Effectiveness of seasonal influenza vaccination in community-dwelling elderly people: an individual participant data meta-analysis of test-negative design case-control studies


Summary

Background Several aggregate data meta-analyses have provided estimates of the effectiveness of influenza vaccination in community-dwelling elderly people. However, these studies ignored the effects of patient-level confounders such as sex, age, and chronic diseases that could bias effectiveness estimates. We aimed to assess the confounder-adjusted effectiveness of influenza vaccines on laboratory-confirmed influenza among elderly people by conducting a global individual participant data meta-analysis.

Methods In this individual participant data meta-analysis, we considered studies included in a previously conducted aggregate data meta-analysis that included test-negative design case-control studies published up to July 13, 2014. We contacted all authors of the included studies on Dec 1, 2014, to request individual participant data. Patients were excluded if their unique identifier was missing, their vaccination status was unknown, their outcome status was unknown, or they had had suspected influenza infection more than once in the same influenza season. Cases were patients with influenza-like illness symptoms who tested positive for at least one of A H1N1, A H1N1 pdm09, A H3N2, or B viruses; controls were patients with influenza-like illness symptoms who tested negative for these virus types or subtypes. Influenza vaccine effectiveness against overall and subtype-specific laboratory-confirmed influenza were the primary and secondary outcomes. We used a generalised linear mixed model to calculate adjusted vaccine effectiveness according to vaccine match to the circulating strains of influenza virus and intensity of the virus activity (epidemic or non-epidemic). Vaccine effectiveness was defined as the relative reduction in risk of laboratory-confirmed influenza in vaccinated patients compared with unvaccinated patients. We did subgroup analyses to estimate vaccine effectiveness according to hemisphere, age category, and health status.

Findings We received 23 of the 53 datasets included in the aggregate data meta-analysis. Furthermore, six additional datasets were provided by data collaborators, which resulted in individual participant data for a total of 5210 participants. A total of 4975 patients had the required data for analysis. Of these, 3146 (63%) were controls and 1829 (37%) were cases. Influenza vaccination was significantly effective during epidemic seasons irrespective of vaccine match status (matched adjusted vaccine effectiveness 44–38%, 95% CI 22–63–60–01; unmatched adjusted vaccine effectiveness 20–00%, 95% CI 3–46–33–68; analyses in the imputed dataset). Seasonal influenza vaccination did not show significant effectiveness during non-epidemic seasons. We found substantial variation in vaccine effectiveness across virus types and subtypes, with the highest estimate for A H1N1 pdm09 (53–19%, 10–25–75–58) and the lowest estimate for B virus types (–1–52%, –39–58 to 26–16). Although we observed no significant differences between subgroups in each category (hemisphere, age, and health status), influenza vaccination showed a protective effect among elderly people with cardiovascular disease, lung disease, or aged 75 years and younger.

Interpretation Influenza vaccination is moderately effective against laboratory-confirmed influenza in elderly people during epidemic seasons. More research is needed to investigate factors affecting vaccine protection (eg, brand-specific or type-specific vaccine effectiveness and repeated annual vaccination) in elderly people.

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Introduction

The ability of inactivated seasonal influenza vaccines to reduce the risk of influenza and influenza-related complications—referred to as influenza vaccine effectiveness—in the high-risk group of elderly people varies significantly from season to season depending on factors such as intensity of influenza virus activity, interval between vaccination and symptom onset, vaccine match to the circulating viruses, and influenza virus types and subtypes.\(^1\)\(^2\) Importantly, individual characteristics of patients such as age and presence of chronic medical disorders (eg, cardiovascular and respiratory diseases) could also affect vaccine effectiveness.\(^3\)\(^4\)
Evidence before this study

In November, 2014, we published an aggregate data meta-analysis of test-negative design studies assessing the effectiveness of seasonal influenza vaccination in elderly people—the first such meta-analysis to our knowledge. For the aggregate data meta-analysis, we did a broad literature search (MEDLINE, Embase, and the Cochrane library) for test-negative design articles published up to July 13, 2014. We included studies if raw data for vaccination status and outcome in people aged 60 years and older were reported or if raw data were provided by the investigators on request. If studies reported raw data for vaccination status and outcome for more than one influenza season, we considered each influenza season as a separate dataset in the meta-analysis. Although we considered the effect of vaccine match and epidemic condition, adjustment for potential individual-level confounders was not possible.

Therefore, to provide adjusted effectiveness estimates that are directly comparable with the aggregate data meta-analysis, we contacted all authors whose studies were included in the aggregate data meta-analysis and did an individual participant data (IPD) meta-analysis. We received 29 (55%) of 53 potential datasets from our previous meta-analysis with individual data on 5210 (44%) of 11 848 patients. Patients were excluded if (1) their unique identifier was missing, (2) their vaccination status was unknown (3) their outcome status (being a laboratory-confirmed case or test-negative control) was unknown, or (4) they had had multiple observations in the same influenza season.

Added value of this study

To our knowledge, this study is the first global IPD meta-analysis assessing effectiveness of influenza vaccination in elderly people. Adjusted estimates of vaccine effectiveness in this study were lower than in the aggregate data meta-analysis (20–44% vs 36–52%) during epidemic seasons, but were still significant. This difference highlights the importance of adjustment for potential confounders to monitor effectiveness of seasonal vaccination, even in test-negative design studies. Additionally, influenza vaccination showed a protective effect among elderly people with cardiovascular disease, lung disease, and those aged 75 years and younger, emphasising the need for vaccination in this high-risk population.

Implications of all the available evidence

Some meta-analyses of observational studies have been done to estimate effectiveness of seasonal influenza vaccination in elderly people. Susceptibility of these studies to confounding bias, as well as limitations of aggregated-data meta-analyses, could provide biased estimates. Global IPD meta-analysis should be pursued to provide adjusted effectiveness estimates and explore the effects of brand-specific or type-specific vaccine effectiveness and repeated annual vaccination on influenza vaccine protection.

To estimate contemporary seasonal vaccine effectiveness and explore the variation in vaccine performance across populations, test-negative design (TND) case-control studies are regularly being done worldwide. In this type of study design, vaccination status is compared between patients presenting with influenza-like illness symptoms who tested positive for influenza (laboratory-confirmed cases) and patients with influenza-like illness symptoms who tested negative (controls). Compared with conventional case-control or cohort designs, TND studies appear to be less susceptible to bias that arises from differences in health care-seeking behaviour between cases and controls and the use of non-specific outcome measurements, such as influenza-like illness symptoms and acute respiratory tract infection.

We did an aggregate data meta-analysis of TND studies and found that seasonal influenza vaccination was moderately effective against laboratory-confirmed influenza in elderly people (aged ≥60 years). Additionally, another aggregate data meta-analysis of TND studies found substantial variation in vaccine effectiveness across influenza virus types and subtypes among adults aged 60 years and older. Although both meta-analyses included a large number of TND studies and considered the geographical spread of influenza virus activity (epidemic condition), vaccine match, and virus types or subtypes, an important limitation was that individual patient-level confounders such as sex, age, smoking behaviour, and chronic medical disorders could not be adjusted for owing to the aggregated structure of the data. Moreover, vaccine effectiveness among subgroups of elderly people who might be at increased risk of influenza-related complications (eg, age >75 years or presence of chronic medical disorders) could not be estimated from the crude aggregated data. As an observational study, TND does not involve randomisation of the vaccination, which means baseline characteristics of vaccinated and non-vaccinated patients could differ systematically—potentially obscuring the real effects of influenza vaccination.

To overcome the limitations of the aggregated data meta-analysis, explore individual level factors affecting vaccine effectiveness, and adjust for the potential individual level confounders, we did an individual participant data (IPD) meta-analysis estimating overall and type-specific vaccine effectiveness in different subgroups of elderly people using data from the studies included in our aggregate data meta-analysis.

Methods

Search strategy and selection criteria

The search strategy, review process, selection criteria, and studies included in the aggregate data meta-analysis have
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