

Influenza vaccination: a ‘shot’ at INVESTing in cardiovascular health

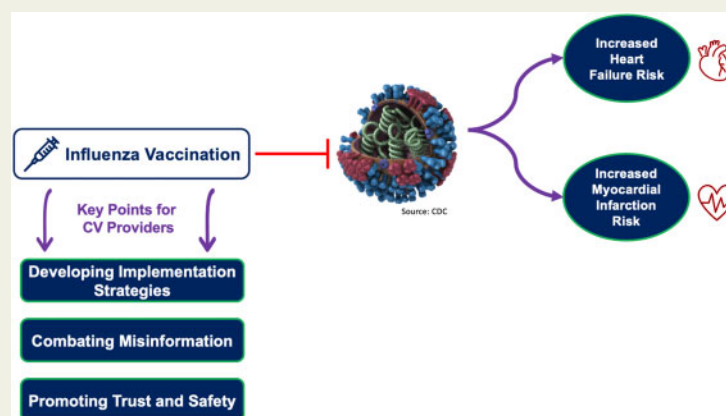
Ankeet S. Bhatt^{1†}, Orly Vardeny^{2†}, Jacob A. Udell³, Jacob Joseph^{1,4},
KyungMann Kim⁵, and Scott D. Solomon^{1*}

¹Division of Cardiology, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, 75 Francis Sreet, Boston, MA 02115, USA; ²Center for Care Delivery and Outcomes Research, Minneapolis VA Health Care System, University of Minnesota, MN, USA; ³Peter Munk Cardiac Centre, Toronto General Hospital, Toronto, ON, Canada; ⁴Department of Medicine, Boston VA, Boston, MA, USA; and ⁵Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI, USA

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The link between viral respiratory infection and non-pulmonary organ-specific injury, including cardiac injury, has become increasingly appreciated during the current coronavirus disease 2019 (COVID-19) pandemic. Even prior to the pandemic, however, the association between acute infection with influenza and elevated cardiovascular risk was evident. The recently published results of the NHLBI-funded INfluenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated (INVESTED) trial, a 5200 patient comparative effectiveness study of high-dose vs. standard-dose influenza vaccine to reduce cardiopulmonary events and mortality in a high-risk cardiovascular population, found no difference between strategies. However, the broader implications of influenza vaccine as a strategy to reduce morbidity in high-risk patients remain extremely important, with randomized controlled trial and observational data supporting vaccination in high-risk patients with cardiovascular disease. Given a favourable risk-benefit profile and widespread availability at generally low cost, we contend that influenza vaccination should remain a centrepiece of cardiovascular risk mitigation and describe the broader context of underutilization of this strategy. Few therapeutics in medicine offer seasonal efficacy from a single administration with generally mild, transient side effects, and exceedingly low rates of serious adverse effects. Infection control measures such as physical distancing, hand washing, and the use of masks during the COVID-19 pandemic have already been associated with substantially curtailed incidence of influenza outbreaks across the globe. Appending annual influenza vaccination to these measures represents an important public health and moral imperative.

Graphical Abstract



Keywords

Influenza vaccination • Heart failure • Myocardial infarction • Cardiovascular prevention

* Corresponding author. Tel: 857-307-1960, Fax: 857-307-1944, Email: ssolomon@bwh.harvard.edu

† These authors contributed equally to this work.

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The link between viral respiratory infection and non-pulmonary organ-specific injury, including cardiac injury, has become increasingly appreciated during the current coronavirus disease 2019 (COVID-19) pandemic. Even prior to the pandemic, however, the association between acute infection with the influenza virus and elevated cardiovascular risk was evident, with data supporting annual influenza vaccination as a potential risk mitigation strategy. Influenza infection is caused by a family of viruses transmitted through respiratory droplets and contributes to nearly a million hospitalizations and over 30 000 deaths annually in the USA.¹ Influenza infection can induce powerful inflammatory responses, and increases in inflammatory cytokines during acute illness have been biologically linked with accelerated atherogenesis and direct myocardial depression.² Randomized clinical trial data have demonstrated that influenza vaccination reduces the risk of cardiovascular death in a population with recent myocardial infarction or planned percutaneous coronary intervention.³ A large meta-analysis found influenza vaccination was associated with reductions in cardiovascular events in patients with atherosclerotic cardiovascular disease, with greater effects in those with recent acute coronary syndromes.⁴ Observational data in patients with heart failure (HF) have also found strong associations between annual influenza vaccination and reductions in all-cause mortality, cardiovascular mortality, and hospitalizations compared with a propensity score-matched cohort.⁵

Based on the concept that influenza infection may increase the risk for adverse cardiovascular events in a high-risk population, the INfluenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated heart failure (INVESTED) trial studied two doses of a simple preventive strategy in 5260 high-risk cardiovascular patients. INVESTED assessed the comparative effectiveness of two vaccine formulations, high-dose vaccine vs. standard-dose vaccine, to determine if high-dose vaccine substantially reduced the risk of the composite of death from any cause or cardiopulmonary hospitalizations. High-dose influenza vaccine was developed to overcome reduced vaccine-induced immune responses with ageing and is FDA approved in older adults, and was shown in a large, randomized clinical trial to reduce polymerase chain reaction-confirmed influenza compared with standard dose.⁶ Patients with cardiovascular disease have also demonstrated reduced humoral response to vaccine, which was overcome with a higher-dose formulation in a pilot trial.⁷ The INVESTED found that high-dose vaccination did not significantly reduce all-cause mortality or cardiopulmonary hospitalizations in this high-risk group as compared with standard-dose vaccination.⁸ These results were consistent for secondary endpoints and for pre-specified subgroups of interest.

How do we integrate the findings of the INVESTED trial into our understanding of the role of influenza vaccination in reducing risk in patients with cardiovascular disease, and in determining which influenza vaccine formulations might be better for our cardiovascular patients? First, the role for influenza vaccine in reducing cardiopulmonary events needs to be considered in the context of the active comparator design in INVESTED. INVESTED compared two dose formulations of influenza vaccination and did not include a placebo group. The clear efficacy data and strong recommendations supporting vaccination in this population from the Centers for Disease Control and Prevention limited the ability to test vaccine against placebo.⁹ Thus, all participants in INVESTED were vaccinated, and while

events were similar in both vaccine dosing groups, the trial results are moot on the degree of benefit of any vaccination vs. non-vaccination. The total number of hospitalizations ascribed to influenza, or even pneumonia, was low in INVESTED compared with the large number of cardiovascular hospitalizations. The fact that influenza hospitalizations were vastly outnumbered by other types of hospitalizations suggests that the *attributable* risk of influenza illness *per se* in this high-risk population may be low in comparison with other competing reasons for adverse events, thereby potentially contributing to the lack of difference in the primary endpoint studied.

Additional factors may have also contributed to the lack of additional benefit from high-dose vaccine as tested in INVESTED. First, the overall effectiveness of the vaccine during the study period was relatively low. Influenza vaccine effectiveness is influenced by the extent of the match between antigens contained in the vaccine and circulating influenza strains, in addition to patient-specific factors such as age, comorbidities, and previous exposure history. Vaccine effectiveness during the 2016–17 and 2017–18 influenza seasons (the first two seasons included in INVESTED) varied between 29% and 40% (and was even lower for older adults), and with the exception of the 2014–15 influenza season, was the lowest since 2007–08. These factors may have further attenuated the effectiveness of vaccination during the study period. However, whether low overall effectiveness would have contributed to lower *comparative* effectiveness of the two vaccine formulations is unclear.

Should the results of INVESTED dampen our enthusiasm for influenza vaccination in this population? We certainly do not believe so. That high dose was no more effective than standard-dose vaccine in reducing the clinical outcomes assessed in INVESTED does not diminish the role of influenza vaccination of either formulation in the slightest, nor does it counteract prior evidence showing high-dose influenza vaccine reduced influenza illness. Randomized and high-quality observational data have suggested vaccination reduces events as compared with no vaccination among high-risk cardiovascular patients. Observational data have suggested influenza vaccination may provide similar efficacy to other more recognized approaches in cardiovascular disease prevention, including smoking cessation.⁶ Indeed, few therapeutics in medicine offer seasonal efficacy from a single administration with generally mild, transient side effects, and exceedingly low rates of serious adverse effects. In addition, influenza vaccine is available at low cost and accessible even in resource-constrained areas.

Acknowledging imperfect data, the scales tip in favour of annual influenza vaccination nearly every time. This is especially important in the context of the current COVID-19 pandemic, which has exposed the interrelatedness of our societies in accelerating disease spread. Today, a clear public health priority supporting influenza vaccination among all eligible individuals over 6 months of age carries even greater importance. Even during years of lower vaccine effectiveness, preventing mild to moderate, self-limited influenza illness experienced more commonly in immunocompetent, lower-risk patients may diminish risks of transmission to individuals with higher-risk profiles. Infection control measures such as physical distancing, hand washing, and the use of masks have already been associated with substantially curtailed incidence of influenza outbreaks across the globe.¹⁰ Appending annual influenza vaccination to these measures represents an important public health and moral imperative.

Table 1 Influenza vaccination rates in the year prior to randomization in INVESTED

	Percent vaccinated in prior year (%)	
	Qualified by MI (N = 1960)	Qualified by HF (N = 3289)
Age group		
Age <65 years	37	53
Age ≥65 years	60	72
Sex		
Men	50	65
Women	50	63
Country		
Canada	48	62
USA	53	65
Randomization year		
2016–17	52	69
2017–18	53	67
2018–19	47	60

HF, heart failure; INVESTED, INfluenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated heart failure trial; MI, myocardial infarction.

Given the clear one-sided calculation favouring the benefits of vaccination over risks, paired with important common-sense public health considerations, promoting vaccination should remain a central priority for all eligible persons, including high-risk patients with cardiovascular disease. With this perspective, why has routine, yearly vaccination proved so challenging to implement? Despite near universal support for vaccination in contemporary cardiovascular guidelines,^{11,12} vaccination rates among high-risk cardiovascular patients have remained disappointingly low. Among HF patients in the American Heart Association's Get with the Guidelines-HF registry, vaccination refusal rates incrementally increased from the 2012–13 to 2016–17 influenza seasons, with over 20% of eligible patients refusing vaccination during the study period.¹³ Trial data from a contemporary, otherwise well-treated HF population demonstrated influenza vaccination rates of only 53% among North American participants.¹⁴ Despite marked ambient risk, the vaccination rate at any dose among INVESTED participants in the year prior to randomization was 59%. Rates were particularly low among participants less than age 65 with these high-risk conditions, and surprisingly lower than would be expected for a population that would agree to participate in a comparative effectiveness study on influenza vaccination a year later (Table 1). Despite compelling evidence for benefit, significant socioeconomic and demographic disparities also exist in vaccination rates among high-risk cardiovascular patients.¹⁵ Misinformation on the risks of vaccination, in addition to unverified claims of excessive harm and continued fears regarding risk of contracting influenza infection from vaccination have likely contributed to public hesitance.

While ongoing placebo-controlled trials may further define the efficacy of vaccination in high-risk cardiovascular patients, the

totality of data to date support early, routine vaccination irrespective of dose formulation. Significant opportunities remain to define and test optimal implementation strategies in general. These implementation strategies may be further generalizable to other public health efforts, including vaccination efforts for other illnesses. In the context of the COVID-19 pandemic, and the possibility for seasonal vaccination needs, such investments in an effective implementation strategies would be expected to provide significant public health benefit. Similarly, while the pandemic has highlighted the promise of vaccination as a preventative strategy, it has also delineated gaping systems-based issues surrounding ensuring effective access, promoting vaccine deployment, and combating public hesitancy. Lessons learned during the COVID-19 pandemic may inform ongoing influenza vaccination efforts and vice-versa. Clinician-facing nudges may be critical to engage cardiovascular health-care providers in promoting vaccine safety and trust among their patients. Strategies may borrow heavily from diverse disciplines including behavioural economics, sociology, and implementation science. Refined counselling initiatives, expanded educational programmes, reductions in barriers to vaccination and expanded access, and additional pragmatic incentives, particularly among high-risk patients, may prove vital (Graphical abstract). Prioritizing influenza vaccination remains a critical 'shot' to mitigate risk and improve cardiovascular health.

Data availability

Data will be available to qualified researchers on the NIH Biolinc website on 11/17/2022 as per NIH guidelines.

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