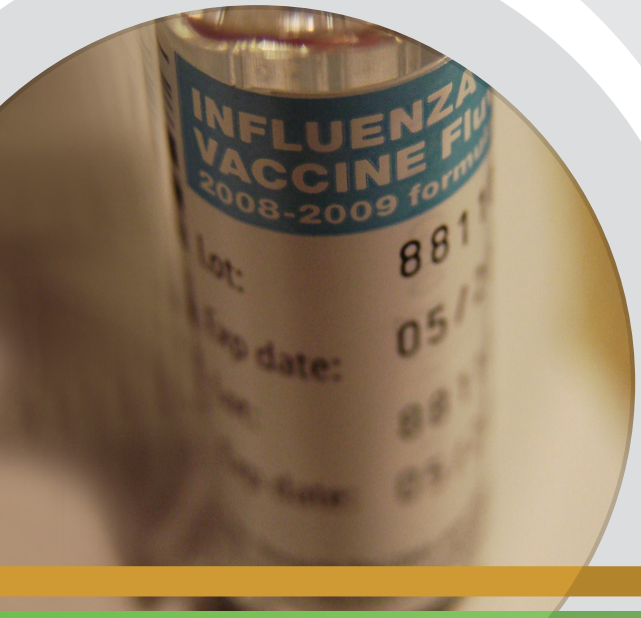

TECHNICAL REPORT

ECDC scientific advice on seasonal influenza vaccination of children and pregnant women

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ECDC scientific advice on seasonal influenza vaccination of children and pregnant women

This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Bruno Ciancio and produced by Pallas health research and consultancy, Rotterdam, Netherlands. Pallas conducted the systematic literature review on burden of influenza in children and pregnant women for the purpose of the expert meeting and this guidance report.

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Contents

Abbreviations

CAIV-T	Cold-adapted influenza vaccine, trivalent
CI	Confidence interval
GP	General practitioner
ILI	Influenza-like illness
LAIV	Live attenuated influenza vaccine
RCT	Randomised controlled trial
TIV	Trivalent inactivated vaccine

1 Executive summary

Aim

The aim of this guidance document is to provide EU/EEA Member States and EU bodies with relevant information to make an informed decision on routine vaccination of healthy children and pregnant women with seasonal influenza vaccine. The options presented in this document are based on a systematic review of the literature and the opinions of a group of independent experts; the expert group also provided additional literature.

The aims of the systematic review were to collect, critically appraise and summarise:

- European data and data from other Western countries on burden of seasonal and pandemic influenza (e.g. incidence, hospitalisations, mortality, and complications) in children and pregnant women;
- European data and data from other Western countries on burden of seasonal and pandemic influenza in young children when their contacts are vaccinated;
- European data only on the safety, efficacy, effectiveness and cost effectiveness of available seasonal and pandemic influenza vaccines in children and pregnant women.

Methods

PubMed and Embase were used to collect relevant articles that were published between August 2000 and August 2010 and contained data collected in the year 2000 or later (i.e. articles that contained only data from before the year 2000 were excluded). Furthermore, an additional PubMed search for articles from three key authors (i.e. Fiore AE, Jamieson DJ, Neuzil KM) was undertaken, and some additional articles were retrieved by hand search (i.e. identified in another included paper) and other databases. Since annual vaccination of children with known risk factors for severe influenza is recommended in all EU countries, this topic was not included in the systematic literature review; nevertheless it was discussed at an expert meeting.

All possible relevant papers were critically appraised using the CoCanCPG[i] checklists (Annex V). Articles judged to be of insufficient quality were excluded. Examples include:

- reviews or meta-analyses in which no description of the methodology was included, or the search was not sufficiently rigorous to identify all relevant articles;
- randomised controlled trials in which the randomisation process was not described or not well executed, which could lead to bias;
- a surveillance study in which the source population was not well defined.

A meeting with experts from Europe and the USA was held in Stockholm on 15 and 16 June 2011.

In preparation of the meeting, the experts read the report of the systematic review. Furthermore, the experts could provide literature, or data from other data sources in addition to the literature and data included in the systematic review. During the expert meeting, the following topics were discussed: burden of influenza in children and pregnant women, vaccine effectiveness and safety, main pros and cons with regard to vaccination of these groups in the European context, and gaps in knowledge.

[i] The CoCanCPG (Coordination of Cancer Clinical Practice Guidelines) was originally designed for developing cancer guidelines, but the criteria are also applicable to studies that address other research questions.

Results and conclusions

What are the advantages and disadvantages of the following vaccine strategy options in the European context?

Universal immunisation of all children aged six months to 18 years without contraindications to vaccination.

Pros:

- Universal immunisation can potentially reach children who have underlying conditions, but are unaware of these and would be missed by targeted vaccination programmes.
- Vaccinating all children would lead to herd immunity thus reducing overall transmission of influenza. The extent of herd immunity produced by different immunising schedules has been estimated by mathematical modelling. However, herd immunity is difficult to investigate and there is little data available on herd immunity after influenza vaccination.

Cons:

- The burden of influenza in children five to 18 years old is considerably lower than the burden in younger children. Therefore the benefits of also vaccinating older children will be lower compared with only vaccinating children aged six months to four years, since fewer hospitalisations/deaths can be prevented.

Universal immunisation of children aged six months to four years without contraindications to vaccination.

Pros:

- The literature review found that the burden of influenza in Western countries is higher in children aged six months to four years than in children aged five to 18 years.
- Data from non-European studies suggested that influenza hospitalisations in children aged six months to four years are comparable with that in elderly or adults with underlying conditions, for whom vaccination is recommended in Europe.
- Assuming the vaccine is effective in children, it can be inferred that vaccination of all children aged six months to four years would lead to a reduction of the major influenza complications in this age group, e.g. secondary bacterial infections such as pneumonia and otitis media. This could be an important consideration especially in countries that have high levels of antibiotic resistance.

Cons:

- When countries consider introducing universal influenza vaccination of children, special attention should be paid to how this could affect the overall childhood vaccination schedule. This can vary from country to country; specific studies to assess parental attitudes towards influenza vaccination, and towards vaccination in general, can be helpful in this context.
- Hardly any European studies on vaccine effectiveness in children have been identified and there are no post-vaccine safety studies.

Targeted immunisation of all children aged six months to 18 years with known risk factors.

Pros:

- All the consulted experts agreed that children with underlying conditions should be vaccinated against seasonal influenza.
- Although the type of underlying conditions and risk factors for severe influenza infection are well defined, new categories may be included as more evidence emerges (e.g. obesity after the 2009 A(H1N1) pandemic).

Annual influenza vaccination of all pregnant women without contraindications to vaccination.

Pros:

- Vaccination could reduce the number of influenza-related hospitalisations and deaths in this group.
- Vaccination of pregnant women can potentially reduce the burden of influenza in children younger than six months old (for whom influenza vaccination and antiviral treatment are not indicated) in two ways:
  - vaccination during pregnancy would reduce the risk of being infected after delivery, thus also reducing the risk of transmission to the child during the first months of life;
  - an RCT conducted in Bangladesh showed proof of concept that transmission of influenza antibodies from the mother to the child takes place and protects the child. Influenza vaccination of the mother during pregnancy was shown to confer protection to the infants also in a number of observational studies. Finally, because both the use of antiviral therapy as well as influenza vaccine are not indicated for use in children younger than six months, there is lack of alternatives to protect these children against influenza, while burden is this group is known to be high.

- Vaccination could reduce the need to treat pregnant women with antivirals. Treatment with antivirals might in theory be more risky than exposure to an inactivated vaccine for which at the moment there are no indications that this causes harm.
- Assuming the vaccine is effective, it may also reduce influenza complications such as secondary bacterial infections. This could be especially important in countries that have high levels of antibiotic resistance.
- During influenza pandemics pregnant women are known to have higher hospitalisation and mortality rates than what should be expected based on population pregnancy rates; this was also observed during the 2009 A(H1N1) pandemic.
- The general view of most experts was that the advantages of vaccinating healthy pregnant women are valid and supported by evidence.
- Although there are no European data on influenza vaccine effectiveness in pregnant women, it can be inferred that vaccine effectiveness is similar to that of healthy women of childbearing age.

Cons:

- Most of the evidence supporting this scientific advice comes from non-European data. More evidence, e.g. from active surveillance systems or large cohort studies, is needed from Europe.

2 Background, aim, expert selection

Background

In 2008, ECDC published an article on risk groups for seasonal influenza, i.e. groups who, if infected with influenza, are more likely to experience severe disease[ii]. This publication was based on the conclusions of a scientific panel that had examined the immunisation of children and concluded that, at the time, data were insufficient to formulate an opinion on childhood vaccination in Europe[iii].

A Recommendation of the European Union (EU) Health Council issued in December 2009 essentially recommended the increased vaccination of risk groups and healthcare workers by the Member States. This Recommendation entailed that ECDC provided guidance on risk groups, in addition to further technical and scientific expertise[iv].

In an article written by ECDC scientists on 'preliminary guidance for developing influenza vaccination recommendations' and published after the 2009 pandemic, the authors argued that the emergence of a new group of viruses (i.e. A(H1N1)pdm09) might change the scientific base[v].

Today, two areas of particular uncertainty remain, namely whether to offer immunisation to children and pregnant women (aside from those with underlying medical conditions).

It should be noted that under its mandate ECDC generally does not issue recommendations; instead, it issues guidance which assists Member States and EU bodies in producing recommendations. Hence the requirement for this guidance was an internal decision of ECDC as part of its ongoing scientific work and in response to the 2009 EU Council Recommendation.

Aim

The aim of this guidance document is to provide EU Member States with relevant information to help in the decision-making process on routine vaccination of healthy children and pregnant women with seasonal influenza vaccine. The options presented in this document are based on a systematic review of the literature and the opinions of a group of independent experts; the expert group also provided additional literature.

Consulted experts

A meeting with international experts was held in Stockholm on 15 and 16 June 2011.

Process of expert selection

As a first step, the ECDC Candidate Expert Directory[vi] was searched for experts with specific expertise in influenza vaccination of children and/or pregnant women. The European Influenza Surveillance Network was also searched using the same criteria. Additional experts were identified by looking at the authors of the articles included in the systematic literature review. An additional Swedish expert with a background in obstetrics and experience in administering influenza vaccines to pregnant women was identified by consulting with the person in charge of influenza at the National Board of Health and Welfare in Stockholm.

[ii] Nicoll A, Ciancio B, Tsolova S, Blank P, Yilmaz C. The scientific basis for offering seasonal influenza immunisation to risk groups in Europe. Euro Surveill. 2008 Oct 23;13(43). pii: 19018. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19018

[iii] Technical report of the scientific panel on vaccines and immunisation. Infant and children seasonal immunisation against influenza on a routine basis during inter-pandemic period. ECDC: Stockholm; 2007. Available from: http://ecdc.europa.eu/en/publications/Publications/0701_TER_Scientific_Panel_on_Vaccines_and_Immunisation.pdf

[iv] Council of the European Union. Council Recommendation of 22 December 2009 on seasonal influenza vaccination (Text with EEA relevance)(2009/1019/EU). Official Journal of the European Union. 2009. L 348/71. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:348:0071:0072:EN:PDF

[v] Nokleby H, Nicoll A. Risk groups and other target groups – preliminary ECDC guidance for developing influenza vaccination recommendations for the season 2010-11. Euro Surveill. 2010 Mar 25;15(12). pii: 19525. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19018

[vi] http://ecdc.europa.eu/en/aboutus/external_experts/Pages/external_experts.aspx

Experts were included based of the following criteria:

- experience in running influenza vaccination programmes for children in a European country;
- experience in issuing seasonal or pandemic influenza vaccine recommendations for pregnant women in a European country;
- international expertise in the field of influenza vaccination of children and pregnant women as documented by their publication record.

Members of the ECDC Advisory Forum were asked whether they had any objections to the proposed expert from his/her country. ECDC invited the expert if there were no objections; otherwise, a different expert was selected.

All experts completed the standard ECDC Annual Declaration of Interest. All declarations were approved by ECDC, and are kept on file at ECDC; they are available on request by writing to influenza@ecdc.eurpoa.eu.

Two ECDC influenza experts were involved in moderating the discussion during the meeting and in writing and reviewing the scientific advice/opinion. Two experts from *Pallas health research and consultancy B.V.* in the Netherlands[vii] acted as rapporteurs and wrote the first draft of the meeting report and the current document.

Table 1. List of participants

Surname	First name	Institute	Country	Date of participation
Ciancio	Bruno	ECDC	Sweden	15 and 16 June
Leino	Tuija	National Institute for Health and Welfare	Finland	15 and 16 June
Mangtani	Punam	London School of Hygiene and Tropical Medicine	UK	15 and 16 June
Neuzil	Kathleen	University of Washington, PATH	USA	15 and 16 June
Nicoll	Angus	ECDC	Sweden	15 and 16 June
Pettersson	Karin	Karolinska Institute	Sweden	15 and 16 June
Sande van der	Marianne	RIVM (National Institute for Public Health and the environment)	The Netherlands	16 June by TC
Shindo	Nahoko	WHO	Switzerland	15 and 16 June

On June 15, the topics with regard to children were discussed; on June 16, the participant discussed topics related to pregnant women.

Evidence assessment

The advice provided in this report is based on the following type of evidence:

- Evidence from a systematic literature review.
- The opinion of an independent group of experts established by ECDC.
- Evidence identified by the group of independent experts but not included in the systematic review because it was outside of its scope (i.e. articles published earlier or later than the inclusion period of the review).

[vii] www.pallashrc.com

3 Systematic review

Aims

The aims of the systematic review were to collect, critically appraise and summarise:

- European data and data from other Western[viii] countries on burden of influenza (e.g. incidence of influenza-like illness (ILI), hospitalisations, mortality, and complications) in children and pregnant women;
- European data and data from other Western countries on the burden of influenza in young children when their contacts are vaccinated;
- European data only on the safety, efficacy, effectiveness and cost effectiveness of available seasonal and pandemic influenza vaccines in children and pregnant women.

Methods

PubMed was used as the core database for the systematic review. Embase was also used for the third aim and for the burden of influenza in pregnant women because literature on this topic was scarce. The PubMed search was conducted for aims 1 and 3 on 28 July 2010, and for aim 2 on 6 October 2010. The Embase search was conducted on 6 October 2010.

Search strings were created for influenza, geographical scope, burden of influenza, vaccine safety, vaccine effectiveness, and cost effectiveness. These search strings were combined with search strings for population, i.e. children, pregnant women and contact of young children. For a detailed description of the search strategies, please refer to Annex 1.

Case reports were excluded. Papers were included if they were published in English, French, German, Italian, Spanish or Dutch between August 2000 and August 2010.

Articles that were published after the year 2000 but included only data from before the year 2000 were excluded. If an article included data from before the year 2000 but also covered susequent years, the article was included.

The results of the PubMed and Embase search were complemented with:

- a search on three relevant key authors in this area: AE Fiore, DJ Jamieson and KM Neuzil: one additional paper to PubMed/Embase on burden of influenza in pregnant women was added;
- a hand search: references of selected articles in the systematic search were checked for additional relevant articles;
- other data sources:
  - European Medicine Agency: www.ema.europa.eu;
  - ESWI (European Scientific Working group on Influenza): www.eswi.org
  - European Centre of Disease Prevention and Control: www.ecdc.europa.eu
  - European Influenza Surveillance Network (EISN): http://www.ecdc.europa.eu/en/activities/surveillance/EISN/Pages/home.aspx
  - EUVAC: www.euvac.net
  - EuroFlu (WHO/Europe Influenza Surveillance): http://www.euroflu.org/index.php
  - Google: www.google.com, with a search on country name + 'influenza' + if necessary, key words from the review objectives such as 'surveillance', 'mortality', 'morbidity'.
  - local national institutes of public health or ministries of health of the countries, for which the Google search did not lead to relevant institutes or data;
  - the library of ECDC's influenza team.

Two researchers independently selected articles of possible relevance for the review. These selected articles were critically evaluated on quality, using the CoCanCPG[ix] checklists (Annex 5). If there was no consensus between the two researchers on whether an article should be included, the article was discussed with a third expert. Articles of insufficient quality were excluded. Examples of insufficient quality were:

- reviews or meta-analyses which lacked a proper description of the methodology;
- reviews or meta-analyses where the search was not sufficiently rigorous to identify all relevant articles;

[viii] 'Western countries' include European countries, the US, Canada, Australia, New Zealand and Japan (high-income countries sharing same economic values, in contrast with middle- and low-income countries).

[ix] The CoCanCPG (Coordination of Cancer Clinical Practice Guidelines) was originally designed for developing cancer guidelines, but the criteria are also applicable to studies that address other research questions.

- randomised controlled trials which did not describe the randomisation process or were judged to not be well executed, which could lead to bias;
- surveillance studies without well defined source populations.

The systematic review yielded a total of 2754 unique articles, of which 496 were selected in the first selection step (i.e. based on title and abstract; the papers that were not selected at this stage did not contain data relevant for this review). Of these 496 articles, 87 were included in evidence tables and text, 78 were not available, and 331 were excluded (i.e. these were of insufficient quality, or did not contain relevant data). The funding source was not considered during the selection phase. Please refer to Annex 2 for an overview of the reasons for exclusion.

Articles reporting data from the 2009 pandemic and those from earlier influenza seasons were summarised separately for two reasons:

- There were significant differences in the risk of severe illness by age and risk group between the two periods.
- During the 2009 pandemic, surveillance than during the years before, which led to an increased number of publications on surveillance data.

Level of evidence

Included studies were ascribed a level of evidence (see Annex 3). This system is used in the Netherlands (CBO, Dutch Institute for Healthcare Improvement) for evidence-based medicine. As surveillance studies are usually not included in such systems, we do not provide a level of evidence for surveillance studies (i.e. studies on burden of influenza).

Limitations

There are several gaps in the literature, some of which are due to restricting the systematic literature review to the past ten years. In general, most European studies refer only to western European countries, while data from eastern European Union countries are lacking. Instead, available evidence and systematic reviews often came from other Western countries, and from expert opinions based on studies conducted before the year 2000.

Articles written in languages other than English, French, German, Italian, Spanish or Dutch may have been missed, which could have disproportionally affected the number of retrieved articles on or from countries in eastern Europe. Data on burden of influenza in pregnancy were largely limited to the pandemic, especially when the data were provided by EU countries. No burden-of-disease studies were found with data on the vaccination of household contacts of young children. Also, no European studies were found which contained data on influenza vaccine efficacy/effectiveness or vaccine safety in pregnant women. In general, European data on vaccine effectiveness in children are limited.

Additional evidence provided by the group of experts

The experts were encouraged to provide additional scientific literature or data from other sources in addition to the literature and data included in the systematic review. Some experts submitted papers that were out of scope of the systematic review, e.g. the articles either referred to other countries than the ones included in the review or were published before 2000/after August 2010. This additional literature was discussed during the expert meeting and included if considered relevant for the purposes of this guidance.

Expert meeting

A meeting with international experts identified by ECDC was held in Stockholm on 15 and 16 June 2011. In preparation for the meeting, the experts had already read the systematic literature review and reviewed the following questions:

Questions concerning children

1. What is the evidence for and against routine influenza vaccination of all children below the age of 18 years in EU countries?

- Burden of disease
- Vaccine effectiveness
- Vaccine safety
- Knowledge gaps in all of the above

2. What are the advantages and disadvantages of the following two vaccine strategy options in the European context?

- Targeted vaccination of all children with known risk factors
- Vaccination of all children without contraindications to vaccination

3. Is it possible/convenient to differentiate the vaccination strategy by age group in order to narrow the age groups for whom universal vaccination might be advisable?

4. What is the best vaccination strategy to protect infants below the age of six months for whom there is no indication for influenza vaccination?

- Vaccination of pregnant women (any data on optimal pregnancy period?)
- Vaccination of contacts

5. What are the main knowledge gaps and areas of uncertainty that require additional research?

Questions concerning pregnant women

1. What is the evidence for and against influenza vaccination of all women who are pregnant during the periods of influenza circulation regardless of the pregnancy trimester and the presence of co-morbidities?

- Burden of disease
- Vaccine effectiveness
- Vaccine safety
- Knowledge gaps in each of the above

2. What are the main knowledge gaps and areas of uncertainty that require additional research?

4 Scientific advice: vaccination of children

This section reviews the specific questions for and against vaccinating children and pregnant women (see end of Section 3 above). For each topic, the results of the systematic review are described first, followed by evidence gleaned from additional literature[x] as provided by the experts. At the end of each topic, a summary of further expert comments as expressed during the meeting is given.

Annex 3 provides a summary of data as taken from the articles included in the systematic review. The tables in Annex 3 do not include data from any of the additional articles that were added by the experts.

4.1 What is the evidence for and against routine influenza vaccination of all children ages 18 years and youngerin EU countries?

a) Burden of disease: evidence from the systematic literature review

The articles selected in the systemic review on burden of influenza in children are summarised in Annex 3, Tables 2 to 17.

2009 pandemic

In the included European studies, children younger than one year of age and children 0–4 years old showed either the highest hospitalisation rate or the highest proportion of cases attributed to influenza[1-3]. A study by Cullen et al. showed similar hospitalisation rates in children 0–4 years and 15–19 years old[4].

The included studies from other Western countries also showed that children below the age of one and children 0–4 years old had the highest hospitalisation rates or proportion of cases[5-12].

In absolute numbers, mortality was low. In three out of five included European studies, none of the children died[4;13;14]. Van 't Klooster et al. showed one death per 200 000 population in children 0–4 and in children 5–14 years old[3]. Donaldson et al. estimated that the highest case fatality rate would be in children 0–4 years old[15]. Over the entire pandemic period in England, four (1%) of 336 fatal pandemic cases were reported in children under six months of age[16].

Studies from other Western countries showed mortality rates of one in 300 000 to 500 000 population in children 0–4 years of age[7;17;18]. The New South Wales Network found that the highest mortality was in children 5–9 years old (1 per 500 000[9]). Paine et al. showed that the proportion of fatal cases of age-specific notified influenza was 0 to less than 1%[10].

Seasonal influenza

One European case series study included in the literature review compared influenza-related hospitalisations in 0–5- and 5–16-year-old children during the influenza seasons 1996/97 to 2001/02[19]: children below five years of age showed the highest proportion of hospitalisation for influenza (81.3%).

The studies from other Western countries showed that children younger than six months[20-31] and children 0–4 years old had the highest hospitalisation rates compared with older children[20-30].

None of the children of 0–4 years old in the included European studies on hospitalised children died of laboratory-confirmed influenza[32-34]. No studies on mortality in older children were found. Mortality was also a rather rare subject in the included studies from other Western countries. Two studies found no deaths in children[20;35]; the other studies found that mortality was higher in children 0–4 years old than in older children[24;26;36].

Additional literature identified by the experts

2009 pandemic

In November 2010, the Lancet published an update of a paper by Donaldson et al.[15] which describes paediatric mortality during the 2009 pandemic in England. The authors identified all paediatric deaths in England related to pandemic influenza infection from 26 June 2009 to 22 March 2010 through daily reporting systems and cross-checking of records. Influenza infection was confirmed by laboratory results or death certificates. In the study, case fatality and population mortality rates were highest in children below the age of one. The mortality rate in children older than one year of age was 14 per 1 000 000. The mortality rate in children 1–17 years old ranged

[x] This additional material does not constitute a complete and systematic overview of the literature.

between four and eight per 1 000 000. Children with severe pre-existing disorders accounted for 64% of all deaths.[37]

Seasonal influenza

Johnson et al. reported on seventeen fatal cases of laboratory-confirmed influenza A in children below 18 years of age in the UK during the 2003/04 influenza season. The median age of fatal cases was two years, with a range from four months to seventeen years. The majority (64%) were under five years of age. Among the sixteen cases for which underlying health status information was available none was recorded as having a known risk factor for severe influenza. During the 2003/04 season, population morbidity rates in young children of up to four years of age were more than twice those of the overall all-age morbidity, indicating substantial disease burden in the young[38].

In the US during the 2003/04 season, 153 influenza-associated deaths among children were reported by 40 State health departments[xi]. The median age of the children was three years, and 96 of them (63%) were younger than five years old. Among the 149 children for whom information on underlying health status was available, 70 (47%) had previously been healthy, 49 (33%) had an high-risk medical condition, and 30 (20%) had other chronic medical conditions not defined as conferring a high risk[39].

Further expert comments

- Burden of influenza in children has been measured using various outcomes such as number of ambulatory visits for a respiratory infection, hospitalisation and mortality. In order to obtain precise estimates of the burden of influenza these outcomes should be laboratory confirmed. In clinical practice laboratory testing is not routinely performed in children with respiratory infections or complications. Reasons include that testing is not routinely used to guide treatment unless results are rapidly available or because influenza is not always suspected as the cause of illness. But even if laboratory tests are conducted, results can be misleading: by the time the illness occurs and influenza is considered as the underlying cause, the virus may have already been cleared from the respiratory tract.
  Although incidence of influenza-related deaths remains an important criterion for making decisions on the vaccination of children, caution in interpreting these data is advisable: deaths directly attributed to influenza are reported infrequently, and the numbers of deaths provided in these studies are most likely underestimates of the true burden of disease. Hospitalisations are reported more frequently, and because of the high cost, hospitalisation is responsible for the largest part of the burden in the various studies.
  Finally, the high number of hospitalisations, especially during the pandemic, should be interpreted with caution because they may have been influenced by other factors than severity of disease. For instance during the 2009/10 pandemic, young children were probably more likely to be hospitalised than during a normal influenza season because parents and clinicians were concerned about unknown risks.
  It should also be noted that paediatric hospital stays during the 2009 pandemic were often short (one to two days), and the most frequent reason for admission was exacerbation of asthma. Reducing hospitalisations might also partly be achieved by reducing unnecessary admission to hospital care.
- A large proportion of the burden of influenza is not apparent through surveillance, partially for the reasons already mentioned above, but also because many parents do not visit a doctor when their child has influenza-like illness.
- Among children, the youngest age groups (i.e. under five years of age) have the highest incidence of disease.
- The number of influenza-related hospitalisations in children younger than five years of age was comparable with the burden in older US adults (over 65 years) or adults with underlying conditions and for whom vaccination is recommended; similar comparative studies have not been conducted in Europe.

b) Vaccine effectiveness and efficacy[xii]: European evidence from the systematic literature review

Three additional studies describing the efficacy of influenza vaccination in children are shown in Table 21. Vaccine-efficacy ranged from 22% to 33% in preventing influenza-like-illnesses[40], and from 83.5% to 88.4% in preventing laboratory-confirmed influenza[41;42].

[xi] In the United States, the reporting of deaths associated with laboratory-confirmed influenza is mandatory. See http://www.cdc.gov/flu/weekly/overview.htm

[xii] Efficacy – an estimate of the likelihood of preventing laboratory-confirmed influenza under optimal circumstances through vaccination – is usually determined through randomised controlled trials.

Effectiveness – the likelihood of preventing laboratory-confirmed influenza through vaccination when applied in the field – is usually determined by observational studies.

Additional literature identified by the experts

At the time of the systematic literature review no European studies on vaccine effectiveness in children were found. In October 2011, a phase III randomised clinical trial was published[43]. The study was conducted during two influenza seasons: 2007/08 in Germany (654 children), and 2008/09 in Germany (2104 children) and Finland (1949 children). The study assessed the safety and efficacy of an MF59-adjuvanted vaccine by comparing it to TIV and a placebo in children between six and less than 72 months of age. The absolute vaccine efficacy rates against all influenza strains were 86% (95% CI, 74 to 93) for the MF59-adjuvant vaccine (adjuvanted TIV), and 43% (95% CI, 15 to 61) for the vaccine without the adjuvant (TIV); the relative vaccine efficacy rate for adjuvanted TIV versus TIV was 75% (95% CI, 55 to 87). The rates of systemic and local reactions to the influenza vaccines with and without the adjuvant were similar in the younger age group (relative risk, 1.04; 95% CI, 0.98 to 1.09), but systemic events in the older age group were more frequent after administration of adjuvanted TIV (63%) than after administration of TIV (44%) or the control vaccine (50%). Serious adverse events were distributed evenly across all three vaccine groups.

Neuzil (one of the independent experts serving on ECDC's expert group panel) and Edwards[44] reviewed the safety, immunogenicity, and efficacy of influenza vaccines in children and discussed the theoretical advantages and disadvantages of a more widespread use of vaccines in healthy and high-risk children. Clinical trials and post-licensure experience have demonstrated that trivalent inactivated influenza vaccine is well-tolerated in children, and the efficacy of the inactivated vaccine has been demonstrated in numerous clinical trials. A large clinical trial demonstrated the tolerability and efficacy of the trivalent live attenuated influenza vaccine (LAIV) in children 15 to 71 months of age. The included studies are mostly non-European studies.

Gruber et al.[45] included 189 school-age children (3−18 years) in a double-blind trial which provided heterotypic protection of 62% and compared it with the protection afforded by a placebo consisting of the influenza B/USSR component of trivalent inactivated vaccine. A single dose of trivalent inactivated vaccine protected school-age children (6 to 19 years of age) from influenza B infection; the rate of protection was 64% against infection and 73% against febrile illness.

In a randomised and blinded pilot study by Hurwitz et al.[46] conducted during the 1996/97 winter flu season, influenza (split virus) trivalent inactivated vaccine was administered to children attending daycare centres. Vaccine efficacy in preventing serologically proven influenza virus infection was 45% (95% CI, -2 to 69) for influenza B, and 31% (95% CI, -95 to 73) for influenza A(H3N2).

Hoberman et al.[47] conducted a randomised, double-blind, placebo-controlled trial in 786 children aged 6 to 24 months. The efficacy of the vaccine against culture-confirmed influenza was 66% (95% CI, 34 to 82) in 1999/2000, and −7% (95% CI, −247 to 67) in 2000/01. Influenza attack rates differed between these two periods. In 1999/2000, culture-proven influenza was identified in 5.5% of the children in the vaccine group and in 15.9% of the children in the placebo group. In 2000/01, 3.6% of the children in the vaccine group had culture-proven influenza versus 3.3% of the children in the placebo group. Small power and a low attack rate in 2000/01 resulted in a broad 95% confidence interval (−247 to 67) and the inability to detect a difference between the vaccine and placebo group.

Further expert comments

- The effectiveness of vaccines can differ between years because of the different strains circulating in the population. The effectiveness of vaccines is partly dependent on the degree of matching between the pre-determined influenza strain used in the vaccine and the circulating vaccine types.
- Even if an influenza vaccine is less effective than desired, vaccination is still the most effective preventive strategy for severe influenza; vaccination has also been shown to reduce hospitalisation in children.
- Evidence on vaccine efficacy and effectiveness in children is limited. Data from available studies show an efficacy/effectiveness comparable to that in the elderly.
- All experts present agreed that children aged six months to 18 years with underlying conditions should be vaccinated against seasonal influenza.

c) Vaccine safety: evidence from the systematic literature review

The articles selected in the systemic review on vaccine safety are summarised in Annex 3 (Table 20).

Overall, the vaccines described in the included literature were well-tolerated; adverse reactions were usually mild or moderate[40;42;48-51]. Of the six studies included, four used trivalent inactivated vaccine (TIV), one used cold-adapted influenza vaccine, trivalent (CAIV-T), and one used live attenuated influenza vaccine (LAIV)[xiii]. Few significant differences between vaccine and control groups were found. In the study of Vesikari et al.[50;51] in Finland, children received two doses of Sub/MF59 vaccine (TIV) in the first year and a booster dose one year later. After

[xiii] Kanra et al. (2004)[48] only mention the vaccine's brand names, not their type. Information on the vaccines was retrieved from the manufacturer's website.

the first and second vaccine dose a significant difference in injection site swelling was found between the Sub/MF59 and split group (p=0.033). A significant difference in injection site pain in children ≥ three years was reported between the Sub/MF59 and split group (p<0.01) after the third vaccine dose. In another study in Finland, a runny nose or nasal discharge occurred in significantly more CAIV-T recipients (82.3%), compared with placebo recipients (75.4%) after the first dose in year one (p=0.001)[42]. Furthermore, in the CAIV-T group, nine possibly, probably, or definitely serious events related to study vaccination were reported compared with five events in the placebo group in the first year of the study. This difference was not statistically significant (P value not reported). In the second year there were two events judged to be possibly, probably, or definitely related to study vaccination in the CAIV-T group. It was not reported in the article whether there were events in the placebo group. No deaths occurred in the included studies.

Additional literature identified by the experts

The experts provided no additional literature.

Further expert comments

Finland and Sweden observed cases of narcolepsy occurring after vaccination with Pandemrix (an AS03-adjuvanted pandemic vaccine) during the 2009 A(H1N1) pandemic. In Europe, a multi-country case-control study is ongoing to investigate the possible epidemiological association between this adverse event and vaccination with Pandemrix. Adjuvanted vaccines, such as Pandemrix, were licensed to use in children during the pandemic. Use of adjuvanted seasonal vaccines in children is very limited. At the time of the expert meeting and writing of the report, only limited evidence was yet available on the association between Pandemrix and narcolepsy.

4.2 What is the best vaccination strategy to protect infants below the age of six months for whom there is no indication for influenza vaccination?

a) Protecting the mother and her unborn child from serious illness: vaccinating pregnant women

Evidence from systematic literature review

No evidence was found in the systematic review, which was restricted to studies conducted in Europe.

Additional literature provided by the experts

Two papers on vaccination of pregnant women were provided by the experts[52;53]. The populations described in the papers are pregnant women from the general population without underlying morbidity. A randomised controlled trial was conducted in Bangladesh to assess the clinical effectiveness of maternal immunisation with inactivated influenza vaccine on influenza illness in infants and mothers. Among infants of mothers who received influenza vaccine, there were fewer cases of laboratory-confirmed influenza than among infants before 24 weeks of age in the control group (six and 16 cases, respectively), with a vaccine effectiveness of 63% (95% CI, 5 to 85). Respiratory illness with fever occurred in 110 infants in the influenza vaccine group and 153 infants in the control group, with a vaccine effectiveness of 29% (95% CI, 7 to 46)[53].

A non-randomised prospective observational cohort study was conducted in Navajo and White Mountain Apache Indian reservations (USA) to assess the effect of seasonal influenza vaccination during pregnancy on laboratory-confirmed influenza in infants up to six months of age. A total of 1160 mother-infant pairs had serum collected and were included in the analysis. The ILI incidence rate was 7.2 and 6.7 per 1000 person-days for infants born to unvaccinated and vaccinated women, respectively. There was a 41% reduction in the risk of laboratory-confirmed influenza virus infection (relative risk, 0.59; 95% CI, 0.37 to 0.93) and a 39% reduction in the risk of ILI hospitalisation (relative risk 0.61; 95% CI, 0.45 to 0.84) for infants born to influenza-vaccinated women compared with infants born to unvaccinated mothers. Infants born to influenza-vaccinated women had significantly higher haemagglutinin inhibition antibody titers at birth and at two to three months of age than infants of unvaccinated mothers for all eight influenza virus strains investigated[52].

Further expert comments

- If a woman is vaccinated during pregnancy, she is less likely to acquire influenza, which in turn reduces the chance of mother-to-child transmission after giving birth and during the first months of life.
- The RCT conducted in Bangladesh showed that influenza antibodies from the mother are transferred to the child.
- The use of antiviral therapy is not licensed in children younger than six months of age. The same applies to influenza vaccines. Therefore, there is a lack of alternatives to protect or treat children younger than six months against influenza, while the burden in this group is high.

- Although evidence from Europe is lacking, there is reassuring evidence from the US, where two million pregnant women were vaccinated against influenza between 2000 and 2003, and only 20 adverse events were reported to VAERS[xiv]. These included nine injection-site reactions and eight systemic reactions (e.g. fever, headache, and myalgias). In addition, three miscarriages were reported, but no causal relationship to vaccination[54] has been established.

b) Vaccination of contacts: evidence from the systematic literature review

The systematic review found no evidence.

Evidence from literature provided by the experts

The experts provided no additional literature.

Further expert comments

- Vaccinating contacts of young children could help prevent transmission of the virus to the infant, but evidence is lacking.

c) What are the main knowledge gaps and areas of uncertainty that require additional research?

The main gaps are the following:

- European data on vaccine-effectiveness in children are limited.
- Large population studies to estimate the burden of influenza by age group have not been conducted in Europe so far.
- Limited data are available from active post-licensing surveillance of severe adverse outcomes associated with seasonal influenza immunisation in Europe.

d) The following is advised:

- Case-based severe influenza surveillance for Europe should be strengthened and should cover more countries. Surveillance should include all age groups in order to allow comparisons between age groups and estimate burden by age. Surveillance data should include information about underlying medical conditions, clinical presentation/severity (lower respiratory tract infection), and clinical outcome.
- In countries that recommend seasonal influenza vaccination in young children (e.g. the USA and Finland), coverage is rather low. There are a number of possible obstacles to seasonal influenza vaccination that need to be eliminated through targeted interventions and focused research investments.
  More evidence on the burden of disease in this age group and on the effectiveness of vaccination is needed to support parents' decision on seasonal influenza vaccination of their children. Furthermore, annual revaccinations and the fact that two doses are needed for first-time vaccinees, are time-consuming and require an additional effort on the part of the parents. This is an important disincentive to increasing vaccination rates in children; supportive actions towards parents should be considered when attempting to increase vaccination coverage in children. If vaccination of young children is recommended, it is advisable to monitor the public opinion on vaccinating children against influenza and against other infections in order to improve strategies to increase or protect achieved vaccination coverage.
- It is advisable that following the introduction of childhood vaccination programmes, population based post-marketing surveillance should be established to monitor vaccine effectiveness, vaccine safety and the impact of vaccination.
- Well-designed RCTs should be conducted to increase the available evidence on vaccine efficacy.

[xiv] The US HHS and FDA Vaccine Adverse Event Reporting System; see http://vaers.hhs.gov/index.

5 Scientific advice: vaccination of pregnant women

5.1 What is the evidence for and against influenza vaccination of all women who are pregnant during the periods of influenza circulation, regardless of the pregnancy trimester and the presence of co-morbidities?

a) Burden of disease: evidence from systematic literature review

The articles selected in the systemic review on burden of influenza in pregnant women are summarised in Annex 3 (Tables 18 and 19).

2009 pandemic

Seventeen studies (six from European countries and 11 from other Western countries) exploring the burden of pandemic influenza A(H1N1) among pregnant women were included. None of the studies included only healthy pregnant women. Nine studies included pregnant women with underlying conditions. Two studies possibly included women with underlying conditions, and six studies did not elaborate on underlying conditions.

Sixteen studies (five from European and 11 from other Western countries) relating to pandemic influenza A(H1N1) hospitalisations among pregnant women (Table 18) were selected; a further eleven studies on mortality (four from European and seven from other Western countries) were included (Table 19).

Two studies (one from Ireland, one from the UK) showed that 4.3% (Ireland) and 6.7% (UK) of the hospitalised cases in the total study group of patients hospitalised for pandemic influenza A(H1N1) were pregnant[2;4]. A Greek and a French study that both investigated ICU admissions reported pregnancy rates at 4.4% (Greece) and 13% (France; 61% of the French cases had underlying conditions)[1;55]. In the Netherlands, 3.5% of non-ICU and 3.8% of ICU admissions with information available were pregnant women[3].

Pregnant women accounted for 5.8% to 13% of the hospitalisations in Australia and the US[6;8;56-58]; 7.2% to 19% of the ICU admissions were due to pandemic influenza in Australia and the US[8;57-60]. Most admissions were pregnant women in the second half or third trimester of pregnancy[8;61-64], while in the UK Nguyen Van-Tam et al. reported that the majority of hospitalised pregnant women were in the second trimester of pregnancy[2]. In a study by Hegawama et al. in Australia, 51% of the pregnant women had underlying conditions[62].

In the Netherlands, none of the pregnant women hospitalised with confirmed influenza during the pandemic died[3]. Two studies reported the proportion of pregnant women among all deaths in hospitalised pandemic cases (France: 2.7%, UK: 6.9%)[1;2]. One study from Greece measured the proportion of pregnant women among all deaths in ICU-admitted pandemic cases (0.7%[2;55]). One study described the complete pandemic period (England) and found that the case fatality rate for pregnant women was 90 per 100 000 clinical cases[16]. In Australia and the US, the proportion of pregnant women among all deaths in pandemic hospitalised cases ranged from 1.6% to 16%[6;8;56;58;59]. The proportion of pregnant hospitalised influenza cases that died ranged from 1.1% to 16.7%[6;8;56;58;63;64]. One study presented mortality per trimester and found that most deaths among pregnant women occurred in the third trimester[64].

Seasonal influenza

No European studies were found in the period of the literature review (articles published in 2000 and after). Two studies (both from the US) reported on outcomes of seasonal influenza in pregnancy[65;66]. In Shiley et al., a total of 503 cases of seasonal influenza with complete records available for review were identified from 1 November 2005 through 1 June 2008 in one hospital. Of these, 381 cases (76%) were diagnosed in hospitalised patients and 122 (24%) during emergency department visits that did not lead to hospital admission. Seven cases were pregnant (1.4%). No pregnant women with seasonal influenza died or required ICU admission. The authors did not report the percentage of pregnant women with underlying conditions. In Rogers et al., 107 hospitalised pregnant women (16% with underlying conditions) diagnosed with influenza A were included (season 2003/04). Twelve per cent of these women developed pneumonia. There were no significant differences between the neonatal outcomes of these pregnant women with influenza A and the outcomes of the general obstetric population[66].

Additional literature provided by the experts

Mak et al. and Blanchard-Rohner and Siegrist reported the findings of systematic literature reviews which concluded that there was evidence of excess morbidity and mortality in pregnant women during seasonal and pandemic influenza[67;68].

In Canada, hospital admission records of women admitted from 1994 to 2000 with a respiratory condition during pregnancy were extracted from the hospitalisation database. Approximately 300 hospitalisations of pregnant women per year were attributed to influenza, of which 140 were in women with co-morbidities. This hospitalisation rate corresponds to 150 (95% CI, 140 to 170) hospitalisations per 100 000 pregnant women per year. An estimated one in 1000 healthy pregnant women were hospitalised due to influenza per year. Pre-existing asthma was the most important risk factor for hospitalisation in pregnant women, accounting for an estimated 450 (95% CI, 300 to 600) admissions per 100 000 pregnant women[69].

In another systematic review, Ortiz et al. found that the odds of hospitalisation for respiratory conditions increased by trimester (from OR 1.4 in the second trimester to OR 4.7 in the third trimester); otherwise healthy women in their third trimester had similar risks to non-pregnant women with chronic co-morbidity conditions[70].

Pierce et al. described the outcomes of pregnancy among a cohort of 272 women in the UK admitted to hospital with confirmed influenza during the second wave of pandemic infection between September 2009 and January 2010. In this cohort, 14% of the women had asthma, and 20% had other co-morbidities than asthma. Perinatal mortality was higher in infants born to infected women (39 (95% CI, 19 to 71) per 1000 total births) than in infants of uninfected women (seven (3–13) per 1000 total births) ($p<0.001$). This was principally explained by an increase in the rate of stillbirth (27 per 1000 total births compared with six per 1000 total births; $p=0.001$). Infected women who delivered preterm were more likely to be infected in their third trimester ($p=0.046$), get admitted to an intensive care unit ($p<0.001$), and have a secondary pneumonia ($p=0.001$) than those who delivered at term[71].

Further expert comments

- In Australia and New Zealand the number of hospitalisations of pregnant women during the pandemic was higher than would be expected based on population distribution (i.e. more than 1 to 1.5%). However, during the pandemic, pregnant women were possibly more closely watched than during seasonal influenza, which could have contributed to the higher proportion of hospitalisations in this group.
- As indicated above, data on burden of disease in pregnant women attributable to seasonal influenza are scarce from European countries. This is partly because surveillance systems usually do not include pregnant women as a specific population during seasonal influenza; instead, they are included in the total population.

b) Vaccine effectiveness: evidence from the systematic literature review

No European studies published in 2000 and after could be retrieved that contained data on influenza vaccine effectiveness in pregnant women.

Additional literature provided by the experts

In their reviews, Mak et al. and Blanchard-Rohner and Siegrist surveyed the literature on influenza vaccination during pregnancy. Many of the included studies focused on the effect of the vaccine to protect young infants against influenza. The studies that used maternal outcomes after vaccination showed a reduction in confirmed influenza or respiratory illness with fever, other studies however failed to show a decreased risk[67;68]. Blanchard-Rohner and Siegrist concluded that influenza vaccination during pregnancy reduced the maternal disease burden[70], while Mak et al. concluded that more evidence was needed on the evaluation of the assumed benefits of vaccinating pregnant women[71].

Further expert comments

- Based on immunogenicity studies there are no indications that vaccine effectiveness is different in pregnant women compared with the general adult population. Although there are immune system adaptations during pregnancy which are responsible for the higher burden of influenza disease, it is unclear whether these have an influence on vaccine effectiveness.
- Data from the Netherlands indicate that an estimated 1500 healthy pregnant women would need to be vaccinated in order to prevent one hospital admission in this group due to seasonal influenza[xv].

[xv] Health Council of the Netherlands. Vaccination of pregnant women against seasonal influenza 2010–2011. Health Council of the Netherlands: The Hague; 2010. Available from: http://www.gezondheidsraad.nl/sites/default/files/201014.pdf

c) Vaccine safety: evidence from the systematic literature review

No European studies published in 2000 and after were retrieved that contained data on influenza vaccine safety in pregnant women.

Additional literature provided by the experts

Tamma et al. conducted a review on safety of influenza vaccination during pregnancy and concluded that the lack of harmful effects of inactivated influenza vaccination on maternal health during pregnancy has been demonstrated in several studies (two RCTs and 10 observational studies)[72]. These studies were non-European studies and/or were published before 2000.

Mak et al. concluded in their review that research on vaccine safety in pregnant women is limited. The few prospective studies of pregnant women suggest that the vaccine is safe[71]. Blanchard-Rohner and Siegrist included ten studies on safety of influenza immunisation during pregnancy. No serious adverse events or increase in adverse pregnancy outcomes were shown in any of these studies[70].

No serious adverse effects of influenza immunisation in pregnancy have been reported in the few published studies on vaccine safety. This evidence is from non-European studies, and data on burden are from before the year 2000. Although evidence from Europe is lacking, there is reassuring evidence from the US, where two million pregnant women were vaccinated against influenza between 2000 and 2003, and only 20 adverse events were reported to the VAERS system. These included nine injection-site reactions and eight systemic reactions (e.g. fever, headache, and myalgias). In addition, three miscarriages were reported, but no causal relationship to vaccination has been established[54].

Further expert comments

- At the moment, there are no indications that vaccinating pregnant women causes harm.
- However, data are on safety are scarce, especially for Europe, since there is no published information on RCTs or large observational studies in Europe.
- If a country should decide to recommend the vaccination of healthy pregnant women, there are some operational issues to consider. Two suggestions were pointed out by the experts:
  - In countries where nearly everyone is registered with a general practitioner (GP), personal invitations by the GP could be an option. The prerequisite for this is that the GP is informed when his or her patients are pregnant.
  - Another option to reach pregnant women is through the midwifery and obstetricians/gynaecologists. In most European countries, pregnant women will visit one of these specialists during their pregnancy.

d) What are the main knowledge gaps and areas of uncertainty that require additional research?

The following main gaps were identified:

- Data from Europe on burden of seasonal influenza in pregnant women (either healthy women or those with underlying conditions).
- Data from Europe on vaccine effectiveness and safety in pregnant women (either healthy women or those with underlying conditions).

e) The following is advised:

- Severe influenza surveillance systems should include pregnant women as a specific category to gain more insight into the burden of influenza in pregnant women. These data should cover all European countries. An alternative approach would be to conduct large multicentre cohort studies which follow up on pregnant women during the influenza seasons and record influenza-related outcomes.
- Hospitalisations and ICU admissions should be added as outcomes in existing surveillance systems or cohort studies, next to mortality. Data on hospitalisations could serve as a marker for differences in influenza outcomes due to differences in healthcare systems.
- Safety studies of women vaccinated with the seasonal influenza vaccine during pregnancy should be conducted in Europe.

6 Additional information

Limitations

The evidence for this advisory report was collected using two different methods, a systematic literature review and literature referrals to additional literature identified by a panel of experts.

The literature search for the systematic part of the review was limited to publications released from 2000 to July 2010. The additional literature provided by the experts proved particularly useful as it allowed the inclusion of relevant evidence that would have otherwise been omitted because of the temporal restrictions of the systematic review. Furthermore, the vaccine-related topics were limited to articles based on European data. Again, the additional literature proved particularly valuable as it provided a broader perspective to the advice formulated here. Unlike the studies included in the systematic review, the literature provided by the experts was neither systematically selected nor critically appraised. Therefore data from these papers are not included in the evidence tables in Annex 2. More evidence on the topics described in this document was becoming available at the time this report was written. Therefore some of the gaps identified here may become less relevant.

Next steps by ECDC

The scientific advice contained in this document will be disseminated by ECDC through the European Commission's Directorate General for Health and Consumers (SANCO), the Health Security Committee's Influenza Section, the ECDC Advisory Forum, the ECDC Vaccine Advisory Group (EVAG); it will also be published on the ECDC website. ECDC monitors influenza vaccine coverage in EU on a routine basis through annual surveys run by the VENICE collaboration (http://venice.cineca.org/). Such surveys include information on the groups for whom vaccination is recommended by national authorities (if collected) and will serve as a tool to monitor the implementation of the advice contained in this document.

Further updates

The systematic part of the review will be updated in two years' time (2014). In the meantime, the ECDC influenza programme will continue to monitor scientific data, analyses and publications and make its findings available through the ECDC Scientific Advances and Public Health Developments series.

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Annex 1. Systematic review of scientific literature

The search strategies used for this publication were developed by Pallas health research and consultancy. The initial selection was based on title and abstracts. Pallas critically appraised full-text articles based on CoCanCPG checklists and then summarised the evidence.

Pallas conducted a search using the search strategies as described below. PubMed search strings were used to identify the amount of articles that needed to be processed during the project. The search strategy was approved by ECDC. PubMed was the core database for the review. Since Embase contains more European journals and pharmacological journals than PubMed, Embase was particularly useful for Aim 3 (see Section 3 above: 'Systematic review'). Embase was also searched for articles on burden of influenza in pregnancy in order to retrieve additional articles since literature on this subject is scarce.

PubMed

Search strategy 1 for influenza

The search string below was used to identify the disease by using medical subject headings [MeSH] and text words [tw]. By using general influenza text words, such as influenza, flu, influenza-like illness and flu-like illness, all subtypes of influenza were supposed to be covered. We added some extra terms for the new pandemic influenza A(H1N1).

(Human influenza [MeSH] OR Influenza A Virus, H1N1 Subtype[MeSH] OR influenza[tw] OR flu[tw] OR influenza-like illness[tw] OR flu-like illness[tw] OR swine flu[tw] OR swine origin influenza[tw] OR 2009 pandemic[tw] OR 2009 pandemic influenza[tw] OR AH1N1v[tw] OR 2009 H1N1[tw])

Search strategy 2 geographical scope

The search for the disease was combined with a search string for European countries.

We selected the articles included in the geographical scope of the review by searching for country names as text words (tag [tw]) or country names in the author's affiliation (tag [ad]).

Therefore the following search string was used for European countries (2a):

(Europe[MeSH] OR Europe*[tw] OR Andorr*[tw] OR Austria*[tw] OR Belgi*[tw] OR Albania*[tw] OR Baltic*[tw] OR Estoni*[tw] OR Latvi*[tw] OR Lithuani*[tw] OR Bosni*[tw] OR Herzegovin*[tw] OR Bulgari*[tw] OR Byelarus*[tw] OR Croatia*[tw] OR Czech*[tw] OR Hungar*[tw] OR Macedonia*[tw] OR Moldov*[tw] OR Montenegr*[tw] OR Poland*[tw] OR Polish*[tw] OR Romania*[tw] OR Russia*[tw] OR Bashkiri*[tw] OR Dagestan*[tw] OR Serbia*[tw] OR Slovaki*[tw] OR Sloveni*[tw] OR Ukrain*[tw] OR Yugoslavi*[tw] OR Finland*[tw] OR Finnish*[tw] OR France*[tw] OR French*[tw] OR German*[tw] OR Gibraltar*[tw] OR Great Britain*[tw] OR Brittish*[tw] OR British*[tw] OR Channel Islands*[tw] OR Guerns*[tw] OR England*[tw] OR English*[tw] OR Hebrid*[tw] OR Ireland*[tw] OR Irish*[tw] OR Scotland*[tw] OR Scotch*[tw] OR Scottish*[tw] OR Wales*[tw] OR Welsh*[tw] OR Greec*[tw] OR Greek*[tw] OR Iceland*[tw] OR Ital*[tw] OR Sicil*[tw] OR Liechtenstein*[tw] OR Luxembourg*[tw] OR Mediterranean Region*[tw] OR Mediterranean Islands*[tw] OR Cyprus*[tw] OR Cipriot*[tw] OR Malta*[tw] OR Monaco*[tw] OR Monas*[tw] OR Netherland*[tw] OR Dutch*[tw] OR Portugal*[tw] OR Portuges*[tw] OR San Marin*[tw] OR Scandinavia*[tw] OR Denmark*[tw] OR Danish*[tw] OR Norwa*[tw] OR Svalbard*[tw] OR Sweden*[tw] OR Swedish*[tw] OR Spain*[tw] OR Spanish*[tw] OR Switzerland*[tw] OR Swiss*[tw] OR Transcaucasia*[tw] OR Armenia*[tw] OR Azerbaijan*[tw] OR Georgia*[tw] OR Vatican*[tw] OR Europe*[ad] OR Andorr*[ad] OR Austria*[ad] OR Belgi*[ad] OR Albania*[ad] OR Baltic*[ad] OR Estoni*[ad] OR Latvi*[ad] OR Lithuani*[ad] OR Bosni*[ad] OR Herzegovin*[ad] OR Bulgari*[ad] OR Byelarus*[ad] OR Croatia*[ad] OR Czech*[ad] OR Hungar*[ad] OR Macedonia*[ad] OR Moldov*[ad] OR Montenegr*[ad] OR Poland*[ad] OR Polish*[ad] OR Romania*[ad] OR Russia*[ad] OR Bashkiri*[ad] OR Dagestan*[ad] OR Serbia*[ad] OR Slovaki*[ad] OR Sloveni*[ad] OR Ukrain*[ad] OR Yugoslavi*[ad] OR Finland*[ad] OR Finnish*[ad] OR France*[ad] OR French*[ad] OR German*[ad] OR Gibraltar*[ad] OR Great Britain*[ad] OR Brittish*[ad] OR British*[ad] OR Channel Islands*[ad] OR Guerns*[ad] OR England*[ad] OR English*[ad] OR Hebrid*[ad] OR Ireland*[ad] OR Irish*[ad] OR Scotland*[ad] OR Scottish*[ad] OR Scotch*[ad] OR Wales*[ad] OR Welsh*[ad] OR Greec*[ad] OR Greek*[ad] OR Iceland*[ad] OR Ital*[ad] OR Sicil*[ad] OR Liechtenstein*[ad] OR Luxembourg*[ad] OR Mediterranean Region*[ad] OR Mediterranean Islands*[ad] OR Cyprus*[ad] OR Cipriot*[ad] OR Malta*[ad] OR Monaco*[ad] OR Monas*[ad] OR Netherland*[ad] OR Dutch*[ad] OR Portugal*[ad] OR Portuges*[ad] OR San Marin*[ad] OR Scandinavia*[ad] OR Denmark*[ad] OR Danish*[ad] OR Norwa*[ad] OR Svalbard*[ad] OR Sweden*[ad] OR Swedish*[ad] OR Spain*[ad] OR Spanish*[ad] OR

Switzerland*[ad] OR Swiss*[ad] OR Transcaucasia*[ad] OR Armenia*[ad] OR Azerbaijan*[ad] OR Georgia*[ad] OR Vatican*[ad])

For the review Aims 1 and 2 the geographical scope was extended outside Europe focusing on the United States, Canada, Australia, New Zealand, and Japan, in order to provide all relevant articles on burden of influenza in children and pregnant women. The above-mentioned search string (2a) was extended to (2b):

("United States"[tw] OR US[tw] OR U.S.A.[tw] OR America*[tw] OR Canad*[tw] OR Austral*[tw] OR New Zealand*[tw] OR Japan*[tw] OR America*[ad] OR "United States"[ad] OR US[ad] OR U.S.A.[ad] OR Canad*[ad] OR Austral*[ad] OR New Zealand*[ad] OR Japan*[ad])

Search strategy 3 for Aim 1: burden of influenza

To identify scientific articles on burden of influenza, we used the search string below, which was combined with the search string for the disease (1) and the geographical scope limited to Europe, the United States, Canada, and Australia (2a and 2b).

(epidemiology[MeSH] OR epidemiology[subheading] OR epidemiology[tw] OR incidence*[tw] OR morbidity*[tw] OR mortality[tw] OR mortality[subheading] OR death*[tw] OR "case-fatality"[tw] OR lethal*[tw] OR hospital*[tw] OR "hospital admission*"[tw] OR visit*[tw] OR complication*[tw] OR pneumonia[tw] OR respiratory disease*[tw] OR respiratory complication*[tw] OR respiratory disorder*[tw] OR respiratory tract infection*[tw] OR chronic disease*[tw] OR chronic disorder*[tw] OR chronic medical condition*[tw] OR asthma exacerbation*[tw] OR asthma[tw] OR diabetes*[tw] OR heart disease*[tw] OR heart disorder*[tw] OR heart failure[tw] OR otitis media[tw] OR ear infection*[tw] OR sinusitis[tw] OR bronchiolitis[tw] OR croup[tw] OR dehydration[tw] OR myositis[tw] OR fetal loss[tw] OR foetal loss[tw] OR fetal death[tw] OR spontaneous abortion OR miscarriage[tw] OR pregnancy termin*[tw])

Search strategy 4 for Aim 2: burden of influenza in young children when contacts are vaccinated

To identify scientific articles on burden of influenza in young children (i.e. between 0 and 59 months old) with vaccinated contacts we used the search string below, which was combined with the search string for disease (1), the geographical scope limited to Europe, the United States, Canada, and Australia (2a and 2b), and the search string for burden of influenza (3).

((Health personnel[MeSH] OR Household contacts[tw] OR caregivers[MeSH] OR caregiver*[tw] OR caretaker[tw] OR nurses[MeSH] OR nurse*[tw] OR physicians[MeSH] OR physician*[tw] OR health care staff[tw] OR carer*[tw] OR healthcare personnel[tw] OR "Disease Transmission, Infectious"[Mesh] OR "Infectious Disease Transmission, Professional-to-Patient"[Mesh] OR family transmission[tw] OR household transmission[tw] OR famil*[tw]) AND (child*[tw] OR infan*[tw] OR pediatr*[tw] OR paediatr*[tw]) AND ("influenza vaccines"[MeSH] OR vaccination[tw] OR vaccin*[tw] OR immunisation[tw] OR immunisation[tw] OR immunogen*[tw] OR immunity*[tw])))

Search strategy 5 for Aim 3: vaccine safety, effectiveness, and cost effectiveness

To identify scientific articles on issues related to vaccine safety, effectiveness, and cost effectiveness of vaccination, we used the search string below, which was combined with the search string for the disease (1) and the geographical scope limited to Europe (2a).

("influenza vaccines"[MeSH] OR vaccination[tw] OR vaccin*[tw] OR immunisation[tw] OR immunisation[tw] OR immunogen*[tw] OR immunity*[tw]) AND (outbreak[tw] OR effectiv*[tw] OR efficacy[tw] OR "cost of illness"[MeSH] OR "attack rate"[tw] OR protection[tw] OR safety[tw] OR AEFI[tw] OR (adverse event[tw] AND immunisation[tw]) OR (adverse event[tw] AND immunisation[tw]) OR neuritis[tw] OR convulsion[tw] OR anaphylaxis[tw] OR encephalitis[tw] OR vasculitis[tw] OR Guillain-Barre syndrome[tw] OR Bell's palsy[tw] OR Bell palsy[tw] OR Bells palsy[tw] OR demyelinating diseas*[tw] OR demyelinating disor*[tw])

Search strategy 6 for population

To identify scientific articles for the population-specific data for year 1 (2010), we used two additional search strategies (see below) that were combined with the search strings 1, 2, 3 and 5.

Search strategy for children aged 6 to 59 months and 5 to 18 years

To identify scientific articles about children (6 months to 18 years), we used the following search string (6a):

(child*[tw] OR infan*[tw] OR adolescen*[tw] OR pediatr*[tw] OR paediatr*[tw] OR juven*[tw])

Search strategy for pregnant women

To identify scientific articles about women who will be or are pregnant during influenza season, we used the following search string (6b):

(Pregnancy[MeSH] OR pregnancy[tw] OR pregnant women[MeSH] OR pregnant women[tw] OR 'Pregnancy Complications, Infectious/prevention and control'[MAJR] OR preconception care[MeSH] OR preconception[tw] OR pregnancy intention[tw])

Limits

We used the following limits:

- NOT (case study OR case studies OR case report*)
- Publication date: last ten years
- Languages: English, French, German, Italian, Spanish, Dutch

Embase

Search strategy 1: influenza

The following search strategy was used to identify the disease, using Emtree terms (/exp) and abstract (:ab):

('influenza virus'/exp OR 'swine influenza virus'/exp OR 'influenza virus a'/exp OR 'influenza virus a h1n1'/exp OR influenza:ab OR flu:ab OR 'influenza-like illness':ab OR 'flu-like illness':ab OR 'swine flu':ab OR 'swine origin influenza':ab OR '2009 pandemic':ab OR '2009 pandemic influenza':ab OR 'ah1n1v':ab OR '2009 h1n1':ab OR influenza:ti OR flu:ti OR 'influenza-like illness':ti OR 'flu-like illness':ti OR 'swine flu':ti OR 'swine origin influenza':ti OR '2009 pandemic':ti OR '2009 pandemic influenza':ti OR 'ah1n1v':ti OR '2009 h1n1':ti)

Search strategy 2: geographical scope

The search for the disease was combined with a search string for European countries.

We selected the articles included in the geographical scope of the review by searching for the country names as abstract (tag ':ab'), title (tag ':ti') or the country names in the author's affiliation (tag ':ad').

Therefore the following search string was used for European countries (2a):

(Europe*:ab OR Andorr*:ab OR Austria*:ab OR Belgi*:ab OR Albania*:ab OR Baltic*:ab OR Estoni*:ab OR Latvi*:ab OR Lithuani*:ab OR Bosni*:ab OR Herzegovin*:ab OR Bulgari*:ab OR Byelarus*:ab OR Croatia*:ab OR Czech*:ab OR Hungar*:ab OR Macedonia*:ab OR Moldov*:ab OR Montenegr*:ab OR Poland*:ab OR Polish*:ab OR Romania*:ab OR Russia*:ab OR Bashkiri*:ab OR Dagestan*:ab OR Serbia*:ab OR Slovaki*:ab OR Sloveni*:ab OR Ukrain*:ab OR Yugoslavi*:ab OR Finland*:ab OR Finnish*:ab OR France*:ab OR French*:ab OR German*:ab OR Gibraltar*:ab OR (Great:ab AND Britain*:ab) OR Brittish*:ab OR British*:ab OR (Channel:ab AND Islands*:ab) OR Guerns*:ab OR England*:ab OR English*:ab OR Hebrid*:ab OR Ireland*:ab OR Irish*:ab OR Scotland*:ab OR Scotch*:ab OR Scottish*:ab OR Wales*:ab OR Welsh*:ab OR Greec*:ab OR Greek*:ab OR Iceland*:ab OR Ital*:ab OR Sicil*:ab OR Liechtenstein*:ab OR Luxembourg*:ab OR (Mediterranean:ab AND Region*:ab) OR (Mediterranean:ab AND Islands*:ab) OR Cyprus*:ab OR Cipriot*:ab OR Malta*:ab OR Monaco*:ab OR Monas*:ab OR Netherland*:ab OR Dutch*:ab OR Portugal*:ab OR Portuges*:ab OR (San:ab AND Marin*:ab) OR Scandinavia*:ab OR Denmark*:ab OR Danish*:ab OR Norwa*:ab OR Svalbard*:ab OR Sweden*:ab OR Swedish*:ab OR Spain*:ab OR Spanish*:ab OR Switzerland*:ab OR Swiss*:ab OR Transcaucasia*:ab OR Armenia*:ab OR Azerbaijan*:ab OR Georgia*:ab OR Vatican*:ab OR Europe*:ad OR Andorr*:ad OR Austria*:ad OR Belgi*:ad OR Albania*:ad OR Baltic*:ad OR Estoni*:ad OR Latvi*:ad OR Lithuani*:ad OR Bosni*:ad OR Herzegovin*:ad OR Bulgari*:ad OR Byelarus*:ad OR Croatia*:ad OR Czech*:ad OR Hungar*:ad OR Macedonia*:ad OR Moldov*:ad OR Montenegr*:ad OR Poland*:ad OR Polish*:ad OR Romania*:ad OR Russia*:ad OR Bashkiri*:ad OR Dagestan*:ad OR Serbia*:ad OR Slovaki*:ad OR Sloveni*:ad OR Ukrain*:ad OR Yugoslavi*:ad OR Finland*:ad OR Finnish*:ad OR France*:ad OR French*:ad OR German*:ad OR Gibraltar*:ad OR (Great:ad AND Britain*:ad) OR Brittish*:ad OR British*:ad OR (Channel:ad AND Islands*:ad) OR Guerns*:ad OR England*:ad OR English*:ad OR Hebrid*:ad OR Ireland*:ad OR Irish*:ad OR Scotland*:ad OR Scottish*:ad OR Scotch*:ad OR Wales*:ad OR Welsh*:ad OR Greec*:ad OR Greek*:ad OR Iceland*:ad OR Ital*:ad OR Sicil*:ad OR Liechtenstein*:ad OR Luxembourg*:ad OR (Mediterranean:ad AND Region*:ad) OR (Mediterranean:ad AND Islands*:ad) OR Cyprus*:ad OR Cipriot*:ad OR Malta*:ad OR Monaco*:ad OR Monas*:ad OR Netherland*:ad OR Dutch*:ad OR Portugal*:ad OR Portuges*:ad OR (San:ad AND Marin*:ad) OR Scandinavia*:ad OR Denmark*:ad OR Danish*:ad OR Norwa*:ad OR Svalbard*:ad OR Sweden*:ad OR Swedish*:ad OR Spain*:ad OR Spanish*:ad OR Switzerland*:ad OR Swiss*:ad OR Transcaucasia*:ad OR Armenia*:ad OR Azerbaijan*:ad OR Georgia*:ad OR Vatican*:ad OR Europe*:ti OR Andorr*:ti OR Austria*:ti OR Belgi*:ti OR Albania*:ti OR Baltic*:ti OR Estoni*:ti OR Latvi*:ti OR Lithuani*:ti OR Bosni*:ti OR Herzegovin*:ti OR Bulgari*:ti OR Byelarus*:ti OR Croatia*:ti OR Czech*:ti OR

Hungar*:ti OR Macedonia*:ti OR Moldov*:ti OR Montenegr*:ti OR Poland*:ti OR Polish*:ti OR Romania*:ti OR Russia*:ti OR Bashkiri*:ti OR Dagestan*:ti OR Serbia*:ti OR Slovaki*:ti OR Sloveni*:ti OR Ukrain*:ti OR Yugoslavi*:ti OR Finland*:ti OR Finnish*:ti OR France*:ti OR French*:ti OR German*:ti OR Gibraltar*:ti OR (Great:ti AND Britain*:ti) OR Brittish*:ti OR British*:ti OR (Channel:ti AND Islands*:ti) OR Guerns*:ti OR England*:ti OR English*:ti OR Hebrid*:ti OR Ireland*:ti OR Irish*:ti OR Scotland*:ti OR Scottish*:ti OR Scotch*:ti OR Wales*:ti OR Welsh*:ti OR Greec*:ti OR Greek*:ti OR Iceland*:ti OR Ital*:ti OR Sicil*:ti OR Liechtenstein*:ti OR Luxembourg*:ti OR (Mediterranean:ti AND Region*:ti) OR (Mediterranean:ti AND Islands*:ti) OR Cyprus*:ti OR Cipriot*:ti OR Malta*:ti OR Monaco*:ti OR Monas*:ti OR Netherland*:ti OR Dutch*:ti OR Portugal*:ti OR Portuges*:ti OR (San:ti AND Marin*:ti) OR Scandinavia*:ti OR Denmark*:ti OR Danish*:ti OR Norwa*:ti OR Svalbard*:ti OR Sweden*:ti OR Swedish*:ti OR Spain*:ti OR Spanish*:ti OR Switzerland*:ti OR Swiss*:ti OR Transcaucasia*:ti OR Armenia*:ti OR Azerbaijan*:ti OR Georgia*:ti OR Vatican*:ti)

For the literature on burden of influenza in pregnancy, the geographical scope was extended outside Europe, focusing on the United States, Canada, Australia, New Zealand and Japan to retrieve all relevant articles. The above-mentioned search string (2a) was extended to (2b):

(US*:ab OR (United:ab AND States*:ab) OR USA*:ab OR America*:ab OR Canad*:ab OR Austral*:ab OR (New:ab AND Zealand*:ab) OR Japan*:ab OR (United:ad AND States*:ad) OR US*:ad OR USA*:ab or America*:ab OR Canad*:ab OR Austral*:ad OR (New:ad AND Zealand*:ad) OR Japan*:ad OR (United:ti AND States:ti) OR US*:ti OR USA*:ti OR America*:ti OR Canad*:ti OR Austral*:ti OR (New:ti AND Zealand*:ti) OR Japan*:ti)

Search strategy 3 for Aim 3: vaccine safety, effectiveness, and cost effectiveness

To identify scientific papers on issues related to vaccine safety, effectiveness, and cost effectiveness of vaccination, we used the search string below, which was combined with the search string for the disease (1) and the geographical scope limited to Europe (2). This limit was set because not all vaccines available in the US are available in Europe (for which the advice in vaccination will be)

'influenza vaccine'/exp OR 'swine influenza vaccine'/exp OR vaccination:ab OR vaccin*:ab OR immunisation:ab OR immunisation:ab OR immunogen*:ab OR immunity*:ab OR vaccination:ti OR vaccin*:ti OR immunisation:ti OR immunisation:ti OR immunogen*:ti OR immunity*:ti AND (outbreak:ab OR effectiv*:ab OR efficacy:ab OR 'attack rate':ab OR protection:ab OR safety:ab OR aefi:ab OR ('adverse event':ab AND immunisation:ab) OR ('adverse event':ab AND immunisation:ab) OR neuritis:ab OR convulsion:ab OR anaphylaxis:ab OR encephalitis:ab OR vasculitis:ab OR 'guillain-barre syndrome':ab OR 'bell palsy':ab OR 'bells palsy':ab OR outbreak:ti OR effectiv*:ti OR efficacy:ti OR 'cost of illness'/exp OR 'attack rate':ti OR protection:ti OR safety:ti OR aefi:ti OR ('adverse event':ti AND immunisation:ti) OR ('adverse event':ti AND immunisation:ti) OR neuritis:ti OR convulsion:ti OR anaphylaxis:ti OR encephalitis:ti OR vasculitis:ti OR 'guillain-barre syndrome':ti OR 'bell palsy':ti OR 'bells palsy':ti OR (demyelin*:ab AND diseas*:ab) OR (demyelin*:ab AND disor*:ab))

Search strategy 4: burden

('epidemiology'/exp OR epidemiology:ab OR incidence:ab OR morbidity:ab OR mortality:ab OR death*:ab OR 'case fatality':ab OR lethal:ab OR hospital*:ab OR 'hospital admission':ab OR visit*:ab OR complication*:ab OR pneumonia:ab OR 'respiratory disease':ab OR 'respiratory complication':ab OR 'respiratory disorder':ab OR 'respiratory tract infection':ab OR 'chronic disease':ab OR 'chronic disorder':ab OR 'chronic medical condition':ab OR 'asthma exacerbation':ab OR asthma:ab OR diabetes:ab OR 'heart disease':ab OR 'heart disorder':ab OR 'heart failure':ab OR 'otitis media':ab OR 'ear infection':ab OR sinusitis:ab OR bronchiolitis:ab OR croup:ab OR dehydration:ab OR myositis:ab OR 'fetal loss':ab OR 'foetal loss':ab OR 'fetal death':ab OR 'spontaneous abortion':ab OR miscarriage*:ab OR (pregnancy:ab OR termin*:ab) OR epidemiology:ti OR incidence:ti OR morbidity:ti OR mortality:ti OR death*:ti OR 'case fatality':ti OR lethal:ti OR hospital*:ti OR 'hospital admission':ti OR visit*:ti OR complication*:ti OR pneumonia:ti OR 'respiratory disease':ti OR 'respiratory complication':ti OR 'respiratory disorder':ti OR 'respiratory tract infection':ti OR 'chronic disease':ti OR 'chronic disorder':ti OR 'chronic medical condition':ti OR 'asthma exacerbation':ti OR asthma:ti OR diabetes:ti OR 'heart disease':ti OR 'heart disorder':ti OR 'heart failure':ti OR 'otitis media':ti OR 'ear infection':ti OR sinusitis:ti OR bronchiolitis:ti OR croup:ti OR dehydration:ti OR myositis:ti OR 'fetal loss':ti OR 'foetal loss':ti OR 'fetal death':ti OR 'spontaneous abortion':ti OR miscarriage*:ti OR (pregnancy:ti OR termin*:ti))

Search strategy 5 for population

To identify scientific papers for the population-specific data for year 1 (2010), we used two additional search strategies (see below) that were combined with the search strings 1 to 4.

Search strategy for children aged 6 to 59 months and 5 to 18 years

To identify scientific papers about children (6 months to 18 years), we used the following search string (4a):

(child*:ab OR infan*:ab OR adolescen*:ab OR pediatr*:ab OR paediatr*:ab OR juven*:ab OR child*:ti OR infan*:ti OR adolescen*:ti OR pediatr*:ti OR paediatr*:ti OR juven*:ti)

Search strategy for pregnant women

To identify scientific papers about women who will be or are pregnant during influenza season, we used the following search string (4b):

('pregnancy'/exp OR pregnancy:ab OR 'pregnant women':ab OR 'Pregnancy Complication'/exp OR 'maternal care'/exp OR preconception:ab OR 'pregnancy intention':ab OR pregnancy:ti OR 'pregnant women':ti OR preconception:ti OR 'pregnancy intention':ti)

Limits

We used the following limits:

- NOT (case study OR case studies OR case report*)
- Publication date: last ten years
- Languages: English, French, German, Italian, Spanish, Dutch

Key authors

As suggested by ECDC, Pallas did an additional PubMed search on the following authors' names:

- "Fiore AE"[author]
- "Jamieson DJ"[author]
- "Neuzil KM"[author]

We used the following limits:

- NOT (case study OR case studies OR case report*)
- Publication date: last ten years
- Languages: English, French, German, Italian, Spanish, Dutch

Hand search

Through hand search (i.e. checking the references of the selected articles for additional relevant articles) Pallas updated key references possibly missed by the search in PubMed and Embase. This was done while completing the evidence tables.

Other data sources

Pallas browsed the following internet sites to identify data relevant to the aims of this review, particularly when data were scarce or not found in the literature:

- European Medicine Agency, www.emea.europa.eu
- ESWI (European Scientific Working group on Influenza), www.eswi.org
- European Centre of Disease Prevention and Control, www.ecdc.europa.eu
- European Influenza Surveillance Network (EISN) http://www.ecdc.europa.eu/en/activities/surveillance/EISN/Pages/home.aspx (formerly the European Influenza Surveillance Scheme (EISS))
- Euvac, www.euvac.net
- EuroFlu (WHO/Europe Influenza Surveillance), http://www.euroflu.org/index.php
- Google (www.google.com), with a search on country name + 'Influenza' + if necessary, key words from the review objectives such as 'surveillance', 'mortality', 'morbidity'.
- Local national institutes of public health or ministries of health of the countries where the Google search did not lead to relevant institutes or data.
- Librabry of ECDC's influenza team

Selection procedure and critical appraisal

Pallas used a three-step selection procedure.

1. First selection step: title and abstract

In selection step 1, all articles retrieved from the search strategies were assessed. Two researchers executed this selection step independently.

The major topics of the articles were assessed by the title and abstract. Articles that did not contain information relevant to the research objectives, in abstract or title, were no selected for full text assessment.

Examples for exclusion were: articles on treatment, animal study, other disease/infection than influenza was topic of article, phase II trial, vaccination coverage, attitude against vaccination, risk perception, study population other than defined in aims, acceptability of vaccination, simulation studies, travel-related pandemic H1N1 cases, case-report, letter to the editor, expert's opinion, and other countries than selected in search strategy.

In a few cases it was doubtful whether the article should be included or excluded. These articles were included and moved to the second selection step.

If an abstract was not available, and the title of that paper suggested that it could be relevant, the paper was selected for the second step.

2. Second selection step: full article

In this step the full text articles, selected in step 1, were assessed. Reasons for exclusion in this step were:

- no relevant information (not possible to determine in selection step 1);
- data on influenza were not presented separately, but in combination with, for example, pneumonia or RSV, or not further specified (e.g. respiratory illness);
- poor quality. The Pallas team critically appraised the methodological quality of the articles using the CoCanCPG checklists (see Appendix 1). The CoCanCPG checklist was chosen because Pallas has experience with this checklist, and it is freely available. This choice was approved by ECDC. To the best of our knowledge, checklists for the critical appraisal of surveillance studies are not available. Appendix II describes the criteria we used to critically appraise surveillance studies. These criteria were based on the criteria for cohort studies, completed with a few other criteria applicable for the purpose of this review. If an article was of poor quality, the article was excluded. Criteria of poor quality were:
  - review or meta-analysis which lacks a description of the methodology, or the search is not sufficiently rigorous to identify all relevant articles;
  - randomised controlled trial in which the randomisation process is not described or not well executed, which could lead to bias;
  - surveillance study in which the source population is not well defined;
- data on burden or vaccination that are older than the year 2000;
- 75% or more of the children/pregnant women had underlying disease, and data were not separately presented for healthy cases vs. cases with underlying disease;
- if a review on vaccination was of good quality, but contained mainly non-European studies, the review was excluded; European studies included in this review were retrieved and critically appraised.

In Appendix 3 the exclusion table for selection step 2 is given. For each article excluded in the second step, a brief statement is provided on the main reason for exclusion. This way the selection procedure is transparent and ensures reproducibility. The exclusion table provides a tool for ECDC to evaluate the selection procedure.

Articles that were not excluded in this step were selected for inclusion in the evidence tables (Annex 3).

3. Third selection step: full article for production of evidence tables

While producing the evidence tables, some additional papers were excluded and added to the exclusion table. This includes articles that only described the first few months of the pandemic while more complete papers for the same country were available, a number of fewer than 100 hospitalised cases in pandemic studies, results from only one school or hospital while larger population data were available, articles retrieved from review studies that were of poor quality.

Annex 2. Reasons for exclusion

PubMed and hand search

1	Acs 2005	The content of this article does not provide data that meet the objectives
2	Ajayi-Obe 2008	This article does not describe results for the population of interest
3	Al Hajjar 2010	The article does not meet the CoCanCPG requirements for conducting a systematic review
4	American Academy of Pediatrics Committee on Infectious Diseases 2004	The article describes an advice that is not based on a systematic review
5	Anderson 2001	The content of this article does not provide data that meet the objectives
6	Anderson 2002	This article does not describe results for the population of interest
7	Anderson 2003	This article does not describe results for the population of interest
8	Anderson 2005	The content of this article does not provide data that meet the objectives
9	Ansaldi 2004	This article does not describe results for the population of interest
10	Ansaldi 2005	This article does not meet the CoCanCPG requirements for conducting a cohort study
11	Arias 2003	The content of this article does not provide data that meet the objectives
12	Arostegi Kareaga 2005	This article does not describe results for the population of interest
13	Aull 2007	This article does not describe results for the population of interest
14	Badia Llach 2006	The content of this article does not provide data that meet the objectives
15	Baguelin 2010	This concerns a modelling study
16	Barr 2005	The content of this article does not provide data that meet the objectives
17	Baydur 2004	The content of this article does not provide data that meet the objectives
18	Beard 2006	The content of this article does not provide data that meet the objectives
19	Belgian Working Group on Influenza A(H1N1) 2009	The content of this article does not provide data that meet the objectives
20	Bender 2009	The content of this article does not provide data that meet the objectives
21	Beyer 2002	The content of this article does not provide data that meet the objectives
22	Bigl 2002	This article does not describe results for the population of interest
23	Blake 2009	The article describes an advice that is not based on a systematic review
24	Bobo 2009	The article does not meet the CoCanCPG requirements for conducting a systematic review
25	Bourgeois 2009	The methods section is not clear
26	Bourgeois 2006	The content of this article does not provide data that meet the objectives
27	Boyd 2006	The article does not meet the CoCanCPG requirements for conducting a systematic review
28	Bramley 2009	The article does not meet the CoCanCPG requirements for conducting a systematic review
29	Brouard 2007	The article does not meet the CoCanCPG requirements for conducting a systematic review
30	Bryant 2010	The content of this article does not provide data that meet the objectives
31	Burgner 2005	The content of this article does not provide data that meet the objectives
32	Bürkle 2010	The article does not meet the CoCanCPG requirements for conducting a systematic review
33	Calatayud 2010	The study population described in this article is too small to include in the review, data only from only one school in London
34	Calitri 2010	The study population described in this article is too small to include in the review
35	Callaghan 2010	The content of this article does not provide data that meet the objectives
36	Calvo Rey 2005	This article does not describe results for the population of interest
37	Calvo 2006	The study population described in this article is too small to include in the review
38	Carmona 2010	The article describes a Phase II trial
39	Carrat 2006	This is a modelling study
40	Castilla 2005	This article does not describe results for the population of interest
41	CDC 2009	Another selected article describes the same study population but presents more complete or more recent data

42	CDC 2003	This article does not describe results for the population of interest
43	CDC 2004	This article does not describe results for the population of interest
44	CDC 2004	This article does not describe results for the population of interest
45	CDC 2004	This article does not describe results for the population of interest
46	CDC 2004	This article does not describe results for the population of interest
47	CDC 2006	This article does not describe results for the population of interest
48	CDC 2008	The results in this article are described in another article
49	CDC 2009	The results in this article are described in another article
50	CDC 2009	The content of this article does not provide data that meet the objectives
51	CDC 2009	This article does not describe results for the population of interest
52	CDC 2010	This article does not describe results for the population of interest
53	Chandran 2005	The article does not meet the CoCanCPG requirements for conducting a systematic review
54	Chen 2009	The article does not meet the CoCanCPG requirements for conducting a systematic review
55	Chung 2007	The content of this article does not provide data that meet the objectives
56	Committe on Infectious Diseases. American Academy of Pediatrics 2002	The article describes an advice that is not based on a systematic review
57	Coleman 2006	The content of this article does not provide data that meet the objectives
58	Cox 2004	The article does not meet the CoCanCPG requirements for conducting a systematic review
59	Cox 2006 J Womens Health	This article does not describe results for the population of interest
60	Cox 2006 Obstet Gynecol	The content of this article does not provide data that meet the objectives
61	Crighton 2004	The content of this article does not provide data that meet the objectives
62	Crighton 2007	The content of this article does not provide data that meet the objectives
63	Crum-Cianflone 2009	The content of this article does not provide data that meet the objectives
64	D'Agaro 2008	This article does not describe results for the population of interest
65	Daley 2000	This article does not describe results for the population of interest
66	David 2005	This article does not describe results for the population of interest
67	De Donno 2007	This article does not describe results for the population of interest
68	Delore 2006	The article does not meet the CoCanCPG requirements for conducting a systematic review
69	Dickinson 2002	The content of this article does not provide data that meet the objectives
70	Dodds 2007	The content of this article does not provide data that meet the objectives
71	Doyle 2006	This concerns a modelling study
72	Durando 2010	The article does not meet the CoCanCPG requirements for conducting a systematic review
73	Ehlken 2005	The data in this study are derived from another included study
74	Ellis 2003	The content of this article does not provide data that meet the objectives
75	Eriksson 2000	The content of this article does not provide data that meet the objectives
76	Esposito 2008	The article does not meet the CoCanCPG requirements for conducting a systematic review
77	Esposito 2009	The article does not meet the CoCanCPG requirements for conducting a systematic review
78	Fairbrother 2010	Another selected article describes the same study population but presents more complete or more recent data
79	Falagas 2010	The articles included in this review are judged/described seperately
80	Falchi 2008	The content of this article does not provide data that meet the objectives
81	Fleming 2005	The study period described in the article does not include the period of the review
82	Fleming 2005	The content of this article does not provide data that meet the objectives
83	Fleming 2007	This article does not describe results for the population of interest
84	Fleming 2008	The article does not meet the CoCanCPG requirements for conducting a systematic review
85	Forster 2003	More complete data is available for this country
86	Frank 2010	The article does not meet the CoCanCPG requirements for conducting a systematic review
87	Fujii 2002	This article does not describe results for the population of interest
88	Gabutti 2004	This article does not describe results for the population of interest

89	García-García 2006	The article does not meet the CoCanCPG requirements for conducting a systematic review
90	Gautier 2008	The content of this article does not provide data that meet the objectives
91	Giezeman 2009	The content of this article does not provide data that meet the objectives
92	Girard 2010	The article does not meet the CoCanCPG requirements for conducting a systematic review
93	Glezen 2002	The article does not meet the CoCanCPG requirements for conducting a systematic review
94	Glezen 2004	The study period described in the article does not include the period of the review
95	Goddard 2004	The content of this article does not provide data that meet the objectives
96	Goldrick 2004	The content of this article does not provide data that meet the objectives
97	Griffin 2004	More complete data is available for this country
98	Grose 2004	The article does not meet the CoCanCPG requirements for conducting a systematic review
99	Groupe de Travail 2005	The article does not meet the CoCanCPG requirements for conducting a systematic review
100	Groupe de Travail 2005	The article does not meet the CoCanCPG requirements for conducting a systematic review
101	Grupo de Trabajo 2010	This article described a systematic review, but the evidence is solely based on expert opinions
102	Guarner 2006	This article does not describe results for the population of interest
103	Guillain-Barre syndrome study group 2000	This article does not describe results for the population of interest
104	Hackett 2009	The study population described in this article is too small to include in the review
105	Hannoun 2004	The content of this article does not provide data that meet the objectives
106	Hanslik 2010	No clear description of methodology-study partly based on estimations
107	Hara 2007	The content of this article does not provide data that meet the objectives
108	Harper 2004	The study period described in the article does not include the period of the review
109	Health Protection Agency and Health Protection Scotland New Influenza A(H1N1) Investigation Teams 2009	More complete data is available for this country
110	Healy 2006	The content of this article does not provide data that meet the objectives
111	Hehme 2002	This article does not describe results for the population of interest
112	Heikkinen 2006	The article does not meet the CoCanCPG requirements for conducting a systematic review
113	Heikkinen 2006	The article does not meet the CoCanCPG requirements for conducting a systematic review
114	Heininger 2003	The article does not meet the CoCanCPG requirements for conducting a systematic review
115	Henrickson 2004	The content of this article does not provide data that meet the objectives
116	Heron 2007	This article does not describe results for the population of interest
117	Heron 2007	The content of this article does not provide data that meet the objectives
118	Herzog 2009	The article does not meet the CoCanCPG requirements for conducting a systematic review
119	Hjalmarsson 2009	This article does not describe results for the population of interest
120	Hoskins 1973	The study period described in the article does not include he period of the review
121	Hoyert 2005	The content of this article does not provide data that meet the objectives
122	Hoyert 2006	The content of this article does not provide data that meet the objectives
123	Hsieh 2006	The content of this article does not provide data that meet the objectives
124	Hunter 2005	More complete data is available for this country
125	Iskander 2007	The article does not meet the CoCanCPG requirements for conducting a systematic review
126	Iskander 2009	The content of this article does not provide data that meet the objectives
127	Iwane 2004	The study population described in this article is too small to include in the review
128	Jaber 2010	The articles included in this review are judged/described seperately
129	Jamieson 2009	More complete data is available for this country

130	Jansen 2007	This article does not describe results for the population of interest
131	Jansen 2008	The content of this article does not provide data that meet the objectives
132	Jefferson 2005	The results in this article are described in another article
133	Jefferson 2008	The articles about Europe included in this review are judged/described seperately
134	Jensen 2004	The content of this article does not provide data that meet the objectives
135	Jensen-Fangel 2004	The content of this article does not provide data that meet the objectives
136	Joiner 2002	This article does not describe results for the population of interest
137	Jouvet 2010	This article does not describe results for the population of interest
138	Kappagoda 2000	This article does not describe results for the population of interest
139	Kelly 2009	This article does not describe results for the population of interest
140	Kikuchi 2007	This article does not describe results for the population of interest
141	Kotikoski 2002	The content of this article does not provide data that meet the objectives
142	Kroll 2006	The content of this article does not provide data that meet the objectives
143	Kumar 2009	This article does not describe results for the population of interest
144	Kunzi 2009	This article does not meet the CoCanCPG requirements on describing a cohort study
145	Kwong 2006	The content of this article does not provide data that meet the objectives
146	Laibl 2005	The article does not meet the CoCanCPG requirements for conducting a systematic review
147	Lambert 2005	The content of this article does not provide data that meet the objectives
148	Lambert 2007	This article does not describe results for the population of interest
149	Lapinsky 2010	The article does not meet the CoCanCPG requirements for conducting a systematic review
150	Larcombe 2010	The study population described in this article is too small to include in the review
151	Laundy 2003	This article does not describe results for the population of interest
152	Lee 2010	This article does not describe results for the population of interest
153	Lee 2010	This article does not describe results for the population of interest
154	Lemay 2008	The content of this article does not provide data that meet the objectives
155	Lenglet 2007	The content of this article does not provide data that meet the objectives
156	Leroux-Roels 2009	The article does not meet the CoCanCPG requirements for conducting a systematic review
157	Li 2007	The article does not meet the CoCanCPG requirements for conducting a systematic review
158	Li 2007	This article does not describe results for the population of interest
159	Li 2009	The article does not meet the CoCanCPG requirements for conducting a systematic review
160	Lister 2009	The content of this article does not provide data that meet the objectives
161	Loughlin 2003	The study period described in the article does not include the period of the review
162	Louie 2006	This article does not describe results for the population of interest
163	Louie 2009	The results in this article are described in another selected article that will be included in the evidence table
164	Lum 2009	The content of this article does not provide data that meet the objectives
165	Macey 2003	This article does not describe results for the population of interest
166	Mahlmeister 2009	The content of this article does not provide data that meet the objectives
167	Mak 2008	The content of this article does not provide data that meet the objectives
168	Manzoli 2007	The articles about Europe included in this review are judged/described seperately
169	Marchetti 2007	This study concerns a modelling study
170	Marès 2010	The article describes an advice that is not based on a systematic review
171	Mares Bermudez 2010	This article does not meet the CoCanCPG requirements for conducting a systematic review
172	Martin 2009	Another selected article describes the same study population but presents more complete or more recent data
173	Mashiba 2004	The study population described in this article is too small to include in the review, data from only one hospital
174	Matsuzaki 2006	The study period described in the article does not include the period of the review

175	Matsuzaki 2007	The content of this article does not provide data that meet the objectives
176	Mazick 2010	The content of this article does not provide data that meet the objectives
177	Meier 2000	The study period described in the article does not include the period of the review
178	Meijer 2006	This article does not describe results for the population of interest
179	Meijer 2007	This article does not describe results for the population of interest
180	Meissner 2001	The article does not meet the CoCanCPG requirements for conducting a systematic review
181	Meissner 2007	The article describes an advice that is not based on a systematic review
182	Meury 2004	The content of this article does not provide data that meet the objectives
183	Minino 2001	The content of this article does not provide data that meet the objectives
184	Minino 2006	The content of the article does not provide data for the objectives
185	Minino 2007	The content of this article does not provide data that meet the objectives
186	Mizuta 2004	The content of this article does not provide data that meet the objectives
187	Molinari 2007	The content of this article does not provide data that meet the objectives
188	Monto 2002	The article does not meet the CoCanCPG requirements for conducting a systematic review
189	Moore 2006	This article does not describe results for the population of interest
190	Morishima 2002	The content of this article does not provide data that meet the objectives
191	Munoz 2002	The article does not meet the CoCanCPG requirements for conducting a systematic review
192	Murakami 2007	This article does not describe results for the population of interest
193	National Advisory Committee on Immunisation (NACI) 2005	The article describes an advice that is not based on a systematic review
194	National Advisory Committee on Immunisation (NACI) 2006	The article describes an advice that is not based on a systematic review
195	Navarro-Mari 2003	This article does not describe results for the population of interest
196	Negri 2005	The articles about Europe included in this review are judged/described seperately
197	Newall 2008	The content of this article does not provide data that meet the objectives
198	Nicholson 2003	The content of this article does not provide data that meet the objectives
199	Nicoll 2008	The content of this article does not provide data that meet the objectives
200	Nicoll 2010	The article describes an advice that is not based on a systematic review
201	No authors listed 2005	This article does not describe results for the population of interest
202	No authors listed Arch Dis Child 2002	The content of this article does not provide data that meet the objectives
203	No authors listed Can Commun Dis Rep 2006	Another selected article describes the same study population but presents more complete or more recent data
204	No authors listed N.S.W.Public Health Bull 2002	This article does not describe results for the population of interest
205	No authors listed N.S.W.Public Health Bull 2003	This article does not describe results for the population of interest
206	No authors listed Wkly Epidemiol Rec 2002	The content of this article does not provide data that meet the objectives
207	No authors listed Wkly Epidemiol Rec, Epidemiological summary... 2009	This article does not describe results for the population of interest
208	No authors listed Wkly Epidemiol Rec, Human infection... 2009	The article describes an advice that is not based on a systematic review
209	Nougairède 2010	This article does not describe results for the population of interest
210	Nougairède 2010	This article does not describe results for the population of interest
211	Novel influenza A(H1N1) investigation team 2009	The results in this article are described in another article
212	Odaira 2009	This article does not describe results for the population of interest
213	Ohta 2007	This article does not describe results for the population of interest
214	Okumura 2005	The content of this article does not provide data that meet the objectives
215	Olson 2007	The content of this article does not provide data that meet the objectives
216	O'Riordan 2010	This article does not describe results for the population of interest
217	Ostlund 2004	The study period described in the article does not include the period of the review
218	Paget 2003	This article does not describe results for the population of interest
219	Paget 2005	The content of this article does not provide data that meet the objectives

220	Peltola 2002	The content of this article does not provide data that meet the objectives
221	Peltola 2003	The study period described in the article does not include the period of the review
222	Pineda Solas 2006	The article describes an advice that is not based on a systematic review
223	Pitman 2007	This article does not describe results for the population of interest
224	Plessa 2010	The study population described in this article is too small to include in the review
225	Ploin 2003	More complete data is available for this country
226	Podda 2003	The article does not meet the CoCanCPG requirements for conducting a systematic review
227	Podewils 2005	This article does not meet the CoCanCPG requirements for conducting a cohort study
228	Poland 2001	The article does not meet the CoCanCPG requirements for conducting a systematic review
229	Pons-Catalano 2003	The content of this article does not provide data that meet the objectives
230	Principi Emerg Infect Dis 2004	The article does not meet the CoCanCPG requirements for conducting a systematic review
231	Principi Arch Dis Child 2004	The content of this article does not provide data that meet the objectives
232	Principi Lancet Infect Dis 2004	This article does not meet the CoCanCPG requirements for conducting a systematic review
233	Principi Pedatr Infect Dis J 2003	The results in this article are described in another article
234	Prisco 2002	This article does not describe results for the population of interest
235	Quach 2003	This article does not describe results for the population of interest
236	Ramet 2007	The article does not meet the CoCanCPG requirements for conducting a systematic review
237	Rebmann 2008	The article does not meet the CoCanCPG requirements for conducting a systematic review
238	Regan Euro Surveill 2002	This article does not describe results for the population of interest
239	Reina 2005	The article does not meet the CoCanCPG requirements for conducting a systematic review
240	Rello 2009	The study population described in this article is too small to include in the review
241	Rennels 2002	This article does not meet the CoCanCPG requirements for conducting a systematic review
242	Reyes 2007	Another selected article describes the same study population but presents more complete or more recent data
243	Reyes 2008	Another selected article describes the same results
244	Rezza 2006	This article does not describe results for the population of interest
245	Richards 2005	The article describes an advice that is not based on a systematic review
246	Ritz 2008	The article does not meet the CoCanCPG requirements for conducting a systematic review
247	Rizzo 2009	The content of this article does not provide data that meet the objectives
248	Roberts 2006	More complete data is available for this country
249	Rodríguez 2010	The content of this article does not provide data that meet the objectives
250	Rothberg 2008	The article does not meet the CoCanCPG requirements for conducting a systematic review
251	Rubín 2010	This article describes a case serie or case report
252	Ryan 2006	The content of this article does not provide data that meet the objectives
253	Salo 2006	This is a modelling study
254	Sasaki 2005	This article does not describe results for the population of interest
255	Satpathy 2009	The article does not meet the CoCanCPG requirements for conducting a systematic review
256	Savidan 2008	The articles about Europe included in this review are judged/described seperately
257	Schanzer 2006	The content of this article does not provide data that meet the objectives
258	Schmitt-Grohe 2001	This article does not meet the CoCanCPG requirements for conducting a clinical trial
259	Sebastian 2008	The content of this article does not provide data that meet the objectives
260	Sebastian 2009	The article does not meet the CoCanCPG requirements for conducting a systematic review
261	Sessa 2001	This article does not describe results for the population of interest

262	Silvennoinen 2009	This article does not meet the CoCanCPG requirements for conducting a cohort study
263	Sivaprakasam 2008	The content of this article does not provide data that meet the objectives
264	Smith Cochrane Database Syst Rev 2006	The results in this article are described in another article
265	Smith MMWR Recomm Rep 2006 2006	The article describes an advice that is not based on a systematic review
266	Stowe 2009	The content of this article does not provide data that meet the objectives
267	Stuart 2009	The article describes an advice that is not based on a systematic review
268	Studahl 2003	The article does not meet the CoCanCPG requirements for conducting a systematic review
269	Sugaya 2002	This article does not describe results for the population of interest
270	Surveillance Group for New Influenza A(H1N1) Virus Investigation and Control in Spain 2009	This article does not describe results for the population of interest
271	Sypsa 2009	This concerns a modelling study
272	Szucs 2004	The article does not meet the CoCanCPG requirements for conducting a systematic review
273	Takanashi 2009	The study population described in this article is too small to include in the review
274	Takano 2009	The content of this article does not provide data that meet the objectives
275	Teo 2005	The article does not meet the CoCanCPG requirements for conducting a systematic review
276	Terebuh 2003	The article does not meet the CoCanCPG requirements for conducting a systematic review
277	Thompson 2003	The content of this article does not provide data that meet the objectives
278	Thompson 2004	The study period described in the article does not include the period of the review
279	Thompson 2006	The content of this article does not provide data that meet the objectives
280	Toovey 2008	The study period described in the article does not include the period of the review
281	Toschke 2008	The content of this article does not provide data that meet the objectives
282	Trollfors 2006	The article does not meet the CoCanCPG requirements for conducting a systematic review
283	Turbelin 2009	The content of this article does not provide data that meet the objectives
284	Turner 2003	The content of this article does not provide data that meet the objectives
285	Uphoff 2004	This article does not describe results for the population of interest
286	Vabret 2010	The article does not meet the CoCanCPG requirements for conducting a systematic review
287	Vaillant 2009	This article does not describe results for the population of interest
288	Vajo 2008	The study population described in this article is too small to include in the review
289	van der Wouden 2005	The results in this article are described in another article
290	van der Zee 2000	The study period described in the article does not include the period of the review
291	van Esso Arbolave 2006	The study population described in this article is too small to include in the review
292	van Zeijl 2004	The content of this article does not provide data that meet the objectives
293	Vesikari 2008	The article does not meet the CoCanCPG requirements for conducting a systematic review
294	Vynnycky 2008	This concerns a modelling study
295	Wahlberg 2003	The content of this article does not provide data that meet the objectives
296	Wang 2010	The article does not meet the CoCanCPG requirements for conducting a systematic review
297	Wareing 2001	The article does not meet the CoCanCPG requirements for conducting a systematic review
298	Wareing 2002	The content of this article does not provide data that meet the objectives
299	Watanabe 2003	The study population described in this article is too small to include in the review
300	Weil-Olivier 2004	The article does not meet the CoCanCPG requirements for conducting a systematic review
301	Weir 2003	The content of this article does not provide data that meet the objectives

302	Wesselius-de Casparis 1972	The study period described in the article does not include the period of the review
303	Whitley 2006	The article does not meet the CoCanCPG requirements for conducting a systematic review
304	Williams 2004	The article does not meet the CoCanCPG requirements for conducting a systematic review
305	Winzer 2009	This article does not describe results for the population of interest
306	Woo 2010	The article does not meet the CoCanCPG requirements for conducting a systematic review
307	Woods 2005	The article describes an advice that is not based on a systematic review
308	Wutzler 2006	The article does not meet the CoCanCPG requirements for conducting a systematic review
309	Yamanaka 2006	The content of this article does not provide data that meet the objectives
310	Zambon 2001	The study period described in the article does not include the period of the review
311	Zhao 2007	The content of this article does not provide data that meet the objectives
312	Zimmerman 2005	The content of this article does not provide data that meet the objectives

Embase

1	Black, 2004	The content of this article does not provide data that meet the objectives
2	Black, 2009	This article does not meet the CoCanCPG requirements for conducting a systematic review
3	Boyce, 2000	This article does not meet the CoCanCPG requirements for conducting a systematic review
4	Brent, 2006	This article does not meet the CoCanCPG requirements for conducting a systematic review
5	Bueno Campaña, 2010	The study population described in this article is too small to include in the review
6	Ehrlich, 2010	This article is a supplement
7	Hibbert, 2007	The content of this article does not provide data that meet the objectives
8	Lina, 2000	This article does not meet the CoCanCPG requirements for conducting a randomised controlled trial
9	Lindsay 2006	The study period described in the article does not include the period of the review
10	Lopez 2010	The content of this article does not provide data that meet the objectives
11	Munoz, 2005	The content of this article does not provide data that meet the objectives
12	Tamma 2010	The content of this article does not provide data that meet the objectives
13	Tamma 2009	This article does not meet the CoCanCPG requirements for conducting a systematic review
14	Tosh, 2008	This article does not meet the CoCanCPG requirements for conducting a systematic review
15	Tsai, 2010	The content of this article does not provide data that meet the objectives

Key authors

1	Neuzil Arch Pediatr Adolesc Med 2002	The study population described in this article is too small to include in the review, data from only one elementary school
2	Neuzil J Infect Dis 2002	The study period described in the article does not include the period of the review
3	Hartert 2003	The study period described in the article does not include the period of the review
4	Rasmussen 2008	The article does not meet the CoCanCPG requirements for conducting a systematic review

Annex 3. Summary tables

Table 2. Laboratory-confirmed pandemic influenza A(H1N1) incidence in children 0–4 years old

Author, year	Country	Season	Study population	No. of cases*	Outcome measure	Age group (years)	Results
Europe							
Donaldson, 2009[15]	England	2009 (July-Nov)	population of England, all ages	NA	estimated cumulative incidence per 100 000 population	< 1 1-4	1 000 1,100
Gilsdorf 2009[73]	Germany	2009 (April-Aug)	population of Germany, all ages	first 9,950 cases	cumulative incidence per 100 000 population	Up to 2	5.5
Hahné, 2009[74]	The Netherlands	2009 (April-June)	population of the Netherlands, all ages	51 indigenous cases	proportion of cases	0-4	4%
Poggensee 2010[75]	Germany	2009 (April-Nov)	population of Germany, all ages	53,968	proportion of cases	0-4	4%
Levy-Bruhl, 2009[76]	France	2009 (April-July)	population of France, all ages	90 indigenous cases	proportion of cases	0-9	30%
McLean 2010[14]	UK	2009 (April-June)	population of the UK, all ages (FF100 project)	392	proportion of cases	< 1 1-5	0.8% 9.2%
Other Western countries							
Appuhamy 2009[77]	Australia	2009 (April-June)	population of Queensland, all ages	593	cumulative incidence per 100 000 population	0-4	21.6
CDC, Ritger, 2009[6]	US	2009 (April-July)	Chicago residents, all ages	1,557	cumulative incidence per 100 000 population	0-4	113
Paine 2010[10]	New Zealand	2009 (April-Nov)	population of New Zealand, all ages	3,186	cumulative incidence per 100 000 population	< 1 1-4	223 97
Baker, 2009[78]	New Zealand	2009 (April- Aug)	population of New Zealand, all ages	3,179	cumulative incidence per 100 000 population	< 1	218.5
Reed 2009[79]	US	2009 (April-July)	population of the US, all ages	NA	estimated cumulative incidence (90% CI) per 100 000 population	0-4	1,870 (1,122-3,505)
Kelly, 2009[80]	Australia	2009 (April-July)	population of Victoria, all ages	221	proportion of cases	0-4	3%
New South Wales public health network 2009[9]	Australia	2009 (May-Aug)	population of New South Wales, all ages	5,106	relative risk (comparison with the general population)	0-4	1

** All cases were laboratory-confirmed cases.*

Table 3. Laboratory-confirmed pandemic influenza A(H1N1) incidence in children ≥ 5 years old

Author, year	Country	Season	Study population	No. of cases*	Outcome measure	Age group	Results
Europe							
Gilsdorf 2009[73]	Germany	2009 (April-Aug)	population of Germany, all ages	first 9,950 cases	cumulative incidence per 100 000 population	15-19	90
Donaldson 2009[15]	England	2009 (July-Nov)	population of England, all ages	NA	estimated cumulative incidence per 100 000 population	5-14	3,100
Poggensee 2010[75]	Germany	2009 (April-Nov)	population of Germany, all ages	53,968	proportion of cases	5-14	32%
McLean 2010[14]	UK	2009 (April-June)	population of the UK, all ages (FF100 project)	392	proportion of cases	6-15	42.3%

Author, year	Country	Season	Study population	No. of cases*	Outcome measure	Age group	Results
Levy-Bruhl, 2009[76]	France	2009 (April-July)	population of France, all ages	90 indigenous cases	proportion of cases	10-19	31%
Hahné, 2009[74]	The Netherlands	2009 (April-June)	population of the Netherlands, all ages	51 indigenous cases	proportion of cases	5-9 10-14 15-19	22% 16% 12%
Other Western countries							
CDC, Ritger[6]	US	2009 (April-July)	Chicago residents, all ages	1,557	incidence rate per 100 000 population	5-14	147
Appuhamy 2009[77]	Australia	2009 (April-June)	population of Queensland, all ages	593	cumulative incidence per 100 000 population	5-9 10-14 15-19	16.8 28.7 27.6
Paine 2010[10]	New Zealand	2009 (April-Nov)	population of New Zealand, all ages	3,186	cumulative incidence per 100 000 population	5-9 10-14 15-19	84 92 127
Kelly, 2009[80]	Australia	2009 (April-July)	population of Victoria, all ages	221	proportion of cases	15-19	37%
New South Wales Public Health network 2009[9]	Australia	2009 (May-Aug)	population of New South Wales, all ages	5,106	relative risk (comparison with the general population)	5-9 10-14 15-19	1.6 1.7 1.4

** All cases were laboratory-confirmed cases.*

Table 4. Laboratory-confirmed pandemic influenza A(H1N1) hospitalisations in children 0–4 years old

Author, year	Country	Season	No. of hospitalisations in total study group*	Outcome measure	Age group (years)	Results
Europe						
Cullen, 2009[4]	Ireland	2009 (April-Oct)	205 hospitalisations, all ages	hospitalisation rate per 100 000 population	0-4	9.7
Van 't Klooster 2010[3]	the Netherlands	2009 (June-Dec)	1,962 hospitalisations (non-ICU), all ages	hospitalisation (non-ICU) rate per 100 000 population	0-4	62.7
Fuhrman, 2010[1]	France	2009 (July-Nov)	514 hospitalised patients, 244 severe cases, all ages	rate of admission to ICU per 100 000 population	< 1	2.03
Koliou, 2009[13]	Cyprus	2009 (June-Aug)	5 hospitalised patients < 16 yrs	proportion hospitalisation of influenza cases	0-16	11% (5/45)
Nguyen-Van-Tam, 2010[2]	UK	2009 (April - Sept)	631 hospitalisations, all ages	proportion of hospitalised influenza cases	< 1 1-4	7% 9%
Fuhrman, 2010[1]	France	2009 (July-Nov)	514 hospitalised patients, 244 severe cases, all ages	proportion of hospitalised severe influenza cases	< 1 1-14	7% 13%
Other Western countries						
Baker, 2009[78]	New Zealand	2009 (April-Aug)	972 hospitalisations, all ages	hospitalisation rate per 100 000 population	< 1	149.8
CDC (Ritger), 2009[6]	US	2009 (April-July)	205 hospitalisations, all ages	hospitalisation rate per 100 000 population	0-4	25
CDC (Brammer), 2010[7]	US	2009 (Aug-Jan)		hospitalisation rate per 100 000 population	0-4	59
New South Wales Public Health Network 2009[9]	Australia	2009 (May-Sept)	1,214 hospitalisations, all ages	hospitalisation rate per 100 000 population	0-4	56.5
Reed, 2009[79]	US	2009 (April-July)	2,768 estimated hospitalisations, < 5 yrs	estimated hospitalisation rate (90% CI) per 100 000 population	0-4	13.0 (8.8-20.2)

Author, year	Country	Season	No. of hospitalisations in total study group*	Outcome measure	Age group (years)	Results
Presanis, 2009[11]	US	2009 (April-July)	259 hospitalisations, < 5 yrs	estimated proportion of cases that result in hospitalisation (95% CI)	0-4	2.45 (1.10%-5.56%)
Bettinger, 2010[5]	Canada	2009 (May-Aug)	235 hospitalised patients <16 yrs	proportion of hospitalised patients	< 3 months 3-5 months 6-23 months 2-5 yrs	6.4% 3.8% 20.9% 28.1%
Jain, 2009[8]	US	2009 (May-June)	272 hospitalisations, all ages	proportion of hospitalised patients	0-2 2-4	8% 7%
Tuite, 2010[12]	Canada	2009 (April-June)	140 hospitalisation, all ages	risk (odds ratio (95% CI) of hospital admission	< 1 1-11	5.86 (2.65-12.94) 1.46 (0.95-2.26)

** All cases were laboratory-confirmed cases.*

Table 5. Laboratory-confirmed pandemic influenza A(H1N1) hospitalisations in children ≥5 years old

Author, year	Country	Season	No. of hospitalisations in total study group*	Outcome measure	Age group (years)	Results
Europe						
Cullen, 2009[4]	Ireland	2009 (April-Oct)	205 hospitalisations, all ages	hospitalisation rate per 100 000 population	5-9 10-14 15-19	6.1 4.7 10.2
Van 't Klooster 2010[3]	the Netherlands	2009 (June-Dec)	1,962 hospitalisations (non-ICU), all ages	hospitalisation (non-ICU) rate per 100 000 population	5-14	19.3
Nguyen-Van-Tam, 2010[2]	UK	2009 (April - Sept)	631 hospitalisations, all ages	proportion of hospitalised patients	5-15	20%
Other Western countries						
CDC (Ritger), 2009[6]	US	2009 (April-July)	205 hospitalisations, all ages	hospitalisation rate per 100 000 population	5-14	11
CDC (Brammer), 2010[7]	US	2009 (Aug-Jan)		hospitalisation rate per 100 000 population	5–17	25
Paine, 2010[10]	New Zealand	2009 (April-Nov)	1,008 hospitalised patients, any age	hospitalisation rate per 100 000 population	5-9 10-14 15-19	17 19 23
New South Wales, 2009[9]	Australia	2009 (May-Sept)	1,214 hospitalisations, all ages	hospitalisation rate per 100 000 population	5-9 10-14 15-19	15.8 9.6 13.6
Presanis, 2009[11]	US	2009 (April-July)	232 hospitalisations, 5-17 yrs	estimated proportion of cases that result in hospitalisation (95% CI)	5-17	0.61% (0.27%-1.34%)
Bettinger, 2010[5]	Canada	2009 (May-Aug)	235 hospitalised patients <16 yrs	proportion of hospitalised patients	6-12 13-15	26.8% 14%
Jain, 2009[8]	US	2009 (May-June)	272 hospitalisations, all ages	proportion of hospitalised patients	5-9 10-17	11% 18%
Tuite, 2010[12]	Canada	2009 (April-June)	140 hospitalisation, all ages	risk (odds ratio (95% CI) of hospital admission	12-18	0.45 (0.26-0.81)

** All cases were laboratory-confirmed cases.*

Table 6. Laboratory-confirmed pandemic influenza A(H1N1) mortality in children 0-4 years old

Author, year	Country	Season	Study population	Influenza hospitalisations	No. of fatal cases	Outcome measure	Age group (years)	Results
Europe								
Van 't Klooster, 2010[3]	The Netherlands	2009 (June-Dec)	population of the Netherlands, all ages	1,962	53	mortality rate per 100 000 population	0-4	0.54
Donaldson 2009[15]	England	2009 (July-Nov)	population of England, all ages	NR	138	estimated case fatality rate (range) per 100 000 cases	< 1 1-4	30 (2-260) 27 (3-120)
						proportion of children among deaths	< 1 1-4	2 of 138 (1%) 7 of 138 (5%)
Cullen, 2009[4]	Ireland	2009 (April-Oct)	population of Ireland, all ages	205	4	proportion of children among deaths	0-4	0%
Fuhrman, 2010[1]	France	2009 (July-Nov)	population of France, all ages	514	37 fatal cases in hospitalised population	proportion of children among deaths	< 1	2 of 37 (5%)
						proportion fatal cases of age-specific hospitalised severe influenza cases	< 1	2 of 16 (12.5%)
Koliou, 2009[13]	Cyprus	2009 (June-Aug)	children of Cyprus, < 16 yrs	5	0	proportion of children among deaths	0-4	0%
McLean, 2010[14]	UK	2009 (April-June)	population of the UK, all ages	NR	0	proportion of children among deaths	0-4	0%
Pebody, 2010[16]	England	April 2009 – March 2010	Population on England, all ages	NR	336 fatal cases with information on age	Proportion of children among deaths	6 months	4 of 336 (1%)
Other Western countries								
CDC, 2010 (Brammer)[7]	US	2009 (Aug-Jan)	large sample of the population, all age	NR	1,779	mortality rate per 100 000 population	0-4	0.31
Kamigaki 2009[18]	Japan	2009 (April-Dec)	population of Japan, all ages	10,487	85	mortality rate per 100 000 population	0-4	0.2
New South Wales Public Health network 2009[9]	Australia	2009 (May-Aug)	population of New South Wales, Australia, all ages	1,214	48	mortality rate per 100 000 population	0-4	0.0
Presanis, 2009[11]	US	2009 (April-July)	population of Milwaukee and New York City, all ages	259	132	estimated proportion of cases that result in death (95% CI) in total US population	0-4	0.026% (0.006%-0.092%)
CDC (Shannon)2009[17]	US	2009 (April-Aug)	population of US, < 18 yrs	NR	36	proportion of children among deaths	0-4	7 of 36 (19%)
Bettinger, 2010[5]	Canada	2009 (May-Aug)	paediatric patients in Canada, < 16 yrs	253	2	proportion of deaths among reported cases in age group	0-6 months 6-23 months 2-5 yrs	0 of 24 (0%) 0 of 39 (0%) 0 of 66 (0%)
Paine, 2010[10]	New Zealand	2009 (April-Nov)	population of New Zealand, all ages	263	19	proportion of children among deaths	<1 1-4	0 of 19 (0%) 1 of 19 (5.3%)
						proportion of deaths among reported cases in age group	<1 1-4	0 of 143 (0%) 1 of 230 (<1%)

Table 7. Laboratory-confirmed pandemic influenza A(H1N1) related mortality in children ≥ 5 years old

Author, year	Country	Season	Study population	Influenza hospitalisations	No. of fatal cases	Outcome measure	Age group (years)	Results
Europe								
Van 't Klooster, 2010[3]	Netherlands	2009 (June-Dec)	population of Netherlands, all ages	1,962	53	mortality rate per 100 000 population	5-14	0.45
Donaldson 2009[15]	England	2009 (July-Nov)	population of England, any age	NR	138	estimated case fatality rate (range) per 100 000 cases	5-14	11 (3-36)
						proportion of children among deaths	5-14	20 of 138 (14%)
Cullen, 2009[4]	Ireland	2009 (April-Oct)	population of Ireland, all ages	205	4	proportion of children among deaths	5-15	0%
Fuhrman, 2010[1]	France	2009 (July-Nov)	population of France, any age	514	37 fatal cases in hospitalised population	proportion of children among deaths	1-14	3 of 37 (8%)
					244 hospitalised severe influenza cases	proportion of deaths among age-specific hospitalised severe influenza cases	1-14	3 of 32 (9.4%)
Koliou, 2009[13]	Cyprus	2009 (June-Aug)	children of Cyprus, < 16 yrs	5	0	proportion of children among deaths	5-16	0%
McLean, 2010[14]	UK	2009 (April-June)	population of the UK, all ages	NR	0	proportion of children among deaths	5-15	0%
Nguyen-Van-Tam, 2010[2]	UK	2009 (April-Sept)	hospitalised patients in the UK, all ages	631	29	case fatality rate in hospitalised patients	0-15	3.5%
Other Western countries								
CDC, 2010 (Brammer)[7]	US	2009 (Aug-Dec)	large sample of the population, all age	NR	1,779	mortality rate per 100 000 population	5-18	0.26
Kamigaki 2009[18]	Japan	2009 (April-Dec)	population of Japan, all ages	10,487	85	mortality rate per 100 000 population	5-9 10-14 15-19	0.1 0.07 0.02
New South Wales Public Health network 2009[9]	Australia	2009 (May-Aug)	population of New South Wales, Australia, all ages	1,214	48	mortality rate per 100 000 population	5-9 10-14 15-19	0.2 0.0 0.0
Presanis, 2009[11]	US	2009 (April-July)	population of Milwaukee and New York City, all ages	232	132	estimated proportion of cases that result in death (95% CI) in total US population	5-17	0.010% (0.003%-0.031%)
CDC (Shannon), 2009[17]	US	2009 (April-Aug)	population of US, < 18 yrs	NR	36	proportion of children among deaths	5-17	29 of 36 (81%)
Fielding, 2009[59]	Australia	2009 (May-Sept)	population of Victoria, Australia, all ages	NR	24	proportion of children among deaths	0-18	3 of 24 (12.5%)
Paine, 2010[10]	New Zealand	2009 (April-Nov)	population of New Zealand, any age	263	19	proportion of children among deaths	5-9 10-14 15-19	1 of 19 (5.3%) 0 of 19 (0%) 0 of 19 (0%)

Author, year	Country	Season	Study population	Influenza hospitalisations	No. of fatal cases	Outcome measure	Age group (years)	Results
						proportion of fatal cases of age-specific notified influenza cases	5-9 10-14 15-19	1 of 241 (<1%) 0 of 279 (0%) 0 of 410 (0%)
Bettinger, 2010[5]	Canada	2009 (May-Aug)	paediatric patients in Canada, < 16 yrs	235	2	proportion of deaths among reported cases in age group	6-12 13-16	2 of 63 (3%) 0 of 33 (0%)

Table 8. Complications of laboratory-confirmed pandemic influenza A(H1N1) in children

Author, year	Country	Season	Study population	No. of included cases	Age group (years)	Outcome measure	Results
Europe							
Nguyen-Van-Tam, 2010[2]	UK	2009 (April-Sept)	Hospitalised patients in the UK, all ages	226 hospitalised children	< 18	proportion of cases with pneumonia	37 of 106* (35%)
Other Western countries							
Bettinger, 2010[5]	Canada	2009 (May-Aug)	Children < 16 yrs in Canada	324 hospitalised cases	< 16	proportion of cases with: • Lower respiratory tract manifestations** • Febrile/afebrile seizures • Encephalitis • Aseptic meningitis	 67% 4% 1% <1%

** Chest radiographic results were recorded in 106 children*

*** Lower respiratory tract manifestations are either respiratory distress, wheezing or radiologically confirmed pneumonia.*

Table 9. Seasonal influenza-like-illness incidence in children 0–4 years old

Author, year	Country	Season	Study population	Sample size	Outcome measure	Age group (years)	Results
Europe							
Castilla 2006[81]	Spain	2004-2005	population of Navarra	22,339 inhabitants	cumulative incidence of ILI consultations per 100 000 inhabitants	0-4	3,950
Dijkstra 2009[82]	The Netherlands	1986-2007	population of Netherlands, all ages	NA	annual incidence range of ILI consultations per season per 100 000 population	< 5	1,550 (2002-2003) – 10,110 (1988-1989)
Paget 2010[83]	England Italy The Netherlands Spain	2002-2008	population of England, Italy, Netherlands, and Spain, all ages	NA	average incidence of ILI consultations per 100 000 population	0-4	England: 354 Italy: 9229 Netherlands: 925 Spain: 2,156
Heikkinen 2003[84]	Finland	2000-2001	children < 13 years old in area of Turku University Hospital	1,338	cumulative attack rate	0-13	18.8%
Payne 2005[85]	Sweden	Week 7 (14-20 February), 2005	random sample of the Swedish population, all ages	2,119	One-week prevalence of self-reported influenza	0-4	15.6% (95% CI: 8.3 to 22.8)
Other Western countries							
Fluwatch Project (Macey) 2001[86]	Canada	2000-2001	population of Canada, all ages	NA	ILI peak incidence per 100 000 population	≤ 5	2,500

Author, year	Country	Season	Study population	Sample size	Outcome measure	Age group (years)	Results
Squires 2000[87]	Canada	1999-2000	population of Canada, all ages	NA	• cumulative incidence of ILI consultations per 100 000 • proportion of cases	1-4 1-4	7,800 16.2%
Public Health Agency of Canada 2006[28]	Canada	2004-2005	population of Canada, all ages	NA	• ILI consultations peak incidence per 100 000 • proportion of cases among total group	0-4	14,900 12.4% of total cases
Kawado 2007[88]	Japan	2002-2005	Population of Japan, all ages	NA	estimated annual incidence per 100 000 population, range	0-14 females 0-14 males	22,340 – 46,170 23,870 – 49,040

Table 10. Seasonal influenza-like-illness incidence in children ≥ 5 years old

Author, year	Country	Season	Study population	Sample size	Outcome measure	Age group (years)	Results
Europe							
Castilla 2006[81]	Spain	2004-2005	population of Navarra	22,339 inhabitants	cumulative incidence per 100 000 inhabitants	5-14	5,040
Paget 2010[83]	England Italy Netherlands Spain	2002-2008	population of England, Italy, Netherlands, and Spain, all ages	NA	average incidence of ILI consultations per 100 000 population	5-14	England: 315 Italy:8,915 Netherlands: 632 Spain: 2,955
Payne 2005[85]	Sweden	Week 7 (14-20 February), 2005	random sample of the Swedish population, all ages	2,119	prevalence of self-reported influenza	5-14	13.0% (95% CI, 8.5 to 17.5)
Other Western countries							
Fluwatch Project (Macey) 2001[86]	Canada	2000-2001	population of Canada, all ages	NA	ILI peak incidence per 100 000 population	5-19	2,700
Public Health Agency of Canada 2006[28]	Canada	2004-2005	population of Canada, all ages	NA	ILI consultations peak incidence per 100 000	5-19	10,300
Squires 2000[87]	Canada	1999-2000	population of Canada, all ages	NA	ILI cumulative incidence per 100 000	5-9 10-14	6,100 NR
					• proportion of cases	5-9 10-14	3.4% 1.9%

Table 11. Seasonal influenza-like-illness or laboratory-confirmed incidence in children 0–18 years old

Country	Season	Study population	Outcome measure	Age group (years)	Results
Europe					
England[a]	2002-2005	population of England, all ages	peak ILI consultation rates per 100 000 population	0-4 5-14	2002-2003: 54 2003-2004: 157 2004-2005: 62 2002-2003: 59 2005-2006: 97.6
France[b]	2005-2008	population of France, all ages	proportion of cases	0-14	2005: 28.5% 2006: 44.1% season 2006-2007: 33.7% season 2007-2008: 32.7%
Sweden[d]	2006-2008	population of Sweden, all ages	observed and expected number of cases[xvi]	0-4 5-14	observed 2006-2007: 43 expected 2006-2007: 43 observed 2007-2008: 26 expected 2007-2008: 32 observed 2006-2007: 69 expected 2006-2007: 87 observed 2007-2008: 71 expected 2007-2008: 65

[xvi] 'Expected' is the number of cases that would have occurred if the cases were evenly distributed in relation to the population of

Country	Season	Study population	Outcome measure	Age group (years)	Results
Other Western countries					
Australia[e]	2001-2008	population of Australia, all ages	notification of laboratory-confirmed influenza rate per 100 000 population, range	< 1 0-4 5-9	2003-2006: 75-257 2001-2008: 32.1-166 2001: 11.6 2007: 68 2008: 54
Canada[f]	2000-2008	population of Canada, all ages	proportion of laboratory confirmed cases (range)	0-4 5-9 10-14	22% (11-33%) 9% (3-20%) 6% (2-19%)
New Zealand[g]	2003-2009	population of New Zealand, all ages	average weekly ILI consultation rates per 100 000 population, range	< 1 1-4 5-19	44-136.5 52.4-173.9 40.4-93.6

[a] *http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/SeasonalInfluenza/EpidemiologicalData/07influsInfluenzaannualreports/)*

[b] *Bilans annuels 2005-2008, Le réseau Sentinelles, http://websenti.b3e.jussieu.fr/sentiweb/?rub=39*

[c] *http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/*

[d] *http://www.smittskyddsinstitutet.se/publikationer/arsrapporter-och-verksamhetsberattelser/smis-arsrapporter-om-influensasasongen/)*

[e] *http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-ozflu-2010.htm*

[f] *http://www.phac-aspc.gc.ca/fluwatch/archive-eng.php*

[g] *http://www.surv.esr.cri.nz/virology/influenza_annual_report.php*

Table 12. Laboratory-confirmed seasonal influenza hospitalisations in children 0–4 years old

Author, year	Country	Season	No. of hospitalisations in total study group	Outcome measure	Age group (years)	Results
Europe						
Forster, 2004[89]	Germany	1999-2001	77 hospitalisations, < 3 yrs	annual hospitalisation rate (95% CI) per 100 000 population	< 3	123 (90-163)
Heikkinen, 2004[90]	Finland	2000-2002	1 hospitalisation, < 13 yrs	annual hospitalisation rate per 100 000 population	< 3	135
Ploin, 2007[33]	France	2001-2002	28 hospitalisations, < 3 yrs	hospitalisation rate per 100 000 population	< 1 1-2 2-3	237 44 23
Montes, 2005[32]	Spain	2001-2004	49 hospitalisations, < 5 yrs	3 year hospitalisation rate range per 100 000 population	< 6 months 6-11 months 1-< 2 2-< 5	0-730 0-170 30-110 10-80
Rojo, 2006[34]	Spain	1996-2003	146 hospitalisation, < 3 yrs	8 year annual hospitalisation rate range per 100 000 population	< 3	11-154
Weigl, 2002[19]	Germany	1996-2001	122 (infl. A) hospitalisations, ≤16 yrs	proportion of cases due to influenza A	0-1 > 1-2 > 2-5	24.5% 23.5% 33.3%
Other Western countries						
CDC (Gershman), 2005[22]	US	2004-2005	238 hospitalisations, < 18 yrs	hospitalisation rate per 100 000 population	< 6 months 6-23 months 2-4	183.0 66.3 28.9
Grijalva, 2006; Grijalva, 2006 [91;92]	US	2003-2005	NR	hospitalisation rate per 100 000 population of two consecutive years	< 6 months 6-23 months 2-5	438-910 96-300 20-80

the respective age groups.

Author, year	Country	Season	No. of hospitalisations in total study group	Outcome measure	Age group (years)	Results
CDC (Dhara), 2005; CDC Blanton, 2007; CDC (Epperson), 2008; CDC (Peebles), 2009[21;23-25]	US	2004-2009	NR	4 year of hospitalisation rate range per 100 000 population	NVSN 0-4 EIP 0-4	 14.6-70 16.2-40.3
Poehling, 2006[31]	US	2000-2004	160 hospitalisations, < 5 yrs	4 years range of hospitalisation rate (95% CI) per 100 000 population	< 6 months 6-23 months 2-5	230-720 40-150 4-60
Dawood, 2010[26]	US	2003-2008	4015 hospitalisation, < 18 yrs	5 years range of hospitalisation rate per 100 000 population	< 6 months 6-23 months 2-4	90-300 30-110 10-40
D'Onise, 2008[93]	Australia	1996-2006	649 hospitalisations, < 5 yrs	11 years range of hospitalisation rate per 100 000 population	< 1 1 2 3 4	11.6-289.0 5.8-198.5 0-123.2 5.4-60.4 0-50.9
Hassan, 2009[27]	US	2003 (Jan-Dec)	20,618 hospitalisations without chronic diseases, <18 yrs	proportion of hospitalised cases without chronic diseases	0-5 months 6-23 months	23% 22%
PHAC, 2006; Reyes 2007; Burton, 2008; Reyes, 2008[20;28-30]	Canada	2004-2008	1608 hospitalisations, < 16 yrs	4 years range of proportion of hospitalised patients	0-5 months 6-23 months 2-4	14,2%-23,0% 24,3%-31,7% 20,2%-27.3%

Table 13. Laboratory-confirmed seasonal influenza hospitalisations in children ≥5 years old

Author, year	Country	Season	No. of hospitalisations in total study group	Outcome measure	Age group (years)	Results
Europe						
Weigl, 2002[19]	Germany	1996-2001	122 (infl. A) hospitalisations, ≤ 16 yrs	proportion of cases due to influenza A	> 5-16	18.6%
Other Western countries						
CDC (Gershman), 2005[22]	US	2004-2005	238 hospitalisations, < 18 yrs	hospitalisation rate per 100 000 population	5-17 yrs	6.1
CDC (Dhara), 2005; CDC (Blanton), 2007; CDC (Epperson), 2008; CDC (Peebles), 2009 [21;23-25]	US	2004-2009	NR	4 year range hospitalisation rate per 100 000 population	EIP 5-17	2.3-6
Dawood, 2010[26]	US	2003-2008	4015 hospitalisation, < 18 yrs	5 year range of hospitalisation rate per 100 000 population	5-17 yrs	3-8
Public Health Agency of Canada, 2006; Reyes 2007; Burton, 2008; Reyes, 2008[20;28-30]	Canada	2004-2008	1608 hospitalisations, < 16 yrs	4 year range of proportion of hospitalised patients	5-15 yrs	24.5%-34,2%
Hassan, 2009[27]	US	2003 (Jan-Dec)	20,618 hospitalisation without chronic diseases, <18 yrs	proportion of hospitalised cases without chronic diseases	2-18 yrs	55%

Table 14. Laboratory-confirmed seasonal influenza-related mortality in children 0–4 years old

Author, year	Country	Season	Study population	Influenza hospitalisations	No. of fatal cases	Outcome measure	Age group (years)	Results
Europe								
Montes, 2005[32]	Spain	2001-2004	children hospitalised in a province in Spain, <5 yrs	49	0	proportion of children among deaths	0-4	0%
Rojo, 2006[34]	Spain	1996-2003	hospitalised patients in a hospital in Madrid, <3 yrs	146	0	proportion of children among deaths	0-2	0%
Ploin, 2007[33]	France	2002 (4 wks peak of epidemic)	children visiting a paediatric emergency department, <3 yrs	283	0	number of fatal influenza cases during follow up	0-2	0%
Other Western countries								
Burton, 2008[20]	Canada	2006-2007	paediatric patients <16 yrs, large sample of paediatric hospitals in Canada	371	2	proportion of children among deaths	0-4	0%
Dawood, 2010[26]	US	2003-2008	large sample of US children <18 yrs	4,015	17	proportion of children among deaths	< 6 months 6-23 months 2-4 yrs	3 of 17(18%) 1 of 17 (6%) of 17 (18%)
Roberts, 2006[35]	Canada	(Jan) 2004-(April) 2005	children <16 yrs within the metropolitan Toronto and Peel region	184	0	proportion of children among deaths	0-4	0%
D'Onise, 2008[93]	Australia	1996-2006	paediatric population in South Australia, <5 yrs	649	4	proportion of fatal cases among hospitalised influenza cases	0-4	4 of 649 (<1%)
Finelli, 2008; CDC (Epperson), 2008[24;36]	US	2004-2008	all children <18 yrs in the US	NR	249	proportion of fatal influenza cases, range 4 seasons	< 6 months 6-23 months 2-4 yrs	11%-17% 8%-28% 10%-20%

Table 15. Laboratory-confirmed seasonal influenza-related mortality in children ≥ 5 years old

Author, year	Country	Season	Study population	Influenza hospitalisations	No. of fatal cases	Outcome measure	Age group (years)	Results
Other Western countries								
Dawood, 2010[26]	US	2003-2008	Representative sample of US children < 18 yrs	4,015	17	proportion of children among deaths	5-17	10 (59%)
						proportion of deaths among hospitalised cases	0-17	17 of 4015 (<1%)
Roberts, 2006[35]	Canada	(Jan) 2004-(April) 2005	children < 16 yrs within the metropolitan Toronto and Peel region	184	0	proportion of children among deaths	5-15	0%
CDC, (Epperson), 2008; Finelli, 2008[24;36]	US	2004-2008	all children <18 yrs in the US	NR	249	proportion of fatal influenza cases, range 4 seasons	5-17	43-58%

Author, year	Country	Season	Study population	Influenza hospitalisations	No. of fatal cases	Outcome measure	Age group (years)	Results
PHAC 2006; Reyes, 2007; Reyes, 2008; Burton, 2008 [20;28-30]	Canada	2004-2008	Representative sample of population <16 yrs, Canada	1,608	11	4 seasonal mean (range) case fatality rate	0-15	0.7% (0.4%-1.3%)

Table 16. Complications of laboratory-confirmed seasonal influenza in children 0–5 years old

Author, year	Country	Season	Study population	No. of included cases	Age group (years)	Outcome measure	Results
Europe							
Forster, 2004	Germany	1999–2001	Paediatric patients of paediatric practices and referral children's hospitals in four cities in Germany	54 outpatients 77 inpatients	< 3	Proportion of outpatients with: • Croup • Bronchiolitis • Bronchitis • Pneumonia Proportion of inpatients with: • Croup • Bronchiolitis • Bronchitis • Pneumonia • Apnoea	 4.2% 2.7% 5.5% 5.1% 4.3% 2.8% 9.2% 4.0% 2.3%
Montes, 2005	Spain	2001–2004	Children who were hospitalised for more than 24 hours with confirmed influenza virus infection in three regions of Spain	49 children	< 5	Proportion of cases with: • Bronchiolitis • Pneumonia • Bronchitis • Croup • ARI • Febrile syndrome with only minor respiratory symptoms (rhinorrhea, cough)	 24.5% 18.4% 6.1% 2.0% 26.5% 22.4%
Ploin, 2007	France	2002	Children <36 months visiting the paediatric emergency department of a hospital in Lyon	283 children	< 3	Proportion of cases with: • Rhinopharyngitis • Isolated fever • Otitis media • Bronchitis • Pneumonia	 54% 22% 6% 6% 0.4%
Rojo, 2006	Spain	1996–2003	Hospitalised children <3 years in a hospital in Madrid	117 hospitalised cases	< 3	Proportion of cases with: • Pneumonia • Acute otitis media	 21% 8.5%
Other Western countries							
Krief, 2009	US	1998–2001	Infants in five different paediatric emergency departments	123 infants	< 60 days of age	Proportion of cases with: • Urinary tract infections • Wheezing • Bronchiolitis • Lobar pneumonia	 2.4% 1.6% 6.5% 2.8%
Poehling 2006	US	2002–2004	Patients of hospitals in two US counties	160 hospitalised cases	< 5	Proportion of cases with: • Otitis media • Pneumonia • Seizures	 28% 6% 1%

Table 17. Complications of laboratory-confirmed seasonal influenza in children 0–18 years old

Author, year	Country	Season	Study population	No. of included cases	Age group (years)	Outcome measure	Results
Europe							
Heikkinen, 2004[90]	Finland	2000-2002	Children <13 years in Finland	370 children	< 13	Proportion of cases with: • Acute otitis media • Pneumonia • Sinusitis	 23% 2.4% 3.5%
Lahti, 2006[95]	Finland	1980-2003	Paediatric patients of Department of Paediatrics, Turku University Hospital	936 children	0-16	Proportion of cases with: • Pneumonia • Acute otitis media	 14% 43%
Ros Aranal, 2008[96]	Spain	2002-2006	Children with influenza admitted to the Miguel Servet Children's Hospitals in Zaragoza, Spain	178 hospitalised cases	< 15	Proportion of cases with: • Upper respiratory tract infection • Acute otitis media • Bronchitis/bronchiolitis • Pneumonia • Gastroenteritis • Myositis	 30.6% 27% 16.9% 10.5% 7.6% 1.7%
Tsolia, 2006[97]	Greece	2003-2005	Outpatients >6 months to <14 yrs of a hospital and seven paediatric practices in Athens area	573 outpatients	> 6 months-<14 yrs	Proportion of cases with: • Otitis media • Bronchial- asthma • Pneumonia • Croup • Febrile seizures	 15% 8% 1.7% 1.7% 1.6%
Weigl, 2002[19]	Germany	1996-2001	Children admitted to one of the local paediatric hospitals with any acute respiratory infection in Kiel	102 influenza A patients	0-16	Proportion of influenza A cases with: • Otitis media • Severe anaemia • Syncope	 25% 1% 1%
				14 influenza B patients		Proportion of influenza B cases with: • Otitis media • Myositis of the calf • Muscles	 0% 7.1%
Other Western countries							
Burton, 2008[20]	Canada	2006-2007	Children < 16 yrs in Canada	371 hospitalised cases	< 16	Proportion of cases with: • Respiratory distress • Pneumonia • Croup • Otitis media • Myositis • Bacterial co-infection	 42% 17% 3% 2% 2% 7%
Dawood, 2010[26]	US	2003-2008	Children < 18 yrs in the US	4015 hospitalised cases	< 18	Proportion of cases with: • Pneumonia • Bacterial coinfection	 36% 2%
Finelli, 2008[36]	US	2004-2005	All influenza-associated death of patients <18 yrs in the US	47 deaths	0-17	Proportion of influenza-associated deaths with: • Bacterial coinfection	 6%
		2005-2006		46 deaths	0-17	Bacterial coinfection	15%
		2006-2007		73 deaths	0-17	Bacterial coinfection	35%
Newland, 2007[98]	US	2000-2004	Paediatric patients admitted to a Hospital in Philadelphia	842 hospitalised cases	0-18*	Proportion of cases with: • Seizures • febrile seizures • seizures with fever • other seizures • encephalopathy • Post-infectious encephalopathy	 7% 3% 1% 2% 1% 0%

Author, year	Country	Season	Study population	No. of included cases	Age group (years)	Outcome measure	Results
Schrag, 2006[99]	US	2003-2004	Hospitalised children <18 years in 54 counties, including >100 hospitals, in the US	1,161 patients with influenza-related hospitalisation not admitted to ICU	0-17	Proportion of cases not admitted to ICU with: • Bacterial coinfection • Pneumonia • Bronchiolitis	 0.5% 22% 6%
				147 patients with influenza-related hospitalisation admitted to ICU	0-17	Proportion of cases admitted to ICU with: • Bacterial coinfection • Pneumonia • Bronchiolitis	 6% 34% 3%

** 36 of the 842 cases were ≥ 18 years old.*

Table 18. Pandemic influenza A(H1N1) hospitalisations in pregnancy

Author, year	Country	Season	No. of hospitalisations in total study group*	Outcome measure	Trimester	Results
Europe						
CDC, 2010[55]	Greece	2009/2010 (May-Feb)	294 (ICU admissions)	Proportion of pregnant women	-	4.4%
Cullen, 2009[4]	Ireland	2009 (April-Oct)	180	Proportion pregnant women	-	6.7%
Fuhrman, 2010[1]	France	2009 (July-Nov)	244 severe cases of whom 117 women	Proportion pregnant women: • hospitalised women; • ICU cases	-	 15.4%; 13%
Nguyen Van-Tam, 2010[2]	UK	2009 (April-Sept)	631	• Proportion of pregnant women • Proportion of pregnant women in study population 16-44 yrs; • expected prevalence in source population	1st 2nd 3rd unknown -	0.3% 2.1% 1.3% 0.6% 18% of admissions 6%
Van 't Klooster 2010[3]	The Netherlands	2009 (June-Dec)	• 1 722 non-ICU admissions (with information available) • 211 ICU admissions (with information available)	Proportion of pregnant women	1st 2nd 3rd Total 1st 2nd 3rd Total	0.2% 0.9% 2.1% 3.5% 0.5% 0.5% 2.4% 3.8%
Other Western countries						
ANZIC, 2009[60]	Australia; New Zealand	2009 (June-August)	722 ICU admissions	Proportion pregnant women	-	9.1%
ANIZC, 2010[61]	Australia	2009 (June-August)	209 childbearing age (15-44 yrs old) admitted to ICU	Proportion of pregnant/postpartum women admitted to ICU	- < 20 weeks ≥ 20 weeks Postpartum	31% 15.6% 76.6% 7.8%
CDC, 2009[6]	US (Chicago)	2009 (April-July)	205	Proportion pregnant women	-	7%
Creanga, 2010[56]	US	2009 (May-June)	976	• Proportion pregnant women • Hospitalisation rate pregnant women per 100 000 population • Hospitalisation rate non-pregnant reproductive-aged women per 100 000 population	- - -	6.4% 55.3 7.7

Author, year	Country	Season	No. of hospitalisations in total study group*	Outcome measure	Trimester	Results
Denholm, 2010[57]	Australia	2009 (May-July)	112 of which 27 admitted to ICU	Proportion of pregnant women: • hospitalisations • ICU admissions	-	 13% 19%
Fielding, 2009[59]	Australia	2009 (April-Sept)	415 of which 108 ICU admissions	Proportion of pregnant cases: • Ward-based • ICU admissions		 6.3% 8.3%
Hewagama, 2010[62]	Australia	2009 (May-July)	43 pregnant women	• Proportion pregnant women per trimester • Proportion ICU admissions • Estimated hospitalisation rate	1st 2nd > 28 wks > 37 wks - 2nd 3rd	5% 30% 28% 37% 18.6% 0.21% 0.46%
Jain, 2009[8]	US	2009 (May-June)	272 hospitalisations of which 67 ICU admissions	Proportion of pregnant women: • hospitalised • ICU • Proportion pregnant women per trimester	- 1st 2nd 3rd	 7% 9% 11% 17% 67%
Kelly, 2009[58]	Australia	2009 (May-Oct)	4833 of which 650 ICU admitted	Proportion pregnant women: • hospitalisations; • Rate per 100 000 • ICU admissions • Rate per 100 000		 5.8% 117.2 47 19.8
Louie, 2010[63]	US	2009 (April-August)	239 women reproductive age	Proportion of pregnant women: • hospitalisations • Proportion pregnant women per trimester • ICU admission	 1st 2nd 3rd	39.3% 5% 37% 57% 19%
Siston, 2010[64]	US	2009 (April-Aug)	509 pregnant women of which 115 ICU admitted	Proportion of pregnant women: • hospitalisations • ICU admissions	 1st 2nd 3rd Unknown 1st 2nd 3rd Unknown	 5.9% 29.7% 41.8% 22.6% 7.0% 33.0% 44.3% 15.6%

** All cases were laboratory-confirmed cases.*

Table 19. Pandemic influenza A(H1N1) mortality in pregnancy

Author, year	Country	Season	Study population	No. of fatal cases in total study group*	Outcome measure	Trimester	Results
Europe							
CDC, 2010[55]	Greece	2009/2010 (May-Feb)	294 ICU admissions	140	• Proportion pregnant women among deaths • Proportion of pregnant cases that died	- -	1 of 140 (0.7%) 1 of 13 (7.7%)
Fuhrman, 2010[1]	France	2009 (July-Nov)	224 hospital admissions	37	• Proportion pregnant women among deaths • Proportion of pregnant cases that died	- -	1 of 37 (2.7%) 1 of 18 (5.6%)

Author, year	Country	Season	Study population	No. of fatal cases in total study group*	Outcome measure	Trimester	Results
Nguyen-Van-Tam, 2010[2]	UK	2009 (April-Sept)	631 hospital admissions	29	• Proportion pregnant women among deaths • Proportion of pregnant cases that died	- -	2 of 29 (6.9%) 2 of 27 (7%)
Pebody, 2010[16]	England	April 2009 – March 2010	Population of England, all ages	308 fatal cases with information on risk factors	• Proportion pregnant women among deaths • Case fatality rate (per 100 000 clinical cases)	-	10 of 308 (3%) 90
Van 't Klooster 2010[3]	The Netherlands	2009 (June-Dec)	2,186 hospital admissions (ICU and non-ICU)	53	Proportion pregnant women among deaths	-	0 of 53 (0%)
Other Western countries							
CDC, 2009[6]	US	2009 (April-July)	205 hospitalised cases	7	• Proportion pregnant women among deaths • Proportion of pregnant cases that died	- -	14.3% 1 of 14 (7.1%)
Creanga, 2010[56]	US	2009 (May-June)	976 hospitalised cases	47	• Proportion pregnant women among deaths • Proportion of pregnant cases that died	- -	4.3% 2 of 62 (3.2%)
Fielding, 2009[59]	Australia	2009 (April-Sept)	415 hospitalised cases	24	Proportion pregnant women among deaths		4.2%
Jain, 2009[8]	US	2009 (May-June)	272 hospitalised cases	19	• Proportion pregnant women among deaths • Proportion of pregnant cases that died	- -	16% 3 of 18 (16.7%)
Kelly, 2009[58]	Australia	2009 (May-Oct)	4833 hospitalised cases	186	• Proportion pregnant women - rate per 100 000 • Proportion of pregnant cases that died	- -	1.6% 1.3 3 of 278 (1.1%)
Louie, 2010[63]	US	2009 (April-Aug)	239 hospitalised women reproductive age	25	• Proportion pregnant women among deaths • Maternal mortality ratio • Proportion of pregnant cases that died	- -	32%; 4.3 8 of 94 (8.5%)
Siston, 2010[64]	US	2009 (April-Aug)	788 H1N1 pregnant cases of which 509 hospitalised	30	Proportion: • Pregnant women • Hospitalisations • Proportion of pregnant deaths per trimester	- 1st 2nd 3rd	 3.8% 5.9% 10% 30% 60%

** All cases were laboratory-confirmed cases.*

Table 20. Safety of influenza vaccines in children

Author, year	Country	N	Vaccine type	Control	Outcome measure	Age group (months)	Results*
Esposito 2006[40]	Italy	303	Inactivated, trivalent, virosome-formulated subunit influenza vaccine	No vaccination	% of children with systemic/local AE	2-5 years	After first dose vs. second dose • Fever: 11.9% vs. 5.0% • Sneezing: 24.3% vs. 15.3% • Cough: 16.8% vs. 7.9% • Vomiting: 5.9% vs. 2.5% • Erythema/tenderness: 6.9% vs. 7.9% • Total: 29.2% vs. 14.9%
Kanra, 2004[48]	Germany; Italy; Turkey	453	Virosome-adjuvanted	Split vaccine	% subjects with at least one systemic/local AE	6 to 71	≥ 1 systemic event virosome vs. split • 1st dose: 8.5% vs. 7.4% • 2nd dose: 4.6% vs. 7.0% • ≥1 local event virosome vs. split • 1st dose:8.9% vs. 4.8% • 2nd dose:4.6% vs. 5.1%
Vesikari, 2006[49]	Finland	197	LAIV	Placebo	% of subjects with solicited events within 10 days of vaccination	9-36	Vaccine vs. placebo • Rhinorrhea/nasal congestion: 80.2% vs.75.3% • Cough: 50.5% vs. 50.5% • Fever ≥38 °C: 51.2% vs. 51.2%
Vesikari, 2006[42]	Belgium; Finland; Israel; Spain; United Kingdom	Year 1: 1616 Year 2: 1090	CAIV-T	Placebo	• % of subjects with reactogenicity events (first dose year 1) • AEs (first dose year 1) • serious AEs possibly/ definitely vaccine related	6 to < 36	CAIV-T vs. placebo; runny nose/nasal discharge: • 82.3 vs. 75.4%, (p=0.001) • Headache: 15.0 vs. 8.9% • Fever of >37.5 °C: 32.0 vs. 27.8% • Fever: 8.7% vs. 7.2% • Rhinitis:8.2% vs. 8.0% • Cough: 6.4% vs. 7.9% – year 1: 9 vs. 5 subjects – year 2: 2 subjects in CAIV-T group
Vesikari, 2009[51]	Finland	222	Sub/MF59	Split vaccine	% subjects with solicited local/systemic reactions; AEs** (possibly/probably vaccine related)	6 to < 36	Sub/MF59 vs. split • Tenderness: 45% vs. 34% • Erythema: 35 vs. 27% • Induration: 16 vs. 14% • Irritability: 41 vs. 33% • Sleepiness: 27 vs. 19% • Analgesic/antipyretic use: 26 vs. 23% • swelling 12% vs. 5%, (p=0.033) • 21 children in each group had a possibly/probably vaccine related AE
Vesikari, 2009[50]	Finland	89	Sub/MF59	Split vaccine	% subjects with solicited local/systemic reactions, AEs	16 to < 48	Sub/MF59 vs. split • Any: 79% vs. 59% • Local: 70% vs. 46% • Systemic: 42% vs. 37% • Other: 21% vs. 9% • Any AE: 70% vs. 76% • At least possibly/probably related AEs: 23% vs. 4% • Serious AEs: 0% vs. 0% • injection site pain in children ≥ 3 years old, p<0.01

** The p-value was only mentioned if the result was significant. ** AE: Adverse Event: as defined/described in evidence table.*

Table 21. Efficacy* of influenza vaccination in children

Author, year	Country	N	Vaccine type	Control	Outcome measure	Age group (years)	Results
Esposito, 2006[40]	Italy	303	Inactivated, trivalent, virosome-formulated subunit influenza vaccine	No vaccination	Vaccine-efficacy in preventing influenza-like-illness	2-5	Upper respiratory tract infections: 33% Lower respiratory tract infections: 22% Febrile respiratory illnesses: 26%
Salleras, 2006[41]	Spain	1951	Virosomal subunit inactivated influenza vaccine	No vaccination	Vaccine-efficacy in preventing influenza	3-14	88.4%
Vesikari, 2006[42]	Belgium; Finland; Israel; Spain	Year 1: 1616 Year 2: 1090	CAIV-T	No vaccination	Vaccine-efficacy in preventing influenza	6 to < 36 months	Year 1: 83.5% (against subtype influenza virus similar to vaccine); 83.8% (against subtypes influenza virus not similar to vaccine) Year 2: 89.0% (against subtype influenza virus similar to vaccine); 85.3% (against subtypes influenza virus not similar to vaccine)

** Vaccine-efficacy: incidence rate in the vaccinated group divided by the incidence rate in the control group.*

Table 22. Cost effectiveness of influenza vaccination in children

Author, year	Country	N	Vaccine type	Control	Outcome measure	Age group (years)	Results
Esposito, 2006[40]	Italy	303	Inactivated, trivalent, virosome-formulated subunit influenza vaccine	No vaccination	Net present value (from the individual perspective)	2-5	EUR +131.43
					Cost-benefit ratio (from the individual perspective)		1.29
Navas, 2007[100]	Spain	1000	Subunit virosomal influenza vaccine	No vaccination	Net present value (from the societal perspective)	3-14	EUR +7587.03
					Cost benefit ratio (from the societal perspective)		1.80
					Net present value (from the provider perspective)		EUR -1460.51
Salleras, 2009[101]	Spain	1000	Subunit virosomal influenza vaccine	No vaccination	Reduction in cost-generating events	3-14	• Paediatric consultations: 212.5 visits • Consumption of antibiotics and antipyretics: 58 consumptions • Loss days of schooling avoided: 1039 days • Loss work days avoided: 158.5 days
					net present value		EUR +21,551.62
					benefit-cost ratio (from a family perspective)		2.15

Annex 4. Levels of evidence

	Intervention	Diagnostic accuracy study	Harm/side effects*, aetiology, prognosis
A1	Meta-analysis or systematic review containing at least two trials of level A2, where the results of individual trials are consistent.		
A2	Randomised comparative clinical trials of good quality (randomised, double-blind, controlled trials) of sufficient size and consistency.	Research evaluated with reference test ('gold standard') which met predefined cut-off values and an independent appraisal of test results and the gold standard, with a sufficient number of patients with both an index test and reference standard test.	Prospective cohort study with a sufficient sample size and follow-up; adequately controlled for confounding and no selective follow-up.
B	Randomised clinical trials of moderate (weak) quality or insufficient size or other comparative trials (non-randomised, cohort studies, patient-control studies)	Research evaluated with reference test, but not with all characteristics mentioned at level A2.	Prospective cohort study, but not with all characteristics mentioned at level A2.
C	Non-comparative trials		
D	Expert opinion		

** This classification is only applicable in situations where controlled trials are not possible due to ethical or other reasons. If a controlled trial is possible, the classification of intervention must be used.*

Annex 5. CoCanCPG checklists for critical appraisal of literature

Systematic reviews/meta-analyses
Internal validity
The study addresses an appropriate and clearly focused question
A description of the methodology used is included
The literature search is sufficiently rigorous to identify all the relevant studies
Study quality is assessed and taken into account
Data extraction is clearly described
The most important characteristics from the original research is described
There are enough similarities between the studies selected to make combining them reasonable
Statistical pooling is correctly performed
Statistical heterogeneity is adequately taken into account
Study quality is taken into account
Overall assessment of the study
Are the results of the systematic review valid?
Are the results of the systematic review applicable to the patient group targeted in the search question?
Comments
Include or exclude
If exclusion, give reason

Randomised Controlled Trials
Internal validity
The study addresses an appropriate and clearly focused question
The assignment of subjects to treatment groups is randomised
An adequate concealment method is used
Subjects are kept blind about treatment allocation
Outcome assessors are kept blind about treatment allocation
The treatment and control groups are similar at the start of the trial
The only difference between groups is the treatment under investigation
All relevant outcomes are measured in a standard, valid and reliable way
All the subjects are analyzed in the groups to which they were randomly allocated (intention to treat)
Overall assessment of the study
Are the results of the study review valid?
Are the results of the study applicable to the patient group targeted in the search question?
Comments
Include or exclude
If exclusion, give reason

Cohort study
Internal validity
The study addresses an appropriate and clearly focused question
The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation
The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis
Comparison by exposure status is made between full participants and those lost to follow up

The outcomes are clearly defined
The assessment of outcome is made blind to exposure status
The measure of assessment of exposure is reliable
The main potential confounders are identified and taken into account in the design and analysis
Overall assessment of the study
Are the results of the study valid?
Are the results of the study applicable to the patient group targeted in the search question?
Comments
Include or exclude
If exclusion, give reason

Case-control study
Internal validity
The study addresses an appropriate and clearly focused question
The cases and controls are taken from comparable populations
The same exclusion criteria are used for both cases and controls
Cases are clearly defined and differentiated from controls
Case ascertainment is performed blind from the exposure status
Exposure status is measured in a standard, valid and reliable way
The main potential confounders are identified and taken into account in the design and analysis
Overall assessment of the study
Are the results of the study valid?
Are the results of the study applicable to the patient group targeted in the search question?
Comments
Include or exclude
If exclusion, give reason

Diagnostic accuracy study
Internal validity
The index test being studied is clearly specified
The index test is compared with a reference standard
The reference standard is likely to correctly classify the target condition
The spectrum of the included patients is representative of the patients who will receive the test in practice
Selection criteria are clearly described
The time period between reference standard and index test is short enough to be reasonably sure that the target condition did not change between the two tests
The whole sample or a random selection of the sample received verification using the reference standard of diagnosis
Patients received the same reference standard regardless of the index test result
The reference standard is independent of the index test (i.e. the index test did not form part of the reference standard)
The execution of the index test is described in sufficient detail to permit replication of the test
The same clinical data were available when test results were interpreted as would be available when the test is used in practice
Uninterpretable/ intermediate test results are reported
Withdrawals from the study are explained
Overall assessment of the study
Are the results of the systematic review valid?
Are the results of the systematic review applicable to the patient group targeted in the search question?
Comments
Include or exclude
If exclusion, give reason