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TECHNICAL REPORT

OF THE SCIENTIFIC PANEL ON VACCINES AND IMMUNISATION

**Use of pneumococcal polysaccharide
vaccine for subjects over 65 years of age
during an inter-pandemic period
Stockholm, January 2007**



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 regulation¹, 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 pneumococcal disease in persons aged 65 years and older in the Member State considering the implementation of a vaccine programme using a 23-valent pneumococcal polysaccharide vaccine (PPV23)?
- Is PPV23 safe and efficacious?
- What is the duration of protection?
- Who should receive PPV23?
- How effective is PPV23 in preventing disease in an open population?
- What is the cost-effectiveness of a PPV23 programme in the country?
- Are there indirect effects of universal vaccination of children with 7-valent pneumococcal conjugate vaccine on the disease burden in the elderly?

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?

¹ 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.

THE SCIENTIFIC PANEL ON VACCINES AND IMMUNISATION

Coordinated from ECDC by Pier Luigi Lopalco and Johan Giesecke



Olin, Patrick
Chairman

Pediatrician, Principal investigator for pertussis vaccine trials & DG Research Project EUSAFEVAC. Until 2003 Swedish WHO EPI manager. ETAGE member to VPI programme, WHO Euro and intermittently short term WHO consultant in Bosnia & Herzegovina

Swedish Institute of
Infectious Disease Control



Dagan, Ron

Pediatrician, Director of the Pediatric Infectious Disease Unit.
Research: epidemiology of vaccine preventable diseases; prevention of respiratory tract infections and antibiotic resistance by vaccination; prevention of pneumococcal infections (otitis, pneumonia)

Ben-Gurion University, and
Soroka University Medical
Center, Beer-Sheva, Israel



Mau, Jochen

Biomathematician, Chair of Statistics and Biomathematics in Medicine.
Teaching: quantitative medicine (2nd clinical year),
Research: biostochastics, risk analysis, research methodology, evidence quantification

Heinrich Heine University,
Medical Faculty,
Duesseldorf, Germany



Navarro-Alonso, Jose Antonio

Pediatrician, Head of Health Protection Service in Murcia Region. Responsible for the regional immunisation programme (policy, implementation and evaluation)
Member of the Spanish Ministry of Health Vaccines Board

General Directorate of
Health, Murcia Region,
Spain



Nuorti, Juha Pekka

Medical Epidemiologist, the Respiratory Diseases Branch, National Center for Immunisation and Respiratory Diseases, CDC. Vaccine-preventable diseases, pneumococcal vaccines and epidemiology of pneumococcal infections

CDC, Atlanta, United States



Pfleiderer, Carsten Michael

Virologist, Rapp or Co-Rapp for most of the centrally authorised vaccines. Acting as a Coordinator for virtually all EMEA scientific advice relating to vaccines. Major involvement in national and EU-activities in relation to biological threats and pandemic preparedness

Paul Ehrlich Institute,
Germany



Tozzi, Alberto Eugenio

Pediatrician, Clinical epidemiology, research in epidemiology of vaccine preventable diseases, vaccine safety, surveillance of infectious diseases, control of hospital infections, preparation of hospital guidelines, epidemiology and evidence-based medicine training

Bambin Gesù' Research
Hospital, Rome, Italy



Usonis, Vytautas

Pediatrician, Vilnius University. Teaching of paediatric infectious diseases (PID). Research in the area of vaccinology. Member of national and international advisory boards in vaccination

Vilnius University, Lithuania



Van Eden, Willem

Immunologist, MD with specialty training in medical microbiology. Responsible for the training of MDs and VMDs in immunology. Running research programmes in infection, vaccines and immunomodulation of inflammatory diseases

Utrecht University, The
Netherlands



Weil-Olivier, Catherine Sylvie

Pediatrician, member of *groupe technique des anti-infectieux* (AFSSAPS) for registration of vaccines; member of Comité technique des vaccinations for planning and national strategies

Paris University, France

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1. EXECUTIVE SUMMARY

In 2005, seventeen of the 25 EU Member States had recommended administration of the 23-valent pneumococcal polysaccharide vaccine (PPV23) to all individuals aged 65 years or older. This document reviews the public health considerations that form the basis for the immunisation policy.

1. Pneumococcal-related diseases are significant causes of illness and account for a large number of hospitalisations and deaths among persons aged 65 years and older in European countries. The incidence of invasive pneumococcal disease (defined as isolation of *Streptococcus pneumoniae* from a normally sterile body site such as blood or cerebrospinal fluid) is highest in older adults and the case-fatality ratio is approximately 10–20%.

Although the exact incidence of pneumococcal pneumonia without bacteremia (non-invasive infection) is not known, *Streptococcus pneumoniae* is considered the leading bacterial cause of pneumonia and is estimated to cause up to one third of pneumonia hospitalisations in adults.

2. The 23-valent pneumococcal polysaccharide vaccine has been shown to be moderately effective in preventing invasive pneumococcal disease among the general elderly population. However, its effect on the risk of invasive disease in the high risk elderly may be smaller.

Although some recent studies have obtained conflicting results, the vaccine has not been demonstrated to prevent pneumococcal pneumonia without bacteremia in this age group.

3. Universal immunisation of elderly persons with PPV23 to prevent invasive pneumococcal disease is supported by the fact that most economic evaluations suggest it is a cost-effective public health strategy in European countries and compares favorably with other standard preventive practices. Most studies also conclude that a universal, age-based vaccination strategy seems more cost-effective than a high risk-based strategy and will result in higher vaccine uptake.

4. Providing PPV23 routinely for all residents of nursing homes and other long-term care facilities may reduce the risk of outbreaks of invasive pneumococcal infections among institutionalised persons.

5. On the basis of currently available data on the duration of vaccine-induced protection, one time revaccination has been recommended for persons aged 65 years and older if they received the vaccine more than five years previously and were aged less than 65 years at the time of primary vaccination. There is currently insufficient evidence to support a recommendation to give a second dose of PPV23 for persons who received their first dose at age 65 or older. More data are needed regarding the optimal timing and schedule of revaccination as well as the clinical safety and effectiveness of more than one time revaccination with PPV23.

6. High quality population-based surveillance data are critical to ascertain pre-vaccination epidemiology, serotype distribution and the pneumococcal-related disease burden in European countries, to enable evidence-based decisions about the most appropriate vaccination strategy and to evaluate programme impact.

Countries considering pneumococcal vaccination programmes are advised to develop national goals, objectives and targets for vaccination coverage and reduction of illness and death due to pneumococcal disease in the elderly through immunisation.

The Scientific Panel advises that countries ensure the surveillance systems are in place or are developed to monitor national and local trends in pneumococcal disease and to monitor the impact of pneumococcal vaccines on disease incidence and to detect changes in the prevalence of antibiotic resistance and pneumococcal serotype distribution.

Additional considerations

Post-licensure surveillance studies in North America have demonstrated that routine use of the 7-valent pneumococcal conjugate vaccine (PCV7) in children has resulted in a substantial reduction of invasive pneumococcal-related diseases and antibiotic resistance in older adults through reduced transmission of vaccine serotypes and development of herd immunity.

Several European countries have recently implemented or are in the process of implementing routine PCV7 childhood immunisation. The magnitude of the expected direct and indirect effects will be influenced by the local distribution of pneumococcal serotypes, the extent of replacement disease caused by non-vaccine serotypes, the vaccination strategy and coverage achieved, as well as other factors, and should therefore be evaluated in each country.

Adult-formulated pneumococcal conjugate vaccines remains a research issue pending data from clinical efficacy trials and cost-effectiveness studies.



2. INTRODUCTION

The 23-valent pneumococcal polysaccharide vaccine (PPV23) has been recommended in some European countries for groups at high risk of invasive pneumococcal disease (IPD) for over two decades but these targeted high risk groups vary substantially in different EU countries¹. The evidence base for PPV23 immunisation programmes also varies from country to country and has not been systematically compiled. Many European countries have recently implemented programmes for universal PPV23 vaccination of all individuals aged 65 years and older and by 2005, seventeen of the 25 EU Member States had such a recommendation¹. However, in 2003 the Netherlands refrained from recommending PPV23 for elderly persons, based on evaluation of several systematic reviews²⁻⁷.

This document outlines an approach that can be used for the systematic evaluation of those factors that should be considered when deciding whether to introduce universal vaccination of persons aged 65 years and older with PPV23. It is intended to help public health immunisation programmes to determine whether PPV23 vaccination is an effective public health strategy in a given jurisdiction and what can be expected at the population level when PPV23 is used in routine practice. The panel considered available evidence in the following categories:

- a) The state of scientific evidence for each topic identified.
- b) Gaps in evidence and the unanswered research questions.
- c) The epidemiological and other data needed at local level to make a policy change.

3. LOCAL BURDEN OF PNEUMOCOCCAL DISEASE IN PERSONS AGED 65 YEARS AND OLDER

Numerous studies confirm that infection with *Streptococcus pneumoniae* remains a major cause of illness and death in all age groups and is the most common bacterial cause of community-acquired pneumonia in the elderly in developed countries⁸. The exact burden of pneumococcal disease, however, is often difficult to assess because of the limitations of available clinical diagnostics to identify the infecting organism in non-bacteremic pneumonia. There is substantial variation in observed rates of invasive pneumococcal disease (defined as isolation of *S. pneumoniae* from a normally sterile body site such as blood or CSF) among European countries^{9, 10} with the overall reported incidence ranging from 0.4 to 20 /100,000/year¹¹. These differences are thought to reflect a combination of epidemiological differences in patient populations as well as health care factors such as administering antibiotics before admission, variation in diagnostic practices such as frequency of obtaining blood cultures from pneumonia patients, different case definitions, reporting practices and surveillance systems. Since the mid-1990s the proportion of pneumococcal isolates resistant to macrolide antibiotics has increased in many European countries from a few percent to 5–35%^{12–14}.

Surveillance of pneumococcal disease in Europe

According to a recent survey of European national public health institutes, surveillance systems for invasive pneumococcal disease in Europe are very heterogeneous and many countries lack adequate surveillance systems¹¹. Although the EU has adopted a standard case definition for IPD, case definitions are not standardised across Europe and few countries routinely collect vaccination status of cases. The proportion of invasive pneumococcal disease caused by serotypes included in PPV23 as well as the 7-valent pneumococcal conjugate vaccine (PCV7) is often lacking because serotyping may not be universally available. Pneumococcal vaccination effectiveness is expected to differ depending on the pneumococcal serotype distribution in a particular population. In some sentinel surveillance programmes, invasive disease is sometimes not distinguished from non-invasive disease syndromes and in some countries, parallel surveillance systems exist.

Surveillance data are critical to ascertain pre-vaccination epidemiology and disease burden of IPD and to make decisions about whether and how to introduce pneumococcal vaccines. Country-specific population-based data are needed to determine morbidity, mortality and hospitalisations for different pneumococcal disease-related outcomes in elderly persons including:

- invasive pneumococcal disease (bacteremia, meningitis);
- non-bacteremic pneumococcal pneumonia and all-cause pneumonia;
- antimicrobial resistance among *S. pneumoniae* isolates and pneumococcal serotype distribution;



- standard case definitions for IPD and case data collection to allow comparisons across European countries.

If local data are not available, data from similar populations could be used as an approximation to assist in decision-making.

Based on the review of evidence on the local disease burden, national goals, objectives and targets for the reduction of pneumococcal disease in the elderly should be developed. Detailed descriptions of local pre-vaccination epidemiology and baseline information on the burden of pneumococcal disease are needed to enable an evaluation of the potential impact of vaccination strategies. Surveillance systems should be in place or developed to monitor national and local trends in pneumococcal disease and to monitor the impact of pneumococcal vaccines on disease incidence and detect changes in the prevalence of antibiotic resistance and serotype distribution.

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4. SAFETY, EFFICACY AND EFFECTIVENESS OF PPV23

Safety

Based on almost 30 years of clinical experience, PPV23 is generally considered safe. Mild, transient local side effects are relatively common after administration but moderate systemic reactions and more severe local reactions are rare^{8, 15}.

Vaccine efficacy in prospective clinical trials

Although multiple randomised clinical trials have evaluated PPV23 efficacy, the degree of protection remains a topic of some controversy. Ten contemporary prospective clinical trials of PPV23 conducted among elderly persons and high risk adults have shown no protective effect against pneumococcal pneumonia and a small but statistically insignificant effect against pneumococcal bacteremia^{8, 15-18}. However, some experts consider these trials too small to have sufficient statistical power to rule out false negative results¹⁹. Further, the specificity of diagnosis of non-bacteremic pneumonia may be inadequate to allow estimating efficacy in trials using pneumococcal pneumonia as the endpoint.

Five published meta-analyses have attempted to determine PPV23 efficacy by pooling results of individual randomised and quasi-randomised clinical trials but the findings of these meta-analyses have also been inconclusive. In summary, most authorities agree that the evidence from the clinical trials and meta-analyses suggests that PPV23 provides moderate protection against invasive pneumococcal disease in the general elderly population, whereas it has a smaller effect on risk of disease in the high risk elderly. The vaccine appears to have little or no effect against pneumonia²⁰.

Vaccination effectiveness in observational studies

Most observational studies (case-control, indirect cohort, retrospective cohort) have suggested a protective effect of PPV23 against invasive pneumococcal disease. Four case-control studies, three indirect cohort studies and one retrospective cohort study found significant aggregate effectiveness estimates of about 50–80% for the prevention of bacteremia or invasive pneumococcal disease in elderly people in developed countries. Vaccine effectiveness estimates appear to diminish with increasing age⁸.

Evidence from recent studies supports the recommendation to vaccinate elderly persons and high risk adults: a retrospective cohort study of 1,898 elderly persons with chronic lung disease in Minnesota found that pneumococcal vaccination was associated with fewer hospitalisations for pneumonia, fewer deaths, and direct medical care cost savings²¹. The findings of a recent retrospective cohort study among 1,428 Group Health Cooperative members in Seattle, all 65 years of age and older, also supported the effectiveness of PPV23 for the prevention of bacteremia. However, pneumococcal vaccination did not alter the risk of non-bacteremic pneumonia²². A community intervention study conducted in Stockholm, Sweden, found that a combined influenza and pneumococcal vaccination programme of



persons aged 65 and older resulted in a 57% reduction in all-cause mortality in the vaccinated cohort (n=100,242) in addition to lower rates of influenza, pneumococcal pneumonia and invasive pneumococcal disease^{23, 24}. In addition, some recent studies have suggested that pneumococcal vaccination may be also associated with a lower risk of hospitalisation for pneumonia, a faster resolution of symptoms, and a shorter hospital stay in adults with community-acquired pneumococcal pneumonia^{25–28}.

The limitations of the PPV23 in protecting elderly persons and high risk adults against pneumococcal-related diseases are widely recognised. In the United States, the Advisory Committee on Immunization Practices (ACIP) recommended vaccinating adults with PPV23 primarily on the basis of available evidence from observational studies which have demonstrated the effectiveness of PPV23 in preventing pneumococcal bacteremia in elderly and high risk adults⁸. The vaccine's moderate effectiveness against bacteremia alone was considered sufficient justification for the recommendation. In addition, a cost-effectiveness analysis found that PPV23 saves costs for elderly people in the prevention of bacteremia alone^{29, 30}. The ACIP considered the evidence about the vaccine's effectiveness against non-bacteremic pneumonia inconclusive.

The population effects of all immunisation programmes should be evaluated. There are few data available on the effectiveness of PPV23 in reducing disease incidence in open populations²⁴. Also, PPV23 has not been shown to reduce nasopharyngeal carriage of *S. pneumoniae* and no indirect effects have been observed. Providing PPV23 routinely for residents of nursing homes and other long-term care facilities may reduce outbreaks of antibiotic-resistant pneumococci among institutionalised persons^{31–33}.

5. DURATION OF VACCINE-INDUCED PROTECTION

Following vaccination with PPV23, antibody levels decline after 5–10 years and they decrease more rapidly in some groups than others. However, the relation of antibody levels and protection against disease is uncertain. Therefore, the ability to define the need for revaccination on the basis of antibody levels is limited. Two epidemiological studies provide estimates of the duration of protection against invasive disease. One study suggested that vaccination may provide protection for at least nine years among those vaccinated with a median age of 57 years³⁴. Another study reported estimates of decreased effectiveness as the interval post-vaccination increased, particularly among persons aged 85 years or more³⁵.

Immunogenicity and safety after first revaccination

Revaccination is associated with an increase in self-limiting local injection site reactions compared with first vaccination^{36–38}. This risk, however, does not represent a contraindication to revaccination with PPV23 in recommended groups. Limited data are available on the safety of three or more doses of PPV23³⁹.

The effectiveness of the first revaccination as well as the duration of possible protection are currently unknown. Available data do not indicate substantial increase in antibody levels in the majority of revaccinated elderly persons. Additional data are needed on safety (potential for hyporesponsiveness with multiple doses of polysaccharide antigen) and immunogenicity of revaccination with more than one dose of PPV23 and the optimal timing and frequency of revaccination. Additional unanswered questions include whether lowering the age for universal vaccination with PPV23 to age 50–64 years is justifiable from scientific and programmatic perspectives (public health impact, cost-effectiveness, feasibility of implementation)⁴⁰. A recent study suggested that expanding the age-based recommendation to include persons aged 50–64 years might only prevent an additional 5–7% of invasive pneumococcal disease in the United States compared with the current high risk-based vaccination recommendation⁴¹. However, there are programmatic advantages to age-based recommendations which have been shown to result in higher vaccination coverage than a high risk-based strategy.

6. ISSUES RELATED TO COST-EFFECTIVENESS AND PROGRAMME IMPLEMENTATION

Several economic evaluation analyses have been conducted in European countries and they generally found that routine pneumococcal vaccination of elderly persons is relatively cost-effective and potentially cost-saving to the health care sector and society⁴²⁻⁴⁵. Recent economic evaluations in five European countries and the US have suggested that the vaccine may be cost-effective on the basis of its effectiveness against invasive disease^{30, 42}. In addition, a recent analysis in the UK suggested that routine vaccination of all elderly might be more cost-effective than the strategy of vaccinating high-risk groups⁴⁴. The uncertainties around vaccination effectiveness estimates, however, play a major role in the analyses. The results of a cost-effectiveness analysis also depend on the local disease burden including the number of hospitalisations and deaths attributable to pneumococcal disease and local health care costs.

Many programme implementation issues will be country-specific. Despite existing national recommendations, the uptake of PPV23 in many European countries has been low, possibly reflecting concerns about the vaccine's effectiveness and consequent lack of programmes to promote the vaccine. The issues surrounding acceptability of a vaccination programme (whether providers will administer the vaccine, people willing to receive it), feasibility of programme implementation given existing resources, sustainability and general issues related to adult immunisation (i.e. how to improve the coverage of PPV23) should be evaluated separately. In general, offering pneumococcal vaccine with influenza vaccination should improve pneumococcal vaccination coverage. Many individuals aged 65 years and over who received influenza vaccine reported never having received pneumococcal vaccination. In the US, strategies such as standing orders, reminder and recall systems and offering vaccination to hospitalised patients before discharge have all been shown to improve vaccination coverage in adults⁴⁶ but few data are available from European countries.

7. FUTURE PERSPECTIVES

Use of pneumococcal vaccines to reduce morbidity and mortality from bacterial pneumonia in an influenza pandemic

Bacterial pneumonia is an important complication of seasonal and pandemic influenza and during previous pandemics, secondary bacterial pneumonia has been an important cause of morbidity and mortality. *S. pneumoniae* superinfection complicates many cases of influenza and some bacterial pneumonia caused by *S. pneumoniae* can be prevented by immunisation⁴⁷. Issues related to the role of pneumococcal vaccines in pandemic influenza preparedness activities may include: logistics of mass vaccination with PPV23 during a pandemic; vaccine supply; shelf life; and need for cold storage. Nevertheless, increasing the current use of pneumococcal vaccines among the age groups for which it is universally recommended (i.e. persons aged under two years (PCV7) and those aged 65 and older (PPV23)) could reduce the burden of pneumococcal disease and can also be expected to benefit persons susceptible to influenza.

Indirect effects of universal vaccination of children with 7-valent pneumococcal conjugate vaccine (PCV7) on the disease burden in the elderly

Routine immunisation of infants with PCV7 began in 2000 in the United States. Despite shortages in vaccine supply and incomplete vaccination coverage during 2001–04, the incidence of invasive pneumococcal disease (IPD) decreased dramatically in children aged under five years compared with the period pre-vaccination. Rates of IPD also decreased in non-immunised adults, including persons aged 65 years and older, likely due to reduced transmission of vaccine serotypes and development of herd immunity^{48–51}.

A routine childhood PCV7 immunisation programme in the US has resulted in reduced carriage of serotypes included in the vaccine not only in children^{47, 52–54}, but also in adults⁵⁵. The decreased transmission has resulted in a substantial reduction in vaccine type and overall invasive pneumococcal disease (IPD) in non-vaccinated age groups, including persons aged 65 and older^{50, 51}. In 2003, for each prevented case in the target age group, 2.2 cases were prevented through indirect vaccine effects (herd immunity)⁴⁹. Furthermore, a reduction in carriage of antibiotic-resistant *S. pneumoniae* in adults was observed after initiation of the vaccination programme in the US⁵⁵, as well as a reduction in IPD caused by antibiotic-resistant *S. pneumoniae* in adults^{56, 57}. Currently no data are available to suggest an effect on non-bacteremic pneumonia in the elderly following vaccination of children.

Pneumococcal conjugate vaccines have not reduced the prevalence of overall pneumococcal carriage and the decrease in vaccine serotypes has been associated with an increased carriage of non-vaccine types^{54, 58}. The percentage increase in IPD caused by non-vaccine serotypes has been significant in some groups, such as HIV-infected persons and the elderly^{50, 59} but as the absolute rate increases of non-vaccine types are small compared with



reduction in vaccine types, the impact of replacement on the overall disease burden continues to be small. Continued surveillance is important to monitor the emergence of non-vaccine serotypes that may reduce the benefits of vaccination in some populations. Currently two new conjugate vaccines are being developed for use in children (a 10-valent and a 13-valent vaccine). Future extended conjugate vaccine formulations should include the replacement serotypes to sustain vaccine impact.

Updated economic analyses which incorporated the observed herd effects in the US indicate substantially improved cost-effectiveness of the immunisation programme. The potential magnitude of an indirect effect in European countries will depend on the burden of childhood and adult disease attributable to conjugate vaccine serotypes and other epidemiologic and health care-related factors such as immunisation strategy, coverage achieved, and population composition. Several European countries have recently introduced universal PCV7 immunisation programmes which are likely to provide significant health benefits for both children and adults.

Development of pneumococcal conjugate vaccines for use in adults

Conjugate vaccines are currently being developed for use in adults. Preliminary results with the newly developed 13-valent CRM₁₉₇ PCV have shown good immunogenicity but efficacy data are not available for adults. As the data on conjugate vaccine in adults are currently limited (including safety of respective doses, the numbers of doses needed in the elderly), the benefits and cost-effectiveness of PCVs in adults in general, and the elderly in particular, have still to be established. Thus as long as the PPV23 contains more serotypes than PCVs, and the safety and efficacy of PCVs in adults is not established, continuing use of PPV23 in persons aged 65 years or over remains a recommended public health strategy.

REFERENCES

1. Pebody RG, Leino T, Nohynek H, Hellenbrand W, Salmaso S, Ruutu P. 'Pneumococcal vaccination policy in Europe.' *Euro Surveill.* 2005 Sep;10(9):174–8.
2. Assendelf WJ, Scholten RJ, Offringa M. 'Pneumococcal vaccination for the elderly in The Netherlands? Assessment of the quality and content of available comparative studies.' *Neth J Med.* 2004 Feb;62(2):36–44.
3. Cornu C, Yzebe D, Leophonte P, Gaillat J, Boissel JP, Cucherat M. 'Efficacy of pneumococcal polysaccharide vaccine in immunocompetent adults: a meta-analysis of randomized trials.' *Vaccine.* 2001 Sep 14;19(32):4780–90.
4. Fine MJ, Smith MA, Carson CA, Meffe F, Sankey SS, Weissfeld LA, et al. 'Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomized controlled trials.' *Arch Intern Med.* 1994 Dec 12–26;154(23):2666–77.
5. Hutchison BG, Oxman AD, Shannon HS, Lloyd S, Altmayer CA, Thomas K. 'Clinical effectiveness of pneumococcal vaccine. Meta-analysis.' *Can Fam Physician.* 1999 Oct;45:2381–93.
6. Moore RA, Wiffen PJ, Lipsky BA. 'Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials.' *BMC Fam Pract.* 2000;1:1.
7. Watson L, Wilson BJ, Waugh N. 'Pneumococcal polysaccharide vaccine: a systematic review of clinical effectiveness in adults.' *Vaccine.* 2002 May 22;20(17–18):2166–73.
8. CDC. 'Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP).' *MMWR Recomm Rep.* 1997 Apr 4;46(RR–8):1–24.
9. Fedson DS, Scott JA. 'The burden of pneumococcal disease among adults in developed and developing countries: what is and is not known.' *Vaccine.* 1999 Jul 30;17 Suppl 1:S11–8.
10. Hausdorff WP, Feikin DR, Klugman KP. 'Epidemiological differences among pneumococcal serotypes.' *Lancet Infect Dis.* 2005 Feb;5(2):83–93.
11. Pebody RG, Hellenbrand W, F DA, Ruutu P. 'Pneumococcal disease surveillance in Europe.' *Euro Surveill.* 2006 Sep 20;11(9).
12. Garcia-Rey C, Aguilar L, Baquero F, Casal J, Dal-Re R. 'Importance of local variations in antibiotic consumption and geographical differences of erythromycin and penicillin resistance in *Streptococcus pneumoniae*.' *J Clin Microbiol.* 2002 Jan;40(1):159–64.
13. Perez-Trallero E, Fernandez-Mazarrasa C, Garcia-Rey C, Bouza E, Aguilar L, Garcia-de-Lomas J, et al. 'Antimicrobial susceptibilities of 1,684 *Streptococcus pneumoniae* and 2,039 *Streptococcus pyogenes* isolates and their ecological relationships: results of a 1-year (1998–1999) multicenter surveillance study in Spain.' *Antimicrob Agents Chemother.* 2001 Dec;45(12):3334–40.
14. Reinert RR, Al-Lahham A, Lemperle M, Tenholte C, Briefs C, Haupts S, et al. 'Emergence of macrolide and penicillin resistance among invasive pneumococcal isolates in Germany.' *J Antimicrob Chemother.* 2002 Jan;49(1):61–8.
15. Ortvist A. 'Pneumococcal vaccination: current and future issues.' *Eur Respir J.* 2001 Jul;18(1):184–95.
16. Dear K, Holden J, Andrews R, Tatham D. 'Vaccines for preventing pneumococcal infection in adults.' *Cochrane Database Syst Rev.* 2003(4):CD000422.
17. Fedson DS. 'The clinical effectiveness of pneumococcal vaccination: a brief review.' *Vaccine.* 1999 Jul 30;17 Suppl 1:S85–90.
18. Mangtani P, Cutts F, Hall AJ. 'Efficacy of polysaccharide pneumococcal vaccine in adults in more developed countries: the state of the evidence.' *Lancet Infect Dis.* 2003 Feb;3(2):71–8.
19. Fedson DS, Liss C. 'Precise answers to the wrong question: prospective clinical trials and the meta-analyses of pneumococcal vaccine in elderly and high-risk adults.' *Vaccine.* 2004 Feb 25;22(8):927–46.



20. Melegaro A, Edmunds WJ. 'The 23-valent pneumococcal polysaccharide vaccine. Part I. Efficacy of PPV in the elderly: a comparison of meta-analyses.' *Eur J Epidemiol.* 2004;19(4):353–63.
21. Nichol KL, Baken L, Wuorenma J, Nelson A. 'The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease.' *Arch Intern Med.* 1999 Nov 8;159(20):2437–42.
22. Jackson LA, Neuzil KM, Yu O, Benson P, Barlow WE, Adams AL, et al. 'Effectiveness of pneumococcal polysaccharide vaccine in older adults.' *N Engl J Med.* 2003 May 1;348(18):1747–55.
23. Christenson B, Hedlund J, Lundbergh P, Ortqvist A. 'Additive preventive effect of influenza and pneumococcal vaccines in elderly persons.' *Eur Respir J.* 2004 Mar;23(3):363–8.
24. Christenson B, Lundbergh P, Hedlund J, Ortqvist A. 'Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study.' *Lancet.* 2001 Mar 31;357(9261):1008–11.
25. Conaty S, Watson L, Dinnes J, Waugh N. 'The effectiveness of pneumococcal polysaccharide vaccines in adults: a systematic review of observational studies and comparison with results from randomised controlled trials.' *Vaccine.* 2004 Aug 13;22(23-24):3214–24.
26. Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J. 'Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia.' *Clin Infect Dis.* 2006 Apr 15;42(8):1093–101.
27. Mykietiuk A, Carratala J, Dominguez A, Manzur A, Fernandez-Sabe N, Dorca J, et al. 'Effect of prior pneumococcal vaccination on clinical outcome of hospitalized adults with community-acquired pneumococcal pneumonia.' *Eur J Clin Microbiol Infect Dis.* 2006 Jul;25(7):457–62.
28. Vila-Corcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodriguez T, et al. 'Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study.' *Clin Infect Dis.* 2006 Oct 1;43(7):860–8.
29. Fedson DS. 'Pneumococcal vaccination for older adults: the first 20 years.' *Drugs Aging.* 1999;15 Suppl 1:21–30.
30. Sisk JE, Moskowitz AJ, Whang W, Lin JD, Fedson DS, McBean AM, et al. 'Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people.' *Jama.* 1997 Oct 22–29;278(16):1333–9.
31. Nuorti JP, Butler JC, Crutcher JM, Guevara R, Welch D, Holder P, et al. 'An outbreak of multidrug-resistant pneumococcal pneumonia and bacteremia among unvaccinated nursing home residents.' *N Engl J Med.* 1998 Jun 25;338(26):1861–8.
32. Quick RE, Hoge CW, Hamilton DJ, Whitney CJ, Borges M, Kobayashi JM. 'Underutilization of pneumococcal vaccine in nursing home in Washington State: report of a serotype-specific outbreak and a survey.' *Am J Med.* 1993 Feb;94(2):149–52.
33. Tan CG, Ostrawski S, Bresnitz EA. 'A preventable outbreak of pneumococcal pneumonia among unvaccinated nursing home residents in New Jersey during 2001.' *Infect Control Hosp Epidemiol.* 2003 Nov;24(11):848–52.
34. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. 'Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations.' *Jama.* 1993 Oct 20;270(15):1826–31.
35. Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, et al. 'The protective efficacy of polyvalent pneumococcal polysaccharide vaccine.' *N Engl J Med.* 1991 Nov 21;325(21):1453–60.
36. Jackson LA, Benson P, Sneller VP, Butler JC, Thompson RS, Chen RT, et al. 'Safety of revaccination with pneumococcal polysaccharide vaccine.' *Jama.* 1999 Jan 20;281(3):243–8.

37. Lackner TE, R GH, J JH, Davey C, Guay DR. 'Pneumococcal polysaccharide revaccination: immunoglobulin g seroconversion, persistence, and safety in frail, chronically ill older subjects.' *J Am Geriatr Soc.* 2003 Feb;51(2):240–5.
38. Torling J, Hedlund J, Konradsen HB, Ortqvist A. 'Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. Vaccine.' 2003 Dec 8;22(1):96–103.
39. Walker FJ, Singleton RJ, Bulkow LR, Strikas RA, Butler JC. 'Reactions after 3 or more doses of pneumococcal polysaccharide vaccine in adults in Alaska.' *Clin Infect Dis.* 2005 Jun 15;40(12):1730–5.
40. Sisk JE, Whang W, Butler JC, Sneller VP, Whitney CG. 'Cost-effectiveness of vaccination against invasive pneumococcal disease among people 50 through 64 years of age: role of comorbid conditions and race.' *Ann Intern Med.* 2003 Jun 17;138(12):960–8.
41. Greene CM, Kyaw MH, Ray SM, Schaffner W, Lynfield R, Barrett NL, et al. 'Preventability of invasive pneumococcal disease and assessment of current polysaccharide vaccine recommendations for adults: United States, 2001–2003.' *Clin Infect Dis.* 2006 Jul 15;43(2):141–50.
42. Ament A, Baltussen R, Duru G, Rigaud-Bully C, de Graeve D, Ortqvist A, et al. 'Cost-effectiveness of pneumococcal vaccination of older people: a study in 5 western European countries.' *Clin Infect Dis.* 2000 Aug;31(2):444–50.
43. Mangtani P, Roberts JA, Hall AJ, Cutts FT. 'An economic analysis of a pneumococcal vaccine programme in people aged over 64 years in a developed country setting.' *Int J Epidemiol.* 2005 Jun;34(3):565–74.
44. Melegaro A, Edmunds WJ. 'The 23-valent pneumococcal polysaccharide vaccine. Part II. A cost-effectiveness analysis for invasive disease in the elderly in England and Wales.' *Eur J Epidemiol.* 2004;19(4):365–75.
45. Postma MJ, Heijnen ML, Jager JC. 'Cost-effectiveness analysis of pneumococcal vaccination for elderly individuals in The Netherlands.' *Pharmacoeconomics.* 2001;19(2):215–22.
46. Shefer A, Briss P, Rodewald L, Bernier R, Strikas R, Yusuf H, et al. 'Improving immunization coverage rates: an evidence-based review of the literature.' *Epidemiol Rev.* 1999;21(1):96–142.
47. Brundage JF. 'Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness.' *Lancet Infect Dis.* 2006 May;6(5):303–12.
48. CDC. 'Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP).' *MMWR Recomm Rep.* 2000 Oct 6;49(RR-9):1–35.
49. CDC. 'Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States, 1998–2003.' *MMWR Morb Mortal Wkly Rep.* 2005 Sep 16;54(36):893–7.
50. Lexau CA, Lynfield R, Danila R, Pilishvili T, Facklam R, Farley MM, et al. 'Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine.' *Jama.* 2005 Oct 26;294(16):2043–51.
51. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. 'Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine.' *N Engl J Med.* 2003 May 1;348(18):1737–46.
52. Hennessy TW, Singleton RJ, Bulkow LR, Bruden DL, Hurlburt DA, Parks D, et al. 'Impact of heptavalent pneumococcal conjugate vaccine on invasive disease, antimicrobial resistance and colonization in Alaska Natives: progress towards elimination of a health disparity.' *Vaccine.* 2005 Dec 1;23(48–49):5464–73.



53. Moore MR, Hyde TB, Hennessy TW, Parks DJ, Reasonover AL, Harker-Jones M, et al. 'Impact of a conjugate vaccine on community-wide carriage of nonsusceptible *Streptococcus pneumoniae* in Alaska.' *J Infect Dis.* 2004 Dec 1;190(11):2031–8.
54. Pelton SI, Loughlin AM, Marchant CD. 'Seven valent pneumococcal conjugate vaccine immunization in two Boston communities: changes in serotypes and antimicrobial susceptibility among *Streptococcus pneumoniae* isolates.' *Pediatr Infect Dis J.* 2004 Nov;23(11):1015–22.
55. Hammitt LL, Bruden DL, Butler JC, Baggett HC, Hurlburt DA, Reasonover A, et al. 'Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an explanation of trends in invasive pneumococcal disease.' *J Infect Dis.* 2006 Jun 1;193(11):1487–94.
56. Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A, et al. 'Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*.' *N Engl J Med.* 2006 Apr 6;354(14):1455–63.
57. Stephens DS, Zughaier SM, Whitney CG, Baughman WS, Barker L, Gay K, et al. 'Incidence of macrolide resistance in *Streptococcus pneumoniae* after introduction of the pneumococcal conjugate vaccine: population-based assessment.' *Lancet.* 2005 Mar 5–11;365(9462):855–63.
58. Dagan R, Givon-Lavi N, Zamir O, Sikuler-Cohen M, Guy L, Janco J, et al. 'Reduction of nasopharyngeal carriage of *Streptococcus pneumoniae* after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers.' *J Infect Dis.* 2002 Apr 1;185(7):927–36.
59. Flannery B, Heffernan RT, Harrison LH, Ray SM, Reingold AL, Hadler J, et al. 'Changes in invasive Pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization.' *Ann Intern Med.* 2006 Jan 3;144(1):1–9.

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