Herd effect from influenza vaccination in non-healthcare settings: a systematic review of randomised controlled and observational studies

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Abstract

**Background:** Influenza vaccine programs are expected to have a herd effect and protect close contacts of vaccinated persons from influenza virus infection.

**Methods:** We searched MEDLINE, EMBASE, CINAHL, Global Health and CENTRAL from inception to March 2014 for studies assessing the protective effect of influenza vaccination versus no vaccination on influenza virus infections in contacts. We excluded studies conducted in a health care setting, and ecological and modelling studies. We evaluated risk of bias and applied GRADE to assess the level of evidence. We calculated odds ratio (OR) and 95% confidence intervals (CI) using a random-effects model.

**Results:** Out of 43,082 screened articles, nine randomized controlled trials (RCTs) and four observational studies were eligible. Most studies were conducted in North America (n=7). Among RCTs, no significant herd effect on the occurrence of influenza in contacts could be found (OR 0.62, 95% CI 0.34-1.12). However, two additional RCTs that were supporting a herd effect, however, the data available was insufficient for inclusion in the meta-analysis. There was only little data available for the other outcomes. We did not find any evidence for a herd effect for prevention of hospital admission, pneumonia, or mortality from RCTs.

**Risk of bias:** The RCTs scored on average 4.3 when assessed against 7 domains with a Newcastle-Ottawa Scale.

Study selection, data extraction, risk of bias assessment:

- **Independent screening, data extraction and risk of bias assessment by two reviewers**
- **Risk of bias:**
  - Cochrane Review Collaboration’s tool for RCTs
  - Newcastle-Ottawa scale for observational studies (scale 1-9, 9 = lowest risk of bias)
- **Overall level of evidence assessed using GRADE**
- **Meta-analysis was conducted using random-effects model, separately for RCTs and observational studies**

**Conclusions**

We found an overall low level of evidence supporting an indirect or herd effect of influenza vaccines in preventing influenza infection in vaccinated persons’ contacts.

Observational studies showed a significant effect, the summary estimate from RCTs, however, did not show a statistically significant effect.

Data on a herd effect on outcomes other than influenza virus infection were sparse, due to either outcomes that were not measured or due to inadequate power to detect a difference.

The best evidence supporting a herd effect was reported by Loeb et al. in a study at community level in Hutterites. The other studies were at higher risk of bias and/or observational in design.

**Limitations**

- Only very few studies that were designed to measure the indirect effects of influenza vaccination were published
- Statistically significant heterogeneity that could not be explained by our a priori defined subgroup analyses
- Risk of bias in the majority of study which further decreased the level of evidence

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**Methods**

**Inclusion criteria:**

- Search of MEDLINE, EMBASE, CINAHL, CENTRAL through March 7, 2014.
- Studies assessing the protective effect of influenza vaccination versus no influenza vaccination (either no vaccination, placebo, or alternative vaccine) on contacts of any age groups in a non-healthcare setting were eligible.
- The definition of contacts was broad and included anyone in the same community, school, or household.
- Designs of interest included RCTs and observational studies including quasi-experimental, cohort, case-control, and cross-sectional designs.
- The primary outcome was influenza disease in non-vaccinated contacts exposed to influenza-vaccinated persons or non-vaccinated persons.
- Evidence of influenza virus infection was defined as laboratory-confirmed (serology, culture, antigen, NAAT) or influenza-like illness within a period of laboratory confirmed circulation of influenza.

**Results**

- Out of 43,082 records identified in our search, we identified 7 relevant RCTs and 4 observational studies.
- In RCTs, the point estimate was in favour of the existence of a herd effect in preventing influenza infection, but failed to achieve statistical significance (OR 0.62, 95% CI 0.34-1.12; Figure 1). In observational studies, however, we found a significant effect (OR 0.57, 95% CI 0.43-0.77; Figure 2).
- We identified two additional RCTs that were supporting a herd effect, however, the data available was insufficient for inclusion in the meta-analysis.
- There was only little data available for the other outcomes. We did not find any evidence for a herd effect on outcomes other than influenza virus infection.
- Observational studies showed a significant effect, the summary estimate from RCTs, however, did not show a statistically significant effect.
- Data on a herd effect on outcomes other than influenza virus infection were sparse, due to either outcomes that were not measured or due to inadequate power to detect a difference.

**Discussion**

We found an overall low level of evidence supporting an indirect or herd effect of influenza vaccines in preventing influenza infection in vaccinated persons’ contacts.

Observational studies showed a significant effect, the summary estimate from RCTs, however, did not show a statistically significant effect.

Data on a herd effect on outcomes other than influenza virus infection were sparse, due to either outcomes that were not measured or due to inadequate power to detect a difference.

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**Limitations**

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- Risk of bias in the majority of study which further decreased the level of evidence.

**Conclusions**

Herd effects are expected with influenza vaccine programs, but there are few studies that quantify the indirect effects of vaccination. We found low-level evidence supporting a herd effect of the influenza vaccine on influenza infections in close contacts of vaccinated persons, with better evidence from studies conducted in a community level. Further rigorous studies are needed in order to better understand under which circumstances vaccination may prevent influenza infections and its complications in contacts.