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Review

Effectiveness of 2009 pandemic influenza A(H1N1) vaccines: A systematic review and meta-analysis

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ABSTRACT

Background: The clinical effectiveness of monovalent influenza A(H1N1)pdm09 vaccines has not been comprehensively summarised. We undertook a systematic review and meta-analysis to assess vaccine effectiveness (VE) for adjuvanted and unadjuvanted vaccines.

Methods: We searched healthcare databases and grey literature from 11 June 2009 to 12 November 2014. Two researchers independently assessed titles and abstracts to identify studies for full review. Random effects meta-analyses estimated the pooled effect size of vaccination compared to placebo or no vaccination for crude and adjusted odds ratios (OR) to prevent laboratory confirmed influenza illness (LCI) and related hospitalization. VE was calculated as (1-pooled OR) * 100. Narrative synthesis was undertaken where meta-analysis was not possible.

Results: We identified 9229 studies of which 38 at moderate risk of bias met protocol eligibility criteria; 23 were suitable for meta-analysis. Pooled adjusted VE against LCI with adjuvanted and unadjuvanted vaccines both reached statistical significance (adjuvanted: VE = 80%; 95% confidence interval [CI] 59–90%; unadjuvanted: VE = 66%; 95% CI 47–78%); in planned secondary analyses, VE in adults often failed to reach statistical significance and pooled point estimates were lower than observed in children. Overall pooled adjusted VE against hospitalization was 61% (95% CI 14–82%); in planned secondary analyses, adjusted VE attained statistical significance in adults aged 18–64 years and children for adjuvanted vaccines. Adjuvanted vaccines were significantly more effective in children compared to adults for both outcomes.

Conclusions: Adjuvanted and unadjuvanted monovalent influenza A(H1N1)pdm09 vaccines were both effective in preventing LCI. Overall, the vaccines were also effective against influenza-related hospitalization. For both outcomes adjuvanted vaccines were more effective in children than in adults.

Contents

Abbreviations: CI, confidence interval; LCI, laboratory-confirmed influenza illness; OR, odds ratio; RT-PCR, reverse-transcriptase polymerase chain reaction.

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1. Background

The first ever global deployment of pandemic influenza vaccines was in response to the influenza A(H1N1) pandemic in 2009–10. Whilst many individual studies have supported the effectiveness of these vaccines in different populations and geographical areas, all have been observational designs and several were underpowered or calculated crude estimates of effectiveness without adjustment for confounding. Two previous systematic reviews and meta-analyses of 2009–10 vaccine against clinical endpoints exist, but were conducted too soon following the pandemic to capture all relevant information [1,2]. Furthermore, Yin et al. did not calculate adjusted pooled estimates and Osterholm et al. did not subject their findings to meta-analysis [1,2]. A third systematic review reported only on serological endpoints [3]. At this point in time it is unlikely that further novel data on the effectiveness of monovalent influenza A(H1N1) pdm09 vaccines will be published.

Comprehensive summaries of the available data are required to inform future public health policies for pandemic vaccine procurement and deployment, and the potential benefits of seasonal influenza vaccination in children. Here we report a systematic review and meta-analysis, which includes a substantial amount of data not included in prior meta-analyses, to assess the efficacy and effectiveness of inactivated monovalent influenza A(H1N1)pdm09 intramuscular vaccines versus placebo or no vaccination to prevent laboratory confirmed influenza illness (LCI), hospitalization and mortality due to infections with the vaccinated strain of influenza. We specified research questions *a priori* to separately estimate these outcomes for adjuvanted and unadjuvanted vaccines [4]. Given the reported potential association between narcolepsy and administration of AS03 adjuvanted monovalent influenza A (H1N1)pdm09 vaccine, our study may inform the discussion regarding risk-to-benefit of immunisation [5–8].

2. Methods

We followed guidance on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9]. The study protocol was registered with the National Institute for Health Research international prospective register of systematic reviews (PROSPERO) [4].

2.1. Definitions and outcomes

We defined the study population as people of all ages, from any setting and included both healthy individuals and those with pre-existing medical conditions. The interventions of interest were vaccination with inactivated adjuvanted or unadjuvanted monovalent intramuscular vaccines, which contained influenza A/California/7/2009 (H1N1)-like virus. We did not include data on live attenuated influenza vaccines (LAIV) or multi-valent preparations which included the pandemic strain. When studies reported using inactivated vaccine and LAIV in different subjects [10–12], we did not include the data on LAIV in meta-analyses. Comparator groups included people who received placebo or who were not vaccinated. Outcome measures were prevention of reverse transcriptase PCR (RT-PCR) or viral culture confirmed influenza A(H1N1)pdm09 illness, hospitalization and mortality. We excluded studies which only evaluated non-specific outcomes such as influenza-like illness or all-cause mortality. We assessed experimental and observational studies and systematic reviews +/− meta-analysis using the eligibility criteria defined in the study protocol [4].

2.2. Search strategy

Healthcare databases and sources of grey literature were searched in November 2014 and April 2016 (no new studies identified) using a pre-specified search strategy considering relevant papers published from June 2009 and pertaining to the influenza A(H1N1)pdm09 pandemic period (11 June 2009 to 10 August 2010) [4] (outlined in Supplementary Material). Two reviewers (LL and SS) independently screened studies for inclusion using a three-stage sifting approach and extracted data using a piloted template (see Supplementary Material), referring to CRB or JSN-V-T for resolution of any discordance.

2.3. Risk of bias assessment

We used the Cochrane Collaboration tool to assess risk of bias in prospective cohort studies, whilst the Newcastle-Ottawa scale was used to critique other eligible observational studies in the three domains of selection of study groups, comparability of the groups

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