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A summary of the Advisory Committee for Immunization Practices (ACIP) use of a benefit-risk assessment framework during the first year of COVID-19 vaccine administration in the United States

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Abstract

To inform Advisory Committee for Immunization Practices (ACIP) COVID-19 vaccine policy decisions, we developed a benefit-risk assessment framework that directly compared the estimated benefits of COVID-19 vaccination to individuals (e.g., prevention of COVID-19-associated hospitalization) with risks associated with COVID-19 vaccines. This assessment framework originated following the identification of thrombosis with thrombocytopenia syndrome (TTS) after Janssen COVID-19 vaccination in April 2021. We adapted the benefit-risk assessment framework for use in subsequent policy decisions, including the adverse events of myocarditis and Guillain-Barre syndrome (GBS) following mRNA and Janssen COVID-19 vaccination respectively, expansion of COVID-19 vaccine approvals or authorizations to new age groups, and use of booster doses. Over the first year of COVID-19 vaccine administration in the United States (December 2020–December 2021), we used the benefit-risk assessment framework to inform seven different ACIP policy decisions. This framework allowed for rapid and direct comparison of the benefits and potential harms of vaccination, which may be helpful in informing other vaccine policy decisions. The assessments were a useful tool for decision-making but required reliable and granular data to stratify analyses and appropriately focus on populations most at risk for a specific adverse event. Additionally, careful decision-making was needed on parameters for data inputs. Sensitivity analyses were used where data were limited or uncertain; adjustments in the methodology were made over time to ensure the assessments remained relevant and applicable to the policy questions under consideration.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

[1]Methodology for the calculation of ICU admissions and deaths prevented by vaccination and risks of vaccination remained the same as described in Box 1.

[2]Compared to full vaccine series.

Keywords

COVID-19 vaccination; Benefits; Risks; ACIP; Vaccine policy

1. Introduction

In response to the COVID-19 pandemic, unprecedented efforts were invested in the successful development, authorization, licensure, and introduction of COVID-19 vaccines. In the United States, the Food and Drug Administration (FDA) is the regulatory authority for vaccines. During a public health emergency, FDA may use Emergency Use Authorizations (EUA) to provide access to vaccines prior to licensure, provided that the FDA determines that the known and potential benefits of the vaccine outweigh the known and potential risks. Following FDA's EUA or licensure of a COVID-19 vaccine, the Centers for Disease Control and Prevention (CDC) publishes public health recommendations for vaccine use informed by advice from the Advisory Committee for Immunization Practices (ACIP). ACIP employs Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to systematically assess the certainty of available data on benefits and risks of vaccinations, and the Evidence to Recommendations (EtR) Framework to guide its deliberations [1]. As part of the criteria for issuing an EUA, the Phase III clinical trials data for COVID-19 vaccines demonstrated favorable safety and efficacy profiles [2]. However, clinical trials have limited ability to detect rare adverse events; therefore, CDC initiated robust post-authorization COVID-19 vaccine safety surveillance and research [3,4]. Furthermore, an ACIP COVID-19 Vaccine Safety Technical Work Group (VaST) was established to rapidly review post-authorization vaccine safety data [5].

As COVID-19 vaccines were introduced, ACIP needed to consider new data from post-authorization safety surveillance and make rapid evidence-based decisions regarding benefits and risks given the available data on COVID-19 epidemiology, vaccine effectiveness (VE), and vaccine safety. No standard methodology existed for benefit-risk assessments; thus, we rapidly developed methods, including visualizations inspired by a University of Cambridge analysis on the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine [6]. Similar methods have since been used by other National Immunization Technical Advisory Groups and FDA [7–13]. Here, we review the benefit-risk assessments developed for use with COVID-19 vaccination policy questions, including the methods and modifications of the framework during the first year of COVID-19 vaccine administration in the United States and considerations for input selection, sensitivity analyses, and lessons learned.

2. Benefit-risk assessments: Methods overview and applications to COVID-19 vaccination program

Benefit-risk assessments were conducted for seven policy questions during the first year of the U.S. COVID-19 vaccination program (December 2020–December 2021) (Table 1). We developed methods in April 2021 following reports of a new and clinically serious adverse event of thrombosis with thrombocytopenia syndrome (TTS) among Janssen COVID-19

vaccine recipients [14]. These methods were adapted as a systematic framework to subsequent adverse events and other COVID-19 vaccine policy questions. The assessments used a Microsoft Excel tool developed to calculate estimates of the individual benefits and risks of COVID-19 vaccination. The assessment of benefits was based on four inputs from U.S. data: 1) incidence of COVID-19-associated hospitalization, including occurrence of serious disease (i.e., proportion of hospitalizations resulting in intensive care unit [ICU] admission or death); 2) proportion of the population currently vaccinated; 3) period over which benefits of vaccination accrue (i.e., analytic time horizon); and 4) expected VE during the time horizon (Box 1).

To calculate the estimated COVID-19-associated hospitalizations prevented by vaccination, we used COVID-19-associated hospitalization rates from the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET), an active, population-based surveillance system that collects data on laboratory-confirmed COVID-19-associated hospitalizations among children and adults through a network of over 250 acute-care hospitals in 14 states, representing approximately 10% of the U.S. population [15]. These data are available by age and sex. COVID-NET also provided the frequencies of ICU admissions and deaths among hospitalized cases, by age and sex, obtained by medical chart abstraction on a representative sample of hospitalized patients. The CDC Immunization Data Lake, a de-identified COVID-19 vaccination data repository, provided the national-level number of vaccinated persons, by age, sex, and vaccine product, at the time of each benefit-risk analysis [16]. Denominator data for calculating vaccine coverage were obtained from 2019 census population projections, accessed through CDC Wide-ranging ONline Data for Epidemiologic Research (WONDER) [17]. The analytic time horizon and VE estimates varied for each assessment, based on the policy question under consideration, the current understanding of VE and waning, and SARS-CoV-2 variants circulating at the time.

Data inputs for risks were based on two U.S. vaccine safety monitoring systems, which were enhanced during the COVID-19 vaccination program: the Vaccine Adverse Events Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). VAERS is a spontaneous reporting system, co-managed by CDC and FDA, designed to detect potential vaccine safety signals. Vaccine providers are required by FDA and the provider agreement for the CDC COVID-19 Vaccination Program to report certain adverse events to VAERS; VAERS staff review reports of selected adverse events after COVID-19 vaccinations and apply case definitions, including defined risk intervals after vaccination, to verify the adverse event [18–20]. Adverse event reporting rates may be calculated from VAERS data and vaccine doses administered to assess risk. VSD, a collaboration between CDC and integrated healthcare systems, uses electronic health record data for vaccine safety surveillance and epidemiologic research. VSD conducts near real-time surveillance for pre-specified health outcomes after COVID-19 vaccinations [21,22]. While VAERS reporting rates are generally considered less robust than VSD data for risk assessment, VAERS data were frequently used for benefit-risk assessments because risk data were available for specific ages and sex stratifications (e.g., myocarditis in males aged 16–17 years) and newly recognized, rare adverse events (e.g., TTS). VAERS reporting rates were compared to the available VSD data and sensitivity analyses were used when differences in estimated risk between the two systems were observed. Risks were quantified and expressed as events per

doses administered. Adverse events evaluated included TTS, myocarditis/pericarditis, and Guillain-Barré syndrome (GBS).

Benefit and risk data inputs were stratified if appropriate for the risks being evaluated, based on evidence of higher risk of the adverse events in specific age and sex groups, and differential risk of COVID-19-associated hospitalization by age and sex. All assessments calculated benefits and risks per one million doses. When analyses were stratified, the assessment remained per million doses per stratum, which allowed for easy comparison, visualization, and interpretation. We summarized results of the benefit-risk assessments overall and by subgroup, in tabular format and graphic displays, directly comparing the benefits to harms calculated. Examples of visuals developed to communicate results to ACIP can be found in the supplemental figures. We presented each assessment to the ACIP COVID-19 Vaccines Work Group and subsequently to the full ACIP at public meetings. The presentations from these public meetings can be found on the ACIP webpage [23].

2.1. TTS following Janssen COVID-19 vaccination

On April 13, 2021, FDA and CDC recommended a temporary pause on the use of Janssen COVID-19 vaccine after reports of cerebral venous sinus thrombosis (CVST) was seen in combination with low levels of blood platelets (thrombocytopenia); this finding was subsequently recognized to be a manifestation of TTS [24,25]. TTS is a rare and potentially life-threatening condition characterized by low platelets and thrombosis. In the 10 days following the pause, ACIP convened two public emergency meetings to review the reported cases of TTS and consider the benefits and risks of Janssen COVID-19 vaccination. To inform this discussion, we developed a benefit-risk assessment that directly compared the estimated benefits of vaccination with the estimated risk of TTS following vaccination, per 1 million doses administered.

For the calculation of benefits, we assumed that all COVID-19-associated hospitalizations occurred among unvaccinated persons due to the high efficacy observed in the COVID-19 vaccine clinical trials, for which waning had not yet been observed [26–28]. This initial assumption was supported by COVID-NET data from January 1–June 30, 2021, which showed that only 3% of laboratory-confirmed COVID-19-associated hospitalizations among adults occurred among vaccinated people [29]. To obtain hospitalization rates among the unvaccinated alone, we calculated the proportion of the population that was unvaccinated using the number of vaccine doses administered and divided the overall rates by this proportion at risk.

For the TTS benefit-risk assessment, a 30-day analytic time horizon for benefits was selected. At the time of the Janssen COVID-19 vaccination pause, most jurisdictions were in phase 1c (i.e., persons aged 65–74 years, persons aged 16–64 years with high risk medical conditions, and non-frontline essential workers) or phase 2 (i.e., all persons aged ≥ 16 years not previously recommended for vaccination) of vaccine allocation [30]. Based on estimates of the limited mRNA COVID-19 vaccine availability in the United States at the time and the pause that had been placed on the Janssen COVID-19 vaccine, we assumed that potential vaccinees would have to wait an additional 30 days for vaccination with a different product if the use of Janssen COVID-19 vaccine was not resumed. VE against

hospitalization was assumed to be 90% based on Phase 3 clinical trial data [28,31]. We also assumed that hospitalization incidence was equal in males and females; therefore, we used overall hospitalization rates, ICU admissions, and deaths, by age group.

The risk assessed for Janssen COVID-19 vaccination was compiled from VAERS surveillance of reported TTS cases. Each case was classified according to a case definition and adjudicated by experts in the Clinical Immunization Safety Assessment (CISA) project, including hematologists; CISA experts considered clinical factors, including interval from vaccination, in determining if a case was consistent with TTS [14]. Risk was calculated per million doses administered by age group and sex.

The balance of risks and benefits varied by age and sex because TTS cases were primarily identified among women aged 18–49 years. Among women aged 18–49 years, the benefit-risk assessment found that for every 1 million doses of the Janssen COVID-19 vaccine administered, 297 hospitalizations, 56 ICU admissions, and six deaths related to COVID-19 could be prevented over 30 days, compared with seven expected TTS cases (Table 2, Supplemental Fig. 1) [32]. The benefits (prevention of severe and fatal COVID-19 cases) outweighed the risks (expected TTS cases after vaccination) in all populations. On April 23, 2021, based on this benefit-risk assessment and other evidence presented, ACIP reaffirmed its interim recommendation for the use of the Janssen COVID-19 vaccine in all persons aged ≥ 18 years [14]. ACIP emphasized the importance of education about TTS risk for vaccination providers and the public, recommended treatment for suspected cases, and recommended consideration of the availability of other COVID-19 vaccine options, particularly for women aged 18–49 years. It was recognized at the time that the benefit-risk assessment might be updated as needed to reflect changes in the COVID-19 pandemic and additional information on TTS risk after COVID-19 vaccination.

2.2. Myocarditis following mRNA COVID-19 vaccination

A safety signal of myocarditis/pericarditis following mRNA COVID-19 vaccination emerged in May 2021 [33]. Myocarditis is an inflammation of the heart muscle; if accompanied by pericarditis, an inflammation of the thin tissue surrounding the heart (the pericardium), it is referred to as myopericarditis. We used myocarditis to refer to myocarditis, pericarditis, or myopericarditis. Given that the event was reported most frequently in adolescent and young adult males (aged 12–29 years) and the data for myocarditis risk in VAERS were more robust than for TTS, a benefit-risk analysis was developed that incorporated additional, narrower age groups. Additionally, the impact of sex on anticipated benefits was incorporated in this assessment using age and sex-specific incidence rates as inputs. For the TTS assessment, benefits of vaccination were based only on COVID-19 hospitalizations, ICU admissions, and deaths averted, as the higher severity of TTS was more directly comparable to these outcomes. Patients with myocarditis after mRNA COVID-19 vaccines had a median hospitalization of 1–2 days and most had great symptom improvement by hospital discharge [34,35]. Therefore, due to the lower severity of myocarditis, we also included the benefit of preventing cases of COVID-19 as an outcome, with case incidence inputs from case-based surveillance [36]. VE against infection and hospitalization were set at 95%, based on Phase 3 trial data [26,27]. The analytic time

horizon was extended to 120 days because there was no alternative vaccine available to adolescents and there was strong evidence that vaccine protection against hospitalization persisted ≥ 120 days [37,38].

Risk of myocarditis was calculated based on the number of cases reported to VAERS with onset within seven days of vaccination and recorded doses administered in the CDC vaccination data repository. Myocarditis cases reported to VAERS among persons aged < 30 years in whom COVID-19 vaccines had been received were reviewed at CDC and confirmed to meet a standard case definition [34,35]. Risk was reported as cases per 1 million doses for each of first and second mRNA vaccine doses, by age and sex group. The highest risk of myocarditis was observed following dose 2 in young men. Smaller cell sizes and relatively small case counts in VSD precluded analyzing the data in the narrower age groups used in the VAERS analyses; however, we compared VSD rates in broader age groups to those reported by VAERS to assess agreement between the two safety surveillance systems.

We presented the benefit-risk assessment to ACIP on June 23, 2021 (Supplemental Fig. 2) [39]. ACIP determined that the calculated benefits of mRNA COVID-19 vaccination outweighed the risks of myocarditis in all analytic groups [35]. However, the balance of benefits and risks varied by age and sex because cases of myocarditis were primarily identified among males aged < 30 years, and the risks of poor outcomes related to COVID-19 increase with age. Per 1 million second doses of mRNA COVID-19 vaccine administered to males aged 12–29 years, 11,000 COVID-19 cases, 560 hospitalizations, 138 ICU admissions, and six deaths due to COVID-19 could be prevented, compared with 39–47 expected myocarditis cases after COVID-19 vaccination (Table 3).

2.3. TTS, myocarditis, and GBS and benefit-risk review of all COVID-19 vaccines

GBS following Janssen COVID-19 vaccination was identified in July 2021 primarily in males aged 50–64 years [40]. GBS is a rare autoimmune and neurologic disorder characterized by ascending weakness and paralysis and by laboratory findings of increased cerebrospinal fluid protein with normal numbers of cells. The ACIP COVID-19 Vaccines Work Group requested a combined benefit-risk assessment that considered the risk of TTS, myocarditis, and GBS following all authorized COVID-19 vaccines to date, using previous assumptions and methodology. Vaccine-specific risks were considered. Data to estimate the risks for Janssen COVID-19 vaccination were 1) the number of GBS patients reported to VAERS within 42 days of Janssen COVID-19 vaccination per million doses administered through June 30, 2021 and 2) the number of patients with TTS reported to VAERS and meeting the case definition that occurred after Janssen vaccination per million doses administered through July 8, 2021. The risk of mRNA COVID-19 vaccination was the number of patients reported to VAERS that met the case definition for myocarditis after receipt of dose 2, per million doses administered.

On July 22, 2021, ACIP reviewed the updated benefit-risk assessment after Janssen and mRNA COVID-19 vaccination. ACIP determined that, overall, the benefits of COVID-19 vaccination in preventing COVID-19 morbidity and mortality outweighed the risks of specific adverse (clinically serious) events in adults aged ≥ 18 years [41]. As with the previous analyses, the balance of benefits and risks varied by age and sex because cases of

each adverse event were primarily identified in subgroups of age and sex (i.e., males aged 50–64 for GBS; females aged 30–39 for TTS; and males aged 18–29 years for myocarditis) (Table 2 and Table 3). ACIP continued to recommend Janssen and mRNA COVID-19 vaccination but emphasized that benefit-risk assessments for COVID-19 vaccines could be updated to reflect changes in epidemiology of the COVID-19 pandemic and additional information on the risk for serious adverse events after vaccination.

2.4. Pfizer-BioNTech Biologics License Application (BLA)

In August 2021, an updated benefit-risk assessment was conducted for myocarditis specific to the Pfizer-BioNTech COVID-19 vaccine, prompted by FDA's approval of the Biologics License Application (BLA) of the vaccine for use in persons aged ≥ 16 years as a primary series (i.e., superseding the EUA). Weekly hospitalization rates were unstable in the younger age groups because few hospitalization events occurred. Therefore, we used averaged weekly rates from the weeks ending July 10–July 31, 2021. At the time of the analysis, the Delta variant surge was causing rates of SARS-CoV-2 infection and hospitalization to increase rapidly; to account for this and the lag in data availability, incidence rates were multiplied by 1.5, and hospitalization rates were multiplied by 3. At the peak of the Delta variant case surge, incident rates were twice as high and hospitalization rates were four times as high as the rates available at the time of the assessment, suggesting the multipliers used were reasonable adjustments to the available data. Otherwise, methods were similar to benefit-risk assessments previously described.

The benefit-risk assessment presented to ACIP on August 30, 2021 [42] showed that the benefits of vaccination with Pfizer-BioNTech COVID-19 vaccine outweighed the risk of myocarditis. Per 1 million second doses of mRNA COVID-19 vaccine administered to males aged 16–17 years (i.e., the group with highest risk of myocarditis), 56,700 COVID-19 cases, 500 hospitalizations, 170 ICU admissions, and four deaths due to COVID-19 could be prevented, compared with 73 expected myocarditis cases after COVID-19 vaccination (Table 3). After a systematic review of all available safety data and a meta-analysis of global VE estimates [43], the ACIP revised its interim recommendation to a standard recommendation for use of the Pfizer-BioNTech COVID-19 vaccine in persons aged ≥ 16 years for the prevention of COVID-19 [44].

2.5. Pfizer-BioNTech, Moderna, and Janssen COVID-19 boosters

When ACIP considered a COVID-19 vaccine booster dose in September and October 2021, the ACIP COVID-19 Work Group requested a benefit-risk assessment to evaluate whether the incremental benefit gained by a booster dose outweighed the potential risk of myocarditis. The application of the assessment required methodologic changes to account for 1) incident COVID-19 cases and hospitalizations among the vaccinated and 2) the relative VE provided by a booster dose (Box 2). At the time of the analysis, SARS-CoV-2 infections among vaccinated people were common; we sought to determine how many infections after vaccination a booster dose might prevent [45]. We used the vaccine screening method to calculate the proportion of COVID-19 cases and hospitalizations occurring among the unvaccinated and vaccinated, using vaccine coverage and VE estimates [46]. The age-specific, 2-dose VE estimates were derived by averaging effectiveness

estimates across four CDC platforms [45,47–49]. We used an overall VE estimate to predict the proportion of hospitalizations occurring among vaccinated and unvaccinated persons and used vaccine-specific estimates to calculate the estimated benefits expected from vaccination with each specific COVID-19 vaccine. Overall hospitalization rates were also stratified by vaccination status.

The assessment was stratified into broad age groups, selected for their potential to inform age-based COVID-19 vaccine recommendations. A 180-day analytic time horizon was used to mirror the policy question of booster dose receipt ≥ 6 months after completion of a primary series. No estimates of vaccine efficacy or effectiveness against COVID-19 hospitalization for the booster dose were available. Therefore, informed by the SARS-CoV-2 antibody levels in booster recipients in clinical trials and early observational data from Israel [50,51], we assumed that a booster dose would return VE to the level seen in the clinical trials. Risk of myocarditis following a booster dose was also unavailable, so we employed the conservative assumption that risk would be equivalent to the higher risk observed following dose 2.

In addition to the standard presentation of the benefit-risk assessment, we extended the assessment to calculate number needed to vaccinate (NNV), which facilitated a comparison of the benefits of primary series versus booster doses [52,53]. The benefits of a booster dose of the Pfizer-BioNTech, Moderna, or Janssen COVID-19 vaccines outweighed the anticipated risks; however, the benefits of primary series vaccination were much larger than the benefits of a booster dose (Supplemental Table, Supplemental Fig. 3). During ACIP meetings in September and October 2021, ACIP voted in favor of the use of a COVID-19 vaccine booster dose after completion of an mRNA primary series for persons aged ≥ 65 years, persons aged 50–64 years with underlying medical conditions, and persons aged ≥ 18 years who reside in long-term care settings. Use of a booster dose for persons aged 18–49 years with underlying medical conditions and for persons aged 18–64 years at high risk for COVID-19 exposure and transmission because of occupational or institutional setting was recommended based on individual benefits and risks. Additionally, ACIP voted in favor of a COVID-19 vaccine booster dose for persons aged ≥ 18 years who received primary vaccination with Janssen COVID-19 vaccine [50]. Recommendations for a booster dose were later expanded to additional groups [54].

2.6. EUA for Pfizer-BioNTech vaccine in children aged 5–11 years

When ACIP considered the EUA for Pfizer-BioNTech COVID-19 vaccines in children aged 5–11 years in November 2021, we returned to the original benefit-risk assessment methodology (Box 1), as there was no primary series vaccination established in the population to consider. We assumed high efficacy against infection (90%) and hospitalization (95%), based on the high efficacy seen against symptomatic illness in the Phase 3 trial [55]. Due to the relatively high rates of infection and hospitalization in this age group at the time of the assessment, we used recent and pandemic average age and sex-specific case incidence and hospitalization rates. Benefits were calculated over a 180-day time horizon. For harms, because myocarditis rates in 5–11-year-old children were unknown, potential risks were described based on the epidemiology of viral myocarditis in

this age group, which has lower rates of viral myocarditis than adolescents, and rates of vaccine-associated myocarditis in adolescents aged 12–15 years. No specific risk estimates were incorporated for children aged 5–11 years.

Due to uncertainty about the risk of myocarditis in children, there was no calculated direct comparison of benefits and harms for this policy question. However, we used the benefit-risk assessment to contextualize the anticipated benefits [56] (Table 3). The assessment was also used for NNV calculations. On November 2, 2021, after a systematic review of available data, including GRADE assessment of the clinical trial data, the ACIP made an interim recommendation for use of the Pfizer-BioNTech COVID-19 vaccine in children aged 5–11 years [57].

2.7. Janssen COVID-19 vaccine safety

In December 2021, COVID-19 Vaccines Work Group and the ACIP reviewed an updated benefit-risk assessment of COVID-19 vaccines. Reports of TTS cases and deaths had continued, despite ongoing education on groups most at risk and appropriate treatment. For this assessment, use of the screening method to estimate COVID-19 hospitalization rates by vaccination status was no longer needed because hospitalization rates stratified by vaccination status were available from COVID-NET, simplifying the methodology (Box 3) [58]. VE estimates came from the Investigating Respiratory Viruses in the Acutely Ill (IVY) Network and were notably lower than the efficacy estimates previously used [59]. Benefits were calculated over a 180-day time horizon, the known duration of protection at the time. We evaluated all previously considered harms using TTS, GBS, and myocarditis rates from VAERS. A detailed review of TTS cases following Janssen COVID-19 vaccination occurring before August 31, 2021, including a description of rates, patient characteristics, and clinical course, was presented to ACIP and used in the benefit-risk analysis [60].

In this assessment, the benefits and harms of each available vaccine were directly compared for the first time [61]. The estimated benefits of the Janssen COVID-19 vaccine outweighed the risks when compared with no vaccine for all persons aged ≥ 18 years (Table 2). However, when compared with the benefit-risk balance for mRNA COVID-19 vaccines, the Janssen COVID-19 vaccine prevented fewer COVID-19 hospitalizations (Tables 2, 3, Supplemental Fig. 4). In addition, more severe, long-term health impacts from TTS and GBS were noted after Janssen COVID-19 vaccination, compared with the apparently less severe myocarditis-associated outcomes after mRNA COVID-19 vaccination. On December 16, 2021, ACIP voted unanimously for a recommendation for preferential use of mRNA COVID-19 vaccines over the Janssen COVID-19 vaccine for the prevention of COVID-19 for persons aged ≥ 18 years [62].

3. Considerations for input selection, sensitivity analyses, and lessons learned

To appropriately capture the issues relevant to each policy question, it was important to identify informative analytic strata and appropriate data inputs. The utility of each assessment depended on the availability of data reflecting the current epidemiology, which

could be sufficiently stratified by age and sex to examine the benefit-risk differences of interest.

We focused the initial assessments on broad age groups defined by the safety signal. As the epidemiologic and safety data became more robust, we observed that, in some cases, additional stratification demonstrated relevant differences in results. For example, we observed that sex-specific hospitalization rates had a meaningful impact on the estimated benefits accrued, which was particularly important when the adverse event of interest was more common among a specific sex. Likewise, while early analyses used overall estimates of the proportion of COVID-19 hospitalizations that would result in ICU admission or death, later analyses used age- and sex-specific values for these inputs after meaningful differences were noted.

The benefit-risk assessments were highly sensitive to the incidence rate inputs; COVID-19-associated hospitalization rates have varied widely over time. Therefore, careful consideration of the time frames from which hospitalization rates would be selected was important for the validity of the results. To reflect current epidemiology, we based initial analyses on the hospitalization rates estimated from the most recent week of available data. As we moved toward more finely stratified analyses and inclusion of younger age groups with less stable hospitalization rates, we used average incidence over the previous month. At later stages of the pandemic, amid ongoing variability of incidence, we used both recent epidemiology and pandemic-average estimates as the primary analysis, to provide a more comprehensive estimate of the benefit-risk balance under different epidemiologic circumstances.

The analytic time horizon varied with the policy question. For most analyses, we used 4 to 6 months based on the expected duration of protection by the vaccines at the time. Selection of a time horizon should incorporate what is known about waning VE, health outcome prevented by vaccination, and anticipated changes in disease epidemiology (e.g., SARS-CoV-2 variants). Vaccine-associated risks occur in the days to weeks after vaccination, while immunologic benefits of vaccination continue to accrue over the entire analytic time horizon. Therefore, assessments with shorter time horizons will have more certainty around the data inputs, but may underestimate benefits, which are artificially truncated at the end of the time horizon. We used sensitivity analyses to explore the uncertainty resulting from simplifications such as using static VE and incidence rates over the analytic time horizon.

We typically performed, but did not always present, sensitivity analyses for each assessment with varying assumptions for incidence, VE, or risks. To account for heterogeneity in incidence across time and locations, we often used a range of incidence rates approximating the highest and lowest rates observed throughout the pandemic or a range of the highest and lowest state-specific incidence rates at the time of the assessment. These rates were typically 3-fold higher and lower than primary analysis. For booster dose evaluations, when relative VE and vaccine risks were not known, we also relied heavily on sensitivity analyses. For these assessments, we varied VE inputs, with restoration to the efficacy seen in the primary series clinical trial as the upper limit and current primary series VE estimates as the lower limit. For risks, we typically used reporting rates of adverse events from VAERS due to

the system's ability to provide data for narrow age groups. Because VAERS is a passive surveillance system, which may lead to underreporting, we compared the rates to those seen in VSD and accounted for any differences through sensitivity analyses. Sensitivity analyses were also performed using risk data from additional surveillance systems and international data when available. For the booster discussions, for which no myocarditis data were available, we assumed myocarditis rates were equivalent to those seen after the second dose in the primary series (i.e., the dose for which myocarditis risk is the highest) but performed and presented sensitivity analyses assuming rates were half that of a second dose and twice that of a second dose.

The benefit-risk assessment method has limitations. First, the accuracy of the assessment of benefits depends on the availability of robust, high-quality, data from the target population with sufficient granularity to support age and sex-stratified analyses. Our assessments relied on COVID-NET hospitalization data, which may not be representative of the entire United States and may include hospitalizations for which COVID-19 was not a primary reason for admission. Second, the assessments assume static VE and incidence rates over the analytic time horizon. However, waning VE has been observed and COVID-19 hospitalization rates have varied widely throughout the pandemic. Sensitivity analyses have been important for exploring the impacts that changes in VE and incidence rate assumptions may have had on results. Third, these assessments did not account for prior COVID-19 infection or hybrid immunity, though incidence rates are derived from population-based surveillance, which does not stratify by prior infection. Fourth, the assessments described in this paper only consider the individual-level, direct benefits of vaccination. However, the benefits of vaccination extend beyond those received by the vaccinee, with population-level, indirect benefits due to potential reductions in transmission and reduced strain on the healthcare system and workforce. Direct benefit-risk assessments, as presented here, and population-level modeling are complementary ways to consider the overall benefits of vaccination [14,63]. Fifth, the assessments only focused on short-term outcomes, limiting the benefit accrual to the analytic time horizon, and not accounting for long-term outcomes of COVID-19, such as post-COVID conditions, or possible adverse events. The focus on short-term outcomes accrued during a specified time horizon likely resulted in an underestimate of vaccine benefits. Sixth, limitations in the VAERS and VSD systems applied to the risk assessments. VAERS is subject to reporting biases; the data quality and completeness of VAERS reports and available medical records are variable [64]. VSD surveillance may have limited statistical power required for assessment of rare outcomes or narrow strata, requires that outcomes and risk intervals be pre-specified, and is also susceptible to biases [65].

4. Conclusions

We conducted benefit-risk assessments using a framework to inform seven different policy questions over the first year of COVID-19 vaccine availability in the United States. When safety signals were identified, these assessments provided a mechanism to rapidly compare the direct benefits and risks of COVID-19 vaccination. The assessments were adjusted as new information, such as changing SARS-CoV-2 epidemiology or risk profiles, became available. Use of the benefit-risk assessment expanded to include the calculation of NNV, a summary measure that allowed ACIP to compare the anticipated benefits of different

policy choices. The framework provided a rapid, flexible alternative to more traditional modeling methods, supplying crucial estimates of the benefit-risk balance of vaccination in an emergency setting. The method was shared with FDA colleagues, who modified our framework to develop benefit-risk assessments using different data inputs and assumptions independently [13].

The COVID-19 vaccine benefit-risk assessment framework has been a critical tool for ACIP policy discussions and decision-making during the COVID-19 pandemic, as it allowed for rapid turnaround and flexible implementation. The framework could be modified for use in other vaccine policy decisions and may be useful for other advisory groups as new products are introduced to the market and evaluated during future public health emergencies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

Abbreviations:

ACIP	Advisory Committee for Immunization Practices
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
COVID-NET	COVID-19-Associated Hospitalization Surveillance Network
CVST	cerebral venous sinus thrombosis
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
EtR	Evidence to Recommendations
GBS	Guillain-Barre syndrome

GRADE	Grading of Reć ommendations Assessment, Development, and Evaluation
ICU	Intensive care unit
IVY	Investigating Respiratory Viruses in the Acutely Ill
NNV	number needed to vaccinate
TTS	thrombosis with thrombocytopenia syndrome
VAERS	Vaccine Adverse Events Reporting System
VaST	Vaccine Safety Technical Work Group
VE	vaccine effectiveness
VSD	Vaccine Safety Datalink
WONDER	Wide-ranging ONline Data for Epidemiologic Research

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Box 1

Benefit-risk assessment framework for primary series vaccination assuming no hospitalizations among the vaccinated – April 2021 through August 2021

Benefits of vaccination, calculated overall and by age- and sex-specific groups

Prevention of COVID-19-associated hospitalization

Incidence of COVID-19 hospitalizations, per person, per day **– I**

Proportion unvaccinated **– P_u**

Daily incidence in unvaccinated **– $I_u = I / P_u$**

Analytic time horizon **– T**

Number of vaccine doses for which benefits will be calculated (*per million in all assessments*) **– D**

Vaccine effectiveness against hospitalization **– VE**

Hospitalized cases preventable during time horizon *(per million vaccine doses)* **– $H_p = I_u \times T \times D \times VE$**

Prevention of COVID-19-associated ICU admission

Proportion of hospitalized cases resulting in ICU admission **– C_h**

ICU admissions preventable during time horizon *(per million vaccine doses)* **– $C_p = H_p \times C_h$**

Prevention of COVID-19-associated death

Proportion of hospitalized cases resulting in Death **– M_h**

Deaths preventable during time horizon *(per million vaccine doses)* **– $M_p = H_p \times M_h$**

Risks of vaccination, calculated overall and by age- and sex-specific groups

Number of specific adverse events during risk interval **– N**

Number of vaccine doses administered **– D_a**

Risk of specific adverse events during risk interval, by number of doses used for calculation of benefits (*per million vaccine doses)* **– $R = N / D_a \times D$**

Box 2

Benefit-risk assessment framework for primary series and booster doses accounting for hospitalizations among the vaccinated– September 2021 through November 2021.

Benefits of vaccination, calculated overall and by age- and sex-specific groups[1]

Prevention of COVID-19-associated hospitalization

Population – N

Vaccinated population – N_v

Proportion vaccinated – $P_v = N_v / N$

Proportion unvaccinated – $P_u = 1 - P_v$

Overall primary series vaccine effectiveness against hospitalization – VE_{op}

Vaccine specific primary series vaccine effectiveness against hospitalization – VE_{vp}

Booster dose relative vaccine effectiveness against hospitalization[2] – VE_b

Proportion of COVID-19 hospitalizations occurring among the vaccinated[3]
$P_{vh} = \frac{P_v(1 - VE_{op})}{P_v(1 - VE_{op}) + P_u}$

Overall incidence of COVID-19 hospitalizations, per person, per day – I

Daily incidence in vaccinated – $I_v = I \times P_{vh} \times \frac{N}{N_v}$

Daily incidence in unvaccinated – $I_u = I \times (1 - P_{vh}) \times \frac{N}{N_v - N}$

Analytic time horizon – T

Number of vaccine doses for which benefits will be calculated (*per million in all assessments*) – D

COVID-19 hospitalizations preventable by primary series during time horizon *(per million vaccine doses)* $H_p = I_u \times T \times D \times VE_{vp}$

COVID-19 hospitalizations preventable by a booster dose during time horizon *(per million vaccine doses)* – $H_b = I_v \times T \times D \times VE_b$

Number needed to vaccinate

Number needed to vaccinate with primary series to prevent one COVID-19-associated hospitalization – $NNV = D / H_p$

Appendix A. Supplementary material
Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.07.037.
[3]Equation based on the screening method [46].

Number needed to vaccinate with booster dose to prevent one COVID-19-associated hospitalization $-NNV = D/H_b$

Box 3

Benefit-risk assessment framework using hospitalization rates by vaccination status– December 2021.

Benefits of vaccination, calculated overall and by age- and sex-specific groups[1]

Prevention of COVID-19-associated hospitalization

Primary series vaccine effectiveness against hospitalization $-VE_p$

Booster dose relative vaccine effectiveness against hospitalization $-VE_b$

Daily incidence in vaccinated $-I_v$.

Daily incidence in unvaccinated $-I_u$

Analytic time horizon $-T$

Number of vaccine doses for which benefits will be calculated (*per million in all assessments*) $-D$

COVID-19 hospitalizations preventable by primary series during time horizon *(per million vaccine doses)* $-H_p = I_u \times T \times D \times VE_p$

COVID-19 hospitalizations preventable by a booster dose during time horizon *(per million vaccine doses)* $-H_b = I_v \times T \times D \times VE_b$

[1]Methodology for the calculation of ICU admissions and deaths prevented by vaccination and risks of vaccination remained the same as described in Box 1.

Table 1

Policy considerations, data inputs, and key assumptions from benefit-risk assessments during the first year of COVID-19 vaccine use in the United States.

Policy consideration	Date of ACIP meeting	Data inputs									Key assumptions	Narrative
		Age strata (years)	Case incidence	Hospitalization incidence[1]	VE against infection, primary series	VE against hospitalization, primary series	VE against infection, booster	VE against hospitalization, booster	Harms	Analytic time horizon		
1. TTS following Janssen COVID-19 vaccination [14,32]	April 2021	18–49 ≥50	N/A	Weekly hospitalization rate from COVID-NET week ending March 27, 2021	N/A	90%	N/A	N/A	TTS reporting rates from VAERS	30 days	All COVID-19 hospitalizations occurring among unvaccinated; COVID-19 hospitalization incidence equal among males and females	Short analytic time horizon used to account for the delay in vaccination that may occur if Janssen vaccine was taken off the market. Large age strata used to allow for risk estimates of a rare adverse event.
2. Myocarditis following mRNA COVID-19 vaccination [35,39]	June 2021	12–17 18–24 25–29 30–39 40–49 50–64 ≥65	Weekly incidence rate from CDC case-based surveillance week ending May 22, 2021	Weekly hospitalization rate from COVID-NET week ending May 22, 2021	95%	95%	N/A	N/A	Myocarditis reporting rates from VAERS	120 days	Used age- and sex-specific hospitalization rates, ICU admissions, and deaths	120-day analytic time horizon used because there was no alternative vaccine in adolescents however VE and incidence rates beyond 4 months were too uncertain to project static estimates further into the future.
3. TTS, myocarditis, and GBS and benefit risk review of all COVID-19 vaccines [41]	July 2021	18–39 40–49 50–64 ≥65	Weekly incidence rate from CDC case-based surveillance week ending June 26, 2021	Weekly hospitalization rate from COVID-NET week ending June 26, 2021	Janssen: 66% mRNA: 95%	Janssen: 90% mRNA: 95%	N/A	N/A	Janssen: TTS, GBS reporting rates from VAERS mRNA: Myocarditis reporting	120 days	Used age- and sex-specific hospitalization rates, ICU admissions, and deaths	

Policy consideration	Date of ACIP meeting	Data inputs									Key assumptions	Narrative
		Age strata (years)	Case incidence	Hospitalization incidence[1]	VE against infection, primary series	VE against hospitalization, primary series	VE against infection, booster	VE against hospitalization, booster	Harms	Analytic time horizon		
									rates from VAERS			
4. Pfizer-BioNTech BLA [42,44]	August 2021	16 −17 18–24 25–29	Weekly incidence rate from CDC case-based surveillance week ending July 31, 2021	Weekly hospitalization rate from COVID-NET averaged from weeks ending July 10-July 31, 2021	95%	95%	N/A	N/A	Myocarditis reporting rates from VAERS	120 days	Used age- and sex-specific hospitalization rates, ICU admissions, and deaths	Due to rapidly increasing incidence rates at the time of the analysis, incidence rates were increased by 1.5 times and hospitalization rates were increased by 3 times. Additionally, to obtain stable estimates in these younger age groups, we averaged hospitalization rates from 4 consecutive weeks.
5. Pfizer-BioNTech, Moderna, and Janssen COVID-19 boosters [50,52,53]	September and October 2021	18–29 30–49 50–64 ≥65	Weekly incidence rate from CDC case-based surveillance week ending September 11, 2021	Weekly hospitalization rate from COVID-NET week ending August 21, 2021	18–29: 78% 30–49: 78% 50–64: 80% ≥65: 78%	18–29: 91% 30–49: 90% 50–64: 90% ≥65: 85%	90%	95%	Primary series myocarditis reporting rates from VAERS following mRNA vaccination	180 days	Used age- and sex-specific hospitalization rates, ICU admissions, and deaths; Booster VE based on the assumption that a booster dose would return VE to that seen after the primary series	Used four CDC platforms to get an averaged age and vaccine specific VE estimates [45,47–49]. Also presented sensitivity analyses with hypothetical pre-booster VE estimates and varied incidence rates. Used the calculated hospitalizations prevented per million doses to calculate

Policy consideration	Date of ACIP meeting	Data inputs									Key assumptions	Narrative
		Age strata (years)	Case incidence	Hospitalization incidence[1]	VE against infection, primary series	VE against hospitalization, primary series	VE against infection, booster	VE against hospitalization, booster	Harms	Analytic time horizon		
												number needed to vaccinate for primary series and booster doses.
6. EUA for Pfizer-BioNTech COVID-19 vaccine in children aged 5–11 years [56,57]	November 2021	5–11	Weekly incidence rate from CDC case-based surveillance week ending September 11, 2021 and pandemic average rate	Weekly hospitalization rate from COVID-NET week ending September 11, 2021 and pandemic average rate	90%	95%	N/A	N/A	Myocarditis rates in this age group were unknown, but potential risks were described based on epidemiology of viral myocarditis in this age group and vaccine associated myocarditis rates seen in aged 12 – 15 years	180 days	Used age- and sex-specific hospitalization rates, ICU admissions, and deaths using both recent epidemiology and pandemic average rates.	
7. Janssen COVID-19 vaccine safety [61,62][2]	December 2021	18–49 50–64 ≥65	N/A	Weekly hospitalization rate from COVID-NET week ending November 13, 2021	N/A	Janssen 18–49: 73 50–64: 69 >65: 76 mRNA 18–49: 92 50–64: 92 ≥65: 88	N/A	N/A	Janssen: TTS, GBS reporting rates from VAERS mRNA: Myocarditis reporting rates from VAERS	180 days	Used age, sex, and vaccination status specific hospitalization rates, ICU admissions, and deaths using recent epidemiology	

Abbreviations: BLA: Biologics Licensing Application; EUA: Emergency Use Authorization; ICU: Intensive care unit; GBS: Guillain-Barré syndrome; TTS: Thrombosis with thrombocytopenia syndrome; VAERS; Vaccine Adverse Events Reporting System.

[1]Percentages of hospitalizations that resulted in ICU admission and death were taken from pandemic average estimates.

[2]Benefit-risk assessment of mRNA COVID-19 vaccines was presented in comparison to the benefit-risk assessment of the Janssen COVID-19 vaccine.

Table 2

Estimated individual-level Janssen (Johnson & Johnson) COVID-19 vaccine benefits (prevented cases, hospitalizations, ICU admissions, deaths) and harms (GBS and TTS cases) per million doses of vaccine for three assessments, United States, 2021.

Policy consideration and month of benefit-risk assessment	Sex/age group (years)	Benefits: COVID-19 outcomes prevented[1]				Harms: adverse events[2]	
		Cases	Hospitalizations	ICU admissions	Deaths	GBS	TTS
Assessment 1: TTS following Janssen COVID-19 vaccination, April 2021	**Females**						
	18–49	–	297	56	6	NA	7
	≥50	–	2,454	661	394	NA	1
	Males						
	18–49	–	272	51	6	NA	1
	≥50	–	2,821	760	471	NA	0
Assessment 3: TTS, myocarditis, and GBS and benefit-risk review of all COVID-19 vaccines, July 2021	**Females**						
	18–29	8,900	700	50	5	1	4–5
	30–49	10,100	900	140	20	6–7	8–10
	50–64	12,100	1,600	350	120	7–8	3–4
	≥65	29,000	5,900	1,250	840	8–10	0
	Males						
	18–29	6,600	300	60	3	2	2–3
	30–49	7,600	650	150	25	7–8	1–2
	50–64	10,100	1,800	480	140	14–17	1–2
	≥65	36,600	11,800	3,300	2,300	7–8	0
Assessment 7: Janssen COVID-19 vaccine safety, December 2021 [3]	**Females**						
	18–49	–	3,729	–	–	5	9
	50–64	–	11,181	–	–	7	5
	≥65	–	24,149	–	–	9	2
	Males						
	18–49	–	2,421	–	–	6	3
	50–64	–	12,189	–	–	16	2
	≥65	–	32,801	–	–	8	0

Abbreviations: ICU: Intensive care unit; GBS: Guillain-Barré syndrome; TTS: Thrombosis with thrombocytopenia syndrome.

[1] Outcomes prevented by vaccination compared to those who were unvaccinated.

[2] Ranges presented for harms are based on ±10% of the reporting rate.

[3] Benefit-risk assessment of mRNA COVID-19 vaccines was presented in comparison to the benefit-risk assessment of the Janssen COVID-19 vaccine.

Table 3

Estimated individual-level mRNA COVID-19 vaccine benefits (prevented cases, hospitalizations, ICU admissions, deaths) and harms (myocarditis cases) per million doses of vaccine, United States, 2021.

Policy consideration and month of benefit-risk assessment	Sex/age group (years)	Benefits: COVID-19 outcomes prevented[1]				Harms: adverse events[2]
		Cases	Hospitalizations	ICU admissions	Deaths	Myocarditis
Assessment 2: Myocarditis following mRNA COVID-19 vaccination, June 2021	**Females**					
	12–29	12,500	922	73	6	4–5
	12–17	8,500	183	38	1	8–10
	18–24	14,000	1,127	93	13	4–5
	25–29	15,000	1,459	87	4	2
	Males					
	12–29	11,000	560	138	6	39–47
	12–17	5,700	215	71	2	56–69
	18–24	12,000	530	127	3	45–56
	25–29	15,000	936	215	13	15–18
Assessment 3: TTS, myocarditis, and GBS and benefit risk review of all COVID-19 vaccines, July 2021	**Females**					
	18–29	12,800	750	50	5	3–4
	30–49	14,600	950	140	20	1–2
	50–64	17,500	1,700	375	125	1
	≥65	32,000	6,200	1300	900	<1
	Males					
	18–29	9,600	300	60	3	22–27
	30–49	11,000	700	160	25	5–6
	50–64	14,700	1,900	500	150	1
	≥65	52,700	12,500	3,500	2,400	<1
Assessment 4: Pfizer-BioNTech BLA, August 2021	**Females**					
	16–17	77,800	520	100	4	8
	18–24	107,000	3,000	240	21	3
	25–29	105,000	4,100	240	16	1

Policy consideration and month of benefit-risk assessment	Sex/age group (years)	Benefits: COVID-19 outcomes prevented[1]				Harms: adverse events[2]
		Cases	Hospitalizations	ICU admissions	Deaths	Myocarditis
	Males					
	16–17	56,700	500	170	4	73
	18–24	75,200	1,000	230	2	39
	25–29	76,000	2,200	490	44	12
Assessment 6: EUA for Pfizer-BioNTech COVID-19 vaccine in children aged 5–11 years, November 2021	**Females**					
	5–11	57,301	191	–	60	–
	Males					
	5–11	56,954	226	–	72	–
Assessment 7: Janssen COVID-19 vaccine safety [3], December 2021	**Females**					
	18–49	–	4,700	–	–	2
	50–64	–	14,908	–	–	1
	≥65	–	27,962	–	–	0
	Males					
	18–49	–	3,052	–	–	13
	50–64	–	16,251	–	–	1
	≥65	–	37,980	–	–	1

Abbreviations: BLA: Biologics Licensing Application; EUA: Emergency Use Authorization; ICU: Intensive care unit;

[1] Outcomes prevented by vaccination compared to those who were unvaccinated.

[2] Ranges presented for harms are based on ±10% of the reporting rate.

[3] Benefit-risk assessment of mRNA COVID-19 vaccines was presented in comparison to the benefit-risk assessment of the Janssen COVID-19 vaccine.