TECHNICAL REPORT

Review of the scientific literature on drivers and barriers of seasonal influenza vaccination coverage in the EU/EEA

www.ecdc.europa.eu

ECDC TECHNICAL REPORT

Review of the scientific literature on drivers and barriers of seasonal influenza coverage in the EU/EEA

This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Teymur Noori and produced by Luciana Brondi, Martin Higgins, Dermot Gorman, Duncan McCormick, Alison McCallum (NHS Lothian, Edinburgh, Scotland, UK) and Sheila Fisken (Information Services, University of Edinburgh, Scotland, UK).

Suggested citation: European Centre for Disease Prevention and Control. Review of scientific literature on drivers and barriers of seasonal influenza vaccination coverage in the EU/EEA. Stockholm: ECDC; 2013.

Stockholm, November 2013

ISBN 978-92-9193-498-0

doi 10.2900/89599

Catalogue number TQ-02-13-331-EN-N

Contents

Tables

Abbreviations and glossary

CDC	US Centers for Disease Control and Prevention
CI	Confidence Interval
C-RCT	Cluster Randomized Controlled Trial
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
GATE	adapted checklist proposed by NICE for the appraisal of studies of public health interventions
EU	European Union
GPs	General Practitioners
HCWs	Healthcare Workers
NICE	National Institute for Health and Care Excellence
NHS	UK National Health Service
RR	Risk Ratio
RCT	Randomized Controlled Trial
VENICE	Vaccine European New Integrated Collaboration Effort
WHO	World Health Organization

Executive summary

Every winter, influenza epidemics cause significant morbidity and mortality throughout Europe. High-risk groups such as older people, individuals with chronic diseases, pregnant women and small children are most affected by these epidemics. Healthcare workers (HCW) are also at high risk of influenza transmission to and from patients. Seasonal vaccination against flu viruses reduces the burden of disease in these groups and has been widely available in most EU/EEA countries for several years. However, uptake of seasonal influenza vaccination for target groups in most of these countries still falls short of the 75% coverage target established by the European Council of Ministers in 2009.

We conducted a systematic review to identify significant evidence on drivers of and barriers to seasonal influenza vaccination of relevance to the EU/EEA. We focused on the high-risk groups which have been identified by ECDC as those where high coverage of seasonal flu vaccination is important.

Evidence from published empirical research forms the core of this review. We searched the Medline/PubMed, EMBASE, Cochrane Library (DARE, NHS EED and HTA) databases. A detailed search strategy developed in consultation with an information specialist was used to search Medline and EMBASE. We covered all English language papers published between 2008 and 2012.

Two authors selected articles of possible relevance for the review. A detailed screening form was developed and tested for this purpose. For the 'title and abstract' screen and the 'full text' screen, 10% per cent of the articles were independently assessed and the level of agreement evaluated. There was excellent agreement between both reviewers.

A total of 4 981 articles were initially retrieved through Medline, EMBASE and Cochrane. After all the screening processes, 26 were included for data abstraction and appraisal in the final evidence tables. Data appraisal was conducted by two authors using standard checklists and disagreements were discussed and resolved. Studies included were then rated to indicate their quality following the process outlined in the NICE Public Health Guidance Methods Manual [1]. To create the evidence tables we used systematic reviews and randomised controlled trials (RCTs) for the evaluation of interventions to increase uptake of flu seasonal vaccine. To identify facilitating factors other than interventions, we used evidence from studies with designs such as case control, cohort or cross-sectional surveys, and mainly from studies highly relevant to the European context.

For the elderly population and healthcare workers, there is published evidence on specific types of interventions to increase the uptake of seasonal flu vaccination. For population of patients with chronic conditions, the evidence is scattered as there are not enough high quality studies in the different groups of chronically ill people and therefore transferability of conclusions between groups and in patients with multiple morbidity, requires further testing. For pregnant women and children, the evidence we found was scarce and quite low in quality and permitted fewer conclusions.

We present the main results of our review by targeted group.

Elderly people

In elderly people, there is insufficient evidence for some interventions but personalised postcards or phone calls are considered effective. Home visits, and having facilitators, may be effective. Reminders to physicians alone are not effective and good quality evidence from one RCT in Japan found positive effects in the elderly population when community pharmacists personally advocated for flu vaccination.

Observational studies suggest that individuals who are older than 85 or married, who use medical services more frequently or who suffer from a chronic disease are more likely to get vaccinated. These studies also suggest that having a case manager as part of an interdisciplinary team in a healthcare practice, and lowering the age limit for vaccination might be effective in increasing vaccination rates. Barriers to vaccination include social disadvantage, smoking, and lack of social support.

Individuals with chronic medical conditions

The conclusions for this subpopulation depend to a certain extent on which kind of chronic condition they suffer from. In addition, most of the interventions were conducted in the USA and some assessment of effectiveness in different healthcare systems is required. Interventions such as reminder/recall systems seem to increase influenza vaccination in asthmatic children, although adding educational messages with reminders might not increase uptake in patients with asthma. While previous studies with chronically ill children and other populations have shown the effectiveness of electronic health reminders/alerts in improving uptake of services, the USA study selected showed only modest and non-significant effect in immunisation for influenza among asthmatic children.

Other drivers and barriers explored by observational studies in this subpopulation suggest that misperceptions about the vaccine might be a barrier to receiving vaccination. Low grade evidence from the UK shows a modest, significant coverage increase (8%) in high-risk patients under 65 when a lead staff member plans the flu campaign, and when a written performance report is produced during the vaccination campaign and results are shared with those involved in the vaccination efforts.

Healthcare workers

There is plenty of evidence on interventions to improve vaccine uptake in this group. One systematic review identified five types of intervention:

- education or promotion
- improved access to vaccination
- legislation or regulation
- measurement or feedback
- role models.

In non-hospital settings, campaigns with more components, specifically education/promotion and improved access to vaccines, had significant positive effects in vaccine uptake, more than doubling the rates in the intervention group compared to the control (risk ratio 2.26, 95% CI, 1.96–2.39), and reaching high coverage (68.5%) in the intervention group. In hospital settings, education/promotion and improved access to vaccination were the most common interventions but never raised vaccination rates above 90%. Other RCTs published since the systematic review are broadly in line with review findings in that they show little evidence that interventions such as education or promotion improved access to vaccination, measurement or feedback, or that role models are on their own effective measures to reach 90% vaccination among HCWs.

Evidence from two observational studies from the USA suggests mandatory vaccine policies are more successful in improving rates of vaccination above 95% than relying on enabling approaches.

Pregnant women

There was no good quality evidence on interventions in this group. As for other drivers and barriers explored in observational studies, very low grade evidence from a cross-sectional study suggests that standing orders[i], role models, and HCW education might improve rates of coverage. Electronic reminders and education of providers might be useful. Inconsistent advice from healthcare providers may also pose a barrier to vaccine uptake in this population.

[i] Standing orders allow professionals who are not physicians (e.g. nurses or pharmacists) to give vaccinations without direct physician involvement at the time of the vaccination.

Children

The evidence for interventions targeting this group is scarce and weak. We found no systematic reviews or RCTs investigating interventions.

There is low grade evidence from the USA. Cross-sectional studies focused on parents' attitudes and views. Common reasons why parents choose to have children vaccinated include:

- prevention of influenza
- physicians' recommendation
- reduced influenza symptoms.

Two studies from the USA and one from the UK provide some indicators for future research, although these surveys all contain notable respondent bias. Potential reasons why parents may choose not to have children vaccinated include:

- low perception of risk of catching the disease
- concern about safety and efficacy of vaccines
- flu vaccine containing thiomersal.

Adults in general

We also present some relevant evidence on the adult population in general since not all studies focused specifically on our target groups. Low grade evidence from a cluster RCT (C-RCT) in the USA shows that electronic reminders might help improving flu vaccination rates in adults if they can access the internet and use it regularly.

As for drivers and barriers explored in observational studies, low grade evidence from a survey carried out in 11 European countries suggest that countries with high per capita income have significantly higher rates of coverage in adults. Awareness that influenza is a serious illness, advice from a family doctor and the wish not to transmit influenza to family members and friends seems to facilitate uptake. Adults who did not think themselves likely to catch influenza or who had never considered vaccination before were less likely to be vaccinated. In addition, having to pay for vaccines is also a barrier, especially in the poorer countries.

List of evidence statements

Elderly people

Evidence statement 1

Different types of interventions in elderly people have been analysed by a high quality systematic review [2]. There was marked heterogeneity among the interventions studied and therefore many results could not be pooled. There is insufficient evidence for most of the interventions, however:

- There is ample, although low quality, evidence that reminders work. Normal reminder postcards or letters (10 RCTs) and personalised postcards or phone calls (11 RCTs) are considered effective with entire 95% CI >1.
- Home visits may be effective.
- Facilitators within the clinics may be effective (3 of 4 RCTs 95% CI>1)
- Reminders to physicians alone (only 1 out of 4 RCTs had positive effects) are not effective.

There is good quality evidence from one C-RCT in Japan showing an increased rate of vaccination among elderly people when community pharmacists personally advocated for flu vaccination, with a difference of 8.7% in uptake (95% CI = 2.2-15.2%) [3].

Evidence statement 2

There is moderate evidence from one case control study involving 11 European countries suggesting that having a case manager in an interdisciplinary team might be a facilitator for higher uptake of flu vaccine in elderly people [4]. The same finding is repeated in a recent cross-sectional survey in 795 UK General Practitioner clinics [5].

Low grade to moderate evidence from a large Italian study and a combined Ireland and Northern Ireland study suggests that being 85 or older increases the likelihood of getting the vaccine [6]. Suffering from severe chronic disease is also a strong determinant according to the Italian survey. The Italian survey also suggests that good social support significantly increases the odds of influenza vaccine use [7]. In the Ireland and Northern Ireland study, being married and greater usage of hospital and community services also increase vaccine uptake. Low grade to moderate evidence from a large Spanish study suggests that lowering the age limit might increase vaccination coverage in all groups [8].

Moderate evidence from an Italian national survey shows that social disadvantage and being a smoker might determine low uptake of flu vaccine [9].

Chronic conditions

Evidence statement 3

Low grade evidence from Esposito [10] indicates that reminder/recall systems seem to increase influenza vaccination in asthmatic children (rates increased from at least 10% to a maximum of 21% in all groups). Receiving a reminder from a paediatrician from the clinic and getting the vaccine in the same clinic increased uptake rates from 40 to 61.1% with RR=1.26 (1.01–1.58).

There is moderate evidence from the USA that an added educational message with reminders might not increase uptake in patients with asthma [11].

Although previous studies with chronically ill children have shown the effectiveness of electronic health reminders alerts in improving vaccine uptake, moderate evidence from studies from the USA show only a modest improvement [12] with a small non-significant (3.4%) increase in uptake (95%CI 1.4% to 9.1%). These results might not be directly transferable to the European context.

Evidence statement 4

Evidence from the USA shows that misperceptions about the vaccine might be a barrier to vaccination in this population. Perception that vaccination can actually cause the flu (adults: 48%; children 39%), and concerns about side-effects might be barriers to vaccination [11].

A large, one season only, UK General Practice cross-sectional survey suggests a significant coverage increase of 8% in high risk patients under 65 when a lead member is planning the flu campaign and when a written performance report is produced (very low grade)[5].

Healthcare workers

Evidence statement 5

The systematic review identified five types of intervention: education or promotion; improved access to vaccine; legislation or regulation; measurement or feedback; and role models. There is mixed evidence about the success of these interventions. The main findings are as follows:

- In non-hospital settings, campaigns with more components, specifically education/promotion and improved access to vaccination, had higher impact with risk ratios > 1. In one, the coverage was highest when each worker had a personal interview with a member of the study team, with an average risk ratio of being vaccinated in the intervention group of 2.16 (1.96–2.43). Two other 2 RCTs found an even higher positive effect when adding role models to education and improved access, with average risk ratios of 7.06 (5.67-8.78) and 8.05 (6.30-10.30). However, the vaccine uptake in the intervention group was below 40%.
- In hospital settings, education/promotion and improved access to vaccination were the most common interventions but never raised vaccination rates above 90%
- Small studies which rely on mandatory compliance indicate vaccination rates can be increased above 90% [13].

The other intervention RCTs published since the systematic review [14 15] are broadly in line with review findings as they show little evidence that interventions such as education or promotion, improved access to vaccination, measurement or feedback, or role models, are on their own effective measures to reach 90% vaccination among HCWs.

Evidence statement 6

Evidence from two observational studies suggests mandatory vaccine policies are more successful in improving rates of vaccination above 95% [16 17]. There are however ethical and legal obstacles associated with mandatory programmes.

Evidence statement 7: Pregnant women

We identified no high quality RCTs or systematic reviews that investigated interventions for increasing uptake of flu vaccination among pregnant women. Most studies captured by our search were cross-sectional. Very low grade evidence from one cross-sectional study suggests that standing orders, role models, and HCW education might improve rates of coverage [18]. Very low grade evidence suggests the usefulness of electronic reminders to providers increase uptake [19] and provider education [20]. Very low grade evidence suggests that inconsistent advice from healthcare providers might pose a barrier to vaccine uptake in this population [21].

Evidence statement 8: Children

We identified no high quality RCTs or systematic reviews that investigated interventions, barriers or facilitators for increasing uptake of flu vaccination among children. Cross-sectional studies from the USA and UK investigating parents' attitudes and views provide some low quality evidence which serve as indicators for future research.

Common reasons why parents choose to have children vaccinated include:

- prevention of influenza
- physicians' recommendation
- reduced influenza symptoms

Potential reasons why parents may choose not to have children vaccinated include:

- low perception of the risk of catching the disease
- concern about safety and efficacy of vaccines
- flu vaccine containing thiomersal

Evidence statement 9: Adult population

Low grade evidence from the USA shows that electronic reminders might help improve flu vaccination rates in adults if they can access the internet and use it regularly [22].

In one survey (low grade evidence) undertaken in 11 European countries, being older, and being older with a chronic condition is a determinant of vaccine uptake. Countries with high per capita income have significantly higher rates of coverage in adults. Awareness that influenza is a serious illness, advice from a family doctor (in 8 of 11 countries), and the wish not to transmit influenza to family members and friends seem to facilitate uptake. Adults who did not feel likely to catch influenza or who had never considered vaccination before were less likely to be vaccinated. Having to pay for vaccines is a barrier, especially in poorer countries [23].

Background

The 2009 Council of the European Union Recommendation (Recommendation 2009/1019/EU of 22 December 2009)[i] on seasonal influenza vaccination encouraged countries to implement measures that would increase seasonal influenza vaccination uptake to at least 75% for defined older age groups, and, if possible, for other risk groups. These targets were intended to be reached by the 2014–2015 winter season.

Following the Council Recommendation, several key high-risk groups were identified as important for increased coverage of seasonal flu vaccination. These are:

- Older age groups (usually 65 years and older)
- Pregnant women (not all Member States)
- Children below two or below five years of age (not all Member States)
- Healthcare workers (HCWs)
- Individuals over six months of age with chronic medical conditions, particularly the following:
  - chronic respiratory diseases
  - chronic cardiovascular diseases
  - chronic metabolic conditions
  - chronic renal and hepatic diseases
  - persons with acquired of congenital immunodeficiency
  - persons with a compromised respiratory function
  - persons with morbid obesity

The outputs from the Vaccine European New Integrated Collaboration Effort (VENICE) project are key to understanding the subsequent developments and trends in influenza vaccination in Europe. The VENICE survey describes aspects of the seasonal influenza immunisation policies implemented in the European Union (EU) Member States, Norway and Iceland, and collects available vaccination uptake data for the risk groups and HCWs. The most recent VENICE report [24] covers the 2010–11 influenza season and shows great variation between countries. Vaccination rates for over 65s are highest in the Netherlands at 80.6% as opposed to 1.1% in Estonia. Seven countries reported vaccination uptake rates in healthcare workers; it ranged from 14% in Norway to 63.9% in Romania. Only five countries reported on the clinical risk groups; uptake was 29.4% in Portugal and 68.9% in the Netherlands. The coverage in pregnant women was only reported in two countries, 3.6% in Romania, and 36.6% for healthy and 56.6% for at-risk women in England. Portugal reported 82.9% coverage for residents of long-term care stay facilities and Slovakia reported 85.4%; no other countries reported this type of coverage.

VENICE demonstrates that different systems, protocols and policies are implemented throughout the region with different risk group definitions being used. For example, the World Health Organization Regional Office for Europe (WHO–EURO) [25] priority groups for seasonal influenza vaccination included elderly persons over a nationally defined age limit, irrespective of other risk factors. However, although Norway, Iceland and all the countries in the EU recommend seasonal influenza vaccination of elderly people, the definition of older age groups varies amongst them. Most of the countries (19 out of 28) recommend the vaccine for individuals aged 65 and older, but others have lower age criteria. Seven countries recommend vaccinination for children (Latvia, Malta, Austria, Estonia, Poland, Slovenia, Slovakia) but not all of them for all ages of children.

All 28 countries recommend the vaccination of patients with chronic medical conditions of the heart and lungs, haematological or metabolic disorders, immuno-suppression due to diseases or treatment, and renal disease. But three of the countries exclude those with HIV/AIDS. Vaccination is recommended for individuals suffering from hepatic and neurological diseases and for those taking long-term aspirin in 19 countries and in nine countries for those with morbid obesity.

Healthcare workers are considered a target group for vaccination by most of the countries and nearly half of these countries also recommend the vaccination of poultry industry workers.

The new report shows that now 19 of the 28 countries recommend the vaccination for all pregnant women and three of them for pregnant women with another clinical risk condition.

New risk groups were included to the recommendations for influenza vaccine after the influenza pandemic occurred (2009–2010). Nineteen countries added those with neurological diseases and nine countries added morbidly obese individuals.

[i] The Council of the European Union Recommendation 2009/1019/EU of 22 December 2009 on seasonal influenza vaccination. Available here: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:348:0071:0072:EN:PDF

Nonetheless, a substantial gap between the official recommendations to vaccinate individuals at risk and the actual vaccination rates in these groups still exist.

Of all countries responding to the survey, 18 reported that no national action plan (NAP) was adopted in their country and seven countries updated previously developed plans. Two countries reported that a national plan had been adopted. This shows no change compared to the previous VENICE survey.

Although the VENICE survey collects valuable information about projected changes in national policies, it is not a source of information about how vaccination services are organised or measures taken to promote vaccination uptake within responding countries. Therefore, the present review of the literature seeks to fill a gap in knowledge about successful interventions to improve vaccination coverage in target groups in the region. The main focus will be on Europe and English language peer-reviewed published literature, although highly relevant data from elsewhere in the world (notably USA, Canada and Australia) were also included.

Objectives and key questions

The main objective was to review critically the evidence on the barriers and drivers of seasonal influenza vaccination coverage in the EU/EEA.

Key questions addressed in the review are:

- What are the drivers and barriers for increased seasonal flu vaccination coverage in the various risk/target groups in the EEA?
- How can the current low rates of healthcare workers' influenza vaccination coverage be improved?
- Can we identify examples of good practice from the literature that increase vaccination uptake in all groups?
- What are the current gaps in research on the drivers and barriers to increase seasonal flu vaccination coverage?

Methodology

This review was conducted in six stages and the review team met on several occasions to decide on key aspects of the work:

- literature search
- screening
- data abstraction/appraisal
- evidence synthesis
- report writing
- paper drafting.

1. Literature search

The search focused mainly on published empirical literature, although a few unpublished ('grey') papers from the empirical literature and contextual literature were also included in the discussion.

Electronic searches:

Evidence from published empirical research forms the core of this review. Relevant studies from a range of disciplines were identified by using appropriate search terms and a range of databases both specified in the search strategy described below. The starting point was existing reviews of the evidence of effectiveness of measures to improve vaccination rates such as those published by NICE and the Cochrane Collaboration. During all phases of our review, particular attention was paid to existing reviews and articles addressing health inequalities, since this is a fundamental element in public health practice and in vaccination programmes. Resources, such as Methodological Standards For The Conduct Of New Cochrane Intervention Reviews (MECIR), which address these issues were utilised [26].

We performed an initial scoping exercise to identify the extent of the literature and the relevant MeSH and keywords. During this iterative process the search strategy was refined and re-tested. From these searches a 'gold set' of references was identified and the strategies were tested to confirm whether the search strategy retrieved this set.

We searched Medline using Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (1946 to Present). The Medline and Embase search were both carried out on the 26 of November 2013 and a more detailed Medline search strategy for the review is described in Annex 1.

Further searches were carried out using Embase (Ovid SP interface) and The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and the Cochrane Controlled Trials Register). Detailed strategies are available on request. The reference lists of included papers were scanned to identify further relevant studies.

We searched the Medline/PubMed, EMBASE, Cochrane Library (DARE, NHS EED and HTA) databases. The EMBASE and Cochrane Library search strategies were adapted from the Medline search. The search strategy described in Annex 1 was refined through an iterative process and in consultation with an information specialist in order to identify potentially relevant papers in different databases. We made sure the electronic search retrieved relevant papers which related to our main priority groups for vaccination (older age group, chronic medical conditions, pregnant women, healthcare workers and children under five).

Both quantitative and qualitative studies have been selected. We filtered the results of our electronic search and based the final report on English language papers. Initially the time limits of the search covered studies published between 2002 and November 2012.

Other resources:

Preliminary results of studies still underway, such as the ongoing VENICE work are also described. In addition, we have contacted some experts in the area and they have directed us to unpublished research that is relevant to the review; after quality appraisal a few of these references were included.

2. Screening

Refworks-COS 2010, by ProQuest was the software used to manage references. A flowchart describing the several screening steps for selection of evidence can be seen in Annex 2 of this report.

The review-level material to be included in our review was screened, quality assessed, data extracted and integrated into the evidence reviews according to the following the process outlined in the NICE Public Health Guidance Methods Manual [27]. For the Cochrane library, one author carried out the screening. For this database, each one of the 47 documents retrieved by the search was title and abstract screened. Then a small proportion of these (6) were fully screened using an adapted version of the review–level material screen form presented in the NICE Manual. After the final review, three systematic reviews from this database were found relevant to our key questions and added to the other articles.

For the Medline and EMBASE search, we subdivided the screening into three steps which was carried out by two authors. A first step eliminated the bulk of irrelevant material and a second step used inclusion and exclusion criteria agreed by the review team. These are the details of each step:

First step

After running the electronic search on Medline and Embase, we identified 4 911 studies matching our search strategy. A first step carried out by one of the authors eliminated the bulk of irrelevant material by reviewing all titles and some abstracts using the inclusion and exclusion criteria agreed by the review team. This first step of the screening reduced the number of studies to 912.

For the second step of the screening, we developed a basic screening form to use. To validate the screening form, two authors independently reviewed a random selection of papers retrieved by our main electronic search until 100% agreement was reached. This ensured consistency of selection criteria used by different reviewers.

Second step

After the first screening, two authors reviewed all the titles and abstracts of the remaining 912 articles identified by the first step using the standard screening form mentioned before. Each of the authors reviewed half of the articles and 10 % of them were independently double checked for consistency. The level of agreement found was excellent (Kappa statistics > 0.75) [1].

All abstracts that did not address the research questions were eliminated. The abstracts selected had to satisfy the following criteria:

Participants:
Studies or reviews included should involve our target groups; older age groups (60 and older or 65 and older); or persons with chronic medical conditions (as set out above); or healthcare workers; or pregnant women; or children below two; or children below five years of age.

Outcomes:
The outcome of the article should be an increase, a decrease or no change in influenza vaccination coverage rates in different target/risk groups. Studies looking at intention to get vaccinated were only selected if they were considered highly relevant.

Drivers and barriers:
Studies and reviews looking at reasons for an increase, a decrease and no change in vaccination coverage rates in our selected groups were included; in this case, drivers (either interventions or other contextual factors) positively affecting vaccination coverage, and barriers (or hazard factors) which can decrease vaccination coverage.

Study design:
Randomised controlled trials (RCT) and systematic reviews of interventions were considered the 'gold standard' for providing information on the impact of interventions (drivers). Studies with different designs looking at interventions were also reviewed to provide answers to our research questions, in line with the methodological standards produced by Cochrane methodology groups. These include well-conducted observational and qualitative studies looking at drivers and barriers for increased vaccination coverage.

Third step

Once the title and abstract screening was finished, and 399 articles had been selected, the review team decided to focus on the material published after 2008. Having excluded all the previous articles we retrieved copies of the full 225 articles or reports remaining. Two authors conducted a full text screening of these 225 articles. Each author reviewed half of the articles and 10 % of them were independently double checked for consistency. The level of agreement during the full text screening was good (Kappa statistics = 0.71) and reasons for any disagreement were explored. After this step, 76 articles including three Cochrane reviews already selected remained. After a final assessment of quality and relevance to the European context, 26 of them were included in the review to produce evidence statements. The main reasons for exclusion at this point were articles irrelevant to the European context, flawed designs or reports and studies using very small unrepresentative samples. A list of the studies excluded during full text review screening along with the main reason for exclusion will be provided.

3. Data abstraction/appraisal

To create the evidence tables we mainly used systematic reviews and RCTs for the interventions to increase uptake of the flu seasonal vaccine. For facilitators in general (not necessarily interventions) and barriers we also used evidence from studies with other designs including case control, cohort or cross sectional surveys, but mainly studies which were considered relevant to the European context. Empirical studies or systematic reviews included in the main part of this review were critically appraised and rated to indicate their quality following the process outlined in the NICE Public Health Guidance Methods Manual [28] .

Quality appraisal electronic checklists were used for this purpose. For the primary studies the forms used were adapted versions of the GATE adapted checklist proposed by NICE for the appraisal of public health interventions. The GATE checklist has the advantage of being an electronic form and therefore facilitates sharing, storage of data, and also linkage with other documents [29]. We used a slightly adapted version of the SIGN checklist for systematic reviews [30].

After appraisal, the included studies were rated based on the number of criteria met. The scores or rates produced reflect the risk of potential bias coming from their design and execution.

The contextual literature cited in the final session of the report was evaluated for quality but not rated. Two members of the research team appraised and rated the included papers, where each full paper was initially appraised by one reviewer and checked by the second reviewer.

Once agreement was reached, the levels of evidence and grading set out in the NICE Public Health Guidance Methods Manual [28] were applied to each study, according to the following grades:

Study quality

++ All or most of the methodology checklist criteria have been fulfilled. Where they have not been fulfilled, the conclusions are thought very unlikely to alter.

+ Some of the methodology checklist criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.

– Few or no methodology checklist criteria have been fulfilled. The conclusions of the study are thought likely or very likely to alter.

The studies included in the final review report were also appraised in terms of applicability to the EU/EEA context.

4. Evidence synthesis

The synthesis of the evidence for the 26 selected studies contains three main aspects:

- a description of the studies selected, including all the main characteristics including methods, participants, interventions and outcomes.
- an evaluation of the risk of bias for each study presented.
- a description of the effects of interventions and hazard factors, including a summary of findings for the main comparison.

The review data was summarised mainly in the evidence tables, although some narrative comments have been provided. We structured the results section according to the type of evidence used. Evidence on interventions was grouped together and only systematic reviews and RCTs were used to produce evidence statements. For facilitators in general and barriers to vaccination, other study designs were also used.

Findings from the evidence tables and revised analysis were synthesised and used as the basis for a number of evidence statements relating to each key question. The statement terminology reflect the judgement of the strength (quantity, type and quality) of evidence as stated in the NICE Public Health Guidance Methods Manual [28] (See Chapter 5, under item 5.5) and also its applicability to the EU/EEA context.

Contextual literature identified during the search and screening stage of the review was also consulted to identify its potential contribution to each key theme. It was included in the final report as necessary, in order to set the review findings in a wider context.

Results

Evidence is presented according to the different target or risk groups: elderly people, persons with chronic medical conditions, healthcare workers, pregnant women and children. However, we also presented relevant data on studies conducted with adult populations, although not all the results in these studies are separated according to our target groups.

Study quality grade codes (++, +, -) are presented in the second column of the evidence table and follow the NICE methodology, as mentioned in the methods section of this document, under data abstraction/appraisal.

The evidence for the final 26 studies which remained are presented mainly in the evidence tables and divided depending on the type of evidence, either a systematic review or RCT or other types of studies.

Table 1. Included studies according to targeted population

Targeted population		Intervention/studies	
Elderly people	Interventions	• Increasing community demand • Increasing access • Provider- or system-based • Advocacy by a community pharmacist	Thomas et al. 2010 (systematic review) [2] Usami, 2009 [3]
	Barriers and other facilitators	Various:	Onder, 2008 [4] Chiatti, 2010 [31] Jimenez-Garcia, 2012 [8] Crawford, 2011 [6] Blank, 2009 [23] Dexter, 2012 [5] La Torre, 2010 [9]
People with chronic diseases	Interventions	Reminder/recall system: Post Reminders: Electronic reminders to physicians:	Esposito, 2009 [10] Walter, 2008 [11] Fiks, 2008 [12]
	Barriers and other facilitators	Misperceptions about vaccine safety and fear of side effects: Various, including aspect of flu organisation campaign:	Walter, 2008 [11] Dexter, 2012 [5]
Pregnant women	Interventions	There are no high quality RCTs or systematic reviews	
	Barriers and other facilitators	Facilitator: consistent advice from providers. Barriers: Efficacy and availability of vaccine, personal safety and safety of unborn child:	Mouzoon, 2010 [18] Riley, 2011 [19] McCarthy, 2012 [21] Panda, 2011 [20]
Children	Interventions	There are no high quality RCTs or systematic reviews.	
	Barriers and other facilitators	Facilitators: prevention of influenza, physicians' recommendation, reduced influenza symptoms. Barriers: low perception of risk, concern about safety and efficacy, thimerosal.	Flood, 2010 [32] Flood, 2011 [33] Brown, 2010 [34]
Healthcare worker	Interventions	Single interventions: • Education or promotion • Improved access to vaccine Legislation or regulation • Measurement or feedback • Role models Combined interventions: • Education and improved access to vaccine • Education and access and legislation and role model • Improved access and measurement/feedback	Lam et al, 2010 (systematic review) [13] Rothan-Tondeur et al, 2011 [14] Chapman, 2010
	Barriers and other facilitators	Improving access and mandatory policy	Rakita, 2010 [16] Quan, 2012 [17]
Adult population in general	Interventions	Health Maintenance Electronic Reminders	Wright, 2012 [22]
	Barriers and other facilitators	Socioeconomic and personal determinants	Blank, 2009 [35,23]

Elderly people

One systematic review and one cluster randomized controlled trial were selected as relevant evidence for interventions to increase the seasonal flu vaccination uptake among elderly people [2 3]. There is ample low quality evidence that reminders work, and limited and very low quality evidence that educating patients is effective. Therefore there is insufficient evidence for most of the interventions. But personalised postcards or phone calls are considered effective and home visits, and facilitators in clinics, may be effective. The review also concluded that reminders to physicians are not.

A cluster RCT conducted in Japan showed an increase of 8.7% in uptake when community pharmacists personally advocated for vaccines with older people. [3].

Table 2. Evidence table: interventions to increase flu seasonal vaccination coverage in the elderly population

Author and country of study	Design, quality grade, sample	Intervention and grade of evidence	Number of participants intervention (I) and control (C) and outcomes.	Results and final conclusion
Evidence statement 1: Different types of interventions elderly populations have been analysed by a high quality systematic review [2]. There was marked heterogeneity amongst the interventions studied and therefore many results could not be pooled. There is insufficient evidence for most of the interventions but: • ample although low quality evidence that *reminders work.* Normal reminder postcard or letter (10 RCTs) and personalized postcards or phone calls (11 RCTs) are considered effective with *entire 95% CI >1.* • home visits *may be* effective. • facilitators within the clinics may be effective as well (3 of 4 RCTs 95% >1) • reminders to physicians (only 1 out of 4 RCTs had positive effects) are not effective. There is good quality evidence from one C-RCT in Japan showing an increase rate of vaccination in the elderly when community pharmacists personally advocated for flu vaccination, with a difference of only 8.7% in uptake (95% CI = 2.2-15.2%) [3].				
Thomas et al., 2010 [2] Primary studies per country: US (25), Canada (7), Australia (4), UK (4), Denmark, Spain, Puerto Rico and New Zealand, one each.	Cochrane Systematic Review ++ Sample: 44 RCTs (of which 18 were cluster-RCTs).Only 14 of them ain or after 2000. 33 RCTs were at high risk of bias and no recommendations for practice can be drawn from them. Sample: 44 RCTs	A. Increasing community demand: (a) Reminders to participants (Low grade) (b)Tailored reminders to Participants (Low grade) (c) Educating and vaccinating participants + offer of Vaccination (Very Low grade) (d) Health risk appraisal + offer of vaccination (Low grade)	10 RCTs; 30,377 (I); 162,609 (C). 3 of 10 RCTs showed positive effects. With entire 95% CI >1. 11 RCTs; 40,301; (I); 166,927 (C). 6 of 11 RCTs positive effects. With entire 95% CI >1. 2 RCTs; 293; (I); 321 (C). Pooled OR 3.29 (95% CI 1.91 to 5.66); P <0.0001 1 RCT; 1228; (I); 781 (C). OR 2.17 (95% CI 1.70 to 2.77); P <0.00001	The Cochrane review conducted by Thomas evaluated 44 studies, mainly published before 2000, with a large proportion at high risk of bias and at least half from the USA. There is ample low quality evidence that reminders work and limited and very low quality evidence that educating patients is effective.
		B. Increasing access: (a)Home visits (Moderate grade) (b)Free vaccine (Very low grade)	2 RCTs were pooled; 710; (I); 1402 (C). OR 1.30 (95% CI 1.05 to 1.61); P = 0.01* 2 RCTs; 1125; (I); 1126 (C).	Two of the four home visit interventions (both with 95% CI above unity), but one a small study. Heterogeneity.

Author and country of study	Design, quality grade, sample	Intervention and grade of evidence	Number of participants intervention (I) and control (C) and outcomes.	Results and final conclusion
		C. Provider- or system-based Interventions: (a)Reminders to Physicians (Moderate grade) (b)Facilitators working with practices (Moderate grade). (c) Education and feedback to physicians (Very low grade) (d) Financial incentives to physicians (Low grade)	4 RCTs; 979; (I); 2437 (C). 1 of 4 RCTs showed positive effect with entire 95% CI >1 4 RCTs; 95,987; (I); 90,272 (C). 3 of 4 RCTs showed positive effect with entire 95% CI >1 3 RCTs; 15,017; (I); 15,323 (C). Only 1 RCT had entire 95% CI above unity. 2 RCTs; 1559; (I); 1256 (C). Pooled OR 2.22 (95% CI 1.77 to 2.77); P <0.0001	Data could not be pooled, heterogeneity. Facilitators: Data could not be pooled, heterogeneity. Not clear if is not known whether facilitators working to increase vaccination uptake only would have higher vaccination uptake than those responsible for increasing several outcomes. Education and feedback: high risk of bias.
Usami, 2009 [3] Japan	Cluster RCT ++ N=84 community pharmacies recruited	Impact of community pharmacist advocacy on Flu vac uptake	911 (I) and 952 (C) Diff in uptake 8.7% (95%CI=2.2-15.2%)	Old study, well conducted. Depended on elderly who visited a pharmacy, not home bound. Showed increase uptake using personal advocacy by a community pharmacist.

** Plus two studies were not pooled due to heterogeneity of the interventions (first, OR 8.15 (95% CI 3.28 to 20.*

29); P <0.00001 and second: OR 0.98 (95% CI 0.64 to 1.50), P = 0.92;

Seven studies, mainly large cross-sectional surveys (Table 3), offered some lower quality evidence. A case control study conducted by Onder in 2011[4], suggests that having a case manager and interdisciplinary team makes it more likely that patients will receive seasonal flu vaccination, OR: 2.08 (1.81–2.39).

Low grade to moderate evidence from a large Italian study [7] and a combined Ireland and Northern Ireland [6] study suggests that being 85 or older increases the likelihood of getting vaccinated. Suffering from severe chronic disease is also a strongest determinant according to the Italian survey. The Italian survey also suggests that social support significantly increases the odds of influenza vaccine use. In the all-Ireland study, being married and greater usage of hospital and community services also increase vaccine uptake. Low grade to moderate evidence from a large Spanish study suggests that lowering age limit might increase vaccination coverage in all groups [8]. Another large sample cross sectional survey in Italy highlights social disadvantages and being a smoker as important determinants of low uptake of flu vaccine [9].

Table 3. Evidence table: barriers and facilitators for increased flu seasonal vaccination coverage in the elderly population

Author and country of study	Design, quality grade, sample	Intervention	Number of participants intervention (I) and control (C) and outcomes	Results and final conclusion
Evidence statement 2: There is moderate evidence from one case control study involving 11 European countries suggesting that having a case manager in an interdisciplinary team might be a facilitator for higher uptake of flu vaccine in elderly people [4]. The same finding is repeated in a recent cross sectional survey in 795 UK General Practitioner clinics [5]. Low grade to moderate evidence from a large Italian study and a combined Ireland and Northern Ireland study suggests that being 85 or older increases the likelihood of getting the vaccine [6]. Suffering from severe chronic disease is also a strong determinant according to the Italian survey. The Italian survey also suggests that good social support significantly increases the odds of influenza vaccine use [7]. In the Ireland and Northern Ireland study, being married and greater use of hospital and community services also increase vaccine uptake. Low grade to moderate evidence from a large Spanish study suggests that lowering age limit might increase vaccination coverage in all groups [8]. Moderate evidence from an Italian national survey shows that social disadvantages and being a smoker might predict low uptake of flu vaccine [9].				
Onder, 2008 [4] 11 different European countries	Case control, + N=4007 elders	Case Management and preventive strategies like flu vaccination	1539 (I) and 2468 (C) OR: 2.08 (1.81–2.39)	Integrated community care programme implemented by an interdisciplinary team including a case manager associated with higher rate of use of preventive strategies including flu vaccination.
Chiatti, 2011 [7] Italy	Cross sectional, + n=25,183	Socioeconomic determinants in older adults (Health and use of health care in Italy National Survey)	Strongest determinants: Being over 85-year old (OR = 1.99; 95% CI 1.77 - 2.21) Suffering from a severe chronic disease (OR = 2.06; 95% CI 1.90 - 2.24)	Italian cross sectional survey with large representative sample. Being 85 or older and suffering from severe chronic disease are the strongest determinants. Also, relying on neighbours' support or on privately paid home help is associated with a higher likelihood of vaccine uptake. Suggests also that being unmarried and living in larger households are barriers.
Jimenez-Garcia, 2012, [8] Spain	Two consecutive cross sectional surveys, + First sample: 7,496 Second:7,686	Lowering age limit for flu vaccine to ≥60 years increase coverage rate	Increase of coverage rate in individuals with chronic conditions: 60-64 (IRR 1.18; 95% CI,1.01—1.54) ≥ 65 (IRR 1.07; 95% CI,1.0—1.14)	Multivariate analysis showed that regions that lowered age limit increased vaccination rates for all age groups, but especially for those 60 or plus with chronic conditions. No significant changes were detected in regions that did not lower the age limit.
Crawford, 2011 [6] Ireland and Northern Ireland	Survey, + N= 2,033	Effect of patient characteristics upon uptake of the influenza vaccination	OR older age 1.6, (95% CI 1.3–2.1)	Both countries with high vaccination rates (Northern Ireland 78% and Ireland 72%). Higher rates of vaccination were found among older people, those who were married and those who made greater use of hospital and community services.
Blank, 2009b [23] UK, Germany, Italy, France, Spain, Austria, Czech Republic, Finland, Ireland, Poland and Portugal	Cross sectional survey, + N= 2000/country	Representative survey during the two consecutive influenza seasons: 2006/07 and 2007/08.	OR older age 1.6, (95% CI 1.3–2.1)	Coverage rates in elderly varied from 13.9% (95% CI 6.9, 20.9%) in Poland, the highest in the UK (70.2, 95% CI 65.2e76.2%). Higher rates of vaccination were found among older people. Elderly with chronic conditions achieved higher rates in all countries.
Dexter, 2012 [5] UK	Cross sectional survey + N= 795 GP practices	Survey to identify practices strategies associated with high flu vaccination rates	OR 1.45, (95% CI 1.10–1.92)	Representative sample although response rate 27.5%. Coverage rates in increase 7% when strategies are implemented. Lead member planning flu campaign, producing performance report, sending personal invitation letter and only stopping vaccination when targets are reached. Having a member of staff identifying eligible patients independently predicted higher rates in this group.

Author and country of study	Design, quality grade, sample	Intervention	Number of participants intervention (I) and control (C) and outcomes	Results and final conclusion
La Torre, 2010 [9] Italy	Cross sectional national health survey, + N= 128,040	Social inequalities determining vaccine uptake	Multivariate analysis of socioeconomic determinants.	Representative Italian national sample. High coverage rates in the elderly (62.5%). Socio-economic disadvantages lower the OR for vaccine uptake. Area of residence was significantly associated with uptake, the island the lowest and the North east region the highest. Smokers were found to have much lower ORs for vaccine uptake

People with chronic conditions

For this group, three RCTs (Table 4) evaluating interventions in patients with asthma were selected. An Italian study evaluated different types of reminder calls and vaccine uptake in asthmatic children, showing a positive effect of reminder calls, especially if made by the doctor who normally cares for that child [10]. Moderate evidence from the USA suggests that postcard reminders might not be very effective in increasing uptake in asthmatic patients [11]. A second American study, also with children suffering from asthma, shows only modest effects using electronic health reminder alerts to physicians [12].

Table 4. Evidence table: interventions to increase flu seasonal vaccination coverage in individuals suffering from chronic conditions

Author and country of study	Design, quality grade, sample	Intervention and grade of evidence	Number of participants intervention (I) and control (C) and outcomes.	Results and final conclusion
Evidence statement 3: Low grade evidence from Esposito [10] that reminder/recall systems seem to increase influenza vaccination in asthmatic children (rates increased from at least 10% to a maximum of 21% in all groups). Receiving a reminder from paediatrician from the clinic and getting the vaccine in the same clinic increased the rates from 40 to 61.1% with RR=1.26 (1.01-1.58). However, the increase in uptake reaches less than 62%. Moderate evidence from USA that added educational messages included with reminders might not increase uptake in patients with asthma [11]. Although previous studies with chronically ill children have shown the effectiveness of electronic health reminders alerts in improving vaccine, moderate evidence from USA shows only a modest non-significant improvement [12] with small (3.4%) increase in uptake (95%CI: -1.4% to 9.1%). Results might not be directly transferable to the European context.				
Esposito, 2009 [10] Italy	RCT, + N=285	Reminder calls: Group 1 (unrelated paediatrician and vaccine in another clinic) Group 2 (paediatrician from clinic, vaccine in another clinic): Group 3 (paediatrician from clinic, vaccine in same clinic)	75 (I) and 33 (C) All three groups had significant increase in uptake from one year to another. Group 1 (35.5% to 49.5%) baseline = *1* RR Group 2 (38.1% to 49.5%) *1.02* (0.80–1.30) RR Group 3 (40.0% to 61.1%) *1.26* (1.01–1.58)	Small study, referral centre in a rich part of Italy, fairly rigorous. Reminder/recall systems seem to increase influenza vaccination in asthmatic children (in all groups studied during the two years). The reminder call was significantly more effective when made by a paediatrician who usually takes care of the child and the vaccine is administered at the same clinic.
Walter, 2008 [11] USA	RCT, + n=8912 first year n=8355 next year	Interventions: 1:Postcard Reminder 2:Postcard Reminder plus Message	Approximately half received 1 half 2. Uptake increase: -Intervention sites 4.5%(SD 3.2%) -Non intervention sites: 4.0% (SD4.5%) P=0.55	Asthma patients, both children and adults. Low coverage rates for two years. Non-significant small increase. Type of postcard reminder used remained non-significant as a predictor of vaccination.
Fiks, 2008 [12] USA	RCT, + Baseline year: 10.667 Study year: 11.919	Electronic health reminders alerts to physicians	Baseline year: 5338(C) 5329(I) Intervention year: 5809(C) 6110(I) Increase in uptake 4.0% (95%CI: -1.3% to 9.1%)	Modest and non-significance increase in uptake. Only 65% of children with asthma who were seen for any reason at a study site during the previous year had 1 sick or well visit during the study year influenza season (eligible). They were mainly males, had received influenza vaccine previously, and had private insurance.

We selected three studies (Table 5) looking at barriers and other facilitators for vaccine uptake in this population. One, a convenience survey conducted during a RCT with asthmatic patients, suggests that misperceptions about vaccine safety and fear of side effects might be important barriers [11]. The other study, a UK-based cross-sectional survey looking at strategies used by GP practices to increase their vaccine uptake, found higher uptake in high-risk individuals (younger than 65) when a lead practice member planned the flu campaign and a written performance report is produced [5]. Lastly, in a large European survey (moderate grade evidence) undertaken in five European countries, being older and being older with a chronic condition is a determinant of vaccine uptake [35].

Table 5. Evidence table: barriers and facilitators for increased flu seasonal vaccination coverage in individuals suffering from chronic conditions

Author and country of study	Design, quality grade, sample	Intervention	Number of participants intervention (I) and control (C) and outcomes.	Results and final conclusion
Evidence statement 4: Evidence from the USA shows that misperceptions about the vaccine might be a barrier to receive vaccination in this population. Perception that vaccine can actually cause the flu (adults: 48%; children 39%), and also concerns about side-effects might be barrier for vaccination [11]. Large, one season only, UK general Practice cross sectional survey suggests a significant coverage increase of 8% in high risk patients under 65 when a lead member is planning the flu campaign and when a written performance report is produced (very low grade) [5].				
Walter, 2008 [11] USA	convenience sample survey within RCT, +	Asthmatic patients and reasons for not getting the vaccine	4 440(I); 3 752(C); 4 154(I); 4 201(C);	Low coverage rates in both seasons. Administrative databases underestimated vaccine coverage if people received it outside their primary care provider. Coverage higher in whites compared to blacks and non-whites. Also, those with no medical insurance and younger than 65 had lower coverage. Decline of vaccine uptake during adolescence. Perception that vaccine causes the flu as cause for not getting vaccine (adults: 48%; children 39%), and also concerns about side-effects.
Dexter, 2012 [5] UK	Cross sectional, + survey, N= 795 GP practices	Survey to identify practices strategies associated with high flu vaccination rates	OR 1.37, (95% CI 1.10–1.71)	Only one season evaluated; 8% higher coverage rates in risk patients under 65 when strategies are implemented. Lead member planning flu campaign, producing written performance report.
Blank, 2009 [35] UK, Germany, Italy, France, and Spain.	Cross sectional, + N= 2000 interviews/country (high 58% response rates)	Household survey, 5 countries for seven influenza seasons, from 2001/2002 to 2007/2008.	Being elderly and suffering from a chronic medical condition were powerful predictors for getting vaccinated in all five countries. No pooled OR presented.	Across all five countries, vaccination rates in the predefined target groups decreased to some extent (elderly) or increased slightly (chronically ill and health care workers). The barriers and drivers are presented for the whole adult population interviewed, not per target group (see under Adult population studies).

Healthcare workers

Our search identified a systematic review from 2010 and RCTs published thereafter. Only 12 studies met inclusion criteria for the systematic review [13] and none of these reported increased rates above the 90% recommended threshold for HCW vaccination rates. Relatively few studies met inclusion criteria which meant pooling data was impractical. There was also a limited number of studies combining interventions (e.g. an education programme alongside new regulations pertaining to vaccination). Among excluded studies, the authors of the systematic review note a propensity toward cross-sectional or uncontrolled before and after studies.

In addition to the systematic review, we identified three good quality intervention studies.

Rothan-Tondeur et al [36] describes Programme 1 of the VESTA cluster RCT study of HCW vaccination rates in France. Earlier results from this cluster RCT [37] are included in Lam's review [13]. The intervention was an educational programme that aimed to reduce fears and appeal to altruism to persuade HCWs to be vaccinated. Although vaccination rates increased overall, there was no significant difference between the rates in the intervention and control groups.

In the 2011 article, Rothan-Tondeur describes a two-step intervention [14]. Programme one, which is primarily education, failed to increase vaccination rates (as reported above). Programme two, instituted one year later, focused on education and a 'personal satisfaction' component designed to promote self-protection. Programme two showed a statistically significant increase in vaccination rates among the intervention group from 31% to 44%. But the authors note that there are a number of flaws in the study design: it has not demonstrated long-term efficacy; there appears to be potential for contamination as well as a Hawthorne effect or unmeasured variables as vaccination rates improved in control as well as intervention clusters.

Chapman et al [15] provide a brief summary of a small RCT undertaken at Rutgers Medical School which tested opt-out versus opt-in as a means of increasing HCW vaccination rates. Four hundred and eighty staff received an email with a date and time for vaccination and 45% of HCW who were asked to opt-out received the vaccination, and 33% of those who were asked to opt-in received the vaccination.

Table 6. Evidence table: interventions to increase flu seasonal vaccination coverage among healthcare workers

Author and country of study	Design, quality grade, sample	Intervention and grade of evidence	Number of participants, intervention (I) and control (C) and outcomes.	Results and final conclusion
Evidence statement 5: The systematic review identified five types of intervention: education or promotion; improved access to vaccine; legislation or regulation; measurement or feedback; role models. There is mixed evidence about the success of these interventions. Main findings are as follows: • In non-hospital settings, campaigns with more components, specifically education/promotion and improved access to vaccine, had higher impact with risk ratios > 1. In one of them, the coverage was highest when each worker had a personal interview with a member of the study team, with an average risk ratio of being vaccinated in the intervention group of 2.16 (1.96-2.43). Two other 2 RCTs found an even higher positive effects when adding role models to education and improved access , with average risk ratios of 7.06 (5.67-8.78) and 8.05 (6.30-10.30), but the vaccine uptake in the intervention group was below 40%. • In hospital settings, education/promotion and improved access to vaccine were the most common interventions but never raised vaccination rates above 90% • Small studies which rely on mandatory compliance indicate vaccination rates can be increased above 90% [13]. The other intervention RCTs published since the systematic review [14 15] are broadly in line with review findings as they show little evidence that interventions such as education or promotion, improved access to vaccine, measurement or feedback, role models are on their own effective measures to reach 90% vaccination among HCWs.				

Author and country of study	Design, quality grade, sample	Intervention and grade of evidence	Number of participants, intervention (I) and control (C) and outcomes.	Results and final conclusion
Lam et al., 2010 [13] Canada (Studies conducted in the USA, Canada, the United Kingdom, Germany and France.)	Cochrane Systematic Review ++ Sample: 12 studies included, 6 C-RCTs, 4 before and after studies, 2 interrupted time series Authors note that there are many potential biases due to study design, notably a lack of baseline characteristics of study groups There was considerable heterogeneity which means recommendations cannot be generalised.	A. Education or promotion	C-RCTs: 2,046 (I), 3,276 (C); 2/3 effective RCTs: 850 (I), 846 (C); 1/5 effective Before-after: 12,937 (I), 2,628 (C); 2/3 effective	There is little evidence that education and promotion is effective. The intervention appears to be marginally more successful in non-hospital settings (2/3 studies) In hospitals there is conflicting evidence: five studies show no effect while three (two before and after and one small RCT) show an improvement in HCW vaccination rates.
		B. Improved access to vaccine	C-RCT: 832 (I), 1,517 (C); 1/1 effective Before-after: 3,349 (I), 1,659 (C); ½ effective	One non-hospital study and one of two hospital studies suggest improved access is an effective intervention.
		C. Legislation or regulation;		No studies eligible
		D. Measurement or feedback		No studies eligible
		E. Role models		No studies eligible
		Combined interventions		
		F. Education and improved access to vaccine	C-RCT: 1 743 (I), 2 532 (C); 2/2 effective Before-after: 10 086 (I), 6 214 (C); ¾ effective In one of them, 68.5% uptake compared to 31.7% (RR 2.16 (1.96-2.39))	Five (2 C-RCTs and 3 before and after) of six studies show this combination is an effective intervention. RRs range from 1.20 in the biggest study to 2.43 in the smallest.
		G. Education and access and legislation and role model	CRCT: 3 336 (I), 3 440 (C); 2/2 effective Year 1: RR 7.06 (5.57-8.78) to 10.30 Year 2: RR 8.05(6.30-10.30)	Two C-RCTs report RRs of 7.06 and 8.05 but vaccination rates were still below 50% in the intervention group.
		H. Improved access and measurement/feedback	Before-after: 195 (I), 176 (C); 0/1 effective	One before and after suggest this was not an effective intervention: RR of 0.94.
Rothan-Tondeur et al [14], 2011 France	Cluster RCT, - N=1 814 HCW in 20 interventional group and 2 435 HCW in 23 control group	VESTA Cluster RCT study of HCW vaccination	1 814 (I) and 2 435 (C) They show a positive effect from a combined education and improved access intervention.	Earlier results from this cluster RCT are included in Lam's review.[13] This study showed an increase in vaccination rates among the intervention group from 31% to 44%. The intervention was an educational programme that aimed to reduce fears and appeal to personal satisfaction to persuade HCWs to be vaccinated.
Chapman et al [15], 2010 USA	RCT, + N=480 HCW	Opt-out of vaccination	45% of HCW who were asked to opt-out received the vaccination. 33% of HCW who were asked to opt-in received the vaccination	Opting out appears to be a more effective vaccination approach than opting in. Overall vaccination rates are still low.

Two observational studies reported on the introduction of mandatory vaccination programmes. Rakita et al [16] report on the introduction of mandatory flu vaccination at the Virginia Mason Medical Centre in Seattle, Washington where vaccination has been mandatory since 2005–06 (in 2003–04, the rate was 54% and 2004–05, it was 29.5%, the lower rate perhaps attributable to vaccine supply shortages). Education, role models and increasing access/provision are part of the intervention. In all five years since mandatory vaccination was implemented, vaccination rates have been 97.5% or higher. There were 4 588 staff accounted for in year one and 4 967 in year five. It is not reported how vaccination status was recorded. The study notes that the intervention is time and resource intensive but that costs reduce after the second year.

Quan et al [17] report on five years of intervention at the University of California Irvine healthcare system. In years one to three, increased access/provision of vaccines and employee declination policies were introduced. Vaccination rate peaked at 62.9% in year two. In year four, mandatory vaccination was introduced as was a measurement/feedback component. In year five, more measurement and feedback was introduced. All vaccinated staff received a plastic coloured tag which is attached to their identity badge to signal compliance. Non-compliance is recorded on declination forms. Year four vaccination rates were 86.7%, year five vaccination rates were 91.2%. Staff numbers ranged from 6 414 to 6 734 over the five years.

Table 7. Evidence table: barriers and facilitators of increased flu seasonal vaccination coverage among healthcare workers

Author and country of study	Design, quality grade, sample	Intervention and grade of evidence	Number of participants, intervention (I) and control (C) and outcomes.	Results and final conclusion
Evidence statement 6: Evidence from two observational studies suggests mandatory vaccine policies are more successful to improve rates of vaccination above 95% [16 17]. But there are ethical and legal obstacles associated with mandatory programmes.				
Rakita, 2010 [16] USA	Before and after using Cross sectional surveys. – N=588 staff (in year one) and 4 967 (year five)	Mandatory vaccination program	In five years, vaccination rates have been 97.5% or higher.	In five years, vaccination rates have been 97.5% or higher. In 2003-04, the rate was 54% and 2004-05, it was 29.5% (perhaps attributable to vaccine supply shortages). It is not reported how vaccination status was recorded. The study notes that the intervention is time and resource intensive but that costs reduce after the second year.
Quan et al [17] USA	Series of cross sectional surveys and a study on attitudes and beliefs N=6 414 to 6 734 (range during the 5 years)	2006–2011 influenza seasons. Serial campaigns that include a mandatory HCP vaccination policy	62.9%, in year two 86.7%, year four 91.2%, year five	Vaccination rate peaked at 62.9% in year two. In year four, mandatory vaccination was introduced as was a measurement/feedback component. In year five, more measurement and feedback was introduced. Non-compliance is recorded on declination forms. Year four vaccination rates were 86.7%, year five vaccination rates were 91.2%.

Pregnant women

Our search for relevant studies addressing pregnant women and vaccination in children resulted in no RCTs or systematic reviews. However, we identified a number of cross-sectional studies (Table 6) and audits of patient data that may offer some ideas for future researchers. It is notable that many of these interventions focus directly on healthcare workers to influence pregnant women. None of the studies included were European.

Cross-sectional studies provide some indicators for future research although these surveys all contain potential for recall/respondent bias. Potential barriers to vaccination include:

- concern about risk to unborn baby
- concern about risk to self
- concern about safety and efficacy of vaccines
- lack of availability of vaccine
- lack of or inconsistent advice/offer from healthcare professional

There is weak evidence from cross-sectional studies and audits of clinical data about barriers to vaccination. Efficacy and availability of vaccine, personal safety and safety of unborn child are most commonly cited as barriers [21 38]. Interventions focus on healthcare workers to improve their knowledge of current practice and guidelines and also to increase their provision of vaccine. Interventions focus on pregnant women to increase their knowledge and understanding. Panda et al, Mouzoon et al and McCarthy et al included an educational intervention focused on healthcare workers in their studies [18 20 21].

Panda performed a physician education programme based on materials suggested by doctors the previous year. Their patient responses recorded more availability of vaccines (32.1% to 55%) from doctors and more vaccines offered by their doctor (28% to 51.1%) [20]. This study is weakened by lack of attribution and recall bias. Mouzoon and colleagues studied an intervention that included role models, education and training for healthcare workers as well as introduction of standing orders for immunisation. Although they report increases in patient vaccination rates, they do not present data which allows assessment of the healthcare worker initiatives [18]. McCarthy reported on an educational programme for healthcare workers. Their cross sectional study showed that some barriers to vaccination of pregnant women may be modifiable. Risk to baby, risk to self and lack of vaccine availability were the main barriers in their 2010 survey. Each of these reasons featured less often in barriers mentioned in the 2011 survey [21].

Table 8. Evidence table: barriers and facilitators of increased flu seasonal vaccination coverage among pregnant women

Author and country of study	Design, quality grade, sample	Intervention and grade of evidence	Number of participants intervention (I) and control (C) and outcomes.	Results and final conclusion
Evidence statement 7: We identified no high quality RCTs or systematic reviews that investigated interventions for increasing uptake of flu vaccination among pregnant women. Most studies captured by our search were cross-sectional. Very low grade evidence from a cross sectional study suggests that standing orders, role models, and HCW education might improve rates of coverage [18]. Very low grade evidence suggests the usefulness of electronic reminders to providers increase uptake [19] and of provider education [20]. Very low grade evidence suggests that inconsistent advice from health care providers might pose a barrier to vaccine uptake in this population [21].				
Mouzoon et al, 2010 [18] USA	Retrospective audit of clinical records, - N=20 233 records retrieved	Role model ("Vaccination Champions"), Education and training for physicians and nurses, Standing Orders 2003-2004 through 2008-2009	Vaccination levels increased from 2.5% to a high point of 46.5% in 2007-2008, dropping to 37.4% in 2008-2009.	It is hard to identify which aspects of this intervention were particularly effective but authors report significant improvements in uptake. Authors note higher rates of vaccination among women in trimesters two and three. Authors suggest that drop may be attributable to clinic closures associated with Hurricane Ike which lasted up to three weeks
Riley et al, 2011 [19] USA	Before and after cross-sectional, - N=varied during baseline, intervention and post intervention (144, 115 and 169)	Do electronic clinical reminders improve vaccination rates for pregnant women?	Pre intervention: 144/66% uptake Intervention 1: 115/79% uptake Intervention 2: 169/84% uptake	This study looked at records of all patients seen by two doctors. It shows increased vaccinations rates. There is no control and no indication of the extent to which patients were representative
McCarthy et al, 2012 [21] Australia	Repeat cross-section, - N=212 (2010) N=240 (2011)	Staff education Patient information	2010: 212/30% uptake 2011: 240/40% uptake	This study took a baseline and repeat survey one year later after a staff education programme and introduction of patient leaflets. There is no way of attributing causality. No control was used.
Panda et al, 2011 [20] USA	Repeat cross-section, **-** N=520 (2007-08) N=480 (2008-09)	Staff education and information Increased availability of vaccine	2007-2008: 19% were vaccinated & 28% reported staff offered the vaccine 2008-2009: 31% uptake and 51% reported staff offered.	No control.

Children

There are no RCTs or systematic reviews on interventions to increase vaccination rates among children. Few studies collect data from children. Instead most studies ask about parents' attitudes and intentions; as these types of questions are not interventions, observational studies can provide worthwhile information.

Table 9. Evidence table: barriers and facilitators of increased flu seasonal vaccination coverage among children

Author and country of study	Design, quality grade, sample	Intervention and grade of evidence	Number of participants intervention (I) and control (C) and outcomes.	Results and final conclusion
Flood et al, 2010 [32] USA	Web survey based on stratified group from representative sample of American parents -	Parents' decision-making	500 participants. Authors stratify results according to parents' intention to get child vaccination and parents' own vaccination behaviours. Parents are high likelihood, medium likelihood, low likelihood.	Parental perception that influenza represents a major threat to their children was an indicator that they intended to vaccinate and vice-versa. Authors suggest that parents classified as medium likelihood may be worth targeting to increase vaccination rates. There was a correlation of 0.63 (Pearson) between parental intention and previous child vaccination. Drivers for vaccination: • prevention of influenza • physicians' recommendation • reduced influenza symptoms Parents who report low likelihood of vaccinating children generally perceive risk of disease to be lower and express most concerns about safety and effectiveness of vaccine. Barriers to vaccination: • Flu vaccine containing thiomersal
Flood et al, 2011 [33] USA	Web survey based on stratified group from representative sample of American parents	Parents' preferences regarding vaccine attributes	500 participants	The most common reason for choosing vaccines is perception of efficacy and safety (presence of thiomersal)
Brown et al, 2010 [34] UK	Web survey of convenience sample of parents, -	Parents' attitudes about risks of vaccination	142 participants	Participants would accept a higher risk of their child catching a disease than they would of their child reacting to a vaccine, would consider a number of symptoms/signs as less serious if they were caused by a disease than if they were caused by a vaccine reaction. They would regard as acceptable a longer duration of symptoms/signs as a consequence of disease than as a consequence of vaccine reaction. It follows that vaccine reactions which objectively appear less unpleasant than or equally unpleasant to disease outcomes may be perceived by parents to be sufficient to warrant vaccine refusal.

Adult population studies

We included evidence from studies focusing on barriers and facilitators in a wider population than our targeted ones.

One RCT in the USA shows that electronic reminders to patients might help improve flu vaccination rates in adults [22]. The study population was mainly white and access and use of a computer and internet was a prerequisite. Blank published two reports in 2009 on predictors of vaccination in Europe. Both of these publications have some duplicated data.

One study reports on data from 11 European countries during two seasons and highlights differences in coverage across Europe. It shows higher vaccination rates in higher income countries compared to lower income ones. It suggests that a major driving factor for getting vaccinated might be awareness that influenza is a serious illness as well as the advice from a family doctor. Also, the desire not to transmit influenza to a family members or friends seems to be a driver. For barriers, people responded they did not feel likely to catch influenza or that they had never considered vaccination before. Lack of access to free vaccination might also be a barrier [23].

The second study reports on five European countries for seven influenza seasons, (from 2001/2002 to 2007/2008) and finds very similar results, confirming the bigger sample study [35]. The findings from both studies confirm previously published European evidence (not included in this review since it was published before 2008).

Table 10. Barriers and facilitators to increased flu vaccination uptake in adults, in general

Author and country of study	Design/ Quality grade of evidence, sample size	Intervention	Number of participants intervention (I) and control (C) and outcomes.	Results and final conclusion
Evidence statement 9: Low grade evidence from the USA shows that electronic reminders might help improving flu vaccination rates in adults if they can access the internet and use it regularly [22]. In one survey (low grade evidence) carried in 11 European countries being older and being older with a chronic condition is a determinant of vaccine uptake. Countries with high per capita income have significantly higher rates of coverage in adults. Awareness that influenza is a serious illness, advice from a family doctor (8/11) and the wish not to transmit influenza to family members and friends seems to facilitate uptake. Adults who did not feel likely to catch influenza or that they had never considered vaccination before were less likely to be vaccinated as well. Also, having to pay for vaccines might be a barrier, especially in poorer countries [23].				
Wright, 2012 [22] USA	Cluster RCT, + N=815	Health Maintenance Electronic Reminders:	396 (I); 460 (C); Odd Ratio: 1.83, p=0.023	No report on our target groups, just adults as a whole. Health Maintenance reminders, when provided directly to patients via a secure electronic connected personal health journal, improved the rates of flu vaccinations in adults. Patients were mainly white and had health insurance. Not many of the eligible population would have access to and use to internet.
Blank, 2009 [23] UK, Germany, Italy, France, Spain, Austria, Czech Republic, Finland, Ireland, Poland and Portugal.	Cross sectional survey, + N≅ 2000 representative adults per country (mainly older than 15)	None Survey during two seasons, during seasons 2006/07 and 2007/08.	Coverage (2007/08): General pop, range from 9.5% to 28.7% ; Countries with low per capita national income versus high (17.7% and 22.3%)	High coverage in high income countries and lower in lower income countries. The financing of the vaccine was named as an important problem in the group of poorer countries. Awareness that influenza is a serious illness was mentioned in all eleven countries as a major driving factor. Other important reasons for getting vaccinated were the advice from a family doctor (8/11) and the wish not to transmit influenza to family members and friends (7/11). For barriers, people responded they did not feel likely to catch influenza (10/11) or that they had never considered vaccination before.
Blank, 2009 [35] UK, Germany, Italy, France, and Spain.	Cross sectional, + N= 2 000 interviews/country (high 58% response rates)	Household survey, 5 countries for seven influenza seasons, from 2001/2002 to 2007/2008	Being elderly and suffering from a chronic medical condition were powerful predictors for getting vaccinated in all five countries. No pooled OR presented.	The most powerful motivation for getting vaccinated in all countries was advice from a family doctor (58.6%) and the perception of influenza as a serious illness (51.9%). The major reasons why individuals did not become vaccinated were (1) the feeling of not being likely to catch influenza (39.5%) and (2) never having considered the option of being vaccinated (35.8%).

Discussion

Elderly people

The Cochrane systematic review published by Thomas in 2010 was the main piece of evidence used to derive the evidence statements for this group [2]. This high quality review evaluated 44 RCTs, only 14 of which were published after 2000. More than half of the RCTs were conducted in the USA. Therefore, caution should be taken when deriving recommendations based on this review to the current European context. This review has not included studies published during or after the 2009 pandemic. From our reading of current literature, it is not clear how the pandemic has affected perception, attitudes and beliefs in different contexts towards seasonal vaccination and further research is still needed to assess that.

Although the findings from the cluster RCT conducted in Japan, which showed an increase of 8.7% in uptake when community pharmacists personally advocated for vaccines, are encouraging [3], they are unlikely to be completely transferable to the European context. Moreover, all the participants in the trial had to be able to attend a community pharmacy, and therefore these findings have low applicability to the very ill or home-bound elderly population. The role of cultural and socio economic determinants in this Japanese elderly population should not be underestimated when deriving recommendations to the European context.

The findings of the several observational studies looking at barriers and facilitators for flu vaccine uptake in the elderly European population should also be taken with caution since they are limited by their design. Further research looking into the highlighted socioeconomic determinants among elderly people is, however, warranted. Socioeconomic characteristics of different European countries and regions, cultural differences and differing national health systems are likely to have an impact on vaccination rates and the transferability of research findings from one setting to another. These aspects should be taken into account when recommendations and new policies are being developed. It is also important to remember that countries of the EU/EEA that have already achieved high coverage rates for elderly people and any further improvements in coverage in this case might prove more challenging.

An RCT focused on older African Americans using vaccine safety messages demonstrated some effectiveness in changing vaccine beliefs [39]. However, this study only analysed intention to get vaccinated and might not be transferable to the European context.

A cross-sectional survey of 795 GP practices in England [5] suggests that clear leadership and performance measures are effective in increasing uptake in the elderly and other eligible patients. This study had a large sample but a low response rate of self-reported questionnaires.

Chronic conditions

We found four RCTs of moderate quality which looked at interventions in this group. One, in Italy, showed a positive and quite important effect of reminder calls for asthmatic children [10]. It is not clear how applicable these results are to the rest of Europe and how costly this may be. Also, although there is wider literature in reminder calls, the applicability to this setting requires further research. It might also prove logistically difficult to designate the same doctor to follow the child, to call the parents and then give the vaccine, since this was the most effective intervention in the Italian study in asthmatic children [10], with vaccine uptake going from 40 to 61.1% (with RR=1.26 (1.01–1.58)).

Another RCT in the USA, again in children with asthma, showed only modest effects using electronic health reminders alerts to physicians [12]. In other populations, such as older people, reminders to physicians were considered ineffective as well [2].

There is ample evidence that the use of reminders targeting patients have a small, positive effect in increasing flu seasonal vaccination coverage in certain populations, such as older people [2]. However, an American RCT suggests that adding an educational message to postcard reminders might not be very effective in asthmatic patients (both children and adults) [11]. Unpublished data from the UK suggests that sending an invitation letter for the seasonal influenza vaccine to the under 65 year at risk groups might improve their uptake by 6.3% (95% CI: 3.1-9.5), by a modest, albeit statistically significant, increase [40].

It is plausible that interventions to increase the uptake among people with chronic conditions depend also on the type of chronic condition, the age and gender and socioeconomic status. Therefore, further research into this population, and the population with multiple morbidity [41] is still required.

Healthcare workers

For this population, our review retrieved a large number of studies, a systematic review of evidence [13] and some RCTs, including one in France [14 15]. There is ample evidence on some of the interventions used to increase vaccination rates in this population.

Although there is evidence that education or promotion, better access to vaccines, legislation or regulation and/or role models ('vaccine champion') were associated with significant positive effects, especially in non-hospital settings, the increases in vaccination coverage did not reach the recommended 90%. Due to heterogeneity, the systematic review was not able to pool data. The effect of pandemic influenza was not assessed either.

The findings of the two other RCTs published since the systematic review are broadly in line with review findings. There is a risk of bias in the French study as some organisations actively sought involvement in the study after it had started. Although these RCTs provide some evidence that interventions such as education or promotion, improved access to vaccine, measurement or feedback, and role models are effective, each one of these strategies on their own are unlikely to increase vaccination coverage above 90% in HCWs.

Other observational studies reported suggest that mandatory vaccine policies are more successful to improve rates of vaccination above 95%. However, the applicability of this evidence to the European context is not clear. Ethical and legal obstacles might be barriers to this kind of approach.

Pregnant women

After the emergence of the pandemic influenza A(H1N1) virus in 2009, concerns about the risk of influenza in pregnant women have increased. Vaccination could reduce the number of influenza-related hospitalisations and deaths in this group and the burden of the disease in children under six months [42]. Yet, levels of vaccination in this group remain low.

Unfortunately, our search for relevant studies addressing pregnant women and vaccination in children resulted in no RCTs or systematic reviews. This meant that we had to adjust our criteria so that we could provide some overview of research targeting these population groups. Petticrew and Roberts [43] and Ogilvie et al [44] have highlighted the potential limitations of relying on a traditional hierarchy of evidence when evaluating social interventions. These authors note that incorporating information from a wider range of study designs may provide suggestions for future research without committing reviewers to making unsustainable claims about evidence quality. Bambra [45] has suggested that producing a review that summarises 'best available evidence' for many public health interventions requires judgements about study quality and availability.

There are a number of methodological difficulties which limit the ability of researchers to study pregnant women's receptiveness and uptake of flu vaccine. Timing is a problem, as pregnancy lasts nine months and many flu vaccination programmes are seasonal lasting six to nine months. Depending on the timing of pregnancy, some pregnant women will be immunised in the spring and the autumn and other women will be missing immunisation activities altogether as a result of late prenatal care and delivery before vaccine programmes run in the autumn. Therefore women have different periods of 'exposure' when vaccination will be available to them. It is also difficult to recruit pregnant women prospectively without doing this through primary care or a formal population level advance 'consent for consent' process. It is possible to design randomised trials relating to increased uptake of vaccination among pregnant women but we have not been able to identify them within the timescale of this study.

The cross-sectional studies and variation of audits of patient data presented in the results section may offer some ideas for future research in this target group.

Children

Most studies addressing uptake of influenza vaccine among children ask about parents' attitudes and intentions; while these types of questions are not directly addressing interventions, good quality observational studies can provide worthwhile information. It is notable that few studies collect data from children. Although most children are too young to consent to immunisation, in some jurisdictions recommendations are for all children to receive a vaccination. Many teenagers are capable of informed consent and guidance reflects this.

Bhat-Schelbert et al [46] conducted focus groups with healthcare providers, parents, teenagers and marketing professionals investigating drivers and barriers to child influenza vaccination. Common barriers to vaccination include: lack of knowledge or misinformation about why they should receive a vaccination; a variety of reasons why the vaccine is unnecessary often premised on fears about vaccine safety and institutional coercion; and practical barriers such as the awkwardness of finding time within a working week to take a healthy child to receive a vaccination in a 9am to 5pm clinic. The groups suggested that health promotion, perceived benefit and trust, better information, and logistical facilitators were likely to increase the rates of vaccination.

One of the studies we selected conducted 28 interviews with 6–12 year olds to gauge their knowledge about and attitudes towards flu vaccination and also to gauge their perceptions of risk in relation to flu [47]. Overall, most children said that flu vaccination was a good thing. Some of the children expressed a preference for nasal spray vaccination delivery. While knowledge about flu and vaccines was related to age, those aged eight and older were more likely to identify potential side-effects such as fever, runny noses, tiredness or headaches.

It should be noted that many of the barriers to vaccination suggested in these studies are similar to those highlighted by Mills et al in their systematic review of qualitative studies investigating parental beliefs about vaccination in general:

> We identified that parents, in many of the studies, held beliefs that vaccines cause ill health. They expressed specific concerns about both the short- and long-term adverse effects associated with vaccination. Parents also expressed a substantial level of distrust of the medical community, and identified several problems with access that impeded vaccination. Many parents also reported poor communication with health care staff, unpleasant staff, and being unaware of the vaccination schedule [48].

Limitations

There are some limitations to our review. We covered a recent and restricted time period and may have missed some evidence published outside this period. We also restricted the language of publication to English and might have missed relevant evidence published in other languages, especially European ones. For example, very few eastern European articles were retrieved. Because of the short time limit for this review, we were not able to independently screen and appraise all pieces of evidence and that might have led to bias. Even considering that our level of agreement when a sizeable proportion of the evidence was independently assessed was good, the fact that the systematic screening of the grey literature and websites was limited means that we might have missed some unpublished relevant work.

Conclusions

The conclusions for each one of the high risk groups differ and are presented separately.

Elderly people

In this sub-population, there is insufficient evidence for some interventions; however, personalised postcards or phone calls are considered effective and home visits, and having facilitators, may be effective. Reminders to physicians are not effective. Good quality evidence from one RCT in Japan shows positive effects in the elderly when community pharmacists personally advocated for flu vaccination.

Other drivers and barriers are suggested by various observational studies conducted in Europe. Those elderly individuals who are older than 85, or are married, or use medical services more frequently or suffer from a chronic disease are more likely to get vaccinated. Having a case manager in an interdisciplinary team in a healthcare practice and lowering the age limit for vaccination might be effective in increasing vaccine uptake. Other barriers suggested are social disadvantage, smoking, and not having social support.

Chronic conditions

The conclusions for this sub-population depend to a certain extent on the nature of the chronic condition. Interventions like reminder/recall systems seem to increase influenza vaccination in asthmatic children. Added educational message with reminder alerts might not increase uptake in patients with asthma. Although previous studies with chronically ill children and other populations have shown the effectiveness of electronic health reminder alerts, a study selected from the USA showed only modest and non-significant effect in asthmatic children. Most of these results come from the USA and might not be directly transferable to the European context.

Other drivers and barriers explored by observational studies in this subpopulation suggest that misperceptions about the vaccine might be a barrier to receive vaccination. Beliefs like the perception that vaccination can actually cause the flu and also concerns about side-effects might play a role. Low grade evidence from the UK shows a modest, significant coverage increase (8%) in high risk patients under 65 when a lead staff member is planning the flu campaign and when a written performance report is produced.

Healthcare workers

There is plenty of evidence on interventions to improve uptake of vaccination in this group. One systematic review identified five types of intervention: education or promotion; improved access to vaccine; legislation or regulation; measurement or feedback; and role model. In non-hospital settings, campaigns with more components, specifically education/promotion and improved access to vaccine, had higher risk ratios and positive significant effects in vaccine uptake. In hospital settings, education/promotion and improved access to vaccine were the most common interventions but never raised vaccination rates above 90%. Other RCTs published since the systematic review are broadly in line with review findings in that they show little evidence that interventions such as education or promotion, improved access to vaccine; measurement or feedback, role models are on their own effective measures to reach 90% vaccination among HCWs.

Evidence from two observational studies from the USA suggests mandatory vaccine policies are more successful at increasing rates of vaccination above 95%.

Pregnant women

The evidence for this group is scarce and weak. We found no systematic reviews or RCTs investigating interventions.

Other drivers and barriers were explored in observational studies; very low grade evidence from cross sectional studies suggests that standing orders, role models, and HCW education might improve rates of coverage. Electronic reminders and education of providers might be useful. Also, inconsistent advice from healthcare providers might pose a barrier to vaccine uptake in this population.

Children

As for pregnant women, the evidence for this group is scarce and weak. We found no systematic reviews or RCTs investigating interventions.

There is low quality evidence from the USA. Most cross-sectional studies focused on parents' attitudes and views. Common reasons why parents choose to have children vaccinated include:

- prevention of influenza
- physicians' recommendation
- reduced influenza symptoms

Low quality evidence from two studies from the USA and one UK study provide some indicators for future research although these surveys all contain notable respondent bias. Potential reasons why parents may choose not to have children vaccinated include:

- low perception of risk of catching the disease
- concern about safety and efficacy of vaccines
- flu vaccine containing thiomersal

Adults

We also present some relevant evidence on adult population in general since not all studies focused specifically on our target groups. Very low grade evidence from a cluster RCT in the USA shows that electronic reminders might help improving flu vaccination rates in adults if they can access the internet and use it regularly.

As for drivers and barriers explored in observational studies, low grade evidence (survey) carried out in 11 European countries suggest that countries with high per capita income have significantly higher rates of coverage in adults. Awareness that influenza is a serious illness, advice from a family doctor and the wish not to transmit influenza to family members and friends seems to facilitate uptake. Adults who did not feel likely to catch influenza or that they had never considered vaccination before were less likely to be vaccinated as well. Also, having to pay for vaccines is a barrier, especially in poorer countries.

Differences between protocol and review

The main reasons for departure from the protocol were time and resource constraints.

We did not look at cost-effectiveness studies and our literature review did not retrieve many relevant papers. So, the key question 'What are the most effective and cost effective interventions already used by governments and healthcare organisations to identify risk groups and increase their uptake of vaccination? Under what circumstances and for which groups do they work best?' was not explored.

Our final list of articles covered studies published between 2008 and 2012 instead of 2002 and 2012. We did not include CINAHL in our electronic search, but all other databases are included.

We also did not systematically search organisational websites like the United States Centers for Disease Control (CDC) and WHO.

In the second step of the screening process, instead of two authors independently reviewing all 912 titles and abstracts selected, 10% of the articles were independently reviewed and the level of agreement between authors measured. There was excellent agreement (as mentioned before) and therefore no action was required.

Two members of the research team appraised and rated the included papers, where each full paper was initially appraised by one reviewer and checked by the second reviewer. However, given time and resources restriction, during the data appraisal process, we did not carry out independent assessment of a proportion of these papers. There were, however, frequent discussions amongst the review team about the data appraisal and quality assessment occurred during this step of the process.

References

1. Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 The Cochrane Collaboration, 2011.
2. Thomas RE, Russell ML, Lorenzetti DL. Systematic review of interventions to increase influenza vaccination rates of those 60 years and older. Vaccine 2010;28(7):1684–701.
3. Usami T, Hashiguchi M, Kouhara T, Ishii A, Nagata T, Mochizuki M. Impact of community pharmacists advocating immunization on influenza vaccination rates among the elderly. Yakugaku Zasshi - Journal of the Pharmaceutical Society of Japan 2009;129(9):1063–68.
4. Onder G, Liperoti R, Bernabei R, Landi F. Case management, preventive strategies, and caregiver attitudes among older adults in home care: results of the ADHOC study. Journal of the American Medical Directors Association 2008;9(5):337–41.
5. Dexter LJ, Teare MD, Dexter M, Siriwardena AN, Read RC. Strategies to increase influenza vaccination rates: outcomes of a nationwide cross-sectional survey of UK general practice. BMJ Open 2012;2(3).
6. Crawford VL, O'Hanlon A, McGee H. The effect of patient characteristics upon uptake of the influenza vaccination: a study comparing community-based older adults in two healthcare systems. Age & Ageing 2011;40(1):35–41.
7. Chiatti C, Barbadoro P, Lamura G, Pennacchietti L, Di Stanislao F, D'Errico MM, et al. Influenza vaccine uptake among community-dwelling Italian elderly: results from a large cross-sectional study. BMC Public Health 2011;11(Journal Article):207.
8. Jimenez-Garcia R, Hernndez-Barrera V, Rodriguez-Rieiro C, de Andres AL, Miguel-Diez J, Trujillo IJ, et al. Are age-based strategies effective in increasing influenza vaccination coverage?: the Spanish experience. Human vaccines & Immunotherapeutics 2012;8(2):228–33.
9. La Torre G, Iarocci G, Cadeddu C, Boccia A. Influence of sociodemographic inequalities and chronic conditions on influenza vaccination coverage in Italy: results from a survey in the general population. Public Health 2010;124(12):690–97.
10. Esposito S, Pelucchi C, Tel F, Chiarelli G, Sabatini C, Semino M, et al. Factors conditioning effectiveness of a reminder/recall system to improve influenza vaccination in asthmatic children. Vaccine 2009;27(5):633–35.
11. Walter EB, Hellkamp AS, Goldberg KC, Montgomery D, Patterson B, Dolor RJ. Improving influenza vaccine coverage among asthmatics: A practice-based research network study. Journal of Clinical Outcomes Management 2008;15(5):227–34.
12. Fiks AG, Hunter KF, Localio AR, Grundmeier RW, Bryant-Stephens T, Luberti AA, et al. Impact of electronic health record-based alerts on influenza vaccination for children with asthma. Pediatrics 2009;124(1):159–69.
13. Lam PP, Chambers LW, MacDougall DM, McCarthy AE. Seasonal influenza vaccination campaigns for health care personnel: systematic review. CMAJ Canadian Medical Association Journal 2010;182(12):E542–8.
14. Rothan-Tondeur M, Filali-Zegzouti Y, Golmard JL, De Wazieres B, Piette F, Carrat F, et al. Randomised active programs on healthcare workers' flu vaccination in geriatric health care settings in France: the VESTA study. Journal of Nutrition, Health & Aging 2011;15(2):126-32.
15. Chapman GB, Li M, Colby H, Yoon H. Opting in vs opting out of influenza vaccination. JAMA 2010;304(1):43-44.
16. Rakita RM, Hagar BA, Crome P, Lammert JK. Mandatory influenza vaccination of healthcare workers: a 5-year study. Infection Control & Hospital Epidemiology 2010;31(9):881-88.
17. Quan K, Tehrani DM, Dickey L, Spiritus E, Hizon D, Heck K, et al. Voluntary to mandatory: evolution of strategies and attitudes toward influenza vaccination of healthcare personnel. Infection Control & Hospital Epidemiology 2012;33(1):63–70.
18. Mouzoon ME, Munoz FM, Greisinger AJ, Brehm BJ, Wehmanen OA, Smith FA, et al. Improving influenza immunization in pregnant women and healthcare workers. American Journal of Managed Care 2010;16(3):209–16.
19. Riley M, Galang S, Green LA. The impact of clinical reminders on prenatal care. Family medicine 2011;43(8):560–65.
20. Panda B, Stiller R, Panda A. Influenza vaccination during pregnancy and factors for lacking compliance with current CDC guidelines. Journal of Maternal-Fetal & Neonatal Medicine 2011;24(3):402–06.
21. McCarthy EA, Pollock WE, Nolan T, Hay S, McDonald S. Improving influenza vaccination coverage in pregnancy in Melbourne 2010-2011. Australian & New Zealand Journal of Obstetrics & Gynaecology 2012;52(4):334–41.
22. Wright A, Poon EG, Wald J, Feblowitz J, Pang JE, Schnipper JL, et al. Randomized controlled trial of health maintenance reminders provided directly to patients through an electronic PHR. Journal of General Internal Medicine 2012;27(1):85–92.
23. Blank PR, Schwenkglenks M, Szucs TD. Vaccination coverage rates in eleven European countries during two consecutive influenza seasons. Journal of Infection 2009;58(6):446–58.

24. O'Flanagan D, Cotter S, Mereckiene J, Consortium. obotVI. Seasonal influenza vaccination in EU/EEA, influenza season 2010-11. Vaccine Europe New Integrated Collaboration Effort II, 2012.

25. WHO/Europe. WHO/Europe recommendations on influenza vaccination during the 2011-2012 winter season. . Copenhagen: WHO, 2011.

26. Cochrane EPOC (Effective Practice and Organisation of Care Group). MECIR (Methodological standards for the conduct of new Cochrane Intervention Reviews), 2012.

27. National Institute for Health and Clinical E. Methods for the development of NICE public health guidance. 2nd ed, 2009.

28. Beale SJ, Bending MW, Trueman P, Naidoo B. Should we invest in environmental interventions to encourage physical activity in England? An economic appraisal. The European Journal of Public Health 2012.

29. Jackson R, Ameratunga S, Broad J, Connor J, Lethaby A, Robb G, et al. The GATE frame: critical appraisal with pictures. Evid Based Med 2006;11(2):35–8.

30. SIGN (Scottish Intercollegiate Guidelines Network). SIGN 50 (A guideline developer's handbook). Revised edition. Edinburgh: Scottish Intercollegiate Guidelines Network/HIS, 2011.

31. Chiatti C, Di Rosa M, Barbadoro P, Lamura G, Di Stanislao F, Prospero E. Socioeconomic determinants of influenza vaccination among older adults in Italy. Preventive Medicine 2010;51(3-4):332–33.

32. Flood EM, Rousculp MD, Ryan KJ, Beusterien KM, Divino VM, Toback SL, et al. Parents' decision-making regarding vaccinating their children against influenza: A web-based survey. Clinical therapeutics 2010;32(8):1448–67.

33. Flood EM, Ryan KJ, Rousculp MD, Beusterien KM, Divino VM, Block SL, et al. Parent preferences for pediatric influenza vaccine attributes. Clinical pediatrics 2011;50(4):338–47.

34. Brown KF, Kroll JS, Hudson MJ, Ramsay M, Green J, Vincent CA, et al. Omission bias and vaccine rejection by parents of healthy children: implications for the influenza A/H1N1 vaccination programme. Vaccine 2010;28(25):4181–85.

35. Blank PR, Schwenkglenks M, Szucs TD. Disparities in influenza vaccination coverage rates by target group in five European countries: trends over seven consecutive seasons. Infection 2009;37(5):390–400.

36. Rothan-Tondeur M, Filali-Zegzouti Y, Belmin J, Lejeune B, Golmard JL, de Wazieres B, et al. Assessment of healthcare worker influenza vaccination program in French geriatric wards: a cluster-randomized controlled trial. Aging-Clinical & Experimental Research 2010;22(5-6):450–55.

37. Lemaitre M, Meret T, Rothan-Tondeur M, Belmin J, Lejonc JL, Luquel L, et al. Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. J Am Geriatr Soc 2009;57(9):1580–6.

38. Ahluwalia IB, Singleton JA, Jamieson DJ, Rasmussen SA, Harrison L. Seasonal influenza vaccine coverage among pregnant women: pregnancy risk assessment monitoring system. Journal of Women's Health 2011;20(5):649–51.

39. Wray RJ, Buskirk TD, Jupka K, Lapka C, Jacobsen H, Pakpahan R, et al. Influenza vaccination concerns among older blacks: a randomized controlled trial. American Journal of Preventive Medicine 2009;36(5):429–34.e6.

40. Stirling AS, McMenamim J, Cromie D, Patterson T, Robertson C. Evaluation of the under 65 Scottish National Invitation for Flu Pilot (U-SNIFF): Draft interim report, 2012. 2012.

41. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. The Lancet. 2012; 380, 9836, 37–43

42. European Centre for Disease Prevention and Control. ECDC scientific advice on seasonal influenza vaccination of children and pregnant women. Stockholm: ECDC, 2012.

43. Petticrew M, Roberts H. Evidence, hierarchies, and typologies: horses for courses. J Epidemiol Community Health 2003;57(7):527–29.

44. Ogilvie D, Egan M, Hamilton V, Petticrew M. Systematic reviews of health effects of social interventions: 2. Best available evidence: how low should you go? Journal of Epidemiology and Community Health 2005;59(10):886–92.

45. Bambra C. Real world reviews: a beginner's guide to undertaking systematic reviews of public health policy interventions. Journal of Epidemiology and Community Health 2011;65(1):14–19.

46. Bhat-Schelbert K, Lin CJ, Matambanadzo A, Hannibal K, Nowalk MP, Zimmerman RK. Barriers to and facilitators of child influenza vaccine - perspectives from parents, teens, marketing and healthcare professionals. Vaccine 2012;30(14):2448–52.

47. Flood EM, Block SL, Hall MC, Rousculp MD, Divino VM, Toback SL, et al. Children's perceptions of influenza illness and preferences for influenza vaccine. Journal of Pediatric Health Care 2011;25(3):171–79.

48. Mills E, Jadad AR, Ross C, Wilson K. Systematic review of qualitative studies exploring parental beliefs and attitudes toward childhood vaccination identifies common barriers to vaccination. J Clin Epidemiol 2005;58(11):1081–8.

Annex 1. Electronic database search strategies, MEDLINE (OVID 1946 to present), conducted on the 26.11.2012

1.Influenza, Human/

2. exp influenzavirus a/ or exp influenzavirus b/ or influenzavirus c/

3. influenza.tw.

4. influenzal.tw.

5. flu.tw.

6. 1 or 2 or 3 or 4 or 5

7. exp Immunization/

8. (immuni* or vaccin*).tw.

9. Vaccines/

10. Immunization Programs/

11. exp drug delivery systems/ and exp vaccines/

12. exp VACCINATION/

13. 7 or 8 or 9 or 10 or 11 or 12

14. 6 and 13

15. Influenza Vaccines/

16. 14 or 15

17. health promotion/ or healthy people programs/

18. health education/ or consumer health information/ or health literacy/

19. Patient Education as Topic/

20. health surveys/ or behavioral risk factor surveillance system/ or population surveillance/ or sentinel surveillance/ or health care surveys/ or interviews as topic/ or focus groups/ or lot quality assurance sampling/ or narration/ or questionnaires/ or disease notification/

21. exp Epidemiologic Research Design/

22. Pamphlets/

23. Health Services Accessibility/

24. "Health Services Needs and Demand"/

25. barrier*.tw.

26. facilitat*.tw.

27. qualitative research/

28. questionnaire*.tw.

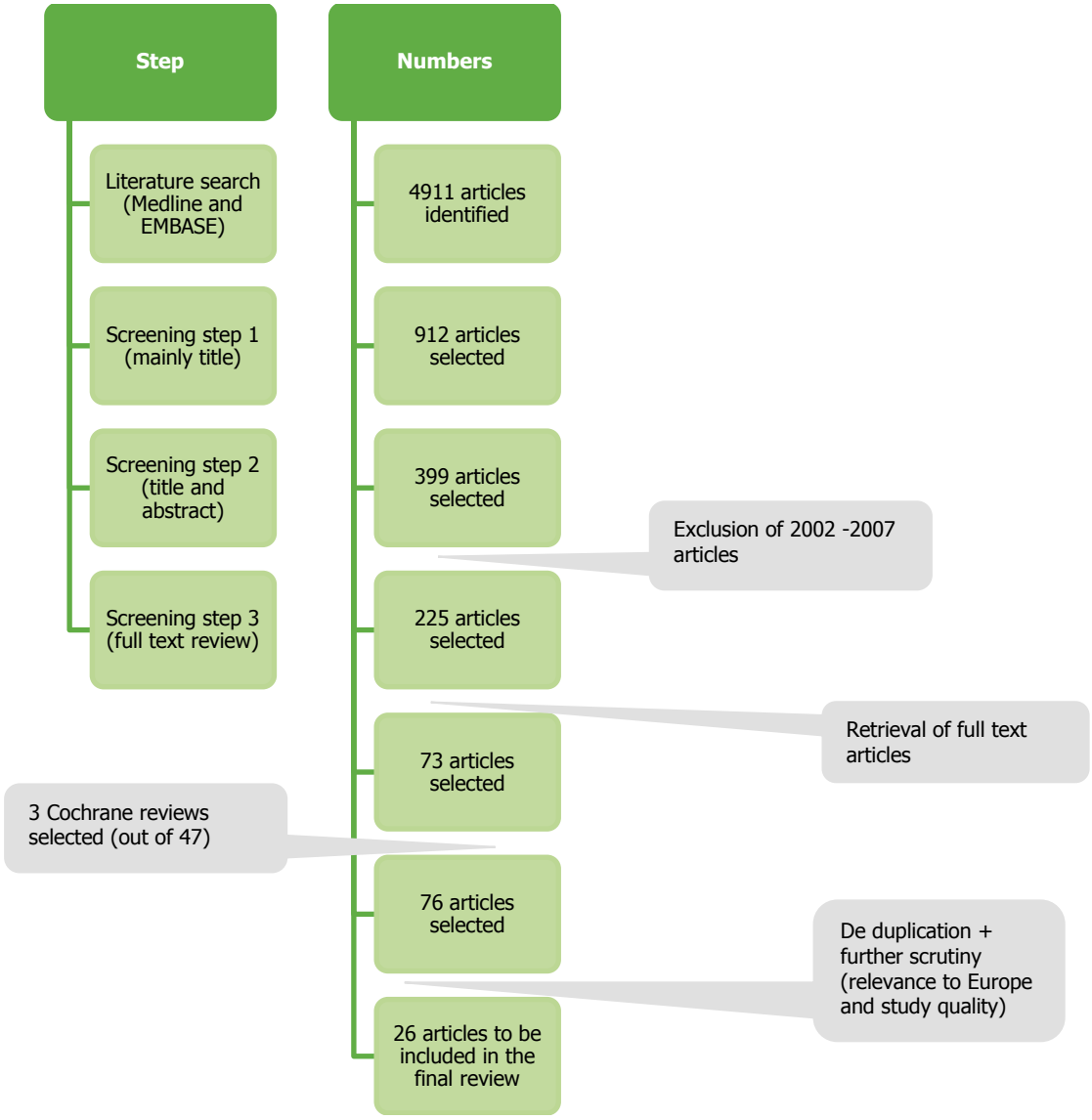
29. risk factors/

30. (vaccin* adj (uptake* or coverage*)).tw.

31. "patient acceptance of health care"/ or exp patient compliance/ or patient participation/ or treatment refusal/

32. access to information/ or advertising as topic/ or communication barriers/ or health communication/ or information dissemination/ or information literacy/ or information seeking behavior/ or reminder systems/ or social networking/
33. Motivation/
34. exp Health Behavior/
35. Health Policy/
36. marketing/ or advertising as topic/ or "marketing of health services"/ or social marketing/
37. Healthcare Disparities/
38. Vulnerable Populations/
39. exp Community Health Services/
40. or/17-39
41. 16 and 40
42. limit 41 to (english language and yr="2002 -Current")

Annex 2. Evidence selection: review of the scientific literature on drivers and barriers of seasonal influenza vaccination coverage in the EU/EEA



Annex 3. Authors and contributions

Luciana Brondi (LB), Senior Honorary Technical Consultant, NHS Lothian.

Sheila Fisken (SF), Liaison Librarian (Medicine), Information Services, University of Edinburgh

Dermot Gorman (DG), Consultant in Public Health Medicine, NHS Lothian

Martin Higgins (MH), Senior Researcher, NHS Lothian

Alison McCallum (AM), Director of Public Health & Health Policy, NHS Lothian.

Duncan McCormick (DM), Consultant in Public Health Medicine, NHS Lothian

Teymur Noori (TN), Expert in monitoring and evaluation of public health programmes, ECDC.

Responsible for the design of the review: LB, DG, AM, DM.

Responsible for data extraction: LB, SF, MH.

Responsible for the assessment of study quality and outcomes: LB, MH.

Responsible for the first draft: LB, MH.

Responsible for the final draft: all authors.