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SHORT REPORT
Low-dose aspirin use does not diminish the immune response to monovalent H1N1 influenza vaccine in older adults

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SUMMARY

Non-steroidal anti-inflammatory drugs (NSAIDs) may inhibit antibody production by peripheral blood mononuclear cells; one consequence of this could be decreased effectiveness of vaccines in NSAID users. Because many older adults use low-dose aspirin for primary or secondary prevention of coronary events, any inhibitory effect of aspirin on vaccine immune response could reduce the benefits of vaccination programmes in older adults. We tested whether immune response to vaccination differed between users vs. non-users of low-dose aspirin, using data from four randomized trials of monovalent 2009 pandemic influenza A(H1N1) vaccine. Geometric mean haemagglutination inhibition antibody titres were not significantly lower in low-dose aspirin users compared to non-users. Our results provide reassurance that influenza vaccination effectiveness is probably not reduced in older adults taking chronic low-dose aspirin.

Key words: Anti-inflammatory agents, human influenza, non-steroidal, vaccines.

In adults, advanced age is associated with a decreased immune response to inactivated influenza vaccines. However, in older adults there is considerable heterogeneity in the immune response which is poorly explained [1]. Inflammation is an important component of vaccine-induced immune responses [2], suggesting that factors that influence the inflammatory response may also influence the immune response to vaccinations. Such an association is supported by a randomized placebo-controlled trial of prophylactic paracetamol (acetaminophen) for prevention of vaccine febrile reactions in infants, in which acetaminophen administration was associated with significantly lower post-vaccination antibody levels to several routinely administered childhood vaccines [3]. In addition, *in vitro* studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) may inhibit antibody production by peripheral blood mononuclear cells [4].

The generalizability of the findings from *in vitro* studies and infant studies to older adults is unclear, as two small randomized trials in older adults found no association between receipt of acetaminophen *vs.* placebo on serum antibody concentrations following influenza vaccination [5, 6]. However, given that 35–55% of adults aged $\geqslant$65 years use aspirin for primary or secondary prevention of coronary events [7, 8], any inhibitory effect of aspirin on vaccine immune response could reduce the benefit of vaccination programmes in older adults. To assess the possible influence of chronic aspirin use on the immune response to influenza vaccine in older adults, we compared serum antibody concentrations between older

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adults taking aspirin and those not taking aspirin in four clinical trials of monovalent pandemic 2009 H1N1 [A(H1N1)pdm] vaccines [9–11].

This study was classified as not requiring Institutional Review Board (IRB) approval by Group Health Research Institute's IRB, as it used only data recorded in a manner such that subjects cannot be identified by the investigators, either directly or through identifiers.

Study setting and population. This study was a meta-analysis of independent subject data from four influenza vaccine phase II clinical trials conducted by the National Institutes of Health's Vaccine Treatment and Evaluation Unit (VTEU) network. These were: (*a*) a trial of inactivated, non-adjuvanted, monovalent A(H1N1)pdm vaccine given before, with, or after licensed trivalent influenza vaccine (TIV) (NCT00943878); (*b*) two trials of inactivated, non-adjuvanted, monovalent A(H1N1)pdm vaccines (NCT00943488 and NCT00943631) at varying doses [9]; and (*c*) a trial of inactivated monovalent A(H1N1)pdm vaccine at varying doses with and without AS03 adjuvant (NCT00963157) [10]. All four studies enrolled healthy, non-pregnant adults aged $\geqslant$18 years who had no history of A(H1N1)pdm infection or A(H1N1)pdm vaccination. For the current study, we restricted the study populations to participants who were aged $\geqslant$50 years at the time of trial enrolment and who had haemagglutination inhibition (HI) assay results at day 21 after vaccination. The trials involved administration of multiple vaccinations during the study period; in this assessment we evaluated the immune response to the first study vaccination, and restricted the study population to participants who received active A(H1N1)pdm vaccine (and not placebo) as the first study vaccination.

Exposure and covariate data. At trial enrolment, all participants were interviewed to verify eligibility and determine demographics, comorbid illnesses, and medication history. For medication history, participants were asked to list all medications taken within the 28 days prior to enrolment, and to provide dates for start of use for each medication and stop dates for medications not in use at the time of enrolment. Queried medications included prescription drugs, over-the-counter medications, vitamins, and supplements. The exposure of interest was low-dose aspirin, defined as self-reported regular, ongoing use of low-dose aspirin for cardiovascular prevention. Chronic or intermittent use of aspirin for other purposes, such as pain relief, was classified as not low-dose aspirin use. Subjects also reported comorbid illnesses. Covariates of interest for the present study included age at vaccination, receipt of 2009–2010 seasonal TIV, body mass index (BMI) calculated from measured height and weight at vaccination, selected self-reported illnesses and medications, and aspirin contraindication (defined as self-reported history of gastrointestinal bleeding, hypercoagulable state, anaemia secondary to ulcer, kidney disease, gout, or allergy to aspirin).

Outcome. The outcome of interest is the HI antibody titre 21 days after receipt of first study influenza vaccination. Testing was performed by Southern Research (Birmingham, USA).

Analysis. We characterized the study population by the distribution of exposure, outcomes, and covariates, stratified by the study product received in each of the four trials. For the primary analysis, we used a linear mixed model to evaluate the association between log-transformed HI titre and low-dose aspirin use, adjusting for age, study product received, and receipt of seasonal 2009–2010 TIV, with random effects for each clinical trial. The secondary analysis expanded on this modelling by adding indicator variables for covariates associated with both low-dose aspirin use and with HI titre in the descriptive analyses. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., USA).

A total of 1597 individuals from the four clinical trials were eligible for this study, ranging from 296 to 577 eligible individuals per trial. Across the four trials, the mean age of study participants was 66·5 years, and 43% of study subjects reported regular use of low-dose aspirin (range across trials, 37–47%). Low-dose aspirin use was more common in older study subjects and in those reporting a history of acute myocardial infarction, coronary artery disease, diabetes, high cholesterol, hypertension, and transient ischaemic attack. Subjects reporting use of low-dose aspirin were more likely to report use of ACE inhibitors, beta-blockers, calcium channel blockers, and statins, and were less likely to report use of non-low-dose aspirin. Due to random assignment of study vaccines, low-dose aspirin users were evenly distributed across the study vaccines, as were age, comorbidities, and concomitant medications.

Combining subjects across all treatment groups and trials, HI geometric mean titre (GMT) was higher in users of low-dose aspirin [133·8, 95% confidence interval (CI) 119·7–149·6] than in non-users (119·2, 95% CI 117·9–134·6), but this difference was not statistically significant. Trends were observed between GMT HI and several covariates. Subjects with higher BMI or history of thrombosis and users of furosemide or calcium channel blockers tended to have higher GMT HI, while subjects with history of acute myocardial infarction or aspirin contraindications and users of acetaminophen and non-low-dose aspirin tended to have lower GMT HI.

After adjusting for study vaccine, age, and receipt of seasonal TIV in a model with random effects for clinical trial, use of low-dose aspirin was not significantly associated with HI antibody titre, with GMT HI being 0·96-fold lower in subjects using low-dose aspirin ($P = 0·69$). Additional adjustment for potentially confounding medications and comorbidities did not meaningfully change these results, with GMT HI being 0·95-fold lower in those using low-dose aspirin ($P = 0·62$).

In this meta-analysis of randomized trial data, we found no evidence that use of low-dose aspirin is associated with lower immunogenicity of monovalent influenza A(H1N1)pdm vaccination. Influenza vaccination is the cornerstone of the United States' approach to reducing influenza-related morbidity and mortality, with up to 45% of adults aged 50–64 years, and up to 70% of adults aged $\geqslant$65 years, receiving seasonal influenza vaccine in a typical year [12]. A large percentage of older adults also use aspirin for primary or secondary prevention of coronary events [7, 8] in addition to the use of aspirin and other NSAIDs for pain relief. If use of aspirin or other NSAIDs inhibits antibody production after vaccination, vaccine effectiveness could be reduced in aspirin users, a group which tends to include individuals at high risk for influenza complications due to comorbid illnesses. Our results suggest that use of low-dose aspirin in older adults does not inhibit antibody production following influenza vaccination.

Several limitations of this study need to be considered. First, data on use of low-dose aspirin, other concomitant medications, and comorbid illnesses were collected by subject self-report. Our results may have been biased due to misclassification of exposure status or important potential confounders. Second, the studies used in this analysis only tested immunogenicity of monovalent A(H1N1)pdm influenza virus vaccines in study subjects. Our results may not generalize to other vaccines, including seasonal influenza vaccine. Third, we evaluated multiple vaccine formulations which could reduce the generalizability of our results to standard-dose non-adjuvanted vaccines typically used in the United States. Strengths of this study include the systematic collection, prior to vaccination, of information on concomitant medications and health history, and the large study size, which gave us power to detect even small differences in GMT HI between users and non-users of low-dose aspirin. For comparison, two prior randomized trials of acetaminophen use and influenza vaccination in older adults enrolled $\leqslant$100 subjects [5, 6], compared to nearly 1600 in this study.

Although one randomized trial found that immune response to vaccines may be blunted in children receiving post-vaccination acetaminophen [3], our study found no statistically significant or clinically meaningful difference in GMT HI between low-dose aspirin users and non-users following monovalent influenza A(H1N1)pdm vaccination. These results provide reassurance that influenza vaccination effectiveness is probably not reduced in older adults taking chronic low-dose aspirin.

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DECLARATION OF INTEREST

None.

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