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REVIEW ARTICLE

After adjusting for bias in meta-analysis seasonal influenza vaccine remains effective in community-dwelling elderly☆

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Abstract

Objective: To compare the performance of the bias-adjusted meta-analysis to the conventional meta-analysis assessing seasonal influenza vaccine effectiveness among community-dwelling elderly aged 60 years and older.

Study Design and Setting: Systematic literature search revealed 14 cohort studies that met inclusion and exclusion criteria. Laboratory-confirmed influenza, influenza-like illness, hospitalization from influenza and/or pneumonia, and all-cause mortality were study outcomes. Potential biases were identified using bias checklists. The magnitude and uncertainty of biases were assessed by expert opinion. Pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using random effects model.

Results: After incorporating biases, overall effect estimates regressed slightly toward no effect, with the largest relative difference between conventional and bias-adjusted ORs for laboratory-confirmed influenza (OR, 0.18; 95% CI: 0.01, 3.00 vs. OR, 0.23; 95% CI: 0.03, 2.04). In most of the studies, CIs widened reflecting uncertainties about the biases. The between-study heterogeneity reduced considerably with the largest reduction for all-cause mortality ($I^2 = 4\%$, $P = 0.39$ vs. $I^2 = 91\%$, $P < 0.01$).

Conclusion: This case study showed that after addressing potential biases influenza vaccine was still estimated effective in preventing hospitalization from influenza and/or pneumonia and all-cause mortality. Increasing the number of assessors and incorporating empirical evidence might improve the new bias-adjustment method.

Keywords: Meta-analysis; Bias adjustment; Observational studies; Seasonal influenza; Vaccination; Community-dwelling elderly

1. Introduction

As seasonal influenza vaccination is standard care for older adults in most of the developed countries, conducting a randomized controlled trial (RCT) to estimate its effectiveness would be considered unethical. Therefore, apart from the limited number of older RCTs [1−3], the main evidence about influenza vaccine effectiveness comes from observational studies. Such studies are prone to bias because of lack of concealed randomization and different baseline characteristics between the vaccinated and the unvaccinated groups [4,5]. It has been shown that confounding by indication (also known as selection bias or healthy user effect), if not properly adjusted for in observational studies, could lead to an invalid estimate of vaccine effectiveness [6]. Moreover, some studies gave evidence for the presence of selection bias in most of the cohort studies assessing seasonal influenza vaccine effectiveness in the elderly population [7,8]. Combining evidence from observational studies by using standard methods of meta-analysis will compound this issue [9]. For instance, the most recently conducted meta-analysis assessing influenza vaccine effectiveness in elderly population [10] found a high level of heterogeneity between studies, which could be partly explained by unadjusted

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What is new?

- After incorporating the effect of internal and external biases, between-study heterogeneity reduced considerably.
- In this case study, bias-adjustment method enables us to identify the potential biases and to arrive at more appropriate estimates, possibly at the cost of less precision.
- Standard methods of meta-analysis do not take into account the effects of biases in observational studies. Bias-adjustment methods can be used to quantify the effects of such biases in future meta-analytic case studies.

sources of biases. It has been suggested that meta-analyses of observational studies are prone to bias because they pool the results from studies of differing quality (internal bias) and relevance (external bias) [11].

Although biases could partly be addressed by using quality scores through sensitivity analysis, it has been shown that weighing the analysis by quality scores is inadequate [12,13], and sensitivity analysis is not applicable when the number of included studies is low. Furthermore, it might be possible to use meta-regression techniques to investigate possible explanations of heterogeneity. However, this is only a good strategy when a relatively large number of studies are included in the meta-analysis [4].

To resolve these limitations, a novel bias-adjustment meta-analysis method has been proposed recently by Turner et al. [14]. This method provides a technique to adjust for internal and external biases through a process of eliciting and incorporating expert opinion with the results of the included studies in the meta-analysis. To estimate seasonal influenza vaccine effectiveness in the community-dwelling elderly against influenza and influenza-related outcomes, we first conducted a conventional meta-analysis of cohort studies (which are considered high in the hierarchy of observational studies). Secondly, we applied the bias-adjustment method to quantify the potential biases in the conventional meta-analysis. Finally, we compared the performance of the 2 methodological approaches and discussed their advantages and disadvantages.

2. Methods

2.1. Conventional meta-analysis

2.1.1. Search strategy

We searched MEDLINE, EMBASE, and the Cochrane library before September 2011 to identify cohort studies assessing influenza vaccine effectiveness. The search strategy consisted the following search terms: (“Influenza Vaccines”[Mesh] OR “Influenza, Human/epidemiology”[Mesh] OR “Influenza Human/immunology”[Mesh] OR “Influenza, Human/mortality”[Mesh] OR “Influenza, Human/prevention and control”[Mesh] OR “Influenza, Human/transmission”[Mesh] OR Influenza vaccine*[tiab] OR (Influenza OR flu [tiab])) AND (Vaccine* OR immuni* OR inocul* OR efficacy OR effectiveness [tiab]) AND (old* OR age*OR elderly [tiab] OR older persons [tiab] OR senior* [tiab]) AND (Clinical Trial [Mesh] OR “Case-Control Studies”[Mesh] OR “Cohort Studies” [Mesh] OR observational studies [tiab]). Only cohort studies assessing seasonal inactivated influenza vaccine effectiveness among community-dwelling elderly on laboratory-confirmed influenza, influenza-like illness (ILI), hospitalizations from influenza and/or pneumonia, and all-cause mortality were included. In our study, laboratory-confirmed influenza was defined as influenza confirmed by viral isolation, or virus nucleic acid detected in a clinical specimen, or when influenza-specific antibody response was measured. ILI was defined as a sudden onset of high fever, cough (usually dry), headache, muscle and joint pain, severe malaise (feeling unwell), sore throat, and runny nose or a code R80 according to the International Classification of Primary Care. Hospitalization from influenza and/or pneumonia was considered as an outcome when it was coded according to the International Classification of Diseases (ICD) version-10 as J12-18, J69.0, A48.1, J10.0, J10.1, J10.8, J11.0, J11.8, according to ICD version-9 (ICD-9-CM) as 480−487 or when hospitalization because of pneumonia was reported by the patient. All-cause death was recorded when it was reported as such in the reviewed studies.

2.1.2. Data extraction

Two reviewers (MD and GG) independently extracted data on the study population, characteristics of the participants, sample size, length of follow-up, inclusion and exclusion criteria for vaccinated and unvaccinated individuals, content and antigenic match of the administered vaccines, description of viral circulation, epidemic condition, and outcomes. If information regarding the vaccine strains and epidemic condition was not available in the studies, we extracted this information from the World Health Organization (WHO) Web site [15].

2.1.3. Statistical analyses

The extracted raw data on vaccination status and outcomes from the cohort studies were entered into the Cochrane RevMan Software (version 5.2) [16]. Where applicable, the adjusted odds ratios (ORs) were used to back calculate the adjusted number of events by using the formula $r_{1adj} \approx (OR_{adj}) \times (r_2/n_2) \times n_1$, where r_{1adj} is the adjusted number of events in the intervention group, OR_{adj} is the adjusted effect size given in the original study, r_2 is the number of events in the control group, n_2 is the total number of participants in the control group, and n_1 is the