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INFLUENZA-ASSOCIATED ACUTE MYOCARDIAL INFARCTION AND ISCHEMIC STROKE: IMPACT OF VACCINATION. REVIEW.

Medicine

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ABSTRACT

Acute infections have long been noted to be associated with an increased risk of acute myocardial infarction (MI). In recent years, myriad studies have demonstrated that viral respiratory infections and seasonal influenza in particular, confer a significantly increased risk of both myocardial infarction and ischemic stroke (IS). Men, older patients, and patients with prior atherosclerotic vascular disease are especially vulnerable to influenza-associated vascular events, and the risk appears to be greatest on the first and second week following infection. Several intriguing mechanisms have been implicated, including an inflammation-associated prothrombotic state and effects of cytokines on the stability of pre-existing atherosclerotic plaques. The causal association between influenza and vascular events is strongly supported by several studies that clearly show that the incidence of MI and IS was roughly halved in patients vaccinated against influenza. Since vaccine hesitancy remains prevalent and the goals of 70-75% people vaccinated had not been reached, educating patients on the potential of preventing "heart attack and stroke" may help overcome suboptimal influenza vaccine uptake in the population.

KEYWORDS

Influenza; Influenza vaccination; Vaccine hesitancy; Vaccine coverage; Acute myocardial infarction; Ischemic stroke; Primary prevention

Most influenza outbreaks begin abruptly and manifest attack rates of 10-20% of the general population (1). The remarkable mutations of these viruses allow them to often escape recognition by the host's immune system and replicate, spreading between people by droplet infection and causing a wide spectrum of clinical manifestations from nearly asymptomatic to severe, life-threatening illness in the host (2, 3). Thus, seasonal influenza infections remain a major cause of morbidity and mortality worldwide. Elderly patients are especially vulnerable and as many as 90% of influenza-related deaths occur among senior citizens (4). Other common concurrent risk factors of poor outcome may add to the risk of elderly (≤65 years of age) patients. These common risk factors include residents of long-term care facilities, obesity, glucocorticoid or other immunosuppressive medications, chronic lung or heart or kidney disease, and neuromuscular disorders (5).

Seasonal influenza vaccination in adults and in the elderly in particular, constitutes an effective mode of reducing influenza-associated morbidity and mortality. The US Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for all individuals six months of age and older (6). However, vaccine effectiveness is far from 100% (7) and in the elderly may be just 39% (95% CI: 29.4-47.8%) due to immunesenescence, although clearly effective in preventing 75% of influenza-related death (8). In addition, vaccine coverage remains quite far from set targets such as the "At least 75% in the elderly" of the European Union Council (9). The NHIS survey showed an increase in influenza vaccination coverage among adults aged ≥19 years, but the overall yield was 44.8% (10). Among adults aged 65 and over, 69% had a recent influenza vaccine, less if they were poor, more if their age was over 75 years (11). In view of their substantially increased risk of adverse outcomes including mortality (3, 12), such suboptimal coverage is highly significant. Even among the large proportion of US adults with significant underlying medical conditions such as COPD, diabetes, or heart disease that confer a special risk of more severe disease and complications (13), influenza vaccination coverage is quite low (14).These missed opportunities are highly important since wide coverage not only protects individuals directly, but is also protective for communities by reducing transmission and the risk of infection of other in an exponential form, so called "herd immunity" (15).

Barriers to influenza vaccine uptake and methods to increase coverage

An unwillingness to vaccinate has remained prevalent over time despite unequivocal recommendations. Among predictors of vaccination, socio-demographic variables which are non-modifiable including age, gender, and ethnicity have been reported to play an important role (16). In addition, individual patient's attitudes often determine vaccine acceptance, including perceptions of personal susceptibility to influenza, perceptions of its severity, belief in the effectiveness of the vaccine, experience with the vaccine in previous seasons, worry about possible adverse effects of the vaccine, as well as issues of availability and cost. Other potential patient factors include occupation, marital status and health literacy. Thus, a variety of barriers had been identified (17) and vaccine uptake rate is also related in part to primary care physician recommendation and other initiatives to overcome vaccine hesitancy.

How can influenza vaccination coverage be improved? A recent meta-analysis identified and examined a total of 61 randomized controlled trials (RCTs) involving 1,055,337 participants (18), providing important insights into what interventions were more likely to increase influenza vaccination rates. Prominent successful interventions tested (albeit in a single study) included invitations by clinic receptionists; nurses or pharmacists educating and nurses vaccinating patients; and medical students counseling patients. Many other sorts of interventions proved useful including simple or personalized reminders; customized or form letters, health risk appraisals, home visits by healthcare workers in different team composition, making vaccine free to the patients, as well as physician-centered interventions such as payment, competition, or chart reminders (18). Nevertheless, vaccine hesitancy remains prevalent (19) and "real world" uptake cannot replicate the achievement of carefully conducted RCTs.

Influenza and increased risk of acute myocardial infarction (AMI) and ischemic stroke (IS)

In 1971/2 a British physician observed an increase in hospital admissions for AMI during an influenza outbreak. A subsequent study revealed significantly increased AMI mortality in 'influenza weeks' vs. 'control' weeks (20). Much later, a case-control study showed that influenza vaccination may be protective against AMI (21), but the association remained controversial (22). The seminal study by Smeeth et al. provided for the first time robust evidence on the association, its scope, and postulated pathogenesis (23). Using a case-series method, based on the extensive UK General Practice Research Database, the risk of either a first AMI or stroke in the initial days after a "systemic respiratory tract infection" was found to be significantly increased yielding incidence ratio of 4.95 (95% CI 4.43- 5.53) for AMI and 3.19 (95% CI 2.81-3.62) for stroke, waning with the distance from the acute infection. The findings supported the concept that systemic inflammation itself alters the probability of the occurrence of a vascular event, possibly due to a short-term alteration of endothelial function or other mechanisms such as changes in plaque composition in persons who have had a fairly stable degree of atherosclerosis for many years (23).

Since then, fairly extensive research provided confirmation as well as further, more specific information. For example, a case-control study reported a strong association between recent respiratory infection and (within 7 days) both AMI (odds ratio 2.1) and stroke (OR 1.92) (24). Notably, in these early studies, respiratory infections were not

specified, controls could not be comparable to cases with certainty, and the mechanism remained speculative. A decade later however, more solid data was forthcoming. Kwong et al. found an excess incidence of laboratory-confirmed influenza (and non-influenza acute respiratory infections as well) in the week preceding AMI (25). A time-series analysis of hospital admissions for both conditions found them to coincide significantly with a variety of viral respiratory infections including influenza (26). In the ARIC study, both inpatient infections (14-day OR 12.83) and outpatient infections (14-day OR 3.29) were strong triggers of incident coronary heart disease, and inpatient infection was also an unequivocal trigger of IS (27, 28). With accumulating research data, it became apparent that the influenza-associated risk applied specifically to IS, with OR 2.88 (95% CI 1.86-4.47) in the first 15 days post influenza-like illness (28, 29); that most AMI were non-ST elevation; and that men, patients≥65 years, and patients with previous vascular diseases were especially prone (30). The mechanism involves a cluster of changes. First, systemic inflammatory and immune response can promote plaque instability by release of inflammatory cytokines and proteolytic enzymes within atherosclerotic plaques. Second, during infection, platelet activation, endothelial dysfunction and decreased fibrinolysis can be found, facilitating thrombosis. Third, biomechanical stress, and increased metabolic demands add to the risk of thrombosis (23, 31). Thus, acute influenza can be considered a non-traditional cardiovascular risk factor, as elegantly confirmed in a recent study (32).

As mentioned above, influenza is also associated with an increased risk of IS, reported even in "young stroke" (33). Infection during the preceding week was significantly more common among adults at any age who had IS vs. matched controls, and again, respiratory tract infections dominated (34). The association was strongly supported by a wide range of clinical studies, as well as experimental animal models (35).

Influenza vaccination ameliorates risk of acute vascular events

The remarkable effect of influenza vaccination on the incidence of acute vascular events (both cardiac and CNS) highlights a convenient and accessible mode of prevention, provided an increased influenza vaccination uptake can be achieved. Grau et al. found more than 50% reduction in the risk of stroke/TIA among vaccinated patients after careful adjustment for confounding factors (30). Lavallee et al. found a very similar effect (OR= 0.50) (36), and an American study of two large cohorts of >280,000 community-dwelling elderly patients of whom >50% had been vaccinated, reported that vaccination against influenza was associated with a 19% reduction in the risk of hospitalization for cardiac disease, IS reduction of 16-23% , and a 48-50% reduction in the risk of death from all causes (37). An important prospective cohort study from Hong Kong, recruiting outpatients aged ≥65 years demonstrated a clear cut benefit for those who received both pneumococcal and influenza vaccination: At week 64, they experienced fewer deaths (HR 0.65), fewer IS (HR 0.67), and AMI (HR 0.52), compared with similar but unvaccinated subjects (38). A meta-analysis encompassing 6 studies and 6735 elderly patients (mean age, 67 years) concluded that influenza vaccination was associated with a lower risk of composite cardiovascular events: 2.9% vs. 4.7% (RR 0.64) (39). Thus, we can state with confidence that timely influenza vaccination reduced major adverse cardiovascular events (aIR 0.5) and cardiovascular mortality (aIR 0.5) (30, 40). This remained true when patients with diabetes, CKD, COPD or CHF were separately investigated. Event-naive patients as well as patients previous MI/IS shared significant prevention benefits (40).

Using the influenza / vascular events association to promote vaccination of elderly patients

Can this information be utilized for increasing vaccine uptake in the elderly population?

Currently, no single method is known of changing patients' often-negative 'idee fixe' about being vaccinated (41). Recently, we approached 100 consenting community-dwelling patients ≥65 years old (all fully insured, free vaccine) asking them 5 short questions:

1. Have you been vaccinated against influenza last year?
2. Do you intend to be vaccinated this year?
3. If not, can you explain why not?
4. Do you know that influenza increases your immediate risk of heart attack and stroke?
5. Do you know that this risk is effectively mitigated by getting the influenza vaccine?

Following the last question, a short vivid verbal instruction on influenza and risk of "heart attack and stroke", and prevention by vaccination was given by a physician. Within a week, question No. 2 was repeated by another person, and 6 weeks later the charts of the patients unwilling to be vaccinated before instruction were checked for influenza vaccination.

No patient refused to participate. Mean age was 73.9±6.5 years (median 73 years, range 65-94), 54% were female and 43% were smokers (current or past). Many patients had a history of symptomatic CAD (39%), CVA (12%), and PAD (4%). Diabetes mellitus (31%) and/or hypertension (84%) were highly prevalent. In 2017, 54% had been vaccinated against influenza, only 47% planned to be vaccinated in 2018. Reasons cited for refusal included fear of adverse reactions [27], falling ill despite being vaccinated [7], and perceived low personal risk of infection [19]. *None* of the 100 was aware of the association of influenza with an increased risk of vascular events or its amelioration by timely influenza vaccination. Of the 53 patients who were *not* going to be vaccinated, 34 (64% of 53) changed their mind when asked again following a short physician-administered verbal instruction on the first encounter. All encounters were completed in ≤5 minutes. Chart review 6 weeks later indicated that 27 had already been vaccinated (51% of the 53 unwilling patients) (Figure 1) (42).

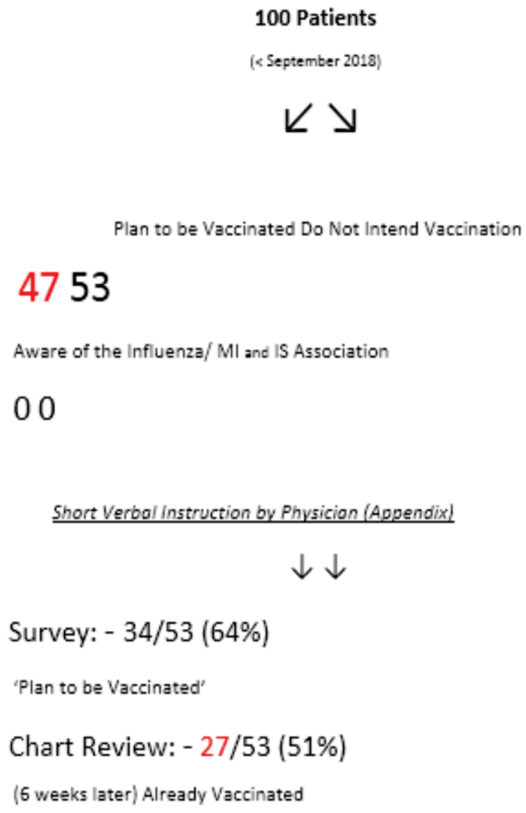

Figure 1. Flow chart of the patients included in the study.

In conclusion, having noticed many patients who have changed their lifetime habits (e.g. heavy smoking, sedentary lifestyle) *after* myocardial infarction or an ischemic stroke and the prevalent fear of these dreaded outcomes, we examined awareness of the influenza/vascular events association and its potential to encourage vaccination uptake among elderly patients. Since an educational advice given by a physician has high impact, a personal patient-physician contact was deemed essential. As reported above, our current level of knowledge suffices to educate patients on the potential benefits of influenza vaccination for cardiovascular prevention. The need for this is self-evident, as none of the patients in the study was aware neither of the increased risk of "heart attack and stroke" associated with influenza, nor of the ability of a timely seasonal

influenza vaccination to reduce much of the risk.

Vascular disease risk factors and ASCVD are highly prevalent in the elderly and in our cohort, making them especially vulnerable to influenza-associated vascular events. Once told of the risk which appears to be roughly halved by being vaccinated (40), 34/53 (64%) patients who thought of skipping the vaccine, changed their attitude and actual vaccination was later recorded in 27 patients (~half of the initially 'unwilling' patients, 79% of those 34 who changed their attitude). Additional patients may have taken the vaccine at a later date. Thus, a short verbal educational intervention by a clinician, pointing out the increased risk of serious vascular events was sufficient to convince 64% of unwilling patients to change their attitude. Vaccination was actually undertaken in at least 51%. This is in line with the findings that individual educational initiatives embedding new knowledge were the most successful in addressing vaccine hesitancy (43) and brief physician counselling can lead to long-term smoking cessation (44). Results may be possibly extrapolated to patients under 65 years, which may be especially helpful if prior ASCVD or multiple risk factors exists but need to be confirmed in a future prospective study.

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