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Vaccines and cardiovascular outcomes: lessons learned from influenza epidemics

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Cardiovascular disease (CVD) is the leading cause of death in the world and is largely preventable. An increasing amount of evidence suggests that annual influenza vaccination reduces CVD-related morbidity and mortality. Despite various clinical guidelines recommending annual influenza vaccination for the general population for influenza-like illness risk reduction, with a particular emphasis on people with CVD, vaccination rates fall consistently below the goal established by the World Health Organization. This review outlines the importance of influenza vaccination, mechanisms of cardiovascular events in influenza, summarizing the available literature on the effects of influenza vaccine in CVD and the benefits of influenza vaccine during the COVID-19 pandemic.

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Introduction

While the global estimates of influenza disease frequently emphasize the burden of respiratory symptoms, epidemiological data have shown the effects of influenza on cardiovascular disease (CVD) outcomes.[1] According to the World Health Organization (WHO), influenza kills up to 650 000 people annually and remains among the top 10 leading causes of mortality for all ages, particularly for those with one or more comorbid conditions like CVD.[2] Before the coronavirus disease 2019 (COVID-19), an estimated 29 million people in the USA contracted influenza between 2018 and 2019 flu season, hospitalizations numbered close to 380 000 and fatalities exceeded 27 000.[3] All-cause influenza-attributable mortality was estimated to be 25.4 per 100 000 population and 118.2 per 100 000 for adults aged 65 years in the 2017–18 influenza season in Europe.[4]

Therefore, the WHO and the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices make annual recommendations for the composition of the influenza vaccine to manufacturers. Various clinical guidelines recommend annual influenza vaccination for the general population for influenza-like illness risk reduction, with particular emphasis on people with CVD.[5–7] The European Society of Cardiology guidelines (ESC-2019) and the American Heart Association and the American College of Cardiology (AHA/ACC-2006) joint guidelines suggest a Class I (Level of Evidence B) recommendation for influenza vaccination for all patients with CVD.[5,8]

The economic burden of seasonal influenza is substantial concerning direct healthcare and indirect societal costs, stemming from the associated morbidity and mortality with estimated productivity losses.[4] Therefore, given the critical relevance of this issue, we reviewed the sources of evidence to understand the mechanism of CVD complications associated with influenza, the effects of influenza vaccine on CVD based on randomized and observational studies, global trends and predictors associated with the vaccination uptake, and potential implications and relevance to the current COVID-19 pandemic.

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Mechanism of cardiovascular events in influenza

Studies conducted in the early 1900s following the influenza pandemic revealed a relationship between the increase in major adverse cardiovascular events (MACE), notably myocardial infarction (MI) and stroke, coinciding with or soon following an influenza epidemic.[9,10] A century later, in 2017, influenza remains a significant cause of CVD complications. One in eight patients hospitalized with influenza had an acute cardiovascular (CV) event, with 31% of those requiring intensive care and 7% ultimately dying in the USA.[11] Atherosclerosis is an inflammatory response culminating in a plaque comprised of a core rich in lipids, pro-inflammatory cells and cytokines, and a fibrous cap. It is thought that influenza acts by a cascade of biological events, including the inflammatory release of cytokines that causes a pro-thrombotic state, atherosclerotic plaque destabilization and subsequent thrombosis, immune complex deposition in atherosclerotic plaques, and increased macrophage circulation leading to coronary vascular events. In addition, physiological effects such as hypoxia and tachycardia can further mediate iscahemia in subcritical stenosed vessels (*Figure 1*).[12–14] Other mechanisms include sympathetic nervous system activation with subsequent effects on vascular tone with vasoconstriction; epithelial dysfunction; insufficient coronary artery blood flow with fever and tachycardia, volume overload, and arrhythmia.[2,15] Finally, influenza produces direct effects on the heart to cause myocarditis. Histopathological and molecular studies on influenza-infected mice have shown that the virus can be isolated from heart tissue and that its presence leads to local inflammatory changes.[16]

Effects of influenza vaccine on CVD

Randomized controlled trials

Multiple randomized controlled trials (RCTs) have shown inconsistent results regarding the effects of influenza vaccination in patients with CVD (*Table 1*). The Flu Vaccination Acute Coronary Syndrome (FLUVACS) study was a single-blind RCT of 301 patients with MI or stable CAD scheduled for PCI.[17] The FLUVACS showed a significantly lower CV death rate with the vaccine than the placebo at 1 year (6.2 vs. 17.7%, $P=0.002$).[17,37,38] On the other hand, Influenza Vaccination in Secondary Prevention from Coronary Ischemic Events in Coronary Artery Disease (FLUCAD) study found no improvement in CV death after influenza vaccination at 12 months (3.0 vs. 5.8%, $P=0.13$). However, the rates of coronary ischaemic events over 12 months were significantly lower with the vaccine than placebo (6.02 vs. 9.97%, $P=0.04$).[18] The Efficacy of Influenza Vaccine in Reducing Cardiovascular Events in Patients with Coronary Artery Disease (IVCAD) trial found no reduction in CV death or MI at 1 year with the vaccine vs. placebo (29 vs. 26%, $P=0.60$).[39] In contrast, the study by Phrommintikul and colleagues[20] was a prospective randomized open-label trial that showed a lower risk of major CV events [unadjusted hazard ratio (HR) 0.70 (95% CI: 0.57–0.86)] but no reduction in CV death.

Evidence exists that elderly patients with underlying CVD may mount a less vigorous response to standard-dose influenza vaccination.[40,41] The Influenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated Heart Failure (INVESTED) study compared standard-dose with high-dose influenza vaccination in patients with recent MI or heart failure (HF) hospitalization in patients (mean age: 66 years) and found no reduction in all-cause mortality or cardiopulmonary hospitalizations compared with the standard dose [HR, 1.06 (95% CI: 0.97–1.17)].[21] The Influenza Vaccine to Prevent Adverse Vascular Events (IVVE) trial evaluated influenza vaccination among patients with symptomatic HF and reported that influenza vaccination did not reduce the primary composite outcome at 36 months [HR, 0.93 (95% CI: 0.81–1.07)]. The IAMI (Influenza Vaccination After Myocardial Infarction) study, a double-blind, randomized clinical trial to test whether influenza vaccination given early after admission for MI or high-risk CAD can reduce MACE within 12 months of the index event, has shown that the primary outcome was lower in the vaccine vs. control [HR, 0.72 (95% CI: 0.52–0.99)]. The vaccinated group also experienced fewer secondary outcomes of all-cause mortality [HR, 0.59 (95% CI: 0.39–0.89)] and CV mortality [HR, 0.59 (95% CI: 0.39–0.90)].[24] The authors subsequently pooled their results with the FLUCAD, FLUVACS, and study by Phrommintikul *et al.* to find a 49% relative risk (RR) reduction in CV mortality [HR, 0.51 (0.36–0.71)].[17,18,20,24]

Observational studies

Several observational studies have studied the association between the vaccine and CV outcomes (*Table 1*).[31,35,42–46] A self-controlled case-series study has shown reduction in acute MI [RR, 0.68 (95% CI: 0.60–0.78)] at 1–14 days after vaccination compared with the baseline period [RR, 0.82 (95% CI: 0.75–0.90)] at 29–59 days. Early seasonal vaccinations showed more pronounced reductions in MI.[42] Another population-based case–control study examined the association of influenza vaccination with a reduced risk of out-of-hospital primary cardiac arrest [odds ratio (OR), 0.51 (95% CI: 0.33–0.79)].[45] In the older cohort (>65 years), during the 1998–99 and 1999–2000 influenza seasons. Vaccination was associated with a reduction in the risk of hospitalization for cardiac disease [OR, 0.81 (95% CI: 0.73–0.89)], cerebrovascular disease [OR, 0.84 (95% CI: 0.72–0.97)] during the 1998–99 season as well as 1999–2000 season [OR, 0.77 (95% CI: 0.66–0.89)]. There was also a reduction in the risk of all-cause death [OR, 0.52 (95% CI: 0.47–0.57)] during the 1998–99 and [OR, 0.50 (95% CI: 0.46–0.55)] 1999–2000 seasons.[46]

The United Kingdom General Practice Research Database (2001 and 2007) showed that influenza vaccination was associated with a reduced rate of acute MI [adjusted OR, 0.81 (95% CI: 0.77–0.85)]. Early seasonal influenza vaccination was associated with a lower rate of acute MI [adjusted OR, 0.79 (95% CI: 0.75–0.83)] than vaccination during the late season [adjusted OR, 0.88 (95% CI: 0.79–0.97)].[44] The Denmark data showed that for patients with HF, vaccination was associated with a reduced risk of both all-cause [adjusted HR, 0.82 (95% CI: 0.81–0.84)] and CV death [adjusted HR, 0.82 (95% CI: 0.81–0.84)].

Meta-analyses of randomized clinical trials and observational studies

Given considerable variability in the results of randomized and observational studies regarding the efficacy of the influenza vaccine for CVD prevention, meta-analyses of

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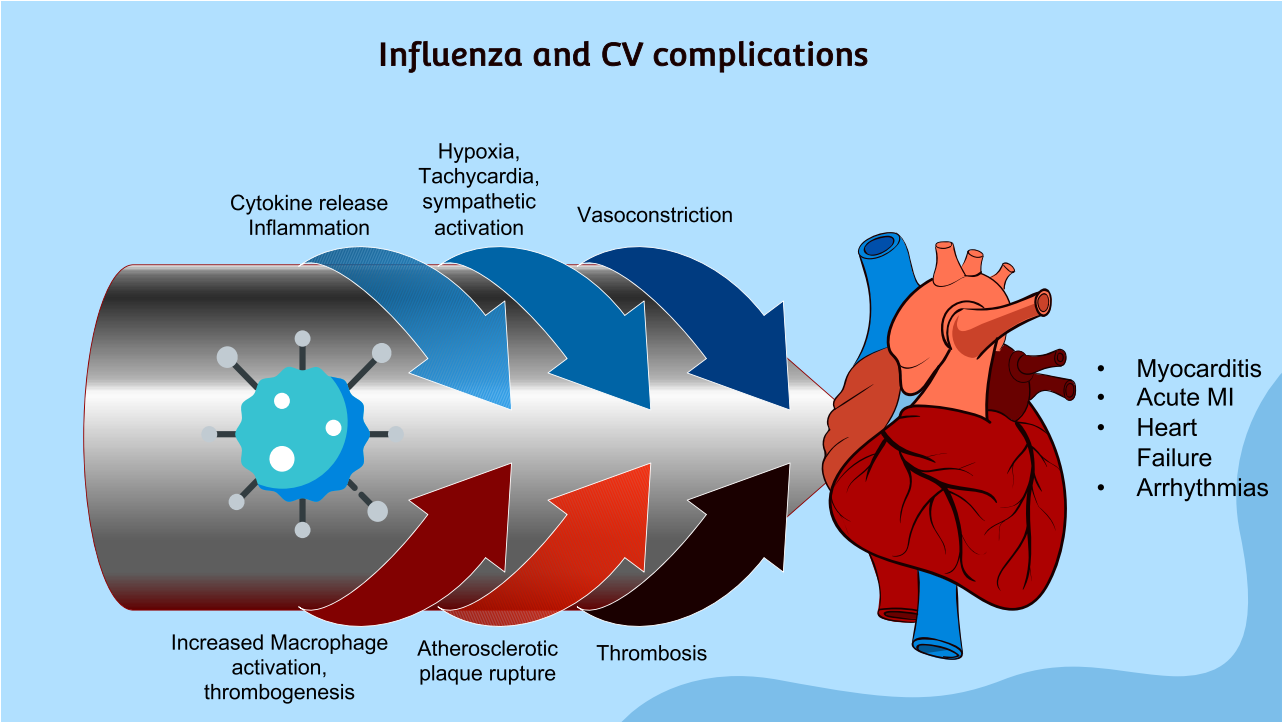

Figure 1 Influenza and CV complications.

randomized and observational studies have been conducted. A Cochrane review showed a reduction in CV mortality with the influenza vaccine in patients with CVD [RR, 0.45 (95% CI: 0.26–0.76)].[47] A more recent meta-analysis of 4 randomized clinical trials and 12 observational studies in patients with CVD showed a significant reduction in all-cause [RR, 0.75 (95% CI: 0.60–0.93)] and CV mortality [RR, 0.82 (95% CI: 0.80–0.84)], and MACE [RR, 0.87 (95% CI: 0.80–0.94)] at a median follow-up of 20 months.[48] Even more up-to-date meta-analysis of 8 trials (14 420 patients) confirmed that influenza vaccine vs. control was associated with a significant 25% lower risk of MACE [RR, 0.75 (95% CI: 0.57–0.97)].[49] In relative terms, these risk reductions are comparable in size effect with guideline-directed therapy in CVD (*Table 2*).[49]

Prevalence and predictors of influenza vaccine uptake

The WHO sets a global target of 75% vaccination uptake,[56] however, only 50% of US adults were vaccinated during influenza season between 2020 and 2021.[57] Similarly, the prevalence of vaccination was only 44% in Europe among elderly adults (≥65 years) between 2016 and 2017,[58] and 15% in the general population and 37.3% among high-risk groups in Asian counties between 2008 and 2018.[56] *Figure 2* demonstrates a global review of vaccine uptake between 2009 and 2020. A US Behavioral Risk Factor Surveillance System (BRFSS, 2016–19) study estimated that the prevalence of influenza vaccine in individuals with atherosclerotic CVD was 54% for Whites, 45% for Blacks, and 42% for Hispanic adults ($P < 0.001$).[60] Various studies have discussed barriers associated with the low uptake of vaccines (*Table 3*). For instance, the BRFSS studies suggested that fear of adverse reactions was the primary deterrent for the under-utilization of the influenza vaccine. Besides persistent vaccine hesitancy and misinformation, under-utilization was also considered attributable to the limited effectiveness of the existing influenza vaccine, which has ranged from 10 to 60% in estimated effectiveness in recent years.[70] Due to natural antigenic drift, predicting the viral strain makeup to include in the standard seasonal influenza vaccine is challenging and is an imprecise science.[71] If the prediction is inaccurate, the effectiveness of the seasonal influenza vaccine may be low.

The effectiveness of the influenza vaccine also depends on other clinical factors, such as the age and comorbidities of the recipient. In 2018–19, the adjusted vaccine effectiveness for all influenza vaccines across all age groups was only 29%, creating more vaccine hesitancy among the general public.[72] Due to current vaccine development strategies, it has become challenging to facilitate the rapid mass production of vaccines in response to new circulating mutations of influenza viruses.[2] Finally, racial and geographic disparities may also explain gaps in vaccine uptake.

Relevance during the COVID-19 pandemic

COVID-19 was declared a pandemic by the WHO on 11 March 2020, with an overall case-fatality ratio of ~2.3%.[2] Influenza infection and COVID-19 share a similar initial clinical presentation,[73] though COVID-19 appears more transmissible.[74] Unlike influenza, COVID-19 is associated with a ~10-fold higher hospitalization rate and a ~5 to 10 times higher mortality rate.[73,75,76] One study showed the highest mortality (69.4%) among patients with elevated troponin-T and underlying CVD, followed by patients with

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Table 1 Baseline characteristics of the studies

Study	Groups	*n*	Age	Females (%)	HTN (%)	DM (%)	HLD (%)	Obesity (%)	Smokers (%)	Follow-up (months)	Primary outcome
Randomized clinical trials											
FLUVACS[17] (2004)	Vaccine	145	64.0	29.7	59.3	19.3	–	–	45.5	12	Favourable
	Control	147	65.0	26.5	45.6	17.0	–	–	42.9		
FLUCAD[18] (2008)	Vaccine	325	58.8	28.9	69.7	19.8	–	–	20.7	12	Unfavourable
	Control	333	58.1	26.1	63.4	20.7	–	–	16.3		
IVCAD[19] (2009)	Vaccine	141	54.9	34.0	82.0	–	83.0	–	–	12	Unfavourable
	Control	137	54.5	33.0	84.0	–	90.0	–	–		
Phrommintikul *et al.*[20] (2011)	Vaccine	221	65.0	39.0	63.1	29.0	44.3	–	13.7	12	Favourable
	Control	218	67.0	48.0	61.6	32.1	49.5	–	10.3		
INVESTED[21] (2021)	Vaccine	2630	65.5	27.3	75.7	37.2	68.4	48.4	18.4	28	Unfavourable
	Control	2630	65.5	28.8	78.4	37.1	69.4.	48.8	16.0		
IVVE[22,23] (2022)	Vaccine	2560	57.4	52.1	64.9	22.3	16.4	–	–	36	Unfavourable
	Control	2569	57.0	50.8	64.9	23.0	16.6	–	–		
IAMI[24] (2021)	Vaccine	1272	60.1	18.6	52.0	22.4	34.0	–	35.5	12	Favourable
	Control	1260	59.6	17.9	47.6	19.7	32.7	–	35.4		
Observational studies											
Diego *et al.*[25] (2009)	Vaccine	860	76.7	52.0	66.7	32.1	–	24.0	6.5	40	Favourable
	Control	480	75.5	53.8	60.6	32.7	–	17.7	8.1		
Liu *et al.*[26] (2012)	Vaccine	2760	74.8	41.7	80.5	54.4	42.9	–	–	48	Favourable
	Control	2288	75.7	48.2	76.2	53.2	38.8	–	–		
Wu *et al.*[27] (2014)	Vaccine	2087	71.9	1.5	–	–	–	–	–	12	Favourable
	Control	429	68.3	1.6	–	–	–	–	–		
Kopel *et al.*[28] (2014)	Vaccine	501	75.8	44.0	73.0	45.0	–	23.0	32.0	48	Unfavourable
	Control	1463	74.1	45.0	72.0	45.0	–	24.0	29.0		
Blaya-Nova'kova' *et al.*[29] (2016)	Vaccine	1016	76.0	60.3	70.0	25.9	42.6	22.7	–	48	Favourable
	Control	1016	76.5	61.9	69.7	24.7	42.3	22.1	–		
Vardeny *et al.*[30] (2016)	Vaccine	1769	67.9	19.8	68.9	40.9	–	–	–	27	Favourable
	Control	6630	62.7	22.3	71.2	32.9	–	–	–		
Modin *et al.*[31] (2019)	Vaccine	78 379	73.7	43.6	36.7	16.7	–	–	–	44.4	Favourable
	Control	55 669	72.8	44.8	40.3	14.9	–	–	–		
Wu *et al.*[32] (2019)	Vaccine	4350	76.3	35.1	90.1	53.7	57.6	–	–	12	Favourable
	Control	4350	76.2	34.6	89.9	53.5	56.6	–	–		
Kaya *et al.*[33] (2017)	Vaccine	265	60.0	28.3	35.1	24.0	–	–	–	15	Favourable
	Control	391	63.0	27.6	34.3	21.0	–	–	–		
Jackson *et al.*[34] (2002)	Vaccine	1016	–	34.9	49.3	24.1	–	–	23.3	27.6	Unfavourable
	Control	362	–	27.3	42.8	17.1	–	–	41.4		
Lavallee *et al.*[35] (2014)	Vaccine	5054	70.0	39.7	82.7	29.5	51.4	–	19.3	24	Unfavourable
	Control	5054	69.9	40.0	82.9	29.9	51.6	–	19.5		
Mohseni *et al.*[36] (2017)	Vaccine	59	74.7	49.9	–	–	–	–	–	12	Favourable
	Control	202	74.7	49.9	–	–	–	–	–		

HTN, hypertension; DM, diabetes mellitus; HLD, hyperlipidemia; *n*, number of patients; FLUVACS, Flu Vaccination Acute Coronary Syndrome; FLUCAD, Influenza Vaccination in Secondary Prevention from Coronary Ischemic Events in Coronary Artery Disease; IVCAD, Influenza Vaccine in Reducing Cardiovascular Events in Patients with Coronary Artery Disease; INVESTED, Influenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated Heart Failure; IVVE, Influenza Vaccine to Prevent Adverse Vascular Events; IAMI, Influenza Vaccination After Myocardial Infarction.

elevated troponin-T and no underlying CVD (37.5%).[77] Another Danish study showed that the incidence of ischaemic stroke was 10 times higher, and the incidence of acute MI was 5 times higher during the 14 days after COVID-19 diagnosis compared with the control interval.[78]

Benefits of influenza vaccine during COVID-19

Some studies have postulated the underlying mechanisms of COVID-19-related CVD injury overlapping with influenza infection, such as cytokine-mediated plaque destabilization, direct myocardial injury, and increased metabolic demand.[2,78] Studies have also shown an association between influenza vaccination status and COVID-19-related morbidity, hospitalization, and mortality.[79–81] A Brazilian study reported that patients with COVID-19 who received inactivated influenza vaccine experienced on average 7% lower odds of needing intensive care treatment, 17% lower need for invasive respiratory support, and 16% lower mortality than non-vaccinated patients.[81] Protective effects were more prominent when the vaccine was administered after the onset of symptoms as well as among younger patients.[81] An Italian study found that the higher influenza vaccination rates were associated with fewer deaths

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Table 2 Barriers of influenza vaccine uptake

Study	Desire to avoid medication	Vaccine not obligatory/not needed/lack of healthcare worker advice	Fear of side effects	Belief that vaccine is ineffective and/or unsafe
Sagor (2018)[50]	✓	✓	✓	✓
Korani (2015)[51]			✓	✓
Abu-Rishey (2016)[52]				✓
El Khoury (2015)[53]		✓		
Kravos (2015)[54]		✓	✓	
Bodeker (2015)[55]		✓	✓	
Sheldenkar (2019)[56]				✓

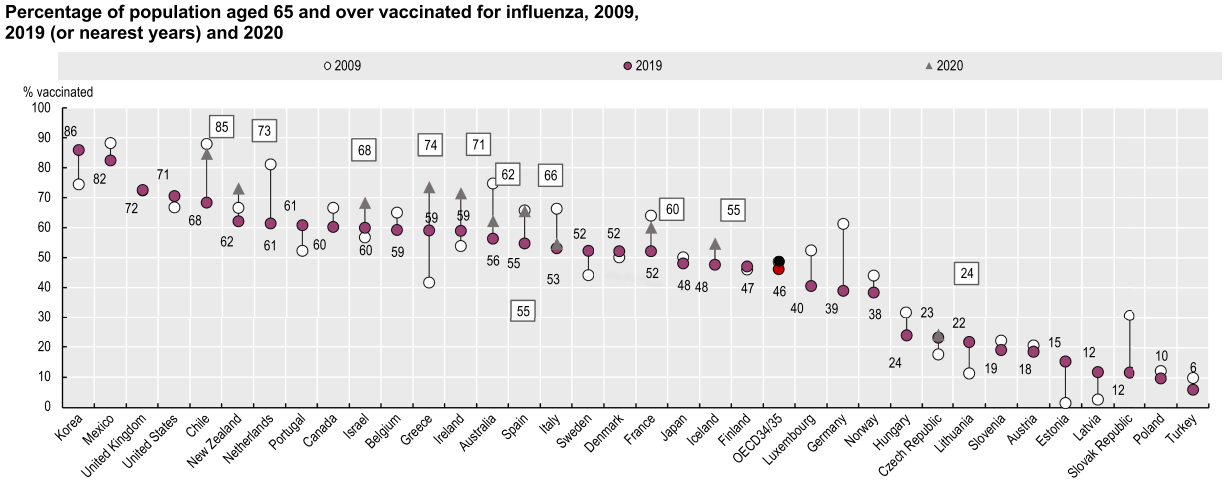

Figure 2 Percentage of the population, aged 65 years and above, vaccinated for influenza, 2009, 2019 (or nearest years), and 2020. *Note*: A 3-year average for Iceland and Luxembourg for all years but 2020. Data are estimated for Norway. *Source*: OECD Health Statistics (2021).[59]

Table 3 Efficacy of guideline-directed interventions and influenza vaccine in the prevention of major adverse cardiovascular events and/or mortality

Coronary intervention	Prevention	Intervention efficacy (%)
Smoking cessation[61,62]	Secondary	32-43
Statins[63]	Secondary	19-30
Beta-blockers[64,65]	Secondary	15-31
Angiotensin receptor inhibitors[65-69]	Secondary	17-25
Influenza[48,49]	Secondary	18-41

from COVID-19; with each 1% increase in influenza vaccination among adults aged >65 years, the regional death rate of COVID-19 decreased by 0.34.[80] A meta-analysis showed that influenza vaccination was associated with a reduced risk of COVID-19 infection [RR, 0.83 (95% CI: 0.76-0.90)] and hospitalization [RR, 0.71 (95% CI: 0.59-0.84)]. Further analysis suggested that the tetravalent influenza vaccine may be associated with a reduced risk of COVID-19 infection [RR, 0.74 (95% CI: 0.65-0.84)].[82] A Brazilian study among pregnant women showed that the influenza vaccines could confer protection against severe COVID-19 infection.[83]

The benefit of influenza vaccination appears more critical during the COVID-19 pandemic, particularly if patients with COVID-19 are at risk of superimposed secondary infection with influenza. There are reports of respiratory viral and bacterial coinfections,[84-87] and vaccination reduces the risk of influenza and may offer some incremental cardiorespiratory protection.[2] Some studies have suggested that influenza vaccination could be used as a temporary measure to reduce the severity of COVID-19, especially in conjunction with vaccines against SARS-CoV-2.[79,80] Certain vaccines lead to protection against other infections through trained immunity for up to 1 year and in the case of live vaccines for up to 5 years.[88] Furthermore, influenza vaccination itself would generate sustained immunity that enhances immunity against SARS-CoV-2.[82]

Conclusion

Influenza remains a global healthcare challenge, and a syndemic of COVID-19 and influenza would create significant issues for clinical management, diagnosis, and strain upon global health resources. While various time-series assessments have shown downstream CV effects with every future worldwide respiratory virus epidemic,[9,10] our knowledge of predicting the next pandemic and its agent of origin remains insufficient.[89] This focused review evaluated the impact of influenza on CV morbidity and mortality and reviewed the evidence establishing the

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efficacy of the influenza vaccine in patients with CVD. Furthermore, studies have highlighted co-protection mediated by the influenza vaccine among patients with COVID-19, providing a unique opportunity to control the burden of CVD complications during the current pandemic.

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Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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