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Review

Does consecutive influenza vaccination reduce protection against influenza: A systematic review and meta-analysis

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ABSTRACT

Introduction: Vaccination against influenza on an annual basis is widely recommended, yet recent studies suggest consecutive vaccination may reduce vaccine effectiveness (VE).
Purpose: To assess whether when examining the entirety of existing data consecutive influenza vaccination reduces VE compared to current season influenza vaccination.
Data sources: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to April 26, 2017; citations of included studies.
Study selection: Randomized, controlled trials (RCTs) and observational studies of children, adults and/or the elderly that reported laboratory-confirmed influenza infection over 2 or more consecutive influenza seasons were eligible.
Data extraction: Data related to study characteristics, participant demographics, cases of influenza infection by vaccination group and risk of bias assessment was extracted in duplicate.
Data synthesis: Five RCTs involving 11,987 participants did not show a significant reduction in VE when participants vaccinated in two consecutive seasons (VE 71%, 95% CI 62–78%) were compared to those vaccinated in the current season (VE 58%, 95% CI 48–66%) (odds ratio [OR] 0.88, 95% CI 0.62–1.26, $p = 0.49$, $I^2 = 39\%$). Twenty-eight observational studies involving 28,627 participants also did not show a reduction (VE 41%, 95% CI 30–51% compared to VE 47%, 95% CI 39–54%; OR 1.14, 95% CI 0.98–1.32, $p = 0.09$, $I^2 = 63\%$). Results from subgroup analyses by influenza type/subtype, vaccine type, age, vaccine match and co-morbidity support these findings; however, dose–response results were inconsistent. Certainty in the evidence was assessed to be very low due to unexplained heterogeneity and imprecision.
Limitations: Included studies with relatively small sample sizes; summary VE and OR estimates were derived from raw and unadjusted data.
Conclusion: Available evidence does not support a reduction in VE with consecutive influenza vaccination.
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Contents

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1. Introduction

Influenza is a significant contributor to morbidity and mortality globally, causing approximately 300,000 to 500,000 deaths every year [1–4]. It is widely accepted that vaccination, which is estimated to be about 60% effective in preventing influenza, is an important public health strategy [5–7]. Since 1960, public health agencies have recommended annual influenza vaccination [5,8–10]. Populations at high risk for complications were first prioritized for vaccination followed by recommendations in the U.S. and other countries that anyone over the age of 6 months that wishes to avoid infection with influenza be vaccinated [8,10–12]. Because of minor changes in the haemagglutinin surface protein of the virus, recommendations concerning vaccine composition are updated annually. This way, there is a better match between the antigens in the vaccine and those of circulating influenza strains [4,5].

Recent observational studies however have raised concern that consecutive influenza vaccination may blunt or reduce the effectiveness of vaccination in a current year [13–18]. This finding was first raised in the 1970s during school outbreaks of influenza where children who received multiple vaccinations were at higher risk than children vaccinated for the first time [19]. Several different immunological explanations for these findings have been posited [19–22]. Together, these data along with biological plausibility, have raised concern about the policy of annual vaccination. To examine this issue, we conducted a systematic review to assess whether when examining the entirety of existing data, consecutive influenza vaccination reduces vaccine effectiveness (VE) compared to current season vaccination.

2. Methods

A protocol for the present systematic review and meta-analysis was registered with PROSPERO, https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017059893 [23]. Decisions regarding criteria for study inclusion, outcomes, search methods for identification of studies, data collection, risk of bias, evaluation of the quality of evidence and analysis were established a priori. The PRISMA statement was used to guide reporting of this review [24].

2.1. Data sources and searches

MEDLINE (OVID interface, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, 1946 to Present), EMBASE (OVID interface, 1974 to Present) and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Search strategies were tailored to each database (Appendix 1A-C of Supplementary Materials). No restrictions based on study design, language or publication date were employed in the searches to minimize publication bias [25]. Included studies were however limited to the English language to facilitate retrieval of full-texts [26,27]. Searches were conducted on February 9 (MEDLINE and CENTRAL) and February 10 (EMBASE), 2017. Each of the searches was rerun on April 26, 2017 as 4 new relevant publications were identified after completion of the initial searches. Citations of included studies were also reviewed to minimize the risk of failing to include relevant studies.

Pairs of reviewers independently screened titles, abstracts and full-texts of records identified by our searches for possible inclusion. If necessary, consensus was reached through discussion amongst the review pair.

2.2. Study selection

Randomized controlled trials (RCTs), quasi-RCTs and observational studies were eligible for inclusion. Studies of any population that experienced influenza-like illness, consistent with symptomatic acute respiratory infection, for which vaccination status was reported were included [28]. All vaccine types were included and were categorized as inactivated influenza vaccine (IIV), live-attenuated influenza vaccine (LAIV) or other (e.g. high-dose vaccine). Laboratory-confirmed influenza, tested by polymerase chain reaction (PCR) or viral culture was the primary outcome. Studies reporting influenza based on any confirmatory laboratory test (PCR, viral culture, rise in antibody titres, immunofluorescence assay, rapid antigen testing or a combination of these) were included as a secondary outcome since these additional methods have been shown to be inferior in sensitivity and reliability when compared to PCR and viral culture [29,30]. Influenza was categorized as influenza A/H3N2, A/H1N1 or B whenever possible. Studies reporting the outcome of immunogenicity were not eligible for inclusion because this surrogate measure of vaccine-induced protection may fail to predict the outcome of influenza infection [31,32].

2.3. Data extraction and quality assessment

Following pilot testing, data related to study characteristics, participant demographics, cases of influenza infection by vaccination group and risk of bias assessment was extracted in duplicate.

Risk of bias was assessed using the Cochrane risk of bias tool for RCTs and the Newcastle-Ottawa Scale (NOS) for observational studies [33,34]. According to the classifications outlined in the Cochrane risk of bias tool, the following were evaluated in RCTs: selection bias (random sequence generation and allocation

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