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REVIEW

The Impact of Vaccination on COVID-19, Influenza, and Respiratory Syncytial Virus-Related Outcomes: A Narrative Review

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ABSTRACT

Vaccination represents a core preventive strategy for public health, with interrelated and multifaceted effects across health and socioeconomic domains. Beyond immediate disease prevention, immunization positively influences downstream health outcomes by mitigating complications of preexisting comorbidities and promoting healthy aging. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza virus, and respiratory syncytial virus (RSV) are common respiratory viruses responsible for broad societal cost and substantial morbidity and mortality, particularly among at-risk individuals, including older adults and people with frailty or certain comorbid conditions. In this narrative review, we summarize the overall impact of vaccination for these 3 viruses, focusing on mRNA vaccines, each of which exhibits unique patterns of infection, risk, and transmission dynamics, but collectively represent a target for preventive strategies. Vaccines for COVID-19 (caused by SARS-CoV-2) and influenza are effective against the most severe outcomes, such as hospitalization and death; these vaccines represent the most potent and cost-effective interventions for the protection of population and individual health against COVID-19 and influenza, particularly for older adults and those with comorbid conditions. Based on promising results of efficacy for the prevention of RSV-associated lower respiratory tract disease, the first RSV vaccines were approved in 2023. Immunization strategies should account for various factors leading to poor uptake, including vaccine hesitancy, socioeconomic barriers to access, cultural beliefs, and lack of knowledge of vaccines and disease states. Coadministration of vaccines and combination vaccines, such as multicomponent mRNA vaccines, offer potential advantages in logistics and delivery, thus improving uptake and reducing barriers to adoption of new vaccines. The success of the mRNA vaccine platform was powerfully demonstrated during the COVID-19 pandemic; these and other new approaches show promise as a means to overcome existing challenges in vaccine development and to sustain protection against viral changes over time.

A graphical abstract and video abstract is available with this article.

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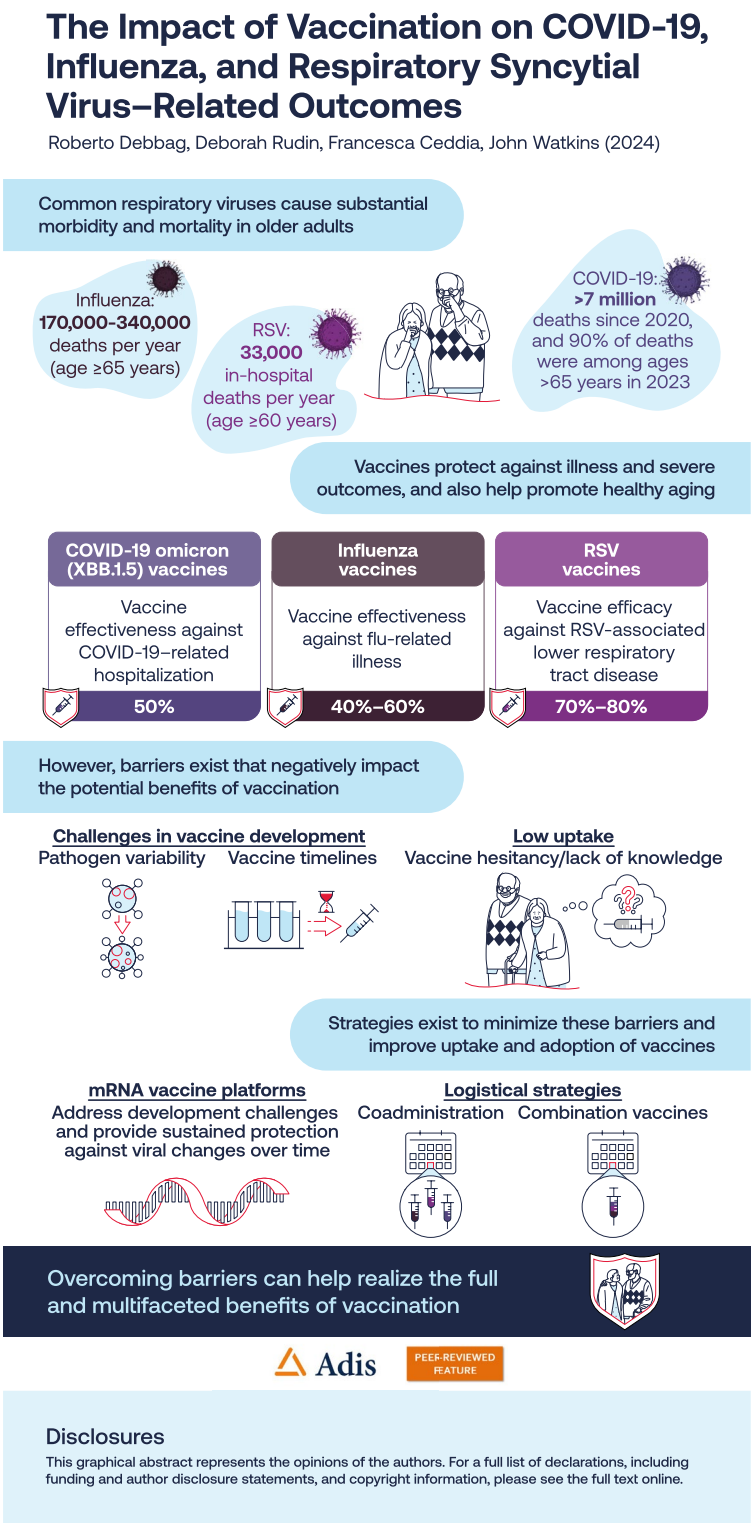
Graphic abstract:



Keywords: COVID-19; Influenza; Older adults; Respiratory syncytial virus; SARS-CoV-2; Vaccination

Key Summary Points
Vaccines for COVID-19, influenza, and RSV are protective against illness, and real-world studies have demonstrated the effectiveness of COVID-19 and influenza vaccines against the most severe outcomes, including hospitalization and death.
Vaccination mitigates exacerbations of preexisting comorbidities and long-term consequences of infection, and a life-course approach to vaccination promotes healthy aging.
Barriers to maximizing impact of vaccination include challenges in vaccine development related to viral and logistical factors, as well as social features contributing to poor uptake, such as vaccine hesitancy and lack of knowledge.
Coadministration of vaccines and combination vaccines, such as multicomponent vaccines that protect against several viruses, offer potential advantages in vaccine logistics, which may improve uptake and reduce barriers to adoption of new vaccines.
New platforms, such mRNA vaccines, may help overcome existing challenges in current non-mRNA vaccine development and sustain protection against viral changes over time.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract and video abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.27096055.

INTRODUCTION

Vaccination is a pillar of public health, heralded for its historic role in preventing and alleviating the global burden of infectious diseases [1, 2]. Worldwide, vaccines are currently estimated to prevent 2–3 million deaths per year; however, a further 1.5 million deaths due to vaccine-preventable diseases could be avoided through increases in vaccine coverage and uptake [3]. Beyond reductions in mortality, the overall impact of vaccines is multidimensional and complex, with interrelated benefits across social, health, and economic domains [2]. In addition to their role in immediate disease prevention, the positive impact of vaccines encompasses mitigating complications as well as exacerbations of preexisting comorbidities following infection, including cardiac and cerebrovascular events and exacerbations of chronic obstructive pulmonary disease (COPD) [4–6]. This positive impact extends to downstream general health outcomes, particularly those associated with aging and frailty, and life-course approach to vaccination can play an important and multifaceted role in healthy aging by modulating immune fitness and promoting the plasticity and resilience of the immune system [7–9]. Even on an individual level, immunization represents one of the most cost-effective interventions in public health, yielding substantial economic benefits across diverse domains and an estimated return on investment of up to 18% in terms of productivity gains and healthcare cost savings [10, 11].

Severe acute respiratory syndrome coronavirus2 (SARS-CoV-2), influenza virus, and respiratory syncytial virus (RSV) are common respiratory viruses responsible for substantial morbidity and mortality, as described in other articles of this supplement. The seasonal and geographical distribution differ between each of these viruses, contributing to variable patterns of circulation according to social dynamics, meteorological factors, and host factors [12–19]. These three viruses present unique public health and clinical challenges but also demonstrate overlapping risks in certain populations, collectively representing a target for

preventive strategies. While these viruses affect all age groups, older adults, those who are frail, and individuals with certain comorbidities are at disproportionate risk of complications and progression to severe disease following infection [20–26]. Many of these underlying medical conditions, such as COPD and diabetes mellitus, represent age-independent common risk factors for severe outcomes for all three respiratory viruses, with higher numbers of coexisting comorbidities associated with increased risk [20, 21, 23, 25]. In addition to impact on health, these three viruses are responsible for major societal costs, driven by direct factors (i.e., hospitalization, intensive care, and inappropriate antibiotic use) and indirect factors (i.e., productivity losses) [27–33].

Existing COVID-19 and influenza vaccines have demonstrated effectiveness against the most severe outcomes, including hospitalization and death, and the first RSV vaccines were approved in 2023 based on positive results of efficacy from clinical trials [34–41]. COVID-19 vaccines, particularly mRNA-based vaccines, have played an important role in the striking downturn of COVID-19–related hospitalizations and deaths compared with the early days of the pandemic, attributable to both averted cases and attenuated severity, leading to improved outcomes following infection [42]. Influenza vaccines provide moderate protection against virologically confirmed influenza; however, this protection fluctuates seasonally and may be greatly reduced or absent due to many factors, including antigenic mismatch with circulating strains and short duration of vaccine-elicited immunity [41, 43–45]. Notably, during the COVID-19 pandemic, cases and viral activity of RSV and influenza decreased to unprecedented low global levels due to the combined effects of multilayer public health interventions [46, 47]. As a consequence of this suppression, children who were very young or born during the winter of 2020–2021 may not have been exposed in their first months of life and remain susceptible to infection by RSV and influenza, potentially driving their epidemiological rebound [48, 49].

Despite the availability of vaccines for COVID-19, influenza, and RSV, and strong evidence supporting their benefit to both individuals and populations, overall adherence to recommendations and vaccine uptake are, in general, universally suboptimal for a variety of reasons, including vaccine hesitancy and logistical challenges [3, 50]. Low uptake in high-risk populations, such as those with certain comorbid conditions, has been attributed to a lack of information or fear of symptoms, and expanding vaccination in this group is key to mitigating the impact of these respiratory viruses [51, 52].

This narrative review aims to comprehensively evaluate the known benefits of vaccination for COVID-19, influenza, and RSV toward reducing morbidity and mortality, promoting healthy aging, and generating broad socioeconomic benefits, while simultaneously highlighting the major challenges and potential future directions of vaccination approaches to overcome developmental and logistical barriers and to reduce disease burden worldwide. Along with other vaccine options for influenza and RSV, mRNA vaccines are highlighted for their ongoing impact on mitigating severe COVID-19–related outcomes and as an important direction for new vaccines.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Impact of COVID-19 Vaccines

Since its zoonotic emergence in December 2019, SARS-CoV-2 has caused more than 774 million cases and more than 7 million deaths, as of March 2024 [53]. Acute SARS-CoV-2 infection is driven by viral replication and generally manifests within 5 days; by contrast, the dysregulated immune response which is the hallmark of severe COVID-19, occurring 7–10 days after symptom onset, leads to acute multiorgan disease, hospitalization, or death [54]. Whereas RSV and influenza have ongoing seasonal impacts, our understanding of endemic

Table 1 Real-world evidence of the impact of COVID-19 vaccines in older adults

Study	Methods	Population	Countries/regions	Interventions	Results
Kopel et al. 2023 [77]	US primary care electronic health records linked to pharmacy/medical claims data, Aug 2022—Feb 2023. Primary endpoint: rVE in preventing COVID-19–related outcomes (hospitalizations and outpatient visits)	Adults ≥ 18 years of age (mean age 58—59 years, 58% female, 40% white), *n* = 2,748,358	United States	(1) Bivalent mRNA-1273.222 (*n* = 1,034,538) (2) Bivalent BNT162b2 (*n* = 1,670,666) mRNA vaccines	Greater rVE for mRNA-1273.222 in preventing COVID-19–related hospitalizations (rVE, 9.8%; 95% CI, 2.6—16.4%) and outpatient visits (rVE, 5.1%; 95% CI, 3.2—6.9%). rVE against both COVID-19–related hospitalizations and outpatient visits increased with increasing age and was greatest in the ≥ 65 years of age subgroup
Wu et al. 2023 [78]	Rapid living systematic evidence review and meta-analysis of the US National Institutes of Health iSearch COVID-19 Portfolio and Embase via OVID until Dec 1, 2022	For VE of a COVID-19 primary vaccination series: 48 studies on SARS-CoV-2 infections; 25 studies on COVID-19–related hospitalizations; and 10 studies on mortality	Europe (14 countries), United States, Canada, Qatar, South Africa, Israel, Singapore, Brazil, Chile, Peru, Thailand	mRNA-1273, BNT162b2, ChAdOx1, Ad26.CoV2.S, CoronaVac	VE of the primary vaccine series against SARS-CoV-2 infections was 83% at 14–42 days after series completion, considered an adequate level, as defined by WHO. VE, decreased through 112 days after vaccination, reaching 47% by 280 days after vaccination. For COVID-19 hospitalizations and mortality, VE levels were adequate at baseline (> 90%), but similarly reduced 112 days after vaccination; although VE remained high over time (> 75%)

Table 1 continued

Study	Methods	Population	Countries/regions	Interventions	Results
Tseng et al. 2023 [79]	Matched prospective cohort study at KPSC health system For ages ≥ 18 years, Aug 31, 2022—Jan 31, 2023. Primary outcome: hospitalization for COVID-19	≥ 6 years of age for inclusion, with matched age group cohorts of 6–17 years, 18–44 years, 45–64 years, 65–74 years, and ≥ 75 years	United States	(1) Bivalent (original and Omicron BA.4/BA.5) mRNA-1273 COVID-19 vaccine (n = 290,292) (2) ≥ 2 doses of original monovalent mRNA COVID-19 vaccination (n = 580,584) (3) COVID-19 unvaccinated group (n = 204,655)	Compared with the ≥ 2 original mRNA vaccine group, the overall rVE against hospitalization for COVID-19 was 70.3% (95% CI, 64.0–75.4%); rVE against SARS-CoV-2 infection requiring emergency department/urgent care and against COVID-19 in-hospital death was 55.0% (95% CI, 50.8–58.8%) and 82.7% (95% CI, 63.7—91.7%), respectively Adjusted rVE was consistent across age, sex, and other demographic factors, with 69.3% (95% CI, 55.2—79.0%) and 71.4% (95% CI, 63.6—77.6%) in 65—74 years and ≥ 75 years age groups, respectively Adjusted rVE was 64.7% (95% CI, 44.0%-—77.7%) and 71.3% (95% CI, 64.5—76.7%) in individuals with and without immunocompromising conditions, respectively

Table 1 continued

Study	Methods	Population	Countries/regions	Interventions	Results
Cheng et al. 2023 [80]	Meta-analysis (22 studies) of reformulated bivalent COVID-19 vaccines (BNT162b2 and mRNA-1273) Subgroup analysis of bivalent vaccines at ≥ 50 years of age and in XBB variant dominant period	Pooled *n* = 39,673,160; subgroup analysis in age ≥ 50 years	United States, Japan, Italy, Denmark, Finland, Norway, Sweden, Palestine, France, South Korea, the Netherlands, United Kingdom, Singapore	(1) Reformulated bivalent COVID-19 vaccine (n = 1,158,5,182) (2) Controls (primarily non-bivalent vaccination)	Protection afforded by bivalent vaccines, compared with monovalent vaccines, was higher for the composite endpoint of hospitalization, death, SARS-CoV-2 infection, and COVID-19 (rVE, 49.7%; 95% CI, 41.4—57.9) in people ≥ 50 years of age and during the period when XBB was predominant (rVE, 49.6%; 95% CI, 27.5—67.8%)
Nab et el. 2023 [81]	Retrospective cohort analysis using the OpenSAFELY platform, Mar 2020—Aug 2022 Crude and sex-standardized and age-standardized wave-specific COVID-19–related death rates and relative risks of COVID-19–related death in population subgroups	Adults ≥ 18 years of age; Wave 1 (Wild-type: Mar—May 2020), *n* = 18,895,870; Wave 2 (Alpha: Sept 2021—Apr 2021), *n* = 19,014,720, Wave 3 (Delta: May—Dec 2021), *n* = 18,932,050; Wave 4 (Omicron: Dec 2021—Apr 2022), *n* = 19,097,970; Wave five (Omicron: Jun—Aug 2022), *n* = 19,226,475	England	Receipt of any COVID-19 vaccine (1—5 doses)	In the first pandemic wave, the highest standardized COVID-19–related death rates were seen in people aged ≥ 80 years and in those with immunocompromising conditions. In later waves, larger decreases (90—91% decrease) in COVID-19–related death rates were seen in groups prioritized for primary SARS-CoV-2 vaccination, including those aged ≥ 80 years and those with neurological disease, learning disability, or severe mental illness

Table 1 continued

Study	Methods	Population	Countries/regions	Interventions	Results
Link-Gelles et al. 2024 (82)	Test-negative case–control study using national Increasing Community Access to Testing CDC data, Sept 21, 2023—Jan 14, 2024	Adults ≥ 18 years of age (n = 9222); subgroup analysis in those aged 18–49 years and ≥ 50 years	United States	Receipt of any updated 2023—2024 monovalent XBB.1.5 vaccine (Moderna, Novavax, Pfizer)	VE was 46% (95% CI, 31—58%) in those aged ≥ 50 years and 57% (95% CI, 48—65%) in those aged 18–49 years During the 60—119 days post-vaccination, VE was 49% (95% CI, 19—68%) for cases with SGTF (representing infection with BA.2.86, JN.1, and sublineages) and 60% (95% CI, 35—75%) for cases with SGTP (representing XBB.1.5 lineages)
Harris et al. 2023 [83]	Retrospective cohort study using Medicare claims linked to customer data from 2 large national pharmacy companies from Dec 11, 2020 to Jul 11, 2021 Study population comprised community-dwelling Medicare fee-for-service beneficiaries aged ≥ 66 years who received an mRNA vaccine as their first COVID-19 vaccine dose during the study period	Adult Medicare fee-for-service beneficiaries aged ≥ 66 years (n = 6,388,196)	United States	(1) mRNA-1273 (n = 2,997,492) (2) BNT162b2 (n = 3,390,704)	After full adjustment, mRNA-1273 vaccine was associated with a lower risk of diagnosed COVID-19 (RR, 0.86; 95% CI, 0.83—0.87); this association was attenuated in individuals categorized as frail (RR, 0.94; 95% CI, 0.89—0.99; P = 0.01 for interaction) Compared with the BNT162b2 vaccine, mRNA-1273 was associated with a lower risk of pulmonary embolism (RR, 0.96; 95% CI, 0.93—1.00) and the composite outcome of any thromboembolic-related event (RR, 0.98; 95% CI, 0.96—1.00)

Table 1 continued

Study	Methods	Population	Countries/regions	Interventions	Results
Xu et al. 2023 [84]	Systematic review and meta-analysis to evaluate the safety of COVID-19 mRNA vaccines (122 studies)	*n* = 5,132,799, subgroup analyses by age and immunocompromised status	United States, Italy, Israel, Japan, Korea, France, Germany, Poland, Saudi Arabia and 17 other countries	(1) mRNA-1273 (2) BNT162b2	The pooled ORs for most AEs were significantly higher in adults than in the elderly for any AE (OR, 2.45; 95% CI, 1.61—3.75), local AEs (OR, 3.58; 95% CI, 2.47—5.19), and any systemic AE (OR, 3.78; 95% CI, 2.26—6.32) Among immunocompromised patients, the pooled ORs of any AEs, any local AEs, and systemic AEs were slightly lower than or similar to those of the healthy controls at 0.6 (95% CI, 0.33–1.11), 0.19 (95% CI, 0.10–0.37), and 0.36 (95% CI, 0.25–0.54), respectively
Kelly et al. 2023 [85]	Prospective cohort study using VHA Corporate Data Warehouse and COVID-19 Shared Resource Comparison. Index date (third booster dose) Jul 1, 2021—Apr 29, 2022; follow-up through May 30, 2022	High-risk adults aged ≥ 18 years receiving care at VHA facilities (*n* = 1,703,189; age ≥ 65 years: 70.3%). Stratified to non-overlapping cohorts of aged ≥ 65 years (13.5%), high-risk comorbid conditions (74.6%), and immunocompromising conditions (11.8%)	United States	3 doses of: (1) BNT162b2 (*n* = 785,235) (2) mRNA-1273 (*n* = 917,954)	Individuals among high-risk populations (aged ≥ 65 years, high-risk comorbid conditions, and/or immunocompromising conditions) who received 3 doses of the BNT162b2 vaccine exhibited a statistically higher relative and absolute risk of hospitalization or death due to COVID-19 pneumonia over a 32-week period compared with those who received 3 doses of the mRNA-1273 vaccine (risk difference, 2.2; 95% CI, 0.9—3.6); no difference was observed in the average-risk population or aged > 65 years subgroup

Table 1 continued

Study	Methods	Population	Countries/regions	Interventions	Results
Wang et al. 2023 [86]	Systematic review and GRADE meta-analysis assessing effectiveness of mRNA-1273 and BNT162b2 COVID-19 vaccines (17 studies)	Adults aged ≥ 18 years with immunocompromising conditions (n = 349,058)	United States, Spain, Singapore, Italy	mRNA-1273 (pooled n = 178,298) BNT162b2 (pooled n = 170,760)	Compared with BNT162b2, mRNA-1273 was associated with a significantly reduced risk of SARS-CoV-2 infection (RR, 0.85; 95% CI, 0.75—0.97; P = 0.0151), severe SARS-CoV-2 infection (RR, 0.85; 95% CI, 0.77—-0.93; P = 0.0009), COVID-19–associated hospitalization (RR, 0.88; 95% CI, 0.79–0.97; P < 0.0001), and COVID-19–associated mortality (RR, 0.63; 95% CI, 0.44–0.90; P = 0.0119)
Ku et al. 2023 [87]	Matched prospective cohort study in KPSC health system, Aug 12, 2021–Jan 31, 2022. Primary outcome: SARS-CoV-2 infection and severe COVID-19 (COVID-19–related hospitalization and death)	Adults ≥ 18 years for inclusion, stratified by age (18–44 years, 45–64 years, 65–74 years, and ≥ 75 years); n = 21,942 (median age, 65 years; 51% female; 47% non-Hispanic White)	United States	mRNA-1273: (1) 3-dose primary series (n = 21,942) (2) 2-dose series (n = 21,942)	Compared with the 2-dose series, the 3-dose series of mRNA-1273 provided improved protection against SARS-CoV-2 infection (adjusted relative VE, 55.0%; 95% CI, 50.8—58.9%), COVID-19 hospitalization (83.0%; 75.4—88.3%), and COVID-19 in-hospital death (87.1%; 30.6—97.6%) Adjusted rVE was numerically higher for persons aged ≥ 75 years compared with those aged 18–44 years (58.5 vs. 49.8, respectively)

Table 1 continued

Study	Methods	Population	Countries/regions	Interventions	Results
Marra et al. 2023 [58]	Systematic literature review and meta-analysis assessing effectiveness of COVID-19 vaccination against long COVID (32 studies)	Pooled $n = 775{,}931$	United States, United Kingdom, Switzerland, India, Brazil, France, Israel, Italy, Morocco, Netherlands, Norway, Saudi Arabia, Scotland, South Africa, Spain, and Turkey	≥ 2 doses of COVID-19 vaccines [mRNA, or vectorial or inactivated viral vaccine, with exception of 1 dose for Janssen (Ad26.COV2.S) vaccine]	Overall, the pooled prevalence of long COVID was 11.8% in the unvaccinated and 5.3% in those who received ≥ 2 doses of vaccine. During the omicron era, the pooled diagnostic OR of long COVID in vaccinated vs. unvaccinated individuals was 0.68 (95% CI, 0.54–0.86)
Lundberg-Morris et al. 2024 [88]	Population-based cohort study using SCIFI-PEARL, a nationwide linked multiregister, observational study of COVID-19 in Sweden	Adults ≥ 18 years of age with COVID-19 first registered between Dec 27, 2020 and Feb 9, 2022 in the 2 largest regions of Sweden ($n = 589{,}722$), with subgroups by age and comorbidities	Sweden	≥ 1 dose or ≥ 2 doses (any combination) of: BNT162b2, mRNA-1273, AZD1222, Ad26.COV2.S, or NVX-CoV2373	Overall, COVID-19 vaccination (≥ 1 dose) before infection was associated with a reduced risk of long COVID (aHR, 0.42; 95% CI, 0.38–0.46; VE, 58%) One dose, 2 doses, and ≥ 3 doses of vaccine were associated with a VE of 21%, 59%, and 73%, respectively. VE was 55% in those aged ≥ 65 years and 55–71% in those with comorbidities cardiovascular, pulmonary, or diabetes

Table 1 continued

Study	Methods	Population	Countries/regions	Interventions	Results
Catala et al. 2024 [89]	A study of the effectiveness of COVID-19 vaccines in preventing long COVID symptoms in adults aged > 18 years	*n* = 1,618,395 (CPRD GOLD), *n* = 5,729,800 (CPRD AURUM), *n* = 2,744,821 (SIDIAP), and *n* = 77,603 (CORIVA)	United Kingdom, Spain, Estonia	≥ 1 dose of BNT162b2, mRNA-1273, ChAdOx1, and Ad26.COV2.S	Vaccination with any COVID-19 first vaccine dose was associated with a reduced risk of developing long COVID across all databases, with meta-analytic calibrated sHRs of 0.54 (95% CI, 0.44–0.67) in CPRD GOLD, 0.48 (0.34–0.68) in CPRD AURUM, 0.71 (0.55–0.91) in SIDIAP, and 0.59 (0.40–0.87) in CORIVA

AE adverse event, *aHR* adjusted hazard ratio, *CDC* US Centers for Disease Control and Prevention, *CPRD* Clinical Practice Research Datalink, *HR* hazard ratio, *KPSC* Kaiser Permanente Southern California, *OR* odds ratio, *RR* relative risk, *rVE* relative vaccine effectiveness, *SCIFI-PEARL* Swedish COVID-19 Investigation for Future Insights–a Population Epidemiology Approach using Register Linkage, *SGTF* S-gene target failure, *SGTP* S-gene target presence, *SIDIAP* Information System for Research in Primary Care, *VE* vaccine effectiveness, *VHA* Veterans Health Administration, *WHO* World Health Organization

SARS-CoV-2 transmission and its cadence of surges is still developing, with future endemicity yet to be determined [13, 55, 56]. Additionally, a succession of highly mutated variant strains and lineages have arisen since the ancestral virus (i.e., alpha, beta, gamma, and delta), with the omicron lineage having obtained global dominance over earlier strains [57]. Since the emergence of ancestral SARS-CoV-2, relatively high levels of infection and cases of symptomatic COVID-19 still occur, although with relatively low incidence of hospitalizations and deaths compared to the pandemic phase [56]. COVID-19 vaccines played an integral role in containing the COVID-19 pandemic and limiting its global impact [34, 58]. However, adults aged ≥ 65 years remain at elevated risk, accounting for 63% of COVID-19 hospitalizations and nearly 90% of in-hospital deaths in the United States in 2023, thus underscoring the importance of age as a risk factor for severe outcomes [59]. Although some countries achieved high levels of vaccination during the pandemic, vaccination rates varied widely, and efforts will be needed to sustain vaccination during the endemic phase of SARS-CoV-2 [60]. Novavax (Nuvaxovid), an adjuvanted protein-based COVID-19 vaccine is authorized for use in those aged ≥ 12 years by the US Advisory Committee on Immunization Practices (ACIP), European Medicines Agency (EMA), and Canadian National Advisory Committee on Immunization [61–63]. However, as of June 30, 2024, mRNA COVID-19 vaccines comprise by a large margin the most frequently administered COVID-19 vaccines in the United States, Europe, and other countries and thus are the focus of this section [64].

In the United States and parts of Europe, two mRNA-based COVID-19 vaccines, mRNA-1273 (Spikevax®; Moderna, Inc., Cambridge, MA, USA) and BNT162b2 (Comirnaty®; Pfizer Inc, New York, NY, USA; BioNTech Manufacturing GmbH, Mainz, Germany), are approved and authorized for use [65–68], while elsewhere other COVID-19 vaccines are available. These two vaccines have been periodically updated since their original authorization and approval to target and enhance protection against newly circulating SARS-CoV-2 variants, most recently

with a monovalent omicron XBB.1.5 component for the 2023–2024 season [65, 66]. Antiviral drugs are available for the treatment of COVID-19; however, the low cost, effectiveness, safety, and broad applicability of vaccines makes immunization an irreplaceable component of COVID-19 control and mitigation [69, 70].

An extensive body of literature has demonstrated the safety, efficacy, and real-world effectiveness of COVID-19 mRNA vaccines, especially for severe outcomes, in both phase 3 clinical trials [71–76] and real-world settings (Table 1) [34–36, 58, 77–89]. A meta-analysis (22 studies, pooled n = 39,673,160) of reformulated variant-targeting COVID-19 vaccines (BNT162b2 and mRNA-1273) found that the protection afforded by bivalent vaccines in people ≥ 50 years of age during the omicron XBB era was higher compared with original vaccines for the composite endpoint of infection, COVID-19 diagnosis, and COVID-19 hospitalization and death [relative vaccine effectiveness (rVE), 49.7%; 95% CI, 41.4–57.9] [80]. These findings support the continued value and importance of updating COVID-19 vaccines to target and provide continued protection against newly emerging SARS-CoV-2 variants. Although evidence suggests that older vaccines against emerging SARS-CoV-2 variants are not as effective in preventing infection, protection against severe outcomes, such as hospitalization and death, remains high [80]. Perhaps because cellular immunity, mediated by memory T cells, can persist long after the waning of humoral immunity, the impact of vaccines appears to last longer for these severe outcomes compared with symptomatic infection, and is resistant to immune escape by emergent strains [90, 91].

Recent evidence has supported the overall importance of COVID-19 vaccination in older and other vulnerable individuals during the omicron era. Bivalent mRNA booster vaccines have demonstrated durable effectiveness of 60–70% against severe COVID-19–related outcomes [79, 92, 93]. An analysis using the OpenSAFELY platform across five pandemic waves spanning nearly 2.5 years in England (through omicron BA.5 dominance) revealed that vaccines and advancements in COVID-19 management substantially decreased population-level COVID-19–related mortality risks during subsequent waves of the pandemic; however, persistent inequalities and vulnerabilities were found among clinical and demographic subgroups, particularly among people with comorbidities or immunocompromising conditions versus those without such conditions [81]. In the first pandemic wave, the highest standardized COVID-19–related death rates were seen in people aged ≥ 80 years and in those with immunocompromising conditions; in later waves, larger decreases (90–91% decrease) in COVID-19–related death rates were seen in groups prioritized for primary SARS-CoV-2 vaccination, including those aged ≥ 80 years and those with neurological disease, learning disability, or severe mental illness [81]. The most recent effectiveness estimates, using Centers for Disease Control and Prevention (CDC) data from the 2023–2024 season, including the omicron XBB lineage and JN.1 variant, show that the updated monovalent XBB.1.5 COVID-19 vaccines were effective, with a rVE of approximately 50% (compared with no updated vaccine) against symptomatic SARS-CoV-2 infection in adults aged ≥ 50 years and vaccine effectiveness (VE) of approximately 50% against COVID-19–related hospitalizations in adults aged ≥ 65 years [82, 94]. Results of comparative effectiveness and safety studies using large, linked claims and electronic health record databases in older US adults suggest that mRNA-1273 may have a lower risk of adverse thromboembolic events and a higher rVE in preventing COVID-19–related outcomes (hospitalizations and outpatient visits) compared with BNT162b2, with a greater protection seen among adults ≥ 65 years of age [77, 83].

Individuals with immunocompromising conditions have been disproportionately affected by COVID-19, with an increased risk of severe outcomes, including breakthrough infection, hospitalization, and death, even with vaccination [95]. Although accounting for only 3.9% of the population of England, immunocompromised people comprised > 20% of COVID-19 hospitalizations, intensive care unit admissions, and deaths in the omicron era, even though > 80% of these individuals have received ≥ 3 doses of a COVID-19 vaccine [96]. Rates of seroconversion and antibody titers following COVID-19

vaccination are significantly lower in individuals with immunocompromising conditions compared with those without immunocompromising conditions, [97] suggesting that modified vaccination approaches may be needed to bolster immune responses in this population. Real-world effectiveness studies in high-risk populations (aged ≥ 65 years, high-risk comorbid conditions, and/or immunocompromising conditions), including data through the omicron era, have demonstrated potentially diminished effectiveness but still favorable effectiveness and safety profiles with updated COVID-19 vaccines in these groups [79, 84, 85, 87]. In a matched cohort study of US adults (median age, 65 years) with immunocompromising conditions, a third dose of mRNA-1273 improved protection against SARS-CoV-2 infection (adjusted relative VE, 55.0%; 95% CI, 50.8–58.9%), COVID-19 hospitalization (83.0%; 75.4–88.3%), and COVID-19 inpatient mortality (87.1%; 30.6–97.6%) compared with two doses [87]. Notably, adjusted relative VE was numerically higher for persons aged ≥ 75 years compared with those aged 18–44 years (58.5 vs. 49.8, respectively), suggesting a slightly enhanced protective effect in this group [87]. Some real-world studies in these populations have shown that mRNA-1273 vaccination compared with BNT162b2 vaccination is associated with a significantly reduced risk of severe outcomes, including breakthrough SARS-CoV-2 infection, severe COVID-19, COVID-19–associated hospitalization, and COVID-19–associated mortality [85, 86]. Overall, enhanced protective measures, such as the use of additional or booster vaccine doses, may be needed for individuals with immunocompromised conditions [86, 98].

Long COVID encompasses a range of potentially debilitating physical and psychological symptoms, likely to be driven by host immune responses, and can affect multiple organ systems and persist for weeks or months beyond the acute phase of COVID-19 [99]. The burden of disease associated with long COVID is large, affecting an estimated 10% of infected individuals or ≥ 65 million people worldwide, with incidence increasing to 50–70% among those hospitalized for COVID-19 [100]. The impact of vaccination on long COVID is not entirely clear, due in part to heterogeneity of case definitions, study methods, and differing time since vaccination; however, studies generally seem to indicate protection associated with vaccination [100]. Meta-analyses among adults ≥ 18 years of age have indicated that receipt of COVID-19 vaccination (BNT162b2, mRNA-1273, Ad26.COV2.S, or ChAdOx1) prior to a diagnosed SARS-CoV-2 infection, may have a significant protective effect against long COVID (overall VE, 30–50%) and against long COVID-associated signs and symptoms such as persistent fatigue and pulmonary disorders [58, 101, 102]. In a large cohort study among adults aged ≥ 18 years in Sweden through the omicron era, VE for the prevention of long COVID was 73% overall after 3 vaccine doses, 55% in those aged ≥ 65 years, and 55–71% in those with comorbidities (cardiovascular, pulmonary, or diabetes) [88]. In a meta-analysis of adults ≥ 18 years of age (41 studies), increasing age and comorbidities were important identified risk factors for developing post-COVID conditions, whereas vaccination with ≥ 2 doses (BNT162b2, mRNA-1273, or ChAdOx1 nCoV-19) had a protective effect [odds ratio (OR), 0.57; 95% CI, 0.43–0.76], highlighting the benefit of vaccination in this key population [103]. A multinational study in European countries found that vaccination with any first vaccine dose (BNT162b2 or ChAdOx1) in adults was associated with an overall VE of 29–52% for the prevention of long COVID, with consistent protection against all age groups, including cohorts aged ≥ 75 years and ≥ 65 years [89]. These results were robust to multiple sensitivity analyses and different definitions of long COVID, including durations of symptoms and clinically diagnosed long COVID [89].

Overall, COVID-19 mRNA vaccines have proven to be the most sustainable and effective public health measure available [104], and were instrumental in mitigating the impact of the pandemic. Although strategies will need to constantly reevaluate the impact of emerging variants on outcomes and durability of protection, cost-effectiveness studies have shown that COVID-19 vaccination programs are uniformly cost-effective across a variety of countries in World Health Organization (WHO) regions [105]. The EMA as well as the US CDC and

ACIP recommend that all persons ≥ 6 months of age receive vaccination with updated mRNA COVID-19 vaccines irrespective of prior vaccination [106–108]. Because individuals can choose the COVID-19 vaccine they receive, it may be important for clinical guidelines to address which populations stand to benefit most from specific updated mRNA vaccines over time.

Impact of Influenza Vaccines

Between 1999 and 2015, influenza virus was responsible for an estimated 0.3 to 0.6 million annual respiratory deaths globally, with the highest rates observed among individuals aged ≥ 75 years [109]. Compared with SARS-CoV-2 and RSV, influenza comprises a diverse family of pathogens and strains, with seasonal patterns that vary between regions and countries, together posing a singular challenge for preventive strategies. Although 4 major types of influenza circulate, only type A (H1N1 and H3N2) causes widespread viral activity and epidemics in humans; type B (Yamagata and Victoria lineages) is more commonly associated with outbreaks in care settings rather than epidemic disease [110]. In the temperate zones of the Northern and Southern Hemispheres, influenza A activity manifests as seasonal disease during the respective winter in each region, whereas tropical zones are sometimes characterized by bimodal seasonality and year-round transmission [19]. Influenza vaccine compositions are thus updated annually by the WHO Global Influenza Surveillance and Response System in response to circulating influenza virus activity [110]. Both quadrivalent and trivalent vaccine formulations have been recommended, although the global absence of the B/Yamagata lineage from circulation in recent years has resulted in the WHO revising recommendations to omit this influenza B component beginning in the 2024–2025 influenza season in the Northern and Southern Hemispheres [110].

Seasonal influenza vaccines are largely manufactured using an egg-based process, although recombinant and cell culture-based options are also available [111], and the overall effectiveness of these vaccines varies by population and season. In the United States, it is estimated that VE among the general population is 40–60% during seasons when vaccines are well-matched to circulating strains [112, 113]. In addition to one cell culture-derived quadrivalent influenza vaccine (QIV) vaccine, a variety of enhanced influenza vaccines are currently available for use in older adults, including two egg-based vaccines and one recombinant protein vaccine (Table 2) [114–117]. Compared with standard-dose vaccines, high-dose vaccines offer significantly greater protection against influenza-like illness and influenza in older adults and may attenuate progression to severe disease (pneumonia, intensive care unit admission, and death) [40]. Although current influenza vaccines may provide moderate protection, vaccine-induced immunity declines over the course of an influenza season, and effectiveness may also vary widely between vaccines and be greatly reduced or absent in some seasons [41, 44, 118].

The relatively variable VE of current influenza vaccines reflects a multitude of viral-, host- (i.e., age and immune function), and vaccine-related factors that impact vaccine performance [113, 118, 119]. Major challenges to VE are related to strain mismatch of vaccines to circulating strains due to egg-adapted mutations acquired during manufacture or antigenic drift occurring during the 6-month production time [45, 113]. Viral adaptations resulting in impaired antibody responses to the circulating strain are a potential consequence of egg-based manufacturing, a time-consuming process that may limit production capacity [43]. Antigenic drift is an inherent feature of influenza viruses that leads to the accumulation of changes in major surface proteins [hemagglutinin (HA) and neuraminidase (NA)] and subsequent evasion of humoral immunity, thus rendering existing vaccines less effective against new strains [120]. Because production times are approximately 6 months from the determination of initial vaccine composition recommendations, antigenically divergent clades from the original target can lead to antigenic mismatch [45]. Host-related factors also challenge influenza VE; people with immunocompromising conditions, including organ transplant, malignancy, or receipt of immunomodulating therapies, are at a heightened

Table 2 Studies of the impact of enhanced and cell-based influenza vaccines in adults

	Enhanced vaccines			Standard-dose vaccines
Vaccine	**Fluzone HD QIV (IIV3-HD) [114]**	**Fluad MF59-adjuvanted QIV (aQIV) [115]**	**Flublok QIV (RIV4) [116]**	**Flucelvax QIV [117]**
Vaccine type	Egg-based	Egg-based, MF59-adjuvanted	Recombinant protein	Cell-based
Dose	60 μg of HA per strain	60 μg (15 μg HA each for the 2 influenza type A and type B strains)	45 μg of recombinant HA per strain (180 μg of protein per dose)	15 μg per 0.5 mL PFS (15 μg hemagglutinin per strain)
Study design	Phase 3b–4 trial comparing IIV3-HD with a standard dose vaccine (IIV3-SD)	Phase 3 trial comparing aQIV with a non-influenza comparator vaccine	Phase 3–4 trial comparing RIV4 with an FDA-approved inactivated vaccine (IIV4)	Phase 3 trial comparing cell culture-derived vaccine (Flucelvax QIV) and egg-based TIV and placebo
Age of study population	≥ 65 years	≥ 65 years	≥ 50 years	18–49 years
Countries	United States and Canada	Bulgaria, Colombia, Czech Republic, Estonia, Latvia, Lithuania, Malaysia, Philippines, Poland, Romania, Thailand, and Turkey	United States	United States, Finland, and Poland
Efficacy	Relative to IIV3-SD, efficacy of IIV3-HD was 24.2% for the primary endpoint of laboratory-confirmed influenza ≥ 14 days post-vaccination Pre-specified superiority criterion was met	Efficacy was 19.8% for the primary endpoint of any RT-PCR–confirmed influenza occurring after day 21 Prespecified success criterion was not met	Relative vaccine efficacy was 30% for the primary endpoint of RT-PCR–confirmed influenza-like illness occurring ≥ 14 days , post-vaccination (any influenza virus type)	Efficacy was 83.8% against vaccine-like strains and 69.5% against all circulating strains for the prevention of laboratory-confirmed influenza ≥ 21 days after vaccination

Table 2 continued

Vaccine	Enhanced vaccines			Standard-dose vaccines
	Fluzone HD QIV (IIV3-HD) [114]	**Fluad MF59-adjuvanted QIV (aQIV) [115]**	**Flublok QIV (RIV4) [116]**	**Flucelvax QIV [117]**
Immunogenicity	For all 3 vaccine strains, HAI antibody GMTs and seroprotection rates at 28 days post-vaccination were significantly higher after vaccination with IIV3-HD than with IIV3-SD	At day 22 post-vaccination, a significantly higher proportion of participants in the aQIV group had HAI antibody GMTs of ≥ 1:40 compared with the non-influenza vaccine comparator group	The proportions of subjects with post-vaccination HAI titers ≥ 1:40 were similar between the 2 vaccine groups	No differences in baseline seroprotection rates, seroconversion rates, and HAI antibody GMTs were seen between the study groups
Safety	The relative risk for experiencing ≥ 1 SAE with IIV3-HD compared with IIV3-SD was 0.92 (95% CI, 0.85–0.99)	SAEs occurred at a similar rate in the aQIV group and comparator group (7.0% and 6.9%, respectively)	Within 6 months after vaccination, 3.4% of the RIV4 group and 3.0% of the IIV4 group had ≥ 1 SAE	No clinically relevant differences in safety and reactogenicity were seen between the 2 vaccine groups, and no SAEs were considered related to the study vaccine

FDA US Food and Drug Administration, *GMT* geometric mean titer, *HA* hemagglutinin, *HAI* hemagglutination inhibition, *HD* high-dose, *QIV* quadrivalent influenza vaccine, *PFS* phosphate-buffered saline, *RIV4* quadrivalent recombinant influenza vaccine, *RT-PCR* real-time polymerase chain reaction, *SAE* serious adverse event, *SD* standard dose, *TIV* trivalent inactivated influenza vaccine

risk of complications following influenza infection, and both vaccination rates and vaccine-mediated immunogenicity are suboptimal in this population [121]. However, vaccine studies often use population or pooled data that may not account for prior exposure, population prevalence of antibodies, and asymptomatic disease; thus, true correlates of protection are difficult to derive and interpret. These challenges associated with the development and implementation of influenza vaccines are inherent in the virology of influenza and suggest a need for new vaccine strategies.

Alternative approaches to overcome limitations of conventional influenza vaccines are under clinical investigation [113]. One such approach is the mRNA platform, which has a simplified and highly scalable manufacturing process compared with conventional vaccines; shortened production timelines could thus enable selection of influenza vaccine strains closer to the start of influenza season, thereby increasing the likelihood of targeting circulating strains and limiting vaccine mismatch [122, 123]. Studies on SARS-CoV-2 mRNA-based vaccines, mRNA-1273 and BNT162b2, have shown that mRNA vaccines can induce strong cellular responses and germinal center reactions, which could improve protection in older adults [124–126]. In addition, the mRNA platform allows for targeting additional antigenic sites, which may broaden protection by improving immunity against more conserved targets, including additional HA antigens and HA plus NA antigens [113, 127, 128]. This concept is being advanced in clinical trials for two candidate mRNA vaccines, mRNA-1010 and mRNA-1012 (ClinicalTrials.gov: NCT05827068), which include additional HA antigens for influenza A.

Published clinical findings on an mRNA influenza vaccine are currently available for the mRNA-1010 vaccine (Moderna), an investigational seasonal influenza vaccine that encodes membrane-bound HA glycoprotein derived of influenza strains recommended by WHO [122]. In a first-in-human randomized, observer-blinded, multicenter, phase 1/2 clinical trial (NCT04956575) in healthy adults aged ≥ 18 years, a single dose of mRNA-1010 elicited HA inhibition antibodies against vaccine-matched strains at 28 days post-vaccination, irrespective of participant age [122]. Compared with a standard-dose influenza vaccine in medically stable adults, mRNA-1010 elicited higher immunogenicity for influenza A strains and comparable immunogenicity for influenza B strains [122]. Overall, mRNA-1010 had an acceptable reactogenicity profile, and most solicited adverse reactions were transient and grade 1 or grade 2 in severity [122].

Routine annual influenza vaccination has been shown to be a highly cost-effective intervention in a variety of settings and in both high-income and low- and middle-income countries, with the greatest impact noted in high-risk groups (adults aged ≥ 65 years and individuals with underlying comorbidities) [129–131]. Further cost-effectiveness studies will be needed to assess the benefits of mRNA-based vaccines against their aforementioned logistical challenges. Currently, the EMA and ACIP recommend that adults aged ≥ 65 years should prioritize receiving one of the following enhanced influenza vaccines: Fluzone HD QIV (HD-IIV4), Flublok QIV (RIV4), or Fluad QIV [132].

Impact of RSV Vaccines

Although the global burden of RSV is highest in children < 5 years of age, older adults and adults with certain underlying comorbidities are at elevated risk of RSV infection and severe outcomes, including hospitalization and death [22–24, 26, 133, 134]. RSV is responsible for an estimated 5.2 million annual cases of RSV-associated acute respiratory infections and 33,000 in-hospital deaths in adults ≥ 60 years of age in high-income countries [135]. The seasonality of RSV varies according to climate and geography; however, RSV is notable for its consistently major annual burden of disease, compared with the highly variable impact of influenza [15, 136]. A cost-effectiveness analysis in the United States showed that an RSV vaccine could be cost-effective and substantially reduce the direct burden of RSV illness among older adults [137].

Recently, improved understanding of the structure of RSV envelope fusion (F) glycoprotein and its stabilization in the prefusion (preF)

conformation has advanced RSV vaccine development [138, 139]. RSV-F glycoprotein mediates fusion and is necessary for RSV infection to occur [140]. RSV preF protein is highly conserved across the two primary cocirculating subtypes of RSV-A and RSV-B, and is the primary target of RSV-neutralizing antibody activity [140], which has led to its use as a key target of RSV vaccine development. Progress toward an RSV vaccine was stalled for several years following clinical trials in previously RSV-naïve infants and children in the 1960s investigating a formalin-inactivated vaccine. Vaccine-associated enhanced disease (VAED) was shown to develop possibly due to the generation of a nonprotective antibody response with low avidity for RSV-F and administration of RSV-F in the post-fusion conformation, which is less stable and generates antibodies with lower neutralizing capacity compared with preF [141]. In children, VAED has been linked to induction of a T-helper 2 (Th2)-biased T-cell response [142–144]. Despite these challenges, two protein-based subunit vaccines [RSVPreF3 (GSK), RSVpreF (Pfizer)] have been approved for the prevention of RSV-associated lower respiratory tract disease (LRTD) in older adults, while RSVpreF has been approved for pregnant persons at 32–36 weeks gestational age to pass on protection to their baby [145, 146]. Additionally, an mRNA-based vaccine, mRNA-1345, was recently approved in the United States for use in adults aged 60 years and older [146].

RSVPreF3 (AREXVY; GSK, Brentford, Middlesex, UK) vaccine, a recombinant $AS01_E$-adjuvanted subunit vaccine containing F protein stabilized in the preF conformation [37], was the first vaccine to receive US Food and Drug Administration (FDA) authorization for the prevention of RSV-associated LRTI. This approval was followed by that for RSVpreF (ABRYSVO®; Pfizer, New York, NY, USA), a bivalent protein subunit vaccine containing conformation-stabilized preF glycoproteins with a sequence derived from RSV-A and RSV-B [147, 148]. In clinical trials, both RSVPreF3 and RSVpreF elicited a ≥ tenfold increase in neutralizing activity and similar durability through 1 year, suggesting substantial durable protection [149, 150]. Both vaccines were efficacious for the prevention of RSV-associated LRTI (RSVPreF3: VE 82.6%; 96.95% CI, 57.9–94.1) and LRTD (RSVpreF: VE 66.7%; 96.66% CI, 28.8–85.8) and were generally well-tolerated (Table 3) [37–39, 150, 151], although the FDA imposed post-marketing pharmacovigilance studies for the evaluation of Guillain–Barré syndrome (both vaccines) and acute disseminated encephalomyelitis (RSVPreF3) risks due to a potential safety signal observed during these trials [152, 153]. An additional RSV vaccine approved in 2024 for use in adults ≥ 60 years of age is mRNA-1345 (Moderna, Cambridge, MA, USA), an mRNA-based vaccine consisting of a lipid nanoparticle–encapsulated mRNA vaccine encoding membrane-anchored preF conformation-stabilized RSV-F glycoprotein derived from the RSV-A strain [39, 146]. The efficacy of mRNA-1345 for the prevention of RSV-associated LRTD was demonstrated in the phase 3 ConquerRSV trial, which showed initial VE of 83.7% (95.88% CI, 66.0–92.2; one-sided $P < 0.001$) and 82.4% (96.36% CI, 34.8–95.3; one-sided $P = 0.008$) for RSV-LRTD with ≥ 2 signs/symptoms and ≥ 3 signs/symptoms, respectively, meeting the prespecified criterion for efficacy (lower boundary of the alpha-adjusted CI > 20%) [39]. The mRNA-1345 vaccine was efficacious across subgroups by age and preexisting comorbidities and protective against both RSV subtypes A and B [39]. No VAED was observed for RSVpreF, RSVPreF3, and mRNA-1345 in any clinical trials [39, 148, 149]. Observational VE data were recently presented at the ACIP meeting in June 2024, which demonstrated that RSV vaccination provided protection against severe RSV disease and RSV-associated emergency visits, hospitalizations, and critical illness in the first season of use among US adults aged ≥ 60 years, similar to the results from clinical trials; however, ongoing monitoring of RSV VE is needed to confirm these findings [158].

The two protein-based vaccines, RSVPreF3 and RSVpreF, were approved by the FDA in May 2023 and by the EMA in June 2023 and August 2023, respectively, for the prevention of RSV-associated LRTD in adults aged ≥ 60 years [152, 153]. RSVpreF was further approved by the FDA in August 2023 for use in pregnant individuals

Table 3 Phase 3 pivotal trials of RSV vaccines in older adults

Vaccine/trial	RSVPreF3 OA/AReSVi-006 [37]	RSVpreF/Renoir [38]	mRNA-1345/ConquerRSV [39]
Vaccine type	Recombinant AS01E-adjuvanted subunit	Protein subunit	mRNA encoding membrane-anchored conformation-stabilized preF
Dose	120 μg of RSVPreF3 antigen and the liposome-based $AS01_E$ adjuvant system containing 25 μg of 3-O-desacyl-4′-monophosphoryl lipid A and 25 μg of *Quillaja saponaria* Molina, fraction 21 (QS21)	120 μg (containing 60 μg each of RSV A and RSV B antigens)	50 μg of mRNA-1345
Study design	Phase 3 trial comparing RSVPreF3 OA to placebo	Phase 3 trial comparing RSVpreF to placebo	Phase 2–3 trial comparing mRNA-1354 to placebo
Age of study population	≥ 60 years	≥ 60 years	≥ 60 years
Countries/regions	17 countries in Africa, Asia, Australia, Europe, and North America	7 countries in Africa, Asia, Europe, and North America	22 countries
Efficacy	Efficacy of RSVPreF3 vaccine in preventing symptomatic, laboratory-confirmed RSV-associated LRTD (primary endpoint) was 82.6% (96.95% CI, 57.9–94.1), which met the prespecified success criterion	Efficacy of RSVpreF vaccine in preventing the first episode of RSV-associated LRTI occurring ≥ 14 days after injection with ≥ 2 symptoms was 66.7%; (96.66% CI, 28.8–85.8) and with ≥ 3 symptoms was 85.7%; (96.66% CI, 32.0–98.7), which met the prespecified success criterion	Efficacy of mRNA-1345 vaccine in preventing RSV-associated LRTD with ≥ 2 symptoms was 83.7% (95.88% CI, 66.0–92.2; one-sided $P < 0.001$) and ≥ 3 symptoms was 82.4% (96.36% CI, 34.8–95.3; one-sided $P = 0.008$)
Immunogenicity	Between baseline and 1 month post-vaccination, the concentrations or titers in the vaccine group increased by a factor of 13.1 for RSVPreF3-specific IgG antibodies, by a factor of 10.2 for RSV A neutralizing antibodies, and by a factor of 8.6 for RSV B neutralizing antibodies	At 1 month post-vaccination, neutralization titers increased ≥ 10.6-fold for RSV A and ≥ 10.3-fold for RSV B compared to baseline across RSVpreF dose levels [150]	Between baseline and 1 month post-vaccination, neutralization titers increased ≥ 10.2-fold for RSV A and ≥ 5.3-fold for RSV B for all dose levels. nAb GMTs remained above baseline through 12 months for all dose levels [151]

Table 3 continued

Vaccine/trial	RSVPreF3 OA/AReSVi-006 [37]	RSVpreF/Renoir [38]	mRNA-1345/ConquerRSV [39]
Safety	In the 6 months post-vaccination, SAEs were reported at a similar rate in RSVPreF3 OA and placebo groups (4.2% and 4.0%, respectively)	At 6 months post-vaccination, there was no difference in the rate of SAEs reported in the RSVpreF and placebo groups (both 2.3%). Two cases of GBS within 7–8 days post-vaccination were observed in two members of the vaccine group	At 6 months post-vaccination, the frequency of unsolicited AEs, including severe AEs, serious AEs (including fatal events), AEs of special interest, medically attended AEs, and AEs leading to trial discontinuation was balanced between the 2 groups

AE adverse event, *IgG* immunoglobulin G, *GBS* Guillain–Barré syndrome, *LRTD* lower respiratory tract disease, *LRTI* lower respiratory tract infection. *OA* older adult, *RSV* respiratory syncytial virus, *RSVpreF* respiratory syncytial virus prefusion F, *SAE* serious adverse event

to prevent LRTD in infants [154]. On June 21, 2023, the ACIP and CDC recommended that adults ≥ 60 years of age may receive a single dose of RSV vaccine, using a shared clinical decision-making approach [155]. Shared decision-making may improve satisfaction and reduce decisional uncertainty among patients, and its benefits may potentially be greatest among populations with the lowest health literacy [156]. The mRNA-1345 vaccine has also received breakthrough status from the FDA and was approved on May 31, 2024, to protect adults aged 60 years and older from LRTD caused by RSV infection [157]. Overall, due to the recent development and approval of RSV vaccines, outcomes and immunogenicity data for these vaccines are much less comprehensive than those for the other respiratory viruses discussed. Along with studies assessing durability of protection and the potential need for booster immunizations, additional long-term real-world effectiveness data will be needed to assess the ongoing impact of RSV vaccines and performance in high-risk groups, including the immunocompromised. Additionally, continued post-marketing studies are necessary to resolve concerns over possible safety signals for Guillain–Barré syndrome and acute disseminated encephalomyelitis with protein-based vaccines. Whether similar requirements will be imposed following the approval of mRNA-1345 remains to be seen. Importantly, the infrastructure for the storage and distribution of RSV vaccines will also need to be developed to support public health initiatives and guidelines endorsing RSV vaccination.

Factors Affecting Differences in Vaccine Uptake

Vaccine uptake within a population, or the number of people vaccinated with a certain dose of vaccine in a specified time period, is a critical metric of protection for high-risk groups, with poor uptake increasing the likelihood that vulnerable individuals, such as older adults or those who have comorbidities or immunocompromising conditions, are susceptible to infections and related severe outcomes

[159–162]. Thus, programs to increase vaccine coverage and uptake should focus on specific at-risk populations, such as those with high-risk conditions and their close contacts or caregivers, particularly in zones of high population density and household overcrowding [163, 164]. Uptake is influenced by various factors, including cultural and socioeconomic elements [50, 165], and vaccination rates differ dramatically across demographic strata, with notable variations by race/ethnicity, religion, and household wealth [166, 167].

One major factor impacting uptake is vaccine hesitancy, a multifaceted phenomenon encompassing the refusal, reluctance, or postponement of accepting vaccination despite the availability of vaccination services; this reluctance may be caused, in part, by vaccine cost and concerns regarding vaccine technology [3, 50]. Furthermore, government support and the political atmosphere exert a variable but substantial influence on vaccine acceptance across different countries [168], and trust in government has been a key issue affecting the success of global vaccination campaigns, as most recently evidenced during the COVID-19 pandemic [169]. In the United States, hesitancy toward COVID-19 vaccination is highest in Black/African Americans and pregnant or breastfeeding women, while lower among men [170]. During the COVID-19 pandemic, influenza vaccination rates were also lowest among Black/African Americans, those of low educational attainment, and poorer individuals [166]. Because demographic inequalities in COVID-19 mortality were reflected in disparities of vaccination coverage, targeted efforts to increase uptake would likely have reduced the mortality burden in these groups [81].

Out-of-pocket cost and relative VE have also been identified as key factors in vaccination decision-making in different regional surveys; higher cost acts as a deterrent to vaccination, but individuals may be willing to pay more for greater VE [171–176]. The cost barrier may be more pronounced among some economically disadvantaged populations compared with other groups, which, in conjunction with higher rates of hesitancy described above, illustrates particular obstacles to vaccination among certain demographic subgroups and those who do not have health insurance [171]. Differences in uptake in population subgroups across different vaccine platforms highlight vulnerabilities and inequities in vaccination coverage, demonstrating the need for public health policy programs to address systemic barriers to vaccine uptake. Furthermore, funding for public health programs and vaccination varies dramatically across countries: to control COVID-19, low- and middle-income countries have depended substantially on donations from developed countries and the COVID-19 Vaccines Global Access initiative [177, 178]. Although more than 70% of the population in high-income countries completed the initial COVID-19 vaccination protocol, only 2% of COVID-19 doses, including boosters, have been administered in low-income countries [177]. Compared with high-income countries, low- and middle-income countries generally have a smaller proportion of older vulnerable individuals but less robust and resilient healthcare systems [177]. These factors are reflected in the cost of immunization delivery, which is the main driver of the gap in successful national vaccination strategies, underlining the central role of strengthening health systems to achieve coverage goals [179].

Variations in vaccination rates are apparent throughout the world. Willingness to receive a COVID-19 vaccine was generally higher in low- and middle-income countries in Asia, Africa, and South America compared with the United States (mean 80.3% vs. 64.6%, respectively); in these countries, desire for personal protection and apprehension over vaccine side effects were the major factors in vaccine acceptance and hesitancy, respectively [180]. In Latin America, individual/group influences have been identified as the primary barrier to vaccination, with low socioeconomic status, lower education, and age contributing to low vaccine uptake, and education and trust in healthcare professionals enhancing vaccine acceptance [174]. A cross-sectional study involving respondents in 10 countries in Asia, Africa, and South America found that female sex, identifying as Muslim, residence in rural areas, non-healthcare-related occupation, and non-receipt of influenza vaccination in the preceding year were significant

predictors of unwillingness to receive the COVID-19 vaccine [167]. In Europe, frequent engagement in the religious practice of praying (compared with never praying) and the holding of anti-elite, populist worldviews, independent of political preferences, increased the likelihood of exhibiting vaccine hesitancy compared with not engaging in praying and not holding those sentiments [168, 181]. These studies highlight the importance of the use of messaging that is adapted to specific regions, countries, and population groups to address population-level factors influencing vaccine uptake.

Individuals with chronic diseases commonly report vaccine hesitancy, despite having an increased risk of direct and indirect complications and exacerbations due to preexisting illness. A survey in the United States found that vaccine hesitancy was reported by nearly 1 in 5 respondents with comorbidities overall; of these respondents, 13.4% had cancer, 19.4% presented with autoimmune diseases, and 17.8% had chronic lung diseases [52]. Individuals with chronic conditions are significantly less likely to receive COVID-19 vaccination compared with those without such conditions, which is primarily attributable to a lack of information, underestimation of personal risk, or fear of symptoms [51]. Tailoring public health messaging may thus reassure individuals with chronic diseases and aid in overcoming their concerns about post-vaccination symptoms and the impact on daily function.

A general lack of understanding regarding the different vaccine platforms involved, complicated by vaccine hesitancy, can also impact vaccine uptake. Hesitancy can vary by vaccine platform, with a reported disconnect between a person's willingness to receive the influenza vaccine compared with the COVID-19 vaccine [182]. Furthermore, although more than one-third of Americans expressed concern about the influenza, RSV, or COVID-19 vaccines, there was no consensus on which of these illnesses was perceived as the most severe, and knowledge about the related conditions varied among individuals [182]. Despite the apparent disconnect reported in this study, coadministration of influenza and COVID-19 vaccines has led to a high uptake of both vaccines in adult populations [183, 184]. However, increasing the uptake among individuals who do not seek vaccination for either COVID-19 or influenza remains a general challenge. Increasing the knowledge and familiarity with newer vaccine technology and the disease state are thus important considerations toward addressing vaccine hesitancy and refusal.

Coadminstration/Combination Respiratory Vaccines

Coinfection by multiple respiratory viruses may increase disease severity of illness, hospitalization rates, and mortality rates; thus, simultaneous protection against SARS-CoV-2, RSV, and influenza viruses is an important public health goal [185–188]. However, the cocirculation of these three viruses potentially complicates immunization schedules, because vaccines should be administered ahead of the start of each viral season [189, 190]. Given the overlapping patterns of risk common to SARS-CoV-2, RSV, and influenza viruses, multicomponent vaccine formulations and vaccine coadministration could streamline vaccination efforts and potentially increase vaccine uptake in key populations [191]. Particularly for those with comorbidities, the recommended immunization schedule in adults is complex, which may be simplified by the coadministration of vaccines [192, 193]. By reducing the number of vaccine consultations, coadministration can also reduce costs and improve compliance [191, 194]. Additionally, because new recommendations for recently authorized/approved vaccines may increase the complexity of vaccine schedules, coadministration can reduce the barrier to adoption and implementation of new vaccines [192].

Currently, coadministration of vaccines in older adults is under examination in several clinical trials, including those investigating COVID-19 (mRNA-1273, BNT162b2, ChAdOx1-nCoV-19, and NVX-CoV2373), influenza, and RSV [183, 195–198] vaccines. Early results have demonstrated that coadministration of vaccines can increase immune responses against the relevant viruses, with an acceptable safety profile [183, 195–197, 199, 200]. The interactions

between these different vaccines have not been fully elucidated, and vaccine efficacy could be negatively affected by immune interference and immune imprinting caused by prior infection or vaccination [201]; however, most studies have demonstrated that coadministration of vaccines elicits adequate levels of antibodies to offer a protective response [197, 202]. Overall, coadministration of vaccines could improve adherence with vaccine recommendations according to age and risk, potentially reduce overall HCRU costs, and facilitate the adoption of new vaccines [191, 192]. Combining multiple vaccines in a single vial could also simplify the chemical logistics (the physicochemical processes occurring during transport that impact vaccine potency) of vaccine administration [203], increasing the combined cost-effectiveness of vaccines and reducing the environmental impact of vaccine packaging and storage.

New vaccine modalities could be an important approach toward development of a multicomponent vaccine that targets these viral pathogens. The mRNA platform can contain multiple mRNAs encoding several antigens in a single vaccine, thus expanding the breadth of protective responses against seasonal influenza or even multiple respiratory infections [204]. A multicomponent mRNA vaccine capable of generating antibodies against numerous antigen targets simultaneously could target highly variable pathogens with antigenically distinct strains, such as influenza, rhinoviruses, and SARS-CoV-2 [204]. The mRNA platform also has a flexible and shortened vaccine development timeline, enabling periodic updates to vaccine compositions that target multiple circulating strains, thereby potentially enhancing coverage against disease [122, 204]. In addition, mRNA vaccines induce durable germinal center reactions and strong cellular immune responses, which could improve protection in older adults [124–126]. Although mRNA vaccines face logistical challenges and stringent cold chain storage needs, which may pose barriers to distribution in certain regions [203], the expanding use of mRNA-based RSV vaccines and the corresponding expansion of cold storage infrastructure could potentially address some of these barriers to use of other mRNA vaccines. mRNA vaccines may exhibit greater reactogenicity than traditional vaccines, and repeated inoculation may be associated with certain adverse reactions, such as hypersensitivity or myocarditis [205, 206]. Nevertheless, mRNA vaccines are generally well-tolerated, severe reactions are rare, and the benefits outweigh the risks, particularly in older and high-risk populations [207]. The success of mRNA-based vaccines against COVID-19 and promising clinical results of mRNA influenza and RSV vaccines have set the stage for the development of a combined respiratory vaccine that could provide protection against all three pathogens.

CONCLUSIONS

For SARS-CoV-2 and influenza, vaccines are the most potent and cost-effective tools available to reduce the risk of severe outcomes, particularly among adults of older age and those with comorbid conditions. Novel vaccines have been approved for the prevention of RSV; however, extended outcomes data are needed to assess their long-term impact. New vaccine technologies, such as mRNA vaccines and vaccine coadministration or combination, are potentially transformative in addressing ongoing viral and logistical barriers to immunization related to these viruses. Overall, the impact of vaccination against vaccine-preventable diseases is multifaceted, with implications beyond direct prevention of disease, as described in the Introduction of this review. These far-reaching positive societal outcomes, which are not always quantifiable or recognized, should be highlighted to support the development of new vaccine technologies and to address challenges with vaccine uptake. Successful population-level vaccination against these viruses, including with mRNA vaccines, may also serve as a protective measure against future and emerging health threats.

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Declarations

Conflict of Interest. Deborah Rudin and Francesca Ceddia are employees of Moderna, Inc., and may hold stock/stock options in the company. John Watkins and Roberto Debbag have no commercial or financial relationships to declare that could be construed as a potential conflict of interest.

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