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REVIEW

Optimal Timing of Vaccination: A Narrative Review of Integrating Strategies for COVID-19, Influenza, and Respiratory Syncytial Virus

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ABSTRACT

Lower respiratory tract infections caused by SARS-CoV-2, influenza, and respiratory syncytial virus (RSV) cause a significant disease burden globally, despite the availability of effective vaccines. Certain populations, such as older adults (≥ 60 years) and individuals of all ages with particular comorbidities, are at increased risk for severe outcomes, including hospitalization and death. National administration schedules for available vaccines against respiratory viruses are not unified, and not all current guidelines are clear and directive, concerning the optimal timing of vaccination. Herein, we formulate an evidence-based position regarding the optimal timing of COVID-19, influenza, and RSV vaccination for older adults and individuals with chronic comorbidities, based on a synthesis of the literature and current guidelines. Vaccination impact and timing were found to be influenced by vaccinee risk factors, including age and comorbidities, and waning vaccine effectiveness and seasonal pathogen burden. Because COVID-19, influenza, and RSV display unique seasonal patterns within and between regions, local epidemiological surveillance of each virus is crucial for determining optimal vaccination timing and guidelines. To maximize the benefits of these respiratory virus vaccines, the timing of peak vaccine effectiveness and period of greatest risk for severe outcomes should be aligned. Thus, COVID-19, influenza, and other recommended vaccines given ahead of the start of the respiratory virus season (or other regionally appropriate time) and co-administered at a single, routine visit represent the optimal approach to protecting at-risk populations. More data will be required to establish the clinical benefit of additional RSV vaccine doses and whether these may be integrated within a seasonal schedule. Coordinated policy decisions that align with strain selection for new and annually reformulated

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vaccines would enable the timely raising of public health awareness, ultimately leading to enhanced vaccine uptake. Implementation strategies will require engagement of healthcare providers and strong, evidence-based public health recommendations for integrated vaccine schedules.

Keywords: Co-administration; COVID-19; Influenza; Lower respiratory tract infection; Older adults; Public health; Respiratory syncytial virus; RSV; SARS-CoV-2; Vaccination

Key Summary Points

Maximizing the benefits of available vaccines for COVID-19, influenza, and RSV requires aligning the timing of peak vaccine effectiveness with the period of greatest health risk.

Optimal timing of vaccination is underpinned by vaccinee risk factors such as age and comorbidities, combined with pathogen seasonal burden and duration of vaccine-elicited protection.

In regions with distinct seasonal patterns, co-administration of COVID-19, influenza, and other recommended vaccines at a single, routine visit ahead of the expected start of the respiratory virus season represents the optimal approach to protecting at-risk adult populations.

Implementation strategies for integrated vaccine schedules in older adults and individuals with comorbid conditions will require further research to inform strong, evidence-based public health recommendations and engagement of healthcare providers.

INTRODUCTION

Despite the availability of effective vaccines, lower respiratory tract infections (LRTIs) caused by SARS-CoV-2, influenza, and respiratory syncytial virus (RSV) are a significant global cause of morbidity and mortality [1–4]. Older adults (age ≥ 60 years), in part as a result of a high prevalence of comorbidities, and individuals of all ages with certain chronic medical conditions are at increased risk for severe outcomes following infection, including hospitalization and death [5–13]. The vaccines that are available to mitigate the impact of these respiratory viruses in vulnerable populations have diverse administration schedules, and specific guidance regarding vaccination timing is limited.

Vaccine recommendations for respiratory viruses vary by region with respect to specific guidance for high-risk groups and clarity on optimal timing to maximize benefit. The optimal timing of vaccination is influenced by vaccinee risk factors (e.g., age and comorbidities), the seasonal incidence of respiratory pathogens, as well as vaccine effectiveness (VE) and waning of immunity [14, 15]. Maximizing the protective benefits of vaccines requires that the timing of peak VE be aligned with the period of greatest risk; to achieve this goal, there is a need to streamline vaccination schedules and develop cohesive guidelines to inform public health policy and clinical practice. In this narrative review, the optimal timing for administration of COVID-19, influenza, and RSV vaccines for older adults and individuals with chronic medical conditions is explored according to available scientific data and current vaccine guidelines, with a focus on vaccinee profiles, pathogen seasonality, and durability of vaccine protection. This narrative review aims to evaluate the existing literature and country-level vaccine recommendations. Limitations are identified and evaluated in the context of how filling these knowledge gaps may inform more inclusive, directive, and cohesive recommendations and policies that maximize vaccination benefits to protect high-risk populations. A major goal was to provide practicable advice and implementation strategies and thus a systematic approach to evaluating the literature was beyond the scope of the current review. Ethical approval was not sought or obtained, as 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.

VACCINEE PROFILE CONSIDERATIONS

Age

Advancing age has been identified as the strongest predictor of severe COVID-19-related outcomes [16–22]. Community incidence of SARS-CoV-2 infection, which may be elevated in long-term care facilities, as well as risk of severe COVID-19, may therefore inform the optimal timing of vaccination [23–25]. Antibody responses against SARS-CoV-2 have been shown to wane more rapidly than T cell immunity [26]. Moreover, humoral responses provide less cross-protection against SARS-CoV-2 variants than cellular immune responses, suggesting that in addition to limiting reinfection, T cell memory may also be critical for preventing severe disease over time [26–28]. SARS-CoV-2 vaccine-induced spike-specific cellular and humoral responses decrease progressively with older (≥ 75 years) age and increasing comorbidity [29]. Furthermore, the immune escape of emergent SARS-CoV-2 variants has contributed to a gradual decline in the protective effects of COVID-19 vaccines [30]. Although VE against omicron XBB- and JN.1-related infection, symptomatic disease, and severe outcomes wanes over time in individuals of all ages following administration of an omicron-containing vaccine, peak vaccine effectiveness is generally lower among older adults [31, 32]. Of note, rates of waning VE against omicron infection and symptomatic disease vary by vaccine product [31]; these data may inform risk-group-specific recommendations with respect to vaccine type, vaccine product, or both that complement vaccine timing guidelines to optimize protection.

Similarly, older age is associated with increased risk for severe outcomes following influenza infection; individuals aged ≥ 65 years account for an estimated 50–70% of hospitalizations and 70–85% of deaths that occur annually as a result of influenza [33]. The World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and European Centre for Disease Prevention and Control (ECDC) recommend that older adults and adults with certain comorbidities should be prioritized for influenza vaccination [34–36]. Studies demonstrate that it is crucial to strike a balance between vaccinating with adequate time to ensure that protection is established before the season begins while also reducing the risk that immunity wanes to levels insufficient for clinical protection later during the season [37].

The WHO notes that RSV is increasingly recognized as an important pathogen in older adults; in 2019, there were an estimated 470,000 RSV-associated hospitalizations and 33,000 in-hospital deaths among adults aged ≥ 60 years residing in high-income countries [38, 39]. This disease burden, which may be underestimated in adults [40, 41], along with an elevated risk of severe outcomes following infection in the elderly [42], suggests that RSV vaccination could confer substantial clinical benefits in this age group.

Comorbid Conditions

The presence of comorbidities is a key risk factor for severe outcomes following infection with SARS-CoV-2, influenza, and RSV [5, 7, 20, 43, 44]; while the prevalence of chronic conditions and multimorbidity (i.e., presence of two or more conditions) increases with advancing age, comorbidities also predict severe outcomes following infection regardless of age [44–46]. The importance of considering chronic conditions as part of vaccinee profile assessment is underscored by the recognition of comorbidities by the WHO, CDC, ECDC, the Global Initiative for Chronic Obstructive Lung Disease (GOLD), and other health organizations as key risk factors for severe outcomes due to respiratory infections [5, 20, 43, 47, 48]. Certain comorbidities are associated with impaired immune responses to vaccination, with the degree of impairment varying according to the conditions present [49–51]. Together with findings that suggest reduced vaccine effectiveness in individuals with comorbidities compared with those without [52], these data suggest that these groups may benefit from tailored strategies, such as specific dosing intervals and administration of vaccines nearer to the expected start of the respiratory virus season.

While the presence of comorbidities is associated with greater clinical severity of respiratory infections overall, specific underlying conditions may place individuals at increased risk of severe outcomes due to SARS-CoV-2, influenza, and RSV infection [53–55]. Certain comorbidities have been established as shared risk factors for severe outcomes due to SARS-CoV-2, influenza, and RSV; however, each respiratory virus is also associated with a unique profile of dominant risk factors [54]. For example, obesity and diabetes have been identified as key risk factors for COVID-19, as they are more common among individuals hospitalized with COVID-19 versus influenza [55–57]. Additional vaccine doses are effective against severe COVID-19-related outcomes among individuals with obesity and diabetes, underscoring the importance of optimally timed vaccination in this population [57–59]. Asthma, cardiovascular disease, and chronic obstructive pulmonary disease are associated with increased risk for severe outcomes due to influenza [5, 55], while key comorbidities associated with increased risk of severe RSV-related outcomes include chronic kidney and respiratory diseases, congestive heart failure, and obesity [60–62]. Although the pathophysiology underlying the differential risk profiles for severe outcomes due to SARS-CoV-2, influenza, and RSV remain to be elucidated, knowledge of the dominant risk factors for each respiratory infection may guide clinicians in stratifying and prioritizing high-risk individuals and groups for vaccination to maximize benefits.

SEASONALITY OF SARS-COV-2, INFLUENZA, AND RSV

The transition of SARS-CoV-2 from a pandemic to an endemic virus presents a challenge in predicting the future seasonality of COVID-19. However, modeling studies using COVID-19 incidence data in the USA and Europe suggest that COVID-19, like other respiratory viruses, may show some degree of seasonality, even with ongoing transmission throughout the year [63, 64]. Two possible patterns have been proposed for temperate areas: an annual peak during the traditional winter viral respiratory season or three annual peaks with a dominant winter peak and two smaller peaks in mid-spring and mid-summer [63, 64]. Similar patterns have been reported in studies using incidence data for other human coronaviruses, with seasonal peak incidence in the late autumn and winter months [65, 66].

Influenza types A and B are responsible for epidemics and outbreaks in humans and thus are targeted in influenza vaccine formulations [34, 67–70]. In temperate regions of the northern and southern hemispheres, influenza tends to manifest as a seasonal disease, with peak cases occurring in the winter months, whereas in tropical regions, influenza activity may occur throughout the year, causing outbreaks of longer duration and greater irregularity, with a higher incidence in rainy seasons [70–72].

RSV is a ubiquitous seasonal respiratory pathogen that cocirculates as two major antigenic subtypes, RSV-A and RSV-B [73]. Similar to influenza, RSV cases tend to peak in temperate regions during the winter months [74, 75]. While RSV seasonality in certain tropical areas parallels that of temperate regions, other tropical areas with higher levels of humidity experience stable case numbers throughout the year [74–76]. Although atypical seasonality was observed for RSV during the COVID-19 pandemic, the 2023 to 2024 season more closely reflected pre-pandemic RSV seasons, and it is therefore expected that vaccination timing coinciding with the late summer or early fall will maximize vaccine benefits during the peak of the RSV season [77, 78].

COVID-19, INFLUENZA, AND RSV VACCINES

Global Vaccine Recommendations

The WHO provides global recommendations for COVID-19 and influenza vaccination [79–81]. As the majority of individuals worldwide have experienced at least one SARS-CoV-2 infection, a simplified, one-dose schedule is recommended for primary COVID-19 immunization to increase

vaccine uptake and provide sufficient protection [79]. In cases where monovalent omicron XBB-containing vaccines are not available, any bivalent variant-containing or WHO emergency-use listed vaccine may be used. This strategy supports the protection of high-risk groups, even in settings of limited vaccine availability. WHO guidelines for certain trivalent egg-, cell culture-, or recombinant-based influenza vaccine components are stratified by hemisphere. For example, the A/Victoria/4897/2022 (H1N1)pdm09-like virus component is recommended for inclusion in influenza vaccines for both hemispheres, whereas A/Thailand/8/2022 (H3N2)-like virus and A/Croatia/10136RV/2023 (H3N2)-like virus components are recommended for the Northern and Southern hemispheres, respectively [80, 81]. By contrast, the WHO does not provide direct recommendations with respect to RSV vaccine type; however, guidelines regarding the quality, safety, and efficacy of RSV vaccines have been issued by the WHO to guide national regulatory authorities and vaccine manufacturers to ensure RSV vaccine development is standardized and to support optimal vaccine use [82, 83].

COVID-19 Vaccines

Vaccination played a critical role in containing the COVID-19 pandemic and reducing its ongoing global disease burden [31, 84–86], and the European Medicines Agency (EMA) and Advisory Committee on Immunization Practices (ACIP) recommend that all persons ≥ 6 months of age receive updated COVID-19 vaccines irrespective of prior vaccination [87–89] (Table 1). A succession of variant strains and lineages have emerged since ancestral SARS-CoV-2, with ongoing mutation necessitating continuous COVID-19 vaccine updates to target the predominant variant [88, 90]. Types of COVID-19 vaccines that are currently available include mRNA- and protein subunit-based vaccines, which have been updated to match and protect against the predominant variants circulating during the 2024–2025 season [91, 92]. Preliminary assessments of relative VE for receipt versus non-receipt of monovalent omicron-containing vaccine showed that the updated monovalent vaccine elicited durable protection against severe COVID-19 among adults aged ≥ 65 years at all evaluated time points up to 4 months post vaccination [87, 88, 93]. Some countries, including the USA, Sweden, Taiwan, Korea, and Japan, have recommended a single additional vaccine dose for individuals at high risk of COVID-19, such as older adults, immunocompromised individuals, and those with comorbidities [30, 94–97]. Although revaccination at least 4 months after the previous dose is necessary to sustain a high level of protection against variants [98], the optimal timing of COVID-19 vaccine doses is still to be determined, dependent on any eventual seasonal patterns, and may vary between individuals on the basis of the complex interplay of risk factors associated with severe illness [23].

Influenza Vaccines

Influenza vaccine composition is updated annually to reflect the expected virus subtype activity, with this monitored by the WHO to recommend the most appropriate vaccine for each season [35, 67, 68, 70]. Trivalent (A/H1N1, A/H3N2, and one influenza B lineage) and quadrivalent (A/H1N1, A/H3N2, B/Victoria, B/Yamagata) inactivated, live, and recombinant influenza vaccines are used; high-dose and adjuvanted formulations are available for certain populations [34, 67, 68, 70]. Since March 2020, there have been no confirmed B/Yamagata lineage infections, leading the WHO and US Food and Drug Administration (FDA) to recommend the exclusion of this presumed extinct lineage from influenza vaccines for the 2024–2025 season [80, 99]. However, not all experts agree on this recommendation, given the uncertainty around the possible resurgence of B/Yamagata, concerns about manufacturing and regulatory issues associated with the trivalent reformulation, and the potential for a negative impact on influenza vaccination campaigns if revised guidance is not adequately communicated [100, 101]. In certain countries, routine annual influenza vaccination is recommended for individuals aged ≥ 6 months (Table 1), with timing of vaccination during the fall or early winter in temperate regions, informed by local seasonal surveillance patterns,

Table 1 Recommendations for COVID-19, influenza, and RSV vaccination in adults in selected countries

Country	Recommendation
COVID-19	
Australia [160]	COVID-19 vaccination recommended for all individuals aged ≥ 18 years and those aged 6 months to < 18 years who are at increased risk of severe COVID-19 One dose is recommended every 6 months for adults ≥ 75 years, and every 12 months for adults aged 65–74 years and individuals aged ≥ 18 years with severe immunocompromise Recommended to consider one dose every 12 months for all adults aged 18–64 years
Canada [161]	COVID-19 vaccination recommended for all adults aged ≥ 65 years and individuals aged ≥ 6 months who have comorbidities associated with increased risk of severe COVID-19 or reside in LTCFs
Germany [156]	Annual vaccination every 12 months (preferably in the autumn) recommended for adults aged ≥ 60 years, residents in LTCFs, individuals aged ≥ 6 months with comorbid conditions including COPD, chronic cardiovascular disease, diabetes, and central nervous system disorders
Italy [162]	Additional dose recommended for adults aged ≥ 60 years, residents of LTCFs, and individuals aged 6 months to 59 years with conditions that increase the risk of severe COVID-19
South Korea [163, 164]	COVID-19 vaccination recommended for all individuals aged ≥ 6 months Additional dose recommended for adults aged ≥ 65 years, residents in LTCFs, and individuals with high-risk conditions
Taiwan [165]	COVID-19 vaccinations recommended for individuals aged ≥ 6 months An additional dose is recommended for adults ≥ 65 years and certain individuals at high-risk of severe disease
UK [166]	The autumn program offered vaccination to older adults residing in long-term care facilities, adults aged ≥ 65 years, and individuals aged ≥ 6 months in a clinical risk group Additional doses were recommended during the Spring 2024 program for adults aged ≥ 75 years and older adults residing in LTCFs
USA [98]	One dose of an updated vaccine is recommended for individuals aged ≥ 6 months irrespective of prior vaccination An additional dose for adults aged ≥ 65 years (≥ 4 months after the first dose)
Influenza	
Australia [167]	Annual influenza vaccination is recommended for all individuals aged ≥ 6 months, with an emphasis on adults aged ≥ 65 years, Aboriginal and Torres Strait Islander individuals (due to increased burden of RSV in this population), and individuals with conditions that increase their risk of severe influenza
Canada [168]	Seasonal influenza vaccination is recommended for all individuals aged ≥ 6 months of age, with a particular focus on adults aged ≥ 65 years, individuals residing in LTCFs, and individuals with chronic conditions including cardiopulmonary disorders, diabetes, and obesity

Table 1 continued

Country	Recommendation
Germany [169]	Annual vaccination (preferably in the autumn) recommended for all adults aged ≥ 60 years, residents in LTCFs, individuals aged ≥ 6 months with comorbid conditions including COPD, chronic cardiovascular disease, diabetes, and chronic neurological diseases
Italy [170]	Annual vaccination recommended for adults aged ≥ 60 years and individuals aged ≥ 6 months to 59 years at increased risk of severe disease due to residence in LTCFs or due to chronic diseases such as diabetes and heart and respiratory conditions
South Korea [171]	Annual influenza vaccination recommended for all individuals aged ≥ 6 months who do not have contraindications Priority groups for vaccination include adults aged ≥ 65 years, residents in LTCFs, pregnant women, individuals aged ≥ 6 months with comorbid conditions including COPD, chronic cardiovascular disease, diabetes, and chronic neurological diseases
Taiwan [172]	Annual vaccination recommended for all individuals aged ≥ 50 years, individuals with comorbidities that are associated with increased risk of severe disease, and individuals that are positioned to maintain viral transmission (e.g., school children, childcare staff, and individuals residing in LTCFs)
UK [173]	Annual vaccination in autumn or early winter recommended for individuals aged ≥ 65 years, residents in LTCFs, and individuals with chronic conditions such as COPD, CKD, and obesity
USA [174]	Routine annual influenza vaccination recommended for all individuals aged ≥ 6 months who do not have contraindications Vaccination of older adults (aged ≥ 65 years) should be avoided during July and August where possible
RSV	
Australia [175]	RSV vaccination is recommended for individuals aged ≥ 75 years, Aboriginal and Torres Strait Islander individuals aged ≥ 60 years (due to increased burden of RSV in this population), and individuals aged ≥ 60 years with medical risk factors for severe disease due to RSV
Canada [176]	RSV vaccination is recommended for all adults aged ≥ 75 years and adults aged ≥ 60 years who reside in LTCFs Vaccination may also be considered for adults aged 60–74 years
Germany [177]	Vaccination recommended for all adults aged ≥ 75 years and for adults aged ≥ 60 years with factors that increase risk of severe disease
Italy [178]	Vaccination recommended for adults aged ≥ 75 years and for adults aged ≥ 60 years with comorbidities
South Korea [179]	RSV vaccine not currently available
Taiwan [180, 181]	The Taiwan CDC does not include RSV as a vaccine-preventable disease; however, with the recent RSV vaccine approvals, it is expected that a public health recommendation for the use of the vaccine is imminent

Table 1 continued

Country	Recommendation
UK [182]	A one-off single dose of an RSV vaccine is recommended for adults aged 75–79 years and a routine program for adults ≥ 75 years of age
USA [183]	A single dose of an RSV vaccine is recommended for all adults aged ≥ 75 years and adults aged 60–74 years who are at increased risk due to the presence of certain chronic conditions (e.g., cardiovascular disease, COPD, and asthma) or residence in nursing homes

The recommendations were accurate as of August 2024 and exclude maternal immunization

CKD chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *LTCF* long-term care facilities, *NA* not available, *RSV* respiratory syncytial virus

to optimize vaccine benefits [35, 36, 67, 70]. Real-world data across four influenza seasons (2016/2017 through 2019/2020) demonstrated intraseasonal waning of VE against influenza illness for standard-dose inactivated influenza vaccines, decreasing from an average of 50% at 14–74 days post vaccination to an average of 17% at 135–194 days post vaccination [102]. Decreasing VE over time may be due to host factors, such as waning immunity, or viral factors, such as antigenic drift causing a change in circulating influenza viruses; more research is warranted to elucidate the mechanisms of declining VE within a single influenza season [102]. As vaccine protection wanes over time, initiation of vaccination programs too early (e.g., during early summer months preceding an influenza season) is not recommended in temperate regions, particularly for adults aged ≥ 65 years among whom optimizing protection across the entire season is vital [34–36].

RSV Vaccines

Immune responses established against natural RSV infection are generally short-lived and only partially protective against subsequent exposure, underscoring the importance of RSV vaccination in high-risk populations [103]. As of July 2024, two recombinant protein-based RSV vaccines had been approved for use in adults aged ≥ 60 years in several countries, with an mRNA-based RSV vaccine approved by the FDA and EMA [104–109]. Preliminary real-world evaluation of the durability of protection afforded by recombinant protein RSV vaccines against RSV-associated lower respiratory tract disease suggest a decrease in protection over time; however, as durability has been demonstrated in randomized, controlled trials at least two seasons [110], there is currently insufficient evidence to determine the appropriate intervals for revaccination. Current recommendations for older adults support a single dose (Table 1), given at any time of the year, with the greatest benefit expected if received just ahead of the expected start of the season in regions where RSV exhibits distinct seasonality [111].

CONSIDERATIONS WHEN FORMULATING RECOMMENDATIONS AND IMPLEMENTATION STRATEGIES

The combined impact of age and chronic health conditions, the varying seasonality of respiratory infections, and the assorted time intervals for the range of recommended adult vaccines point to a need for integrated schedules with optimized timing to maximize protection and encourage uptake in these vulnerable populations. Clinical practice and public health policy guidelines and recommendations must be clear, concise, and accessible to enable informed decision-making; where multiple interventions are available, evidence-based guidance aids prioritization and strategy of when and where to implement the most appropriate intervention to

achieve optimal health outcomes [112]. Strong recommendations from healthcare providers are positively associated with vaccine uptake and, in turn, the likelihood of healthcare providers recommending vaccination to their patients and families is influenced by the strength of vaccination guidelines and trust in authorities that issue them [113, 114]; as such, formulating strong vaccination guidelines is critical. The evolving nature of infectious diseases and vaccine development necessitates agile decision-making from policy makers to ensure that recommendations are dynamically adjusted in the best interest of public health. Ongoing monitoring of disease epidemiology, vaccine safety profiles, and effectiveness is also needed, particularly in the context of high-risk groups.

Public Health Strategies

Global and national vaccine action plans using evidence-based recommendations are needed to realize these suggestions and set out strategies to help achieve the vision of a world where protection against vaccine-preventable disease is realized by all individuals throughout their life course [115, 116]. By setting public health goals and outlining strategies to achieve these goals, the ultimate aim of these vaccine action plans is to influence vaccine development and use [115, 116]. Goals of vaccine action plans that are pertinent to optimal timing of vaccination in older adults include developing innovative vaccines with improved vaccine effectiveness, and potentially addressing the waning immunity that is observed with existing vaccines [115, 116]; increasing public awareness and uptake of life-course vaccinations, which could ensure vaccinations are received at optimal times for maximum protection [115, 116]; and improving monitoring of vaccine-preventable diseases and the impact of vaccination guidelines, which could help to inform optimal vaccination timing [115].

Where multiple vaccines are targeted to pathogens with overlapping seasonality, coordinated efforts ensures simultaneous availability of the vaccines, ultimately streamlining vaccination schedules and potentially enhancing uptake. Delays in the vaccine approval process can contribute to uncertainty surrounding recommendations and vaccine availability, decrease the lead time for public health planning, and reduce the ability of healthcare providers and vaccination clinics to simultaneously administer multiple viral vaccines at a single visit, potentially reducing uptake [117]. Modeling analyses estimate that delays in vaccination substantially impact morbidity and mortality in high-, low-, and middle-income countries, highlighting the importance of minimizing delays, including those arising from delayed vaccine approval processes [118–122]. Coordination of principles and policy decisions among major regional regulatory agencies may facilitate timely submission and approval following strain selection for vaccines requiring annual reformulation; new vaccines, such as mRNA vaccine platforms, may address these challenges via shortened production timelines.

Increasing Vaccination Rates Using Co-administration

The logistics of implementing adult vaccination programs are important factors to consider when aiming to increase accessibility to vaccination and narrow the gap between target and actual vaccination rates. In light of an increasingly complex vaccination schedule in adults, particularly in those with comorbidities, co-administration of vaccines represents one of the most efficient strategies to enhance vaccine uptake, raise compliance with age-appropriate schedules, and implement new vaccines into existing programs [123]. The WHO recommends the co-administration of COVID-19 vaccines with inactivated seasonal influenza vaccines; this approach has several benefits, including enhancing vaccine uptake rates and reducing the number of healthcare visits required to complete the recommended vaccination program, thereby alleviating the burden on individuals and healthcare systems [124–126]. The CDC recommends co-administration of all age-appropriate vaccines at a single healthcare visit, including influenza, RSV, and COVID-19 vaccines, provided there are no contraindications [127]. To date, there is

no evidence that non-live vaccines, including respiratory vaccines, interfere significantly with the immune responses to other vaccines, both non-live and live; any non-live vaccine can generally be administered simultaneously or at any time before or after any other live or non-live vaccine [128, 129]. Most studies supporting co-administration of respiratory vaccines have been conducted for seasonal influenza and COVID-19 vaccines; clinical trials and real-world studies have demonstrated that co-administration of seasonal influenza and COVID-19 vaccines was safe and well tolerated, with no evidence of clinically significant immune interference [124, 130–133]. In clinical trials, co-administration of RSV and quadrivalent influenza vaccines has also been shown to be safe and without immune interference when administered to healthy or medically stable adults aged ≥ 60 years with chronic conditions, or adults with heart failure [134–136]. Together with determining the potential need for revaccination and optimal dosing intervals, the acceptability of co-administering RSV vaccines with others beyond influenza remains to be clarified. Benefits and utilization of co-administration also extend to other vaccines on the adult schedule; for example, co-administration of 20-valent pneumococcal conjugate vaccine in adults aged ≥ 65 years with either influenza or mRNA COVID-19 vaccines was shown to be safe with no immune interference in clinical trials [137–143].

Integration of Vaccine Schedules into Routine Care

Given the growing complexity of adult vaccination schedules, strategies to coordinate vaccination at optimal times should also promote vaccination as a standard, routine component of preventive care, emphasizing its critical role in healthy aging. Vaccine messaging and community engagement, from public health agencies, community partners, and healthcare providers, should occur throughout the year, not just during seasonal peaks, to build trust and increase awareness and uptake [144]. Additionally, other vaccines on the adult immunization schedule that provide multi-year protection and have infrequent formula changes, such as pneumococcal and pertussis vaccines [145], should be offered outside of the fall-winter respiratory viral season to allow vaccination efforts to focus on seasonal activity, such as influenza, COVID, and RSV.

Engaging Providers

Engaging healthcare providers through public–private partnerships, professional training programs, and implementation of best practice guidelines that reflect the recent evidence can strengthen knowledge and clinician capacity toward delivering vaccines per the integrated vaccination schedules suggested here. In clinical scenarios, physicians must often expedite decision-making and select the most appropriate interventions for individual patients on the basis of benefit-risk profiles and cost-effectiveness, both of which may not be immediately apparent without critical appraisal of related guidelines and most recent research [146]. Healthcare providers are among the most credible and influential sources of information regarding vaccines and are frequently relied upon by the public to support decisions around vaccination [114]. Models including decision trees (e.g., clinical decision tree for vaccination based on age, race/ethnicity, comorbidities, and other risk factors), visual aids (e.g., nomogram of age, risk profile, and vaccine type), and digital tools that are underpinned by benefit-risk and cost-effectiveness analyses are useful to guide physicians in evidence-based decision-making, thereby optimizing patient-specific outcomes and increasing vaccination uptake rates [146–149].

RECOMMENDATIONS FOR ADULT VACCINATION

Although the long-term temporal patterns of COVID-19 have yet to be fully elucidated, current data suggest that SARS-CoV-2 will follow a seasonal pattern not dissimilar to that of other common respiratory viruses, with peaks in late autumn and winter months in temperate regions [63–65], and with emerging variants

necessitating continuously updated vaccines [88, 90]. Thus, for COVID-19 and influenza vaccines in older adults and those with comorbidities, an annual schedule in the early autumn in temperate regions that utilizes a combination or co-administration approach may be expected to maximize the positive impact of immunization [150, 151]. Because various factors, including an aging global population and variant emergence causing immune escape, have contributed to the recent waning of vaccine-induced protection against COVID-19 [30], revaccination later in the season may be appropriate to sustain protection in older and comorbid populations. Indeed, as stated earlier, an additional COVID-19 vaccine dose at least 4 months after the first has been recommended for individuals at high risk of COVID-19, such as older adults, immunocompromised individuals, and those with comorbidities in certain countries, including the USA, Sweden, Taiwan, Korea, and Japan [30, 94–97]. Long-term durability data for RSV vaccines are currently lacking; however, interseasonal waning of VE has been observed [110]. As such, should data emerge that demonstrate a clinical benefit of additional RSV vaccine doses, co-administration strategies incorporating these additional doses at seasonally appropriate intervals may augment protection, thus warranting consideration of RSV vaccines for inclusion in the optimal approach to respiratory virus vaccination presented here.

DISCUSSION

Older adults and those with chronic comorbidities are at increased risk for severe outcomes due to LRTIs, and vaccination against SARS-CoV-2, influenza, and RSV is an essential public health tool that contributes to a reduction in disease burden in these populations [2, 3]. Many of the pathogens responsible for LRTIs exhibit a bimodal distribution affecting the youngest and oldest age groups [1]; because grandparents are often involved in the care of young children, vaccination programs addressing both very young and old individuals are important in limiting the bidirectional spread and impact of LRTIs in these vulnerable populations. Furthermore, older adults and those with comorbidities may face substantial barriers to vaccination, including cost, underestimation of personal risk, or fear of adverse reactions similar to viral infection itself. As such, integrating infrequently scheduled vaccines and those not received on an annual basis into existing schedules is crucial in reducing barriers to ensure protection is sustained in this vulnerable population. Although vaccine guidelines for older adults and adults with comorbidities are available from the WHO, ECDC, and CDC [94, 152], many of these do not provide clear and directive recommendations with respect to the optimal timing of vaccination.

Because co-administration is associated with enhanced vaccine uptake, co-administration of age-appropriate recommended vaccines, such as those for COVID-19 and influenza in adults aged ≥ 60 years, is an important strategy for the protection of high-risk groups [123, 153]. In regions with well-defined and overlapping peaks in respiratory virus activity, vaccine co-administration also improves compliance, ensuring all seasonally relevant protection is established ahead of the expected start of the respiratory virus seasons [123]. Additionally, vaccines that are currently administered as a one-time dose, such as RSV vaccines, may be received simultaneously with COVID-19, influenza, or other vaccines at a single visit to reduce schedule complexity and increase the likelihood of vaccine uptake at the optimal time, ultimately increasing protection against vaccine-preventable diseases. Although vaccines with infrequent schedules (e.g., pneumococcal and pertussis vaccines) would ideally be administered outside of seasonal vaccination peaks, these may also be co-administered in cases where this approach would ensure compliance with an age-appropriate vaccination schedule [123]. Crucially, the seasonal patterns of SARS-CoV-2, influenza, and RSV vary among regions, with the distinct winter peaks observed in temperate areas less notable or absent in areas with tropical climates, where year-round activity may occur [76]. Moreover, seasonality may differ for respiratory pathogens within the same regions; for example, in Taiwan, influenza displays a distinct seasonal

peak during the winter months, whereas peak RSV prevalence is not constant across seasons [154]. As such, defining local epidemiological patterns for individual viruses is a necessary step in determining optimal vaccine timing and recommendations. The position presented here that supports seasonally appropriate co-administration of COVID-19, influenza, and other vaccines, such as RSV, in older adults and individuals with comorbidities aligns with guidelines from Australia, the UK, and the USA, among others [153, 155–157].

While this publication offers valuable insights into vaccine timing and coadministration, it is not a systematic review and thus is potentially subject to selection bias. However, the narrative approach enables a broader exploration of key themes and contextual factors. Moreover, guidelines and optimal vaccination timing strategies can vary substantially by region according to difference in disease epidemiology, available healthcare infrastructure, regulatory processes and approvals, as well as public health policies. While the aim of this review was to provide a broad, non-region-specific overview, some country- or vaccine-specific nuances may not have been fully addressed. Finally, gaps remain in the literature with respect to optimal timing of vaccination, particularly for certain populations such as older adults and individuals with certain underlying conditions. Further research, including real-world effectiveness studies and clinical trials, is needed to refine vaccine timing strategies to maximize protection across different populations and settings and may aid in the refinement of more unified vaccination timing recommendations overall. In addition to the anticipated need for annual updates to COVID-19 vaccine composition to match circulating variants, continued monitoring of the effectiveness of updated COVID-19 vaccines, particularly in high-risk populations, will be important to assess the durability of protection and optimal timing [87, 88, 90, 158]. Both the emergence of new SARS-CoV-2 variants and the impact of vaccination may affect the predicted seasonality of COVID-19 [65], with ongoing surveillance data leading to the refinement of vaccination timing according to temporal and regional variation. Compared with vaccines against other pathogens discussed here, data for RSV vaccines are far less comprehensive; however, additional long-term studies may support the evidence-based development of vaccination strategies and a clinical decision-making framework.

CONCLUSIONS

Given the increased burden of COVID-19-, influenza-, and RSV-related morbidity and mortality in older adults and individuals of all ages with comorbidities [5–11, 20, 159], evidence-based timing of vaccination is crucial to maximize the positive impact of vaccination and protect these vulnerable populations. As a step in consolidating vaccine schedules, co-administration enhances uptake by promoting compliance with age- and season-appropriate vaccination programs [123]. Thus, in regions with clear seasonal patterns, co-administration of COVID-19, influenza, and other recommended vaccines at a single visit ahead of the expected start of the respiratory virus season represents the optimal approach to protecting older adults and adults with comorbidities against these respiratory pathogens. Implementing this approach requires both public health strategies that are underpinned by strong, evidence-based recommendations, and the engagement of healthcare providers to strengthen the capacity for integrating updated vaccine schedules into routine care and to increase vaccination rates.

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Declarations

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