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Original Contribution

Risk and Benefit of mRNA COVID-19 Vaccines for the Omicron Variant by Age, Sex, and Presence of Comorbidity: A Quality-Adjusted Life Years Analysis

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The development of the mutant omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the coronavirus disease 2019 (COVID-19) pandemic raised the importance of reevaluating the risk and benefit of COVID-19 vaccines. With a decision tree model, we calculated the benefit-risk ratio and the benefit-risk difference of receiving monovalent messenger RNA (mRNA) COVID-19 vaccine (primary 2 doses, a third dose, and a fourth dose) in the 4–5 months after vaccination using quality-adjusted life years. The analysis was stratified by age, sex, and the presence of comorbidity. Evidence from peer-reviewed publications and gray literature was reviewed on September 16, 2022, to inform the study. Benefit-risk ratios for receipt of the BNT162b2 vaccine (Pfizer-BioNTech) ranged from 6.8 for males aged 12–17 years without comorbidity for the primary doses to 221.3 for females aged ≥65 years with comorbidity for the third dose. The benefit-risk ratios for receipt of the mRNA-1273 vaccine (Moderna) ranged from 7.2 for males aged 18–29 years without comorbidity for the primary doses to 101.4 for females aged ≥65 years with comorbidity for the third dose. In all scenarios of the one-way sensitivity analysis, the benefit-risk ratios were more than 1, irrespective of age, sex, comorbidity status, and type of vaccine, for both primary and booster doses. The benefits of mRNA COVID-19 vaccines in protecting against the omicron variant outweigh the risks, irrespective of age, sex, and comorbidity.

coronavirus disease 2019; COVID-19; quality-adjusted life years; risk; safety; vaccines

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; MIS-C, multisystem inflammatory syndrome in children; QALY, quality-adjusted life year; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

While vaccines are essential to mitigate the impact of the coronavirus disease 2019 (COVID-19) pandemic, vaccine hesitancy threatens the potential impact of vaccination success (1). Messenger RNA (mRNA) vaccines—including BNT162b2, manufactured by Pfizer-BioNTech (Pfizer, Inc., New York, New York; BioNTech SE, Mainz, Germany), and mRNA-1273, manufactured by Moderna, Inc. (Cambridge, Massachusetts)—are widely used globally, especially in high-income countries (2). Although mRNA vaccines are generally very safe and effective, particularly for preventing hospitalization and death due to COVID-19 (2), adverse events following immunization, such as myocarditis and pericarditis, have associated with these vaccines. In the United States, among persons vaccinated with BNT162b2 there were 26.7 reported cases of myocarditis per 100,000 males aged 12–17 years within 21 days after the second dose (3), and many studies have indicated that the risk is higher for mRNA-1273 than for BNT162b2 (3–7). The incidence of postvaccination myocarditis has been lower in females than in males and in older adults compared with younger adults or adolescents (3, 4). The Centers for Disease Control and Prevention conducted a risk-benefit analysis of mRNA COVID-19 vaccines, calculating the number of COVID-19 cases, hospitalizations, and deaths averted (5–8). However, the analysis for vaccine risk was based on passive reporting of adverse events following immunization. While some passive surveillance systems, including the Vaccine Adverse Event Reporting System, monitor adverse events following COVID-19 vaccination, the passive nature of these surveillance systems raises concerns about underreporting,

overreporting, and misreporting (9). In addition, to our knowledge, no analysis comparing the risks and benefits of mRNA COVID-19 vaccines using a single health outcome scale (e.g., quality-adjusted life years (QALYs)) has yet been reported (10). For persons who hesitate to get the vaccine because of concerns about potential adverse events, evaluating the magnitude of the expected benefit versus the potential risks may be helpful in supporting their vaccine decision-making.

On November 26, 2021, the World Health Organization designated the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant B.1.1.529 (omicron) a variant of concern (11). Soon after, the omicron variant replaced previously predominant strains of SARS-CoV-2 (e.g., delta) in many countries (12, 13). Compared with the delta variant, omicron has led to reduced vaccine effectiveness and reduced disease severity, illustrating the importance of considering data specific to omicron when evaluating the risks and benefits of COVID-19 vaccines (14–16).

Our objective in this study was to evaluate the benefits and risks of the mRNA COVID-19 vaccines using a single health outcome scale (QALYs) through the period of widespread circulation of the omicron variant.

METHODS

Model overview

Using the decision tree model presented in Figure 1, we calculated the expected benefits and risks of receiving each of the monovalent mRNA COVID-19 vaccines (BNT162b2 and mRNA-1273), stratifying the results by age, sex, and the presence of comorbidity (≥1 comorbid condition). The study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (17). Age groups used for stratification included 5–11, 12–17, 18–29, 30–49, 50–64, and ≥65 years for monovalent BNT162b2 and 18–29, 30–49, 50–64, and ≥65 years for monovalent mRNA-1273. The bivalent COVID-19 vaccines were not evaluated in this study given the lack of vaccine effectiveness data at the time the study was conducted. The benefits and risks of the primary series (2 doses), a third dose, and a fourth dose were estimated. The comparators and the time horizon in the study were as follows.

1. Less than 5 months (days 14–149) after the primary 2 doses versus no doses.
2. Less than 4 months (days 7–119) after a third dose versus 5–8 months (days 150–262) after the primary doses (no third dose).
3. Less than 4 months (days 7–119) after a fourth dose versus 4–7 months (days 120–232) after a third dose (no fourth dose) for adults.

Both the benefits and the risks of the vaccine were quantified using the QALY, a measure for evaluating health outcomes. QALYs are calculated by multiplying an individual's health utility (a numerical value between 0 and 1) by the expected number of remaining life years (18). US data provided information on age- and sex-specific health utility norms and life expectancy (19, 20). Methods for calculating the risks and benefits of the vaccine are presented in the Web Appendix (available at https://doi.org/10.1093/aje/kwad058).

We examined both published studies and gray literature to identify the values of indicators in the model (Web Table 1) to ensure inclusion of the rapidly evolving evidence regarding COVID-19 vaccines and the omicron variant. When adjusting future QALY changes to present values, the discount rate was 3%, meaning that for each year (n) in the future the health value was multiplied by $(1/(1 + D)^n)$, D being the discount rate (21, 22). The discount rate was applied to QALY loss due to long-term sequelae or death. Cost was not considered in this study. All calculations were conducted using Microsoft Excel 2016 (Microsoft Corporation, Redmond, Washington).

Outcome

Study outcomes were the benefits and risks of vaccination, presented as QALY change per 100,000 vaccinees in the 4–5 months after vaccination, for 1) persons receiving the primary doses (days 14–149 after the second of the 2 primary doses) versus no dose; 2) persons receiving a third dose (days 7–119 after the booster dose) versus no third dose (days 150–262 after the primary doses); and 3) for those aged 18 years or older, persons receiving a fourth dose (days 7–119 after the booster dose) versus no fourth dose (days 120–232 after the third dose). The benefit of the vaccine was measured as the incremental QALYs gained by vaccination, and the risk of the vaccine was the decremental QALYs lost by vaccination. The benefit-risk ratio and the benefit-risk difference for the QALY changes were calculated as follows:

Benefit-risk ratio = incremental QALYs gained by vaccination/decremental QALYs lost by vaccination.

Benefit-risk difference = incremental QALYs gained by vaccination − decremental QALYs lost by vaccination.

Vaccine benefits and COVID-19 burden

In the model, the benefits of vaccination included the prevention of symptomatic nonhospitalized infection, hospitalization, admission to a hospital's intensive care unit (ICU), death due to COVID-19, postacute COVID-19 syndrome, and multisystem inflammatory syndrome in children (MIS-C) by the vaccination during the comparison period. The QALY loss of asymptomatic infection was assumed to be zero in this study. Information on vaccine effectiveness against infection and severe outcomes for the omicron variant was obtained from US data (Web Table 2) (16, 23, 24).

We obtained the age- and sex-specific average incidence rates (per 100,000 person-years) of COVID-19 cases and deaths among the unvaccinated from US data covering the period February 13, 2022–July 2, 2022 to calculate the expected average incidence during the comparison period (25, 26). Age- and sex-specific data on each outcome (asymptomatic infection, symptomatic nonhospitalized infection, hospitalization, ICU admission, and death) for the omicron variant were obtained from US data (27–30).

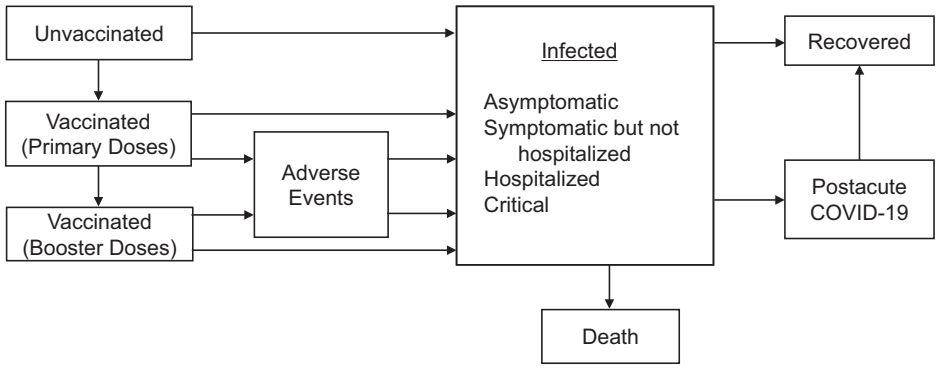

Figure 1. Decision tree model for coronavirus disease 2019 (COVID-19) vaccination. While both the unvaccinated population and the vaccinated population may get infected, the vaccinated population has a reduced chance of becoming infected. Vaccination involves a risk of adverse events. Infection status is divided into 4 groups: asymptomatic, symptomatic but not hospitalized, hospitalized, and critical, with a proportion of the infected population experiencing death. Postacute COVID-19 was only assumed for symptomatic cases.

Because the data on COVID-19 incidence contained both symptomatic and asymptomatic infections, we estimated the incidence of symptomatic COVID-19 cases to calculate the disease burden of nonhospitalized COVID-19 cases. The rates of developing severe outcomes (hospitalization or death) were also stratified by the presence of comorbidity (27, 31). The health disutility and the duration of each COVID-19–related status (nonhospitalized symptomatic infection, hospitalization, ICU admission without mechanical ventilation, ICU admission with mechanical ventilation, death, and postacute COVID-19 syndrome) were obtained from previous literature (30, 32–35). Because of the lack of data regarding COVID-19–specific health disutility for acute cases requiring hospitalization and ICU admission, we obtained information on the health disutility of hospitalization and ICU admission for other infectious disease outcomes (i.e., severe acute respiratory syndrome) (33, 34).

Underestimation of COVID-19 burden was also considered in the model, with underreporting ratios for COVID-19 cases and deaths of 3.40 and 1.32, respectively (36). We obtained data on the health disutility of postacute COVID-19 syndrome among hospitalized cases aged 18 years or older (37). The ratio of the rate of developing persistent symptoms after COVID-19 in children to the rate in adults was multiplied by the postacute COVID-19 QALY loss for adults in order to calculate the estimated QALY loss from postacute COVID-19 for children aged 5–17 years (38).

The Centers for Disease Control and Prevention reported the 7-day average number of reported MIS-C cases, and a US study estimated the incidence of MIS-C between April and June 2020 in 7 US states as 5.1 cases per 100,000 person-months (39, 40). According to these data, the model estimated that the incidence rates of MIS-C from February 13, 2022, to July 2, 2022, were 2.6, 1.8, and 0.7 per 100,000 person-months for persons aged 5–11, 12–15, and 16–20 years, respectively (Web Table 1). Feldstein et al. (41) reported that length of hospital stay among MIS-C cases was 7 days, with 79.6% and 19.9% of patients requiring ICU admission and mechanical ventilation, respectively, which were included in the model. The negative impact of COVID-19–related complications, such as thrombosis and myocarditis, was not included in the model to avoid double-counting of the disease burden. The average QALY loss per event is presented in Web Tables 3–5.

Vaccine risks

Risks of vaccination included anaphylaxis, myocarditis, and other adverse events such as fever, headache, nausea, and local pain (2, 42). To avoid underestimating the impact of adverse events, we used health-care databases and active surveillance systems, instead of passive surveillance systems, to estimate the risks of anaphylaxis and myocarditis, and we used randomized controlled trials to estimate rates of more common adverse events (42–49).

The incidence of anaphylaxis was reported to be higher in females than in males (Web Table 1) (42, 50, 51). The model assumed that all patients with anaphylaxis recovered without long-term complications (52). The incidence of myocarditis after the primary doses (cumulative incidence after dose 1 and dose 2) and a booster dose of BNT162b2 was obtained from US active surveillance data (53). In the case series from the United States and Canada, the median length of hospitalization was 2 days, and 18.7% of patients were admitted to the ICU (54). The US data showed that among 360 cases with myocarditis after COVID-19 vaccination, 81% were fully or probably fully recovered at 143 days (interquartile range, 131–162) after myocarditis onset (55). On the basis of these data, the estimated incidence of myocarditis by age and by sex in our model is presented in Web Table 1. Based on data from persons with heart failure, we assumed a health disutility of −0.2 for those who had not recovered after hospital discharge (19% of all myocarditis cases after COVID-19 vaccination had −0.2 health disutility for 143 days after the onset of myocarditis) (55, 56). However, the long-term prognosis of vaccine-associated myocarditis is unknown. Some reports estimate that up to 20% of persons

with myocarditis unrelated to vaccination develop long-term cardiac dysfunction, although the outcomes of myocarditis following COVID-19 vaccination are reported to be better than those of myocarditis unrelated to vaccination (57, 58). No myocarditis death was considered in the model, given the lack of data regarding the incidence rate of myocarditis death after vaccination.

The rates of developing other, more common adverse events, by grade of adverse events, by age, and by vaccine type, were obtained from the clinical trial data, considering the difference in rates of adverse events between vaccine and placebo groups (43–49). According to a study regarding QALY loss due to adverse events by grade, grade 1 or grade 2 adverse events did not produce significant QALY loss, while grade 3 adverse events had a loss of 0.68 QALYs/1,000 grade 3 events (a grade 3 event prevents daily routine activity or requires use of a pain reliever; a grade 4 event requires an emergency room visit or hospitalization) (59). The age-specific incidence of adverse events (myocarditis, anaphylaxis, and other adverse events) after the fourth dose was assumed to be the same as that after the third dose.

Sensitivity analyses

We conducted one-way sensitivity analyses to explore the impact of indicators with uncertain values and new SARS-CoV-2 variants that might emerge in the future (Web Table 2). The indicators investigated in sensitivity analyses included the incidence of COVID-19 (from the minimum incidence to the maximum weekly incidence between January and July 2022), vaccine effectiveness (23), the long-term effect of myocarditis following vaccination (from resolution at discharge for all cases with myocarditis to lifelong heart failure for 20% of cases with myocarditis), the relative incidence of myocarditis after a booster dose as compared with the primary 2 doses (from 0.08 to 1.35) (53), COVID-19 disease severity (from 45% and 82% reductions in hospitalization and death (vs. the base-case scenario) due to development of protective immunity from prior natural infection to higher severity due to delta variant infection) (30, 60), and the discount rate (0%–5% per year) (21). Details on the uncertainties of these indicators are provided in Web Table 2.

In addition, we conducted a probabilistic sensitivity analysis for the above indicators with 1,000 simulations to evaluate the distribution of benefit-risk ratios in the age group with the lowest benefit-risk ratio in the base-case scenario. In the probabilistic sensitivity analysis, a beta (β) distribution was assumed for vaccine effectiveness, while a β-PERT distribution (PERT stands for "program evaluation and review technique"; the PERT distribution is based on minimal, most likely, and maximal values) was assumed for other indicators (Web Table 6).

Ethics

A review of human subjects research was not required for this study, since we used only publicly available data.

RESULTS

The estimated disease burden of COVID-19 (QALY loss/100,000 unvaccinated population) from February 13, 2022, to July 2, 2022, was larger in older age groups, ranging from 53.3 for males aged 5–11 years without comorbidity to 1,745.9 for females aged ≥65 years with comorbidity (Table 1).

Vaccine benefits (QALY gain/100,000 vaccinees) for primary doses (days 14–149 after the third dose) versus no doses ranged from 22.0 for males aged 5–11 years without comorbidity who received BNT162b2 to 951.4 for females aged ≥65 years with comorbidity who received mRNA-1273 (Web Table 7). For a third dose, the vaccine benefits (days 7–119 after the third dose) ranged from 22.0 for males aged 5–11 years without comorbidity who received BNT162b2 to 708.5 for females aged ≥65 years with comorbidity who received mRNA-1273 (Web Table 7). The benefits were larger for mRNA-1273 than for BNT162b3 across all age, sex, and comorbidity stratifications. On the other hand, the risks from vaccination were higher for mRNA-1273 than for BNT162b3. The highest risk for myocarditis was among males aged 12–17 years after receipt of mRNA-1273 (15.60/100,000 vaccinees after the primary series). The group with the highest vaccine risk was males aged 18–29 years (11.9 and 5.9 QALY loss/100,000 vaccinees for primary doses and a booster dose of the mRNA-1273 vaccine, respectively).

The benefit-risk differences were larger for mRNA-1273 than for BNT162b3 across all age, sex, and comorbidity groups, ranging from 18.7/100,000 vaccinees for males aged 5–11 years without comorbidity for a booster dose of BNT162b2 to 939.8/100,000 vaccinees for females aged ≥65 years with comorbidity for primary doses of mRNA-1273 (Table 1). On the other hand, the benefit-risk ratios were higher for BNT162b2 than for mRNA-1273, ranging from 6.8 for males aged 12–17 years without comorbidity for the primary doses to 221.3 for females aged ≥65 years with comorbidity for the third dose among persons receiving BNT162b2 and ranging from 7.2 for males aged 18–29 years without comorbidity for the primary doses to 101.4 for females aged ≥65 years with comorbidity for the third dose among persons receiving mRNA-1273 (Table 1).

Figure 2 and Web Figure 1 show the results of one-way sensitivity analyses of the benefit-risk ratio for males aged 12–17 years without comorbidity who received primary doses (vs. no dose) and a third dose (vs. no third dose) of BNT162b2, the group with the lowest benefit-risk ratio in the base-case scenario. The benefit-risk ratios were 1 or larger in all scenarios, irrespective of age, sex, and the presence of comorbidity. The results of the probabilistic sensitivity analysis for males aged 12–17 years without comorbidity who received BNT162b2 and males aged 18–29 years without comorbidity who received mRNA-1273 are presented in Figure 3 and Web Figure 2, respectively. In the 1,000 simulations, the probabilities of having benefit-risk ratios greater than 1, greater than 5, and greater than 10 for the primary 2 doses versus no dose for males aged 12–17 years without comorbidity among persons receiving BNT162b2

Table 1. Burden of Coronavirus Disease 2019 and Related Benefit-Risk Ratios According to Age, Sex, and the Presence of Comorbidity, United States, September 16, 2022

Measure, Vaccine, and Age Group, years	Sex and Comorbidity Status			
	Male		Female	
	Comorbidity	No Comorbidity	Comorbidity	No Comorbidity
COVID-19 burden[a]				
5–11	60.2	53.3	68.0	61.8
12–17	88.7	76.0	100.3	88.8
18–29	214.6	176.3	228.4	193.9
30–49	443.0	328.7	451.7	355.3
50–64	1,069.3	679.4	1,040.6	718.3
≥65	1,666.8	1,354.8	1,745.9	1,519.6
Benefit-risk difference[b]				
BNT162b2				
Primary doses vs. no dose[c]				
5–11	25.2	20.8	28.1	24.2
12–17[d]	43.9	36.0	50.4	43.3
18–29	94.2	71.2	99.2	78.5
30–49	210.8	142.2	210.1	152.3
50–64	558.2	324.2	531.5	338.1
≥65	835.2	647.9	858.5	722.7
Third dose vs. no third dose[e]				
5–11	21.2	18.7	23.9	21.6
12–17[d]	32.1	27.5	35.6	31.5
18–29	62.7	49.3	65.7	53.6
30–49	131.9	92.0	131.9	98.3
50–64	336.0	199.9	321.2	208.7
≥65	503.1	394.2	518.5	439.5
Fourth dose vs. no fourth dose[f]				
18–29	35.0	27.4	37.2	30.4
30–49	76.9	54.1	77.5	58.3
50–64	196.5	118.8	189.1	124.8
≥65	300.6	238.4	312.0	266.8
mRNA-1273				
Primary doses vs. no dose[c]				
18–29	98.8	73.9	104.6	82.2
30–49	226.9	152.6	226.7	164.0
50–64	605.6	352.2	577.5	368.0
≥65	912.5	709.7	939.8	792.7
Third dose vs. no third dose[e]				
18–29	75.1	60.1	78.6	65.2
30–49	153.8	109.1	154.2	116.5
50–64	383.9	231.6	367.9	242.0
≥65	575.8	454.0	594.5	506.1
Fourth dose vs. no fourth dose[f]				
18–29	40.4	31.2	43.2	34.9
30–49	91.8	64.3	92.8	69.6
50–64	237.5	143.5	228.8	151.2
≥65	366.4	291.2	381.0	326.5
Benefit-risk ratio				
BNT162b2				
Primary doses vs. no dose[c]				
5–11	23.2	19.4	26.3	22.8
12–17[d]	8.1	6.8	9.5	8.3
18–29	17.3	13.3	18.6	14.9
30–49	38.3	26.2	38.3	28.0
50–64	100.4	58.7	95.6	61.2
≥65	149.8	116.4	153.8	129.7

Table continues

Table 1. Continued

Measure, Vaccine, and Age Group, years	Sex and Comorbidity Status			
	Male		Female	
	Comorbidity	No Comorbidity	Comorbidity	No Comorbidity
Third dose vs. no third dose[e]				
5–11	45.2	39.7	50.8	45.8
12–17[d]	11.3	9.5	13.5	11.8
18–29	24.9	19.4	27.1	21.9
30–49	54.9	38.0	55.4	41.0
50–64	143.2	84.8	136.7	88.5
≥65	214.9	168.2	221.3	187.5
Fourth dose vs. no fourth dose[f]				
18–29	15.5	12.3	16.9	14.0
30–49	33.6	23.9	34.1	25.9
50–64	85.3	52.0	82.1	54.5
≥65	130.0	103.3	134.8	115.4
mRNA-1273				
Primary doses vs. no dose[c]				
18–29	9.3	7.2	10.0	8.1
30–49	20.4	14.0	20.5	15.1
50–64	53.1	31.3	50.6	32.6
≥65	79.4	62.0	81.8	69.1
Third dose vs. no third dose[e]				
18–29	11.7	9.1	12.5	10.2
30–49	25.4	17.8	25.5	19.0
50–64	65.1	38.9	62.3	40.7
≥65	98.2	77.2	101.4	86.1
Fourth dose vs. no fourth dose[f]				
18–29	7.8	6.3	8.4	7.0
30–49	16.8	12.0	16.9	12.9
50–64	41.9	25.7	40.4	27.0
≥65	64.1	51.2	66.6	57.2

Abbreviations: COVID-19, coronavirus disease 2019; mRNA, messenger RNA; QALY; quality-adjusted life year.

[a] Values are presented as QALY loss/100,000 unvaccinated population. The average age at death was assumed to be 23.5 years in the age group 18–29 years, 39.5 years in the age group 30–49 years, 57.0 years in the age group 50–64 years, and 80.0 years in the age group ≥65 years.

[b] Values are presented as QALY gain/100,000 vaccinees.

[c] Comparison between days 14–149 after receiving the primary doses and the corresponding period with no dose.

[d] In cases where the data regarding vaccine benefits or risks of BNT162b2 in persons aged 12–17 years were not available, the data for persons aged 12–15 years were applied.

[e] Comparison between days 7–119 after receiving a third dose and no third dose (days 150–262 since the second dose).

[f] Comparison between days 7–119 after receiving a fourth dose and no fourth dose (days 120–232 since a third dose).

were 100%, 83.9%, and 13.5%, while those for a third dose versus the primary 2 doses were 100%, 97.2%, and 53.6%, respectively (Figure 3).

DISCUSSION

This study demonstrated that the benefits of mRNA vaccines are much larger than the risks, for both the primary series and the booster dose, across all age, sex, and comorbidity status groups. In addition, sensitivity analyses showed that benefits would continue to outweigh risks even in low-incidence, low-severity, or comparatively low-vaccine-effectiveness scenarios. To our knowledge, this study was the first quantitative comparison of the benefits and risks of receiving COVID-19 vaccines using a single health scale, considering the omicron variant. Notably, while the difference in the benefit minus risk for receiving COVID-19 vaccination was expected to be larger for mRNA-1273, the ratio of benefit to risk was larger for BNT162b2. Our study could help individuals of any age and sex make informed decisions about whether to be vaccinated against COVID-19.

Vaccine hesitancy is a serious public health concern, impeding the use of vaccines to mitigate the spread of

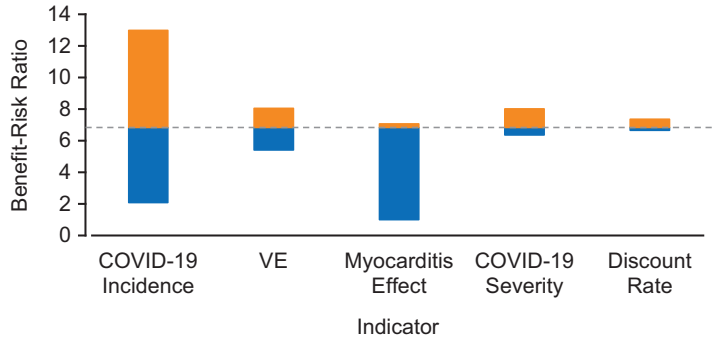

Figure 2. One-way sensitivity analysis of the benefit-risk ratio for coronavirus disease 2019 (COVID-19) vaccination in males aged 12–17 years without comorbidity who received primary doses of BNT162b2, September 16, 2022. The indicators investigated in the sensitivity analysis included the incidence of COVID-19, vaccine effectiveness (VE), the long-term effect of myocarditis following vaccination, COVID-19 disease severity or QALY loss associated with COVID-19, and the discount rate. QALY, quality-adjusted life years.

COVID-19 (1). Some people, especially younger populations, question whether receiving the COVID-19 vaccine would be beneficial for them given their low likelihood of developing severe COVID-19, even if acknowledging the potential benefit of preventing the spread of infection to others (61). A systematic review revealed that major concerns of the vaccine-hesitant population included vaccine safety, perceptions of a low likelihood of contracting vaccine-preventable diseases, perceived low severity of vaccine-preventable diseases, beliefs that vaccines do not work, and overall lack of information (62).

While a recent study found a small number of MIS-C cases after COVID-19 vaccination (63), our study did not include this burden in our analysis because of the remaining uncertainty in causality assessment. Continuous safety monitoring and timely evaluation are necessary as more young children are vaccinated (63).

This study did not investigate children under 5 years of age, given that postlicensure vaccine data had not yet accumulated for this population at the time the study was conducted. A quantitative evaluation of the benefits and risks of COVID-19 vaccination for infants and young children is an important future research topic. In addition, this study did not consider indirect benefits of vaccination, including reduced transmission, alleviation of the burden on the health-care system and workforce through a reduction in the number of severe cases, money saved by replacing treatment with prevention, the larger economic impacts of the

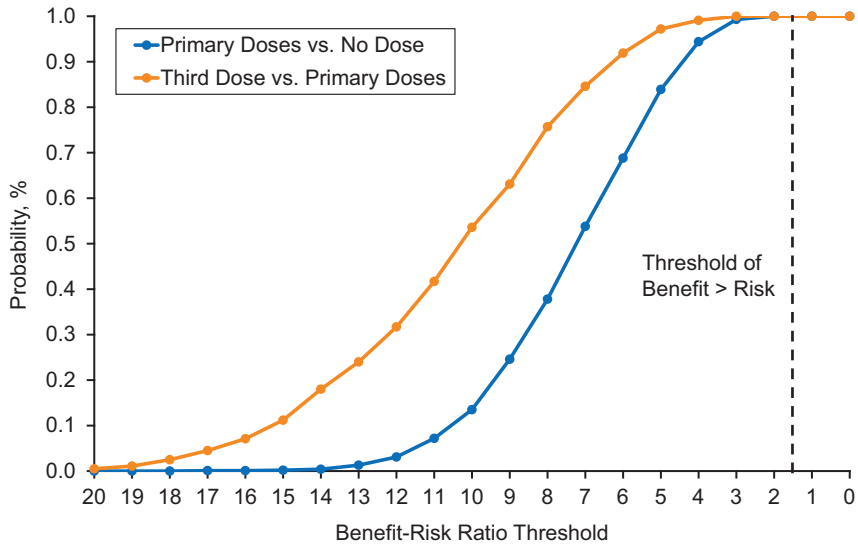

Figure 3. Probabilistic sensitivity analysis of coronavirus disease 2019 (COVID-19) vaccination for males aged 12–17 years without comorbidity who received BNT162b2, September 16, 2022. The probabilistic sensitivity analysis was conducted with 1,000 Monte Carlo simulations. The indicators included the incidence of COVID-19, vaccine effectiveness, the long-term effect of myocarditis following vaccination, the relative incidence of myocarditis after a booster dose as compared with the primary 2 doses, COVID-19 disease severity, and the discount rate. A beta (β) distribution was assumed for vaccine effectiveness, while a β-PERT distribution (program evaluation and review technique) was assumed for other indicators.

pandemic, and so on. Consideration of these factors would only further increase the expected net benefits of vaccination. The study did not account for the impact of herd immunity and therapeutic medications. The risk of an unvaccinated person's becoming infected with SARS-CoV-2 may decline in the future as the vaccine coverage rate in the population is further improved. If more effective therapeutic medications are used in the future, the overall disease burden of COVID-19 may also decrease.

Although the new bivalent COVID-19 vaccine had limited postlicensure data regarding safety and effectiveness at the time this study was conducted, clinical trials showed that the bivalent vaccines had similar safety profiles and potentially better immunogenicity to the omicron B.A.5 variant than the monovalent vaccines (64). This suggests that the new bivalent vaccine may be expected to have similar or better benefit-risk ratios and differences in comparison with the monovalent vaccines. While the data used in the model were mainly derived from US sources, the results may be applied globally. However, the magnitude of the benefit of vaccination varies by country, due to the wide variation in the pandemic situation by country and by region.

This study had some limitations. There were large uncertainties for some indicators in the model, including the population incidence of COVID-19, the incidence of myocarditis for a booster dose, the magnitude of the impact of myocarditis after vaccination (frequency, duration, and health disutility of long-term cardiac dysfunction), and COVID-19–specific health utility for acute cases requiring hospitalization and ICU admission. Evidence regarding booster doses in children and adolescents was relatively scarce at the time the study was conducted. However, sensitivity analyses showed a consistent beneficial result for both primary and booster doses, irrespective of age, sex, and comorbidity status. While this study mainly focused on the population without prior infection, the benefits and risks of vaccination for persons with prior COVID-19 infection may need to be evaluated separately, given that some studies have indicated differences in the risks and benefits of vaccination by history of COVID-19 (65–67). Although there have been case reports of death with myocarditis after COVID-19 vaccination (68), myocarditis death was not considered in the model because of a lack of evidence for calculating the incidence rate of myocarditis death after vaccination.

In conclusion, the benefits of mRNA COVID-19 vaccines (both primary and booster doses) outweigh the risks, irrespective of age, sex, and the presence of comorbidity, and even considering the reduced disease severity and vaccine effectiveness for the omicron variant. While we cannot predict the specifics of future variants, these findings strengthen the recommendation that all eligible persons should stay up to date on COVID-19 vaccinations.

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Data supporting the findings of this study are available within the article or its supplementary materials.

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