EURHEART-D-24-0456-R2
09.05.2025

Vaccination as a New Form of Cardiovascular Prevention
An ESC Clinical Consensus Statement

With the contribution of the European Association of Preventive Cardiology (EAPC), the Association for Acute CardioVascular Care (ACVC), and the Heart Failure Association (HFA) of the ESC

Bettina Heidecker*, German Heart Center of the Charité Berlin, Germany, Berlin Institute of Health, and DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany
Peter Libby, Brigham and Women's Hospital, Boston, Mass., United States
Vassilios S. Vassiliou, University of East Anglia, Norwich, United Kingdom
François Roubille, University of Montpellier, INSERM, France
Orly Vardeny, University of Minnesota, United States
Christian Hassager, Department of Cardiology, Rigshospitalet and Dept of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
Michael A. Gatzoulis, Royal Brompton Hospital and Imperial College, United Kingdom
Mamas A. Mamas, Keele Cardiovascular Research Group, United Kingdom
Leslie T. Cooper, Mayo Clinic Jacksonville, Fla., United States
Felix Schoenrath, Deutsches Herzzentrum der Charité Berlin, Germany and DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany
Marco Metra, Cardiology, University of Brescia, Italy
Offer Amir, Hadassah-Hebrew University Medical Center, Jerusalem, Israel,
Scott Solomon, Brigham and Women's Hospital, Boston,
Ulf Landmesser, German Heart Center of the Charité Berlin, Germany
and
Thomas F. Lüscher*, Royal Brompton & Harefield Hospitals GSTT., Cardiovascular Academic Group, King's College, United Kingdom and Center for Molecular Cardiology, University of Zurich, Switzerland

Key Words: COVID-19 - Infection – Influenza – Pneumococcus - Respiratory Syncitial Virus

* Corresponding author(s):

Thomas F. Lüscher, MD, FRCP, FESC
Royal Brompton and Harefield Hospitals GSTT
Sydney Street
London SW3 6NP, United Kingdom
Tel: +41 (0)44 250 40 93
Fax: + 41 (0)44 250 40 90
Email: cardio@tomluescher.ch

Bettina Heidecker; MD. FESC, FACC
German Heart Center of the Charité Berlin, Germany, Berlin
Campus Benjamin Franklin
Deutsches Herzzentrum der Charité
Hindenburgdamm 30
12203 Berlin
Tel.: +49 30 450 513 725
Fax: +49 30 450 7 513 984
Email: bettina.heidecker@dhzc-charite.de

Abstract

Vaccination is increasingly acknowledged as an effective preventive measure not only against specific infections, but also for the prevention of cardiovascular disease in high-risk patients. Specifically, a growing body of evidence suggests that vaccines against influenza, SARS-CoV-2, respiratory syncytial virus (RSV), herpes zoster, and other viruses significantly reduce infection and for influenza the incidence of major adverse cardiovascular events in vaccinated individuals.

This clinical consensus statement examines the existing literature and accumulated evidence and offers practical clinical advice on vaccination timing and target demographics, specifically addressing complex clinical scenarios with a focus on cardiovascular conditions. It includes guidelines for vaccinating vulnerable populations such as immunosuppressed individuals, patients with congenital heart disease, and pregnant women as well as safety and potential complications of the procedure.

Keywords: Vaccine; cardiovascular events; myocarditis; pneumococcus; influenza; SARS-CoV-2

Introduction

Vaccination is a critical topic in policymaking and healthcare strategies, and generated great discussion in the public arena, in particular since the COVID-19 pandemic. A recent Consensus Document objectively examined the cardiovascular (CV) risks associated with infection by SARS-CoV-2 and its vaccines, addressing public concerns, while highlighting potential mitigation strategies. The pandemic has underscored the CV complications that can arise from viral respiratory infections, which may ultimately increase the risk of myocardial infarction, arrhythmias, heart failure and death. Major cardiovascular events (MACE) as well as heart failure continue to be an overwhelming global public health issue, with heart failure affecting approximately 64 million people worldwide(1-4). In an era of increasing recognition of prevention as crucial for reducing the CV disease (CVD) burden, vaccinations could become a foundational pillar of preventive strategies alongside other established measures.

Therefore, it is essential for healthcare professionals to acquire and maintain a robust understanding of the latest evidence on this topic, in particular indications and application of vaccines and their potential complications. This article provides a comprehensive analysis of the public health implications of CV complications from bacterial and viral infections and summarizes the current evidence on how current vaccines can mitigate untoward CV effects associated with these conditions. Additionally, it evaluates the potential risks associated with vaccination and offers strategies for their management, particularly in vulnerable populations such as

pregnant women, patients with congenital heart disease, and immunocompromised individuals.

Public health impact of cardiovascular disease and prevention strategies

CVD is the leading cause of death globally. Age-standardized CVD mortality varies by region and in 2022 ranged from 73.6 per 100,000 in high-income Asia Pacific to 432.3 per 100,000 in Eastern Europe.(5) Coronary artery disease (CAD) affects over 300 million individuals world-wide, accounting for the largest proportion of mortality, and resulting in the highest disease burden as measured by disability adjusted life years, estimated at 2,276 per 100,000.(5) While incidence rates and mortality have decreased in high-income countries over the last few decades, its prevalence currently at 3,610 per 100,000, will continue to climb due to the obesity epidemic and its metabolic risk factors as well an aging population.(5) Thus, CVD will continue to substantially impact society and health care systems. Prevention strategies beyond those currently used are therefore paramount to reduce the overall burden of CVD.

A comprehensive prevention plan for CVD encompasses both behavioral and biological factors. Among classical CV risk factors, exposure to elevated levels of low density lipoprotein cholesterol accounts for approximately 40% of deaths due to CAD frequently associated with vascular and systemic inflammation.(6, 7) Elevated levels of inflammatory biomarkers, such as hs-CRP or IL-6 have also been associated with the risk for atherosclerotic cardiovascular disease on top of classical CV risk factors.(8) Any infection is associated with a burst of inflammation. Therefore, preventing inflammation offers novel avenue for CV risk reduction.

Viral and bacterial infections increase risk for MACE

Awareness has grown of the impact of viral and bacterial infection on the CV system and the extent to which infectious diseases can trigger CV morbidity and mortality. Indeed, pulmonary and systemic infections may influence CV health in a variety of ways, e.g. by increasing myocardial oxygen consumption and predisposing to ischemic events in patients at risk, by stimulating inflammatory pathways that may trigger coronary plaque rupture or erosion, and by depressing myocardial contractile function leading to or exacerbated heart failure. A recent study suggested that approximately 3% of deaths and 5% of hospitalizations with influenza or pneumonia may be attributed to influenza in patients with heart failure(9).

Influenza has long been associated with increased CV risk; the population attributable risk of influenza for CAD has been estimated at 3.9% (95% CI 2.5-5.3%)(10). Data from the *Atherosclerosis Risk in Communities* (ARIC) study suggested that each 5% increase in monthly influenza activity was associated with a 24% increase in hospitalization rates.(11) SARS-CoV-2 contributed to a substantial increase in CV risk, especially early in the COVID-19 pandemic when population immunity was exceedingly low (figure 1).(12-16) Other respiratory infections, including respiratory syncytial virus (RSV), parainfluenza, adenovirus and pneumococcal pneumonia have also been associated with increased CV morbidity and mortality.(17, 18)

Influenza and other respiratory infections increase the risk of MACE and heart failure through a variety of mechanisms, including induction of local and systemic proinflammatory and prothrombotic pathways destabilizing coronary plaques, and worsening of myocardial contractile function,(19) leading to heart failure exacerbation, increasing myocardial oxygen consumption and in turn inducing ischemia, triggering arrhythmias, and/or resulting in myocarditis. Influenza, may directly infect coronary endothelial and smooth muscle cells.(20) In mice, endothelial infection results in decreased endothelial nitric oxide synthase expression.(20) Influenza A H3N2 can persist in atherosclerotic plaques and in the myocardium(21) up to several weeks following infection.(22) Infection also induces an enhanced production and release of proinflammatory cytokines and chemokines, which may destabilize the cap of atherosclerotic plaques.(20) Furthermore, infection may activate local and systemic proinflammatory and prothrombotic mediators including tissue factor among others, thereby increasing the risk of intravascular clot formation and MACE.

Mechanisms of cardiovascular events after infection

Various mechanisms activated in acute and chronic infections may trigger or worsen CV events.(23) In that regard, Chlamydia species or viruses, notably Herpes, may infect CV tissues and in turn potentiate atherogenesis.(24, 25) However, a series of well-conducted randomized antibiotic trials using agents targeting Chlamydia revealed neutral results.(26) While viral nucleic acid and proteins can localize within atherosclerotic plaques, their causal role in atherogenesis either through direct infection of arterial tissues or leukocytes within atheromata is uncertain.(27) (23)Thus,

chronic viral presence as a cause or facilitator of atherosclerotic plaques, while intriguing, remains unsubstantiated.

The relationship of acute infections to CV events also remains inconclusive. For example, in SARS-CoV-2, the angiotensin converting enzyme-2 receptor for this virus appears expressed primarily in pericytes of the myocardial microvasculature rather than myocardial cells themselves. Nevertheless, scant evidence supports direct infection of endothelial cells by SARS-CoV-2, and the receptor for virus entry does not appear abundant in intrinsic vascular cells or in cardiomyocytes.

While direct cardiac tissue infection remains rather uncertain as a cause of CV events associated with acute or chronic infections, ample evidence supports indirect effects(28, 29). Most infections will elicit local and systemic release of cytokines as well as protein mediators of inflammation, immunity and thrombus formation(28, 29). Moreover, pathogen-associated molecular patterns (PAMPs) derived from bacteria or viruses can activate molecular pathways in CV cells. For example, bacterial lipopolysaccharides (LPS), the principal endotoxins of Gram-negative bacteria, elicit the expression of cytokines such as tumor necrosis factor (TNF) or various interleukins (IL), among them IL-1 and IL-6, primarily via their ligation of Toll-like receptor 4 that is expressed in macrophages.(28) IL-1 refers to 2 cytokines, IL-1α and IL-1β, which signal through a common receptor, IL-1 receptor type I(29) that may mediate inflammatory changes in target cells, among them production of matrix metalloproteases capable of digesting components of the plaque's protective fibrous cap.

Age and pre-existing CV disease are important risk factors for death during and after acute viral infections. For example, between 2013 and 2017, the influenza-attributable excess death rate in Italy varied by virus strain and season, but consistently the death rate in those over 65 was 5 times that in younger persons, possibly because of the presence of occult or manifest CVD in the elderly(30). In a meta-analysis of over 9000 individuals, influenza was associated with a 5.4% risk of death in patients with history of acute coronary syndromes (ACS), while vaccine against influenza was associated with a lower risk of death by 45%(31).

Prevention of cardiovascular events through vaccination

Vaccination is pivotal in preventing viral and bacterial infections and thus their potentially adverse CV sequelae.(32-34)

Vaccines against viruses: Influenza vaccines reduce the risk of infection with influenza viruses by up to 60% and early trials supported evidence for a reduction in cardiovascular complications following the infection.(35-37) Vaccinated individuals exhibit a 30% reduction in MACE,(38) although observational studies appear to overestimate the benefit compared to randomized controlled trials (RCT).(39, 40)Notably, most previous RCTs studied inactivated influenza vaccines.

Large meta-analyses, observational studies, and a randomized trial yielded similar results, with vaccination resulting in fewer MACE compared to no vaccination or to placebo.(32)·(33)·(34)

Both observational studies and RCTs have evaluated influenza vaccination in patients who had suffered an acute myocardial infarction (AMI) and were vaccinated

during the index hospitalization and documented even under these circumstances an up to 41% reduction in CV mortality (**Table 1, Figure 2**).(41) However, it has to be noted that the IAMI trial was underpowered as it was stopped early due to the COVID-19 pandemic.

The largest published randomized placebo-controlled study to date on influenza vaccines was the IVVE study with >5000 individuals enrolled.(42) The IVVE study was conducted in patients with stable heart failure, of which 30% had ischemic etiology.

The study was neutral for its primary endpoint, but there was reduction in secondary outcomes including pneumonia and hospitalisations.(42) However, non-fatal myocardial infarction, non-fatal stroke, all-cause hospitalisation, and hospitalisation for heart failure were not significantly reduced (Table 1).(42)

High-dose influenza vaccine was compared to standard-dose vaccine in the INVESTED trial in 5,260 patients with high CV risk (**Table 1**).(43) High dose vaccine did not reduce cardiopulmonary hospitalizations or death compared with standard dose vaccine. The authors suggested that the very high number of events in this high-risk population may have diluted a potential benefit of high dose vaccine. In contrast, high-dose vaccine compared with standard dose was associated with reduced CV and respiratory events in lower-risk elderly.(44)

The ongoing DANFLU-2 study (Clinical Trials.gov: ID NCT05517174) is co-powered to assess cardiovascular events and will address this hypothesis (table 1). Results from the corresponding feasibility study DANFLU-1 have already been published (table 1).(45, 46) The **DANFLU-2 Trial** (*A Pragmatic Randomized Trial to evaluate the Effectivness of high-dose Quadrivalent Influenza Vaccine vs. standard-dose Quadrivalent Influenza Vaccine in older adults*) has in the meantime recruited over 300'000 individuals 1 : 1 to either high- or

low-dose quadrivalent Influenza vaccines into a registry based, pragmatic trial with mortality and hospitalizations as primary endpoint and will be reported shortly.

The IAMI trial investigated whether influenza vaccination reduces cardiovascular events in patients with acute myocardial infarction.(34) In a post-hoc analysis comparing early-season vs. late-season vaccination, there was no statistically significant difference in vaccine effectiveness against adverse cardiovascular outcomes at one year.(34) Both early and late vaccination resulted in similar reductions in all-cause death, MI, or stent thrombosis compared to placebo.(34) Although the benefit on all-cause mortality appeared slightly greater with early vaccination, the difference was not statistically significant. (34)

Herpes zoster or shingles has also been associated with CV complications including AMI, stroke and transient ischemic attack (TIA), in particular during the first month following reactivation. A herpes zoster vaccine is more than 90% efficient in preventing the disease(47) and also associated with a strong, over 50% reduction in CV events.(48)

RSV mainly affects children and adults over 60 years of age, particularly those with comorbidities including CV conditions. Cardiac events can occur in 20% of individuals with a prior cardiac condition during an acute infection.(49) In the elderly, the vaccine is 89% effective in preventing lung infections(50) and may also reduce subsequent cardiac events, but solid evidence is still missing. The **DAN-RSV trial** (*Vaccine Effectiveness of a Bivalent RSV Prefusion-F-based Vaccine for preventing RSV Hospitalizations in Older Adults*) is a pragmatic, open label trial that randomized over 130'000 elderly individuals 1:1 to either an RSV vaccine or no RSV vaccine with hospitalisation as the primary endpoint. The results will be reported shortly.

Vaccines against SARS-CoV-2 are effective against infection, with efficacy varying depending on the type of the vaccine and the SARS-CoV-2 strain.(51) Overall, the available vaccines reduce the severity of infection, hospitalization and death.(51) Furthermore, patients with any CVD including heart failure have a much more severe course(15, 16, 52) and an around 30% higher risk of developing long COVID.(53) Vaccination reduces the risk of long COVID by 43%(54),(55).

Finally, human papillomavirus (HPV) infection is also associated with up to a 4-fold risk for atherosclerotic CVD, CAD and stroke.(56) An HPV vaccine appears effective in almost 100% of individuals(57) with one study has shown normalization of the excess CV risk in vaccinated women.(58) Further research is needed to evaluate, if HPV also puts men at higher risk for cardiovascular complications.

Vaccines against bacteria

Vaccination with pneumococcal vaccine is 60-70% effective in preventing an invasive disease course.(59) Furthermore, a meta-analysis has shown that vaccination with the pneumococcal polysaccharide vaccine led to a 10% reduction in any CV event including MI in those of 65 years of age or older.(60)

Recommendations of the European Society of Cardiology (ESC), American College of Cardiology (ACC)/American Heart Association (AHA) guidelines

Chronic Coronary Syndromes: The *2024 ESC Guidelines for the Management of Chronic Coronary Syndromes (CCS)* recommend vaccination against influenza, pneumococcal disease and other widespread infections, e.g. COVID-19 in patients with CCS*(61).* The *2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease* state that "*In patients with*

CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death."(62) They further state: "*In patients with CCD, COVID-19 vaccination is recommended per public health guidelines to reduce COVID-19 complications, and in patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death*."(62) The ACC/AHA Guidelines recommend annual influenza vaccination in patients with ACS without a contraindication to reduce the risk of death and MACE.(63) Thus, international guidelines all recommend influenza vaccinations, particularly in the elderly. The US, but not the ESC Guidelines also recommend pneumococcal vaccination in this population

Heart Failure: The *2021 ESC Guidelines on the Diagnosis and Treatment of Acute and Chronic Heart Failure* recommended that influenza and pneumococcal vaccinations should be considered to prevent heart failure hospitalizations(64). The *AHA/ACC 2022 Guidelines for Heart Failure* note that vaccination was associated with lower risk in observational and randomized trials and state that "*Patients with heart failure should learn to take medications as prescribed, restrict sodium intake, stay physically active, and get vaccinations*."(65) The recommendations further state that "*In patients with heart failure, vaccinating against respiratory illnesses is reasonable to reduce mortality*." (65) The AHA/ACC 2022 guidelines do further note that "*patients with heart failure are uniquely susceptible to poor outcomes in the setting of SARS-CoV-2 infection and should be vaccinated against COVID-19*."(65)

Cardiovascular risks of vaccination

Acute reactions to vaccines: Serious adverse reactions to most vaccinations are very rare with reported incidences below 10 per 100.000,(66) but are more common among

younger individuals.(66) These adverse reactions include myocarditis and pericarditis as well as even less commonly anaphylaxis, immune thrombocytopenia, and encephalitis/meningitis. (66) On the other hand, flu-like symptoms and especially local vaccine adverse reactions may often occur.(43) After influenza vaccination about 25% experience injection site pain.(43) While in a placebo-controlled trial such local reactions were more common after influenza vaccination in the active arm, serious adverse events were similar in both type and incidence and in the placebo groups.(34) Mild to moderate adverse reactions after an influenza vaccine has been related to a reduced risk of cardiopulmonary hospitalization and all-cause mortality in patients with a CVD.(43) Rare anaphylactic reactions to vaccines should be promptly treated as any other anaphylactic reactions. The same holds true for other severe reactions to vaccines. There are no proven specific treatments for vaccine related serious adverse reactions and as such treatment is mainly symptomatic in nature.

Myocarditis after SARS-CoV-2 vaccine: A recent Consensus Document comprehensively summarized the risks of developing myocarditis after SARS-CoV-2 vaccine.(67) Overall, younger individuals have a higher risk of myocarditis in the context of a vaccination against COVID-19 compared to older ones, whom may need vaccination more.(67) Also, myocarditis is more common in young men(67) than in young females, similar to the prevalence of classic myocarditis.(68) It merits emphasis that the risk of developing myocarditis from COVID-19 is 6 times higher than developing myocarditis from the vaccine.(67, 69) Most cases are mild and resolve spontaneously, though rare instances of severe cases have been reported(67).

The mechanisms of myocarditis following vaccination are not well understood. Circulating spike protein have been described in patients with myocarditis.(67, 70) In another study anti-IL-R1 antibodies were elevated in 75% of 14–21-year-old myocarditis patients(71). In contrast, other studies on antibody reaction to the vaccines have demonstrated a robust anti-viral antibody response, but no increase in overall

autoantibody reactivity compared to control groups.(72) Similar to other forms of myocarditis innate immune cells in the heart following rechallenge with antigen through a second dose of vaccine may activate a robust TLR4 and inflammasome mediated, IL-1β pathway driving myocarditis through trained immunity.(73)

Management of vaccine-associated myocarditis: If myocarditis is suspected based on cardiac symptoms such as chest pain within a few weeks of vaccination, testing should include and ECG, troponin, serum natriuretic peptides (BNP or NT-proBNP), and echocardiography.(67) Abnormal results that suggest cardiac injury should prompt cardiac magnetic resonance imaging (CMR) in hemodynamically stable patients.(67) In rare cases with clinically significant arrhythmias or cardiogenic shock, endomyocardial biopsy (EMB) may be useful to confirm myocarditis and exclude more clinically aggressive forms such as giant cell myocarditis(67, 74).

Heart failure and arrhythmias associated with COVID-19 vaccination should be treated according to the respective guidelines.(64, 75, 76) Anti-inflammatory treatments have uncertain value especially in mild cases that often resolve within a few days to weeks. Colchicine may be considered for patients with pericarditis and chest pain and in the context of myopericarditis with normal left ventricular function. As for other forms of myocarditis, exercise cessation is advised for 3-6 months after an episode of vaccine-associated myocarditis(67, 77).

Advice on when, how and who to vaccinate

When, how, and whom to vaccinate remain crucial concerns in daily practice and do require special care and attention (**Table 2**).

Influenza Vaccination: In the United States and China, health authorities recommend a routine annual influenza vaccination for all individuals ≥6 months of age who do not have contraindications(78, 79). In Europe, vaccination recommendations vary according to countries, but are generally limited to persons aged 65 years or older or to those at increased risk of severe disease and influenza-related complications. Vaccination is especially important for people at higher risk of serious influenza complications, e.g. individuals with specific chronic medical conditions, pregnant women, the elderly and healthcare workers.(80) A number of European countries have initiated programs to vaccinate children aged 6-59 months.(80) Recommendations for health care professionals vary substantially.

The ESC Guidelines recommend annual influenza vaccination for patients with established CV disease.(81) This has been particularly reinforced in the last guidelines on heart failure(81) and CAD(82, 83) as the vaccination against influenza has been well established as particularly safe. In CAD, the ESC Guidelines recommend an annual influenza vaccination in patients with stable atherosclerotic cardiovascular disease(82, 83). Furthermore, the ACC/AHA Guidelines recommend annual influenza vaccination in patients with ACS without a contraindication to reduce the risk of death and MACE(63). Vaccine is associated with a reduction of acute MI, an improved prognosis in patients with heart failure, and decreased CV risk in adults aged 65 years and older, as reported in several consistent metanalyses.(84) Above all, influenza vaccination given early after an AMI(34) or in high-risk CAD (35) decreases all-cause and CV death, at one year. These results driven by consistent large trials led to propose influenza vaccination for all patients admitted for ACS, preferentially during index hospitalization.

Obviously, a licensed and age-appropriate vaccine should be used, following national or local approvals. Studies have been designed to compare high-doses versus low-doses of influenza vaccines, but no specific recommendations have been proposed until now. Depending on the seasons and industrial developments, the following types of vaccines are available: Inactivated influenza vaccines, recombinant influenza vaccine, and live attenuated influenza vaccine.

Pneumococcal Vaccination: Recommendations for pneumococcal vaccine allow some flexibility. Indeed, patients can be eligible to receive both pneumococcal conjugated and polysaccharidic vaccines (PCV13 and PPV23 respectively), sequentially, or only PPV23 in specific conditions, and soon new vaccines with only one dose will become available(59). PCV 13 contains 13 pneumococcal serotypes, whereas the 23-valent unconjugated polysaccharide vaccine PPV 23 contains 23 pneumococcal serotypes(59). The combination of the two vaccines (PCV13 and PPV23) makes it possible to obtain a higher immune response than the use of PPV23 alone(59). Persons vaccinated using the previous sequence may receive a repeat injection of PPV23 after 5 years(59). Persons vaccinated for more than one year with PPV23 will receive PCV13 and a revaccination with PPV23 at least 5 years after the last PPV23(59). The necessity of subsequent revaccination is not currently established but is advised by infectious disease specialists.(59)

In the United States and the United Kingdom, health authorities recommend pneumococcal vaccination in patients older than 65 years. It is also recommended after 65 years and earlier in high-risk immunocompetent patients, such as those with chronic CV disease (except hypertension). Based on expert opinion, the ESC Guidelines recommends pneumococcal vaccination in patients with heart failure.(81)

COVID-19 Vaccination: Most countries recommend COVID-19 vaccination in patients with chronic diseases, including CV conditions. The COVID-19 epidemiology is changing fast and new recommendations should be considered, not only regarding the patients prioritized, but also regarding novel vaccines and the virus types circulating within a specific population. The utility of RNA vaccines compared to more classical technologies remain a matter of debate.

General recommendations are well supported also for patients with CV disease. All patients irrespectively of age, sex or comorbidities should follow the recommendations given for the general population. Patients older than 65 years and patients with comorbidities, especially heart failure and CAD, but also diabetes or other immunocompromised situations, should be more strictly advised to get protected.

Other vaccines: Other vaccines are currently under evaluation by national or local health authorities, including vaccines against RSV or herpes zoster. In that regard, a randomized controlled trial studying RSV vaccine in 130 000 individuals is currently underway (ClinicalTrials.gov: ID NCT06684743). These approaches will have to be evaluated in the context of CV disease prevention. Specific sequential or simultaneous schedules have to be evaluated and the hope is to propose combined vaccines, for instance a „winter“ vaccine grouping protection against several viruses to simplify administration.

In practice: Based on the overall increasing evidence for the effectiveness of influenza vaccination in reducing cardiovascular events(85), the influenza vaccine carries a Class IA recommendation in the ESC Guidelines.(81) Similar to statins, this intervention is effective, safe, and inexpensive and it has a substantial impact on this vulnerable population. Classically, vaccination is considered the responsibility of

primary care physicians. However, this strategy does not appear to be optimal given the low current vaccination rates, suggesting that other health-providers should be involved in the future. Every opportunity should be taken to vaccinate patients either during a routine visit or hospitalization, even for acute conditions. The first step to improve vaccination coverage is to improve informing patients, families and health care providers about evidence-based important benefits and low risks of the intervention. Implementation research is underway to study the most effective means to improve vaccination coverage nationwide.(86) In that regard, a study in Denmark evaluated a governmental letter system to deliver electronic letters to individuals of age 65 and older to inform them about the benefits of the influenza vaccine.(86, 87) Overall, the magnitude of effectiveness of this intervention was modest(87), highlighting that offering vaccination during direct patient contact should become a priority in the clinical setting.

Special risk groups and vulnerable populations

An infection specialist should always be consulted before considering vaccinating a patient with a suppressed immune system. Live vaccines are in general contraindicated in immunocompromised patients and inactivated, nonconjugated vaccines may not induce sufficient antibody production. Recent acute cardiac illness does however not seem to be of concern regarding vaccination. A large, randomised clinical trial has proven that influenza vaccination is safe and reduces total and cardiovascular mortality when given within 72 hours of an acute MI. This effect seems to be especially pronounced in non-ST elevation MI (NSTEMI) patients with more comorbidities compared to STEMI patients.(34) It thus seems safe and practical to

introduce a potential vaccination programme already during the in-hospital phase of an acute cardiac condition – although only proven safe and effective for patients with an MI.

Vaccination During Pregnancy: Inactivated vaccines, not containing a live version of the virus they are protecting against, are generally safe during pregnancy (**Table 3**).(88) In contrast, live virus vaccines such as MMR and chickenpox are generally contra-indicated as they can cross the placenta and infect the fetus. However, there is no evidence that any live vaccine may cause birth defects. Live vaccines should therefore be given before or after pregnancy, the latter right after delivery, even during lactation, if indicated.(89)

Some vaccines, such as the tetanus vaccine, are safe during pregnancy if necessary (**Table 2**).

***Congenital heart disease (CHD)*:** Patients with moderate to severe and/or cyanotic CHD and those with pulmonary arterial hypertension (PAH) are advised to have annual influenza vaccination in the fall. There have been no reports of particular concerns regarding COVID-19 vaccination on CHD patients.

Patients with functional asplenia syndrome, commonly -but not exclusively- present with right atrial isomerism (duplication of right sided structures and associated "asplenia"), should receive peunomococcal vaccination (PPV-23) after the age of 2, and have it repeated every 5 years thereafter. Patients with 22q deletion (Di George

Syndrome), a congenital disorder characterized by cellular immune deficiency should generally avoid live vaccines.(90)

It remains unclear as to whether thymectomy, often performed during neonatal cardiac surgery, is a contra-indication for live vaccines.(91) Patients should consult with their CHD Team. Regarding thymectomy, there is often poor documentation in the surgical notes, a practice that must improve as it may have implications on patients.

***Vaccination and heart transplantation (HTX)*:** Heart transplant recipients represent a unique population with heightened susceptibility to infections due to immunosuppression. Vaccination plays a critical role in preventing diseases and reducing the risk of infectious complications post-transplantation. In a large Swiss cohort study of solid organ transplant recipients, 11.9% experienced vaccination preventable infections.(92) Importantly, there was significant morbidity and mortality associated with these infections.(92) Despite this, only around 60% of all transplant candidates undergo pneumococcal vaccination(93) highlighting the need for optimized immunization strategies. Also, a nationwide cohort study in Denmark of solid organ transplant recipients undergoing influenza vaccine reported a reduced risk of all-cause pneumonia admission (aHR, 0.83; 95% CI, 0.69-0.99; p = 0.035) and all-cause mortality (aHR, 0.60; 95% CI, 0.47-0.76; p = 0.001) in vaccinated individuals.(94) The investigators also pointed out that overall vaccination coverage was low (48%) and that vaccination should become a priority in the care of transplant recipients given its benefits.(94) Current International Society for Heart and Lung Transplantation (ISHLT) guidelines recommend completion of live virus vaccination, including measles, mumps and rubella (MMR), varicella, herpes zoster and rotavirus, at least four weeks prior to

transplantation (table 4). Inactivated vaccines including SARS-CoV-2, influenza, pneumococcal, tetanus, pertussis, hepatitis A and B, and human papillomavirus vaccines, should be completed at least two weeks before transplantation (table 4).(95-97) Unfortunately, in these often severely ill patients with secondary organ failure, the response to many vaccines is impaired.(98) Although live attenuated vaccines are generally avoided after transplantation, small studies in pediatric patients after liver transplantation showed good safety profile and efficacy with live attenuated vaccines for measles, mumps rubella and varicella zoster.(99, 100) After transplantation, vaccination is usually not performed within the first 3 to 6 months.(95)

During the SARS-CoV-2 pandemic and with influenza vaccination seroconversion was achieved as early as one month after transplantation, if no induction therapy with a B or T-cell-depleting agent has been carried out.(101, 102) Even after vaccination, heart transplant recipients should continue to adhere to infection prevention measures recommended by health authorities, such as wearing masks, practicing hand hygiene, and avoiding crowded settings, due to their increased vulnerability to infections and decreased seroresponsiveness. Especially steroids, high doses of mycophenolate mofetil and belatacept in maintenance immunosuppressive regimens have been associated with a lower rate of antibody response to vaccination.(55, 102) To ensure an adequate protection from infections, vaccination strategies are also crucial for close contacts.(98)

Influenza in HTX*:* Influenza vaccine with inactivated virus is safe and effective without increasing the risk of either rejection episodes or infections.(101) Health authorities recommend for an annual vaccination that can be administered as early as one month after transplantation to ensure adequate vaccination during influenza

season. The response in transplant recipients is reported to be lower compared with healthy subjects, with 70% of patients having virus specific IGGs.(103, 104)

***Human papillomavirus (HPV) in HTX*:** Transplant recipients are at increased risk of HPV related malignancies. The HPV vaccine should be administered without any age or sex restrictions, if possible, pre-transplantation(105). Vaccination after transplantation can still be beneficial, and it should be considered as part of post-transplant care. The HPV vaccine is available in several formulations, including bivalent, quadrivalent, and nonavalent vaccines. Theoretically, it is advised to consider the nonavalent vaccine as the first choice in solid organ transplant recipients due to its broad coverage of HPV genotypes.(105)

***Pneumococcus in HTX**:* Pneumococcal vaccination should be administered to heart transplant recipients as part of routine care prior to or 3 months at the earliest after heart transplantation and is as safe as it is in non-transplanted patients.(106) Adult heart transplant recipients should receive both the pneumococcal conjugate vaccine (PCV15) and the pneumococcal polysaccharide vaccine (PPSV23) to provide comprehensive protection against pneumococcal disease.(106)

***SARS-CoV-2 in HTX**:* The International Society for Heart and Lung Transplantation (ISHLT) COVID-19 Task Force, advises to delay the SARS-CoV-2 vaccination for at least 1 month after heart transplantation and at least 3 months from the use of T-cell depleting agents or specific B-cell depletion agents.(102) In general, detectable antibodies against the receptor-binding domain of the spike protein of the SARS-CoV-2 virus are demonstrated in 10% to 57% and cellular response in 10% to 70% of HT recipients following 2 doses of mRNA vaccines. Increased intensity of immunosuppression, use of antimetabolites such as mycophenolate, and agents that

inhibit B-cell response are associated with reduced immunogenicity. Despite suboptimal seroconversion rates, vaccination was associated with reduced risk of death from COVID-19 when compared to unvaccinated transplant recipients.(107) The third dose of mRNA vaccination in transplant recipients is associated with an increase in detectable humoral response ranging from 55% to 68%. However, specific heart transplant data in this setting has been sparse as previous studies included only 28 HT patients and HT-specific results were not reported.(108)

***Further direction in HTX*:** Novel vaccine formulations, including high-dose influenza vaccines and adjuvanted vaccines, have demonstrated enhanced immunogenicity in immunocompromised individuals, potentially addressing the diminished vaccine response observed in heart transplant recipients. Furthermore, the development of mRNA vaccines has revolutionized vaccine delivery, offering the prospect of improved efficacy and safety profiles.

Limited data on vaccine effectiveness and safety in this specific population underscore the need for further research to guide evidence-based recommendations. Additionally, logistical challenges, such as vaccine availability, accessibility, and vaccine hesitancy among transplant recipients, their relatives and healthcare providers, pose significant hurdles to achieving high vaccination coverage rates. By optimizing vaccination practices, we can mitigate the burden of vaccine-preventable infections and improve long-term outcomes in this vulnerable population.

Existing Knowledge Gaps

Influenza vaccination demonstrates a significant protective effect in the acute post-MI period supported by the IAMI trial and a meta-analysis of other randomized controlled

trials,(41),(32) but only a modest benefit in stable CAD and stable heart failure, as demonstrated in IVVE, and indirectly in the INVESTED and the DANFLU-1 trial.

Its protective effect on hard outcomes after MI exceeds its impact on influenza infection alone and appears to persist beyond the influenza season. This raises important research questions: What are the additional effects/mechanisms of influenza vaccine in addition to preventing respiratory infection? Should influenza vaccination be administered year-round? Should MI patients receive a booster, if vaccinated earlier in the season? Additionally, emerging evidence suggests that influenza and other vaccines may reduce inflammation through trained immunity mechanisms.(109) (110) Additional evidence from randomized, placebo-controlled trials is necessary for other types of vaccines such as herpes zoster to assess the potential benefits of vaccination against the most common viruses linked to cardiovascular events. Furthermore, mechanistic studies are needed to gain deeper insight into why these types of vaccines reduce the risk of MACE.

Summary and Outlook

Vaccination has been among the greatest achievements of science-based medicine and has prevented millions of patients from infections and premature death. Beyond prevention infection and its sequelae, vaccinations have profound effects on the CV risk and as such should be considered the fourth pilar of medical CV prevention besides antihypertensives, lipid lowering drugs and medications that treat diabetes. International guidelines support such a concept and recommend vaccination in patients at risk for MACE such as those with coronary artery disease and heart failure.

Nevertheless, several knowledge gaps remain. While evidence of influenza, SARS-CoV-2 and pneumococcus is reasonably solid, more data are required for other vaccinations. Furthermore, while there are trials and large registries for common CV

conditions, less is known in patients with rarer diseases. Thus, further trials are needed with some vaccinations and in CV patient populations other than those with coronary artery disease and/or heart failure.

Acknowledgements

We thank Maximilian Müller for his support designing the graphical abstract.

References

1. Khan MS, Shahid I, Bennis A, Rakisheva A, Metra M, Butler J. Global epidemiology of heart failure. Nature reviews Cardiology. 2024.
2. Magnussen C, Ojeda FM, Leong DP, Alegre-Diaz J, Amouyel P, Aviles-Santa L, et al. Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality. The New England journal of medicine. 2023;389(14):1273-85.
3. Mohebi R, Chen C, Ibrahim Nasrien E, McCarthy Cian P, Gaggin Hanna K, Singer Daniel E, et al. Cardiovascular Disease Projections in the United States Based on the 2020 Census Estimates. Journal of the American College of Cardiology. 2022;80(6):565-78.
4. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. European journal of heart failure. 2020;22(8):1342-56.
5. Mensah GA, Fuster V, Murray CJL, Roth GA, Global Burden of Cardiovascular D, Risks C. Global Burden of Cardiovascular Diseases and Risks, 1990-2022. Journal of the American College of Cardiology. 2023;82(25):2350-473.
6. Pirillo A, Norata GD. The burden of hypercholesterolemia and ischemic heart disease in an ageing world. Pharmacol Res. 2023;193:106814.
7. Libby P, Hansson GK. From Focal Lipid Storage to Systemic Inflammation: JACC Review Topic of the Week. Journal of the American College of Cardiology. 2019;74(12):1594-607.
8. Kaptoge S, Seshasai SR, Gao P, Freitag DF, Butterworth AS, Borglykke A, et al. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. European heart journal. 2014;35(9):578-89.
9. Modin D, Claggett B, Johansen ND, Solomon SD, Trebbien R, Grove Krause T, et al. Excess Mortality and Hospitalizations Associated With Seasonal Influenza in Patients With Heart Failure. Journal of the American College of Cardiology. 2024;84(25):2460-7.
10. Chaves SS, Nealon J, Burkart KG, Modin D, Biering-Sorensen T, Ortiz JR, et al. Global, regional and national estimates of influenza-attributable ischemic heart disease mortality. EClinicalMedicine. 2023;55:101740.

11. Kytomaa S, Hegde S, Claggett B, Udell JA, Rosamond W, Temte J, et al. Association of Influenza-like Illness Activity With Hospitalizations for Heart Failure: The Atherosclerosis Risk in Communities Study. JAMA Cardiol. 2019;4(4):363-9.
12. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020;5(7):831-40.
13. Modin D, Claggett B, Sindet-Pedersen C, Lassen MCH, Skaarup KG, Jensen JUS, et al. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. Circulation. 2020;142(21):2080-2.
14. Bhatt AS, Jering KS, Vaduganathan M, Claggett BL, Cunningham JW, Rosenthal N, et al. Clinical Outcomes in Patients With Heart Failure Hospitalized With COVID-19. JACC Heart failure. 2021;9(1):65-73.
15. Tomasoni D, Inciardi RM, Lombardi CM, Tedino C, Agostoni P, Ameri P, et al. Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the Cardio-COVID-Italy multicentre study. European journal of heart failure. 2020;22(12):2238-47.
16. Inciardi RM, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. European heart journal. 2020;41(19):1821-9.
17. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. The New England journal of medicine. 2004;351(25):2611-8.
18. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. The New England journal of medicine. 2018;378(4):345-53.
19. Ito T, Akamatsu K, Fujita SI, Kanzaki Y, Ukimura A, Hoshiga M. Transient depression of myocardial function after influenza virus infection: A study of echocardiographic tissue imaging. PloS one. 2019;14(8):e0221628.
20. Haidari M, Wyde PR, Litovsky S, Vela D, Ali M, Casscells SW, et al. Influenza virus directly infects, inflames, and resides in the arteries of atherosclerotic and normal mice. Atherosclerosis. 2010;208(1):90-6.
21. Naghavi M, Wyde P, Litovsky S, Madjid M, Akhtar A, Naguib S, et al. Influenza infection exerts prominent inflammatory and thrombotic effects on the atherosclerotic plaques of apolipoprotein E-deficient mice. Circulation. 2003;107(5):762-8.
22. Lin YH, Platt MP, Gilley RP, Brown D, Dube PH, Yu Y, et al. Influenza Causes MLKL-Driven Cardiac Proteome Remodeling During Convalescence. Circulation research. 2021;128(5):570-84.
23. Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V, et al. Inflammation, Immunity, and Infection in Atherothrombosis: JACC Review Topic of the Week. Journal of the American College of Cardiology. 2018;72(17):2071-81.
24. Libby P, Egan D, Skarlatos S. Roles of infectious agents in atherosclerosis and restenosis: an assessment of the evidence and need for future research. Circulation. 1997;96(11):4095-103.
25. Hemmat N, Ebadi A, Badalzadeh R, Memar MY, Baghi HB. Viral infection and atherosclerosis. Eur J Clin Microbiol Infect Dis. 2018;37(12):2225-33.
26. Andraws R, Berger JS, Brown DL. Effects of antibiotic therapy on outcomes of patients with coronary artery disease: a meta-analysis of randomized controlled trials. Jama. 2005;293(21):2641-7.

27. Rossmann A, Henderson B, Heidecker B, Seiler R, Fraedrich G, Singh M, et al. T-cells from advanced atherosclerotic lesions recognize hHSP60 and have a restricted T-cell receptor repertoire. Exp Gerontol. 2008;43(3):229-37.
28. Maier W, Altwegg LA, Corti R, Gay S, Hersberger M, Maly FE, et al. Inflammatory markers at the site of ruptured plaque in acute myocardial infarction: locally increased interleukin-6 and serum amyloid A but decreased C-reactive protein. Circulation. 2005;111(11):1355-61.
29. Sims JE, Smith DE. The IL-1 family: regulators of immunity. Nature reviews Immunology. 2010;10(2):89-102.
30. Rosano A, Bella A, Gesualdo F, Acampora A, Pezzotti P, Marchetti S, et al. Investigating the impact of influenza on excess mortality in all ages in Italy during recent seasons (2013/14-2016/17 seasons). Int J Infect Dis. 2019;88:127-34.
31. Behrouzi B, Bhatt DL, Cannon CP, Vardeny O, Lee DS, Solomon SD, et al. Association of Influenza Vaccination With Cardiovascular Risk: A Meta-analysis. JAMA Netw Open. 2022;5(4):e228873.
32. Udell JA, Zawi R, Bhatt DL, Keshtkar-Jahromi M, Gaughran F, Phrommintikul A, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. Jama. 2013;310(16):1711-20.
33. Modin D, Jørgensen ME, Gislason G, Jensen JS, Køber L, Claggett B, et al. Influenza Vaccine in Heart Failure. Circulation. 2019;139(5):575-86.
34. Fröbert O, Götberg M, Erlinge D, Akhtar Z, Christiansen EH, MacIntyre CR, et al. Influenza Vaccination After Myocardial Infarction: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. Circulation. 2021;144(18):1476-84.
35. Phrommintikul A, Kuanprasert S, Wongcharoen W, Kanjanavanit R, Chaiwarith R, Sukonthasarn A. Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome. European heart journal. 2011;32(14):1730-5.
36. Gurfinkel EP, Leon de la Fuente R, Mendiz O, Mautner B. Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) Study. European heart journal. 2004;25(1):25-31.
37. Ciszewski A, Bilinska ZT, Brydak LB, Kepka C, Kruk M, Romanowska M, et al. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. European heart journal. 2008;29(11):1350-8.
38. Omidi F, Zangiabadian M, Shahidi Bonjar AH, Nasiri MJ, Sarmastzadeh T. Influenza vaccination and major cardiovascular risk: a systematic review and meta-analysis of clinical trials studies. Scientific reports. 2023;13(1):20235.
39. Liu R, Fan Y, Patel A, Liu H, Du X, Liu B, et al. The association between influenza vaccination, cardiovascular mortality and hospitalization: A living systematic review and prospective meta-analysis. Vaccine. 2024;42(5):1034-41.
40. Modin D, Lassen MCH, Claggett B, Johansen ND, Keshtkar-Jahromi M, Skaarup KG, et al. Influenza vaccination and cardiovascular events in patients with ischaemic heart disease and heart failure: A meta-analysis. European journal of heart failure. 2023;25(9):1685-92.
41. Maniar YM, Al-Abdouh A, Michos ED. Influenza Vaccination for Cardiovascular Prevention: Further Insights from the IAMI Trial and an Updated Meta-analysis. Current cardiology reports. 2022;24(10):1327-35.
42. Loeb M, Roy A, Dokainish H, Dans A, Palileo-Villanueva LM, Karaye K, et al. Influenza vaccine to reduce adverse vascular events in patients with heart failure: a multinational

randomised, double-blind, placebo-controlled trial. Lancet Glob Health. 2022;10(12):e1835-e44.
43. Peikert A, Claggett BL, Udell JA, Joseph J, Hegde SM, Kim K, et al. Influenza Vaccine Immune Response in Patients With High-Risk Cardiovascular Disease: A Secondary Analysis of the INVESTED Randomized Clinical Trial. JAMA Cardiology. 2024;9(6):574-81.
44. DiazGranados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine. 2015;33(38):4988-93.
45. Christensen J, Johansen ND, Janstrup KH, Modin D, Skaarup KG, Nealon J, et al. Time of day for vaccination, outcomes, and relative effectiveness of high-dose vs. standard-dose quadrivalent influenza vaccine: A post hoc analysis of the DANFLU-1 randomized clinical trial. J Infect. 2024;89(5):106276.
46. Johansen ND, Modin D, Nealon J, Samson S, Salamand C, Loiacono MM, et al. A Pragmatic Randomized Feasibility Trial of Influenza Vaccines. NEJM Evid. 2023;2(2):EVIDoa2200206.
47. . https://wwwcdcgov/vaccines/vpd/shingles/public/shingrix/.
48. Mbinta JF, Wang AX, Nguyen BP, Paynter J, Awuni PMA, Pine R, et al. Herpes zoster vaccine safety in the Aotearoa New Zealand population: a self-controlled case series study. Nature Communications. 2023;14(1):4330.
49. Woodruff RC, Melgar M, Pham H, Sperling LS, Loustalot F, Kirley PD, et al. Acute Cardiac Events in Hospitalized Older Adults With Respiratory Syncytial Virus Infection. JAMA Internal Medicine. 2024;184(6):602-11.
50. https://www.cdc.gov/rsv/vaccines/older-adults.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fvpd%2Frsv%2Fpublic%2Folder-adults.html.
51. Thomas SJ, Moreira ED, Jr., Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. The New England journal of medicine. 2021;385(19):1761-73.
52. Anker SD, Butler J, Khan MS, Abraham WT, Bauersachs J, Bocchi E, et al. Conducting clinical trials in heart failure during (and after) the COVID-19 pandemic: an Expert Consensus Position Paper from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European heart journal. 2020;41(22):2109-17.
53. Pilishvili T, Gierke R, Fleming-Dutra KE, Farrar JL, Mohr NM, Talan DA, et al. Effectiveness of mRNA Covid-19 Vaccine among U.S. Health Care Personnel. The New England journal of medicine. 2021;385(25):e90.
54. Tsampasian V, Elghazaly H, Chattopadhyay R, Debski M, Naing TKP, Garg P, et al. Risk Factors Associated With Post−COVID-19 Condition: A Systematic Review and Meta-analysis. JAMA Internal Medicine. 2023;183(6):566-80.
55. Rosano G, Jankowska EA, Ray R, Metra M, Abdelhamid M, Adamopoulos S, et al. COVID-19 vaccination in patients with heart failure: a position paper of the Heart Failure Association of the European Society of Cardiology. European journal of heart failure. 2021;23(11):1806-18.
56. Cheong HS, Chang Y, Kim Y, Kwon MJ, Cho Y, Kim B, et al. Human papillomavirus infection and cardiovascular mortality: a cohort study. European heart journal. 2024;45(12):1072-82.
57. https://www.cdc.gov/vaccines/vpd/hpv/hcp/vaccines.html.

58. Liang X, Chou OHI, Cheung BMY. The Effects of Human Papillomavirus Infection and Vaccination on Cardiovascular Diseases, NHANES 2003-2016. The American journal of medicine. 2023;136(3):294-301.e2.
59. https://www.cdc.gov/vaccines/vpd/pneumo/hcp/about-vaccine.html.
60. Marra F, Zhang A, Gillman E, Bessai K, Parhar K, Vadlamudi NK. The protective effect of pneumococcal vaccination on cardiovascular disease in adults: A systematic review and meta-analysis. Int J Infect Dis. 2020;99:204-13.
61. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. European heart journal. 2024.
62. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2023;148(9):e9-e119.
63. Rao SV, O'Donoghue ML, Ruel M, Rab T, Tamis-Holland JE, Alexander JH, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2025;151(13):e771-e862.
64. Authors/Task Force M, McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. European journal of heart failure. 2022;24(1):4-131.
65. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032.
66. Altman NL, Berning AA, Mann SC, Quaife RA, Gill EA, Auerbach SR, et al. Vaccination-Associated Myocarditis and Myocardial Injury. Circulation research. 2023;132(10):1338-57.
67. Heidecker B, Dagan N, Balicer R, Eriksson U, Rosano G, Coats A, et al. Myocarditis following COVID-19 vaccine: incidence, presentation, diagnosis, pathophysiology, therapy, and outcomes put into perspective. A clinical consensus document supported by the Heart Failure Association of the European Society of Cardiology (ESC) and the ESC Working Group on Myocardial and Pericardial Diseases. European journal of heart failure. 2022.
68. Thevathasan T, Kenny MA, Gaul AL, Paul J, Krause FJ, Lech S, et al. Sex and Age Characteristics in Acute or Chronic Myocarditis: A Descriptive, Multicenter Cohort Study. JACC: Advances. 2024;3(4):100857.
69. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. The New England journal of medicine. 2021;385(12):1078-90.
70. Yonker LM, Swank Z, Bartsch YC, Burns MD, Kane A, Boribong BP, et al. Circulating Spike Protein Detected in Post-COVID-19 mRNA Vaccine Myocarditis. Circulation. 2023;147(11):867-76.
71. Thurner L, Kessel C, Fadle N, Regitz E, Seidel F, Kindermann I, et al. IL-1RA Antibodies in Myocarditis after SARS-CoV-2 Vaccination. The New England journal of medicine. 2022;387(16):1524-7.

72. Jaycox JR, Lucas C, Yildirim I, Dai Y, Wang EY, Monteiro V, et al. SARS-CoV-2 mRNA vaccines decouple anti-viral immunity from humoral autoimmunity. Nature Communications. 2023;14(1):1299.
73. Moorlag S, Roring RJ, Joosten LAB, Netea MG. The role of the interleukin-1 family in trained immunity. Immunological reviews. 2018;281(1):28-39.
74. Basso C. Myocarditis. The New England journal of medicine. 2022;387(16):1488-500.
75. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European heart journal. 2023;44(37):3627-39.
76. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. European heart journal. 2022;43(40):3997-4126.
77. Patriki D, Baltensperger N, Berg J, Cooper LT, Kissel CK, Kottwitz J, et al. A Prospective Pilot Study to Identify a Myocarditis Cohort who may Safely Resume Sports Activities 3 Months after Diagnosis. Journal of cardiovascular translational research. 2021;14(4):670-3.
78. Grohskopf LA, Alyanak E, Ferdinands JM, Broder KR, Blanton LH, Talbot HK, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021-22 Influenza Season. MMWR Recomm Rep. 2021;70(5):1-28.
79. [Technical guidelines for seasonal influenza vaccination in China (2023-2024)]. Zhonghua Liu Xing Bing Xue Za Zhi. 2023;44(10):1507-30.
80. https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/seasonal-influenza-vaccines.
81. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European heart journal. 2021;42(36):3599-726.
82. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. European heart journal. 2021;42(34):3227-337.
83. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European heart journal. 2020;41(3):407-77.
84. Gupta R, Quy R, Lin M, Mahajan P, Malik A, Sood A, et al. Role of Influenza Vaccination in Cardiovascular Disease: Systematic Review and Meta-Analysis. Cardiol Rev. 2023.
85. Davidson JA, Banerjee A, Douglas I, Leyrat C, Pebody R, McDonald HI, et al. Primary prevention of acute cardiovascular events by influenza vaccination: an observational study. European heart journal. 2023;44(7):610-20.
86. Lassen MCH, Johansen ND, Vaduganathan M, Bhatt AS, Lee SG, Modin D, et al. Electronically Delivered Nudges to Increase Influenza Vaccination Uptake in Older Adults With Diabetes: A Secondary Analysis of the NUDGE-FLU Trial. JAMA Netw Open. 2023;6(12):e2347630.
87. Johansen ND, Vaduganathan M, Bhatt AS, Lee SG, Modin D, Claggett BL, et al. Electronic nudges to increase influenza vaccination uptake in Denmark: a nationwide, pragmatic, registry-based, randomised implementation trial. Lancet. 2023;401(10382):1103-14.

88. Siu W, Sinilaite A, Papenburg J. Summary of the National Advisory Committee on Immunization (NACI) Updated Guidance on Influenza Vaccination During Pregnancy. Can Commun Dis Rep. 2024;50(3-4):86-92.
89. Razai MS, Mansour R, Ravindran P, Freeman S, Mason-Apps C, Morris J, et al. Facilitators and barriers to vaccination uptake in pregnancy: A qualitative systematic review. PloS one. 2024;19(4):e0298407.
90. Mustillo PJ, Sullivan KE, Chinn IK, Notarangelo LD, Haddad E, Davies EG, et al. Clinical Practice Guidelines for the Immunological Management of Chromosome 22q11.2 Deletion Syndrome and Other Defects in Thymic Development. Journal of clinical immunology. 2023;43(2):247-70.
91. Leone DM, Park HJ, Unlu S, Gurvitz M, Kang I, Elder RW. T Cell Response to Influenza Vaccination Remains Intact in Adults with Congenital Heart Disease Who Underwent Early Thymectomy. Int J Cardiol Congenit Heart Dis. 2022;8.
92. Walti LN, Mugglin C, Mombelli M, Manuel O, Hirsch HH, Khanna N, et al. Vaccine-Preventable Infections Among Solid Organ Transplant Recipients in Switzerland. JAMA Network Open. 2023;6(4):e2310687-e.
93. Dendle C, Stuart RL, Mulley WR, Holdsworth SR. Pneumococcal vaccination in adult solid organ transplant recipients: A review of current evidence. Vaccine. 2018;36(42):6253-61.
94. Harboe ZB, Modin D, Gustafsson F, Perch M, Gislason G, Sorensen SS, et al. Effect of influenza vaccination in solid organ transplant recipients: A nationwide population-based cohort study. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2022;22(10):2409-17.
95. Velleca A, Shullo MA, Dhital K, Azeka E, Colvin M, DePasquale E, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2023;42(5):e1-e141.
96. Danzinger-Isakov L, Kumar D, Practice ASTIDCo. Guidelines for vaccination of solid organ transplant candidates and recipients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009;9 Suppl 4:S258-62.
97. Peled Y, Ducharme A, Kittleson M, Bansal N, Stehlik J, Amdani S, et al. International Society for Heart and Lung Transplantation Guidelines for the Evaluation and Care of Cardiac Transplant Candidates-2024. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2024.
98. Vigano M, Beretta M, Lepore M, Abete R, Benatti SV, Grassini MV, et al. Vaccination Recommendations in Solid Organ Transplant Adult Candidates and Recipients. Vaccines (Basel). 2023;11(10).
99. Pittet LF, Verolet CM, McLin VA, Wildhaber BE, Rodriguez M, Cherpillod P, et al. Multimodal safety assessment of measles-mumps-rubella vaccination after pediatric liver transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2019;19(3):844-54.
100. Posfay-Barbe KM, Pittet LF, Sottas C, Grillet S, Wildhaber BE, Rodriguez M, et al. Varicella-zoster immunization in pediatric liver transplant recipients: safe and immunogenic. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(11):2974-85.

101. Perez-Romero P, Bulnes-Ramos A, Torre-Cisneros J, Gavalda J, Aydillo TA, Moreno A, et al. Influenza vaccination during the first 6 months after solid organ transplantation is efficacious and safe. Clin Microbiol Infect. 2015;21(11):1040 e11-8.
102. https://www.ishlt.org/docs/default-source/default-document-library/2022-10-ishlt-covid19-vaccination-pre-exposure-prophylaxis-in-hltx.pdf?sfvrsn=2544395b_1
103. White-Williams C, Brown R, Kirklin J, St Clair K, Keck S, O'Donnell J, et al. Improving clinical practice: should we give influenza vaccinations to heart transplant patients? The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2006;25(3):320-3.
104. Lagler H, Wenisch JM, Tobudic S, Gualdoni GA, Rodler S, Rasoul-Rockenschaub S, et al. Pandemic influenza A H1N1 vaccine in recipients of solid organ transplants: immunogenicity and tolerability outcomes after vero cell derived, non-adjuvanted, whole-virion vaccination. Vaccine. 2011;29(40):6888-93.
105. Vinkenes E, Nielsen MA, Blaakaer J. Is there evidence for efficacy of human papillomavirus vaccination in solid organ transplant recipients? Eur J Obstet Gynecol Reprod Biol X. 2019;4:100015.
106. Kobayashi M, Pilishvili T, Farrar JL, Leidner AJ, Gierke R, Prasad N, et al. Pneumococcal Vaccine for Adults Aged >/=19 Years: Recommendations of the Advisory Committee on Immunization Practices, United States, 2023. MMWR Recomm Rep. 2023;72(3):1-39.
107. Aslam S, Ison MG. SARS-CoV-2 vaccination in heart transplantation: What we do and do not know. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2022;41(2):158-60.
108. Peled Y, Ram E, Lavee J, Sternik L, Segev A, Wieder-Finesod A, et al. BNT162b2 vaccination in heart transplant recipients: Clinical experience and antibody response. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2021;40(8):759-62.
109. Aïdoud A, Gana W, Poitau F, Fougère B, Angoulvant D. Does the influenza A vaccine have a direct atheroprotective effect? Archives of cardiovascular diseases. 2022;115(6-7):331-4.
110. Hjelholt AJ, Bergh C, Bhatt DL, Fröbert O, Kjolby MF. Pleiotropic Effects of Influenza Vaccination. Vaccines. 2023;11(9):1419.
111. Xu S-w, Ilyas I, Weng J-p. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. Acta Pharmacologica Sinica. 2023;44(4):695-709.

Figure legends

Graphical abstract: Both healthy individuals (top middle box) and susceptible risk groups (lower middle box) are protected through specific vaccines from pathogens associated with an increase cardiovascular risk (left box), but potentially also from cardiovascular events as well (right box)

Figure 1: Pathogens such as COVID-19 by inhalation of the virus affect number of organs in the body (left picture). Organ damage is determined by the balance between the activation of hazardous mechanisms (orange) and protective mechanisms (dark blue). Modified from: https://www.nature.com/articles/s41401-022-00998-0(111)

Figure 2: Reduction of cardiovascular events through influenza vaccination myocardial infarction.

Results from the IAMI trial: Kaplan-Meier event curves of the influenza vaccine and placebo groups for the primary composite end point of all-cause death, myocardial infarction, or stent thrombosis in a time-to-event analysis (A) for all-cause death, (B) cardiovascular death, (C) and for myocardial infarction (D). The study was stopped early due to the COVID-19 pandemic and was underpowered as a consequence. Abbreviations: AMI: Acute myocardial infarction; CV: cardiovascular. *From: Fröbert at al, Circulation, 2021*(34)

1
2
3