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

Charles R Beck,[a] Bruce C McKenzie,[a] Ahmed B Hashim,[a] Rebecca C Harris,[b] Arina Zanuzdana,[c] Gabriel Agboado,[d] Elizabeth Orton,[e] Laura Béchard-Evans,[f] Gemma Morgan,[g] Charlotte Stevenson,[h] Rachel Weston,[i] Mitsuru Mukaigawara,[b] Joanne Enstone,[a] Glenda Augustine,[j] Mobasher Butt,[k] Sophie Kim,[l] Richard Puleston,[a] Girija Dabke,[m] Robert Howard,[n] Julie O'Boyle,[n] Mary O'Brien,[o] Lauren Ahyow,[j] Helene Denness,[p] Siobhan Farmer,[q] Jose Figureroa,[r] Paul Fisher,[s] Felix Greaves,[t] Munib Haroon,[u] Sophie Haroon,[v] Caroline Hird,[v] Rachel Isba,[w] David A Ishola,[x] Marko Kerac,[y] Vivienne Parish,[z] Jonathan Roberts,[g] Julia Rosser,[aa] Sarah Theaker,[ab] Dean Wallace,[ab] Neil Wigglesworth,[ac] Liz Lingard,[ad] Yana Vinogradova,[e] Hiroshi Horiuchi,[ae] Javier Peñalver,[f] Jonathan S Nguyen-Van-Tam[a]

[a]Division of Epidemiology and Public Health, University of Nottingham, Nottingham, United Kingdom. [b]Global Influenza Programme, World Health Organization, Geneva, Switzerland. [c]Department of Public Health Medicine, University of Bielefeld, Bielefeld, Germany. [d]Public Health Directorate, NHS Blackpool, Blackpool, United Kingdom. [e]Division of Primary Care, University of Nottingham, Nottingham, United Kingdom. [f]Freelance, World Health Organization, Geneva, Switzerland. [g]South West (North) Health Protection Unit, Health Protection Agency, Gloucester, United Kingdom. [h]Cumbria and Lancashire Health Protection Unit, Health Protection Agency, Chorley, United Kingdom. [i]Health Protection Agency Yorkshire and Humber, Health Protection Agency, Leeds, United Kingdom. [j]Public Health Directorate, NHS Leicestershire County, Leicester, United Kingdom. [k]Department of Medicine, Brighton and Sussex University Hospital NHS Trust, Brighton, United Kingdom. [l]Law School, Harvard University, Cambridge, Massachusetts, United States of America. [m]Hampshire and Isle Of Wight Health Protection Unit, Health Protection Agency, Fareham, United Kingdom. [n]Public Health Directorate, NHS Nottingham City, Nottingham, United Kingdom. [o]Public Health, Wessex Deanery, Winchester, United Kingdom. [p]Public Health Directorate, NHS Derbyshire County, Chesterfield, United Kingdom. [q]Public Health, Mersey Deanery, Liverpool, United Kingdom. [r]Medical School, Harvard University, Boston, Massachusetts, United States of America. [s]Public Health Directorate, Solihull NHS Primary Care Trust, Solihull, United Kingdom. [t]School of Public Health, Imperial College London, London, United Kingdom. [u]Childrens Services, Leicester Partnership Trust, Leicester, United Kingdom. [v]Health Protection Agency East Midlands, Health Protection Agency, Nottingham, United Kingdom. [w]Medical School, Lancaster University, Lancaster, United Kingdom. [x]Department of Infection and Population Health, University College London, London, United Kingdom. [y]Centre for International Health and Development, University College London, London, United Kingdom. [z]Public Health Directorate, NHS Northamptonshire, Northampton, United Kingdom. [aa]Public Health Directorate, NHS Halton and St. Helens, Widnes, United Kingdom. [ab]Public Health Directorate, NHS Nottinghamshire County, Mansfield, United Kingdom. [ac]Public Health Directorate, NHS East Lancashire, Nelson, United Kingdom. [ad]Health Protection Agency North East, Health Protection Agency, Newcastle upon Tyne, United Kingdom. [ae]Faculty of Medicine, Tokyo Medical and Dental University, Tokyo, Japan.

Correspondence: Dr Charles Beck. Division of Epidemiology and Public Health, University of Nottingham, Nottingham, United Kingdom Email: charles.beck@nottingham.ac.uk or Professor Jonathan Nguyen-Van-Tam, email: jvt@nottingham.ac.uk.

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.[1,2] 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.[2–6]

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.[7,8]

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).[7–9] 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.[2,10] 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.[7,8]

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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	I^2 (%)	P value of I^2
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; (S), seasonal; (P), pandemic; ES, effect size; CI, confidence interval; SC1, seroconversion ($\geq$4 fold rise post-vaccination); SC2, seroconversion (<1:40 to $\geq$1:40 haemagglutination inhibition titre); SP, seroprotection ($\geq$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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Conflicts of interest

The University of Nottingham Health Protection Research Group is currently in receipt of research funds from

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GlaxoSmithKline (GSK). The group has recently accepted an unrestricted educational grant for influenza research from F. Hoffmann-La Roche. Research on influenza funded by an unrestricted educational grant from AstraZeneca is also underway. The aforementioned funding received from GSK, F. Hoffmann-La Roche and Astra Zeneca did not support any aspect of this study. JSN-V-T has received funding to attend influenza-related meetings, lecture and consultancy fees and research funding from several influenza antiviral drug and vaccine manufacturers. All forms of personal remuneration ceased in September 2010, but influenza-related research funding from GlaxoSmithKline, F. Hoffmann-La Roche and Astra Zeneca remains current. He is a former employee of SmithKline Beecham plc. (now GlaxoSmithKline), Roche Products Ltd, and Aventis-Pasteur MSD (now Sanofi Pasteur MSD), all prior to 2005, with no outstanding pecuniary interests by way of shareholdings, share options or accrued pension rights. AZ has received fees for participating in review activities from the Global Influenza Programme, World Health Organization. JE has received consultancy fees from GSK.

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