Vaccines for Covid-19: Effectiveness and Value

Draft Evidence Report

APRIL 7, 2026

Prepared for

NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

AN ICER PROGRAM

ICER Staff	Modeling Team
David M. Rind, MD, MSc Chief Medical Officer Institute for Clinical and Economic Review **Avery McKenna, BS** Research Lead Institute for Clinical and Economic Review **Marina Richardson, PhD, MSc** Associate Director, HTA Methods and Health Economics Institute for Clinical and Economic Review **Marie Phillips, BA** Health Economics Research Assistant Institute for Clinical and Economic Review **Sophia Cassim, BA** Research Assistant Institute for Clinical and Economic Review **Dan Ollendorf, PhD, MPH** Chief Scientific Officer and Director of HTA Methods and Engagement Institute for Clinical and Economic Review	**University of Colorado** **R. Brett McQueen, PhD** Associate Professor Skaggs School of Pharmacy and Pharmaceutical Sciences University of Colorado Anschutz Medical Campus **Antal Zemplenyi, PhD** Visiting Research Associate Skaggs School of Pharmacy and Pharmaceutical Sciences University of Colorado Anschutz Medical Campus **Harry Gyimah Gyamfi, MSc** Research Assistant Skaggs School of Pharmacy and Pharmaceutical Sciences University of Colorado Anschutz Medical Campus *The role of the University of Colorado is limited to the development of the cost-effectiveness model, and the resulting ICER report does not necessarily represent the view of the University of Colorado.* **Consultant** **Lisa A. Prosser, PhD** Marilyn Fisher Blanch Research Professor of Pediatrics University of Michigan

ICER's value assessments are free from financial conflicts of interest from health care companies. As an organization, we value transparency and hold ourselves, and our collaborators, to high standards for conducting our work. Our full policy to manage potential conflicts of interest can be found here. You can find ICER's Code of Ethics here. Any conflicts reported by the authors of this report or expert reviewers can be found on page v.

DATE OF PUBLICATION: April 7, 2026

How to cite this document: Rind DM, McQueen RB, Zemplenyi A, McKenna A, Prosser L, Richardson M, Phillips M, Gyamfi HG, Cassim S, Ollendorf D. Vaccines for Covid-19: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, April 7, 2026. https://icer.org/assessment/covid-19-2025/

David M. Rind served as the lead author on the report. Avery McKenna led the systematic review and authorship of the comparative clinical effectiveness section of this report with the support of Sophia Cassim. R. Brett McQueen, Antal Zemplenyi, and Harry Gyimah Gyamfi developed the cost-effectiveness model and authored the corresponding sections in collaboration with Lisa Prosser and Marina Richardson. Marie Phillips conducted the analysis for the budget impact model. Dan Ollendorf provided methodologic guidance on the clinical and economic sections. We would also like to thank Evan Amelchenko, Madeline Booth, Chloe Fandetti, Anna Geiger, and Natalya Salganik for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit ICER's website.

The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 22% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. The only life science company relevant to this review who participates in this program is Sanofi. A complete list of funders and more information on ICER's support, is available on the funding page of the ICER website.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About New England CEPAC

New England CEPAC (NE CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. NE CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care. The NE CEPAC Panel is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value medical interventions.

The findings contained within this report are current as of the date of publication. The systematic literature review search was run on December 17, 2025 and weekly news surveillance is conducted to identify new literature. A formal update to the search will be conducted between the Draft and Evidence report. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the initial draft evidence report:

Expert Reviewers

Rebecca Kirch, JD
Executive Vice President of Policy and Programs, National Patient Advocate Foundation
Board Chair, Care Camps Foundation

Eric A. Meyerowitz, MD
Associate Professor of Medicine, Montefiore Medical Center

Ashleigh Tuite, PhD, MPH, MSc
Manager, Health Economics and Modelling
Public Health Agency of Canada

Rochelle Walensky, MD, MPH
Professor of Medicine, Harvard Medical School
Medical Advisor, Vaccine Integrity Project

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions or iterations of the report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from whom we requested input, or who have submitted public comments so far, please visit: https://icer.org/assessment/covid-19-2025/

Conflict of Interest Disclosures for the Report

Table 1. ICER Authors and External Collaborators Conflict of Interest Disclosures

ICER Staff and External Collaborators	Conflict of Interest
Sophia Cassim, BA Research Assistant Institute for Clinical and Economic Review	No conflicts to disclose.
Harry Gyimah Gyamfi, MSc Research Assistant Skaggs School of Pharmacy and Pharmaceutical Sciences University of Colorado Anschutz Medical Campus	No conflicts to disclose.
Avery McKenna, BS Research Lead Institute for Clinical and Economic Review	No conflicts to disclose.
R. Brett McQueen, PhD Associate Professor Skaggs School of Pharmacy and Pharmaceutical Sciences University of Colorado Anschutz Medical Campus	Dr. McQueen received compensation from Sanofi for a special speaker series in April 2024 and January 2026 related to the cost-effectiveness of screening for type 1 diabetes and fees for reviewing a project attempting to improve early diagnosis of type 1 diabetes.
Dan Ollendorf, PhD, MPH Chief Scientific Officer and Director of HTA Methods and Engagement Institute for Clinical and Economic Review	No conflicts to disclose.
Marie Phillips, BA Health Economics Research Assistant Institute for Clinical and Economic Review	No conflicts to disclose.
Lisa A. Prosser, PhD Marilyn Fisher Blanch Research Professor of Pediatrics University of Michigan	No conflicts to disclose.
Marina Richardson, PhD, MSc Associate Director, HTA Methods and Health Economics Institute for Clinical and Economic Review	No conflicts to disclose.
David M. Rind, MD, MSc Chief Medical Officer Institute for Clinical and Economic Review	No conflicts to disclose.
Antal Zemplenyi, PhD Visiting Research Associate Skaggs School of Pharmacy and Pharmaceutical Sciences University of Colorado Anschutz Medical Campus	No conflicts to disclose.

Table 2. Expert Reviewers of the Draft Evidence Report Conflict of Interest Disclosures

Expert Reviewer	Conflict of Interest
Rebecca Kirch, JD Executive Vice President of Policy and Programs, National Patient Advocate Foundation Board Chair, Care Camps Foundation	No conflicts to disclose.
Eric A. Meyerowitz, MD Associate Professor of Medicine, Montefiore Medical Center	Dr. Meyerowitz reported financial support to his institution from Moderna for clinical trial of mRNA-1345.
Ashleigh Tuite, PhD, MPH, MSc Manager, Health Economics and Modelling Public Health Agency of Canada	No conflicts to disclose.
Rochelle Walensky, MD, MPH Professor of Medicine, Harvard Medical School Medical Advisor, Vaccine Integrity Project	No conflicts to disclose.

Table of Contents

List of Acronyms and Abbreviations Used in this Report

%	Percent
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians & Gynecologists
ACP	American College of Physicians
AE	Adverse event
AESI	Adverse event of special interest
aHR	Adjusted hazard ratio
AHRQ	Agency for Healthcare Research and Quality
aOR	Adjusted odds ratio
AR	Adverse report
aRD	Adjusted risk difference
CDC	Center for Disease Control and Prevention
CDR	Clinical Trial Diversity Rating
CE	Cost effectiveness
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CKD	Chronic Kidney Disease
COVID-NET	Coronavirus Disease 2019 (COVID-19) Hospitalization Surveillance Network
COVID-19	Coronavirus Disease 2019
ED	Emergency department
evLYs	Equal value of life years
FDA	Food and Drug Administration
GMT	Geometric mean titers
HIDI	Health Improvement Distribution Index
HR	Hazard Ratio
ICU	Intensive Care Unit
IR	Incidence ratio
IRR	Incidence rate ratio
MAAE	Medically attended adverse event
MACE	Major Adverse Cardiovascular Event
ME/CFS	Myalgic Encephalomyelitis or Chronic Fatigue Syndrome
MMWR	Morbidity and Mortality Weekly Reports
Mo	Months
mRNA	Messenger ribonucleic acid
N	Total number
NR	Not reported
NE	Not estimated
PCC	Post-covid condition
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PDUFA	Prescription Drug User Fee Act
PIMMC	Potentially Immune-Mediated Medical Conditions
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RR	Risk Ratio
rVE	Relative vaccine effectiveness
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event

TEAE	Treatment emergent adverse event
UC	Urgent Care
US	United States
VA	Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine effectiveness
VFC	Vaccines for Children Program
VSD	Vaccine Safety Datalink
WAC	Wholesale Acquisition Cost
Yrs	Years

Executive Summary

In Wuhan, China, in December 2019, patients began to present with atypical pneumonia.[1] Over the next several months, the disease that would be called Covid-19 and was caused by the virus SARS-CoV-2 spread around the world as a pandemic, disrupting life in nearly every country. More than 1.2 million people died of Covid-19 in the United States (US).[2]

On April 30, 2020, the first Trump Administration launched operation Warp Speed to quickly produce a vaccine for Covid-19.[3,4] In mid-November 2020, vaccines using messenger RNA (mRNA) technology developed by Pfizer and BioNTech and by Moderna were found to be approximately 95% effective.[5-7] These and other vaccines were rolled out in early 2021 and by June 2021, more than 300 million vaccine doses were administered in the US.[8] These vaccines dramatically affected the course of the pandemic. Booster vaccines to address waning immunity and vaccine modifications to address viral variants were developed, and over time the vast majority of people in the US received vaccines, had experienced prior infection(s) with SARS-CoV-2, or both, creating a population that was no longer immunologically naïve. In this setting, early data from randomized trials of mRNA and other vaccines, including the FDA-approved Novavax spike protein vaccine,[9] provide only limited information about the current effects of immunization in the US population.

Four vaccines for Covid-19 are currently available in the US: Spikevax® (Moderna); mNEXSPIKE® (Moderna); COMIRNATY® (Pfizer, BioNTech); and Nuvaxovid® (Sanofi, an updated version of the prior Novavax vaccine). Recent recommendations from the Advisory Committee on Immunization Practices (ACIP) generally recommend vaccination for people age 65 and older and for those 6 months or older but younger than 65 with at least one underlying condition that puts them at risk for severe Covid-19.[10,11] Some professional associations and state public health departments have promulgated guidance that is more aligned with prior ACIP guidance that recommended Covid-19 vaccination for all persons ages six months or older.[12-14]

Updated vaccines are expected to be available again in the fall of 2026. In this report, we examine the best available evidence on the likely comparative effectiveness and cost effectiveness of vaccination for Covid-19 in the 2026–2027 season, with a focus on subgroups at varying risk from Covid-19 when examining comparative effectiveness.

We performed a systematic review of the evidence that identified the original randomized trials and large amounts of observational data since 2020; this is discussed in the main report and in the supplement. In the absence of recent trials, we had a strong preference for the most recent data available; older data were felt to necessarily be low quality evidence for most outcomes due to the degree of indirectness to the current population living in the US that has been repeatedly exposed to Covid-19 antigens and seen continued decreases in rates of severe illness.[15] As such, we chose to focus primarily on three well-conducted observational studies examining vaccine effectiveness in

the 2024-2025 season. These included two studies using a "test-negative" design, a type of case-control study that can provide relative vaccine effectiveness, that we refer to as "The Adult CDC Study" and "The Childhood CDC Study" in this report.[16,17] The third study, central to anchoring our results, we refer to as "The VA Study".[18] This is a cohort study that, unlike the case-control studies, can provide absolute effectiveness as well as relative effectiveness and that we felt was at very low risk for bias or confounding. However, the population was predominantly male with a mean age of 71 and so was necessarily indirect evidence for estimating effects in many other groups, which leads to uncertainties.

The changing epidemiology of Covid-19 provides additional uncertainties. Table ES.1 shows annual hospitalization rates associated with Covid-19 in a range of age groups; however hospitalizations have been declining year over year. It is possible that rates of serious Covid-19 will decline further in the 2026–2027 season or that the emergence of new strains could lead to an increase in serious disease.[19]

Table ES.1. Estimated Annual Covid-19-Associated Hospitalization Rates In 2024–2025[15]

Age Category	Rate per 100,000
<6 Months	250
6–12 Months	130
1–2 Years	70
2–4 Years	20
5–17 Years	9
18–29 Years	22
30–39 Years	30
40–49 Years	39
50–64 Years	80
65–74 Years	210
75–84 Years	540
>84 Years	1,200

We estimated the benefits of vaccination assuming this same epidemiology for the 2026–2027 season and from the efficacy seen in the above studies, and present these results as numbers of people who need to be vaccinated to prevent one hospitalization or one death as shown in Table ES.2.

Table ES.2. Estimated Vaccine Effectiveness for Preventing Hospitalization and Death

Population	Fewer Hospitalizations Per 1,000 Vaccinated Persons	Vaccinations Needed to Prevent One Hospitalization*	Fewer Deaths Per 1,000 Vaccinated Persons	Vaccinations Needed to Prevent One Death*
Young Adults	0.06	16,000	0.02	55,000
Adults 50–64	0.22	4,500	0.06	15,000
Adults 65+†	0.75	1,300	0.22	4,500
Adults 85+	3.36	300	0.99	1,000
Children 5–18	0.05	20,000	NE	NE
Children 2–5	0.15	6,600	NE	NE
Children 1–2	0.53	1,900	NE	NE
Children 6–12 Months	0.99	1,000	NE	NE
Young Pregnant Women	0.21	4,800	0.06	16,000
Older Pregnant Women	0.29	3,500	0.08	12,000
Comorbidities In People Under 65‡	0.17	6,000	0.05	20,000
People Under 65 With CKD	0.13	7,900	0.04	27,000

CKD: chronic kidney disease, NE: not estimated due to data limitations

*Rounded estimates

†Estimates of fewer hospitalizations/deaths per 1,000 persons for adults 65+ were from The VA Study

‡Comorbidities other than CKD

We feel that the evidence for these estimates is best for older adults as this most closely matches the group in The VA Study where we have high-quality evidence. Our estimates in other adults are primarily extrapolated from The VA Study, and this extrapolation is particularly uncertain in groups such as young adults and pregnant women. Results in children were extrapolated mainly from The Childhood CDC Study, and efficacy from vaccinating pregnant mothers for their infants younger than six months (numeric efficacy not estimated) was based on data from earlier in the pandemic and from biologic plausibility.

We did not consider reduction of transmission or prevention of prolonged symptoms after mild illness as a benefit of Covid-19 vaccination in the 2026–2027 season given the low quality evidence for such effects. We did not find adequate evidence on efficacy comparing the vaccines to each other.

We examined both trial and observational data for evidence of minor and serious harms from vaccination. Minor harms such as fever and malaise are relatively common and there is some evidence that they are more common with mRNA vaccines than with Nuvaxovid. Serious harms are extremely rare. Adolescent boys and young men were at increased risk for myocarditis after vaccination early in the pandemic but this risk has not been seen more recently. The reasons for this decrease are not clear and we considered that there were still some uncertainties around

myocarditis when making evidence ratings for this population. We found no material evidence for other serious harms occurring at a frequency that would affect our evidence ratings.

Our evidence ratings are shown in Table ES.3 and the rationale for these ratings is described in the report. Uncertainties about rates of serious disease in the 2026–2027 season affect all these ratings. We intentionally made conservative choices about the relative effectiveness of Covid-19 in preventing events in deciding on these evidence ratings.

Table ES.3. Evidence Ratings

Population	Intervention*	Comparator	Evidence Rating
Adults 18–65 (Excluding Men Ages 18–24)	Vaccine	No Vaccine	C+
Adults 65+	Vaccine	No Vaccine	B+
Males 12–24	Vaccine	No Vaccine	P/I
Children 5–18 (Excluding Boys 12–18)	Vaccine	No Vaccine	C+
Children 2–5	Vaccine	No Vaccine	C+
Children 1–2	Vaccine	No Vaccine	C++
Children 6–12 Months	Vaccine	No Vaccine	B+
Vaccination During Pregnancy	Vaccine	No Vaccine	B+
People With Comorbidities Under Age 65	Vaccine	No Vaccine	C++
People Living in the US in 2026	Any of 4 vaccines	Each other	I

*Intervention: Updated 2026–2027 Covid-19 Vaccine, Comparator: No Updated 2026–2027 Covid-19 Vaccine
Note: In comparing vaccination for Covid-19 with no vaccination in various groups/subgroups, we are not distinguishing in our overall ratings among the four available vaccines

While these evidence ratings represent our judgement of the evidence for the likely net benefit of Covid-19 vaccination for the 2026-2027 season, we note that these ratings are not recommendations or policy suggestions. Vaccination is a public health intervention and those who make such recommendations need to consider clarity and ease of implementation when designing policies.

We performed a cost-effectiveness analysis of Covid-19 vaccines for the 2026–2027 season. This analysis builds on the cost-effectiveness model by Prosser (2025) which informed ACIP deliberations during the 2023–2024 vaccination season.[20] The replicated model incorporates updated vaccine effectiveness estimates based on more recent observational data. Key drivers of the cost-effectiveness estimates include vaccine effectiveness against hospitalization and the probability of hospitalization from Covid-19. Weighted results (i.e., by age and risk) suggest that, at current prices, Covid-19 vaccination for the 2026–2027 season would meet commonly cited cost-effectiveness thresholds, driven primarily by reducing hospitalizations in people ages 50 and older.

1. Background

In Wuhan, China, in December 2019, patients began to present with atypical pneumonia.[1] Over the next several months, the disease that would be called Covid-19 and was caused by the virus SARS-CoV-2 spread around the world as a pandemic, disrupting life in nearly every country. More than 1.2 million people died of Covid-19 in the United States (US).[2] Reported worldwide deaths were greater than seven million,[2] however estimates looking at excess mortality suggest the actual number of deaths was much larger.[21]

By early January 2020, SARS-CoV-2 had been genetically sequenced.[22] On April 30, 2020, the first Trump Administration launched operation Warp Speed to quickly produce a vaccine for Covid-19.[3,4] In mid-November 2020, vaccines using messenger RNA (mRNA) technology developed by Pfizer and BioNTech and Moderna were found to be approximately 95% effective, with data published in December 2020.[5-7] These and other vaccines were rolled out in early 2021 and by June 2021, more than 300 million vaccine doses were administered in the US.[8] Although these vaccines dramatically affected the course of the pandemic, by the summer of 2021 the "Delta" variant of SARS-CoV-2 became widespread and could be transmitted even by vaccinated patients.[23] Booster vaccines to address waning immunity and vaccine modifications to address viral variants were developed, and over time the vast majority of people in the US received vaccines, had experienced prior infection(s) with SARS-CoV-2, or both, creating a population that was no longer immunologically naïve. In this setting, early data from randomized trials of mRNA and other vaccines, including the FDA-approved Novavax spike protein vaccine,[9] provide only limited information about the current effects of immunization in the US population.

Four vaccines for Covid-19 are currently available in the US: Spikevax® (Moderna); mNEXSPIKE® (Moderna); COMIRNATY® (Pfizer, BioNTech); and Nuvaxovid® (Sanofi, an updated version of the prior Novavax vaccine). As of August 2025, the Food and Drug Administration (FDA) labels were changed to state that the vaccines are approved for use in all individuals who are 65 years of age and older, and individuals under 65 with at least one underlying condition that puts them at risk for severe Covid-19 outcomes (minimum indicated age: six months for Spikevax, five years for COMIRNATY, and 12 years for Nuvaxovid and mNEXSPIKE).[24-27] Recent recommendations from the Advisory Committee on Immunization Practices (ACIP) as of September 2025 generally follow the revised FDA labels.[10,11] Some professional associations and state public health departments have promulgated guidance that is more aligned with prior ACIP guidance that recommended Covid-19 vaccination for all persons ages six months or older.[12-14]

Updated vaccines are expected to be available again in the fall of 2026. In this report, we examine the best available evidence on the likely comparative effectiveness and cost effectiveness of vaccination for Covid-19 in the 2026-2027 season, with a focus on subgroups at varying risk from Covid-19 when examining comparative effectiveness.

Table 1.1. Interventions of Interest

Intervention	Vaccine Platform	Delivery Route	Prescribing Information
Comirnaty	mRNA	Intramuscular	Ages 5+ years: Single 0.3 mL dose
Spikevax	mRNA	Intramuscular	Ages 6 months–23 months: Primary series: two 0.25 mL doses separated by 1 month interval OR single 0.25 mL dose for those with ≥2 prior doses Ages 2 years–11 years: Single 0.25 mL dose Ages 12+ years: Single 0.5 mL dose
mNexspike	mRNA	Intramuscular	Ages 12+ years: Single 0.2 mL dose
Nuvaxovid	Protein-based	Intramuscular	Ages 12+ years: Single 0.5 mL dose

mL: milliliter, mRNA: messenger RNA

2. Patient and Other Stakeholder Input

During this review, we sought input from diverse stakeholders, including individuals considering vaccine benefits and risks, patients experiencing residual Covid-19 symptoms, patient advocates, clinicians, researchers, and manufacturers of the vaccines. This section summarizes feedback gathered during calls with patient and general community stakeholders (vaccine candidates, patients, and patient advocacy organizations) and clinical experts. ICER looks forward to continued engagement with stakeholders throughout the review to refine our understanding of the clinical effectiveness and value of vaccinations for Covid-19.

2.1. Patient Community Insights

Essentially all people can be considered patient stakeholders for the purpose of this review, as Covid-19 was pandemic and is now endemic. Everyone living in the US needs to decide whether to receive vaccination for Covid-19 in the 2026–2027 season.

That said, we spoke with individuals from certain groups at higher risk for complications from Covid-19 or from vaccination for Covid-19. We heard from patients who are immunocompromised from treatment of autoimmune conditions about increased concerns of contracting Covid-19 but also, for some patients, needing to avoid vaccination because of concerns of inducing a flare of an autoimmune condition. We heard about the experience early in the pandemic of certain medications for autoimmune conditions becoming unavailable because they were being inappropriately given to people with Covid-19. Additionally, we heard that shortages of other medications for autoimmune conditions were caused by the use of these medications for severe Covid-19. This led some patients to be angry at those who did not get vaccinated for Covid-19 as they felt those unvaccinated took on unnecessary risks for Covid-19 and eventually needed medications that would otherwise have been available to people with autoimmune conditions. In both situations, some patients deteriorated due to lack of medications and never returned to their prior level of health.

We also heard from older individuals; while there are some who are skeptical of vaccination, most are convinced of vaccine benefits. We heard that the lack of promotion of updated vaccines can cause older individuals to miss a Covid-19 vaccine simply because they did not realize it was available. We also heard that greater cost sharing has made some individuals have to weigh perceived benefits against significant monetary outlays to get vaccinated.

We heard from individuals in the African American community that there was initially a great deal of skepticism about vaccination and more generally about Covid-19. These individuals were clear that they could not speak for the community as a whole but that prior harms to the community by the scientific and medical establishments continue to create uncertainties about whether their best interests are being adequately considered. They worried about what might happen in a future pandemic.

We also heard about concerns for particular populations, such as those living in long-term group settings, who are at increased risk for spread of Covid-19 from resident to resident.

We also spoke with representatives from groups that focus, at least in part, on Long Covid and heard concerns both about the individual burden of post-acute sequelae of Covid-19 as well as the large numbers of individuals experiencing these sequelae. We heard about stigma from medical providers and others not accepting Long Covid as a real condition. We heard strong support for vaccination to prevent Long Covid and belief that frequency of Long Covid increases with repeated infections, making vaccination important even in those who have tolerated Covid-19 in the past. We heard worries that vaccine hesitancy may increase the risk for children developing Long Covid. We also heard concerns that in those who already have Long Covid, vaccination may cause flares of the condition. We heard beliefs that post-acute sequelae affect people differently, and that there may be groups of symptoms/syndromes that can occur alone or in combination. We also heard that it can be difficult to access adequate information and education about Long Covid informed by good research. Similarly, it can be hard to find medical care for Long Covid that is appropriately based in evidence and research.

We reached out to various groups that express skepticism of vaccines in general, but were unable to arrange discussions. We spoke with an individual living in an area and with prior work in a field where there has been more vaccine hesitancy. He is not a general vaccine skeptic but chose to never get vaccinated for Covid-19 because of his concerns about that vaccine in particular. He worried that the trials of the vaccines were too rushed and could have missed serious long-term harms. He also noted that the political conflicts around the vaccine also contributed to his decision not to get vaccinated; he reported being bothered by politics on both sides of the vaccine debate. He noted that given the development of more evidence over time, he would likely now be on the fence about getting the vaccine if rates of serious Covid-19 were similar to what they were at the beginning of the pandemic; greater experience with vaccine safety has provided him with some reassurance.

Conversely, we spoke with an individual living in an area and working in a field where there is wide vaccine acceptance. She has two teenage sons and described that while she had heard about concerns around myocarditis, she discounted these as being very low risk to her sons compared with the risks of Covid-19, and so has ensured that her sons received the Covid-19 vaccination every year. She, too, had thoughts about the politics around Covid-19 and wondered whether having an administration that is more skeptical of vaccines might lead to the development of vaccines with decreased safety and/or effectiveness, though she ultimately concluded this was not a reasonable worry.

2.2. Health Equity Considerations

Early in the pandemic, it was noted that Black Americans had significantly greater concerns about the Covid-19 vaccines than White Americans.[28] Since in the US, race is correlated with socioeconomic status, and risk factors for severe Covid-19 were correlated with lower socioeconomic status, this created important health equity considerations where those at greater risk of severe Covid-19 were less willing to be vaccinated.[28]

More recently, it is less clear that there are important associations between race and vaccination; however, correlations continue between lower income and lower vaccination rates.[29] Although overall risk from Covid-19 is much lower than early in the pandemic, there may still be health equity considerations if vaccination helps prevent serious outcomes of Covid-19 and those with lower incomes are less likely to receive vaccination.

2.3. Clinical Expert Insights

Clinical experts felt that data remain inadequate to conclude that vaccination for Covid-19 helps prevent transmission in the current era.

There was general consensus among experts that effectiveness of vaccines for prevention of Covid-19 is modest and wanes relatively quickly; there was also consensus that protection was greater against severe Covid-19 outcomes (e.g., hospitalization) than against less severe outcomes.

Most experts felt that universal annual vaccination for Covid-19 was not needed. We heard varying beliefs from clinical experts about the importance of vaccinating children for Covid-19, though most experts felt that vaccinating young children was important, with one describing that a person's first exposure should be through vaccination rather than infection. There was also some belief that vaccination of pregnant women provided some protection for newborns, although experts varied in how strong they felt the evidence was for this.

We heard from experts that myocarditis as a vaccine complication has decreased over time, but there was disagreement among experts about whether this reflected changes in the vaccine schedule, changes in the vaccine, avoidance of vaccination by those at greater risk, or whether the explanation for this decrease is not understood.

We spoke with an expert in vaccine hesitancy who noted that better studies demonstrating the safety and effectiveness of current vaccination for Covid-19 should not be expected to change large numbers of people's minds as there would be continuing distrust of such evidence.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Scope of Review

We evaluated the clinical effectiveness of four Covid-19 vaccines compared to each other and to not receiving an updated vaccine for Covid-19. The population of interest for our review was people living in the United States in 2026, with a focus on evidence on effectiveness and harms within subpopulations defined by age (young children, adolescents, boys aged 12 to 18 and young adult men, pregnant women, adults under 65 years old, and adults age 65 years and older) and comorbid conditions (e.g., pulmonary conditions, cardiovascular disease, immunocompromising conditions, diabetes, obesity, neurologic conditions, and serious mental illness). Our outcomes of interest included serious illness from Covid-19, hospitalization, emergency department/urgent care visits, Long Covid and permanent harms from Covid-19, and fetal injury from Covid-19. We also sought and reviewed evidence on adverse events including myocarditis and pericarditis, Guillain-Barre syndrome, and short-term minor adverse events including fever and malaise (i.e., reactogenicity). The full protocol for the review is available in Supplement Section D1.

Evidence Base

Data Sources

A primary research question for this review was to assess the net health benefit of receipt of an updated vaccine for Covid-19 versus not receiving an updated vaccine in 2026.

We sought the best available evidence for vaccine effectiveness and safety, both for individual vaccines and across all vaccines for Covid-19. Our search identified the original randomized trials and subsequent booster studies, observational studies reporting on effectiveness and safety using cohort, case-control, and self-controlled case series study designs, and safety surveillance studies using large databases such as the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD). We also sought information on recent epidemiological data for Covid-19 through publicly available surveillance systems that are routinely updated, such as the CDC COVID-NET Hospitalization tracker (see Supplement Section A for more detail on COVID-NET). A description of our search process and results is outlined in Supplement Section D2 and key evidence tables for both randomized trials and observational data are in Supplement Section D3.

Although randomized trials provided the best evidence for effectiveness early in the pandemic, absolute and relative effects seen in these trials do not apply to the broad US population that has either previously received vaccinations, been infected with strains of SARS-CoV-2 one or more times, or both. In the absence of recent trials, we sought the best observational data, preferring data that could provide absolute estimates of benefit when available.

Given the continuing and evolving exposure to Covid-19 antigens both from circulating virus and from vaccination, we also had a strong preference for the most recent data available; older data were felt to necessarily be low quality evidence for most outcomes due to the degree of indirectness to the current population living in the US that has been repeatedly exposed to Covid-19 antigens and seen continued decreases in rates of severe illness.[15] As such, we chose to focus on a small number of well-conducted recent observational studies even though we include in the Supplement D3 a large number of older observational studies that were identified.

We had limited ability to compare specific vaccines to each other when looking at efficacy as most observational studies did not support such comparisons. Some more recent data comparing adverse events across vaccine preparations were available and we also considered adverse events seen in the original randomized trials of the vaccines.

In the absence of data on absolute benefits, we sought observational data providing relative estimates of benefit and applied these estimates to the known epidemiology of Covid-19 in recent months. For subgroups where evidence even on relative benefit was limited, we looked for evidence on whether relative population vaccine effects could be applied in those subgroups. We also extrapolated from outcomes (such as hospitalization), that were frequently better captured in subgroups, to other outcomes such as mortality.

A common technique used to measure relative vaccine effectiveness is the "test-negative" design. This is a variant of a case-control study and so provides effectiveness based on an odds ratio. Patients with a possible Covid-19 illness are tested for Covid-19 without regard to vaccine status and rates of vaccination are compared in those who test positive and negative. Vaccine effectiveness is calculated as one minus the odds ratio. We identified two test-negative studies that report the most recent effectiveness estimates during the 2024–2025 season for adults over age 18 ("The Adult CDC Study") and children aged nine months to 17 years old ("The Childhood CDC Study").[16,17] These studies utilize two CDC-supported networks (IVY and VISIONARY) to evaluate vaccine effectiveness and are generally representative of the US population. The study designs for these two studies are described in Supplement Table D3.37. Of note, because vaccine effectiveness will only be captured in patients who present for evaluation, and given that sicker patients and those with better access to care are more likely to be evaluated, the vaccine effectiveness estimates are likely to be enriched for effectiveness in more severe disease and those with higher socioeconomic status.[30] This can result in incorrect estimates of vaccine effectiveness in less severe

disease if effectiveness varies across disease severity. As such, wherever possible we compared relative effects from test-negative studies with other sources of evidence.

A central study for anchoring results in our review was Cai 2025 ("The VA Study").[18] As such, we are providing details about the conduct of this study. The VA Study examined the effectiveness of the 2024–2025 Covid-19 vaccine among veterans who could have received the vaccine between September 3, 2024 and December 31, 2024 using electronic health records from the Department of Veterans Affairs. Study outcomes included Covid-19 associated emergency department visits, hospitalizations, or deaths in the six months after vaccination. The study design and analysis have particular strengths in reducing concerns about residual confounding, which is why we highlight this study; however, concerns about generalizability to other populations remain and are examined as we discuss results. Participants were 295,971 adult veterans who received influenza vaccination during the period in question; 164,132 participants chose to also receive Covid-19 vaccination on the same day (intervention cohort) and 131,839 chose to only receive the influenza vaccine (control cohort). We note that all participants were willing to receive a vaccination against a respiratory virus and so were choosing only between receiving or not receiving an additional vaccination against a different respiratory virus. Nearly all intervention cohort participants received an mRNA vaccine against Covid-19. Table 3.1 below shows negative control results across both influenza and non-influenza outcomes. The combination of the way participants were enrolled and the results of these negative controls (i.e., risks that did not differ between the intervention and control cohorts) provide substantial reassurance about the absence of significant residual confounding. In particular, it is very unlikely that the overall health, risk for Covid-19, or risk for serious outcomes from Covid-19 were importantly different between the intervention cohort and the control cohort.

Table 3.1. Negative Outcome Control Analyses From The VA Study[18]

Negative Outcome Controls	Risk Ratio (95% CI)
SARS-Cov-2 Test Positive Within 10 Days of T_0	1.00 (0.68, 1.46)
Emergency Department Visit for Renal Colic/Kidney Stone*	0.94 (0.73, 1.19)
Emergency Department Visit for Ankle Sprain*	1.08 (0.58, 1.85)
Clinical Encounter for Tinnitus or Hearing Aid Fitting*	1.01 (0.96, 1.06)
Seasonal Influenza-Associated Negative Outcome Controls	
Influenza-Associated Emergency Department Visit	1.00 (0.89, 1.11)
Influenza-Associated Hospitalization	0.98 (0.78, 1.20)
Composite of Influenza-Associated Emergency Department Visit, Hospitalization, or Death	1.00 (0.89, 1.11)
Influenza Test Positivity	1.01 (0.91, 1.10)
Receipt of Influenza Testing	0.98 (0.95, 1.00)

CI: confidence interval, T_0: time zero

*6-month outcome after T_0

Estimating Vaccine Effectiveness

High-quality recent data are available on Covid-19 hospitalizations in the US.[15] For most subgroups and for most outcomes other than hospitalizations, we had to extrapolate from available evidence on the epidemiology of Covid-19 and the effectiveness of vaccination, given the low quality of the majority of the observational evidence available. We used the following general approach to arrive at such estimates:

1) We used recent data on Covid-19 hospitalizations in the US for subgroups of interest. These were available for most subgroups.
2) We used a conservative estimate of effectiveness of Covid-19 vaccination based on The VA Study and The Adult and Childhood CDC Studies and applied this to hospitalizations to find an estimate of absolute reduction in hospitalizations from vaccination.
3) Using The VA Study, we calculated the ratio of absolute risk differences for emergency department visits to hospitalizations and mortality to hospitalizations and applied these ratios to the reduction in hospitalizations in step two to extrapolate these other two outcomes.

This extrapolation can be seen with the numbers used in the discussion of effectiveness in adults in Section 3.2. Extrapolation calculations can be found in Supplement Tables D2.1–D2.2. Data from The VA Study, Adult CDC, and Childhood CDC Studies can be found in Supplement Tables D3.37–D3.45. We discuss the limitations of such extrapolations in the section on Uncertainties and Controversies and these limitations are an important aspect of our eventual evidence ratings.

3.2. Results

Epidemiology

Rates of symptomatic and asymptomatic Covid-19 vary over time and also across geographic locations even within the US as do the specific strains of SARS-CoV-2 that predominate.[19]

At the beginning of 2024 there were very high levels of SARS-CoV-2 viral activity in wastewater nationally. Since then, there has been a general downward trend in viral activity levels with expected increases during peak seasons (summer/winter). Throughout 2025, levels generally fluctuated between low, moderate, and high. As of February 2026, national levels are described as low.[31]

It was estimated that in the 2024–2025 season (October 2024 to September 2025), there were 14.1 to 20.7 million Covid-19 illnesses, 3.4 to 4.8 million outpatient visits, 390,000 to 550,000 hospitalizations, and 45,000 to 64,000 deaths in the United States.[31] Table 3.2 shows rates of hospitalization across age groups.

Table 3.2. Estimated Annual Covid-19-Associated Hospitalization Rates In 2024–2025[15]

Age Category	Rate per 100,000
<6 Months	250
6–12 Months	130
1–2 Years	70
2–4 Years	20
5–17 Years	9
18–29 Years	22
30–39 Years	30
40–49 Years	39
50–64 Years	80
65–74 Years	210
75–84 Years	540
>84 Years	1,200

Clinical Benefits

Vaccine Effectiveness

Throughout this report, we discuss "relative vaccine effectiveness" as a number between 0 and 1. If relative vaccine effectiveness for an outcome was 1, that outcome would not occur in people who were vaccinated; if relative vaccine effectiveness was 0, those vaccinated and unvaccinated would have the same rate of the outcome.

As an example, if 40 out of 100 unvaccinated people are hospitalized and 10 out of 100 vaccinated people are hospitalized, relative vaccine effectiveness for hospitalization is 0.75. This is calculated as the rate in the unvaccinated minus the rate in the vaccinated divided by the rate in the unvaccinated, or (0.4 - 0.1)/0.4. This means that the vaccine is preventing 75% of hospitalizations that would have otherwise occurred.

Prevention of Serious Disease

The following table presents our estimates of prevention of hospitalization and death with Covid-19 vaccination. The explanations for these estimates as well as the uncertainties in the results are presented in the following sections below.

Table 3.3. Estimated Vaccine Effectiveness for Preventing Hospitalization and Death

Population	Fewer Hospitalizations Per 1,000 Vaccinated Persons	Vaccinations Needed to Prevent One Hospitalization*	Fewer Deaths Per 1,000 Vaccinated Persons	Vaccinations Needed to Prevent One Death*
Young Adults	0.06	16,000	0.02	55,000
Adults 50–64	0.22	4,500	0.06	15,000
Adults 65+†	0.75	1,300	0.22	4,500
Adults 85+	3.36	300	0.99	1,000
Children 5–18	0.05	20,000	NE	NE
Children 2–5	0.15	6,600	NE	NE
Children 1–2	0.53	1,900	NE	NE
Children 6–12 Months	0.99	1,000	NE	NE
Young Pregnant Women	0.21	4,800	0.06	16,000
Older Pregnant Women	0.29	3,500	0.08	12,000
Comorbidities In People Under 65‡	0.17	6,000	0.05	20,000
People Under 65 With CKD	0.13	7,900	0.04	27,000

CKD: chronic kidney disease, NE: not estimated due to data limitations

*Rounded estimates

†Estimates of fewer hospitalizations/deaths per 1,000 persons for adults 65+ were from The VA Study

‡Comorbidities other than CKD

Adults Under Age 65

As discussed elsewhere, we believe our best evidence on current effectiveness of vaccination for preventing serious clinical outcomes from Covid-19 in adults in the US comes from the VA Study.[18] Table 3.4 shows absolute risks and risk differences for Covid-19 associated emergency department (ED) visits, hospitalizations, and deaths per 1,000 people considering Covid-19 vaccination.

Table 3.4. Absolute Risk and Risk Differences at Six months in 2024–2025 Season from The VA Study*[18]

Outcome	Risk in No Vaccine Group	Risk in Vaccine Group	Risk Difference (95% CI)
Covid-19-Associated Emergency Department Visit	6.24	4.42	1.83 (1.08, 2.76)
Covid-19-Associated Hospitalization	1.91	1.16	0.747 (0.344, 1.30)
Covid-19-Associated Death	0.349	0.125	0.220 (0.049, 0.691)

CI: confidence interval, %: percent

*Data presented as per 1,000 persons

The mean age of participants in The VA Study was 71; however 67,300 participants were under age 65. We do not have reductions in individual outcomes of ED visits, hospitalizations, and deaths in this younger cohort; however the reduction in a composite of these outcomes was smaller in those under 65 than those ages 65 to 75 and those over 75 (1.3 fewer composite events per 1,000 participants versus 2.4 fewer and 2.7 fewer, respectively) (see Supplement Table D3.45).

The relative effectiveness of vaccination at reducing ED visits for the population in The VA Study was 29.3%. The Adult CDC Study, using a test-negative design and examining the 2024 to 2025 time frame, found similar estimates of relative effectiveness.[16] The study found 33% effectiveness against ED or urgent care (UC) visits in the entire adult cohort (median age 58 among case patients and 53 among control patients); effectiveness was also 30% among those under 65.

In The VA Study, relative effectiveness against hospitalization and against death were both better than the effectiveness against the composite endpoint (28.3%) (see Supplement Table D3.41). Given this, and given the results of The Adult CDC Study, we think it is reasonable to assume at least a 28% relative effectiveness in adults under age 65 for prevention of ED visits, hospitalizations, and deaths as a conservative estimate.

We have detailed data on rates of hospitalization associated with Covid-19 in the 2024-2025 season from the CDC COVID-NET surveillance system.[15] Rates ranged from approximately 22 hospitalizations per 100,000 young adults per year to approximately 80 hospitalizations per 100,000 adults ages 50 to 64. Applying the estimated relative effectiveness of 0.28, we get absolute reductions in hospitalizations ranging from approximately 0.06 fewer hospitalizations from vaccinating 1,000 younger adults to approximately 0.22 fewer hospitalizations from vaccinating 1,000 adults ages 50 to 64.

In The VA Study, absolute reductions in ED visits were 2.45 times the reductions in hospitalizations, and reductions in mortality were 0.29 times the reductions in hospitalizations. This gives conservative estimates of 0.14 fewer ED visits and 0.02 fewer deaths per 1,000 vaccinated younger adults and 0.55 fewer ED visits and 0.06 fewer deaths per 1,000 vaccinated adults ages 50 to 64.

Older Adults

Given the mean age of 71 in The VA Study, we feel that the estimates of risk reduction seen in that study can be appropriately applied to a population of older adults and taken as slightly conservative estimates given that the population also included those under 65. The VA Study found that per 1,000 patients, vaccination resulted in 1.8 fewer ED visits, 0.75 fewer hospitalizations, and 0.22 fewer deaths.[18]

The Adult CDC Study found similar estimates of relative effectiveness in those over age 65 to what was seen in the VA Study for the entire population.[16] Prevention of ED or UC visits was 35% versus

29.3% for ED visits in the VA Study, and prevention of hospitalization among immunocompetent participants was approximately 45% versus 39%.

These results support using the estimates from The VA Study and are also reassuring that The Adult CDC Study provides reasonable estimates of relative effectiveness.

As in other age groups, risk varies over the age range. Data from the 2024 to 2025 season found that rates of hospitalization were 2.6 times higher for those age 75 to 84 compared with those 65 to 74 and were nearly six times higher for those 85 and older.[15]

Ages 5 to 18 Years

This age range appears to be a particularly low risk group, with hospitalization rates from the 2024–2025 season of approximately 9 per 100,000.[15] The Childhood CDC study estimated vaccine effectiveness of 0.56 (95% CI: 0.35 to 0.70) for prevention of ED and UC visits in this population.[17] If we assume this same effectiveness against hospitalization, we would estimate 0.05 fewer hospitalizations per 1,000 vaccinated older children and teenagers.

Ages 2 to 5 Years

This age range appears to have risks for hospitalization similar to young adults, with hospitalization rates from the 2024–2025 season of approximately 20 per 100,000.[15] The Childhood CDC study estimated vaccine effectiveness of 0.76 (95% CI: 0.58 to 0.87) for prevention of ED and UC visits in children nine months to less than age five.[17] If we assume this same effectiveness against hospitalization, we would estimate 0.15 fewer hospitalizations per 1,000 vaccinated younger children.

Ages 1 to 2 Years

This age range appears to be at increased risk for hospitalization with hospitalization rates from the 2024–2025 season of approximately 70 per 100,000.[15] The Childhood CDC study estimated vaccine effectiveness of 0.76 (95% CI: 0.58 to 0.87) for prevention of ED and UC visits in children nine months to less than age five.[17] If we assume this same effectiveness against hospitalization, we would estimate 0.53 fewer hospitalizations per 1,000 vaccinated younger children.

Ages 6 to 12 Months

This age range also appears to be at increased risk, with hospitalization rates from the 2024–2025 season of approximately 130 per 100,000.[15] We do not have good estimates of vaccine effectiveness for this age range; as noted above, The Childhood CDC study estimated vaccine effectiveness of 0.76 (95% CI: 0.58 to 0.87) for prevention of ED and UC visits in children nine

months to less than age five.[17] If we assume this same effectiveness against hospitalization in this population, we would estimate 0.99 fewer hospitalizations per 1,000 vaccinated older infants.

Children of Women Vaccinated During Pregnancy

Young infants are at high risk for hospitalization with rates higher than for any age group less than age 75.[15] Hospitalization rates from the 2024–2025 season were approximately 250 per 100,000.[15] Infants younger than six months of age are too young to receive Covid-19 vaccine.

Vaccination during pregnancy could potentially improve outcomes of the child by preventing illness during pregnancy and during the first six months of life, when maternal antibodies could be protective against Covid-19 in the child. Third trimester administration of Covid-19 vaccine results in significant levels of antibodies in cord blood.[32] Observational studies suggest that administration of influenza or pertussis vaccine to pregnant women is protective against disease caused by those viruses in young infants.[33,34] There is some evidence that vaccination of pregnant mothers decreases the risk of infection in infants, including greater protection with higher levels of antibodies in the infant which makes this more likely to be causal.[35] A recent cohort study from Norway examining outcomes from 2021 through 2023 concluded that maternal vaccination reduced the risk of hospital evaluation for Covid-19 in newborns, with protection waning over six months.[36] In this study, vaccination did not appear to reduce the likelihood of hospital evaluation for other infections, which makes confounding less likely, however first trimester vaccination had the same benefit as second and third trimester vaccination, which would be unexpected and does raise concerns for residual confounding.

We do not have high quality studies assessing the potential benefits for young infants in 2026 of vaccinating their mothers while pregnant. The best available evidence appears to be biologic plausibility, extrapolating from the high risk from Covid-19, the evidence for transplacental antibody transfer after Covid-19 maternal vaccination, and the likely benefits of other maternal vaccinations. Lower quality observational data support this conclusion but, particularly with more recent studies, we worry that there may be residual confounding as pregnant women who choose to get vaccinated may differ in important ways from pregnant women who choose not to get vaccinated (see Supplement Tables D3.54–D3.57).[34,37-41]

Pregnant Women

Pregnancy has been considered a risk factor for more severe manifestations of Covid-19.[42] A study looking at the influence of pregnancy on Covid-19 outcomes in a post-pandemic period (May 2023 through December 2024) found that pregnant women had similar rates of infection with Covid-19 compared with non-pregnant women, but that pregnancy increased the risk of hospitalization with Covid-19 (relative risk 3.4).[42]

Hospitalization rates from the 2024–2025 season were approximately 22 per 100,000 for people ages 18 to 29 and 30 per 100,000 for people 30 to 39.[15] If this relative risk persists, we might anticipate hospitalization rates for pregnant women ages 18 to 29 of 75 per 100,000 and of 102 per 100,000 for those ages 30 to 39. Assuming vaccine effectiveness of 0.28, we would expect 0.21 fewer hospitalizations per 1,000 younger pregnant women and 0.29 fewer hospitalizations per 1,000 older pregnant women.

Extrapolating further, using the relative effects in The VA Study, we would expect 0.51 and 0.71 fewer ED visits per 1000 younger and older pregnant women, and expect 0.06 and 0.08 fewer deaths per 1000 younger and older pregnant women. As discussed below, this extrapolation is using data from a very different population and adds substantial uncertainties. However, we did not find estimates that we felt were more reliable for the 2026 to 2027 season.

Supplement Tables D3.54–D3.57 outline studies identified that report on vaccine effectiveness and safety for pregnant women and infants.

Comorbidities

In The VA Study, comorbidities that significantly increased the risk of the composite endpoint (Covid-19 associated ED visit, hospitalization, or death) in unvaccinated patients included cardiovascular disease, cerebrovascular disease, chronic kidney disease (CKD), chronic lung disease, and immunocompromised state.[18] In all these conditions, the relative effectiveness of vaccination against the composite endpoint was greater than our conservative estimate of 28%. We note, however, that these conditions increase with increasing age and the published results were uncontrolled for age. Risks in these conditions are shown in Table 3.5.

Table 3.5. Composite Endpoint: Subgroup Analyses of Comorbid Conditions in The VA Study*[18]

Comorbidity	Risk in No Vaccine Group	Risk in Vaccine Group	Risk Difference
Cardiovascular Disease	10.22	6.56	3.63 (2.07, 5.56)
Cerebrovascular Disease	11.42	7.54	3.86 (1.30, 7.21)
Chronic Kidney Disease	8.60	5.56	3.03 (1.63, 4.76)
Chronic Lung Disease	11.38	7.21	4.17 (2.31, 6.40)
Immunocompromised	11.83	7.74	4.08 (1.83, 6.82)

*Data presented as per 1,000 persons

In this study, in those not receiving Covid-19 vaccination, the risk of the composite endpoint was approximately twice as high in those with the condition as those without, with the exception of CKD, where the risk was approximately 50% higher than in those without CKD (see Table 3.6).

Table 3.6. Relative Risk of the Composite Endpoint in The VA Study by Comorbid Condition[18]

Comorbidity	Relative Risk vs. Absence of Comorbidity*
Cardiovascular Disease	1.95
Cerebrovascular Disease	1.94
Chronic Kidney Disease	1.51
Chronic Lung Disease	2.18
Immunocompromised	2.12

*Calculated by dividing risk with the comorbid condition by the risk without the comorbid condition among unvaccinated people.

In the absence of better data on the absolute risks of events with each of these conditions in younger adults, we are estimating by using 2024–2025 season data from the CDC Covid-19-Associated Hospitalization Surveillance Network (COVID-NET).[15] There were approximately 30 hospitalizations per 100,000 adults ages 18 to 49 from Covid-19. If we double the risk for comorbidities other than CKD, we would estimate 60 hospitalizations per 100,000 adults with comorbidities other than CKD and 45 hospitalizations for those with CKD. Applying the estimated relative effectiveness of 0.28, we get absolute reductions in hospitalizations ranging from approximately 0.17 fewer hospitalizations from vaccinating 1,000 adults with comorbidities other than CKD and 0.13 fewer hospitalizations from vaccinating 1,000 adults with CKD.

Using the extrapolation applied above in The VA Study, absolute reductions in ED visits were 2.45 times the reductions in hospitalizations, and reductions in mortality were 0.29 times the reductions in hospitalizations, we get estimates of 0.41 fewer ED visits and 0.05 fewer deaths per 1,000 vaccinated adults with comorbidities other than CKD and estimates of 0.31 fewer ED visits and 0.04 fewer deaths per 1,000 vaccinated adults with CKD.

Transmission

Vaccination against respiratory viruses in low-risk individuals is sometimes considered as a strategy to reduce risk in people at higher risk because of age or comorbidities.[43] In July 2021, spread of Covid-19 by and between vaccinated individuals occurred in Provincetown, MA and called into question the effectiveness of vaccination for Covid-19 in preventing transmission.[44] While some data from the pandemic show decreased infectivity of vaccinated individuals,[45,46] it is unclear whether reduction in transmission of Covid-19 is an important benefit of vaccination in 2026.

Prolonged Symptoms After Mild Disease

Prolonged symptoms after serious Covid-19 can occur for multiple reasons including post-intensive care unit (ICU) syndromes, severe deconditioning, and irreversible organ damage. Prolonged symptoms can occur after recognized viral illnesses such as with influenza or Epstein Barr Virus, or can occur in the absence of known infection with definitions of various syndromes such as Myalgic

Encephalomyelitis or Chronic Fatigue Syndrome (ME/CFS).[47,48] The syndrome of Long Covid has been defined very broadly but includes patients with similar syndromes to ME/CFS as well as Postural Orthostatic Tachycardia Syndrome (POTS; a syndrome involving intolerance to an upright posture).[49] One definition of Long Covid from the National Academies of Sciences, Engineering, and Medicine can be found in Supplement Section A.

A difficulty in interpreting evidence on vaccination for prevention of prolonged symptoms after mild disease with Covid-19 is the lack of reliable information on rates of mild or asymptomatic infection with SARS-CoV-2. In the absence of higher quality evidence, given no good denominator, we have only very low-quality evidence on how well vaccination prevents mild symptoms of Covid-19 and very low-quality evidence on whether vaccination prevents prolonged symptoms after infection that is asymptomatic or results in only mild disease. Some studies have suggested vaccination reduced rates of Long Covid early in the pandemic (see Supplement Table D3.67).[50-52]

This lack of evidence does not mean that such benefits do not exist, but including them as important benefits of vaccination would be speculative.

Harms

Short Term Adverse Events

Evidence on short-term local and systemic adverse reactions (also referred to as reactogenicity) were primarily derived from the pivotal randomized trials of the four vaccines: BNT162b2 (Comirnaty), mRNA-1273 (Spikevax), mRNA-1283 (mNexspike), and NVX-CoV-2373 (Nuvaxovid). The vaccine brand names will be used throughout this section for clarity as we are making distinctions among the vaccine products. Additional safety data from pivotal, booster, and other safety studies are presented in Supplement Tables D3.2–D3.36.

The most commonly reported local reactions across all vaccine trials were pain at injection site, axillary swelling, redness, and tenderness. The most commonly reported systemic adverse events across all vaccine trials were headache, fatigue, and muscle pain. Participants in the safety subsets of the trials highlighted below recorded adverse events in an electronic diary for seven days after each injection. Table 3.7 below outlines key local and systemic adverse events for dose two of the pivotal trials for Comirnaty (aged 16 to 55), Spikevax (18+), and Nuvaxovid (18+), and a first dose of mNexspike compared to a dose of Spikevax in previously vaccinated individuals (12+ years old). Across the trials, there were more reactogenic events after the second dose of the primary series compared with the first dose and we chose to focus on the second-dose data.

For Comirnaty, adults experienced the highest rates of reactogenicity, and older adults, young children, and adolescents reported less frequent reactions.[7,53,54] For Spikevax, adults and

adolescents had similarly high reaction levels and young children and older adults reported slightly fewer local and systemic reactions.[55-58] For mNexspike, adverse events rates were generally similar across age groups compared to Spikevax but slightly lower for some reactions (e.g., pain at the injection site).[59] For Nuvaxovid, adults and adolescents experienced similarly high rates of reactogenicity and older adults reported fewer events.[9,60,61] In line with current FDA label indications for mNexspike and Nuvaxovid, safety data for children under the age of 12 were not reported in the initial trials. More detail on systemic and local adverse events across randomized and booster trials can be found in Supplement Tables D3.2–D3.34.

Table 3.7. Key Safety after Second Dose of Primary Vaccine Series[7,56,59,60]

Vaccine	Comirnaty		Spikevax		mNexspike		Nuvaxovid	
Study	Polack 2020		Sahly 2021		Chalkias 2025		Dunkle 2021	
Arm	BNT162b2	Placebo	mRNA-1273	Placebo	mRNA-1283	mRNA-1273	NVX-CoV-2373	Placebo
Timeframe	Seven Days After Injection							
Local, %								
Pain at Injection Site	78	12	88	17	69	78	60	14
Redness	6	1	9	0.5	2	4	7	0.4
Swelling	6	0	12	0.4	4	6	6	0.3
Tenderness	NR	NR	NR	NR	NR	NR	73	16
Systemic, %								
Chills	35	4	44	6	23	20	NR	NR
Headache	52	24	59	24	44	41	44	20
Fatigue	59	23	65	24	50	49	50	22
Fever	16	0	16	0.3	6	5	6	0.3
Muscle Pain	37	8	NR	NR	NR	NR	48	12
Nausea/Vomiting	2	1	19	7	12	11	3	3

NR: not reported, %: percent

In booster doses across vaccines, adverse event rates lowered with additional vaccination. It is unknown whether this is the result of a biological effect, less complete ascertainment, or under enrollment of individuals who had poor reactions to the initial vaccine doses. It is also unknown whether repeated doses of the same vaccine may result in less adverse events over time (see the mRNA-1273 arms for Sahly 2021 and Chalkias 2025 above).

We identified several small randomized control trials (RCTs) (sample sizes ranging from ~130 to 750) that sought to compare reactogenicity among currently available vaccines given as booster doses, specifically *between protein-based vaccines* (Nuvaxovid) and *mRNA vaccines* (Comirnaty, Spikevax, mNexspike), and *between two mRNA vaccines* (Comirnaty and Spikevax) These studies evaluated booster doses and enrolled participants who previously received heterologous (different vaccine types between doses, e.g. mRNA followed by protein-based) or homologous (same vaccine type between doses, e.g. mRNA followed by mRNA) vaccine regimens with a variety of approved

vaccines.[62-66] Among small trials comparing Comirnaty and Spikevax, fewer reactogenicity events were observed with Comirnaty.[62,66] Three studies found that there were fewer reports of reactogenicity with receipt of a Nuvaxovid vaccine compared to mRNA vaccination.[63-65] (see Supplement Table D3.36).

In addition, recent observational studies have sought to evaluate reactogenicity differences in a real-world population. It is important to note that participants included in these studies have previously received series of homologous or heterologous vaccines and may be more likely to seek out a different vaccine based on prior experiences with vaccine reactogenicity.

A pre-print from a manufacturer-sponsored prospective study (SHIELD) reported rates of reactogenicity among 588 health care workers and first responders who self-selected either the 2024–2025 Nuvaxovid or Comirnaty vaccine found there were fewer reactogenicity symptoms and a lower mean global impairment score (i.e., impacts on work, family life, etc.) among people who received Nuvaxovid.[67] No differences between vaccines were observed after seven days. This is aligned with the 2019nCoV-406 study, which found fewer reactogenicity events reported in booster doses of protein-based compared to mRNA-based Covid-19 vaccines.[68]

We identified numerous vaccine surveillance studies that used databases such as Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD), and Moderna Global Safety Database. These studies report on safety across age groups and help identify new safety signals (see Supplement Section D3). Recent surveillance studies have not revealed new safety signals beyond what has been previously understood.

Myocarditis and Pericarditis

After initial doses of mRNA Covid-19 vaccines in 2020–2021, cases of myocarditis, inflammation of the heart muscle, were identified across the population but particularly among boys aged 12 to 18 years old and young men. Myocarditis and pericarditis, inflammation of the lining surrounding the heart, often occur together and can be referred to as myopericarditis or myocarditis/pericarditis. Vaccine studies have not routinely clearly distinguished these entities. We are reporting what was recorded in studies; FDA warnings for these vaccines also mention pericarditis.[24-27]

In the VSD database, the highest incidence of myocarditis among people 12 to 39 years old within a week of mRNA vaccination was after the second dose of the original monovalent vaccine in the 2020–2021 season (38 per 1,000,000 doses) and the first booster dose in 2021 to 2022 (25 per 1,000,000 doses). These data were not stratified by sex. The VSD and VAERS database did not identify increased risk of myocarditis with the 2022 to 2023, 2023 to 2024, or 2024 to 2025 updated vaccine formulations. In the 2024–2025 season, data from VSD reported 2 cases per 1,000,000 doses which aligns with background rates of myocarditis in this age group.[69] Data from FDA's

Biologics Effectiveness and Safety System (BEST) reported a myocarditis rate of 26.9 cases per 1,000,000 doses in boys and men aged 12 to 24 and a rate of 8.4 cases per 1,000,000 doses in all persons aged six months to 64 years old in the seven days following vaccine administration.[69] These results likely provide an upper limit for the risk of clinically important myocarditis with vaccination for Covid-19.

Real-world evidence on various vaccination formulations over the past six years does identify cases of myocarditis associated with Covid-19 vaccination, however, incidence has appeared to decrease to the background rate. Two recent studies conducted in the US of the 2023-2024 mRNA vaccine formulation did not identify an increased risk of myocarditis with Covid-19 vaccination.[70,71] Supplement Tables D3.60–D3.63 report observational studies identified that report on myocarditis/pericarditis in boys and young men and other age groups.

Harms in Pregnancy

As pregnant women were not included in the initial clinical trials evaluating Covid-19 vaccines, observational studies have sought to evaluate the safety profile among pregnant women and their infants. Numerous observational studies evaluating vaccine safety among pregnant women have not identified an increased risk of miscarriage, post-partum hemorrhage, pre-term delivery, or maternal death among pregnant women.[72-75] In addition, many observational studies have not identified increased risk of perinatal or neonatal death, low birth weight, or congenital anomalies (see Supplement Tables D3.54–D3.57).[37,76-80] These findings are in alignment with a 2024 living systematic review and meta-analysis that evaluated over 600,000 participants across 177 studies and found that while the majority of evidence has low certainty, Covid-19 vaccination was not associated with increased risk of maternal or infant harm.[81]

Guillain-Barre Syndrome

Guillain-Barre syndrome is a rare disorder in which the immune system damages the nerves. An estimated 3,000 to 6,000 people develop it each year in the US. There was a small increased risk of Guillain-Barre syndrome identified with previously developed viral vector Covid-19 vaccines that are no longer available in the US.[82] There was no safety signal for Guillain-Barre in the clinical trials for Comirnaty, Spikevax, or mNexspike but there have been cases identified after mRNA vaccination in post-marketing and observational studies. However, no clear evidence of an increased risk has been established. In the Novavax clinical trials, there was one serious case of Guillain-Barre syndrome that was reported after the first dose administration.[27] The observational studies identified that report on Guillain-Barre syndrome in relation to Covid-19 vaccination are outlined in Supplement Tables D3.64–D3.65.

Subgroup Analyses and Heterogeneity

We discuss multiple subgroups above defined by age ranges, comorbidities, pregnancy status, and, in the case of harms, sex. We note here that in the original randomized trials, there was no effect modification observed in vaccine efficacy by sex or race.[6,7,9,55-61,83,84]

Uncertainty and Controversies

- We do not have large randomized trials of vaccination for Covid-19 in the post-pandemic era. In the absence of such trials, we focused heavily on what we felt was the best available evidence for recent effectiveness, The VA Study, balanced by comparisons to the two large CDC cohort studies in adults and children. For the reasons discussed above, we feel The VA Study provides high quality evidence for the effectiveness of Covid-19 vaccination in the 2024–2025 season in the population studied. However, these estimates are importantly indirect to many other populations in 2024–2025 and to all populations in the 2026–2027 season. As the degree of indirectness increases, particularly when extrapolating to younger populations, to younger populations with comorbidities, and to pregnant women, the degree of uncertainty in estimates increases. This is reflected in our evidence ratings.

- For most subgroups we have estimates of recent epidemiology for hospitalizations from Covid-19, but limited or no high-quality estimates of mortality from Covid-19. We have extrapolated as discussed above, but it is likely that these will somewhat overestimate or underestimate rates of events in some subgroups.

- We intentionally used a conservative estimate of vaccine effectiveness of 0.28 when performing extrapolations. Most studies suggest that vaccine effectiveness is higher for more serious events (including mortality) and lower for less serious events (such as mild illness). Vaccination is a preventive strategy and we believe that conservative estimates are appropriate when data are limited in the area of prevention. Rates of serious infection with Covid-19 have been declining rapidly. For a three-month period from the beginning of October until the end of December, hospitalization rates for Covid-19 per 100,000 were 77.0 in 2023 but declined to 33.5 in 2024 and 16.2 in 2025.[15] We did not include an estimate of further declines for the 2026–2027 season; in making that choice we were making "optimistic" estimates of benefit based on expected cases of Covid-19. Others, however, may wish to examine results with more optimistic estimates. We note that that while The VA Study found a vaccine effectiveness rate of 0.28 for a composite endpoint, the effectiveness estimate for mortality was more than twice this (effectiveness of 0.64; 95% CI: 0.23 to 0.85). To help provide a likely upper bound for reductions in mortality in various subgroups, in Table 3.8 below we present the expected reductions in deaths per 1000 vaccinated people if we assume triple the reduction in deaths (effectiveness of 0.84;

essentially the upper limit of the 95% CI from The VA Study). We note, however, that those wishing to use these more optimistic estimates might consider extrapolating to a lower rate of serious infections in the 2026–2027 season.

Table 3.8. Optimistic Expected Reductions in Death Per 1,000 Vaccinated People and Vaccines Needed to Prevent One Death: Triple Reduction Assumption

Population	Expected Reductions in Death (Optimistic)	Vaccines Needed to Prevent One Death* (Optimistic)	Vaccines Needed to Prevent One Death* (Baseline)
Younger Adults	0.06	18,000	55,000
Adults 50–64	0.18	5,100	15,000
Adults 65+	0.66	1,500	4,500
Adults 85+	2.97	340	1,000
Children 5–18	NE	NE	NE
Children 2–5	NE	NE	NE
Children 1–2	NE	NE	NE
Children 6–12 Months	NE	NE	NE
Young Pregnant Women	0.18	5,400	16,000
Older Pregnant Women	0.24	4,000	12,000
Comorbidities In People Under 65†	0.15	6,700	20,000
People With CKD	0.12	9,000	27,000

CKD: chronic kidney disease, NE: not estimated due to data limitations

*Rounded estimates

†Comorbidities other than CKD

- The strains of Covid-19 have been changing over time. A variant with extensive spike protein mutations has been recently found to be circulating in the US.[19] This necessarily creates uncertainties about the 2026–2027 season. We note that some experts pointed out that among the possibilities is that another severe pandemic strain could emerge. Were that to occur, the net clinical benefit of an effective vaccine would be much greater than we are assuming in this report.

- Conversely, as discussed above, the severity of Covid-19 appears to be declining over time. While we used recent estimates of disease severity (hospitalizations) for most subgroups, it is possible that by the 2026–2027 season, severity will be even lower, which would reduce the net benefits of vaccination. However, as noted, we attempted to include some of this uncertainty by using conservative estimates of vaccine effectiveness.

- It is unclear whether there is still an excess risk of myocarditis/pericarditis with Covid-19 vaccination. There has been a decline in reported cases. This may reflect changes in the vaccine schedule (longer duration between initial doses), changes in vaccine formulations, changes in background immunity, decisions by individuals about whether to receive vaccination, or other unrecognized changes over time. Although the decline is likely real, if it

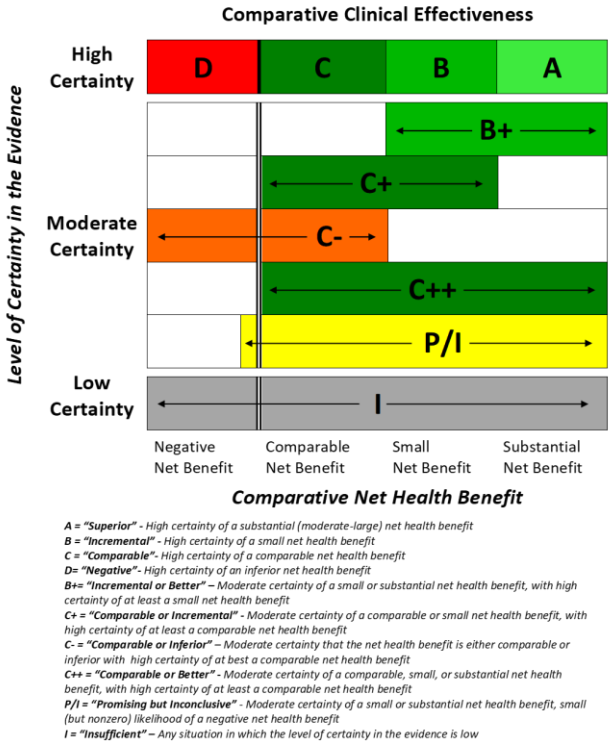
reflects individual decisions to avoid vaccination (for instance, by parents of teenage boys, individuals with prior severe reactions, or individuals with family members who had severe reactions), evaluations of vaccine net benefit would still need to consider this risk.

- Even for epidemiologic data on Covid-19-associated hospitalizations, there are uncertainties about causality. Some hospitalized patients found to have Covid-19 will have been hospitalized for reasons unrelated to Covid-19. Other patients may have an illness triggered by Covid-19, such as a heart failure exacerbation, without Covid-19 having been tested for or detected. A methodology for determining causality among patients hospitalized with a positive test for SARS-CoV-2 has been published.[85] Data presented in September 2025 at a meeting of the ACIP reported that high percentages of children (89%), adults ages 50 to 64 (83%) and adults 65 and older (91%) who were hospitalized with positive tests for SARS-CoV-2 in the 2024–2025 season were hospitalized because of Covid-19.[86] The percentage was somewhat lower in adults ages 18 to 49 (69%).

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1.) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



In comparing vaccination for Covid-19 with no vaccination in various groups/subgroups, we are not distinguishing in our overall ratings among the four available vaccines, although we are commenting on areas where vaccine differences could affect these ratings. We note that when we look at more recent data on vaccine effectiveness, most patients received an mRNA vaccine and so outcomes are not being driven by the net effects of Nuvaxovid. For example, in The VA Study, more than 99% of participants vaccinated for Covid-19 received one of two mRNA vaccines.[18] Randomized trials early in the pandemic suggested similar efficacy of the vaccines.[6,7,9] However, it is possible that vaccine effectiveness could differ in the 2026–2027 season. In making group evidence ratings we are assuming that any differences in effectiveness would not change these ratings, but readers should recognize that estimates of effectiveness for Nuvaxovid are likely more uncertain than for the mRNA vaccines. These uncertainties are reflected in our ratings of the evidence between/among vaccines.

For all the vaccines, our evidence ratings assume that vaccination does not have an important impact on the risk of transmitting Covid-19. Given the lack of convincing evidence, we feel this is

appropriate. Additionally, it means that the evidence ratings are considering only individual net health benefit from vaccination or, in the case of pregnant women, benefit only to the mother and baby. If vaccination does substantially reduce transmission, a population perspective would conclude that there is greater net health benefit from individual vaccinations.

We also feel that there is no convincing evidence linking Covid-19 vaccination to development of Guillain-Barre syndrome. These evidence ratings assume there is no causal link.

The distinction between "incremental" and "substantial" net health benefits in the ICER rating system is necessarily subjective. ICER has not previously reported on vaccinations. Covid-19 vaccination is a preventive intervention. If the major benefit is only for the individual vaccinated and it does not have an important benefit in preventing disease transmission, Covid-19 vaccination can reasonably be compared with preventative therapies in areas that ICER has examined such as cardiovascular disease. A well-studied preventive intervention is statin therapy to prevent major adverse cardiovascular events (MACE). A meta-analysis of randomized trials found that statins used for primary prevention reduce MACE by about 25%.[87] Guidelines for primary prevention use different risk cut points at which to recommend statin therapy, but virtually all guidelines pick a ten-year risk of 5% or greater. A patient with a ten-year risk of 4% could expect an approximately 1% reduction in MACE over a decade, or a reduction of 0.1% in one year. In this report, for populations where, even with uncertainties, we did not think the absolute benefit of vaccination in preventing a serious case of Covid-19 could exceed 0.1% in one year, we considered the benefits of vaccination at most incremental. Where they could exceed 0.1% in one year, we included the possibility that the benefits were substantial.

Adults Ages 18 to 64 (Excluding Men Ages 18 to 24):

The current risk of severe disease from Covid-19 is small, though it does start to increase somewhat around age 50. We estimate that approximately 16,000 younger healthy adults would need to be vaccinated to prevent one hospitalization and approximately 55,000 to prevent one death. For adults ages 50 to 64, these estimates are approximately 4,500 to prevent one hospitalization and approximately 15,000 to prevent one death.

Serious harms from Covid-19 vaccination are extremely rare, however minor harms (e.g., one-to-two days of malaise) are common and must be considered given the relatively small estimated benefits of vaccination in this population of younger, healthy adults.

Given the uncertainties in the estimates of benefits in this population of healthy adults, particularly for the 2026–2027 season if rates of serious Covid-19 continue to decline, we feel the net benefit of Covid-19 vaccination versus no vaccination is "Comparable or Incremental" (**C+**). The net health

benefit will be larger in people who do not experience significant side effects with vaccination and in those over age 50 but still would be unlikely to be greater than incremental.

Older Adults:

We believe The VA Study provides high quality evidence for the effectiveness of mRNA Covid-19 vaccination in a population with a mean age of 71 in the 2024–2025 season. Approximately 1,300 older adults would need to be vaccinated to prevent one hospitalization and approximately 4,500 to prevent one death. As noted, serious harms of Covid-19 vaccination are extremely rare.

The risk of hospitalization goes up substantially as people age. Using our extrapolations, for those 85 and older we would expect that approximately 300 adults would need to be vaccinated to prevent one hospitalization and 1,000 to prevent one death.

Given the uncertainties about the risk of serious Covid-19 in the 2026–2027 season, we feel the net benefit of Covid-19 vaccination versus no vaccination is "Incremental or Better" (**B+**) for a broad population of older adults and increases as people age. For those over age 85, the net health benefit in the 2026–2027 season is likely to be substantial. For all older age groups, it is unclear from the available evidence how much the effects of age are independent of comorbidities or, instead, reflect the association of age with comorbidities.

Children Ages 5 to 18 (Excluding Boys Ages 12 to 18):

This is a low-risk population, but there is some evidence that vaccine effectiveness may be higher than in older populations. We estimate that approximately 20,000 children in this age range would need to be vaccinated to prevent one hospitalization; deaths are uncommon and vaccine effectiveness for prevention of death is uncertain. Serious harms from Covid-19 vaccination are extremely rare.

Given the uncertainties about the risk of serious Covid-19 in the 2026–2027 season, we feel the net benefit of Covid-19 vaccination for this population is "Comparable or Incremental" (**C+**).

Males Ages 12 to 24:

The risk of serious Covid-19 in this population is low and is described in the sections above. The FDA labels for Covid-19 vaccinations all mention the risk of myocarditis/pericarditis, and the mRNA vaccines include a risk of 2.7 cases per 100,000 males ages 12 to 24, or approximately one case for every 37,000 males in this age range vaccinated. As discussed above, most cases of myocarditis/pericarditis after vaccination are mild and recovery is typically rapid. Cases of myocarditis/pericarditis have declined over time for uncertain reasons. Some people feel this is due to the change in the vaccine schedule or to prior exposure to the antigens, however it is also

possible that this decline reflects decisions about who should receive vaccine given concerns about myocarditis/pericarditis.

Given the above considerations, as well as the uncertainties about the risk of serious Covid-19 in the 2026–2027 season, we consider the net health benefit of Covid-19 vaccination in males ages 12 to 24 to be "Promising but Inconclusive" (**P/I**).

Children Ages 2 to 5:

As with older children, there is some evidence that vaccine effectiveness may be higher than in older populations. Risk appears similar to that in young adults. We estimate that approximately 6,600 children in this age range would need to be vaccinated to prevent one hospitalization; deaths are uncommon and vaccine effectiveness for prevention of death is uncertain. Serious harms from Covid-19 vaccination are extremely rare.

Given the uncertainties in the estimates of benefits in this population, particularly for the 2026–2027 season, we feel the net benefit of Covid-19 vaccination is "Comparable or Incremental" (**C+**).

Children Ages 1 to 2:

This is a group at moderately increased risk from Covid-19 and, as with other children, there is some evidence that vaccine effectiveness may be higher than in older populations. We estimate that approximately 1,900 children in this age range would need to be vaccinated to prevent one hospitalization; vaccine effectiveness for prevention of death is uncertain. Serious harms from Covid-19 vaccination are extremely rare.

Given the uncertainties in the estimates of benefits in this population, particularly for the 2026–2027 season, we feel the net benefit of Covid-19 vaccination is "Comparable or Better" (**C++**).

We note, however, that for children who have never been vaccinated previously and have never been infected with SARS-CoV-2, it is likely that the net health benefits are at least incremental and could be substantial.

Children Ages 6 to 12 Months:

This is a population with increased risk and, as with other children, there is some evidence that vaccine effectiveness may be higher than in older populations. We estimate that approximately 1,000 children in this age range would need to be vaccinated to prevent one hospitalization. We lack adequate data on mortality and vaccine effectiveness for prevention of death. Serious harms from Covid-19 vaccination are extremely rare.

Given the uncertainties about the risk of serious Covid-19 in the 2026–2027 season, we feel the net benefit of Covid-19 vaccination for older infants is "Incremental or Better" (**B+**).

Vaccination During Pregnancy:

In considering net health benefit for vaccination during pregnancy, we are taking the perspective of benefits and harms both for the mother and the child with the assumption that this will be the likely perspective of most pregnant women. We note, however, that other perspectives are possible.

We estimate that approximately 4,800 younger pregnant women and approximately 3,500 older pregnant women would need to be vaccinated to prevent one hospitalization; these numbers to prevent one death are approximately 16,000 and approximately 12,000, respectively.

As discussed above, young infants are at higher risk from Covid-19 than any age group younger than 75. It is biologically plausible given evidence on antibody levels in young infants after maternal vaccination that third-trimester vaccination could provide important protection for infants.

The risk of serious harms from vaccination appears low. However, fever during embryogenesis has been shown in animal models to be teratogenic. While some human studies have also suggested teratogenicity from fever, the evidence is inconsistent.[88]

Given the uncertainties about the risk of serious Covid-19 in the 2026–2027 season, we feel the net benefit, from a combined mother/child perspective, of maternal third trimester Covid-19 vaccination is "Incremental or Better" (**B+**). We are less certain about vaccination early in pregnancy during embryogenesis when fever from vaccination could potentially be teratogenic and consider the evidence insufficient. Vaccination after embryogenesis, but before the third trimester, is likely to be beneficial for the mother but not provide substantial protection through young infancy.

Comorbidities:

As noted above, we are uncertain how much of the effect of comorbidities is independent of the association between age and comorbidities. The presence of comorbidities substantially increases the risk of serious Covid-19: in The VA Study there was an approximate doubling of the composite endpoint of Covid-19 associated ED visit, hospitalization, or death in people with cardiovascular disease, cerebrovascular disease, chronic lung disease, or immunocompromise; there was an approximately 50% greater risk of the composite endpoint in those with CKD.

We estimate that approximately 6,000 people under age 65 with cardiovascular disease, cerebrovascular disease, chronic lung disease, or immunocompromise would need to be vaccinated to prevent one hospitalization and that approximately 20,000 would need to be vaccinated to prevent one death. We estimate that approximately 7,900 people under age 65 with CKD would need to be vaccinated to prevent one hospitalization and that approximately 27,000 would need to be vaccinated to prevent one death.

Serious harms from Covid-19 vaccination are extremely rare.

Given the uncertainties about the risk of serious Covid-19 in the 2026–2027 season and the large uncertainties in the extrapolations for this population, we feel the net benefit of Covid-19 vaccination in people under 65 with cardiovascular disease, cerebrovascular disease, chronic lung disease, CKD, or who are immunocompromised is "Comparable or Better" (**C++**).

Comparison Among Vaccines:

There are substantial uncertainties when trying to compare Covid-19 vaccines for the 2026–2027 season. A randomized trial of two of the mRNA vaccines (Spikevax and mNexspike) that enrolled patients in the spring and summer of 2023 found similar efficacy and adverse events between the vaccines.[59] Our ability to extrapolate from the earlier placebo-controlled randomized trials of the individual vaccines is limited. We suspect that the mRNA vaccines have similar effectiveness and harms. We are less certain about the relative effectiveness of Nuvaxovid in the current era as The VA Study had few patients who received Nuvaxovid; there is some evidence from the early randomized trials and from more recent observational data that Nuvaxovid may have fewer minor adverse events.[67] We feel that for all comparisons of net health benefit among the four available vaccines, the evidence is "Insufficient" (**I**).

Table 3.9. Evidence Ratings

Population	Intervention*	Comparator	Evidence Rating
Adults 18–65 (Excluding Men Ages 18–24)	Vaccine	No Vaccine	C+
Adults 65+	Vaccine	No Vaccine	B+
Males 12–24	Vaccine	No Vaccine	P/I
Children 5–18 (Excluding Boys 12–18)	Vaccine	No Vaccine	C+
Children 2–5	Vaccine	No Vaccine	C+
Children 1–2	Vaccine	No Vaccine	C++
Children 6–12 Months	Vaccine	No Vaccine	B+
Vaccination During Pregnancy	Vaccine	No Vaccine	B+
People With Comorbidities Under Age 65	Vaccine	No Vaccine	C++
People Living in the US in 2026	Any of 4 vaccines	Each other	I

B+: "Incremental or Better", Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit; C+: "Comparable or Incremental", Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit; C++: "Comparable or Better", Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit; P/I: "Promising but Inconclusive", Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit; I: "Insufficient", Any situation in which the level of certainty in the evidence is low

*Intervention: Updated 2026-2027 Covid-19 Vaccine, Comparator: No Updated 2026-2027 Covid-19 Vaccine

Note: In comparing vaccination for Covid-19 with no vaccination in various groups/subgroups, we are not distinguishing in our overall ratings among the four available vaccines.

4. Long-Term Cost Effectiveness

4.1. Methods Overview

The aim of this analysis was to estimate the cost-effectiveness of Covid-19 vaccines that will be updated for the 2026–2027 season. This analysis builds on the cost-effectiveness model by Prosser (2025) which informed ACIP deliberations during the 2023–2024 vaccination season, the first period for which Covid-19 was considered endemic and an annual vaccination program was considered.[20] The replicated model incorporates updated vaccine effectiveness estimates based on more recent observational data. A hypothetical cohort of individuals entered the model at the start of the season and were assigned to vaccination or no vaccination. Vaccine effectiveness was applied to reduce the risk of clinical events over the entire season. The base-case analysis used a decision tree with a one-year cycle, followed by a Markov model to estimate the quality of life and cost impacts from long-term severe sequelae that may extend beyond year one. While Covid-19 circulates year-round without the clear seasonal pattern observed for other respiratory illnesses such as influenza and respiratory syncytial virus (RSV), we focused on one-year impacts aligned with annual vaccination recommendations and the structure of available vaccine effectiveness (VE) and surveillance data (see Section 4.2 below for further detail). Alive individuals then exit the decision tree and enter the Markov model in one of three health states: 1) alive with no sequelae; 2) alive with non-severe sequelae; 3) and alive with severe sequelae, split into subgroups of patients with and without an ICU admission (see Figure 4.1). In addition to modeling the impacts of severe long-term sequelae, the Markov model accounts for unrelated health care costs, all-cause mortality, and quality of life for the remainder of the lifetime horizon.

As illustrated in Figure 4.1, the decision tree begins with a comparison between two strategies: Updated Covid-19 Vaccination (2026–2027) and No Updated Covid-19 Vaccination (2026–2027). Each strategy leads to three primary disease outcome pathways noted above. The first pathway represents individuals who remain free of Covid-19 infection throughout year one and consequently develop no long-term sequelae. These individuals experience only age-specific background mortality with baseline quality of life for the remainder of the lifetime horizon after moving to the Markov model (alive with no sequelae).

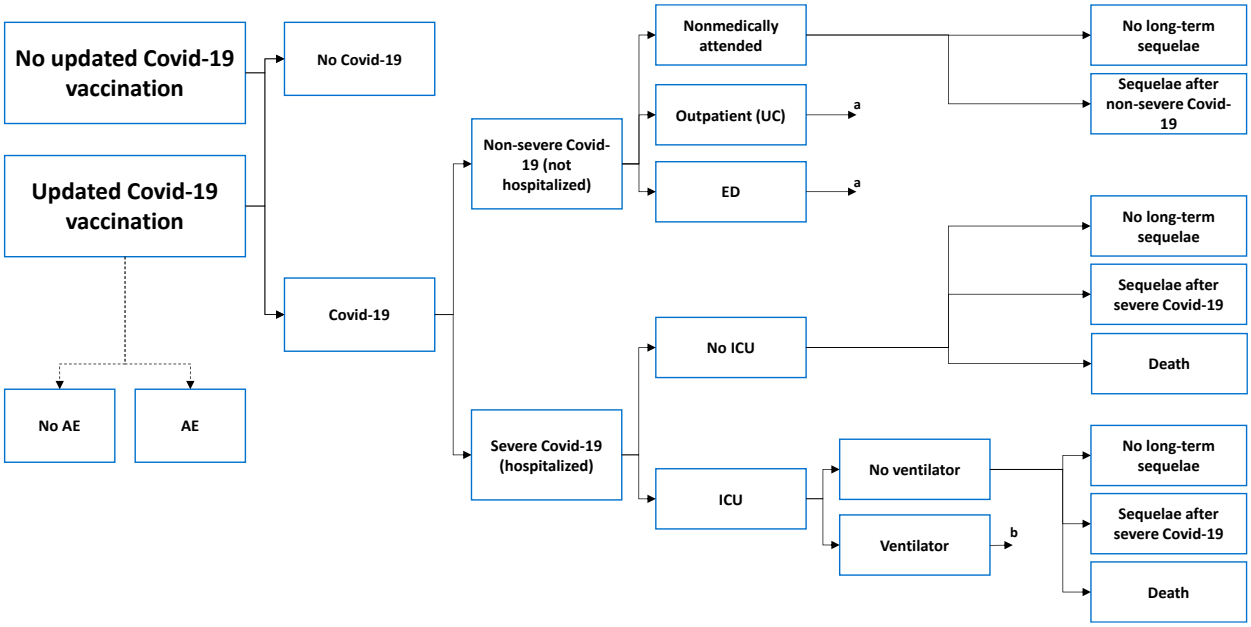
The second pathway captures non-severe Covid-19 (not requiring hospitalization), which branches into three health care utilization patterns: no medical attention sought, outpatient or urgent care visits, and emergency department visits. Patients in each of these arms face a probability of developing long-term sequelae after non-severe Covid-19, which assumed cost and quality-of-life impacts through year one and no excess mortality at any point (alive with non-severe sequelae).

The third major pathway involves severe Covid-19 that requires hospitalization. This pathway splits into two branches based on whether patients were admitted to the intensive care unit (ICU). Patients who were hospitalized and not admitted to the ICU may experience long-term sequelae after severe Covid-19. Those who were admitted to the ICU were further categorized based on their need for mechanical ventilation. Both ICU subgroups (with and without mechanical ventilation) carry risks of severe sequelae—including post-ICU syndrome and organ damage—as well as death. Sequelae after severe Covid-19 were modeled in the lifetime Markov model to extend the time to resolve severe long-term sequelae (alive with severe sequelae split into subgroups of patients with and without an ICU visit).

Long-term sequelae were modeled separately depending on whether they followed non-severe or severe Covid-19. Sequelae after non-severe Covid-19 encompass post-viral syndromes such as Myalgic Encephalomyelitis and Chronic Fatigue Syndrome (ME/CFS) and postural orthostatic tachycardia syndrome (POTS). These were modeled over a one-year period with associated utility decrements and ongoing health care costs, but no excess mortality. Sequelae resulting from severe Covid-19 may present similar post-viral symptoms but are characterized by additional complications. These complications include persistent organ damage (such as pulmonary, renal, and cardiovascular) following hospitalization, as well as post-intensive care syndrome after ICU admission. The reductions in quality of life and health care costs for this group were estimated to reflect the greater functional impairment linked to these conditions. Given limited available data on long-term sequelae, we assumed a resolution period of three years with decrements to quality of life and increases in costs to manage sequelae after severe Covid-19. However, we only assumed excess mortality in year one due to lack of evidence on persistent mortality risk among patients with such complications. Detailed parameter ranges and sensitivity analyses are reported in Supplement E2.

For individuals who receive an updated Covid-19 vaccine, the model incorporated vaccine-related adverse events (AEs such as myocarditis and reactogenicity). Vaccinated individuals either experience no AEs or develop AEs, with particular attention to myocarditis given its age- and sex-specific risk profile (i.e., higher in young males), as well as anaphylaxis.

Figure 4.1. Model Structure



AE: adverse event, ED: emergency department, ICU: intensive care unit, UC: urgent care, M: Markov Model for long-term sequelae

Notes: [a]Outpatient/urgent care and emergency department encounters may result in: no long-term sequelae, sequelae after non-severe Covid-19, [b]ICU encounters with mechanical ventilation may result in: no long-term sequelae, sequelae after severe Covid-19, or Covid-19 attributable death.

Cost-effectiveness was estimated using incremental cost-effectiveness ratios, with incremental analyses comparing Updated Covid-19 Vaccination (2026–2027) to No Updated Covid-19 Vaccination (2026–2027). The base-case analysis was conducted from the health care system perspective (i.e., focus on direct medical care costs only). The results were weighted by the size of each age and risk subgroup to reflect the composition of the vaccine-eligible population (Supplement E6). A scenario analysis used a modified societal perspective with productivity impacts. Model outcomes included total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLYs) gained, and total costs for each intervention over a lifetime time horizon. The model outcomes also included hospitalizations averted. Costs and outcomes were discounted at 3% per year.

4.2. Key Model Assumptions and Inputs

Our model includes several assumptions stated below.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Vaccine effectiveness (VE) represents incremental protection above baseline immunity from prior vaccination and/or infection.	Real-world VE estimates are derived from observational studies conducted in populations with pre-existing immunity. Applying VE as incremental protection avoids double-counting baseline risk reductions.
Base-case VE for the 2026–2027 season is assumed equal to observed real-world VE from the 2024–2025 season (JN.1-lineage), applied to ED/UC encounters, hospitalization, and death.	At the time of analysis, 2026-2027-specific VE data are unavailable. The most recent season provides the best empirical evidence and is consistent with prior economic evaluations.
A time-weighted average VE is applied over the 2026–2027 season. VE is not modeled as time-varying within year one, and waning beyond year one is not explicitly modeled.	The model focuses on a single season with an annual cycle. Using a seasonal average VE provides a simple approximation that aligns with available data and prevents over-parameterization. In achieving this seasonal average, we included evidence on both waning immunity and fewer cases of Covid-19 during the second six months of the modeled year.
The effect of receiving a second vaccine dose is not modeled separately. VE inputs are assumed to reflect the effectiveness of seasonal Covid-19 vaccination as observed in real-world studies, which predominantly reflect receipt of a single 2024–2025 dose.	Real-world VE studies informing the model do not reliably stratify effectiveness by dose number and, in several cases, explicitly exclude individuals receiving more than one seasonal dose. As a result, VE estimates are best interpreted as representing a single-dose seasonal strategy. Modeling dose-specific effects is not supported by available data.
Adverse events (AEs) are modeled if they are either 1) common or 2) rare but clinically serious (e.g., myocarditis) with potential for hospitalization. Modeled AE costs included short-term productivity losses (missed work) in the modified societal perspective analysis.	Focusing on clinically meaningful adverse events enhances model simplicity while accurately capturing relevant costs and disutility.
Severe sequelae and non-severe sequelae are mutually exclusive health states determined by acute illness severity (hospitalized vs. non-hospitalized).	Patients with multiple sequelae are classified according to the most severe pathway. Additive utility decrements from concurrent sequelae are not modeled due to limited evidence.
Decrements to quality of life and increases in costs to manage long-term sequelae after Covid-19 were assumed to resolve after one year for individuals with a non-severe Covid-19 episode, and after three years for those with severe Covid-19. Excess mortality from severe sequelae was assumed only for year one.	With limited evidence on the resolution of symptoms from severe sequelae, we made conservative assumptions based on expert clinical opinion.

Table 4.2 summarizes key model inputs. Epidemiologic parameters were derived via back-calibration from CDC 2024–2025 US Covid-19 burden estimates, which reflect cumulative seasonal event counts in a partially vaccinated population. Back-calibration was performed separately within each age stratum using age-specific rates for ICU admission and ventilation from Yehoshua et al. (2024), age-specific vaccine coverage from CDC VaxView, and age-specific vaccine effectiveness estimates from Cai et al. (2025).[18] For each stratum, unvaccinated-arm probabilities were calculated by adjusting observed population-level rates for the prevailing mix of vaccinated and unvaccinated individuals; vaccinated-arm probabilities were then derived by applying the corresponding effectiveness estimates. Conditional probabilities governing severity progression among hospitalized patients were derived from Yehoshua et al. (2024).[89]

The modeled population comprised individuals eligible for vaccination based on age and high-risk status. For adults aged ≥65 years, the full age group was included regardless of comorbidity status (N=61,179,918). For those aged 18 to 64 years, eligibility was restricted to individuals with at least one comorbidity associated with severe Covid-19 per CDC criteria, yielding high-risk proportions of 27.4% (ages 18–49, N=39,424,898) and 63.4% (ages 50–64, N=39,392,528). For individuals under 18, asthma prevalence was used as a proxy for high-risk status, consistent with the approximately 7% prevalence of childhood asthma reported in national survey data, yielding modeled populations of 1,347,058 (ages 6 months–4 years), 2,285,961 (ages 5–11 years) and 2,088,847 (ages 12–17 years). The total modeled population was 145,719,209, representing approximately 43% of the US population. Outcomes were estimated separately for each age group using age-specific event rates and vaccine effectiveness, then pooled by weighting each subgroup's results by its share of the total modeled population.

Vaccine effectiveness inputs were sourced primarily from Cai et al. (2025),[18] which reported effectiveness of updated 2024–2025 Covid-19 vaccines against a range of outcomes in a US population. Vaccine effectiveness estimates from Cai et al. (2025) reflected approximately six months of follow-up. To project VE over the full model year, a waning multiplier (0.773) was derived based on the area under the VE-time curve over 365 days relative to the observed 180-day window, assuming linear decline to zero after the study period and weighting each half of the year by the share of 2024–2025 COVID-19 hospitalizations occurring in that period per CDC COVID-NET surveillance data.[90] The multiplier was applied uniformly to all subgroup-specific VE estimates. Full details are provided in the Vaccine Effectiveness section of the Supplement E2.

VE against outpatient visits was approximated using the reported effectiveness against ED/urgent care encounters (≥18 years: 22.7%; 6 months–17 years: 47.0%), in the absence of ambulatory-specific estimates. VE against hospitalization was 30.3% in adults and 47.0% in those aged 6 months–17 years. The adult estimate was applied to ICU admission given the absence of ICU-specific VE data. VE against death was 49.5%. Once these inputs were applied and averaged on a population-wide basis, the model produced an average effectiveness estimate similar to the

composite endpoint referenced in the Comparative Clinical Effectiveness section. Our approach estimated hospitalization (ICU and non-ICU) and ventilation rates similar to those observed in the VA study. Because of the way we structured this model, had we applied the composite endpoint universally to all outcomes, we would have underestimated the rate of severe Covid-19 and its related outcomes.

As an internal consistency check, the outputs of the six age-specific subgroup models were aggregated and compared with CDC Covid-19 burden estimates. Specifically, the predicted numbers of hospitalizations and deaths across subgroups were summed and examined against CDC-reported totals to ensure that the overall outcome distribution generated by the model was consistent with national surveillance estimates (Supplement E7. Model Validation).

Health-related quality of life was modeled using health state utilities for long-term Covid-19 sequelae and event-based utility decrements for acute illness and adverse events. Utilities for long-term sequelae of non-severe Covid-19 were informed by observational studies of Long Covid, while lower utilities for long-term sequelae of severe Covid-19 were informed by health-related quality of life studies of ICU survivors, demonstrating greater impairment.

Myocarditis and anaphylaxis were modeled as rare acute vaccine-associated adverse events with short-term health care costs and temporary quality-of-life loss. Acute cases incurred a one-time episode cost and a limited disutility corresponding to the symptomatic period. Consistent with CDC follow-up data, most cases are expected to resolve within months, and the base-case analysis assumed no long-term costs or disutility beyond the acute phase. We also modeled the impact of reactogenicity (e.g., short-term fever and malaise) using a disutility with a higher incidence of symptoms for mRNA-based vaccines.

Vaccine acquisition costs were based on CDC-published per-dose prices for the 2025–2026 season, with separate public-sector and private-sector prices combined using a weight for those participating in the Vaccines for Children (VFC) Program. For pediatric doses (ages 12–17) eligible for the VFC program, CDC-published public-sector prices were available for Spikevax, Comirnaty, and Nuvaxovid. Because no CDC-listed VFC price exists for mNEXSPIKE in the 12 to 17 years age group, the mNEXSPIKE pediatric price was estimated by applying the ratio of the Spikevax pediatric price to the Spikevax adult price to the mNEXSPIKE adult prices.

Table 4.2. Key Model Inputs

Parameter	Age Group*	Base Case	Source
Annual Probability of Symptomatic Covid-19 (No Vaccination)	All ages	0.0512	CDC 2024-2025 US Covid-19 Burden Estimate, US Census,[91,92] Authors' estimation
Annual Probability of Outpatient/ED Visits (No Vaccination)	All ages	0.0134	
Annual Probability of Hospitalization (Subgroups) (No Vaccination)	6 mo–11 yrs	0.0005	COVID-NET Surveillance System, 2024-25,[91] Authors' estimation
	12–17 yrs	0.0002	
	18–49 yrs	0.0008	
	50–64 yrs	0.0025	
	≥65 yrs	0.0062	
Vaccine Effectiveness (Outpatient/ED Encounter)	≥18 yrs	22.7%	Cai et al. 2025[18]
Vaccine Effectiveness (Outpatient/ED Encounter)	<18 yrs	47.0%	MMWR CDC study, 2025; Estimated as the weighted average of effectiveness for 9 mo–4 yrs and 5–17 yrs[17]
Vaccine Effectiveness (Hospitalization With or Without ICU)	≥18 yrs	30.3%	Cai et al. 2025[18]
	<18 yrs	47.0%	Assumption: same as for Outpatient/ED
Vaccine Effectiveness (Death)	All ages	49.5%	Cai et al. 2025[18]
HR Due to Death From Sequelae Given Severe Covid-19 and No ICU	All	1.00	Assumption based on interactions with clinical experts
Time Until Increased Mortality Persists in Sequelae Given Severe Covid-19 and No ICU, Yrs	All	1.00	
HR Due To Death From Sequelae Given Severe Covid-19 and ICU	All	1.00	
Time Until Increased Mortality Persists in Sequelae Given Severe Covid-19 and ICU, Yrs	All	1.00	
Time To Resolve: Sequelae Given Non-Severe Covid-19, Yrs	All	1.00	
Time To Resolve: Sequelae Given Severe Covid-19 and No ICU, Yrs	All	3.00	
Time To Resolve: Sequelae Given Severe Covid-19 and ICU, Yrs	All	3.00	
Symptomatic Covid Utility Decrement	All ages	0.006	Prosser et al. 2025[20]
Hospitalized Covid Non-ICU Utility Decrement	All ages	0.027	

Parameter	Age Group*	Base Case	Source
Hospitalized Covid ICU Utility Decrement	All ages	0.054	
Reactogenicity Utility Decrement	All ages	0.0004	
Myocarditis Utility Decrement	All ages	0.0100	
Anaphylaxis Utility Decrement	All ages	0.0137	
Spikevax Price	6 mo–11 yrs 12–17 yrs 18 yrs+	$103 $112 $142	CDC, weighted public/private price applied for the pediatric population[93]
Comirnaty Price	5–11 yrs 12–17 yrs 18 yrs+	$73 $113 $137	CDC, weighted public/private price applied for the pediatric population[93]
Nuvaxovid Price	12–17 yrs 18 yrs+	$122 $168	CDC, weighted public/private price applied for the pediatric population[93]
mNEXSPIKE	12–17 yrs 18 yrs+	$139 $177	CDC, weighted public/private price applied for the pediatric population[93] The mNEXSPIKE pediatric price is assumed based on the ratio of the Spikevax pediatric price to the adult price.
Cost Of Hospitalization (Non-ICU)	≥65 yrs	$22,444	Prosser et al. 2025[20]
Cost Of ICU Stay (No Ventilator)	≥65 yrs	$25,240	Prosser et al. 2025[20]
Cost Of ICU Stay (Ventilator)	≥65 yrs	$60,064	Prosser et al. 2025[20]
Covid-19-Related Cost of Mortality	≥65 yrs	$22,540	Jiao & Basu 2021[94]
Future Unrelated Costs	≥65 yrs	$11,087	Jiao & Basu 2021[94]

CDC: Centers for Disease Control and Prevention, ED: emergency department, ICU: intensive care unit, MMWR: Morbidity and Mortality Weekly Report, mo: months, yrs: years

*Age groups from 6 months to 64 years include individuals with at least one underlying condition, representing high-risk populations.

The table presents key input parameters. A complete list of parameters, including subgroup-specific values, can be found in Supplement E2.

4.3. Results

Base-Case Results

The average per person total discounted costs, quality-adjusted life years (QALYs), equal value of life years (evLYs), life years (LYs), and hospitalizations are detailed in Table 4.3. The results are weighted by the prevalence of each subgroup reported in Supplement E6 (i.e., age and risk level based on comorbid conditions). For vaccines with a labeled indication of ≥12 years (Nuvaxovid,

mNEXSPIKE), the no-vaccination arm includes the 6 months to 11 years population to ensure a consistent comparator denominator when computing total costs and QALYs for the pooled analysis; no vaccine costs or benefits are attributed to this age group in the intervention arm. The effectiveness of vaccines were estimated during one season, demonstrating small incremental differences in total costs, QALYs, evLYs, and LYs. For example, Nuvaxovid and mNEXSPIKE have different reactogenicity rates but are only accounted for over one day.

Table 4.3. Results for the Base-Case for Covid-19 Vaccines Updated for the 2026-2027 Season Compared to No Updated Vaccine Among 6 Months–64 Years of Age At High-Risk And ≥65 Years of Age

Treatment	Intervention Acquisition Costs*	Intervention-Related Costs†	Non-Intervention Costs‡	Total Costs*	Hospitalizations per 100,000	QALYs	evLYs	Life Years
No Vaccine	$0	$0	$120,090	$120,144	353	15.101056	15.101056	17.749889
Spikevax	$140	$36	$120,052	$120,282	245	15.103559	15.103560	17.752705
Comirnaty	$134	$36	$120,052	$120,276	246	15.103559	15.103560	17.752705
Nuvaxovid	$163	$26	$120,052	$120,295	246	15.103598	15.103599	17.752705
mNEXSPIKE	$172	$35	$120,052	$120,314	246	15.103559	15.103560	17.752705

evLYs: equal value of life years, QALY: quality-adjusted life year
Results are weighted by the following age groups where indicated: high risk 6 months to 4 years of age (N=1,347,058), high risk 5–11 years of age (N=2,285,961), high risk 12–17 years of age (N=2,088,847), high risk 18–49 years of age (N=39,424,898), high risk 50–64 years of age (N=39,392,528), and 65+ years of age (N=61,179,918).
*Based on weighted average price including the vaccines for children program
†Intervention-related costs include vaccine administration and adverse event management costs. The costs for Spikevax and Comirnaty are slightly different, which is not displayed due to rounding.
‡Non-intervention costs include Covid-19 management-based costs (e.g., inpatient admission), unrelated medical costs, and mortality costs.

Table 4.4 presents the discounted incremental results for Covid-19 vaccines updated for the 2026 to 2027 season compared to no updated vaccine among 6 months-64 years of age at high-risk and ≥65 years of age, including cost per QALY, cost per evLY, cost per LY, and cost per hospitalization avoided. The results are rounded to the nearest thousand US dollars. Given the similarity in outcomes, differences in incremental results by vaccine were manifested nearly entirely in differences in weighted vaccine price.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Base-Case Population‡	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*	Cost per Hospitalization Avoided
Spikevax	6 mo–64 yrs high risk, 65+	No vaccine†	$55,000	$55,000	$49,000	$129,000
Comirnaty	6 mo–64 yrs high risk, 65+		$53,000	$53,000	$47,000	$124,000
Nuvaxovid†	6 mo–64 yrs high risk, 65+		$60,000	$60,000	$54,000	$142,000
mNEXSPIKE†	6 mo–64 yrs high risk, 65+		$68,000	$68,000	$60,000	$160,000

evLYs: equal value of life years, mo: months, QALY: quality-adjusted life year, yrs: years

*Based on weighted average price including the vaccines for children program

†The comparator of no vaccine is adjusted for appropriate indicated age groups. In addition, because Nuvaxovid and mNEXSPIKE are FDA-indicated only for age 12+, no vaccination was assumed for individuals age 6 months – 11 years.

‡ Results are weighted by the following age groups where indicated: 65+ years of age (N=61,179,918), high risk 50-64 years of age (N=39,392,528), high risk 18-49 years of age (N=39,424,898), high risk 12-17 years of age (N=2,088,847), high risk 6 months to 11 years of age (N=3,633,018).

Heterogeneity and Subgroups

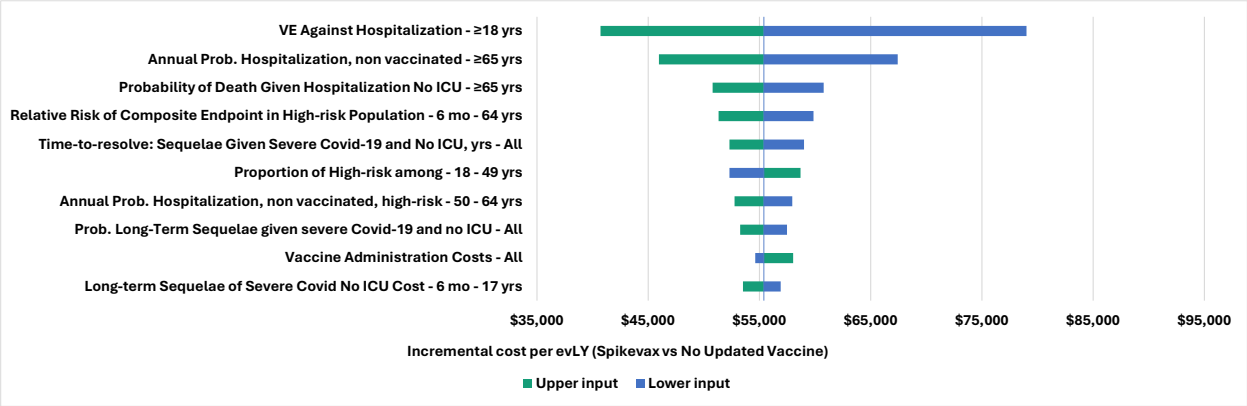
Cost-effectiveness results varied across age subgroups and were broadly consistent with the findings from the clinical evidence review. Results were most favorable in adults aged 65 years and older, and also favorable in high-risk adults aged 50–64 years. In younger and lower-risk populations, results were less favorable, consistent with the smaller absolute benefit suggested by the clinical evidence. Detailed subgroup results are provided in the Supplement (Section E6).

Sensitivity Analyses

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available estimates of parameter uncertainty (e.g., standard errors or plausible parameter ranges).

Figure 4.2 demonstrates the impact of varying inputs on incremental cost-effectiveness ratios with evLYs as the outcome. Given the most influential parameters are similar across vaccines when compared against no vaccine, we provide one example below (Spikevax vs. No Updated Vaccine); the rest of the tornado diagrams are available in the Supplement. Key drivers of the cost-effectiveness estimates include vaccine effectiveness against hospitalization and the probability of hospitalization conditional on Covid-19 exposure. Other drivers were related to mortality and time to resolving long-term sequelae.

Figure 4.2. Tornado Diagram for Spikevax versus No Updated Vaccine



VE: vaccine effectiveness; ICU: intensive care unit; evLY: equal value of life year

Probabilistic sensitivity analyses were also performed by jointly varying multiple model parameters over 1,000 simulations. Table 4.5 presents the probability of reaching certain cost-effectiveness thresholds for each intervention compared to no vaccine using cost per evLY.

Table 4.5. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Covid-19 Vaccines Updated for the 2026–2027 Season Compared to No Updated Vaccine Among 6 Months–64 Years of Age At High-Risk And ≥65 Years Of Age

	Cost Effective at $50,000 per evLY Gained*	Cost Effective at $100,000 per evLY Gained*	Cost Effective at $150,000 per evLY Gained*	Cost Effective at $200,000 per evLY Gained*
Spikevax	31%	100%	100%	100%
Comirnaty	37%	100%	100%	100%
Nuvaxovid	19%	100%	100%	100%
mNEXSPIKE	8%	99%	100%	100%

evLYs: equal value of life years

*Based on weighted average price including the Vaccines For Children program

Scenario Analyses

We conducted several scenario analyses to examine the uncertainty and potential variations in the findings. Results of the scenario analyses examined are outlined below in Table 4.6; cost-effectiveness remained below commonly-cited benchmarks in nearly all scenarios.

Scenario 1: **Modified Societal Perspective**

In addition to direct medical costs, this scenario incorporated productivity losses due to illness and caregiving, as well as productivity loss associated with vaccine-related reactogenicity.

Scenario 2: **Lower Bound of Illness and Hospitalization Rate (i.e., Lower Bound of Confidence Interval)**

The base-case disease burden parameters were derived from 2024–2025 surveillance data, applied to a modeled 2026–2027 season. Given the observed downward trend in Covid-19 incidence and hospitalization rates in recent years, this scenario reflects a plausible extrapolation of that trend by setting all probabilities to the lower bound of their respective confidence intervals. The annual probability of symptomatic Covid-19 was reduced from 5.1% to 4.1%, and age-specific hospitalization probabilities in the unvaccinated population were reduced from 0.047% to 0.038% (ages 6 months–11 years), 0.020% to 0.016% (ages 12–17 years), 0.082% to 0.066% (ages 18–49 years), 0.261% to 0.207% (ages 50–64 years), and 0.650% to 0.505% (ages ≥65 years).

Scenario 3: 5-Year Time Horizon

The analytic horizon was shortened from lifetime to five years, limiting the capture of downstream costs and health outcomes.

Scenario 4: **Exclusion of Unrelated Medical Costs**

Future medical costs unrelated to Covid-19 that accrue during life-years gained were excluded from the analysis.

Scenario 5: **Every Child Assumed to be Eligible for the Vaccines for Children (VFC) Program (52% in Base Case; 100% in Scenario)**

The proportion of children eligible for the VFC program, a federally funded program through which providers purchase vaccines at the CDC contract price, was increased from 52% (base case) to 100%, reflecting a scenario of full public program coverage for the pediatric population.

Table 4.6. Scenario Analysis Results

Treatment	Base-Case Results (per evLY)*	Scenario Analysis 1 (per evLY)*	Scenario Analysis 2 (per evLY)*	Scenario Analysis 3 (per evLY)*	Scenario Analysis 4 (per evLY)*	Scenario Analysis 5 (per evLY)*
Spikevax	$55,000	$131,000	$72,000	$126,000	$46,000	$55,000
Comirnaty	$53,000	$128,000	$69,000	$119,000	$43,000	$53,000
Nuvaxovid	$60,000	$59,000	$77,000	$134,000	$50,000	$59,000
mNEXSPIKE	$68,000	$142,000	$87,000	$158,000	$58,000	$68,000

evLYs: equal value of life years

*Based on weighted average price including the Vaccines For Children program

Threshold Analyses

Tables 4.7 and 4.8 present the unit price needed for each vaccine to reach commonly cited cost-effectiveness thresholds when compared to no vaccine.

Table 4.7. QALY-Based Threshold Analysis Results

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
Spikevax	6 mo–11 yrs 12–17 yrs 18 yrs+	$103 $112 $142	$127	$253	$380	$506
Comirnaty	5–11 yrs 12–17 yrs 18 yrs+	$73 $113 $137	$128	$255	$381	$507
Nuvaxoid	12–17 yrs 18 yrs+	$122 $168	$142	$273	$403	$533
mNEXSPIKE	12–17 yrs 18 yrs+	$139 $177	$130	$259	$387	$515

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Table 4.8. evLY-Based Threshold Analysis Results

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per evLY Gained	Unit Price to Achieve $100,000 per evLY Gained	Unit Price to Achieve $150,000 per evLY Gained	Unit Price to Achieve $200,000 per evLY Gained
Spikevax	6 mo–11 yrs 12–17 yrs 18 yrs+	$103 $112 $142	$127	$253	$380	$506
Comirnaty	5–11 yrs 12–17 yrs 18 yrs+	$73 $113 $137	$128	$255	$381	$507
Nuvaxovid	12–17 yrs 18 yrs+	$122 $168	$142	$273	$403	$533
mNEXSPIKE	12–17 yrs 18 yrs+	$139 $177	$130	$259	$387	$515

evLY: equal value of life year, mo: months, WAC: wholesale acquisition cost, yrs: years

Model Validation

Please see Supplement Section E7 for model validation details.

Prior Economic Models

Please see Supplement Section E8 for a summary of prior economic models.

Uncertainty and Controversies

- We relied on the best available real-world evidence for vaccine effectiveness given the absence of large randomized trials in the post-pandemic era of Covid-19. As described in the Comparative Clinical Effectiveness section, The VA Study provided the best available evidence for the 2024–2025 season.[18] It is important to note this evidence is limited in its generalizability to a broader population outside of the VA as well as populations in the 2026–2027 season.

- A key input driver behind incremental cost-effectiveness was the probability of hospitalizations estimated through the COVID-NET Surveillance System for the 2024–2025 season.[91] This probability estimate is notably smaller than those estimated from studies during and briefly after the pandemic era. According to CDC COVID-NET surveillance data,[90] crude Covid-19-associated hospitalization rates fell from 637 per 100,000 in 2021–2022 to 308 in 2022–2023, 243 in 2023–2024, and 123 in 2024–2025. Therefore, cost-effectiveness ratios are higher than previously estimated by Prosser et al. (2025) because the baseline

level of hospitalizations is lower,[20] driving the potential gains in cost offsets and improvements in quality and quantity of life downward compared with a higher baseline level of hospitalizations.

- Data were lacking for epidemiology in multiple subgroups, particularly for the pediatric population. We made some simplifying assumptions around key epidemiologic data on the number of high-risk patients indicated for vaccinations. The lack of evidence also prevented additional scenario analyses in subgroups.

- We deviated from the Comparative Clinical Effectiveness section (Section 3) in applying disaggregated effectiveness estimates across endpoints including applying a higher effectiveness estimate for more severe events (e.g., hospitalizations and death). Once these inputs are applied and averaged across the population, however, the model output produces an average effectiveness estimate similar to the composite endpoint referenced in the Comparative Clinical Effectiveness section. For example, when the tree is averaged, we estimate a range of composite effectiveness of 29.5% (18 to 49 years of age), 29.9% (50 to 64 years of age), and 31.1% (65 years of age and up). In other words, the outputs between the Comparative Clinical Effectiveness and cost-effectiveness results rely on a similar composite impact across all outcomes.

- Consistent with the Comparative Clinical Effectiveness section, we did not identify evidence for modeling transmission effects between individuals. The model captures only the direct benefits of vaccination to the vaccinated individual, including reductions in health care utilization, hospitalization, and death. The model produced hospitalization outputs similar to what was observed in the 2024–2025 season.

- The model assumes a single annual vaccine dose and does not capture the potential benefit of bi-annual administration, which has been discussed as a strategy for the highest-risk groups, including older adults and immunocompromised individuals, given rapid VE waning and the absence of a single defined Covid-19 season. The net impact on cost-effectiveness of additional doses is uncertain, as any incremental clinical benefit would need to be weighed against the costs of additional vaccination.

4.4. Summary and Comment

Key drivers of the cost-effectiveness estimates include vaccine effectiveness against hospitalization and the probability of hospitalization conditional on Covid-19 exposure. Weighted results (i.e., by age and risk) suggest that one course of Covid-19 vaccination for the 2026–2027 may add costs to the health care system at current prices but would also meet commonly cited cost-effectiveness thresholds, driven primarily by reducing hospitalizations in individuals greater than or equal to 50 years of age who contributed the greatest weight to the results.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the interventions in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There are particular obligations to people with this condition because of disease severity and/or unmet need with currently available therapies.	Vaccines for Covid-19 have been available for five years; as such, we consider this category not applicable for this review.
There are particular obligations to people with this condition because it disproportionately affects those from a racial/ethnic group that have not been equitably served by the health care system.	As noted above, Covid-19 severity is typically worse in people who have comorbidities including hypertension and chronic kidney disease. These conditions are more common in people with lower socioeconomic status and lower socioeconomic status is associated with underserved racial/ethnic groups.
Apart from issues around disease severity/unmet need and race/ethnicity, there are other particular obligations to people with this condition.	Particularly early in the pandemic, many frontline workers were from populations with lower socioeconomic status and worked in jobs that did not have the possibility of remote work. Additionally, health care workers were a group that took on particular risks and obligations early in the pandemic.
Vaccination for Covid-19 is likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life.	Vaccination for Covid-19 is unlikely to produce substantial improvements in caregiver quality of life for the vast majority of people who are vaccinated and their potential caregivers.
If payment/cost were not an issue, vaccination for Covid-19 would be likely to improve access to treatment because of its method of delivery and/or treatment setting.	Not applicable for this review.
Other: As determined pre-meeting by ICER team based on input from patients, clinical experts, and appraisal committee members.	This section may be updated based on input received during public comment.

ICER did not calculate the Health Improvement Distribution Index (HIDI) because the relative rates of disease in different ethnic groups have been varying over time and estimates are uncertain.

6. Health Benefit Price Benchmark

ICER does not provide a Health Benefit Price Benchmark as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmark that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness analyses were used to calculate the blended potential total budgetary impact of an Updated Covid-19 vaccination (2026–2027) (Spikevax, mNEXSPIKE, COMIRNATY, and Nuvaxovid) for the US population. For new drugs, the aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. Because this potential budget impact analysis evaluates vaccines, we did not include such a threshold analysis, given that the threshold generally informs the use of a new therapy in a candidate population of diagnosed patients. Because the candidate population for Covid-19 vaccines is any individual between the ages of 6 months and 64 years with at least one risk factor for severe disease, as well as all individuals age 65 and older, the budget impact threshold is less relevant. Furthermore, the Covid-19 vaccines have been available on the market for several years, so our typical analysis forecasting how budgets may be impacted moving forward does not apply. Therefore, we focused this budget impact analysis on estimating the cumulative annual per patient blended budget impact of the Covid-19 vaccines compared to no vaccination, and we did not conduct a threshold analysis.

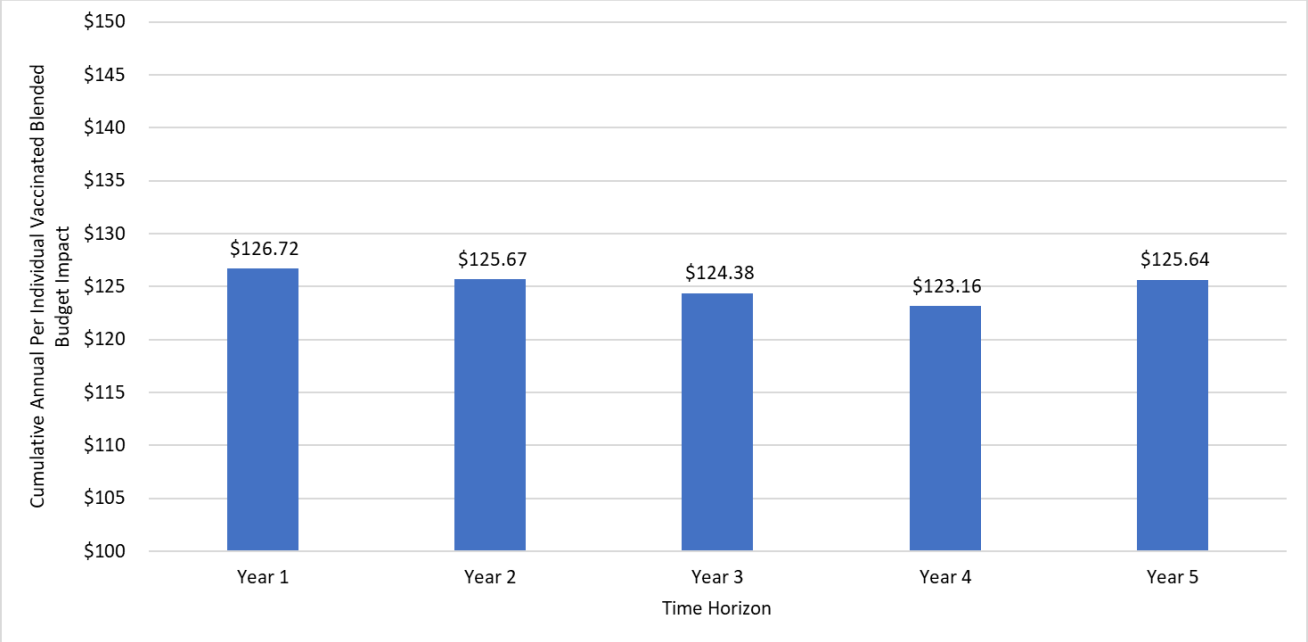
This potential budget impact analysis included the estimated number of individuals in the US who would be vaccinated with any of the Covid-19 vaccines in scope within one year. To estimate the size of the US population anticipated to receive an updated 2026–2027 Covid-19 vaccine, we used inputs for the percentage of adults and children who received the 2025–2026 Covid-19 vaccine (17.5% and 9% respectively), as well as the percentage of adults and children who definitely plan to get the Covid-19 vaccine (7.6% and 3.2%) according to CDC vaccination intent survey data.[95] Applying these sources to the total adult and child populations in the US averaged over the next five years (271.9 million and 69.7 million) results in estimates of roughly 76.7 million total eligible individuals in the US (68.2 million adults and 8.5 million children).[96] For the purposes of this analysis, we assumed that all of these individuals were vaccinated in year one. To determine the blended potential budget impact of an updated 2026–2027 Covid-19 vaccine, we used a weighted average of year one costs based on 2025 US sales data for each vaccine. The estimated market share in the US was 9% Spikevax, 22% mNexspike, 67% Comirnaty, and 3% Nuvaxovid.[97]

7.2. Results

Figure 7.1 illustrates the blended cumulative annual per patient treated budget impact for an updated 2026–2027 Covid-19 vaccine compared to no updated Covid-19 vaccine. This analysis assumes that all vaccinations occur in year one only. Years two through five do not include the costs or benefits of annual revaccination but include the cumulative costs of vaccination in Year one and other costs such as averted health care costs.

Using the weighted average of the CDC-published private-sector prices for the 2025–2026 season, the estimated cumulative annual per individual vaccinated blended budget impact was $127 in year one, and $126 by year five. The cumulative annual budget impact decreased each year from year one to year four and then increased moderately in year five. This trend was due to the vaccines' prevention of long-term sequelae for a maximum of three years in the cost-effectiveness model. After that, the moderately higher cumulative costs for an updated 2026–2027 Covid-19 vaccine from year four to year five were due to more patients being alive from receipt of an updated vaccine and no additional cost-offsets from the prevention of long-term sequelae.

Figure 7.1. Cumulative Annual Per Individual Vaccinated Blended Budget Impact



References

1. Centers for Disease C, Prevention. Outbreak of pneumonia of unknown etiology (PUE) in Wuhan, China. *HAN ; 424*. 2020;(424)Health Alert Network.
2. WHO. WHO COVID-19 dashboard. Accessed 10/29, 2025. https://data.who.int/dashboards/covid19/deaths?n=o
3. Remarks by President Trump at the Operation Warp Speed Vaccine Summit. 2020. https://trumpwhitehouse.archives.gov/briefings-statements/remarks-president-trump-operation-warp-speed-vaccine-summit/
4. Trump Administration Collaborates With Moderna to Produce 100 Million Doses of COVID-19 Investigational Vaccine. 2020. https://www.war.gov/News/Releases/Release/article/2309561/trump-administration-collaborates-with-moderna-to-produce-100-million-doses-of/
5. David J. Sencer CDC Museum. CDC Museum COVID-19 Timeline. Accessed 10/29, 2025. https://www.cdc.gov/museum/timeline/covid19.html
6. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. Feb 4 2021;384(5):403-416. doi:10.1056/NEJMoa2035389
7. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. Dec 31 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577
8. Mathieu HR, Lucas Rodés-Guirao, Cameron Appel, Daniel Gavrilov, Charlie Giattino, Joe Hasell, Bobbie Macdonald, Saloni Dattani, Diana Beltekian, Esteban Ortiz-Ospina, and Max Roser. Coronavirus (COVID-19) Vaccinations. Our World in Data. https://ourworldindata.org/covid-vaccinations#article-citation
9. Heath PT, Galiza EP, Baxter DN, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *N Engl J Med*. Sep 23 2021;385(13):1172-1183. doi:10.1056/NEJMoa2107659
10. Centers for Disease Control and Prevention. Healthcare Professionals: Adult Immunization Schedule by Age. https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-age.html
11. ACIP Recommends COVID-19 Immunization Based on Individual Decision-making. 2025. Accessed 3/1/2026. https://www.hhs.gov/press-room/acip-recommends-covid19-vaccination-individual-decision-making.html
12. Committee on Infectious Diseases. Recommendations for COVID-19 Vaccines in Infants, Children, and Adolescents: Policy Statement. *Pediatrics*. 2025;156(5)doi:10.1542/peds.2025-073924
13. Massachusetts 2025-2026 Respiratory Illness Season: COVID-19 Vaccine Recommendations (2025).
14. American Association of Family Physicians. AAFP Announces Fall Immunization Recommendations, Reaffirming Commitment to Vaccine Safety and Public Health. https://www.aafp.org/news/media-center/statements/aafp-announces-fall-immunization-recommendations-reaffirming-commitment-to-vaccine-safety-and-public-health.html
15. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) Hospitalization Surveillance Network (COVID-NET). Accessed 02/28, 2026. https://www.cdc.gov/covid/php/covid-net/index.html

16. Link-Gelles R, Chickery S, Webber A, et al. Interim Estimates of 2024-2025 COVID-19 Vaccine Effectiveness Among Adults Aged >/=18 Years - VISION and IVY Networks, September 2024-January 2025. *MMWR Morb Mortal Wkly Rep*. Feb 27 2025;74(6):73-82. doi:10.15585/mmwr.mm7406a1
17. Irving SA, Rowley EAK, Chickery S, et al. Effectiveness of 2024-2025 COVID-19 Vaccines in Children in the United States - VISION, August 29, 2024-September 2, 2025. *MMWR Morb Mortal Wkly Rep*. Dec 11 2025;74(40):607-614. doi:10.15585/mmwr.mm7440a1
18. Cai M, Xie Y, Al-Aly Z. Association of 2024-2025 Covid-19 Vaccine with Covid-19 Outcomes in U.S. Veterans. *N Engl J Med*. Oct 23 2025;393(16):1612-1623. doi:10.1056/NEJMoa2510226
19. Shakya M, Ma KC, Hughes LJ, et al. Early Detection and Surveillance of the SARS-CoV-2 Variant BA.3.2 - Worldwide, November 2024-February 2026. *MMWR Morb Mortal Wkly Rep*. Mar 19 2026;75(10):130-137. doi:10.15585/mmwr.mm7510a1
20. Prosser LA, Perroud J, Chung GS, et al. The cost-effectiveness of vaccination against COVID-19 illness during the initial year of vaccination. *Vaccine*. 2025/02/27/ 2025;48:126725. doi:https://doi.org/10.1016/j.vaccine.2025.126725
21. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. *Lancet*. Apr 16 2022;399(10334):1513-1536. doi:10.1016/s0140-6736(21)02796-3
22. Chan JF-W, Kok K-H, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections*. 2020/01/01 2020;9(1):221-236. doi:10.1080/22221751.2020.1719902
23. Brown CM, Vostok J, Johnson H, et al. Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings — Barnstable County, Massachusetts, July 2021. *MMWR Morb Mortal Wkly Rep*. 2021;
24. COMIRNATY (COVID-19 Vaccine, mRNA) Prescribing Information - August 2025. Pfizer-BioNTech. (2025).
25. Spikevax (COVID-19 Vaccine, mRNA) Prescribing Information - August 2025. Moderna. (2025).
26. mNEXSPIKE (COVID-19 Vaccine, mRNA) Prescribing Information - August 2025. Moderna. (2025).
27. Nuvaxovid (COVID-19 Vaccine, adjuvanted) Prescribing Information - August 2025. Novavax. (2025).
28. Dhanani LY, Franz B. A meta-analysis of COVID-19 vaccine attitudes and demographic characteristics in the United States. *Public Health*. Jun 2022;207:31-38. doi:10.1016/j.puhe.2022.03.012
29. Dinero RE, Monti WB, Kmush BL. Regional political climate's moderating role in the association between political conservatism and COVID-19 vaccine hesitancy in the United States. *PLoS One*. 2026;21(2):e0342063. doi:10.1371/journal.pone.0342063
30. Dean N, Amin AB. Test-Negative Study Designs for Evaluating Vaccine Effectiveness. *Jama*. Jul 9 2024;332(2):163-164. doi:10.1001/jama.2024.5633
31. Centers for Disease Control and Prevention. Preliminary Estimates of Covid-19 Burden. Accessed 3/1, 2026. https://www.cdc.gov/covid/php/surveillance/burden-estimates.html

32. Rottenstreich A, Zarbiv G, Oiknine-Djian E, et al. Timing of SARS-CoV-2 vaccination during the third trimester of pregnancy and transplacental antibody transfer: a prospective cohort study. *Clin Microbiol Infect*. Mar 2022;28(3):419-425. doi:10.1016/j.cmi.2021.10.003
33. Rowe SL, Leder K, Perrett KP, et al. Maternal Vaccination and Infant Influenza and Pertussis. *Pediatrics*. Sep 2021;148(3)doi:10.1542/peds.2021-051076
34. Havers FP, Whitaker M, Chatwani B, et al. COVID-19-Associated Hospitalizations and Maternal Vaccination Among Infants Aged <6 Months - COVID-NET, 12 States, October 2022-April 2024. *MMWR Morb Mortal Wkly Rep*. Sep 26 2024;73(38):830-836. doi:10.15585/mmwr.mm7338a1
35. Cardemil CV, Cao Y, Posavad CM, et al. Maternal COVID-19 Vaccination and Prevention of Symptomatic Infection in Infants. *Pediatrics*. Mar 1 2024;153(3)doi:10.1542/peds.2023-064252
36. Eide HN, Håberg SE, Næss Ø E, Stephansson O, Magnus MC. COVID-19 mRNA Vaccination in Pregnancy and Risk of Infection in Early Childhood. *Pediatrics*. Mar 20 2026;doi:10.1542/peds.2025-073661
37. Mensah AA, Stowe J, Jardine JE, et al. COVID-19 Vaccine Safety in Pregnancy, A Nested Case-Control Study in Births From April 2021 to March 2022, England. *Bjog*. Dec 2024;131(13):1882-1893. doi:10.1111/1471-0528.17949
38. Peretz-Machluf R, Hirsh-Yechezkel G, Zaslavsky-Paltiel I, et al. Obstetric and Neonatal Outcomes following COVID-19 Vaccination in Pregnancy. *Journal of Clinical Medicine*. 2022;11(9):2540.
39. Lipschuetz M, Guedalia J, Cohen SM, et al. Maternal third dose of BNT162b2 mRNA vaccine and risk of infant COVID-19 hospitalization. *Nature Medicine*. 2023/05/01 2023;29(5):1155-1163. doi:10.1038/s41591-023-02270-2
40. Danino D, Ashkenazi-Hoffnung L, Diaz A, et al. Effectiveness of BNT162b2 Vaccination During Pregnancy in Preventing Hospitalization for Severe Acute Respiratory Syndrome Coronavirus 2 in Infants. *The Journal of Pediatrics*. 2023;254:48-53.e1. doi:10.1016/j.jpeds.2022.09.059
41. Goldshtein I, Steinberg DM, Kuint J, et al. Association of BNT162b2 COVID-19 Vaccination During Pregnancy With Neonatal and Early Infant Outcomes. *JAMA Pediatrics*. 2022;176(5):470-477. doi:10.1001/jamapediatrics.2022.0001
42. Regan A, Coates M, Sullivan SG, Rowe S, Munoz FM, Arah O. P-1594. Incidence and Severity of Post-Pandemic SARS-CoV-2 Infection during Pregnancy. *Open Forum Infect Dis*. Jan 2026;13(Suppl 1)
43. Jefferson T, Smith S, Demicheli V, Harnden A, Rivetti A, Di Pietrantonj C. Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. *Lancet*. Feb 26-Mar 4 2005;365(9461):773-80. doi:10.1016/s0140-6736(05)17984-7
44. Siddle KJ, Krasilnikova LA, Moreno GK, et al. Transmission from vaccinated individuals in a large SARS-CoV-2 Delta variant outbreak. *Cell*. Feb 3 2022;185(3):485-492.e10. doi:10.1016/j.cell.2021.12.027
45. Lyngse FP, Mølbak K, Denwood M, et al. Effect of vaccination on household transmission of SARS-CoV-2 Delta variant of concern. *Nat Commun*. Jun 30 2022;13(1):3764. doi:10.1038/s41467-022-31494-y

46. Madewell ZJ, Yang Y, Longini IM, Jr., Halloran ME, Dean NE. Household Secondary Attack Rates of SARS-CoV-2 by Variant and Vaccination Status: An Updated Systematic Review and Meta-analysis. *JAMA Netw Open*. Apr 1 2022;5(4):e229317. doi:10.1001/jamanetworkopen.2022.9317
47. Buchwald DS, Rea TD, Katon WJ, Russo JE, Ashley RL. Acute infectious mononucleosis: characteristics of patients who report failure to recover. *Am J Med*. Nov 2000;109(7):531-7. doi:10.1016/s0002-9343(00)00560-x
48. Hickie I, Davenport T, Wakefield D, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *Bmj*. Sep 16 2006;333(7568):575. doi:10.1136/bmj.38933.585764.AE
49. Ely EW, Brown LM, Fineberg HV. Long Covid Defined. *N Engl J Med*. Nov 7 2024;391(18):1746-1753. doi:10.1056/NEJMsb2408466
50. Yousaf AR, Mak J, Gwynn L, et al. COVID-19 Vaccination and Odds of Post–COVID-19 Condition Symptoms in Children Aged 5 to 17 Years. *JAMA Network Open*. 2025;8(2):e2459672-e2459672. doi:10.1001/jamanetworkopen.2024.59672
51. Di Fusco M, Sun X, Allen KE, et al. Effectiveness of BNT162b2 BA.4/5 Bivalent COVID-19 Vaccine against Long COVID Symptoms: A US Nationwide Study. *Vaccines (Basel)*. Feb 11 2024;12(2)doi:10.3390/vaccines12020183
52. Wu Q, Zhang B, Tong J, et al. Real-world effectiveness and causal mediation study of BNT162b2 on long COVID risks in children and adolescents. *eClinicalMedicine*. 2025;79doi:10.1016/j.eclinm.2024.102962
53. Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. *New England Journal of Medicine*. 2022;386(1):35-46. doi:doi:10.1056/NEJMoa2116298
54. Frenck RW, Klein NP, Kitchin N, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. *New England Journal of Medicine*. 2021;385(3):239-250. doi:doi:10.1056/NEJMoa2107456
55. Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents. *New England Journal of Medicine*. 2021;385(24):2241-2251. doi:doi:10.1056/NEJMoa2109522
56. Sahly HME, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. *New England Journal of Medicine*. 2021;385(19):1774-1785. doi:doi:10.1056/NEJMoa2113017
57. Anderson EJ, Creech CB, Berthaud V, et al. Evaluation of mRNA-1273 Vaccine in Children 6 Months to 5 Years of Age. *New England Journal of Medicine*. 2022;387(18):1673-1687. doi:doi:10.1056/NEJMoa2209367
58. Creech CB, Anderson E, Berthaud V, et al. Evaluation of mRNA-1273 Covid-19 Vaccine in Children 6 to 11 Years of Age. *New England Journal of Medicine*. 2022;386(21):2011-2023. doi:doi:10.1056/NEJMoa2203315
59. Chalkias S, Dennis P, Petersen D, et al. Efficacy, immunogenicity, and safety of a next-generation mRNA-1283 COVID-19 vaccine compared with the mRNA-1273 vaccine (NextCOVE): results from a phase 3, randomised, observer-blind, active-controlled trial. *Lancet Infect Dis*. Nov 2025;25(11):1230-1242. doi:10.1016/s1473-3099(25)00236-1

60. Dunkle LM, Kotloff KL, Gay CL, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. *New England Journal of Medicine*. 2022;386(6):531-543. doi:doi:10.1056/NEJMoa2116185
61. Áñez G, Dunkle LM, Gay CL, et al. Safety, Immunogenicity, and Efficacy of the NVX-CoV2373 COVID-19 Vaccine in Adolescents: A Randomized Clinical Trial. *JAMA Network Open*. 2023;6(4):e239135-e239135. doi:10.1001/jamanetworkopen.2023.9135
62. E.U. Covat-Aged study group obotVc, Stemler J, Yeghiazaryan L, et al. Immunogenicity, reactogenicity, and safety of a second booster with BNT162b2 or full-dose mRNA-1273: A randomized VACCELERATE trial in adults aged ≥75 years (EU-COVAT-1-AGED Part B). *International Journal of Infectious Diseases*. 2024;146doi:10.1016/j.ijid.2024.107161
63. Kelly E, Greenland M, de Whalley PCS, et al. Reactogenicity, immunogenicity and breakthrough infections following heterologous or fractional second dose COVID-19 vaccination in adolescents (Com-COV3): A randomised controlled trial. *Journal of Infection*. 2023;87(3):230-241. doi:10.1016/j.jinf.2023.06.007
64. Mazarakis N, Toh ZQ, Neal E, et al. The immunogenicity, reactogenicity, and safety of a bivalent mRNA or protein COVID-19 vaccine given as a fourth dose. *Journal of Infection*. 2025;90(3)doi:10.1016/j.jinf.2025.106447
65. McLeod C, Dymock M, Flanagan KL, et al. The Platform Trial in Covid-19 priming and BOOsting: The immunogenicity, reactogenicity, and safety of licensed COVID-19 vaccinations administered as a second booster in BNT162b2 primed individuals aged 18-<50 and 50-<70 years old. *Journal of Infection*. 2024;89(6)doi:10.1016/j.jinf.2024.106346
66. Janssen C, Cachanado M, Ninove L, et al. Immunogenicity and reactogenicity of heterologous and homologous mRNA-1273 and BNT162b2 vaccination: A multicenter non-inferiority randomized trial. *EClinicalMedicine*. Jun 2022;48:101444. doi:10.1016/j.eclinm.2022.101444
67. Yoon S, Phillips A, Calhoun S, et al. *mRNA and Protein Subunit COVID-19 Vaccine Reactogenicity and the Relationship to Productivity for Healthcare Workers and First Responders*. 2025.
68. Rousculp MD, Hollis K, Ziemiecki R, et al. Reactogenicity Differences between Adjuvanted, Protein-Based and Messenger Ribonucleic Acid (mRNA)-Based COVID-19 Vaccines. *Vaccines*. 2024;12(7):802.
69. Update on CDC's COVID-19 Vaccine Safety Monitoring, June 2025. (2025).
70. Pan Y, Han Y, Zhou C, et al. Evaluating the safety of XBB.1.5-containing COVID-19 mRNA vaccines using a self-controlled case series study. *Nature Communications*. 2025/07/15 2025;16(1):6514. doi:10.1038/s41467-025-61613-4
71. Sun JW, Dodge LE, Kim EJ, et al. Risk of adverse events after Omicron XBB-adapted BNT162b2 COVID-19 vaccination in the United States. *Vaccine*. Jan 25 2025;45:126629. doi:10.1016/j.vaccine.2024.126629
72. McClymont E, Blitz S, Forward L, et al. The Role of Vaccination in Maternal and Perinatal Outcomes Associated With COVID-19 in Pregnancy. *Jama*. 2026;335(2):154-162. doi:10.1001/jama.2025.21001
73. Sheth SS, Vazquez-Benitez G, DeSilva MB, et al. Coronavirus Disease 2019 (COVID-19) Vaccination and Spontaneous Abortion. *Obstet Gynecol*. May 2 2025;146(1):129-137. doi:10.1097/aog.0000000000005904

74. Moro PL, Carlock G, Fifadara N, et al. Safety monitoring of bivalent mRNA COVID-19 vaccine among pregnant persons in the vaccine adverse event reporting System - United States, September 1, 2022 - March 31, 2023. *Vaccine*. Apr 2 2024;42(9):2380-2384. doi:10.1016/j.vaccine.2024.02.084
75. Moro PL, Olson CK, Clark E, et al. Post-authorization surveillance of adverse events following COVID-19 vaccines in pregnant persons in the vaccine adverse event reporting system (VAERS), December 2020 - October 2021. *Vaccine*. May 26 2022;40(24):3389-3394. doi:10.1016/j.vaccine.2022.04.031
76. Suseeladevi AK, Denholm R, Retford M, et al. COVID-19 vaccination and birth outcomes of 186,990 women vaccinated before pregnancy: an England-wide cohort study. *Lancet Reg Health Eur*. Oct 2024;45:101025. doi:10.1016/j.lanepe.2024.101025
77. Jorgensen SCJ, Drover SSM, Fell DB, et al. Association between maternal mRNA covid-19 vaccination in early pregnancy and major congenital anomalies in offspring: population based cohort study with sibling matched analysis. *BMJ Med*. 2024;3(1):e000743. doi:10.1136/bmjmed-2023-000743
78. Kim K, Bolormaa E, Gwak E, et al. Maternal Exposures to COVID-19 Vaccine and Adverse Birth Outcomes: National Population Study in Korea. *J Korean Med Sci*. May 5 2025;40(17):e63. doi:10.3346/jkms.2025.40.e63
79. Denoble AE, Vazquez-Benitez G, Sheth SS, et al. Coronavirus Disease 2019 (COVID-19) Vaccination and Stillbirth in the Vaccine Safety Datalink. *Obstet Gynecol*. Aug 1 2024;144(2):215-222. doi:10.1097/aog.0000000000005632
80. Hall C, Lanning J, Romano CJ, Bukowinski AT, Gumbs GR, Conlin AMS. COVID-19 vaccine initiation in pregnancy and risk for adverse neonatal outcomes among United States military service members, January-December 2021. *Vaccine*. Apr 2 2025;51:126894. doi:10.1016/j.vaccine.2025.126894
81. Ciapponi A, Berrueta M, Argento FJ, et al. Safety and Effectiveness of COVID-19 Vaccines During Pregnancy: A Living Systematic Review and Meta-analysis. *Drug Safety*. 2024/10/01 2024;47(10):991-1010. doi:10.1007/s40264-024-01458-w
82. Centers for Disease Control and Prevention. Guillain-Barre Syndrome (GBS) and Vaccines. Accessed 3/1, 2026. https://www.cdc.gov/vaccine-safety/about/guillain-barre.html
83. Hui A-M, Li J, Zhu L, et al. Immunogenicity and safety of BNT162b2 mRNA vaccine in Chinese adults: A phase 2 randomised clinical trial. *The Lancet Regional Health – Western Pacific*. 2022;29doi:10.1016/j.lanwpc.2022.100586
84. Grassi CM, Feng J, Wahid R, et al. Immunogenicity and safety of a SARS-CoV-2 N-terminal domain and receptor-binding domain monovalent XBB.1.5 vaccine in Japanese participants. *Vaccine*. 2026/01/01/ 2026;69:127960. doi:https://doi.org/10.1016/j.vaccine.2025.127960
85. Taylor CA, Whitaker M, Patton ME, et al. Trends in COVID-19-Attributable Hospitalizations Among Adults With Laboratory-Confirmed SARS-CoV-2-COVID-NET, June 2020 to September 2023. *Influenza Other Respir Viruses*. Nov 2024;18(11):e70021. doi:10.1111/irv.70021
86. Centers for Disease Control and Prevention. Updates to COVID-19 epidemiology. Accessed March 28, 2026. https://www.cdc.gov/acip/downloads/slides-2025-09-18-19/02-Srinivasan-covid-508.pdf

87. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. Jan 31 2013;2013(1):Cd004816. doi:10.1002/14651858.CD004816.pub5
88. Sass L, Urhoj SK, Kjærgaard J, Dreier JW, Strandberg-Larsen K, Nybo Andersen AM. Fever in pregnancy and the risk of congenital malformations: a cohort study. *BMC Pregnancy Childbirth*. Dec 8 2017;17(1):413. doi:10.1186/s12884-017-1585-0
89. Yehoshua A, Cook AD, Di Fusco M, et al. Health outcomes and economic burden among patients with a COVID-19-associated hospitalization in the United States during the predominance of the XBB and JN.1 omicron lineages. *J Med Econ*. Jan-Dec 2024;27(1):1372-1378. doi:10.1080/13696998.2024.2416873
90. CDC. Centers for Disease Control and Prevention: Weekly Rates of Laboratory-Confirmed COVID-19 Hospitalizations from the COVID-NET Surveillance System. Updated February 5, 2026. https://data.cdc.gov/Public-Health-Surveillance/Weekly-Rates-of-Laboratory-Confirmed-COVID-19-Hosp/6jg4-xsqq/about_data
91. Centers for Disease Control and Prevention. Preliminary Estimates of COVID-19 Burden. https://www.cdc.gov/covid/php/surveillance/burden-estimates.html
92. United States Census Bureau. The United States population. https://www.census.gov/
93. CDC. CDC Vaccine Price List. https://archive.cdc.gov/#/details?url=https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/2025/2025-12-02.html
94. Jiao B, Basu A. Catalog of Age- and Medical Condition-Specific Healthcare Costs in the United States to Inform Future Costs Calculations in Cost-Effectiveness Analysis. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jul 2021;24(7):957-965. doi:10.1016/j.jval.2021.03.006
95. Centers for Disease Control. Vaccination Trends. 2026;
96. US Census Bureau. 2023 National Population Projections Tables. 2023;
97. IPD Analytics. Life-Cycle Insights. 2025;
98. World Health Organization. Coronavirus disease (COVID-19). Accessed 3/1, 2026. https://www.who.int/health-topics/coronavirus#tab=tab_1
99. Ely EW, Brown LM, Fineberg HV. Long Covid Defined. *New England Journal of Medicine*. 2024;391(18):1746-1753. doi:doi:10.1056/NEJMsb2408466
100. Ludwig S, Zarbock A. Coronaviruses and SARS-CoV-2: A Brief Overview. *Anesth Analg*. Jul 2020;131(1):93-96. doi:10.1213/ane.0000000000004845
101. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. *BMC Med Res Methodol*. Nov 6 2021;21(1):241. doi:10.1186/s12874-021-01440-5
102. Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F. The how's and what's of vaccine reactogenicity. *NPJ Vaccines*. 2019;4:39. doi:10.1038/s41541-019-0132-6
103. Ottersen T, Førde R, Kakad M, et al. A new proposal for priority setting in Norway: Open and fair. *Health Policy*. Mar 2016;120(3):246-51. doi:10.1016/j.healthpol.2016.01.012
104. van de Wetering EJ, Stolk EA, van Exel NJ, Brouwer WB. Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. *Eur J Health Econ*. Feb 2013;14(1):107-15. doi:10.1007/s10198-011-0346-7

105. Stolk EA, van Donselaar G, Brouwer WB, Busschbach JJ. Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. *Pharmacoeconomics*. 2004;22(17):1097-107. doi:10.2165/00019053-200422170-00001
106. Qaseem A, Obley A, Harrod C, Wilt T, Carroll K, Humphrey L. COVID-19 Vaccines for 2025–2026 in Adults Who Are Not Pregnant or Immunocompromised: Rapid Practice Points From the American College of Physicians. *Annals of Internal Medicine*. 2026;0(0):null. doi:10.7326/annals-25-05026 %m 41730216
107. American College of Obstetricians & Gynecologists. Maternal Immunizations. *Obstetrics & Gynecology*. 2026:10.1097/AOG.0000000000006230. doi:10.1097/aog.0000000000006230
108. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med*. Mar 1 1997;126(5):376-80.
109. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current
110. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Mar 29 2021;372:n71. doi:10.1136/bmj.n71
111. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj*. Oct 12 2016;355:i4919. doi:10.1136/bmj.i4919
112. Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *Cmaj*. 2020;192(32):E901-E906.
113. Agboola FW, AC. A Framework for Evaluating the Diversity of Clinical Trials. *Journal of Clinical Epidemiology*. 2024:111299.
114. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. Updated January 31, 2020. https://icer.org/evidence-rating-matrix/
115. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care*. Jun 2010;48(6 Suppl):S145-52. doi:10.1097/MLR.0b013e3181d9913b
116. Chalkias S, Pragalos A, Akinsola A, et al. Safety and Immunogenicity of SARS-CoV-2 Spike Receptor-Binding Domain and N-Terminal Domain mRNA Vaccine. *The Journal of Infectious Diseases*. 2025;231(4):e754-e763. doi:10.1093/infdis/jiaf022
117. Thomas SJ, Moreira ED, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. *New England Journal of Medicine*. 2021;385(19):1761-1773. doi:doi:10.1056/NEJMoa2110345
118. Thomas SJ, Perez JL, Lockhart SP, et al. Efficacy and safety of the BNT162b2 mRNA COVID-19 vaccine in participants with a history of cancer: subgroup analysis of a global phase 3 randomized clinical trial. *Vaccine*. 2022/03/01/ 2022;40(10):1483-1492. doi:https://doi.org/10.1016/j.vaccine.2021.12.046
119. Muñoz FM, Sher LD, Sabharwal C, et al. Evaluation of BNT162b2 Covid-19 Vaccine in Children Younger than 5 Years of Age. *New England Journal of Medicine*. 2023;388(7):621-634. doi:doi:10.1056/NEJMoa2211031

120. Moreira ED, Kitchin N, Xu X, et al. Safety and Efficacy of a Third Dose of BNT162b2 Covid-19 Vaccine. *New England Journal of Medicine*. 2022;386(20):1910-1921. doi:doi:10.1056/NEJMoa2200674
121. Simões EAF, Klein NP, Sabharwal C, et al. Immunogenicity and Safety of a Third COVID-19 BNT162b2 mRNA Vaccine Dose in 5- to 11-Year Olds. *Journal of the Pediatric Infectious Diseases Society*. 2023;12(4):234-238. doi:10.1093/jpids/piad015
122. Sher LD, Boakye-Appiah JK, Hill S, et al. Bivalent Omicron BA.4/BA.5 BNT162b2 Vaccine in 6-Month- to <12-Year-Olds. *Journal of the Pediatric Infectious Diseases Society*. 2024;13(8):421-429. doi:10.1093/jpids/piae062
123. Usdan L, Patel S, Rodriguez H, et al. A Bivalent Omicron-BA.4/BA.5-Adapted BNT162b2 Booster in ≥12-Year-Olds. *Clinical Infectious Diseases*. 2023;78(5):1194-1203. doi:10.1093/cid/ciad718
124. Clinicaltrials.gov. Special Investigation for Booster Dose of Comirnaty in Children Ages 6 Months Though 4 Years. https://clinicaltrials.gov/study/NCT06130410
125. Figueroa AL, Ali K, Berman G, et al. Safety and immunogenicity of an mRNA-1273 vaccine booster in adolescents. *Hum Vaccin Immunother*. Dec 2025;21(1):2436714. doi:10.1080/21645515.2024.2436714
126. Figueroa AL, Ali K, Berman G, et al. Safety and durability of mRNA-1273–induced SARS-CoV-2 immune responses in adolescents: results from the phase 2/3 TeenCOVE trial. *eClinicalMedicine*. 2024;74doi:10.1016/j.eclinm.2024.102720
127. Figueroa AL, Torres D, Reyes-Acuna C, et al. Safety and immunogenicity of a single-dose omicron-containing COVID-19 vaccination in adolescents: an open-label, single-arm, phase 2/3 trial. *The Lancet Infectious Diseases*. 2025;25(2):208-217. doi:10.1016/S1473-3099(24)00501-2
128. Baden LR, El Sahly HM, Essink B, et al. Long-term safety and effectiveness of mRNA-1273 vaccine in adults: COVE trial open-label and booster phases. *Nature Communications*. 2024/08/29 2024;15(1):7469. doi:10.1038/s41467-024-50376-z
129. Berthaud V, Creech CB, Rostad CA, et al. Safety and Immunogenicity of an mRNA-1273 Booster in Children. *Clinical Infectious Diseases*. 2024;79(6):1524-1532. doi:10.1093/cid/ciae420
130. Heath PT, Galiza EP, Baxter DN, et al. Safety and Efficacy of the NVX-CoV2373 Coronavirus Disease 2019 Vaccine at Completion of the Placebo-Controlled Phase of a Randomized Controlled Trial. *Clinical Infectious Diseases*. 2022;76(3):398-407. doi:10.1093/cid/ciac803
131. Áñez G, McGarry A, Woo W, et al. Safety and immunogenicity of four sequential doses of NVX-CoV2373 in adults and adolescents: A phase 3, randomized, placebo-controlled trial (PREVENT-19). *Vaccine*. 2025/08/13/ 2025;61:127362. doi:https://doi.org/10.1016/j.vaccine.2025.127362
132. Andersen KM, McColgan MD, Mateus JS, et al. BNT162b2 XBB.1.5-Adapted Single Dose Vaccine Uptake and Effectiveness in Children Aged 5-17 Years Using Linked Claims and Vaccine Registries in California and Louisiana. *J Pediatr*. Nov 2025;286:114778. doi:10.1016/j.jpeds.2025.114778
133. Tartof SY, Frankland TB, Puzniak L, et al. BNT162b2 XBB Vaccine for COVID-19 Among Children 5-17 Years of Age. *JAMA Network Open*. 2024;7(12):e2449944-e2449944. doi:10.1001/jamanetworkopen.2024.49944

134. Gwak E, Choe S-A, Bolormaa E, et al. Relative effectiveness of homologous NVX-CoV2373 and BNT162b2 COVID-19 vaccinations in South Korea. *Vaccine*. 2025/01/01/ 2025;43:126503. doi:https://doi.org/10.1016/j.vaccine.2024.126503
135. Andersen KM, Ahi T, Mateus JS, et al. 2024-2025 BNT162b2 COVID-19 vaccine effectiveness in non-immunocompromised adults: mid-season estimates from vaccine registries in two states linked to administrative claims. *Vaccine*. Aug 30 2025;62:127534. doi:10.1016/j.vaccine.2025.127534
136. Jayawardena I, Dean NE, Witrick B, Litwin AH, Rennert L. 2024-2025 COVID-19 mRNA Vaccine Effectiveness against Severe Disease. *J Infect Dis*. Mar 2 2026;doi:10.1093/infdis/jiag137
137. Vicic N, Bogdanov A, Zheng Z, et al. Evaluating the Effectiveness of 2024-2025 Seasonal mRNA-1273 Vaccination Against COVID-19-Related Hospitalizations and Medically Attended COVID-19 Among Adults Aged ≥ 18 years in the United States: An Observational Matched Cohort Study. *Infect Dis Ther*. Mar 2026;15(3):701-714. doi:10.1007/s40121-025-01292-2
138. Kopel H, Nguyen VH, Bogdanov A, et al. COMPARATIVE EFFECTIVENESS OF THE BIVALENT COVID-19 MRNA VACCINES, MRNA1273-222 AND BNT162B2, IN ADULTS WITH CHRONIC LUNG DISEASES IN THE UNITED STATES. *CHEST*. 2024;166(4):A3903-A3904. doi:10.1016/j.chest.2024.06.2357
139. Link-Gelles R, Rowley EAK, DeSilva MB, et al. Interim Effectiveness of Updated 2023-2024 (Monovalent XBB.1.5) COVID-19 Vaccines Against COVID-19-Associated Hospitalization Among Adults Aged ≥18 Years with Immunocompromising Conditions - VISION Network, September 2023-February 2024. *MMWR Morb Mortal Wkly Rep*. Mar 28 2024;73(12):271-276. doi:10.15585/mmwr.mm7312a5
140. Copland E, Patone M, Saatci D, et al. Safety outcomes following COVID-19 vaccination and infection in 5.1 million children in England. *Nature Communications*. 2024/05/27 2024;15(1):3822. doi:10.1038/s41467-024-47745-z
141. Ahn B, Shin SH, Hwang MJ, et al. Epidemiological Characteristics and Outcome of Myocarditis and Pericarditis Temporally Associated With BNT162b2 COVID-19 Vaccine in Adolescents: Korean National Surveillance. *J Korean Med Sci*. Dec 23 2024;39(49):e317. doi:10.3346/jkms.2024.39.e317
142. Straus W, Urdaneta V, Esposito DB, et al. Analysis of Myocarditis Among 252 Million mRNA-1273 Recipients Worldwide. *Clin Infect Dis*. Feb 8 2023;76(3):e544-e552. doi:10.1093/cid/ciac446
143. Karlstad Ø, Hovi P, Husby A, et al. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. *JAMA Cardiology*. 2022;7(6):600-612. doi:10.1001/jamacardio.2022.0583
144. Faksova K, Walsh D, Jiang Y, et al. COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals. *Vaccine*. Apr 2 2024;42(9):2200-2211. doi:10.1016/j.vaccine.2024.01.100
145. Nasreen S, Jiang Y, Lu H, et al. Risk of Guillain-Barré syndrome after COVID-19 vaccination or SARS-CoV-2 infection: A multinational self-controlled case series study. *Vaccine*. Jul 11 2025;60:127291. doi:10.1016/j.vaccine.2025.127291

146. Bishara H, Arbel A, Barnett-Griness O, et al. Association Between Guillain-Barré Syndrome and COVID-19 Infection and Vaccination: A Population-Based Nested Case-Control Study. *Neurology*. Nov 14 2023;101(20):e2035-e2042. doi:10.1212/wnl.0000000000207900
147. Kitano T, Salmon DA, Dudley MZ, Saldanha IJ, Thompson DA, Engineer L. Age- and sex-stratified risks of myocarditis and pericarditis attributable to COVID-19 vaccination: a systematic review and meta-analysis. *Epidemiologic Reviews*. 2024;47(1):1-11. doi:10.1093/epirev/mxae007
148. Censi S, Bisaccia G, Gallina S, Tomassini V, Uncini A. Guillain-Barré syndrome and COVID-19 vaccination: a systematic review and meta-analysis. *J Neurol*. Mar 2024;271(3):1063-1071. doi:10.1007/s00415-024-12186-7
149. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama*. Sep 13 2016;316(10):1093-103. doi:10.1001/jama.2016.12195
150. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Aug 2019;22(8):931-941. doi:10.1016/j.jval.2019.02.009
151. Rosas IO, Benitez A, McKinnell JA, et al. Long-Term Clinical Outcomes of Adults Hospitalized for COVID-19 Pneumonia. *Emerg Infect Dis*. Jun 2025;31(6):1158-1168. doi:10.3201/eid3106.241097
152. Ayenew T, Gete M, Gedfew M, et al. Prevalence of Post-intensive care syndrome among intensive care unit-survivors and its association with intensive care unit length of stay: Systematic review and meta-analysis. *PLoS One*. 2025;20(5):e0323311. doi:10.1371/journal.pone.0323311
153. Statistics NCfH. *Percentage of ever having asthma for children under age 18 years, United States, 2019—2024*. 2026. https://wwwn.cdc.gov/NHISDataQueryTool/SHS_child/index.html
154. Boersma P, Black LI, Ward BW. Prevalence of Multiple Chronic Conditions Among US Adults, 2018. *Prev Chronic Dis*. Sep 17 2020;17:E106. doi:10.5888/pcd17.200130
155. Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. *Jama*. Oct 12 2021;326(14):1390-1399. doi:10.1001/jama.2021.15072
156. Goddard K, Hanson KE, Lewis N, Weintraub E, Fireman B, Klein NP. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. *Ann Intern Med*. Dec 2022;175(12):1169-1771. doi:10.7326/M22-2274
157. Prosser LA, Payne K, Rusinak D, Shi P, Uyeki T, Messonnier M. Valuing health across the lifespan: health state preferences for seasonal influenza illnesses in patients of different ages. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jan 2011;14(1):135-43. doi:10.1016/j.jval.2010.10.026
158. Morrow AJ, Sykes R, McIntosh A, et al. A multisystem, cardio-renal investigation of post-COVID-19 illness. *Nat Med*. Jun 2022;28(6):1303-1313. doi:10.1038/s41591-022-01837-9

159. Fust K, Kohli M, Joshi K, et al. Modeling the cost-effectiveness of the next-generation COVID-19 mRNA-1283 vaccine in the United States. *J Med Econ*. Dec 2026;29(1):574-593. doi:10.1080/13696998.2026.2624967
160. Neba R, Pedaprolu LS, Neba B, Sambamoorthi U. Long COVID Is Associated with Excess Direct Healthcare Expenditures Among Adults in the United States. *Healthcare (Basel)*. Oct 27 2025;13(21)doi:10.3390/healthcare13212704

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Covid-19: Infectious disease caused by the SARS-CoV-2 virus. The disease can cause a range of respiratory symptoms (e.g., cough, shortness of breath), systemic symptoms (e.g., fever, muscle ache), and symptoms involving other organ systems (e.g., loss of taste or smell, gastrointestinal symptoms), most of which are mild/moderate and resolve but some people will experience serious illness that requires medical attention.[98]

COVID-NET: A CDC surveillance system that tracks laboratory-confirmed Covid-19 hospitalizations for children and adults. It is a part of the Respiratory Virus Hospitalization Surveillance Network (RESP-NET). It covers 14 states, representing an estimated 12% of the United States (US) population and is generally similar to the broader US population in regard to demographics. A case in COVID-NET is defined as lab-confirmed SARS-CoV-2 if the person lives in a COVID-NET surveillance area and has a positive test (by a lab-based molecular, antigen, or serology test) within 14 days before or during hospitalization. The online dashboard is updated weekly and can be filtered by season, age group, race and ethnicity, sex, and site.[15]

Long Covid: Research on Long Covid etiology and risk factors are ongoing. Many clinical experts acknowledge that the definition of Long Covid may continue to evolve as more is understood. As of 2024, the National Academies of Sciences, Engineering, and Medicine defines Long Covid as an "infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least three months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems."[99]

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) refers to the virus responsible for Covid-19 illness. The first infection in people was identified in 2019.[100]

MACE: Major adverse cardiovascular events (MACE) is a common composite outcome used in clinical research. The definition of MACE can vary depending on the study but commonly includes myocardial infarction, stroke, and cardiovascular-related death.[101]

Reactogenicity: A group of adverse events occurring as a result of inflammatory responses to a vaccination, which can be categorized as a local reaction (e.g., injection site pain) or a systemic reaction (e.g., fever).[102]

Vaccine Effectiveness: Evaluates how protective a vaccination is in a real-world population outside a controlled clinical trial in regard to reductions in illness, hospitalization, and death.[101] In the VA study, vaccine effectiveness was calculated using 1–Risk Ratio and was reported as a percent.[18] As population immunity increases, vaccine effectiveness will decrease even in the absence of any other effects (i.e., in a completely immune population, vaccine effectiveness will be zero).

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[103] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[104,105] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above one suggest that more health may be gained on the relative scale in the subpopulation of interest when

compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5). We did not calculate a HIDI for this review.

A2. Potential Cost-Saving Measures in Covid-19

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, please reference ICER's Value Assessment Framework). These services are ones that would not be directly affected by therapies for Covid-19 (e.g., intensive care unit [ICU] admission for Covid-19), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of Covid-19 beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with Covid-19 that could be reduced, eliminated, or made more efficient. No suggestions were received.

A3. Patient Input on Clinical Trial Design

We did not ask for a written explanation of how manufacturers engaged patients in the design of their clinical trials for this review given the unique circumstances under which these trials were conducted amidst the Covid-19 pandemic.

B. Stakeholder Input: Supplemental Information

B1. Patient Community Insights: Methods

ICER invited a range of patient organizations (focused on Long Covid, chronic illness, those serving older Americans, those focused on pro-vaccine and anti-vaccine advocacy, and those focused on access to affordable care) to share their perspectives on the Covid-19 vaccines. We requested support from a range of organizations and ICER's Patient Council to connect with individuals for interviews. Ultimately, we spoke with two patient organizations focused on Long Covid, two people with immunocompromising conditions, two people who are older than 65 years old with comorbid conditions, one person who expressed Covid-19 vaccine hesitancy, and one parent of teenage sons.

B2. Clinical Expert Input: Methods

We spoke with various infectious disease clinical experts including former members of ACIP.

C. Clinical Guidelines

Advisory Committee on Immunization Practices (ACIP)

As of September 2025, ACIP recommended that Covid-19 vaccination should be determined by shared clinical decision-making for all individuals six months and older. ACIP emphasizes that there is a more favorable risk-benefit profile for individuals who are at increased risk for severe Covid-19 compared to individuals who are not at increased risk.[10,11]

American College of Physicians (ACP)[106]

The 2026 ACP recommendation for Covid-19 in people who are not pregnant and who are not immunocompromised is:

- Adults 65+ years old should receive an updated 2025–2026 mRNA-based Covid-19 vaccine
- Adults 18 to 64 years old at increased risk for severe Covid-19 should receive an updated 2025–2026 mRNA-based Covid-19 vaccine
- Adults 18 to 64 years old who are not at increased risk for severe Covid-19 may consider receiving an updated 2025-2026 mRNA-based Covid-19 vaccine

American Academy of Pediatrics (AAP)[12]

The 2026 AAP recommendation for Covid-19 in children and adolescents is a single dose of an age-appropriate 2025-2026 Covid-19 vaccine in those at high risk of severe Covid-19. This includes:

- Infants and children 6 months to 23 months old
- Children 2 to 18 years old who are in the following risk groups: children at high risk of severe Covid-19, children who are residents of long-term care facility or other congregate setting, children who were never vaccinated against Covid-19, and children who have household contacts at high risk for severe Covid-19
- Children 6 months to 18 years old who are moderately or severely immunocompromised

American College of Obstetricians & Gynecologists (ACOG)[107]

The 2026 ACOG recommendation for Covid-19 vaccination is that all individuals who are pregnant or will be pregnant during the fall/winter respiratory illness season should receive an annual Covid-19 vaccination. The recommendation does not specify a certain Covid-19 vaccine product and does not specify a specific trimester but encourages vaccination to be done as soon as possible for both maternal and fetal health.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

Populations

The population of interest for this review is people living in the United States in 2026.

Data permitting, we evaluated the evidence on effectiveness and harms within subpopulations defined by:

- Sociodemographic factors (e.g., sex, age, race, ethnicity), such as:
  - Young children (e.g., 6 months–2 years, 2–5 years, 5–11 years)
  - Adolescents (12–18 years)
  - Boys ages 12–18 years and young adult men
  - Pregnant women
  - Adults under age 65
  - Adults ages 65 and older
- Comorbid conditions including:
  - Pulmonary conditions such as asthma and chronic obstructive pulmonary disease (COPD)
  - Cardiovascular disease
  - Immunocompromise, including:
    - Immunocompromising conditions
    - Immunocompromise after hematopoietic stem cell transplantation
    - Immunocompromise from medications after solid organ transplantation
    - Immunocompromise from medications for immune-related medical conditions
  - Diabetes
  - Obesity
  - Neurologic conditions
  - Serious mental illness

Interventions

The full list of interventions is as follows:

- COMIRNATY (Covid-19 vaccine, mRNA)
- Spikevax (Covid-19 vaccine, mRNA)
- mNEXSPIKE (Covid-19 vaccine, mRNA)
- Nuvaxovid (Covid-19 vaccine, adjuvanted)

Comparators

Data permitting, we compared these vaccines to each other and to not receiving an updated vaccine for Covid-19.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Covid-19
    - Serious illness from Covid-19
    - Hospitalization
    - Emergency department/urgent care visits
    - Mortality
    - Risk of transmitting SARS-CoV-2
    - Long Covid and permanent harms from Covid-19
    - Fetal injury from Covid-19
    - Adverse events including:
        - Short-term minor adverse events including fever and malaise (i.e., reactogenicity)
        - Myocarditis and pericarditis
        - Guillain-Barre syndrome
        - Fetal injury from Covid-19 immunization
- Other Outcomes
    - Asymptomatic SARS-CoV-2 infection

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the US.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size will be included. High-quality comparative observational studies with a sample size greater than 50,000 will also be included. Smaller high-quality observational studies that address specific subpopulations or research questions of interest may be considered.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

Section and Topic	Item #	Checklist Item
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		

Section and Topic	Item #	Checklist Item
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on vaccines for Covid-19 followed established best research methods.[108,109] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[110] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, and public data repositories for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

Table D1.2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

#	Search Terms
1	exp COVID-19/ or exp SARS-COV-2/
2	(COVID* or coronovir* or coronavir* or SARS* or 2019-nCoV or "2019 nCoV" or 2019nCoV or nCov 2019 or "Severe Acute Respiratory Syndrome Coronavirus 2" or HCoV* or ((corona* or corono*) adj1 (virus* or viral* or virinae*))).ti,ab
3	1 or 2
4	("Abdavomeran" OR "biontech COVID-19 vaccine" OR "biontech-pfizer COVID-19 vaccine" OR "BNT 162" OR "BNT 162A1" OR "BNT 162B1" OR "BNT 162b2" OR "BNT 162b3" OR "BNT 162c2" OR "BNT162" OR "BNT162a1" OR "BNT162b1" OR "BNT162b2" OR "BNT162b2 Omicron JN.1 mRNA Drug Substance" OR "BNT162b3" OR "BNT162c2" OR "Comirnaty" OR "COMIRNATY JN.1" OR "Comirnaty LP.8.1" OR "Comirnaty RTU" OR "famtozinameran" OR "LP.8.1-adapted monovalent Covid-19 vaccine" OR "Pfizer Covid 19 Vaccine" OR "Pfizer-BioNTech COVID-19 Vaccine" OR "raxtozinameran" OR "riltozinameran" OR "SARS-CoV-2/Covid-19 vaccine" OR "tozinameran").ti,ab.
5	("2019 nCoV Vaccine mRNA 1273" OR "2019-nCoV vaccine" OR "2019-nCoV Vaccine (Moderna)" OR "2019-nCoV vaccine mRNA1273" OR "andusomeran" OR "Coronavirus Vaccine (Moderna)" OR "COVID-19 Vaccine Moderna" OR "COVID-19 vaccine mRNA1273" OR "COVID-19 vaccine mRNA-1273" OR "CX 024414" OR "CX024414" OR "Elasomeran" OR "M 1273" OR "M1273" OR "messenger RNA1273" OR "messenger RNA1273 vaccine" OR "Moderna COVID 19 Vaccine" OR "Monovalent XBB.1.5 COVID-19 Vaccine" OR "mRNA 1273" OR "mRNA 1273.211" OR "mRNA 1273.251" OR "mRNA 1273.712" OR "mRNA1273" OR "mRNA1273 vaccine" OR "mRNA-1273.167" OR "mRNA-1273.214" OR "mRNA-1273.222" OR "mRNA1273.251" OR "mRNA-1273.351" OR "mRNA-1273.529" OR "mRNA-1273.617" OR

#	Search Terms
	"mRNA-1273.617.2" OR "mRNA1273.712" OR "mRNA-1273.815" OR "novel coronavirus vaccine" OR "Spikevax" OR "Spikevax BA.1" OR "TAK 919" OR "TAK919").ti,ab.
6	("mNexspike" OR "mRNA 1283" OR "SARS-CoV-2/Covid-19 vaccine").ti,ab.
7	("COVID-19 vaccine Novavax" OR "Covovax" OR "Novavax COVID-19 Vaccine" OR "Novavax COVID-19 vaccine, adjuvanted" OR "Novavax vaccine" OR "Nuvaxovid" OR "nuvaxovid xbb.1.5" OR "nvx cov 2373" OR "NVX CoV2373" OR "NVX CoV2601" OR "NVXCoV2373" OR "NVX-CoV2373 COVID-19 vaccine" OR "nvx-cov2373 vaccine" OR "SARS-CoV-2 rS" OR "SARS-CoV-2/Covid-19 vaccine" OR "TAK 019").ti,ab.
8	4 OR 5 OR 6 OR 7
9	3 AND 8
10	9 NOT (animals not (humans and animals)).sh.
11	10 NOT (clinical trial protocol or Clinical Trial, Veterinary or letter OR autobiography OR bibliography OR biography OR comment OR case report OR case reports OR congresses OR consensus development conference OR dictionary OR directory OR editorial OR encyclopedia OR festschrift OR guideline OR interactive tutorial).pt
12	11 NOT (case report or guideline or simulation model or primate or murine or in vitro or cell line or protein structure or molecular docking or molecular dynamics or animal model or rodent or viral genome).ti,ab
13	Remove duplicates from 12

Search Ran: 12/17/25

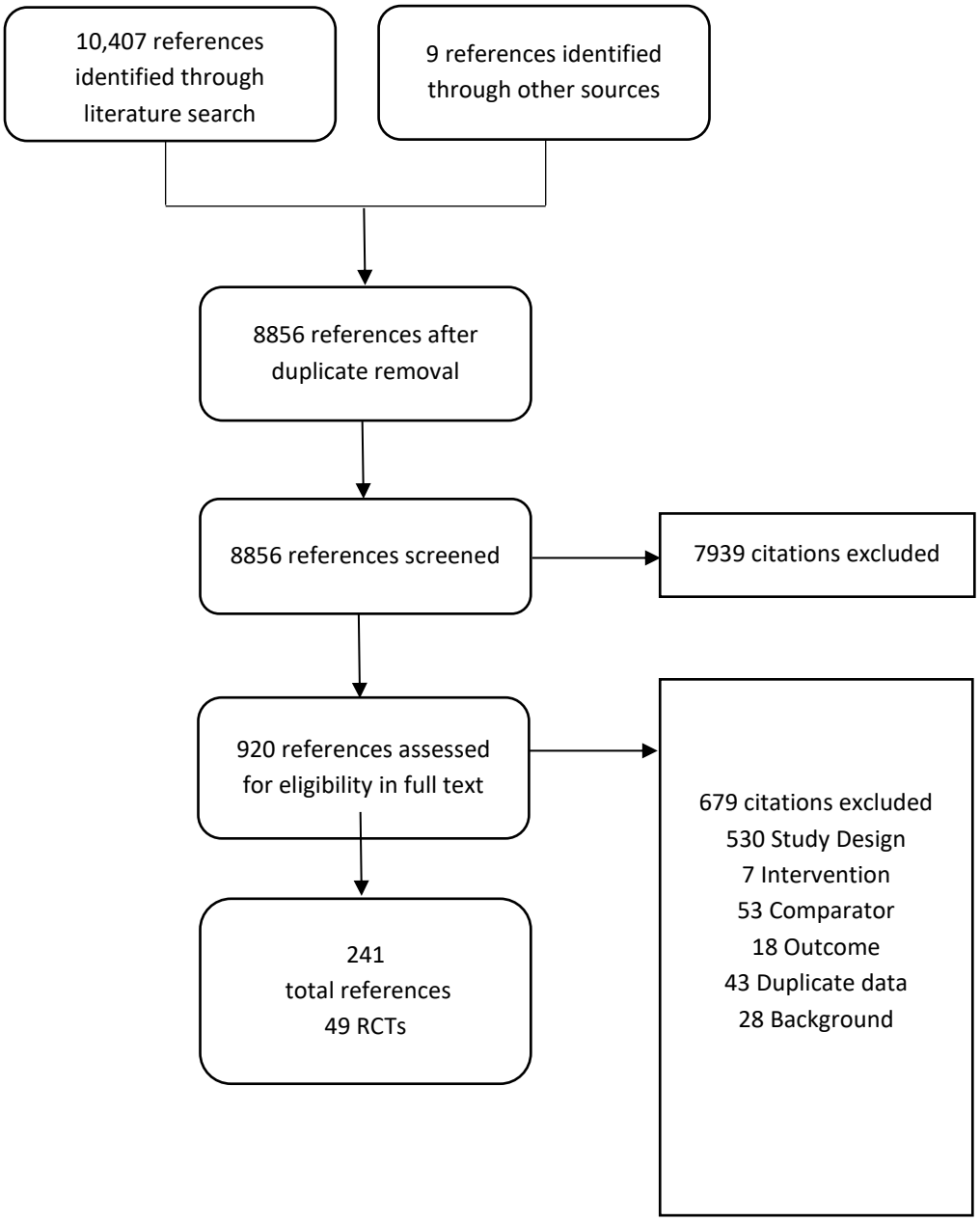
Table D1.3. Search Strategy of EMBASE SEARCH

#	Search Terms
1	'coronavirus disease 2019'/exp OR 'coronavirus disease 2019':ti,ab
2	(COVID* OR coronavir* OR coronovir* OR SARS* OR HCoV* OR 'nCov 2019' OR '2019-nCoV infection' OR '2019 nCoV' OR 2019nCoV OR 'severe acute respiratory syndrome 2' OR ((corona* or corono*) NEAR/1 (virus* or viral* or virinae*))):ti,ab
3	#1 OR #2
4	('Abdavomeran' or 'biontech COVID-19 vaccine' or 'biontech-pfizer COVID-19 vaccine' or 'BNT 162' or 'BNT 162A1' or 'BNT 162B1' or 'BNT 162b2' or 'BNT 162b3' or 'BNT 162c2' or 'BNT162' or 'BNT162a1' or 'BNT162b1' or 'BNT162b2' or 'BNT162b2 Omicron JN.1 mRNA Drug Substance' or 'BNT162b3' or 'BNT162c2' or 'Comirnaty' or 'COMIRNATY JN.1' or 'Comirnaty LP.8.1' or 'Comirnaty RTU' or 'famtozinameran' or 'LP.8.1-adapted monovalent Covid-19 vaccine' or 'Pfizer Covid 19 Vaccine' or 'Pfizer-BioNTech COVID-19 Vaccine' or 'raxtozinameran' or 'riltozinameran' or 'SARS-CoV-2/Covid-19 vaccine' or 'tozinameran'):ti,ab
5	('2019 nCoV Vaccine mRNA 1273' or '2019-nCoV vaccine' or '2019-nCoV Vaccine (Moderna)' or '2019-nCoV vaccine mRNA1273' or '2019-nCoV vaccine mRNA-1273' or 'andusomeran' or 'COVID-19 Vaccine Moderna' or 'COVID-19 vaccine mRNA1273' or 'COVID-19 vaccine mRNA-1273' or 'CX 024414' or 'CX024414' or 'Elasomeran' or 'M 1273' or 'M1273' or 'messenger RNA1273' or 'messenger RNA1273 vaccine' or 'Moderna COVID 19 Vaccine' or 'Monovalent XBB.1.5 COVID-19 Vaccine' or 'mRNA 1273' or 'mRNA 1273.211' or 'mRNA 1273.251' or 'mRNA 1273.712' or 'mRNA Coronavirus Vaccine (Moderna)' or 'mRNA1273' or 'mRNA1273 vaccine' or 'mRNA-1273.167' or 'mRNA-1273.214' or 'mRNA-1273.222' or 'mRNA1273.251' or 'mRNA-1273.251' or 'mRNA-1273.351' or 'mRNA-1273.529' or 'mRNA-1273.617' or 'mRNA-1273.617.2' or 'mRNA1273.712' or 'mRNA-1273.815' or 'novel coronavirus vaccine' or 'Spikevax' or 'Spikevax BA.1' or 'TAK 919' or 'TAK919'):ti,ab
6	('mNexspike' or 'mRNA 1283' or 'SARS-CoV-2/Covid-19 vaccine'):ti,ab
7	('COVID-19 vaccine Novavax' or 'Covovax' or 'Novavax COVID-19 Vaccine' or 'Novavax COVID-19 vaccine, adjuvanted' or 'Novavax vaccine' or 'Nuvaxovid' or 'nuvaxovid xbb.1.5' or 'nvx cov 2373' or 'NVX CoV2373' or 'NVX CoV2601' or 'NVXCoV2373' or 'NVX-CoV2373 COVID-19 vaccine' or 'nvx-cov2373

#	Search Terms
	vaccine' or 'NVXCoV2601' or 'NVX-CoV2705' or 'SARS-CoV-2 rS' or 'sars-cov-2 rs vaccine' or 'SARS-CoV-2/Covid-19 vaccine' or 'TAK 019'):ti,ab
8	#4 OR #5 OR #6 OR #7
9	#3 AND #8
10	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
11	#9 NOT #10
12	#11 NOT (‘case reports’/it OR ‘clinical trial protocol’/it OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
13	#12 NOT (‘case report’ OR ‘simulation model’ OR ‘primate’ OR ‘murine’ OR ‘in vitro’ OR ‘cell line’ OR ‘protein structure’ OR ‘animal model’ OR ‘rodent’ OR ‘viral genome’):ti,ab
14	#13 AND [english]/lim
15	#14 NOT [medline]/lim

Search Ran: 12/17/25

Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for Covid-19 Vaccines



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, Minnesota); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also evaluated FDA and CDC documents related to the four Covid-19 vaccines These included the manufacturer's submission to the agency, internal FDA review documents, prescribing information, and ACIP meeting materials. All literature that did not undergo a formal peer review process is described separately.

Additional detail on study selection can be found in Supplement Section D2 below.

Data Extraction

Data were extracted into Microsoft Word and Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for the key observational studies that informed estimates for vaccine effectiveness in this review using criteria published in Risk of Bias In Non-randomized Studies – of Interventions Tool (ROBINS-I).[111] We used the ROBINS-I Version 2 that was updated in November 2025. Risk of bias was assessed by study outcome for each of the following aspects of the trials: confounding, classification of interventions, selection of participants, deviation from intended interventions, missing data, measurement of outcome, and selection of reported result. Two

reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer.

To assess the risk of bias in trials, we rated the categories as: "low risk of bias," "moderate risk of bias," "serious risk of bias" or "critical risk of bias." Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: There is the possibility of uncontrolled confounding that has not been controlled for (given the observational nature of the study), but otherwise little or no concern about bias in the result.*

Moderate risk of bias*: There is some concern about bias in the result, although it is not clear that there is an important risk of bias.*

Serious risk of bias*: The study has some important problems: characteristics of the study give rise to a serious risk of bias in the result*

Critical risk of bias: *The study is very problematic: characteristics of the study give rise to a critical of bias in the result, such that the result should generally be excluded from evidence syntheses.*

We examined the risk of bias for the primary outcome for each trial: composite endpoint of ED visit, hospitalization, and death (Cai 2025) and lab-confirmed Covid-19-associated ED or urgent care encounter (Irving 2025, Link-Gelles 2025). See Table D1.3.

Table D1.3. Risk of Bias Assessment using ROBINS-I

Studies (Author, Year)	Confounding	Classification of Interventions	Selection of Participants	Deviation from Intended Interventions	Missing Data	Measurement of Outcome	Selection of Reported Result	Overall Risk of Bias
Cai 2025	**Low**	**Low**	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**
	Comment: Study has an active comparator design, conducted inverse probability weighting for 184 covariates, presented numerous sensitivity analyses to address potential confounding, and emulated a target trial. The population was US veterans with a mean age of 71 and were 70% white and were required to have received a 2023–2024 vaccine which may reflect a population that utilizes health services more.							
Link-Gelles 2025	**Moderate**	**Low**	**Moderate**	**Low**	**Moderate**	**Low**	**Low**	**Moderate**
	Comment: Study adjusted for sex, race, age, calendar time, and geographic region. Other potential confounders were not measured. There were clear inclusion and exclusion criteria using electronic health records through two networks. Limited information provided on missing data.							
Irving 2025	**Moderate**	**Low**	**Moderate**	**Low**	**Moderate**	**Low**	**Low**	**Moderate**
	Comment: Study adjusted for sex, race, age, calendar time, and geographic region. Other potential confounders were not measured. There were clear inclusion and exclusion criteria using electronic health records through one networks. Limited information provided on missing data.							

Evaluation of Subgroup Credibility

We did not evaluate the credibility of clinically relevant subgroup analyses (aka effect modification analyses) using criteria published in the Instrument for the Credibility of Effect Modification ANalyses (ICEMAN) tool (Version 1.1).[112] This tool is used for randomized controlled trials and meta-analyses. The most recent evidence on effectiveness for our review of Covid-19 vaccines comes from observational studies. We did evaluate the primary RCTs for short-term adverse events but did not extract efficacy estimates as we do not believe they apply to current estimates on vaccine effectiveness, and therefore did not look at subgroups by efficacy that may have been explored in the RCTs.

Evaluation of Clinical Trial Diversity

Given the broad population in scope for this review and the evidence base for vaccines for Covid-19, we did not evaluate the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[113]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[114,115]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include: “Covid-19 Vaccine,” “Comirnaty,” “BNT162b2,” “Spikevax”, “mRNA-1273”, “mNexspike”, “mRNA-1283,” “Nuvaxovid” and “NVX-CoV2373”. We sought studies which would have met our inclusion criteria, and for which no findings have been published. We did not identify any studies.

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized qualitatively in the body of the evidence report and in the evidence tables below in Supplement Section D3.

D2. Additional Clinical Evidence

Table D2.1. Estimating Effectiveness: Calculations for Hospitalization

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6
Population	**CDC Hospitalization Estimate per 1,000 persons**	**Vaccine Relative Effectiveness**	**Fewer Hospitalizations per 1,000 persons**	**Vaccinations Needed to Prevent One Hospitalization**	**Vaccinations Needed to Prevent One Hospitalization (Rounded)**
Young Adults	0.22	0.28	0.0616	16233.76623	16000
Adults 50 - 64	0.8	0.28	0.224	4464.285714	4500
Adults 65+	NE	0.28	0.75	1333.333333	1300
Adults 85+	12	0.28	3.36	297.6190476	300
Children 5 - 18	0.09	0.56	0.0504	19841.26984	20000
Children 2 - 5	0.2	0.76	0.152	6578.947368	6600
Children 1 - 2	0.7	0.76	0.532	1879.699248	1900
Children 6 - 12 months	1.3	0.76	0.988	1012.145749	1000
Young Pregnant Women	0.75	0.28	0.21	4761.904762	4800
Older Pregnant Women	1.02	0.28	0.2856	3501.40056	3500
Comorbidities in People Under 65	0.6	0.28	0.168	5952.380952	6000
People with CKD	0.45	0.28	0.126	7936.507937	7900

CDC: Centers for Disease Control and Prevention, CKD: chronic kidney disease, NE: not estimated

- Column 1: Subpopulation of interest
- Column 2: CDC Hospitalization estimates are from 2024 – 2025 Covid-19 Season from COVID-NET
- Column 3: Vaccine Relative Effectiveness estimates are from the relevant publications (0.28: Cai 2025; 0.56 and 0.76: Irving 2025)
- Column 4: Calculated by multiplying Column 2 and 3
- Column 5: Calculated using 1 / fewer hospitalizations per 1,000 persons
- Column 6: Column 5 values rounded to two significant digits

For the population of adults 65+, we felt the risk difference in hospitalizations (0.75 per 1,000 persons) from the VA study was applicable and therefore did not calculate in an estimate based on CDC hospitalization estimates and vaccine effectiveness.

Table D2.2. Estimating Effectiveness: Calculations for Deaths

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6
Population	**Fewer Hospitalizations per 1,000 persons**	**Reductions in Mortality / Reductions in Hospitalization**	**Fewer Deaths per 1,000 persons**	**Vaccines Needed to Prevent One Death**	**Vaccines Needed to Prevent One Death (Rounded)**
Young Adults	0.0616	0.294511379	0.018141901	55121.01535	55000
Adults 50 - 64	0.224	0.294511379	0.065970549	15158.27922	15000
Adults 65+	0.75	0.294511379	0.22	4545.454545	4500
Adults 85+	3.36	0.294511379	0.989558233	1010.551948	1000
Children 5 - 18	0.0504	NE	NE	NE	NE
Children 2 - 5	0.152	NE	NE	NE	NE
Children 1 - 2	0.532	NE	NE	NE	NE
Children 6 - 12 months	0.988	NE	NE	NE	NE
Young Pregnant Women	0.21	0.294511379	0.06184739	16168.83117	16000
Older Pregnant Women	0.2856	0.294511379	0.08411245	11888.84645	12000
Comorbidities in People under 65	0.168	0.294511379	0.049477912	20211.03896	20000
People with CKD	0.126	0.294511379	0.037108434	26948.05195	27000

CKD: chronic kidney disease, NE: not estimated due to data limitations

- Column 1: Subpopulation of interest
- Column 2: Calculated by multiplying the CDC hospitalization estimate and vaccine relative effectiveness (see table above)
- Column 3: Calculated using the risk differences for Covid-19 associated death and hospitalization per 1,000 persons from the VA Study (0.22 / 0.747)
- Column 4: Calculated by multiplying Column 2 and 3
- Column 5: Calculated using 1 / fewer deaths per 1,000 persons
- Column 6: Column 5 values rounded to two significant digits

Systematic Literature Review Results

Our search yielded 10,407 references and we identified nine references from other sources. After de-duplication, 8,856 references were screened at the title/abstract level. 920 references were reviewed at the full-text level and 241 were included as they aligned with our PICOTS criteria.

We were interested in randomized or non-randomized controlled trials with any sample size to evaluate short-term adverse events. Efficacy outcomes from these trials were not abstracted. We included high-quality comparative observational studies with a sample size greater than 50,000 to try to identify the best, most recent evidence on vaccine effectiveness. In the absence of large comparative observational studies for subpopulations of interest, we considered small high-quality observational studies that address specific subpopulations or research questions of interest to our review (ideally with a sample size >1,000). Given the amount of evidence on vaccine effectiveness for the four vaccines of interest and the evolving nature of SARS-CoV-2 variants and strains, studies that presented evidence on effectiveness from 2023 to present were prioritized during the full-text screening to align best with the research questions for this review.

Our search identified the original randomized trials and subsequent booster studies, observational studies reporting on effectiveness and safety using cohort, case-control, and self-controlled case series study designs, and safety surveillance studies using large databases such as the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD). We also sought information on recent epidemiological data for Covid-19 through publicly available surveillance systems (e.g., the CDC COVID-NET Hospitalization tracker) that are routinely updated.

The most recent, high-quality observational studies reporting on vaccine effectiveness are highlighted in the main section of the report. This includes Cai 2025, Irving 2025, and Link-Gelles 2025. Supporting studies for specific subgroups are cited in the main report where relevant.

Section D3: Order of Tables

In Section D3 below, numerous evidence tables are outlined as a result of our systematic literature review. The bulleted list below outlines the broader categories that the evidence tables are organized within.

- Pivotal Trials and Related Studies for Short-Term Adverse Events
    - Study Design: Table D3.1
    - Comirnaty: Tables D3.2–D3.13
    - Spikevax: Tables D3.14–D3.23
    - mNexspike: Supplement Tables D3.24–D3.29
    - Nuvaxovid: D3.30–D3.35
    - Multiple Vaccines: D3.36
- Evidence Tables for Key Observational Studies informing Vaccine Effectiveness
    - Study Design: Table D3.37
    - Cai 2025: Tables D3.38, D3.41, D3.45
    - Irving 2025: Tables D3.39, D3.42
    - Link-Gelles 2025: Tables D3.40, D3.43
- Additional Observational Studies Identified for Key Subgroups of Interest

    - Young Children (6 months – 11 years old): Tables D3.46–D3.47
    - Adolescents (12–17 years old): Tables D3.48–D3.49
    - Adults over 18 years old: Tables D3.50–D3.51
    - Adults over 55–65 years old: Tables D3.52–D3.53
    - Pregnant Women: Tables D3.54–D3.57
    - People with Comorbid Conditions: Tables D3.58–D.359
- Additional Observational Studies for Key Outcomes of Interest
    - Myocarditis and Pericarditis in Boys and Young Men: Tables D3.60–D3.61
    - Myocarditis and Pericarditis in Other Age Groups: Tables D3.62–D3.63
    - Guillain-Barre Syndrome: Tables D3.64–D3.65
    - Long-Covid: Tables D3.66–D3.67

Section D3: Observational Study Section Information

The subsections for observational studies identified from the systematic literature review are organized in a way to efficiently identify studies that report data on specific subpopulations of interest for this review.

For the sections "Additional Observational Studies Identified for Key Subgroups of Interest" and "Additional Observational Studies Identified for Key Outcomes of Interest," each subsection begins with a table that outlines the references identified that report on the specific subpopulation of interest. These tables are not mutually exclusive. If a study reports on multiple subpopulations of interest, the study is repeated in each table where relevant (e.g., if a study stratifies vaccine effectiveness by adolescents 12 to 17 and adults 18+ it will be included in both tables).

The reference tables describe study title, author last name and year of publication, vaccine type, study type, and data range. For vaccine type, if multiple vaccines are listed then data in the study is stratified by vaccine type. If there are multiple vaccines evaluated in a study, but results are not stratified by vaccine type and are rather presented as an overall estimate, this cell will read: multiple (not stratified). The data range column refers to the timeframe that the data in a particular study was collected. To best align references with Covid-19 seasons, the data ranges were categorized in terms of vaccine seasons and span across two years (i.e., Fall 2020 to Spring 2021, Fall 2021 to Spring 2022, Fall 2022 to Spring 2023, etc.)

Where relevant, a second table follows the primary reference table that highlights key results from select trials within a particular subpopulation or for a particular outcome.

For myocarditis/pericarditis, there are two sections. One that focuses on evidence on myocarditis/pericarditis for boys and young men as this is of particular interest for this review. The

second table focuses on data for other age groups. There may be overlap in studies between these if a study has stratified data both on boys and young men and other age groups.

D3. Evidence Tables

Pivotal Trials and Related Studies for Short-Term Adverse Events

Table D3.1. Study Design

Trial Name (NCT)	Study Design & Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
COMIRNATY (BNT162b2)				
Polack. NEJM. 2020[7] **NCT04368728**	Phase II/III multinational, placebo-controlled, observer-blinded, pivotal efficacy trial N=43,548	1:1 ratio, 2 doses 21 days apart 1) 30 µg of BNT162b2 (0.3 ml volume per dose) 2) Placebo Follow-up: 2 months	**Inclusion**: ·Adults 16 years of age or older who were healthy or had stable chronic medical conditions **Exclusion**: ·A medical history of Covid-19 ·Treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.	·Efficacy of BNT162b2 against confirmed Covid-19 [at least 7 days after the second dose] ·Efficacy in participants with and without evidence of prior infection ·Efficacy of BNT162b2 against severe Covid-19 ·Solicited, specific local or systemic AEs and use of antipyretic or pain medication [7 days after each dose of vaccine or placebo] ·Unsolicited AEs [1 month after the second dose] ·Unsolicited SAEs [6 months after the second dose]
Walter. NEJM. 2022[53] **NCT04816643**	Phase I, dose-finding study N= 48 Ongoing Phase II-III randomized trial N=2268	<u>Phase I</u> 2 doses, 21 days apart planned dose level (10 µg, 20 µg, and 30 µg) of BNT162b2 <u>Phase II-III</u> 2:1 ratio, 2 doses, 21 days apart 1)10 µg of BNT162b2 2) Placebo	**Inclusion:** ·Male or female participants ≥6 months to <12 years of age, at the time of randomization ·Negative urine pregnancy test for female participants **Exclusion:** ·Receipt of medications intended to prevent Covid-19. ·Previous or current diagnosis of MIS-C. ·History of severe adverse reaction associated with a vaccine and/or severe allergic reaction ·Immunocompromised individuals with	·SARS-CoV-2 GMTs [7 days after the second dose] ·Ratio of GMT [1 month after the second dose] ·Geometric mean fold rises [baseline to 1 month after the second dose] ·Ratio of confirmed Covid-19 illness without evidence of prior SARS-CoV-2 infection [7 days after the second dose] ·Ratio of confirmed Covid-19 illness with and without evidence of prior SARS-CoV-2 infection [7 days after the second dose]

Trial Name (NCT)	Study Design & Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
		Follow up: 2 years	known or suspected immunodeficiency ·Previous vaccination with any coronavirus vaccine.	
Hui. Lancet. 2022[83]	Phase II, randomized, double-blind, placebo-controlled trial N=959	3:1, 2 doses, 21 days apart <u>18-55</u> 1) 30 µg of BNT162b2 2) Placebo <u>56-85</u> 1) 30 µg of BNT162b2 2) Placebo Follow-up: 6 months	**Inclusion:** ·Healthy Chinese adults aged 18−85 years with a negative SARS-CoV-2 antibody test at screening, including those with a pre-existing stable condition **Exclusion:** ·Symptoms of Covid-19 ·Known infection with human immunodeficiency virus, hepatitis B or C virus (according to medical history) ·Known or suspected immunodeficiency or treatment with immunosuppressive therapy ·Treatment with medications intended to prevent Covid-19	·GMT and seroconversion rate [1 month after dose 2] ·GMT and SCR of neutralizing antibodies [1 week and 6 months after dose 2] ·Geometric mean fold rise in neutralizing antibody [1 week and at 1 month, 6 months after dose 2] ·GMT, SCR, GMFR of S1-binding IgG protein level [1 week, 1 month, 6 months after dose 2] ·Local and systemic solicited events, antipyretic medication use [14 days following each injection] ·Unsolicited TEAEs [dose 1 up to 1 month after dose 2] ·Serious AEs [6 months after dose 2]
SPIKEVAX (mRNA-1273)				
Ali. NEJM. 2021[55] **Teen COVE** **NCT04649151**	Ongoing Phase II-III, observer-blinded, placebo-controlled trial N=3,726	1:1 ratio, 2 doses, 21 days apart 1) 30 µg of BNT162b2 (0.3 ml volume per dose) 2) Placebo	**Inclusion:** ·Male and female adolescents between the ages of 12 and 17 years considered to be in good general health **Exclusion:** ·Pregnancy or breast-feeding ·Acute illness or fever 24 hours before or at screening ·Previous administration of an investigational vaccine against SARS-CoV-2 or current treatment with investigational agents for prophylaxis against Covid-19	·GMT ratio of pseudovirus neutralizing antibody titers and serologic response in adolescents in Phase II with those of young adult recipients in the efficacy Phase III trial [28 days after receipt of the second injection] ·Incidence of SARS-CoV-2 infection, asymptomatic SARSCoV-2 infection, and Covid-19 [14 days after second injection] ·Solicited local and systemic ARs [7 days after injection] ·Unsolicited AEs [days 1 through 28 after each injection] ·Medically attended, leading to withdrawal, serious AEs, data on MIS-C [until end of trial]

Trial Name (NCT)	Study Design & Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
Sahly. NEJM. 2021[56] **COVE** **NCT04470427***	Phase III, observer-blinded, randomized, placebo-controlled trial N=30,415	1:1 ratio, 2 doses ≥18 to <65 years and not at risk, ≥18 to <65 years and at risk, and ≥65 years 1) 100 µg of mRNA-1273 2) Placebo	**Inclusion:** ·18 years of age or older with no known history of SARS-CoV-2 infection and with locations or circumstances that put them at an appreciable risk of SARS-CoV-2 infection **Exclusion:** ·Acutely ill or febrile 72 hours prior to or at Screening or dosing ·Pregnant or breastfeeding ·Known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients ·Immunosuppressive or immunodeficient state	·mRNA-1273 vaccine efficacy in preventing a first occurrence of Covid-19 [at least 14 days after dose 2] ·mRNA-1273 vaccine efficacy in preventing severe Covid, Covid-19 after first dose, Covid-19 regardless of prior SARS-CoV-2 infection [at least 14 days after dose 2]
Anderson. NEJM. 2022[57] **KidCOVE** **NCT04796896**	Ongoing Phase II/III trial Part 1: dose selection Part 2: Observer-blinded, placebo-controlled evaluation	3:1 ratio, 2 doses, 28 days apart 1) 2 25 µg of mRNA-1273 2) Placebo	**Inclusion:** ·Healthy children, including children with stable chronic conditions **Exclusion:** ·Children with a known recent history of SARS-CoV-2 infection ·Received an investigational or approved SARS-CoV-2–related vaccine ·Known hypersensitivity to vaccine components or excipients	·Incidence of Covid-19 and SARS-CoV-2 infection after administration of mRNA-1273 or placebo ·Solicited local and systemic ARs [within 7 days after each injection] ·Unsolicited AEs [within 28 days after each injection] ·AEs leading to nonreceipt of the second injection, discontinuation from the trial, or both; SAEs, MAAES, AESIs, and SARS-CoV-2 infection assessed [day 1 through trial completion]
Creech. NEJM. 2022[58] **KidCOVE** **NCT04796896**		Part 1 and part 2 of the trial in the cohort of 6 to 11 year-old children		

Trial Name (NCT)	Study Design & Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
mNEXSPIKE (mRNA-1283)				
Chalkias. Lancet. 2025[59] **Next COVE** **NCT05815498**	Phase III, randomized, observer-blind, active-controlled study N=11,417	1:1 ratio, single dose 1) 10 µg of mRNA-1283.222 (0.2 mL) 2) 50 µg of mRNA-1273.222 (0.5 mL) Follow up: 1 year	**Inclusion:** ·12 and older ·Medically stable ·Received any authorized or otherwise approved Covid-19 vaccination more than 90 days before the screening visit **Exclusion:** ·Chronic diseases requiring ongoing medical intervention within the 2 months before enrollment ·Immunocompromising conditions or medications ·Any malignancy within 5 years of screening ·Positive SARS-CoV-2 lateral flow or rapid antigen or PCR test in the 90 days before screening	·Non-inferior rVE of mRNA-1283 compared with mRNA-1273 to prevent the first event of a US CDC–defined Covid-19 episode [14 days after vaccination] ·Geometric mean concentration ratios (GMRs) and seroresponses against omicron BA.4/BA.5 and original SARS-CoV-2 D614G [day 29] ·Solicited local and systemic AEs [7 days after injection] ·Unsolicited AEs [until 28 days after injection]
Grassi. Vaccines. 2026[84] **NCT05397223**	Phase III randomized, observer-blinded study N=689	1:1 ratio, single dose 1) 10 µg of mRNA-1283.815 (0.2mL) 2) 50 µg of mRNA-1273.815 (0.5 mL)	**Inclusion:** ·Japanese individuals aged ≥12 years who were medically stable and had previously received a primary series of a Covid-19 vaccine ·Japanese individuals aged ≥18 years were required to have received ≥1 booster dose of a Covid-19 vaccine **Exclusion:** ·Covid-19 vaccination or SARSCoV-2 infection within 90 days of screening ·Use of systemic immunosuppressants for a total of >14 days within the 180 days prior to screening	·Geometric mean ratio of mRNA-1283.815 10 µg vs. 50 µg [Day 29] ·Solicited local and systemic adverse reactions [15 min after vaccination up to 6 days] ·Unsolicited AEs [28 days after dose] ·Medically attended AEs, AEs of special interest, SAEs, and AEs leading to withdrawal [throughout study]

Trial Name (NCT)	Study Design & Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
Chalkias. IDSA. 2025 [116] **NCT05137236**	Phase IIa, 2 part, dose-ranging study Part A: observer-blind, stratified, randomized study Part B: OL N=340	Part A 1:1:1:1:1:1, 2 doses 1)2.5 µg mRNA-1283 2)5 µg of mRNA-1283 3)10 µg of mRNA-1283 4)5 µg of mRNA-1283.211 5) 10 µg of mRNA-1283.211 6)50 µg of mRNA-1273 Follow-up: 12 months	**Inclusion:** ·Healthy adults at least 18 years old ·Received second dose of mRNA-1273 primary series ≥6 months prior to screening and enrollment **Exclusion:** · Has symptomatic acute or unstable chronic disease requiring medical or surgical care ·History of myocarditis/pericarditis/myopericarditis within 2 months prior to screening ·Use of systemic immunosuppressants for >14 days within 6 months prior to screening	·Symptomatic and asymptomatic SARS-CoV-2 infection and Covid-19 cases [14 days after study vaccination] ·Frequency and grade of solicited local and systemic ARs [through 7 days after vaccination] ·Unsolicited TEAEs [28 days after vaccination] SAEs, MAAEs, AEs leading to study participation withdrawal, AESI [day 1 to end of study] ·Serum neutralizing antibody titers [Days 1, 29, 91, 181, 366]

Trial Name (NCT)	Study Design & Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
NUVAXOVID (NVX-CoV2373)				
Dunkle. NEJM. 2021[60] **NCT04611802**	Phase III, randomized, observer-blinded, placebo-controlled trial N=25,452	2:1 ratio, 2 doses, 21 days apart 1) NVX-CoV2373 (5 µg of SARS-CoV-2 recombinant spike protein adjuvanted with 50 µg of Matrix-M), 0.5-ml 2) Placebo Follow up: 2 months	**Inclusion:** · Adults ≥18 years of age at screening who are considered at substantial risk of exposure to and infection with SARS-CoV-2 **Exclusion**: ·Unstable acute or chronic illness ·Participation in research involving an investigational product (drug/biologic/device) administered within 45 days prior to first study vaccination ·History of a previous laboratory-confirmed diagnosis of SARS-CoV-2 infection or Covid-19. ·Received any vaccine within 4 days prior to first study vaccination or planned receipt of any vaccine before Day 49 ·Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) or therapy that causes clinically significant immunosuppression	·Efficacy of NVX-CoV2373 for the prevention of a first occurrence of RT-PCR–confirmed symptomatic mild, moderate, or severe Covid-19 [at least 7 days after the second dose] ·Efficacy of NVX-CoV2373 for the prevention of RT-PCR–confirmed Covid-19 cases caused by SARS-CoV-2 that was neither a variant of concern nor a variant of interest ·Efficacy against moderate and severe Covid-19 ·Solicited local and systemic AEs [7 days after each injection] ·Unsolicited AEs [first dose through 28 days after the second dose]
Heath, NEJM. 2021[9]	Phase III, randomized, observer-blinded, placebo-controlled trial N=14,039	1:1 ratio, 2 doses, 21 days apart 1) 5-µg doses of NVX-CoV2373 2) Placebo Follow up: 1 year	**Inclusion:** ·Men and nonpregnant women between the ages of 18 and 84 years who were healthy or had stable chronic medical conditions, including HIV and cardiac and respiratory diseases **Exclusion:** ·History of documented Covid-19 treated with immunosuppressive therapy ·Diagnosis of an immunodeficient condition	·Efficacy of the NVX-CoV2373 vaccine against the first occurrence of virologically confirmed symptomatic mild, moderate, or severe Covid-19 among participants who were seronegative at baseline [at least 7 days after the second dose] ·Solicited local and systemic AEs [7 days after each dose] ·Unsolicited AEs [first dose through 28 days after the second dose] ·SAEs, AESI, MAAEs [first dose through 1 year after the second dose]

Trial Name (NCT)	Study Design & Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
Anez. JAMA. 2023[61] **NCT04611802**	Phase III, randomized, observer-blinded, placebo-controlled trial N=2,247	2:1 ratio, 2 doses, 21 days apart 1) NVX-CoV2373 (5 µg recombinant SARS-CoV-2 rS plus 50 µg Matrix-M adjuvant) 2) Placebo	**Inclusion:** ·Healthy adolescents aged 12 through 17 years or those with stable chronic medical conditions including chronic pulmonary, kidney, or cardiovascular disease; type 1 or 2 diabetes; or well-controlled HIV infection that did not necessitate substantive changes in medications in the 2 months prior to enrollment ·Not currently undergoing workup of undiagnosed illness that could lead to diagnosis of a new condition **Exclusion:** ·Previous laboratory-confirmed SARS-CoV-2 infection ·Known immunosuppression	·Solicited local and systemic AEs [7 days after each injection] ·Unsolicited AEs [first dose through 28 days after 2nd dose] ·SAEs, AESIs, MAAEs [first dose until the end of the study] ·Neutralizing antibodies specific to SARS-CoV-2 [Day 0 and Day 35 serum samples] ·Efficacy of NVX-CoV2373 in preventing first episode of RT-PCR-confirmed symptomatic mild/moderate/severe Covid-19 [at least 7 days after 2nd dose]

AE: adverse event, AESI: adverse event of special interest, AR: adverse reaction, GMT: geometric mean titers, MAAE: medically attended adverse event, N: number, RT-PCR: Reverse Transcription Polymerase Chain Reaction, rVE: relative vaccine effectiveness, SAE: serious adverse event, TEAE: treatment emergent adverse events

*For NCT04470427, we focused on data from the Sahly 2021 publication as it presented the final results.

Comirnaty

Table D3.2. Comirnaty: Overall Safety for Pivotal Phase III Trials[7,54,117,118]

Vaccine		Comirnaty									
NCT		NCT04368728									
Author, Year		Polack 2020		Frenck 2021				Thomas 2021		Thomas 2022	
Trial Phase		Pivotal Phase III		Phase III				Phase III		Phase III	
Subgroup (Years)		≥18 to <65		12-15		16-25		16+		Cancer Participants 12+	
Arm		BNT162b2 (30 µg)	Placebo	BNT162b-2 (30 µg)	Placebo	BNT162b-2 (30 µg)	Placebo	BNT162b2 (30 µg)	Placebo	BNT162b-2 (30 µg)	Placebo
N		21,621*	21,631	1131	1129	536	561	21,926	21,921	1,898	1,908
AEs	Any	5770 (26.7)	2638 (12.2)	68 (6)	67 (5.9)	58 (10.8)	45 (8)	6617 (30.2)	3048 (13.9)	669 (35.2)	336 (17.6)
	Related	4484 (20.7)	1095 (5.1)	33 (2.9)	21 (1.9)	33 (6.2)	12 (2.1)	5241 (23.9)	1311 (6)	487 (25.7)	116 (6.1)
	Severe	240 (1.1)	139 (0.6)	7 (0.6)	2 (0.2)	9 (1.7)	3 (0.5)	262 (1.2)	150 (0.7)	39 (2.1)	25 (1.3)
	Life-Threatening	21 (0.1)	24 (0.1)	1 (0.1)	1 (0.1)	0	0	21 (0.1)	26 (0.1)	3 (0.2)	6 (0.3)
SAEs	Any	126 (0.6)	111 (0.5)	4 (0.4)	2 (0.4)	1 (0.1)	2 (0.4)	127 (0.6)	116 (0.5)	47 (2.5)	25 (1.3)
	Related	4 (0)	0	0	0	0	0	3 (0)	0	2 (0.1)	0
	Severe	71 (0.3)	68 (0.3)	2 (0.2)	0	2 (0.4)	1 (0.2)	71 (0.3)	66 (0.3)	25 (1.3)	14 (0.7)
	Life-Threatening	21 (0.1)	23 (0.1)	0	1 (0.1)	0	0	21 (0.1)	26 (0.1)	3 (0.2)	6 (0.3)
AEs Leading To Withdrawal/ Discontinuati-on	Any	37 (0.2)	30 (0.1)	2 (0.2)	0	1 (0.2)	2 (0.2)	32 (0.1)	36 (0.2)	6 (0.3)	4 (0.2)
	Related	16 (0.1)	9 (0)	1 (0.1)	0	1 (0.2)	0	13 (0.1)	11 (0.1)	3 (0.2)	1 (<0.1)
	Severe	13 (0.1)	9 (0)	1 (0.1)	0	1 (0.2)	0	10 (<0.1)	10 (<0.1)	1 (<0.1)	0
	Life-Threatening	3 (0)	6 (0)	1 (0.1)	0	0	0	3 (<0.1)	3 (<0.1)	1 (<0.1)	3 (0.2)
Death		2 (0)	4 (0)	0	0	0	0	3 (<0.1)	5 (<0.1)	1	2

AE: adverse event, N: total number, NA: not applicable, NR: not reported, SAE: serious adverse event, TEAE: treatment emergent adverse event

*From dose 1 to 1 month after dose 2

Table D3.3. Comirnaty: Overall Safety for Pivotal Phase II and III Trials[53,83,119]

Vaccine		Comirnaty								
NCT		NCT04816643						NCT04649021		
Author, Year		Walter 2022*		Munoz 2023†				Hui 2022*		
Trial Phase		Pivotal Phase II-III		Phase II-III				Phase II		
Subgroup		5-11 yrs		6 mo to <2 yrs		2-4 yrs		18-55 yrs	56-85 yrs	All
Arm		BNT162b2 (10 µg)	Placebo	BNT162b2 (3 µg)	Placebo	BNT162b2 (3 µg)	Placebo	BNT162b2 (30 µg)	BNT162b2 (30 µg)	Placebo
N		1,518	750	1178	598	1835	915	389	331	239
AEs	Any	166 (10.9)	69 (9.2)	355 (30.1)	162 (27.1)	344 (18.7)	171 (18.7)	56 (14.4)	23 (7)	19 (8)
	Related	46 (3)	16 (2.1)	55 (4.7)	21 (3.5)	37 (2)	18 (2)	41 (10.5)	17 (5.1)	9 (3.8)
	Severe	2 (0.1)	1 (0.1)	12 (1)	10 (1.7)	9 (0.5)	6 (0.7)	NR	NR	NR
	Life-Threatening	0	0	0	1 (0.2)	0	0	NR	NR	NR
SAEs	Any	1 (0.1)	1 (0.1)	17 (1.4)	14 (2.3)	12 (0.7)	8 (0.9)	0	0	0
	Related	0	0	0	1 (0.2)	1 (0.1)	0	0	0	0
	Severe	1 (0.1)	1 (0.1)	8 (0.7)	9 (1.5)	5 (0.3)	3 (0.3)	NR	NR	NR
	Life-Threatening	0	0	0	1 (0.2)	0	0	NR	NR	NR
AEs Leading to Withdrawal / Discontinuation	Any	0	0	3 (0.3)	0	3 (0.2)	1 (0.1)	NR	NR	NR
	Related	NR	NR	3 (0.3)	0	2 (0.1)	1 (0.1)	0	0	0
	Serious	NR	NR	0	0	1 (0.1)	0	NR	NR	NR
	Severe	NR	NR	1 (0.1)	0	1 (0.1)	1 (0.1)	NR	NR	NR
	Life-Threatening	NR	NR	0	0	0	0	NR	NR	NR
Vaccine Discontinuation	TEAE	NR	NR	NR	NR	NR	NR	2 (0.5)	2 (0.6)	2 (0.8)
AESI	Any	NR	NR	NR	NR	NR	NR	0	0	0
	Related	NR	NR	NR	NR	NR	NR	0	0	0
Death		0	0	0	0	0	0	NR	NR	NR

AE: adverse event, N: total number, NA: not applicable, NR: not reported, SAE: serious adverse event, TEAE: treatment emergent adverse event, yrs: years

*From dose 1 to 1 month after dose 2

†From dose 1 to 1 month after dose 3

Table D3.4. Comirnaty: Systemic Safety for Pivotal Phase III Trial[7,54,118]

Vaccine		Comirnaty									
NCT		NCT04368728									
Author, Year		Polack 2020*‡				Frenck 2021*§				Thomas 2022	
Trial Phase		Pivotal Phase III				Phase III				Phase III	
Subgroup (Years)		16 to 55		>55		12 to 15#		16 to 25		12+	
Arm		BNT162b2 (30 µg)	Placebo	BNT162b2 (30 µg)	Placebo	BNT162b2 (30 µg)	Placebo	BNT162b2 (30 µg)	Placebo	BNT162b2 (30 µg)	Placebo
N	Dose 1	8,183				1131	1129	537†	561	1,898	1,908
	Dose 2					1124	1117				
Arthralgia	Dose 2	NR	NR	NR	NR	NR	NR	NR	NR	33 (1.7)	12 (0.6)
Chills	Dose 1	14	6	6	3	317 (28)	113 (10)	25	9	NR	NR
	Dose 2	35	4	23	3	472 (42)	78 (7)	40	4	119 (6.3)	12 (0.6)
Diarrhea	Dose 1	11	12	8	7	90 (8)	79 (7)	11	11	NR	NR
	Dose 2	10	8	8	6	67 (6)	44 (4)	8	5	23 (1.2)	16 (0.8)
Fatigue	Dose 1	47	33	34	23	679 (60)	463 (41)	60	39	NR	NR
	Dose 2	59	23	51	17	742 (66)	279 (25)	66	23	129 (6.8)	41 (2.1)
Fever	Dose 1	4	1	1	0	113 (10)	11 (1)	7	1	NR	NR
	Dose 2	16	0	11	0	224 (20)	11 (1)	17	0	129 (6.8)	3 (0.2)
Headache	Dose 1	42	34	25	18	622 (55)	395 (35)	54	37	NR	NR
	Dose 2	52	24	39	14	731 (65)	268 (24)	61	24	116 (6.1)	34 (1.8)
Joint Pain	Dose 1	11	6	9	6	113 (10)	79 (7)	13	5	NR	NR
	Dose 2	22	5	19	4	180 (16)	56 (5)	22	4	NR	NR
Muscle Pain	Dose 1	21	11	14	8	271 (24)	147 (13)	27	14	NR	NR
	Dose 2	37	8	29	5	360 (32)	89 (8)	41	10	NR	NR
Myalgia	Dose 2	NR	NR	NR	NR	NR	NR	NR	NR	111 (5.8)	12 (0.6)
Use of Antipyretic Medication	Dose 1	28	14	20	12	418 (37)	113 (10)	32	11	NR	NR
	Dose 2	45	13	38	10	573 (51)	100 (9)	46	12	NR	NR
Nausea/Vomiting	Dose 1	1	1	0	1	34 (3)	11 (1)	2	2	NR	NR
	Dose 2	2	1	1	0	34 (3)	11 (1)	3	2	NR	NR

N: total number, NR: not reported
*Total number of each arm is not available, data presented are percentages
†Overall 16-25 year population is 1,875 for BNT12b2 and 1,913 for placebo
‡Solicited adverse events
§Unsolicited adverse events
#Back calculated N's

Table D3.5. Comirnaty: Systemic Safety for Phase II and III Trials[53,83,119]

Vaccine		Comirnaty								
NCT		NCT04816643						NCT04649021		
Author, Year		Walter 2022*		Munoz 2023				Hui 2022*†		
Trial Phase		Pivotal Phase II-III		Phase II-III				Phase II		
Subgroup		5 to 11		6 Mo to <2 Yr		2 to 4		18-55 Yrs	56-85 Yrs	All
Arm		BNT162b2 (10 µg)	Placebo	BNT162b2 (3 µg)	Placebo	BNT162b2 (3 µg)	Placebo	BNT162b2 (30 µg)	BNT162b2 (30 µg)	Placebo
N	Dose 1	1,511	748	1173	595	1825	909	389	331	239
	Dose 2	1,501	749	1147	591	1779	878	387	328	237
	Dose 3	NA	NA	365	170	552	262	NA	NA	NA
Chills	Dose 1	76 (5)	30 (5)	NR	NR	2	2	36 (9.3)	13 (3.9)	1 (0.4)
	Dose 2	150 (10)	30 (4)	NR	NR	3	3	118 (30.5)	59 (18)	0
	Dose 3	NA	NA	NR	NR	3	3	NA	NA	NA
Decreased Appetite	Dose 1	NR	NR	22	21	NR	NR	NR	NR	NR
	Dose 2	NR	NR	22	18	NR	NR	NR	NR	NR
	Dose 3	NA	NA	20	14	NR	NR	NA	NA	NA
Diarrhea	Dose 1	91 (6)	30 (4)	NR	NR	8	8	11 (2.8)	3 (0.9)	2 (0.8)
	Dose 2	75 (5)	37 (5)	NR	NR	7	7	5 (1.3)	2(0.6)	0
	Dose 3	NA	NA	NR	NR	5	5	NA	NA	NA
Drowsiness	Dose 1	NR	NR	27	29	NR	NR	NR	NR	NR
	Dose 2	NR	NR	24	21	NR	NR	NR	NR	NR
	Dose 3	NA	NA	20	13	NR	NR	NA	NA	NA
Fatigue	Dose 1	514 (34)	232 (31)	NR	NR	30	31	45 (11.6)	24 (7.3)	5 (2.1)

Vaccine		Comirnaty								
NCT		NCT04816643						NCT04649021		
Author, Year		Walter 2022*		Munoz 2023				Hui 2022*†		
Trial Phase		Pivotal Phase II-III		Phase II-III				Phase II		
Subgroup		5 to 11		6 Mo to <2 Yr		2 to 4		18-55 Yrs	56-85 Yrs	All
Arm		BNT162b2 (10 µg)	Placebo	BNT162b2 (3 µg)	Placebo	BNT162b2 (3 µg)	Placebo	BNT162b2 (30 µg)	BNT162b2 (30 µg)	Placebo
	Dose 2	585 (39)	180 (24)	NR	NR	26	23	112 (28.9)	50 (15.2)	4 (1.7)
	Dose 3	NA	NA	NR	NR	24	22	NA	NA	NA
Fever	Dose 1	45 (3)	7 (1)	7	7	5	5	25 (6.4)	11 (3.3)	1 (0.4)
	Dose 2	105 (7)	7 (1)	7	6	5	5	150 (38.8)	62 (18.9)	0
	Dose 3	NA	NA	7	6	5	4	NA	NA	NA
Headache	Dose 1	332 (22)	180 (24)	NR	NR	4	5	34 (8.7)	12 (3.6)	4 (1.7)
	Dose 2	420 (28)	142 (19)	NR	NR	5	4	97 (25.1)	37 (11.3)	0
	Dose 3	NA	NA	NR	NR	5	4	NA	NA	NA
Irritability	Dose 1	NR	NR	51	47	NR	NR	NR	NR	NR
	Dose 2	NR	NR	47	41	NR	NR	NR	NR	NR
	Dose 3	NA	NA	44	38	NR	NR	NA	NA	NA
Joint Pain	Dose 1	45 (3)	30 (5)	NR	NR	1	2	16 (4.1)	2 (0.6)	1 (0.4)
	Dose 2	75 (5)	30 (4)	NR	NR	1	1	37 (9.6)	14 (4.3)	0
	Dose 3	NA	NA	NR	NR	1	1	NA	NA	NA
Muscle Pain	Dose 1	136 (9)	52 (7)	NR	NR	2	2	25 (6.4)	8 (2.4)	2 (0.8)
	Dose 2	180 (12)	52 (7)	NR	NR	3	2	55 (14.2)	21 (6.4)	1 (0.4)
	Dose 3	NA	NA	NR	NR	2	2	NA	NA	NA
Use of Antipyretic Medication	Dose 1	211 (14)	60 (8)	24	20	11	9	NR	NR	NR
	Dose 2	300 (20)	60 (8)	21	19	10	8	NR	NR	NR
	Dose 3	NA	NA	19	17	9	7	NA	NA	NA
Vomiting	Dose 1	30 (2)	7 (1)	NR	NR	3	3	1 (0.3)	1 (0.3)	0
	Dose 2	30 (2)	7 (1)	NR	NR	3	3	6 (1.6)	4 (1.2)	0
	Dose 3	NA	NA	NR	NR	2	4	NA	NA	NA

N: total number, NA: not applicable, NR: not reported, mo: months, yr: years

*Back calculated N's

†Solicited adverse events

Table D3.6. Comirnaty: Local Safety for Pivotal Phase III Trials[7,54,118]

Vaccine		Comirnaty									
NCT		NCT04368728									
Author, year		Polack 2020[*§]				Frenck 2021[†]				Thomas 2022	
Trial Phase		Pivotal Phase III				Phase III				Phase III	
Subgroup (Years)		16 to 55		>55		12 to 15[#]		16 to 25		12+	
Arm		BNT162b2 (30 µg)	Placebo	BNT162b2 (30 µg)	Placebo	BNT162b2 (30 µg)	Placebo	BNT162b2 (30 µg)	Placebo	BNT162b2 (30 µg)	Placebo
N	Dose 1	8,183				1131	1129	537[‡]	561	1,898	1,908
	Dose 2					1124	1117				
Erythema / Redness	Dose 1	5	1	5	1	6	6	1	1	NA	NA
	Dose 2	6	1	7	1	5	6	1	0	28 (1.5)	2 (0.1)
Lymphadenopathy	Dose 1	64 (0.3%) vaccine recipients vs. 6 (<0.1%) placebo recipients				9 / 1131 (0.8%)	2 / 1129 (0.2%)	1 / 536 (0.2%)	0	NA	NA
	Dose 2									NR	NR
Pain at Injection Site	Dose 1	83	14	71	9	86	NR	NR	16	NA	NA
	Dose 2	78	12	66	8	79	78	18	12	266 (14.0)[‡]	26 (1.4)
Swelling	Dose 1	6	0	7	1	7	8	1	1	NA	NA
	Dose 2	6	0	7	1	5	7	1	0	21 (1.1)	1 (<0.1)

N: total number, NA: not applicable, NR: not reported

*Solicited adverse events

†Unsolicited adverse events

‡Overall 16-25 year population is 1,875 for BNT162b2 and 1,913 for placebo

‡Study also reports pain: 69 (3.6) for BNT162b2 and 10 (0.5) for placebo

§Total number of each arm is not available, data presented are percentages

#Back calculated N's

Table D3.7. Comirnaty: Local Safety for Pivotal Phase II and Phase III Trials[53,83,119]

Vaccine		Comirnaty								
NCT		NCT04816643						NCT04649021		
Author, year		Walter 2022*		Munoz 2023				Hui 2022*†		
Trial Phase		Pivotal Phase II-III		Phase II-III				Phase II		
Subgroup		5 to 11 Yrs		6 Mo to <2 Yr		2 to 4 Yrs		18-55 Yrs	56-85 Yrs	All
Arm		BNT162b2 (10 µg)	Placebo	BNT162b2 (3 µg)	Placebo	BNT162b2 (3 µg)	Placebo	BNT162b2 (30 µg)	BNT162b2 (30 µg)	Placebo
N	Dose 1	1,511	748	1159	591	1813	905	389	331	239
	Dose 2	1,501	749	1137	590	1772	877	387	328	237
	Dose 3	NA	NA	365	170	552	262	NA	NA	NA
Erythema / Redness	Dose 1	227 (15)	45 (6)	11	7	9	8	18.5	9.4	0
	Dose 2	285 (19)	37 (5)	9	7	11	6	10.6	7	0
	Dose 3	NA	NA	7	5	11	3	NA	NA	NA
Pain at Injection Site	Dose 1	1118 (74)	232 (31)	NR	NR	NR	NR	69.2	38.4	1.7
	Dose 2	1066 (71)	217 (29)	NR	NR	NR	NR	63.1	37.5.	3.8
Swelling	Dose 1	151 (10)	22 (3)	4	3	4	3	23.1	10.6	0.8
	Dose 2	225 (15)	22 (3)	4	2	6	2	16.5	8.8	0
	Dose 3	NA	NA	3	2	3	1	NA	NA	NA
Tenderness	Dose 1	NR	NR	17	11	31	21	NR	NR	NR
	Dose 2	NR	NR	15	8	31	20	NR	NR	NR
	Dose 3	NA	NA	16	12	27	13	NA	NA	NA

mo: months, N: total number, NA: not applicable, NR: not reported, yrs: years

*Back calculated N's

†Solicited adverse events

Table D3.8. Comirnaty: Overall Safety for Booster Trials[120-122]

Vaccine			Comirnaty					
NCT			NCT04955626		NCT04816643	NCT05543616		
Author, Year			Moreira 2022		Simoes 2023	Sher 2024		
Trial Phase			Phase III Booster #1 (Dose 3)		Phase II/III Booster #1 (Dose 3)	Phase III OL		
Subgroup (Years)			≥16		5-11	6 Mo - <2 Yrs	2-5	5 - <12
Arm			BNT162b2 (30 µg)*	Placebo	BNT162b2 (10 µg)	BNT162b2 (3 µg)	BNT162b2 (3 µg)	BNT162b2 (10 µg)
N			5,055	5,020	401	92	218	113
Unsolicited AEs Regardless of Relationship to Study Vaccination	All		1,263 (25.0)	326 (6.5)	36 (9)	13	9.2	6.2
	Serious		16 (0.3)	24 (0.5)	2 (0.5)‡	0	0.5	0
	Severe		NR	NR	1 (0.2)	NR	NR	NR
	Life Threatening		NR	NR	0	0	0	0
	Fatal		0	1 (<0.1)	0	NR	NR	NR
	Medically-Attended		NR	NR	0‡	NR	NR	NR
	Leading to Study Discontinuation		0	1 (<0.1)	NR	0	0	0
	AESI		NR	NR	16 (3.9)	NR	NR	NR
		Covid-19	0	1 (<0.1)†	NR	NR	NR	
		MIS-C	NR	NR	0	0	0	0
		Other	NR	NR	0	NR	NR	NR
		Lymphadenopathy	135 (2.7)	2 (<0.1)	1 (0.2)	NR	NR	NR
		Myocarditis	0	0	0	0	0	0
		Rash	NR	NR	1 (0.2)	NR	NR	NR
Unsolicited AEs Related to Study Vaccination	All		1,182 (23.4)	205 (4.1)	19 (4.7)	1.1	1.4	0.9
	Serious		3 (<0.1)	2 (<0.1)	0	NR	NR	NR
	Fatal		0	0	0	NR	NR	NR
	Leading to Study Discontinuation		0	0	0	NR	NR	NR
	Leading to Study Vaccine Discontinuation		NR	NR	0	NR	NR	NR
	Severe		0.1	<0.1	0	NR	NR	NR
	PIMMC		NR	NR	0	NR	NR	NR

Vaccine			Comirnaty					
NCT			NCT04955626		NCT04816643	NCT05543616		
Author, Year			Moreira 2022		Simoes 2023	Sher 2024		
Trial Phase			Phase III Booster #1 (Dose 3)		Phase II/III Booster #1 (Dose 3)	Phase III OL		
Subgroup (Years)			≥16		5-11	6 Mo - <2 Yrs	2-5	5 - <12
Arm			BNT162b2 (30 µg)*	Placebo	BNT162b2 (10 µg)	BNT162b2 (3 µg)	BNT162b2 (3 µg)	BNT162b2 (10 µg)
	AESI		NR	NR	16 (4.0)	NR	NR	NR
		MIS-C	NR	NR	0	0	0	0
		Lymphadenopathy	0	0	14 (3.5)	NR	NR	NR
		Myocarditis	0	0	0	0	0	0

AE: adverse events, AESI: adverse events of special interest, MIS-C: multisystem inflammatory syndrome in children, mo: months, N: total number, NA: not applicable, NR: not reported, PIMMC: Potential Immune-Mediated Medical Conditions, yrs: years

*Data for participants with stable human immunodeficiency virus infection were analyzed separately.

†Covid-19 pneumonia

‡From dose 3 to safety data cutoff

Table D3.9. Comirnaty: Overall Safety for Booster Trials[123,124]

Vaccine		Comirnaty					
NCT		NCT05472038					NCT06130410
Author, Year		Usdan 2024 (Bivalent BNT162b2-Omi.BA.4/BA.5)					Clinicaltrials.gov
Trial Phase		Phase II/III Booster #2 (Dose 4)					Booster #2 (Dose 4)
Subgroup (Years)		12-17	18-55		≥56		6 Mo-4 Yrs
Arm		BNT162b2 (30 µg)	BNT162b2 (30 µg)	BNT162b2 (60 µg)	BNT162b2 (30 µg)	BNT162b2 (60 µg)	Monovalent BNT162b2 (XBB.1.5)
N		107	313	110	306	102	25
Unsolicited AEs Regardless of Relationship to Study Vaccination	All	8 (7.5)	19 (6.1)	9 (8.2)	21 (6.9)	7 (6.9)	5 (20)
	Serious	0	1 (0.3)	0	2 (0.7)	0	0
	Severe	0	1 (0.3)	0	2 (0.7)	0	NR
	Life Threatening	0	0	0	0	0	NR

Vaccine			Comirnaty					
NCT			NCT05472038					NCT06130410
Author, Year			Usdan 2024 (Bivalent BNT162b2-Omi.BA.4/BA.5)					Clinicaltrials.gov
Trial Phase			Phase II/III Booster #2 (Dose 4)					Booster #2 (Dose 4)
Subgroup (Years)			12-17	18-55		≥56		6 Mo-4 Yrs
Arm			BNT162b2 (30 µg)	BNT162b2 (30 µg)	BNT162b2 (60 µg)	BNT162b2 (30 µg)	BNT162b2 (60 µg)	Monovalent BNT162b2 (XBB.1.5)
	Fatal		0	0	0	0	0	0
	Leading to Study Discontinuation		0	0	0	0	0	NR
	AESI	Covid-19	2	4	3	4	0	NR
		Lymphadenopathy	0	0	0	0	0	NR
		Myocarditis	0	0	0	0	0	NR
Unsolicited AEs Related to Study Vaccination	All		6 (5.6)	12 (3.8)	3 (2.7)	6 (2)	1 (1)	1 (4)
	Serious		0	0	0	0	0	0
	Fatal		0	0	0	0	0	0
	Leading to Study Discontinuation		0	0	0	0	0	NR
	Severe		0	0	0	0	0	NR
	AESI	Lymphadenopathy	7 (0.7)					NR
		Myocarditis	0	0	0	0	NR	NR

AE: adverse events, AESI: adverse events of special interest, N: total number, NR: not reported

Table D3.10. Comirnaty: Systemic Safety for Booster Trials[120-122]

Vaccine							
NCT		**NCT04955626**		**NCT04816643**	**NCT05543616**		
Author, Year		**Moreira 2022**		**Simoes 2023**	**Sher 2024**		
Trial Phase		**Phase II/III Booster #1 (Dose 3)[*‡]**		**Phase III Booster #1 (Dose 3)[†]**	**Phase III OL Booster #2 (Dose 4)[*]**		
Subgroup		**≥16 Yrs**		**5-11 Yrs**	**6 Mo - <2 Yrs**	**2 - <5 Yrs**	**5 - <12 Yrs**
Arm		**BNT162b2 (30 µg)[*]**	**Placebo**	**BNT162b2 (10 µg)**	**BNT162b2 (3 µg)**	**BNT162b2 (3 µg)**	**BNT162b2 (10 µg)**
N (%)		**5,055**	**5,020**	**371**	**89-92**	**217-218**	**111**
Chills	**Dose 1**	233 (4.6)	9 (0.2)	41 (11)	NR	5	9
Decreased appetite	**Dose 1**	9 (0.2)	0	NR	20	NR	NR
Diarrhea	**Dose 1**	NR	NR	19 (5)	NR	5	4
Drowsiness	**Dose 1**	NR	NR	NR	20	NR	NR
Fatigue	**Dose 1**	365 (7.2)	61 (1.2)	170 (46)	NR	31	41
Fever	**Dose 1**	242 (4.8)	7 (0.1)	26 (7)	9	7	5
Headache	**Dose 1**	255 (5)	48 (1)	126 (34)	NR	4	25
Irritability	**Dose 1**	NR	NR	NR	36	NR	NR
Joint Pain	**Dose 1**	NR	NR	NR	NR	1	9
Malaise	**Dose 1**	35 (0.7)	4 (0.1)	NR	NR	NR	NR
Muscle Pain	**Dose 1**	NR	NR	67 (18)	NR	3	14
Myalgia	**Dose 1**	239 (4.7)	20 (0.4)	NR	NR	NR	NR
Nausea/Vomiting	**Dose 1**	11 (0.2)	2 (<0.1)	7 (2)	NR	5	4

mo: months, N: total number, NR: not reported, yrs: years

*AEs reported ≤7 days

†AEs reported <1st month of admin

‡Back calculated N's

Table D3.11. Comirnaty: Systemic Safety for Booster Trials[123,124]

Vaccine		Comirnaty						
NCT		NCT05472038					NCT06130410	
Author, Year		Usdan 2024					Clinicaltrials.gov	
Trial Phase		Phase II/III Booster #2 (Dose 4)*					Booster (4th Dose)†	
Subgroup (Years)		12-17	18-55		≥56		<2	>2-4
Arm		BNT162b2 (30 µg)	BNT162b2 (30 µg)	BNT162b2 (60 µg)	BNT162b2 (30 µg)	BNT162b2 (60 µg)	Booster	Booster
N (%)		107	309-310	110	300-301	101-102	15	10
Any Systemic Event	Dose 1	NR	NR	NR	NR	NR	4 (26.7)	2 (20)
Chills	Dose 1	23	22	27	12	23	NR	NR
Diarrhea	Dose 1	7	11	13	10	7	NR	NR
Fatigue	Dose 1	67	61	69	39	53	NR	NR
Fever	Dose 1	9	5	12	4	14	NR	NR
Headache	Dose 1	51	47	45	31	36	NR	NR
Joint Pain	Dose 1	12	15	25	12	15	NR	NR
Muscle Pain	Dose 1	26	30	42	18	23	NR	NR
Use of antipyretic medication	Dose 1	34	34	52	25	39	NR	NR
Nausea/Vomiting	Dose 1	3	2	2	1	3	NR	NR

N: total number, NR: not reported

*AEs reported ≤7 days

†AEs reported ≤28 days

Table D3.12. Comirnaty: Local Safety for Booster[120-122]

Vaccine		Comirnaty					
NCT		NCT04955626		NCT04816643	NCT05543616		
Author, Year		Moreira 2022		Simoes 2023	Sher 2024		
Trial Phase		Phase II/III Booster #1 (Dose 3)*‡		Phase III Booster #1 (Dose 3)†	Phase III OL Booster #2 (Dose 4)*		
Subgroup		≥16 Yrs		5-11 Yrs	6 Mo - <2 Yrs	2-5 Yrs	5 - <12 Yrs
Arm		BNT162b2 (30 µg)*	Placebo	BNT162b2 (10 µg)	BNT162b2 (3 µg)	BNT162b2 (3 µg)	BNT162b2 (10 µg)
N (%)		5,055	5,020	371	90-92	218	111
Axillary Swelling	Dose 1	13 (0.3)	1 (<0.1)	NR	NR	NR	NR
Erythema	Dose 1	22 (0.4)	0	NR	NR	NR	NR
Lymphadenopathy	Dose 1	135 (2.7)	2 (<0.1)	NR	NR	NR	NR
Pain	Dose 1	135 (2.7)	15 (0.3)	NR	NR	NR	NR
Pain at injection site	Dose 1	651 (12.9)	78 (1.6)	274 (74)	NR	30	64
Redness	Dose 1	NR	NR	59 (16)	8	6	7
Swelling	Dose 1	21 (0.4)	1 (<0.1)	59 (16)	5	4	5
Tenderness	Dose 1	NR	NR	NR	12	NR	NR

mo: months, N: total number, NR: not reported, yrs: years

*AEs reported ≤7 days

†AEs reported <1st month of admin

‡Back calculated N's

Table D3.13. Comirnaty: Local Safety for Booster Trials[123,124]

Vaccine		Comirnaty						
NCT		NCT05472038					NCT06130410	
Author, Year		Usdan 2024					Clinicaltrials.gov	
Trial Phase		Phase II/III Booster #2 (Dose 4)*					Booster (4th Dose)†	
Subgroup (Years)		12-17	18-55		≥56		<2	>2-4
Arm		BNT162b2 (30 µg)	BNT162b2 (30 µg)	BNT162b2 (60 µg)	BNT162b2 (30 µg)	BNT162b2 (60 µg)	Booster	Booster
N (%)		107	309-310	110	300-301	101-102	15	10
Any Local AR	Dose 1	NR	NR	NR	NR	NR	5 (33.3)	7 (70.0)
Pain at Injection Site	Dose 1	70	76	94	57	71	NR	NR
Redness	Dose 1	6	6	11	4	7	NR	NR
Swelling	Dose 1	7	7	15	3	9	NR	NR

N: total number, NR: not reported

*AEs reported ≤7 days

†AEs reported ≤28 days

Spikevax

Table D3.14. Spikevax: Overall Safety for Pivotal Phase II and III Trials[55,56]

Vaccine			Spikevax							
NCT			NCT04649151		NCT04470427					
Author, Year			Ali 2020		Sahly 2021					
Trial Phase			Pivotal Phase II-III		Pivotal Phase III					
Subgroup			12-17 Yrs		Overall		≥18 - <65 Yrs		≥65 Yrs	
Arm			mRNA-1273 (30 µg)	Placebo	mRNA-1273 (100 µg)	Placebo	mRNA-1273 (100 µg)	Placebo	mRNA-1273 (100 µg)	Placebo
N			2,482	1,238	15,166	15,151	11,406	11,402	3,760	3,749
Any Solicited AR	Overall	Dose 1	2381 (95.9)	806 (65.1)	13317 (87.8)	7285 (48.1)	10262 (90)	5737 (50.3)	3055 (81.3)	1548 (41.3)
		Dose 2	2405 (97.1)	680 (55.7)	13556 (92.3)	6255 (42.9)	10252 (93.2)	4921 (45.0)	3304 (89.5)	1334 (36.6)

Vaccine		Spikevax							
NCT		NCT04649151		NCT04470427					
Author, Year		Ali 2020		Sahly 2021					
Trial Phase		Pivotal Phase II-III		Pivotal Phase III					
Subgroup		12-17 Yrs		Overall		≥18 - <65 Yrs		≥65 Yrs	
Arm		mRNA-1273 (30 µg)	Placebo	mRNA-1273 (100 µg)	Placebo	mRNA-1273 (100 µg)	Placebo	mRNA-1273 (100 µg)	Placebo
N		2,482	1,238	15,166	15,151	11,406	11,402	3,760	3,749
AE	Related	19 (0.8)*	5 (0.4)	NR	NR	NR	NR	NR	NR
SAEs	Any	0	0	NR	NR	NR	NR	NR	NR
	Related	0	0	NR	NR	NR	NR	NR	NR
AESI	Any	0	0	NR	NR	NR	NR	NR	NR
Death		0	0	16 (0.1)‡	16 (0.1)	NR	NR	NR	NR

AE: adverse event, AESI: adverse event of special interest, AR: adverse report, N: total number, NR: not reported, SAEs: serious adverse event, yrs: years

*Unsolicited adverse events that were medically attended and considered related to study vaccine, none led to discontinuation

†Special interest of MIS-C (multisystem inflammatory syndrome in children)

‡Not related to vaccine

Table D3.15. Spikevax: Overall Safety for Pivotal Phase II and III Trials[57,58]

Vaccine		Spikevax					
NCT		NCT04796896					
Author, Year		Anderson 2022*				Creech 2022*	
Trial Phase		Phase II-III				Phase II-III	
Subgroup		2-5 Yrs		6 to 23 Months		6-11 Yrs	
Arm		mRNA-1273 (25 µg)	Placebo	mRNA-1273 (25 µg)	Placebo	mRNA-1273 (50 µg)	Placebo
N		2,938	959	1,596	526	3,004	993
Any Solicited AR	Dose 1	2332 (78.9)	641 (66.1)	1469 (84.1)	460 (79)	2868 (95.5)	681 (68.6)
	Dose 2	2478 (84.3)	603 (62.9)	1329 (83.3)	381 (72.4)	2899 (97)	646 (66.7)
SAEs	Any	0	0	0	0	NR	NR
	Related	NR	NR	NR	NR	0	0

Vaccine		Spikevax					
NCT		NCT04796896					
Author, Year		Anderson 2022*				Creech 2022*	
Trial Phase		Phase II-III				Phase II-III	
Subgroup		2-5 Yrs		6 to 23 Months		6-11 Yrs	
Arm		mRNA-1273 (25 µg)	Placebo	mRNA-1273 (25 µg)	Placebo	mRNA-1273 (50 µg)	Placebo
N		2,938	959	1,596	526	3,004	993
AESI	Any	5 (0.2)	1 (<0.1)	3 (0.2)	0	3 (<0.1)	2 (0.2)
Death		0	0	0	0	0	0

AESI: adverse event of special interest, AR: adverse report, N: total number, NR: not reported, SAEs: serious adverse event, yrs: years

*Solicited adverse events

Table D3.16. Spikevax: Systemic Safety for Pivotal Phase II and III Trials [55,56]

Vaccine		Spikevax							
NCT		NCT04649151		NCT04470427					
Author, Year		Ali 2020		Sahly 2021					
Trial Phase		Pivotal Phase II-III		Pivotal Phase III					
Subgroup (Years)		12-17		Overall		≥18 - <65		≥65	
Arm		mRNA-1273 (30 µg)	Placebo	mRNA-1273 (100 µg)	Placebo	mRNA-1273 (100 µg)	Placebo	mRNA-1273 (100 µg)	Placebo
N	Dose 1	2,482	1,238	15,166	15,151	11,406	11,402	3,760	3,749
	Dose 2	2,478	1,220	14,691	14,578	11,000	10,929	3,691	3,649
Any Systemic Event	Dose 1	1701 (68.5)	687 (55.5)	8316 (54.8)	6397 (42.2)	6499 (57)	5063 (44.4)	1817 (48.3)	1334 (35.6)
	Dose 2	2134 (86.1)	561 (46)	11678 (79.5)	5343 (36.7)	9023 (82)	4208 (38.5)	2655 (71.9)	1135 (31)
Arthralgia	Dose 1	371 (15)	143 (11.6)	2510 (16.6)	1784 (11.8)	1892 (16.6)	1327 (11.6)	618 (16.4)	457 (12.2)
	Dose 2	716 (28.9)	113 (9.3)	6303 (42.9)	1579 (10.8)	5010 (45.6)	1180 (10.8)	1293 (35.1)	399 (10.9)
Chills	Dose 1	456 (18.4)	138 (11.1)	1251 (8.3)	878 (5.8)	1050 (9.2)	730 (6.4)	201 (5.3)	148 (4)
	Dose 2	1066 (43)	97 (8)	6500 (44.3)	813 (5.6)	5357 (48.7)	662 (6.1)	1143 (31)	151 (4.1)
Fatigue	Dose 1	1188 (47.9)	453 (36.6)	5636 (37.2)	4133 (27.3)	4385 (38.5)	3281 (28.8)	1251 (33.3)	852 (22.7)

Vaccine		Spikevax							
NCT		NCT04649151		NCT04470427					
Author, Year		Ali 2020		Sahly 2021					
Trial Phase		Pivotal Phase II-III		Pivotal Phase III					
Subgroup (Years)		12-17		Overall		≥18 - <65		≥65	
Arm		mRNA-1273 (30 µg)	Placebo	mRNA-1273 (100 µg)	Placebo	mRNA-1273 (100 µg)	Placebo	mRNA-1273 (100 µg)	Placebo
N	Dose 1	2,482	1,238	15,166	15,151	11,406	11,402	3,760	3,749
	Dose 2	2,478	1,220	14,691	14,578	11,000	10,929	3,691	3,649
	Dose 2	1679 (67.8)	353 (28.9)	9607 (65.4)	3418 (23.5)	7453 (67.8)	2701 (24.7)	2154 (58.4)	717 (19.6)
Fever	Dose 1	63 (2.5)	12 (1)	112 (0.7)	44 (0.3)	102 (0.9)	37 (0.3)	10 (0.3)	7 (0.2)
	Dose 2	302 (12.2)	12 (1)	2276 (15.5)	43 (0.3)	1909 (17.4)	38 (0.3)	367 (9.9)	5 (0.1)
Headache	Dose 1	1106 (44.6)	477 (38.5)	4950 (32.6)	4026 (26.6)	4028 (35.3)	3303 (29)	922 (24.5)	723 (19.3)
	Dose 2	1739 (70.2)	370 (30.3)	8637 (58.8)	3427 (23.5)	6929 (63)	2775 (25.4)	1708 (46.3)	652 (17.9)
Myalgia	Dose 1	668 (26.9)	205 (16.6)	3442 (22.7)	2069 (13.7)	2700 (23.7)	1625 (14.3)	742 (19.7)	444 (11.9)
	Dose 2	1154 (46.6)	153 (12.5)	8529 (58.1)	1824 (12.5)	6789 (61.7)	1425 (13)	1740 (47.2)	399 (10.9)
Nausea/Vomiting	Dose 1	281 (11.3)	110 (8.9)	1262 (8.3)	1075 (7.1)	1068 (9.4)	908 (8)	194 (5.2)	167 (4.5)
	Dose 2	591 (23.9)	106 (8.7)	2794 (19)	941 (6.5)	2355 (21.4)	807 (7.4)	439 (11.9)	134 (3.7)

N: total number

Table D3.17. Spikevax: Systemic Safety for Pivotal Phase II and III Trials[57,58]

Vaccine		Spikevax							
NCT		NCT04796896							
Author, Year		Anderson 2022						Creech 2022	
Trial Phase		Phase II-III						Phase II-III	
Subgroup		24-36 Mo		37 Mo-5 Yrs		6 to 23 Mo		6-11 Yrs	
Arm		mRNA-1273 (25 µg)	Placebo	mRNA-1273 (25 µg)	Placebo	mRNA-1273 (25 µg)	Placebo	mRNA-1273 (50 µg)	Placebo
N	Dose 1	942	320	2,013	650	1,746	582	3,004	993
	Dose 2	963	330	1,975	629	1,596	526	2,988	969
Any Systemic Event	Dose 1	612 (65)	198 (61.9)	983 (48.8)	290 (44.6)	1334 (76.4)	421 (72.3)	1740 (57.9)	518 (52.2)
	Dose 2	651 (67.6)	194 (58.8)	1163 (58.9)	234 (37.2)	1174 (73.6)	350 (66.5)	2335 (78.1)	485 (50.1)
Arthralgia	Dose 1	NR	NR	124 (6.2)	32 (4.9)	NR	NR	260 (8.7)	75 (7.6)
	Dose 2	NR	NR	168 (8.5)	28 (4.5)	NR	NR	482 (16.1)	84 (8.7)
Chills	Dose 1	NR	NR	129 (6.4)	40 (6.2)	NR	NR	309 (10.3)	67 (6.7)
	Dose 2	NR	NR	245 (12.4)	31 (4.9)	NR	NR	904 (30.3)	74 (7.6)
Decreased Appetite	Dose 1	225 (23.9)*	71 (22.3)*	NR	NR	524 (30.2)*	152 (26.2)*	NR	NR
	Dose 2	294 (30.5)*	69 (20.9)*	NR	NR	510 (32.1)*	132 (25.1)*	NR	NR
Fatigue	Dose 1	NR	NR	807 (40.1)	236 (36.3)	NR	NR	1298 (43.2)	334 (33.6)
	Dose 2	NR	NR	956 (48.4)	185 (29.4)	NR	NR	1925 (64.5)	335 (34.6)
Fever	Dose 1	106 (11.3)	25 (7.8)	155 (7.7)	33 (5.1)	191 (11)	49 (8.4)	99 (3.3)	15 (1.5)
	Dose 2	182 (18.9)	35 (10.6)	316 (16)	28 (4.5)	232 (14.6)	44 (8.4)	714 (23.9)	19 (2)
Headache	Dose 1	NR	NR	231 (11.5)	78 (12)	NR	NR	938 (31.2)	306 (30.8)
	Dose 2	NR	NR	310 (15.7)	51 (8.1)	NR	NR	1622 (54.3)	275 (28.4)
Irritability	Dose 1	513 (54.5)†	163 (51.1)†	NR	NR	1175 (67.6)†	361 (62.1)†	NR	NR
	Dose 2	523 (54.3)†	148 (44.8)†	NR	NR	1021 (64.3)†	307 (58.5)†	NR	NR
Myalgia	Dose 1	NR	NR	200 (9.9)	60 (9.2)	NR	NR	438 (14.6)	96 (9.7)
	Dose 2	NR	NR	310 (15.7)	47 (7.5)	NR	NR	843 (28.2)	105 (10.8)
Sleepiness	Dose 1	285 (30.3)	92 (28.8)	NR	NR	645 (37.1)	217 (37.3)	NR	NR
	Dose 2	347 (36)	89 (27)	NR	NR	558 (35.1)	175 (33.3)	NR	NR

Vaccine		Spikevax							
NCT		NCT04796896							
Author, Year		Anderson 2022						Creech 2022	
Trial Phase		Phase II-III						Phase II-III	
Subgroup		24-36 Mo		37 Mo-5 Yrs		6 to 23 Mo		6-11 Yrs	
Arm		mRNA-1273 (25 µg)	Placebo	mRNA-1273 (25 µg)	Placebo	mRNA-1273 (25 µg)	Placebo	mRNA-1273 (50 µg)	Placebo
N	Dose 1	942	320	2,013	650	1,746	582	3,004	993
	Dose 2	963	330	1,975	629	1,596	526	2,988	969
Nausea/Vomiting	Dose 1	NR	NR	137 (6.8)	50 (7.7)	NR	NR	325 (10.8)	107 (10.8)
	Dose 2	NR	NR	194 (9.8)	30 (4.8)	NR	NR	716 (24)	97 (10)

mo: months, N: total number, NR: not reported, yrs: years

*Loss of appetite

†Irritability/crying

Table D3.18. Spikevax: Local Safety for Pivotal Phase II and III Trials[55,56]

Vaccine		Spikevax							
NCT		NCT04649151		NCT04470427					
Author, Year		Ali 2020		Sahly 2021					
Trial Phase		Pivotal Phase II-III		Pivotal Phase III					
Subgroup (Years)		12-17		Overall		≥18 - <65		≥65	
Arm		Spikevax (30 µg)	Placebo	Spikevax (100 µg)	Placebo	Spikevax (100 µg)	Placebo	Spikevax (100 µg)	Placebo
N	Dose 1	2,482	1,238	15,166	15,151	11,406	11,402	3,760	3,749
	Dose 2	2,478	1,220	14,691	14,578	11,000	10,929	3,691	3,649
Any Local AR	Dose 1	2339 (94.2)	455 (36.8)	12765 (84.2)	3009 (19.9)	9961 (87.4)	2436 (21.4)	2804 (74.6)	573 (15.3)
	Dose 2	2314 (93.4)	398 (32.6)	13029 (88.7)	2757 (18.9)	9936 (90.3)	2262 (20.7)	3093 (83.8)	495 (13.6)
Axillary Swelling	Dose 1	578 (23.3)	101 (8.2)	1553 (10.2)	722 (4.8)	1322 (11.6)	567 (5)	231 (6.1)	155 (4.1)
	Dose 2	519 (21)	61 (5)	2092 (14.2)	571 (3.9)	1777 (16.2)	474 (4.3)	315 (8.5)	97 (2.7)
Erythema / Redness	Dose 1	334 (13.5)	8 (0.6)	445 (2.9)	77 (0.5)	354 (3.1)	54 (0.5)	91 (2.4)	23 (0.6)
	Dose 2	484 (19.5)	11 (0.9)	1274 (8.7)	68 (0.5)	989 (9)	53 (0.5)	285 (7.7)	15 (0.4)

Vaccine		Spikevax							
NCT		NCT04649151		NCT04470427					
Author, Year		Ali 2020		Sahly 2021					
Trial Phase		Pivotal Phase II-III		Pivotal Phase III					
Subgroup (Years)		12-17		Overall		≥18 - <65		≥65	
Arm		Spikevax (30 µg)	Placebo	Spikevax (100 µg)	Placebo	Spikevax (100 µg)	Placebo	Spikevax (100 µg)	Placebo
N	Dose 1	2,482	1,238	15,166	15,151	11,406	11,402	3,760	3,749
	Dose 2	2,478	1,220	14,691	14,578	11,000	10,929	3,691	3,649
Lymphadenopathy	Dose 1	108 (4.3)*	5 (0.4)	NR	NR	NR	NR	NR	NR
Pain at Injection Site	Dose 1	2310 (93.1)	431 (34.8)	12688 (83.7)	2665 (17.6)	9908 (86.9)	2183 (19.1)	2780 (73.9)	482 (12.9)
	Dose 2	2290 (92.4)	370 (30.3)	12964 (88.3)	2486 (17.1)	9893 (89.9)	2048 (18.7)	3071 (83.2)	438 (12)
Swelling	Dose 1	403 (16.2)	12 (1)	935 (6.2)	65 (0.4)	766 (6.7)	42 (0.4)	169 (4.5)	23 (0.6)
	Dose 2	509 (20.5)	12 (1)	1807 (12.3)	60 (0.4)	1399 (12.7)	46 (0.4)	408 (11.1)	14 (0.4)

AR: adverse report, N: total number, NR: not reported

*Unsolicited AE up to 28 days after any injection

Table D3.19. Spikevax: Local Safety for Pivotal Phase II and III Trials[57,58]

Vaccine		Spikevax					
NCT		NCT04796896					
Author, Year		Anderson 2022				Creech 2022	
Trial Phase		Phase II-III				Phase II-III	
Subgroup		2-5 Yrs		6 to 23 Mo		6-11 Yrs	
Arm		mRNA-1273 (25 µg)	Placebo	mRNA-1273 (25 µg)	Placebo	mRNA-1273 (50 µg)	Placebo
N	Dose 1	2,957	970	1,746	582	3,004	993
	Dose 2	2,938	959	1,596	526	2,988	969
Any Local AR	Dose 1	1874 (63.4)	407 (42)	775 (44.4)	193 (33.2)	2814 (93.7)	480 (48.3)
	Dose 2	2157 (73.4)	404 (42.1)	868 (54.4)	159 (30.2)	2849 (95.3)	490 (50.6)
Axillary Swelling	Dose 1	205 (6.9)	56 (5.8)	102 (5.9)	26 (4.5)	465 (15.5)	84 (8.5)
	Dose 2	267 (9.1)	31 (3.2)	148 (9.3)	28 (5.3)	537 (18)	65 (6.7)

Vaccine		Spikevax					
NCT		NCT04796896					
Author, Year		Anderson 2022				Creech 2022	
Trial Phase		Phase II-III				Phase II-III	
Subgroup		2-5 Yrs		6 to 23 Mo		6-11 Yrs	
Arm		mRNA-1273 (25 µg)	Placebo	mRNA-1273 (25 µg)	Placebo	mRNA-1273 (50 µg)	Placebo
N	Dose 1	2,957	970	1,746	582	3,004	993
	Dose 2	2,938	959	1,596	526	2,988	969
Erythema/Redness	Dose 1	164 (5.5)	14 (1.4)	150 (8.6)	24 (4.1)	349 (11.9)	13 (1.3)
	Dose 2	259 (8.8)	15 (1.6)	215 (13.5)	20 (3.8)	559 (18.7)	10 (1)
Lymphadenopathy	Dose 1	NR	NR	NR	NR	480 (16)*	90 (9)*
	Dose 2	NR	NR	NR	NR	538 (18) *	68 (7)*
Pain at Injection Site	Dose 1	1813 (61.4)	382 (39.4)	652 (37.4)	175 (30.1)	2796 (93.1)	465 (46.8)
	Dose 2	2099 (71.4)	395 (41.2)	738 (46.2)	135 (25.7)	2832 (94.8)	480 (49.5)
Swelling	Dose 1	134 (4.5)	17 (1.8)	146 (8.4)	15 (2.6)	354 (11.8)	12 (1.2)
	Dose 2	240 (8.2)	11 (1.1)	243 (15.3)	11 (2.1)	507 (17)	12 (1.2)

AR: adverse report, mo: months, N: total number, NR: not reported, yrs: years

*Back calculated N's

Table D3.20. Spikevax: Overall Safety for Booster Trials[125-127]

Vaccine			Spikevax		
NCT			NCT04649151		
Author, Year			Figueroa 2024 (Part 1A & 1B)	Figueroa 2025 (Part 1C)	Figueroa 2025 (Part 3)
Trial Phase			Ongoing Phase II/III	OL Booster (Dose 3)	Phase III OL
Subgroup (Years)			12-17	12-17	12-17
Arm			mRNA-1273 (100 µg)[*]	mRNA-1273 (50 µg)[†]	mRNA-1273 (50 µg)[‡]
N			2,577	1,405	379
Solicited AEs			NR	1278 (94.6)[§]	229 (61)[#]
Unsolicited AEs Regardless of Relationship to Study Vaccination	All		1,427 (55.4)	209 (14.9)	49 (13)
	Serious		22 (0.9)	0	2 (1)
	Severe		50 (1.9)	4 (0.3)	3 (1)
	Fatal		0	0	0
	Medically-Attended		1,014 (39.3)	119 (8.5)	36 (9)
	Leading to Study Discontinuation		0	0	0
	Leading to Study Vaccine Discontinuation		3 (0.1)	0	NR
	AESI		13 (0.5)	NR	0
		MIS-C	0	0	0
		Other	13 (0.5)	NR	NR
		Myocarditis	0	0	0
Unsolicited AEs Related to Study Vaccination	All		391 (15.2)	59 (4.2)	14 (4)
	Serious		0	0	0
	Fatal		0	0	0
	Medically-Attended		29 (1.1)	2 (0.1)	7 (2)
	Leading to Study Discontinuation		0	0	0
	Leading to Study Vaccine Discontinuation		1 (<0.1)	0	NR
	Severe		15 (0.6)	3 (0.2)	1 (<1)
	AESI		NR	0	0
		Covid-19	0	NR	NR

Vaccine			Spikevax		
NCT			NCT04649151		
Author, Year			Figueroa 2024 (Part 1A & 1B)	Figueroa 2025 (Part 1C)	Figueroa 2025 (Part 3)
Trial Phase			Ongoing Phase II/III	OL Booster (Dose 3)	Phase III OL
Subgroup (Years)			12-17	12-17	12-17
Arm			mRNA-1273 (100 µg)*	mRNA-1273 (50 µg)†	mRNA-1273 (50 µg)‡
N			2,577	1,405	379
		MIS-C	0	0	0
		Myocarditis	0	0	0
		Other	0	NR	NR

AE: adverse event, AESI: adverse event of special interest, N: total number, NR: not reported

*Total participants include 2486 who received mRNA-1273 and 91 who initially received placebo and then crossed over to receive mRNA-1273. Adverse events reported after injection 1 through Day 394.

†Participants were offered a homologous mRNA-1273 50-µg booster ≥5 months after receiving dose 2 of the mRNA-1273 primary series

‡Participants received two 50 µg doses of mRNA-1273.222 (ancestral strain Wuhan-Hu-1 and omicron subvariants BA.4 and BA.5), 6 months apart. TEAE reported up to 28 days after vaccination.

§N=1,351

#N=378

Table D3.21. Spikevax: Overall Safety for Booster Trials[128,129]

Vaccine			Spikevax			
NCT			NCT04470427		NCT04796896	
Author, Year			Baden 2024		Berthaud 2024	
Trial Phase			OL Booster (Part C)		Booster #1 (Dose 3)	
Subgroup (Years)			18+		6 Mo - 5 Yrs	6 - 11 Yrs
Arm			mRNA-1273 (100 µg)*	mRNA-1273 (100 µg)†	mRNA-1273 (10 µg)	mRNA-1273 (25 µg)
N			9,647	9,952	153	2,519
Unsolicited AEs Regardless of Relationship to Study Vaccination	All		3,303 (34.2)	3,140 (31.6)	39 (25.5)	374 (14.8)
	Serious		42 (0.4)	58 (0.6)	1 (0.7)	11 (0.4)
	Severe		NR	NR	0	17 (0.7)
	Fatal		1 (<0.1)	5 (<0.1)	0	0
	Medically-Attended		940 (9.7)	1004 (10.1)	87 (56.9)	1053 (41.8)
	Leading to Study Discontinuation		1 (<0.1)	5 (<0.1)	0	0
	AESI		NR	NR	2 (1.3)	12 (0.5)
		MIS-C	NR	NR	0	0
		Myocarditis	NR	NR	0	0
Unsolicited AEs Related to Study Vaccination	All		2,424 (25.1)	2,173 (21.8)	5 (3.3)	83 (3.3)
	Serious		3 (<0.1)	1 (<0.1)	0	0
	Fatal		0	0	0	0
	Medically-Attended		107 (1.1)	99 (1)	0	20 (0.8)
	Leading to Study Discontinuation		0	0	0	0
	Severe		37 (0.4)	28 (0.3)	0	8 (0.3)
	AESI		NR	NR	0	0
		MIS-C	NR	NR	0	0
		Myocarditis	1‡	NR	0	0

AE: adverse event, AESI: adverse event of special interest, mo: months, N: total number, NR: not reported, yrs: years

*Adverse events reported ≤28 days after booster

†Offered participants an opportunity to receive the primary series (if they received placebo in Part A).

‡Occurred on day 1 post-booster and resolved at day 72

Table D3.22. Spikevax: Systemic Safety for Booster Trials[125,127-129]

Vaccine		Spikevax						
NCT		NCT04470427		NCT04649151		NCT04796896		
Author, year		Baden 2024		Figueroa 2025 (Part 1C)	Figueroa 2025 (Part 3) §	Berthaud 2024		
Trial Phase		OL Booster (Part C)		OL Booster (Dose 3)	Phase III OL	Booster #1 (Dose 3)		
Subgroup		≥18 Yrs		12-17 Yrs	12-17 Yrs	6-23 Mo	2-5 Yrs	6-11 Yrs
Arm		mRNA-1273 (100 µg)*	mRNA-1273 (100 µg)†	mRNA-1273 (50 µg) ‡	mRNA-1273 (50 µg)	10 µg Booster	10 µg Booster	25 µg Booster
N (%)		9,647	9,952	1,351	378	122	31	2,487
Any Systemic Event	Dose 1	NR	NR	1027 *(76)*	150 (40)	97 (63.4)		1523 (61.3)
Arthralgia	Dose 1	NR	NR	324 *(24)*	38 *(10)*	NR	2 *(8)*	274 *(11)*
Chills	Dose 1	327 (3.4)	242 (2.4)	405 *(30)*	19 *(5)*	NR	2 *(8)*	299 *(12)*
Loss of Appetite	Dose 1	NR	NR	NR	NR	32 *(26)*	5 (17)	NR
Sleepiness	Dose 1	NR	NR	NR	NR	34 (28)	10 *(33)*	NR
Fatigue	Dose 1	694 (7.2)	630 (6.3)	783 *(58)*	46 (12)	NR	10 *(32)*	1129 (45.4)
Fever	Dose 1	304 (3.2)	188 (1.9)	81 *(6)*	30 *(8)*	13 *(11)*	1 *(3)*	174 *(7)*
Headache	Dose 1	486 (5.0)	419 (4.2)	757 *(56)*	104 (28)	NR	6 *(20)*	895 (36)
Irritability/Crying	Dose 1	NR	NR	NR	NR	63 *(52)*	21 *(67)*	NR
Myalgia	Dose 1	279 (2.9)	215 (2.2)	540 *(40)*	59 (16)	NR	4 *(12)*	472 *(19)*
Myocarditis	Dose 1	1 (<0.1)	0	NR	NR	NR	NR	NR
Nausea/Vomiting	Dose 1	NR	NR	230 *(17)*	19 *(5)*	NR	1 *(4)*	298 *(12)*

mo: months, N: total number, NR: not reported, yrs: years

*Adverse events reported ≤28 days after booster

†Offered participants an opportunity to receive the primary series (if they received placebo in Part A).

‡Participants were offered a homologous mRNA-1273 50-µg booster ≥5 months after receiving dose 2 of the mRNA-1273 primary series. Adverse events reported ≤7 days.

§Participants received two 50 µg doses of mRNA-1273.222 (ancestral strain Wuhan-Hu-1 and omicron subvariants BA.4 and BA.5), 6 months apart. TEAE reported up to 28 days after vaccination.

Note: Italicized data are digitized and N's are back calculated

Table D3.23. Spikevax: Local Safety for Booster Trials[125,127-129]

Vaccine		Spikevax						
NCT		NCT04470427		NCT04649151		NCT04796896		
Author, year		Baden 2024		Figueroa 2025 (Part 1C)	Figueroa 2025 (Part 3) §	Berthaud 2024		
Trial Phase		OL Booster (Part C)		OL Booster (Dose 3)	Phase III OL	Booster #1 (Dose 3)		
Subgroup		≥18 Yrs		12-17 Yrs	12-17 Yrs	6-23 Mo	2-5 Yrs	6-11 Yrs
Arm		mRNA-1273 (100 µg)*	mRNA-1273 (100 µg)†	mRNA-1273 (50 µg)‡	mRNA-1273 (50 µg)	10 µg Booster	10 µg Booster	25 µg Booster
N (%)		9,647	9,952	1,351	378	122	31	2,487
Any Local AR	Dose 1	NR	NR	*92*	169 (45)	75 (49)		2,243 (90.3)
Axillary Swelling	Dose 1	NR	NR	*28*	43 (11)	6 *(5)*	1 *(3)*	622 *(25)*
Erythema	Dose 1	NR	NR	*9*	11 *(3)*	13 *(11)*	1 *(3)*	249 (10)
Pain	Dose 1	362 (3.8)	277 (2.8)	*90*	161 (43)	50 *(39)*	18 *(58)*	2221 *(89.3)*
Pain at injection site	Dose 1	1,330 (13.8)	1,247 (12.5)	NR	NR	NR	NR	NR
Swelling	Dose 1	NR	NR	*13*	11 *(3)*	15 *(12)*	3 *(9)*	249 (10)

mo: months, N: total number, NR: not reported, yrs: years

*Adverse events reported ≤28 days after booster

†Offered participants an opportunity to receive the primary series (if they received placebo in Part A).

‡Participants were offered a homologous mRNA-1273 50-µg booster ≥5 months after receiving dose 2 of the mRNA-1273 primary series. Adverse events reported ≤7 days.

§Participants received two 50 µg doses of mRNA-1273.222 (ancestral strain Wuhan-Hu-1 and omicron subvariants BA.4 and BA.5), 6 months apart. TEAE reported up to 28 days after vaccination.

Italicized data are digitized and N's are back calculated

mNexspike

Table D3.24. mNexspike: Overall Safety for Pivotal Phase III Trials[59,84]

Vaccine		mNexspike vs. Spikevax			
NCT				NCT05397223	
Author, Year		Chalkias. Lancet. 2025		Grassi 2026	
Trial Phase		Pivotal Phase III		Phase III	
Subgroup (Years)		12+		12+ (Japan Only)	
Arm		mRNA-1283.222 (10 µg)	mRNA-1273.222 (50 µg)	mRNA-1283.815 (10 µg)	mRNA-1273.815 (50 µg)
N		5,701	5,705	343	346
Any Solicited AR	Dose 1	4571 (80.2)	4781 (83.8)	307 (89.5)	331 (95.7)
SAEs	Any	NR	NR	0	0
AEs Leading to Withdrawal/Discontinuation	Any	3 (<0.1)	2 (<0.1)	0	0
	Related	NR	NR	0	0
	Serious	NR	NR	0	0
	Severe	NR	NR	0	0
	Life-Threatening	NR	NR	0	0
Vaccine Discontinuation	TEAE	NR	NR	0	0
	Treatment-Related TEAE	NR	NR	0	0
AESI	Any	3 (0.05)*	6 (0.1)	0	0
	Related	1 (0.02)	0	NR	NR
Death		5 (0.1)	10 (0.2)	0	0

AESI: adverse event of special interest, AR: adverse report, N: total number, NR: not reported, SAEs: serious adverse event

*Unsolicited adverse event

Table D3.25. mNexspike: Systemic Safety for Pivotal Phase III Trials[59,84]

Vaccine	mNexspike vs. Spikevax

NCT				NCT05397223	
Author, Year		Chalkias. Lancet. 2025		Grassi 2026	
Trial Phase		Pivotal Phase III		Phase III	
Subgroup (Years)		12+		12+ (Japan Only)	
Arm		mRNA-1283.222 (10 µg)	mRNA-1273.222 (50 µg)	mRNA-1283.815 (10 µg)	mRNA-1273.815 (50 µg)
N	Dose 1	5,701	5,705	343	346
Any Systemic Event	Dose 1	3672 (64.4)	3664 (64.2)	*59.6*	*76.6*
Arthralgia	Dose 1	1696 (29.7)	1577 (27.6)	*31.7*	*35.8*
Chills	Dose 1	1293 (22.7)	1127 (19.8)	*20.8*	*31.2*
Fatigue	Dose 1	2876 (50.4)	2798 (49)	*51.2*	*63.7*
Fever	Dose 1	317 (5.6)	254 (4.5)	*7*	*12.7*
Headache	Dose 1	2519 (44.2)	2349 (41.2)	*42.4*	*56*
Myalgia	Dose 1	2178 (38.2)	2114 (37)	*34.9*	*39.9*
Nausea/Vomiting	Dose 1	691 (12.1)	625 (11)	*7.7*	*8.8*

N: total number

Note: Italicized data are digitized

Table D3.26. mNexspike: Local Safety for Pivotal Phase III Trials[59,84]

Vaccine	mNexspike vs. Spikevax	
NCT		NCT05397223
Author, Year	Chalkias. Lancet. 2025	Grassi 2026

Trial Phase		Pivotal Phase III		Phase III	
Subgroup (Years)		12+		12+ (Japan Only)	
Arm		mRNA-1283.222 (10 µg)	mRNA-1273.222 (50 µg)	mRNA-1283.815 (10 µg)	mRNA-1273.815 (50 µg)
N	Dose 1	5,701	5,705	343	346
Any Local AR	Dose 1	4007 (70.3)	4473 (78.4)	*86.4*	*95.2*
Axillary Swelling	Dose 1	1123 (19.7)*	1047 (18.4)*	*24.6*	*26.1*
Erythema / Redness	Dose 1	123 (2.2)	225 (3.9)	*4*	*11.2*
Pain at Injection Site	Dose 1	3905 (68.5)	4419 (77.5)	*85*	*94.7*
Swelling	Dose 1	206 (3.6)	359 (6.3)	*9.7*	*15*

AR: adverse report, N: Total number

*Axillary swelling or tenderness

Note: Italicized data are digitized

Table D3.27. mNexspike: Overall Safety for Booster Trial[116]

Vaccine		mNexspike					
NCT		NCT05137236					
Author, Year		Chalkias IDSA 2025					
Trial Phase		Phase II Part A Booster #1 (Dose 3)*					
Vaccine		mRNA-1283			mRNA-1283.211		mRNA- 1273
Arm		2.5 µg	5 µg	10 µg	5 µg	10 µg	50 µg
N		57	64	56	52	54	57
Unsolicited AEs Regardless of Relationship to Study Vaccination	All	13 (22.8)	9 (14.1)	12 (21.4)	13 (25.0)	7 (13.0)	9 (15.8)
	Serious	2 (3.5)	1 (1.6)	2 (3.6)	3 (5.8)	3 (5.6)	2 (3.5)
	Severe	2 (3.5)	1 (1.6)	3 (5.4)	3 (5.8)	1 (1.9)	0
	Fatal	0	0	0	0	0	0
	Medically-Attended	28 (49.1)	29 (45.3)	31 (55.4)	27 (51.9)	21 (38.9)	26 (45.6)
	Leading to Study Discontinuation	0	0	0	0	0	0
	AESI	2 (3.5)	1 (1.6)	0	0	0	0
Unsolicited AEs Related to Study Vaccination	All	5 (8.8)	0	1 (1.8)	2 (3.8)	2 (3.7)	1 (1.8)
	Serious	0	0	0	0	0	0

Vaccine			mNexspike					
NCT			NCT05137236					
Author, Year			Chalkias IDSA 2025					
Trial Phase			Phase II Part A Booster #1 (Dose 3)*					
Vaccine			mRNA-1283			mRNA-1283.211		mRNA- 1273
Arm			2.5 µg	5 µg	10 µg	5 µg	10 µg	50 µg
N			57	64	56	52	54	57
	Fatal		0	0	0	0	0	0
	Medically-Attended		0	0	0	0	0	1 (1.8)
	Leading to Study Discontinuation		0	0	0	0	0	0
	Severe		0	0	0	0	0	0
	AESI		0	0	0	0	0	0
		Myocarditis	0	0	0	0	0	0

AE: adverse event, AESI: adverse event of special interest, N: total number

*Adverse events reported ≤7 days

Table D3.28. mNexspike: Systemic Safety for Booster Trial[116]

Vaccine	mNexspike		
NCT	NCT05137236		
Author, year	Chalkias IDSA 2025		
Trial Phase	Phase II Part A Booster #1 (Dose 3)*		
Subgroup	mRNA-1283	mRNA-1283.211	mRNA-1273

Arm		2.5 µg	5 µg	10 µg	5 µg	10 µg	50 µg
N (%)		314†					
Arthralgia	Dose 1	*24*	*29*	*31*	*33*	*23*	*39*
Chills	Dose 1	*12*	*11*	*32*	*30*	*11*	*32*
Fatigue	Dose 1	*42*	*47*	*51*	*45*	*49*	*59*
Fever	Dose 1	*0*	*5*	*2*	*9*	*0*	*6*
Headache	Dose 1	*41*	*43*	*46*	*60*	*39*	*58*
Myalgia	Dose 1	*26*	*35*	*38*	*33*	*35*	*56*
Nausea/Vomiting	Dose 1	*8*	*13*	*10*	*15*	*5*	*29*

N: total number

*Adverse events reported ≤7 days

†The solicited safety set comprised 314 (92.4%) participants in part A

Note: Italicized data are digitized

Table D3.29. mNexspike: Local Safety for Booster Trial[116]

Vaccine	mNexspike					
NCT	NCT05137236					
Author, Year	Chalkias IDSA 2025					
Trial Phase	Phase II Part A Booster #1 (Dose 3)*					
Subgroup	mRNA-1283			mRNA-1283.211		mRNA-1273
Arm	2.5 µg	5 µg	10 µg	5 µg	10 µg	50 µg
N (%)	314†					

Axillary Swelling	**Dose 1**	*12*	*27*	*24*	*15*	*19*	*12*
Pain at Injection Site	**Dose 1**	*57*	*62*	*68*	*58*	*65*	*83*
Redness	**Dose 1**	*0*	*2*	*2*	*4*	*3*	*6*
Swelling	**Dose 1**	*0*	*6*	*4*	*2*	*3*	*10*

N: total number

*Adverse events reported ≤7 days

†The solicited safety set comprised 314 (92.4%) participants in part A

Note: Italicized data are digitized

Nuvaxovid

Table D3.30. Nuvaxovid: Overall Safety for Pivotal Phase III Trials[9,60,61,130]

Vaccine		**Nuvaxovid**							
NCT						**NCT04611802**			
Author, Year		**Heath 2021**		**Heath 2023**		**Dunkle 2021**		**Anez 2023**	
Trial Phase		**Pivotal Phase III**		**Phase III**		**Pivotal Phase III**		**Phase III**	
Subgroup (Years)		**18-84**		**18-84**		**18+**		**12-17**	
Arm		**NVX-CoV2373 (5 µg)**	**Placebo**	**NVX-CoV2373**	**Placebo**	**NVX-CoV2373 (5 µg)**	**Placebo**	**NVX-CoV2373 (5 µg)**	**Placebo**
N		**2,310***		**7,569**	**7,569**	**19,729‡**	**9,853**	**1,487#**	**745**
AEs	**Any**	25.3†	20.5†	2075 (27.4) †	1649 (21.8) †	3216 (16.3)	1456 (14.8)	236 (15.9)	116 (15.6)
	Related	NR	NR	880 (11.6)	369 (4.9)	798 (4)	239 (2.4)	43 (2.9)	7 (0.9)
	Severe	1	0.8	88 (1.2)	87 (1.1)	244 (1.2)	106 (1.1)	6 (0.4)	2 (0.3)
	Severe Related	NR	NR	15 (0.2)	5 (<0.1)	55 (0.3)	10 (0.1)	0	0
SAEs	**Any**	NR	NR	59 (0.8)	61 (0.8)	169 (0.9)	94 (1)	7 (0.5)	2 (0.3)
	Related	0.5	0.5	NR	NR	NR	NR	NR	NR
AEs Leading to Withdrawal / Discontinuation	**Any**	NR	NR	18 (0.2)	13 (0.2)	60 (0.3)	13 (0.1)	0	0
	Related	NR	NR	3 (<0.1)	1 (<0.1)	14 (0.1)	2 (<0.1)	0	0
MAAE	**Any**	NR	NR	355 (4.7)	336 (4.4)	1387 (7)	651 (6.6)	96 (6.5)	51 (6.8)
	Related	NR	NR	36 (0.5)	17 (0.2)	88 (0.4)	30 (0.3)	5 (0.3)	3 (0.4)

Vaccine		Nuvaxovid							
NCT						NCT04611802			
Author, Year		Heath 2021		Heath 2023		Dunkle 2021		Anez 2023	
Trial Phase		Pivotal Phase III		Phase III		Pivotal Phase III		Phase III	
Subgroup (Years)		18-84		18-84		18+		12-17	
Arm		NVX-CoV2373 (5 µg)	Placebo	NVX-CoV2373	Placebo	NVX-CoV2373 (5 µg)	Placebo	NVX-CoV2373 (5 µg)	Placebo
N		2,310*		7,569	7,569	19,729‡	9,853	1,487#	745
	Serious Related	NR	NR			5 (<0.1)	0	0	0
Vaccine Discontinuation	TEAE	0.3	0.3	23 (0.3)	28 (0.4)	57 (0.3)	16 (0.2)	1 (<0.1)	1 (0.1)
	Treatment-Related TEAE	NR	NR	7 (<0.1)	8 (0.1)	10 (0.1)	3 (<0.1)	0	0
AESI	Any	0.1	0.3	NR	NR	NR	NR	NR	NR
	Any PIMMC	NR	NR	6 (<0.1)	9 (0.1)	16 (0.1)	3 (<0.1)	0	0
	Treatment Related to PIMMC	NR	NR	NR	NR	10 (0.1)	1 (<0.1)	0	0
	Relevant to Covid-19	NR	NR	12 (0.2)§	35 (0.5)	4 (<0.1)	4 (<0.1)	0	0
	Treatment-Related to Covid-19	NR	NR	NR	NR	0	0	0	0
Death		1	1	4	3	9 (0.5)	5 (0.5)	0	0

AE: adverse event, AESI: adverse event of special interest, AR: adverse report, MAAE: medically attended adverse event, N: total number, NR: not reported, PIMMC: potentially immune-mediated medical conditions, SAEs: serious adverse event, TEAE; treatment emergent adverse event

*Solicited AE safety population

†Unsolicited adverse events

‡Safety population received both dose 1, dose 2, or both

§None considered related to study vaccine

#Safety analysis set

Table D3.31. Nuvaxovid: Systemic Safety for Pivotal Phase III Trials[9,60,61]

Vaccine		Nuvaxovid					
NCT				NCT04611802			
Author, Year		Heath 2021		Dunkle 2021		Anez 2023	
Trial Phase		Pivotal Phase III		Pivotal Phase III		Phase III	
Subgroup (Years)		18-84		18+		12-17	
Arm		NVX-CoV2373 (5 µg)	Placebo	NVX-CoV2373 (5 µg)	Placebo	NVX-CoV2373 (5 µg)	Placebo
N	Dose 1	2,310*		19,729	9,853	1,487‡	745
	Dose 2			19,104	9,422	NA	NA
Any Systemic Event	Dose 1	45.7	36.3	8614 (47.66)	3562 (40)	800 (55.2)	296 (40.8)
	Dose 2	64	30	11906 (69.47)	2969 (35.87)	1038 (74.5)	198 (28.9)
Fatigue	Dose 1	19.4	17	4632 (25.63)	1993 (22.38)	350 (24.2)	113 (15.6)
	Dose 2	40.3	15	8486 (49.51)	1811 (21.88)	695 (49.9)	100 (14.6)
Fever	Dose 1	2†	1†	66 (0.37)	33 (0.37)	11 (0.8)	5 (0.7)
	Dose 2	4.8†	1†	973 (5.68)	23 (0.28)	235 (16.9)	1 (0.1)
Headache	Dose 1	24.5	21	4505 (24.93)	2028 (22.78)	440 (30.4)	181 (24.9)
	Dose 2	40	18	7618 (44.45)	1625 (19.63)	793 (56.9)	119 (17.3)
Joint Pain	Dose 1	6	5	1388 (7.68)	590 (6.63)	102 (7)	35 (4.8)
	Dose 2	16.8	4.8	3809 (22.22)	567 (6.85)	226 (16.2)	21 (3.1)
Malaise	Dose 1	11	8	2660 (14.72)	1037 (11.65)	215 (14.8)	67 (9.2)
	Dose 2	30	8	6674 (38.94)	1018 (12.3)	560 (40.2)	51 (7.4)
Muscle Pain	Dose 1	21.4	13	4102 (22.7)	1188 (13.34)	492 (34)	114 (15.7)
	Dose 2	40.3	9	8240 (48.08)	1001 (12.09)	683 (49)	82 (12)
Nausea/Vomiting	Dose 1	5	5.5	1152 (6.37)	488 (5.48)	113 (7.8)	56 (7.7)
	Dose 2	10.5	3	3	3	277 (19.9)	33 (4.8)

N: total number

*Solicited AE safety population

†Elevated temperature

‡Safety analysis set

Table D3.32. Nuvaxovid: Local Safety for Pivotal Phase III Trials[9,60,61]

Vaccine		Nuvaxovid					
NCT				NCT04611802			
Author, Year		Heath 2021		Dunkle 2021		Anez 2023	
Trial Phase		Pivotal Phase III		Pivotal Phase III		Phase III	
Subgroup (Years)		18-84		18+		12-17	
Arm		NVX-CoV2373 (5 µg)	Placebo	NVX-CoV2373 (5 µg)	Placebo	NVX-CoV2373 (5 µg)	Placebo
N	Dose 1	2,310*		19,729	9,853	1,487†	745
	Dose 2			19,104	9,422	NA	NA
Any Local AR	Dose 1	57.6	17.9	10475 (57.96)	1881 (21.13)	948 (65.5)	207 (28.5)
	Dose 2	79.6	16.4	13525 (78.91)	1797 (21.71)	1050 (75.3)	141 (20.6)
Erythema/Redness	Dose 1	2	0.5	164 (0.91)	27 (0.3)	15 (1)	5 (0.7)
	Dose 2	8.2	0.5	1138 (6.64)	29 (0.35)	104 (7.5)	0
Pain at Injection Site	Dose 1	29.3	9	6211 (34.37)	986 (11.07)	648 (44.6)	126 (17.4)
	Dose 2	51.2	8.6	10227 (59.67)	1141 (13.78)	850 (61)	102 (14.9)
Swelling	Dose 1	0.5	0.5	154 (0.85)	24 (0.27)	20 (1.4)	3 (0.4)
	Dose 2	7.2	0.5	1056 (6.16)	25 (0.3)	111 (8)	1 (0.1)
Tenderness	Dose 1	53.3	14	9450 (52.59)	1494 (16.78)	817 (56.4)	153 (21.1)
	Dose 2	76.4	12.5	12584 (73.42)	1312 (15.85)	909 (65.2)	97 (14.1)

AR: adverse report, N: total number

*Solicited AE safety population

†Safety analysis set

Table D3.33. Nuvaxovid: Overall Safety for Booster Trial[131]

Vaccine		Nuvaxovid			
NCT		NCT04611802			
Author, Year		Anez 2025			
Trial Phase		Phase III Booster #1 / 2 (Doses 3 / 4)*			
Subgroup (Years)		12-17		18+	
Arm		NVX-CoV2373 (Dose 3)	NVX-CoV2373 (Dose 4)	NVX-CoV2373 (Dose 3)	NVX-CoV2373 (Dose 4)
N		1,499	205	13,354	359
Solicited AEs		1251 (83.5)	163 (79.5)	10,545 (79.0)	280 (78.0)
Unsolicited AEs Regardless of Relationship to Study Vaccination	All	87 (5.8)†	7 (3.4)†	669 (5)†	7 (1.9)†
	Serious	9 (0.6)†	3 (1.5)†	397 (3)†	4 (1.1)†
	Severe	9 (0.6)†	0	48 (0.4)†	0
	Fatal	0	0	25 (0.2)	1 (0.3)
	Medically-Attended	43 (2.9)	NA	681 (5.1)	6 (1.7)
	Leading to Study Discontinuation	0	NA	27 (0.2)	1 (0.3)
	PIMMC	0	0	24 (0.2)	0
	AESI Relevant to Covid-19	0	0	9 (<0.1)	0
Unsolicited AEs Related to Study Vaccination	All	17 (1.1)†	1 (0.5)†	100 (0.7)†	0
	Serious	0	0	5 (<0.1)†	0
	Fatal	0	0	0	0
	Medically-Attended	3 (0.2)	0	35 (0.3)	0
	Leading to Study Discontinuation	0	NA	0	0
	Severe	1 (<0.1)	0	11 (<0.1)†	0
	PIMMC	0	0	2 (<0.1)	0
	AESI Relevant to Covid-19	0	0	0	0

AE: adverse event, AESI: adverse event of special interest, N: total number, NA: not applicable, PIMMC: Potential Immune-Mediated Medical Conditions

*TEAE through end of study

†Adverse events through 28 days after dose

Table D3.34. Nuvaxovid: Systemic Safety for Booster Trial[131]

Vaccine		Nuvaxovid			
NCT		NCT04611802			
Author, Year		Anez 2025			
Trial Phase		Phase III Booster #1 / 2 (Doses 3 / 4)			
Subgroup (Years)		12-17		≥18	
Arm		NVX-CoV2373 (Dose 3)	NVX-CoV2373 (Dose 4)	NVX-CoV2373 (Dose 3)	NVX-CoV2373 (Dose 4)
N (%)		1,251	163	10,545	280
Any Systemic Event	Dose 1	1,013 (81)	132 (81)	7,602 (72.1)	171 (61.1)
Fatigue	Dose 1	717 (57.3)	87 (53.4)	5,543 (52.9)	127 (45.4)
Fever	Dose 1	211 (16.9)	18 (11.0)	811 (7.7)	13 (4.6)
Headache	Dose 1	790 (63.1)	95 (58.3)	4,803 (45.5)	89 (31.8)
Joint Pain	Dose 1	275 (22.0)	29 (17.8)	2,768 (26.2)	57 (20.4)
Malaise	Dose 1	566 (45.2)	83 (50.9)	4,312 (40.9)	100 (35.7)
Muscle Pain	Dose 1	754 (60.3)	100 (61.3)	5,440 (51.6)	115 (41.1)
Nausea/Vomiting	Dose 1	292 (23.3)	37 (22.7)	1,255 (11.9)	18 (6.4)

N: total number

Table D3.35. Nuvaxovid: Local Safety for Booster Trial[131]

Vaccine		Nuvaxovid			
NCT		NCT04611802			
Author, year		Anez 2025			
Trial Phase		Phase III Booster #1 / 2 (Doses 3 / 4)			
Subgroup (Years)		12-17		≥18	
Arm		NVX-CoV2373 (Dose 3)	NVX-CoV2373 (Dose 4)	NVX-CoV2373 (Dose 3)	NVX-CoV2373 (Dose 4)
N (%)		1,251	163	10,545	280
Any Local AR	Dose 1	969 (77.5)	122 (74.8)	8332 (79)	200 (71.4)
Pain	Dose 1	812 (64.9)	106 (65)	6453 (61.2)	137 (48.9)

Vaccine		Nuvaxovid			
NCT		NCT04611802			
Author, year		Anez 2025			
Trial Phase		Phase III Booster #1 / 2 (Doses 3 / 4)			
Subgroup (Years)		12-17		≥18	
Arm		NVX-CoV2373 (Dose 3)	NVX-CoV2373 (Dose 4)	NVX-CoV2373 (Dose 3)	NVX-CoV2373 (Dose 4)
N (%)		1,251	163	10,545	280
Redness	Dose 1	129 (10.3)	13 (8)	953 (9)	31 (11.1)
Swelling	Dose 1	119 (9.5)	9 (5.5)	873 (8.3)	27 (9.6)
Tenderness	Dose 1	828 (66.2)	102 (62.6)	7698 (73)	187 (66.8)

N: total number

Table D3.36. Safety Summary of RCTs Comparing Vaccines

Trial Name	Study Design	Arms	Key Safety Results
VACCELERATE[62]	Phase II multinational, randomized controlled trial in adults ≥75 years old	Second booster dose of either: 1) BNT162b2 30 µg (n=135) 2) mRNA-1273 100 µg (n=135)	Vaccine-related AE (Grade 1) • mRNA-1273: 30% • BNT162b2: 39% Vaccine-related AE (Grade 2) • mRNA-1273: 25% • BNT162b2: 16% Pain at the injection site (most frequent AE) • mRNA-1273: 51% • BNT162b2: 48% Fatigue • mRNA-1273: 38% • BNT162b2: 23%

Trial Name	Study Design	Arms	Key Safety Results
Com-COV3[63]	Phase II multicenter single-blind randomized controlled trial in adolescents	After a first dose of BNT162b2 30 µg: 1) BNT162b2 30 µg (n=48) 2) BNT162b2 10 µg (n=47) 3) NVX-CoV2373 (n=37)	• More solicited systemic AES in BNT-30 and NVX groups • Solicited local reactions least common in NVX group • Most reactions mild to moderate, no clear difference in frequency of severe reactions
Mazarakis 2025[64]	Single-blind parallel group randomized controlled trial in adults	A fourth dose of either: 1) mRNA-1273 (n=177) 2) NVX-CoV-2373 (n=176)	Any local and systemic reactions (Grade 1 – 4) • mRNA-1273: 90% • NVX-CoV-2373: 74% Serious reactions (Grade 3 – 4) • mRNA-1273: 6.2% • NVX-CoV-2373: 5.1%
PICOBOO[65]	Randomized, adaptive study in adults 50-70 years old	Second booster dose of: 1) BNT162b2 (n=51) 2) mRNA-1273 (n=52) 3) NVX-CoV-2373 (n=52)	Pain at the injection site • BNT162b2: 86% • mRNA-1273: 88% • NVX-CoV-2373: 42% Headache • BNT162b2: 51% • mRNA-1273: 63% • NVX-CoV-2373: 35% Fever • BNT162b2: 6% • mRNA-1273: 4% • NVX-CoV-2373: 4%

Trial Name	Study Design	Arms	Key Safety Results
Janssen 2022[66]	Open-label randomized trial of heterologous and homologous vaccination	Participants received a second dose of either BNT162b2 or mRNA-1273 and groups were split by primary dose 1) BNT162b2/BNT162b2 (n=94) 2) BNT162b2/mRNA-1273 (n=96) 3) mRNA-1273/ mRNA-1273 (n=97) 4) mRNA-1273/BNT162b2 (n=103)	• Participants who received a second dose of mRNA-1273 has higher rates of adverse reactions and general symptoms compared to participants who received BNT162b2 (p<0.0001)

AE: adverse event, N: total number, %: percentage

Key Observational Data for Vaccine Effectiveness

Table D3.37. Study Design[16-18]

Trial Name (NCT)	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
Cai. NEJM. 2025[18]	Observational study using EHRs of the Department of Veterans Affairs N=295,971 Follow-up: 6 months	1) Received 2024-2025 COVID-19 vaccine and 2024-2025 seasonal influenza vaccine on same day 2) Received 2024-2025 seasonal influenza vaccine only	**Inclusion:** · ≥18 years old · Had at least one primary care physician encounter within the VA system in the 18 months before vaccination · Clinical encounter for vaccination within the VA system between September 3, 2024 to December 31, 2024 · Received at least one dose of the 2023-2024 season COVID-19 vaccine within the VA system	Covid-19-associated emergency department or urgent care visit [24 hours before or after a positive test] Covid-19-associated hospitalization [inpatient admission occurring within 2 days before to 7 days after a positive test] Covid-19-associated death [within 30 days after a positive test]

Trial Name (NCT)	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
			Exclusion: · Received a COVID-19 vaccine within 90 days before the date of enrollment · Had a laboratory-confirmed positive test for SARS-CoV-2 or seasonal influenza within 90 days before enrollment	
Irving. MMWR. 2025[17] **VISION**	Multisite EHR-based network	1) Patients with an ED/UC encounter for COVID-19–like illness and receipt of a positive SARS-CoV-2 molecular or antigen test result 2) Patients with an ED/UC encounter for COVID-19–like illness and receipt of a negative SARS-CoV-2 molecular test result	**Inclusion:** · Eligible immunocompetent children and adolescents aged 9 months–17 years who visited a participating ED/UC during August 29, 2024-September 2, 2025 **Exclusion:** · Received a 2024– 2025 COVID-19 vaccine dose <7 days before their index date · Received a 2024-2025 COVID-19 vaccine dose <2 months after receiving any previous COVID-19 vaccine dose · Covid-19 case patients: received a positive test result for influenza virus or respiratory syncytial virus at time of their ED/UC encounter	2024–2025 COVID-19 VE against COVID-19-associated ED/UC visits among children aged 9 months-4 years and 5-17 years
Link-Gelles. MMWR. 2025[16] **VISION and IVY Networks**	VISION: multisite EHR-based network including 373	1) Received a positive SARS-CoV-2 molecular or antigen test result	**Inclusion:** · Adults aged ≥18 years with COVID-19 like illness	· Effectiveness of 2024–2025 COVID-19 vaccines was estimated against COVID-

Trial Name (NCT)	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Key Outcomes
	ED/UCs and 241 hospitals in 8 states IVY: multicenter, inpatient network of 26 hospitals in 20 US states	2) Received a negative SARS-CoV-2 molecular test result.	· Had a medical encounter at an ED/UC (VISION only) · Hospitalized (VISION and IVY) **Exclusion:** · Received a 2024–2025 COVID-19 vaccine <7 days or ≥120 days before their eligible ED/UC encounter or hospitalization · Received a 2024-2025 COVID-19 vaccine dose <2 months after receiving a previous COVID-19 vaccine dose · Immunocompetent persons who had received more than 1 2024-2025 COVID-19 vaccine dose · Covid-19 case patients: received a positive test result for influenza virus or respiratory syncytial virus at time of their ED/UC encounter	19–associated ED/UC) visits during September 2024–January 2025 among adults aged ≥18 years (VISION only) · Effectiveness of 2024–2025 COVID-19 vaccination against COVID-19–associated hospitalization among adults aged ≥65 year · Effectiveness of 2024–2025 COVID-19 vaccination against COVID-19–associated hospitalization among adults aged ≥65 year with immunocompromising conditions (IVY only)

ED: emergency department, EHR: electronic health record, UC: urgent care

Table D3.38. Baseline Characteristics for Cai 2025[18]

Cai. 2025. VA Study				
Arm			**Covid-19 Vaccine**	**No Covid-19 Vaccine**
N			**164,132**	**131,839**
Demographic Characteristics	**Age, Year**	**Mean (SD)**	71.45 (10.66)	71.47 (10.89)
	Sex, n (%)	**Male**	151,291 (92.18)	121,375 (92.06)
		Female	12,841 (7.82)	10,464 (7.94)
	Race, n (%)	**White**	116,159 (70.77)	92,866 (70.44)
		Black	41,733 (25.43)	33,925 (25.73)
		Other	6,240 (3.80)	5,048 (3.83)
	Smoking Status, n (%)	**Never Smoked**	61,375 (37.39)	49,850 (37.81)
		Former Smoker	72,337 (44.07)	57,902 (43.92)
		Current Smoker	30,420 (18.53)	24,087 (18.27)
	Area Deprivation Index Score*	**Mean (SD)**	51.98 (19.88)	52.26 (19.8)
	Care Assessment Need Score†	**Mean (SD)**	0.19 (0.16)	0.19 (0.16)
	VA Frailty Index Score‡	**Mean (SD)**	0.15 (0.10)	0.15 (0.10)
Formulation of 2024–2025 Seasonal Influenza Vaccine — no. (%)	**High-Dose Formulation for Adults ≥65 yr of Age**		122,547 (74.66)	96,339 (73.07)
	Standard-Dose Formulation		41,585 (25.34)	35,500 (26.93)
Covid-19 Vaccine Formula, n (%)	**Covid-19 Vaccine Original Series**		161,224 (98.23)	129,492 (98.22)
	Covid-19 Vaccine 2021–2022 Formula		152,160 (92.71)	121,891 (92.45)
	Covid-19 Vaccine 2022–2023 Formula		125,812 (76.65)	100,132 (75.95)
	Covid-19 Vaccine 2023–2024 Formula		164,132 (100)	131,839 (100)
Coexisting Conditions, n (%)	**Cardiovascular Disease**		38,645 (23.55)	31,338 (23.77)
	Cerebrovascular Disease		15,527 (9.46)	12,553 (9.52)
	Chronic Lung Disease		31,465 (19.17)	25,390 (19.26)
	Diabetes		45,846 (27.93)	36,856 (27.96)
	Gastrointestinal Disease		14,259 (8.69)	11,606 (8.80)
	Hyperlipidemia		36,592 (22.29)	29,430 (22.32)
	Immunocompromised Status		20,678 (12.60)	16,753 (12.71)

Cai. 2025. VA Study				
Arm			**Covid-19 Vaccine**	**No Covid-19 Vaccine**
N			**164,132**	**131,839**
	Peripheral Artery Disease		4,037 (2.46)	3,287 (2.49)
Laboratory or Vital-Sign Measures	**Body-Mass Index**	**Mean (SD)**	30.08 (6.07)	30.04 (6.09)
	eGFR, ml/min/1.73 m^2	**Mean (SD)**	73.31 (19.86)	73.23 (20.15)
	Glycated Hemoglobin, %	**Mean (SD)**	6.18 (1.09)	6.17 (1.08)
	Hemoglobin, g/dl	**Mean (SD)**	13.17 (3.60)	13.17 (3.57)
	HDL cholesterol, mg/dl	**Mean (SD)**	47.67 (14.64)	47.65 (14.75)
	LDL cholesterol, mg/dl	**Mean (SD)**	84.95 (34.46)	85.12 (34.24)

eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, n: number, N: total number, SD: standard deviation, VA: Veteran's Affairs, yr: years

*The scores range from 1 to 100, with a higher score representing greater deprivation.

†The score indicates the predicted risk of death within 90 days, ranging from 0 to 1.

‡The measure is based on 31 conditions, ranging from 0 to 1.

Table D3.39. Baseline characteristics for Irving 2025[17]

Irving. MMWR. 2025.				
		Total Encounters	**COVID-19 Case-Patients**	**COVID-19 Control Patients**
Aged 9 Months - 4 Years				
N, (%)		44,541 (100)	1,292 (100)	43,249 (100)
Female, n (%)		19,648 (44)	564 (44)	19,084 (44)
Race and Ethnicity	**Black or African American, Non-Hispanic**	6,008 (13)	139 (11)	5,869 (14)
	White, Non-Hispanic	15,855 (36)	476 (37)	15,379 (36)
	Hispanic or Latino, Any Race	14,199 (32)	391 (30)	13,808 (32)
	Other, Non-Hispanic*	7,390 (17)	247 (19)	7,143 (17)
	Unknown†	1,089 (2)	39 (3)	1,050 (2)
	Any	1,859 (4)	12 (1)	1,847 (4)
	Moderna	396 (21)	2 (17)	394 (21)

Irving. MMWR. 2025.				
		Total Encounters	**COVID-19 Case-Patients**	**COVID-19 Control Patients**
Aged 9 Months - 4 Years				
2024–2025 COVID-19 Vaccine Receipt‡	**Pfizer-BioNTech**	1,463 (79)	10 (83)	1,453 (79)
Aged 5 - 17 years				
N, (%)		53,467 (100)	1,325 (100)	52,142 (100)
Female, n (%)		26,561 (50)	687 (52)	25,874 (50)
Race and Ethnicity	**Black or African American, Non-Hispanic**	7,290 (14)	166 (13)	7,124 (14)
	White, Non-Hispanic	22,896 (43)	603 (46)	22,293 (43)
	Hispanic or Latino, Any Race	14,961 (28)	346 (26)	14,615 (28)
	Other, Non-Hispanic *	7,585 (14)	193 (15)	7,392 (14)
	Unknown †	735 (1)	17 (1)	718 (1)
2024–2025 COVID-19 Vaccine Receipt ‡	**Any**	2,488 (5)	26 (2)	2,462 (5)
	Moderna	434 (17)	5 (19)	429 (17)
	Novavax	5 (0)	0 (NR)	5 (0)
	Pfizer-BioNTech	2,049 (82)	21 (81)	2,028 (82)

n: number, N: total number

*Combines people who reported non-Hispanic ethnicity, American Indian or Alaska Native, Asian, Middle Eastern or North African, Native Hawaiian or Pacific Islander, other races not listed, and multiple races.

†Includes people with missing race and ethnicity in their electronic health record.

‡Received during 7-179 days before the index date.

Table D3.40. Baseline Characteristics for Link-Gelles 2025[16]

Link-Gelles. 2025. VISION and IVY Networks										
Data Source		**VISION**			**VISION**			**IVY**		
Outcome		**ED / UC Encounters**			**Hospitalizations**			**Hospitalizations**		
Subpopulation		**All Adults Aged ≥18 Years**			**All Adults Aged ≥65 Years**			**Immunocompetent Adults Aged ≥65 Years**		
Characteristic		**Total**	**COVID-19 Case-Patients**	**COVID-19 Control Patients**	**Total**	**COVID-19 Case-Patients**	**COVID-19 Control Patients**	**Total**	**COVID-19 Case-Patients**	**COVID-19 Control Patients**
N		**137,543**	**10,459**	**127,084**	**34,411**	**2,846**	**31,565**	**1,929**	**683**	**1,246**
2024–2025 COVID-19 Vaccination Status and Time Interval	**No 2024–2025 Dose**	118,517 (86)	9,545 (91)	108,972 (86)	27,623 (80)	2,540 (89)	25,083 (79)	1,635 (85)	614 (90)	1,021 (82)
	7–119 Days Earlier	19,026 (14)	914 (9)	18,112 (14)	6,788 (20)	306 (11)	6,482 (21)	294 (15)	69 (10)	225 (18)
	7–59 Days Earlier	10,269 (7)	480 (5)	9,789 (8)	3,904 (11)	179 (6)	3,725 (12)	146 (8)	41 (6)	105 (8)
	60–119 Days Earlier	8,757 (6)	434 (4)	8,323 (7)	2,884 (8)	127 (4)	2,757 (9)	148 (8)	28 (4)	120 (10)
Median Age, yrs (IQR)		53 (34–72)	58 (37–74)	53 (34–71)	78 (72–84)	79 (73–86)	78 (71–84)	77 (71–84)	78 (72, 85)	76 (70, 83)
Age Group, yrs	**18 - 64**	88,858 (65)	6,113 (58)	82,745 (65)	NR	NR	NR	NR	NR	NR
	≥65	48,685 (35)	4,346 (42)	44,339 (35)	34,411 (100)	2,846 (100)	31,565 (100)	1,929 (100)	683 (100)	1,246 (100)
Female Sex		83,641 (61)	6,275 (60)	77,366 (61)	18,274 (53)	1,412 (50)	16,862 (53)	1,050 (54)	374 (55)	676 (54)
Race and Ethnicity	**Black or African American, NH**	15,003 (11)	794 (8)	14,209 (11)	2,575 (7)	156 (5)	2,419 (8)	370 (19)	120 (18)	250 (20)
	White, NH	83,282 (61)	7,256 (69)	76,026 (60)	25,811 (75)	2,281 (80)	23,530 (75)	1,223 (63)	447 (65)	776 (62)
	Hispanic or Latino, Any Race	20,461 (15)	1,255 (12)	19,206 (15)	2,640 (8)	183 (6)	2,457 (8)	184 (10)	59 (9)	125 (10)
	Other, NH	14,014 (10)	897 (9)	13,117 (10)	2,858 (8)	188 (7)	2,670 (8)	89 (5)	34 (5)	55 (4)
	Unknown*	4,783 (3)	257 (2)	4,526 (4)	527 (2)	38 (1)	489 (2)	63 (3)	23 (3)	40 (3)

Link-Gelles. 2025. VISION and IVY Networks									
Data Source	**VISION**			**VISION**			**IVY**		
Outcome	**ED / UC Encounters**			**Hospitalizations**			**Hospitalizations**		
Subpopulation	**All Adults Aged ≥18 Years**			**All Adults Aged ≥65 Years**			**Immunocompetent Adults Aged ≥65 Years**		
Characteristic	**Total**	**COVID-19 Case-Patients**	**COVID-19 Control Patients**	**Total**	**COVID-19 Case-Patients**	**COVID-19 Control Patients**	**Total**	**COVID-19 Case-Patients**	**COVID-19 Control Patients**
N	**137,543**	**10,459**	**127,084**	**34,411**	**2,846**	**31,565**	**1,929**	**683**	**1,246**
No. of Organ Systems With A Chronic Medical Condition, Median (IQR)†	0 (0–1)	0 (0–1)	0 (0–1)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2, 4)	2 (2, 3)	3 (2, 4)
Immunocompromised‡	NR	NR	NR	8,192 (24)	598 (21)	7,594 (24)	NR	NR	NR

ED: emergency department, IQR: inter quartile range, N: total number, NH: non-hispanic, NR: not reported, UC: urgent care, yrs: years

*For VISION, refers to patients' EHR missing race and ethnicity data. For IVY, refers to patients who did not report race or ethnicity.

†For VISION this includes pulmonary, cardiovascular, cerebrovascular, neurologic or musculoskeletal, hematologic, endocrine, renal, and gastrointestinal. For IVY, this includes IVY pulmonary, cardiovascular, neurologic, hematologic, endocrine, kidney, gastrointestinal, and autoimmune.

‡Immunocompromised status is not included in ED or UC encounters due to the possibility of an incomplete discharge diagnosis code. In IVY, immunocompromised adults weren't included in vaccine effectiveness calculations due to a limited sample size.

Table D3.41. Key Efficacy for Cai 2025[18]

Cai NEJM 2025						
	Vaccine Season	Timepoint	Vaccine Effectiveness, Percent (95% CI)*	Risk in Covid-Vaccine Group (95% CI)	Risk in No-Covid-Vaccine Group (95% CI)	Risk Difference (95%CI) †
			Percent	Per 10,000 Persons	Per 10,000 Persons	Per 10,000 Persons
Covid-19–Associated Emergency Department Visit	**2024 - 2025**	**6 Months**	29.3 (19.1, 39.2)	44.15 (40.98, 47.56)	62.39 (55.62, 70.75)	18.32 (10.84, 27.57)
Covid-19–Associated Hospitalization			39.2 (21.6, 54.5)	11.55 (10.01, 13.33)	19.06 (15.14, 24.39)	7.47 (3.44, 13.04)
Covid-19–Associated Death			64.0 (23.0, 85.8)	1.25 (0.78, 2.05)	3.49 (1.98, 8.07)	2.20 (0.49, 6.91)
Covid-19–Associated Composite Outcome			28.3 (18.2, 38.2)	46.04 (42.80, 49.53)	64.20 (57.36, 72.64)	18.23 (10.69, 27.52)

CI: confidence interval

*The difference of 1 subtracted from the RR (the risk in the Covid-vaccine group divided by the risk in the no-Covid-vaccine group).

†The difference of the risk in the no-Covid-vaccine group subtracted from the risk in the Covid-vaccine group

Table D3.42. Key Efficacy for Irving 2025[17]

Lab-Confirmed COVID-19–Associated Emergency Department or Urgent Care Encounters Among Children							
		Total Encounters, No.	Days Since Last Dose Among Vaccinated Persons, No.		Positive SARS-Cov-2 Test Results, No. (Column %)	VE, % (95% CI)*	
			Median (IQR)	Maximum		Unadjusted	Adjusted*
Children Aged 9 Months - 4 Years							
Primary VE Estimates†	**No 2024–2025 COVID-19 Dose (Ref)**	42,682	407 (290–675)	1,474	1,280 (99)	Ref	Ref
	≥1 2024–2025 COVID-19 Dose, 7–179 Days Earlier	1,859	78 (42–118)	179	12 (1)	79 (63–88)	76 (58–87)

Lab-Confirmed COVID-19–Associated Emergency Department or Urgent Care Encounters Among Children							
		Total Encounters, No.	Days Since Last Dose Among Vaccinated Persons, No.		Positive SARS-Cov-2 Test Results, No. (Column %)	VE, % (95% CI)*	
			Median (IQR)	Maximum		Unadjusted	Adjusted*
Sensitivity VE estimates, Extended VE interval‡	**No 2024–2025 COVID-19 Dose (Ref)**	42,682	407 (290–675)	1,474	1,280 (99)	Ref	Ref
	≥1 2024–2025 COVID-19 Dose, 7–299 Days Earlier	2,207	91 (49–147)	296	15 (1)	78 (63–87)	77 (62–86)
Relaxed Vaccination History Requirement§	**No 2024–2025 COVID-19 Dose (Ref)**	44,314	422 (289–695)	1,575	1,312 (98)	Ref	Ref
	≥1 2024–2025 COVID-19 Dose, 7–179 Days Earlier	3,029	73 (38–112)	179	32 (2)	65 (50–75)	66 (51–76)
Children Aged 5 - 17 Years							
Primary VE Estimates†	**No 2024–2025 COVID-19 Dose (Ref)**	50,979	986 (722–1,135)	1,633	1,299 (98)	Ref	Ref
	≥1 2024–2025 COVID-19 Dose, 7–179 Days Earlier	2,488	84 (44–124)	179	26 (2)	60 (40–73)	56 (35–70)
Sensitivity VE Estimates, Extended VE Interval§	**No 2024–2025 COVID-19 Dose (Ref)**	50,979	986 (722–1,135)	1,633	1,299 (97)	Ref	Ref
	≥1 2024–2025 COVID-19 Dose, 7–299 Days Earlier	3,152	105 (55–167)	299	44 (3)	46 (27–60)	45 (25–59)
By Age Group: 5 - 11 years	**No 2024–2025 COVID-19 Dose (Ref)**	31,508	883 (595–1,050)	1,633	645 (98)	Ref	Ref
	≥1 2024–2025 COVID-19 Dose, 7–179 Days Earlier	1,443	85 (44–126)	179	13 (2)	57 (24–75)	51 (14–72)

Lab-Confirmed COVID-19–Associated Emergency Department or Urgent Care Encounters Among Children							
		Total Encounters, No.	Days Since Last Dose Among Vaccinated Persons, No.		Positive SARS-Cov-2 Test Results, No. (Column %)	VE, % (95% CI)*	
			Median (IQR)	Maximum		Unadjusted	Adjusted*
By Age Group: 12 - 17 years	No 2024–2025 COVID-19 Dose (Ref)	19,471	1,056 (835–1,191)	1,552	654 (98)	Ref	Ref
	≥1 2024–2025 COVID-19 Dose, 7–179 Days Earlier	1,045	82 (44–122)	179	13 (2)	64 (37–79)	61 (31–78)

CI: confidence interval, VE: vaccine effectiveness, %: percent, No.: number

*Calculated by taking (1 − adjusted odds ratio) × 100%.

†Vaccinated group included children who received a 2024-2025 dose as an initial series or as an additional vaccine. The compactor included children who did not receive a 2024-2025 dose or any prior COVID-19 vaccination.

‡Included 44,889 encounters.

§Vaccinated group included children who received ≥1 2024-2025 dose. The comparator included children who did not receive a 2024-2025 dose, regardless of prior vaccination.

Table D3.43. Key Efficacy for Link-Gelles 2025[16]

Covid-19-Associated Emergency Department / Urgent Care Visit					
		COVID-19 Case Patients, No. (%)	COVID-19 Control Patients, No. (%)	Median Interval Since Last Dose for Vaccinated, Days (IQR)	VE %* (95% CI)
≥18 Years	No 2024–2025 Dose†	9,545 (91)	108,972 (86)	998 (539–1,142)	Ref
	Received 7–119 Days Earlier	914 (9)	18,112 (14)	55 (32–80)	33 (28–38)
	Received 7–59 Days Earlier	480 (5)	9,789 (8)	33 (20–46)	36 (29–42)
	Received 60–119 Days Earlier	434 (4)	8,323 (7)	82 (71–97)	30 (22–37)
18 - 64 Years	No 2024–2025 Dose†	5,860 (96)	76,792 (93)	1,042 (751–1,180)	Ref
	Received 7–119 Days Earlier	253 (4)	5,953 (7)	53 (29–77)	30 (20–39)
	Received 7–59 Days Earlier	134 (2)	3,379 (4)	32 (20–45)	36 (23–46)

Covid-19-Associated Emergency Department / Urgent Care Visit					
		COVID-19 Case Patients, No. (%)	**COVID-19 Control Patients, No. (%)**	**Median Interval Since Last Dose for Vaccinated, Days (IQR)**	**VE %* (95% CI)**
	Received 60–119 Days Earlier	119 (2)	2,574 (3)	81 (70–95)	21 (5–35)
≥65 Years	**No 2024–2025 Dose**	3,685 (85)	32,180 (73)	750 (346–1,076)	Ref
	Received 7–119 Days Earlier	661 (15)	12,159 (27)	57 (33–82)	35 (29–41)
	Received 7–59 Days Earlier	346 (8)	6,410 (14)	34 (21–47)	36 (28–44)
	Received 60–119 Days Earlier	315 (7)	5,749 (13)	83 (71–97)	34 (25–42)
Covid-19-Associated Hospitalization					
VISION, Immunocompetent	**No 2024–2025 Dose†**	2,016 (90)	19,198 (80)	775 (357–1,084)	Ref
	Received 7–119 Days Earlier	232 (10)	4,773 (20)	53 (30–77)	45 (36–53)
	Received 7–59 Days Earlier	129 (6)	2,759 (12)	33 (20–46)	42 (30–52)
	Received 60–119 Days Earlier	103 (5)	2,014 (8)	81 (70–94)	48 (36–58)
VISION, Immunocompromised	**No 2024–2025 Dose†**	524 (88)	5,885 (78)	720 (343–1,064)	Ref
	Received 7–119 Days Earlier	74 (12)	1,709 (22)	53 (31–78)	40 (21–54)
IVY, Immunocompetent	**No 2024–2025 Dose†**	614 (90)	1,021 (82)	—^{§}	Ref
	Received 7–119 Days Earlier	69 (10)	225 (18)	60 (31–85)	46 (26–60)
	Received 7–59 Days Earlier	41 (6)	105 (8)	31 (20–45)	42 (14–61)
	Received 60–119 Days Earlier	28 (4)	120 (10)	85 (72–98)	47 (17–67)

CI: confidence interval, Ref: reference, IQR: inter quartile range, VE: vaccine effectiveness

*Calculated by comparing the odds of 2024–2025 Covid-19 vaccination among case-patients and control patients using the following equation: (1 – adjusted odds ratio) x 100%.

†Includes people who did not receive a 2024–2025 Covid-19 vaccine dose.

Table D3.44. Secondary Efficacy for Cai 2025[18]

Trial	Outcome	Time Interval	Vaccine Effectiveness (95 CI%)*	Risk Difference (95 CI %)†	Risk In COVID-19 Vaccine (95 CI%)	Risk In No COVID-19 Vaccine (95 CI%)
Cai NEJM 2025	**Composite Endpoint**	1 to 60 days	37.1% (19.5%, 49.9)	7.98 (3.42, 12.80)	13.48 (11.71, 15.42)	21.54 (17.16, 25.99)
		61 to 120 days	32.5% (14.3%, 45.6%)	8.75 (3.13, 14.75)	18.20 (16.12, 20.44)	27.06 (21.61, 32.60)
		121 to 180 days	21.4% (0.3%, 37.0%)	3.95 (0.04, 8.03)	14.45 (12.59, 16.48)	18.46 (14.84, 22.12)

CI: confidence interval

*The difference of 1 subtracted from the risk ratio (the risk in COVID-19 vaccine group divided by the risk in no COVID-19 vaccine group.

†The difference of the risk in no COVID-19 vaccine group subtracted from the risk in COVID-19 vaccine group.

Table D3.45. Subgroup for Cai 2025[18]

Subgroup	Sample Size			Vaccine Effectiveness*	Risk Difference†	Risks	
	Total	COVID-19 Vaccine	No COVID-19 Vaccine			COVID-19 Vaccine	No COVID-19 Vaccine
Age							
<65	67,300	37,890	29,410	27.7% (5.2% to 46.3%)	13.16 (2.10 to 27.00)	34.73 (29.26 to 41.62)	48.05 (38.33 to 60.23)
65-75	95,004	53,491	41,513	35.4% (18.6% to 50.0%)	24.20 (10.70 to 41.31)	44.16 (38.95 to 50.28)	68.44 (55.65 to 84.28)
>75	133,667	72,751	60,916	33.5% (20.3% to 45.3%)	26.91 (14.26 to 42.08)	53.65 (48.58 to 59.35)	80.81 (68.69 to 94.80)
Cardiovascular Disease							
No	222,983	125,487	97,496	23.2% (12.0% to 34.1%)	12.23 (5.71 to 19.91)	40.12 (36.66 to 43.91)	52.28 (46.79 to 58.94)
Yes	72,988	38,645	34,343	35.6% (22.5% to 47.6%)	36.33 (20.73 to 55.63)	65.59 (57.85 to 74.53)	102.15 (88.74 to 119.00)
Cerebrovascular Disease							
No	266,334	148,605	117,729	26.7% (17.4% to 36.0%)	15.76 (9.48 to 23.23)	43.07 (39.79 to 46.61)	58.83 (53.46 to 65.19)
Yes	29,637	15,527	14,110	33.7%	38.64	75.38	114.21

Subgroup	Sample Size			Vaccine Effectiveness*	Risk Difference†	Risks	
	Total	COVID-19 Vaccine	No COVID-19 Vaccine			COVID-19 Vaccine	No COVID-19 Vaccine
				(13.3% to 51.6%)	(12.95 to 72.09)	(62.67 to 90.73)	(92.79 to 143.46)
Chronic Kidney Disease							
No	220,638	123,433	97,205	24.6% (13.9% to 35.3%)	14.11 (7.19 to 22.34)	42.98 (39.36 to 46.91)	57.08 (51.34 to 64.09)
Yes	75,333	40,699	34,634	35.1% (21.8% to 47.7%)	30.32 (16.32 to 47.61)	55.61 (48.65 to 63.65)	86.04 (74.05 to 101.01)
Chronic Lung Disease							
No	237,160	132,667	104,493	23.2% (12.2% to 34.0%)	12.15 (5.86 to 19.77)	39.98 (36.63 to 43.63)	52.16 (46.80 to 58.57)
Yes	58,811	31,465	27,346	36.4% (23.3% to 48.9%)	41.71 (23.14 to 64.03)	72.06 (63.06 to 82.46)	113.82 (98.39 to 133.23)
Immunocompromised Status							
No	255,985	143,454	112,531	25.5% (15.5% to 35.2%)	14.28 (7.89 to 21.67)	41.65 (38.34 to 45.23)	55.89 (50.62 to 62.33)
Yes	39,986	20,678	19,308	34.4% (18.0% to 49.2%)	40.82 (18.31 to 68.17)	77.39 (65.94 to 90.72)	118.33 (99.92 to 142.61)

Note: risks and risk differences are reported as per 10,000 persons at 6 months

*The difference of 1 subtracted from the RR (the risk in COVID-19 vaccine group divided by the risk in no COVID-19 vaccine group).

†The difference of the risk in the no COVID-19 vaccine group subtracted from the risk in the COVID-19 vaccine group.

Observational Studies Identified for Key Subgroups of Interest

Young Children (6 Months to 11 Years)

Table D3.46. Observational Trials Identified Reporting Effectiveness and/or Safety for Young Children

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Vascular and inflammatory diseases after COVID-19 infection and vaccination in children and young people in England: a retrospective, population-based cohort study using linked electronic health records.	Sampri 2025	Comirnaty	Cohort	2020 - 2022	Safety
Results of safety monitoring of BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine in U.S. children aged 5-17 years	Hu 2022	Comirnaty	Cohort	2021 - 2022	Safety
OpenSAFELY: Effectiveness of COVID-19 Vaccination in Children and Adolescents.	Andrews 2026	Comirnaty	Cohort	2021 - 2022	Safety
Risk of adverse events after covid-19 in Danish children and adolescents and effectiveness of BNT162b2 in adolescents: cohort study.	Kildegaard 2022	Comirnaty	Cohort	2021 - 2022	Safety
Pediatric safety assessment of BNT162b2 vaccination in a multistate hospital-based electronic health record system in the USA: a retrospective analysis.	Matson 2023	Comirnaty	Cohort	2021 - 2022	Safety
Maternal third dose of BNT162b2 mRNA vaccine and risk of infant COVID-19 hospitalization.	Lipschuetz 2023	Comirnaty	Cohort	2021 - 2022	Safety
Real-world effectiveness and causal mediation study of BNT162b2 on long COVID risks in children and adolescents	Wu 2025	Comirnaty	Cohort	2021 - 2022	Effectiveness; Safety
BNT162b2 COVID-19 vaccination uptake, safety, effectiveness, and waning in children and young people aged 5-11 years in Scotland.	Rudan 2025	Comirnaty	Cohort	2022 - 2023	Effectiveness; Safety
BNT162b2 XBB.1.5-Adapted Single Dose Vaccine Uptake and Effectiveness in Children Aged 5-17 Years Using Linked Claims and Vaccine Registries in California and Louisiana.	Andersen 2025	Comirnaty	Cohort	2023 - 2024	Effectiveness

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Effectiveness of BNT162b2 Vaccination During Pregnancy in Preventing Hospitalization for Severe Acute Respiratory Syndrome Coronavirus 2 in Infants.	Danino 2023	Comirnaty	Case-control	2021 - 2022	Effectiveness
Effectiveness of the Original BNT162b2 Messenger RNA Vaccine Against COVID-19 Omicron Infection in Children Aged 6 Months to 4 Years in Japan	Aizawa 2025	Comirnaty	Case-control	2022 - 2023	Effectiveness
Receipt of BNT162b2 Vaccine and COVID-19 Ambulatory Visits in US Children Younger Than 5 Years.	Tartof 2023	Comirnaty	Case-control	2022 - 2023	Effectiveness
BNT162b2 XBB Vaccine for COVID-19 Among Children 5-17 Years of Age.	Tartof 2024	Comirnaty	Case-control	2023 - 2024	Effectiveness
Febrile Seizure Risk Following Monovalent COVID-19 mRNA Vaccination in US Children Aged 2-5 Years	Anderson 2024	Spikevax	Cohort	2022-2023	Safety
Global Safety Assessment of Adverse Events of Special Interest Following 2 Years of Use and 772 Million Administered Doses of mRNA-1273	Urdaneta 2024	Spikevax	Surveillance Study: Moderna GSDB	2020 - 2022	Safety
Reported Adverse Events Following SARS-CoV-2 Vaccinations in the Canadian Province of Alberta and Associated Risk Factors: A Retrospective Cohort Study	Mansou 2024	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety
Maternal Exposures to COVID-19 Vaccine and Adverse Birth Outcomes: National Population Study in Korea.	Kim 2025	Comirnaty; Spikevax	Cohort	2022 - 2023	Safety
Safety Monitoring of Bivalent COVID-19 mRNA Vaccines Among Recipients 6 Months and Older in the United States.	Lloyd 2025	Comirnaty; Spikevax	Cohort	2022 - 2023	Safety
mRNA COVID-19 vaccine safety among children and adolescents: a Canadian National Vaccine Safety Network cohort study	Soe 2024	Comirnaty; Spikevax	Cohort	2021 - 2023	Effectiveness
BNT162b2 Versus mRNA-1273 Vaccines: Comparative Analysis of Long-Term Protection Against SARS-CoV-2 Infection and Severe COVID-19 in Qatar.	Chemaitelly 2024	Comirnaty; Spikevax	Cohort	2023 - 2024	Effectiveness
Serious Adverse Drug Reactions to COVID-19 Vaccines in the Pediatric Population: A Retrospective,	Nazar 2025	Comirnaty; Spikevax	Cross-sectional	2020 - 2023	Safety

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Cross-Sectional Study Utilizing the Eudravigilance Database for the European Economic Area					
Safety outcomes following COVID-19 vaccination and infection in 5.1 million children in England.	Copland 2024	Comirnaty; Spikevax	Self-controlled Case Series	2021 - 2022	Safety
Real-life safety profile of mRNA vaccines for COVID-19: An analysis of VAERS database.	Santi Laurini 2023	Comirnaty; Spikevax	Surveillance Study: VAERS	2020 - 2021	Safety
COVID-19 Vaccine Reactogenicity Among Young Children	Madni 2024	Comirnaty; Spikevax	Surveillance Study: CDC C19VPR	2022 - 2023	Safety
Safety of Ancestral Monovalent BNT162b2, mRNA-1273, and NVX-CoV2373 COVID-19 Vaccines in US Children Aged 6 Months to 17 Years.	Hu 2024	Comirnaty; Spikevax; Nuvaxovid	Cohort	2019 - 2023	Safety
Safety of Monovalent BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and NVX-CoV2373 (Novavax) COVID-19 Vaccines in US Children Aged 6 months to 17 years	Hu 2023	Comirnaty; Spikevax; Nuvaxovid	Cohort	2022 - 2023	Safety
Effectiveness of 2024–2025 COVID-19 Vaccines in Children in the United States — VISION, August 29, 2024–September 2, 2025	Irving 2025	Comirnaty; Spikevax; Nuvaxovid	Case-control	2024-2025	Effectiveness
COVID-19 vaccine initiation in pregnancy and risk for adverse neonatal outcomes among United States military service members, January–December 2021	Hall 2025	Multiple (not stratified)	Cohort	2020 - 2021	Safety
Cardiac Complications After SARS-CoV-2 Infection and mRNA COVID-19 Vaccination - PCORnet, United States, January 2021-January 2022.	Block 2022	Multiple (not stratified)	Cohort	2021 - 2022	Safety

C19VPR: Covid-19 Vaccine Pregnancy Registry, GSDB: Global Safety Database, VAERS: Vaccine Adverse Event Reporting System

Table D3.47. Details for Select Studies for Young Children

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Andersen 2025[132]	US	2023 – 2024	Comirnaty	Retrospective Cohort using HealthVerity Claims from California and Louisiana N=2,449,261	34,389 children aged 5 – 17 who received an XBB.1.5-adapated BNT162b2 vaccine. 40% were aged 12 – 17	Adjusted Vaccine Effectiveness among children 5 -11 • Covid-19 ED or UC Visit: 60% (95%CI: 10%, 82%) • ED, UC, or Hospitalization: 61% (95%CI: 12%, 82%) • Any ARI, ED, or UC Visit: 31% (95%CI: 23%, 38%) No Covid-19 associated hospitalizations in vaccinated group
Tartof 2024[133]	US	2023 – 2024	Comirnaty	Test-negative case control study N=15,233	9,834 participants 5 – 11 years old, 1,125 of which received Comirnaty	Adjusted Vaccine Effectiveness Against Hospital Admission, ED or UC visit (all test results): • 68% (11%, 88%)

ARI: acute respiratory infection, CI: confidence interval, ED: emergency department, N: total number, UC: urgent care, %: percent

Adolescents (12 to 17 Years)

The studies below report on either effectiveness or safety of Covid-19 vaccines for Adolescents. Studies that report only on myocarditis/pericarditis or Guillain-Barre Syndrome are described in separate sections below.

Table D3.48. Observational Trials Identified Reporting Effectiveness and/or Safety for Adolescents

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Vascular and inflammatory diseases after COVID-19 infection and vaccination in children and young people in England: a retrospective, population-based cohort study using linked electronic health records.	Sampri 2025	Comirnaty	Cohort	2020 - 2022	Safety
Safety and effectiveness of BNT162b2 mRNA Covid-19 vaccine in adolescents.	June Choe 2022	Comirnaty	Cohort	2021-2022	Effectiveness; Safety
OpenSAFELY: Effectiveness of COVID-19 Vaccination in Children and Adolescents.	Andrews 2026	Comirnaty	Cohort	2021 - 2022	Effectiveness; Safety
Real-world effectiveness and causal mediation study of BNT162b2 on long COVID risks in children and adolescents	Wu 2025	Comirnaty	Cohort	2021 - 2022	Effectiveness; Safety
Risk of adverse events after covid-19 in Danish children and adolescents and effectiveness of BNT162b2 in adolescents: cohort study.	Kildegaard 2022	Comirnaty	Cohort	2021 - 2022	Safety
Results of safety monitoring of BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine in U.S. children aged 5-17 years	Hu 2022	Comirnaty	Cohort	2021 - 2022	Safety
Safety of the BNT162b2 COVID-19 Vaccine in Children Aged 5 to 17 Years.	Hu 2023	Comirnaty	Cohort	2021 - 2022	Safety
Pediatric safety assessment of BNT162b2 vaccination in a multistate hospital-based electronic health record system in the USA: a retrospective analysis.	Matson 2023	Comirnaty	Cohort	2021 - 2022	Safety
BNT162b2 XBB.1.5-Adapted Single Dose Vaccine Uptake and Effectiveness in Children Aged 5-17 Years Using Linked Claims and Vaccine Registries in California and Louisiana.	Andersen 2025	Comirnaty	Cohort	2023 - 2024	Effectiveness
Adolescent vaccination with BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccine and effectiveness against COVID-19: National test-negative case-control study, England	Powell 2021	Comirnaty	Case-control	2021 - 2022	Effectiveness
BNT162b2 XBB Vaccine for COVID-19 Among Children 5-17 Years of Age.	Tartof 2024	Comirnaty	Case-control	2023 - 2024	Effectiveness

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
COVID-19 Vaccine Safety First Year Findings in Adolescents.	Hesse 2023	Comirnaty	Surveillance Study: VAERS	2021 - 2022	Safety
Global Safety Assessment of Adverse Events of Special Interest Following 2 Years of Use and 772 Million Administered Doses of mRNA-1273	Urdaneta 2024	Spikevax	Surveillance Study: Moderna GSDB	2020 - 2022	Safety
Vaccine efficacy of NVX-CoV2373 against SARS-CoV-2 infection in adolescents in the USA: an ancillary study to a phase 3, observer-blinded, randomized, placebo-controlled trial.	Deming 2025	Nuvaxovid	Cohort	2021 - 2022	Effectiveness; Safety
mRNA COVID-19 vaccine safety among children and adolescents: a Canadian National Vaccine Safety Network cohort study	Soe 2024	Comirnaty; Spikevax	Cohort	2021 - 2023	Effectiveness; Safety
Reported Adverse Events Following SARS-CoV-2 Vaccinations in the Canadian Province of Alberta and Associated Risk Factors: A Retrospective Cohort Study	Mansou 2024	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety
Near real-time surveillance of safety outcomes in US COVID-19 vaccine recipients aged 12 to 64 years.	Lloyd 2022	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety
BNT162b2 Versus mRNA-1273 Vaccines: Comparative Analysis of Long-Term Protection Against SARS-CoV-2 Infection and Severe COVID-19 in Qatar.	Chemaitelly 2024	Comirnaty; Spikevax	Cohort	2023 - 2024	Effectiveness
Safety outcomes following COVID-19 vaccination and infection in 5.1 million children in England.	Copland 2024	Comirnaty; Spikevax	Self-controlled Case Series	2021 - 2022	Safety
Effect of COVID-19 Vaccination on Thyroid Disease in 7 Million Adult and 0.2 Million Adolescent Vaccine Recipients	Bea 2025	Comirnaty; Spikevax	Self-controlled Case Series	2021 - 2022	Safety
Real-life safety profile of mRNA vaccines for COVID-19: An analysis of VAERS database.	Santi Laurini 2023	Comirnaty; Spikevax	Surveillance Study: VAERS	2020 - 2021	Safety
Adverse Events and Safety Profile of the COVID-19 Vaccines in Adolescents: Safety Monitoring for Adverse Events Using Real-World Data	Lee 2022	Comirnaty; Spikevax	Surveillance Study: VAERS	2021 - 2022	Safety

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Short-Term Relative Effectiveness of Homologous NVX-CoV2373 and BNT162b2 COVID-19 Vaccinations in South Korea	Gwak 2024	Comirnaty; Nuvaxovid	Cohort	2022	Safety
Safety of Monovalent BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and NVX-CoV2373 (Novavax) COVID-19 Vaccines in US Children Aged 6 months to 17 years	Hu 2023	Comirnaty; Spikevax; Nuvaxovid	Cohort	2022 - 2023	Safety
Determinants of COVID-19 vaccine-induced myocarditis	Rose 2024	Comirnaty; Spikevax; Nuvaxovid	Surveillance Study: VAERS	2022 - 2023	Safety
Effectiveness of 2024–2025 COVID-19 Vaccines in Children in the United States — VISION, August 29, 2024–September 2, 2025	Irving 2025	Comirnaty; Spikevax; Nuvaxovid	Case-control	2024-2025	Effectiveness

GSDB: Global Safety Database, VAERS: Vaccine Adverse Event Reporting System

Table D3.49. Details for Select Studies for Adolescents

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Andersen 2025[132]	US	2023 – 2024	Comirnaty	Retrospective Cohort using HealthVerity Claims from California and Louisiana N=2,449,261	34,389 children aged 5 – 17 who received an XBB.1.5-adapated BNT162b2 vaccine. 60% were aged 12 – 17	Adjusted Vaccine Effectiveness among children 12 – 17 • Covid-19 ED or UC Visit: 64% (95%CI: 33%, 81%) • ED, UC, or Hospitalization: 65% (95%CI: 35%, 81%) • Any ARI, ED, or UC Visit: 29% (95%CI: 21%, 37%) No Covid-19 associated hospitalizations in vaccinated group
Tartof 2024[133]	US	2023 – 2024	Comirnaty	Test-negative case control study N=15,233	5,399 participants 12 – 17 years old, 264 of which received Comirnaty	Adjusted Vaccine Effectiveness Against Hospital Admission, ED or UC visit (all test results): • 63% (20%, 83%)

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Gwak 2024[134]	South Korea	2023	Comirnaty; Nuvaxovid	Retrospective cohort study among ≥ 12 year olds using Korea Disease Control and Prevention Agency Covid-19 National Health Insurance Service (K-COV-N) Database N= 137,845	Homologous Primary Series 1) NVX-CoV-2373 (n=104,004) 2) BNT162b2 (n=33,841)	Adjusted Hazard Ratios for any lab-confirmed or severe SAR-CoV-2 infection following homologous primary series and booster: **30 Days: Primary Series** • Any: 0.9 (95%CI: 0.86, 0.95) • Severe: 0.62 (95%CI: 0.37, 1.04) **30 Days: Booster** • Any: 0.85 (95%CI: 0.7, 1.04) • Severe: 0.55 (95%CI: 0.13, 2.27) **180 Days: Primary Series** • Any: 0.9 (95%CI: 0.87, 0.93) • Severe: 0.65 (95%CI: 0.48, 0.88) **180 Days: Booster** • Any: 1.15 (95%CI: 1.01, 1.3) • Severe: 0.39 (95%CI: 0.2, 0.75)

ARI: acute respiratory infection, CI: confidence interval, ED: emergency department, N: total number, UC: urgent care, %: percent

Adults Over 18 Years Old

Table D3.50. Observational Trials Identified Reporting Effectiveness and/or Safety for Adults Over 18

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Differences in Long-COVID Symptoms between Vaccinated and Non-Vaccinated (BNT162b2 Vaccine) Hospitalized COVID-19 Survivors Infected with the Delta Variant	Fernández-de-las-Peñas 2022	Comirnaty	Cohort	2020 - 2021	Safety
Safety of BNT162b2 mRNA COVID-19 Vaccine Batches: A Nationwide Cohort Study.	Hviid 2025	Comirnaty	Cohort	2020 - 2023	Safety
Adverse Events Following the BNT162b2 mRNA COVID-19 Vaccine (Pfizer-BioNTech) in Aotearoa New Zealand.	Walton 2023	Comirnaty	Cohort	2021 - 2022	Safety
Prevalence of Adverse Events Reported Following the First Dose of COVID-19 Vaccines in Bahia State, Brazil, from 2021 to 2022	Saavedra 2025	Comirnaty	Cohort	2021 - 2022	Safety

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Effectiveness of BNT162b2 BA.4/5 Bivalent COVID-19 Vaccine against Long COVID Symptoms: A US Nationwide Study	Di Fusco 2024	Comirnaty	Cohort	2022 - 2023	Safety
Impact of Bivalent BA.4/5 BNT162b2 COVID-19 Vaccine on Acute Symptoms, Quality of Life, Work Productivity and Activity Levels among Symptomatic US Adults Testing Positive for SARS-CoV-2 at a National Retail Pharmacy	Di Fusco 2023	Comirnaty	Cohort	2022 - 2023	Effectiveness
Effectiveness of BNT162b2 XBB.1.5 vaccine in immunocompetent adults using tokenization in two U.S. states.	Andersen 2025	Comirnaty	Cohort	2023 - 2024	Effectiveness
2024-2025 BNT162b2 COVID-19 vaccine effectiveness in non-immunocompromised adults: mid-season estimates from vaccine registries in two states linked to administrative claims.	Andersen 2025	Comirnaty	Cohort	2024 - 2025	Effectiveness
Vaccine Effectiveness of BNT162b2 and CoronaVac against SARS-CoV-2 Omicron BA.2 in CKD.	Cheng 2024	Comirnaty	Case-control	2021 - 2022	Effectiveness
Effectiveness of BNT162b2 XBB Vaccine Against XBB and JN.1 Sublineages	Tartof 2024	Comirnaty	Case-control	2023 - 2024	Effectiveness
Effectiveness of BNT162b2 XBB vaccine in the US Veterans Affairs Healthcare System	Caffrey 2024	Comirnaty	Case-control	2023 - 2024	Effectiveness
Early effectiveness of the BNT162b2 KP.2 vaccine against COVID-19 in the US Veterans Affairs Healthcare System.	Appaneal 2025	Comirnaty	Case-control	2024 - 2025	Effectiveness
Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection.	Patone 2021	Comirnaty	Self-controlled Case Series	2020 - 2021	Safety
Risk of adverse events after Omicron XBB-adapted BNT162b2 COVID-19 vaccination in the United States	Sun 2025	Comirnaty	Self-controlled Case Series	2023 - 2024	Safety
mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial.	Oosting 2021	Spikevax	Cohort	2020 - 2021	Safety
Effectiveness of the 2023-2024 Omicron XBB.1.5-containing mRNA COVID-19 Vaccine (mRNA-1273.815) in Preventing COVID-19-related Hospitalizations and Medical Encounters Among Adults in the United States	Kopel 2024	Spikevax	Cohort	2023 - 2024	Effectiveness
Evaluating the Effectiveness of mRNA-1273.815 Against COVID-19 Hospitalization Among Adults Aged ≥ 18 Years in the United States	Wilson 2025	Spikevax	Cohort	2023 - 2024	Effectiveness

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Effectiveness of 2023-2024 Mrna-1273 Xbb.1.5 Vaccine Against Covid-19 Associated Hospitalizations and Medically Attended Covid-19 in the United States	Zheng 2025	Spikevax	Cohort	2023 - 2024	Effectiveness
Evaluating the Effectiveness of 2024-2025 Seasonal mRNA-1273 Vaccination Against COVID-19-Associated Hospitalizations and Medically Attended COVID-19 among adults aged ≥ 18 years in the United States	Wilson 2025	Spikevax	Cohort	2024 - 2025	Effectiveness
Evaluating the Effectiveness of 2024-2025 Seasonal mRNA-1273 Vaccination Against COVID-19-Related Hospitalizations and Medically Attended COVID-19 Among Adults Aged ≥ 18 years in the United States: An Observational Matched Cohort Study	Vicic 2026	Spikevax	Cohort	2024 - 2025	Effectiveness
Global Safety Assessment of Adverse Events of Special Interest Following 2 Years of Use and 772 Million Administered Doses of mRNA-1273	Urdaneta 2024	Spikevax	Surveillance Study: Moderna GSDB	2020 - 2022	Safety
Cohort study of cardiovascular safety of different COVID-19 vaccination doses among 46 million adults in England.	Ip 2024	Comirnaty; Spikevax	Cohort	2020 - 2022	Safety
Surveillance for Adverse Events After COVID-19 mRNA Vaccination.	Klein 2021	Comirnaty; Spikevax	Cohort	2020 - 2021	Safety
Pulmonary embolism after SARS-CoV-2 vaccination	Zethelius 2024	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety
Adverse outcomes of SARS-CoV-2 infection with delta and omicron variants in vaccinated versus unvaccinated US veterans: retrospective cohort study.	Bohnert 2023	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety
Reported Adverse Events Following SARS-CoV-2 Vaccinations in the Canadian Province of Alberta and Associated Risk Factors: A Retrospective Cohort Study	Mansou 2024	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety
Short-Term Relative Effectiveness of Homologous NVX-CoV2373 and BNT162b2 COVID-19 Vaccinations in South Korea	Gwak 2024	Comirnaty; Nuvaxovid	Cohort	2021 - 2022	Safety
Cardiovascular events following coronavirus disease 2019 vaccination in adults: a nationwide Swedish study	Xu 2025	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety
Risk of Adverse Events Following Monovalent Third or Booster Dose of COVID-19 mRNA Vaccination in U.S. Adults Ages 18 Years and Older	Shoaibi 2024	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals.	Faksova 2024	Comirnaty; Spikevax	Cohort	2022 - 2023	Safety
Comparative Effectiveness of Bivalent (Original/Omicron BA.4/BA.5) COVID-19 Vaccines in Adults	Kopel 2023	Comirnaty; Spikevax	Cohort	2022 - 2023	Effectiveness
COMPARATIVE EFFECTIVENESS OF THE BIVALENT COVID-19 MRNA VACCINES, MRNA1273-222 AND BNT162B2, IN ADULTS WITH CHRONIC LUNG DISEASES IN THE UNITED STATES	Kopel 2024	Comirnaty; Spikevax	Cohort	2022 - 2023	Effectiveness
Comparative Effectiveness of the Bivalent (Original/Omicron BA.4/BA.5) mRNA COVID-19 Vaccines mRNA-1273.222 and BNT162b2 Bivalent in Adults with Underlying Medical Conditions in the United States	Kopel 2024	Comirnaty; Spikevax	Cohort	2022 - 2023	Effectiveness
Real-world effectiveness of NVX-CoV2373 and BNT162b2 mRNA COVID-19 vaccination in South Korea	Gwak 2024	Comirnaty; Nuvaxovid	Cohort	2022 - 2023	Effectiveness
BNT162b2 Versus mRNA-1273 Vaccines: Comparative Analysis of Long-Term Protection Against SARS-CoV-2 Infection and Severe COVID-19 in Qatar.	Chemaitelly 2024	Comirnaty; Spikevax	Cohort	2023 - 2024	Effectiveness
Evaluating the safety of XBB.1.5-containingCOVID-19 mRNA vaccines using a self-controlled case series study	Pan 2025	Comirnaty; Spikevax	Self-controlled Case Series	2023 - 2024	Safety
Analysis of Allergy and Hypersensitivity Reactions to COVID-19 Vaccines According to the EudraVigilance Database.	Romantowski 2024	Comirnaty; Spikevax	Case-control	2022 - 2023	Safety
Real-life safety profile of mRNA vaccines for COVID-19: An analysis of VAERS database.	Santi Laurini 2023	Comirnaty; Spikevax	Surveillance Study: VAERS	2020 - 2021	Safety
Reactogenicity within 2 weeks after mRNA COVID-19 vaccines: Findings from the CDC v-safe surveillance system.	Chapin-Bardales 2021	Comirnaty; Spikevax	Surveillance Study: CDC V-Safe	2020 - 2021	Safety
Cardiac adverse drug reactions to COVID-19 vaccines. A cross-sectional study based on the Europe-wide data.	Nazar 2024	Comirnaty; Spikevax; Nuvaxovid	Cross-sectional	2021 - 2022	Safety
Early Estimates of Updated 2023-2024 (Monovalent XBB.1.5) COVID-19 Vaccine Effectiveness Against Symptomatic SARS-CoV-2 Infection Attributable to Co-Circulating Omicron Variants Among Immunocompetent Adults - Increasing Community Access to Testing Program, United States, September 2023-January 2024.	Link-Gelles 2024	Comirnaty; Spikevax; Nuvaxovid	Case-control	2023 - 2024	Effectiveness

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Neuro-Ophthalmic Adverse Events of COVID-19 Infection and Vaccines: A Nationwide Cohort Study.	Han 2023	Multiple (not stratified)	Cohort	2021 - 2022	Safety
Bivalent Boosters and Risk of Postacute Sequelae Following Vaccine-Breakthrough SARS-CoV-2 Omicron Infection: A Cohort Study	Wee 2025	Multiple (not stratified)	Cohort	2021 - 2023	Safety
Monovalent XBB.1.5 COVID-19 vaccine effectiveness against hospitalisations and deaths during the Omicron BA.2.86/JN.1 period among older adults in seven European countries: A VEBIS-EHR network study.	Nunes 2024	Multiple (not stratified)	Cohort	2023 - 2024	Effectiveness
Effectiveness of 2023–2024 COVID-19 vaccines against COVID-19–associated hospitalizations among adults aged ≥18 years with end stage kidney disease — United States, September 2023–April 2024	Payne 2025	Multiple (not stratified)	Cohort	2023 - 2024	Effectiveness
Effectiveness of the 2023–2024 Formulation of the COVID-19 Messenger RNA Vaccine	Shrestha 2024	Multiple (not stratified)	Cohort	2023 - 2024	Effectiveness
Effectiveness of the 2023-to-2024 XBB.1.5 COVID-19 Vaccines Over Long-Term Follow-up	Ioannau 2025	Multiple (not stratified)	Cohort	2023 - 2024	Effectiveness
Association of 2024–2025 Covid-19 Vaccine with Covid-19 Outcomes in U.S. Veterans	Cai 2025	Multiple (not stratified)	Cohort	2024-2025	Effectiveness
2024-2025 COVID-19 mRNA Vaccine Effectiveness against Severe Disease	Jayawardena 2026	Multiple (not stratified)	Cohort	2024 - 2025	Effectiveness
Estimated 2023-2024 COVID-19 Vaccine Effectiveness in Adults	Link-Gelles 2025	Multiple (not stratified)	Case-control	2022 - 2023	Effectiveness
Effectiveness of Updated 2023-2024 (Monovalent XBB.1.5) COVID-19 Vaccination Against SARS-CoV-2 Omicron XBB and BA.2.86/JN.1 Lineage Hospitalization and a Comparison of Clinical Severity-IVY Network, 26 Hospitals, October 18, 2023-March 9, 2024.	Ma 2024	Multiple (not stratified)	Case-control	2023 - 2024	Effectiveness
Interim Effectiveness of Updated 2023–2024 (Monovalent XBB.1.5) COVID-19 Vaccines Against COVID-19–Associated Hospitalization	Link-Gelles 2024	Multiple (not stratified)	Case-control	2023 - 2024	Effectiveness

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Among Adults Aged ≥18 Years with Immunocompromising Conditions — VISION Network, September 2023–February 2024					
Interim Estimates of 2024–2025 COVID-19 Vaccine Effectiveness Among Adults Aged ≥18 Years — VISION and IVY Networks, September 2024–January 2025	Link-Gelles 2025	Multiple (not stratified)	Case-control	2024 - 2025	Effectiveness
Neurological Events Reported after COVID-19 Vaccines: An Analysis of VAERS.	Frontera 2022	Multiple (not stratified); Comirnaty; Spikevax	Surveillance Study: VAERS	2020 - 2021	Safety
COVID-19 Vaccine Adverse Events in the United States: A Temporal and Spatial Analysis	Li 2024	Multiple (not stratified)	Surveillance Study: VAERS	2021 - 2022	Safety
COVID-19–Associated Hospitalizations Among U.S. Adults Aged ≥18 Years — COVID-NET, 12 States, October 2023–April 2024	Taylor 2024	Multiple (not stratified)	Surveillance Study: COVID-NET	2023 - 2024	Effectiveness

GSDB: Global Safety Database, VAERS: Vaccine Adverse Event Reporting System, V-Safe: Vaccine Safety Monitoring System

Table D3.51. Details for Select Studies for Adults 18+

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Andersen 2025[135]	US	2024 – 2025	Comirnaty	Retrospective Cohort Study using administrative claims data N=6.9 million	People who received 2024 – 2025 BNT162b2 vaccine	Covid-19 Associated Hospitalization, Age ≥ 18 • Received vaccine: 719,540, No vaccine: 27,288,381 • Adjusted VE: 41% (95%CI: 2%, 64%)
Jayawardena 2026[136]	US	2024 – 2025	Multiple mRNA (not stratified)	Retrospective Cohort using EHR records in South	Of 157,888 individuals identified, 10,041 received	In people less than 65 years old: Vaccine Effectiveness • ED or severe care: 48.5% (95%CI: -12.0, 76.3) • Hospitalizations: 45.5% (95%CI: -95.3, 84.8)

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
				Caroline Health System N=157,988	updated 2024 – 2025 vaccine Final Matched Sample: 30,080	
Vicic 2026[137]	US	2024 – 2025	Spikevax	Matched Cohort Study N=1.1 million	596,248 people who received mRNA-1273 KP.2 vaccine were matched 1:1 to unvaccinated people	**In people ≥18** Vaccine Effectiveness • Hospitalization: 45.2% (95%CI: 37.7%, 51.8%) • Medically Attended Covid-19: 33.1% (95%CI: 30.6%, 35.4%)

CI: confidence interval, ED: emergency department, N: total number, VE: vaccine effectiveness, %: percent

Adults Over 55 to 65 Years Old

Table D3.52. Observational Trials Identified for Adults Over 55 to 65 Years Old

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Effectiveness of BNT162b2 XBB.1.5 vaccine in immunocompetent adults using tokenization in two U.S. states.	Andersen 2025	Comirnaty	Cohort	2023 - 2024	Effectiveness
2024-2025 BNT162b2 COVID-19 vaccine effectiveness in non-immunocompromised adults: mid-season estimates from vaccine registries in two states linked to administrative claims.	Andersen 2025	Comirnaty	Cohort	2024 - 2025	Effectiveness
Effectiveness of BNT162b2 XBB vaccine in the US Veterans Affairs Healthcare System	Caffrey 2024	Comirnaty	Case-control	2023 - 2024	Effectiveness
Early effectiveness of the BNT162b2 KP.2 vaccine against COVID-19 in the US Veterans Affairs Healthcare System.	Appaneal 2025	Comirnaty	Case-control	2024 - 2025	Effectiveness
Myocardial Infarction, Stroke, and Pulmonary Embolism After BNT162b2 mRNA COVID-19 Vaccine in People Aged 75 Years or Older.	Jabagi 2022	Comirnaty	Self-controlled Case Series	2020 - 2021	Safety

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection.	Patone 2021	Comirnaty	Self-controlled Case Series	2020 - 2021	Safety
Effectiveness of 2023-2024 Mrna-1273 Xbb.1.5 Vaccine Against Covid-19 Associated Hospitalizations and Medically Attended Covid-19 in the United States	Zheng 2025	Spikevax	Cohort	2023 - 2024	Effectiveness
Evaluating the Effectiveness of mRNA-1273.815 Against COVID-19 Hospitalization Among Adults Aged ≥ 18 Years in the United States	Wilson 2025	Spikevax	Cohort	2023 - 2024	Effectiveness
Effectiveness of the 2023-2024 Omicron XBB.1.5-containing mRNA COVID-19 Vaccine (mRNA-1273.815) in Preventing COVID-19-related Hospitalizations and Medical Encounters Among Adults in the United States	Kopel 2024	Spikevax	Cohort	2023 - 2024	Effectiveness
Evaluating the Effectiveness of 2024-2025 Seasonal mRNA-1273 Vaccination Against COVID-19-Associated Hospitalizations and Medically Attended COVID-19 among adults aged ≥ 18 years in the United States	Wilson 2025	Spikevax	Cohort	2024 - 2025	Effectiveness
Evaluating the Effectiveness of 2024-2025 Seasonal mRNA-1273 Vaccination Against COVID-19-Related Hospitalizations and Medically Attended COVID-19 Among Adults Aged ≥ 18 years in the United States: An Observational Matched Cohort Study	Vicic 2026	Spikevax	Cohort	2024 – 2025	Effectiveness
Global Safety Assessment of Adverse Events of Special Interest Following 2 Years of Use and 772 Million Administered Doses of mRNA-1273	Urdaneta 2024	Spikevax	Surveillance Study: Moderna GSDB	2020 - 2022	Safety
Comparative Risks of Potential Adverse Events Following COVID-19 mRNA Vaccination Among Older US Adults.	Harris 2023	Comirnaty; Spikevax	Cohort	2020 - 2021	Effectiveness; Safety
Reported Adverse Events Following SARS-CoV-2 Vaccinations in the Canadian Province of Alberta and Associated Risk Factors: A Retrospective Cohort Study	Mansou 2024	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety
Comparative Safety of BNT162b2 and mRNA-1273 Vaccines in a Nationwide Cohort of US Veterans.	Dickerman 2022	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety
Risk of Adverse Events Following Monovalent Third or Booster Dose of COVID-19 mRNA Vaccination in U.S. Adults Ages 18 Years and Older	Shoaibi 2024	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Surveillance of COVID-19 vaccine safety among elderly persons aged 65 years and older.	Wong 2023	Comirnaty; Spikevax	Cohort	2021 - 2022	Safety
Comparative Effectiveness of Bivalent (Original/Omicron BA.4/BA.5) COVID-19 Vaccines in Adults	Kopel 2023	Comirnaty; Spikevax	Cohort	2022 - 2023	Effectiveness
Effectiveness of the BNT162b2 and mRNA-1273 JN.1-adapted vaccines against COVID-19-associated hospitalisation and death: a Danish, nationwide, register-based, cohort study.	Hansen 2025	Comirnaty; Spikevax	Cohort	2024 - 2025	Effectiveness
Reactogenicity within 2 weeks after mRNA COVID-19 vaccines: Findings from the CDC v-safe surveillance system.	Chapin-Bardales 2021	Comirnaty; Spikevax	Surveillance Study: CDC V-Safe	2020 - 2021	Safety
Real-life safety profile of mRNA vaccines for COVID-19: An analysis of VAERS database.	Santi Laurini 2023	Comirnaty; Spikevax	Surveillance Study: VAERS	2020 - 2021	Safety
Evaluation of potential adverse events following COVID-19 mRNA vaccination among adults aged 65 years and older: Two self-controlled studies in the U.S.	Shoaibi 2023	Comirnaty; Spikevax	Self-controlled Case Series	2020 - 2022	Safety
Monovalent XBB.1.5 COVID-19 vaccine effectiveness against hospitalisations and deaths during the Omicron BA.2.86/JN.1 period among older adults in seven European countries: A VEBIS-EHR Network Study	Nunes 2024	Multiple (not stratified)	Cohort	2023 - 2024	Effectiveness
Monovalent XBB.1.5 COVID-19 vaccine effectiveness against hospitalisations and deaths during the Omicron BA.2.86/JN.1 period among older adults in seven European countries: A VEBIS-EHR network study.	Nunes 2024	Multiple (not stratified)	Cohort	2023 - 2024	Effectiveness
Comparative effectiveness of monovalent XBB.1.5 containing covid-19 mRNA vaccines in Denmark, Finland, and Sweden: target trial emulation based on registry data	Andersson 2024	Multiple (not stratified)	Cohort	2023 - 2024	Effectiveness
Association of 2024–2025 Covid-19 Vaccine with Covid-19 Outcomes in U.S. Veterans	Cai 2025	Multiple (not stratified)	Cohort	2024-2025	Effectiveness
2024-2025 COVID-19 mRNA Vaccine Effectiveness against Severe Disease	Jayawardena 2026	Multiple (not stratified)	Cohort	2024 - 2025	Effectiveness

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Data Type
Estimated 2023-2024 COVID-19 Vaccine Effectiveness in Adults	Link-Gelles 2025	Multiple (not stratified)	Case-control	2022 - 2023	Effectiveness
Monovalent mRNA XBB.1.5 vaccine effectiveness against COVID-19 hospitalization in Quebec, Canada: Impact of variant replacement and waning protection during 10-month follow-up	Carazo 2025	Multiple (not stratified)	Case-control	2023 - 2024	Effectiveness
Interim Estimates of 2024–2025 COVID-19 Vaccine Effectiveness Among Adults Aged ≥18 Years — VISION and IVY Networks, September 2024–January 2025	Link-Gelles 2025	Multiple (not stratified)	Case-control	2024 - 2025	Effectiveness
COVID-19–Associated Hospitalizations Among U.S. Adults Aged ≥18 Years — COVID-NET, 12 States, October 2023–April 2024	Taylor 2024	Multiple (not stratified)	Surveillance Study: COVID-NET	2023 - 2024	Effectiveness

GSDB: Global Safety Database, VAERS: Vaccine Adverse Event Reporting System, V-Safe: Vaccine Safety Monitoring System

Table D3.53. Details for Select Studies for Adults 55-65+

Author & Year Published	Location	Data Year Range	Vaccine	Study Design & N	Study Arms	Key Results
Andersen 2025[135]	US	2024 – 2025	Comirnaty	Retrospective Cohort Study using administrative claims data N= 6.9 million	People who received 2024 – 2025 BNT162b2 vaccine	Covid-19 Associated Hospitalization, Age ≥ 50 • Received vaccine: 459,439, No vaccine: 10,830,028 • Adjusted VE: 45% (95%CI: 6%, 68%) Covid-19 Associated Hospitalization, Age ≥ 65 • Received vaccine: 230,842, No vaccine: 4,333,219 • Adjusted VE: 46% (95%CI: 3%, 70%)
Jayawardena 2026[136]	US	2024 – 2025	Multiple mRNA (not stratified)	Retrospective Cohort using EHR records in South Caroline Health System	Of 157,888 individuals identified, 10,041 received updated 2024 – 2025 vaccine	In people 65+ years or older: Vaccine Effectiveness • ED or severe care: 39.4% (95%CI: 11.1, 58.8) • Hospitalizations: 46.3% (95%CI: 10.8, 67.6)

Author & Year Published	Location	Data Year Range	Vaccine	Study Design & N	Study Arms	Key Results
				N=157,988	Final Matched Sample: 30,080	
Vicic 2026[137]	US	2024 – 2025	Spikevax	Matched Cohort Study N=1.1 million	596,248 people who received mRNA-1273 KP.2 vaccine were matched 1:1 to unvaccinated people	**In people 65+ years or older** Vaccine Effectiveness • Hospitalization: 47.1% (95%CI: 39.3%, 53.8%) • Medically Attended Covid-19: 37.5% (95%CI: 34.8%, 40.2%) **In people 18-94 high-risk / ≥ 65** Vaccine Effectiveness • Hospitalization: 44.9% (95%CI: 37.0%, 51.7%) • Medically Attended Covid-19: 34.0% (95%CI: 31.4%, 36.5%)

CI: confidence interval, ED: emergency department, N: total number, VE: vaccine effectiveness, %: percent

Pregnant Women

Table D3.54. Observational Trials Identified for Pregnant Women Subpopulation (N=30)

Title	Author and Publication Year	Vaccine Type	Study Type	Data Year Range
Obstetric and Neonatal Outcomes following COVID-19 Vaccination in Pregnancy	Peretz-Machluf 2022	Comirnaty	Cohort	2020 - 2021
Safety of COVID-19 vaccination in pregnant women: A study of the adverse perinatal outcomes.	Kugelman 2023	Comirnaty	Cohort	2020 - 2021
Association of BNT162b2 COVID-19 Vaccination During Pregnancy With Neonatal and Early Infant Outcomes.	Goldshtein 2022	Comirnaty	Cohort	2021 - 2022
Effectiveness of a third BNT162b2 mRNA COVID-19 vaccination during pregnancy: a national observational study in Israel.	Guedalia 2022	Comirnaty	Cohort	2021 - 2022
Maternal third dose of BNT162b2 mRNA vaccine and risk of infant COVID-19 hospitalization.	Lipschuetz 2023	Comirnaty	Cohort	2021 - 2022

Title	Author and Publication Year	Vaccine Type	Study Type	Data Year Range
Effectiveness of BNT162b2 Vaccination During Pregnancy in Preventing Hospitalization for Severe Acute Respiratory Syndrome Coronavirus 2 in Infants.	Danino 2023	Comirnaty	Case-control	2021 - 2022
Association of BNT162b2 SARS-CoV-2 vaccination during pregnancy with postnatal outcomes in premature infants.	Tamir-Hostovsky 2024	Comirnaty	Case-control	2021 - 2022
COVID-19 mRNA vaccine in pregnancy: Results of the Swiss COVI-PREG registry, an observational prospective cohort study.	Favre 2022	Comirnaty; Spikevax	Cohort	2021 - 2022
COVID-19 Vaccination During Pregnancy and Major Structural Birth Defects.	Rowe 2025	Comirnaty; Spikevax	Cohort	2021 - 2022
Safety of COVID-19 vaccines in pregnancy: a Canadian National Vaccine Safety (CANVAS) network cohort study.	Sadarangani 2022	Comirnaty; Spikevax	Cohort	2021 - 2022
mRNA COVID-19 vaccination early in pregnancy and the risk of spontaneous abortion in an international pregnancy registry.	Mansour 2023	Comirnaty; Spikevax	Cohort	2021 - 2022
Maternal Exposures to COVID-19 Vaccine and Adverse Birth Outcomes: National Population Study in Korea.	Kim 2025	Comirnaty; Spikevax	Cohort	2022 - 2023
Coronavirus Disease 2019 (COVID-19)Vaccination and Spontaneous Abortion	Sheth 2025	Comirnaty; Spikevax	Case-control	2020 - 2021
Coronavirus Disease 2019 (COVID-19)Vaccination and Stillbirth in the VaccineSafety Datalink	Denoble 2024	Comirnaty; Spikevax	Case-control	2021 - 2022
Post-authorization surveillance of adverse events following COVID-19 vaccines in pregnant persons in the vaccine adverse event reporting system (VAERS), December 2020 - October 2021.	Moro 2022	Comirnaty; Spikevax	Surveillance Study: VAERS	2020 - 2021
Safety monitoring of bivalent mRNA COVID-19 vaccine among pregnant persons in the vaccine adverse event reporting System - United States, September 1, 2022 - March 31, 2023.	Moro 2024	Comirnaty; Spikevax	Surveillance Study: VAERS	2022 - 2023
COVID-19 vaccine initiation in pregnancy and risk for adverse neonatal outcomes among United States military service members, January–December 2021	Hall 2025	Multiple (not stratified)	Cohort	2020 - 2021
The effect of COVID-19 vaccination and booster on maternal-fetal outcomes: a retrospective multicenter cohort study	Piekos 2022	Multiple (not stratified)	Cohort	2021 - 2022

Title	Author and Publication Year	Vaccine Type	Study Type	Data Year Range
A population-based matched cohort study of major congenital anomalies following COVID-19 vaccination and SARS-CoV-2 infection.	Calvert 2023	Multiple (not stratified)	Cohort	2021 - 2022
COVID-19 vaccination and birth outcomes of 186,990 women vaccinated before pregnancy: an England-wide cohort study	Suseeladevi 2024	Multiple (not stratified)	Cohort	2021 - 2022
COVACPREG, a French prospective cohort study of women vaccinated against COVID-19 during pregnancy	Lacroix 2025	Multiple (not stratified)	Cohort	2021 - 2022
BNT162b2 mRNA COVID-19 vaccine effectiveness in pregnancy: Emulating trial NCT04754594 using observational data from Norwegian health registries.	Zidan 2025	Multiple (not stratified)	Cohort	2021 - 2022
COVID-19 vaccination during pregnancy is not associated with an increased risk of severe postpartum hemorrhage	Magnus 2024	Multiple (not stratified)	Cohort	2021 - 2022
Comparison of Perceived Adverse Events After COVID- 19 Vaccination Between Pregnant and Non pregnant Women Using Two Cohort Studies in the Netherlands	Woesternberg 2025	Multiple (not stratified)	Cohort	2021 - 2022
The Role of Vaccination in Maternal and Perinatal Outcomes Associated With COVID-19 in Pregnancy.	McClymont 2026	Multiple (not stratified)	Cohort	2021 - 2022
Post–Acute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) After Infection During Pregnancy	Metz 2024	Multiple (not stratified)	Cohort	2021 - 2023
COVID-19 mRNA Vaccination in Pregnancy and Risk of Infection in Early Childhood	Eide 2026	Multiple (not stratified)	Cohort	2021-2023
Association between maternal mRNA covid- 19 vaccination in early pregnancy and major congenital anomalies in offspring: population based cohort study with sibling matched analysis	Jorgensen 2024	Multiple (not stratified)	Cohort	2022 - 2023
COVID- 19 Vaccine Safety in Pregnancy, A Nested Case–Control Study in Births From April 2021 to March 2022, England	Mensah 2024	Multiple (not stratified)	Case-control	2021 - 2022
Safety of COVID-19 vaccines in pregnancy: a VAERS based analysis.	Santi Laurini 2023	Multiple (not stratified)	Surveillance Study: VAERS	2021 - 2022
COVID-19–Associated Hospitalizations and Maternal Vaccination Among Infants Aged <6 Months — COVID-NET, 12 States, October 2022–April 2024	Havers 2024	Multiple (not stratified)	Surveillance Study: COVID-NET	2023 - 2024

Table D3.55. Outcomes Reported in Trials for Pregnant Women – Maternal Effectiveness and Safety

Author & Year Published	Covid Infection	Hospitalization	ICU Admission	Spontaneous Abortion	Maternal Death	Post-Partum Hemorrhage
McClymont 2026	✓	✓	✓			
Guedalia 2022	✓	✓			✓	
Mensah 2024	✓		✓			
Moro 2024	✓	✓		✓		✓
Magnus 2024						✓
Sadarangani 2022	✓	✓		✓		
Zidan 2025	✓	✓				
Favre 2022				✓		
Mansour 2023				✓		
Sheth 2025				✓		
Santi Laurini 2023				✓		
Moro 2022	✓	✓		✓	✓	✓

ICU: intensive care unit

Table D3.56. Outcomes Reported in Trials for Pregnant Women / Infants – Effectiveness and Safety

Author & Year Published	Pre-term Birth	Perinatal Death	Neonatal Death	Stillbirth	Low Birth Weight	Hospitalization / ICU Admission	Congenital Anomaly
McClymont 2026	✓						
Mensah 2024	✓	✓	✓	✓	✓	✓	
Piekos 2022	✓			✓	✓		
Moro 2024	✓			✓	✓	✓	
Sadarangani 2022	✓			✓			
Suseeladevi 2024	✓			✓	✓		
Favre 2022	✓					✓	
Kugelman 2023	✓			✓		✓	
Peretz-Machluf 2022	✓		✓	✓		✓	
Santi Laurini 2023	✓	✓		✓			
Moro 2022	✓		✓	✓	✓	✓	✓
Havers 2024						✓	

Author & Year Published	Pre-term Birth	Perinatal Death	Neonatal Death	Stillbirth	Low Birth Weight	Hospitalization / ICU Admission	Congenital Anomaly
Jorgensen 2024							✓
Kim 2025	✓						✓
Calvert 2023							✓
Rowe 2025							✓
Denoble 2024				✓			
Lipshuetz 2023	✓	✓				✓	✓
Danino 2023						✓	
Goldshtein 2022	✓	✓			✓	✓	
Hall 2025	✓				✓	✓	
Eide 2026						✓	

ICU: intensive care unit

Table D3.57. Details for Select Studies on Pregnancy

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Maternal Effectiveness and Safety						
McClymont 2026[72]	Canada	2021 - 2022	Multiple (not separated)	Population-level surveillance using CANCOVID-Preg Database N= 19,899	1) Vaccinated (n=14,367) (80% prior to pregnancy, 20% during pregnancy) 2) Unvaccinated (n=5,532)	**Vaccination associated with a lower risk of:** **Hospitalization:** - Delta: RR 0.38 (95%CI 0.30 - 0.48) Absolute Risk Difference [ARD] 8.7% (95%CI: 7.3% - 10.2%) - Omicron: RR 0.38 (95%CI: 0.27-0.53); ARD 3.8% (95%CI: 2.4% - 5.2%) **Critical Care Unit Admission:** - Delta: RR 0.10 (95%CI: 0.04-0.26); ARD 2.4% (95%CI: 1.8% - 2.9%) - Omicron: RR 0.10 (95%CI: 0.03-0.29); ARD 0.85% (95%CI: 0.27% - 1.44%) **Pre-term Birth:** - Delta: RR 0.80 (95%CI: 0.66-0.98); ARD 1.8% (95%CI, 0.3% - 3.4%)

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
						- Omicron: RR 0.64 (95%CI: 0.52-0.77); ARD 4.1% (95%CI, 2.0% - 6.2%).
Mensah 2024[37]	UK	2021-2022	Comirnaty, Spikevax, Chadox1	Case-control N=514,013	1.) Unvaccinated pregnant participants 2.) Vaccinated pregnant participants	**Comirnaty** Odds of Admission to ICU: aOR = 0.88 (95%CI: 0.77 - 1.00) Odds of Low birthweight: aOR = 0.89 (95%CI: 0.82 - 0.97) Odds of Pre-term birth: aOR = 0.86 (95%CI: 0.83 - 0.90) Odds of Stillbirth: aOR = 0.85 (95%CI: 0.69 - 1.05) Odds of Neonatal Death: aOR = 1.32 (95%CI: 0.89 - 1.97) Odds of Perinatal Death: aOR = 0.94 (0.78 - 1.14) **Spikevax** Odds of Admission to ICU: aOR = 0.65 (95%CI: 0.52 - 0.81) Odds of Low birthweight: aOR = 0.80 (95%CI: 0.70 - 0.92) Odds of Pre-term birth: aOR = 0.86 (95%CI: 0.81 - 0.93) Odds of Stillbirth: aOR = 0.97 (95%CI: 0.71 - 1.32) Odds of Neonatal Death: aOR = 1.37 (95%CI: 0.76 - 2.48) Odds of Perinatal Death: aOR = 1.12 (0.84 - 1.49)
Suseeladevi 2024[76]	UK	2021-2022	Comirnaty, Chadox1	Cohort study N=186,990	1.) Vaccinated before pregnancy 2.) Not Vaccinated before pregnancy	Covid-19 vaccination within 12 months before pregnancy was associated lower risk of: • Very and extremely preterm birth: aHR:0.74 (95%CI:0.63, 0.88) • Small for- gestational age: 0.94 (95%CI: 0.88, 1.00) • Stillbirth risk in those receiving an mRNA vaccine: 0.72 95%CI: 0.52, 1.00) Incidence of venous thromboembolism during pregnancy was higher amongst women receiving a viral vector, but not an mRNA vaccine (1.54 [1.10, 2.16] and 1.02 [0.70, 1.50], respectively).
Infant Effectiveness and Safety						

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Jorgensen 2024[77]	Canada	2021-2023	Comirnaty, Spikevax	Population based cohort study with sibling matched analysis N=69,132	1) Maternal Covid-19 vaccination (n=34,181) 2) No maternal Covid-19 vaccination (n=34,951)	**Overall: Vaccination vs. No Vaccination** Congenital Malformation aPR: 0.89 (95%CI: 0.79 - 1.01) **Comirnaty vs. No Vaccination** Congenital Malformation aPR: 0.91 (0.80 - 1.04) **Spikevax vs. No Vaccination** Congenital Malformation aPR: 0.88 (0.65 - 1.21)
Kim 2025[78]	South Korea	2022	Comirnaty, Spikevax	Retrospective cohort study N=106,692	1.) Covid-19 Vaccination during pregnancy (n=8,966) 2.) No Covid-19 Vaccination during pregnancy	**Overall: Vaccination vs. No Vaccination** Preterm Birth OR: 1.03 (95%CI: 0.77 - 1.36) Congenital Malformations OR: 0.90 (95%CI: 0.72 - 1.12) **Comirnaty vs. No Vaccination** Preterm Birth OR: 0.72 (95%CI: 0.63 - 0.82) Congenital Malformation OR: 0.98 (95%CI: 0.88 - 1.09) **Spikevax vs. No Vaccination** Preterm Birth OR: 0.82 (95%CI: 0.66 - 1.03) Congenital Malformation OR: 0.90 (95%CI 0.74 - 1.10)
Denoble 2024[79]	US	2021 - 2022	Comirnaty, Spikevax, J&J	Matched Case-control study in Vaccine Safety Datalink N=1098	1) Stillbirths (n=276) 2) Live births (n=822)	**Overall: Vaccination vs. No Vaccination** 38.4% stillbirths versus 39.3% live births in vaccinated individuals aOR: 1.02 (95%CI: 0.76 - 1.37) No association between vaccination and stillbirth by number of vaccine doses during pregnancy or vaccination within 6 weeks before stillbirth compared with no vaccination. **Comirnaty vs. No Vaccination** Stillbirth aOR: 1.00 (95%CI: 0.69 - 1.43)

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
						Spikevax vs. No Vaccination Stillbirth aOR: 1.00 (95%CI: 0.62 - 1.62)
Hall 2025[80]	US	2021	Comirnaty, Spikevax, Ad26.Cov2s	Retrospective cohort study N=7,184	1.) Exposed to first COVID-19 vaccine during pregnancy (n=2,867) 2.) Unexposed to any COVID-19 vaccine in pregnancy (n=4,317)	**Preterm Birth (<37 wk gestation) aHR:** 1.02 (95%CI: 0.83 - 1.26) **Low Birthweight aHR:** 1.01 (95%CI: 0.80 - 1.28) **Neonatal ICU Admission aRR:** 0.90 (95%CI: 0.75 - 1.07)
Peretz-Macluf 2022[38]	Israel	2021	Comirnaty	Retrospective Cohort study N=3,700	1) Vaccinated (n=3,240) 2) Unvaccinated	• Vaccine was not significantly associated with increased risk of neonatal adverse outcomes including respiratory complications and NICU hospitalization
Havers 2024[34]	US	2022 – 2024	mRNA (not specified)	COVID-NET Surveillance Study	1) Infants with maternal vaccination (n=144) 2) Infants with no maternal vaccination during pregnancy (n=921)	Percentage of hospitalized infants whose mothers were vaccinated significantly decreased from 17.6% (132 of 745) during 2022–23 to 4.3% (12 of 320) during 2023–24 (p<0.001)
Lipshuetz 2023[39]	Israel	2021 – 2022	Comirnaty	Cohort Study	1) Born to mothers	- Among 48,868 live-born infants included in the analysis, rates of Covid-19 hospitalization were 0.4%, 0.6% and 0.7%

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
				N=48,868	vaccinated with 2 doses >5 months prior to delivery (n=13,364) 2) Born to mothers vaccinated with 3 doses >5 months prior to delivery (n=22,321) 3) Born to unvaccinated mothers (n=13,273)	in the third-dose, second-dose and unvaccinated groups, respectively. - Compared to the second dose, the third dose was associated with reduced infant hospitalization with estimated effectiveness of 53% (95% CI: 36 to 65%). - Greater protection was associated with a shorter interval between vaccination and delivery. - A third maternal dose during pregnancy reduced the risk of infant hospitalization for Covid-19 during the first 4 months of life, supporting clinical and public health guidance for maternal booster vaccination to prevent infant Covid-19 hospitalization.

aHR: adjusted hazard ratio, aOR: adjusted odds ratio, aRD: adjusted risk difference, aRR: adjusted risk ratio, CI: confidence interval, ICU: intensive care unit, n: number, N: total number, RR: risk ratio, %: percent

Comorbid Conditions

Table D3.58. Observational Trials Identified for Comorbid Conditions Subpopulation

Title	Author and Publication Year	Vaccine Type	Comorbid Condition	Observational Study	Data Range
BNT162b2 vaccine effectiveness in chronic kidney disease patients—an observational study	Bielopolski 2022	Comirnaty	CKD	Cohort	2020 - 2021
Vaccine Effectiveness of BNT162b2 and CoronaVac against SARS-CoV-2 Omicron BA.2 in CKD.	Cheng 2024	Comirnaty	CKD	Case-control	2021 - 2022
mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or	Oosting 2021	Spikevax	Patients with solid tumors receiving active systemic therapy	Cohort	2020 - 2021

Title	Author and Publication Year	Vaccine Type	Comorbid Condition	Observational Study	Data Range
chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial.					
Effectiveness of 2023-2024 Mrna-1273 Xbb.1.5 Vaccine Against Covid-19 Associated Hospitalizations and Medically Attended Covid-19 in the United States	Zheng 2025	Spikevax	Immunocompromised*	Cohort	2023 - 2024
Evaluating the Effectiveness of mRNA-1273.815 Against COVID-19 Hospitalization Among Adults Aged ≥ 18 Years in the United States	Wilson 2025	Spikevax	High-risk; Immunocompromised†	Cohort	2023 - 2024
Real-world effectiveness of NVX-CoV2373 COVID-19 vaccine in immunocompromised individuals in South Korea (pre-print)	Gwak 2025	Nuvaxovid	Rheumatologic/inflammatory disorders; Solid organ malignancy; Hematologic malignancy; Organ or stem cell transplant	Cohort	2022 - 2023
Comparative Effectiveness of the Bivalent (Original/Omicron BA.4/BA.5) mRNA COVID-19 Vaccines mRNA-1273.222 and BNT162b2 Bivalent in Adults with Underlying Medical Conditions in the United States	Kopel 2024	Comirnaty; Spikevax	Diabetes; Cerebro/cardiovascular disease; Chronic Lung Disease; Immunocompromised‡; CKD	Cohort	2022 - 2023
COMPARATIVE EFFECTIVENESS OF THE BIVALENT COVID-19 MRNA VACCINES, MRNA1273-222 AND BNT162B2, IN ADULTS WITH CHRONIC LUNG DISEASES IN THE UNITED STATES (conference abstract)	Kopel 2024	Comirnaty; Spikevax	Chronic Lung Disease	Cohort	2022 - 2023
Effectiveness of 2023–2024 COVID-19 vaccines against COVID-19–associated hospitalizations among adults aged ≥18 years with end stage kidney disease — United States, September 2023–April 2024	Payne 2025	Multiple (not stratified)	End stage kidney disease	Cohort	2023 - 2024

Title	Author and Publication Year	Vaccine Type	Comorbid Condition	Observational Study	Data Range
Interim Effectiveness of Updated 2023–2024 (Monovalent XBB.1.5) COVID-19 Vaccines Against COVID-19–Associated Hospitalization Among Adults Aged ≥18 Years with Immunocompromising Conditions — VISION Network, September 2023–February 2024	Link-Gelles 2024	Multiple (not stratified)	Immunocompromising Conditions§	Case-control	2023 - 2024

CKD: Chronic kidney disease

*Included cancer, HIV, primary immunodeficiencies, solid or blood transplant, receiving immunosuppressive medications

†High risk included lung disease, cardiovascular disease, chronic kidney disease, diabetes mellitus type 1 and 2, mood disorders, dementia, obesity, pregnancy, current and former smoker. Immunocompromising conditions included cancer, primary immunodeficiency, HIV, organ or stem cell transplant, recent use of immunosuppressive therapies. Hospitalization rates not stratified by specific groups.

‡Included cancer, human immunodeficiency virus, primary immunodeficiencies/other immunocompromising conditions, solid organ or blood stem cell transplantation, stem cell transplantation, use of immunosuppressive medications

§Included hematological malignancy, solid malignancy, transplant, rheumatologic/inflammatory disorders, other intrinsic immune condition or immunodeficiency.

Table D3.59. Details for Select Studies on People with Comorbid Conditions

Author and Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Kopel 2024[138]	US	2022-2023	Comirnaty; Spikevax	Retrospective, observational cohort study Population: Individuals ≥18 years of age with ≥1 underlying medical condition associated with an increased risk of severe outcomes from COVID-19 as defined by the CDC* N = 1,962,547	1) Spikevax: 757,572 2) Comirnaty: 1,204,975	**Relative Vaccine Effectiveness (higher percentage = favors Spikevax)** **COVID-19 Related Hospitalizations** -Diabetes 15.1% (8.7%-21.0%) -Cerebro- /CVD 14.7% (9.0-20.1%) -Chronic lung disease 11.9% (5.1-18.2%) -Immunocompromised 15.0% (7.2-22.2%) -CKD 8.4% (0.5%-15.7%) **COVID-19-related outpatient encounter** -Diabetes 3.7% (1.2%-6.2%) -Cerebro- /CVD 7.4% (4.9-9.8%)

Author and Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
						-Chronic lung disease 3.1% (0.4-5.7%) -Immunocompromised 4.8% (1.8-7.7%) -CKD 7.6% (4.1%-11.0%)
Link-Gelles 2024[139]	US	2023 – 2024	Multiple (not stratified)	Retrospective, case-control trial using VISION network (multisite EHR-based network that utilizes a test-negative design to estimate COVID-19 VE) Population: Adults with Immunocompromising Conditions†	1) Case-patients were persons who received a positive SARS-CoV-2 test result (n=1,392) 2) Control patients were those who received a negative SARS-CoV-2 test result (n=13,194)	**No updated dose (reference group):** Among 11,990 individuals, 10% tested positive for SARS-CoV-2 with a median of 587 days since last dose, serving as the reference group for vaccine effectiveness estimates. **Received updated dose:** Among 2,596 individuals, 8% tested positive with a median of 56 days since last dose, corresponding to an unadjusted VE of 27% (95% CI 14 to 37) and adjusted VE of 36% (95% CI 25 to 46).

CI: confidence interval, CKD: chronic kidney disease, CVD: cardiovascular disease, N: total number, VE: vaccine effectiveness, %: percent

*Included cancer, human immunodeficiency virus, primary immunodeficiencies/other immunocompromising conditions, solid organ or blood stem cell transplantation, stem cell transplantation, use of immunosuppressive medications

†Included hematological malignancy, solid malignancy, transplant, rheumatologic/inflammatory disorders, other intrinsic immune condition or immunodeficiency.

Observational Studies Identified for Key Outcomes of Interest

Myocarditis and Pericarditis in Boys and Young Men

Table D3.60. Observational Trials Reporting on Myocarditis/Pericarditis in Boys and Young Men

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range
Myocarditis or Pericarditis Events After BNT162b2 Vaccination in Individuals Aged 12 to 17 Years in Ontario, Canada.	Buchan 2023	Comirnaty	Cohort	2020 - 2021
Risk of myocarditis requiring hospitalization following Covid-19 mRNA booster vaccinations	Arbel 2023	Comirnaty	Cohort	2021 - 2022
Epidemiological Characteristics and Outcome of Myocarditis and Pericarditis Temporally Associated With BNT162b2 COVID-19 Vaccine in Adolescents: Korean National Surveillance.	Ahn 2024	Comirnaty	Cohort	2022 - 2023
Safety outcomes following COVID-19 vaccination and infection in 5.1 million children in England.	Copland 2024	Comirnaty	Self-controlled Case Series	2021 - 2022
Myocarditis after mRNA-1273 vaccination: A population-based analysis of 151 million vaccine recipients worldwide	Straus 2021	Spikevax	Safety Surveillance	2020 - 2021
Evaluation and Adjudication of Case Reports of Myocarditis After mRNA-1273 Vaccination	Urdaneta 2023	Spikevax	Safety Surveillance: Moderna GSDB	2020 - 2022
Analysis of Myocarditis Among 252 Million mRNA-1273 Recipients Worldwide.	Straus 2023	Spikevax	Safety Surveillance: Moderna GSDB	2021 - 2022
Epidemiology of Myocarditis and Pericarditis Following mRNA Vaccination by Vaccine Product, Schedule, and Interdose Interval Among Adolescents and Adults in Ontario, Canada.	Buchan 2022	Comirnaty; Spikevax	Cohort	2020 - 2021
SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents.	Karlstad 2022	Comirnaty; Spikevax	Cohort	2020 - 2021

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range
Booster Vaccination with SARS-CoV-2 mRNA Vaccines and Myocarditis Risk in Adolescents and Young Adults: A Nordic Cohort Study of 8.9 Million Residents	Hviid 2022	Comirnaty; Spikevax	Cohort	2021 - 2022
Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases.	Wong 2022	Comirnaty; Spikevax	Cohort	2021 - 2022
Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines.	Le Vu 2022	Comirnaty; Spikevax	Case-control	2020 - 2021
Post-marketing active surveillance of myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines in persons aged 12-39 years in Italy: a multi-database, self-controlled case series study	Massari 2022	Comirnaty; Spikevax	Self-controlled Case Series	2020 - 2021
Risk of myocarditis after three doses of COVID-19 mRNA vaccines in the United States, 2020-2022: A self-controlled case series study.	Lai 2024	Comirnaty; Spikevax	Self-controlled Case Series	2021 - 2022
Myocarditis and/or pericarditis risk after mRNA COVID-19 vaccination: A Canadian head to head comparison of BNT162b2 and mRNA-1273 vaccines.	Abraham 2022	Comirnaty; Spikevax	Safety Surveillance: CAEFISS	2020 - 2021
Adverse Events and Safety Profile of the COVID-19 Vaccines in Adolescents: Safety Monitoring for Adverse Events Using Real-World Data	Lee 2022	Comirnaty; Spikevax	Safety Surveillance: VAERS	2021 - 2022
Risks of Myocarditis and Pericarditis Following Vaccination with SARS-CoV-2 mRNA Vaccines in Japan: An Analysis of Spontaneous Reports of Suspected Adverse Events.	Kobayashi 2023	Comirnaty; Spikevax	Safety Surveillance	2021 - 2022
A Pharmacoepidemiological Study of Myocarditis and Pericarditis Following the First Dose of mRNA COVID-19 Vaccine in Europe.	Tome 2023	Comirnaty; Spikevax	Safety Surveillance: EudraVigilance	2021 - 2022

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range
SARS-CoV-2 mRNA vaccine-related myocarditis and pericarditis: An analysis of the Japanese Adverse Drug Event Report database.	Takada 2025	Comirnaty; Spikevax	Safety Surveillance: JADER	2022 - 2023
Cardiac Complications After SARS-CoV-2 Infection and mRNA COVID-19 Vaccination - PCORnet, United States, January 2021-January 2022.	Block 2022	Multiple (not stratified)	Cohort	2021 - 2022

CAEFISS: Canadian Adverse Events Following Immunization Surveillance System, GSDB: Global Safety Database, JADER: Japanese Adverse Drug Event Report

Table D3.61. Details for Select Studies on Myocarditis/Pericarditis In Boys and Young Men

Author and Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Copland 2024[140]	England	2021 – 2022	Comirnaty Spikevax	Self-controlled Case Series N= 5.1 million	5-11 years old: 1.8 million 12-17 years old: 3.3 million 4.3 million young adults aged 18-24 used as comparison	Over 99.9% received BNT162b2 vaccine so results are focused on that vaccine. • Increased risk of myocarditis after the first dose of BNT162b2 was only observed in females (IRR 4.01; 95% CI: 1.33 to 12.09; excess events per million: 3; 95% CI: 1 to 4) • Increased risk following the second dose was observed in males only (IRR 2.87; 95% CI: 1.50 to 5.51; excess events per million: 9; 95% CI: 4 to 11)
Ahn 2024[141]	South Korea	2021 – 2023	Comirnaty	Retrospective cohort N=3,709,063	1) First Dose (N=3,541,856) 2) Second Dose (N=3,398,431)	IR of myocarditis/pericarditis within 42 days of vaccination Dose: 1.8 (1.24, 2.53) Dose 2: 5.01 (4.12, 6.17) Dose 3: 4.59 (3.05, 6.62)

Author and Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
					3) Third Dose (N=1,194,953)	Mild: 3.24 (2.72, 3.83) Severe: 0.33 (1.82, 0.56)
Straus 2023[142]	Global	2020 – 2022	Spikevax	Surveillance study N=477,932	Identified 3017 cases of myocarditis/myopericarditis	Males 12-17: RR of 1.3 (0.98, 1.77) Males 18-24: RR of 3.1 (2.68, 3.58)
Karlstad 2022[143]	Nordic Countries	2020 – 2021	Comirnaty Spikevax	4 population-based cohort studies combined using meta-analysis N=23,122,522	Identified 1077 myocarditis events and 1149 pericarditis events	Adjusted IRRs for males 16 to 24 years of age: 5.31 (95% CI: 3.68 to 7.68) for 2nd dose of BNT162b2 13.83 (95% CI: 8.08 to 23.68) for 2nd dose of mRNA-1273 Excess number of myocarditis events per 100,000 vaccines in 28 day risk period: BNT: [Dose 1] 1.55 (95% CI: 0.70 to 2.39) events, [Dose 2] 5.55 (95% CI: 3.70 to 7.39) events mRNA: [Dose 1} 1.75 (95% CI: −0.20 to 3.71) events, [Dose 2] 18.39 (95% CI: 9.05 to 27.72) Heterologous schedule: 27.49 (95% CI: 14.41 to 40.56) events

CI: confidence interval, IR: incidence rate, IRR: incidence rate ratio, N: total number, RR: risk ratio, %: percent

Myocarditis and Pericarditis in other Age Groups

Table D3.62. Observational Trials Reporting on Myocarditis/Pericarditis in Other Age Groups

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Subgroups Presented
Myocarditis or Pericarditis Events After BNT162b2 Vaccination in Individuals Aged 12 to 17 Years in Ontario, Canada.	Buchan 2023	Comirnaty	Cohort	2020 - 2021	Adolescents

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Subgroups Presented
Myocarditis after Covid-19 Vaccination in a Large Health Care Organization.	Witberg 2021	Comirnaty	Cohort	2020 - 2021	Adults
Vascular and inflammatory diseases after COVID-19 infection and vaccination in children and young people in England: a retrospective, population-based cohort study using linked electronic health records.	Sampri 2025	Comirnaty	Cohort	2020 - 2022	Young Children, Adolescents
Risk of adverse events after covid-19 in Danish children and adolescents and effectiveness of BNT162b2 in adolescents: cohort study.	Kildegaard 2022	Comirnaty	Cohort	2021 - 2022	Young Children, Adolescents
Incidence rates of myocarditis and pericarditis within 30 days following homologous and heterologous BNT162b2 vaccinations in individuals 5-40 years of age.	Kumwichar 2024	Comirnaty	Cohort	2021 - 2022	Adolescents, Adults
Prognosis of Myocarditis Developing After mRNA COVID-19 Vaccination Compared With Viral Myocarditis.	Lai 2022	Comirnaty	Cohort	2021 - 2022	Adolescents, Adults
Risk of myocarditis requiring hospitalization following Covid-19 mRNA booster vaccinations	Arbel 2023	Comirnaty	Cohort	2021 - 2022	Adolescents, Adults
Epidemiological Characteristics and Outcome of Myocarditis and Pericarditis Temporally Associated With BNT162b2 COVID-19 Vaccine in Adolescents: Korean National Surveillance.	Ahn 2024	Comirnaty	Cohort	2022 - 2023	Adolescents
Safety outcomes following COVID-19 vaccination and infection in 5.1 million children in England.	Copland 2024	Comirnaty	Self-controlled Case Series	2021 - 2022	Young Children, Adolescents
Risk of adverse events after Omicron XBB-adapted BNT162b2 COVID-19 vaccination in the United States	Sun 2025	Comirnaty	Self-controlled Case Series	2023 - 2024	Adults
Myocarditis after mRNA-1273 vaccination: A population-based analysis of 151 million vaccine recipients worldwide	Straus 2021	Spikevax	Safety Surveillance	2020 - 2021	Adolescents, Adults, Older Adults
Global Safety Assessment of Adverse Events of Special Interest Following 2 Years of Use and 772 Million Administered Doses of mRNA-1273	Urdaneta 2024	Spikevax	Safety Surveillance: Moderna GSDB	2020 - 2022	Young Children, Adolescents, Adults, Older Adults

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Subgroups Presented
Evaluation and Adjudication of Case Reports of Myocarditis After mRNA-1273 Vaccination	Urdaneta 2023	Spikevax	Safety Surveillance: Moderna GSDB	2020 - 2022	Young Children, Adolescents, Adults, Older Adults
Analysis of Myocarditis Among 252 Million mRNA-1273 Recipients Worldwide.	Straus 2023	Spikevax	Safety Surveillance: Moderna GSDB	2021 - 2022	Adolescents, Adults, Older Adults
Epidemiology of Myocarditis and Pericarditis Following mRNA Vaccination by Vaccine Product, Schedule, and Interdose Interval Among Adolescents and Adults in Ontario, Canada.	Buchan 2022	Comirnaty; Spikevax	Cohort	2020 - 2021	Adolescents, Adults
SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents.	Karlstad 2022	Comirnaty; Spikevax	Cohort	2020 - 2021	Adolescents, Adults
A multiprovincial retrospective analysis of the incidence of myocarditis or pericarditis after mRNA vaccination compared to the incidence after SARS-CoV-2 infection.	Naveed 2024	Comirnaty; Spikevax	Cohort	2020 - 2021	Adolescents, Adults
Comparative Risks of Potential Adverse Events Following COVID-19 mRNA Vaccination Among Older US Adults.	Harris 2023	Comirnaty; Spikevax	Cohort	2020 - 2021	Older Adults
SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study.	Husby 2021	Comirnaty; Spikevax	Cohort	2020 - 2021	Adolescents, Adults
SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study.	Husby 2021	Comirnaty; Spikevax	Cohort	2020 - 2021	Adolescents, Adults
Booster vaccination with SARS-CoV-2 mRNA vaccines and myocarditis in adolescents and young adults: a Nordic cohort study.	Hviid 2024	Comirnaty; Spikevax	Cohort	2021 - 2022	Adolescents, Adults
A population-based assessment of myocarditis after messenger RNA COVID-19 booster vaccination among adult recipients.	Naveed 2023	Comirnaty; Spikevax	Cohort	2021 - 2022	Adults
COVID-19 Vaccination-Related Pericarditis: A Korean Nationwide Study.	Lee 2024	Comirnaty; Spikevax	Cohort	2021 - 2022	Adolescents, Adults
Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases.	Wong 2022	Comirnaty; Spikevax	Cohort	2021 - 2022	Adults
Incidence Rates and Clinical Characteristics of Patients With Confirmed Myocarditis or Pericarditis Following COVID-19 mRNA	Luo 2023	Comirnaty; Spikevax	Cohort	2021 - 2022	Adults, Older Adults

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Subgroups Presented
Vaccination: Experience of the Veterans Health Administration Through 9 October 2022					
Observed versus expected rates of myocarditis after SARS-CoV-2 vaccination: a population-based cohort study.	Naveed 2022	Comirnaty; Spikevax	Cohort	2021 - 2022	Adolescents, Adults, Older Adults
Risk of Adverse Events Following Monovalent Third or Booster Dose of COVID-19 mRNA Vaccination in U.S. Adults Ages 18 Years and Older	Shoaibi 2024	Comirnaty; Spikevax	Cohort	2021 - 2022	Adults, Older Adults
Surveillance of COVID-19 vaccine safety among elderly persons aged 65 years and older.	Wong 2023	Comirnaty; Spikevax	Cohort	2021 - 2022	Older Adults
mRNA COVID-19 vaccine safety among children and adolescents: a Canadian National Vaccine Safety Network cohort study	Soe 2024	Comirnaty; Spikevax	Cohort	2021 - 2023	Young Children, Adolescents
COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals.	Faksova 2024	Comirnaty; Spikevax	Cohort	2022 - 2023	Adults
Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines.	Le Vu 2022	Comirnaty; Spikevax	Case-control	2020 - 2021	Adolescents, Adults
Influence of mRNA Covid-19 vaccine dosing interval on the risk of myocarditis	Le Vu 2024	Comirnaty; Spikevax	Case-control	2020 - 2022	Adolescents, Adults
Serious Adverse Drug Reactions to COVID-19 Vaccines in the Pediatric Population: A Retrospective, Cross-Sectional Study Utilizing the Eudravigilance Database for the European Economic Area	Nazar 2025	Comirnaty; Spikevax	Cross-sectional	2020 - 2023	Young Children
Post-marketing active surveillance of myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines in persons aged 12-39 years in Italy: a multi-database, self-controlled case series study	Massari 2022	Comirnaty; Spikevax	Self-controlled Case Series	2020 - 2021	Adolescents, Adults
Risk of myocarditis following sequential COVID-19 vaccinations by age and sex	Patone 2021	Comirnaty; Spikevax	Self-controlled Case Series	2020 - 2021	Adults
Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection.	Patone 2022	Comirnaty; Spikevax	Self-controlled Case Series	2020 - 2021	Adults
Risk of Myocarditis After Sequential Doses of COVID-19 Vaccine and SARS-CoV-2 Infection by Age and Sex.	Patone 2022	Comirnaty; Spikevax	Self-controlled Case Series	2020 - 2021	Adolescents, Adults

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Subgroups Presented
Risk of myocarditis after three doses of COVID-19 mRNA vaccines in the United States, 2020-2022: A self-controlled case series study.	Lai 2024	Comirnaty; Spikevax	Self-controlled Case Series	2021 - 2022	Adolescents, Adults
Risk of myocarditis and pericarditis after a COVID-19 mRNA vaccine booster and after COVID-19 in those with and without prior SARS-CoV-2 infection: A self-controlled case series analysis in England.	Stowe 2023	Comirnaty; Spikevax	Self-controlled Case Series	2021 - 2022	Adolescents, Adults
Evaluating the safety of XBB.1.5-containingCOVID-19 mRNA vaccines using a self-controlled case series study	Pan 2025	Comirnaty; Spikevax	Self-controlled Case Series	2023 - 2024	Adults
Myocarditis and pericarditis following COVID-19 vaccination: Inequalities in age and vaccine types	Li 2021	Comirnaty; Spikevax	Surveillance Study: VAERS & CDC Covid Tracker	2020 - 2021	Adolescents, Adults, Older Adults
Myocarditis and/or pericarditis risk after mRNA COVID-19 vaccination: A Canadian head to head comparison of BNT162b2 and mRNA-1273 vaccines.	Abraham 2022	Comirnaty; Spikevax	Safety Surveillance: CAEFISS	2020 - 2021	Adults
Myocarditis and pericarditis in individuals exposed to the Ad26.COV2.S, BNT162b2 mRNA, or mRNA-1273 SARS-CoV-2 vaccines.	Pareek 2023	Comirnaty; Spikevax	Surveillance Study: VAERS	2020 - 2021	Adults
Comparative assessment of myocarditis and pericarditis reporting rates related to mRNA COVID-19 vaccines in Europe and the United States.	Hatziantoniou 2022	Comirnaty; Spikevax	Surveillance Study: VAERS and EudraVigilance	2020 - 2021	Adults, Older Adults
Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021.	Oster 2022	Comirnaty; Spikevax	Safety Surveillance: VAERS	2020 - 2021	Adolescents, Adults
A Pharmacoepidemiologic Study of Myocarditis and Pericarditis Following the First Dose of mRNA COVID-19 Vaccine in Europe.	Tome 2023	Comirnaty; Spikevax	Safety Surveillance: EudraVigilance	2021 - 2022	Adolescents, Adults, Older Adults
Risk of Myocarditis and Pericarditis Following Coronavirus Disease 2019 Messenger RNA Vaccination—A Nationwide Study	Su 2022	Comirnaty; Spikevax	Safety Surveillance	2021 - 2022	Adolescents, Adults
Risk of myocarditis and pericarditis following BNT162b2 and mRNA-1273 COVID-19 vaccination.	Goddard 2022	Comirnaty; Spikevax	Safety Surveillance	2021 - 2022	Adults
Risks of Myocarditis and Pericarditis Following Vaccination with SARS-CoV-2 mRNA Vaccines in Japan: An Analysis of Spontaneous Reports of Suspected Adverse Events.	Kobayashi 2023	Comirnaty; Spikevax	Safety Surveillance	2021 - 2022	Adolescents, Adults

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Subgroups Presented
Adverse Events and Safety Profile of the COVID-19 Vaccines in Adolescents: Safety Monitoring for Adverse Events Using Real-World Data	Lee 2022	Comirnaty; Spikevax	Safety Surveillance: VAERS	2021 - 2022	Adolescents
Near real-time surveillance of safety outcomes in US COVID-19 vaccine recipients aged 12 to 64 years.	Lloyd 2022	Comirnaty; Spikevax	Safety Surveillance	2021 - 2022	Adolescents, Adults
SARS-CoV-2 mRNA vaccine-related myocarditis and pericarditis: An analysis of the Japanese Adverse Drug Event Report database.	Takada 2025	Comirnaty; Spikevax	Safety Surveillance: JADER	2022 - 2023	Adolescents, Adults, Older Adults
COVID-19 vaccine associated myocarditis in Norway - a nationwide validation study	Skinningsrud 2024	Comirnaty; Spikevax	Validation Study	2020 - 2022	Adults
Cardiac adverse drug reactions to COVID-19 vaccines. A cross-sectional study based on the Europe-wide data.	Nazar 2024	Comirnaty; Spikevax; Nuvaxovid	Cross-sectional	2021 - 2022	Adults
Safety of Monovalent BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and NVX-CoV2373 (Novavax) COVID-19 Vaccines in US Children Aged 6 months to 17 years	Hu 2023	Comirnaty; Spikevax; Nuvaxovid	Cohort	2022 - 2023	Young Children, Adolescents
Determinants of COVID-19 vaccine-induced myocarditis	Rose 2024	Comirnaty; Spikevax; Nuvaxovid	Safety Surveillance: VAERS	2022 - 2023	Young Children, Adolescents, Adults, Older Adults
Cardiac Complications After SARS-CoV-2 Infection and mRNA COVID-19 Vaccination - PCORnet, United States, January 2021-January 2022.	Block 2022	Multiple (not stratified)	Cohort	2021 - 2022	Young Children, Adolescents
Long-Term Prognosis of Patients With Myocarditis Attributed to COVID-19 mRNA Vaccination, SARS-CoV-2 Infection, or Conventional Etiologies	Semenzato 2024	Multiple (not stratified)	Cohort	2021 - 2022	Adolescents, Adults
Acute myocarditis following a third dose of COVID-19 mRNA vaccination in adults.	Simone 2022	Multiple (not stratified)	Cohort	2021 - 2022	Adults
Myocarditis and pericarditis in adolescents after first and second doses of mRNA COVID-19 vaccines.	Foltran 2022	Multiple (not stratified)	Case Series	2021 - 2022	Adolescents
Acute myocarditis following covid-19 mrna vaccination	Simone 2021	Multiple (not stratified)	Self-controlled Case Series	2020 - 2021	Adults

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range	Subgroups Presented
RISK OF RECURRENT MYOCARDITIS FOLLOWING COVID-19 MRNA VACCINATION IN ADULTS WITH PRIOR HISTORY	Simone 2022	Multiple (not stratified)	Self-controlled Case Series	2021 - 2022	Adults

CAEFISS: Canadian Adverse Events Following Immunization Surveillance System, GSDB: Global Safety Database, JADER: Japanese Adverse Drug Event Report, VAERS: Vaccine Adverse Event Reporting System

Table D3.63. Details for Select Studies on Myocarditis/Pericarditis in Other Age Groups

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Copland 2024[140]	England	2021 – 2022	Comirnaty	Self-controlled Case Series N=5.1 million	5-11 years old: 1.8 million 12-17 years old: 3.3 million 4.3 million young adults aged 18-24 used as comparison	Over 99.9% received BNT162b2 vaccine so results are focused on that vaccine. No increased risk in children 5 – 11. In 12-17-year-olds: • estimated 3 (95% CI: 0 to 5) and 5 (95% CI: 3 to 6) additional cases of myocarditis per million following a first and second dose with BNT162b2, respectively. In adolescents, no statistically significant increased risk of myocarditis with BNT162b2 vaccination observed but an increased risk of hospital admission for myocarditis following first or second dose BNT162b2 was observed The increased risk of myocarditis after the first dose of BNT162b2 was only observed in females (IRR 4.01 95% CI: 1.33 to 12.09; excess events per million: 3; 95% CI: 1 to 4), while the increased risk following the second dose was observed in males only (IRR 2.87; 95% CI: 1.50 to 5.51; excess events per million: 9; 95% CI: 4 to 11)
Sun 2025[71]	US	2023 – 2024	Comirnaty	Self-controlled Case Series N=113,459	People who received BNT162b2 XBB vaccine	Myo/Pericarditis Relative Incidence: 1.5 (95% CI: 0.22, 12.61)

Author & Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Pan 2025[70]	US	2023 – 2024	Comirnaty Spikevax	Self-controlled Case Series N=244,494	People who received XBB1.5-containing Covid-19 mRNA vaccines in the US	Incidence Rate Ratio for Myo/Pericarditis: - Comirnaty: 0.39 (95% CI: 0.06 to 1.44) - Spikevax: 0.45 (95% CI: 0.13 to 1.16)

CI: confidence interval, IRR: incidence rate ratio, N: total number, %: percent

Guillain-Barre Syndrome

Table D3.64. Observational Trials Reporting on Guillain-Barre Syndrome

Title	Author and Publication Year	Vaccine Type	Observational Study	Data Range
Risk of adverse events after covid-19 in Danish children and adolescents and effectiveness of BNT162b2 in adolescents: cohort study.	Kildegaard 2022	Comirnaty	Cohort	2021 - 2022
Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection.	Patone 2021	Comirnaty	Self-controlled Case Series	2020 - 2021
COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals.	Faksova 2024	Comirnaty; Spikevax	Cohort	2022 - 2023
Neurological Events Reported after COVID-19 Vaccines: An Analysis of VAERS.	Frontera 2022	Comirnaty; Spikevax	Surveillance Study: VAERS	2020 - 2021
Post-marketing active surveillance of Guillan Barré Syndrome following vaccination with anti-COVID-19 vaccines in persons aged ≥12 years in Italy: A multi-database self-controlled case series study	Morciano 2023	Comirnaty; Spikevax	Self-controlled Case Series	2020 - 2021
Risk of Guillain-Barre Syndrome Following COVID-19 Vaccines: A Nationwide Self-Controlled Case Series Study.	Le Vu 2023	Comirnaty; Spikevax	Self-controlled Case Series	2020-2022
Safety outcomes following COVID-19 vaccination and infection in 5.1 million children in England.	Copland 2024	Comirnaty; Spikevax	Self-controlled Case Series	2021 - 2022
Surveillance of COVID-19 vaccine safety among elderly persons aged 65 years and older.	Wong 2023	Comirnaty; Spikevax	Surveillance Study	2021 - 2022
Reports of Guillain-Barre Syndrome After COVID-19 Vaccination in the United States.	Abara 2023	Comirnaty; Spikevax	Surveillance Study: VAERS	2021 - 2022
Risk of Guillain-Barre syndrome after COVID-19 vaccination or SARS-CoV-2 infection: A multinational self-controlled case series study.	Nasreen 2025	Multiple (not stratified)	Self-controlled Case Series	2020-2023
Association Between Guillain-Barre Syndrome and COVID-19 Infection and Vaccination: A Population-Based Nested Case-Control Study.	Bishara 2023	Multiple (not stratified)	Case-control	2021 - 2022

Title	Author and Publication Year	Vaccine Type	Observational Study	Data Range
Incidence of Guillain-Barre syndrome following SARS-CoV-2 immunization: Analysis of a nationwide registry of recipients of 81 million doses of seven vaccines.	Garcia-Grimshaw 2022	Multiple (not stratified)	Surveillance Study	2020 - 2021
Guillain-Barré Syndrome after COVID-19 Vaccination in the Vaccine Safety Datalink	Hanson 2021	Multiple (not stratified)	Surveillance Study: VSD	2020 - 2021
Incidence of Guillain-Barre Syndrome After COVID-19 Vaccination in the Vaccine Safety Datalink.	Hanson 2022	Multiple (not stratified)	Surveillance Study: VSD	2020 - 2021

VAERS: Vaccine Adverse Event Reporting System, VSD: Vaccine Safety Datalink

Table D3.65. Details for Select Studies on Guillain-Barre Syndrome

Author and Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
Faksova 2024[144]	Global	2022 - 2023	Comirnaty; Spikevax	Cohort study using Global Vaccine Data Network of 99 million vaccinated individuals	1) BNT162b2: 183 million doses 2) mRNA-1273: 36 million doses 3) ChAdOx1: 23 million doses	Observed versus Expected Ratios from Dose 1 • BNT162b2: 0.9 (95%CI: 0.79, 1.03) • mRNA-1273: 0.95 (95%CI: 0.65, 1.34) • ChAdOx1: 2.49 (95%CI: 2.15, 2.87) Lower OE with additional doses observed
Nasreen 2025[145]	Global	2020-2023	Multiple (not separated)	Self-controlled Case Series using Global Vaccine Data Network	From electronic data sources, 2,086 GBS cases who received 4,329 doses of any Covid-19 vaccine Medical records reviewed for 410 cases	• Increased risk of confirmed GBS after Vaxzevria/Covishield vaccinations • Decreased risk of GBS (level of certainty 1-4) after Comirnaty/Tozinameran and CoronaVac and Sinovac • Increased risk observed after SARS-CoV-2 infection

Author and Year Published	Location	Data Year Range	Vaccine	Study Design and N	Study Arms	Key Results
					489 cases of GBS post SARS-Cov-2 infection	
Bishara 2023[146]	Israel	2021 - 2022	Multiple (not separated)	Nested case-control in a cohort N=3,193,951	People 16+ years old without a prior diagnosis of GBS from largest health care provider in Israel 10 randomly selected controls were matched to each case of GBS on age and sex	76 patients diagnosed with GBS during follow-up (6 weeks), matched with 760 controls • Cov-19 vaccination in 10.5% of cases and 17.9% of controls • Odds ratio for GBS associated with SARS-CoV-2 infection: 6.3 (95%CI: 2.55, 15.56) • Odds ratio for GBS associated with Covid-19 vaccination: 0.41 (95%CI: 0.17, 0.96)

CI: confidence interval, GBS: Guillain-Barre syndrome, N: total number, OE: observed over expected, %: percent

Long-Covid

Table D3.66. Studies Identified For Long Covid

Title	Author and Publication Year	Vaccine Type	Study Type	Data Range
Real-world effectiveness and causal mediation study of BNT162b2 on long COVID risks in children and adolescents	Wu 2025	Comirnaty	Cohort	2021 - 2022
Association of COVID-19 Vaccination With Risk of Medically Attended Postacute Sequelae of COVID-19 During the Ancestral, Alpha, Delta, and Omicron Variant Eras	Swift 2025	Multiple (not specified)	Cohort	2021 - 2022
Effectiveness of BNT162b2 BA.4/5 Bivalent COVID-19 Vaccine against Long COVID Symptoms: A US Nationwide Study	Di Fusco 2024	Comirnaty	Cohort	2022 - 2023
COVID-19 Vaccination and Odds of Post-COVID-19 Condition Symptoms in Children Aged 5 to 17 Years	Yousaf 2025	Multiple (not stratified)	Case-control	2021 - 2022

Table D3.67. Details for Select Studies on Long-Covid

Author and Year Published	Location	Data Year Range	Vaccine	Study Design	Study Arms	Key Results
Wu 2025[52]	US	2021 - 2022	Comirnaty	Cohort Study using RECOVER PCORnet electronic health records N=386,219	All vaccinated participants received BNT162b2 1) Adolescents 12 – 20 in Delta phase (N=112,590, 88,811 vaccinated) 2) Children 5 – 11 in Omicron phase (N=188,894, 101,277 vaccinated)	**Vaccine Effectiveness** • Adolescents in Delta: 95.4% (95%CI: 90.9%, 97.7%) • Children in Omicron: 60.2 (95%CI: 40.3%, 73.5%) • Adolescents in Omicron: 75.1% (95%CI: 50.4%, 87.5%) Direct effect of vaccination (beyond impact on SARS-CoV-2 infection was no statistically significant across all 3 cohorts. VE is primarily driven by reducing risk of infection.

Author and Year Published	Location	Data Year Range	Vaccine	Study Design	Study Arms	Key Results
					3) Adolescents 12 – 20 in Omicron phase (N=84,735, 37,724 vaccinated)	
Yousaf 2025[50]	US	2021 - 2022	Multiple (not specified)	Case-control study of children enrolled in longitudinal pediatric cohort evaluating post-covid-19 condition (PCC) N=622	1) Case Participants (n=28) 2) Control Participants (n=594)	COVID-19 vaccination was associated with decreased odds of: • 1 or more PCC symptoms (adjusted odds ratio [aOR], 0.43; 95% CI: 0.19 to 0.98) and • 2 or more PCC symptoms (aOR, 0.27; 95% CI: 0.10 to 0.69).

aOR: adjusted odds ratio, CI: confidence interval, N: total number, PCC: post-covid condition, VE: vaccine effectiveness, %: percent

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Title/Trial Sponsor	Study Design	Patient Population	Primary Outcomes	Estimated Completion Date
Comirnaty				
A Study to Learn About BNT162b2 (LP.8.1)-Adapted Vaccine Against SARS-CoV-2 in Children 5 Through 11 Years of Age That Are Considered at Higher Risk of Severe COVID-19 **NCT07222384**	Phase III OL 1) BNT162b2 (2025/2026 formulation) N=343	Children 5-11 years old with at least 1 underlying stable medical condition	·Local reactions [up to 7 days after dose] ·Systemic events [up to 7 days after dose] ·AEs [up to 7 days after dose] ·SAEs [within 6 months after dose] ·Geometric mean fold rises [before vaccination to 1 month after dose]	7/31/2026
A Study to Learn About COVID-19 RNA-Based Variant-Adapted Vaccine Candidate(s) Against SARS-CoV-2 in Participants Ages 12 Through 64 Years Considered at Higher Risk of Severe COVID-19, and Participants Ages ≥65 Years **NCT07069309**	Phase III OL 1) 30 µg of BNT162b2 (2025/2026 strain) Estimated N=760	Participants 12-64 with at least 1 underlying medical condition Cohort 1: ≤18 years Cohort 2: ≤12 years	·Local reactions [up to 7 days after dose] ·Systemic events [up to 7 days after dose] ·AEs [up to 1 month after dose] ·SAEs [within 6 months after dose] ·Geometric mean fold rises [before vaccination to 2 weeks after dose] ·Seroresponse [2 weeks after dose] ·Geometric mean fold rises [before vaccination to 1 month after dose]	5/5/2026
A Study to Learn About a COVID-19 Vaccine in Healthy Adults 50 Through 64 Years of Age **NCT07300839**	Phase III, randomized, double-blind, placebo-controlled study 1) BNT162b2 2) Placebo Estimated N=25, 500	Healthy adults between 50-64 years old	·Local reactions or systemic events [within 7 days after dose] ·AEs [Day 1 to 4 weeks after dose] ·SAEs [Day 1 to 6 months after dose] ·First episode of confirmed COVID-19 cases [Day 0 to at least 6 months post-dose]	7/31/26

Title/Trial Sponsor	Study Design	Patient Population	Primary Outcomes	Estimated Completion Date
Spikevax				
Effectiveness of mRNA-1273 Variant-Containing Vaccine Formulation Against Severe Outcomes in Adults Aged 50-64 Years Without Risk Factors for Severe COVID-19 (DAN-COVID) **NCT07279766**	Phase IV, randomized trial 1) mRNA-1273 2) No COVID-19 vaccine Estimated N=28,500	Healthy adults between 50-64 years old	·Medically attended COVID-19 [≥14 days after initially booked study visit date until 6 months after initially booked study visit date]	8/1/2026
Bringing Optimized COVID-19 Vaccine Schedules To Immunocompromised Populations (BOOST-IC): an Adaptive Randomized Controlled Clinical Trial (BOOST-IC) **NCT05556720**	Phase III, randomized, quadruple-blinded study <u>People living with HIV</u> 1) 50 ug Spikevax 2) 30 ug of Comirnaty <u>Solid organ transplant recipients</u> 1) 50 ug of Spikevax 2) 30ug of Comirnaty 3) TBC <u>People with Haematological</u> Neoplasms 1) 50 ug of Spikevax 2) 30 ug of Comirnaty 3) TBC Estimated N=960	·≥16 years old ·Have completed at least 3 months prior, 3- to 8-doses of an Australian TGA approved SARS-CoV-2 vaccine (including mRNA [Pfizer or Moderna], ChAdOx1 [Oxford/Astra Zeneca] or protein [Novavax]) ·Fit the criteria to be included in one of the following 3 populations: Infected with HIV; Current recipient of a solid organ transplant ·Undergoing chemotherapy, immunotherapy and/or targeted therapy	·Geometric mean concentration of anti-spike SARS-CoV-2 IgG antibody (AU/ml) [28 days after completion of trial vaccines]	12/31/2026

Title/Trial Sponsor	Study Design	Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Assess Long-term Outcomes of Myocarditis Following Administration of COVID-19 mRNA Vaccine (SPIKEVAX) **NCT06189053**	Retrospective observational cohort 1) Post-vaccine myocarditis 2) All other myocarditis N=1,500	·Participants with a diagnosis of myocarditis between December 18, 2020, and October 31, 2026, ·Participants will be required to have at least 30 days of medical history to assess SPIKEVAX exposure.	Number of participants with major adverse clinical outcomes, persistent cardiac abnormality, reporting symptoms of chest pain, returning to normal activities [up to 5 years]	10/31/2028
mNexspike				
A Study to Evaluate the Efficacy and Safety of mRNA-1283 and mRNA-1273 in Participants 50 to 64 Years of Age Without High-Risk Conditions for Severe Coronavirus Disease 2019 (COVID-19) **NCT07266558**	Phase IV, randomized observer-blind, placebo-controlled study 1) mRNA-1273 2) mRNA-1278 3) Placebo Estimated N=30,000	Healthy adults between 50 to 64 years	·VE of mRNA-1273 to prevent first event of symptomatic COVID-19 [Day 1 through 181] ·VE of mRNA-1283 to prevent first event of symptomatic COVID-19 [Day 1 through 181] ·Number of participants with unsolicited AEs, SAEs, MAAEs, AESIS, AEs leading to discontinuation [Day 1 through 181]	6/16/27
The Impact of COVID-19 on Maternal and Neonatal Outcomes **NCT05197621**	Prospective observational cohort 1) Pregnant women who are planning to receive an mRNA COVID vaccine Estimated N=300	All pregnant women, aged 14-55, receiving prenatal care from Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center, who are planning to receive an mRNA COVID vaccine and/or a third dose booster during their pregnancy, or patients who have had a positive COVID-19 test during their pregnancy or at the time of admission to Labor & Delivery.	·Evaluation of biospecimens from recently delivered pregnant women and neonates who were diagnosed with COVID-19 during their pregnancy [Study enrollment up to 1 year after sample collection]	5/5/28

Title/Trial Sponsor	Study Design	Patient Population	Primary Outcomes	Estimated Completion Date
Nuvaxovid				
COVID-19 Booster Study in Healthy Adults in Australia **NCT05658523**	Phase III, double-blind, randomized study 1) 25 µg of mRNA-1273.214 2) 5 µg of Novavax 3) No vaccine N=496	·Adults ≥18 years who have received their third dose of COVID-19 at least 6 months previously No confirmed SARS-CoV-2 infection on PCR or RAT within the last 3 months	·SARS-CoV-2 Specific Immunoglobulin (Ig)G Antibodies at 28-days Post Booster Vaccination [28 days post booster vaccination] ·Total incidence of solicited reactions (systemic and local) [7 days post booster vaccination]	4/1/26
A Study to Evaluate the Efficacy and Safety of mRNA-1283 and mRNA-1273 in Participants 50 to 64 Years of Age Without High-Risk Conditions for Severe Coronavirus Disease 2019 (COVID-19) **NCT07266558**	Phase IV, randomized, observer-blind, placebo-controlled trial 1)mRNA-1273 2)mRNA-1283 3)Placebo Estimated N=30,000	·Healthy adults between 50 to 64 years old without underlying medical conditions	·Effectiveness of mRNA-1273 to prevent first event of symptomatic COVID-19 [Day 1 through 181] ·Effectiveness of mRNA-1283 to prevent first event of symptomatic COVID-19 [Day 1 through 181] ·Number of participants with unsolicited AEs [Day 1 through 28] ·Number of participants with SAEs, MAAEs, AESIs, AEs leading to discontinuation [Day 1 through 181]	6/16/27

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

AE: adverse event, AESI: adverse event of special interest, IgG: Immunoglobulin G, MAAE: medically attended adverse event, N: total number, OL: open label, SAE: serious adverse event, VE: vaccine effectiveness

D5. Previous Systematic Reviews and Technology Assessments

We identified many systematic literature reviews or meta-analyses evaluating the effectiveness and safety of Covid-19 vaccines in various populations, three of which are summarized below.

Ciapponi A., et al. (2024) "Safety and effectiveness of Covid-19 Vaccines During Pregnancy: A Living Systematic Review and Meta-Analysis Pregnancy"[81]

This living systematic review and meta-analysis aimed to evaluate the safety and effectiveness COVID-19 vaccines provided to pregnant individuals. The review included 177 studies, with 137 studies presenting data on safety, effectiveness, and immunogenicity of COVID-19 vaccines in pregnant individuals and their infants. Across 10 different COVID-19 vaccines identified, BNT162b2 and mRNA-1273 were the most commonly assessed. Among those who received at least one dose of the COVID-19 mRNA vaccine, there were a lower risk of stillbirth compared with those who did not receive one (75–83%). Additionally, the authors did not find a higher risk of miscarriage or abortion among vaccinated pregnant women who received at least one dose during pregnancy. In regard to infant safety, the authors did not find an increased risk of congenital malformations, incidence of preterm infants or small for gestational age cases, or NICU hospitalizations. For vaccine effectiveness, across variants the estimated VE was 72% (95% CI: 42 to 86) with mRNA vaccines, 49% (95% CI: 0 to 74) with viral vector vaccines, and 61% (95% CI: 0 to 93) with inactivated vaccine. The authors not there is low-certainty evidence supporting a mother's vaccination in reducing severe or hospitalized COVID-19 in their infants. The authors acknowledge the limitations of utilizing observational studies, including the inevitable risk of bias and confounding factors. Therefore, further research using larger sample sizes across varying sociodemographic is necessary to monitor the vaccine safety and effectiveness of an at risk population.

Kitano T., et al. (2025) "Age-and Sex-Stratified Risks of Myocarditis and Pericarditis Attributable to Covid-19 Vaccination: A Systematic Review and Meta-Analysis"[147]

This systematic review and meta-analysis aimed to stratify its assessment of Covid-19 associated myocarditis and pericarditis by age, sex, vaccine dose, and vaccine type. The review included 17 observational studies. The authors found the risk ratios to be the highest among young men who received mRNA vaccines, particularly in the second dose. Based on vaccine type, the RR for all doses of BNT162b2 was 9.83 in 12-17 years old boys compared to 7.07 for mRNA-1273 in 18-24 years old young men. For the BNT162b2 vaccine, the attributable risk was largest in 12-17 years old boys (10.18 per 100 000 doses; 95% CI: 0.50 to 19.87). For the mRNA-1273 vaccine, the attributable risk was largest in 18-24 years old men (20.02 per 100 000 doses; 95% CI: 10.47 to 29.57). Limitations include heterogeneity for risk after the second dose, lack of standardization in case definitions, and studies only reporting RRs or ARs.

Censi, S., et al. (2024) "Guillain-Barre Syndrome and COVID-19 Vaccination: A Systematic Review and Meta-Analysis"[148]

This systematic review and meta-analysis aimed to explore the occurrence of GBS within 42 days after COVID-19 vaccination. The review included 15 studies, leading the model to assess 1.25 GBS cases per million vaccines doses (95% CI: 0.21 to 2.83). The first dose was associated with a risk ratio of 2.6 (95% CI: 0.42 to 15.92) compared to the second dose. The authors portray the rate of GBS to be five times higher for adenovirus-vectored vaccines compared to mRNA vaccines. For mRNA vaccines, the risk ratio of GBS resulted in 0.32 (95% CI: 0.23 to 0.47). The authors identified 28 deaths across 524 GBS cases, resulting the model portraying 0.1 (95% CI: 0.00 to 0.75) deaths per million doses of COVID-19 vaccine.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type Of Impact (Add Additional Domains, As Relevant)	Included In This Analysis From […] Perspective?		Notes On Sources (If Quantified), Likely Magnitude & Impact (If Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	X	Pediatric only
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.[149]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[150]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The economic evaluation focuses on populations eligible for seasonal Covid-19 vaccination in the United States (US). The primary analysis is based on the US population eligible for vaccination, with subgroup analyses to explore heterogeneity in vaccine effectiveness and economic outcomes across age and selected high-risk clinical subgroups.

Primary Analysis:

Vaccine-eligible US population: 6 months to 64 years with high-risk factors, as well as individuals aged 65 and over

Subgroup Analyses:

- Individuals with at least one comorbidity by age groups (high-risk)
    - 6 months–4 years
    - 5–11 years
    - 12–17 years
    - 18–64 years
- Individuals aged ≥65 years

Treatment Strategies

The list of vaccines was developed with input from patient organizations, clinicians, manufacturers, and payers on which vaccines to include. The full list of vaccines is as follows:

- COMIRNATY (Covid-19 vaccine, mRNA)
- Spikevax (Covid-19 vaccine, mRNA)
- mNEXSPIKE (Covid-19 vaccine, mRNA)
- Nuvaxovid (Covid-19 vaccine, adjuvanted)

Timing:

- Administered in fall 2026

Administration Setting:

- 90.5% pharmacy
- 9.5% physician office

Comparator

The comparator for these interventions:

- No receipt of updated 2026–2027 Covid-19 vaccine dose

E2. Model Inputs and Assumptions

Key model inputs and assumptions are listed in Section 4.2. Additional inputs are described below.

Clinical Inputs

Table E2.1. Model Population Characteristics

Parameter	Subgroup	Value
Cohort Average Age	≥65 yrs	71 yrs
	50–64 yrs	57 yrs
	18–49 yrs	34 yrs
	12–17 yrs	15 yrs
	5-11 yrs	8 yrs
	6 mo – 4 yrs	2 yrs
Percent Female	All	50.51%

mo: months, yrs: years

Epidemiologic Parameters

Epidemiologic parameters related to the probability of symptomatic Covid-19 and its outcomes were derived via back-calibration from CDC 2024–2025 US Covid-19 burden estimates,[91] which represent cumulative seasonal event counts in a partially vaccinated population. All back-calibration was performed separately within each age stratum; no aggregate incidence proportions were derived for the full vaccine-eligible (6m+) population. Age-specific hospitalization rates in the mixed (vaccinated and unvaccinated) population were derived from Yehoshua et al. (2024) raw hospitalization counts apportioned to corresponding US Census population denominators.[89] Age-specific vaccine coverage values were applied (5% for ages 6m to 17y; 14.1% for 18–49y; 24.8% for 50–64y; 44.6% for ≥65y, per CDC VaxView), and VE against hospitalization was varied by age group per Cai et al. (NEJM 2025) (47% for ages 6m to 17; 30.3% for 18 to 49y, 50 to 64y and for ≥65y). For each stratum, the back-calibration formula $R_{unvax}=R_{pop} / [(1 - c) + c \times (1 - VE)]$ was applied to recover the unvaccinated-arm hospitalization probability, where R_{pop} denotes the observed population-level hospitalization rate in the mixed (partially vaccinated) population, c denotes the age-specific vaccine coverage proportion, and VE denotes vaccine effectiveness against hospitalization. Vaccinated-arm probabilities were derived by applying the corresponding VE estimates. Emergency department visit VE was used as a proxy for outpatient visit rates in the absence of ambulatory-specific estimates. VE against death (64%) was drawn from Cai et al. and applied uniformly across adult age groups.[18] Conditional probabilities governing severity progression among hospitalized patients, including ICU admission, invasive mechanical ventilation given ICU admission, and in-hospital mortality, were derived from Yehoshua et al. (2024) using patient-level counts.[89] The probability of developing Covid-19-related events in high-risk individuals aged six months to 64 years was assumed to be twice that of the general population (range: 1.5 to 2.5×), consistent with estimates in Section 3.2, Table 3.5.

Table E2.2. Epidemiological Data

Probability Type	Age Group	Base Case	Lower Bound	Upper Bound	Source
Annual Probability of Symptomatic Covid-19	All ages	5.12%	4.12%	6.04%	CDC 2024-2025 US Covid-19 Burden Estimate, US Census;[91,92] Authors' estimation
Annual Probability of ED Visits, Non-Vaccinated	All ages	0.62%	0.51%	0.75%	
Annual Probability of Outpatient Visits, Non-Vaccinated	All ages	0.72%	0.58%	0.86%	
Annual Probability of Hospitalization, Non-Vaccinated	6mo – 11yrs	0.05%	0.04%	0.06%	COVID-NET Surveillance System, 2024-25;[91] Authors' estimation
	12-17yrs	0.02%	0.02%	0.02%	
	18 - 49yrs	0.08%	0.07%	0.10%	

Probability Type	Age Group	Base Case	Lower Bound	Upper Bound	Source
	50-64yrs	0.25%	0.21%	0.31%	
	65yrs+	0.62%	0.50%	0.75%	
Relative Risk of Composite Endpoint In High-Risk Population	6mo - 64yrs	200%	150%	250%	Assumption, based on Table 3.5. in Section 3.2. Results

CDC: Centers for Disease Control and Prevention, mo: months, US: United States, yrs: years

Composite endpoint refers to the first occurrence of any of the three outcomes: ED visit, hospitalization, death.

Table E2.3. Conditional Probabilities

Probability Type	Age Group	Base Case	Lower Bound	Upper Bound	Source
Probability of Long-Term Sequelae Given Non-Severe Covid-19	All	7.20 %	5.85%	8.67%	Prosser et al.[20]
Probability of Long-Term Sequelae Given Severe Covid-19 and No ICU	All	22.00 %	17.8%	26.5%	Assumption based on[151]
Probability of Long-Term Sequelae Given Severe Covid-19 and ICU	All	25.00 %	20.3%	30.1%	Assumption based on[152]
Probability of ICU Admission Given Hospitalization	6mo—17yrs	22.46 %	18.2%	27.0%	Yehosha et al. 2024[89]
	18—49yrs	18.15 %	14.7%	21.8%	
	50—64yrs	21.98 %	17.8%	26.4%	
	65yrs+	16.92 %	13.7%	20.4%	
Probability of Ventilator Assistance Given ICU Admission	6mo—17yrs	30.26 %	24.5%	36.3%	
	18—49yrs	37.21 %	30.1%	44.6%	
	50—64yrs	43.61 %	35.2%	52.2%	
	65yrs+	38.51 %	31.1%	46.2%	
Probability of Death Given Hospitalization No ICU	6m—17yrs	0.00 %	0.0%	0.0%	
	18—49yrs	0.69 %	0.6%	0.8%	
	50—64yrs	2.80 %	2.3%	3.4%	
	65yrs+	11.84 %	9.6%	14.3%	
Probability of Death Given ICU Admission	6m—17yrs	1.10 %	0.9%	1.3%	
	18—49yrs	7.21 %	5.9%	8.7%	
	50—64yrs	13.16 %	10.7%	15.8%	

Probability Type	Age Group	Base Case	Lower Bound	Upper Bound	Source
	65yrs+	19.21 %	15.6%	23.1%	
Proportion Of High-Risk Among 6mo-11yrs	6mo—11yrs	7.00 %	5.7%	8.4%	Assumed based on CDC data on asthma prevalence [153]
Proportion Of High-Risk Among 12-17yrs	12—17yrs	7.00 %	5.7%	8.4%	
Proportion Of High-Risk Among 18-49yrs	18—49yrs	27.45 %	NA	NA	Boersma et al. 2020[154]
Proportion Of High-Risk Among 50-64yrs	50—64yrs	63.38 %	NA	NA	

CDC: Centers for Disease Control and Prevention, ICU: intensive care unit, NA: not available, mo: months, yrs: years

Vaccine Effectiveness

Table E2.4. Vaccine Effectiveness Inputs by Outcomes

Vaccine Effectiveness Outcome	Subgroup	Base Case (%)*	Lower Bound	Upper Bound	Source
ED/UC Encounter	6 months–17 years	47.0	30.6	62.8	MMWR CDC study, 2025,[17] Weighted average of 9 mo-4 years and 5-17 years, adjusted for 1 year waning
	≥18 years	22.7	14.8	30.3	Cai et al. 2025,[18] adjusted for 1 year waning
Hospitalization and ICU	6 months–17 years	47.0	30.6	62.8	Assumption: same as for Outpatient/ED
	≥18 years	30.3	16.7	42.2	Cai et al. 2025,[18] adjusted for 1 year waning
Death	All ages	49.5	17.8	66.4	Cai et al. 2025,[18] adjusted for 1 year waning

ED: emergency department, CDC: Centers for Disease Control and Prevention, ICU: intensive care unit, MMWR: Morbidity and Mortality Weekly Report, VE: vaccine effectiveness, UC: urgent care

*Relative risk reduction

Calibration of Vaccine Effectiveness Against Death

In the model, mortality outcomes are derived from a chain of conditional probabilities, including hospitalization, ICU admission given hospitalization, and death given ICU or non-ICU hospitalization,

sourced from Yehoshua et al. (2024).[89] Because vaccine effectiveness against death operates multiplicatively through this chain rather than as a single direct reduction, the implied model-level VE against death may not equal the empirically observed estimate of 64% from Cai et al. (2025).[18] To address this, a calibration factor was applied to the conditional probability of death in the vaccinated arm only: 0.60 for adults aged ≥18 years and 0.92 for individuals aged 6 months to 17 years. These values were solved to ensure that the resulting implied VE against death matched the 64% target from Cai et al., and were confirmed by computing the model-level VE for each age stratum. The probabilities for the unvaccinated arm were not altered. The calibration factor is treated as a fixed parameter and is not varied in sensitivity analyses.

Long-Term Sequelae: Markov Model Parameters

Long-term sequelae were modeled using a Markov structure with annual cycles extending from year two through the lifetime horizon, with individuals entering health states based on the disease severity in the decision tree: sequelae after non-severe Covid-19, sequelae after severe Covid-19 without ICU admission, and sequelae after severe Covid-19 with ICU admission. In the absence of empirical long-term follow-up data specific to the 2024–2025 season, all parameters were derived from clinical assumption. Time to resolution was one year (range: 1 to 3) for non-severe sequelae and three years (range: 1 to 5) for both severe non-ICU and ICU sequelae. Excess mortality was modeled in a conservative way via hazard ratios applied over a defined post-infection window: 1.00 (range: 1.00–1.05) for one year (range: 1 to 2 years) in severe non-ICU sequelae, and 1.00 (range: 1.00–1.10) for one year (range: 1 to 2 years) in ICU sequelae, with base-case values set to 1.00 given uncertainty in excess mortality in contemporary vaccinated populations. All parameters were varied independently in one-way deterministic sensitivity analyses.

Table E2.5. Inputs Used For Modeling Long-Term Sequelae

Vaccine Effectiveness Outcome	Subgroup	Base Case (%)*	Lower Bound	Upper Bound	Source
HR Due To Death From Sequelae Given Severe Covid-19 And No ICU	All	1.00	1.00	1.05	Assumption
Time Until Increased Mortality Persists In Sequelae Given Severe Covid-19 And No ICU, Yrs	All	1.00	1.00	2.00	Assumption
HR Due To Death From Sequelae Given Severe Covid-19 And ICU	All	1.00	1.00	1.10	Assumption
Time Until Increased Mortality Persists In Sequelae Given Severe Covid-19 And ICU, Yrs	All	1.00	1.00	2.00	Assumption
Time To Resolve: Sequelae Given Non-Severe Covid-19, Yrs	All	1.00	1.00	3.00	Assumption
Time To Resolve: Sequelae Given Severe Covid-19 And No ICU, Yrs	All	3.00	1.00	5.00	Assumption

Vaccine Effectiveness Outcome	Subgroup	Base Case (%)*	Lower Bound	Upper Bound	Source
Time To Resolve: Sequelae Given Severe Covid-19 And ICU, Yrs	All	3.00	1.00	5.00	Assumption

ICU: intensive care unit, Yrs: years

Adverse Events

Reactogenicity, anaphylaxis, and myocarditis were modeled as vaccine-associated adverse events. Reactogenicity was defined as systemic reaction (fever) and modeled as a transient event occurring shortly after vaccination. Event rates were differentiated by vaccine type: 16% for mRNA vaccines (Comirnaty, Spikevax, mNEXSPIKE) and 5.9% for Nuvaxovid in individuals aged ≥12 years, with the mRNA rate halved to 8% for children aged 6 months to 11 years. Each reactogenicity event incurs a one-time QALY decrement and, under the modified societal perspective, a one-day productivity loss reflecting short-term work absence.

Anaphylaxis was modeled as a rare acute event applicable across all age groups, with an incidence of 0.0050 per 1,000 doses. A probability of death given anaphylaxis was included, with a base-case value of 0% and an upper bound of 0.966% explored in sensitivity analyses.

Myocarditis was modeled as a rare acute adverse event in individuals aged 18 to 39 years, consistent with the known age-specific risk profile. Incidence was 0.00238% in the 18 to 29 year age group and 0.00087% in the 30 to 39 year age group. Acute cases incur a one-time episode cost and a limited QALY decrement corresponding to the symptomatic period. Consistent with CDC follow-up data indicating resolution within months for most cases, no long-term costs or disutility were assumed beyond the acute phase in the base case, and no excess mortality was attributed to myocarditis.

Thrombosis and Guillain–Barré syndrome were considered but excluded from the base-case model due to insufficient data to reliably parameterize incidence, costs, and outcomes.

Table E2.6. Adverse Event Incidence Rates

Adverse Events	Subgroup	Base Case (%)*	Lower Bound (%)	Upper Bound (%)	Source
Reactogenicity - Systemic (Fever) mRNA Vaccines	≥12 years	16.0	12.8	19.2	Based on Table 3.6 in section 3.2, Polack et al. 2020,[7] Sanly et al. 2021[56]
	6 mo–11 yrs	8.0	NA	NA	Assumption: 50% of the mRNA vaccine-related reactogenicity rate of the 12-year-old and over population

Reactogenicity - Systemic (Fever) Nuvaxovid	≥12 yrs	5.9	NA	NA	Based on Table 3.6 in section 3.2, Dunkle et al. 2022[60]
Anaphylaxis	All	0.00050	0.00032	0.00074	Prosser et al,[20] Klein et al. 2021[155]
Probability Of Death Given Anaphylaxis	All	0.00000	0.00000	0.96600	Prosser et al.[20]
Myocarditis	18-29 yrs	0.00238	0.00085	0.00838	Prosser et al.,[20] Goddard et al 2022[156]
	30-39 yrs	0.00087	0.00008	0.00375	Prosser et al.[20]

mo: months, NA: not available, yrs: years

Health State Utilities

Health-related quality of life was modeled using event-based QALY decrements for acute illness and adverse events, and health state utility values for long-term Covid-19 sequelae. For acute illness, decrements increased with severity, from 0.006 for non-hospitalized symptomatic illness to 0.027 for non-ICU hospitalization and 0.054 for critical illness, all sourced from Prosser et al. (2025). Long-term sequelae states were assigned utility values that decreased with severity of the index event, reflecting greater and more persistent impairment following ICU care relative to non-ICU hospitalization or non-severe illness; these were informed by published observational studies of long Covid and ICU survivors, supplemented by authors' assumptions. For adverse events, QALY decrements were applied for reactogenicity (0.0004, equivalent to approximately one day of symptomatic illness), anaphylaxis (0.0137), and myocarditis (0.010, based on an assumed disutility applied over the acute illness period). No long-term disutility was assigned to adverse events beyond the acute phase. Uncertainty in all utility parameters was explored in one-way and probabilistic sensitivity analyses.

Table E2.7. Utilities

Parameter	Subgroup	Base Case	Lower Bound	Upper Bound	Source
Acute Covid-19 Illness (Utility Decrement)					
Symptomatic Illness, Non-Hospitalized	All ages	0.006	0.004	0.008	Prosser et al. 2025[20]
Hospitalization, Non-ICU	All ages	0.027	–	–	
Critical Illness (ICU)	All ages	0.054	–	–	
Long-Term Covid-19 Sequelae (Health State Utility)					
Sequelae After Non-Severe Covid-19	All ages	0.691	0.548	0.817	Authors' assumption
Sequelae After Severe Covid-19, No ICU	All ages	0.651	0.519	0.773	
Sequelae After Severe Covid-19, ICU	All ages	0.631	0.50	0.75	
Vaccine-Associated Adverse Events (Utility Decrement)					
Reactogenicity (Systemic Reaction)	All ages	0.0004	0.0003	0.0005	Prosser et al.,[20] assumption

Parameter	Subgroup	Base Case	Lower Bound	Upper Bound	Source
Anaphylaxis	All ages	0.0137	0.005	0.04	Prosser et al.,[20,157]
Myocarditis	All ages	0.01	0.005	0.04	Prosser et al.[20,158]

ICU: intensive care unit, NA: not available

Cost Inputs

All costs used in the model were updated to 2026 USD.

Vaccine Costs

Vaccine acquisition costs are based on CDC-published per-dose prices for the 2025–2026 season, with separate public-sector and private-sector prices combined using a weight for those participating in the Vaccines for Children Program. mNEXSPIKE pricing aligns with Moderna's Covid-19 vaccine price structure for adults aged ≥12 years.

Table E2.8. Vaccine Prices

Vaccine	Vaccine Type	Age Group	CDC Cost/Dose	Private Sector Cost/Dose	Source
Spikevax	Pediatric	12+ yrs	$83.76	$141.80	CDC, weighted public/private price applied for the pediatric population,[93] mNEXSPIKE adult price is sourced from Fust et al. 2026,[159] mNEXSPIKE pediatric price is assumed based on the ratio of the Spikevax pediatric price to the adult price.
Spikevax	Pediatric	6 mo - 11 yrs	$78.23	$129.00	
mNEXSPIKE	Pediatric	12+ yrs	$104.62	$177.12	
Comirnaty	Pediatric	12+ yrs	$91.75	$136.75	
Comirnaty	Pediatric	5 - 11 yrs	$69.38	$77.00	
Nuvaxovid	Pediatric	12+ yrs	$79.21	$168.35	
Spikevax	Adult	12+ yrs	n/a	$141.80	
mNEXSPIKE	Adult	12+ yrs	n/a	$141.80	
Comirnaty	Adult	12+ yrs	n/a	$136.75	
Nuvaxovid	Adult	12+ yrs	n/a	$168.35	

CDC: Centers for Disease Control and Prevention, n/a: not applicable, mo: months, yrs: years
Note: CDC prices reflect Vaccines for Children (VFC) pricing, and private sector prices reflect commercial acquisition costs. A weighted price will be applied only to pediatric age groups. Adult age groups are assumed to incur private sector prices only; although VFC eligibility extends through age 18, this overlap is not explicitly modeled for simplicity.

Other Direct Medical Costs

Cost inputs reflect direct medical costs for vaccine administration, acute Covid-19 care, and post-acute management, primarily sourced from Prosser (2025) (Table E2.9) and uniformly inflated to 2026 USD using a GDP deflator–based adjustment. Outpatient visit, ED, hospitalization, and critical care costs are applied by age group and increase substantially with care intensity;[20] the six months to 17 years age group was assigned the same hospitalization and ICU costs as the 18 years to 49 years group by assumption. Post-discharge care is applied as a single all-ages cost. Terminal care costs are included for deaths and decrease with age. Long-term sequelae costs are applied by severity pathway: an annual cost for non-severe sequelae, an annual cost for severe sequelae without ICU admission based on non-IPF interstitial lung disease as a proxy, and a lifetime cost for ICU survivors, all applied uniformly across age groups. Future unrelated health care costs are included under both perspectives as age-specific annual costs, ranging from approximately $2,000 per year in children to $11,000 in adults aged ≥65 years. Detailed inputs are shown in Table E2.9.

Table E2.9. Direct Medical Costs

Parameter	Subgroup	Base Case	Lower	Upper	Source
Vaccination					
Vaccine Administration (Per Dose)	All ages	$20	$18	$27	CMS 2025 Fee Schedule, CPT 90471
Outpatient & Emergency Care					
Outpatient Visit	6 mo–17 yrs	$404	$402	$408	Assumption (same as 18–49 yrs)
	18–49 yrs	$404	$402	$408	Prosser et al[20]
	50–64 yrs	$413	$410	$417	Prosser et al[20]
	≥65 yrs	$425	$420	$430	Prosser et al[20]
ED Visit	All ages	$633	$587	$1,426	Prosser et al[20]
Antiviral Therapy (NirmatrelvirRitonavir)	All ages	$576	$0	$1,304	Prosser et al[20]
Hospitalization					
Hospitalization, Non-ICU	6 mo–17 yrs	$35,343	$30,985	$39,701	Assumption (same as 18–49 yrs)
	18–49 yrs	$35,343	$30,985	$39,701	Prosser et al[20]
	50–64 yrs	$35,712	$34,186	$37,238	Prosser et al[20]

Parameter	Subgroup	Base Case	Lower	Upper	Source
	≥65 yrs	$22,444	$22,061	$22,827	Prosser et al[20]
ICU Stay, No Mechanical Ventilation	6 mo–17 yrs	$40,392	$32,736	$48,049	Assumption (same as 18–49 yrs)
	18–49 yrs	$40,392	$32,736	$48,049	Prosser et al[20]
	50–64 yrs	$50,792	$43,772	$57,813	Prosser et al[20]
	≥65 yrs	$25,240	$24,357	$26,123	Prosser et al[20]
ICU Stay, With Mechanical Ventilation	6m–17 yrs	$266,785	$183,009	$350,561	Assumption (same as 18–49 yrs)
	18–49 yrs	$266,785	$183,009	$350,561	Prosser et al[20]
	50–64 yrs	$183,908	$152,452	$215,366	Prosser et al[20]
	≥65 yrs	$60,064	$55,116	$65,012	Prosser et al[20]
Post-Discharge Care	All ages	$11,447	$9,158	$13,738	Prosser et al[20]
Covid-19-Related Cost of Mortality	6m–11 yrs	$45,538	$26,029	$70,414	Jiao & Basu 2021[94]
	12–17 yrs	$42,304	$24,180	$65,413	
	18–49 yrs	$35,476	$20,278	$54,855	
	50–64 yrs	$27,211	$15,553	$42,075	
	≥65 yrs	$22,180	$12,678	$34,296	
Adverse Events					
Systemic Reactogenicity – Physician Visit	All ages	$99	$90	$126	Prosser et al[20]
Anaphylaxis – Hospitalization	All ages	$5,473	$4,378	$6,568	Prosser et al[20]
Myocarditis – Hospitalization	All ages	$82,533	$66,026	$99,039	Prosser et al[20]
Long-Term Sequelae					
Non-Severe Covid-19 Sequelae (Long Covid), Annual Cost	All ages	$4,098	$1,619	$6,578	Neba et al 2025[160]
Severe Covid-19 Sequelae, No ICU (Annual Cost)	All ages	$20,000	$11,432	$30,925	Authors' assumption based on non-IPF ILD cost
Severe Covid-19 Sequelae, ICU	All ages	$25,000	$14,290	$38,657	Prosser et al[20]
Future Unrelated Health Care Costs (Annual)					
Unrelated Health Care Costs	6 mo–11 yrs	$2,029	$1,160	$3,138	Jiao & Basu 2021[94]
	12–17 yrs	$2,282	$1,304	$3,529	
	18–49 yrs	$3,797	$2,170	$5,871	

Parameter	Subgroup	Base Case	Lower	Upper	Source
	50–64 yrs	$7,764	$4,438	$12,005	
	≥65 yrs	$11,087	$6,337	$17,144	

ICU: intensive care unit, mo: months, yrs: years

Productivity Costs

Productivity losses were included under the modified societal perspective. Work time lost was valued using age-specific daily wage rates; for adults aged ≥65 years, a lower residual value was applied to reflect continued economic contributions beyond formal employment, consistent with Prosser (2025).[20] A separate caregiver productivity loss was applied for pediatric patients as a percentage of the adult wage.

Productivity losses were applied across five categories. First, vaccination time was captured as recipient time spent traveling and waiting, weighted by the proportion vaccinated at physician offices versus pharmacies per CDC COVIDVaxView. Second, work days lost due to adverse events were applied in the year of vaccination: one day for systemic reactogenicity, one day (base case) for anaphylaxis, and four days for myocarditis. Third, productivity loss from acute Covid-19 illness was calculated from the duration of acute illness, the proportion of illness days associated with work absence (50%), and the time spent on outpatient or ED visits and testing. Fourth, productivity losses were applied to individuals residing in long-term sequelae states throughout the lifetime model horizon, with 50% of sequelae days assumed to carry productivity loss across all three severity pathways.

Fifth, premature mortality incurred a permanent productivity loss. In contrast to the single discounted lifetime productivity loss per death used by Prosser (2025),[20] the present model applied an annual productivity value in each Markov cycle following death, consistent with the lifetime model structure. For adults aged 18 to 64 years, the annual value was approximated using the US median income (Bureau of Labor Statistics, 2025). For adults aged ≥65 years, the annual value was derived by taking Prosser's undiscounted lifetime productivity loss estimate, spreading it over 15 years, and annualizing, yielding a lower per-year figure that reflects the residual economic contributions of this age group. Detailed inputs are shown in Table E2.10.

Table E2.10. Inputs for Estimating Productivity Loss

Parameter	Subgr -oup	Base Case	Lower Bound	Upper Bound	Source
Wage Inputs					
Mean Hourly Earnings	≥18 yrs	$37	$23	$54	Prosser et al 2025.[20]
Daily Productivity Value	18–49 yrs	$120	–	–	Prosser et al. 2025[20]

Parameter	Subgr-oup	Base Case	Lower Bound	Upper Bound	Source
Daily Productivity Value	50–64 yrs	$135	–	–	Prosser et al. 2025[20]
Daily Productivity Value	≥65yr-s	$42	–	–	Prosser et al. 2025[20]
Caregiver Productivity Loss (As % Of Adult Wage)	6m–17yrs	30%	24%	36%	Authors' assumption
Vaccination					
Recipient Time, Physician Office Visit	All ages	1.19 h	0.17 h	2.00 h	Prosser et al. 2025[20]
Recipient Time, Pharmacy	All ages	0.25 h	0.08 h	0.50 h	Prosser et al. 2025[20]
Proportion Vaccinated At Physician's Office	All ages	9.5%	–	–	CDC COVIDVaxView
Proportion Vaccinated At The Pharmacy	All ages	90.5%	–	–	CDC COVIDVaxView
Adverse Events (Work Days Lost)					
Systemic Reactogenicity	All ages	1 day	–	–	Prosser et al 2025,[20] Assumption
Anaphylaxis	All ages	1 day	1 day	3 days	Prosser et al. 2025[20]
Myocarditis	All ages	4 days	0 days	14 days	Prosser et al. 2025[20]
Acute Covid-19 Illness					
Duration Of Acute Illness	All ages	4.6 days	3.6 days	5.7 days	Prosser et al. 2025[20]
Proportion Of Illness Days With Productivity Loss	All ages	50%	–	–	Prosser et al. 2025[20]
Patient Time, Outpatient Visit	All ages	1.08 h	0.54 h	1.62 h	Prosser et al. 2025[20]
Patient Time, ED Visit	All ages	6.4 h	2.8 h	14.6 h	Prosser et al. 2025[20]
Covid-19 Test Recipient Time	All ages	0.5 h	0.25 h	1.5 h	Prosser et al. 2025[20]
Long-Term Sequelae					
Proportion With Productivity Loss, Non-Severe Sequelae	All ages	50%	–	–	Authors' assumption
Proportion With Productivity Loss, Severe Sequelae (No ICU)	All ages	50%	–	–	Authors' assumption
Proportion With Productivity Loss, Severe Sequelae (ICU)	All ages	50%	–	–	Authors' assumption
Premature Mortality					
Annual Productivity Loss Due to Death	18–64y	$63,000	–	–	BLS median earnings 2025
Annual Productivity Loss Due to Death	≥65y	$17,000	–	–	Authors' estimation based on Prosser et al. 2025[20]

ED: emergency department, h: hours, ICU: intensive care unit, n/a: not applicable, USD: US dollars, yrs: years

E3. Results

Base-case results as well as scenario analyses are described in Section 4.3 of the report.

E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional evLY.

Figure E4.1. Tornado Diagram for Cost per evLY for Spikevax versus No Updated Vaccine

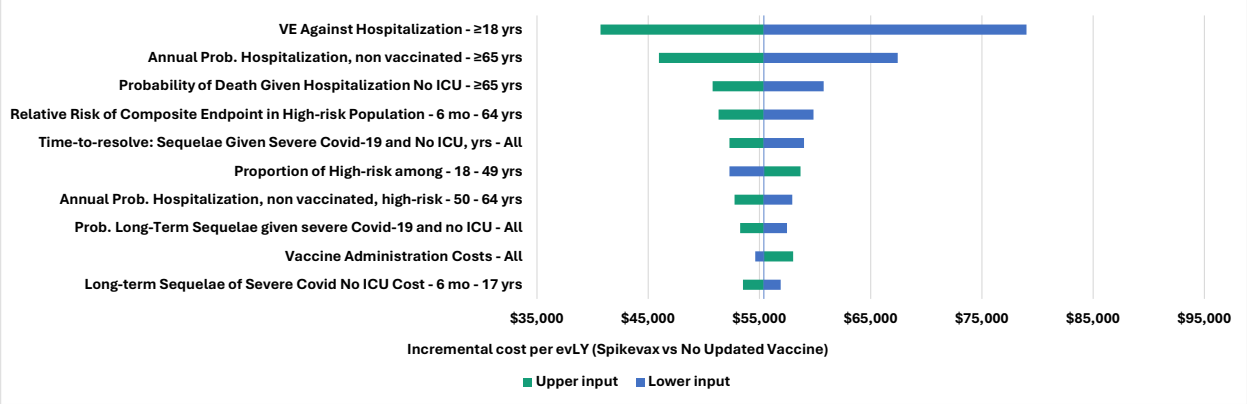


Figure E4.2. Tornado Diagram for Cost per evLY for Comirnaty versus No Updated Vaccine

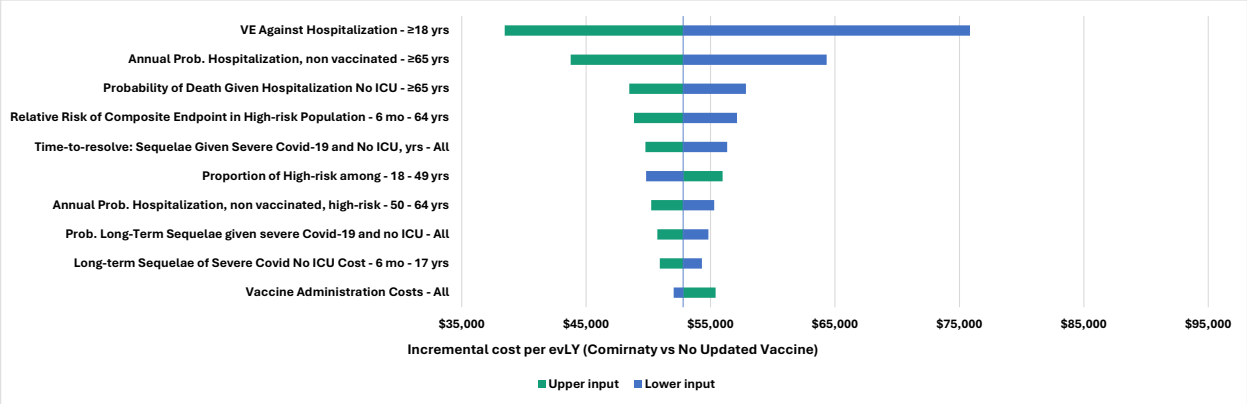


Figure E4.3. Tornado Diagram for Cost per evLY for Nuvaxovid versus No Updated Vaccine

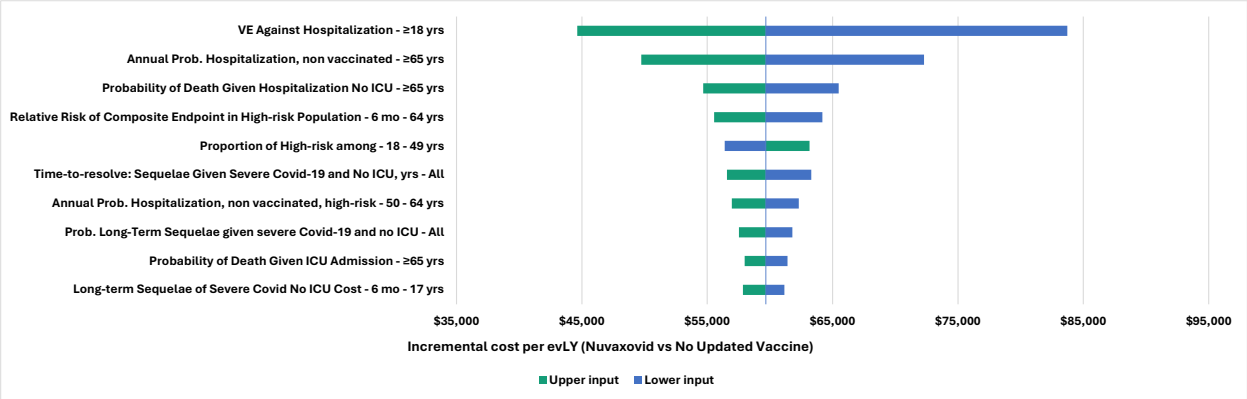


Figure E4.4. Tornado Diagram for Cost per evLY for mNEXSPIKE versus No Updated Vaccine

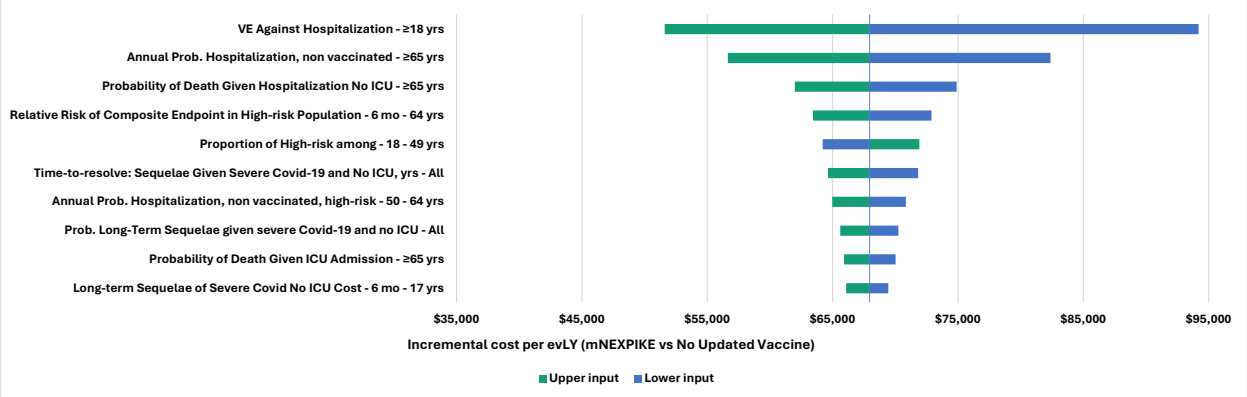


Table E4.1. Tornado Diagram Inputs and Results for Spikevax versus No Vaccine

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
VE Against Hospitalization - ≥18 yrs	$79,009	$40,710	0.167	0.422
Annual Prob. Hospitalization, Non-Vaccinated - ≥65 yrs	$67,439	$45,976	0.005	0.007
Probability of Death Given Hospitalization No ICU - ≥65 yrs	$60,784	$50,794	0.096	0.143
Relative Risk of Composite Endpoint in High-risk Population - 6 mo - 64 yrs	$59,862	$51,332	1.500	2.500
Time-to-Resolve: Sequelae Given Severe Covid-19 and No ICU, yrs - All	$59,005	$52,312	1.000	5.000

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Proportion of High-Risk Among - 18 - 49 yrs	$52,316	$58,693	0.222	0.330
Annual Prob. Hospitalization, Non-Vaccinated, High-Risk - 50 - 64 yrs	$57,962	$52,768	0.002	0.003
Prob. Long-Term Sequelae Given Severe Covid-19 and No ICU - All	$57,489	$53,278	0.178	0.265
Vaccine Administration Costs - All	$54,629	$58,029	$18	$27
Long-Term Sequelae of Severe Covid No ICU Cost - 6 mo - 17 yrs	$56,909	$53,521	$11,432	$30,925

CE: cost-effectiveness, ICU: intensive care unit, ICU: intensive care unit, mo: months, yrs: years

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E4.2. Tornado Diagram Inputs and Results for Comirnaty versus No Vaccine

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
VE Against Hospitalization - ≥18 yrs	$75,847	$38,449	0.167	0.422
Annual Prob. Hospitalization, Non-Vaccinated - ≥65 yrs	$64,332	$43,762	0.005	0.007
Probability of Death Given Hospitalization No ICU - ≥65 yrs	$57,850	$48,470	0.096	0.143
Relative Risk of Composite Endpoint in High-Risk Population - 6 mo - 64 yrs	$57,121	$48,849	1.500	2.500
Time-to-resolve: Sequelae Given Severe Covid-19 and No ICU, yrs - All	$56,330	$49,766	1.000	5.000
Proportion of High-risk among - 18 - 49 yrs	$49,826	$55,963	0.222	0.330
Annual Prob. Hospitalization, Non-Vaccinated, high-risk - 50 - 64 yrs	$55,286	$50,234	0.002	0.003
Prob. Long-Term Sequelae Given Severe Covid-19 and No ICU - All	$54,832	$50,724	0.178	0.265
Long-term Sequelae of Severe Covid No ICU Cost - 6 mo - 17 yrs	$54,297	$50,921	$11,432	$30,925
Vaccine Administration Costs - All	$52,030	$55,398	$18	$27

CE: cost-effectiveness, ICU: intensive care unit, ICU: intensive care unit, mo: months, yrs: years

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E4.3. Tornado Diagram Inputs and Results for Nuvaxovid versus No Vaccine

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
VE Against Hospitalization - ≥18 yrs	$83,725	$44,625	0.167	0.422
Annual Prob. Hospitalization, Non-Vaccinated - ≥65 yrs	$72,291	$49,739	0.005	0.007

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Probability of Death Given Hospitalization No ICU - ≥65 yrs	$65,488	$54,675	0.096	0.143
Relative Risk of Composite Endpoint in High-Risk Population - 6 mo - 64 yrs	$64,188	$55,547	1.500	2.500
Proportion of High-Risk Among - 18-49 yrs	$56,398	$63,159	0.222	0.330
Time-to-Resolve: Sequelae Given Severe Covid-19 and No ICU, yrs - All	$63,294	$56,567	1.000	5.000
Annual Prob. Hospitalization, Non-Vaccinated, High-Risk - 50 - 64 yrs	$62,306	$56,963	0.002	0.003
Prob. Long-Term Sequelae Given Severe Covid-19 and No ICU - All	$61,787	$57,521	0.178	0.265
Probability of Death Given ICU Admission - ≥65 yrs	$61,404	$57,981	0.156	0.231
Long-Term Sequelae of Severe Covid No ICU Cost - 6 mo-17 yrs	$61,145	$57,839	$11,432	$30,925

CE: cost-effectiveness, ICU: intensive care unit, mo: months, yrs: years

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E4.4. Tornado Diagram Inputs and Results for mNEXSPIKE versus No Vaccine

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
VE Against Hospitalization - ≥18 yrs	$94,204	$51,609	0.167	0.422
Annual Prob. Hospitalization, Non-Vaccinated - ≥65 yrs	$82,383	$56,642	0.005	0.007
Probability of Death Given Hospitalization No ICU - ≥65 yrs	$74,903	$61,990	0.096	0.143
Relative Risk of Composite Endpoint in High-risk Population - 6 mo - 64 yrs	$72,895	$63,434	1.500	2.500
Proportion of High-risk among - 18 - 49 yrs	$64,216	$71,926	0.222	0.330
Time-to-Resolve: Sequelae Given Severe Covid-19 and No ICU, yrs - All	$71,819	$64,632	1.000	5.000
Annual Prob. Hospitalization, Non-Vaccinated, High-Risk - 50-64 yrs	$70,845	$64,969	0.002	0.003
Prob. Long-Term Sequelae Given Severe Covid-19 and no ICU - All	$70,241	$65,618	0.178	0.265
Probability of Death Given ICU Admission - ≥65 yrs	$70,026	$65,917	0.156	0.231
Long-term Sequelae of Severe Covid No ICU Cost - 6 mo-17 yrs	$69,445	$66,087	$11,432	$30,925

CE: cost-effectiveness, ICU: intensive care unit, mo: months, yrs: years

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E4.5. Results of Probabilistic Sensitivity Analysis for Spikevax versus No Vaccine

	Spikevax Mean	No Vaccine Mean	Incremental
Costs	$120,264	$120,125	$139
QALYs	15.091702	15.089175	0.002527
QALYs 95% CrI	(14.732626, 15.418743)	(14.729861, 15.416229)	(0.00191, 0.003353)
evLYs	15.091703	15.089175	0.002527
evLYs 95% CrI	(14.732627, 15.418743)	(14.729861, 15.416229)	(0.001911, 0.003354)
Incremental CE Ratio	$55,054 per evLY and $55,073 per QALY		

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year, CrI: credible interval

Table E4.6. Results of Probabilistic Sensitivity Analysis for Comirnaty versus No Vaccine

	Comirnaty Mean	No Vaccine Mean	Incremental
Costs	$120,258	$120,125	$133
QALYs	15.091702	15.089175	0.002527
QALYs 95% CrI	(14.732626, 15.418743)	(14.729861, 15.416229)	(0.00191, 0.003354)
evLYs	15.091703	15.089175	0.002528
evLYs 95% CrI	(14.732627, 15.418743)	(14.729861, 15.416229)	(0.001911, 0.003355)
Incremental CE Ratio	$52,476 per evLY and $52,495 per QALY		

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year, CrI: credible interval

Table E4.7. Results of Probabilistic Sensitivity Analysis for Nuvaxovid versus No Vaccine

	Nuvaxovid Mean	No Vaccine Mean	Incremental
Costs	$120,278	$120,125	$152
QALYs	15.091741	15.089175	0.002566
QALYs 95% CrI	(14.732661, 15.418771)	(14.729861, 15.416229)	(0.001947, 0.003393)
evLYs	15.091742	15.089175	0.002566
evLYs 95% CrI	(14.732662, 15.418772)	(14.729861, 15.416229)	(0.001947, 0.003394)
Incremental CE Ratio	$59,328 per evLY and $59,348 per QALY		

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year, CrI: credible interval

Table E4.8. Results of Probabilistic Sensitivity Analysis for mNEXSPIKE versus No Vaccine

	mNEXSPIKE Mean	No Vaccine Mean	Incremental
Costs	$120,296	$120,125	$171
QALYs	15.091702	15.089175	0.002527
QALYs 95% CrI	(14.732626, 15.418742)	(14.729861, 15.416229)	(0.00191, 0.003353)
evLYs	15.091703	15.089175	0.002527
evLYs 95% CrI	(14.732627, 15.418743)	(14.729861, 15.416229)	(0.001911, 0.003355)
Incremental CE Ratio	$67,484 per evLY and $67,508 per QALY		

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year, CrI: credible interval

E5. Scenario Analyses

Scenario analyses are available in Section 4 of the main report.

E6. Heterogeneity and Subgroups

Subgroup results are shown in Tables E6.1 to E6.5. Each subgroup is stratified by age and high risk based on at least one comorbid condition according to data from the CDC.

Table E6.1. Modeled Population by Subgroups

Subgroup	High-Risk Proportion	Modeled Population (N)	% of Total US Population	% of Total Modeled Population
6 Months–4 Years, High Risk	1.6%	1,347,058	0.4%	0.9%
5–11 Years, High Risk	2.7%	2,285,961	0.7%	1.6%
12–17 Years, High Risk	2.5%	2,088,847	0.6%	1.4%
18–49 Years, High Risk	46.6%	39,424,898	11.7%	27.1%
50–64 Years, High Risk	46.6%	39,392,528	11.6%	27.0%
≥65 Years (All)		61,179,918	18.1%	42.0%
Total Modeled Population	–	145,719,209	43.1%	100%

High-risk defined as ≥1 comorbidity associated with severe Covid-19 per CDC criteria. All adults aged ≥65 years are included regardless of comorbidity status. Total US population denominator: 339,640,651 (US Census Bureau 2024).

Subgroup-specific inputs include age-varying hospitalization rates, vaccine effectiveness (39% in adults aged 18–64 years to 66% in children aged 6 months to 11 years, per Cai et al.), and lower reactogenicity rates in children aged 6 months to 11 years. The wide variation in ICERs across subgroups reflects differences in absolute disease risk. In the 12 to 17-year age group, mRNA vaccines appear less effective and more costly under QALY and evLY metrics due to very low absolute mortality risk and a small net QALY loss from reactogenicity.

Table E6.2. Results for the Subgroup of 65 Years of Age or Older

Treatment	Base-Case Population	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per Hospitalization Avoided
Spikevax	65+ years of age N=61,179,918	No vaccine	$27,000	$27,000	$24,000	$73,000
Comirnaty			$26,000	$26,000	$23,000	$70,000
Nuvaxovid			$30,000	$30,000	$27,000	$82,000
mNEXSPIKE			$34,000	$34,000	$30,000	$92,000

Table E6.3. Results for the Subgroup of High Risk 50–64 Years of Age or Older

Treatment	Base-case population	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per Hospitalization Avoided
Spikevax	High risk 50-64 years of age N=39,392,528	No vaccine	$102,000	$102,000	$93,000	$161,000
Comirnaty			$98,000	$98,000	$90,000	$155,000
Nuvaxovid			$112,000	$112,000	$106,000	$183,000
mNEXSPIKE			$131,000	$131,000	$120,000	$207,000

Table E6.4. Results for the Subgroup of High Risk 18–49 Years of Age

Treatment	Base-Case Population	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per Hospitalization Avoided
Spikevax	High risk 18-49 years of age N=39,424,898	No vaccine	$888,000	$888,000	$716,000	$641,000
Comirnaty			$859,000	$859,000	$693,000	$620,000
Nuvaxovid			$800,000	$800,000	$791,000	$709,000
mNEXSPIKE			$1,087,000	$1,087,000	$876,000	$785,000

Table E6.5. Results for the Subgroup of High Risk 12–17 Years of Age

Treatment	Base-Case Population	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per Hospitalization Avoided
Spikevax	High risk 12-17 years of age N=2,088,847	No vaccine	Less effective, more costly	Less effective, more costly	$19,105,000	$1,476,000
Comirnaty			Less effective, more costly	Less effective, more costly	$19,347,000	$1,495,000
Nuvaxovid			$33,961,000	$33,954,000	$19,166,000	$1,481,000
mNEXSPIKE			Less effective, more costly	Less effective, more costly	$22,993,000	$1,776,000

Table E6.6. Results for the Subgroup of High Risk 5-11 Years of Age

Treatment	Base-case population	Compa-rator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per hospitalization avoided
Spikevax	High risk 5-11 years of age N=2,285,960	No vaccine	$40,882,000	$40,852,000	$6,637,000	$531,000
Comirnaty			$2,291,000	$2,291,000	$4,518,000	$362,000

Note: mNEXSPIKE and Nuvaxovid are not indicated for this population

Table E6.7. Results for the Subgroup of High Risk 6 Months to 11 Years of Age

Treatment	Base-Case Population	Compa-rator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per Hospitalization Avoided
Spikevax	High risk 6 months to 4 years of age N=1,347,058	No vaccine	$36,248,000	$36,225,000	$6,476,000	$531,000

Note: Comirnaty, mNEXSPIKE and Nuvaxovid are not indicated for this population

E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted by comparing with Prosser et al. 2025.[20] As hospitalization rates were a key driver of the model, modeled hospitalization rates per 100,000 in the unvaccinated arm were compared with the corresponding rates reported in Prosser (2025). Modeled rates were lower across all adult age groups, ranging from approximately 22% lower in the 50 to 64 years group to 55% lower in the ≥ 65 years group. This pattern is expected: CDC COVID-NET surveillance data for the 2024–2025 season show hospitalization rates approximately one-third of those observed in the 2022–2023 season used in Prosser et al. 2025, reflecting declining disease severity and increased population immunity over time. The direction and magnitude of the difference are therefore consistent with the updated epidemiologic inputs used in the present model.

In addition, the absolute event counts generated by the model for the two arms (no updated vaccine and updated vaccine) were compared with CDC 2024–2025 cumulative burden estimates for the total US population. The modeled population covers approximately 145.7 million individuals, adults aged ≥65 years and high-risk individuals aged 6 months to 64 years, representing 42.8% of the total US population. Modeled counts for symptomatic illness, outpatient visits, hospitalizations, and deaths all fell below the corresponding CDC national estimates, as expected given that the modeled population is a subset of the total US population. Notably, the modeled population accounts for approximately 96.5% of nationally estimated hospitalizations and 77.5% of deaths, consistent with the concentration of severe Covid-19 outcomes in older and high-risk groups.

Table E7.1. Absolute Outcomes In Modeled Population versus CDC 2024–2025 US Burden Estimates (Total US Population)

Outcome	Modeled	CDC Burden Estimate	Modeled as % of CDC Estimate
Symptomatic Illness	7,454,961	17,400,000	43%
Outpatient/ED Visits	1,832,225	4,100,000	43%
Hospitalizations	453,494	470,000	96%
Deaths	41,693	54,500	77%

ED: emergency department

E8. Prior Economic Models

Two published cost-effectiveness analyses of Covid-19 vaccination in the US are most relevant to the present model: Prosser et al. (2025),[20] which informed ACIP deliberations for the 2023–2024 season, and Fust et al. (2026),[159] which evaluated mNEXSPIKE for the 2025–2026 season.

Both models share our core structural features: a static decision tree with a one-year horizon, effects over a lifetime and a scenario analysis with societal perspective inputs. Prosser et al. is the direct antecedent to our model; we mostly replicated its structure, VE waning approach, and EQ-5D utility estimates for acute-phase illness. Our results differ primarily because we apply substantially lower symptomatic illness and hospitalization rates reflecting the 2024–2025 surveillance data, which show Covid-19 burden approximately one-third of that observed in the 2022–2023 period used by Prosser et al. Additional updates include VE inputs from Cai et al. (2025),[18] hospitalization costs from Yehoshua et al. (2024) in place of the older MarketScan estimates, and an expanded scope covering children and vaccine-specific inputs (e.g., prices, reactogenicity rate).[89]

Fust et al. (2026) use a similar structure and also source hospitalization costs from Yehoshua et al 2024.[159] The primary differences are their restriction to high-risk 12–64-year-olds and adults ≥65 (excluding the high-risk population under 12 that we include), the use of RCT-derived relative VE estimates for mNEXSPIKE versus mRNA-1273 (which we assumed equal), and the application of post-discharge mortality probabilities from a separate meta-analysis rather than direct COVID-NET mortality data. Their base-case incremental cost-effectiveness ratio of $16,247 per QALY gained (2025 USD) for mNEXSPIKE versus no vaccination is directionally consistent with our findings, though not directly comparable given these differences.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy. ICER's methods for estimating potential budget impact are described in detail in the Value Assessment Framework.