ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

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
Stockholm, January 2007

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BACKGROUND

The main task of the Scientific Advice Unit (SAU) of the European Centre for Disease Control (ECDC) is to provide sound and independent technical and scientific advice. This is accomplished through the collaboration of a strong scientific core within the Centre with leading European scientists in the relevant disciplines.

According to ECDC founding regulation*, the Unit can be supported in its scientific work by *ad hoc* Scientific Panels selected following a well defined procedure, from among those who have expressed their interest to work with the ECDC by responding to the ECDC call for scientists across the Member States.

The current report has been produced by an *ad hoc* Panel established in June 2006 to advise on replies to specific questions requested by Member States.

In discussions between the Head of Unit for Scientific Advice, the Panel, and the MS raising the questions, they were re-formulated to be:

- What is the local burden of influenza in children?
- To what extent are split or subunit influenza vaccines immunogenic, safe and efficacious in children?
- Are there indirect benefits to the community (herd immunity, reducing community transmission, etc) from vaccinating children against influenza?
- What is the cost-effectiveness of influenza vaccination programme in children?

For each specific issue identified, the Scientific Panel attempted to answer the following three questions:

- What is the state of scientific evidence for each topic identified?
- Where are the gaps in evidence and what are the unanswered research questions?
- What data would the EU Member States need to make a policy change?

* Article 6 of Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European Centre for Disease Prevention and Control.

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EXECUTIVE SUMMARY

Annual influenza vaccination of risk groups has been common practice in Europe and elsewhere for many years. Routine influenza immunisation of healthy children has been recommended in some countries, to reduce morbidity among children with the potential additional benefit of reducing the spread of disease and thus indirectly protect adults at high risk of severe influenza.

Introduction of routine influenza vaccination of children will be considered in the near future in a number of EU Member States. As indicated in this document there are important knowledge gaps to be resolved before such programmes may be introduced to include all children.

This document addresses issues key to whether routine influenza vaccination of children should be considered in European countries. In the Annex recent cost-effectiveness analyses are reviewed. Programmatic issues, vaccine logistics and other implementation issues are not *per se* covered here.

Key issues and knowledge gaps

1. The burden of influenza in children has recently been recognised, albeit with some inter-country variation. The risk of severe influenza illness is highest among infants below six months of age and high among older infants. However, data for young children, particularly under two years of age, are scant from European countries.

- Therefore, a first step towards any decision on the introduction of routine influenza immunisation for children in any European country is to determine the specific national profile of the disease burden such as incidence rates and morbidity by age groups.
- ECDC is advised to establish standardised case definitions including improved laboratory tests, guidelines for, and coordination efforts to collect baseline epidemiological data focussing on children.

2. The available scientific data suggest that inactivated trivalent vaccines, split or subunit, are safe and well tolerated in healthy children over six months of age.

- However, careful post-licensure surveillance of rare serious adverse events should be part of any newly introduced routine immunisation programme in infants and older children.

3. Little data exist on any potential long term adverse effects of reiterated annual immunisations. Therefore:

- annual revaccinations pose a particular issue within a routine programme for children aiming at very high coverage;
- reiterated annual immunisations in children require careful follow-up.

4. For children 1–18 years of age, combined, efficacy has been demonstrated. In the latest meta-analysis[†] efficacy against laboratory-confirmed influenza across all age groups was estimated at 59% (95% CI 31–71%).

- There are few age-specific data on efficacy in pre-school children, especially between one and two years of age, and no data below one year of age.

5. Two doses of trivalent inactivated influenza vaccines are recommended to previously unvaccinated infants and children according to the European core summary of product characteristics. However:

- the optimal dosage and schedule in infants and children is presently not well established;
- no controlled immunogenicity (nor efficacy) trials have been conducted in infants and children so far with any split or subunit influenza vaccine licensed in the EU through the Mutual Recognition Procedure (MRP).

6. Product specific clinical evaluation in immunologically naïve as well as primed infants and children should be performed for new vaccines in order to:

- define the number of doses and dosage needed to achieve protective immunity by age group;
- determine the effect of annual revaccination in infants and children who have had a successful course of primary immunisation.

7. Published data suggest that routine immunisation of school-age children has an indirect beneficial effect for adults and the elderly in terms of reduced disease burden.

- However, such an indirect effect has not been demonstrated in young children, particularly in infants under six months of age. Quantification of the preventable burden is difficult to assess. Generalisation between different settings (e.g. countries, age groups) should be done with caution.

8. Cost-effectiveness seems to depend mainly on national social and labour laws regarding parental care of a sick child.

- Whether and when added health risks from vaccination are outweighed by health benefits from averted influenza in healthy children is still an unanswered question.

9. Countries considering influenza vaccination programmes are advised to develop national goals, objectives and targets for vaccination coverage and reduction of illness and death due to influenza disease in different age groups.

[†] Demicheli V, Di Pietrantonj C, Harnden A, Jefferson T, Matheson NJ, Rivetti. The Cochrane collaboration. Vaccines for preventing influenza in healthy children (Review). The Cochrane library, 2006, issue 3. Available at: www.thecochranelibrary.com.

General recommendation

The Expert Panel advises ECDC, together with national experts, to initiate a concerted action to address knowledge gaps:

- It should be an integrated function of the planning of any forthcoming routine influenza immunisation of children.
- Funding of such efforts could be considered by all EU Member States and by the European Commission through DG Research and/or DG Sanco.
- Collaboration with manufacturers could also be sought to address such knowledge gaps.

INTRODUCTION

Annual influenza vaccination of risk groups has been common practice in Europe and elsewhere for many years. During the last 10–20 years, influenza immunisation of children has been introduced in some countries[1,2] to reduce morbidity among children with the potential additional benefit of reducing the spread of disease and thus indirectly protecting adults at high risk of severe influenza. Similar recommendations have been published by independent European vaccination experts[3]. On the other hand the Conseil Supériur D'Hygiene in Belgium argues against introducing routine seasonal influenza immunisation for children[4].

This document addresses issues key to whether routine influenza vaccination of children should be considered in European countries. A brief review of recent published cost-effectiveness analyses are presented in the Annex. However, programmatic issues, vaccine logistics and other implementation issues are not *per se* covered. Guidelines for adding a vaccine to a national immunisation programme have recently been issued by WHO[5].

Efficacy and effectiveness

The terms *efficacy*[‡§] and *effectiveness*[**] are unfortunately often used synonymously. In this document we use the following definitions and distinctions:

Absolute efficacy is the percentage reduction of the rate of influenza in immunised as compared to unimmunised individuals, measured under ideal conditions such as a randomised controlled trial (RCT). Ideally *efficacy* is given for a primary laboratory-confirmed case definition of influenza. Trials also use a number of secondary case definitions for more severe disease, such as pneumonia, otitis and hospitalisation.

In addition, less specific secondary case definitions are used to measure the effect of a vaccine against a clinical case definition such as influenza-like illness (ILI). Such estimates are often given as measures of 'individual effectiveness' and are usually lower than the corresponding estimates of *efficacy* since non-influenza diseases will be included in ILI and since strict monitoring of who were immunised and who became ill generally are not applicable in real conditions. In a clinical trial an intention to treat analysis is often incorrectly used to estimate the effectiveness of a vaccination.

Effectiveness as used in epidemiological studies measures the effect of an immunisation programme expressed as a reduction of the disease burden using similar or the same case definitions as above.

Effectiveness on the population level is influenced by a number of factors besides vaccine *efficacy* such as:

- vaccination coverage;
- age-specific attack rates;
- means of spread of disease, including contagiousness, contact patterns, and indirect protection of unimmunised individuals or *herd immunity*.

Herd immunity[††] is part of the *effectiveness* on the population level but should be distinguished from effectiveness on an individual basis.

‡ Pocock SJ. Clinical Trials: a practical approach. Wiley, 1984.
§ Fine PE, Clarkson JA. Reflections on the efficacy of pertussis vaccines. Rev Infect Dis. 1987; 9: 866–83.
** Mulholland EK, Bjorvatn B. Assessment of Individual Vaccines: Efficacy and Effectiveness, in The Vaccine Book edited by Bloom BR and Lambert PH, Academic Press 2003.
†† Fine PEM. Herd Immunity: History, Theory, Practice. Epidemiol Rev 1993; 15: 265–302.

1. BURDEN OF INFLUENZA IN CHILDREN

The disease burden of influenza infection among children is not well established. Despite numerous statements in recent scientific literature and public health documents as described below, very little scientific data is available, and most publications are based on relatively small-scale local observations.

Historical data shows that children were among the highest victim groups during the influenza pandemics of the 20th century. Although in those European countries reporting age-specific data the highest clinical incidences were observed among children aged 0–14, these were not especially high compared to historical data[6].

The European Influenza Surveillance Scheme (EISS) is a collaborative project which aims to contribute to a reduction in morbidity and mortality due to influenza in Europe by active clinical and virological surveillance of influenza[7,8,9,10]. During the 2004–05 season, 26 countries actively reported data to EISS and the scheme included 30 national reference laboratories, at least 12,000 sentinel physicians and covered a total population of 445 million inhabitants. EISS reported that the highest consultation rates attributable to influenza were generally observed among children aged 0–14[11,12,13]. However, these rates were not especially high compared to the historical data.

Although in the EISS reports the age groups most affected by influenza were 0–4 years and 5–14 years, it should be noted that the estimated consultation rates for the different age groups are influenced by several factors such as consultation behaviour, estimation procedure, case definition, vaccination coverage and obligatory doctors visits for absence from work or school, which may differ between countries[8].

For Italy, reported data[14] indicate that the highest incidence is reported in 0–14 year old children. The overall incidence in that age group varied between 120 to 250 per 1,000 during the 2004–05 season . Hospitalisations were most common below one year of age. However, the Italian authors caution that the reported figures are uncertain due to weaknesses in the present surveillance system, mainly based on clinical reports without laboratory confirmation.

Similar figures are reported in France from the 'Réseau National des Groupes Régionaux d'Observation de la Grippe' with influenza-like illness (ILI) attack rates ranging 72–315 per 1,000 in 0–4 and 128–168 per 1,000 in 5–14 year old children (seasons 2002–03 to 2005–06) [*source*: www.grog.org, in French].

A useful summary of current data on the burden of influenza disease[15], cites hospitalisation data from Lyon, France: Age is an important risk factor for hospitalisation due to influenza, the risk measured as odds ratio (OR) is 9.1 (95% confidence interval, 95% CI 2.06–33.3) in children less than 12 months old compared to 24–36 month old children.

In the Netherlands, where influenza vaccination is not routinely given to children without a medical indication, the annual incidence of ILI-general practitioner (GP) consultations over the past 10 years was highest in children 0–1 year old and varied in this period between 21.0 and 80.3/1,000 per year. In 2005–06 the incidence in this age group was 54.6/1,000 per year, compared to 32.0/1,000 in the age group 1–4 years, 20.6/1,000 in the 5–9 year olds,

15.8/1,000 in the 10–14 year olds and 16.9/1,000 in the 15–19 year olds [*source*: NIVEL]. In 32.2% of randomly collected diagnostic samples of ILI patients in all age groups an influenza virus was found by culture and/or PCR. Influenza virus was detected in one third of sampled children 0–4 years of age [*source*: RIVM/LIS].

A prospective cohort study of respiratory infections in Finland showed the highest average annual rate of influenza, 179/1,000 children, among children less than three years old[16].

Data from the UK for the influenza season 2002–03 showed the highest peak incidence rates in the beginning of the epidemic in children 5–14 years of age, and for 2003–04 in children under five years of age, suggesting that children spread the disease to other age groups [*source*: www.hpa.uk].

In the USA, the Centers for Disease Control and Prevention report that the risks of complications, hospitalisations, and deaths from influenza in the USA are higher among persons aged 65 years and over, young children, and persons of any age with certain underlying health conditions[1]. Children up to six months old have by far the highest annual rates of hospitalisations, ranging from 2.3 to 7.2 per 1,000 during the 2000–04 influenza seasons. Children aged 6–23 months were also at increased risk for influenza-related hospitalisations, 0.6–1.5/1,000. Furthermore, children aged 24–59 months were at increased risk for influenza-related clinic and emergency department visits[17]. Thus, infants and young children are at a great risk for influenza-related complications[18,19,20].

In Canada, children under two years of age have significantly higher hospitalisation rates attributable to influenza than older children and adolescents. The hospitalisation rates of 0.25 per 1,000 for all children and 0.81 per 1,000 for children 0 to 24 months of age were reported in the metropolitan Toronto and Peel region by active surveillance (laboratory confirmed cases), 2004–05[21]. Among 505 children hospitalised with laboratory-confirmed influenza at nine Canadian tertiary care hospitals during the 2003–04 influenza season, 57 percent were younger than two years old. Previously healthy children accounted for 58% of all of the cases. Pulmonary and neurological disorders were the most common underlying chronic conditions. Seizures occurred in 9% of cases. Serious complications included myocarditis (2), encephalopathy (6), and meningitis (1). There were three influenza-related deaths. Mean duration of hospitalisation was 5.3 days. Twelve percent of children required ICU admission, and 6% required mechanical ventilation[22].

Similar distribution in age groups was reported in Asia. The adjusted rates of excess hospitalisation for acute respiratory disease that were attributable to influenza in Hong Kong were 278.5 and 288.2 per 10,000 children of less than one year of age in 1998 and 1999, respectively; 218.4 and 209.3 per 10,000 children from one to under two years of age; 125.6 and 77.3 per 10,000 children two to under five years of age; 57.3 and 20.9 per 10,000 children five to less than 10 years of age; and 16.4 and 8.1 per 10,000 children 10 to 15 years of age[23].

Although influenza is common among children, paediatric mortality related to laboratory confirmed influenza has not been assessed. During the 2003–04 influenza season 153 cases of influenza-associated deaths occurred among US children and 63% of them were younger than five years old[24].

In many cases the diagnosis of influenza in European countries is based only on clinical symptoms and childhood influenza is believed not to be as severe a disease as it is among adults. Therefore it can be assumed that physicians are reluctant to consider influenza as a cause of a child's death. Consequently the reported cases of childhood influenza-related deaths might be imprecise.

Finally, the wide criteria used ILI are weak and unspecific. Respiratory illness criteria are particularly confusing in the under fives due to the overlap of numerous viral respiratory diseases prevalent in infants and pre-school children. Behind the ILI term, a lot of different symptoms are possible, rendering the results prone to critique. As a possible consequence, the impact of influenza vaccine could be underestimated.

Conclusion

The burden of influenza (excess morbidity, serious morbidity, mortality) in children has recently been recognised, albeit with some inter-country variation. The risk of severe influenza illness is highest among infants under six months of age and high among older infants and young children. However, data for these age groups are scant from European countries.

- Therefore, a first step towards any decision on the introduction of routine influenza immunisation for children in any European country is to determine the specific national profile of the disease burden such as incidence rates and morbidity by age group.
- ECDC is advised to establish standardised case definitions including improved laboratory tests, guidelines for, and coordination efforts to collect baseline epidemiological data focussing children.

2. DEVELOPMENT AND IMMUNOGENICITY OF INFLUENZA VACCINES

The development of influenza vaccines dates back to the 1940s shortly after the influenza virus itself was discovered in 1933[25]. These early experimental vaccines consisted of crude preparations of whole influenza virus propagated in mouse lung and chick embryo tissues[26] which was inactivated by formaldehyde. Throughout the following decades inactivated whole virus vaccines were successively refined by introducing efficient purification steps allowing removal of the majority of process-related impurities[27,28] which ultimately resulted in a significantly reduced reactogenicity profile of these vaccines. To achieve higher purity and better tolerability of influenza virus antigens, inactivated split influenza vaccines have been developed. The split vaccines consist of surface antigens (Haemagglutinin (HA) and Neuraminidase (NA)) with only few residual amounts of internal virus proteins[29]. Split inactivated influenza vaccines and also inactivated influenza vaccines – predominantly composed of the viral HA-protein – have now replaced inactivated whole virus vaccines and represent the majority of licensed products available within the EU. Other influenza vaccines including live attenuated influenza vaccines are currently not licensed in the EU.

A continuous development towards the highly purified influenza vaccines has undoubtedly resulted in an excellent safety record and a favourable risk–benefit ratio for split or subunit influenza vaccines.

All influenza vaccines licensed in the EU contain each of the three circulating human influenza viruses, i.e. two influenza A-like viruses, sub-types H1N1 and H3N2, and one influenza B-like virus.

Annual revaccination is needed in order to update specificity of the human immune system with regard to antigenically drifted seasonal influenza viruses.

Effective revaccination requires, however, sufficiently high residual immunity. Individuals with no or low influenza virus specific residual immunity may respond weakly or not at all to a single dose of licensed influenza vaccine leaving those individuals without protective immunity following vaccination. From that perspective influenza vaccines should be highly immunogenic in order to provoke an acceptable immune response irrespective of pre-vaccination titres.

There is, however, a reliable line of evidence that contemporary split or influenza vaccines, while well tolerated, are significantly less immunogenic compared to the previous generation of whole virus vaccines[30,31,32,33,34].

These findings have fundamental implications for the efficient vaccination of unprimed or weakly primed individuals, e.g. infants and children who had never been exposed to circulating influenza viruses and who had never been vaccinated or older individuals without exposure to influenza viruses who were not vaccinated or who received their last influenza vaccine many years ago. Under those circumstances more than a single dose of licensed influenza vaccine might be necessary in order to achieve protective immunity[35]. It is noteworthy that immunological acceptance criteria laid down in the guideline from the

committee for proprietary medicinal products have been established for adults and never been tested for suitability in infants and children.

Conclusion

Two doses of trivalent inactivated influenza vaccines are recommended to previously unvaccinated infants and children according to the European core SPC. However:

- the optimal dosage and schedule in infants and children is presently not well established;
- no controlled immunogenicity (nor efficacy) trials have been conducted in infants and children so far with any split or subunit influenza vaccine licensed in the EU through the Mutual Recognition Procedure (MRP).

3. SAFETY OF SPLIT OR SUBUNIT TRIVALENT INACTIVATED INFLUENZA VACCINES (TVI) AMONG CHILDREN

In low-risk children annual immunisation with inactivated trivalent influenza vaccine (TIV) is generally considered safe, especially with split or subunit vaccines.

Small randomised controlled trials (RCT) conducted in the late 1970s in children aged 3–18 years demonstrated good local and systemic tolerance to inactivated vaccines[36,37,38].

More recently some larger studies have been published. A RCT showed post-vaccination mild fever as the most common systemic adverse events in 4.6–11.5% children aged 1–15 years[39]. Another RCT with 525 children aged 6–24 months found no serious adverse events likely caused by vaccine[40]. While bearing in mind the limitations of passive surveillance systems related to causality, in children less than two years of age the most frequent reports to Vaccine Adverse Event Reporting System (VAERS) between 1990 and 2003 were fever, urticarial rash, seizures and injection site reaction[41]. A large population-based study amongst a cohort of 251,600 US children younger than 18 years of age, using a screening analysis of children in the Vaccine Safety Datalink did not find an increased risk of important medically attended events in emergency, or outpatient, departments during the two weeks immediately after influenza vaccination[42]. With information from subjects included in the Vaccine Safety Datalink, a retrospective, descriptive, population-based study using self-control analysis and chart review of medically attended events in 45,536 children 6–23 months of age who received TIV between 1991 and 2003 showed that very few of the events occurring 0–42 days after vaccination were significantly associated with the vaccine and none of them were serious. This finding applied solely to split or subunit influenza vaccines[43].

A phase IV post-marketing telephone survey including 690 infants and toddlers, without an age-specific control group, targeted to detect adverse events following inactivated influenza vaccination, was conducted in Canada in 2004. The study indicated that influenza vaccine was well tolerated, with fever and fussiness as the most frequent events reported[44].

The safety of two doses of trivalent inactivated vaccine was assessed among 13,383 infants 6–23 months of age of whom 3,697 received vaccines in a retrospective case-control study. Adverse events possibly attributable to influenza vaccination among infants and toddlers were unusual[45].

Regarding administration of multiple doses, a review in 2005 concluded that repeated TIV immunisation in high-risk children seemed to be safe and well tolerated[46].

It is not known whether Guillain-Barre Syndrome (GBS) is a true side effect of vaccination in the years other than 1976, but in such a case the estimated risk of GBS would be of approximately one additional case/1 million vaccinated of all ages[1].

Exceptionally, immediate severe hypersensitivity reactions can occur and usually are caused by residual egg protein. Nevertheless, patients with a mild to moderate egg allergy could safely receive TIV in a 2-dose protocol when the vaccine preparation contains no more than

1.2 micrograms/mL egg protein, according to results from a study in 83 subjects with egg allergies and 124 controls[47].

The majority of influenza vaccines no longer contain thiomersal as a preservative. Few influenza vaccines may still contain thiomersal in trace amounts as residuals in the manufacturing process. The Institute of Medicine recently recognised the 'lack of direct evidence for a biological mechanism and the fact that all well-designed epidemiological studies provide evidence of no association between thiomersal and autism'[48]. However, US officials recommend that thiomersal should be eliminated from any influenza vaccine preparations considered for universal immunisation of infants[49].

Conclusion

The available scientific data suggest that inactivated trivalent vaccines, split or subunit, are safe and well tolerated in healthy children over six months of age.

- However, careful post-licensure surveillance of rare serious adverse events should be part of any newly introduced routine immunisation programme in infants and older children.

Little data exist on potential long-term adverse effects of reiterated annual immunisations:

- thus, annual revaccinations pose a particular issue within a routine programme for children aiming at very high coverage;
- reiterated annual immunisations in children require careful follow-up.

4. EFFICACY OF TRIVALENT INACTIVATED VACCINE (TIV) IN HEALTHY CHILDREN

Efficacy of trivalent inactivated vaccines (TIV) in healthy children 6 months to 18 years of age has been reviewed through the past 20 years of scientific literature, with a focus on age groups of 6–23 months, 2–4 (or five) years, and five (or six) years and over.

The criteria for the primary case definitions used for efficacy are laboratory-confirmed cases with a positive viral culture or serologic criteria (with pre-defined laboratory criteria accepted by EMEA). A secondary case definition is influenza-like illness (ILI) used to express the 'effectiveness' against ILI in terms of reduction of symptomatic cases (without laboratory confirmation). Individual studies and meta-analyses are reviewed.

Individual studies

Targeting healthy children, some studies evaluated efficacy[50,51,52,53,54,55]. In addition, a number of studies evaluated efficacy based on alleviation of ILI[56,57], on alleviation of acute otitis media AOM symptoms[40,58,59,60], or analysed the socio-economic impact of vaccination[61]. The individual studies are presented in Table 1.

The heterogeneity in methodology represents major issues in the interpretation of the individual studies presented in Table 1. Bias renders some studies uninformative or misleading. The huge heterogeneity of studies includes:

- the site: US, Japan, Europe and Turkey[51–62];
- the timing: one or several epidemic seasons[51,55,56];
- study design[51–62];
- age group studied[51,54–58,61,62];
- small sample size, especially noticeable in infants[51–62];
- type of vaccine[51–58,61,62];
- vaccine schedule[51–55,57,58,62];
- vaccine dosage[57,58];
- case definitions[52,53,58,62];
- type of laboratory confirmation[57].

Despite these methodological constraints, TIV efficacy was demonstrated for any age in all studies but one[55] where no significant difference was observed between those vaccinated and the controls. The alleviation of ILI, AOM, and other outcomes was inconstantly demonstrated, especially in very young children.

Table 1. Individual studies

	Method	*Efficacy*
Heikkinen 1991 Finland[59]	RCTs 187 children vaccinated + 187 controls 1–3 years of age Day care centre	Reduction of AOM episodes by 36%
Clements 1995 USA[60]	94 children 6–30 months of age Day care centre TIV subunit; 1 or 2 doses	Significant reduction of AOM episodes by 32% (OR 0.69, 95% CI 0.49–0.98)
Hurwitz 2000 USA, California[52,53]	Randomised trial 149 children 24–60 months of age Day care centres DCC Subunit vaccine 2 doses 1 month apart Criteria: serologically & virological identification ILI with or without fever (≥ 38°C) Follow-up 6 months	Serologically proven influenza infection 45% (95% CI –2, 69) for B 31% (95% CI –95, 73) for A(H3N2) No pre-existing HI antibodies: lower antibody responses to vaccine less likely to develop a serologic response that was protective against infection more likely to develop serologic evidence of influenza infection Respiratory illnesses and febrile respiratory illnesses: no statistically significant reduction among all vaccinated children Pre-vaccination titres for influenza B and A(H3N2) influence : ≤ 5 : –23% (95% CI –56, 3) ≥ 10 : 11% (95% CI –9, 26)
Neuzil KM 2001 USA[51]	RCT, 5 year study 277 included / 791 healthy children 1–16years of age Split-vaccine TIV bivalent the 1st year (A H3N2 / H1N1) then trivalent. Only one dose even when < 9y Children < 3y half dose (eg 0.25ml) N sero-negative children (pre-vaccine serology) 50% : children < 3 years up to 30% : children > 3 up to 6 years	All ages 1 up to 16 years (culture positive influenza) H3N2 : 77.3% (95% CI : 20, 93.5) H1N1 : 91.4% (95% CI : 64, 98) All ages 1 up to 16 years (sero-conversion rates) H3N2 : 67.1% (95% CI : 51, 78) H1N1 : 91,4% (95% CI : 64, 98) Per age group (sero-conversion rates) 1 up to < 6 years HINI : 43.6% (95% CI : – 3.5, 69) H3N2 : 48.5% (95% CI : – 38.5, 81) 6 up to < 11 years H1N1 : 76.1% (95% CI 53, 88) H3N2 : 73.8 % (95% CI 37, – 89)

		11 up to 15 years H1N1 : 80.5% (95% CI : 46.6, 92.9) H3N2 : 70.4% (95% CI –1.2, 91.4)
Colombo 2001 Italy, Sardinia[54]	RCT (vs no treatment) 344 healthy un-primed 1–6 years of age Day care centres DDC > 85% TIV (subunit vaccine) 2 doses Effectiveness criteria ILI Follow-up: 5 months	Sero-conversion (17 children) 100% for H3N2 94% for H1N1 76% for B • Reduction of ILI: 67% (CI95% 0.59-0.74) (unvaccinated: 37.7% vs vaccinated: 12.4%) • Otitis media: p=0.07 vaccinated: no episodes vs control: 3 • DDC absenteeism: p<0.001 Mean overall duration: unvaccinated: 2.3 days vs vaccinated: 0.5 day
Principi 2003 Italy[62]	Prospective study vs placebo 301 children 6 months up to 5 years of age TIV Inflexal	Were significantly (p<0.0001) reduced in vaccinees • febrile ILI • school / DDC absenteeism • antipyretic prescriptions • antibiotic prescriptions
Hoberman 2003 Netherlands[55]	RCTs 786 children 6–24 months of age 50% children < 12 months 2 seasons 1999–2000 411 children Attack rate :15.9% (controls) 2000–01 375 children Attack rate 3.3% (controls) vs vaccinees 3.6% TIV subunit 2 doses x 0.25ml, 4 weeks apart Efficacy criteria fever, AOM or both	Influenza positive cultures 1st year: 66% (95% CI 34, 82%) 2nd year:– 7% (95% CI – 247%, 67%) 1st year results only By age group 6–12 months of age: 63% 13–18 months of age: 66% 19–24 months of age: 69% RTI rates: no differences vaccinees / controls At least one AOM episode: • all ages: no differences vaccinees / controls • in the 19–24 months, tendency for less frequency during influenza & respiratory seasons and significantly lower during the 1-year follow-up. Health care utilisation: no significant differences
Maeda T 2004 abstract only Japan[56]	Randomised trial Healthy 6–24 month children (small effectives) 3 consecutive seasons (2000–02)	No significant difference between vaccinated / controls Attack rates in vaccinated / controls respectively

	Efficacy criteria: Influenza A attack rates infection Follow-up: 4 months	y 2000 : N=27 (14.8%) / N= 32 (12.5%) y 2001 : N=72 (2.8%) / N= 69 (7.2%) y 2002 : N=52 (3.4%) / N= 56 (8.9%)
Kamada 2006 Japan[57]	Case control, multi-centred Culture positive influenza cases enrolled Children 6 months – 13 years of age recruited consecutively, 2300 enrolled Split vaccine : 2 doses > 2 weeks apart Doses vary with age: respectively 0.1, 0.2 and 0.3ml for 6–11 months, 1–5 years and 6–13 years Criteria of inclusion in the culture positive influenza subjects: • any fever > 37.5°C less than 3 days duration • regardless of influenza-like symptoms Due to insufficient cases for H3N2 (n=93) & H1N1 (n=167), analysis restricted to B (n=501) unvaccinated (45.4% > 6 years) older than vaccinated (28.2% > 6 years)	• Fever ≥ 39.6°C and 37.5 – 39.5°C rate of vaccinees respectively 11.4% and 18.1% • Fever > 39.5°C: comparison vaccines / control: crude OR 0.58 (95% CI : 0.34, 1.01; p 0.054) adjusted on age 0.52 (95% CI : 0.30, 0.92; p 0.024) • Vaccination effect statistically independent from that of the aging
Fujieda 2006 Japan[58]	RCTs vs no treatment control group (no request of vaccination by parents) 2913 healthy children < 6 years of age 1512 vaccinees TIV: 2 doses 2–4 weeks apart 0.1ml for < 1 year 0.2ml > 1 year (Japanese recommendation) Clinical case definition: • acute febrile illness ± any respiratory episode	Global vaccine effectiveness: 24% (CI95% : 12, 34) OR Adjustment per temperature level (≥ 39.0°C / < 38°C): higher effectiveness: 29% Per age: ≥ 2 y of age, OR = 0.67 (CI95% 0.56, 0.79) vaccine effectiveness 33% (CI95% : 21, 44) 1.0 up to 5.9 years, adjusted ORs = 0.74 (CI95% 0.63, 0.86) ; vaccine effectiveness 26% < 2 years: ORs = 1.07 (CI95% 0.80, 1.44)

	• frequency of ILI Follow-up: 4 months	< 1year vaccine effectiveness = –84% (-319%, 19%) 1.0–1.9 year vaccine effectiveness = 1% (-36%, 28%)
Ozgur 2006 Turkey[61]	Prospective, single blind study with control group Day care centres 119 healthy 6–60 month children TIV subunit Blind (about the vaccination status) ENT examination of children every 6 weeks Follow-up: 6 months	Against AOM, OME or any OM episode: 51%, 18% and 18% respectively With a significant difference ($p < 0.05$) during influenza season. Overall, AOM & OME frequency significantly lower ($p<0.001$) in vaccinated children during the study period.

RCT randomised control trial
TIV trivalent inactivated vaccine
ILI influenza-like illness
RTI respiratory tract infection
AOM acute otitis media
OME otitis media with effusion
OM otitis media

Table 2. Meta-analysis efficacy/effectiveness

	Methods	*TIV Efficacy*	*TIV Effectiveness*
Demicheli 2006 any country (USSR/Russia) 1966–2004[65]	RCTs / cohorts / case-control Healthy children < 16 years Mostly > 6 years & < 6 years < 2 years (1 study only)	RCTs : 59% (RR 0.41; 0.29, 0.59) < 2 years: TIV not significantly different from placebo Cohorts > 6 years: 64% (RR 0.36, 0.18, 1.11) < 6 years: 66% (RR 0.34; 0.13, 0.89) < 2 years: no better than placebo (RR 0.63; 0.27, 1.47)	RCTs: 36% (RR 0.64; 0.54, 0.76) < 2 years: no evidence Cohort studies all ages: 55% (RR 0.45; 0.29, 0.68) > 6 years: 56% (RR 0.44; 0.29, 0.68). < 6 years: lack of effectiveness (RR 0.41; 0.12, 1.42) <2 years: no data
Jefferson 2005 Up to 2004[64]	14 RCTs (vs placebo / no intervention) 8 cohort 1 case-control study children up to 16 years > 2 & < 2 years	At any age: 65% (vs 79% LAIV) < 2 years: no efficacy (effects similar to placebo)	> 2 years of age: 28% Other outcomes Reduction of long term school absenteeism (RR 0.14; 0.07-0.27) Against secondary cases, hospital stay, AOM, lower

			respiratory tract: no difference / placebo or standard care (lack of statistical power) Reduction in mortality, serious complications, and community transmission of influenza: No studies
Beyer 2002 USA[66]	RCTs all ages (up to 65 years) TIV split / subunit vaccine except one (whole vaccine: Feldman, Johnson in 1–7 years) All with 1 or 2 doses without a booster	OR not significantly different from 1 H3N2 (OR 1.50 ; 0.80-2.82) H1N1 (OR 1.03 ; 0.58-1.82) One study including children + adults: H3N2: 68.8% - 77.8% H1N1: 75.0% -78.6% B: no results	
Negri 2005 USA, Russia, Cuba, Kazakhstan 1990–2003[63]	13 RCTs At least 75% unprimed healthy children ≥ 6 months – 18 years Bi-, tri-valent TIV whole, split or subunit	Any ages 65% culture-confirmed 63% serologically confirmed	Any ages 33% reduction of ILI

Meta-analyses

Two meta-analyses reviewed vaccine trials that assessed efficacy for various case definitions of influenza in healthy children under 16 or 18 years of age up to the years 2000[62] and 2003[63], updated to 2004[64]. In addition, one analysis covered all ages up to 65 years[65]. TIV results are given in Table 2.

According to the most recent meta-analysis[64] overall TIV efficacy was 59% (RR=0.41, 95% CI 0.29–0.59) for all age groups studied in the RCTs. Below two years of age, in only one study with a small sample size[54] TIV efficacy was not significantly different from placebo. In cohort studies, TIV efficacy was 64% (95% CI -11% – 82%) over five years of age, 66% (95% CI 11% – 87%) under six years of age, and no better than placebo (37% point estimate, 95% CI -47% – 73%) in children under two years of age[54].

Comments and discussion

Most studies estimate efficacy using similar criteria as for the primary case definition: culture positive or serologically proven cases. The results are consistent. The same range of overall efficacy around 60% is observed in children 1–18 years of age.

However, heterogeneity of studies renders the results of the meta-analysis uncertain. Few data are available on the circulating epidemic strain, the attack rate and the match with the vaccine strain. The evidence may not be uniform depending on the strain (AH3N3, AH1N1, B), and the match between the tested vaccine and the circulating strains. Due to yearly epidemiological variations, the yearly predominant circulating strain often prevents an assessment of the efficacy for the three strains in a TIV at the same time. The general assumption is, however, that given similar IgG antibody responses measured in immunogenicity studies, efficacy is similar against all three included vaccine strains.

Furthermore, there is a lack of data per age groups in children and particularly few data on children under three years of age.

Not all TIV trials were conducted with a two-dose schedule; most lacked information about any previous vaccination or influenza illness; some had an interval of less than two weeks between the two doses. Such data are necessary to assess, for example, the benefit of a two-dose versus a one-dose schedule. Similarly, more data are required regarding a longer follow-up than the 4–6 month period covered in most studies.

Conclusion

For children 1–18 years of age, combined, efficacy has been demonstrated. In the latest meta-analysis efficacy against laboratory-confirmed influenza across all age groups was estimated at 59% (95% CI 31–71%), but results in each age group show a wide range of point estimates.

Moreover, there are few age-specific data on efficacy, especially between one and two years of age, and no data below one year of age.

5. HERD IMMUNITY OR INDIRECT BENEFITS TO THE COMMUNITY

Universal immunisation of children may limit virus circulation in the community and may provide indirect protection to adults. This effect has been investigated in different settings measuring the efficacy of immunisation in children in protecting contacts or the community at large. A recent systematic review provided a summary of the results of the available studies on the topic of reducing community transmission by TIV as shown below[66].

Table 3. Summary of studies on the indirect effect of TIV immunisation of children on the adult population

Studies on contacts				
Reference	*Study design*	*Target age group for immunisation*	*Outcome*	*Vaccine efficacy*
Gruber, 1985–86	Cluster RCT	Children > 3 years	Culture or serologically confirmed cases of B infection in family contacts	−33% (−399, 44)
Clover, 1986–87	Cluster RCT	Children 3–18 years	Culture or serologically confirmed A infection in family contacts	22%% (−55, 61)
Hurwitz, 1996–97	Cluster RCT	Children 2–5 years	Respiratory tract infections; school-days missed; adult work-days missed; physician visits; antibiotics prescribed; over-counter medications	Any respiratory illness: 16% Respiratory illness with fever: 42% Respiratory illness with fever > 38°: 47%
Colombo, 1995–96	Cluster RCT	Children 1–6 years	Influenza-like illness	No difference
Esposito, 2000–01	Cluster RCT	Children 6 months to 14 years	Respiratory tract infections; medical visits for respiratory tract infections; hospitalisations; antibiotic and antipyretic prescriptions; parental work-days lost; school-days lost	24%
Principi, 2001–02	Cluster RCT	Children 6 months to 5 years	Respiratory tract infections; medical visits for respiratory tract infections; parental work-days lost; help at home	30%
Studies in the community				
Reference	*Study design*	*Target age group for immunisation*	*Outcome*	*Vaccine efficacy*
Monto, 1968–69	Intervention trial comparing two cities	Children 5–19 years	Respiratory tract infection by age group in samples of families from whole city populations	67%

Reichert, 1949–99	Ecological study	Children in school age	Excess all-cause mortality and excess influenza + pneumonia mortality, relative to baseline	Number needed to vaccinate and prevent one death: 420
Ghendon, 2006	Intervention trial comparing four areas	Children 3–17 years	Influenza-like illness and its potential complications in the elderly (>60 years)	Persons in the unvaccinated communities had 3.4 times fewer ILI and 1.7–2.6 times fewer episodes of possible complications of influenza

Modified from Jordan R, 2006[66]

The evidence accumulated so far suggests that universal immunisation of school-age children is effective in preventing the disease in contacts and in the community. However, the available studies have often had problems in study design, have included different vaccine types and different target age groups for immunisation, there have been different matching profiles between the vaccine and the wild circulating strain, and the definition of outcomes has varied. Therefore, the estimation of effectiveness of this strategy is imprecise, and more observational studies would be warranted to quantify the preventable fraction achievable in the adult population with universal immunisation of children of different age groups.

Nonetheless, an increasing number of studies have recently explored the potential herd immunity induced by universal immunisation of children. The assumptions taken in these studies rely on different efficacy figures of influenza vaccines and on different coverage levels[67,68]. Based on other experiences, most models assume a protective efficacy of the influenza vaccine of 70% among children, and an efficacy for infectiousness of 80%.

A simulation model[68] suggests that vaccinating 20% of schoolchildren would reduce influenza-related mortality in the elderly more than would vaccinating 90% of persons over the age of 64. In the scenarios predicted in this work, if limited doses of vaccine were available, vaccinating schoolchildren would be the most efficient approach to reducing overall numbers of influenza cases. Another work[69] yielded similar results with a reduction of 46% of the total cases of influenza given a coverage of 20% among 6 months to 18 year olds, or a reduction of 91% with 80% coverage in the same age group.

A study performed in Massachusetts[70] indicates that during an influenza outbreak, paediatric patients, specifically preschool children aged 3–4 years, receive ambulatory and emergency care earliest. The authors suggested that these patients drive the transmission of the virus to older paediatric patients and to the wider community.

The American Advisory Committee for Immunization Practices has recommended the extension of immunisation to children up to 59 months starting from this year[1]. Extending influenza immunisation to children 6–59 months of age, however, has not been justified by induction of herd immunity in other age groups. This strategy is mainly based on morbidity,

mortality, hospitalisation rates, and number of visits observed in this age group, although this extension is a move toward the goal of annual universal influenza vaccination in the US.

The impact of universal vaccination of children in the community reasonably depends on the efficacy of the vaccine, and on the level of coverage achieved. The availability of a live attenuated vaccine, which exhibits a higher efficacy than TIV, may support this strategy since the same effect in the community may be obtained with a lower coverage.

Provided that universal immunisation of children proves efficacious in preventing influenza in adults, and appropriate studies demonstrate the convenience of universal immunisation of children, ethical issues and acceptability by the families should be explored. A strategy intended to administer a very high number of doses to a new target group would also require a huge amount of resources and adequate information strategies.

Thus, seemingly encouraging results have been obtained through mathematical models or simulations where efficacy estimates of the vaccine in children have been set to 70%. These models support indirect protection of adults and elderly when school-age children are targeted even with coverage as low as 20%. However, note that current models assume vaccine efficacy at the upper range of true efficacy – models should also use more conservative estimates until the model estimate of benefits are proven by real life data (see the Annex on cost-effectiveness for further discussion).

Available data have only shown that routine immunisation of school-age children may reduce the disease burden in adults, including the elderly. There is no data on the effect on the disease burden in the most vulnerable group: infants and young children. The indirect effect of immunising infants and young children is not known. Again such effects will be affected by age-specific incidence rates, contact patterns between age groups and obtained coverage rates.

Although implementation issues are not within the scope of the present document, the feasibility of a vaccination programme in children should be assessed before introduction.

Any universal immunisation of children should be integrated with other existing strategies such as immunisation of high-risk groups, including the elderly. Is there room for two doses in children under 12 years old during the same season and before the peak of the epidemic in autumn, and within the ordinary national childhood immunisation schedule?

A cause of concern is the low vaccine coverage in 6–23 month old children from the USA[71] and Calgary, Canada[72], on the first year of recommendations: 33.4% and 40.6% for one dose or more, respectively.

Conclusion

Published data suggest that routine immunisation of school-age children has an indirect beneficial effect for adults and the elderly in terms of reduced disease burden. However, such an indirect effect has not been demonstrated in young children, particularly in infants below six months of age.

Quantification of the preventable burden is difficult to assess. Generalisation between different settings (e.g. countries, age groups) should be done with caution.

6. COST-EFFECTIVENESS AND RISK ANALYSIS OF TRIVALENT INACTIVATED INFLUENZA VACCINE IN HEALTHY CHILDREN

A review of recently published cost-analyses of routine use of TIV in healthy children is presented in the Annex.

The results from economic analyses with different methodologies, in different subgroups of children, in different settings of health systems, and with more or less optimistic assumptions about medical, epidemiological, and economic cost-relevant factors, including influenza-related mortality and vaccination-induced adverse events, are clearly not uniform. Studies published in 2005 and 2006 are less optimistic in general, due to more conservative assumptions and a wider set of cost factors. Consequently, routine vaccination of all children is presently not seen as saving costs in every societal setting.

Vaccinating healthy children for a primarily community health benefit raises ethical concerns not taken into account in these studies. As the disease burden is particularly high for very young infants, and given that only TIV vaccines are licensed in Europe, routine vaccination of high-risk children of all ages seems to emerge as currently the best justified approach.

Before expanded influenza-virus vaccination programmes for inter-pandemic periods can be recommended to policy decision-makers, research is needed into case-based assessments of the health risks and health benefits that are incurred by healthy children vaccinees, together with the collection of multivariate costs data in EU Member States.

7. ADDITIONAL ISSUES AND CONSIDERATIONS

Which criteria should be considered on a national basis to justify universal immunisation of children?

The primary aim of such a universal immunisation programme, whether directed to all children or to a specific age group of children, should be carefully considered first.

Is the primary aim:

- *to prevent significant morbidity* in the targeted age group; or
- *to reduce spread of the disease* by induction of herd immunity in other age groups?

Addressing the possibility of reaching such aims, this document has highlighted significant knowledge gaps that should be acknowledged and potentially acted upon.

Several gaps mostly concerning quantitative data on efficacy have been identified. Future studies should take into account at least the following factors:

- previous vaccination status;
- vaccine specificity (the product);
- schedule;
- number of doses;
- interval between doses and dosage (half or full dose).

It is known from many inactivated vaccines that an efficient booster response is linked to an efficient primary immunisation usually induced by more than one vaccine dose. Still, efficacy in infants and children previously not exposed to influenza (disease or vaccine) is uncertain or not documented.

This concern is corroborated by very recent clinical data generated with influenza virus strains to which humans are immunologically naive. In particular with the H5N1 subtype, where two doses of up 90 µg of H5N1-HA antigen are needed to mount an acceptable immune response[73]. This is six times more HA antigen compared to licensed inactivated split or subunit vaccine.

There is a need for more effective vaccines: only TIV is currently licensed in the EU Member States. Live attenuated influenza vaccines, LAIV, may provide an improved primary response and also better cross-immunity, at least against related strains.

Conclusions

Product specific clinical evaluation in immunologically naive as well as primed infants and children should be performed for new vaccines in order to:

- define the number of doses and dosage needed to achieve protective immunity by age-group;
- determine the effect of annual revaccination in infants and children who have had a successful course of primary immunisation.

Little data exist on potential long-term adverse effects of reiterated annual immunisations:

- thus, annual revaccinations pose a particular issue within a routine programme for children aiming at very high coverage;
- reiterated annual immunisations in children require careful follow-up.

Countries considering influenza vaccination programmes are advised to develop national goals, objectives and targets for vaccination coverage and reduction of illness and death due to influenza disease in different age groups:

- The Scientific Panel advised that surveillance systems should be in place or be developed to monitor national and local trends in influenza disease and to monitor the impact of influenza vaccines on disease incidence.
- Close monitoring of newly introduced routine influenza immunisation programmes for children or large well-designed field trials would be needed to determine more precisely their effectiveness related to varying immunisation coverage and other factors.
- More research is also needed on assessments of individual health risks and benefits, also important for wider acceptance of vaccinating children, and collection of multivariate costs data, in EU Member States.

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ANNEX
COST-EFFECTIVENESS ANALYSIS OF TRIVALENT INACTIVATED INFLUENZA VACCINATION IN HEALTHY CHILDREN

J Mau

Summary

The results from economic analyses with different methodologies, in different subgroups of children, in different settings of health systems, and with more or less optimistic assumptions about medical, epidemiological, and economic cost-relevant factors, including influenza-related mortality and vaccination-induced adverse events, are clearly not uniform. Studies published in 2005 and 2006 are less optimistic in general, due to more conservative assumptions and a wider set of cost factors. Consequently, routine vaccination of all children must not be seen as cost saving in every societal setting anymore. Vaccinating healthy children for mainly the community health benefits raises ethical concerns and has not been incorporated in these studies, accordingly. As the disease burden is particularly high for the very young, routine vaccination of high-risk children of all ages plus routine vaccination of all children aged 6 to 23 months seems to emerge as currently recommendable from an economic perspective. Before expanded influenza-virus vaccination programmes for inter-pandemic periods can be recommended to policy decision-makers, research into case-based assessments of the health risks and health benefits that are incurred by healthy children vaccinees, and collection of multivariate costs data in EU Member States are needed.

1. Rationale

1.1. Influenza

Influenza is a recurrent epidemic with a high potential of occasional world-wide 'mega-kill'. An adequate level of immunisation in populations is believed to provide a time window that can be used for production and delivery of targeted antiviral drug treatment. Though the issue seems compelling, decision-makers are not prepared to engage into a costly programme of immunisation of a significant part of the population, easily. Nor does the public seem to be prepared to participate in annual vaccination readily.

Previous research found a reduction to one-third of influenza-like illnesses when more than 85% of children were vaccinated (cf. *Monto et al*, 1970), while the Japanese experience amounts to having prevented about 11,000 deaths from pneumonia and influenza per year by routinely vaccinating school-age children (cf. *Reichert et al*, 2001), and modeling studies would imply containment of annual influenza epidemics by vaccination of about 60% of children in the USA (cf. *Elveback et al*, 1976; *Longini et al*, 2000; *Halloran et al*, 2002).

Therefore, targeted immunisation of major spreaders and in pools of high contact rates appears a reasonable strategy in several aspects: (i) reduced incidence in the targeted subpopulation as well as at community level ('herd immunity'), (ii) reduced influenza-related morbidity and mortality in vulnerable subpopulations, (iii) reduced health costs, (iv) increased

productivity, and – last but not least – (v) increased readiness for pandemic situations through expanded production capacity and logistics for vaccine delivery.

With regard to these considerations, immunisation of children, of day care, pre-school and school ages, has come into focus. The discussion has mainly been led in the USA, and been taken up more recently in some other countries. It is led at the levels of evidence that observational studies and mathematical modelling parameterised with 'guesstimates', and sometimes supplemented with data from randomised trials, can provide. The monetary commitment that routine immunisation of children during inter-pandemic periods would entail has motivated economic studies of cost-effectiveness, early.

1.2. Cost-effectiveness analysis

The subject is almost classical, as seen from early textbooks, e.g. *Warner and Luce* (1982). Citing from *Petitti* (1994), methods for quantitative synthesis in medicine comprise meta-analysis, medical decision analysis, and cost-effectiveness analysis; those three components provide a rationale framework for counselling patients, setting clinical procedures, and aiding high-level policy decision making about funding, respectively and jointly, when a choice between alternative medical strategies must be made.

Cost-effectiveness analysis compares decision options primarily in terms of monetary costs. In medicine, it starts with a decision analysis, followed by collection of medical data, often from meta-analyses, and of costs data from health service economic sources, and subsequent comparisons of costs that are entailed by alternative options or actions.

'Cost-effectiveness analysis' as a term may have different interpretations in the medical literature (*Doubilet et al*, 1986) and is sometimes used interchangeably with cost-benefit (*Warner and Luce*, 1982). This motivated a definition of terms in a glossary at the end of the present article. There, definitions that appear closer to common clinical speech are preferred to those that may be used in the health economics literature, somewhat arbitrarily, though.

This paper reviews recently published studies and provides a synthesis.

2. Material and methods

To fix ideas about the kind of results to be expected from C/E analysis, an example taken from *Petitti* (1994) may be instructive: Cost-effectiveness of vaccination against pneumococcal pneumonia in persons older than 65 years had been analysed from the perspective of Medicare, by *Sisk and Riegelman* (1986). It was estimated that net expenditures for vaccination would be between 4,400 and 8,300 USD (1983) *per year of healthy life gained*, and that vaccination would be cost efficient for Medicare if it were administered in a public programme to keep costs of vaccination low. Hence, *cost-effectiveness* is expressed as a *ratio*.

More specifically, a cost-effectiveness ratio may be either absolute or incremental, cf. *Petitti* (1994; Chapter 12): Cost per unit outcome measure is an *absolute C/E* ratio, typical for a non-comparative assessment of costs of a medical intervention; for a comparative assessment of vaccination versus no vaccination, the *incremental C/E* ratio of excess or incremental cost per excess unit outcome, as given in the example above in terms of years of healthy life *gained*, is more appropriate.

To use cost-effectiveness for cost saving has been described as a (common) misuse of terminology, cf. *Doubilet et al* (1986). While helpful for academia, the practitioner will have to bypass such criticism whenever consensus about an outcome of primary interest is lacking. Hence, most studies self-declared as C/E ones will plausibly compare cost savings from vaccination, obtained as costs per case vaccinated minus costs per case unvaccinated, also referred to as 'one-to-one' below. The approach has the additional advantage of avoiding discussions about ascribable costs, or causal cost-intervention relationships that most studies to date cannot withstand. A viable alternative is the general term 'economic study'.

An economic study should start with a *decision tree* that represents the logical structure of the problem, its relevant steps ('nodes') and outcomes of interest. To what extent detailed decision options and decision costs are included in the tree model will depend on the *perspective* of the intended evaluation. Obvious options are the direct payers, i.e. the household and the third-party or insurance industry, and the population or health policy viewpoint which involves impacts on national economy and social security systems, cf. Glossary.

The selected articles were found by a simple search in common medical literature databases. Some full text versions were not available at the time of writing the present paper.

3. Results

3.1. Case-comparison studies

1. White et al (1999) compared individually initiated and group-based vaccination settings with no vaccination as reference in *school-age children* for inactivated influenza virus vaccine, in the USA, and concluded that 'influenza vaccination of school-aged children could result in a net cost savings from a societal perspective and have health benefits within the community'. Direct costs included visit to physician's office for individually initiated (USD 10.00) or group-setting (USD 4.00) vaccination (twice for children aged < 9 years in first year), costs of a physician visit for ill child and for secondary household contacts seeking medical care. Indirect costs included costs of employed caretaker staying with ill child while both parents are at work, costs of lost work when a parent cares for ill child or takes child to physician's office for vaccination, and lost work due to secondary transmission to employed parent. Included probabilities were annual influenza incidences in children (47.7% among <11 years old, 40% among 11–17 year olds), vaccine effectiveness of 56% in preventing influenza-type illness, secondary transmission to adult of 18%, and exposure of two adults in 72% of households, among which 76% of mothers and 97% of fathers would be employed. Included adverse events were low-grade fever (100%) and Guillain-Barré syndrome (1 per million); otitis media was not assumed to be preventable by vaccination in school-aged children. Sensitivity analysis covered uncertainties in costs estimates and variabilities in annual influenza incidence and risks of adverse events, transmission rates, and other probabilities in the model. The group-based setting that did not require parents to incur wage losses, would be more efficient as indirect costs mainly determine monetary benefits of immunisation. *Not included were death from influenza, complications of infection or from vaccination, hospitalisation, costs of transportation, or monetary benefits from herd immunity.*

2. Cohen and Nettleman (2000) did a decision analysis of routine vaccination with inactivated influenza virus vaccine in *pre-school children aged 0.5 to 5 years*, and concluded that vaccination in this subgroup is economically advantageous. Direct costs included visit to physician's office for vaccination (USD 10.00), twice in a child's first year of vaccination, costs of an outpatient visit to pediatrician's office (USD 51.00) or to emergency (USD 124.42) for ill child, costs of outpatient visit to physician's office for secondarily infected adults (USD 69.51), costs of antibiotic use attributable to influenza-like illnesses, costs of hospitalisation related to influenza. Indirect costs included parental wage loss because of child's influenza, parent's secondarily transmitted influenza infection, obtaining child's vaccination, and because of child's otitis media. Included probabilities were an influenza incidence in children aged <6 years of 37%, a vaccine effectiveness of 83% in preventing clinically apparent infections in children aged <5 years and of 32% in reducing otitis media in 6 to 30-month old children, an excess outpatient annual visit rate for influenza of 9.9%, probabilities of outpatient's emergency-room visits for upper respiratory infections of 4.95%, excess antibiotic courses of in 7.2% among pre-school aged children, adult's outpatient clinic visits for illness at 27%, excess influenza-related annual hospitalisation rate of 0.176% per child, probabilities of secondary transmission to adult of 28.6%, and an exposure of two adults in 68% of households where 97% of men and 65% of women would be employed, 24% of the latter only part time, incidence of otitis media during the influenza season of 27.6%. Sensitivity

analysis examined vaccine efficacy and costs, secondary trasmissions, and vaccination adverse events, use of outpatient services for ill child, and number of days spent in bed. Influenza vaccination in this age group would result in net cost savings per child if performed in the general population, and even when indirect costs are ignored; as parental wage loss appears as the most important factor, obtaining vaccination outside traditional work hours would imply highest savings. *Not included were death from influenza, complications of vaccination, or transmission to other children or adults outside the home, or costs of transportation*.

3. Luce et al (2001) used a prospective two-dose placebo-controlled multi-centre randomised trial of a still investigational live attenuated influenza vaccine (LAIV) in *pre-school children* during two seasons for a CE analysis of vaccination. The trial admitted 1,602 *children aged 15 to 71 months* in the first, and 1,358 of these again in the second season. In their analysis they compared individual-initiated and group-based vaccination policies. Frequency and costs of required visits for medical examination, diagnostic tests and treatments were recorded in more detail, though resource utilisation and lost productivity data had still to be obtained from secondary sources as the trial had been planned for efficacy and not for cost-effectiveness. Direct medical costs included costs implied by administration of vaccine (time needed for administration, vaccine), by use of health care resources because of vaccine-related adverse events (medications) or influenza-like illnesses (hospitalisation, days in hospital, visits to obtain medical care – either physician's office or emergency department – diagnostic tests, antibiotic or other prescriptions or OTC medications). Direct non-medical costs included caregiver's transportation for vaccination, for treatment of vaccination adverse events, or for treatment of ILI or culture-confirmed influenza. Indirect costs include caregiver's productivity loss in a wide sense (absent from usual activity) due to obtaining vaccination, treatment of vaccination adverse events, of ILI, or of culture-confirmed influenza. Probabilities of 97.7% and 2.3% were assumed for outpatient visits to physician's office and emergency rooms, respectively, and 0.213% for hospitalisation per ILI episode. The authors concluded that the use of intranasal influenza vaccine can be cost-effective when reduction in ILI fever days is the main outcome of interest; the vaccination of young children can imply costs savings for society in particular when vaccination is delivered in group-based settings such as childcare or elementary school, where vaccination costs can be kept small. *Not included were influenza-related mortality or more severe adverse effects from vaccination.*

4. Pisu et al (2005) used data from a *randomised controlled trial* in 127 and 133 *children from daycare* centres at US Californian naval bases during the 1996–1997 and 1998–1999 influenza seasons, respectively, to compare direct and indirect monetary costs of influenza-related illnesses (without costs of vaccination) between households of IIV vaccinated and unvaccinated children, both from a household and from a societal perspective. They found no statistically significant differences in household costs. In the first season, costs of adult and school-aged sibling contacts were significantly lower and costs of day care children were significantly higher in the vaccinated group; in the second season, no significant difference was seen. Results were similar from a societal perspective. Generalizability of results was said to be limited because of low power. The navy setting might also imply some lack of representativeness for a wider population. [Abstract only.]

5. Meltzer et al (2005) simulated net economic returns from annually vaccinating all children in three hypothetical cohorts, (i) *0.5 to below 2 years*, (ii) *0.5 to below 5 years*, and (iii) *5 to 14 years* of age, under three scenarios for the proportion of high-risk children in a cohort, (a) 0%, (b) 10%, and (c) 100%. Expected net savings were calculated as crude savings from expected numbers of averted outcomes in vaccinated target population minus costs of vaccinating total target population. The expected number of averted outcomes was estimated as excess proportion of influenza-related outcomes times influenza vaccine effectiveness. Excess risks were used throughout to adjust for lack of data about laboratory confirmed influnza. The authors formed *synthetic belief functions* (that they misleadingly referred to as probability distributions) for illness, medical resource use and economic parameters from averages or percentiles available in the literature; synthetic model fitting returned mainly skewed and sometimes bulky shapes of distributions used for simulation. Health outcomes and costs implied from a societal perspective included death, hospitalisation, outpatient visits, home-care using data from *Meltzer et al* (1999); some costs were modeled. Inconsistencies that arose from negative values under simulations for positive parameters; were eliminated by setting negative values to zero, when appropriate. All children presenting to medical service or having home care were assumed to require parental absence from work or other usual activity. The authors predicted net savings only for vaccinating and evaluating the high-risk children, cohorts of {(i),(c)} to {(iii),(c)}, for assumed clinical attack rates of 20 to 40% and vaccination costs between 30 and 60 US$ per dose administered. For the healthy (a) or mainly healthy (b) children cohorts, break-even costs per vaccine dose administered were between 30 and 60 US$, generally similar across the chosen age cohorts (i) to (iii); results depended more on the assumed clinical attack rates, either 20 to 30% or 30 to 40%. The attack rates used by these authors are lower than those assumed in preceding publications (*White et al*, 1999; *Cohen and Nettleman*, 2000). Savings were mainly influenced by the indirect costs attributable to prevented deaths or productivity losses due to child-sick leave, followed by individual costs of vaccination. As the authors studied only the effects for 100% vaccinated cohorts, different vaccination coverages and the pertinent population or community-level effects could be included into their assessment. The authors concluded that influenza virus vaccination should be targeted to the high-risk children for health and monetary benefits from a societal perspective. *Vaccination adverse events or transportation costs were not considered.*

6. Skowronski et al (2006) studied cost-effectiveness of routine vaccination of toddlers (*6 to 23 months*) with respect to reduced hospitalisation rates, which had been the main motivation for the immunisation recommendation issued in 2004 in Canada. *Comparative C/E analysis* was based on an implicit *decision tree model* and done twice, with direct costs only (third-party perspective) and including indirect costs (societal perspective), and comparisons were made between IIV vaccinated and not vaccinated children on a *one-to-one basis.* Direct medical costs included influenza immunisation, vaccine and administration per dose (2 doses required by all in first and by one-third in every later year), physician care at outpatient office or at emergency department, antibiotic prescription, and hospitalisations in medical ward or pediatric intensive care unit. Indirect costs were wage losses in full or part time employment of father or mother. Epidemiologic and demographic parameters were vaccine uptake (100%), some health condition in toddlers (5%), in day care (17%), two-parent households (85%),

number of toddlers per household (1), both parents working (67%), full-time employed fathers and mothers in two-parent households (96% and 66%, resp.), full-time and part-time employed mother in one-parent households (66% and 34%, respectively), and mother absent from work for child immunisation visit (48%), influenza incidence (25%), duration of uncomplicated illness (7 days), incidence of influenza-related AOM (25%, all of which would attend physician), attendance of physician without AOM (40%), physician visit at outpatient office (75%) or emergency department (25%) among non-high-risk and (50% each) among high-risk, antibiotic courses among AOM (100%) and non-AOM (24%), hospitalisations among influenza cases (1%) for 4.6 days, 12% requiring intensive care for another 2.4 days, case fatality related to influenza (0.002%), as direct effects of disease, and secondary transmissions to adult from child in day care (25%), days absent from work for mother to care for ill child (1.95 days) or for adult due to influenza illness from secondary transmission of virus (1.5 days), as indirect effects of disease, and vaccine effectiveness of IIV in toddlers of 66%. It was found that immunisation might not be cost saving, whether in the first (double dose) or in subsequent (single dose) years, as long as attack rates are below 55%, hospitalisation rates below 4%, and costs per dose administered above 7 CDN$ when considering direct costs only. Immunisation might become cost-effective in group settings, where attack rates are high and vaccine administration costs can be low. *Note that adverse events from vaccination or transportation costs were not considered.*

7. Salo et al (2006) compared direct medical costs, direct non-medical costs, and indirect costs due to productivity loss (work absenteeism) between univaccinated and IIV vaccinated *children of age-cohorts 0.5 up to 3 years*, *3 up to 5 years*, *5 up to 7 years*, and *7 to 13 years* in the Finnish society. They assumed vaccine efficacies (VE) of 80% or 60% for all ages. As influenza-related disease outcomes they considered AOM, pneumonia, sinusitis, and severe illness for outpatients and inpatients, apart from uncomplicated course. Most of their input data were from Finnish sources. They concluded that vaccination in all children between 0.5 and 13 yrs was cost saving, even at VE of 60%. When looking at their calculations more closely, the savings in terms of societal costs are marginal 3.04 EUR per vaccinated child 7 to 13 yrs old, with an extra total direct cost of 2.90 EUR (negative saving), simply and only due to vaccination-related transportation costs. Similarly, the impresssive savings in societal costs of 20 to 30 EUR per vaccinated child younger than 7 yrs, decrease from 8 and 4 to 1 EUR savings per vaccinated child in terms of total direct costs (excluding productivity loss) in age groups 0.5 up to 3 yrs, 3 up to 5 yrs, and 5 up to 7 yrs, respectively. *Influenza-related mortality, symptomatic treatment, or vaccination related adverse events and their treatment were not considered.*

8. Prosser et al (2006) did a comparative C/E analysis for routine vaccination of children in different age groups between 0.5 and 17 years, separately for IIV vaccines and LAIVs, on a one-to-one basis according to a societal perspective. They included health benefits in terms of quality of life metrics and the adverse events associated with vaccination into their *decision-tree modeling* (cf. Figure 1). In most epidemiologic parameters they distinguished five age groups, *6 to 23 months*, *2 years*, *3 to 4 years*, *5 to 11 years*, and *12 to 17 years* with pertinent probabilities of influenza incidence, outpatient visit for ill child, AOM incidence for influenza-related medically attended child, outpatient pneumonia or other complication for influenza-related medically attended ill child, hospitalisation for pneumonia or other

respiratory condition due to influenza in children not at high risk, long-term sequelae after influenza-related hospitalisation and mortality among hospitalised cases, vaccine effectiveness in preventing influenza illness (69% for IIV), medically attended vaccination-related adverse events such as injection site reactions or fever, anaphylaxis, or Guillain-Barré syndrome. Influenza-related costs in their model were OTC medications, physician visit for uncomplicated influenza, AOM, non-hospitalised pneumonia, hospitalisations, long-term sequelae after hospitalisation, while vaccination costs included costs of vaccine, its administration, and parent time costs per visit; costs for vaccination-related adverse events were physician visit for injection site reactions, costs for treatment of anaphylaxis and of Guillain-Barré syndrome. Their analysis yields the result that routine vaccination of all children is possibly less cost-effective than vaccination of children aged 0.5 up to 2 years plus all other children at high risk. Their calculations were most sensitive to variations in influenza attack rates and vaccine effectiveness. Comparing their findings with the literature, they have assumed estimates of attack rate, effectiveness and total costs of vaccination that are less favorable to comprehensive vaccination programmes. *Transportation costs were not considered.*

3.2. Population-effects studies

1. Fitzner et al (2001) used *surveillance data* from Hong Kong collected in 1993–94 and a theoretical predictive decision model to analyze cost-effectiveness of vaccinations in parts or in all of the population from individual and societal perspectives; among their five vaccination strategies in the total population, they had included *targeted vaccination of children*. In their decision tree model, they included vaccination coverage of 0.6, susceptibility of 0.88 for the unvaccinated, vaccination efficacy of 0.6, vaccination adverse events in 0.01, incidence among susceptibles of 0.3, symptomatic influenza in 81% of infected, and 68%, 29%, 2% and 0.7% of mild, moderately ill, severely ill cases without and with complications, respectively. (However, breaking all numbers down to children's age groups is beyond the scope of this overview.) Despite the special epidemiologic circumstances in Southern China, where influenza occurs throughout the year and shows much lower hospitalisation and mortality rates than are known from Western countries, the results are interesting because they are in conflict with findings for Western countries. In fact, they predicted that targeted vaccination of the elderly and those at risk from underlying illnesses would be the most cost-effective strategy, saving 1 dollar for 3.78 dollars spent on prevention. Hence, none of the vaccination strategies would be cost-effective from a societal perspective, though vaccination would be cost-effective for a susceptible person. Targeted vaccination would become cost-effective for society, even, when a highly virulent strain could be controlled with an effective vaccine. The authors attribute their conflicting results partly to lower indirect and direct costs of influenza or influenza-like illnesses in Hong Kong than in the USA. In particular, lost productivity was insignificant in Hong Kong because of lower absenteeism and lower average wages, when compared to the USA, and there was little or no recorded influenza-related mortality in Hong Kong.

2. Weycker et al (2005) report a *population simulation study* into the effects of routine vaccination of *children aged 0.5 to 18 years* for the whole population. These authors use a stochastic simulation model of virus transmission and disease burden due to Elveback (cf.

Elveback et al, 1976) and then include direct and indirect economic costs. Epidemiologic direct and indirect effects of vaccination, reduced susceptibility among vaccinees and reduced transmissions to other in community, respectively, were modeled as well as infectiousness in different stages. The (direct) costs of medical care include in- and outpatient medical services, prescriptions and OTC medications, while indirect costs result from influenza-related parental or caregiver's work absenteeism due to adult's own illness or need to care for ill child. Disease burden resulting from the model and entailed direct and indirect costs and implied savings are calculated for three age groups in the total population, children, working adults, and elderly. While presently 5%, vaccine coverages of 20% and 80% in children aged 0.5 to 18 years would then reduce total numbers of influenza cases in the US population by 50% and 90%, respectively, and similar reductions in mortality and economic costs were obtained.

3. Halloran and Longini Jr (2006) discuss how to plan studies of risk/benefit assessments when routine vaccination of school children would come into effect. This is a 'shot' of the evidence, and it can also provide some hints to implementation. Aspects relating to implementation and logistics that touch on a health policy level are also discussed by *Yogev* (2005) and *Greene et al* (2006).

3.3. Systematic overviews

1. Nichol (2003) reviewed the literature on efficacy, effectiveness and cost-effectiveness of inactivated influenza virus vaccines in different subpopulations; among the seven economic studies in children were *White et al* (1999; Nr. 1 in 3.1 above), *Cohen and Nettleman* (2000; Nr. 2 in 3.1 above), *Luce et al* (2001; Nr. 3 in 3.1 above), an earlier study by *Meltzer et al* (1999) for a pandemic scenario, *Fitzner et al* (2001; Nr. 1 in 3.2 above), and a study from Argentina (*Dayan et al*, 2001). She also included a cost-utility analyses done by the Office of Technology Assessment (1981) which had indicated early that influenza vaccination of children might be a low-cost preventive intervention that can yield health benefits among all age groups. The author summarised the evidence on efficacy and effectiveness in children, too: Inactivated influenza virus vaccine was 91% (95%ci: 64–98%) and 77% (95%ci: 20–94%) efficacious in preventing culture confirmed influenza from H1N1 and H3N2 strains, respectively, in a series of randomised controlled trials which had comprised 791 children, 277 under the age of 16 years, between 1985 and 1990, cf. *Neuzil et al* (2001). Another randomised trial in Italy with 344 children aged 1 to 6 years demonstrated 67% (95%ci: 59–74%) reduction in influenza-like illness, cf. *Colombo et al* (2001). Acute otitis media (AOM) which is a major complication of influenza among young children was reduced by 36% in a Finnish trial among vaccinated children, cf. *Heikkinen et al* (1991), and by 31% (OR=0.69; 95%ci: 0.49–0.98) among day care children in North Carolina, cf. *Clements et al* (1995). From the economic studies mentioned above, that author concludes that 'influenza vaccination of children may yield both health and economic benefits during epidemic and pandemic periods. These studies have used different analytic methods, outcomes and costs. Nevertheless, a common theme has emerged – in the United States influenza vaccination of children is probably cost saving if vaccination costs are less than US$ 20–25. ... It is important to note that a substantial portion of economic benefits associated with vaccinating children is due to reductions in parental work loss for care of sick children. The results of cost benefit analyses of childhood influenza vaccination in other countries have varied.'

2. Jordan et al (2006) systematically review the empirical evidence for indirect community benefits from vaccination of children against influenza, based on 8 randomised trials from USA, Italy and Russia, three community studies from USA including also the Japanese experience (*Reichert et al*, 2001), and the economic studies of *White et al* (1999; Nr. 1 in 3.1 above), Cohen and Nettleman (2000; Nr. 2 in 3.1 above) and Luce et al (2001; Nr. 3 in 3.1 above). Much of their scepticism may be attributed to the fact that they invoked rigorous methodological standards known from efficacy trials in drug testing. Their quality criteria for the assessment of the economic studies are surprisingly insensitive to distinct features, then, as they obtained identical answers in most items. While they try to synthesize the evidence from these trials, this author suggests to appreciate their differences in focus and methodology which render the three trials incomparable. As matter of fact, none of the trials included effects on community outside the household with infected children. Even though, those authors' conclusions support the theoretically derived results of *Weycker et al* (2005) reported above in general terms, without specifically suggesting similar quantifications of incurred benefits.

3.4. Other studies

1. Principi et al (2003) conducted a *retrospective study* in 3,771 *children aged <14 years who presented to primary care pediatricians or emergency departments* in Italy with symptoms of respiratory tract infections during the 2001–2002 influenza season. Influenza was verified by virus culture or polymerase chain reaction. Influenza virus was confirmed in 9.3% of children (8.7% and 11.5% in emergency department and in primary care pediatrician subgroups, respectively) for which household contacts data were also collected. Though similar in numbers and duration of hospitalisations and in numbers of additional medical visits, influenza-virus positive children had statistically significantly ($P<0.0001$) longer durations of fever, and accordingly longer absenteeism from day care or school. Numbers of medical visits, days of parental work or siblings' school absenteeism or need for help at home to care for the ill children were significantly larger among household contacts of children with confirmed influenza, while hospitalisations of parents or siblings were not. The authors also reported a *prospective vaccination efficacy trial* in 303 *children aged 0.5 to 5 years* who had been *randomised* before the influenza season started. Among vaccinated children, respiratory tract infections, fever, antibiotic and antipyretic prescriptions and school absenteeism were statistically significantly ($P<0.005$) reduced while the number of hospitalisations was not. Impact on household contacts was similar. Though this study does not involve costs estimates, it provides useful data on pertinent parameters for C/E analyses in a European setting.

3.5 Synthesis

In 2005 and 2006, another six economic studies that had not been included in overviews by *Nichol* (2003; Nr. 1 in 3.3 above) or *Jordan et al* (2006; Nr. 2 in 3.3 above), were published. It is now described whether and how the conclusions drawn in the previous overviews must be modified.

Nichol (2003; Nr. 1 in 3.3 above) concluded that influenza vaccination of children may be cost saving when vaccination costs are kept below some threshold value and economic benefits from vaccinating children would be due to reductions in parental work loss for care of ill child.

She argued from a societal perspective. *Jordan et al* (2006; Nr. 2 in 3.3 above) concluded that vaccinating children may imply health and economic benefits to the community; they partly argued from a health policy perspective.

The studies by *Pisu et al* (2005; Nr. 4 in 3.1 above), *Meltzer et al* (2005; Nr. 5 in 3.1 above), *Skowronski et al* (2006; Nr. 6 in 3.1 above), *Salo et al* (2006; Nr. 7 in 3.1 above), and *Prosser et al* (2006; Nr. 8 in 3.1 above) all supplement the evidence reviewed by *Nichol* (2003; Nr. 1 in 3.3 above); *Weycker et al* (2005; Nr. 2 in 3.2 above) add quantitatively to the results from a health policy viewpoint of *Jordan et al* (2006; Nr. 2 in 3.3 above). The study by *Principi et al* (2003; Nr. 1 in 3.4 above) adds socioeconomic background data from Italy.

Now, *Pisu et al* (2005; Nr. 4 in 3.1 above) would not expect cost savings from vaccinating daycare children, either from a household or a societal perspective; their study might have been underpowered, and the Californian naval base setting will not be typical of most communities in the USA. *Meltzer et al* (2005; Nr. 5 in 3.1 above) had studied the significance of high-risk to non-high-risk ratios in young school, pre-school and daycare children in the US setting and concluded that only vaccination of high-risk children would imply health and monetary benefits. *Skowronski et al* (2006; Nr. 6 in 3.1 above) found that immunisation of toddlers in Canada imply savings in direct costs when threshold values of attack rates, hospitalisations, or costs per dose of vaccines were passed, and immunisation might generally be cost-effective in group settings with their higher attack rates and lower vaccination costs, then. *Salo et al* (2006; Nr. 7 in 3.1 above) considered young school, pre-school and day care children in Finland, and found potential cost savings from vaccination in all age groups; however, they did not include complications from influenza or vaccination, and the Finnish setting might yield too optimistic estimates for other countries. *Prosser et al* (2006; Nr. 8 in 3.1 above) studied all age groups and all costs except for transportations, and concluded that routine vaccination of only high-risk children of any age plus all toddlers could be more cost-effective than routine vaccination of all children.

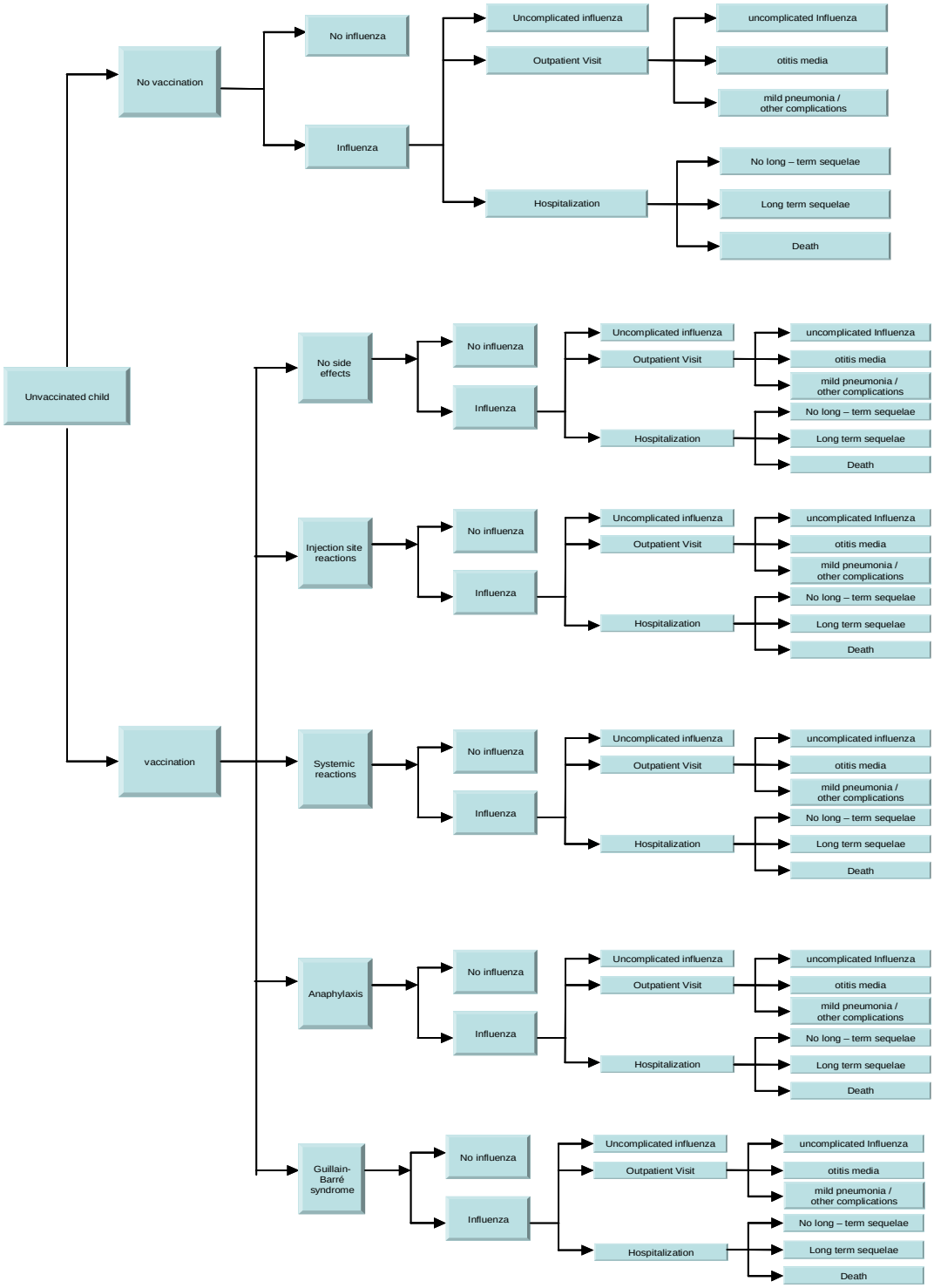

Figure 1: Decision-tree of *Prosser et al* (2006)

4. Discussion

Cost-effectiveness assessment of vaccination would require estimation of an incremental C/E ratio for a primary outcome measure, cf. *Petitti* (1994) for more detail, and *Dinh and Zhou* (2006) and *Wang and Zhao* (2006) for some recent methodology research. Most studies compared only the costs with and without vaccination. Only few studies extrapolated to population effects.

The analyses of the more recent studies tend to produce broadly consistent results with different methodologies when done in settings of comparable health systems, but reveal sensitivity to their assumptions about societal contexts, modelling techniques and data-source validity in the more often conflicting results from studies done in different regions. Most studies did not include adverse events related to vaccinating children, or transportation costs, and apparently no study considered infection of child by secondary transmission from adults in household.

Contrary to former analyses, the 'common theme emerges' (*Nichol*, 2003) now that:

- indirect costs incurred by households are more important than societal costs, and
- vaccinating all children may not imply cost savings under any setting, to say the least.

Most studies compared costs with and without vaccination on a case basis from a mixed household and insurance industry view point; the importance of the household perspective does not appear to be adequately appreciated in its own right, as:

- economic benefits, if any, were most vulnerable to the indirect costs that employed household adults would have to take when obtaining vaccination for healthy child or attending an ill child; in Finland, on the contrary, where wage loss is not a household issue during the few days that influenza would cause work absenteeism, the transportation costs took the place of wage loss in the US;
- the decision to participate in routine influenza vaccination of children will be made at the household level; this observation implies the creation or communication of understandable and rather immediate incentives, then.

Hence, a case-based *assessment* of *health risks and benefits* for the intended vaccinees should be done in the first place, and monetary or health benefits to the household should come next.

The value of sensitivity analyses is very limited as only marginal distributions of costs and health parameters are considered while associations between them are ignored; raising such data would require to conduct *separate multivariate cost studies in different countries*. This could be a theme for a joint research proposal to the European Commission.

5. Conclusion

High-risk children have specific chronic medical conditions, such as cardiac diseases, asthma, diabetes mellitus, or others that imply an increased risk for complicated courses of influenza illness and typically present an indication for vaccination. Very young children have higher

rates of hospitalisation for influenza-related complications which motivated consideration of this age group for immunisation, as well.

Consideration of vaccinating healthy children of younger ages more generally has been motivated by influenza-related health system expenditures, and parental or caregiver's productivity losses, instead. Despite a tendency towards growing belief in the benefits of vaccinating healthy children in some countries, the question arises as to whether it is ethical, and legal, to expose the healthy children in a population to the risks of vaccination for mainly the benefit of the adults, when the risks of complicated courses of influenza illness may generally be minor in children.

As herd immunity is a population benefit enjoyed by many at the expense of exposing relatively few others (the children) to the vaccination risks, the ethical question arises whether the presumably much smaller benefits for vaccinated children will balance the incurred risks to an adequate extent. This mandates a case-based risk/benefit assessment for the intended vaccinees in the first place in which C/E in the total population must not play a role, as health cost savings and protection for the adults cannot justify potentially harmful measures of bodily injury on the children.

Glossary

To fix ideas, some standardised terminology would be helpful since there is no common understanding: some terms used as synonyms by some have very distinct meaning for others. Also, economists and physicians have different interpretations: benefits, for example, would relate to health status improvements for only the latter while they are monetary for the former.

The examples given below in explanation are not exhaustive.

Costs may be direct or indirect, monetary or not, and may be accounted for at an individual or a societal level.

Here, costs are **monetary**, and may occur as either **expenditures** (positive costs) or **savings** (negative costs). **Non-monetary** costs would be either **risks** (positive 'costs') or **benefits** (negative 'costs') in terms of the **health status** and **quality of life**.

Monetary costs; individual, societal; direct, indirect

Direct individual costs then comprise case payments for obtaining or providing medical treatment of influenza and administration of vaccine, including treatment of influenza-like illnesses and side effects of influenza treatment and vaccination; **indirect individual** expenditures would include case-related wage losses, missed education, and also payments for replacements in job, house-keeping, child care, or otherwise.

Direct societal expenditures are global payments for production, public information, training and delivery; **indirect societal** expenditures can be related to legislation, administration, infrastructure, liability, productivity and tax revenue losses, etc.

Risks and benefits; individual, societal; direct, indirect

Individual direct risks and benefits will relate to case burden from influenza, while **individual indirect** risks and benefits will comprise second-line side effects, health status, co-morbidities, and others.

Societal direct risks could involve selection and distribution of an ineffective or contaminated vaccine, shortcomings in supply or distribution ages of adequate vaccines, while benefits would be seen in 'herd immunity', for example; **societal indirect** risks and benefits will include higher and lower levels of population morbidity or mortality, respectively.

Efficiency, utility

Efficiency is optimisation, typically minimisation of the positive costs, per unit of effective outcome.

Utility is the extent to which preferred or desirable outcome outweighs adverse outcome. Its analysis will require a metric of preferences, then.

Perspectives

The **household perspective** incorporates the direct, indirect, medical, and non-medical costs that an intervention or use of medical resources more generally, implies and that are not covered by third-party payers, in particular health insurance or employer. It is the costs that are paid by the household 'out of pocket', as deductions from wages, or as reduced benefits.

The **third-party perspective** incorporates the direct medical costs which includes immunisation (when applicable), medical visits, prescriptions, and hospitalisation, assumed not to be paid by households directly when covered by insurance or employer.

The **societal perspective** would include direct and indirect costs, medical and not medical such as absenteeism from day care or school and productivity losses resulting from adult absenteeism from work due to obtaining immunisation of child (if applicable), ill-child care, or adult illness after secondary transmission of virus; it also includes monetary benefits from productivity gains and from averted costs in the future.

The **health policy perspective** will further include vaccination coverage, health transfer ('herd') effects in a community, or health policy costs of implementing and sustaining a vaccination programme; extending this fully to a **national economy perspective** would imply consideration of potential impacts on tax revenues, labour market, social security systems, and employer's productivity.

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