

Appendix 1: Study protocol

Project title

Influenza vaccine for healthcare workers: a review of the evidence

Authors

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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 <i>(separate terms)</i>	Vaccines influenza immunisation <i>(separate terms)</i>
Randomized Control Trials <i>(as topic)</i> 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, bdspace, 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	<table border="1"> <tr> <td>Participants</td> <td>Persons at higher risk of complication from respiratory infection receiving care from an HCW</td> </tr> <tr> <td>Intervention</td> <td>Influenza vaccination</td> </tr> <tr> <td>Control</td> <td>Not stated</td> </tr> </table>	Participants	Persons at higher risk of complication from respiratory infection receiving care from an HCW	Intervention	Influenza vaccination	Control	Not stated
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 articles (4 RCTs, 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	<table border="1"> <tr> <td>Participants</td> <td>No definition provided</td> </tr> <tr> <td>Intervention</td> <td>Flu vaccination</td> </tr> <tr> <td>Control</td> <td>Not stated</td> </tr> </table>	Participants	No definition provided	Intervention	Flu vaccination	Control	Not stated
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	<table border="0"> <tr> <td>Participants</td> <td>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</td> </tr> <tr> <td>Intervention</td> <td>trivalent inactivated vaccines (TIV)</td> </tr> <tr> <td>Control</td> <td>Placebo or none</td> </tr> </table>	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
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 (CTR) 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	<u>1 study (21)</u> VE = 88% [95% CI: 47, 97] (influenza A) VE = 89% [95% CI: -14, 99] (influenza B)	<u>1 study (38)</u> OR = 0.10 [95% CI: 0.01,0.75] (GPs, aged 30)	<u>1 study (21)</u> VE = 88% [95% CI: 59,96]
Efficacy against clinically-suspected influenza in healthcare workers	<u>1 study (22)</u> 1.8 episodes (vaccine) vs 2 episode (placebo), not statistically different <u>1 study (20)</u> 23% (vaccine) vs. 22% (control), not statistically different	<u>1 study (37)</u> VEf=53% (p = 0.002) <u>1 study (38)</u> OR 0.35 [95% CI: 0.13, 0.96] (GPs, aged 30)	<u>1 study (22)</u> RR=1.14 [95% CI: 0.15-8.52] <u>1 study (20)</u> RR=1.07 [95% CI: 0.62-1.85]
Working days lost for healthcare workers	<u>1 study (21)</u> Mean absence (\pm SD) 0.10 days \pm 0.35 (vaccine) vs 0.21 days \pm 0.75 (control) <u>1 study (22)</u> Mean absence 1.0 day (vaccine) vs 1.4 days (control) p = 0.02 <u>1 study (20)</u> Mean absence (\pm SD) 7.6 hours \pm 12.1 (vaccine) vs.8.2 hours \pm 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	<u>Meta-analysis of 22 studies</u> : VE=62% [95% CI: 56,67] (parenteral inactivated vaccine)	<u>Meta-analysis of unknown number of studies</u> : VE=59% [95% CI: 50, 66] (parenteral inactivated vaccine)	<u>1 study</u> (46) VE= 69.5% [97.5% CI lower bound 55%] <u>1 study</u> (48) VE= 46.3% [97.5% CI lower bound 9.8%] <u>1 meta-analysis</u> (5) Inactivated vaccine: VE=73% [95% CI: 54,84] (matching); VE=44% [95% CI: 33,59] (unmatched) <u>1 study</u> (27) VE=73% [95% CI: 51,85] <u>1 study</u> (56) VE=77% [95% CI:37,92]	<u>1 study</u> (42) VE=72% [95% CI: 55, 82] <u>1 study</u> (46) VE= 70% [95% CI: 55, ?] (CCIV); VE= 63% [95% CI: 47, ?] (TIV) <u>1 study</u> (48) VE= 49% 95% CI: 20,?) <u>1 meta-analysis</u> (5) VE= 73% [95% CI: 54, 84] (matched, inactivated); VE 44% [95% CI: 23, 59] (unmatched) <u>1 study</u> (27) VE=68% [95% CI 46,81] <u>1 study</u> (56): VE=72% [95% CI: 42, 90] <u>1 study</u> (57)_no significant effect	<u>Meta-analysis of 6 studies</u> : VE=59% [95% CI: 51, 67]	<u>Meta-analysis of 25 studies</u> VE=63%, [95% CI: 53,71] (all vaccines)
Efficacy against clinically-suspected influenza in healthy adults	<u>Meta-analysis of 16 studies</u> : VEf=17% [95% CI: 13,22] (parenteral inactivated vaccine)	-	<u>1 meta-analysis</u> (5) VEf=30% [95% CI 17,41] (matched); RR=0.93 [95% CI: 0.79,1.09] (unmatched)	<u>1 meta-analysis</u> (5) VEf= 30% [95% CI: 17,41] (matched)	-	<u>Meta-analysis of 49 studies</u> : 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)	-	<u>1 meta-analysis</u> (5) MD (days)=-0.21 [95% CI:-0.36, -0.05] (matched); Mean difference =0.09 [95% CI: 0.00, 0.18] (unmatched)	<u>1 meta-analysis</u> (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	<p><u>Meta-analysis of 2 RCTs</u> RR = 0.80 [95% CI: 0.31,2.08]</p> <p><u>1 study</u> (17) ($\geq 35\%$ vs $< 35\%$ vaccinated HCWs) - Adjusted OR = 0.07 (0.01–0.98)</p>	-	<p><u>1 study</u> (1) No significant effect <u>1 study</u> (25) 14% (vaccine) vs 34% (control), $p < 0.001$ <u>1 meta-analysis</u> (33) RR=0.87 [0.38,1.99] <u>1 study</u> (34) 72.1% decrease, $p < 0.01$</p>	<p><u>1 meta-analysis</u> (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)</p>	<p><u>1 meta-analysis</u> (33) No significant effect</p>	<p><u>Meta-analysis of 2 studies</u> (1), (16) RD= 0.00 [95% CI:-0.03,0.03] (some patients vaccinated)</p>
Efficacy against clinically-suspected influenza in patients of healthcare workers	<p><u>Meta-analysis of 3 RCTs</u> RR = 0.58 [95% CI: 0.46,0.73]</p> <p><u>1 study</u> (18) ($\geq 15\%$ vs $< 15\%$ vaccinated HCWs) <u>Adjusted RR= 0.3 (0.1–1.2)</u></p>	-	<p><u>1 study</u> (14) RD=-0.09 [95% CI: -0.14, -0.03] (period 1); RD=0.00 [95% CI:-0.06,0.06] (period 2) <u>1 study</u> (26) Spearman rank correlation, $r = 0.379$, $p = 0.459$ (hospital personnel vaccination coverage and no. influenza cases) <u>1 study</u> (15) OR=0.69 [95% CI: 0.52,0.91] <u>1 study</u> (29) OR= 0.28 [95% CI: 0.23–0.32] <u>1 study</u> (16) OR= 0.57 [95% CI:0.34,0.94] (some patients vaccinated) <u>1 study</u> (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) <u>1 meta-analysis</u> (33) RR =0.71 [95% CI: 0.58, 0.88]</p>	<p><u>1 meta-analysis</u> (33) RR =0.14 [95% CI: 0.03,0.6] (some patients vaccinated); RR 0.87 [95% CI: 0.49,1.55] (unvaccinated patients)</p>	<p><u>1 meta-analysis</u> (33) RR =0.14 [95% CI: 0.03,0.6] (some patients vaccinated); No significant effect (unvaccinated patients)</p>	-
Patients of healthcare workers admitted to hospital	<p><u>Meta-analysis of 2 RCTs</u> RR = 0.91 [95% CI: 0.68,1.19]</p>	-	<p><u>1 study</u> (14) RD=-0.02 [95% CI:-0.05, 0.02] (period 1); RD=0.00 [95% CI:-0.03,0.04] (period 2) <u>1 study</u> (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) <u>1 study</u> (15) OR= 1.03 [95% CI:0.76, 1.40] <u>1 study</u> (15) OR=0.90 [95% CI:0.66,1.21] (respiratory illness) <u>1 meta-analysis</u> (33) OR=0.90 [95% CI:0.66 to 1.21]</p>	-	-	<p><u>1 study</u> (15) RD= 0.00 [95% CI: -0.02, 0.03] (respiratory illness)</p>

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	-	-	<u>1 study</u> (1) 20% difference in proportion influenza positive at death, p=0.055 <u>1 study</u> (14) RD=-0.01 [95% CI:-0.02 to 0.01] (period 1); RD=-0.01 [95% CI:-0.03,0.00] (period 2) <u>1 meta-analysis</u> (33) pool of Hayward: OR= 0.72 [95% CI: 0.31,1.70] (ILI)	-	-	<u>Meta-analysis of 2 studies</u> (15), (16) RD= -0.01 [95% CI:-0.05,0.03]
Death caused by complications of influenza in patients	-	-	<u>1 study</u> (15) OR=1.55 [95% CI: 0.59,4.10] (respiratory) <u>1 study</u> (16) OR=0.60 [95% CI: 0.37,0.97] (pneumonia) <u>1 meta-analysis</u> (33) pool of other 2 results: OR= 0.87 [95% CI: 0.47,1.64] (adjusted, pneumonia)	<u>1 meta-analysis</u> (33) RR=0.82 [95% CI: 0.45,1.49] (unadjusted, pneumonia)	<u>1 meta-analysis</u> (33) no significant effect	-
Deaths from all causes in patients	<u>Meta-analysis of 4 RCTs</u> RR = 0.71 [95% CI: 0.59,0.85]	<u>1 study</u> (1) OR= 0.61 [95% CI: 0.36,1.04] <u>1 study</u> (16) OR=0.56 p=0.0013	<u>1 study</u> (1) OR= 0.62 [95% CI: 0.36,1.04] <u>1 study</u> (14) RD=-0.05 [95% CI:-0.07 to -0.02] (period 1); RD=-0.01 [95% CI:-0.04,0.02] (period 2) <u>1 study</u> (15) OR=0.86 [95% CI: 0.72,1.02] <u>1 study</u> (16) OR=0.56 [95% CI: 0.40,0.80] <u>1 meta-analysis</u> (33) pool of other 4 results: OR= 0.68 [95% CI 0.55,0.84] (adjusted)	<u>1 meta-analysis</u> (33) RR=0.66 [95% CI: 0.55,0.79] (unadjusted)	<u>1 meta-analysis</u> (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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