THE SECONDARY BENEFITS OF INFLUENZA VACCINATION

LITERATURE REVIEW

IFA
INTERNATIONAL FEDERATION ON AGEING
Global Connections

VACCINES 4LIFE

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Foreword

Increases in life expectancy around the world due to significant demographic transitions is a cause for celebration yet a longer life in poor health and function is not a prize. According to the World Health Organization, seasonal influenza epidemics are responsible for three to five million serious illnesses and half a million deaths worldwide, with approximately 89 percent of those deaths among individuals aged 65 years and older. The influenza virus also significantly contributes to decline in functional ability amongst older people.

One of the most cost-effective and affordable strategies to reduce the social and economic burden of infectious disease such as influenza is immunization – a strategy often overlooked in the prevention of functional decline in later life. This comprehensive literature review, conducted by Ms. Vyvyan Mishra, seeks coherence through a synthesis of the literature currently available on the secondary protective benefits of influenza vaccination to older adults with particular focus on older people with chronic diseases such as diabetes and chronic lung disease.

It is hoped that this review will assist civil society, ageing organizations, patient organizations representing those with chronic disease, academics and government to gain a deeper understanding not only of the primary effect of influenza vaccination, but of the secondary protective benefits offered by immunization. In turn, the IFA hopes that a concerted effort by stakeholders across sectors and disciplines can translate this important understanding into tangible actions that enable healthy ageing for generations to come.

Sincerely,

Dr Jane Barratt
Secretary General
International Federation on Ageing

CONTENTS

LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
ARI	Acute respiratory illness
CAP	Community-acquired pneumonia
CHD	Coronary heart disease
CHF	Congestive heart failure
CLD	Chronic lung disease
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
ECDC	European Centre for Disease Control and Prevention
GDP	Gross Domestic Product
HD	Heart disease
HF	Heart failure
IFA	International Federation on Ageing
IHD	Ischaemic heart disease
IPD	Invasive pneumococcal disease
IV	Influenza vaccine
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
NCD	Non-communicable disease
PCI	Percutaneous coronary intervention
PPV 23	Valent pneumococcal vaccine
PV	Pneumococcal vaccine
RCT	Randomized controlled trial
SBI	Secondary bacterial infection
TIA	Trans-ischaemic attack
TIV	Trivalent influenza (TIV) vaccine
VTE	Venous thromboembolism
VPD	Vaccine-preventable disease
WHO	World Health Organization

BACKGROUND

Influenza is a global threat, with the risk of an influenza pandemic still very present in the minds of experts around the world. Three pandemics occurred in the 20th century which resulted in millions of deaths worldwide. The fourth pandemic of H1N1 influenza occurred in 2009 and affected countries on all continents.[64] Globally, seasonal epidemics are thought to be responsible for around three to five million cases of severe illness and anywhere from 250,000 to 500,000 deaths. Of these deaths, 89 percent occur in patients aged ≥65 years.

Influenza is a major contributor to functional physical decline and causes exacerbations of pulmonary and cardiovascular disease. [38] It is also the primary cause of increased mortality among patients with underlying chronic co-morbid conditions (such as acute ischemic heart disease, stroke and pneumonia) in the winter season. [38, 52] It therefore poses serious risks to the health, well-being, activity and survival of older adults, particularly those with co-morbidities and frailty.

Foremost amongst the diseases preventable by vaccination is influenza. Immunization is the cornerstone for preventing adverse health outcomes, and vaccination programs are timed to optimize protection during the annual influenza season. Despite widespread influenza vaccination programs, rates of hospitalization for acute respiratory illness and cardiovascular diseases have been increasing in this population during recent annual influenza seasons, [38, 64] while vaccine coverage rates among older adults remain generally poor. [38] There is some evidence, mostly from Europe and the United States, that seasonal influenza vaccination rates are higher in persons with non-communicable diseases (NCDs) than in the general population. Nevertheless, they still fall short of the World Health Organization (WHO) and European Union recommended targets. For example, only one in three adults with heart disease (34 percent) in the United States received influenza vaccination in 2005. [15, 38, 54]

There are a number of barriers to vaccination in the older adult population, which include misconceptions about the adverse effects of the vaccine, [7, 62] a relatively poor awareness of the seriousness of vaccine-preventable diseases (VPDs) such as pneumococcal pneumonia, [30] a prevailing opinion that only childhood immunization programs are a priority, [30, 39] and beliefs in the effectiveness of actions such as exercise and good nutrition, thought to boost well-being and the health of the immune system and to provide protection in themselves against influenza infection. [78] Many healthcare workers share these beliefs, which helps to explain the surprising fact that they too show consistently low vaccination rates year after year across the globe. [54, 81]

Research also indicates a barrier to vaccination is the lack of availability of the vaccine at the medical clinic to which the older adult may routinely go, or at a specialist clinic to which they have been referred to for the management of their NCD. [15] Furthermore, inadequate vaccine surveillance prohibits universal coverage and creates a vacuum of knowledge that, if available, could inform strategies to improve vaccine uptake, effectiveness and safety, as well as healthcare budget savings. [30]

Prevention programs, such as vaccination, are often considered to have only return in the long run; thus, in situations where governments are looking to cut expenditure, they will look for short-term return and stop investing in prevention programs. [58] Moreover, the conventional economic evaluations usually conducted for vaccination generally omit health-related productivity and macroeconomic improvements attributed to health status changes and, consequently, may

not adequately reflect the broader economic benefits of vaccination. [58]

This sub-optimal influenza vaccination uptake by older adults has significant implications because emerging literature suggests that influenza vaccine may have a distinctly protective effect. It has been shown to decrease the likelihood of adverse health events, for example myocardial infarction, cerebrovascular disease and death, although a coherent story about this aspect of immunization is lacking. This report seeks coherence through a synthesis of the literature currently available. It focuses on the secondary benefits of influenza vaccination for older adults living with certain specific NCDs —respiratory and cardiovascular diseases, and diabetes—as well as for frail older adults. Consideration is given to the impact of influenza infection on these conditions, and the potential alleviation and prevention of complications provided by influenza vaccination. Costs and cost-effectiveness are explored, along with gaps in, and limitations to the research. Recommendations for future directions from researchers and reviewers of the literature are also shared.

EXPLORING THE CONNECTIONS

Non-communicable diseases (NCDs) are the most significant cause of premature mortality globally, accounting for 36 million (63 percent) of the 57 million annual deaths and will have an estimated associated cost of over $30 trillion over the next 20 years. [54] The major NCDs—cardiovascular diseases, cancer, chronic obstructive pulmonary disease (COPD) and diabetes—have significant consequences within the WHO European region, for example, accounting for nearly 86 percent of deaths and 77 percent of the disease burden in the region. When combined with the fact that death from influenza is considerably more common in older people and those with co-occurring conditions

(such as heart disease and chronic lung disease), and that in Western Europe the highest mortality rates for pneumonia are in people aged 80 years and over, understanding the connections between NCDs, vaccine-preventable diseases (VPDs) and population ageing becomes imperative toward finding a solution that will positively impact the largest number of people. [30]

The rate of NCDs has seen a steady increase globally in the last decade. Nearly 80 percent of NCD mortality takes place in low- and middle-income countries, where health systems are ill-prepared to deal with the NCD burden effectively. There is sufficient epidemiological evidence confirming that influenza is associated with higher rates of complications, hospitalizations and even deaths in individuals living with NCDs versus the general population. This was particularly notable during the 2009-2010 H1N1 pandemic. In non-pandemic years, 80 percent of people hospitalized for influenza in the USA had one or more underlying medical conditions. [54]

Research indicates that there is abundant information on the primary prevention and control of major NCDs, but little attention has been paid to the interplay of communicable and non-communicable diseases and whether targeted interventions can be mutually beneficial. There is sufficient data to demonstrate that, apart from the fact that some NCDs have an infectious aetiology (e.g. gastric cancer, hepatocellular cancer and cervical cancer), the high burden of infectious diseases and associated chronic inflammation exacerbates risks for other NCDs as well. [54]

The probability of hospitalization for influenza is three times higher in people with diabetes than in the general population. [54] In people with cardiovascular disease, systemic respiratory infections—which are frequently caused by influenza viruses—increase the risk of stroke and heart attacks three- and five-fold respectively in the three days following the

onset of infection. [54, 69] The impact of influenza infection on mortality among high-risk groups is even more pronounced. In the United Kingdom, epidemiological surveillance data from 2010 to 2011 indicated that patients in a risk group due to chronic NCDs had a 10-fold greater risk of mortality due to influenza compared with patients who were not in an at-risk category. [54]

In general, peak periods of mortality among NCD patients coincide with peaks of pneumonia and seasonal influenza. As an example, the risk of dying from acute myocardial infarction and chronic ischaemic heart disease is 1.3 times greater during influenza epidemic weeks. Case fatality rates from Influenza A can be over 30 percent in persons with COPD compared to 0.1 percent or less in the healthy population. [54]

Mortality rates in NCD patients range from ten to 377 per 100,000 influenza cases, depending on the number of high-risk conditions. The highest rates of influenza mortality are noted among people who are 65 years and older. For example, in the United States, influenza infection was responsible for 132.5 per 100,000 person-years for all-cause deaths, 98.3 for underlying respiratory and circulatory deaths, and 22.1 for underlying pneumonia and influenza deaths. If two co-morbid conditions are present (e.g. frailty and high-risk), influenza-related death rates are 100 times greater than in healthy adults. [54]

Despite all the known benefits that influenza vaccination brings, the vaccination coverage remains unacceptably low globally, a fact which leads researchers to argue for an urgent increase in the investigation of potential benefits and risks of influenza vaccination for older adults living with NCDs. [54]

RESPIRATORY DISEASE

Secondary Bacterial Infections (SBIs)

Influenza virus infections remain a significant health burden worldwide, despite available vaccines. Factors that contribute to this include a lack of broad coverage by current vaccines and continual emergence of novel virus strains. Further complicating matters, if influenza viruses infect a host, severe infections can develop when bacterial pathogens invade. Secondary bacterial infections (SBIs) contribute to a significant proportion of influenza-related mortality, with *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Haemophilus influenzae* as major coinfecting pathogens. [50]

Grabowska et al. (2006) confirmed the connection between influenza infection and Invasive Pneumococcal Disease (IPD) through a study that demonstrated a 12 to 20 percent per influenza season increase in IPD cases due to influenza. [20] The incidence of secondary bacterial pneumonia is most common in older adults and those with underlying conditions such as congestive heart disease and chronic bronchitis. [64] Vaccines against bacterial pathogens can reduce co-infection incidence and severity, but few vaccines are available, and those that are available may have decreased efficacy in influenza virus-infected hosts. [70]

"The incidence of secondary bacterial pneumonia is most common in older adults and those with underlying conditions such as congestive heart disease and chronic bronchitis."

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It is largely believed that current influenza vaccines are both effective and cost-saving in the older population. However, while the trivalent inactivated influenza virus vaccine prevents laboratory-confirmed influenza illness in approximately 70 to 90 percent of healthy adults when the vaccine and circulating virus are antigenically similar, the picture for older individuals with one or more NCDs is not as clear. Few placebo-controlled, randomized clinical trials have been performed, and none have been powered enough to study serious outcomes, including mortality. [38]

A large and well-designed placebo-controlled, randomized clinical trial, conducted by Govaert et al. in the Netherlands during the 1991–1992 influenza season, randomly assigned 1,838 healthy volunteers aged 60 years and over to receive either a placebo or a trivalent inactivated influenza virus vaccine. After stratifying by age, the researchers estimated an influenza vaccine effectiveness of 57 percent in people aged 60 to 69 years, but only 23 percent in subjects aged 70 years and older. This result suggests that the effect of the vaccine decreases in this sub-population, which partly reflects changes in the immune system occurring with advancing age. It has not been possible to resolve this issue for obvious ethical reasons. [38]

The majority of those at risk for an SBI are the young (<1 year old) and older adults (>65 years old), and these populations notoriously have weak immune responses toward both infection and vaccination. [70] In the case of older adults, this may be related to immunosenescence, which may impair the immune response to vaccination in older people. [42] Although a person's age is a factor, there is no single cause for immunosenescence. It is the consequence of a compilation of events, including (but not limited to): thymic involution and the immune reduction in thymic output; the continuous re-shaping of the immune repertoire by persistent antigenic challenge; the reduced

production of new B cells and the intrinsic defects arising in resident B cells; the impact of co-morbidities; the nutritional status of the individual and the increase in the frequency of low-grade and chronic inflammation; and dysregulation of hormonal pathways. [39]

There is very little research to indicate the extent of vaccine-induced immunity against the influenza virus and its impact on subsequent SBI incidence and severity. [10, 70] Vaccination-associated reductions in the risk of hospitalization for pneumonia and influenza and death from all causes have been observed in studies in the United States, Canada (Manitoba), the United Kingdom, Spain, Italy and Argentina, with an estimated reduction percentage of 20 to 40 percent. Some studies report a higher protection percentage than this: 30 to 50 percent in studies in Canada, the United States and the United Kingdom. [25, 52]

The 2015 Cochrane Review into influenza vaccination for preventing cardiovascular disease identified four studies that showed influenza infections were significantly reduced by influenza vaccination, three studies which reported that the vaccines produced adequate seroprotection, one study showing that no cases of influenza were seen over the initial six-month follow-up in the intervention or the comparison group, and one study that did not report on the effectiveness of the vaccination against influenza. [14]

Other studies showed that influenza vaccination is similarly effective in reducing the risk of hospitalization for pneumonia or death in healthy older adults and in those with co-existing conditions and reduces morbidity and mortality during influenza seasons. [52]

A common and serious complication of influenza infection is community-acquired pneumonia (CAP), which either results from direct viral infection of the lung parenchyma or from secondary bacterial infections. A German study investigating the impact of prior influenza

vaccination on disease severity and mortality in patients with community-acquired pneumonia (CAP) performed an analysis of an observational, multi-center cohort study initiated by the German competence network for CAP. Patients were analysed separately as an influenza season and off-season cohort. Associations between vaccination status and outcome parameters were evaluated by multivariate analyses.

In the season cohort (2,368 patients), CAP in vaccinated patients was significantly less severe and these patients showed a better overall survival within the six-month follow-up period; while the off-season cohort (2,632 patients) showed no significant influence of vaccination status on CAP severity or disease outcome. The authors concluded that prior influenza vaccination was associated with a less severe clinical course and improved overall long-term survival in patients with CAP during influenza seasons. Several other studies confirm these findings. [52, 74]

Asthma

Respiratory viral infection is an exacerbating factor which may be caused by seasonal influenza viruses. Although people with asthma are not more likely to suffer influenza infections, they may present with more severe symptoms, even in those with mild asthma or with symptoms well controlled by medication. Influenza infection in the lungs may trigger asthma attacks and worsen asthma symptoms, and adults and older people with the condition are more likely to develop pneumonia after having influenza. Asthma is the most common medical condition in adults hospitalized with influenza, and one of the most frequent medical conditions in hospitalized older adults. [72]

Chronic airway inflammation and type 2 immune responses are thought to impair anti-viral immunity in the respiratory tract, resulting in susceptibility to serious influenza illness and associated bacterial infection. Furthermore, influenza infections can lead to severe asthma attacks, often requiring hospitalization. [81]

A 2013 Cochrane systematic review of the effectiveness of influenza vaccination in those with asthma was inconclusive. [81] In contrast, a 2017 systematic review and meta-analysis, which identified 35 studies enrolling 142,519 patients with asthma, noted positive indicators in the cohort who had received vaccination. While the low quality of the body of evidence and the scarcity of studies assessing influenza vaccination in older adults with asthma was noted, the pooled vaccine effectiveness in 1,825 persons with asthma from two test-negative design case-control studies was 45 percent for laboratory-confirmed influenza; and pooled efficacy of live vaccines in reducing influenza was 81 percent. The influenza vaccine prevented 59 to 78 percent of asthma attacks leading to emergency visits and/or hospitalizations. [81]

A matched case-control study in Spain assessed the frequency of hospitalization for influenza in people with asthma aged more than 65 years, against a backdrop of 56.2 percent of older adults (65 years and over) having received influenza vaccination in the 2014–2015 season, with some variations between regions in Spain. Although the researchers found no conclusive evidence of the protective effect of vaccination, they confirmed that vaccinated older people with asthma had fewer symptoms and better outcomes than non-vaccinated patients, recording no deaths during hospitalization or during the first 30 days after discharge in the vaccinated subjects. [72]

Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality and carries a significant disease burden in both primary and secondary care. In 2010, 384 million individuals worldwide were

estimated to have COPD, with a global prevalence of 11.7 percent. COPD is the most common cause of death due to chronic respiratory disease, causing an estimated 2.9 million deaths in 2013. The disease ranks as the third most common cause of death in the United States, and fourth in the United Kingdom and southern Latin America. The prevalence of COPD increases significantly with age and tobacco use and is higher in men than in women. [2]

There is no known cure for COPD, but the symptoms are treatable and disease progression can be delayed. Exacerbations of COPD are characterised by acute worsening symptoms due to airflow restriction resulting from mucus hypersecretion, mucosal swelling and bronchospasm. At least 70 percent of COPD exacerbations are infectious in origin, and respiratory viruses are identified in approximately 30 percent of cases. In a review of the literature, influenza was the second most common virus identified in association with COPD exacerbations. Bacterial and viral co-infections may also occur, and bacterial infection may complicate an initial viral infection. [2, 18]

In view of the role of influenza in contributing to COPD exacerbations, the associated complications and their related healthcare costs, immunization against influenza is recommended by the World Health Organization (WHO), the United States Centers for Disease Control and Prevention, the European Centre for Disease Control and Prevention (ECDC), and numerous national agencies. Descriptive population-based cohort studies have shown that influenza vaccination significantly reduces hospitalizations and mortality in patients with COPD. However, influenza vaccination coverage rates remain below target in many countries. [2] In 2009, influenza vaccination rates among patients with COPD were approximately 56 percent in Spain, 58 percent in the United States, from 26 to 49

percent in Italy, 44 to 59 percent in the United Kingdom, and 57 percent in France. [72]

> *"Descriptive population-based cohort studies have shown that influenza vaccination significantly reduces hospitalizations and mortality in patients with COPD."*
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> Bekkat-Berkani R, Wilkinson T, Buchy P et al.

A Cochrane literature review of randomized controlled trials (RCTs) published by Poole et al. in 2006 reported that influenza vaccination appears to reduce exacerbations of COPD, although this was based on a limited number of reports available. The size of effect was similar to that seen in large observational studies and showed reductions in exacerbations occurring three or more weeks after vaccination. In older, high-risk patients there was an increase in adverse effects with vaccination, but these were seen early and were usually mild and transient. [2, 56, 63]

Bekkat-Berkani et al. (2017) published a systematic literature review of RCTs and observational studies on the seasonal influenza vaccination given to patients with COPD. Most studies were conducted in moderately severe influenza seasons with moderate-to-good matches between circulating strains and vaccine strains. Some studies in the review found no convincing evidence that seasonal influenza vaccination reduced the risk of mortality, including a prospective Spanish cohort study of 1,298 subjects with COPD, in whom seasonal influenza vaccination did not reduce the risk of all-cause mortality each year nor overall during the four-year follow-up period. [2] Similarly, in a retrospective cohort study, influenza

vaccination was not associated with a statistically significant reduction in the risk of all-cause death in the year following immunization. [2, 19] By contrast, other studies demonstrated a protective effect of the vaccine and associated reduction in mortality figures. These included a retrospective study in the United Kingdom, with data from almost 41,000 patients with COPD, which revealed a significant protective effect of seasonal influenza vaccination. Over an average 6.8-year follow-up period between 1988 and 2006, influenza vaccination was associated with a reduced risk of all-cause mortality by 41 percent. [2] Influenza vaccination was concluded to have significantly reduced all-cause mortality, deaths associated with a respiratory event and episodes of acute coronary syndrome and heart failure in COPD patients, as well as heart failure in people 65 years of age or older. The impact of vaccination was greatest in well-matched seasons, and lowest in poorly-matched seasons. [2]

Research in Japan studied the clinical efficacy of combined vaccination with 23-valent pneumococcal vaccine (PV) and influenza vaccine (IV) against pneumonia and acute exacerbation of chronic lung diseases (CLD), in an open-label, randomized, controlled study among 167 adults with CLD over a two-year period. When these subjects were divided into sub-groups, an additive effect of PV with IV in preventing infectious acute exacerbation was significant only in patients with COPD. This effect was noted during the first year after vaccination but not during the second year. [18]

A 2012 Canadian evidence-based review found that influenza vaccination was associated with significantly fewer episodes of influenza-related acute respiratory illness (ARI) in patients with COPD. Overall, the vaccine effectiveness was 76 percent. For categories of mild, moderate or severe COPD the vaccine effectiveness was 84 percent, 45 percent and 85 percent respectively. [64]

Montserrat-Capdevila et al. studied the risk of hospitalization due to exacerbations in 1,323 vaccinated (mean age 75.6 years) and unvaccinated (mean age 57.1 years) Spanish patients with COPD during the 2001-2002 influenza season. They found that the effectiveness of influenza vaccination in preventing hospitalization was 90.8 percent. [2]

A Korean study similarly concluded that influenza vaccination significantly reduced the risk of hospitalization, especially due to acute exacerbation of ischemic heart disease (IHD) and congestive heart failure (CHF), in COPD patients aged 65 years and older. The estimated vaccine effectiveness in these patients was 56.0 percent. [65]

Huang et al. investigated the influenza vaccine effect for IHD occurrence secondary to COPD, employing data spanning 11 years from the Taiwan National Health Insurance cohort research database and analysing the relationships between vaccination and incidence of IHD for COPD patients stratified by age. They found that influenza vaccination was associated with a reduced risk of IHD only in older COPD patients. [28] Similar findings emerged from a retrospective cohort study of 899 patients in Spain with COPD, which reported that influenza vaccination significantly reduced the risk of severe (hospitalized) exacerbations in the year following immunization, with a greater effect in those patients with more severe disease. [2, 19]

An impaired immune response to vaccination and infection in patients with COPD has been described. Immunogenicity in this population may be influenced by immunosenescence in older adults, co-morbidities, and the use of immune-suppressants. Influenza vaccination was immunogenic in patients with COPD in five studies, although only one of these studies compared immune response to vaccine efficacy. [2]

Overall, influenza vaccination was found to have an acceptable safety profile in patients with COPD [2]. In studies with a lung disease sub-group, influenza vaccinations were generally well tolerated. These conclusions applied only to inactivated influenza vaccination. There were significantly more local side-effects and wheezing reported with intramuscular influenza vaccine than with placebo; however, these effects were self-limiting and were outweighed by the longer-term benefits of the vaccination. [56] There was also a significant increase in local effects, ranging from pain at the site of injection to erythema with or without induration, but all effects appeared to be mild and transitory. [56]

The limited evidence from RCTs supports recommendations that influenza vaccination should be used in COPD patients. After two to three weeks, the number of exacerbations per patient and the number of patients with exacerbations were both reduced. The data suggest that COPD patients benefit as much as other older adults. [56]

In summary, acute exacerbations of COPD are one of the most important causes of COPD-related morbidity and mortality, with infectious triggers like influenza playing a major role. In patients with chronic respiratory diseases such as COPD who are at risk of severe complications from influenza infection, vaccination has been shown to decrease influenza incidence, severity, hospitalizations, and mortality by up to 50 percent. [25]

CARDIOVASCULAR DISEASE

In 2008, cardiovascular disease (CVD) became the leading cause of mortality in the world, now noted as causing 13 percent of all deaths globally. [48, 83] As an example, heart failure (HF) currently affects approximately 5.7 million adults in the United States, and is associated with significant morbidity, mortality, and financial burden. [3, 62] Moreover, major adverse cardiovascular events (MACEs), a composite category consisting of cardiovascular diseases and ischaemic stroke, are among the leading causes of morbidity and mortality in the older adult population. [8]

There is a wide interaction between cardiovascular and respiratory pathologies. Given the central role of inflammation as a common final pathway for infectious agents, most acute infections have similar non-specific, injurious effects on the coronary arteries. [22] Respiratory infection is a leading cause of hospitalization among patients with HF, is associated with increased in-hospital mortality rates, [12] and is estimated to trigger 50 percent of HF exacerbations. [3]

> *"Influenza-related death is more common among individuals with CVD than among patients with any other chronic condition."*
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> Davis MM, Taubert K, Benin AL et al.

Epidemiological data indicate that risks for complications, hospitalizations and death from influenza are higher for individuals at the extremes of age (<5 years old, ≥ 65 years old) and for people with chronic medical conditions than for healthy older children and younger adults. [15, 52] Influenza-related death is more common among individuals with CVD than among patients with any other chronic condition. [15]

Influenza Vaccination Coverage in Patients with CVD

Many countries recommend influenza vaccination for patients at increased risk of severe complications from influenza, including those with cardiovascular disease (CVD). However, vaccine coverage remains sub-optimal in this vulnerable population,

irrespective of health campaigns and media attention aimed at improving vaccination rates. [1, 3] The real rate of vaccination against influenza among HF patients across the world varies from close to 80 percent in the Netherlands and the United Kingdom down to 10 to 30 percent in countries such as Korea, Slovakia and Brazil, to less than two percent in China, Russia and Bulgaria. [12] Alarmingly, only one in every three adults with heart disease (34 percent) in the United States received influenza vaccination in 2005. [15] And in a heart failure clinical trial conducted in 47 countries, the use of influenza vaccination ranged from 0 to 77 percent, with only 21 percent of patients overall receiving influenza vaccination within a year of trial enrolment. [80]

The Pathophysiology of Influenza and CVD

The mechanism by which influenza increases the risk of cardiovascular events is unclear. However, evidence is increasingly pointing to a significant link between the influenza virus and the triggering rupture of vulnerable atherosclerotic plaques, [22, 40, 46] closely associated with the pathophysiology of acute coronary syndrome (ACS). The term ACS describes a spectrum of clinical conditions ranging from ST segment elevation myocardial infarction (MI) to non-ST segment elevation MI and unstable angina (ACS without enzyme or marker release). ACS is caused by narrowing and/or obstruction of the coronary arteries mainly due to rupture of atherosclerotic plaques. Inflammation plays a central role in the development of atherosclerosis and in the occurrence of ACS. [22]

The influenza virus has extensive effects on inflammatory and coagulation pathways. [82] Infection with influenza can cause cardiovascular abnormalities by inappropriately activating the 'coagulation cascade', [12, 73] whereby an inflammatory release of cytokines causes a pro-thrombotic state, local disruption of coronary plaques, as well as physiological effects such as

hypoxia and tachycardia. A consequence of this pathophysiology is acute obstruction of coronary arteries that may be otherwise sub-critically stenosed. [48]

Although several infectious agents are thought to increase cardiovascular risk through a cascade of systemic infection and subsequent inflammation, the influenza virus may play a more specific role in triggering acute events by exclusively targeting areas of atherosclerosis and destabilising pre-existing plaques. [14]

Further, influenza has been shown to produce direct effects on the heart. 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. [48]

Exploring the Research

Numerous studies have shown that influenza vaccinations reduce mortality, hospitalization and acute coronary syndromes (ACS) in patients with coronary heart disease (CHD) and/or HF. [12]

The Flu Vaccination Acute Coronary Syndromes (FLUVACS) study in Argentina was one of the first prospective randomized controlled trials to demonstrate the benefit of influenza vaccination in patients with ACS. [15, 77] This single-blind, parallel group, multi-center trial enrolled 200 patients with AMI and 101 patients with elective percutaneous coronary intervention (PCI). After six-month and one-year follow-ups, cardiovascular death remained statistically lower in the vaccine group than the control group; and on analysing the data after two years, a lower incidence of death in the vaccine group was maintained. The beneficial effect was seen mainly in the patients who had experienced an AMI. [62] Additionally, data on subsequent AMI, collected as part of a composite endpoint, showed that there was no effect of the vaccine on the risk of AMI at one year. [82] The FLUVACS researchers found that

influenza vaccination improved the clinical course of CAD and reduced the frequency of coronary ischaemic events. [62] Although FLUVACS had only 301 patients, it is the only RCT based on the recommendations of the European Society of Cardiology, American College of Cardiology and American Heart Association to have vaccinated patients with cardiovascular disease. [51]

The Influenza Vaccination in Secondary Prevention from Coronary Ischemic Events in Coronary Artery Disease (FLUCAD) study conducted in Poland was a randomized, double-blind, placebo-controlled trial of 658 optimally treated patients with coronary artery disease (CAD) with an average age of 59 years. [13, 51, 62, 77] While no significant influence of influenza vaccination on cardiovascular mortality and the incidence of MI was noted, there was a trend to better MACE-free survival in vaccinated patients in comparison to controls. Furthermore, the study found that vaccination against influenza significantly reduced the risk of coronary ischaemic events (MACE or hospitalization for myocardial ischemia) in comparison to the placebo group. In multi-variable analysis, influenza vaccination emerged as an independent factor associated with lower incidence of coronary ischaemic events. [13, 62]

The 2009 IVCAD trial consisted of 281 patients with CAD in a randomized placebo-controlled study during the 2007-2008 influenza season in Iran. No significant difference was found between the two groups at six months, and none of the secondary outcomes (angina severity, coronary artery stenosis score, cardiac ejection fraction, or cardiac adverse events) were "markedly different" between groups. However, there was a significantly higher rate of at least one MACE (ACS, coronary revascularization or CV death) in the placebo group (rates not provided); and patients in the placebo group had a higher rate of influenza infection, but no other adverse events were reported. This unpublished study demonstrated no reduction in cardiovascular death or myocardial infarction. [40, 77] It was noted that the inability to demonstrate a reduction in fatal events within the two trials that studied patients with relatively stable CAD (FLUCAD and IVCAD) may have been a result of a patient population with low absolute rates of subsequent fatal cardiovascular events. [13, 77]

A randomized placebo-controlled trial of 439 post-ACS patients without a history of prior influenza vaccination was conducted in Thailand from 2007 to 2009. The investigators found no difference in cardiovascular death rates between those vaccinated and control patients but did detect a significant benefit in the vaccine group on the composite secondary outcome of all-cause mortality and hospitalization for ACS, HF, or stroke. [3, 55]

A 2013 meta-analysis of six trials which followed 6,735 patients with varying degrees of cardiovascular risk supported the findings of Phrommintikul et al., identifying an association between influenza vaccination and a significantly lower risk of MACEs within one year. This global meta-analysis of RCTs, which studied patients with high cardiovascular risk, identified influenza vaccination as being particularly associated with cardiovascular prevention in patients with recent ACS. Influenza vaccination was also associated with the lowest risk of cardiovascular events in patients with the highest risk. [3, 73, 77]

A Taiwanese study (2000 to 2013), based on complete clinical information on co-morbidities, procedures, medications and vaccination for more than 98 percent of the population, supports the protective effect of influenza vaccination on primary MACEs. Influenza vaccination was associated with a 20 percent reduction in MACEs among patients 65 years and older and showed that the increased risk of those with a diagnosis of influenza was attenuated by influenza vaccination. [8]

In 2017, Mohseni et al. published the results of a self-controlled study on a large population with HF, based on linked primary and secondary health records in England between 1990 and 2013. The authors found that during the year after a patient was vaccinated against influenza, the rate of hospitalization due to CVD was significantly lower than in a year in which the patient was not vaccinated. [12, 49]

In a meta-analysis of more than 12,000 patients from eight RCTs published as a Cochrane Review in 2015, reviewers found a reduction in cardiovascular mortality among patients vaccinated against influenza. It was concluded that influenza vaccination may reduce cardiovascular mortality and combined cardiovascular events, [12] although the authors noted that the studies were small, had a risk of bias and results were inconsistent. [14]

> *"Investigators concluded that influenza vaccination was associated with reduced risk of heart disease and cerebrovascular disease, as well as the risk of death from all causes during influenza seasons."*
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> Harskamp RE and van Ginkel MW.
> Nichol KL, Nordin J, Mullooly J et al.

Nichol et al. conducted research among more than 140,000 members of managed care organizations aged 65 years or older in the United States during the 1998–1999 and 1999–2000 influenza seasons. Over two consecutive years, influenza vaccination reduced the risk of hospitalization for cardiac disease by 19 percent and reduced the risk of hospitalization for cerebrovascular disease by 16 percent. Therefore, the investigators concluded that influenza vaccination was associated with reduced risk of heart disease and cerebrovascular disease, as well as the risk of death from all causes during influenza seasons. [14, 22, 52]

In 2016, a research study published in Taiwan observed the resistance of vaccinated older adults with acute coronary syndrome to air pollution and weather factors. A case-crossover design was applied to 1,835 older adult ACS patients who were 68 years of age or more, had multiple co-morbidities, and had received influenza vaccination at least once. The population was stratified into two groups: 707 had received influenza vaccinations annually for at least the past three years; the remaining 1128 had not. Findings showed that those participants who received continuous influenza vaccination for at least three years displayed a demonstrably greater tolerance to pollutant exposure, as well as to decreased air temperatures during influenza season, compared to those with only one year of influenza vaccination. [27]

Acute Myocardial Infarction (AMI)

The epidemiological relationship between AMI and influenza was first observed in the 1930s, with increased cardiovascular deaths during the influenza seasons. [1] A peak of both influenza and cardiac deaths in winter has consistently been noted since then; [82] and influenza epidemics are associated with increased hospitalization rates for AMI and other cardiovascular-related conditions. [48]

A wealth of retrospective and prospective studies shows a temporal relationship between the two, with influenza respiratory illnesses preceding AMI by a variable time, with the strongest association occurring in the first three days, lasting up to one year. [48, 82] Multiple observational studies have assessed cardiovascular risk during the influenza

season. Estimates from pooled data indicate that influenza infection, influenza-like illness or respiratory tract infection double the risk of myocardial infarction, [1, 40] and the highest risk is among those with established CVD.

While many infections have been studied for their role in triggering vascular events, the most consistent evidence is for influenza. There is compelling evidence for the association between influenza infection and acute myocardial infarction (AMI). [8, 82] Winter peaks in the incidence of AMI have been linked to climate, metabolic factors and infection. Because known risk factors do not fully account for cases of AMI, current interest is focused on the putative link with respiratory infection. Significant increases in AMI occur during peak winter incidence of pneumonia, influenza and influenza-like syndrome, particularly during years dominated by epidemic rather than non-epidemic Influenza A. This association supports the notion that the increase is caused by influenza rather than cold weather. [67] AMI may increase susceptibility to respiratory illness, but the association between AMI and respiratory infection occurring within four weeks prior to the AMI supports infection as a cause of AMI. [67]

If influenza vaccine protects against AMI, the mechanism is through preventing influenza and thereby preventing the possibility of AMI triggered by mechanisms such as the coagulation cascade. An additional putative molecular mechanism for the protective effect of vaccination is that vaccine-induced antibody cross-reacts with a human bradykinin receptor. It is postulated that this interaction could lead to increased levels of nitric oxide, which increases the efficiency of myocardial oxygen use, as well as leading to increased blood flow through vasodilation and possible angiogenesis. [48]

Evidence is accumulating about the effectiveness of influenza vaccination in coronary disease prevention. Observational studies have shown that the protective effectiveness of influenza vaccine against AMI is between 19 and 45 percent. [26, 48, 67] A meta-analysis of case–control studies showed that influenza vaccine has a summary vaccine effectiveness of 29 percent against AMI. [1] In a meta-analysis of RCTs, influenza vaccine was protective against the outcome of AMI, although the pooled estimate was not statistically significant. [82] However, each RCT showed efficacy of influenza vaccine against composite coronary morbidity and mortality outcomes. [13, 48] Another RCT demonstrated that influenza vaccine reduced major cardiovascular events by 10 percent in patients with ACS during a 12-month follow-up period. [55]

Cerebrovascular Accident ('Stroke')

Cerebrovascular accident is a significant cause of death, disability and long-term illness worldwide. Classical risk factors, such as increasing age, hypertension, smoking, diabetes and heart disease account for only 50 to 60 percent of strokes, raising the possibility of other causative factors. Stroke is more common in winter. [66] Several case-control studies have shown increased likelihood of respiratory symptoms one to four weeks before strokes occur, implying that early treatment or prevention of respiratory infection may also prevent stroke. [66]

Many studies have produced results linking influenza vaccination to reduced rates of brain infarction (stroke). One study reports a significant reduction in the risk of cerebrovascular accidents (CVAs) associated with influenza vaccination. [15] After multi-variate analyses, influenza vaccination remains associated with a reduced risk of stroke. [52, 62]

In a matched 1:1 case-control design with data from the United Kingdom (UK) General Practice Research Database, Siriwardena et al. studied approximately 50,000 cases of stroke and trans-ischaemic attacks (TIA)

and found that influenza vaccination was associated with a 24 percent reduction in risk of stroke but not TIAs. [66] The risk of stroke was significantly lower with early (September to mid-November) but not later influenza vaccination (mid-November onwards), perhaps reflecting the seasonal variation of influenza incidence. This study supports the evidence of Udell's systematic review of RCTs, showing that influenza vaccination is associated with a lower risk of MACEs. [66, 77]

Research published in 2009 sought to determine the impact of influenza vaccination on the risk of venous thromboembolism (VTE) through a case-control study involving 1,454 adults enrolled in 11 French centres (2003 and 2007), comprising 727 consecutive cases with a first documented episode of VTE and 727 age- and sex-matched controls. In the case and control groups, 202 (28.2 percent) and 233 (32.1 percent) subjects, respectively, had been vaccinated against influenza during the previous 12 months. After multi-variate regression analysis, the authors concluded that influenza vaccination is associated with a reduced risk of VTE. [86]

Effectiveness and Safety of the Influenza Vaccine for CVD Patients

The effectiveness of influenza vaccination is dependent on many factors, including the age and immunity of recipients and the effectiveness of the vaccine. Respiratory infections have important seasonal variations in many countries, [12] and the effectiveness of annual influenza vaccines varies depending on the vaccine match to circulating strains. [1, 52] Influenza vaccination is predictably most effective when the inactive influenza strains in the vaccine match the circulating strains in the community. In seasons with a poor match, the reductions in hospitalization and death are fewer than in seasons with a good match. [14].

In a matched case–control design with data from the United Kingdom General Practice Research Database of 78,706 patients, researchers noted that early vaccination (September to mid-November in the northern hemisphere) protected against AMI significantly better than later vaccination, and that repeated vaccination (consecutive five seasons) protected better than vaccination only during the current season. [12, 67] The duration of the protective effect of influenza vaccination against cardiovascular events remains controversial. Many studies postulate a span of up to 12 months, while others restrict the protective effect to the epidemiological season, with an understanding that influenza vaccination is likely to be effective only against circulating strains of influenza virus. [12, 67] The timing is also important, with vaccination status being a valid predictor of AMI risk only if the vaccine was administered prior to the AMI event. [1]

> *"...repeated vaccination (consecutive five seasons) protected better than vaccination only during the current season."*
>
> Ciszewski A.
> Siriwardena AN, Gwini SM

Importantly, no study has indicated higher rates of cardiovascular event for individuals who receive influenza vaccination. A multi-year cohort study of more than 39,000 patients with CVD (either MI or CVA) in the United Kingdom found no increased risk of MI or CVA in the 90-day period after influenza vaccination. In fact, incidence rates of MI and CVA were significantly lower in the 28 days after vaccination than in the period immediately preceding vaccination, although these

differences disappeared with adjustment for age. [15, 69]

Concerns about the acute inflammatory response elicited by vaccination soon after cardiovascular events were largely allayed with a cohort study of close to 40,000 patients who had no short-term risk of AMI or stroke after immunization for influenza, pneumococcus or tetanus. [51, 69] Similarly, the FLUVACS study showed that there was no effect from the vaccine on the risk of AMI at one year after vaccination. [13, 69, 82] Studies also demonstrated that, overall, adverse effects in these patients after influenza vaccination were rarely reported; and those that were reported were generally minor and transient. [40]

The Optimal Vaccination Dosage

The best dose and formulation for vaccination of CVD patients remains unclear. A high-dose formulation has been approved in the United States and Canada for medically stable individuals over the age of 65 years, as older adults exhibit blunted immune responses to standard dose vaccination. [80]. Additionally, HF is often accompanied by a depressed immune response. Therefore, a high-dose influenza vaccination for HF patients has been proposed and remains under clinical and immunological evaluation. [12, 80]

The large-scale, randomized clinical trial, INVESTED (Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure) will enrol 9,300 patients with recent MI or HF, to be observed over multiple influenza seasons. The trial will randomize patients to receive standard-dose quadrivalent versus high-dose trivalent influenza vaccination. Measuring all-cause mortality and cardio-pulmonary hospitalization, this will be the largest and longest study to assess whether high-dose influenza vaccine is superior to standard-dose influenza vaccine in reducing cardiopulmonary events in a high-risk cardiovascular population. [3]

Hung et al. (2010) conducted research in Hong Kong into dual vaccination of older adults with chronic illness, using 23-valent pneumococcal (PPV) and trivalent influenza (TIV) vaccines, to ascertain whether the combination would be effective in protecting respiratory, cardiovascular and cerebrovascular disease complications, thereby reducing hospitalization, coronary or intensive care admissions, and death. Of the 36,636 subjects recruited, 7,292 received both PPV and TIV, 2,076 received TIV vaccine alone, 1,875 received PPV alone, and 25,393 were unvaccinated. At week 64 from commencement of the study, dual-vaccines experienced fewer deaths and fewer cases of pneumonia, ischemic stroke and AMI than unvaccinated subjects. Dual vaccination also resulted in fewer coronary and intensive care admissions, compared with unvaccinated subjects. [29] In addition, several large, prospective studies in Sweden and the United States have shown an additive beneficial effect of dual vaccination, with additional reductions in the risk of hospitalization for influenza or pneumonia, and in death. [29]

Clinical and Policy Implications

The widespread influenza activity of 2012–2013 was a strong reminder of the potential cardiovascular complications that may occur in association with a severe respiratory tract infection. Greater attention to prevention of cardiovascular events is therefore imperative to address the specific pathophysiology underlying this complication, particularly in older patients. Influenza vaccination may prevent cardiovascular events via avoidance of atherosclerotic plaque rupture or other forms of cardiac injury in a vulnerable patient and represents a simple once-annual protective therapy to reduce cardiovascular events. This finding has considerable clinical and health policy importance, given the profound underuse of vaccination among the general public and the potential impact this preventive strategy may have on high-risk patients. [77]

DIABETES

Since people with diabetes are at high risk of developing complications from lower respiratory tract infections, annual influenza vaccination has been specifically recommended for decades. Despite this, vaccination levels remain low. [45] One of the major reasons may be that evidence regarding the clinical benefits of such vaccination is conflicting, and protection has been questioned because of a potential decreased T-cell–mediated immune response. [45]

Several studies have sought to establish the effectiveness of influenza vaccination against serious morbidity and mortality in people with diabetes, but the results of these studies are inconsistent. Colquhoun et al. observed that influenza vaccination reduced hospital admissions of diabetic patients during an influenza epidemic in the late 1990s by 79 percent. In 2002, Hak et al. also found significant vaccine effectiveness among the sub-group of older individuals with diabetes, with reductions in hospitalization for influenza or pneumonia or death from any cause ranging from 50 percent in one influenza season to 21 percent in the second season—attributing this level of effectiveness in part to the fact that the predominating influenza strains matched well with the vaccine. In contrast, a study by Heymann et al. in 2004 failed to find positive clinical effects of such vaccination in the sub-group of older individuals with diabetes. [45]

Voordouw et al. reported in a 2005 study that consecutive annual influenza vaccination is associated with a reduction in all-cause mortality risk, particularly in older individuals with diabetes, whereas first vaccination reduced mortality only marginally. [45]

Conversely, a 2006 study of the clinical effectiveness of first and repeat influenza vaccination in adult and older adult diabetic patients concluded that there was clear evidence of substantial clinical benefits from influenza vaccination among adult individuals with diabetes, most with type 2, independent of age or prior vaccine uptake. With good matching of the vaccine to the influenza strains, the study estimated a vaccine effectiveness of 39 percent. [45]

Epidemiologic studies quantifying influenza vaccine protection against severe outcomes for patients with diabetes are scarce and largely inconclusive. A 2015 meta-analysis found in patients aged more than 65 years a pooled vaccine effectiveness of 38 percent for all-cause death and 23 percent for all-cause admission to hospital. However, the authors noted that these conclusions were limited by the small number of studies identified, lack of experimental studies, low quality of evidence and strong residual confounding in most studies; and they did not identify any studies assessing influenza vaccine effectiveness against cardiovascular events in people with diabetes. [79]

Recognising the substantial health burden caused by seasonal influenza in diabetic patients, a 2016 study examined the effectiveness of influenza vaccination against admission to hospital for acute cardiovascular and respiratory conditions and all-cause death in people with type 2 diabetes. In a retrospective cohort study using primary and secondary care data from the Clinical Practice Research Datalink in England over a seven-year period between 2003/04 and 2009/10, 124,503 adults with type 2 diabetes were enrolled in the study. Outcome measures included admission to hospital for acute myocardial infarction (AMI), stroke, HD or pneumonia/influenza, and death. Vaccine recipients were older and had more co-morbid conditions compared with non-recipients.

After adjusting for co-variates and residual confounding, vaccination was associated with significantly lower admission rates for stroke, heart failure and pneumonia or influenza, as well as all-cause death, and a non-

significant change for AMI during the influenza seasons. The research team concluded that in this cohort of patients with type 2 diabetes, influenza vaccination was associated with reductions in rates of admission to hospital for specific cardiovascular events, and that their findings underlined the importance of influenza vaccination as part of comprehensive secondary prevention in this high-risk population. [79]

FRAILTY

Frailty is characterized by cumulative multi-system declines, impaired homeostasis, decreased physiologic reserve, and increased vulnerability to hospitalization, dependency, and premature mortality in older adults. [42] Conceptualizations of frailty encompass a broad range of biological, psychological and social factors that can contribute to susceptibility to vaccine-preventable diseases (VPDs), factors that are often not considered, but which need to be incorporated into a broader definition of healthy ageing. [30] VPDs are also associated with an age-related increase in serious adverse health outcomes, leading to hospitalization, antibiotic misuse, debilitating complications and/or death. [39] When chronic diseases are present, the outcomes can be even more severe and debilitating. [30]

"Those over 65 years of age account for more than 90 percent of the deaths from influenza and are more likely to develop complications, such as pneumonia, following infection than younger individuals."

Lang PO, Aspinall R.

Respiratory infections cause a severe burden in older populations. Foremost among them is influenza, which is associated with considerable morbidity and mortality in older adults and is a major contributor to functional physical decline. [38] Those over 65 years of age account for more than 90 percent of the deaths from influenza and are more likely to develop complications, such as pneumonia, following infection than younger individuals. In the European Union, between 40,000 and 220,000 deaths per year can be attributed to influenza infection, and the highest prevalence occurs among older adults, especially those with chronic medical conditions or immunological disorders, resulting in increased mortality. [39]

A study in Hong Kong found that the functional status of older nursing home residents affects influenza vaccine efficacy; and that the ability of the vaccine to reduce mortality declined with increasingly impaired functional status. However, influenza vaccination significantly reduced all-cause mortality compared with no vaccination. [7] Despite this finding, the immunization rate for influenza remains low among the frail older adult population in Hong Kong. Even after the government funded a monovalent vaccination program for adults aged over 65 in December 2009, less than three percent received the vaccine, owing to the fear of potential adverse effects. [7]

Although the protective effect of influenza vaccination against hospitalization remains controversial, [42] a Taiwanese four-year study of 5,063 frail older adults (frailty as defined by the Adjusted Clinical Group) found that influenza vaccination did provide benefits to frail older adults in relation to both hospitalizations and mortality, with a seven percent reduction in hospitalization. The protective effect for mortality was greater than for hospitalization; and consecutive influenza vaccination provided protection against total hospitalization as well as a far greater protective

effect on mortality than interrupted vaccination. [42]

A Spanish study of more than 200,000 older adults in the influenza seasons of 2011/2012 and 2012/2013 noted a 16 percent lower all-cause mortality in the vaccinated group in comparison to the unvaccinated. [6]

Research into the prevalence and outcomes related to influenza and pneumococcal vaccinations in a large European population of frail old people living in nursing homes, consisting of 3,510 participants with a mean age of 84.6 years and a one-year follow-up to record incidence of mortality, found that the influenza vaccine, and the combination of influenza and pneumococcal vaccines (but not pneumococcal vaccination alone), were associated with a statistically significant reduction in mortality as compared with no vaccination. [57]

Herd Immunity

While most vaccines are designed primarily to directly protect immunized individuals, there is a significant positive effect on close contacts, neighbours, and even the community when sufficient numbers of the population have been immunized. This process, which has been measured and termed "herd immunity", results in a lower infection rate among non-immunized individuals for infections that are transmitted from person-to-person, such as influenza. Thus, not everyone needs to be immunized to control the disease, and individuals who fail or reject vaccination or for whom vaccination is less effective, ineffective, or contra-indicated would be protected indirectly. [38]

The protection afforded by vaccination of older individuals is frequently incomplete because of impaired immune function and/or co-morbid conditions, so vaccination of healthcare workers (including ancillary staff and informal caregivers) has been recommended as an additional or alternative strategy. In studies comparing long-term care facilities in which influenza vaccination to healthcare workers was either routinely offered or not, vaccine uptake was associated with a substantial decrease in mortality among patients. [39]

The caution sounded against herd immunity is that it may have brought about an increase in the average age of infection, especially when the severity of such diseases increases with age. With fewer infections among young children, the burden of the disease is now mainly borne by older adults. Thus, as the current attitudes towards vaccination in most industrialized countries have led to considerable success of childhood vaccination schedules, there has been an accompanying fundamental change in the epidemiology of the common VPDs. While it is widely believed that current immunization strategies save many lives, VPDs still place a considerable burden not only on older adults but also on the healthcare systems of most developed countries. They are also associated with an age-related increase in serious adverse health outcomes, leading to hospitalization, antibiotic misuse, debilitating complications and/or death. [39]

Nonetheless, as current trivalent inactivated influenza virus vaccines do not offer optimal direct protection to older adult populations, protecting them indirectly through the effect of herd immunity or enhancing their immune response in order to offer higher and broader protection could be useful strategies. [38]

COSTS OF INFLUENZA INFECTION AND COST-EFFECTIVENESS OF VACCINATION

Healthcare Burden

Given that a significant proportion of healthcare budgets are expended on the acute

treatment and long-term management of cardiovascular and respiratory diseases, prevention through identifying and mitigating risk factors is a priority. [2, 18, 48, 54, 56]

Estimates of the cost of managing COPD exacerbations range from 40 percent to 90 percent of the total cost of COPD, with a substantial portion attributable to hospitalizations. [2, 18, 63] Costs per year of life saved in the United States range from US$4350 for smoking cessation programs to US$142–760 for statin use in those under 65 years of age. Further gains in prevention of CHD would therefore likely be cost-effective, especially if using a low-cost strategy such as influenza vaccination. [48]

Besides being simple to administer and cost-effective in protecting against influenza and pneumonia, vaccines can also prevent increased morbidity and mortality associated with VPDs in older people and people with chronic diseases that can result in increased care needs, time off work, and additional services (such as rehabilitation) associated with complications. [6, 23, 30, 42]

Cost-Effectiveness

Influenza vaccination is a relatively cheap, safe and evidence-based public health measure that is currently underused in at-risk populations [1, 48] and there is sufficient evidence to demonstrate that vaccination against influenza is one of the most cost-effective public health interventions. [54, 61] According to the WHO, vaccination can reduce influenza-related morbidity by 60 percent and mortality by up to 80 percent. In addition, the indirect benefits from vaccinations may include savings in terms of reduced related healthcare costs due to reduced disease burden. [54]

Vaccination against influenza is particularly beneficial for people living with NCDs as it relates to reduced mortality, hospitalizations and complications. When the impact of vaccination on NCDs was measured in over 35,000 older adults, mortality from stroke, diabetes, COPD and heart disease was lowered by 65 percent, 55 percent, 45 percent and 22 percent respectively. [54]

Other studies demonstrated that seasonal vaccination reduced the risk of hospitalization by as much as 79 percent in diabetics and 54 percent in persons with COPD. Complications, such as heart attacks in cardiovascular or COPD patients, may be reduced by up to 67 percent, [54, 76] and the likelihood of a stroke reduced by 24 percent. Exacerbations of COPD and CAD may also be reduced by vaccination against influenza, with the effect of reducing the healthcare burden. The greatest protection is offered to those people at the highest risk of complications. [3, 14, 41, 43, 46, 48, 49, 54, 55, 66, 67, 71, 77] A study into the efficacy of dual vaccination demonstrated successful prevention of respiratory and cardiovascular diseases, resulting in a significant reduction in the risk of hospitalizations and death, which can be translated to direct medical care cost savings for older adults. [29].

A systematic review and meta-analysis conducted to estimate the disease burden of MACEs and the related direct and indirect costs in ACS patients in Korea (including 882,258 ACS patients obtained from the 2013 population database) concluded that influenza vaccination would prevent 16,514 MACE-related hospitalizations and 2,764 premature deaths in Korea per year, with an overall reduction in costs of US$86.2 million per year from a societal perspective. [73]

COPD occurs predominantly in older people who have smoked and is characterised by progressive airflow obstruction that is largely irreversible. As the disease progresses, exacerbations can occur several times per year, and may require hospital admission. These exacerbations can take several weeks to resolve, during which considerable morbidity can occur and result in significant healthcare costs. Most

studies suggest that vaccination is very cost-effective. In a 1998 study, Nichol et al. estimated that vaccination was associated with a reduction in healthcare costs of about US$171 per year per high-risk person vaccinated. [56]

A Japanese study into the additive effect of pneumococcal and influenza vaccines on acute exacerbations in patients with chronic lung disease noted that estimated costs for hospitalization due to acute exacerbation range from $5,655 to $7,413 in developed countries. Moreover, the reduced frequency (27.2 percent) of acute exacerbation in the PV+IV group in the study, compared to the IV group, had significant economic implications for patients with COPD. [18]

In an economic evaluation conducted in Thailand based on the results of an RCT, the authors concluded that influenza immunization was highly cost-effective in patients with COPD, with a greater cost-benefit in those with more severe underlying disease. [2, 9]

A retrospective cohort study of the effectiveness of influenza vaccination against admission to hospital for acute cardiovascular and respiratory conditions and all-cause death in people with type 2 diabetes found a significant reduction in the health burden for this cohort. Vaccination was associated with lower admission rates for stroke, heart failure and pneumonia or influenza, as well as all-cause death, during the influenza seasons. [79]

In addition to its effectiveness in reducing disease and mortality, the benefits of vaccination have usually been measured in terms of the averted costs of medical care. [58] However, in the longer term it has been suggested that vaccines can increase lifetime productivity due to improved physical capacity, cognition, and capacity to learn and be actively engaged in community. Reductions in mortality and morbidity also contribute to increased consumption and gross domestic product (GDP). For example, preliminary research

suggested that a five-year improvement in life expectancy can translate into 0.3 to 0.5 percent increased annual growth. Other studies have estimated how lives saved could influence future government expenditure on social programs such as health, education and pensions, as well as influence future tax receipts. [58]

> *"In the longer term it has been suggested that vaccines can increase lifetime productivity due to improved physical capacity, cognition, and capacity to learn and be actively engaged in community."*
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> Quilici S, Smith R and Signorelli C.

A study estimated the governmental return on investment for immunizing adults aged 50 years against diphtheria, tetanus, pertussis, seasonal influenza, pneumococcal diseases and herpes zoster in the Netherlands, by considering how such investments influence ongoing tax revenues to government (e.g. income tax, value-added tax, and social insurance contributions). Based on the investment costs of vaccinating adults aged 50 years, vaccination yielded a benefit-cost ratio of 4.09, suggesting a fourfold rate of return for the government. [58]

In summary, vaccination in older adults will contribute to the promotion of healthy ageing, enabling older adults to assist their family with, for instance, childcare, and help maintain functional ability (versus decline) and the related impacts on health and welfare expenditure. [58]

GAPS AND LIMITATIONS

Gaps

Significant knowledge gaps remain in the impact of disease severity and co-morbidity on influenza vaccine effectiveness. [2, 34, 63] For example, there has been no large, adequately powered multi-center RCT testing influenza vaccination for the prevention of cardiovascular events such as AMI or respiratory disease in older adults. [1, 12, 48, 72, 77] Data is sparse for the primary protective effect of the influenza vaccine in older adults with a range of NCDs; [8, 42, 70] few vaccine studies have considered the functional status of older adults; [7] and there is a dearth of research into the impact of influenza vaccination on influenza-related hospitalizations in older patients with co-morbidities. [27, 65]

A systematic review into seasonal influenza vaccination in patients with COPD found no studies describing the impact of influenza vaccination on quality of life measures or treatment costs for COPD patients, and only one new RCT contributed to the body of data on COPD in the ten years since the 2006 Cochrane Review. [2]

RCTs rarely include frail participants. Few placebo-controlled, randomized clinical trials of older adults have been performed, and none have been powered enough to study severe outcomes, including serious morbidity and mortality. [38, 45]

Limitations

The achievement of an accurate assessment of influenza vaccine effectiveness is fraught with considerable methodological and epidemiological challenges. [37, 38] These include, but are not limited to:

a) Accurate assessment of influenza vaccine effectiveness can be a challenge due to varying case definitions, use of different clinical endpoints, and poor correlates of protection in immunogenicity studies. Diagnostic tests for influenza have varying levels of sensitivity and specificity for influenza-like illness. Further complications in diagnosis can occur due to the large number of patients with influenza-like illness who are culture-negative (40 percent). This further distorts the true extent of the disease burden. [38]

b) Defining influenza for research purposes is difficult since clinical definitions, especially involving recall of the participants, are likely to be affected by recall bias. [82]

c) Studies differ by recruitment methods, vaccine ascertainment methods, type of vaccines, and outcome definitions; in some cases, the latter were not described. In particular, the definition and evaluation of asthma exacerbations are important points of variability across studies. Most studies (experimental and observational) recruited children or adults <65 years old. Only a few studies have assessed influenza vaccination in older people with asthma. [81]

d) There is a major problem in defining asthma, asthma type, and asthma intensity. It is not easy to distinguish between influenza symptoms and asthma exacerbations, and medication for influenza infection can exacerbate asthma. Bacterial infection following influenza infection may be mistaken for asthma. Measuring the incidence of a chronic intermittent disease like asthma is difficult, partly because of its complex intermittent natural history. [72]

e) It can often be difficult to distinguish forms of respiratory distress in patients with heart failure. [3]

f) The effectiveness of influenza vaccination is dependent on many factors, including the age and immunity of recipients and the effectiveness of the vaccine. [14]

All meta-analyses studying estimates of influenza vaccine effectiveness have questioned the quality and interpretation of available data. [38, 40] Many investigators comment on the limitations to the value of research through low

power studies with a small number of subjects. [7, 12, 14, 38, 40, 51, 63, 64, 74, 79, 81] Other limitations in the current body of literature stem from the fact that the research is mainly observational, relying on retrospective and epidemiological studies, containing an inherent risk of confounding and bias, which in turn can yield negative, inconsistent and inconclusive results. [6, 12, 55, 66, 85]

Case–control studies are prone to biases from participant selection and measurement of exposure, [1] offering potential for misclassification. [40, 62] Examples of potential bias from controlled participant selection include: 'healthy user bias', whereby 'healthy' people have higher vaccine uptake than 'unhealthy' people and are likely to exhibit a range of healthy behaviours and have better health outcomes regardless of vaccination; 'frailty selection bias', by which more frail people who are closer to death may be less likely to receive influenza vaccine than other people; [38, 79] studies which are limited to defined patient populations where conditions can be controlled; [70] and cohort and case-control analyses in which lower event risks may be confounded by socio-demographic and health factors also associated with influenza vaccination. [15]

Another reported limitation is that the true impact of vaccines on the outcome of polymicrobial infections is difficult to evaluate, in part because there is little systematic surveillance of bacterial co-infections during seasonal influenza, and as a result the limited data cannot be systematically or consistently validated. [3, 32, 70] The apparent protective effects of influenza vaccine against death outside the influenza season, which are shown in some observational studies, suggest residual biases or mechanisms other than influenza prevention. [14] Moreover, most studies on vaccines focus solely on vaccine-induced responses to the pathogen the vaccine was designed to protect against. [70]

There is also an ethical limitation. Since immunization guidelines recommend vaccination for patients with high-risk conditions regardless of age, it is ethically difficult to conduct large, randomised, placebo-controlled trials of influenza vaccination, even though it would appear desirable to do so. [2, 45, 56]

> *"Most studies on vaccines focus solely on vaccine-induced responses to the pathogen the vaccine was designed to protect against [not secondary benefits]."*
>
> Smith AM and Huber VC

This complex set of limitations has led some researchers and reviewers to conclude that there is insufficient evidence to establish that influenza vaccination has a role to play in reducing risk for patients with NCDs. [14, 34, 37, 55] Some question these assertions, maintaining that studies which found no evidence of benefit had low power, poor case ascertainment, misclassification of vaccination status and lack of investigator blinding. [67] Others confidently state that, despite the limited observational evidence, convincing evidence is emerging of a secondary protective role for influenza vaccination. [67]

RECOMMENDATIONS

Future Research

Robust research of greater scope, scale, depth and power than what currently exists is recommended by researchers and reviewers of the literature alike. They see an urgent need for additional higher-quality evidence in order to establish whether the low-cost, annual, safe, easily administered and well-tolerated therapy of influenza vaccination can reduce the risk and

complications of cardiovascular and respiratory disease beyond current therapies. New research needs to be in the form of adequately powered, randomized, controlled, large-scale multi-center trials, with target groups to include older adults. [1, 2, 3, 4, 14, 18, 31, 39, 63, 66, 67, 70, 71, 72, 75, 77]

Additionally, there is a call for a greater understanding of how age-related changes and their interaction with common chronic co-morbid conditions interfere with the vaccine response, including the impact of immunosenescence. [7, 38]

Cost-effectiveness studies are also needed to compare influenza vaccination as primary and secondary prevention, to further inform preventive health policy. [1]

The need to improve the accuracy of influenza vaccine effectiveness estimates should include exploring the strengths and limitations of various comparison periods for model validation, the influence of important potential confounders, and other methods to quantify the impact of potential residual confounding such as sensitivity analyses. [38] Further understanding of disparities in vaccination rates should involve the use of large-registry data, which would also allow for a temporal outlook. [3, 13, 42] Future observational studies must use a more sophisticated methodological approach when investigating a significant bias prone exposure. [37, 38, 66]

There is a substantial gap in the literature with respect to reporting vaccination coverage by race/ethnicity and socio-economic status, even in North America and Europe. [54] More studies are needed to examine socio-economic status and vaccination uptake, casting a wider net than currently exists since available research comes mainly from low- and middle-income countries, such as North America and European nations. Research is currently insufficient for the efficacious design of strategies appropriate to various national levels

of development and the resources available for healthcare systems globally. [54] As NCDs are on the rise in low- and middle-income countries and tend to concentrate in poorer populations, documenting disparities in vaccination is critical. [54]

Routine surveillance of influenza manifestation and effectiveness of influenza vaccination among people with NCDs and other high-risk groups should be performed and shared across all countries to improve vaccine development and coverage rates, and to inform and stimulate further robust research. [54]

Given the high global burden of AMI, and ischaemic heart disease being the leading cause of death and disability in the world, influenza vaccination could be added to other preventive strategies and confer additional population health benefits on AMI prevention. Patients with ACS and IHD are identified as a risk group for serious influenza infection, with many countries recommending vaccination for people with CVD. [1, 73]

Education / Awareness-raising

Health Professionals

Healthcare settings are places that people with NCDs and other high-risk groups tend to frequent; and it is clear that healthcare workers can act as vectors, unknowingly infecting their patients particularly when the infection is asymptomatic. Annual influenza immunization of healthcare workers can both prevent nosocomial infections and decrease the exposure among high-risk groups. However, as noted earlier, vaccination coverage among healthcare workers across the globe is sub-optimal.

The general lack of awareness among healthcare workers and many clinicians of the explicit relationship between influenza vaccinations and NCD management is an important impeding factor in vaccination uptake among the vulnerable groups, especially people

living with NCDs. Therefore, awareness-building campaigns with a strong educational component are key to a better compliance of healthcare workers with current influenza vaccination recommendations. Priority needs to be given to frontline education on vaccination and VPDs. [30] It is also suggested that mandatory immunization for this cohort could be the most effective strategy for increasing the vaccine coverage rate among healthcare workers. [38, 54]

Influenza vaccination campaigns based on educational interventions influence individuals' decision to be vaccinated when they understand the risks associated with influenza and are motivated to protect themselves against the infection. A 2011 study found that wide-reaching communication campaigns were strongly associated with increased influenza immunization coverage. [54] A recommended strategy to increase coverage among high-risk individuals is to target venues frequented by high-risk groups, such as primary and tertiary care settings situated in hospitals or in clinics and physician practices. This is particularly important for NCD patients, who tend to visit clinics more frequently. [54] Given the fact that personal recommendation by a healthcare professional, particularly a family doctor, is the single factor most likely to encourage vaccination, using physicians as role models of healthy behaviours can also be an effective approach to improve vaccination uptake among NCD patients. [54]

There is a growing trend globally to improve access to vaccine through diverse gateways such as pharmacies. For example, Canadian legislation now permits certified pharmacists to administer influenza vaccination to patients in nine of the ten provinces. [40] This indicates a shift towards viewing these professionals as part of the solution, enabling them to identify people with established CVD who may benefit from the influenza vaccine, to educate their customers about the potential CV benefits and, with approved training, to provide the immunization. [24, 40]

Older Adults Living with NCDs

Educating patients about the other benefits of influenza vaccination may subdue negative connotations about the vaccine and subsequently increase vaccination rates. [62] Healthcare professionals should educate and vaccinate patients at any and all opportunities. However, many healthcare providers, including specialists, do not stock influenza vaccine. All providers could assume the responsibility of having that conversation about vaccination status and schedules, providing education, and ensuring that patients have the latest information to decide about vaccination. [1, 11, 15, 42, 45, 49, 52, 62] There is a need to encourage vaccine uptake wherever indicated as, for example, in people with diabetes (a condition which increases the risk of AMI) and existing cardiovascular disease. [79, 82] It is conceded that a paradigm change may be required to encourage clinicians to see influenza vaccine as a cost-effective prevention strategy for patients with CAD. [48]

In order to "market" the benefits of influenza vaccination to the general public, and in particular to older adults with co-morbidities, a recommended solution is to simultaneously acknowledge that a substantial audience segment believes in the effectiveness of the alternative behaviours thought to "boost" the immune system. This argument can be outlined, while framing influenza vaccination in terms of its positive effect on the immune system through a messaging strategy that emphasizes the unique features of the influenza vaccine—namely, that vaccination leads to a very specific immunological response which prevents influenza. [78] The relative advantage of the specificity of the immune response produced by the influenza vaccine can be contrasted with the more general positive effect of behaviours such healthy eating, physical activity, and getting enough sleep on immune

health. In other words, audiences need to be convinced that, by design, vaccination is the ultimate "immune boost", and even a healthy immune system can use help targeting a pathogen as specific as the influenza virus. [78]

> *"Audiences need to be convinced that, by design, vaccination is the ultimate "immune boost", and even a healthy immune system can use help targeting a pathogen as specific as the influenza virus."*
>
> Ulasevich A, Jacobs S, Mbangdadji D et al.

A multi-faceted comprehensive public health strategy must be applied to increase immunization rates. Social media can be employed to enhance community awareness and education about the potential benefits of dual vaccination of influenza and pneumococcal vaccines, alongside health talks by infectious diseases experts. [29]

Because vaccines are both simple to administer and cost-effective, influenza vaccine represents a tool for public health decision-makers to develop evidence-based preventive interventions to avoid adverse influenza infection outcomes. [3, 14, 30, 61]

National and Global Perspectives

Vaccination is a low-cost, potentially lifesaving procedure. It is expected that owing to increasing antibiotic-resistance and global population ageing the role of vaccination will grow rapidly and should become a first line of prevention of avoidable infections and their cardiovascular complications. [12] In that context, public health initiatives are needed to improve the current low vaccine uptake, such as better immunization strategies. [31, 42, 81]

Improving influenza vaccination coverage among people living with NCDs is a complex task, and multiple strategies are needed at national and international levels to achieve the goal of 75 percent vaccination rate. [54] Globally, it is critical to include influenza immunization as part of the monitoring framework for NCDs and to underscore the vaccine's importance in secondary prevention of these diseases. [54] At the national level, strategies should target not only those at high risk of influenza complications, such as NCD patients, but also those at elevated risk of both contracting and transmitting the virus, such as schoolchildren and healthcare workers. [54]

Health Product Gain

Investment in vaccination offers a wide range of social and economic benefits that can potentiate gains for the individual and for society. [58] Hence, additional methods should be considered to capture the full benefits of vaccination, such as assessment of vaccination's impact on absenteeism, presenteeism, or individuals' lifetime earnings. [58]

Health is a key factor for the promotion of social and economic growth at the regional, national and global levels. The vaccine industry and their programs targeted at populations of different ages can contribute substantially to a nation's growth by maintaining and improving healthy behaviours throughout their lives. This will require continuous investment in research and development to protect populations against an increasing number of existing or new vaccine-preventable diseases. There is a clear need for a commitment to vaccination, not only from health authorities but also from governments. [58]

CONCLUSION

It is generally agreed that annual influenza vaccination rates are unacceptably low, and people with NCDs are at high risk of complications, including death, when infected with influenza. [30, 38, 54, 62] Despite the limitations in the research, there is consistent and compelling evidence to suggest that annual influenza vaccination reduces exacerbations of respiratory illness and cardiovascular disease, and diabetes. [48, 51, 67, 77, 82] Annual influenza vaccination is a simple, cost-effective intervention that can decrease all-cause mortality in Given the high global burden of such NCDs as respiratory and cardiovascular disease, and the severity of complications in older people with co-morbidities, prevention through identifying and mitigating risk factors is a priority. [48]

> *"There are few interventions in all of medicine that are as low-cost, low-risk, well tolerated, or easy to administer and with such large potential clinical benefits. Don't we owe it to our patients to offer them this one-shot deal?"*
>
> Vardeny and Solomon

The aim of encouraging new, robust research into the secondary protective benefits of influenza vaccination in older adults is to determine the extent to which the influenza vaccine can promote healthy ageing by limiting or preventing the adverse effects of infection in older people. This will enable a more accurate and proactive engagement in optimal influenza vaccination coverage among older adults, creating opportunities for improvements in their quality of life and concomitant cost-savings in national healthcare budgets.

It is hoped that this synthesis of the literature will assist the scientific community to move towards a deeper understanding not only of the primary protective effect of influenza vaccination against influenza infection, but also of the secondary protective benefits offered by the vaccination.

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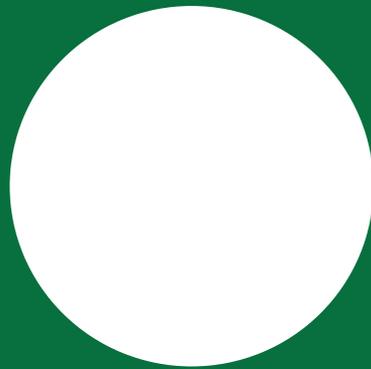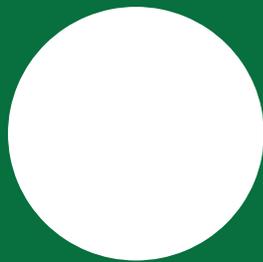
Pictured on front cover: Mr Graeme Prior and Ms Helen Hamlin
Photographed by: Mr Greg Shaw