Influenza vaccination for immunocompromised patients: summary of a systematic review and meta-analysis

Vaccination of immunocompromised patients is recommended in many national guidelines to protect against severe or complicated influenza infection. However, due to uncertainties over the evidence base, implementation is frequently patchy and dependent on individual clinical discretion. We conducted a systematic review and meta-analysis to assess the evidence for influenza vaccination in this patient group. Healthcare databases and grey literature were searched and screened for eligibility. Data extraction and assessments of risk of bias were undertaken in duplicate, and results were synthesised narratively and using meta-analysis where possible. Our data show that whilst the serological response following vaccination of immunocompromised patients is less vigorous than in healthy controls, clinical protection is still meaningful, with only mild variation in adverse events between aetiological groups. Although we encountered significant clinical and statistical heterogeneity in many of our meta-analyses, we advocate that immunocompromised patients should be targeted for influenza vaccination.

Keywords Immunocompromised, influenza, meta-analysis, systematic review, vaccination.

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**Introduction**

Seasonal and pandemic influenza are well documented in producing a significant burden of morbidity and mortality on human health. Patients with reduced immune function due to disease or pharmacotherapy are vulnerable to severe or complicated influenza infection, and national immunisation guidelines commonly recommend this population are vaccinated to protect against such outcomes.\(^2\)\(^\text{,}^2\)\(^\text{,}\)\(^3\)\(^\text{,}\)\(^4\) However, defining a threshold of immunosuppression beyond which vaccination is indicated is problematic, as is the lack of evidence of clinical protection in some immunocompromised patient groups. As a result, the decision to vaccinate such patients is usually devolved to individual clinicians.\(^2\)\(^\text{,}\)\(^5\)\(^\text{,}\)\(^6\)

This article summarises a recently conducted systematic review and meta-analysis which assessed the evidence for influenza vaccination in immunocompromised patients. Two manuscripts arising from this work have been published and report our findings through a public health policy interpretation and a sub-analysis by aetiology of immunocompromise.\(^7\)\(^\text{,}\)\(^8\)

**Methods**

The methodology used in this study has been previously described, and an abbreviated protocol is also available from the National Institute for Health Research international prospective register of systematic reviews (PROSPERO).\(^7\)\(^\text{,}\)\(^9\) We defined the study population according to policy documents published by the World Health Organization and United Kingdom Departments of Health for persons with primary or secondary immunodeficiency.\(^7\)\(^\text{,}\)\(^\text{,}\)\(^10\) Eligible interventions included both 2009 pandemic influenza A (H1N1) and seasonal influenza vaccinations, and comparative groups consisted of vaccinated immunocompetent controls (VICT) or immunocompromised patients who received placebo or no vaccination (PNV). Outcome measures of interest pertained to the prevention of influenza-like illness, laboratory-confirmed influenza infection, serological response and adverse events.

Electronic healthcare databases and grey literature were searched according to a comprehensive strategy prior to screening all identified records against the protocol eligibility criteria. Two reviewers completed this process through sequentially examining the title, abstract and full text of each record. Data extraction and assessments of risk of bias were performed in duplicate, and outcome measures pertaining to the serological response to vaccination were classified according to the EU Committee for Human Medicinal Products criteria for seroconversion and seroprotection.\(^11\) Results were synthesised narratively, and meta-analyses were conducted where feasible initially using a random effects model. Heterogeneity was assessed using \(I^2\) and when low (\(I^2 < 40\%\)) analyses were re-executed using a fixed effects model; but when high (\(I^2 > 85\%\)) analyses were abandoned. The potential risk of publication bias was assessed both visually using Begg’s funnel plot and statistically using Egger’s regression test.

**Results**

Two hundred and nine studies met the protocol eligibility criteria, the majority of which were non-randomised controlled trials and at unclear or high risk of bias. When pooling data for all immunocompromised patients, meta-analyses showed a significantly lower odds of influenza-like illness and laboratory-confirmed influenza infection through vaccinating immunocompromised patients compared with PNV controls. Meta-analysis found no significant difference in the odds of influenza-like illness after vaccinating immunocompromised patients compared with VICT controls; inadequate data were identified to undertake this analysis for laboratory-confirmed influenza infection. The pooled odds of seroconversion (≥4 fold rise in haemagglutination inhibition titre) and seroprotection were lower and reached statistical significance in vaccinated immunocompromised patients compared with VICT controls for seasonal influenza A (H1N1), A (H3N2) and B. An increased pooled odds of seroconversion was shown in vaccinated immunocompromised patients compared with PNV controls, although this did not reach statistical significance for seasonal influenza A (H1N1) and A (H3N2). Table 1 shows the statistical output from those meta-analyses we conducted to inform an overall public health policy interpretation of the evidence.

Considering our sub-analyses by aetiology of immunocompromise, meta-analyses showed significantly lower odds of influenza-like illness post-vaccination in HIV patients, cancer patients and transplant recipients and of laboratory-confirmed influenza in HIV patients, compared with PNV controls. Insufficient data were available to analyse these outcome measures for patients treated with immunosuppressants due to autoimmune or respiratory disease. Pooled odds of seroconversion and seroprotection were typically lower in HIV patients, cancer patients and transplant recipients, compared with VICT controls.

Publication bias was detected in a minority of analyses, and narrative synthesis supported our quantitative findings. We did not identify consistent evidence of safety concerns, and the included studies reported that vaccination was generally well tolerated, with variation in mild adverse events between aetiologies. There was limited evidence of a transient increase in viraemia and a decrease in CD4% in HIV patients although this was not accompanied by a worsening of clinical symptoms. Further exposition of the evidence including statistical detail from our meta-analyses of outcome measures stratified by aetiology of immunocompromise has been published elsewhere.\(^7\)\(^\text{,}\)\(^8\)
Table 1. Summary of primary meta-analyses: influenza-like illness, laboratory-confirmed influenza infection and serological response

| Outcome measure | Influenza subtype | Comparator | Number of studies | Pooled ES (95% CI) | P value of ES | I² (%) | P value of I² |
|-----------------|-------------------|------------|-------------------|-------------------|--------------|--------|--------------|
| Clinical protection | ILI | N/A | PNV | 7 | 0.23 (0.16–0.34) | <0.001 | 22.0 | NS |
|                 | ILI | N/A | VICT | 2 | 0.62 (0.22–1.78) | NS | 12.3 | NS |
|                 | LCII | N/A | PNV | 2 | 0.15 (0.03–0.63) | 0.01 | 50.4 | NS |
| Serological response | SC1 | A (H1N1) (S) | VICT | 50* | 0.55 (0.43–0.71) | <0.001 | 53.2 | <0.001 |
|                 | SC1 | A (H3N2) | VICT | 47* | 0.55 (0.41–0.73) | <0.001 | 66.9 | <0.001 |
|                 | SC1 | B | VICT | 44* | 0.48 (0.36–0.62) | <0.001 | 54.3 | <0.001 |
|                 | SC1 | A (H1N1) (S) | PNV | 3 | 3.90 (0.42–36.64) | NS | 77.8 | 0.01 |
|                 | SC1 | A (H3N2) | PNV | 3 | 10.93 (0.92–129.80) | NS | 82.5 | 0.003 |
|                 | SC1 | B | PNV | 2 | 9.17 (1.05–79.97) | 0.05 | 72.7 | NS |
|                 | SC2 | A (H1N1) (S) | VICT | 6 | 0.65 (0.39–1.09) | NS | 13.6 | NS |
|                 | SC2 | A (H3N2) | VICT | 8 | 0.60 (0.25–1.43) | NS | 63.9 | 0.007 |
|                 | SC2 | B | VICT | 8 | 0.42 (0.19–0.94) | 0.04 | 69.8 | 0.002 |
|                 | SP | A (H1N1) (P) | VICT | 2 | 0.22 (0.02–2.75) | NS | 80.4 | 0.02 |
|                 | SP | A (H1N1) (S) | VICT | 37* | 0.36 (0.26–0.51) | <0.001 | 56.9 | <0.001 |
|                 | SP | A (H3N2) | VICT | 35* | 0.39 (0.26–0.59) | <0.001 | 64.1 | <0.001 |
|                 | SP | B | VICT | 37* | 0.37 (0.25–0.53) | <0.001 | 65.1 | <0.001 |

*= some studies contributed two sets of data included in this meta-analysis; ILI, influenza-like illness; LCII, laboratory-confirmed influenza infection; SC1, seroconversion (≥4 fold rise post-vaccination); SC2, seroconversion (≥1:40 to ≥1:40 haemagglutination inhibition titre); SP, seroprotection (≥1:40 haemagglutination inhibition titre post-vaccination); VICT, vaccinated immunocompetent controls; PNV, placebo or no vaccination; NS, not statistically significant; N/A, not applicable.

**Conclusion**

Our systematic review and meta-analysis show that the serological response to influenza vaccination of immunocompromised patients is generally weaker than healthy controls, although the level of clinical protection afforded is perhaps comparable, whilst not associated with excess harm. Due to the potential for bias and confounding in the studies included and the presence of clinical and statistical heterogeneity in many of the meta-analyses, we suggest the quality of evidence reviewed is generally weak, although the directions of effect are largely consistent (in favour of vaccination). We advocate that clinical judgement remains important when discussing the benefits and safety profile of influenza vaccination with immunocompromised patients. Infection prevention and control strategies including national and international public health policy should recommend that immunocompromised patients are targeted for influenza vaccination.

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