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Influenza vaccination for healthcare workers in the UK: appraisal of systematic reviews and policy options

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Abstract

Background: The UK Department of Health recommends annual influenza vaccination for healthcare workers, but uptake remains low. For staff, there is uncertainty about the rationale for vaccination and evidence underpinning the recommendation.

Objectives: Clarify the rationale, and evidence-base, for influenza vaccination of healthcare workers from the occupational health, employer, and patient safety perspectives.

Design: Systematic appraisal of published systematic reviews

Results: The quality of the 11 included reviews was variable; some included exactly the same trials but made conflicting recommendations.

Three reviews assessed vaccine effects in healthcare workers and found one trial reporting a vaccine efficacy of 88%. Six reviews assessed vaccine effects in healthy adults and vaccine efficacy was consistent with a median of 62% (95% CI 56 to 67).

Two reviews assessed effects on working days lost in healthcare workers (three trials), and three reported effects in healthy adults (four trials). The meta-analyses presented by the most recent reviews do not reach standard levels of statistical significance, but may be misleading as individual trials suggest benefit with wide variation in size of effect. The 2013 Cochrane review reported absolute effects close to zero for laboratory-confirmed influenza, and hospitalization for patients, but excluded data on clinically-suspected influenza and all-cause mortality which had shown potentially important effects in previous editions. A more recent systematic review reports these effects as a 42% reduction in clinically-suspected influenza (95% CI 27 to 54), and a 29% reduction in all-cause mortality (95% CI 15 to 41).

Conclusions: The evidence for employer and patient safety benefits of influenza vaccination is not straightforward, and has been interpreted differently by different systematic review authors. Future uptake of influenza vaccination among healthcare workers may benefit from a fully transparent guideline process by a panel representing all relevant stakeholders, which clearly communicates the underlying rationale, evidence-base, and judgements made.

Article summary

Strengths and limitations of this study

This study unpicks the three main perspectives justifying health workers being vaccinated against influenza, and the evidence of an effect for each. This includes the occupational perspective, examining the effect on illness; the employer perspective, examining working days lost; and the patient safety perspective, examining the effect on transmission to patients.

The analysis draws on published systematic reviews, which draw on a similar population of trials, and summaries the results and the consistency of their conclusions.

We conclude from an occupational health perspective, there is consistency in the effect of the vaccine in preventing illness; for the employer perspective, some meta-analyses are misleading and the individual trials all seem to show a reduction in days lost; and for an effect on patient safety, the results are conflicting and unclear.

The study does not aim to provide recommendations, but suggests a conceptual framework and evidence summaries that may help frame a guideline development process to provide clear messages to help health workers make informed decisions.

Background

The UK Department of Health (DH) currently recommends that all healthcare workers (HCWs) in direct contact with patients or clients are vaccinated against influenza each year (1,2). Although this policy is not enforced, an aspirational target of 75% vaccination coverage has been set for all hospital and community services, and has recently been linked to additional funding known as 'winter pressure funds' (3).

Despite this target, vaccination coverage among HCWs remains low, at 50.6% during the 2015/2016 season and 54.9% during the 2014/2015 season (4,5). A systematic review on self-reported reasons for non-uptake of flu vaccine by HCWs identified two major factors: a wide range of misconceptions or lack of knowledge about influenza infection; and lack of convenient access to vaccine (6). On the reasons for accepting influenza vaccine, self-protection was the most important reason. We were interested in the degree of misconceptions by health workers in the literature. We noted that systematic reviews and related papers, often draw on the same body of evidence, reached different conclusions, and wondered whether this may perhaps contribute to the muddle, rather than helping (7,8,9).

In this paper we sought to unpick the different rationales for vaccination, and summarise the evidence base for each through a critical appraisal and summary of all the available relevant systematic reviews. To do this we developed a conceptual framework (Figure 1). This presents the two main policy options available to the UK DH, and the rationale and evidence requirements for each:

1. Offer vaccination to all HCWs – This policy takes an occupational health perspective, which could be justified by evidence of increased risk of influenza among staff. Healthcare workers would require reliable evidence on the efficacy and safety of the vaccine, and could opt-in or out of vaccination.
2. Frame vaccination as a 'professional responsibility' and target high vaccination coverage – This policy could be justified from either an employer perspective: if vaccination reduced sick leave and service disruption, or a patient safety perspective: if there were evidence that vaccination of HCWs reduced influenza in vulnerable patients.

The current policy as stated in the 2015/6 Flu Plan and Annual Flu Letter refers to both the occupational health and patient safety perspectives: to protect HCWs themselves from influenza, and to reduce the risk of passing the virus on to vulnerable patients (5,10).

Methods

The protocol for this evidence appraisal is included in Appendix 1. We aimed to include all systematic reviews, published in English language journals, which evaluate the effects of influenza vaccination in either healthy adults (over 18 years old), or HCWs (nurses, doctors, nursing and medical students, other health professionals including ancillary staff) of all ages. We sought evidence of effects on laboratory-confirmed influenza and clinically-suspected influenza (the occupational health perspective), working days lost (the employer perspective), and laboratory-confirmed influenza, clinically-suspected influenza, death, or hospitalization of patients (the patient safety perspective).

Search methods for identification of systematic reviews

Two authors (MK and AK) independently searched Medline, Embase, CINAHL, AMED and HMIC for all systematic reviews from January 1990 to December 2015. Search terms were "Influenza Vaccine", "adult", "healthcare worker", "doctor", "nurse", "effectiveness", "efficacy", "absence", "systematic review" and "meta-analysis" (Appendix 2). Bibliographies of retrieved articles were also searched to identify additional reviews.

Data collection and analysis

Two authors (MK and AK) independently reviewed titles and abstracts for inclusion in the review, applied the inclusion criteria, and extracted data onto a standardised form. For each included review, we extracted information on: the review objectives, perspective, search strategy, inclusion criteria, outcome measures, included studies, risk of bias of included studies, results, and conclusions.

Where possible, we only extracted data for inactivated parenteral vaccines, as per the current UK influenza vaccination programme. Where this distinction was not clear we extracted data for all vaccines. In addition, where possible, we only extracted data for seasonal influenza vaccination. Where this distinction was not clear we extracted data for all vaccine schedules. Two reviewers (MK and AK) independently checked data extraction for agreement. A third reviewer (DS) was consulted to resolve disagreements.

Two authors (MK and AK) independently appraised the methodological quality of each review using the AMSTAR tool for appraising systematic reviews (11). Disagreements were resolved through discussion and where necessary through appraisal by a third author (DS). The AMSTAR tool required us to make judgments about how well the systematic review authors applied 11 methodological techniques to reduce bias and error in their reviews. While these criteria are likely to identify reviews with major flaws, they are less effective at detecting errors in interpretation.

Where possible, outcome data are presented as vaccine efficacy (VE) expressed as a percentage using the formula: VE = 1-Relative Risk (RR), with 95% confidence intervals (95% CI). Where relative risk was not presented, data is presented as reported in the source systematic review. The number needed to vaccinate (NNV) to prevent one case of influenza in healthy adults and HCWs was calculated using the formula: NNV = 1/absolute risk reduction, with 95% confidence intervals. To estimate the impact from an economic perspective, the number of prevented working days lost was calculated per 100 HCWs.

We also extracted the authors' inferences or recommendations.

Results

The search identified 2,483 unique citations of which 2,371 were excluded after screening the title, and a further 91 were excluded after screening the abstract. The full inclusion criteria were applied to 23 full text articles, of which 11 were included. Of the 12 excluded papers, 10 were excluded as they were not systematic reviews, one was a previous version of a review already included and one did not include data on HCWs or healthy adults (Figure 2; Appendix 3). One review was supported by an influenza vaccine manufacturer (12) and the rest by public bodies or agencies (Table 1).

Of the 11 included systematic reviews: three evaluated the effects of influenza vaccination in HCWs (12,13,14) and six in healthy adults (14,15,16,17,18,19); five evaluated the effects in patients (13,14,20,21,22); and five evaluated the effects of vaccination on days off work (12,13,14,16,19); (Table 1, appendix 4 and 5). Two Cochrane reviews were included; the main analysis includes only the most recent version of the review, but where necessary we refer back to the earlier editions.

Table 1: Characteristics of included systematic reviews

Review ID	Funding source	Search period / end date	Perspective reported			Populations of interest	Included vaccines	Included study designs	Number of relevant studies
			Occupational health	Employer	Patient safety				
Burls 2006	European Scientific Working Group on Influenza	Until June 2004	Yes (HCWs)	Yes	Yes	HCW; Patients (High risk)	Any	All	5
Michiels 2011	National Institute for Health and Disability Insurance in Belgium	Jan 2006 to March 2011	Yes (HCWs and healthy adults)	Yes	Yes	HCW; Healthy adults (16-65 years); Patients (no further definition)	Trivalent inactivated	RCTs & non-RCT	10
Ng 2011	None stated	Date of launch to March 2011	Yes (HCWs)	Yes	No	HCW	Any	RCTs & non-RCTs	3
Demicheli 2014	None stated	Date of launch to May 2013	Yes (healthy adults)	Yes	No	Healthy adults (16-65 years)	Inactivated parenteral	RCTs & quasi-RCTs	20
DiazGranados 2012	Authors employees of Sanofi Pasteur	Until Oct 2011	Yes (healthy adults)	No	No	Healthy adults (non-elderly)	Inactivated parent, live attenuated intranasal, adjuvant or recombinant	RCTs & quasi-RCTs	20
Feroni 2011	None stated	Date of launch to March 2011	Yes (healthy adults)	Yes	Yes	Patients (no further definition); Healthy adults	Any	SRs and RCTs	6
Osterholm 2012	Alfred P Sloan Foundation	Jan 1967 to Feb 2011	Yes (healthy adults)	No	No	Healthy adults (18-46 years)	Any	RCTs & observational studies	7
Villari 2004	Italian Ministry of Health and the Emilia Romagna Regional Health Agency	Jan 1966 Dec 2002	Yes (healthy adults)	No	No	Healthy adults (mainly 16-65 years)	Any	RCTs & quasi-RCTs	26
Ahmed 2014	None stated	Jan 1948 to June 2012	No	No	Yes	Patients in healthcare facilities	Inactivated or live attenuated	RCTs, cohort, case-control studies	6
Dolan 2012	World Health Organization Global Influenza Programme	Not stated	No	No	Yes	Patients (at high risk of respiratory infection)	Any	RCTs & observational studies (cross sectional/ cohort)	16
Thomas 2013	None stated	Date of launch to March 2013	No	No	Yes	Patients (aged >60ys living in institutions)	Any	RCTs & non-randomized controlled studies	3

1. Occupational health perspective: effect on illness

In healthcare workers

Three reviews directly evaluate vaccine efficacy among HCWs (12,13,14), (table 2; appendix 6).

Methodological quality of reviews: Ng 2011 was the most up-to-date review, and was judged to be a high quality review against the AMSTAR criteria, with only minor limitations (table 3). Both Burls 2006 and Michiels 2011 have major limitations (table 3).

Included studies: Ng 2011 and Burls 2006 included the same three RCTs enrolling 967 participants. Michiels 2011 included two trials, both different to those included by Ng 2011 and Burls 2006, and describes both as RCTs although one is clearly non-randomized (23). Neither of these trials is mentioned in the list of excluded studies presented by Ng 2011.

Results: Ng 2011 and Burls 2006 report a vaccine efficacy of 88% against laboratory-confirmed influenza, based on a single trial among 264 hospital HCWs, although Burls 2006 presents the result stratified by influenza virus type (24). Ng 2011 and Burls 2006 both report that the effects on clinically-suspected influenza were not statistically significant across two trials (25,26). In an additional RCT among 356 dental students reported by Michiels 2011 (27), vaccine efficacy against clinically-suspected influenza was 53% (P = 0.03; table 2).

Consistency of conclusions: Although they evaluated exactly the same three trials, and present similar summaries, Ng 2011 and Burls 2006 made very different inferences: Burls 2006 recommended health worker vaccination 'as a priority', while Ng 2011 stated that 'no definitive conclusion' could be made (table 2). The strong recommendation by Burls 2006 may be influenced by their additional findings related to protecting patients and reducing days off work described below.

Table 2: Vaccination effects in healthcare workers (the occupational health perspective)

Review ID	Population	Laboratory confirmed influenza		Clinically suspected influenza		Systematic Review authors conclusions	
		No. of studies (participants)	Efficacy (95% CI)	No. of studies (participants)	Efficacy (95% CI)	On efficacy	For policy
Ng 2011	**HCW**	1 RCT (359)	88% (59 to 96)	2 RCTs (606)	No significant effect in either study	'No definitive conclusion on the effectiveness of influenza vaccinations in HCWs'	'Further research is necessary to evaluate whether annual vaccination is a key measure to protect HCWs'
Burls 2006	**HCW**	1 RCT (361)	88% (47 to 97) Inf. A 89% (14 to 99) Inf. B	2 RCTs (606)	No significant effect in either study	'Vaccination was highly effective'	'Effective implementation should be a priority'[1]
Michiels 2011	**HCW**	1 non-RCT (262)	90% (25 to 99)	1 RCT (346)	53% (NS) P=0.002	None stated	None stated
Demicheli 2014	**Healthy adults**	22 RCTs (51,724)	62% (56 to 67)	16 (25,795)	17% (13 to 22)	'Influenza vaccines have a very modest effect in reducing influenza symptoms'	'Results seem to discourage the utilisation of vaccination against influenza in healthy adults as a routine public health measure.'[2]
DiazGranados 2012	**Healthy adults**	Not stated	59% (50 to 66)	-	-	'Influenza vaccines are efficacious'	None stated
Osterholm 2012	**Healthy adults**	6 (31,892)	59% (51 to 67)	-	-	'Influenza vaccines provide moderate protection against confirmed influenza'	None stated
Villari 2004	**Healthy adults**	25 (18,920)	63% (53 to 71)	49 (46,022)	22% (16 to 28)	'Estimates (of effect) vary substantially'	'Further trials…are needed to provide definitive answers for policy-makers
Michiels 2011	**Healthy adults**	14 (21,616)	44% to 73% (range)	19 (19,046)	No significant effect	'Inactivated influenza vaccine shows efficacy in healthy adults'	None stated
Feroni 2011	**Healthy adults**	5 (43,830)	44% to 77% (range)	18 (19,046)	7% to 30% (range)	'Inactivated vaccines are effective at reducing infection'	None stated

[1] Burls 2006: This conclusion may be influenced by the reported effects on protecting patients and days off work in tables 3 and 4 respectively.
[2] Demicheli 2014: This conclusion is influenced by the additional findings of no demonstrable effect on complications such as pneumonia or transmission.

Table 3: AMSTAR assessments of methodological quality

AMSTAR Criteria	Burls 2006	Michiels 2011[1]	Ng 2011	Demicheli 2014	Diaz Granados 2012	Feroni 2011[1]	Osterholm 2012	Villari 2004	Ahmed 2014	Dolan 2012	Thomas 2013
1. 'A priori' design?	No	No	No	Yes	No	No	No	No	No	Yes	Yes
2. Duplicate study selection and extraction?	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
3. Comprehensive literature search?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
4. Did they attempt to find unpublished studies and grey literature?	Yes	No	Yes	Yes	No	No	No	Yes	No	No	Yes
5. List of studies (included and excluded) provided?	No	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes
6. Characteristics of included studies provided?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Scientific quality of included studies assessed and documented?	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
8. Scientific quality of included studies used appropriately in formulating conclusions?	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
9. Appropriate methods used to combine the findings of studies?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Likelihood of publication bias assessed?	No	No	No	No	Yes	No	No	Yes	No	No	Yes
11. Conflict of interest stated?	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Total risk score*	**5**	**6**	**9**	**10**	**7**	**5**	**4**	**9**	**7**	**7**	**11**

* Note all questions score 1 point for a 'yes' answer

[1] Michiels 2011 and Feroni 2011 are mainly overviews of reviews and so the AMSTAR criteria may be poorly applicable.

In healthy adults

In addition, six reviews report vaccine efficacy in healthy adults, which may reasonably be extrapolated to HCWs (12,13,16,17,18), (Table 2, appendix 7).

Methodological quality of reviews: Of the most recent reviews, Demicheli 2014 was a high quality review with only minor limitations, while DiazGranados 2012, Osterholm 2012, Michiels 2011 and Feroni 2011 had some or major limitations (table 3).

Included studies: Demicheli 2014 included 20 trials of inactivated parenteral vaccines. The other reviews included between six and 26 studies, influenced by different inclusion criteria and search dates. Michiels 2011 only included studies of trivalent inactivated vaccines, Osterholm 2012 only included studies in people aged 18 to 46 years, and Feroni 2011 and Michiels 2011 summarize the results of the previous version of the Demicheli Cochrane review (Jefferson 2010), (28) plus a few additional trials.

Results: Demicheli 2014, DiazGranados 2012, Osterholm 2012 and Villari 2004 report very similar vaccine efficacy against laboratory-confirmed influenza despite differences in the number of included trials (62%, 59%, 59% and 63% respectively). Of these only Demicheli 2014 and Villari 2004 report vaccine efficacy against clinically-suspected influenza, which is much lower (17% and 22% respectively). The remaining two reviews rely largely on the results of Jefferson 2010 but only report the range of effects across trials.

Consistency of conclusions: All six reviews conclude that the vaccine is effective at preventing laboratory-confirmed influenza. However, Demicheli 2014 states that 'the results of this review provide no evidence for the utilisation of vaccination against influenza in healthy adults as a routine public health measure', perhaps basing this on their judgement that this efficacy was too low, or on their additional findings that vaccination did not reduce complications of influenza. The oldest review (Villari 2004) called for more trials, and the remaining four reviews did not make any policy recommendations.

2. Employer perspective: effect on working days lost

In healthcare workers

Two reviews described above (Ng 2011 and Burls 2006), include the same three trials, and report the impact of vaccinating HCW on working days lost.

Methodological quality: see above.

Results: Ng 2011 reports a meta-analysis of two of these trials which does not reach standard levels of statistical significance (MD -0.08 days, 95% CI -0.19 to 0.02, I^2 = 0%, two trials, 540 participants), and states that the third trial could not be included in the meta-analysis due to the way the data was presented. However, Burls 2006 reports that the third trial found a statistically significant reduction in working days lost of 0.4 (P = 0.02) (Table 4).

In healthy adults

One Cochrane review reports effects on working days lost in healthy adults (Demicheli 2014), and two other systematic reviews (Michiels 2011 and Feroni 2011) simply present the results from an earlier version of Demicheli 2014 (Jefferson 2010) (Table 4).

Methodological quality: see above.

Results: The 2010 version of the Cochrane review (Jefferson 2010) reported statistically significant effects on working days lost, but the 2014 version (Demicheli 2014) did not, even though there were no additional trials.

In Jefferson 2010, the authors combined studies where the vaccine was a good match with the circulating virus (MD -0.21 working days lost, 95% CI -0.36 to -0.05; 4 trials, 4263 participants), and a poor match (MD 0.09, 95% CI 0.00 to 0.18, one trial, 1130 participants); and present an overall mean reduction of 0.13 working days lost (Jefferson 2010). In the updated version (Demicheli 2014), the authors removed one study conducted during the 1960s pandemic which had a large effect on working days lost, and present an overall mean reduction of 0.04 working days lost. This result does not reach standard levels of statistical significance when using a random effects model (95% CI -0.14 to 0.06), but becomes statistically significant when a fixed effects model is used (95% CI -0.06 to -0.01). This difference occurs due to the large variation in the size of the effect in individual trials, and consideration of the trials individually is probably more informative than the meta-analysis: of the four studies where the vaccine was a good match with

the circulating virus, two reported large effects (MD -0.44 and -0.74 respectively), and two reported more modest effects (MD -0.08 and -0.04 respectively). All four results reached standard levels of statistical significance.

Table 4: Vaccination effects on the health system (the employer perspective)

Review ID	Population	Days off work		Review authors conclusions	
		Number of studies (participants)	Mean difference (days)	On efficacy	For policy
Ng 2011	**HCW**	2 (540)	–0.08 (95% CI –0.19 to 0.02) (3rd study not included in meta-analysis)	'No definitive conclusion on the effectiveness of influenza vaccinations in HCWs'	'Further research is necessary to evaluate whether annual vaccination is a key measure to protect HCWs'
Burls 2006	**HCW**	3 (967)	Statistically significant difference in only one of the three studies (MD 0.4 days, P=0.02)	'Vaccination was highly effective'	'Effective implementation should be a priority'[1]
Demicheli 2014	**Healthy adults**	4 (3,726)	Good match - 3 studies (2596) MD= -0.09 (-0.19 to 0.02) Matching absent/unknown - 1 study (1130) MD = 0.09 (0.00-0.18)	'A modest effect on time off work'	'No evidence for the utilisation of vaccination against influenza in healthy adults as a routine public health measure'[2]
Michiels 2011	**Healthy adults**	Not stated	Not stated (refers to Jefferson 2010)	None stated	None stated
Feroni 2011	**Healthy adults**	1 meta-analysis including 5 studies (5393)	Good match - 0.21 Matching absent/unknown - 0.09 (refers to Jefferson 2010)	'May be marginally more effective than placebo'.	None stated

[1] Burls 2006: This conclusion may be influenced by the reported effects on vaccine efficacy and protecting patients in tables 2 and 3 respectively.

2 Demicheli 2014: This conclusion is influenced by the additional findings of no demonstrable effect on complications such as pneumonia or transmission

3. Patient safety perspective: effects on patients and clients

Six reviews report the impact of vaccinating HCWs on their patients or clients (13,14,16,20,21,22), (Table 5, appendix 8).

Methodological quality of reviews: One of the two most recent reviews (Thomas 2013) was of high methodological quality and had only minor limitations (table 3). The remaining reviews all have some major limitations.

Included studies: Thomas 2013 evaluated the effects of vaccinating HCW on people aged over 60 years living in residential care settings or hospitals, and included four cluster-RCTs (7558 participants) and one cohort study (12,742 participants). Ahmed 2014 and Dolan 2012 both evaluate the same four cluster-RCTs plus some additional observational studies. Burls 2006 only includes two of the cluster RCTs included in Thomas 2013, and Michiels 2011 and Feroni 2011 summarise the findings of an earlier version of Thomas 2013 (Thomas 2010) (29).

Results: Thomas 2013 reports absolute effect estimates close to zero for laboratory-confirmed influenza (Risk Difference (RD) 0.00, 95% CI -0.03 to 0.03; two trials, 752 participants), hospitalization (RD 0.00, 95% CI -0.02 to 0.02; one trial, 3400 participants), and death due to lower respiratory tract infection (RD -0.02, 95% CI -0.06 to 0.02; two trials, 4459 participants). Thomas 2013 states that they chose not to present results on clinically-suspected influenza and all-cause mortality because 'these are not the effects the vaccines were produced to address', and give further reasons why they believe this is important in appendices. They did, however, include these outcomes in their previous version (Thomas 2010), and three of the other reviews simply refer to the results for these outcomes reported in the Cochrane review (Dolan 2012, Michiels 2011, and Feroni 2011). Dolan 2012 also presents the results of three observational studies which report statistically significant effects on clinically-suspected influenza. Ahmed 2014 analyzes the same four RCTs, but includes the two additional outcomes with statistically significant and quantitatively important effects: a reduction in clinically-suspected influenza of 42% (95% CI 27 to 54, three trials, 7031 participants), and a reduction in all-cause mortality of 29% (95% CI 15 to 41, four trials, 8468 participants).

Conclusions: Thomas 2013 and the earlier version of this Cochrane review concluded that they 'did not identify a benefit of healthcare worker vaccination'. Dolan 2013 concludes a 'likely protective effect for patients' (based mainly on the outcomes of the earlier edition of the Cochrane review), and that the evidence base is 'sufficient to sustain current policy'. Ahmed 2014 concludes vaccinating healthcare professionals 'can enhance patient safety'.

Table 5: Vaccination effects in patients or clients of HCW (the patient safety perspective)

		Laboratory confirmed influenza		Clinically suspected influenza		Other statistically significant effects	Review authors conclusions	
Review ID	**Patient group**	**No. of studies (participants)**	**Efficacy (95% CI)**	**No. of studies (participants)**	**Efficacy**		**On efficacy**	**For policy**
Burls 2006	Those at risk. No further definition	Not reported	Not reported	Not reported	Not reported	Deaths from all-cause mortality OR=0.56 p=0.0013	'Vaccination was highly effective'[3]	'Effective implementation should be a priority'[1]
Michiels 2011	No further definition	Refers to 2010 version of Thomas 2013	No statistically significant effect	Refers to 2010 version of Thomas 2013	No statistically significant effect	Deaths from all-cause mortality Effectiveness=34% [95% CI: 21-45]	'There is little evidence that immunisation is effective in protecting patients'4	'Should not be mandatory at present'
Feroni 2011	People aged at least 60 years in long-term care facilities	2 RCTs Refers to 2011 version of Thomas 2013	No statistically significant effects	Refers to 2011 version of Thomas 2013	86% where some patients vaccinated to no significant effect where patients unvaccinated	Deaths from all-cause mortality RR=0.66 [95% CI: 0.55,0.79 (unadjusted)	'Influenza vaccination of both healthcare workers and the older people in their care may be more effective at reducing influenza-like illness in older people living in institutions, although vaccination of healthcare workers alone may be no more effective'	None stated
Ahmed 2014	Patients in healthcare facilities. No further definition.	2 RCTs (752) 1 observational study	RCTs - No statistically significant effects Observational study (≥35% vs <35% vaccinated HCWs) - Adjusted OR = 0.07 (0.01–0.98)	3 RCTs (7,031) 1 observational study	RCTs - 42% [95% CI 27-54] Observational study – no significant effect	Deaths from all-cause mortality RR = 0.71 [95% CI 0.59-0.85]	'Healthcare professional influenza vaccination can enhance patient safety'	None stated
Dolan 2012	At high risk of respiratory infection	2 RCTs (752) 2 observational studies (not stated)	RD 0.00 (-0.03 to 0.03) Observational studies found statistically significant effects	3 RCTs (not stated) 2 observational studies (not stated)	RCTs and observational studies: Statistically significant effects	Deaths from all-cause mortality OR= 0.68 [95% CI 0.55,0.84] (adjusted)	'A likely protective effect for patients'[2]	'The existing evidence base is sufficient to sustain current recommendations for vaccinating HCWs'
Thomas 2013	Aged >60ys living in institutions)	2 RCTs (752)	RD 0.00 (-0.03 to 0.03)	Not reported	Not reported	Not reported	'Did not identify a benefit of healthcare worker vaccination'[1]	'Does not provide reasonable evidence to support the vaccination of healthcare workers'

[1] Thomas 2013 also reports no statistically significant effects on hospitalization, or deaths due to lower respiratory tract infection. The authors chose not to present data on clinically suspected influenza or all-cause mortality as they doubt the validity of these measures when there is no effect on influenza.

[2] Dolan 2013: This conclusion is based on statistically significant findings on clinically suspected influenza and all cause mortality reported in an early version of Thomas 2013 but excluded from the most recent version of the review.

[3] Burns 2006 only presents data on all-cause mortality from two cluster-RCTs. It reports that both trials found statistically significant effects but notes problems with the analysis in both trials.

Discussion

Occupational health perspective: The efficacy of influenza vaccination against laboratory-confirmed influenza is remarkably consistent across reviews, at around 60% in healthy adults. It seems reasonable to extrapolate this effect to HCWs (who are themselves often 'healthy adults'), and indeed the single trial directly assessing efficacy in HCWs is consistent with this. Using the median efficacy of 62%, and the median risk of influenza in the control groups of 4%, vaccination would prevent approximately 2.5 episodes of influenza per 100 HCW vaccinated (a NNV to prevent one case of influenza of around 40 (95% CI 36 to 52). The decision about whether to offer vaccination to all healthcare workers (figure 1; vaccine policy one), would then depend on a value judgement as to whether this effect was considered worthwhile, and further evidence that the vaccine was safe, acceptable to HCWs, and affordable to the health service.

Employer perspective: The most recent reviews in both HCWs and all healthy adults present meta-analyses which do not reach standard levels of statistical significance. However, these may be misleading due to either failure to include all the trials, or the wide variation in effect size seen in the individual trials. While even the conservative estimate of four working days saved per 100 people vaccinated (taken from the latest Cochrane review) would inevitably reduce some disruption to the health workforce, estimates of how much this would save or cost the NHS are needed, and are beyond the scope of this review.

Patient safety perspective: It is not unreasonable to postulate that vaccinating HCWs with an effective vaccine will reduce transmission of influenza to patients. However, the data available from trials, the data presented in reviews, and the conclusions reached by authors are somewhat confusing. The best supportive evidence seems to come from analyses of vaccine efficacy against clinically-suspected influenza and all-cause mortality, which were present in Ahmed 2014 and the 2010 version of the Cochrane review, although discounted in the conclusions reached and then removed from the latest version of the Cochrane review despite showing important effects. While we accept that these outcomes have limitations, we are unsure if excluding them was the right decision, especially if trials are adequately blinded, and the data on laboratory-confirmed influenza are insufficient to exclude effects. In a fully transparent process, these data would be clearly presented alongside an evaluation of the certainty of the evidence (assessed by GRADE) for consideration by the reader or the guideline panel, rather than the authors simply deciding to exclude it.

The direct evidence (from systematic reviews of randomised controlled trials), for employer or patient safety effects which would lead to policy option two (framing high vaccination coverage as a professional responsibility), is nuanced, and has suffered from being the subject of multiple systematic review teams, making different inferences from the same data. Occasionally these authors have stepped beyond the brief of systematic reviews to make recommendations based on author judgements (30) which have only served to muddy the waters and add to the confusion surrounding vaccination. Evidence of effects from systematic reviews is only one component of evidence-informed policy making, and judgements about the relative importance of different outcomes, or the clinical importance of estimated effects, are best made by a panel who adequately represent all important stakeholder groups, including patients, carers and HCWs, such as Joint Committee on Vaccination and Immunisation (JCVI).

Strengths and limitations of this paper: This paper did not aim to undertake an appraisal of the quality of evidence for each of the policy relevant outcomes. This would have comprised doing our own systematic review, and clearly there are already enough of these. Rather we have concentrated on appraising the existing systematic reviews, and unpicking the reasons for the inconsistencies between their conclusions. We also did not aim to make judgements or recommendations of our own, as we are not the right people to do so, and this would simply add to the confusion around vaccination. We would, however, encourage dialogue between the Cochrane review teams and the relevant policy makers to ensure that future editions include all the outcomes relevant to decision making, and a transparent appraisal of the quality of evidence using the GRADE approach.

We chose to include only systematic reviews in English, as these are most likely to have influenced HCWs and policy makers in the UK, although further reviews in other languages may exist and be important to policies elsewhere. We

chose to restrict our analysis to inactivated parenteral vaccines where possible as this is what is recommended in the UK.

Conclusions
HCWs are increasingly used to seeing, and demanding to see, the evidence base for the healthcare interventions they are asked to provide, or make themselves subject to. Consequently, influenza vaccination uptake may benefit from a fully transparent guideline process, which makes explicit the underlying rationale, evidence base, values, preferences and judgements, which inform the current or future policy. This process would draw on all available direct evidence from systematic reviews and the most up-to-date research, but may also utilize indirect evidence such as health system data on working days lost due to influenza.

List of abbreviations
HCWs – Healthcare workers
JCVI – Joint Committee on Vaccination and Immunisation
MD – Mean difference
NHS – National Health Service
NNV – Number needed to vaccinate
RCT – Randomised controlled trial
RD – Risk difference
RR – Relative risk
VE – Vaccine efficacy

Declaration of competing interests
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; MK, AK, SG are employed by Public Health England; PG has an honorary contract with Public Health England; and PG and DS are employed by a grant that supports Cochrane.

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Authors' contributions
SG initiated the development of this paper. All authors had substantial contributions to conception and design of the paper, and interpretation of the data. MK and AK collected and analysed the data. PG proposed the appraisal structure and DS developed the conceptual framework. MK drafted the manuscript and all authors contributed to developing the manuscript. All authors have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

MK is responsible for the overall content as guarantor. MK affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

No additional data is available.

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Figure 1: perspectives for benefit of influenza vaccination of health workers, evidence required and policy framing for each
26x13mm (300 x 300 DPI)

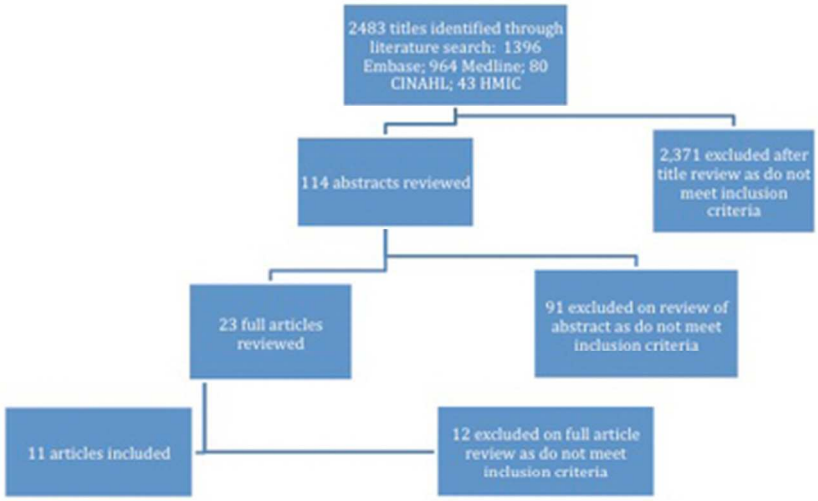

Figure 2: flow chart of search process
36x36mm (300 x 300 DPI)

Appendix 1: Study protocol

Project title

Influenza vaccine for healthcare workers: a review of the evidence

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Introduction

Influenza-like illness (ILI) is caused by a variety of viral respiratory which are not clinically distinguishable from one another. A small proportion (8-15%) of ILI is caused by the influenza virus (Nicholson et al, 1997).

The UK Department of Health recommends influenza vaccination for all healthcare workers (HCWs) in direct contact with patients or clients by their employers (PHE, 2013b). The premise for providing influenza vaccination to HCWs is to protect them and their patients by reducing transmission in the healthcare setting. By reducing the number of health care workers that develop the disease, the vaccine could also reduce time off work with sickness, particularly at a time when demand for healthcare is high.

Despite the UK policy, influenza vaccination coverage in UK healthcare workers remains poor. Uptake rates were 46% during the 2012/13 influenza season (PHE, 2013a). Reasons for this appear to be based on low perceived personal benefits, safety and efficacy concerns and access (Chen et al, 2012; Rubin et al, 2011). Publications in the medical press questioning the benefit of influenza vaccination in healthcare workers may have also impacted on rates of uptake (Doshi, 2013; McCartney, 2011).

Various systematic reviews have been undertaken considering the impact of influenza vaccination on healthcare workers and healthcare settings, which have been used to inform guidance and opinion, but their recommendations vary. In addition, reviews considering the impact on healthy adults are also

frequently cited in the discussions of the effectiveness of flu vaccination in healthcare workers, as most healthcare workers are healthy adults.

Systematic reviews are themselves subject to bias and error, and thus it is important that reviews are appraised against best standards. We therefore examined the quality of existing systematic reviews and the robustness of their conclusions in relation to HCW in the UK.

Aim

To critically appraise and summarise current evidence relating to the effects of influenza vaccination of healthcare workers and the impact on healthcare settings

Review design

Types of studies

Systematic reviews and meta-analysis

Types of participants

Healthcare workers (nurses, doctors, nursing and medical students, other health professionals, cleaners, porters and volunteers) of all ages or healthy adults (over 18 years old)

Types of interventions

Vaccination of healthcare workers or healthy adults with any inactivated parenteral vaccine, as per the current UK regime

Types of outcome measure

Primary outcomes

Outcomes for healthcare workers:

- Cases of laboratory confirmed influenza by viral isolation and/or serological supporting evidence, plus a list of likely respiratory symptoms
- Cases of influenza-like illness clinically defined from a list of likely respiratory and systemic signs and symptoms within the epidemic period (the six month winter period if not better specified)
- Working days lost

Secondary outcomes

Outcomes for healthy adults:

- Cases of laboratory confirmed influenza by viral isolation and/or serological supporting evidence, plus a list of likely respiratory symptoms
- Cases of influenza-like illness clinically defined from a list of likely respiratory and systemic signs and symptoms within the epidemic period (the six month winter period if not better specified)
- Working days lost

Outcomes for patients of healthcare workers:

- Cases of laboratory confirmed influenza by viral isolation and/or serological supporting evidence, plus a list of likely respiratory symptoms
- Cases of influenza-like illness clinically defined from a list of likely respiratory and systemic signs and symptoms within the epidemic period (the six month winter period if not better specified)
- Cases of influenza admitted to hospital
- Cases of influenza-like illness admitted to hospital
- Death caused by influenza or its complications
- Deaths from all causes

Search methods for identification of studies

Electronic searches

Medline, Embase, CINAHL, AMED and HMIC will be searched by two authors independently (MK and AK) for all systematic reviews and RCTs from January 1990 to July 2013. Search terms will be:

Search methods for identification of studies

Electronic searches

Medline, Embase, CINAHL, AMED and HMIC will be searched by two authors independently (MK and AK) for all systematic reviews and RCTs from January 1990 to December 2013. Search terms will be:

- "Influenza Vaccine"[MeSH] OR ((influenza OR flu) AND (vaccin* OR immuni* OR inoculat*))ti.ab.
- adult* OR ((health* OR Hospital*) AND (staff* OR work* OR personn*)) OR doctor* OR nurs* OR physician* OR "health personnel" [MeSH] OR "nurse" [MeSH] OR "physician" [MeSH] OR "adult" [MeSH]
- (effect* OR effica* OR absen* OR "work* day* lost")ti.ab.

- ("Randomi* Control* Trial*" OR "RCT" OR "Systematic review" OR "meta-analysis")ti.ab OR ("Randomized Controlled Trial" OR "Review" OR "Meta-Analysis") [Publication Type] OR ("Randomized Controlled Trials" OR "Systematic review" OR "meta-analysis") [MeSH]

For the MeSH search terms, these will need to be undertaken on an individual basis for each database. The detail is listed in Table 1 below. Additionally, the MeSH terms will be searched in "Any Field", the publication type terms will be searched for in "Publication Type" and all other terms will be searched for in "Title and Abstract".

Medline	Embase	CINAHL	AMED	HMIC
Influenza Vaccines	influenza vaccine	Influenza Vaccine	Influenza Vaccination *(separate terms)*	Vaccines influenza immunisation *(separate terms)*
Randomized Control Trials *(as topic)* RANDOMIZED CONTROLLED TRIAL	controlled clinical trial	Randomized Control Trials	Randomized Controlled Trials	Randomised controlled trials
	systematic review	Systematic Review	N/A	Systematic Reviews
Meta-Analysis	meta analysis	Meta Analysis	Meta Analysis	Meta Analysis

Table 1: MeSH search terms for each database

Medline	Embase	CINAHL	AMED	HMIC
Health personnel	Health care personnel	Health personnel	Health personnel	Health service staff
Physicians	Nurse	Physicians	Physicians	Health professionals
Nurses Adult	Physician adult	Nurses Adult	Nurses adult	Medical staff Nurses adults

Table 2: Healthcare worker search terms for each database

Searching other resources

MK and AK will search bibliographies of retrieved articles.

Data collection and analysis

Selection of studies

Two review authors (MK and AK) will independently review the abstracts using the following inclusion criteria.

- Systematic review or meta-analysis
- Influenza vaccination of healthcare worker or healthy adult
- Morbidity and mortality of healthcare worker or healthy adult or patients or impact on healthcare service (e.g. working days lost)

Data extraction and management

Two review authors (MK and AK) will apply the inclusion criteria all identified and retrieved articles and extracted data from included studies into a standardised form in duplicate. The extracted data includes:

- Aim
- Search strategy - Electronic databases, To date, Key words, Language
- Inclusion criteria – Design, Population, Interventions in intervention group, Interventions in control group
- Outcome measures - Primary outcome measures, Secondary outcome measures
- Included studies
- Outcomes
    - Cases of laboratory confirmed influenza by viral isolation and/or serological supporting evidence, plus a list of likely respiratory symptoms in healthcare workers
    - Cases of influenza-like illness clinically defined from a list of likely respiratory and systemic signs and symptoms within the epidemic period (the six month winter period if not better specified) in healthcare workers
    - Working days lost in healthcare workers
    - Cases of laboratory confirmed influenza by viral isolation and/or serological supporting evidence, plus a list of likely respiratory symptoms in healthy adults
    - Cases of influenza-like illness clinically defined from a list of likely respiratory and systemic signs and symptoms within the epidemic period (the six month winter period if not better specified) in healthy adults
    - Working days lost in healthy adults
    - Cases of laboratory confirmed influenza by viral isolation and/or serological supporting evidence, plus a list of likely respiratory symptoms in patients
    - Cases of influenza-like illness clinically defined from a list of likely respiratory and systemic signs and symptoms within the epidemic period (the six month winter period if not better specified) in patients
    - Cases of influenza admitted to hospital in patients
    - Cases of influenza-like illness admitted to hospital in patients

- Death caused by influenza or its complications in patients
- Deaths from all causes in patients

Two review authors (MK and AK) will independently check data extraction and disagreements will be resolved by third author (DS).

Assessment of risk of bias in included studies

Assessment of methodological quality for systematic reviews will be carried out using the AMSTAR tool for systematic reviews (Shea et al, 2007). Assessment of methodological quality for RCTs identified will be carried out using the Cochrane Collaboration's risk of bias tool for RCTs (Cochrane Collaboration, 2008).

Method of dissemination of findings

The authors hope to publish the findings in a peer-review journal .

Appendix 2: full search terms

- "Influenza Vaccine"[MeSH] OR ((influenza OR flu) AND (vaccin* OR immuni* OR inoculat*))ti.ab.
- adult* OR ((health* OR Hospital*) AND (staff* OR work* OR personn*)) OR doctor* OR nurs* OR physician* OR "health personnel" [MeSH] OR "nurse" [MeSH] OR "physician" [MeSH] OR "adult" [MeSH]
- (effect* OR effica* OR absen* OR "work* day* lost")ti.ab.
- ("Randomi* Control* Trial*" OR "RCT" OR "Systematic review" OR "meta-analysis")ti.ab OR ("Randomized Controlled Trial" OR "Review" OR "Meta-Analysis") [Publication Type] OR ("Randomized Controlled Trials" OR "Systematic review" OR "meta-analysis") [MeSH]

Appendix 3: Table of excluded studies

Identified paper	Reason for exclusion
Carman et al., 2000 (1)	Randomised controlled trial
Gatwood et al., 2010 (2)	Not a systematic review
Hitzeman et al., 2010 (3)	Not a systematic review
Jefferson et al., 2002 (4)	Not a systematic review
Jefferson et al., 2010 (5)	Previous version of included review
Lau et al., 2012 (6)	Does not include healthcare workers or healthy adults
Loeb et al., 2011 (7)	Not a systematic review
Manzoli et al., 2012 (8)	Systematic review of reviews
Nichol et al., 1999 (9)	Not a systematic review
Nichol et al., 2008 (10)	Not a systematic review
Prato et al., 2010 (11)	Not a systematic review
Riphagen-Dalhuisen et al., 2013 (12)	Not a systematic review

Appendix 4: Characteristics of included reviews for vaccinating healthcare workers

Study ID		**Ahmed 2014 (13)**
Aim		To evaluate the effect of healthcare personnel influenza vaccination on mortality, hospitalization, and influenza cases in patients of healthcare facilities
Databases searched		Medline, embase, CINAHL, web of science, Cochrane library
Key words used in search		Healthcare workers; health care personnel; health personnel; medical staff/hospital; influenza vaccines
End search date		June 2012
Language		Any
Study types included		RCTs, cohort studies, case-control studies
Inclusion criteria	Participants	Patients of healthcare facilities
	Intervention	Inactivated or live attenuated influenza vaccination
	Control	No vaccine or vaccination with influenza vaccination with lower rates of uptake
Outcome measures		Mortality, hospitalisation, cases of influenza in patients
Tool to assess quality of included studies		Cochrane collaboration assessment of bias, GRADE
Number of studies included		4 RCTs and 2 observational studies
Quality of included studies		Laboratory confirmed influenza– very serious risk of bias; clinically confirmed influenza – serious bias; Mortality - No serious bias; Hospitalisation – no serious bias; GRADE assessment of outcome (quality of evidence): laboratory confirmed influenza – very low; clinically confirmed influenza – low; hospitalisation – low; mortality - moderate
Included studies		(1), (14), (15), (16), (17), (18)
Summary of conclusions		Healthcare personnel influenza vaccination can enhance patient safety.
Study ID		**Burls 2006** (19)
Aim		To investigate effectiveness, cost-effectiveness and factors affecting uptake, and an economic evaluation of flu vaccination for HCWs
Databases searched		Cochrane library, CINAHL, NHSEED, HEED, DARE, MEDLINE, EMBASE
Key words used in search		influenza; health personnel; health care worker; health worker; care giver; physician; medical staff; nurses; nursing home; homes for the aged; residential home; vaccination; influenza vaccine
End search date		June 2004
Language		No language restrictions
Study types included		Any
Inclusion criteria	Participants	HCWs in hospitals, nursing homes or the community in contact with high-risk individuals
	Intervention	Influenza vaccination
	Control	No vaccination, placebo or vaccine unrelated to influenza
Outcome measures		In high-risk contacts: Culture or serologically confirmed influenza; all-cause mortality; mortality attributed to influenza/pneumonia; influenza-like illness; influenza-related morbidity; cost or cost-effectiveness In HCW population: Effectiveness; adverse events; acceptability; uptake; methods of attaining uptake; absenteeism
Tool to assess quality of included studies		Not assessed
Number of studies included		18 overall, 5 included in this review
Quality of included studies		2 cluster RCTs of reasonable quality, 2 RCTs of good quality, one not assessed

Included studies		(20), (21), (22), (1), (16)
Summary of conclusions		Vaccination of HCWs against influenza protects HCWs and provides indirect protection to the high-risk
Study ID		**Dolan 2013** (23)
Aim		Investigate effect of vaccinating HCWs on patient groups most vulnerable to severe or complicated respiratory illness
Databases searched		Embase, cinahl, medline, central, pubmed, jstage, bdsp, eastview, index F, Elibrary, WHO global index medicus, WHO portal of clinical trials
Key words used in search		Not stated
End search date		Not stated
Language		Chinese, English, French, Japanese, Portuguese, Russian, or Spanish
Study types included		Any experiment, observational study, or systematic review
Inclusion criteria	Participants	Persons at higher risk of complication from respiratory infection receiving care from an HCW
	Intervention	Influenza vaccination
	Control	Not stated
Outcome measures		Cases/consultations, death or hospitalization for acute respiratory disease, influenza, ILI, in patients of HCW
Tool to assess quality of included studies		Cochrane Collaboration tool for experimental studies Downs & Black tool for observational studies US Agency for Healthcare Research and Quality tool for systematic reviews
Number of studies included		14 primary research article s (4 cRCTs, 10 observational studies) and 2 systematic reviews
Quality of included studies		Six assessed with Cochrane collaboration tool - 2 low risk of bias; 2 moderate risk of bias; 2 high risk of bias 7 assessed with Downs and Black Tool - scores ranged from 3-10 out of 27 (low scores = high bias). 2 assessed with agency for healthcare research and quality tool - low risk for bias
Included studies		(19), (1), (16), (24), (25), (14), (26), (15), (27), (28), (29), (30), (31), (32), (33), (34)
Summary of conclusions		Consistency in the direction of effect was observed across several different outcome measures, suggesting a likely protective effect for patients in residential care settings
Study ID		**Feroni 2011** (35)
Aim		To investigate the effectiveness of vaccines to prevent influenza
Databases searched		Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment (HTA) database
Key words used in search		Not stated
End search date		March 2011
Language		No language restrictions
Study types included		Systematic reviews and RCTs
Inclusion criteria	Participants	No definition provided
	Intervention	Flu vaccination
	Control	Not stated
Outcome measures		Mortality; prevention of influenza (influenza or influenza-like illness); prevention of complications (e.g., pneumonia, hospitalisation); time to return to normal activities (time off school, time off work); and adverse effects
Tool to assess quality of included studies		Not done

Number of studies included		1 systematic review
Quality of included studies		Not stated
Included studies		(33)
Summary of conclusions		Influenza vaccination of both healthcare workers and the older people in their care may be more effective at reducing influenza-like illness in older people living in institutions, although vaccination of healthcare workers alone may be no more effective. Influenza vaccination of both healthcare workers and the older people, or of healthcare workers alone, may be no more effective at reducing laboratory-confirmed influenza in older people living in institutions (very low-quality evidence). Influenza vaccination of healthcare workers may be no more effective at reducing deaths from pneumonia in the older people in their care living in institutions, but it may be more effective at reducing all-cause mortality in those older people
Study ID		**Michiels 2011** (36)
Aim		To investigate efficacy, effectiveness and risks of the use of inactivated influenza vaccines in children, healthy adults, elderly individuals and individuals with co-morbidities
Databases searched		Cochrane Central Register of Controlled, PubMed
Key words used in search		influenza vaccines, humans, Clinical Trial, Meta-Analysis, Randomised Controlled Trial, Controlled Clinical Trial, Guideline
End search date		March 2011
Language		English or French
Study types included		Randomised controlled trials and controlled clinical trials
Inclusion criteria	Participants	Adults (16–65 years), healthy children (under 16 years), elderly (over 65 years), pregnant women, healthcare workers and individuals of all ages with chronic medical conditions
	Intervention	trivalent inactivated vaccines (TIV)
	Control	Placebo or none
Outcome measures		Efficacy (against laboratory-proven influenza), effectiveness (against influenza-like illness)
Tool to assess quality of included studies		AMSTAR for systematic reviews; Cochrane Risk of bias tool for RCTs
Number of studies included		36 studies in article including Eleven Cochrane reviews, one additional meta-analysis, 14 RCTs and 3 CCTs were included; 3 relevant studies included
Quality of included studies		1 systematic review low risk of bias; 1 RCT and 1 CCT with high risk of bias
Included studies		(37), (38), (33)
Summary of conclusions		Inconsistent results are found in studies among children younger than 6 years, individuals with COPD, institutionalised elderly, elderly with co-morbidities and healthcare workers in elderly homes, which might be explained by unknown biases.
Study ID		**Ng 2011** (39)
Aim		To evaluate the effectiveness of influenza vaccines in preventing laboratory-confirmed influenza infections, influenza-like illness (ILI), and reducing working days lost among HCWs
Databases searched		British Nursing Index; CAJ Full-text Database; CBMdisc; Chinese Medical Current Contents; CINAHL Database; Clinical Evidence; All databases within the Cochrane Library; EBM Reviews; EMBASE; Journals@Ovid; Lippincott Williams & Wilkins Total Access Collection; MD Consult (Core Collection); Medline; Science Citation Index Expanded; Science Direct e online journals by Elsevier Science; Wiley Encyclopedia of Biomedical Engineering
Key words used in search		influenza vaccines (influenza, human/prevention and control; influenza vaccin*; inoculation; immuni*), effectiveness (efficacy), health personnel (medical staff; nursing staff; allied health occupations; nurses' aides; health worker*; health care worker*; healthcare provider*) and health facilities (hospitals; long-termcare; residential facilities).
End search date		March 2011
Language		English or Chinese

Study types included		RCTs
Inclusion criteria	Participants	All groups of healthcare workers in all healthcare settings
	Intervention	Any kind of influenza vaccination
	Control	Placebo/vaccine other than the influenza vaccine/no intervention
Outcome measures		Laboratory-confirmed influenza infection, influenza-like illness, reducing working days lost among HCWs, Associated adverse effects
Tool to assess quality of included studies		Cochrane handbook for systematic reviews
Number of studies included		3
Quality of included studies		The methodological quality employed in two of the included trials was rated as high, and one was rated as moderate
Included studies		(21), (20), (22)
Summary of conclusions		There is no definitive conclusion on the effectiveness of influenza vaccinations in HCWs because of the limited number of related trials
Study ID		**Thomas 2013** (40)
Aim		To investigate the effects of vaccinating healthcare workers on the incidence of laboratory-proven influenza, pneumonia, death from pneumonia and admission to hospital for respiratory illness in those aged 60 years or older that they care for
Databases searched		Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Web of Science
Key words used in search		Influenza Vaccines; Immunization; Health Personnel ; Health Services for the Aged
End search date		March 2013
Language		No language restrictions
Study types included		RCTs and non-RCTs (cohort or case-control studies)
Inclusion criteria	Participants	Healthcare workers (nurses, doctors, nursing and medical students, other health professionals, cleaners, porters and volunteers who have regular contact with those aged 60 years or older) of all ages, caring for those aged 60 years or older in institutions such as nursing homes, LTCIs or hospital wards
	Intervention	Any influenza vaccine given alone or with other vaccines, in any dose, preparation, or time schedule
	Control	Placebo or with no intervention
Outcome measures		Outcomes in those aged 60 years or older in long term care institutions: Cases of influenza in those aged 60 years or older confirmed by viral isolation or serological supporting evidence (or both), plus a list of likely respiratory symptoms; Lower respiratory tract infection; Admission to hospital for respiratory illness; Deaths caused by respiratory illness
Tool to assess quality of included studies		Cochrane Collaboration's 'Risk of bias' tool for RCTs; Newcastle-Ottawa Scales for non-RCTs
Number of studies included		3
Quality of included studies		Two high risk of bias, one moderate risk of bias
Included studies		(1), (15), (16)
Summary of conclusion		This review does not provide reasonable evidence to support the vaccination of healthcare workers to prevent influenza in those aged 60 years or older resident in LTCIs

Appendix 5: Characteristics of included reviews for vaccinating healthy adults

Study ID		**Demicheli 2014 (41)**
Aim		To investigate the effects(efficacy, effectiveness and harm) of vaccines against influenza in healthy adults
Databases searched		Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed) and EMBASE, journal Vaccine
Key words used in search		Industry; Influenza A virus; Influenza B virus; Influenza Vaccines adverse effects; therapeutic use; Influenza, Human;prevention & control; virology; Publication Bias; Research Support as Topic
End search date		May 2013
Language		No language restrictions
Study types included		RCT or quasi-RCT
Inclusion criteria	Participants	Healthy individuals aged 16 to 65 years
	Intervention	Live, attenuated or killed vaccines or fractions thereof administered by any route, irrespective of antigenic configuration (inactivated parenteral vaccines only included in this review)
	Control	Placebo or no intervention
Outcome measures		Numbers and seriousness (complications and working days lost) of symptomatic influenza and influenza-like illness (ILI) cases (Harms not included in this review)
Tool to assess quality of included studies		Cochrane Handbook for Systematic Reviews of Interventions; Newcastle-Ottawa Scales
Number of studies included		20 studies assessing effects for inactivated parenteral vaccine
Quality of included studies		5 low risk, 12 unclear risk and 3 high risk of bias
Included studies		(42), (43), (44), (45), (46), (47), (48), (49), (50), (51), (52), (53), (54), (55), (56), (57), (58), (59), (20), (60)
Summary of conclusions		The preventive effect of parenteral inactivated influenza vaccine on Influenza vaccines have a very modest effect in reducing influenza symptoms in healthy adults, and a modest effect on time off work. The results of this review provide no evidence for the utilisation of vaccination against influenza in healthy adults as a routine public health measure.
Study ID		**Diaz Granados 2012** (61)
Aim		To investigate the efficacy of seasonal influenza vaccines in children and non-elderly adults; to compare the estimates with meta-analyses
Databases searched		Medline, EmBase
Key words used in search		“Influenza vaccines” and “Influenza, Human/prevention & control” using “Randomized Controlled Trial” or “Controlled Clinical Trial”
End search date		October 2011
Language		English, French, Spanish, and Russian
Study types included		Randomized or quasi-randomized controlled trial
Inclusion criteria	Participants	Healthy children or non-elderly adults
	Intervention	Seasonal influenza vaccine (inactivated parenteral, live attenuated intranasal, adjuvanted or recombinant)
	Control	Placebo, inactive control or no intervention
Outcome measures		Incidence of laboratory-confirmed influenza illness
Tool to assess quality of included studies		JADAD score
Number of studies included		30 studies in article, 20 relevant studies included investigating inactivated parenteral vaccination

Quality of included studies		5 studies (16.7%) considered of low quality, 7 studies (23.3%) considered of moderate quality, and 18 studies (60%) considered of high quality
Included studies		(44), (62), (42), (43), (63), (46), (47), (64), (65), (48), (66), (50), (67), (68), (56), (57), (69), (58), (70), (71)
Summary of conclusions		Influenza vaccines are efficacious, but efficacy estimates depend on many variables including type of vaccine and age of vaccinees, degree of matching of the circulating strains to the vaccine, influenza type, and methods of case ascertainment
Study ID		**Feroni 2011** (35)
Aim		To investigate the effectiveness of vaccines to prevent influenza
Databases searched		Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment (HTA) database
Key words used in search		Not stated
End search date		March 2011
Language		No language restrictions
Study types included		Systematic reviews and RCTs
Inclusion criteria	Participants	No definition provided
	Intervention	Flu vaccination
	Control	Not stated
Outcome measures		Mortality; prevention of influenza (influenza or influenza-like illness); prevention of complications (e.g., pneumonia, hospitalisation); time to return to normal activities (time off school, time off work); and adverse effects
Tool to assess quality of included studies		Not done
Number of studies included		1 systematic review, 4 cluster RCTs and 1 cohort study
Quality of included studies		Not stated
Included studies		(5), (46), (48), (68), (56)
Summary of conclusions		Influenza vaccination is more effective than placebo or no intervention at reducing the proportion of people with confirmed influenza in healthy individuals aged 14 to 60 years (high-quality evidence)
Study ID		**Michiels 2011** (36)
Aim		To investigate efficacy, effectiveness and risks of the use of inactivated influenza vaccines in children, healthy adults, elderly individuals and individuals with co-morbidities
Databases searched		Cochrane Central Register of Controlled, PubMed
Key words used in search		influenza vaccines, humans, Clinical Trial, Meta-Analysis, Randomised Controlled Trial, Controlled Clinical Trial, Guideline
End search date		March 2011
Language		English or French
Study types included		Randomised controlled trials and controlled clinical trials
Inclusion criteria	Participants	Adults (16–65 years), healthy children (younger than 16 years), elderly (65 years or older), pregnant women, healthcare workers and individuals of all ages with chronic medical conditions
	Intervention	Trivalent inactivated vaccines (TIV)
	Control	Placebo or none
Outcome measures		Efficacy (against laboratory-proven influenza), effectiveness (against influenza-like illness)

Tool to assess quality of included studies		AMSTAR for systematic reviews; Cochrane Risk of bias tool for RCTs
Number of studies included		36 studies in article including Eleven Cochrane reviews, one additional meta-analysis, 14 RCTs and 3 CCTs were included; 7 relevant studies included
Quality of included studies		1 systematic reviews low risk of bias; 4 RCTs with low risk of bias; 2 RCTs with moderate risk of bias
Included studies		(5), (42), (46), (48), (68), (56), (57)
Summary of conclusions		The inactivated influenza vaccine has been proven effective in preventing laboratory-confirmed influenza among healthy adults
Study ID		**Osterholm 2012** (72)
Aim		To assess the efficacy and effectiveness of licensed influenza vaccines in the USA
Databases searched		Medline
Key words used in search		influenza, human and vaccine; case-control study, cohort study, attenuated vaccine, clinical trial, vaccination, randomized controlled trial, phase IV clinical trial
End search date		February 2011
Language		English
Study types included		RCTs and observational studies
Inclusion criteria	Participants	Healthy adults aged 18–46
	Intervention	Influenza vaccine
	Control	Placebo or vaccine other than influenza
Outcome measures		Efficacy or effectiveness
Tool to assess quality of included studies		Not assessed
Number of studies included		17 studies in article, 7 relevant studies included
Quality of included studies		Not assessed
Included studies		(44), (43), (46), (48), (68), (56), (57)
Summary of conclusions		Influenza vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons.
Study ID		**Villari 2004** (73)
Aim		To investigate potential sources of heterogeneity of efficacy estimates of influenza vaccine in healthy adults
Databases searched		Medline, Cochrane Controlled Trials Register (CCTR) and EMBASE
Key words used in search		influenza, flu, vaccine/s, vaccination, efficacy, effectiveness, prevention and control
End search date		End of 2002
Language		English
Study types included		Randomized or quasi-randomized control trials
Inclusion criteria	Participants	At least 70% of participants with age range between 15 and 65 years and without medical conditions that would place them at high risk for complications of influenza
	Intervention	Any influenza vaccines in humans
	Control	Placebo or control vaccines
Outcome measures		Vaccine efficacy for prevention of clinically and/or laboratory confirmed cases of influenza
Tool to assess quality of included studies		Chalmers scale and Jadad scale

Number of studies included	26 studies
Quality of included studies	Briefly described but not given for individual papers. Not able to assess overall quality of papers
Included studies	(21), (20), (22), (63), (47), (65), (50), (67), (58), (45), (74), (53), (55), (75), (76), (77), (78), (79), (54), (80), (81), (82), (59), (83), (84), (85)
Summary of conclusions	Statistically significant benefit of influenza vaccination in prevention of clinically and laboratory confirmed cases of influenza as well as a statistically significant heterogeneity among the individual studies. Given the importance of a reliable estimate of influenza vaccination efficacy from an health policy point of view, further clinical trials, that are likely to be of high quality and that should be designed in order to facilitate future pooled analyses, are warranted.

Appendix 6: Vaccination effects in healthcare workers (the occupational health perspective): In health care workers

Study ID	**Burls 2006** (19)	**Michiels 2011** (36)	**Ng 2011** (39)
Efficacy against laboratory-confirmed influenza in healthcare workers	1 study (21) VE = 88% [95% CI: 47, 97] (influenza A) VE = 89% [95% CI: -14, 99] (influenza B)	1 study (38) OR = 0.10 [95% CI: 0.01,0.75] (GPs, aged 30)	1 study (21) VE = 88% [95% CI: 59,96]
Efficacy against clinically-suspected influenza in healthcare workers	1 study (22) 1.8 episodes (vaccine) vs 2 episode (placebo), not statistically different 1 study (20) 23% (vaccine) vs. 22% (control), not statistically different	1 study (37) VEf=53% (p = 0.002) 1 study (38) OR 0.35 [95% CI: 0.13, 0.96] (GPs, aged 30)	1 study (22) RR=1.14 [95% CI: 0.15-8.52] 1 study (20) RR=1.07 [95% CI: 0.62-1.85]
Working days lost for healthcare workers	1 study (21) Mean absence (±SD) 0.10 days±0.35 (vaccine) vs 0.21 days±0.75 (control) 1 study (22) Mean absence 1.0 day (vaccine) vs 1.4 days (control) p = 0.02 1 study (20) Mean absence (±SD) 7.6 hours±12.1 (vaccine) vs.8.2 hours±18.3 (control)		Meta-analysis of 2 studies (20), (21) Mean difference= -0.08 [95% CI: -0.19,0.02]

CI=Confidence intervals; RR=relative risk; SD=standard deviation; VE=vaccine efficacy; VEf=vaccine effectiveness

Appendix 7: Vaccination effects in healthcare workers (the occupational health perspective): in healthy adults

Study ID	**Demicheli 2014** (41)	**DiazGranados 2012** (61)	**Feroni 2011** (35)	**Michiels 2011** (36)	**Osterholm 2012** (72)	**Villari 2004** (73)
Efficacy against laboratory-confirmed influenza in healthy adults	Meta-analysis of 22 studies: VE=62% [95% CI: 56,67] (parenteral inactivated vaccine)	Meta-analysis of unknown number of studies: VE=59% [95% CI: 50, 66] (parenteral inactivated vaccine)	1 study (46) VE= 69.5% [97.5% CI lower bound 55%] 1 study (48) VE= 46.3% [97.5% CI lower bound 9.8%] 1 meta-analysis (5) Inactivated vaccine: VE=73% [95% CI: 54,84] (matching); VE=44% [95% CI: 33,59] (unmatched) 1 study (27) VE=73% [95% CI: 51,85] 1 study (56) VE=77% [95% CI:37,92]	1 study (42) VE=72% [95% CI: 55, 82] 1 study (46) VE= 70% [95% CI: 55, ?] (CCIV); VE= 63% [95% CI: 47, ?] (TIV) 1 study (48) VE= 49% 95% CI: 20,?] 1 meta-analysis (5) VE= 73% [95% CI: 54, 84] (matched, inactivated); VE 44% [95% CI: 23, 59] (unmatched) 1 study (27) VE=68% [95% CI 46,81] 1 study (56): VE=72% [95% CI: 42, 90] 1 study (57) no significant effect	Meta-analysis of 6 studies: VE=59% [95% CI: 51, 67]	Meta-analysis of 25 studies VE=63%, [95% CI: 53,71] (all vaccines)
Efficacy against clinically-suspected influenza in healthy adults	Meta-analysis of 16 studies: VEf=17% [95% CI: 13,22] (parenteral inactivated vaccine)	-	1 meta-analysis (5) VEf=30% [95% CI 17,41] (matched); RR=0.93 [95% CI: 0.79,1.09] (unmatched)	1 meta-analysis (5) VEf= 30% [95% CI: 17,41] (matched)	-	Meta-analysis of 49 studies: VE=22%, [95% CI: 16,28] (all vaccines)
Working days lost for healthy adults	Good match - 3 studies (2596) MD= -0.09 (-0.19 to 0.02) Matching absent/unknown - 1 study (1130) MD = 0.09 (0.00-0.18) (parenteral inactivated vaccine)	-	1 meta-analysis (5) MD (days)=−0.21 [95% CI:−0.36, −0.05] (matched); Mean difference =0.09 [95% CI: 0.00, 0.18) (unmatched)	1 meta-analysis (5) MD (days)=−0.21 [95% CI:−0.36, −0.05] (matched)	-	-

CCIV=cell cultured derived inactivated subunit influenza vaccine; CI=confidence intervals; MD=mean difference; RR=relative risk; TIV=egg derived inactivated subunit influenza vaccine; VE=vaccine efficacy; VEf=vaccine effectiveness

Appendix 8: Vaccination effects in patients or clients of HCW (the patient safety perspective)

Study ID	**Ahmed 2014** (13)	**Burls 2006** (19)	**Dolan 2013** (23)	**Feroni 2011** (35)	**Michiels 2011** (36)	**Thomas 2013** (40)
Efficacy against laboratory confirmed influenza in patients of healthcare workers	Meta-analysis of 2 RCTs RR = 0.80 [95% CI: 0.31,2.08] 1 study (17) (≥35% vs <35% vaccinated HCWs) - Adjusted OR = 0.07 (0.01–0.98)	-	1 study (1) No significant effect 1 study (25) 14% (vaccine) vs 34% (control), p<0.001 1 meta-analysis (33) RR=0.87 [0.38,1.99] 1 study (34) 72.1% decrease, p<0.01	1 meta-analysis (33) RR=0.80 [95% CI: 0.39,1.64] (some patients vaccinated); RR 1.37 [95% CI: 0.22 to 8.36] (unvaccinated patients)	1 meta-analysis (33) No significant effect	Meta-analysis of 2 studies (1), (16) RD= 0.00 [95% CI:-0.03,0.03] (some patients vaccinated)
Efficacy against clinically-suspected influenza in patients of healthcare workers	Meta-analysis of 3 RCTs RR = 0.58 [95% CI: 0.46,0.73] 1 study (18) (≥15% vs <15% vaccinated HCWs) Adjusted RR= 0.3 (0.1–1.2)	-	1 study (14) RD=–0.09 [95% CI: –0.14, –0.03] (period 1); RD=0.00 [95% CI:–0.06,0.06] (period 2) 1 study (26)Spearman rank correlation, r = 0.379, p = 0.459 (hospital personnel vaccination coverage and no. influenza cases) 1 study (15) OR=0.69 [95% CI: 0.52,0.91) 1 study (29) OR= 0.28 [95% CI: 0.23–0.32] 1 study (16) OR= 0.57 [95% CI:0.34,0.94] (some patients vaccinated) 1 study (30) RR=0.19 [95% CI: 0.10,0.36] (high vs low vaccination rate, season 1) ; RR = 0.51 [95% CI: 0.25,1.04] (season 2) 1 meta-analysis (33) RR =0.71 [95% CI: 0.58, 0.88]	1 meta-analysis (33) RR =0.14 [95% CI: 0.03,0.6] (some patients vaccinated); RR 0.87 [95% CI: 0.49,1.55] (unvaccinated patients)	1 meta-analysis (33) RR =0.14 [95% CI: 0.03,0.6] (some patients vaccinated); No significant effect (unvaccinated patients)	-
Patients of healthcare workers admitted to hospital	Meta-analysis of 2 RCTs RR = 0.91 [95% CI: 0.68,1.19]	-	1 study (14) RD=−0.02 [95% CI:−0.05, 0.02] (period 1); RD=0.00 [95% CI:−0.03,0.04] (period 2) 1 study (14) For ILI - RD=−0.02 [95% CI:−0.03 to 0.00] (period 1); RD=0.00 [95% CI:−0.02,0.02] (period 2) 1 study (15) OR= 1.03 [95% CI:0.76, 1.40] 1 study (15) OR=0.90 [95% CI:0.66,1.21] (respiratory illness) 1 meta-analysis (33) OR=0.90 [95% CI:0.66 to 1.21]	-	-	1 study (15) RD= 0.00 [95% CI: -0.02, 0.03] (respiratory illness)

Appendix 8: Vaccination effects in patients or clients of HCW (the patient safety perspective) - continued

Study ID	**Ahmed 2014** (13)	**Burls 2006** (19)	**Dolan 2013** (23)	**Feroni 2011** (35)	**Michiels 2011** (36)	**Thomas 2013** (40)
Death caused by influenza in patients	-	-	1 study (1)20% difference in proportion influenza positive at death, p=0.055 1 study (14) RD=−0.01 [95% CI:−0.02 to 0.01] (period 1); RD=-0.01 [95% CI:−0.03,0.00] (period 2) 1 meta-analysis (33) pool of Hayward: OR= 0.72 [95% CI: 0.31,1.70] (ILI)	-	-	Meta-analysis of 2 studies (15), (16) RD= -0.01 [95% CI:-0.05,0.03]
Death caused by complications of influenza in patients	-	-	1 study (15) OR=1.55 [95% CI: 0.59,4.10] (respiratory) 1 study (16) OR=0.60 [95% CI: 0.37,0.97] (pneumonia) 1 meta-analysis (33) pool of other 2 results: OR= 0.87 [95% CI: 0.47,1.64] (adjusted, pneumonia)	1 meta-analysis (33) RR=0.82 [95% CI: 0.45,1.49] (unadjusted, pneumonia)	1 meta-analysis (33) no significant effect	-
Deaths from all causes in patients	Meta-analysis of 4 RCTs RR = 0.71 [95% CI: 0.59,0.85]	1 study (1) OR= 0.61 [95% CI: 0.36,1.04] 1 study (16) OR=0.56 p=0.0013	1 study (1) OR= 0.62 [95% CI: 0.36,1.04] 1 study (14) RD=−0.05 [95% CI:−0.07 to -0.02] (period 1); RD=-0.01 [95% CI:−0.04,0.02] (period 2) 1 study (15) OR=0.86 [95% CI: 0.72,1.02] 1 study (16) OR=0.56 [95% CI: 0.40,0.80] 1 meta-analysis (33) pool of other 4 results: OR= 0.68 [95% CI 0.55,0.84] (adjusted)	1 meta-analysis (33) RR=0.66 [95% CI: 0.55,0.79 (unadjusted)	1 meta-analysis (33) Effectiveness=34 % [95% CI: 21-45]	-

CI=Confidence intervals; RD=risk difference; RR=relative risk; VE=vaccine efficacy; VEf=vaccine effectiveness

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4, appendix 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, Appendix4 and 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3,4,5 appendix 6,7,8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Influenza vaccination for healthcare workers in the UK: appraisal of systematic reviews and policy options

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Keywords: Influenza vaccination, flu vaccination, healthcare workers, NHS

Abstract

Background: The UK Department of Health recommends annual influenza vaccination for healthcare workers, but uptake remains low. For staff, there is uncertainty about the rationale for vaccination and evidence underpinning the recommendation.

Objectives: Clarify the rationale, and evidence-base, for influenza vaccination of healthcare workers from the occupational health, employer, and patient safety perspectives.

Design: Systematic appraisal of published systematic reviews

Results: The quality of the 11 included reviews was variable; some included exactly the same trials but made conflicting recommendations.

Three reviews assessed vaccine effects in healthcare workers and found one trial reporting a vaccine efficacy of 88%. Six reviews assessed vaccine effects in healthy adults and vaccine efficacy was consistent with a median of 62% (95% CI 56 to 67).

Two reviews assessed effects on working days lost in healthcare workers (three trials), and three reported effects in healthy adults (four trials). The meta-analyses presented by the most recent reviews do not reach standard levels of statistical significance, but may be misleading as individual trials suggest benefit with wide variation in size of effect. The 2013 Cochrane review reported absolute effects close to zero for laboratory-confirmed influenza, and hospitalization for patients, but excluded data on clinically-suspected influenza and all-cause mortality which had shown potentially important effects in previous editions. A more recent systematic review reports these effects as a 42% reduction in clinically-suspected influenza (95% CI 27 to 54), and a 29% reduction in all-cause mortality (95% CI 15 to 41).

Conclusions: The evidence for employer and patient safety benefits of influenza vaccination is not straightforward, and has been interpreted differently by different systematic review authors. Future uptake of influenza vaccination among healthcare workers may benefit from a fully transparent guideline process by a panel representing all relevant stakeholders, which clearly communicates the underlying rationale, evidence-base, and judgements made.

Article summary

Strengths and limitations of this study

This study unpicks the three main perspectives justifying health workers being vaccinated against influenza, and the evidence of an effect for each. This includes the occupational perspective, examining the effect on illness; the employer perspective, examining working days lost; and the patient safety perspective, examining the effect on transmission to patients.

The analysis draws on published systematic reviews, which draw on a similar population of trials, and summaries the results and the consistency of their conclusions.

We conclude from an occupational health perspective, there is consistency in the effect of the vaccine in preventing illness; for the employer perspective, some meta-analyses are misleading and the individual trials all seem to show a reduction in days lost; and for an effect on patient safety, the results are conflicting and unclear.

The study does not aim to provide recommendations, but suggests a conceptual framework and evidence summaries that may help frame a guideline development process to provide clear messages to help health workers make informed decisions.

Background

The UK Department of Health (DH) currently recommends that all healthcare workers (HCWs) in direct contact with patients or clients are vaccinated against influenza each year (1,2). Although this policy is not enforced, an aspirational target of 75% vaccination coverage has been set for all hospital and community services, and has recently been linked to additional funding known as 'winter pressure funds' (3).

Despite this target, vaccination coverage among HCWs remains low, at 50.6% during the 2015/2016 season and 54.9% during the 2014/2015 season (4,5). A systematic review on self-reported reasons for non-uptake of flu vaccine by HCWs identified two major factors: a wide range of misconceptions or lack of knowledge about influenza infection; and lack of convenient access to vaccine (6). On the reasons for accepting influenza vaccine, self-protection was the most important reason. We were interested in the degree of misconceptions by health workers in the literature. We noted that systematic reviews and related papers, often draw on the same body of evidence, reached different conclusions, and wondered whether this may perhaps contribute to the muddle, rather than helping (7,8,9).

In this paper we sought to unpick the different rationales for vaccination, and summarise the evidence base for each through a critical appraisal and summary of all the available relevant systematic reviews. To do this we developed a conceptual framework (Figure 1). This presents the two main policy options available to the UK DH, and the rationale and evidence requirements for each:

1. Offer vaccination to all HCWs – This policy takes an occupational health perspective, which could be justified by evidence of increased risk of influenza among staff. Healthcare workers would require reliable evidence on the efficacy and safety of the vaccine, and could opt-in or out of vaccination.
2. Frame vaccination as a 'professional responsibility' and target high vaccination coverage – This policy could be justified from either an employer perspective: if vaccination reduced sick leave and service disruption, or a patient safety perspective: if there were evidence that vaccination of HCWs reduced influenza in vulnerable patients.

The current policy as stated in the 2015/6 Flu Plan and Annual Flu Letter refers to both the occupational health and patient safety perspectives: to protect HCWs themselves from influenza, and to reduce the risk of passing the virus on to vulnerable patients (5,10).

Methods

The protocol for this evidence appraisal is included in Appendix 1. We aimed to include all systematic reviews, published in English language journals, which evaluate the effects of influenza vaccination in either healthy adults (over 18 years old), or HCWs (nurses, doctors, nursing and medical students, other health professionals including ancillary staff) of all ages. We sought evidence of effects on laboratory-confirmed influenza and clinically-suspected influenza (the occupational health perspective), working days lost (the employer perspective), and laboratory-confirmed influenza, clinically-suspected influenza, death, or hospitalization of patients (the patient safety perspective).

Search methods for identification of systematic reviews

Two authors (MK and AK) independently searched Medline, Embase, CINAHL, AMED and HMIC for all systematic reviews from January 1990 to December 2015. Search terms were "Influenza Vaccine", "adult", "healthcare worker", "doctor", "nurse", "effectiveness", "efficacy", "absence", "systematic review" and "meta-analysis" (Appendix 2). Bibliographies of retrieved articles were also searched to identify additional reviews.

Data collection and analysis

Two authors (MK and AK) independently reviewed titles and abstracts for inclusion in the review, applied the inclusion criteria, and extracted data onto a standardised form. For each included review, we extracted information on: the review objectives, perspective, search strategy, inclusion criteria, outcome measures, included studies, risk of bias of included studies, results, and conclusions.

Where possible, we only extracted data for inactivated parenteral vaccines, as per the current UK influenza vaccination programme. Where this distinction was not clear we extracted data for all vaccines. In addition, where possible, we only extracted data for seasonal influenza vaccination. Where this distinction was not clear we extracted data for all vaccine schedules. Two reviewers (MK and AK) independently checked data extraction for agreement. A third reviewer (DS) was consulted to resolve disagreements.

Two authors (MK and AK) independently appraised the methodological quality of each review using the AMSTAR tool for appraising systematic reviews (11). Disagreements were resolved through discussion and where necessary through appraisal by a third author (DS). The AMSTAR tool required us to make judgments about how well the systematic review authors applied 11 methodological techniques to reduce bias and error in their reviews. While these criteria are likely to identify reviews with major flaws, they are less effective at detecting errors in interpretation.

Where possible, outcome data are presented as vaccine efficacy (VE) expressed as a percentage using the formula: VE = 1-Relative Risk (RR), with 95% confidence intervals (95% CI). Where relative risk was not presented, data is presented as reported in the source systematic review. The number needed to vaccinate (NNV) to prevent one case of influenza in healthy adults and HCWs was calculated using the formula: NNV = 1/absolute risk reduction, with 95% confidence intervals. To estimate the impact from an economic perspective, the number of prevented working days lost was calculated per 100 HCWs.

We also extracted the authors' inferences or recommendations.

~~**Patient involvement**~~

~~Patients, carers and lay people were not involved in the design, development of outcome measures or any other part of this study. The development of the research question was informed by healthcare professionals' priorities, who are in this case, the patients.~~

Results

The search identified 2,483 unique citations of which 2,371 were excluded after screening the title, and a further 91 were excluded after screening the abstract. The full inclusion criteria were applied to 23 full text articles, of which 11 were included. Of the ~~and~~ 12 ~~were~~ excluded papers, 10 were excluded as they were not systematic reviews, one was a previous version of a review already included and one did not include data on HCWs or healthy adults (Figure 2; Appendix 3). One review was supported by an influenza vaccine manufacturer (12) and the rest by public bodies or agencies (table 1).

Of the 11 included systematic reviews: three evaluated the effects of influenza vaccination in HCWs (12,13,14) and six in healthy adults (14,15,16,17,18,19); five evaluated the effects in patients (13,14,20,21,22); and five evaluated the effects of vaccination on days off work (12,13,14,16,19); (table 1, appendix 4 and 5). Two Cochrane reviews were included; the main analysis includes only the most recent version of the review, but where necessary we refer back to the earlier editions.

Table 1: Characteristics of included systematic reviews

Review ID	Funding source	Search period / end date	Perspective reported			Populations of interest	Included vaccines	Included study designs	Number of relevant studies
			Occupational health	Employer	Patient safety				
Burls 2006	European Scientific Working Group on Influenza	Until June 2004	Yes (HCWs)	Yes	Yes	HCW; Patients (High risk)	Any	All	5
Michiels 2011	National Institute for Health and Disability Insurance in Belgium	Jan 2006 to March 2011	Yes (HCWs and healthy adults)	Yes	Yes	HCW; Healthy adults (16-65 years); Patients (no further definition)	Trivalent inactivated	RCTs & non-RCT	10
Ng 2011	None stated	Date of launch to March 2011	Yes (HCWs)	Yes	No	HCW	Any	RCTs & non-RCTs	3
Demicheli 2014	None stated	Date of launch to May 2013	Yes (healthy adults)	Yes	No	Healthy adults (16-65 years)	Inactivated parenteral	RCTs & quasi-RCTs	20
DiazGranados 2012	Authors employees of Sanofi Pasteur	Until Oct 2011	Yes (healthy adults)	No	No	Healthy adults (non-elderly)	Inactivated parent, live attenuated intranasal, adjuvant or recombinant	RCTs & quasi-RCTs	20
Feroni 2011	None stated	Date of launch to March 2011	Yes (healthy adults)	Yes	Yes	Patients (no further definition); Healthy adults	Any	SRs and RCTs	6
Osterholm 2012	Alfred P Sloan Foundation	Jan 1967 to Feb 2011	Yes (healthy adults)	No	No	Healthy adults (18-46 years)	Any	RCTs & observational studies	7
Villari 2004	Italian Ministry of Health and the Emilia Romagna Regional Health Agency	Jan 1966 Dec 2002	Yes (healthy adults)	No	No	Healthy adults (mainly 16-65 years)	Any	RCTs & quasi-RCTs	26
Ahmed 2014	None stated	Jan 1948 to June 2012	No	No	Yes	Patients in healthcare facilities	Inactivated or live attenuated	RCTs, cohort, case-control studies	6
Dolan 2012	World Health Organization Global Influenza Programme	Not stated	No	No	Yes	Patients (at high risk of respiratory infection)	Any	RCTs & observational studies (cross sectional/ cohort)	16
Thomas 2013	None stated	Date of launch to March 2013	No	No	Yes	Patients (aged >60ys living in institutions)	Any	RCTs & non-randomized controlled studies	3

1. Occupational health perspective: effect on illness

In healthcare workers

Three reviews directly evaluate vaccine efficacy among HCWs (12,13,14), (table 2~~3~~; appendix 6).

Methodological quality of reviews: Ng 2011 was the most up-to-date review, and was judged to be a high quality review against the AMSTAR criteria, with only minor limitations (table 3~~2~~). Both Burls 2006 and Michiels 2011 have major limitations (table 3~~2~~).

Included studies: Ng 2011 and Burls 2006 included the same three RCTs enrolling 967 participants. Michiels 2011 included two trials, both different to those included by Ng 2011 and Burls 2006, and describes both as RCTs although one is clearly non-randomized (23). Neither of these trials is mentioned in the list of excluded studies presented by Ng 2011.

Results: Ng 2011 and Burls 2006 report a vaccine efficacy of 88% against laboratory-confirmed influenza, based on a single trial among 264 hospital HCWs, although Burls 2006 presents the result stratified by influenza virus type (24). Ng 2011 and Burls 2006 both report that the effects on clinically-suspected influenza were not statistically significant across two trials (25,26). In an additional RCT among 356 dental students reported by Michiels 2011 (27), vaccine efficacy against clinically-suspected influenza was 53% (P = 0.03; table 2~~3~~).

Consistency of conclusions: Although they evaluated exactly the same three trials, and present similar summaries, Ng 2011 and Burls 2006 made very different inferences: Burls 2006 recommended health worker vaccination 'as a priority', while Ng 2011 stated that 'no definitive conclusion' could be made (table 2~~1~~). The strong recommendation by Burls 2006 may be influenced by their additional findings related to protecting patients and reducing days off work described below.

Table 2: AMSTAR assessments of methodological quality

AMSTAR Criteria	Burls 2006	Michiels 2011[‡]	Ng 2011	Demicheli 2014	Diaz Granados 2012	Feroni 2011[‡]	Osterholm 2012	Villari 2004	Ahmed 2014	Dolan 2012	Thomas 2013
1. 'A priori' design?	No	No	No	Yes	No	No	No	No	No	Yes	Yes
2. Duplicate study selection and extraction?	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
3. Comprehensive literature search?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
4. Did they attempt to find unpublished studies and grey literature?	Yes	No	Yes	Yes	No	No	No	Yes	No	No	Yes
5. List of studies (included and excluded) provided?	No	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes
6. Characteristics of included studies provided?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Scientific quality of included studies assessed and documented?	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
8. Scientific quality of included studies used appropriately in formulating conclusions?	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
9. Appropriate methods used to combine the findings of studies?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Likelihood of publication bias assessed?	No	No	No	No	Yes	No	No	Yes	No	No	Yes
11. Conflict of interest stated?	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Total risk score*	**5**	**6**	**9**	**10**	**7**	**5**	**4**	**9**	**7**	**7**	**11**

* Note all questions score 1 point for a 'yes' answer

‡ Michiels 2011 and Feroni 2011 are mainly overviews of reviews and so the AMSTAR criteria may be poorly applicable.

Table 223: Vaccination effects in healthcare workers (the occupational health perspective)

Review ID	Population	Laboratory confirmed influenza		Clinically suspected influenza		Systematic Review authors conclusions	
		No. of studies (participants)	Efficacy (95% CI)	No. of studies (participants)	Efficacy (95% CI)	On efficacy	For policy
Ng 2011	**HCW**	1 RCT (359)	88% (59 to 96)	2 RCTs (606)	No significant effect in either study	'No definitive conclusion on the effectiveness of influenza vaccinations in HCWs'	'Further research is necessary to evaluate whether annual vaccination is a key measure to protect HCWs'
Burls 2006	**HCW**	1 RCT (361)	88% (47 to 97) Inf. A 89% (14 to 99) Inf. B	2 RCTs (606)	No significant effect in either study	'Vaccination was highly effective'	'Effective implementation should be a priority'[1]
Michiels 2011	**HCW**	1 non-RCT (262)	90% (25 to 99)	1 RCT (346)	53% (NS) P=0.002	None stated	None stated
Demicheli 2014	**Healthy adults**	22 RCTs (51,724)	62% (56 to 67)	16 (25,795)	17% (13 to 22)	'Influenza vaccines have a very modest effect in reducing influenza symptoms'	'Results seem to discourage the utilisation of vaccination against influenza in healthy adults as a routine public health measure.'[2]
DiazGranados 2012	**Healthy adults**	Not stated	59% (50 to 66)	-	-	'Influenza vaccines are efficacious'	None stated
Osterholm 2012	**Healthy adults**	6 (31,892)	59% (51 to 67)	-	-	'Influenza vaccines provide moderate protection against confirmed influenza'	None stated
Villari 2004	**Healthy adults**	25 (18,920)	63% (53 to 71)	49 (46,022)	22% (16 to 28)	'Estimates (of effect) vary substantially'	'Further trials…are needed to provide definitive answers for policy-makers
Michiels 2011	**Healthy adults**	14 (21,616)	44% to 73% (range)	19 (19,046)	No significant effect	'Inactivated influenza vaccine shows efficacy in healthy adults'	None stated
Feroni 2011	**Healthy adults**	5 (43,830)	44% to 77% (range)	18 (19,046)	7% to 30% (range)	'Inactivated vaccines are effective at reducing infection'	None stated

[1] Burls 2006: This conclusion may be influenced by the reported effects on protecting patients and days off work in tables 3 and 4 respectively.
[2] Demicheli 2014: This conclusion is influenced by the additional findings of no demonstrable effect on complications such as pneumonia or transmission.

Table 3: AMSTAR assessments of methodological quality

AMSTAR Criteria	Burls 2006	Michiels 2011[1]	Ng 2011	Demicheli 2014	Diaz Granados 2012	Feroni 2011[1]	Osterholm 2012	Villari 2004	Ahmed 2014	Dolan 2012	Thomas 2013
1. 'A priori' design?	No	No	No	Yes	No	No	No	No	No	Yes	Yes
2. Duplicate study selection and extraction?	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
3. Comprehensive literature search?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
4. Did they attempt to find unpublished studies and grey literature?	Yes	No	Yes	Yes	No	No	No	Yes	No	No	Yes
5. List of studies (included and excluded) provided?	No	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes
6. Characteristics of included studies provided?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Scientific quality of included studies assessed and documented?	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
8. Scientific quality of included studies used appropriately in formulating conclusions?	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
9. Appropriate methods used to combine the findings of studies?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Likelihood of publication bias assessed?	No	No	No	No	Yes	No	No	Yes	No	No	Yes
11. Conflict of interest stated?	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Total risk score*	5	6	9	10	7	5	4	9	7	7	11

* Note all questions score 1 point for a 'yes' answer

[1] Michiels 2011 and Feroni 2011 are mainly overviews of reviews and so the AMSTAR criteria may be poorly applicable.

In healthy adults

In addition, six reviews report vaccine efficacy in healthy adults, which may reasonably be extrapolated to HCWs (12,13,16,17,18), (Table ~~3~~2, appendix 7).

Methodological quality of reviews: Of the most recent reviews, Demicheli 2014 was a high quality review with only minor limitations, while DiazGranados 2012, Osterholm 2012, Michiels 2011 and Feroni 2011 had some or major limitations (table ~~2~~3).

Included studies: Demicheli 2014 included 20 trials of inactivated parenteral vaccines. The other reviews included between six and 26 studies, influenced by different inclusion criteria and search dates. Michiels 2011 only included studies of trivalent inactivated vaccines, Osterholm 2012 only included studies in people aged 18 to 46 years, and Feroni 2011 and Michiels 2011 summarize the results of the previous version of the Demicheli Cochrane review (Jefferson 2010), (28) plus a few additional trials.

Results: Demicheli 2014, DiazGranados 2012, Osterholm 2012 and Villari 2004 report very similar vaccine efficacy against laboratory-confirmed influenza despite differences in the number of included trials (62%, 59%, 59% and 63% respectively). Of these only Demicheli 2014 and Villari 2004 report vaccine efficacy against clinically-suspected influenza, which is much lower (17% and 22% respectively). The remaining two reviews rely largely on the results of Jefferson 2010 but only report the range of effects across trials.

Consistency of conclusions: All six reviews conclude that the vaccine is effective at preventing laboratory-confirmed influenza. However, Demicheli 2014 states that 'the results of this review provide no evidence for the utilisation of vaccination against influenza in healthy adults as a routine public health measure', perhaps basing this on their judgement that this efficacy was too low, or on their additional findings that vaccination did not reduce complications of influenza. The oldest review (Villari 2004) called for more trials, and the remaining four reviews did not make any policy recommendations.

2. Employer perspective: effect on working days lost

In healthcare workers

Two reviews described above (Ng 2011 and Burls 2006), include the same three trials, and report the impact of vaccinating HCW on working days lost.

Methodological quality: see above.

Results: Ng 2011 reports a meta-analysis of two of these trials which does not reach standard levels of statistical significance (MD -0.08 days, 95% CI -0.19 to 0.02, I^2 = 0%, two trials, 540 participants), and states that the third trial could not be included in the meta-analysis due to the way the data was presented. However, Burls 2006 reports that the third trial found a statistically significant reduction in working days lost of 0.4 (P = 0.02) (Table 4).

In healthy adults

One Cochrane review reports effects on working days lost in healthy adults (Demicheli 2014), and two other systematic reviews (Michiels 2011 and Feroni 2011) simply present the results from an earlier version of Demicheli 2014 (Jefferson 2010) (Table 4).

Methodological quality: see above.

Results: The 2010 version of the Cochrane review (Jefferson 2010) reported statistically significant effects on working days lost, but the 2014 version (Demicheli 2014) did not, even though there were no additional trials.

In Jefferson 2010, the authors combined studies where the vaccine was a good match with the circulating virus (MD -0.21 working days lost, 95% CI -0.36 to -0.05; 4 trials, 4263 participants), and a poor match (MD 0.09, 95% CI 0.00 to 0.18, one trial, 1130 participants); and present an overall mean reduction of 0.13 working days lost (Jefferson 2010). In the updated version (Demicheli 2014), the authors removed one study conducted during the 1960s pandemic which had a large effect on working days lost, and present an overall mean reduction of 0.04 working days lost. This result does not reach standard levels of statistical significance when using a random effects model (95% CI -0.14 to 0.06), but becomes statistically significant when a fixed effects model is used (95% CI -0.06 to -0.01). This difference occurs due to the large variation in the size of the effect in individual trials, and consideration of the trials individually is probably more informative than the meta-analysis: of the four studies where the vaccine was a good match with

the circulating virus, two reported large effects (MD -0.44 and -0.74 respectively), and two reported more modest effects (MD -0.08 and -0.04 respectively). All four results reached standard levels of statistical significance.

Table 4: Vaccination effects on the health system (the employer perspective)

Review ID	Population	Days off work		Review authors conclusions	
		Number of studies (participants)	Mean difference (days)	On efficacy	For policy
Ng 2011	**HCW**	2 (540)	–0.08 (95% CI –0.19 to 0.02) (3rd study not included in meta-analysis)	'No definitive conclusion on the effectiveness of influenza vaccinations in HCWs'	'Further research is necessary to evaluate whether annual vaccination is a key measure to protect HCWs'
Burls 2006	**HCW**	3 (967)	Statistically significant difference in only one of the three studies (MD 0.4 days, P=0.02)	'Vaccination was highly effective'	'Effective implementation should be a priority'[1]
Demicheli 2014	**Healthy adults**	4 (3,726)	Good match - 3 studies (2596) MD= -0.09 (-0.19 to 0.02) Matching absent/unknown - 1 study (1130) MD = 0.09 (0.00-0.18)	'A modest effect on time off work'	'No evidence for the utilisation of vaccination against influenza in healthy adults as a routine public health measure'[2]
Michiels 2011	**Healthy adults**	Not stated	Not stated (refers to Jefferson 2010)	None stated	None stated
Feroni 2011	**Healthy adults**	1 meta-analysis including 5 studies (5393)	Good match - 0.21 Matching absent/unknown - 0.09 (refers to Jefferson 2010)	'May be marginally more effective than placebo'.	None stated

[1] Burls 2006: This conclusion may be influenced by the reported effects on vaccine efficacy and protecting patients in tables 2 and 3 respectively.

2 Demicheli 2014: This conclusion is influenced by the additional findings of no demonstrable effect on complications such as pneumonia or transmission

3. Patient safety perspective: effects on patients and clients

Six reviews report the impact of vaccinating HCWs on their patients or clients (13,14,16,20,21,22), (Table 5, appendix 8).

Methodological quality of reviews: One of the two most recent reviews (Thomas 2013) was of high methodological quality and had only minor limitations (table 3~~2~~). The remaining reviews all have some major limitations.

Included studies: Thomas 2013 evaluated the effects of vaccinating HCW on people aged over 60 years living in residential care settings or hospitals, and included four cluster-RCTs (7558 participants) and one cohort study (12,742 participants). Ahmed 2014 and Dolan 2012 both evaluate the same four cluster-RCTs plus some additional observational studies. Burls 2006 only includes two of the cluster RCTs included in Thomas 2013, and Michiels 2011 and Feroni 2011 summarise the findings of an earlier version of Thomas 2013 (Thomas 2010) (29).

Results: Thomas 2013 reports absolute effect estimates close to zero for laboratory-confirmed influenza (Risk Difference (RD) 0.00, 95% CI -0.03 to 0.03; two trials, 752 participants), hospitalization (RD 0.00, 95% CI -0.02 to 0.02; one trial, 3400 participants), and death due to lower respiratory tract infection (RD -0.02, 95% CI -0.06 to 0.02; two trials, 4459 participants). Thomas 2013 states that they chose not to present results on clinically-suspected influenza and all-cause mortality because 'these are not the effects the vaccines were produced to address', and give further reasons why they believe this is important in appendices. They did, however, include these outcomes in their previous version (Thomas 2010), and three of the other reviews simply refer to the results for these outcomes reported in the Cochrane review (Dolan 2012, Michiels 2011, and Feroni 2011). Dolan 2012 also presents the results of three observational studies which report statistically significant effects on clinically-suspected influenza. Ahmed 2014 analyzes the same four RCTs, but includes the two additional outcomes with statistically significant and quantitatively important effects: a reduction in clinically-suspected influenza of 42% (95% CI 27 to 54, three trials, 7031 participants), and a reduction in all-cause mortality of 29% (95% CI 15 to 41, four trials, 8468 participants).

Conclusions: Thomas 2013 and the earlier version of this Cochrane review concluded that they 'did not identify a benefit of healthcare worker vaccination'. Dolan 2013 concludes a 'likely protective effect for patients' (based mainly on the outcomes of the earlier edition of the Cochrane review), and that the evidence base is 'sufficient to sustain current policy'. Ahmed 2014 concludes vaccinating healthcare professionals 'can enhance patient safety'.

Table 5: Vaccination effects in patients or clients of HCW (the patient safety perspective)

		Laboratory confirmed influenza		Clinically suspected influenza		Other statistically significant effects	Review authors conclusions	
Review ID	**Patient group**	**No. of studies (participants)**	**Efficacy (95% CI)**	**No. of studies (participants)**	**Efficacy**		**On efficacy**	**For policy**
Burls 2006	Those at risk. No further definition	Not reported	Not reported	Not reported	Not reported	Deaths from all-cause mortality OR=0.56 p=0.0013	'Vaccination was highly effective'[3]	'Effective implementation should be a priority'[1]
Michiels 2011	No further definition	Refers to 2010 version of Thomas 2013	No statistically significant effect	Refers to 2010 version of Thomas 2013	No statistically significant effect	Deaths from all-cause mortality Effectiveness=34% [95% CI: 21-45]	'There is little evidence that immunisation is effective in protecting patients'4	'Should not be mandatory at present'
Feroni 2011	People aged at least 60 years in long-term care facilities	2 RCTs Refers to 2011 version of Thomas 2013	No statistically significant effects	Refers to 2011 version of Thomas 2013	86% where some patients vaccinated to no significant effect where patients unvaccinated	Deaths from all-cause mortality RR=0.66 [95% CI: 0.55,0.79 (unadjusted)	'Influenza vaccination of both healthcare workers and the older people in their care may be more effective at reducing influenza-like illness in older people living in institutions, although vaccination of healthcare workers alone may be no more effective'	None stated
Ahmed 2014	Patients in healthcare facilities. No further definition.	2 RCTs (752) 1 observational study	RCTs - No statistically significant effects Observational study (≥35% vs <35% vaccinated HCWs) - Adjusted OR = 0.07 (0.01–0.98)	3 RCTs (7,031) 1 observational study	RCTs - 42% [95% CI 27-54] Observational study – no significant effect	Deaths from all-cause mortality RR = 0.71 [95% CI 0.59-0.85]	'Healthcare professional influenza vaccination can enhance patient safety'	None stated
Dolan 2012	At high risk of respiratory infection	2 RCTs (752) 2 observational studies (not stated)	RD 0.00 (-0.03 to 0.03) Observational studies found statistically significant effects	3 RCTs (not stated) 2 observational studies (not stated)	RCTs and observational studies: Statistically significant effects	Deaths from all-cause mortality OR= 0.68 [95% CI 0.55,0.84] (adjusted)	'A likely protective effect for patients'[2]	'The existing evidence base is sufficient to sustain current recommendations for vaccinating HCWs'
Thomas 2013	Aged >60ys living in institutions)	2 RCTs (752)	RD 0.00 (-0.03 to 0.03)	Not reported	Not reported	Not reported	'Did not identify a benefit of healthcare worker vaccination'[1]	'Does not provide reasonable evidence to support the vaccination of healthcare workers'

[1] Thomas 2013 also reports no statistically significant effects on hospitalization, or deaths due to lower respiratory tract infection. The authors chose not to present data on clinically suspected influenza or all-cause mortality as they doubt the validity of these measures when there is no effect on influenza.

[2] Dolan 2013: This conclusion is based on statistically significant findings on clinically suspected influenza and all cause mortality reported in an early version of Thomas 2013 but excluded from the most recent version of the review.

[3] Burns 2006 only presents data on all-cause mortality from two cluster-RCTs. It reports that both trials found statistically significant effects but notes problems with the analysis in both trials.

Discussion

Occupational health perspective: The efficacy of influenza vaccination against laboratory-confirmed influenza is remarkably consistent across reviews, at around 60% in healthy adults. It seems reasonable to extrapolate this effect to HCWs (who are themselves often 'healthy adults'), and indeed the single trial directly assessing efficacy in HCWs is consistent with this. Using the median efficacy of 62%, and the median risk of influenza in the control groups of 4%, vaccination would prevent approximately 2.5 episodes of influenza per 100 HCW vaccinated (a NNV to prevent one case of influenza of around 40 (95% CI 36 to 52). The decision about whether to offer vaccination to all healthcare workers (figure 1; vaccine policy one), would then depend on a value judgement as to whether this effect was considered worthwhile, and further evidence that the vaccine was safe, acceptable to HCWs, and affordable to the health service.

Employer perspective: The most recent reviews in both HCWs and all healthy adults present meta-analyses which do not reach standard levels of statistical significance. However, these may be misleading due to either failure to include all the trials, or the wide variation in effect size seen in the individual trials. While even the conservative estimate of four working days saved per 100 people vaccinated (taken from the latest Cochrane review) would inevitably reduce some disruption to the health workforce, estimates of how much this would save or cost the NHS are needed, and are beyond the scope of this review.

Patient safety perspective: It is not unreasonable to postulate that vaccinating HCWs with an effective vaccine will reduce transmission of influenza to patients. However, the data available from trials, the data presented in reviews, and the conclusions reached by authors are somewhat confusing. The best supportive evidence seems to come from analyses of vaccine efficacy against clinically-suspected influenza and all-cause mortality, which were present in Ahmed 2014 and the 2010 version of the Cochrane review, although discounted in the conclusions reached and then removed from the latest version of the Cochrane review despite showing important effects. While we accept that these outcomes have limitations, we are unsure if excluding them was the right decision, especially if trials are adequately blinded, and the data on laboratory-confirmed influenza are insufficient to exclude effects. In a fully transparent process, these data would be clearly presented alongside an evaluation of the certainty of the evidence (assessed by GRADE) for consideration by the reader or the guideline panel, rather than the authors simply deciding to exclude it.

The direct evidence (from systematic reviews of randomised controlled trials), for employer or patient safety effects which would lead to policy option two (framing high vaccination coverage as a professional responsibility), is nuanced, and has suffered from being the subject of multiple systematic review teams, making different inferences from the same data. Occasionally these authors have stepped beyond the brief of systematic reviews to make recommendations based on author judgements (30) which have only served to muddy the waters and add to the confusion surrounding vaccination. Evidence of effects from systematic reviews is only one component of evidence-informed policy making, and judgements about the relative importance of different outcomes, or the clinical importance of estimated effects, are best made by a panel who adequately represent all important stakeholder groups, including patients, carers and HCWs, such as Joint Committee on Vaccination and Immunisation (JCVI).

Strengths and limitations of this paper: This paper did not aim to undertake an appraisal of the quality of evidence for each of the policy relevant outcomes. This would have comprised doing our own systematic review, and clearly there are already enough of these. Rather we have concentrated on appraising the existing systematic reviews, and unpicking the reasons for the inconsistencies between their conclusions. We also did not aim to make judgements or recommendations of our own, as we are not the right people to do so, and this would simply add to the confusion around vaccination. We would, however, encourage dialogue between the Cochrane review teams and the relevant policy makers to ensure that future editions include all the outcomes relevant to decision making, and a transparent appraisal of the quality of evidence using the GRADE approach.

We chose to include only systematic reviews in English, as these are most likely to have influenced HCWs and policy makers in the UK, although further reviews in other languages may exist and be important to policies elsewhere. We

chose to restrict our analysis to inactivated parenteral vaccines where possible as this is what is recommended in the UK.

Conclusions

HCWs are increasingly used to seeing, and demanding to see, the evidence base for the healthcare interventions they are asked to provide, or make themselves subject to. Consequently, influenza vaccination uptake may benefit from a fully transparent guideline process, which makes explicit the underlying rationale, evidence base, values, preferences and judgements, which inform the current or future policy. This process would draw on all available direct evidence from systematic reviews and the most up-to-date research, but may also utilize indirect evidence such as health system data on working days lost due to influenza.

List of abbreviations

HCWs – Healthcare workers
JCVI – Joint Committee on Vaccination and Immunisation
MD – Mean difference
NHS – National Health Service
NNV – Number needed to vaccinate
RCT – Randomised controlled trial
RD – Risk difference
RR – Relative risk
VE – Vaccine efficacy

Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; MK, AK, SG are employed by Public Health England; PG has an honorary contract with Public Health England; and PG and DS are employed by a grant that supports Cochrane.

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Authors' contributions

SG initiated the development of this paper. All authors had substantial contributions to conception and design of the paper, and interpretation of the data. MK and AK collected and analysed the data. PG proposed the appraisal structure and DS developed the conceptual framework. MK drafted the manuscript and all authors contributed to developing the manuscript. All authors have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

MK is responsible for the overall content as guarantor. MK affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

No additional data is available.

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