

23-valent pneumococcal polysaccharide vaccine; core references

Within each section the papers are listed in chronological order. Summaries are provided when available.

Epidemiology of pneumococcal disease

Adegbola RA, Hill PC, Secka O, Ikumapayi UN, Lahai G, Greenwood BM, Corrah T. Serotype and antimicrobial susceptibility patterns of isolates of *Streptococcus pneumoniae* causing invasive disease in The Gambia 1996-2003. *Trop Med Int Health* 2006 Jul;11(7):1128-35.

OBJECTIVES: To describe the characteristics of pneumococcal isolates obtained from patients with invasive pneumococcal disease in The Gambia. **METHODS:** Pneumococcal isolates were obtained from children aged < or =6 years with invasive pneumococcal disease during a Haemophilus influenzae vaccine effectiveness study (1997-2002) and from patients with invasive pneumococcal disease admitted to the MRC hospital, Fajara, for routine care (1996-2003). Isolates were identified, serotyped and tested for antibiotic susceptibility. **RESULTS:** Five hundred and thirty one pneumococcal isolates were obtained from 518 patients; 55 (10.6%) patients died; 415 isolates (79%) were from blood culture, 84 (16%) from CSF, and 42 (8%) from lung aspirates. Forty serogroups and serotypes were identified; six accounted for 64% and 16 for 86% of all episodes; 33.7% were of serotypes 1 and 5. 23.5% were of a 7-valent vaccine serotype, 57.1% were of a 9-valent vaccine serotype; 56% were of a 7-valent serogroup and 78% were of a 9-valent serogroup. There was a significant increase in the proportion of isolates of non-vaccine serogroup with increasing age ($P < 0.0001$). Antibiotic resistance had not significantly increased over time; but intermediate non-susceptibility to penicillin had risen and resistance to chloramphenicol had fallen in isolates of vaccine serotype compared with those of non-vaccine serotype. **CONCLUSIONS:** The majority of invasive pneumococcal disease in The Gambia is caused by pneumococci of relatively few serogroups. A conjugate vaccine would be expected to reduce the pneumococcal disease burden substantially and to have a beneficial effect on pneumococcal antibiotic resistance to penicillins.

Lexau CA, Lynfield R, Danila R, Pilishvili T, Facklam R, Farley MM, Harrison LH, Schaffner W, Reingold A, Bennett NM, Hadler J, Cieslak PR, Whitney CG. Active Bacterial Core Surveillance Team. 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.

CONTEXT: A conjugate vaccine targeting 7 pneumococcal serotypes was licensed for young children in 2000. In contrast to the 23-valent polysaccharide vaccine used in adults, the 7-valent conjugate vaccine affects pneumococcal carriage and transmission. Early after its introduction, incidence of invasive pneumococcal disease declined among older adults, a group at high risk for pneumococcal disease. **OBJECTIVE:** To determine among adults aged 50 years or older whether incidence of invasive pneumococcal disease, disease characteristics, or the spectrum of patients acquiring these illnesses have changed over the 4 years since pneumococcal conjugate vaccine licensure. **DESIGN, SETTING, AND POPULATION:** Population-based surveillance of invasive pneumococcal disease in 8 US geographic areas (total population, 18,813,000), 1998-2003. **MAIN OUTCOME MEASURES:** Incidence of invasive pneumococcal disease by pneumococcal serotype and other characteristics; frequency among case patients of comorbid conditions and other factors influencing mortality. **RESULTS:** Incidence of invasive pneumococcal disease among adults aged 50 years or older declined 28% (95% confidence interval [CI], -31% to -24%), from 40.8 cases/100,000 in 1998-1999 to 29.4 in 2002-2003. Among those aged 65 years or older, the 2002-2003 rate (41.7 cases/100,000) was lower than the Healthy People 2010 goal (42 cases/100,000). Among adults aged 50 years or older, incidence of disease caused by the 7 conjugate vaccine serotypes declined 55% (95% CI, -58% to -51%) from 22.4 to 10.2 cases/100,000. In contrast, disease caused by any of the 16 serotypes only in polysaccharide vaccine did not change, and disease caused by serotypes not in either vaccine increased somewhat, from 6.0 to 6.8 cases/100,000 (13%; 95% CI, 1% to 27%). Between 1998-1999 and 2002-2003, the proportion of case-patients with human immunodeficiency virus infection increased from 1.7% (47/2737) to 5.6% (124/2231) ($P < .001$), and those with any comorbid condition that is an indication for pneumococcal polysaccharide vaccination increased from 62.3% (1842/2955) to 72.0% (1721/2390) ($P < .001$). **CONCLUSIONS:** Our findings indicate that use of conjugate vaccine in children has substantially benefited older adults. However, persons with certain comorbid conditions may benefit less than healthier persons from the indirect effects of the new vaccine.

Immune response, efficacy/effectiveness, and safety

Moberley S, Holden J, Tatham D, Andrews R. Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev.* 2008 Jan 23;(1):CD000422.

BACKGROUND: Diseases caused by *Streptococcus pneumoniae* (*S. pneumoniae*) continue to cause substantial morbidity and mortality throughout the world. Whilst pneumococcal polysaccharide vaccines (PPV) have the potential to prevent disease and death, the degree of protection afforded against various clinical endpoints and within different populations is uncertain. **OBJECTIVES:** To assess the effectiveness of PPV in preventing disease or death in adults. Adverse events were not assessed. **SEARCH STRATEGY:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2007, Issue 2); MEDLINE (January 1966 to June 2007); and EMBASE (1974 to June 2007). **SELECTION CRITERIA:** A) Randomised controlled trials (RCTs) comparing PPV with placebo, control vaccines, or no intervention. B) Non-RCTs assessing PPV effectiveness against invasive pneumococcal disease (IPD). **DATA COLLECTION AND ANALYSIS:** A) RCTs: trial quality assessment was conducted by two review authors and data extracted by three authors; odds ratios (OR) and 95% confidence intervals (CI) were estimated using a random-effects model. B) Non-RCTs: study quality, including measures to control for confounding, was assessed and data extracted by two review authors; OR and 95% CI were calculated using a random-effects model following the conversion of each study outcome to a log OR and standard error. **MAIN RESULTS:** Twenty-two studies met our inclusion criteria (15 RCTs involving 48,656 participants and 7 non-RCTs involving 62,294 participants). Meta-analysis of the RCTs found strong evidence of PPV efficacy against IPD with no statistical heterogeneity (OR 0.26, 95% CI 0.15 to 0.46; random-effects model, $I^2 = 0\%$). Efficacy against all cause pneumonia was inconclusive with substantial statistical heterogeneity (OR 0.71, 95% CI 0.52 to 0.97; random-effects model, $I^2 = 87.3\%$). PPV was not associated with substantial reductions in all-cause mortality (OR 0.87, 95% CI 0.69 to 1.10; random-effects model, $I^2 = 75.3\%$). Vaccine efficacy against primary outcomes appeared poorer in adults with chronic illness but the difference was not statistically significant. Non-RCTs provided evidence for protection against IPD in populations for whom the vaccine is currently utilised (OR 0.48, 95% CI 0.37 to 0.61; random-effects model, $I^2 = 31.4\%$). **AUTHORS' CONCLUSIONS:** This meta-analysis provides evidence supporting the recommendation for PPV to prevent IPD in adults. The evidence from RCTs is less clear with respect to adults with chronic illness. This might be because of lack of effect or lack of power in the studies. The meta-analysis does not provide compelling evidence to support the routine use of PPV to prevent all-cause pneumonia or mortality.

Scott P, Egger M, Huss A. Effectiveness of pneumococcal polysaccharide vaccine: systematic review and meta-analysis of randomised controlled trials. *In press, CMAJ* Oct 17, 2008.

De Vito C, Manzoli L, Marzuillo C, Anastasi D, Boccia A, Villari P. A systematic review evaluating the potential for bias and the methodological quality of meta-analyses in vaccinology. *Vaccine* 2007;25:8794-806.

A systematic review was undertaken to produce an annotated bibliography of meta-analyses in vaccinology and to evaluate their methodological quality. Based on our evaluation using the Oxman and Guyatt index, the methodological quality of the 121 meta-analyses included in this study is not satisfactory. The most frequent limitations include non-comprehensive bibliographic research; bias in the selection of the studies; lack of quality assessment of individual studies; absence of evaluation of heterogeneity among studies and publication bias. The methodological quality significantly increases with the year of publication and with declared financial support, without differences between profit and non-profit support. Meta-analyses with a higher Oxman and Guyatt quality score are more likely to include only randomized trials and to explore appropriately potential sources of heterogeneity. Most of the methodological deficiencies of meta-analyses in vaccinology could be corrected easily, and meta-analysts should improve the methodological quality of their work to maintain their impact on policy decisions.

Johnstone J, Marrie TJ, Eurich DT, Majumdar SR. Effect of pneumococcal vaccination in hospitalized adults with community-acquired pneumonia. *Arch Intern Med* 2007;167:1938-1943.

BACKGROUND: Although 23-valent polysaccharide pneumococcal vaccine (PPV) does not prevent community-acquired pneumonia (CAP), it might still improve outcomes in those who develop pneumonia. We tested this hypothesis using a population-based cohort of hospitalized patients with CAP. **METHODS:** From

2000 to 2002, we prospectively collected data on all adults with CAP admitted to 6 hospitals in Capital Health, the largest integrated health delivery system in Canada. Polysaccharide pneumococcal vaccine status was ascertained by interview, medical record review, and contact with physicians and community health offices. The primary outcome was the composite of in-hospital mortality or intensive care unit (ICU) admission. Multivariable regression was used to determine the independent association between PPV use and outcomes, after adjusting for patient characteristics, pneumonia severity, and propensity scores. RESULTS: Of the 3415 patients with CAP (median age, 75 years), 46% were female, 62% had severe pneumonia, and 22% had prior PPV. Overall, 624 patients died or were admitted to an ICU. Polysaccharide pneumococcal vaccine was protective from reaching this composite end point (73/760 [10%] vs 551/2655 [21%] for unvaccinated patients; $P < .001$), mostly a result of reduced ICU admission (2/760 [$<1\%$] vs 349/2655 [13%]). The propensity-adjusted odds of death or ICU admission was 0.62 (95% confidence interval, 0.42-0.92; $P = .02$) for patients who had received PPV. Only 215 of 2416 patients (9%) eligible for PPV at hospital discharge were vaccinated. CONCLUSIONS: Patients with CAP who had prior PPV had about a 40% lower rate of mortality or ICU admission compared with those who were not vaccinated. This provides additional support for recommending PPV to those at risk of pneumonia.

O'Brien KL, Hochman M, Goldblatt D. Combined schedules of pneumococcal conjugate and polysaccharide vaccines: is hyporesponsiveness an issue? *Lancet Infect Dis.* 2007 Sep;7(9):597-606.

Streptococcus pneumoniae is a major cause of morbidity and mortality in children less than 5 years of age. Prevention of pneumococcal disease and death in children in the developing world through vaccination with recently developed, highly efficacious pneumococcal conjugate vaccines (PCVs) is now possible. Schedules combining PCV with 23-valent pneumococcal polysaccharide vaccine (PPV23) have been studied and proposed as a means to expand disease protection against serotypes not included in the PCVs. Studies of group A and C meningococcal polysaccharide vaccine and repeated doses of PPV23 in adults and children have shown that a state of immune tolerance, or hyporesponsiveness, can develop to repeated polysaccharide vaccine antigen exposures. In this Review, we describe the evidence for and against this hyporesponsiveness and explore the possible mechanisms for such an occurrence.

Mykietiuk A, Carratalà J, Domínguez A, Manzur A, Fernández-Sabé N, Dorca J, Tubau F, Manresa F, Gudiol F. 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.

The aim of this study was to evaluate the effect of prior pneumococcal vaccination on the clinical outcome of 554 consecutive hospitalized adults with community-acquired pneumococcal pneumonia from 1995 to 2004, 61 of whom had been vaccinated in the 5 years before admission. Outcome variables that were compared in vaccinated and unvaccinated adults included the occurrence of bacteremia, the time to resolution of pneumonia symptoms, the length of hospital stay, and mortality. Prior pneumococcal vaccination was associated with a lower risk of bacteremia (odds ratio 0.46, 95% CI 0.22-0.98). Compared with unvaccinated patients, vaccine recipients had better clinical outcomes, which included a faster resolution of pneumonia symptoms. The median length of hospital stay was shorter in vaccinated patients (8.0 vs. 9.0 days; $p=0.032$). Overall case-fatality rates did not differ significantly between groups (1.6% vs. 6.2%; $p=0.233$). In conclusion, prior pneumococcal vaccination appears to be associated with a lower risk of bacteremia, a faster time to resolution of symptoms, and a shorter hospital stay in adults with pneumococcal pneumonia. The findings presented here provide additional support to the current vaccine recommendations and should encourage healthcare providers to increase pneumococcal vaccine coverage among targeted adult populations.

Manoff S, Liss C, Caulfield MJ, Boslego J, Romero-Steiner S, Rajam G, Glass N, Whitney CG, Carlone GM, and the Pneumococcal Revaccination Study Group. Revaccination with a 23-valent pneumococcal polysaccharide vaccine induces elevated and persistent functional antibody responses in adults ≥ 65 years of age. Presented at the 12th International Congress on Infectious Diseases, Lisbon, Portugal, June 2006. (No abstract available).

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;42:1093-1101.

BACKGROUND: Vaccination with pneumococcal polysaccharide reduces the incidence of bacteremic pneumococcal disease in adults. We investigated the impact of prior pneumococcal vaccination on in-hospital mortality and the probability of respiratory failure among hospitalized adults with community-acquired pneumonia. **METHODS:** Consecutive individuals hospitalized with community-acquired pneumonia (diagnosed by International Classification of Diseases, Ninth Revision, Clinical Modification codes 480.0-487.0) at 109 community and teaching hospitals in the United States were identified using the Quality and Resource Management System, a database constructed by Tenet HealthCare to improve the quality of patient care. Vaccination status, comorbidities, and outcomes were abstracted by case managers concurrently with patient care. Associations between vaccination, survival, and respiratory failure were defined using multivariable logistic regression models. **RESULTS:** Of 62,918 adults hospitalized with community-acquired pneumonia between 1999 and 2003, 7390 (12%) had a record of prior pneumococcal vaccination. Vaccine recipients were less likely to die of any cause during hospitalization than were individuals with no record of vaccination (adjusted odds ratio [OR], 0.50; 95% confidence interval [CI], 0.43-0.59), even after adjustment for the presence of comorbid illnesses, age, smoking, and influenza vaccination and under varying assumptions about missing vaccination data. Vaccination also lowered the risk of respiratory failure (adjusted OR, 0.67; 95% CI, 0.59-0.76) and other complications and reduced median length of stay by 2 days, compared with nonvaccination ($P < .001$). **CONCLUSIONS:** Prior vaccination against pneumococcus is associated with improved survival, decreased chance of respiratory failure or other complications, and decreased length of stay among hospitalized patients with community-acquired pneumonia. These observations reinforce current efforts to improve compliance with existing pneumococcal vaccination recommendations for adults.

Zhogolev SD, Ogarkov PI, Mel'nichenko PI. [The prophylaxis of nonhospital pneumonia using 23-valent pneumococcus vaccine in the military collectives] *Voen Med Zh.* 2004 Dec;325(12):35-43, 96.

Basing on the results obtained during the study of risk factor effect and extra-hospital pneumonia (EHP) etiology in servicemen in order to prevent this nosologic form the complex of prophylactic and antiepidemic measures was developed. The effective measure of EHP pneumonia prophylaxis in military collectives proved to be the polysaccharide 23-valent pneumococcus vaccine "Pneumo-23". After immunization of about 14 000 servicemen on the average EHP incidence has 3 times decreased with vaccine efficiency coefficient up to 74.23%. The more considerable decrease in EHP incidence was observed during the combined use of pneumococcus and influenzal vaccines: the efficiency was 78.5%.

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;22:927-46.

Ten prospective clinical trials conducted in elderly and high-risk adults have failed to show that pneumococcal vaccine prevents pneumococcal bacteraemia and all pneumonia. Several of these trials focused on unrepresentative populations and most had serious methodological problems. Few adequately considered sample size requirements in pre-trial planning. Retrospective sample size calculations based on the findings of the individual trials showed that none was large enough to rule out false negative results. Five published meta-analyses have attempted to determine the efficacy of pneumococcal vaccine by pooling the results of the individual clinical trials. The resulting study populations often were not representative of the populations of elderly and high-risk adults for whom vaccination is recommended. The meta-analysts often omitted clinical trials that should have been evaluated, included other trials that should have been omitted and miscounted the numbers of subjects and outcome events in the individual trials. Retrospective sample size calculations showed that none of the meta-analyses included an adequate number of person years of observation to rule out false negative results. The prospective clinical trials and meta-analyses of pneumococcal vaccine in elderly and high-risk adults have been inconclusive, but they should not be regarded as negative studies. The clinical effectiveness of vaccination in preventing pneumococcal bacteraemia in elderly and high-risk adults has been demonstrated in observational studies, and vaccination is cost-effective. This evidence is sufficient to justify wider use of pneumococcal vaccine.

Conaty S, Watson L, Dinnes J, and 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;22(23-24): p. 3214-24.

The use of pneumococcal polysaccharide vaccine has remained controversial since licensure, especially in the elderly. Observational studies form much of the evidence base. We conducted a systematic review of observational studies and compared results with those obtained from an earlier review of randomised controlled trials (RCTs). Estimates of protection against invasive disease from observational studies were consistent, homogenous and compatible with sparse information obtained from RCTs. Studies were of moderate quality. From 13 observational studies the estimate of vaccine efficacy against invasive disease was 53% (46-59%) compared with 38% (-4 to 63%) from nine RCTs. Estimates of protection against all-cause pneumonia were based on fewer, heterogeneous studies that were not consistent with the findings from RCTs for this outcome. From five studies combined efficacy was 32% (7-50%) compared with 3% (-16 to 19%) from 13 RCTs.

Töröling 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.

Revaccination with the 23-valent pneumococcal polysaccharide vaccine (PPV) has remained controversial due to lack of immunological data and fear of side effects. We re-vaccinated 61 elderly patients (median age 75 years), who had a history of hospital treatment for pneumonia, with PPV on average 5.3 years after their primary vaccination. Revaccination resulted in significant increases of the geometric mean antibody concentration (GMC) and the geometric mean antibody fold increase (GMFI), although to lower levels than after primary vaccination. 36/61 (59%) of the patients responded with a GMFI of ≥ 2 to ≥ 2 of six serotypes. Local reactions to revaccination were common (63%), but mild, and there were no serious adverse events. We conclude that revaccination of elderly with PPV after 5-10 years is safe and induce a significant immune response in a majority of persons.

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. *Lancet Infect Dis*. 2003 Feb;3(2):71-8.

We review studies on the efficacy against disease caused by *Streptococcus pneumoniae* of the 23-valent polysaccharide pneumococcal vaccine in adult populations in the more developed countries. Meta-analyses of primary vaccine trials have attempted to reduce uncertainty from lack of power. Vaccine efficacy calculated from studies in South African gold-miners and in Papua New Guinea, with high attack rates and differing serotype patterns, cannot automatically be applied to more developed countries. Meta-analyses will overestimate a protective effect if this clinical heterogeneity is ignored. Meta-analyses limited to trials in the more developed setting show no protective effect against pneumococcal pneumonia and a non-significant protective effect against bacteraemia. Lack of a specific diagnosis limits the ability to detect a protective effect against pneumococcal pneumonia. Most, but not all, observational studies confirm a protective effect against bacteraemia. An effect on mortality in more developed countries has yet to be documented.

Jackson LA, Benson P, Sneller VP, Butler JC, Thompson RS, Chen RT, Lewis LS, Carlone G, DeStefano F, Holder P, Lezhava T, Williams WW. Safety of revaccination with pneumococcal polysaccharide vaccine. *JAMA*. 1999 Jan 20;281(3):243-8.

CONTEXT: Revaccination of healthy adults with pneumococcal polysaccharide vaccine (PPV) within several years of first vaccination has been associated with a higher than expected frequency and severity of local injection site reactions. The risk of adverse events associated with revaccination of elderly and chronically ill persons 5 or more years after first vaccination, as is currently recommended, has not been well defined. **OBJECTIVE:** To determine whether revaccination with PPV at least 5 years after first vaccination is associated with more frequent or more serious adverse events than those following first vaccination. **DESIGN:** Comparative intervention study conducted between April 1996 and August 1997. **PARTICIPANTS:** Persons aged 50 to 74 years either who had never been vaccinated with PPV (n = 901) or who had been vaccinated once at least 5 years prior to enrollment (n = 513). **INTERVENTION:** PPV vaccination. **MAIN OUTCOME MEASURES:** Postvaccination local injection site reactions and prevaccination concentrations of type-specific antibodies. **RESULTS:** Those who were revaccinated were more likely than those who received their first vaccinations to report a local injection site reaction of at least 10.2 cm (4 in) in diameter within 2 days of vaccination: 11% (55/513) vs 3% (29/901) (relative risk [RR], 3.3; 95% confidence interval [CI], 2.1-5.1). These reactions

resolved by a median of 3 days following vaccination. The highest rate was among revaccinated patients who were immunocompetent and did not have chronic illness: 15% (33/228) compared with 3% (10/337) among comparable patients receiving their first vaccinations (RR, 4.9; 95% CI, 2.4-9.7). The risk of these local reactions was significantly correlated with prevaccination geometric mean antibody concentrations. CONCLUSIONS: Physicians and patients should be aware that self-limited local injection site reactions occur more frequently following revaccination compared with first vaccination; however, this risk does not represent a contraindication to revaccination with PPV for recommended groups.

Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA* 1993;270(15):1826-31.

OBJECTIVE--To determine pneumococcal polysaccharide vaccine efficacy in selected populations at risk for serious pneumococcal infection for whom vaccination is currently recommended and to assess duration of protection after vaccination. DESIGN--Vaccine efficacy was estimated using indirect cohort analysis to compare the proportion of pneumococcal infections caused by serotypes included in the vaccines of vaccinated and unvaccinated persons who were identified during 14 years of national surveillance. SETTING--Hospital laboratories in the United States that submitted pneumococcal isolates to the Centers for Disease Control and Prevention between May 1978 and April 1992. PARTICIPANTS--A total of 2837 persons older than 5 years who had pneumococcus isolated from blood or cerebrospinal fluid. RESULTS--Overall efficacy for preventing infection caused by serotypes included in the vaccine was 57% (95% confidence interval [CI], 45% to 66%). Efficacy among persons with diabetes mellitus was 84% (95% CI, 50% to 95%); with coronary vascular disease, 73% (95% CI, 23% to 90%); with congestive heart failure, 69% (95% CI, 17% to 88%); with chronic pulmonary diseases, 65% (95% CI, 26% to 83%); and with anatomic asplenia, 77% (95% CI, 14% to 95%). Efficacy was not documented for patients with alcoholism or cirrhosis, sickle cell disease, chronic renal failure, lymphoma, leukemia, or multiple myeloma, although sample sizes were small for these groups. Efficacy for immunocompetent persons older than 65 years was 75% (95% CI, 57% to 85%). Efficacy did not decline with increasing interval after vaccination: 5 to 8 years after vaccination it was 71% (95% CI, 24% to 89%), and 9 years or more after vaccination it was 80% (95% CI, 16% to 95%). CONCLUSIONS--Intensified efforts to improve pneumococcal vaccine coverage among certain populations for whom vaccination is currently recommended is indicated, but universal revaccination is not warranted at this time.

Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, Adair RK, Clemens JD. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 1991 Nov 21;325(21):1453-60.

BACKGROUND. Although the protective efficacy of pneumococcal polysaccharide vaccine has been demonstrated in randomized trials in young African gold miners, there has been controversy about its efficacy in older Americans at risk for serious pneumococcal infections. To assess the vaccine's protective efficacy against invasive pneumococcal infections, we conducted a hospital-based case-control study of the efficacy of pneumococcal vaccine in adults with a condition recognized to be an indication for receiving the vaccine. METHODS. From 1984 to 1990, adults in whom *Streptococcus pneumoniae* was isolated from any normally sterile site were identified by prospective surveillance in the microbiology laboratories of 11 large hospitals; those with an indication for pneumococcal vaccine were enrolled as case patients. For each case patient, one control was matched according to age, underlying illness, and site of hospitalization. We contacted all providers of medical care to ascertain each subject's history of immunization with pneumococcal vaccine. Isolates of *S. pneumoniae* were serotyped by an investigator unaware of the subject's vaccination history. RESULTS. Thirteen percent of the 1,054 case patients and 20 percent of the 1,054 matched controls had received pneumococcal vaccine (P less than 0.001). When vaccine was given in either its 14-valent or its 23-valent form, its aggregate protective efficacy (calculated as a percentage: 1 minus the odds ratio of having been vaccinated times 100) against infections caused by the serotypes represented in the vaccine was 56 percent (95 percent confidence interval, 42 percent to 67 percent; P less than 0.00001) for all 983 patients infected with a serotype represented in the vaccine, 61 percent for a subgroup of 808 immunocompetent patients (95 percent confidence interval, 47 percent to 72 percent; P less than 0.00001), and 21 percent for a subgroup of 175 immunocompromised patients (95 percent confidence interval, -55 percent to 60 percent; P = 0.48). The vaccine was not efficacious against infections caused by serotypes not represented in the vaccine (protective efficacy, -73 percent; 95 percent confidence interval, -263 percent to 18 percent; P = 0.15). CONCLUSIONS. Polyvalent pneumococcal vaccine

is efficacious in preventing invasive pneumococcal infections in immunocompetent patients with indications for its administration. This vaccine should be used more widely.

PPV23 and HIV

Peñaranda M, Falco V, Payeras A, Jordano Q, Curran A, Pareja A, Samperiz G, Dalmau D, Ribera E, Riera M. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. *Clin Infect Dis.* 2007 Oct 1;45(7):e82-7.

BACKGROUND: Polysaccharide pneumococcal vaccine (PPV) is recommended among human immunodeficiency virus (HIV)-infected patients, although its effect in reducing the incidence of pneumonia or invasive pneumococcal disease is not well established. Our objective was to determine the effectiveness of 23-valent PPV in HIV-infected adults and the risk factors for pneumococcal pneumonia or invasive pneumococcal disease. **METHODS:** We performed a retrospective case-control study in 4 Spanish hospitals for the period from January 1995 through December 2005 using the HIV database from each hospital to identify case patients with *Streptococcus pneumoniae* disease and control subjects without a history of pneumococcal infection. **RESULTS:** A total of 184 case patients and 552 control subjects were identified. The factors associated with pneumococcal disease in bivariate analysis were active injection drug use (odds ratio [OR], 3.33; 95% confidence interval [CI], 2-5.55), alcoholism (OR, 3.03; 95% CI, 1.86-4.91), chronic obstructive pulmonary disease (OR, 2.58; 95% CI, 1.3-5.1), cirrhosis (OR, 6.05; 95% CI, 3.2-11.4), antiretroviral therapy (OR, 0.23; 95% CI, 0.16-0.32), trimethoprim-sulfamethoxazole prophylaxis (OR, 0.66; 95% CI, 0.45-0.97), viral load <5000 copies/mL (OR, 0.38; 95% CI, 0.26-0.54), and previous PPV (OR, 0.39; 95% CI, 0.24-0.65). Risk factors for pneumococcal disease in multivariate analysis were cirrhosis (OR, 5.64; 95% CI, 2.53-12.53), chronic obstructive pulmonary disease (OR, 2.90; 95% CI, 1.21-6.94), and alcoholism (OR, 2.15; 95% CI, 1.11-4.19), whereas protective factors were receipt of antiretroviral therapy (OR, 0.23; 95% CI, 0.14-0.36) and receipt of pneumococcal vaccine (OR, 0.44; 95% CI, 0.22-0.88), even in patients with CD4 lymphocyte counts <200 cells/microL. **CONCLUSIONS:** Antiretroviral therapy and PPV have a significant, independent protective effect against pneumococcal disease, regardless of CD4 lymphocyte count; thus, all patients with HIV infection should be vaccinated with PPV to prevent pneumococcal disease.

Flannery B, Heffernan RT, Harrison LH, Ray SM, Reingold AL, Hadler J, Schaffner W, Lynfield R, Thomas AR, Li J, Campsmith M, Whitney CG, Schuchat A. 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. *Ann Intern Med.* 2006 Jan 3;144(1):1-9.

BACKGROUND: Adults infected with HIV have high rates of invasive pneumococcal disease. Introduction of pneumococcal conjugate vaccine for children could affect disease among HIV-infected adults. **OBJECTIVE:** To compare invasive pneumococcal disease among HIV-infected adults before and after the introduction of a pediatric conjugate vaccine. **DESIGN:** Active laboratory-based surveillance in an adult population of 10.8 million, including 38,314 living with AIDS. **SETTING:** 7 Active Bacterial Core surveillance areas in the United States. **PATIENTS:** All surveillance-area residents 18 to 64 years of age with *Streptococcus pneumoniae* isolated from a sterile site between 1998 and 2003. **MEASUREMENTS:** Ratio of the number of cases of invasive pneumococcal disease among HIV-infected adults to the estimated number of adults 18 to 64 years of age living with AIDS; serotype-specific subset analyses; and comparison of periods before and after introduction of conjugate vaccine by using exact tests. **RESULTS:** Of 8582 cases of invasive pneumococcal disease in adults, 2013 (24%) occurred among persons infected with HIV. Between baseline (1998 to 1999) and 2003, the ratio of invasive pneumococcal disease in HIV-infected adults to the number of adults living with AIDS in the surveillance areas decreased from 1127 to 919 cases per 100 000 AIDS population, a reduction of 19% ($P = 0.002$). Among HIV-infected adults, the ratio for disease caused by pneumococcal serotypes included in the conjugate vaccine decreased 62% ($P < 0.001$), although the ratio for disease caused by nonvaccine serotypes increased 44% ($P < 0.001$). **LIMITATIONS:** Ratios are proxy measures of incidence rates. The denominator of surveillance-area residents living with HIV infection was not available. **CONCLUSIONS:** Introduction of the pediatric conjugate vaccine was associated with an overall decrease in invasive pneumococcal disease among HIV-infected adults, despite increased disease caused by nonvaccine serotypes.

Breiman RF, Keller DW, Phelan MA, Sniadack DH, Stephens DS, Rimland D, Farley MM, Schuchat A, Reingold AL. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. Arch Intern Med. 2000 Sep 25;160(17):2633-8

BACKGROUND: We conducted a retrospective case-control study to evaluate effectiveness of pneumococcal vaccine against invasive disease among adults with human immunodeficiency virus (HIV) infection in San Francisco, Calif, and Atlanta, Ga. **METHODS:** Case patients were 18- to 55-year-old subjects with HIV infection who were admitted to selected hospitals in Atlanta or San Francisco from February 1992 to April 1995 from whom *Streptococcus pneumoniae* was isolated from a normally sterile site. Controls were HIV-infected patients of similar age matched to cases by hospital of admission and CD4 lymphocyte count (<0.20, 0.20-0.499, >=0.50 x 10⁹/L [$<200, 200-499, \geq 500$ cells/mm³]) or clinical stage of acquired immunodeficiency syndrome. Case and control subjects were restricted to persons known to have HIV infection before hospital admission. Analysis used matched univariate and conditional logistic regression. **RESULTS:** One hundred seventy-six case patients and 327 controls were enrolled. By univariate analysis, persons with pneumococcal disease were more likely to be black, be current smokers, and have close contact with children. Adjusted for these factors and CD4 cell count, pneumococcal vaccine effectiveness was 49% (95% confidence interval [CI], 12%-70%). Adjusting for all variables and key interaction terms, vaccine effectiveness among whites was 76% (95% CI, 35%-91%), whereas effectiveness among blacks was 24% (95% CI, -50% to 61%). Among controls, vaccination was significantly less common among blacks (29% vs 45%; $P<.005$). **CONCLUSIONS:** Pneumococcal vaccine demonstrated protection against invasive pneumococcal infections among white but not black HIV-infected adults. Failure to demonstrate effectiveness among blacks may be due to limited power because of low use of the vaccine in this population, immunization at more advanced stages of immunosuppression, or unmeasured factors. These data support current recommendations for use of pneumococcal vaccine in HIV-infected persons and highlight a clear need for strategies to improve vaccine-induced protection.

French N, Nakiyingi J, Carpenter LM, Lugada E, Watara C, Moi K, Moore M, Antvelink D, Mulder D, Janoff EN, Whitworth J, Gilks CF. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. Lancet. 2000 Jun 17;355(9221):2106-11.

BACKGROUND: Infection with *Streptococcus pneumoniae* is a frequent and serious problem for HIV-immunosuppressed adults. Vaccination is recommended in the USA and Europe, but there are no prospective data that show vaccine efficacy. **METHODS:** 1392 (937 female) HIV-1-infected adults in Entebbe, Uganda, were enrolled. 697 received 23-valent pneumococcal polysaccharide vaccine and 695 received placebo. The primary endpoint was first event invasive pneumococcal disease. Secondary endpoints included vaccine serogroup-specific invasive disease, all (probable and definite) pneumococcal events, all-cause pneumonia, and death. **FINDINGS:** First invasive events occurred in 25 individuals (24 bacteraemias, one pyomyositis), 15 in the vaccine arm and ten in the placebo arm (hazard ratio [HR] 1.47; 95% CI 0.7-3.3). 22 isolates (88%) were of vaccine-specific serogroups with 15 events in the vaccine arm compared with seven in the placebo arm (HR 2.10; 0.9-5.2). All pneumococcal events had a similar distribution (20 vs 14; HR 1.41; 0.7-2.8) though all-cause pneumonia was significantly more frequent in the vaccine arm (40 vs 21; HR 1.89; 1.1-3.2). Mortality was unaffected by vaccination. **INTERPRETATION:** 23-valent pneumococcal polysaccharide vaccination is ineffective in HIV-1-infected Ugandan adults and probably has little, or no, public health value elsewhere in sub-Saharan Africa. Increased rates of pneumococcal disease in vaccine recipients may necessitate a reappraisal of this intervention in other settings.

PPV23 and influenza

Morens DM, Taubenberger JK, Fauci AS. Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness. J Infect Dis. 2008 Aug 18. [Epub ahead of print].

Toschke AM, Arenz S, von Kries R, Puppe W, Weigl JA, Höhle M, Heininger U. No temporal association between influenza outbreaks and invasive pneumococcal infections. *Arch Dis Child.* 2008 Mar;93(3):218-20.

OBJECTIVE: To assess whether the influenza peak in populations precedes the annual peak for invasive pneumococcal infections (IPI) in winter. **DESIGN:** Ecological study. Active surveillance data on influenza A and IPI in children up to 16 years of age collected from 1997 to 2003 were analysed. **SETTING:** Paediatric hospitals in Germany. **Patients:** Children under 16 years of age. **RESULTS:** In all years under study, the influenza A season did not appear to affect the IPI season ($p = 0.49$). Specifically, the influenza peak never preceded the IPI peak. **CONCLUSION:** On a population level there was no indication that the annual influenza epidemic triggered the winter increase in the IPI rate or the peak of the IPI distribution in children.

McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin Microbiol Rev* 2006;19(3):571-82.

Bacterial infections following influenza are an important cause of morbidity and mortality worldwide. Based on the historical importance of pneumonia as a cause of death during pandemic influenza, the increasingly likely possibility that highly pathogenic avian influenza viruses will trigger the next worldwide pandemic underscores the need to understand the multiple mechanisms underlying the interaction between influenza virus and bacterial pathogens such as *Streptococcus pneumoniae*. There is ample evidence to support the historical view that influenza virus alters the lungs in a way that predisposes to adherence, invasion, and induction of disease by pneumococcus. Access to receptors is a key factor and may be facilitated by the virus through epithelial damage, by exposure or up-regulation of receptors, or by provoking the epithelial regeneration response to cytotoxic damage. More recent data indicate that alteration of the immune response by diminishing the ability of the host to clear pneumococcus or by amplification of the inflammatory cascade is another key factor. Identification and exploration of the underlying mechanisms responsible for this synergism will provide targets for prevention and treatment using drugs and vaccines.

Brundage JF. Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness. *Lancet Infect Dis* 2006;6(5):303-12.

It is commonly believed that the clinical and epidemiological characteristics of the next influenza pandemic will mimic those of the 1918 pandemic. Determinative beliefs regarding the 1918 pandemic include that infections were expressed as primary viral pneumonias and/or acute respiratory distress syndrome, that pandemic-related deaths were the end states of the natural progression of disease caused by the pandemic strain, and that bacterial superinfections caused relatively fewer deaths in 1918 than in subsequent pandemics. In turn, response plans are focused on developing and/or increasing inventories of a strain-specific vaccine, antivirals, intensive care beds, mechanical ventilators, and so on. Yet, there is strong and consistent evidence of epidemiologically and clinically important interactions between influenza and secondary bacterial respiratory pathogens, including during the 1918 pandemic. Countermeasures (eg, vaccination against pneumococcal and meningococcal disease before a pandemic; mass uses of antibiotic(s) with broad spectrums of activity against common bacterial respiratory pathogens during local epidemics) designed to prevent or mitigate the effects of influenza-bacterial interactions should be major focuses of pandemic-related research, prevention, and response planning.

Talbot TR, Poehling KA, Hartert TV, Arbogast PG, Halasa NB, Edwards KM, Schaffner W, Craig AS, Griffin MR. Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. *Am J Med.* 2005 Mar;118(3):285-91.

BACKGROUND: Seasonal fluctuation in the incidence of invasive pneumococcal disease has been attributed to winter virus exposure (e.g., influenza and respiratory syncytial virus [RSV]). Evidence of a direct correlation of invasive pneumococcal disease with laboratory-confirmed virus seasons, however, is limited. Using two prospective surveillance networks, the temporal relation between invasive pneumococcal disease and isolation of circulating winter viruses was explored. **METHODS:** Episodes of invasive pneumococcal disease in five Tennessee counties were collected prospectively from January 1995 through June 2002. Virus seasons were defined using prospective laboratory-based surveillance. Correlation between weekly identification of invasive pneumococcal disease and laboratory isolation of RSV and influenza, as well as comparisons of the frequencies of invasive pneumococcal disease episodes during viral and nonviral seasons were determined. **RESULTS:** A

total of 4147 invasive pneumococcal disease episodes were identified. Weekly frequency of invasive pneumococcal disease correlated directly with the weekly frequency of isolation of RSV ($r = 0.56$, $P < 0.001$) and influenza ($r = 0.40$, $P < 0.001$). The average weekly frequency of invasive pneumococcal disease during RSV and influenza seasons was higher than during the nonviral seasons ($P < 0.001$ for each year). **CONCLUSION:** Weekly episodes of invasive pneumococcal disease correlated temporally with laboratory-confirmed weekly isolation of RSV and influenza, and the incidence of invasive pneumococcal disease was increased when these viruses were circulating in the community.

PPV23 and pregnancy

Quiambao BP, Nohynek HM, Käyhty H, Ollgren JP, Gozum LS, Gepanayao CP, et al. Immunogenicity and reactogenicity of 23-valent pneumococcal polysaccharide vaccine among pregnant Filipino women and placental transfer of antibodies. *Vaccine* 2007;25:4470-7.

This randomized, controlled study among pregnant women evaluated the prevaccination distribution of anti-pneumococcal (Pnc) antibodies (Ab), the immunogenicity and reactogenicity of Pnc polysaccharide vaccine, and transplacental transfer of Ab. The Pnc vaccine group (N=106) received Pnc PS vaccine, Hemophilus influenzae type b conjugate vaccine and tetanus toxoid; the control group (N=54) received tetanus toxoid only. Sera and cord blood were assayed for anti-pnc Ab using enzyme immunoassay. In the Pnc vaccine group, anti-Pnc Ab rose by 3- to 9-fold and was significantly higher in cord blood. In evaluating Pnc conjugate vaccines, the concentration of 0.35 microg/ml is suggested as the protective threshold against invasive disease. Around 90% of mothers had this level pre-vaccination. Considering the decay of passively acquired Ab and the growth of the infant, an Ab level in cord blood of at least 4.4 microg/ml is needed if infants are to be protected up to 4 months of age. Cord blood anti-Pnc Ab was above this level in 60% and 10% of the Pnc vaccine and control groups, respectively. Maternal immunization with Pnc polysaccharide vaccine can provide prolonged protection through passively acquired Ab.

Shann F. Giving pneumococcal vaccine to mothers. *Vaccine* 2007;25:6147.
(No abstract available).

Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, Lumbiganon P, Desimone JA, Baxter J, and Tolosa JE. Pneumococcal vaccination during pregnancy for preventing infant infection. *Cochrane Database Syst Rev*, 2006(1): p. CD004903.

BACKGROUND: Each year at least one million children worldwide die of pneumococcal infections. The development of bacterial resistance to antimicrobials adds to the difficulty of treatment of diseases and emphasizes the need for a preventive approach. Newborn vaccination schedules could substantially reduce the impact of pneumococcal disease in immunized children, but does not have an effect on the morbidity and mortality of infants less than three months of age. Pneumococcal vaccination during pregnancy may be a way of preventing pneumococcal disease during the first months of life before the pneumococcal vaccine administered to the infant starts to produce protection. **OBJECTIVES:** To assess the effect of pneumococcal vaccination during pregnancy for preventing infant infection. **SEARCH STRATEGY:** We searched the Cochrane Pregnancy and Childbirth Group Trials Register (June 2004), CENTRAL (The Cochrane Library, Issue 2, 2004), MEDLINE (January 1966 to June 2004), EMBASE (January 1985 to June 2004), and reference lists of articles. **SELECTION CRITERIA:** Randomized controlled trials in pregnant women comparing pneumococcal vaccine with placebo or doing nothing or with another vaccine to prevent infant infections. **DATA COLLECTION AND ANALYSIS:** Two authors independently assessed methodological quality and extracted data using a data collection form. Study authors were contacted for additional information. **MAIN RESULTS:** Three trials (280 participants) were included. There was no evidence that pneumococcal vaccination during pregnancy reduces the risk of neonatal infection (one trial, 149 pregnancies, relative risk (RR) 0.51; 95% confidence interval (CI) 0.18 to 1.41). Although the data suggest an effect in reducing pneumococcal colonisation in infants by 16 months of age (one trial, 56 pregnancies, RR 0.33; 95% CI 0.11 to 0.98), there was no evidence of this effect in infants at two months of age (RR 0.28; 95% CI 0.02 to 5.11) or by seven months of age (RR 0.32; 95% CI 0.08 to 1.29). **AUTHORS' CONCLUSIONS:** There is insufficient evidence to support whether pneumococcal vaccination during pregnancy could reduce infant infections.

Lehmann D, Pomat WS, Riley ID, Alpers MP. Studies of maternal immunisation with pneumococcal polysaccharide vaccine in Papua New Guinea. *Vaccine* 2003;21:3446-3450.

In two studies, pneumococcal polysaccharide (Pnc PS) vaccine was given to more than 400 pregnant Papua New Guinean women. No deleterious effects were found. The vaccine prevented acute lower respiratory infection (ALRI) among offspring in utero or aged 1-17 months at the time of maternal immunisation, suggesting protection through breast feeding. Serum IgG antibody titres were higher in vaccinated than unvaccinated groups for 2-4 months after delivery and no immune suppression, evaluated by the response to subsequent Pnc PS vaccination, was detected. Breast milk IgA to four serotypes was 1.1-1.8 times higher in immunised than unimmunised women for 6 months postpartum. Given results from several developing countries, large-scale safety and efficacy trials are now justified. Postpartum maternal immunisation is another intervention under consideration.

Lehmann D, Pomat WS, Combs B, Dyke T, Alpers M. Maternal immunization with pneumococcal polysaccharide vaccine in the highlands of Papua New Guinea *Vaccine* 2002;20:1837-45.

In Tari, Southern Highlands Province (SHP), Papua New Guinea (PNG), pneumococcal polysaccharide (Pnc PS) vaccine was offered to women at 28-38 weeks gestation. Blood samples were collected for measurement of pneumococcal antibody titres prior to immunization, from mother and cord at delivery and from their children at ages 1-3 and 4-6 months; samples were also collected in a subset of children before and 1 month after Pnc PS vaccine was given at age 8-9 months. Serum was collected from unimmunized women and their children at delivery and from children of unimmunized women at the same ages in infancy. There were no differences in neonatal or post-neonatal mortality rates or congenital abnormalities in the children of 235 immunized and 202 unimmunized women. There was a significant increase in antibody titres to pneumococcal serotypes 5, 14 and 23F in immunized women but not for serotype 7F. Geometric mean titres (GMTs) of antibodies for serotypes 5 and 23F were significantly higher in children of immunized women than in the unimmunized group up to age 2 months and for serotype 14 significantly higher to age 4 months. Maternal immunization did not significantly affect the children's capacity to make antibody responses to immunization with Pnc PS vaccine in infancy. The findings of this study and those in several other developing countries provide support for the concept of Pnc PS maternal immunization and justify the planning of large-scale efficacy trials.

Cost-Effectiveness

Smith KJ, Zimmerman RK, Lin CJ, Nowalk MP, KF-S, McEllistrem MC, Roberts MS. Alternative strategies for adult pneumococcal polysaccharide vaccination: A cost-effectiveness analysis. *Vaccine* 2008;11(Mar 10):1420-31.

Pneumococcal polysaccharide vaccination (PPV) to prevent invasive pneumococcal disease (IPD) is recommended at age 65 for most persons in the US. We used a Markov model to examine alternative PPV strategies, finding that vaccination at ages 50 and 65 prevented more IPD than present vaccination policies; four decennial vaccinations were most effective. The present vaccination policy costs \$3341/QALY gained, vaccinations at 50/65 cost \$23,120/QALY and four vaccinations (50/60/70/80) cost \$54,451/QALY; results were sensitive to vaccine uptake assumptions, with current policy no longer favored at present vaccination rates. PPV at ages 50/65 may be clinically and, depending on cost-effectiveness criterion used, economically favored over present vaccination recommendations.

Grading quality of evidence

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer TT, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 Jun 19;328(7454):1490.

Users of clinical practice guidelines and other recommendations need to know how much confidence they can place in the recommendations. Systematic and explicit methods of making judgments can reduce errors and improve communication. We have developed a system for grading the quality of evidence and the strength of recommendations that can be applied across a wide range of interventions and contexts. In this article we present a summary of our approach from the perspective of a guideline user. Judgments about the strength of a recommendation require consideration of the balance between benefits and harms, the quality of the evidence, translation of the evidence into specific circumstances, and the certainty of the baseline risk. It is also important to consider costs (resource utilisation) before making a recommendation. Inconsistencies among systems for grading the quality of evidence and the strength of recommendations reduce their potential to facilitate critical appraisal and improve communication of these judgments. Our system for guiding these complex judgments balances the need for simplicity with the need for full and transparent consideration of all important issues.

Policy issues

Use of pneumococcal polysaccharide vaccine for subjects over 65 years of age during and inter-pandemic period. Technical Report of the Scientific Panel on Vaccines and Immunization, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden. Available at (<http://www.ecdc.eu.int>), 18 January 2007

Centers for Disease Control and Prevention. October 2006-September 2007. MMWR 2006; 55(40): p. Q1-Q4.

Levine OS, O'Brien KL, Knoll M, Adegbola RA, Black S, Cherian T, Dagan R, Goldblatt D, Grange A, Greenwood B, Hennessy T, Klugman KP, Madhi SA, Mulholland K, Nohynek H, Santosham M, Saha SK, Scott JA, Sow S, Whitney CG, Cutts F. Pneumococcal vaccination in developing countries. *Lancet*. 2006 Jun 10;367(9526):1880-2. (No abstract available).

Feikin DR, Feldman C, Schuchat A, Janoff EN. Global strategies to prevent bacterial pneumonia in adults with HIV disease. *Lancet Infect Dis*. 2004 Jul;4(7):445-55.

We examined the peer-reviewed literature on the burden of bacterial pneumonia and the effectiveness of interventions for its prevention among HIV-infected adults in developed and developing countries. Bacterial pneumonia rates were up to 25-fold higher among HIV-infected adults than in the general community, with rates increasing as CD4⁺ T-cell count decreases. In developed countries, cohort studies showed that highly active antiretroviral therapy (HAART) had the most consistent effect on reducing pneumonia. In a prospective cohort and case-control studies from these regions, pneumococcal polysaccharide vaccine reduced pneumococcal disease in certain subgroups, particularly those with higher CD4⁺ T cells/microL. In patients with fewer than 200 CD4⁺ T cells/microL, antimicrobial prophylaxis was usually effective in reducing pneumonia. In sub-Saharan Africa, randomised controlled trials concluded that co-trimoxazole prophylaxis decreased rates of bacterial pneumonia, but pneumococcal polysaccharide vaccine prevented neither pneumonia nor invasive pneumococcal disease. Although not yet fully evaluated in Africa, based on experience in industrialised nations, use of HAART in Africa may have substantial potential to prevent bacterial pneumonia.

Prevention of Pneumococcal Disease - Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. Recommendations and Reports Series (RR) 1997;46:No.RR-8.