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The association of adult vaccination with the risk of cerebrovascular ischemia: A systematic review and meta-analysis

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ABSTRACT

There is mounting evidence supporting infection as an independent risk factor for ischemic stroke (IS), while preliminary data indicate that vaccination may prevent IS. We performed a systematic review and meta-analysis of available randomized clinical trials (RCTs) or prospective observational cohorts reporting associations of influenza vaccination (IV) and/or pneumococcal vaccination (PV) with IS. We identified a total of 12 studies (543,311 patients; 47.4% vaccinated). Vaccination was not related to the risk of IS (RR = 1.06, 95%CI: 0.74–1.51, p = 0.77), with no significant differences (p = 0.26) among RCTs (RR = 0.66, 95%CI: 0.30–1.47) and observational studies (RR = 1.11, 95%CI: 0.76–1.61). Evidence of considerable heterogeneity was identified within observational studies (I^2 = 98%), but not within RCTs (I^2 = 0%). In subgroup analyses according to vaccination type, IV was associated with a significantly lower risk of IS (RR = 0.87, 95%CI: 0.79–0.96, p = 0.004) with moderate evidence of heterogeneity (I^2 = 53%). No association was seen for PV (RR = 1.38, 95%CI: 0.60–3.16, p = 0.45), where considerable heterogeneity was identified (I^2 = 97%). In the additional adjusted analyses of observational studies, vaccination tended to be associated with lower risk of IS (HRadjusted = 0.87; 95%CI: 0.75–1.01; p = 0.07). The findings of this meta-analysis indicate that IV may be associated with a lower risk of IS. This association was not reproduced for PV or the combination of two vaccines. Substantial heterogeneity was detected across observational studies for all outcome events, while moderate to low heterogeneity was identified across included RCTs. These preliminary findings require independent validation in large RCTs.

1. Introduction

The role of systemic infection as a trigger for cerebrovascular diseases is complex and still remains incompletely understood [1]. Observational data indicate that previous infectious disease is reported in approximately one out of ten patients hospitalized for acute ischemic stroke (AIS) and is independently associated with increased stroke severity [2]. Data from a prospective population-based stroke registry suggest a seasonal trend for AIS with a significant increase in incidence within two weeks after influenza infection [3]. In two American case-control studies, recent respiratory tract infections were significantly associated with an increased risk of large-vessel and/or cardioembolic AIS [4,5], especially in patients without vascular risk factors [5]. Case-control study results also suggest an increased risk for AIS within the first week after an infection on both pediatric [6], adult [7,8], and elderly populations [9], while highlight under vaccination as an independent risk factor for the aforementioned association [6]. Nevertheless, the limited studies that have evaluated the association of vaccination with the risk of IS in the settings of randomized controlled trials (RCTs) or prospective cohort studies have reported contradictory

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results [10].

In view of the former considerations, we performed a systematic review and meta-analysis evaluating the association of influenza and pneumococcal vaccination with the risk of IS and other cardiovascular outcomes.

2. Methods

2.1. Trial identification and data abstraction

This meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses [11]. Eligible prospective observational cohort studies or RCTs reporting the occurrence of cerebral ischemic events (IS/TIA) in patients receiving influenza and/or pneumococcal vaccination and controls during the follow-up period were identified by searching MEDLINE, SCOPUS and the CENTRAL Register of Controlled Trials. The combination of search strings that was used in all database searches included the terms: “vaccination”, “immunization”, “vaccine”, “influenza”, “pneumococcal”, “acute ischemic stroke”, “stroke” and “cerebral ischemia”. No language, date range or other restrictions were imposed. Last literature search was conducted on March 1st, 2017. The complete search algorithm used in MEDLINE search is available in the Online Supplement. Reference lists of all articles that met the inclusion criteria and of all relevant review articles were examined to identify studies that may have been missed by the database search. Literature search was performed by three independent reviewers (AHK, MFI & MTM) and potentially eligible studies were scanned independently by the aforementioned reviewers to include only prospective observational cohort studies or RCTs reporting the occurrence of cerebral ischemic events in influenza/pneumococcal vaccinated and control subjects. We excluded from the final analysis: 1. retrospective cohort studies, 2. case-control studies, 3. case series, 4. case reports, 5. studies reporting vaccination other than against influenza or pneumococcus, 6. studies performed on pediatric population, 7. studies not providing the outcomes of interest and 8. studies with overlapping data.

Outcome events of interest including IS, myocardial ischemic events and cardiovascular deaths were extracted for the duration of follow-up in each included study independently by the authors that performed the literature search (AHK, MFI & MTM). Additional data were also extracted from a recently published meta-analysis on the association between influenza vaccination and cardiovascular outcomes in high-risk patients [12]. In case of any disagreement between authors during the literature search or data extraction process the corresponding author was consulted (GT) and disagreement was finally resolved with consensus.

We used a predefined 7-point quality control to address biases in each included RCT. For each quality item, the corresponding risk of bias was categorized as low, high or unclear according to the suggestions by Higgins et al. [13]. We also used the Newcastle-Ottawa Scale for assessing the quality of non-randomized studies in meta-analyses tool for each observational study that met our inclusion criteria. High-quality ratings are identified with a star and studies can earn a maximum of 9 star-points. A maximum of one star can be awarded for each item within the selection and exposure/outcome categories and a maximum of two stars for the comparability category [14]. Quality control and bias identification were performed by two independent reviewers (AHK, GT) and all emerging conflicts were resolved with consensus.

2.2. Statistical analyses

For all reported events during each eligible study period we calculated the corresponding risk ratios (RRs) to express the comparison of event occurrence risk among vaccinated patients and controls. Where applicable we also extracted data on the corresponding reported hazard ratios adjusted for potential confounders ($HR_{adjusted}$). In all pairwise meta-analyses, RR or HR values lower than 1 denote that vaccination has a favorable effect on the prevention of adverse cardiovascular events. A random-effects model (DerSimonian Laird) was used to calculate the pooled RRs. The equivalent z test was performed for each pooled RR/HR, and if $p < 0.05$ it was considered statistically significant.

Heterogeneity between studies was assessed with the Cochran Q and I^2 statistics. For the qualitative interpretation of heterogeneity, I^2 values of at least 50% were considered to represent substantial heterogeneity, while values of at least 75% indicated considerable heterogeneity, as per the Cochrane Handbook [15]. Publication bias (i.e. assessment of bias across studies) was evaluated both graphically using a funnel plot [16], and with the Egger's statistical test for funnel plot asymmetry [17].

After the overall analyses we performed additional subgroup analyses according to study type (RCT or observational cohort) and vaccination used (influenza, pneumococcal or both). The mixed-effects model was used to calculate both the pooled point estimate in each subgroup and the overall estimates. According to the mixed-effects model, we used a random-effects model (DerSimonian Laird) to combine studies within each subgroup and a fixed effect model (Mantel–Haenszel method) to combine subgroups and estimate the overall effect. We assumed the study-to-study variance (tau-squared) to be the same for all subgroups. Tau-squared was first computed within subgroups and then pooled across subgroups [18].

Statistical analyses were conducted using Review Manager (RevMan) Version 5.2 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) and Comprehensive Meta-analysis Version 2 software (Borenstein M, Hedges L, Higgins J, Rothstein H, Biostat, Englewood NJ, 2005).

3. Results

3.1. Study selection and study characteristics

A systematic search of MEDLINE and SCOPUS databases yielded 486 and 611 results respectively. Subsequent search in the CENTRAL Register of Controlled Trials retrieved no additional RCTs. After removing duplicates, the titles and abstracts from the remaining 810 studies were screened; 24 potentially eligible studies for the meta-analysis were retained. The full-text versions of the aforementioned 24 studies were reviewed and 9 studies were excluded (Table e-1) due to a case-control design (n = 6) or provision of either data from a pediatric population (n = 1) or overlapping data (n = 2). Three additional studies were excluded because they either reported vaccination against a pathogen other than influenza or pneumococcus (n = 1) or did not provide data on the outcomes of interest (n = 2). In the final evaluation of the literature search results, there was no conflict or disagreement between reviewers and the 12 studies that met the study protocol's inclusion criteria were included in the qualitative and quantitative synthesis (Fig. 1) [19–30]. The characteristics of included studies, comprising a total of 543,311 patients (47.4% vaccinated) are summarized in Table 1. Included studies consisted of 5 placebo-controlled RCTs [19–23] and 7 prospective observational studies [24–30]. Influenza vaccination was reported in 8 of the study protocols [19–23,27,28,30], pneumococcal vaccination in 2 study protocols [24,29], while both pneumococcal and influenza vaccination was performed in 2 study protocols [25,26]. One of the included observational study protocols reported data on two separate cohorts that each was prospectively followed up for a one year period (1998–1999 & 1999–2000), and thus data from these two cohorts were pooled separately.