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

Merav Kliner,1 Alex Keenan,2 David Sinclair,3 Sam Ghebrehewet,2 Paul Garner3

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: To 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. 3 reviews assessed vaccine effects in healthcare workers and found 1 trial reporting a vaccine efficacy (VE) of 88%. 6 reviews assessed vaccine effects in healthy adults, and VE was consistent with a median of 62% (95% CI 56 to 67). 2 reviews assessed effects on working days lost in healthcare workers (3 trials), and 3 reported effects in healthy adults (4 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 0 for laboratory-confirmed influenza, and hospitalisation 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.

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 influenza 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.7–9

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 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 2015–2016 Influenza Plan and Annual Influenza Letter refers to 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 online supplementary 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 hospitalisation 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’, ‘health-care worker’, ‘doctor’, ‘nurse’, ‘effectiveness’, ‘efficacy’, ‘absence’, ‘systematic review’ and ‘meta-analysis’ (see online supplementary 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 judgements 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% CIs. Where RR was not presented, data are 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% CIs. 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 2483 unique citations of which 2371 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, 1 was a previous version of a review already included and 1 did not include data on HCWs or healthy adults (figure 2, see online supplementary 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 HCWs12–14 and six in healthy adults;14–15 five evaluated the effects in patients13 14 20–22 and five evaluated the effects of vaccination on days off work12–14 16 19 (table 1, see online supplementary appendices 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.

Occupational health perspective: effect on illness
In healthcare workers
Three reviews directly evaluate VE among HCWs12–14 (table 2; see online supplementary appendix 6).

Methodological quality of reviews: Ng and Lai12 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). Burls et al13 and Michiels et al14 have major limitations (table 3).

Included studies: Ng and Lai12 and Burls et al13 included the same three randomised controlled trials (RCTs) enrolling 967 participants. Michiels et al14 included two trials, both different to those included by Ng and Lai12 and Burls et al,13 and describe both as RCTs although one is clearly non-randomised.23 Neither of these trials is mentioned in the list of excluded studies presented by Ng and Lai.12

Results: Ng and Lai12 and Burls et al13 report a VE of 88% against laboratory-confirmed influenza, based on a single trial among 264 hospital HCWs, although Burls et al13 presents the result stratified by influenza virus type.25 Ng and Lai12 and Burls et al13 report that the effects on clinically suspected influenza were not statistically significant across two trials.26 27 In an additional RCT among 356 dental students reported by Michiels et al,14 28

Figure 1 Perspectives for benefit of influenza vaccination of health workers, evidence required and policy framing for each.

Figure 2 Flow chart of search process.
| Review ID | Funding source | Search period/end date | Perspective reported | Populations of interest | Included vaccines | Included study designs | No. of relevant studies |
|-----------|----------------|-----------------------|----------------------|------------------------|-------------------|-----------------------|------------------------|
| Burls et al<sup>3</sup> | European Scientific Working Group on Influenza | Until June 2004 | Yes (HCWs) | HCW; patients (high risk) | Any | All | 5 |
| Michiels et al<sup>4</sup> | National Institute for Health and Disability Insurance in Belgium | January 2006 to March 2011 | Yes (HCWs and healthy adults) | HCW; healthy adults (16–65 years); patients (no further definition) | Trivalent inactivated | RCTs and non-RCTs | 10 |
| Ng and Lai<sup>12</sup> | None stated | Date of launch to March 2011 | Yes (HCWs) | HCW | Any | RCTs and non-RCTs | 3 |
| Demicheli et al<sup>19</sup> | None stated | Date of launch to May 2013 | Yes (healthy adults) | Healthy adults (16–65 years) | Inactivated parenteral | RCTs and quasi-RCTs | 20 |
| DiazGranados et al<sup>15</sup> | Authors employees of Sanofi Pasteur | Until October 2011 | Yes (healthy adults) | Healthy adults (non-elderly) | Inactivated parent, live attenuated intranasal, adjuvant or recombinant | RCTs and quasi-RCTs | 20 |
| Ferroni and Jefferson<sup>16</sup> | None stated | Date of launch to March 2011 | Yes (healthy adults) | Patients (no further definition); healthy adults | Any | SRs and RCTs | 6 |
| Osterholm et al<sup>17</sup> | Alfred P Sloan Foundation | January 1967 to February 2011 | Yes (healthy adults) | Healthy adults (18–46 years) | Any | RCTs and observational studies | 7 |
| Villari et al<sup>18</sup> | Italian Ministry of Health and the Emilia Romagna Regional Health Agency | January 1966 to December 2002 | Yes (healthy adults) | Healthy adults (mainly 16–65 years) | Any | RCTs and quasi-RCTs | 26 |
| Ahmed et al<sup>22</sup> | None stated | January 1948 to June 2012 | No | Patients in healthcare facilities | Inactivated or live attenuated | RCTs, cohort, case–control studies | 6 |
| Dolan et al<sup>23</sup> | WHO Global Influenza Programme | Not stated | No | Patients (at high risk of respiratory infection) | Any | RCTs and observational studies (cross sectional/cohort) | 16 |
| Thomas et al<sup>31</sup> | None stated | Date of launch to March 2013 | No | Patients (aged >60 years living in institutions) | Any | RCTs and non-RCTs | 3 |

HCWs, healthcare workers; RCTs, randomised controlled trials; SRs, systematic reviews.
Table 2 Vaccination effects in healthcare workers (the occupational health perspective)

| Review ID     | Population | Laboratory-confirmed influenza | Clinically suspected influenza | SR authors’ conclusions |
|---------------|------------|--------------------------------|--------------------------------|--------------------------|
|               |            | No. of studies (participants) | Efficacy (95% CI)             | No. of studies (participants) | Efficacy (95% CI) | On efficacy | For policy |
|               |            |                                |                                |                          |                          |             |            |
| Ng and Lai12  | 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 | 'Effective implementation should be a priority'* |
| Burls et al13 | HCW        | 1 RCT (361)                    | 88% (47 to 97) Inf. A          | 2 RCTs (606)             | No significant effect in either study | 'Vaccination was highly effective' | None stated | None stated |
| Michiels et al14 | HCW    | 1 non-RCT (262)                | 90% (25 to 99)                 | 1 RCT (346)             | 53% (NS) p=0.002 | None stated | None stated |
| Demicheli et al15 | 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 usage of vaccination against influenza in healthy adults as a routine public health measure.'† | None stated |
| DiazGranados et al16 | Healthy adults | Not stated | 59% (50 to 66) | – | – | 'Influenza vaccines are efficacious' | None stated |
| Osterholm et al17 | Healthy adults | 6 (31 892) | 59% (51 to 67) | – | – | 'Influenza vaccines provide moderate protection against confirmed influenza' | None stated |
| Villari et al18 | 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 policymakers' | None stated |
| Michiels et al14 | 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 |
| Ferroni and Jefferson16 | 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 |

*This conclusion may be influenced by the reported effects on protecting patients and days off work in tables 3 and 4, respectively.†

†This conclusion is influenced by the additional findings of no demonstrable effect on complications such as pneumonia or transmission.†

HCW, healthcare worker; RCTs, randomised controlled trials; SR, systematic review.
Table 3  AMSTAR assessments of methodological quality

| AMSTAR criteria                                      | Burls et al | Michiels et al | Ng and Lat | Demicheli et al | Diaz Granados et al | Ferroni and Jefferson | Osterholm et al | Villari et al | Ahmed et al | Dolan 2012 | Thomas et al |
|------------------------------------------------------|-------------|----------------|------------|----------------|---------------------|------------------------|----------------|--------------|-------------|-------------|-------------|
| 1. 'A priori' design?                                 | No          | Yes            | No         | Yes            | No                  | No                     | No             | No           | Yes         | Yes         | Yes         |
| 2. Duplicate study selection and extraction?          | Yes         | Yes            | Yes        | No             | No                  | No                     | Yes            | 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                     | Yes            | No           | No          | Yes         | 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                     | Yes            | 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            | Yes          | Yes         | Yes         | Yes         |
| Total risk score*                                    | 5           | 6              | 9          | 10             | 7                   | 5                      | 4              | 9            | 7           | 7           | 11          |

*Michiels et al and Ferroni and Jefferson are mainly overviews of reviews and so the AMSTAR criteria may be poorly applicable.
†Note all questions score 1 point for a ‘yes’ answer.
VE 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 and Lai\textsuperscript{12} and Burls \textit{et al}\textsuperscript{25} made very different inferences: Burls \textit{et al}\textsuperscript{25} recommended health worker vaccination ‘as a priority’, whereas Ng and Lai\textsuperscript{12} stated that ‘no definitive conclusion’ could be made (table 2). The strong recommendation by Burls \textit{et al}\textsuperscript{25} may be influenced by their additional findings related to protecting patients and reducing days off work described below.

**In healthy adults**

In addition, six reviews report VE in healthy adults, which may reasonably be extrapolated to HCWs\textsuperscript{12 13 16–18} (table 2, see online supplementary appendix 7).

**Methodological quality of reviews:** Of the most recent reviews, Demicheli \textit{et al}\textsuperscript{19} was a high-quality review with only minor limitations, whereas DiazGranados \textit{et al}\textsuperscript{15} Osterholm \textit{et al}\textsuperscript{17} Michiels \textit{et al}\textsuperscript{14} and Ferroni and Jefferson\textsuperscript{16} had some or major limitations (table 3).

**Included studies:** Demicheli \textit{et al}\textsuperscript{19} included 20 trials of inactivated parenteral vaccines. The other reviews included between 6 and 26 studies, influenced by different inclusion criteria and search dates. Michiels \textit{et al}\textsuperscript{14} only included studies of trivalent inactivated vaccines, Osterholm \textit{et al}\textsuperscript{17} only included studies in people aged 18–46 years and Ferroni and Jefferson\textsuperscript{16} and Michiels \textit{et al}\textsuperscript{14} summarise the results of the previous version of the Demicheli Cochrane review\textsuperscript{19 29} plus a few additional trials.

**Results:** Demicheli \textit{et al}\textsuperscript{19} DiazGranados \textit{et al}\textsuperscript{15} Osterholm \textit{et al}\textsuperscript{17} and Villari \textit{et al}\textsuperscript{28} report very similar VE against laboratory-confirmed influenza despite differences in the number of included trials (62%, 59%, 59% and 63%, respectively). Of these only Demicheli \textit{et al}\textsuperscript{19} and Villari \textit{et al}\textsuperscript{28} report VE against clinically suspected influenza, which is much lower (17% and 22%, respectively). The remaining two reviews rely largely on the results of Jefferson \textit{et al}\textsuperscript{28} 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 \textit{et al}\textsuperscript{19} 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\textsuperscript{18} called for more trials, and the remaining four reviews did not make any policy recommendations.

**Employer perspective: effect on working days lost**

**In healthcare workers**

Two reviews described above\textsuperscript{12 13} include the same three trials and report the impact of vaccinating HCW on working days lost.

**Methodological quality:** see above.

**Results:** Ng and Lai\textsuperscript{12} reports a meta-analysis of two of these trials, which does not reach standard levels of statistical significance (mean difference (MD) −0.08 days, 95% CI −0.19 to 0.02, I\textsuperscript{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 were presented. However, Burls \textit{et al}\textsuperscript{25} 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\textsuperscript{19} and two other systematic reviews\textsuperscript{14 16} simply present the results from an earlier version of Demicheli \textit{et al}\textsuperscript{19} (ref. 28) (table 4).

**Methodological quality:** see above.

**Results:** The 2010 version of the Cochrane review\textsuperscript{29} reported statistically significant effects on working days lost, but the 2014 version\textsuperscript{19} did not, even though there were no additional trials.

In the study of Jefferson \textit{et al}\textsuperscript{29} 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\textsuperscript{29}. In the updated version\textsuperscript{19}, the authors removed one study conducted during the 1968s 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.

**Patient safety perspective: effects on patients and clients**

Six reviews report the impact of vaccinating HCWs on their patients or clients\textsuperscript{13 14 16 20–22} (table 5, see online supplementary appendix 8).

**Methodological quality of reviews:** One of the two most recent reviews\textsuperscript{21} was of high methodological quality and had only minor limitations (table 3). The remaining reviews all have some major limitations.

**Included studies:** Thomas \textit{et al}\textsuperscript{21} 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 \textit{et al}\textsuperscript{22} and Dolan \textit{et al}\textsuperscript{23} evaluate the same four cluster-RCTs plus some additional
observational studies. Burls et al. only includes two of the cluster-RCTs included in Thomas et al. and Michiels et al. and Ferroni and Jefferson summarise the findings of an earlier version of Thomas et al.

Results: Thomas et al. 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), hospitalisation (RD 0.00, 95% CI −0.02 to 0.02; 1 trial, 3400 participants) and death due to lower respiratory tract infection (RD −0.02, 95% CI −0.06 to 0.02; 2 trials, 4459 participants). Thomas et al. state 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, and three of the other reviews simply refer to the results for these outcomes reported in the Cochrane review (Dolan et al. and Michiels et al.).

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

| Review ID | Population | Days off work | Mean difference (days) | Review authors’ conclusions |
|-----------|------------|---------------|------------------------|-----------------------------|
| Ng and La  | HCW        | 2 (540)       | −0.08 (95% CI −0.19 to 0.02) (third study not included in meta-analysis) | 'No definitive conclusion on the effectiveness of influenza vaccinations in HCWs' |
| Burls et al. | HCW    | 3 (967)       | Statistically significant difference in only one of the three studies (MD 0.4 days, p=0.02) | 'Vaccination was highly effective' |
| Demicheli et al. | Healthy adults | 4 (3726) | Good match—three studies (2596), MD=−0.09 (−0.19 to 0.02) Matching absent/unknown—one study (1130), MD=0.09 (0.00 to 0.18) | 'A modest effect on time off work' |
| Michiels et al. | Healthy adults | Not stated | Not stated (refers to Jefferson 2010) | None stated |
| Ferroni and Jefferson | Healthy adults | 1 meta-analysis including 5 studies (5393) | Good match—0.21 Matching absent/unknown—0.09 (refers to Jefferson 2010) | None stated |

Table conclusions: Thomas et al. and the earlier version of this Cochrane review concluded that they ‘did not identify a benefit of healthcare worker vaccination’. Dolan et al. 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 et al. concludes vaccinating healthcare professionals ‘can enhance patient safety’.

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 ~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 HCWs (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.
| Review ID | Patient group | Laboratory-confirmed influenza | Clinically suspected influenza | Other statistically significant effects | Review authors’ conclusions |
|-----------|---------------|-------------------------------|-------------------------------|----------------------------------------|-----------------------------|
|           |               | No. of studies (participants) | Efficacy (95% CI) | No. of studies (participants) | Efficacy | On efficacy | For policy |
| Burls et al<sup>3</sup> | 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’<sup>+</sup> | ‘Effective implementation should be a priority’<sup>†</sup> |
| Michiels et al<sup>4</sup> | No further definition | Refers to 2010 version of Thomas et al<sup>1</sup> | No statistically significant effect | Refers to 2010 version of Thomas et al<sup>1</sup> | No statistically significant effect | Deaths from all-cause mortality Effectiveness=34% (95% CI 21 to 45) | ‘There is little evidence that immunisation is effective in protecting patients’ | ‘Should not be mandatory at present’ |
| Ferroni and Jefferson<sup>16</sup> | People aged at least 60 years in long-term care facilities | Two RCTs | No statistically significant effects | Refers to 2011 version of Thomas et al<sup>1</sup> | 86% where some patients vaccinated to no significant effect where patients unvaccinated | Deaths from all-cause mortality, RR=0.66 (95% CI 0.55 to 0.79) (unadjusted) | None stated |
| Ahmed et al<sup>22</sup> | Patients in healthcare facilities. No further definition | Two RCTs (752) | RCTs—No statistically significant effects Observational study (≥35% vs ≤35% vaccinated HCWs)—adjusted OR=0.07 (0.01 to 0.98) | Three RCTs (7031) | RCTs—42% (95% CI 27 to 54) Observational study—no significant effect | Deaths from all-cause mortality, RR=0.71 (95% CI 0.59 to 0.85) | None stated |

Continued
The existing evidence base is sufficient to sustain a protective effect for patients‡. Deaths from all-cause mortality, OR=0.68 (95% CI 0.55 to 0.84) was present in Ahmed et al22 as a result of the 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 National Health Service are needed and are beyond the scope of this review.

**Employer perspective**

The most recent reviews in 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 National Health Service 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 VE against clinically suspected influenza and all-cause mortality, which were present in Ahmed et al22 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. Although 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 RCTs), 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,31 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 policymaking, 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 policymakers 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 policymakers 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 use indirect evidence such as health system data on working days lost due to influenza.

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REFERENCES
1. Department of Health, Public Health England, NHS England. The national flu immunisation programme 2014/15 (updated 28 April 2014; cited 3 December 2014). https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/316007/FIUmmunisationLetter2014_accessible.pdf
2. Public Health England, NHS England. Seasonal flu vaccine uptake in healthcare workers: 1 September 2015 to 31 January 2016 (published 18 February 2016). https://www.gov.uk/government/statistics/seasonal-flu-vaccine-uptake-in-healthcare-workers-1-september-2015-to-31-january-2016 (accessed 25 May 2016).
3. British Medical Association. BMA criticises staff flu-jab funding link (updated 9 October 2014; cited 18 May 2016). http://www.bma.org.uk/news-views-analysis/news/2014/october/bma-criticises-staff-flu-jab-funding-link
4. Public Health England. Seasonal influenza vaccine uptake amongst frontline healthcare workers (HCWs) in England Winter season 2015 to 2016 (updated May 2016; cited 26 May 2016). https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/526041/Seasonal_influenza_vaccine_uptake_HCWs_2015_16_Annual_Report.pdf
5. Public Health England, NHS England. Flu plan: winter 2015 to 2016. (updated March 2015; cited 17 September 2015). https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/418038/Fiu_Plan_Winter_2015_to_2016.pdf
6. Hollmeyer HG, Hayden F, Poland G, et al. Influenza vaccination of health care workers in hospitals—a review of studies on attitudes and predictors. Vaccine 2009;27:3935–44
7. McCartney M. Show us the evidence for the flu jab. Pulse Today, 19 October 2011 (cited 7 August 2014). http://www.pulsetoday.co.uk/show-us-the-evidence-for-the-flu-jab/12911759.article
8. McCartney M. What use is mass flu vaccination? BMJ 2014;349:g6182.
9. Doult P. Influenza: marketing vaccine by marketing disease. BMJ 2013;346:f3037.
10. Department of Health, Public Health England, NHS England. The national flu immunisation programme 2015 to 2016: supporting letter (updated 27 March 2015, cited 17 September 2015). https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/418428/Annual_flu_letter_24_03_15_FINALv3_para9.pdf
11. Shea B, Bouter L, Peterson J, et al. Development of a measurement tool to assess systematic Reviews (AMSTAR). PLoS One 2007;2:e150
12. Ng AN, Lai CK. Effectiveness of seasonal influenza vaccination in healthcare workers: 1 September 2015 to 31 January 2016. J Hosp Infect 2011;79:279–86.
13. Burls A, Jordan R, Barton P, et al. Vaccinating healthcare workers against influenza to protect the vulnerable—is it a good use of healthcare resources? A systematic review of the evidence and an economic evaluation. Vaccine 2006;24:4212–21.
14. Michiels B, Govaerts F, Remmen R, et al. A systematic review of the evidence on the effectiveness and risks of inactivated influenza vaccines in different target groups. Vaccine 2011;29:9159–70.
15. DiazGranados CA, Denis M, Plotkin S. Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: a systematic review with meta-analyses of controlled trials. Vaccine 2012;31:49–57.
16. Ferroni E, Jefferson T. Influenza. Clin Evid (Online) 2011 pii 0911.
17. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:36–44.
18. Villari P, Manzoli L, Boccia A. Methodological quality of studies and patient age as major sources of variation in efficacy estimates of influenza vaccination in healthy adults: a meta-analysis. Vaccine 2004;22:3475–86.
19. Demicheli V, Jefferson T, Al-Ansary L, et al. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2014;(3):CD001269.
20. Dolan GP, Harris RC, Clarkson M, et al. Vaccination of healthcare workers to protect patients at increased risk of acute respiratory disease: summary of a systematic review. *Influenza Other Respir Viruses* 2013;7(Suppl 2):93–6.

21. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions. *Cochrane Database Syst Rev* 2013;(7):CD005187.

22. Ahmed F, Lindley MC, Allred N, et al. Effect of influenza vaccination of healthcare personnel on morbidity and mortality among patients: systematic review and grading of evidence. *Clin Infect Dis* 2014;58:50–7.

23. Dolan GP, Harris RC, Clarkson M, et al. Vaccination of health care workers to protect patients at increased risk for acute respiratory disease. *Emerg Infect Dis* 2012;18:1225–34.

24. Michiels B, Philips H, Coenen S, et al. The effect of giving influenza vaccination to general practitioners: a controlled trial. *BMC Med* 2006;4:17.

25. Wilde J, McMillan J, Serwint J, et al. Effectiveness of influenza vaccine in health care professionals: a randomized trial. *JAMA* 1999;281:908–13.

26. Weingarten S, Staniloff H, Ault M, et al. Do hospital employees benefit from the influenza vaccine? A placebo-controlled clinical trial. *J Gen Intern Med* 1988;3:32–7.

27. Saxén H, Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of health care workers. *Pediatr Infect Dis J* 1999;18:779–83.

28. Hui L, Rashwan H, bin Jaafar M, et al. Effectiveness of influenza vaccine in preventing influenza-like illness among Faculty of Dentistry staff and students in University Kebangsaan Malaysia. *Healthc Infect* 2008;13:4–9.

29. Jefferson T, Di Pietrantonj C, Rivetti A, et al. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev* 2010;(7):CD001269.

30. Thomas R, Jefferson T, Lasserson T. Influenza vaccination for healthcare workers who work with the elderly. *Cochrane Database Syst Rev* 2010;(2):CD005187.

31. Cochrane Handbook. Chapter 12: Interpreting results and drawing conclusions (cited 8 October 2014). http://handbook.cochrane.org/v5.0.0/chapter_12/12_interpreting_results_and_drawing_conclusions.htm