Influenza Vaccination and Major Adverse Vascular Events in High Risk Patients

Running title: Johnstone et al.; Influenza vaccination and risk of vascular events

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Abstract:

**Background** - We sought to determine the association between influenza vaccination and major adverse vascular events, as the association remains uncertain.

**Methods and Results** - 31,546 participants were enrolled from 40 countries. Eligibility included age $\geq 55$ years and known vascular disease. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, or stroke during 4 influenza seasons (2003-2007). Influenza vaccination was associated with a lower risk of the outcome during three influenza seasons (defined using WHO FluNet reports); 2004-2005 (adjusted OR (aOR) 0.62 [95% CI 0.50 – 0.77]), 2005-2006 (aOR 0.69 [95% CI 0.53 – 0.91]) and 2006-2007 (aOR 0.52 [95% CI 0.42 – 0.65]); the same years circulating influenza matched the vaccine antigen. In 2003-2004, there was an incomplete match between circulating influenza and the vaccine antigen and there was no association between influenza vaccination and the outcome (aOR 0.96 [95% CI 0.73-1.27]). However, tests of potential biases in the analyses revealed associations between influenza vaccination and the outcome during non-influenza seasons except 2003-2004. Summary OR in the influenza season (OR 0.65 [95% CI 0.58 – 0.74]) and non-influenza season (OR 0.66 [95% CI 0.57 – 0.76]) were almost identical. Reduction in risk of non-cardiovascular death associated with the influenza vaccine ranged from 73% to 79%.

**Conclusions** - Although initial analyses suggest that influenza vaccination was associated with reduced risk of major adverse vascular events during influenza seasons when the influenza vaccine matched the circulating virus, sensitivity analyses revealed that risk of bias remained. A randomized trial is needed to definitively address this question.

**Key words:** heart failure; infection; myocardial infarction; prevention; stroke
Introduction

It is well established that deaths due to acute myocardial infarction as well as stroke mortality increase by approximately 10% to 15% in the winter months\(^1,2\). Influenza, which circulates during winter months, may be an important causative factor for this increase in vascular mortality. Several observational studies have established an association between influenza infection and major adverse vascular events\(^3-6\). Mechanisms that have been postulated to explain this increased risk include the precipitation of plaque rupture, endothelial dysfunction, reactivation of other latent infections leading to plaque rupture, fever associated tachycardia and metabolic derangements related to infection including elevation of triglycerides and serum glucose levels\(^7\).

Whether immunizing high-risk patients against influenza reduces major vascular events is uncertain\(^1\). Observational studies that have evaluated the association between influenza vaccination and major adverse vascular events such as myocardial infarction and stroke have had conflicting results\(^7-17\). A meta-analysis of two small randomized trials showed no significant difference of immunization in preventing acute myocardial infarction or cardiac death, although point estimates of effect tended towards protection and a recent small open-label randomized trial showed a reduction in major adverse vascular events in influenza vaccinated patients with a history of acute coronary syndrome\(^1,18-21\).

We sought to determine whether influenza vaccination was associated with a reduction in major adverse vascular events using a large clinical database consisting of prospectively collected data from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trials\(^22-24\).
Methods

Study population

Participants in the ONTARGET/ TRANSCEND trials were ≥55 years and had a history of known vascular disease or diabetes mellitus with documented end-organ damage\textsuperscript{22}. These two double blind, placebo-controlled randomized trials were conducted from 2002 to 2007 in order to examine the efficacy of an angiotensin receptor blocker (Telmisartan) and an angiotensin converting enzyme inhibitor (Ramipril) alone versus in combination (ONTARGET) and an angiotensin receptor blocker (Telmisartan) versus placebo in participants intolerant to angiotensin converting enzyme inhibitors (TRANSCEND) in reducing cardiovascular outcomes\textsuperscript{22-24}. Patients with symptomatic congestive heart failure, uncontrolled hypertension, history of a heart transplant, those with a major non-cardiac illness expected to reduce life expectancy or interfere with study participation, and those with significant disability precluding regular follow-up visits were excluded\textsuperscript{22}.

In total, 31,546 participants were recruited from 733 sites in 40 countries over the study period. Participants were reviewed 6 weeks after enrollment and then every 6 months for up to 5.5 years (median 56 months). In total, 99.8% of participants were followed until the primary outcome occurred or the end of study. The study was approved by the ethics review board of local institutions in all countries. All participants provided written informed consent.

Influenza Vaccination

Annual immunization status with trivalent influenza vaccine was determined using a self-reported questionnaire at the study enrollment visit, 2-year follow-up visit and end of study visit. Self-reported questionnaire has been shown to be a highly accurate method for determining influenza vaccination status in adults\textsuperscript{25}. Influenza vaccine is reformulated annually to include...
antigens from influenza strains anticipated to circulate in the ensuing influenza season. We therefore analyzed the ONTARGET/TRANSCEND database as a series of 4 cohorts each corresponding to an influenza season. For example, the 2003-2004 cohort included all patients enrolled in the study by June 1, 2003 and followed until May 31, 2004. The following cohorts were included: 2003-2004, 2004-2005, 2005-2006 and 2006-2007. An important limitation of using self-reported questionnaires is that we were only able to determine if an individual patient had been vaccinated against influenza for a given season and not the date of vaccination. We did not conduct analyses for the 2002-2003 influenza season because too few participants were enrolled. Participants who developed the primary outcome or died (from any cause) were excluded from subsequent analysis.

Primary Outcome

The primary outcome was a composite of major adverse vascular events, including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. All study outcomes were prospectively adjudicated by a central committee blinded to study medications allocation and influenza vaccination status with the use of standardized criteria.

Statistical Analysis

Baseline characteristics for each influenza season were stratified according to history of influenza vaccination and compared using $\chi^2$ or Fisher’s exact test or Student’s t-test as appropriate. Logistic regression models were used to estimate the unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between influenza vaccination and the composite primary outcome during each influenza season (2003-2007). Complete cases analysis was performed in the event of missing data as there was far less than 10% missing values for all variables; missing influenza vaccination status ranged from 0.36% in the 2006-
2007 cohort to 1.5% in the 2003-2004 cohort. We defined influenza season for the southern hemisphere as June 1 – November 30 and as December 1 – May 31 for the northern hemisphere. The dates encompassed the peak influenza activity for all participating countries; influenza surveillance was gathered using the World Health Organization Global Influenza Surveillance Network, FluNet reports\textsuperscript{26}.

To avoid lack of independence associated with counting multiple outcomes, only the first outcome was counted. Models were adjusted for potential confounding variables including history of coronary artery disease, diabetes, hypertension, stroke, admission to a nursing home and use of ASA, beta-blocker, lipid lowering drug, ACE inhibitor or angiotensin II inhibitor. We also created a propensity score for influenza vaccine use to reduce the effect of bias on the basis of a tendency for healthier persons to be vaccinated against influenza\textsuperscript{27,28}. The propensity score included the following variables: age, sex, body mass index, ethnicity, education, vitamin use, smoking history, alcohol use and history of pneumococcal vaccination. The co-variates included in the propensity score were selected \textit{a priori}. Age, sex, education and markers of healthy living have been associated with influenza vaccination\textsuperscript{29}, thus these were the co-variates chosen for the propensity score. Co-morbidities that are risk factors for influenza infection have also been associated with influenza vaccination, however we did not include this in the propensity score as all patients in the study were at risk of influenza due to co-morbidity based on inclusion criteria.

Seven additional sensitivity analyses were conducted to assess the risk of bias in our study. First, we identified the influenza seasons where the antigen in the vaccine was well-matched to the predominant influenza isolate circulating in the study regions\textsuperscript{30-39}; the hypothesis being that reduction in the primary outcome would only be seen during such well-matched seasons. Second, we conducted analyses during the non-influenza season, postulating that the
influenza vaccine would have less association with the pre-specified outcome in the non-
influenza season compared to the influenza season. Non-influenza seasons were defined as
December 1 – May 31 for the southern hemisphere and June 1 – November 30 for the northern
hemisphere (all weeks not included in the influenza season for a particular study year).

Third, the adjusted OR for each influenza season were combined to create a summary
OR. The adjusted ORs were combined to help improve precision of the estimate and to
determine whether there was heterogeneity within the estimate. Our a priori hypothesis to
explain possible heterogeneity, were differences due to well-matched versus incompletely
matched vaccine seasons. Reduction of heterogeneity and a significant test of interaction on the
basis of well-matched versus incompletely matched vaccine seasons would increase the
confidence in our results. The generalized estimating equation (GEE) approach was used to
account for the correlation between each cohort, as each cohort included similar participants.
A summary OR for the non-influenza seasons was also created. Heterogeneity was tested for
correlated sample. We defined significant heterogeneity as \( p<0.1 \).41

Fourth, we evaluated the effect of influenza vaccination history over several influenza
seasons on our primary outcome. We hypothesized that evidence of mounting immunity and/or
persistent immunity would increase the confidence in our results. Fifth, because we did not have
information on date of influenza vaccination for the patients, and simply classified patients as
influenza vaccinated or not vaccinated for a given season, we could have introduced immortal
time bias into the analyses.42 We therefore restricted analyses of the primary outcome to patients
who had study visit dates during the three months when the vaccine was most likely to have been
given (i.e. October, November and December in the Northern Hemisphere and April, May and
June in the Southern Hemisphere). We hypothesized that if the point estimates in these analyses
were similar to the point estimates from the full analyses, presence of immortal time bias would be less likely.

Sixth, we examined the association between influenza vaccination and all non-cardiovascular deaths. Previous studies of influenza vaccination have demonstrated reductions in all-cause mortality of up to 50%, an implausible reduction given that the proportion of deaths due to influenza is estimated to be 5%\(^4\). This overestimate of vaccine effectiveness has since been attributed to bias\(^4\). Thus we hypothesized that any reduction in mortality associated with the influenza vaccine beyond 5% would be due to bias.

Last, we evaluated the impact of the pneumococcal vaccine on major adverse vascular events. One study found an association between pneumococcal vaccination and risk of cardiovascular outcomes; the authors hypothesized that pneumococcal vaccination may protect against cardiovascular events by reducing the risk of atherosclerosis through prevention of \textit{Streptococcus pneumoniae} infection\(^4\). However there were several limitations of this study and others have not confirmed this association\(^9,12,16,17,45\). Thus, we hypothesized that we would not detect an association between pneumococcal vaccination and major adverse vascular events, and if an association was detected, it would likely be due to confounding bias. The model was adjusted for the following co-variates: coronary artery disease, diabetes, hypertension, stroke, admission to a nursing home and use of ASA, beta-blocker, lipid lowering drug, ACE inhibitor or angiotensin II inhibitor and a propensity score for pneumococcal vaccination which included age, sex, body mass index, ethnicity, education, vitamin use, smoking history, alcohol use and history of influenza vaccination. Statistical analyses were carried out using SAS version 8.2 (SAS Institute Inc, Cary, North Carolina).
Role of the Funding Source

The study sponsor, Boehringer Ingelheim, played no role in the study design, data collection, analysis of the data, interpretation of the data, the writing of the report or decision to submit the paper for publication.

Results

Patient Characteristics

Baseline characteristics of participants in each influenza season, stratified by influenza vaccination status, are presented in Table 1. The proportions of participants receiving the influenza vaccine varied by year, ranging from 28% during the 2005 – 2006 influenza season to 47% during the 2006 – 2007 influenza season. Influenza vaccinated participants were more likely to be older, male, have known coronary artery disease, smoke and receive the pneumococcal vaccine and were less likely to have diabetes, hypertension or history of stroke.

Influenza Vaccination and Risk of Major Adverse Vascular Events

In the unadjusted analysis, influenza vaccination was associated with a reduced risk of the primary outcome during three influenza seasons where the circulating viruses were well-matched with the vaccine antigen: the 2004-2005 influenza season (OR 0.74 [95% CI 0.61 – 0.90], p=0.003), the 2005-2006 influenza season (OR 0.76 [95% CI 0.58 – 1.0], p=0.046) and the 2006-2007 influenza season (OR 0.59 [95% CI 0.48 – 0.73], p=<0.0001)(Table 2). Influenza vaccination was not associated with a reduced risk of the primary outcome during the incompletely matched influenza season; 2003-2004 (OR 1.08 [95% CI 0.83 – 1.40], p=0.55).

The results were similar in the adjusted analysis. There was an associated reduced risk of the primary outcome in the influenza vaccinated group when the influenza virus matched the vaccine
antigen well (2004-2005 (aOR 0.62 [95% CI 0.50 – 0.77]), 2005-2006 (aOR 0.69 [95% CI 0.53 – 0.91]) and 2006-2007 (aOR 0.52 [95% CI 0.42 – 0.65]), but there was no association in 2003-2004 when there was an incomplete vaccine antigen match with the circulating influenza virus (aOR 0.96 [95% CI 0.73-1.27]) (Table 2 and Figure 1A). When we performed the analysis during the non-influenza season, the point estimates were similar to the influenza season (Table 3 and Figure 1B).

The summary OR for the four adjusted OR from the influenza seasons was 0.65 [95% CI 0.58 – 0.74, p<0.001], and there was statistically significant heterogeneity (p=0.003). Heterogeneity remained when only the three well-matched influenza seasons were combined (summary OR 0.60 [95% CI 0.52 – 0.68], p-value for heterogeneity p=0.09). However, the interaction test with the incompletely matched influenza season (adjusted OR 0.96 [95% CI 0.73-1.27] was significant (interaction p=0.003). The summary OR for the four adjusted OR from the non-influenza seasons was 0.66 [95% CI 0.57 – 0.76], p<0.0001, p=0.11 for heterogeneity.

Patient’s influenza vaccination history appeared to influence the primary outcome (Table 4). During the 2006-2007 influenza season, influenza vaccinated patients with a history of prior influenza vaccination during the prior two influenza seasons appeared to have fewer major adverse vascular events than those without a history of vaccination (i.e. evidence of mounting immunity, p-value for trend = 0.0096). Similarly, non-influenza vaccinated patients with a history of influenza vaccination appeared to have fewer major adverse vascular events than those with no vaccination history during the prior to influenza seasons (i.e. evidence of persistent immunity, p-value for trend=0.0085).

Restricting analyses of the association between influenza vaccination and major adverse vascular events to study visits during the three months when influenza vaccination was most
likely to occur to evaluate the possible impact of immortal time bias revealed point estimates similar to the full analyses: 2004-2005 influenza season 14/813 for vaccinated patients versus 44/1181 for non-vaccinated patients (OR 0.45 [95% CI 0.25 – 0.83]), 2005-2006 influenza season 9/673 for vaccinated patients versus 28/1397 for non-vaccinated patients (OR 0.66 [95% CI 0.31 – 1.41]) and 2006-2007 influenza season 3/59 for vaccinated patients versus 24/101 for non-vaccinated patients (OR 0.17 [95% CI 0.05 – 0.60]).

**Influenza Vaccination and Risk of Non-Cardiovascular Deaths**

In adjusted analysis, non-cardiovascular death was associated with the influenza vaccine; associated reductions in risk ranged from 73%-79% (Table 5). Adjusted analysis could not be performed for the 2003-2004 influenza season due to too few deaths during these time periods.

**Pneumococcal Vaccination and Risk of Major Adverse Vascular Events**

There was no association between pneumococcal vaccination and the primary outcome during any of the influenza seasons (Figure 2).

**Discussion**

In this large, prospective, multi-national study, upon initial analyses, we found influenza vaccination to be associated with a reduced risk of major adverse vascular events during the influenza season when compared to non-influenza vaccinated participants, when the predominant circulating influenza virus was well-matched to the influenza antigen contained in the influenza vaccine. These findings support the results of a meta-analysis of two small clinical trials and a recent small open-label trial that have attempted to address whether influenza vaccination reduces major adverse vascular events. Although the meta-analysis of the two trials, in which there were very few events, showed no statistically significant difference in acute
myocardial infarction (16/476 vs. 19/483 for non-vaccinated participants RR 0.84 [95% CI 0.44 – 1.64]) or cardiac death (11/476 vs. 26/483 for non-vaccinated participants RR 0.51 [95% CI 0.15 – 1.76]) the point estimates tended to show protection¹,²⁰. A recent randomized trial evaluated whether the influenza vaccine prevented major adverse vascular events in patients with a history of acute coronary syndromes. In this study, there were fewer events in the vaccinated group (21/221) when compared to non-vaccinated patients (42/218) 1 year following enrollment (unadjusted HR 0.70 [95% CI 0.57-0.86]); however the small size and open-label design may have introduced bias into the results. Indeed, the vaccinated group tended to be younger, more likely to receive timely revascularization for their initial acute coronary syndrome and be on an ACE inhibitor/angiotensin II inhibitor²¹.

We were able to evaluate outcomes over 4 influenza and non-influenza seasons. Indeed, the fact that we found an association between influenza vaccination and major adverse vascular events during well-matched influenza seasons and not for the incompletely matched year (2003-2004 influenza season, adjusted OR 0.96 [95% CI 0.73 – 1.27], p=0.79) increased the confidence in our results. It should be noted that there is evidence that incompletely matched influenza vaccine still provides protection against laboratory confirmed influenza in the elderly⁴⁶, and thus some reduction in vascular events might have been expected, although a substantial reduction in vaccine effectiveness against lab confirmed influenza during the incompletely matched 2003-2004 influenza season has been observed in patients with high-risk medical condition including diabetes and known vascular disease⁴⁷. This could explain why there was no association between the influenza vaccine and our primary outcome during the incompletely matched influenza season.

The findings of an association between influenza vaccination and reduced major adverse
vascular events must be tempered by the fact that the effect sizes during the influenza and non-influenza seasons were similar and the summary odds ratios in the influenza season and non-influenza season were almost identical. One possible explanation is that influenza vaccination protects against major adverse vascular during the non-influenza season because of a carry-over effect; influenza infection may precipitate a cascade of events that could lead to eventual, but not immediate vascular events, particularly cardiovascular death. An alternative and more likely explanation for these results is bias. To our knowledge, no other study has described the association between influenza vaccination and risk of vascular events during non-matched influenza seasons. In fact, only one other study stratified the effect of the influenza vaccine on vascular outcomes over multiple years. This U.S. based study found an association between influenza vaccination and hospitalization for cardiac disease during the 1998-1999 influenza season (adjusted OR 0.81 [95% CI 0.73-0.89]) and 1999-2000 influenza season (adjusted OR 0.81 [95% CI 0.73-0.89]). In both influenza seasons the circulating influenza viruses were well matched with the corresponding vaccine. The association between vaccination and cardiac events outside the influenza seasons was not reported.

Prior observational studies investigating the association between influenza vaccination and major adverse vascular events have been conflicting. These discrepant results are likely explained by bias, as studies of influenza vaccination are at high risk of bias due to fundamental differences between individuals who get vaccinated and those who do not. This bias is sometimes referred to as health vaccinee bias, or healthy user bias as vaccinated individuals tend to be healthier than non-vaccinated individuals. Recommended strategies to reduce bias in studies of influenza vaccination include: 1) adjusting for confounders not typically found in large databases; 2) exploration of the unique seasonality of influenza which enables the detection
of changing effect size over matched and unmatched seasons and when influenza is and is not circulating and 3) avoidance of use of all cause mortality as an outcome\textsuperscript{48}.

In our study, we prospectively collected co-variates and were therefore able to obtain information on variables seldom found in databases. This is in contrast to most other studies which either collected data from administrative and clinical databases or collected few co-variates beyond age, sex, co-morbidities and medications\textsuperscript{7,9,11,12,14-17}. Confidence in our ability to adjust for important confounders increased when we did not detect an association between pneumococcal vaccination and major adverse vascular events. We hypothesized that if an association was detected, it would likely be due to confounding bias given the general lack of effectiveness of the polysaccharide pneumococcal vaccine against other outcomes such as pneumonia\textsuperscript{49,50}; the majority of studies investigating this issue have not found an association\textsuperscript{7,13-17,45}.

Our primary outcome was focused and relevant to our study. Furthermore, our primary outcome was prospectively obtained and adjudicated blindly by a central committee. This is in contrast to many of the other studies, which depended on databases for measurement of outcomes\textsuperscript{7,13-17}. However, to critically evaluate our study for risk of bias, we looked at the associated effect of influenza vaccination on non-cardiovascular death, a very non-specific outcome. Influenza mortality is thought cause approximately 5% of all deaths in the elderly during the winter months\textsuperscript{43}. Thus, we hypothesized that the effect size should not be greater than 5%. In fact, the effect size in our study was far greater than 5% and ranged from 73% to 79%, which raises questions about confounding bias, despite all efforts to control for bias in our study design.

We were also unable to confirm vaccination history with medical records, and some
participants may have been misclassified although vaccination history ascertained by self-report in adults has a high sensitivity and specificity\textsuperscript{25}. We also did not know the date of influenza vaccination, which could lead to immortal time bias. Sensitivity analyses restricting the sample to study visits when influenza vaccination was most likely to occur showed point estimates consistent with the full analyses assessing the association between influenza vaccination and major adverse vascular events, making immortal time bias less likely. We have also assumed that the influenza vaccine administered for a given season contained the antigens recommended by WHO. We did not perform active surveillance for influenza throughout the study period, and therefore did not have individual-level influenza infection data on participants, an important limitation for all of the similar studies that have been conducted\textsuperscript{7-17}. Although our definition of influenza season captured the peak influenza activity for all participating countries, sporadic influenza activity can occur year round. We defined matching as well-matched and incompletely matched between the vaccine and the predominant circulating influenza virus world-wide, although there were likely regional differences in the circulating strain. For example, during the 2004-2005 influenza season, the predominant globally circulating H3N2 virus matched the vaccine virus (A/Fujian/411/2002-like H3N2); however the majority of H3N2 isolates circulating in the Unites States were the A/California/7/2004 which did not match the vaccine virus, biasing the results towards the null hypothesis\textsuperscript{37,38}. In addition, although the external validity of this study is high due to the multi-country enrollment and follow-up over multiple influenza seasons, its generalizability may be limited by the fact that the data were obtained in a trial setting.

Despite our study’s many strengths, it remains uncertain whether the influenza vaccine reduces the risk of major adverse vascular events. It seems unlikely that any observational study will be able to overcome the many potential areas of bias associated with this clinical question.
and this question will only be definitively answered with a trial design. Definitively addressing whether the influenza vaccine reduces the risk of major adverse vascular events is essential; fewer than 50% of patients in this study were vaccinated despite clear guideline recommendations to vaccinate this at risk group and large amounts of resources are necessary to significantly increase vaccine coverage\textsuperscript{51,52}. The question is particularly important to address as the efficacy and effectiveness of the influenza vaccine for other clinically important outcomes in people aged 65 years or older is also uncertain according to a recent Cochrane review\textsuperscript{53}. In conclusion, a large randomized placebo controlled trial is needed to definitively address whether influenza vaccination reduces the risk of major adverse vascular events.

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**Conflict of Interest Disclosures:** None.

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Table 1. Characteristics of participants in each cohort, stratified by influenza vaccination status.

<table>
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<tbody>
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<td></td>
<td>Vaccinated</td>
<td>Not Vaccinated</td>
<td>Vaccinated</td>
<td>Not Vaccinated</td>
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<tr>
<td></td>
<td>n=8566</td>
<td>n=13697</td>
<td>n=11624</td>
<td>n=15253</td>
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<td>Age mean (SD)</td>
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<td>65 (7)</td>
<td>68 (7)**</td>
<td>65 (7)</td>
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<tr>
<td>Female sex</td>
<td>2297 (27)**</td>
<td>4113 (30)</td>
<td>3155 (27)**</td>
<td>4939 (32)</td>
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<td>Current or former smoker</td>
<td>5834 (68)**</td>
<td>8220 (60)</td>
<td>7782 (67)**</td>
<td>8828 (58)</td>
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<td>Alcohol ≥ once per week</td>
<td>4063 (47)**</td>
<td>4982 (36)</td>
<td>5460 (47)**</td>
<td>5160 (34)</td>
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<tr>
<td>CAD</td>
<td>6667 (78)**</td>
<td>10018 (73)</td>
<td>9086 (78)**</td>
<td>10973 (72)</td>
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<td>2972 (35)**</td>
<td>5069 (37)</td>
<td>4006 (34)**</td>
<td>5657 (37)</td>
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<td>Hypertension</td>
<td>5601 (65)**</td>
<td>9683 (71)</td>
<td>7582 (65)**</td>
<td>11067 (73)</td>
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<td>Stroke or TIA</td>
<td>1562 (18)**</td>
<td>2748 (20)</td>
<td>2151 (19)**</td>
<td>3193 (21)</td>
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<td>Medications</td>
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<td>ASA</td>
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<td>10409 (76)</td>
<td>9048 (78)**</td>
<td>11381 (75)</td>
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<tr>
<td>Beta-blocker</td>
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<td>7842 (57)</td>
<td>6860 (59)**</td>
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<td>Lipid agent</td>
<td>6069 (71)**</td>
<td>8403 (61)</td>
<td>8352 (72)**</td>
<td>8899 (58)</td>
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<td>ACE/AIIA</td>
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<td>2153 (16)</td>
<td>2097 (18)**</td>
<td>2404 (16)</td>
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<td>PPV</td>
<td>2082 (24)**</td>
<td>1221 (9)</td>
<td>2794 (24)**</td>
<td>1061 (7)</td>
</tr>
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</table>

SD-standard deviation; Yr – year; CAD – coronary artery disease; TIA – transient ischemic attack; ACE – Angiotensin converting enzyme inhibitor; AIIA – angiotensin II antagonists; PPV – pneumococcal vaccine

*P-value 0.01-0.05
** P-value <0.01
Table 2. Association between influenza vaccination and risk of major adverse vascular events during the influenza season.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Primary outcome in influenza vaccinated n (%)</th>
<th>Primary outcome in non influenza vaccinated n (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted* OR (95% CI)</th>
<th>P-value</th>
<th>Matched**</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-2004</td>
<td>96/8566 (1.1)</td>
<td>142/13697 (1.0)</td>
<td>1.08 (0.83 – 1.40)</td>
<td>0.55</td>
<td>0.96 (0.73-1.27)</td>
<td>0.79</td>
<td>H1N1 – Match</td>
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<tr>
<td>2004-2005</td>
<td>155/11624 (1.3)</td>
<td>274/15253 (1.8)</td>
<td>0.74 (0.61 – 0.90)</td>
<td>0.003</td>
<td>0.62 (0.50-0.77)</td>
<td>&lt;0.0001</td>
<td>H3N2 – Match</td>
</tr>
<tr>
<td>2005-2006</td>
<td>70/7499 (0.93)</td>
<td>231/18876 (1.2)</td>
<td>0.76 (0.58 – 1.00)</td>
<td>0.046</td>
<td>0.69 (0.53-0.91)</td>
<td>0.009</td>
<td>H1N1 – Match</td>
</tr>
<tr>
<td>2006-2007</td>
<td>145/12441 (1.2)</td>
<td>269/13795 (2.0)</td>
<td>0.59 (0.48 – 0.73)</td>
<td>&lt;0.0001</td>
<td>0.52 (0.42-0.65)</td>
<td>&lt;0.0001</td>
<td>H3N2 – Match</td>
</tr>
</tbody>
</table>

*Adjusted by: propensity score for influenza vaccination (body mass index, age, sex, ethnicity, education, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination), history of coronary artery disease, diabetes, hypertension, stroke, admission to a nursing home, or use of ASA, beta-blocker, lipid lowering drugs, ACE inhibitor or angiotensin II inhibitor.

**A match was defined if the majority (≥50%) of the circulating influenza virus was antigenically similar to the vaccine strain. Bolding indicates the predominant influenza isolate(s) circulating in the study regions30-39.

Table 3. Association between influenza vaccination and risk of the major adverse vascular events during the non-influenza season.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Primary outcome in influenza vaccinated n (%)</th>
<th>Primary outcome in non influenza vaccinated n (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted* OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-2004</td>
<td>80/8550 (0.94)</td>
<td>144/13699 (1.05)</td>
<td>0.89 (0.68 - 1.17)</td>
<td>0.40</td>
<td>0.81 (0.61-1.09)</td>
<td>0.16</td>
</tr>
<tr>
<td>2004-2005</td>
<td>112/11581 (0.97)</td>
<td>208/15187 (1.4)</td>
<td>0.70 (0.56 – 0.89)</td>
<td>0.003</td>
<td>0.64 (0.50-0.83)</td>
<td>0.0005</td>
</tr>
<tr>
<td>2005-2006</td>
<td>66/7495 (0.88)</td>
<td>214/18859 (1.1)</td>
<td>0.77 (0.59 - 1.0)</td>
<td>0.07</td>
<td>0.74 (0.56-0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>2006-2007</td>
<td>87/12383 (0.70)</td>
<td>165/13691 (1.2)</td>
<td>0.58 (0.45 - 0.75)</td>
<td>&lt;0.0001</td>
<td>0.50 (0.38-0.67)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjusted by: propensity score for influenza vaccination (body mass index, age, sex, ethnicity, education, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination), history of coronary artery disease, diabetes, hypertension, stroke, admission to a nursing home, or use of ASA, beta-blocker, lipid lowering drugs, ACE inhibitor or angiotensin II inhibitor.
Table 4. Effect of influenza vaccination history on major adverse vascular events in influenza vaccinated and non-vaccinated patients.

<table>
<thead>
<tr>
<th>Influenza Vaccination status (+/-)</th>
<th>Primary Outcome No</th>
<th>Primary Outcome Yes</th>
<th>P-value for trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect of Mounting Immunity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- -</td>
<td>11093 (98.23)</td>
<td>200 (1.77)</td>
<td>0.0096</td>
</tr>
<tr>
<td>- +</td>
<td>1877 (99.05)</td>
<td>18 (0.95)</td>
<td></td>
</tr>
<tr>
<td>- +</td>
<td>1247 (99.05)</td>
<td>12 (0.95)</td>
<td></td>
</tr>
<tr>
<td>+ +</td>
<td>5211 (98.8)</td>
<td>64 (1.2)</td>
<td></td>
</tr>
<tr>
<td>2005-2006 Influenza Season</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- -</td>
<td>N/A</td>
<td>13111 (98.79)</td>
<td>161 (1.21)</td>
</tr>
<tr>
<td>- +</td>
<td>N/A</td>
<td>1637 (98.73)</td>
<td>21 (1.27)</td>
</tr>
<tr>
<td>+ +</td>
<td>N/A</td>
<td>5786 (99.16)</td>
<td>49 (0.84)</td>
</tr>
<tr>
<td><strong>Effect of Persistent Immunity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006-2007 Influenza Season</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- -</td>
<td>N/A</td>
<td>11093 (98.23)</td>
<td>200 (1.77)</td>
</tr>
<tr>
<td>+ -</td>
<td>1462 (96.31)</td>
<td>56 (3.69)</td>
<td></td>
</tr>
<tr>
<td>+ +</td>
<td>544 (98.91)</td>
<td>6 (1.09)</td>
<td></td>
</tr>
<tr>
<td>+ +</td>
<td>5211 (98.8)</td>
<td>64 (1.2)</td>
<td></td>
</tr>
<tr>
<td>2005-2006 Influenza Season</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- -</td>
<td>N/A</td>
<td>13111 (98.79)</td>
<td>161 (1.21)</td>
</tr>
<tr>
<td>+ -</td>
<td>N/A</td>
<td>5506 (98.74)</td>
<td>70 (1.26)</td>
</tr>
<tr>
<td>+ +</td>
<td>N/A</td>
<td>5786 (99.16)</td>
<td>49 (0.84)</td>
</tr>
</tbody>
</table>
Table 5. Association between influenza vaccination and risk of non-cardiovascular death during the influenza season.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Outcome in influenza vaccinated n (%)</th>
<th>Outcome in non influenza vaccinated n (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted* OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-2004 Non-cardiovascular death</td>
<td>1/9210 (0.01)</td>
<td>12/15015 (0.08)</td>
<td>0.14 (0.02-1.04)</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cancer death</td>
<td>0/9377 (0)</td>
<td>5/15271 (0.03)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Death from other causes</td>
<td>1/9407 (0.05)</td>
<td>7/15292 (0.01)</td>
<td>0.23 (0.03-1.89)</td>
<td>0.17</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2004-2005 Non-cardiovascular death</td>
<td>28/12443 (0.23)</td>
<td>89/16562 (0.54)</td>
<td>0.42 (0.27-0.64)</td>
<td>0.0001</td>
<td>0.26 (0.16-0.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cancer death</td>
<td>12/12606 (0.10)</td>
<td>46/16742 (0.27)</td>
<td>0.35 (0.18-0.65)</td>
<td>0.001</td>
<td>0.20 (0.10-0.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death from other causes</td>
<td>16/12656 (0.13)</td>
<td>43/16757 (0.26)</td>
<td>0.49 (0.28-0.87)</td>
<td>0.015</td>
<td>0.33 (0.18-0.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2005-2006 Non-cardiovascular death</td>
<td>7/8051 (0.09)</td>
<td>75/20313 (0.37)</td>
<td>0.23 (0.11-0.51)</td>
<td>0.0002</td>
<td>0.21 (0.10-0.46)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cancer death</td>
<td>5/8087 (0.06)</td>
<td>40/20419 (0.20)</td>
<td>0.32 (0.12-0.80)</td>
<td>0.015</td>
<td>0.27 (0.10-0.69)</td>
<td>0.0065</td>
</tr>
<tr>
<td>Death from other causes</td>
<td>2/8094 (0.02)</td>
<td>35/20457 (0.17)</td>
<td>0.14 (0.03-0.60)</td>
<td>0.008</td>
<td>0.14 (0.03-0.58)</td>
<td>0.0070</td>
</tr>
<tr>
<td>2006-2007 Non-cardiovascular death</td>
<td>34/13286 (0.26)</td>
<td>99/14724 (0.67)</td>
<td>0.38 (0.26-0.56)</td>
<td>&lt;0.0001</td>
<td>0.27 (0.18-0.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cancer death</td>
<td>16/13294 (0.12)</td>
<td>60/14723 (0.41)</td>
<td>0.29 (0.17-0.51)</td>
<td>&lt;0.0001</td>
<td>0.17 (0.10-0.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death from other causes</td>
<td>18/13307 (0.14)</td>
<td>39/14196 (0.27)</td>
<td>0.51 (0.29-0.89)</td>
<td>0.018</td>
<td>0.47 (0.25-0.86)</td>
<td>0.0137</td>
</tr>
</tbody>
</table>

*Adjusted by: propensity score for influenza vaccination (body mass index, age, sex, ethnicity, education, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination), history of coronary artery disease, diabetes, hypertension, stroke, admission to a nursing home, or use of ASA, beta-blocker, lipid lowering drugs, ACE inhibitor or angiotensin II inhibitor.
Figure Legends:

**Figure 1.** A. Association between influenza vaccination and the risk of the primary outcome during the influenza season. B. Association between influenza vaccination and the risk of the primary outcome during the non-influenza season.

**Figure 2.** Association between pneumococcal vaccination and risk of the primary outcome during the influenza season.
<table>
<thead>
<tr>
<th>Year</th>
<th>Adjusted*OR(95% CI);P</th>
<th>Year</th>
<th>Adjusted*OR(95% CI);P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Influenza season</strong></td>
<td></td>
<td><strong>Non-influenza season</strong></td>
<td></td>
</tr>
<tr>
<td>2003-2004</td>
<td>0.96 (0.73 - 1.27); 0.79</td>
<td>2003-2004</td>
<td>0.81 (0.61 - 1.09); 0.16</td>
</tr>
<tr>
<td>2004-2005</td>
<td>0.62 (0.5 - 0.77); &lt;0.0001</td>
<td>2004-2005</td>
<td>0.64 (0.5 - 0.83); 0.0005</td>
</tr>
<tr>
<td>2005-2006</td>
<td>0.69 (0.53 - 0.91); 0.009</td>
<td>2005-2006</td>
<td>0.74 (0.56 - 0.98); 0.04</td>
</tr>
<tr>
<td>2006-2007</td>
<td>0.52 (0.42 - 0.65); &lt;0.0001</td>
<td>2006-2007</td>
<td>0.5 (0.38 - 0.67); &lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjusted by: propensity score for influenza vaccination (body mass index, age, sex, ethnicity, education, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination), history of coronary artery disease, diabetes, hypertension, stroke, admission to a nursing home, or use of ASA, beta-blocker, lipid lowering drugs, ACE inhibitor or angiotensin II inhibitor.
*Adjusted by: propensity score for pneumococcal vaccination (body mass index, age, sex, ethnicity, education, vitamin use, smoking history, alcohol use, history of influenza vaccination), history of coronary artery disease, diabetes, hypertension, stroke, admission to a nursing home, or use of ASA, beta-blocker, lipid lowering drugs, ACE inhibitor or angiotensin II inhibitor.
Influenza Vaccination and Major Adverse Vascular Events in High Risk Patients
Jennie Johnstone, Mark Loeb, Koon K. Teo, Peggy Gao, Leanne Dyal, Lisheng Liu, Alvaro Avezum, Ernesto Cardona-Munoz, Peter Sleight, Robert Fagard and Salim Yusuf

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