Impacts on influenza A(H1N1)pdm09 infection from cross-protection of seasonal trivalent influenza vaccines and A(H1N1)pdm09 vaccines: systematic review and meta-analyses
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CRD summary
The review concluded that during the delay in influenza A H1N1 2009 vaccine production, seasonal influenza vaccination provided moderate protection against confirmed influenza A H1N1 2009 illness. Targeted vaccines were highly effective. The review was generally well conducted but the data had a number of limitations and care should be taken when interpreting the authors' conclusions.

Authors' objectives
To determine the impact of cross-protection from seasonal trivalent influenza vaccines and the impact of pandemic influenza A H1N1 2009 vaccines on pandemic influenza A H1N1 2009 infection.

Searching
EMBASE, MEDLINE, The Cochrane Library, CRD databases, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus were searched to July 2011 for articles in any language. Search terms were reported. Clinical trial registries, relevant journals, and relevant websites were searched. The reference lists of retrieved studies and reviews were searched and study authors were contacted.

Study selection
Randomised controlled trials (RCTs), cohort studies and case-control studies of trivalent influenza vaccines in any population for the seasons 2007 to 2008, 2008 to 2009, or 2009 to 2010 in the northern hemisphere, and 2008 or 2009 in the southern hemisphere, were eligible for inclusion. Controls for RCTs and cohort studies had to be participants who did not receive the vaccine that year or in the previous year. Controls for case-control studies were participants who were influenza A H1N1 2009 laboratory test negative. The outcomes were laboratory-confirmed infection, influenza-like illness, sickness absence, and acute respiratory illness occurring at least 14 days after vaccination. Definitions were provided.

The included studies reported cross-protection from seasonal trivalent influenza vaccine, the effectiveness of influenza A H1N1 2009 vaccines, or both. The age of participants ranged from zero to 84 years, where reported. The study locations included the USA, UK, Australia, Mexico, Canada, China, and Europe. The enrolment period for studies ranged from November 2005 to October 2010.

Two reviewers independently selected studies.

Assessment of study quality
The quality of RCTs was assessed using the Cochrane Collaboration's tool, version 5.1.0, which appraised selection, performance, attrition, detection, and reporting biases. The quality of case-control and cohort studies was assessed using the Newcastle-Ottawa scale, which appraised selection, comparability and exposure. All RCTs and studies were scored as low, moderate or high risk of bias.

Two reviewers independently assessed quality and disagreements were resolved by discussion or consultation with a third reviewer.

Data extraction
Data were extracted on clinical outcomes and used to calculate odds ratios or risk ratios, with 95% confidence intervals. Two reviewers independently extracted data and disagreements were resolved by discussion or consultation with a third reviewer.

Methods of synthesis
Mantel-Haenszel random-effects meta-analysis was used to calculate pooled risk ratios and odds ratios, with 95%
confidence intervals. Statistical heterogeneity was assessed using $I^2$. Publication bias was assessed using funnel plots, the Begg-Mazumdar test, and Duval and Tweedie’s trim and fill method. Sensitivity analysis was conducted by excluding studies with a high risk of bias and those undertaken during the 2009 pandemic.

**Results of the review**

Thirty-three studies were included in the review, with about three million participants. Twenty-one were case-control studies, six were cohort studies, two were RCTs, three were surveillance reports, and one was an outbreak investigation. One RCT was rated at moderate risk of bias and one was rated at low risk of bias. Ten case-control studies had low risk and 11 had moderate risk of bias. Three cohort studies had low risk, three had moderate risk, and one had a high risk of bias.

**Seasonal vaccine**: Compared with no vaccination, seasonal influenza vaccination was not associated with statistically less confirmed influenza A H1N1 2009 illness (OR 0.81, 95% CI 0.58 to 1.13; $I^2$=94%; 13 case-control studies). Sensitivity analysis excluding high- and moderate-risk studies made the results significant in favour of vaccine (OR 0.66, 95% CI 0.48 to 0.91; $I^2$=91%; eight case-control studies). Sensitivity analysis further excluding studies with recruitment early in the pandemic was also statistically significant in favour of vaccine (OR 0.49, 95% CI 0.43 to 0.55; $I^2$=0; five case-control studies). Results in individual RCTs and cohort studies showed mixed effects.

**Pandemic vaccine**: Compared with no vaccination, pandemic influenza vaccination was associated with statistically less confirmed influenza A H1N1 2009 illness (OR 0.14, 95% CI 0.07 to 0.27; $I^2$=81%; 11 case-control studies). Sensitivity analysis excluding high- and moderate-risk studies was significantly in favour of vaccine (OR 0.15, 95% CI 0.08 to 0.28; $I^2$=45%; six case-control studies).

Other results were presented. There was no evidence of publication bias.

**Authors’ conclusions**

During the delay in influenza A H1N1 2009 vaccine production, seasonal influenza vaccination provided moderate protection against confirmed influenza A H1N1 2009 illness. Targeted vaccines were highly effective.

**CRD commentary**

The inclusion criteria were clearly defined and several relevant data sources were searched. Publication bias was assessed and was not detected. Attempts were made to reduce error and bias throughout the review. The quality of the evidence was mixed, with approximately half of the studies deemed at moderate or high risk of bias.

Random-effects meta-analysis was undertaken, but significant statistical heterogeneity was present in many of the meta-analyses, indicating that the data might not have been suitable for pooling, which the authors acknowledged. They also noted that some of the studies used a test-negative case-control design, which could have biased the results.

The review was generally well conducted, but the data had a number of limitations and care should be taken when interpreting the authors’ conclusions.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that research directed toward better, more effective, and universal influenza vaccines was underway and was needed, as there was only moderate cross-protection from trivalent influenza vaccines.

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**Bibliographic details**

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