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Review

Change in the efficacy of influenza vaccination after repeated inoculation under antigenic mismatch: A systematic review and meta-analysis

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ABSTRACT

Objectives: To examine the effects of repeated influenza vaccination on medically-attended influenza (MAI) and acute respiratory illness (ARI) risk according to the antigenic matching between vaccine and circulating virus strains.
Methods: We performed a systematic review and meta-analysis of randomized studies that compared the risk of MAI and ARI between subjects who had been vaccinated for two consecutive seasons (multiple vaccine group) and those who had been vaccinated in the current season and not in the previous season (single vaccine group).
Results: Of 1467 articles identified, eight studies covering ten seasons were included in meta-analyses. Six studies assessed efficacy against MAI in children, yielding the risk ratios (RR) of 2.04 (95% CI 1.29–3.22) when circulating strains mismatched vaccine strains, and 0.64 (0.33–1.22) when circulating strains matched vaccine strains. When stratified by vaccine types, the reduced efficacy was significant for live-attenuated influenza vaccine only. Three studies investigated efficacy against ARI in children, with the RR of 0.96 (0.81–1.15). The results on adults and the elderly were scarce.
Conclusions: Influenza vaccine efficacy against mismatch strains was lower in repeatedly vaccinated children as compared with those vaccinated for the current season only. The scarcity of available studies may call for further randomized controlled trials on repeated influenza vaccination.

Contents

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1. Introduction

Vaccination has been a major preventive measure against influenza to reduce its clinical burden [1]. Because influenza viruses undergo antigenic changes frequently, the World Health Organization (WHO) established sentinel centers around the world to collect samples from patients with influenza-like illness, a group of acute respiratory illnesses characterized by fever, cough, headache, myalgia, and other symptoms, and detect the virus type of circulating strains to determine which strains to include in the vaccine for the upcoming influenza season every year [1]. Annual vaccination is recommended in many countries for the elderly and individuals with specific pathologies, and also for healthy children and adults in the U.S. [2,3].

Although significant efficacy of influenza vaccine has been demonstrated in systematic reviews of randomized controlled trials [1,3,4], which examined the effect of current-season vaccination, relatively fewer studies have been conducted on the effects of repeated vaccination [5]. From 1970s, there has been concern for reduced vaccine efficacy upon repeated vaccination [6–8]. Hoskin et al. showed reduced efficacy in repeatedly vaccinated school children while other studies did not show such trend [5,6,9]. To our knowledge, there has been only one systematic review of randomized trials on the effects of repeated influenza immunization, which showed no evidence of reduced efficacy due to repeated vaccination [5]. However, substantial heterogeneity existed among the included studies [5], raising the possibility that other factors accounted for the overall neutral finding.

Smith et al. suggested that antigenic distance between circulating strains and vaccine strains partly account for the variable vaccine efficacy [10]. Cochrane reviews showed reduced vaccine efficacy when circulating strains mismatched vaccine strains [1,11]. Some serological studies showed reduced immune response upon vaccination with antigenically dissimilar viruses in individuals with a previous vaccination history [12,13]. Some animal studies also showed the reduced development of T-cell immunity in previously vaccinated mice upon novel virus challenge [14,15]. These findings suggest the potential role of antigenic match in modulating the efficacy of repeated influenza vaccination.

To provide the high-quality evidence on the effect of repeated influenza vaccination, we conducted a systematic review and meta-analysis of randomized controlled trials, taking into account the effect of antigenic match between vaccine and circulating strains.

2. Methods

2.1. Data sources and searches

We searched MEDLINE (PubMed) for articles published in English and Japanese between 1/1/1966 and 12/31/2015. The search was done on 11/16/2014 and updated on 7/18/2016. We followed the PRIMA guideline to conduct this systematic review.

The primary outcomes of this systematic review were medically-attended influenza and acute respiratory illness (ARI) because we considered the presence of clinical symptoms to be the important outcomes for patients. We defined ARI as the presence of fever, cough, headache, myalgia, sore throat or other respiratory symptoms. We defined medically-attended influenza as the ARI with laboratory confirmation of influenza virus. The methods of laboratory confirmation of influenza included the detection of viral mRNA through reverse transcription-polymerase chain reaction (RT-PCR), the isolation of influenza virus from culture, and fourfold or greater rises in the titer of serum antibodies against hemagglutinin (a viral surface protein) as measured in the hemagglutination inhibition (HI) assay. We defined vaccine efficacy against medically-attended influenza and ARI as the reduction in the rates of these conditions.

Our full search strategy is described in Supplementary Table 1. The inclusion criteria for our systematic review were as follows: (1) Published randomized controlled trials; (2) Studies with results on the rate of medically-attended influenza and/or ARI; (3) Medically-attended influenza cases confirmed by RT-PCR, viral culture, or serological data; (4) Studies that included subjects who were vaccinated for two consecutive seasons (defined as multiple vaccine group) and those who were vaccinated for one season and not in the previous season (defined as single vaccine group). For the fourth criteria, we included two types of studies: (a) studies where subjects were randomized to vaccine or placebo for the first year and re-randomized for the second year; (b) studies that randomized subjects to vaccine or placebo and reported data on their vaccination status in the previous season.

2.2. Study selection

Two reviewers read titles and abstracts of retrieved studies and selected those that examined the rates of medically-attended influenza and/or ARI. For articles with no abstract, we read full-text articles to determine if they examined the rates in case we were unable to exclude these articles based on their titles only. Then the two reviewers independently applied the inclusion criteria to the selected articles to identify eligible studies. Disagreement was resolved by discussion. At this point, we included studies that provided data on vaccination status within previous two years because we thought that we would be able to obtain data on those who had been vaccinated for two seasons in a row by contacting the authors. We excluded studies with >15% of subjects having chronic illness in the multiple or the single vaccine group and studies that included pregnant women. Because we aimed to examine the public effects of yearly vaccination, we excluded studies that examined the effects of a combination of trivalent and monovalent influenza vaccinations. In addition, we excluded challenge studies because they did not reflect the real-life setting of influenza infection. We also excluded review studies and studies that examined the effects of vaccination on serological parameters.

2.3. Data extraction and quality assessment

Among eligible studies, some did not specify the number of subjects with ARI and/or medically-attended influenza in the multiple vaccine group and the single vaccine group separately. We contacted the authors of these studies by email to request unpublished results. We found that data for two studies were available in the online public domain after contacting an author [16]. Because