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Special article - Review

CONSENSUS DOCUMENT ON THE ROLE OF ADULT VACCINATION IN THE PREVENTION OF CARDIOVASCULAR EVENTS. JOINT STATEMENT BY THE ARGENTINE FEDERATION OF CARDIOLOGY (FAC), ARGENTINE SOCIETY OF CARDIOLOGY (SAC), AND THE ARGENTINE COUNCIL OF CARDIOLOGY RESIDENTS (CONAREC)

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Abstract

Cardiovascular diseases remain the leading cause of death among adults, both in Argentina and worldwide. Numerous studies have established a consistent association between infections –particularly respiratory infections– and an increased risk of cardiovascular events, stroke, arrhythmias, and both cardiovascular and all-cause mortality. The underlying pathophysiological mechanisms include systemic inflammation, immune activation, endothelial dysfunction, prothrombotic states, sympathetic stimulation, and elevated myocardial oxygen demand. In respiratory infections, these effects are further exacerbated by hypoxemia and impaired gas exchange. Such alterations can trigger *de novo* cardiovascular events or exacerbate preexisting conditions, such as ischemic heart disease or heart failure.

In this context, robust evidence supports the safety of vaccines against Influenza, Pneumococcus, Respiratory Syncytial Virus, COVID-19, and Herpes Zoster in adults, including those with established cardiovascular disease or risk factors. Moreover, these vaccines have demonstrated efficacy in reducing cardiovascular events by mitigating infection-related complications. Notably, influenza vaccination has proven safe even during the acute phase of myocardial infarction, when administered during hospitalization.

Despite this strong evidence base, vaccination rates remain suboptimal among individuals with cardiovascular disease, both in Argentina and across Latin America. This consensus document reviews the current evidence linking infections and cardiovascular events, and highlights vaccines as a safe and cost-effective strategy for primary, secondary, and tertiary prevention. It also provides concrete recommendations to improve vaccine coverage and reduce residual cardiovascular risk in the region.

Key words: cardiovascular diseases, vaccination, cardiovascular prevention, infectious disease, public health

Resumen

Documento de consenso sobre el rol de la vacunación en adultos para la prevención de eventos cardiovasculares. Posicionamiento conjunto de la Federación Argentina de Cardiología (FAC), Sociedad Argentina de Cardiología (SAC) y el Consejo Argentino de Residentes de Cardiología (CONAREC)

Las enfermedades cardiovasculares son la principal causa de muerte en adultos, tanto en Argentina como a nivel global. Existe una relación consistente entre las infecciones, especialmente las respiratorias, y un aumento en los eventos cardiovasculares, cerebrovasculares, arritmias, la mortalidad cardiovascular y total. Los mecanismos involucrados incluyen inflamación sistémica, activación inmunitaria, disfunción endotelial, estados protrombóticos, estimulación simpática y aumento de la demanda miocárdica de oxígeno. En el caso de las infecciones respiratorias, se suman además la hipoxemia y el deterioro del intercambio gaseoso. Estas alteraciones pueden precipitar eventos cardiovasculares *de novo* o descompensar enfermedades preexistentes, como cardiopatía isquémica o insuficiencia cardíaca.

Numerosos estudios han demostrado que las vacunas contra influenza, neumococo, virus sincicial respiratorio, COVID-19 y herpes zóster son seguras en adultos, inclusive en aquellos con cardiopatías o factores de riesgo cardiovascular. Asimismo, estas vacunas han demostrado reducir significativamente los eventos cardiovasculares, mitigando muchas de las consecuencias adversas asociadas a las infecciones. En particular, la vacuna antigripal ha demostrado ser segura incluso durante la fase aguda del infarto, cuando se administra durante la hospitalización.

A pesar de esta evidencia, las tasas de vacunación en la población con enfermedad cardiovascular es subóptima, tanto en Argentina como en otros países de la región. Este consenso revisa la evidencia disponible sobre infecciones y eventos cardiovasculares, y posiciona a las vacunas como una estrategia segura y costo-efectiva para la prevención primaria, secundaria y terciaria. Además, se presentan recomendaciones para mejorar las coberturas vacunales y reducir el riesgo cardiovascular residual en nuestro país y la región.

Palabras clave: enfermedades cardiovasculares, vacunación, prevención cardiovascular, enfermedad infecciosa, salud pública

KEY POINTS
Current knowledge

- For decades, infections have been recognized as potential triggers of major cardiovascular events, both during the acute phase and in the weeks to months following recovery.
- Despite being safe and cost-effective preventive strategies, adult vaccination rates remain suboptimal, particularly among high-risk individuals such as those with established cardiovascular disease.

Article's contribution to current knowledge

- Vaccination against influenza, pneumococcus, respiratory syncytial virus, herpes zoster, and COVID-19 prevents severe infection and reduces major adverse cardiovascular events.
- These vaccines are safe in patients receiving antiplatelet or anticoagulant therapy.
- As they do not contain live pathogens, they can be administered safely to transplant recipients and severely immunocompromised individuals.
- No cardiovascular disease or comorbidity constitutes a contraindication to vaccination. In older adults, vaccination contributes to maintaining autonomy and functional independence.

Cardiovascular disease (CVD) remains the leading cause of death worldwide, both in high-income and low- and middle-income countries[1,2]. In Argentina, CVD accounts for nearly twice as many deaths as all forms of cancer combined. This shift, in which non-communicable chronic diseases now exceed infectious diseases as the primary cause of mortality, is referred to as the "epidemiological transition." It has led to increased efforts to reduce the burden associated with cardiovascular conditions[1].

Despite significant advances in preventive treatment, a substantial proportion of individuals continue to experience major cardiovascular events or succumb to cardiovascular causes, despite being on guideline-directed preventive therapy. This phenomenon, known as residual cardiovascular risk, is partly driven by underlying inflammatory states, including those triggered by local or systemic infections[1].

In light of this, the Argentine Federation of Cardiology (FAC), the Argentine Society of Cardiology (SAC), and the Argentine Council of Cardiology Residents (CONAREC) have jointly developed this consensus document to provide a scientific foundation for the use of adult immu-

nization as a strategy for reducing cardiovascular events (Table 1).

Accordingly, this document focuses exclusively on vaccines that demonstrate specific benefits in cardiovascular prevention and does not include those that, while potentially beneficial for adult health, have no evidence of direct cardiovascular benefit.

Relationship between infections, cardiovascular events, and underlying mechanisms

For several decades, acute infections have been recognized as important triggers for cardiovascular and cerebrovascular events[3-5]. The underlying mechanisms include activation of the immune system, leading to systemic inflammation, a prothrombotic state, sympathetic nervous system stimulation, and increased myocardial oxygen demand (Fig. 1)[1,6,7]. These processes contribute to endothelial dysfunction, rupture of atherosclerotic plaques, thrombotic complications, myocardial depression, and heart failure. In certain scenarios, direct myocardial injury may also occur –as in myocarditis– while in respiratory infections, associated hypoxemia may further compromise oxygen delivery to tissues[8-10].

Regardless of the specific pathophysiological mechanism, infections may either precipitate "*de novo*" vascular events in previously healthy individuals or exacerbate pre-existing cardiovascular disease[1,8-10]. These observations have prompted interest in the potential use of antimicrobial agents for the prevention of cardiovascular events. However, a systematic review and meta-analysis including 38 clinical trials with 26 638 participants found no evidence to support the use of antibiotics for cardiovascular prevention[11]. Moreover, available data suggest that macrolides and fluoroquinolones may increase cardiovascular risk in certain contexts[11].

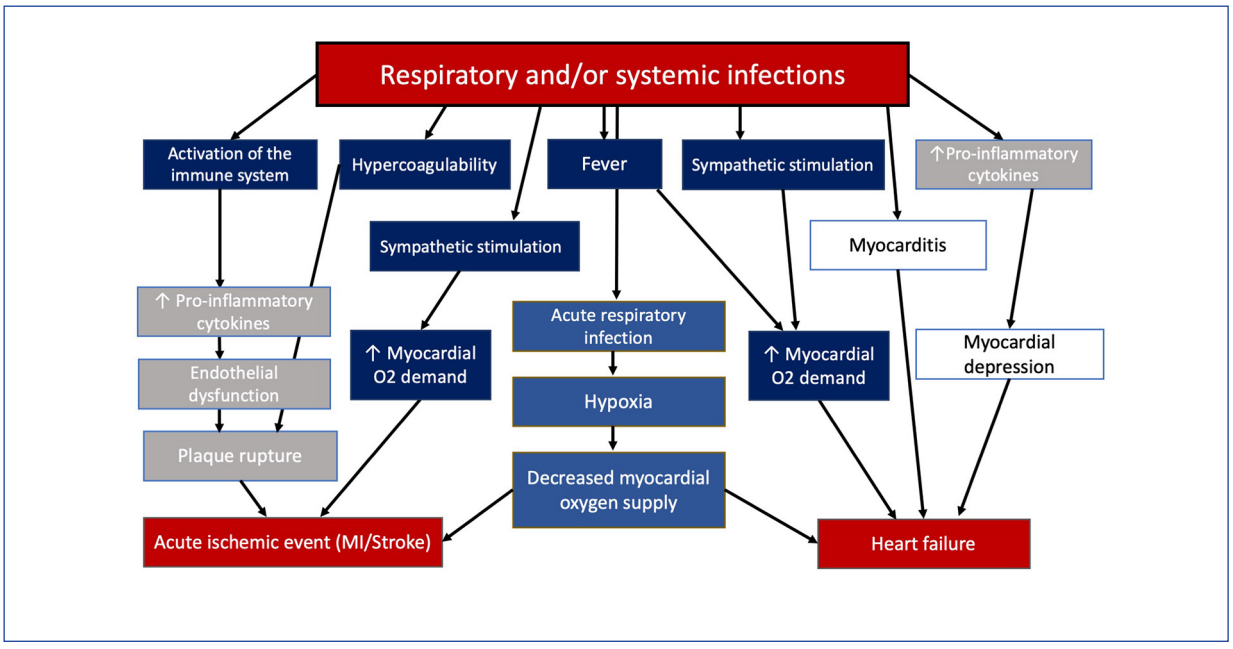
In contrast, vaccines have proven to be highly effective tools for preventing infectious diseases, particularly in their most severe forms. Consequently, the potential role of immunization in reducing cardiovascular events has received growing attention in recent years[1,7].

Table 1 | Practical summary of vaccines for adults with cardiovascular disease

Vaccine	Recommendation	Coverage	Schedule
Influenza vaccine	Priority	Publicly funded	Annual
20-valent pneumococcal conjugate vaccine (PCV20)[Ω]	Priority	Publicly funded	Single dose[δ]
Respiratory syncytial virus (RSV) vaccine	Recommended	Variable cost[ε]	1 dose*
Recombinant zoster vaccine (RZV)	Recommended	Variable cost[ε]	2 doses**
COVID-19 vaccine guidance	Priority	Publicly funded	See national booster
Diphtheria–tetanus toxoid (Td)[π]	Priority	Publicly funded	Every 10 years
Enhanced influenza vaccine (adjuvanted, high-dose, or cell-based)[λ]	Recommended	Variable cost[ε]	Annual

[Ω]*Or the pneumococcal vaccine currently recommended by the National Immunization Schedule*
[δ]*Adults vaccinated before age 65 because of comorbidities should receive a booster after turning 65, provided at least 5 years have elapsed since the initial dose*
[ε]*Not universally covered by the National Immunization Schedule; out-of-pocket cost and insurance coverage vary by plan and patient risk profile*
** Duration of protection is still being determined*
*** Doses are separated by 2–6 months. In candidates for imminent immunosuppression (e.g., before heart or other solid-organ transplantation, or prior to starting chemotherapy), the interval may be shortened to 1 month; specialist follow-up is advised*
[π]*Although do not reduce cardiovascular risk, it is part of the National Immunization Schedule. Keeping patients up to date helps prevent tetanus-related complications after invasive procedures common in cardiology (e.g., device implantation and cardiac surgery)*
[λ] *These formulations offer incremental benefits over standard influenza vaccines; immunization should not be delayed if an enhanced product is not immediately available. The adjuvanted influenza vaccine is included in the National Immunization Schedule and is provided free of charge to adults aged ≥65 years*

Figure 1 | Underlying mechanisms linking respiratory or systemic infections to cardiovascular events. Adapted from reference[1]



O_2: oxygen; MI: myocardial infarction

The role of vaccination in cardiovascular prevention

Influenza

Influenza viruses are classified into four types –A, B, C, and D– though only types A and B are clinically relevant in humans[1,7,12]. Influenza A viruses are further subtyped according to the surface proteins hemagglutinin (H) and neuraminidase (N); while over 130 subtypes have been identified in animals, only a few currently circulate in the human population. Influenza B viruses are grouped into two major lineages –Victoria and Yamagata– with multiple subclades. These viruses are responsible for annual seasonal epidemics, typically occurring during the winter months (April to October in the Southern Hemisphere), although year-round circulation may also occur.

Despite the proven effectiveness of vaccination in preventing severe complications of influenza, more than half of the adults with an indication for immunization remain unvaccinated, both in Argentina and globally[13-16].

Influenza infection and cardiovascular events

Seasonal influenza peaks are associated with an increase in cardiovascular and cerebrovascular events, including acute myocardial infarction (AMI), stroke, heart failure, and arrhythmias[4,5,17,18]. A UK cohort study examined adults following an acute infection or vaccination. Within the first three days after an influenza or influenza-like illness, the adjusted incidence ratio for AMI was 4.95 (95% CI: 4.43–5.53; $p<0.05$), and 3.19 (95% CI: 2.81–3.62; $p<0.05$) for stroke[4]. Elevated risk persisted for up to 90 days post-infection. In contrast, receipt of influenza, pneumococcal, or tetanus vaccines was not associated with an increased vascular event rate.

Another series assessed outcomes following hospitalization for influenza in 925 older adults (≥65 years) in Canada. In-hospital mortality reached 8.4%, while 9.9% of patients experienced severe loss of functional independence, and 8.2% had moderate decline[19].

Cardiovascular impact of influenza vaccination

One of the earliest randomized trials to assess the impact of vaccination in patients with acute coronary syndromes was the FLUVACS trial, conducted in Argentina[20]. At six months, vaccinated patients who had recently suffered a coronary event or undergone complex revascularization had a significantly lower rate of cardiovascular events, a benefit that persisted at one-year follow-up. In 2013, a meta-analysis of six randomized controlled trials involving 6735 high-risk cardiovascular patients found that influenza vaccination reduced the risk of major cardiovascular events by 36% (95% CI: 0.48-0.86; p=0.003)[21]. Subsequent systematic reviews and meta-analyses have confirmed this finding, reporting relative risk reductions ranging from 25% to 36%[18,22-24].

In 2021, a double-blind randomized controlled trial enrolled 2571 patients hospitalized for acute coronary syndrome (ACS) or high-risk percutaneous coronary intervention to receive either the influenza vaccine or a placebo[25]. Participants were vaccinated 24 hours before to 48 hours after their procedure. The vaccinated group experienced a significantly lower all-cause mortality (HR 0.59; 95% CI: 0.39-0.89; p=0.01) and cardiovascular mortality (HR 0.59; 95% CI: 0.39-0.90; p=0.014) at one year[25]. Importantly, no increase in serious or overall adverse events was observed, despite the widespread use of antiplatelet and anticoagulant therapy. In light of these findings and consistent with other studies, influenza vaccination should be implemented as a standard intervention during hospitalization for coronary syndromes[18,22-25].

Regarding heart failure, a Danish cohort study including 134 048 individuals followed for a mean of 3.7 years found that receiving at least one dose of the influenza vaccine was associated with lower all-cause and cardiovascular mortality (HR 0.82; 95% CI: 0.81–0.84) after adjustment for multiple confounders[26]. Additional benefits were observed among those vaccinated early in the autumn and among individuals who received multiple doses across different seasons. The same research group analyzed outcomes among patients with diabetes and found that vaccinated individuals had a reduced risk of all-cause and cardiovascular mortality (HR 0.84; p<0.001), AMI and stroke (HR 0.85; p=0.028), and fewer hospital admissions due to diabetes decompensation (HR 0.89; p=0.006)[27].

A further meta-analysis including one RCT and six observational studies (n=3 167 445) demonstrated a reduction in arrhythmia risk following influenza vaccination (OR 0.82; 95% CI: 0.70-0.97), with an effect on atrial fibrillation (OR 0.94; 95% CI: 0.90-0.98)[28].

Recommendations for influenza vaccination

All individuals with cardiovascular conditions are considered at high risk and should receive annual influenza vaccination, regardless of age[1,2,7]. In addition, all healthcare personnel –including administrative and technical staff– should be immunized each year, as this strategy has been shown to reduce mortality among the patients they care for[29].

In Argentina, individuals at higher risk of complications from influenza are eligible for free annual vaccination without the need for a medical prescription, as influenza vaccination is included in the National Immunization Schedule. These priority groups include:

- Adults aged 65 years and older
- Individuals aged 2 to 64 years with risk factors or underlying comorbidities (Table 2)
- Pregnant women (in any trimester) and women up to 10 days postpartum
- Children aged 6 months to 2 years
- Healthcare and essential workers

While some groups are at increased risk of influenza-related complications, the infection can affect anyone. For this reason—and given the high safety profile of influenza vaccines—the United States, following the H1N1 pandemic, simplified its immunization strategy and now recommends annual vaccination for everyone over 6 months of age[12,30]. This universal approach has the added benefit of reducing viral transmission. In countries with limited healthcare resources, vaccination policies often prioritize the most vulnerable groups based on accessibility, rather than purely scientific considerations.

Hypertension, smoking, and influenza infection

Patients with hypertension or those who smoke are at greater risk of adverse outcomes and mortality if infected with influenza. A large

Table 2 | Populations at risk for influenza complications and with an indication for annual vaccination

Cardiovascular disease
*** Hypertension; heart failure€; coronary artery disease with or without revascularization; prior valve replacement; moderate-to-severe valvular heart disease; pulmonary hypertension; heart transplantation.**
*** Congenital heart disease of any complexity.**
Other clinical conditions
Commonly encountered conditions in cardiology
Diabetes mellitus (any type); chronic respiratory disease (COPD or asthma of any severity); pregnancy (any trimester) and up to 10 days postpartum; obesity (BMI ≥40 kg/m²); chronic kidney disease (especially on dialysis or expected to start dialysis within 6 months); nephrotic syndrome; chronic liver disease (including cirrhosis); solid-organ malignancy under active treatment; recipients of any solid-organ transplant; rheumatologic disease (regardless of current therapy).
Healthcare personnel: all staff working in healthcare settings.
Other indications
- Selected conditions: diaphragmatic hernia; tracheostomy; severe malnutrition; functional or anatomic asplenia (including sickle cell disease); developmental delay (<18 years); neuromuscular disorders with respiratory involvement; major congenital malformations; household contacts of patients with hematologic malignancies or of premature infants <1,500 g.
- Immunodeficiency states: congenital or acquired (including hematologic malignancies); HIV infection; use of immunosuppressive medications (e.g., methotrexate, azathioprine, biologic agents) or high-dose systemic corticosteroids for >14 days. Chronic aspirin therapy in persons <18 years.

COPD: chronic obstructive pulmonary disease; BMI: body mass index; HIV: human immunodeficiency virus
€Irrespective of left ventricular ejection fraction

Danish cohort study examined 608 452 individuals with hypertension receiving at least two antihypertensive agents over nine influenza seasons (2007-2016). After excluding participants with other comorbidities and adjusting for multiple confounders, vaccination was associated with reduced all-cause mortality (HR 0.82; p<0.001), cardiovascular mortality (HR 0.84; p<0.001), and mortality due to myocardial infarction or stroke (HR 0.90; p=0.017)[31]. Based on this and other findings, the 2025 update of the HEARTS in the Americas Initiative-led by the Pan American Health Organization– has incorporated influenza and pneumococcal vaccination as standard interventions for patients with hypertension and high cardiovascular risk, regardless of age[32].

Concerning smoking, a UK study using electronic medical records found that younger smokers were at increased risk of respiratory infections, including influenza (OR 1.32; 95% CI: 1.07-1.64; p=0.01)[33]. Similarly, a multicenter case-control study across 20 hospitals in Spain showed that smokers had a significantly higher risk of hospitalization for influenza than non-smokers, even after adjusting for confounders (adjusted OR 1.32; 95% CI: 1.04-1.68; p=0.02)[34]. Furthermore, passive smoking increase the risk of influenza and other respiratory infections.

Immunization schedule

Due to the antigenic variability of surface proteins in influenza viruses, circulating strains change yearly, necessitating annual vaccination[1,30,35]. The vaccine should ideally be administered at the end of summer or the beginning of autumn (March-April in the Southern Hemisphere), as seroprotection develops within 2–3 weeks, allowing optimal antibody levels before the peak of viral transmission. However, influenza viruses may circulate year-round –even in tropical climates– and some seasons feature early or delayed peaks, or multiple surges. As a result, the most practical recommendation is to vaccinate any at-risk individual at the time of healthcare contact, provided they have not al-

ready received the vaccine during the current season[1,30].

Despite the annual variability in circulating strains, influenza vaccines have demonstrated protective effects even when there is only partial antigenic match[36]. This benefit appears to be more pronounced with enhanced vaccines.

Immunosenescence, inflammation, and types of influenza vaccines

Influenza vaccines are typically classified as either trivalent (containing two influenza A subtypes and one B lineage) or quadrivalent (containing two A subtypes and two B lineages)[1,2,30]. Each year, the World Health Organization (WHO) issues recommendations on the specific viral strains to be included in that season's influenza vaccines.

Older adults often exhibit a diminished response to immunogenic stimuli, a phenomenon known as immunosenescence. This physiological process, which intensifies from around the age of 50, leads to a reduced T- and B-cell response, decreased antibody production, and impaired activation of antigen-presenting cells[1,2,7]. As a result, older individuals are not only more susceptible to infections but also demonstrate a weaker response to standard vaccines. Additionally, this population often exhibits chronic, low-grade systemic inflammation, termed "inflammaging", which further compromises immune function and vaccine efficacy and increases vulnerability to infection[1,2,7].

To address these challenges, enhanced influenza vaccines have been developed. These include adjuvanted vaccines, which contain an oil-in-water emulsion to boost immune response; high-dose vaccines, which contain four times the antigen concentration of standard-dose vaccines; and recombinant vaccines, produced via DNA technology, currently unavailable in Argentina[1,12,30,37].

Adjuvanted influenza vaccines showed superior immunogenicity and clinical effectiveness compared to standard formulations[38-41]. A nested case–control study based on 18 influenza seasons in Italy showed a significant reduction in cardiovascular events among recipients of adjuvanted vaccines compared to those who received non-adjuvanted formulations (OR 0.88; 95% CI: 0.80-0.97)[39]. In Argentina, the adjuvanted influenza vaccine is approved for use in individuals aged 50 and older[42]. Similarly, high-dose influenza vaccines have also demonstrated enhanced immunogenicity and effectiveness in preventing clinical outcomes compared to standard vaccines[43-45]. The DANFLU-1 study, a pragmatic randomized clinical trial conducted in Denmark, compared the relative effectiveness of high-dose quadrivalent influenza vaccine to standard-dose formulations in adults aged 65 to 79. The high-dose vaccine reduced hospitalizations due to pneumonia (relative effectiveness: 64.4%, 95% CI: 24.4%-84.6%; $p<0.05$) and overall mortality (relative effectiveness: 48.9%, 95% CI: 11.5%-71.3%; $p<0.05$)[44]. In Argentina, this vaccine is approved for individuals aged 65 and older.

To date, no prospective randomized trials have directly compared the adjuvanted and high-dose influenza vaccines. Several meta-analyses using indirect comparisons (from differing populations and influenza seasons) have concluded that both vaccines outperform standard-dose formulations, without a clear superiority of one over the other[46-48]. Some observational studies have suggested that adjuvanted vaccines may confer additional benefit over high-dose vaccines[49]. However, given the limitations of observational data, it is advisable to tailor the choice of formulation to the patient's characteristics, vaccine availability, cost considerations, and shared decision-making with the treating physician.

Another strategy to improve vaccine effectiveness is the use of cell-based manufacturing rather than traditional egg-based methods[50]. Cell-based vaccines allow for high viral yields, avoid the use of antibiotics and preservatives, and circumvent adaptive mutations that may alter the viral antigen structure during development in embryonated eggs. This results in greater fidelity to circulating strains and reduced mismatch risk[12,51]. Additionally, they can be produced more rapidly and do not rely on egg supply –an important logistical advantage. Since they do not contain egg proteins, they are also suitable for individuals with egg allergy. Emerging data suggest superior effectiveness compared to conventional vaccines[50].

Adverse effects and contraindications

Adverse reactions are infrequent, occurring in fewer than 15% of vaccine recipients. Most are mild and self-limiting, including local reactions (pain, induration, erythema) or systemic symptoms (fever, malaise, myalgia), typically resolving within 24-48 hours without intervention.

Contraindications to influenza vaccination are rare. These include a history of anaphylaxis to the vaccine or its components, or the development of Guillain–Barré syndrome (GBS) within six weeks of a previous influenza vaccine, after ruling out other causes[2,12,30,52]. It is estimated that GBS occurs in approximately 1.6 cases per million doses administered. As the risk of GBS is four to ten times higher following influenza infection compared to vaccination, a remote history of GBS not linked to vaccination does not constitute a contraindication[52].

Practical considerations for influenza vaccine prescription

- These vaccines contain only inactivated viral components, so they cannot cause influenza. They are safe for immunocompromised individuals, including heart transplant recipients.

- Mild illnesses such as upper respiratory infections, diarrhea, or current antibiotic use are not contraindications to vaccination.

- Protective antibody levels develop 2 to 3 weeks post-vaccination and typically last 6 to 10 months.

- The vaccine can be administered intramuscularly or subcutaneously –even in anticoagulated patients (see below).

- In exceptional cases where a high-risk individual cannot be vaccinated (e.g., due to prior GBS after influenza vaccination), it is essential to immunize close contacts and household members to reduce viral transmission and the risk of infection.

- Enhanced influenza vaccines –adjuvanted, high-dose, or cell-culture-based– are superior to standard formulations. Quadrivalent formulations do not provide additional clinical benefit over trivalent vaccines.

Pneumococcus

Infection with *Streptococcus pneumoniae* (*pneumococcus*) can lead not only to pneumonia but also to other severe conditions such as meningitis and endocarditis. Globally, it remains the leading cause of death from vaccine-preventable diseases[12,53].

This pathogen follows a bimodal distribution, primarily affecting young children, due to the immaturity of their immune systems, and older adults, as a consequence of immunosenescence[1,2,12]. In addition, individuals with chronic illnesses or comorbidities are at increased risk for developing severe pneumococcal infections[12,53]. Notably, the risk factors for invasive pneumococcal disease closely overlap with those associated with severe influenza-related complications (Table 3).

Available vaccines and administration schedules

Currently, four pneumococcal vaccines are available for clinical use in our country:

- 13-valent conjugate vaccine (PCV13), expected to be discontinued during 2025.
- 23-valent polysaccharide vaccine (PPSV23), expected to be discontinued during 2025.
- 15-valent conjugate vaccine (PCV15)
- 20-valent conjugate vaccine (PCV20)

All four vaccines contain capsular polysaccharides derived from different *S. pneumoniae* serotypes; the number in their name corresponds to the number of serotypes covered. The conjugate vaccines (PCV13, PCV15, and PCV20) use a carrier protein that enhances antigen presentation, promoting T-cell activation, immune memory formation, and improved mucosal protection. These immunological features translate into a more robust and durable immune response compared to the unconjugated polysaccharide vaccine[1,12].

Sequential vaccination with PCV13 followed by PPSV23 is more effective than either vaccine alone[2,12]. Based on this evidence, the traditional pneumococcal vaccination strategy involves administering a single dose of PCV13, followed by a dose of PPSV23 one year later[12,54]. However, with the recent inclusion of PCV20

in the National Immunization Schedule, a simplified regimen has been adopted: a single dose of PCV20 can now be administered at any time of the year. Individuals under 65 years of age who are vaccinated due to comorbidities or other risk factors should receive a booster dose after turning 65, provided that at least five years have elapsed since the initial PCV20 dose (Table 4).

Recently, results from a new conjugate pneumococcal vaccine (V116) demonstrated comparable immunogenicity, safety, and tolerability to

Table 3 | Similarities and differences in indications for pneumococcal and influenza vaccination from a cardiology perspective

Indications for both vaccines	* Heart failure€; coronary artery disease with or without revascularization; prior valve replacement; moderate-to-severe valvular heart disease; pulmonary hypertension; heart transplantation. * Congenital heart disease of any complexity. * Age ≥65 years, irrespective of comorbidities*. * Other comorbid conditions listed for influenza vaccination. * Tobacco exposure: current smokers with ≥15 pack-years, or former smokers with ≥10 pack-years who quit within the past 10 years2.
Indications unique to pneumococcal vaccination	* History of invasive pneumococcal disease. * Alcohol use disorder. * Anatomic or functional asplenia. * Cochlear implants or cerebrospinal fluid leaks.
Indications unique to influenza vaccination	* Healthcare personnel * Class III obesity (BMI ≥40 kg/m²)

€Irrespective of left ventricular ejection fraction
**Some scientific societies (e.g., the Argentine Society of Infectious Diseases) recommend lowering the routine age threshold to 60 years for both vaccines*

Table 4 | Recommendations for PCV20 in adults previously vaccinated with PCV13 or PPSV23

Condition	Previous vaccination regimen	Recommended intervention	Alternative
≥65 years or heart transplant recipients	Complete series*	PCV20 at 5 years after the last pneumococcal dose.	---
18–64 years with risk factors	Complete series*	No additional doses until age 65.	---
≥65 years or heart transplant recipients	PCV13 PPSV23	PCV20 12 months after the previous dose.	---
18–64 years with risk factors	PCV13 PPSV23	PCV20 12 months after the previous dose.	PPSV23** PCV13**

PCV: pneumococcal conjugate vaccine; PCV13 (13-valent), PCV20 (20-valent); PPSV23: 23-valent pneumococcal polysaccharide vaccine
** Complete series: PCV13 + PPSV23*
*** Alternative only if PCV20 is not available or per local policy; keep a 12-month interval from the prior pneumococcal dose*

PCV20. This vaccine is expected to become available in our country in the future.

Pneumococcal infection and cardiovascular events

Numerous observational studies have explored the association between pneumococcal disease and cardiovascular complications[55-59]. A nested case-control study analyzed two prospective cohorts –the Cardiovascular Health Study (5,888 participants aged ≥65 years) and the Atherosclerosis Risk in Communities (ARIC) Study (15 792 participants aged 45-64 years)– with a follow-up period of 10 years[56]. The risk of cardiovascular complications following pneumonia was highest during the first 30 days (HR 4.07; 95% CI 2.86-5.27; $p < 0.05$) and remained significantly elevated up to 90 days post-infection (HR 2.94; 95% CI 2.18-3.70; $p < 0.05$)[56]. A systematic review and meta-analysis confirmed that community-acquired pneumonia significantly increased the risk of acute coronary syndrome (OR 3.02; 95% CI 1.88-4.86), stroke (OR 2.88; 95% CI 2.09-3.96), all-cause mortality (OR 3.22; 95% CI 2.42-4.27), and cardiovascular events overall (OR 3.37; 95% CI 2.51-4.53)[57].

Regarding heart failure, the relationship with pneumococcal infection is bidirectional. On one hand, disease progression increases patients' vulnerability to such infections, and the lack of vaccination further elevates morbidity and mortality[58]. On the other hand, pneumococcal infections are a major cause of decompensation in heart failure patients, contributing independently to worse clinical outcomes[59].

Cardiovascular impact of pneumococcal vaccination

A meta-analysis of 11 cohort studies including 332 267 participants found that adults who received the PPSV23 vaccine had a significantly lower risk of major adverse cardiovascular events (MACE) (RR 0.86, 95% CI 0.76-0.97; p=0.016) and cardiovascular mortality (RR 0.92, 95% CI 0.86-0.98; p=0.010)[60]. The protective effect was even more pronounced among older adults (RR 0.80, 95% CI 0.70-0.92; p=0.001) and individuals at high cardiovascular risk (RR 0.92, 95% CI 0.87–0.98; p=0.010).

Another meta-analysis, which included 18 studies and over 716 000 individuals, confirmed these findings. Vaccination was associated with a reduced risk of cardiovascular events overall (RR 0.91, 95% CI 0.84-0.99; p<0.01; I^2=74.6%) and acute myocardial infarction (RR 0.88, 95% CI 0.79-0.98; p<0.01; I^2=75.4%)[61]. In addition, all-cause mortality was significantly lower among vaccinated individuals (RR 0.75, 95% CI 0.66-0.86; p<0.01; I^2=84.1%), with an even greater benefit observed in those aged 65 and older (RR 0.70, 95% CI 0.59-0.84; p<0.01; I^2=77.5%)[61].

Optimal timing for vaccination

Although pneumococcal pneumonia exhibits a seasonal pattern like influenza, local data from Argentina indicate that only 38% of pneumonia cases occur during winter months[2]. Despite this, pneumococcal vaccine uptake remains even lower than that of the influenza vaccine[13,14]. For this reason, vaccination should be recommended during any healthcare encounter with an unvaccinated individual[2,12,35]. Importantly, if a patient is unsure whether they have previously received pneumococcal vaccination –or recalls being vaccinated but cannot confirm the date, a dose of PCV20 (or the available pneumococcal vaccine) should be administered without delay.

Adverse effects and contraindications

Pneumococcal vaccines have an excellent safety profile. The most common side effect is mild local reactogenicity (pain or swelling at the injection site), occurring in approximately 30% of individuals. These reactions are typically self-limiting and do not require medical intervention. Fever is rare, affecting less than 1% of recipients.

The only absolute contraindication is a history of anaphylaxis following a previous dose of the vaccine.

Practical tips for pneumococcal vaccination

- These vaccines contain only purified capsular polysaccharides from *Streptococcus pneumoniae* (with or without protein conjugation), so they cannot cause pneumococcal disease. They are safe for immunocompromised individuals, including heart transplant recipients.

- Mild illnesses such as colds, rhinitis, diarrhea, or the use of antibiotics are not contraindications to vaccination.

- Any patient recently discharged after a pneumonia episode –or who has completed outpatient treatment– can be safely vaccinated without requiring a specific waiting period. This strategy helps prevent missed opportunities for immunization and enhances long-term protection against future infections.

Respiratory syncytial virus

Respiratory syncytial virus (RSV) is a highly contagious, single-stranded RN– virus with global distribution. It is responsible for hundreds of thousands of respiratory infections annually, leading to a substantial number of hospitalizations and deaths worldwide[1,12,62-64]. The populations most vulnerable to RSV infection are those at the extremes of age: infants and young children, as well as older adults –particularly those with underlying comorbidities (Table 5)[62].

Some studies have shown that individuals under 60 years of age with conditions such as heart failure, COPD, diabetes, or chronic kidney disease are at greater risk of developing severe RSV infection and experiencing worse clinical outcomes than older adults without such comorbidities[10,62,65].

RSV infection and cardiovascular events

RSV infection has been associated with major cardiovascular events, both *de novo* and as triggers of acute decompensation in patients with pre-existing conditions[62]. A cohort study examined outcomes in 7998 adults hospitalized for lower respiratory tract infections with laboratory-confirmed diagnoses of influenza (13.7%), COVID-19 (80.3%), or RSV (6.1%)[65]. To reduce bias, analyses were restricted to individuals unvaccinated against COVID-19 or influenza. Approximately 70% of participants had a history of cardiovascular disease. The risk of invasive mechanical ventilation or death was similar between patients with RSV and those with unvaccinated COVID-19 (12.0% vs. 14.1%; p=0.22) or unvaccinated influenza (12.0% vs. 10.3%; p=0.35)[65]. However, RSV patients had significantly higher rates of ventilatory support (30.2% vs. 23.4% for COVID-19 and 22.5% for influenza; p=0.006) and multiorgan dysfunction (31.4% vs. 25.3% and 24.3%, respectively; p=0.02)65.

Another study involving adults ≥50 years hospitalized with laboratory-confirmed RSV infection included 6248 patients (mean age 72.7 years), 56.4% of whom had a history of cardiovascular disease66. Overall, 22.4% of participants experienced a cardiovascular event, occurring in 8.5% of those without prior cardiac disease and in 33.0% of those with known cardiovascular conditions. The most frequent events were heart failure decompensation and acute coronary syndrome, followed by ventricular arrhythmias and hypertensive crisis[66]. Patients experiencing cardiovascular events during RSV infection had significantly higher risks of ICU admission (RR 1.54, 95% CI 1.23-1.93; p<0.01), invasive mechanical ventilation (RR 2.00, 95% CI 1.44-2.79; p<0.01), and in-hospital mortality (RR 1.77, 95% CI 1.36-2.31; p<0.01)[66].

Similarly, a nationwide study from Denmark assessed the risk of cardiovascular events in older adults following RSV infection during the 2022–2023 season[67]. A total of 2655 individuals aged ≥65 years were evaluated for cardiovascular events within 14 days of diagnosis. RSV infection was associated with significantly increased incidence of hospitalization for heart failure (IRR 4.4, 95% CI 2.4-8.1; p<0.001), stroke (IRR 8.1, 95% CI 3.3-20.1; p<0.001), and major cardiovascular events (IRR 5.0, 95% CI 3.2-8.0; p<0.001)67.

Cardiovascular impact of RSV vaccination

The association between RSV infection, cardiovascular complications, and adverse clinical outcomes is well established and biologically plausible[1,10,66,67]. Available vaccines have shown high efficacy in preventing lower respiratory tract infections and severe forms of disease[1,7,12,68]. The adjuvanted RSV vaccine demonstrated 94.1% efficacy (95% CI 62.4%-99.9%) in preventing severe disease, while the bivalent vaccine showed 85.7% efficacy (95% CI 32.0%-98.7%)[1]. In a randomized trial of 131 276 adults ≥60 years (21.8% with cardiovascular disease), assignment to a bivalent RSV vaccine versus placebo yielded a

Table 5 | Comorbidities indicating the need for respiratory syncytial virus vaccination

Cardiovascular disease *(risk profile broadly mirrors influenza)*
*** Heart failure€; coronary artery disease with or without revascularization; prior valve replacement; moderate-to-severe valvular heart disease; pulmonary hypertension; heart transplantation.**
*** Congenital heart disease of any complexity.**
Other clinical conditions
Commonly encountered conditions in cardiology
Diabetes mellitus (any type; irrespective of end-organ damage or current therapy), chronic respiratory disease (COPD or asthma, any severity), obesity (BMI ≥40 kg/m²), chronic kidney disease on dialysis or expected to initiate dialysis in the coming months, chronic liver disease (including cirrhosis), solid-organ malignancy under active treatment, recipients of any solid-organ transplant, rheumatologic disease (regardless of therapy).
Other high-risk conditions
- Age ≥50 years, residence in long-term care facilities; neurologic or neuromuscular disorders causing dysphagia or respiratory muscle weakness (including individuals with tracheostomy), chronic hematologic disorders, congenital or acquired immunodeficiency (hematologic and non-hematologic), HIV infection; use of immunosuppressive medications (e.g., methotrexate, azathioprine, biologic agents) or high-dose systemic corticosteroids for >14 days, additional chronic medical conditions or risk factors that, in the clinician's judgment, may increase the risk of severe RSV disease, such as frailty, suspected but undiagnosed chronic illness, or residence in rural/remote settings with limited access to advanced care[71].

COPD: chronic obstructive pulmonary disease; BMI: body mass index; HIV: human immunodeficiency virus
€Irrespective of left ventricular ejection fraction

9.9% relative reduction in cardiopulmonary hospitalizations at 1 year (95% CI, 0.3–18.7; p=0.04)[69].

Regarding safety, RSV vaccines are well tolerated in patients with cardiac disease. Coadministration with influenza vaccines has proven safe in patients with heart failure and reduced ejection fraction[70].

Types of RSV vaccines and administration schedule

To date, the FDA has approved three vaccines for respiratory syncytial virus (RSV): an adjuvanted vaccine, a bivalent vaccine, and an mRNA-based vaccine[1,12]. In our country, the first two are currently available. Both are based on the prefusion-stabilized form of the RSV fusion (F) glycoprotein. The key difference lies in their composition: the adjuvanted vaccine includes an AS01E adjuvant in combination with the prefusion F protein, whereas the bivalent vaccine contains two distinct prefusion F protein subunits, representing RSV subtypes A and B. Both vaccines have demonstrated favorable safety profiles and high effectiveness against both RSV subtypes, including in older adults and individuals with cardiovascular comorbidities[1,7,12,68].

RSV typically follows a seasonal pattern like that of other respiratory viruses, with peak circulation during autumn and early winter. However, year-round transmission has been reported, and the COVID-19 pandemic has disrupted the usual seasonality of several respiratory viruses, including influenza and RSV. Because both vaccines provide protection lasting over two years, it is reasonable to vaccinate at any time of the year, especially when an opportunity arises to immunize an unvaccinated individual[1,7,12,35,71]. A prior RSV infection should reinforce –rather than delay– vaccination, as natural infection does not confer lasting immunity, and reinfec-

tion may occur as early as two months after recovery[71].

Adverse effects and contraindications

Both RSV vaccines share a similar adverse event profile. The most common reactions include injection site pain, redness, and swelling, along with systemic symptoms such as fatigue (16%-34%), headache, and myalgia or arthralgia[1,12]. Injection site pain tends to be more frequent with the adjuvanted vaccine due to its lipid-based adjuvant. Less commonly, fever (<3%), nausea, diarrhea, or other mild gastrointestinal symptoms may occur. Overall, adverse events are generally mild and self-limited, resolving within 1-2 days. The only absolute contraindication to either vaccine is a history of anaphylaxis to any of its components[71]. Although isolated cases of GBS have been reported following both vaccines, it is important to note that RSV infection itself may act as a trigger for GBS-much like influenza. Consequently, the overall risk– benefit profile strongly supports vaccination[71].

Practical tips for RSV vaccination

- Both vaccines contain only purified proteins from the prefusion F glycoprotein of the respiratory syncytial virus, so they cannot cause RSV infection. They are safe for immunocompromised individuals, including heart transplant recipients.

- Mild illnesses such as the common cold, rhinitis, diarrhea, or the concurrent use of antibiotics do not constitute a contraindication to RSV vaccination.

Herpes zoster

Herpes zoster (HZ) is caused by reactivation of the varicella–zoster virus (VZV) following a prior primary infection. Varicella is highly prevalent, with estimates suggesting that over 90% of the global population aged >50 years has been infected –either symptomatically or asymptomatically[72]. Immunity to HZ is initially acquired after the primary infection; subsequent exposure to individuals with VZV boosts protective antibody levels (Fig. 2)[72].

With advancing age, immunosenescence facilitates HZ reactivation. The estimated incidence is 5.2% (95% CI 4.6%-5.9%) at age 50, increasing to more than doubling among octogenarians[73]. Regardless of age, certain conditions can increase the risk of developing HZ earlier in life (Table 6).

Zoster reactivation and cardiovascular events

An acute episode of HZ typically causes severe, disabling pain –sometimes described as more intense than labor pain– which may persist for weeks or even months[74]. Pain lasting more than 90 days after the resolution of skin lesions is defined as postherpetic neuralgia, the most frequent complication of HZ, affecting up to one-third of patients. This condition can last for years, and in some cases, for life (Fig. 3).

As with other infections, HZ triggers an inflammatory response that may induce endothelial dysfunction, contributing to the development of vascular complications[74]. In this context, HZ has been associated with increased risk of:

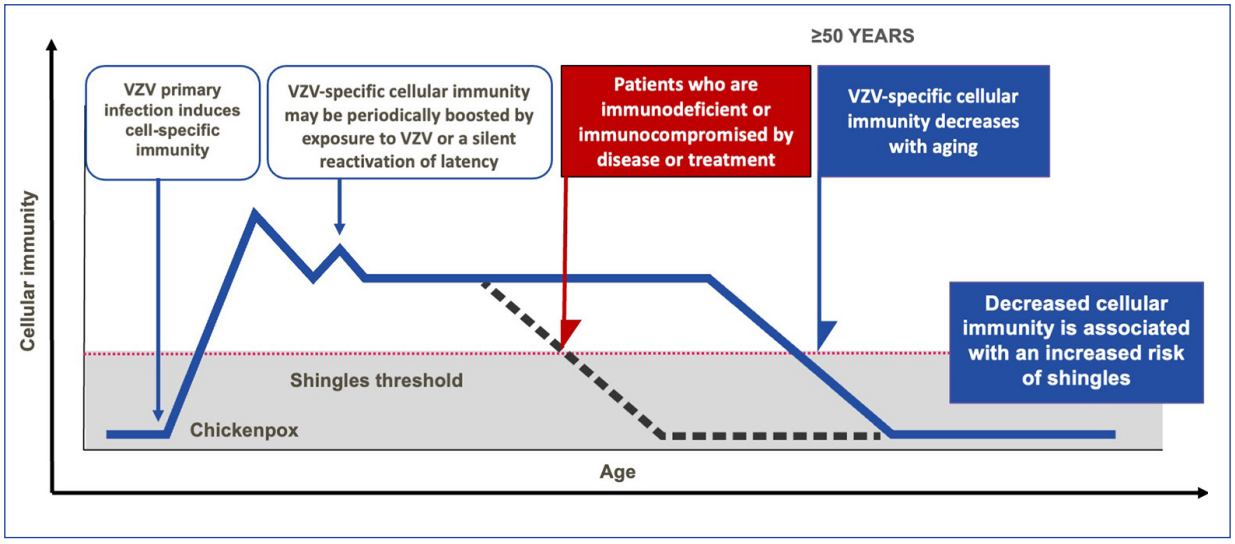
- **Stroke**: The risk peaks during the first week after acute HZ (adjusted incidence rate 2.37, 95% CI 2.17-2.59; $p<0.05$) and declines in the following weeks, reaching 1.55 (95% CI 1.46-1.65; $p<0.05$) by the fourth week[75]. Some studies suggest that the elevated stroke risk may persist for up to one year after HZ[75]. The risk is particularly high in younger patients and in those with ophthalmic HZ[76].

- **Acute Myocardial Infarction (AMI)**: During the first week after HZ onset, the incidence of AMI increases significantly (1.68, 95% CI 1.47-1.92; $p<0.05$), with progressive decline over subsequent weeks to 1.34 (95% CI 0.98-1.82) by week four[74,77].

- **Heart failure (HF)**: Patients with severe HZ requiring hospitalization have a markedly increased risk of HF (HR 2.03, 95% CI 1.62–2.56; $p<0.05$)[77].

Given these associations, some studies have explored the use of antiviral therapy during acute HZ as a strategy to reduce subsequent ischemic risk. However, this approach has not demonstrated efficacy in preventing cardiovascular events[74].

Figure 2 | Schematic of the development of acquired immunity to varicella-zoster virus (VZV) and its decline over time due to immunosenescence and comorbidities. Adapted from reference[72]



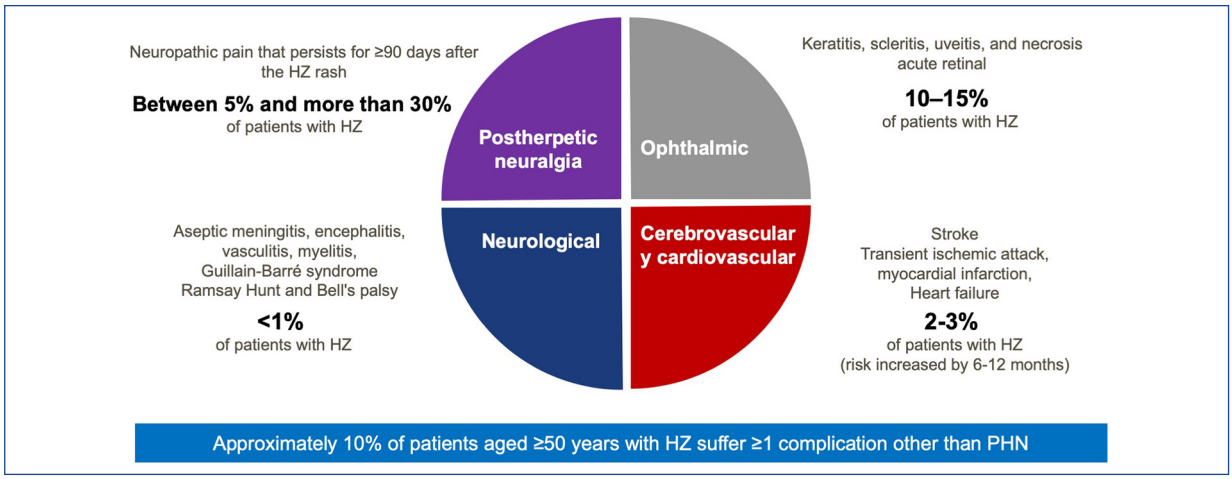
VZV= varicella-zoster virus

Table 6 | Comorbidities and risk factors for herpes zoster reactivation in adults

Comorbidities and conditions
– Age ≥50 years
– Heart failure, NYHA class II–IV
– Pulmonary hypertension
– Moderate-to-severe valvular heart disease
– Diabetes mellitus
– Chronic respiratory disease (COPD or bronchial asthma)
– Chronic kidney disease, especially in patients on dialysis
– Heart transplantation
– Active malignancy
– HIV infection
– Other conditions: depression, chronic liver disease (including alcohol use disorder), connective tissue disease, hematopoietic stem-cell or other solid-organ transplantation, rheumatologic disease (regardless of current therapy).
Immunosuppression and biologic therapies
– Pharmacologic: prolonged or high-dose systemic corticosteroids, biologic agents, including monoclonal antibodies
– Non-pharmacologic: anatomic or functional asplenia

COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; NYHA: New York Heart Association

Figure 3 | Post-herpes zoster complications and their approximate frequencies in immunocompetent adults



HZ= herpes zoster; PHN= postherpetic neuralgia

Cardiovascular impact of herpes zoster vaccination

A large U.S. Medicare cohort study evaluated the effect of the live attenuated HZ vaccine in adults, analyzing 1 603 406 vaccinated individuals and comparing them with an equal number of unvaccinated controls matched through a propensity score model[78]. Vaccinated individuals had a lower risk of ischemic stroke (HR 0.83, 95% CI 0.82-0.84; p<0.001) and hemorrhagic stroke (HR 0.88, 95% CI 0.85-0.91; p<0.001)[78]. Another study compared the impact of the live attenuated and recombinant vaccines on stroke incidence, finding that both the live attenuated (OR 0.77, 95% CI 0.65-0.91; p=0.002) and recombinant vaccines (OR 0.57, 95% CI 0.46-0.72; p<0.001) reduced stroke risk, with the recombinant formulation providing greater benefit[79].

Using the TriNetX network, a propensity-matched analysis compared 7657 recipients of the recombinant vaccine with an equal number of unvaccinated individuals. At three years of follow-up, vaccinated individuals had a lower risk of acute myocardial infarction (RR 0.73, 95% CI 0.5-0.96; p<0.05) and all-cause mortality (RR 0.84, 95% CI 0.74-0.95; p<0.05)[80].

Vaccine types and administration schedule

The first vaccine approved for HZ prevention was the live attenuated virus formulation, which demonstrated only moderate efficacy and was contraindicated in immunosuppressed individuals[7]. Subsequently, the recombinant HZ vaccine –comprising an antigen and an adjuvant– was approved. The inclusion of the adjuvant significantly improved efficacy, reducing the risk of developing HZ in adults aged ≥50 years by 97.2% (95% CI 93.7%-99.0%; p<0.001), with sustained benefit in those aged ≥70 years (89.8%, 95% CI 84.2%-93.7%; p<0.001)[81]. Because it does not contain live virus, the recombinant vaccine can be administered to immunosuppressed individuals (Table 6). To date, it has demonstrated durable serologic protection and clinical efficacy for over 10 years[81].

The recommended schedule consists of an initial dose followed by a booster between 2 and 6 months later[1,35]. In individuals at imminent risk of severe immunosuppression or with an increased likelihood of developing HZ (e.g., before transplantation or initiation of chemotherapy), the second dose may be given as early as 30 days after the first.

Adverse effects and contraindications

Most adverse events with the recombinant vaccine are mild, local, and self-limited. Injection-site pain –attributed to the lipid component of the adjuvant– was reported in 79.1% of participants, with erythema in 39.2% and swelling in 26.3%. Systemic symptoms occurred more frequently in younger age groups: myalgia was reported in 46.3% of individuals aged ≥50 years and in 31.2% of those aged ≥70 years; fever occurred in 21.5% and 12.3% of these groups, respectively. Symptoms are generally transient, resolving spontaneously within 24-48 hours[1,7]. Notably, experiencing adverse events after the first dose does not predict recurrence with the second dose.

The only contraindication is known hypersensitivity to any vaccine component or a history of severe allergic reaction following the first dose.

Practical tips for herpes zoster vaccination

- This vaccine contains only recombinant varicella–zoster virus glycoprotein E with an adjuvant, so it cannot cause herpes zoster. It is safe for immunocompromised individuals, including heart transplant recipients.

- The vaccine is effective in preventing HZ and postherpetic neuralgia (PHN), but it has no therapeutic role once PHN is established.

- If the second dose is missed and more than six months have passed since the first, simply administer the missed dose –there is no need to restart the series.

- If a person believes they have never had varicella, serologic testing is not recommended; vaccination should proceed directly.

- After an acute episode of HZ, vaccination is recommended 6–12 months later. If the patient prefers not to wait, the vaccine may be administered once all skin lesions (vesicles) have resolved.

- Mild illnesses –such as the common cold, rhinitis, diarrhea, or concurrent antibiotic use– do not constitute a contraindication to receiving the HZ vaccine.

COVID-19

In March 2020, infection with the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a global pandemic[12], creating profound challenges for the general population, healthcare professionals, and health systems worldwide[82-89]. Beyond causing severe respiratory disease, COVID-19 has been linked to serious –and often fatal– cardiovascular complications[8,90-92]. These events may result both from direct viral effects and from immune-mediated injury[8,90-92]. Another significant concern is long COVID, in which cardiovascular manifestations such as myocarditis, chest pain, and palpitations have been frequently reported[8,90-92].

The introduction of COVID-19 vaccines dramatically reduced the incidence of severe disease, cardiovascular complications, and infection-related mortality[93]. At the time of drafting this document, no official recommendations were available regarding the optimal vaccination schedule[94]. Most experts currently recommend primary immunization with a single dose of the Moderna mRNA vaccine. The exception applies to immunocompromised patients –such as heart-transplant recipients– who should receive a three-dose primary series. Booster doses may be administered with any of the available vaccines, including the nationally produced recombinant protein subunit vaccine, which has been approved for adults aged 18 years and older and is currently available only in the private sector.

The currently used vaccines have a favorable safety profile. Although there have been reports of cardiovascular adverse events –such as pericarditis and myocarditis, particularly among younger individuals– these occur at low rates (12 cases per million doses) and typically resolve spontaneously[95].

Importantly, SARS-CoV-2 infection itself is associated with much higher rates of cardiovascular complications[8,90-92]. For these reasons, both national and international scientific societies, as well as public health authorities, recommend regular booster vac-

Table 7 | COVID-19 vaccination by risk category

Risk category	Population
High risk	Adults ≥50 years; immunocompromised individuals; pregnant women.
Intermediate risk	Adults <50 years with non–immunocompromising comorbidities (e.g., chronic diseases or obesity); healthcare workers; essential/strategic personnel.
Low risk	Adults <50 years without comorbidities.

Note: Booster timing and product selection should follow current national guidance for each risk category

cination against COVID-19 for high-risk populations, such as older adults and those with cardiovascular disease. The Argentine Society of Infectious Diseases advises annual vaccination for all adults, with semiannual boosters for individuals at high risk of severe infection (Table 7)[94]. Given the evolving epidemiology of COVID-19, booster schedules are currently under review.

Special situations

Adults with congenital heart disease

Adults with congenital heart disease (ACHD) represent a heterogeneous population, given the variability in underlying anatomy, physiology, and whether surgical or interventional correction was performed[2]. Although many patients are successfully treated during childhood, most experience residual sequelae from the disease or prior interventions and often require further procedures in adulthood. As such, they are considered "special hosts" with an increased susceptibility to infections.

While no specific studies have evaluated the cardiovascular impact of vaccines in this population, it is widely accepted that all ACHD patients benefit from vaccination –particularly those with more complex forms. These individuals should receive vaccines against influenza, pneumococcus, and COVID-19 vaccine. For those with the most complex conditions, vaccination against respiratory syncytial virus (RSV) is also recommended. Vaccination against HZ –or RSV vaccination in patients with less complex heart disease– should be determined through shared decision-making between the patient and the care team.

Depending on age and individual risk, ACHD patients may also require additional vaccines not covered in this Consensus, such as hepatitis B or measles–mumps–rubella (MMR).

Patients on anticoagulant or antiplatelet therapy

Patients receiving antiplatelet or anticoagulant therapy are at elevated risk both for infections and thrombotic events. Vaccination in these patients is safe and should *not* be delayed, as postponement often results in missed immunization opportunities.

Practical considerations:

- Apply firm pressure (without rubbing) to the injection site (deltoid region) for 2-5 minutes.

- Either intramuscular or subcutaneous administration can be used, depending on provider experience.

- For patients on vitamin K antagonists (acenocoumarol or warfarin), ensure they are within therapeutic range, ideally with an INR <2.5[2,7].

- For patients on direct oral anticoagulants (DOACs):

* Vaccination can be performed without interrupting therapy, or

* One dose can be omitted based on the specific agent:

- Rivaroxaban or edoxaban: skip the evening dose the night before vaccination.

- Apixaban or dabigatran: skip the morning dose on the day of vaccination.

- Resume the anticoagulant the same evening, regardless of the specific drug used.

Frailty and loss of independence

The relationship between frailty and cardiovascular disease is bidirectional: comorbidities increase frailty, and frailty is associated with worse outcomes in individuals with heart disease[96]. One of the most significant consequences is the loss of independence, which has substantial personal, family, and healthcare system implications. Even mild infections can precipitate marked functional decline in frail older adults, as has also been observed with HZ. Studies indicate that between 10% and 50% of older adults hospitalized for respiratory infections experience loss of independence[19,64]. In this context, vaccination plays a critical role in preventing such decline and preserving functional autonomy.

Egg allergy

True egg allergy affects an estimated 0.2% of adults and 1.3% of children, while anaphylaxis following influenza vaccination occurs at a rate of only 1 case per million doses administered. The benefits of vaccination far outweigh this risk[2]. Furthermore, **pneumococcal, RSV, herpes zoster, and COVID-19 vaccines contain no egg-derived components,** meaning that a history of egg allergy should not be considered a contraindication to their administration.

Practical recommendations:

- Individuals with suspected or mild egg allergy (e.g., limited to urticaria) can safely receive the influenza vaccine without prior testing or special precautions.

- In cases of more severe allergy (extra-cutaneous reactions), vaccination should be performed in a hospital setting with observation for 30–60 minutes, as most allergic reactions occur within the first few minutes post-vaccination.

- Individuals who have experienced a severe reaction to an influenza vaccine should be evaluated by a specialist; in such cases, cell culture–based influenza vaccines are both safe and effective[50].

Vaccine coadministration

Coadministration refers to the simultaneous administration of two or more vaccines at different anatomical sites, without mixing them in the same syringe. This approach does not interfere with antibody production, and delaying vaccination is often associated with missed opportunities for immunization. All vaccines included in this Consensus may be coadministered.

Cost-effectiveness of vaccination

No studies from Argentina or the region have specifically evaluated the cost-effectiveness of vaccines in adults with cardiovascular disease. However, an analysis from the United Kingdom concluded that vaccination against Influenza, Pneumococcus, RSV, and HZ is highly cost-effective in adults and significantly reduces the societal burden of these diseases. The study also estimated that improving vaccination rates could yield savings up to 19 times greater than the initial investment[97].

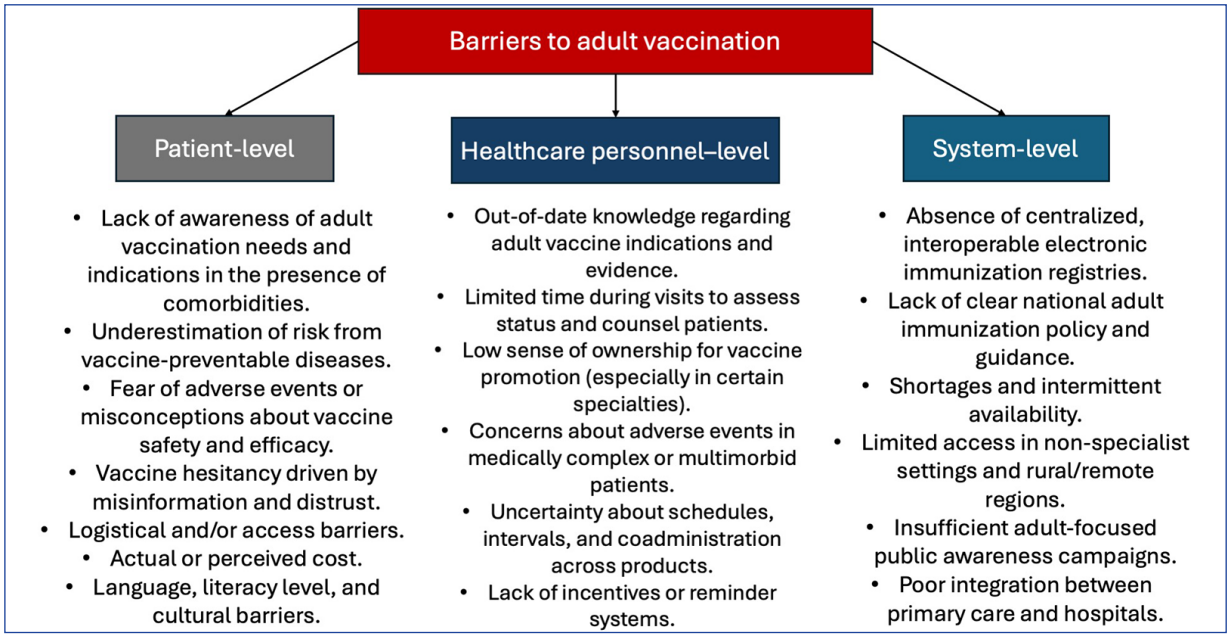
Myths and barriers to vaccination

Adult vaccination faces persistent myths and obstacles that hinder its implementation, even among individuals with cardiovascular disease. Many adults mistakenly believe that vaccines are unnecessary later in life or distrust their safety and effectiveness due to misinformation[98]. In certain settings, practical barriers further limit access (Fig. 4).

One of the leading factors limiting vaccination remains the **absence of a physician's recommendation** (Table 8). Simply prescribing a vaccine is insufficient; it is essential to communicate with clarity and empathy to build patient trust. To support this dialogue, the CDC has proposed the **SHARE** approach, which outlines five steps to improve vaccine acceptance (Table 9 and Appendix 1).

Among the challenges in adult vaccination is achieving sustained implementation. Strategies such as checklists, electronic reminders embedded in medical records, patient messaging, and educational campaigns have been shown to increase vaccination rates. Notably, digital reminders that emphasize the **cardio-**

Figure 4 | Common barriers to adult vaccination.



Tabe 8 | Attitudes toward physician vaccination recommendations and reported barriers to uptake. Adapted from reference[1]

Would be vaccinated if recommended by their physician	85%
Actual vaccination uptake among survey respondents	56%-61%*
Reasons for not being vaccinated	
"My doctor did not recommend it"	57%
"If I feel healthy, I don't need it"	61%
Concern about adverse effects	40%
Financial barriers/cost	17%

**Range varies by vaccine assessed*

Table 9 | SHARE approach for empathetic vaccine counseling in adults

S	***Share***	Share why vaccination is appropriate for this patient—considering age, comorbidities, lifestyle, occupation, and risk factors. Personalize the recommendation so it feels relevant.
H	***Highlight***	Highlight positive experiences and evidence from your practice (benefits, safety, outcomes) to reinforce trust in vaccines.
A	***Address***	Address all questions and concerns using clear, plain language. Validate worries and explain that while infection can still occur, vaccination markedly reduces severity and complications.
R	***Remind***	Remind patients that vaccination protects them and those around them– family, loved ones, and the community, especially the most vulnerable.
E	***Explain***	Explain the costs of not vaccinating: medical complications and hospitalizations, time away from work or family, financial impact, and the risk of transmitting infection to high-risk contacts

Table 10 | Multilevel strategies to optimize adult vaccination coverage

Individual-level interventions (patients)
• Personalized reminders via text, email, or phone to prompt vaccination.
• Plain-language educational materials (leaflets, videos, infographics) emphasizing benefits and safety.
• Community awareness campaigns targeting older adults and other vulnerable groups.
• Engage trusted community leaders (e.g., civic or faith leaders) to promote vaccination.
• Address vaccine hesitancy with empathetic conversations, real patient narratives, and tailored messaging.
• Use every healthcare encounter to vaccinate and coadminister when appropriate; do not require a vaccine card or serologic testing when not clinically necessary.
• Offer practical incentives (e.g., reduced copays/medication costs) for high adherence to vaccination.
• Provide symbolic recognition (certificates, public acknowledgment) for individuals/families with excellent adherence.
• Ethical use of generative AI tools (e.g., chatbots) to deliver up-to-date, empathetic, user-tailored guidance.
Healthcare-professional interventions
• Ongoing training in clinical updates and communication skills, tailored to specialty and role.
• Electronic Health Record-based clinical alerts and automated reminders at the point of care.
• Systematic documentation of each patient's vaccination status.
• Protect time within visits to discuss vaccination.
• Incentives for prescribing/administering vaccines on the national schedule or essential-medication lists (e.g., differential reimbursement, tax relief) and non-financial benefits (recertification points, institutional recognition, access to resources).
• Symbolic awards for clinicians/teams achieving high vaccination rates (e.g., diplomas, internal commendations, mentions at professional meetings).
• Regular audit with constructive feedback to teams on coverage and targets.
Health-system and policy interventions
• Embed vaccination into routine care using standardized protocols or checklists across specialties.
• Maintain unified, easily accessible national electronic registries to track status and recover incomplete series.
• Offer vaccination at alternative sites (shopping centers, parks, clubs, religious centers) with extended hours.
• Simplify access where safe –allow administration without a physician prescription or vaccine card when clinical criteria are met.

vascular benefits of vaccination have proven more effective than usual care.

In 2019, the WHO identified **vaccine hesitancy** as one of the top ten threats to global health, driven by misinformation, low perceived risk, lack of access, and distrust[99]. The most effective interventions for increasing adult vaccination rates are multicomponent strategies and organizational approaches designed to facilitate access (Table 10)[100]. Another major global health threat identified by WHO is the spread of antimicrobial-resistant pathogens, for which vaccines play a critical preventive role.

In this context, there is growing interest in the use of **generative artificial intelligence**, such as large language models, to address questions, detect misinformation, and deliver personalized, empathetic messaging[101]. These tools can identify emotions, tailor responses to the audience's profile, and build trust in vaccination. One study even showed that their responses were rated higher in clarity and empathy than

those of healthcare professionals[101]. Nevertheless, their deployment must be ethical, regulated, and ensure equitable access for all populations.

In conclusion, infections are closely linked to an increased risk of cardiovascular and cerebrovascular events, as well as higher mortality. In the case of respiratory infections, the association with hypoxemia further amplifies this risk. Vaccination has consistently proven to be a safe, effective, and cost-efficient intervention to mitigate these adverse outcomes.

Despite this, adult immunization rates remain alarmingly low –even among those at high cardiovascular risk or with free access to vaccination. Immunizations must be embraced as an **essential strategy** for reducing residual cardiovascular risk (Table 11). Active clinician engagement, fostering empathetic dialogue, practicing active listening, and explaining the cardiovascular benefits of vaccination beyond infectious disease prevention are crucial steps to improving adult immunization rates and achieving comprehensive cardiovascular prevention.

Table 11 | Immunization recommendations for adults with cardiovascular disease

Recomendation	Rec	NE
Prioritize annual influenza vaccination for all individuals with cardiovascular disease	I	A
Prioritize administration of the 20-valent pneumococcal conjugate vaccine (PCV20) for all individuals with cardiovascular disease.	I	B
Respiratory syncytial virus (RSV) vaccination is recommended for individuals with cardiovascular disease.	I	B
Recombinant zoster vaccine (RZV) is recommended for individuals with cardiovascular disease.	I	B
COVID-19 vaccination is recommended for all adults with cardiovascular disease.	I	B
Do not defer vaccination in anticoagulated individuals, as postponement is associated with missed immunization[λ]. The only precaution required is to ensure firm local hemostasis for at least 2 minutes *.	I	B
Mild to moderate allergies to any substance—including urticaria—do not constitute a contraindication and should not delay administration of any of the vaccines included in this Consensus[ε].	I	B
Annual influenza vaccination is recommended for all healthcare personnel (clinical and non-medical-staff), irrespective of individual risk factors.	I	B
Administer a Td (adult formulation) booster every 10 years in adults with cardiovascular disease, as in the general population.	I	C
Maintain empathetic communication with individuals who express vaccine hesitancy, providing clear, accurate information about benefits beyond prevention of infectious diseases.	I	C
All healthcare personnel should actively participate in educating colleagues and patients to reduce vaccine hesitancy and improve coverage in the general population.	I	C

Rec: class of recommendation; LOE: level of evidence; Td: tetanus and diphtheria vaccine
See Appendix 2

[λ]*Vaccination can be performed without interrupting anticoagulation in patients on direct oral anticoagulants (DOACs). For those on vitamin K antagonists (acenocoumarol or warfarin), ensure INR <3.0 (ideally <2.5). If a brief DOAC hold is preferred: omit the evening dose for Rivaroxaban or Edoxaban, or omit the morning dose for Apixaban or Dabigatran. In all cases, restart anticoagulation the same evening after vaccination.*
**Route of administration may be intramuscular or subcutaneous, according to vaccinator experience and preferences.*
[ε]*In individuals with a history of severe allergic reactions (e.g., anaphylaxis or angioedema), perform an individualized assessment prior to vaccination, and administer the vaccine in a healthcare setting equipped to manage severe allergic events.*

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Appendix 1: Frequently asked questions and suggested responses about adult vaccinations

1. "Do I really need vaccines if I feel fine?"

Suggested response:

I'm glad you're well today. Vaccination helps *keep* you well and prevents serious complications. In people with risk factors or heart disease, even "mild" infections can trigger heart attacks, strokes, heart failure decompensation, arrhythmias, or—in severe cases—death. Vaccination protects against risks that aren't always visible but can be significant.

2. "Isn't it better to let my body fight infections naturally?"

Suggested response:

It's a fair question. The immune system is powerful, but infections like influenza or pneumococcal disease can overwhelm it –especially with cardiac conditions. Vaccines safely *prime* your defenses so you're protected without having to endure a severe infection.

3. "What if I have a bad reaction to the vaccine?"

Suggested response:

That concern is understandable. The vaccines I'm recommending have excellent safety profiles. Side effects, when they occur, are usually mild –like arm soreness or fatigue. In contrast, the infections themselves carry far greater risks for your heart.

4. "Can I be vaccinated if I'm on antiplatelet therapy (aspirin, clopidogrel, prasugrel, or ticagrelor)?"

Suggested response:

Yes –you *can and should* be vaccinated. Antiplatelet therapy is not a barrier to any of these vaccines. We simply press on the injection site for a few minutes to minimize a small bruise. Vaccination is especially important because infections increase the risk of heart attack and stroke.

5. "Can I be vaccinated if I'm taking anticoagulants?"

Suggested response:

Yes. We take simple precautions –use a small-gauge needle in the arm and apply firm pressure a bit longer afterward. There's no need to stop your anticoagulant.

6. "Is it dangerous to receive several vaccines at the same visit?"

Suggested response:

No. The immune system can handle multiple vaccines without being overloaded. Coadministration helps you get protected sooner and reduces the chance of missing a dose.

7. "I had the flu once, and it wasn't that bad –why vaccinate?"

Suggested response:

Viruses vary year to year, and a future infection could hit harder—especially for the heart. Influenza vaccination substantially lowers the chance that a flu episode will trigger a cardiac complication.

8. "Why are you insisting on vaccination if I'm not that old?"

Suggested response:

Age isn't the only risk factor. Having heart disease places you at a higher risk regardless of age. Vaccination is a core part of cardiac care-just like medications and blood-pressure control.

9. "What happens if I choose not to vaccinate?"

Suggested response:

It's your decision; my role is to provide clear information. Without vaccination, you remain exposed to infections that can destabilize your cardiac condition. Based on evidence and clinical experience, vaccination adds meaningful protection.

10. "Should I skip vaccination if I have a mild cold, rhinitis, or diarrhea?"

Suggested response:

You can proceed. Mild illnesses without fever don't interfere with vaccine effectiveness. Delaying unnecessarily increases the chance of forgetting and staying unprotected.

11. "Can I get vaccinated if I'm taking antibiotics or recovering from a recent illness?"

Suggested response:

Yes. Neither antibiotics nor recovery from a mild illness diminishes vaccine effectiveness. Timely vaccination helps prevent infections that could complicate your heart condition.

12. "If I get vaccinated, will I never get sick?"

Suggested response:

Vaccines don't eliminate all infections, but they *strongly* reduce the risk of severe disease—the kind that leads to hospitalization, heart attacks, or stroke. Even if you develop mild symptoms, vaccination protects against the most dangerous complications.

13. "Can I be vaccinated if I have or had cancer, an autoimmune disease, or I'm on immunosuppressive therapy?"

Suggested response:

Yes –you *can and should* receive the vaccines that reduce cardiovascular risk (influenza, pneumococcal, RSV, herpes zoster, and COVID-19). These are **non-live** vaccines and have excellent safety profiles. In some cases of high-dose immunosuppression, special schedules or additional doses may be needed. These conditions also raise cardiovascular risk, so you may gain even *more* benefit from vaccination.

14. "Is it true the MMR vaccine causes autism?"

Suggested response:

No. The study that suggested that link was fraudulent and was retracted. Large, high-quality studies show **no association** between vaccines and autism. Vaccination remains essential to protect the heart and brain from infection-related complications.

15. "Don't hygiene and clean water make vaccines unnecessary?"

Suggested response:

Hygiene and safe water help, but many diseases were controlled only after widespread vaccination. If vaccination programs lapse, these infections return—with risks that include severe illness and cardiovascular complications.

16. "Is thimerosal in vaccines dangerous?"

Suggested response:

No. Thimerosal is a preservative used in very small amounts in some multi-dose vials. Robust scientific evidence and international health agencies confirm its safety. Many routine vaccines are also available in thimerosal-free, single-dose presentations.

Appendix 2: Grading of classes of recommendation and levels of evidence for the recommendations issued in the consensus document on the role of adult vaccination in the prevention of cardiovascular events

Classes of recommendation

• **Class I:** Conditions for which there is evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective.

• **Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness or efficacy of a treatment or procedure.

o **Class IIa:** The weight of evidence or opinion is in favor of usefulness or efficacy.

o **Class IIb:** Usefulness or efficacy is less well established.

• **Class III:** Evidence or general agreement indicates that the treatment or procedure is not useful or effective and, in some cases, may be harmful.

Levels of evidence

• **Level of evidence A:** Strong evidence derived from multiple randomized clinical trials or large cohort studies with appropriate design to achieve statistically robust and biologically meaningful conclusions.

• **Level of evidence B:** Data derived from a single randomized clinical trial or from large nonrandomized studies.

• **Level of evidence C:** Consensus of expert opinion.