

Review

Recognizing the Full Clinical and Economic Consequences of Vaccine-Preventable Diseases in Older Adults

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Abstract

Modern public health strategies are undergoing fundamental shifts as global populations age, and vaccination is on the front lines, transitioning from a traditional focus on the pediatric immunization model to a “life-course” vaccination paradigm. Part of this shift is an increased focus on the interaction between infectious disease, vaccination and the various comorbidities that are common in older populations. This narrative review considers recent key clinical, immunological, and health economic studies to discuss the importance of adult immunization to both individual health and the sustainability of healthcare systems and examines how changes in clinical trial design are changing health recommendations. Because the scope of the review touches on multiple fields, pivotal, heavily cited studies have been chosen to illustrate the changing political and scientific landscape of adult vaccination.

Keywords: life-course vaccination; immunosenescence; comorbidities

1. Introduction

Population aging is one of the most profound demographic transformations of the past century. Improvements in sanitation, nutrition, medical care, and public health have substantially increased life expectancy across most regions of the world and, together with declining birthrates, have resulted in a rapid increase in the proportion of older adults within national populations. While this demographic shift is associated with significant improvements in health and economic well-being for individuals, it also presents significant clinical and public health challenges [1]. Different countries are at different stages in this process, but the trend appears to be universal. However, most studies of this issue originate in high-income countries, which are, accordingly, the focus of this review. Increased longevity does not necessarily equate to an equal increase in the years lived in good health; aging is associated with increased risk for multimorbidity, frailty, functional decline, and heightened vulnerability to infectious diseases [2]. Accordingly, a central goal of modern health systems is no longer simply to extend lifespan but also to preserve healthspan, resilience, and quality of life in older age.

Older adults bear a disproportionate burden of chronic illness, including cardiovascular, metabolic and chronic respiratory diseases; malignancy; and neurodegenerative disorders. These comorbidities often coexist, interact, and contribute to increased healthcare utilization, disability, and mortality [2]. Importantly, they are also associated with increased risk of infection with, and worse outcomes from, common vaccine-preventable diseases (VPDs) [3,4]. Respiratory infections such as influenza, pneumococcal disease, coronavirus disease, and respiratory syncytial virus (RSV) are associated with particularly



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severe outcomes in older populations, including hospitalization, decompensation of underlying chronic illnesses, loss of independence, and death [5,6]. In many cases, the impact of infection extends beyond the acute episode, accelerating the development of frailty and contributing to long-term declines in physical and cognitive function [7].

Vaccination thus represents a cornerstone of healthy aging strategies—a way to break the negative feedback loop between chronic comorbidity and infectious disease. Traditionally viewed primarily as a tool to prevent acute infectious disease, adult immunization is now increasingly understood as an intervention with broader implications for supporting healthy longevity [8,9]. By reducing the incidence and severity of vaccine-preventable infections—and preventing downstream exacerbation of chronic, non-infectious disease—vaccination may help interrupt pathways that lead from acute illness to functional decline, institutionalization, and excess mortality in older adults [7].

A life-course immunization approach recognizes that vaccine policy should not be confined to childhood but rather should extend through adulthood and older age, adapting to changing risk profiles and underlying health status, especially in aging societies [10,11]. This recognition is especially important given the expansion of immunization opportunities for older adults, including vaccines against influenza, pneumococcal disease, herpes zoster, COVID-19, and RSV, as well as the development of enhanced formulations designed to overcome reduced immune responsiveness in later life. Such strategies may be particularly beneficial in frail adults and those living with chronic diseases, among whom the clinical and economic consequences of infection are greatest [10,11].

Despite the clear rationale for vaccination in older adults, uptake remains suboptimal in most settings. Barriers include limited awareness of adult vaccine recommendations, recommendations that are narrowly focused on acute infectious disease, inequities in access, vaccine hesitancy, and insufficient integration of immunization into chronic disease management and geriatric care [12,13]. Under-vaccination is especially important in populations with comorbidities, where missed opportunities for prevention may have substantial downstream consequences—consequences that not only fall on individuals but are also increasingly stressing healthcare systems dealing with higher numbers of older patients, requiring complex management [2]. Strengthening adult immunization programs therefore requires not only improved vaccine availability and tailored recommendations but also a reframing of vaccination as an integral component of preventive medicine, healthy aging, and the preservation of resilience.

In this review, I discuss the growing importance of vaccination in aging populations, with particular attention to older adults living with comorbidities and frailty; examine how demographic aging, multimorbidity, and age-related decline in immunity converge to increase both vulnerability to VPDs and the downstream consequences of infection; summarize current evidence on the clinical and public health value of vaccination in later life; and consider how life-course immunization strategies can contribute to extending not only lifespan but also healthspan in an increasingly older world.

2. Immunosenescence and Inflammaging in Older Adults

The increased vulnerability of older adults to infection is, in part, a natural consequence of biological aging. Just as with other physiological systems in the body, the gradual loss of pluripotent or multipotent stem cells eventually degrades the ability of the body to generate new immune cells [14]. However, the immune system in total is inherently adaptive and therefore highly plastic. Thus, the generation of immune memory is affected by exposure to pathogens, allergens and environmental antigens, providing long-lasting memory responses that are unique to each individual's circumstances. Immune memory and function can be further modified by psychosocial factors, such as socioeconomic

status and chronic stress [15–17], or by comorbidities such as diabetes or atherosclerosis, which increase the risk of chronic inflammation and oxidative stress [18]. The loss of new, naïve immune cells from progenitors in the bone marrow and thymus, together with the accumulation of long-term T- and B-cell memory and of senescent or poorly functional immune cell lineages, leads to a reduced ability to respond to new antigens. This process, called immunosenescence, or age-related decline in immune function [19], is associated with altered innate and adaptive immunity, leading to suboptimal phagocytosis, antigen presentation, T-cell and B-cell responses, chemotaxis, and cytotoxicity. It is typically characterized by an increased proportion of activated memory T and B cells compared to naïve cells [20,21]. This leaves older adults disproportionately vulnerable to severe infection and—at least in some cases—diminishes the magnitude and durability of vaccine-induced protection [20,21]. Together with accumulated epigenetic changes, it is also thought to contribute to what is called “inflammaging”, the persistence of chronic, low-level inflammatory responses [22].

These biological changes are affected by, and interact with, comorbidities, polypharmacy, and social determinants of health [23]. The result is that every older individual has a unique “immune fingerprint” or “immunological biography” that reflects their life history; this makes older populations significantly more heterogeneous in their ability to respond to immune challenges than infants or children. Consequently, chronological age alone is a poor marker of vulnerability; biological aging, frailty status, and comorbidity profiles are increasingly recognized as critical determinants of infectious disease risk and vaccine response [24]. Equally importantly, it is well established that infection can act as an exacerbating factor in individuals with comorbidities, in whom infections can, for example, trigger cardiovascular events, worsen glycemic control, and precipitate respiratory or renal decompensation and other adverse outcomes. Unprevented, this can lead to a downward spiral where multimorbid patients are at risk of infections that can worsen their chronic illnesses—in turn, increasing their susceptibility to further infection [23]. There is a positive side to this, however. The plasticity of the immune system offers us the possibility of modulating immune responses by vaccination over the life course—essentially rewriting a person’s “immunological biography” to reduce the risk of VPDs and the long-term physical or mental decline that very often follows infection in older patients.

3. Impact of Vaccine-Preventable Disease on Overall Mortality and Morbidity

The idea that infectious diseases can cause mortality and morbidity beyond that which can be easily ascribed to the acute infection is hardly new. In *Observationes Medicae*, published in 1676, Thomas Sydenham noted that while uncomplicated measles was generally benign, secondary infections (specifically pneumonia and severe diarrhea) were common causes of measles-associated death, typically after measles had run its course [25]. This remains true today [26], though it took over 300 years for the mechanism to be revealed—the induction of what is now called “immune amnesia” due to the elimination of immune memory cells in the wake of measles infection, which leads to increased risk of infection and increased overall mortality [27,28]. While older adults today are likely to be immune to measles, either through vaccination or exposure, other VPDs such as tuberculosis, pneumococcal infection, influenza, COVID-19 and RSV are also associated with excess mortality and morbidity beyond that which can be attributed to acute infection, which leads to increased demand for primary and secondary healthcare [2].

Given that these VPDs are all respiratory pathogens, it comes as no surprise that these infections are associated with an elevated risk of exacerbation of chronic respiratory conditions, such as Chronic Obstructive Pulmonary Disease (COPD) and asthma (Table 1). However, the downstream effects of these infections extend well beyond inflammation of the respiratory tract, with elevated risk for a variety of cardiac, metabolic, cerebrovascular or neurological diseases (Table 1). This table does not attempt to be comprehensive, but it does include some of the most commonly reported complications or downstream effects of these infections, indicating both the breadth and the overlapping nature of the diseases associated with them. The fact that this elevated risk is reduced or absent in vaccinated individuals is consistent with a causal link to infection—though this has yet to be formally proven in most cases.

One notable exception to this is influenza, where randomized controlled trials (RCTs) have provided strong evidence of a causal link between influenza disease and subsequent cardiovascular risk [29], and influenza therefore serves as a good model for examining the evolving role of vaccination as a tool to reduce the health impact of chronic, non-communicable disease. The association between influenza, atherosclerosis and cardiovascular risk was, like the measles example above, identified by observational studies in the late 19th and early 20th centuries, long before the biological mechanisms involved were understood [30,31]. It took almost a century for the mechanism to be defined (Figure 1) and for the beneficial impact of influenza vaccination on cardiovascular risk to be formally investigated [31] and nearly a decade more for these findings to start to be reflected in recommendations for managing cardiovascular disease risk [32,33].

Table 1. Impact of several major VPDs on chronic non-infectious conditions.

Pathogen	Conditions with Significantly Increased Risk in the Immediate Post-Infection Phase	References
Influenza	Acute Myocardial Infarction ¹	[32–35]
	Ischemic Stroke ¹	[33,36,37]
	Arrhythmia ¹	[38]
	Overall Cardiovascular Mortality ¹	[34,35]
	Exacerbation of COPD ¹	[39]
	Exacerbation of Asthma ¹	[40,41]
	Incident Diabetes ¹	[42,43]
RSV	New Onset Dementia ¹	[44,45]
	Acute Myocardial Infarction	[44,46]
	Ischemic stroke	[47,48]
	Arrhythmia	[48,49]
	Acute Heart Failure	[46–48]
	Overall Cardiovascular Mortality	[50]
	Exacerbation of COPD	[51–53]
SARS-CoV-2	Exacerbation of Asthma	[52,53]
	Acute Myocardial Infarction ¹	[54,55]
	Ischemic Stroke ¹	[54,56]
	Arrhythmia ¹	[56,57]
	Overall Cardiovascular Mortality ¹	[56,57]
	Incident Heart Failure ¹	[55,57]
	Incident Diabetes ¹	[58–61]
	New Onset Dementia ¹	[62–65]

Note: ¹. Elevated risk shown to be reduced or eliminated in fully vaccinated individuals.

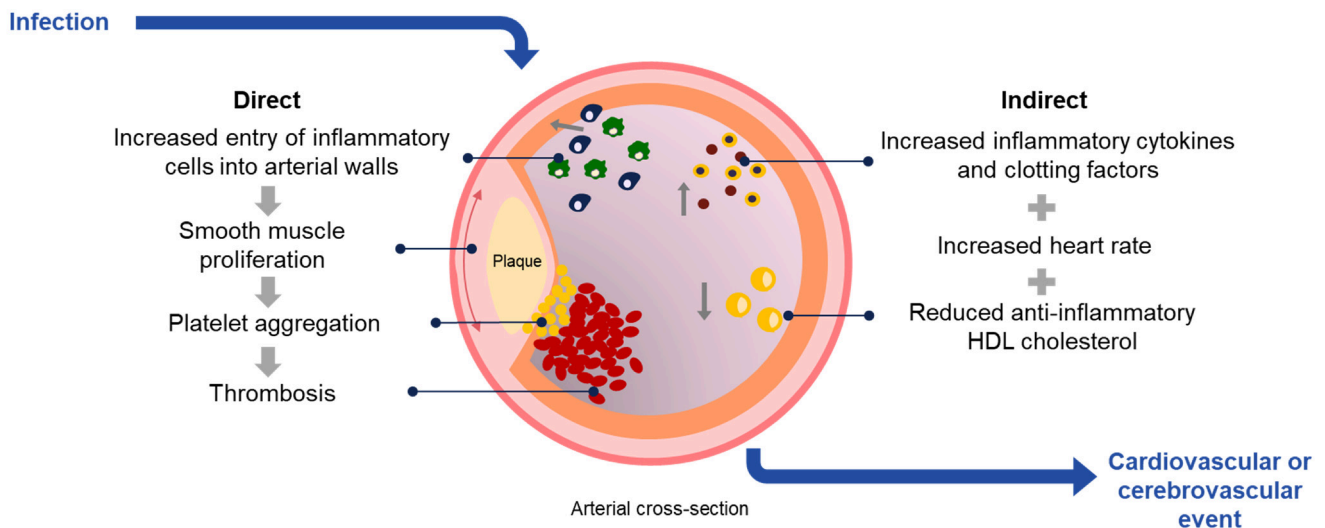


Figure 1. This schematic of a blood vessel shows how infections can lead to cardiovascular or cerebrovascular events by activating both direct and indirect pro-atherosclerotic mechanisms [66,67].

It has been suggested that systemic inflammation, hemodynamic changes, and the pathology induced by local inflammation, vascular remodeling, and chronic arterial changes can increase the risk of subsequent vessel occlusion, leading to ischemia and a cardiovascular or cerebrovascular event. These mechanisms are common to respiratory diseases such as influenza or RSV, as well as other diseases such as herpes zoster [68], and explain the strong association of infection with subsequent elevated risk, as well as the significant reduction in the risk of cardiac disease, stroke and dementia in appropriately vaccinated individuals [45,54,57,69].

4. Progressing to Recommendations for Influenza Vaccination in Older Adults

There are a number of impediments to adult vaccination, both structural and non-structural [12,13], but one that is frequently overlooked is the limited indications and recommendations for vaccination as a general preventive intervention. To take just one example, the fact that it took so long to implement vaccine recommendations that acknowledged the potential benefit of influenza vaccination might seem surprising, given the very strong association between influenza, influenza vaccination and cardiovascular disease seen over decades of observational studies. However, medical recommendations evolve slowly, with the emphasis on a solid base of evidence for a causal effect, and observational studies, no matter how consistent or numerous, are rarely considered sufficient because of the risk of potential unconsidered confounding factors. Influenza vaccines are recommended based on their ability to prevent influenza cases, prevent influenza complications and prevent influenza transmission in the population [70]. A recent meta-analysis found a vaccine efficacy in preventing laboratory-confirmed influenza of 64.3% and 50.1% against strains similar and dissimilar to the vaccine strain, respectively [71]. Definitive evidence for a directly protective role of influenza vaccination was not obtained until the 2020s with the initiation of a series of prospective RCTs. One influential example was the Influenza Vaccination after Myocardial Infarction (IAMI) trial, which found a 41% reduction in cardiovascular mortality among patients with acute myocardial infarction who had been vaccinated against influenza either at admission or shortly afterward [29]. As a well-designed RCT, IAMI was able to provide convincing evidence of a directly protective role of influenza vaccination against cardiovascular disease and mortality. However, for practical reasons, a traditional RCT like this is limited in the number of patients that can be enrolled and followed up with,

and, thus, the obvious step is to enroll those at high risk to ensure that sufficient incident cases are detected to draw robust conclusions. The downside to this approach is that the results are difficult to generalize, as outcomes may only be applicable to the population studied. In the case of IAMI, this was patients with acute myocardial infarction. Other RCTs examining the effect of vaccination on cardiovascular risk have similarly focused on high-risk patient groups [72,73]. Initially, therefore, recommendations for the prevention of cardiac disease by vaccination focused on secondary prevention for those with an existing high-risk profile [32], even though the epidemiological and observational data suggested a broader population-level benefit. This leads to a situation where people at risk are often only recommended vaccination after they have been hospitalized with Major Adverse Cardiovascular Events (MACEs), rather than before, in an attempt to prevent it.

To attempt to bridge this gap, researchers have turned to what are called pragmatic clinical trials (PCTs) [74,75]. Like RCTs, PCTs are prospective, randomized trials, but unlike traditional RCTs that test efficacy under ideal conditions with strictly defined enrollment, PCTs test the effectiveness of a medical intervention in real-world, routine clinical practice and feature participant populations that better represent the general public [43,44]. This means that the results from PCTs can more readily be generalized. The integration of the trial into routine practice and the use of existing administrative healthcare databases also means that enrollment, intervention and follow-up can potentially handle very large patient cohorts. PCTs are typically not used for testing the impact of new interventions, due to the risk of unforeseen adverse events in a diverse patient population, but are ideal for testing the effectiveness of existing interventions. As an example, two such PCTs, DANFLU-2 and GALFLU (conducted in Denmark and Galicia, Spain, respectively), were together able to rapidly enroll and randomize 466,320 individuals 65 years old and older, both with and without existing atherosclerotic cardiovascular disease (ASCVD), for a trial on high-dose influenza vaccines [76]. The results showed a significant reduction in overall cardiovascular hospitalizations of 6.6% using high-dose influenza vaccines compared to the standard dose. Protection against heart failure was particularly marked: patients receiving the high-dose vaccine saw a 21% reduction in hospitalizations for heart failure [76]. Importantly, the reduced risk of MACEs and cardiorespiratory hospitalization was similar for patients with and without a prior history of cardiovascular disease, which suggests that the benefits seen in smaller RCTs conducted in high-risk groups may be broadly applicable to the population as a whole [76]. The direct finding of these studies was that high-dose influenza vaccines in older adults reduced the risk of hospitalizations for cardiorespiratory disease compared to standard vaccination protocols. However, the data also provide strong evidence for a cardioprotective role of vaccination in the general population—the magnitude of which is likely understated due to the use of the standard dose vaccine as a comparator in these PCTs.

It is therefore only very recently that we have started to see these recommendations extended to primary disease prevention [31]. Given the importance of a physician's recommendation for vaccination uptake [77], and the elevated risk that many patients with comorbidities face from infection, the importance of linking vaccination with overall health outcomes can hardly be overstated.

5. Estimating the Full Value of Vaccination

These changes in recommendations show that—for influenza vaccination, at least—the case for vaccination as a primary preventive measure for cardiorespiratory disease is recognized [32,33]. But for other VPDs, the evidence base remains weaker. A medium-sized PCT of RSV vaccination conducted along the same lines as the DANFLU-2 PCT described above (called DAN-RSV) in 131,276 adults aged 60 years or older showed a

significant (2.9%) reduction in all-cause cardiorespiratory hospitalization in the vaccinated cohort, but when broken down into subanalyses, the reductions in all-cause cardiovascular hospitalization or stroke were not statistically significant [47]. This suggests the potential downstream cardiorespiratory benefits of RSV immunization, similar to those observed for influenza, but also highlights the need for very large studies to confirm any such link. Estimations regarding other VPDs and the effects on other conditions such as diabetes or dementia are—for now—reliant on observational or registry studies.

In an attempt to make these estimates more rigorous, researchers have turned to hospital or national databases, which enable the analysis of very large populations. Earlier studies estimated that four common VPDs (influenza, pneumococcal disease, herpes zoster, and pertussis) in adults cost the United States around \$26.5 billion annually [78]. As high as this estimate is, it may understate the overall impact of VPDs, because the analysis did not include all VPDs or the long tail of potential downstream effects, which can occur months or even years after an acute infectious disease episode. Meta-analyses suggest that outcomes from VPD infections were typically worse among high-risk subpopulations and generally associated with increased costs [79]. This conclusion is supported by an analysis of hospitalizations in adults aged 50 years and older between July 2016 and June 2019, using the United States-based de-identified Clinformatics Data Mart Database from Optum. This covered more than 15 million person-years of data and evaluated how VPD infections can affect not just hospitalization with acute disease but also the subsequent impact on adult health trajectory, baseline comorbidities, and functional autonomy [7]. Using individuals enrolled in a health insurance plan, data were collected from 24 months before hospitalization to 1 year after discharge. In that study, 97,057 adults aged 50 years and older who were hospitalized with a primary diagnosis of a non-infectious condition and a secondary diagnosis of a current or near-term VPD (e.g., influenza, pneumococcal disease, herpes zoster, pertussis, or RSV) were matched with 386,978 controls who had no active VPD diagnosis but the same non-infectious diagnosis. Controls were rigorously matched based on exact age, sex, ethnicity, geographic region, baseline healthcare resource utilization, and baseline Charlson Comorbidity Index (CCI) score. Outcomes were evaluated using regression modeling and a Difference-in-Differences (DD) estimator, which allowed us to compare each patient's post-discharge health status directly against their own 24-month pre-index baseline as well as against the controls, isolating the specific health consequences attributable to the VPD from natural age-related decline in health. The clinical impact of a VPD was highly pronounced in the period immediately after infection but persisted for at least a year after diagnosis. The overall risk ratio (RR) for mortality among VPD patients was 4.08 (95% CI 3.98–4.18) at 30 days, compared to control patients without a VPD, and remained significantly elevated (RR = 2.76, 95% CI 2.73–2.80) at the 1-year mark [7]. Strikingly, the relative risk of mortality was highest among younger, healthier cohorts (e.g., ages 50–54 with a baseline CCI of 0), which makes a strong argument for adult vaccination at an earlier age [7]. In addition to increased mortality, a concurrent VPD diagnosis was associated with a much higher risk of developing new chronic conditions. Over the 1-year follow-up, 65–86% of VPD cases developed at least one newly diagnosed comorbidity (such as myocardial infarction, congestive heart failure, stroke, or renal failure), compared to only 13–41% of controls—the wide range reflecting variation among the different subcohorts analyzed [7]. This was associated with a significant increase in mean CCI scores: by 3.23 points in VPD cases compared to 0.89 in controls. Finally, the data suggested that the infection often acted as a tipping point. At 1-year post-discharge, 41% of VPD cases suffered a significant loss of independence compared to 12% of controls. This was seen in an increased reliance on professional home health care for VPD cases compared to controls (25% vs. 9%) or discharge from the hospital into a long-term care

facility (29% vs. 6%) [7]. This study demonstrates that the acute phase of a VPD is only the tip of the iceberg. It appears that preventing hospitalization via routine adult immunization is not simply a case of averting an acute infectious episode; it can be inferred that it may help directly preserve long-term organ function and patient independence and prevent premature cardiovascular or metabolic decline. However, it should be noted that although the study was designed to reduce residual confounding as much as possible, it is never possible to completely eliminate it in observational studies of this kind. Moreover, the exact figures are representative of hospital admissions in the US population and reflect data on outcomes captured by US healthcare providers: they may not be directly applicable to every patient population. Studies replicating this approach in other populations and healthcare systems are needed.

6. Conclusions: The Way Forward

The studies discussed above make a strong, multi-layered case for expanding adult vaccination recommendations but also indicate just how far we have to go. Aging populations mean that it is essential to move from a simple “preventing infection” model to one that both optimizes the use of healthcare resources and prioritizes overall disease prevention and the preservation of long-term health [1]. This approach means reframing vaccines as “Respiratory, Cardiovascular and Metabolic Interventions” rather than purely as tools to prevent acute disease from viral or bacterial infections. As the example of influenza, given above, illustrates, the surest path to change is solid clinical data derived from clinical trials. As discussed, the traditional RCT is not always suited to trials requiring a very large number of participants for the analysis of rare events. However, the development of PCTs, and the rapid growth in the number of PCTs looking at downstream effects of vaccination—including, but not limited to influenza—on chronic disease, offer hope that the data needed to support changes to clinical guidelines can be acquired within the next few years. More effort—particularly for diseases such as dementias, where current treatment and prevention options are limited—in this field is essential.

The hospital admissions data discussed give some indication of the magnitude of the unaccounted effect of VPDs, suggesting that up to 86% of adults aged 50+ may develop a new, major comorbidity (like heart failure, stroke, or renal disease) within a year of a severe VPD episode [7]. So, expanded protocols (e.g., lower age thresholds for vaccination) should be thought of as proactive health promotion: immunizing a 50-year-old should not be seen as just helping to keep them out of the ICU this coming winter; it should also be seen as an active intervention to prevent deterioration in their physical condition over the next decade. More patient database studies of this kind are needed to quantify the unaccounted-for costs of VPDs and the potential benefits of addressing them and to ensure the generalizability of these conclusions. Recognition of the benefits of such analyses by politicians and funding bodies and their translation into policy will be crucial.

However, healthcare administrators often view vaccine programs as an upfront financial cost that has to be balanced against other, competing costs and uncertain future savings [80]. As older populations put healthcare budgets under pressure, this balance grows ever more precarious. By looking at the full burden of disease—and, crucially, by providing more precise economic analysis—vaccine advocates can provide a convincing rationale for expanding vaccine programs for older adults [81]. The World Health Organization has recognized this and built the Full Value of Vaccine Assessment (FVVA) framework to help with such assessments. Studies suggest that even for infections with relatively straightforward clinical management, vaccine-preventable hospitalizations can significantly lower the Incremental Cost-Effectiveness Ratio of vaccination by up to 50.5%, which suggests that the value of vaccination may be underestimated by as much as half [82].

By combining this with the data showing that 41% of VPD patients suffer a permanent loss of independence requiring complex post-acute discharge planning [7], clinicians can build a case for vaccination that also resonates with insurance executives and government officials. Expanding adult vaccination protocols could directly mitigate emergency department gridlock, free up acute-care beds, and reduce the immense resources spent on managing post-infection frailty [7].

Because of the perceived incremental cost, many health systems heavily prioritize vaccines for patients aged 65 and older, leaving the 50–64 cohort with lower coverage. And yet, the relative risk of mortality following a VPD hospitalization is actually highest in the younger, healthier subgroups—those who are ages 50–54 with zero baseline comorbidities [7]. These data suggest that waiting until age 65 to heavily promote adult vaccination may miss the critical window where a VPD does the most radical relative damage to a previously healthy individual's life trajectory and economic productivity.

And while it is important to make an economic argument for vaccination, we should never lose sight of the fact that “prolonging economic activity” and “preventing a deterioration in CCI scores” translates into individuals enjoying longer, healthier lives. Recognizing that adult vaccination has the potential to reduce the risk for, or ameliorate the impact of, multiple chronic conditions means that communicating this message to patients as well as policy-makers remains of critical importance.

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Abbreviations

The following abbreviations are used in this manuscript:

COVID-19	coronavirus disease of 2019
COPD	Chronic Obstructive Pulmonary Disease
FVVA	Full Value of Vaccine Assessment
MACE	Major Adverse Cardiovascular Event
RSV	respiratory syncytial virus
VPD	vaccine-preventable disease

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