

Pneumococcal polysaccharide vaccine has limited efficacy in adults

Clinical question Is the pneumococcal polysaccharide vaccine (PPV) effective for adults?

Bottom line The evidence to support the efficacy of PPV in adults is limited at best. The best studies have not shown a consistent benefit, particularly in the most vulnerable populations that we currently target. The impact of increasing herd immunity due to infant vaccination using conjugate vaccines is another factor, although that is not addressed by this analysis. An accompanying editorial argues that some studies excluded for methodologic limitations should have been included, and vice versa, and called for additional well-designed studies in relevant populations rather than a cessation of the vaccination. (Level of evidence = 1a-)

Synopsis The efficacy of the unconjugated PPV has been questioned in some recent randomized trials. The authors of this meta-analysis set out to investigate the effect of study quality on outcomes. They identified 22 randomized trials and quasirandomized trials (ie, assignment to groups by date of birth) comparing PPV with other vaccines, placebo, or no interventions. Eight studies used the 23-valent PPV, seven were double-blinded, six used adequate concealment of allocation, and only three were both double-blinded and used adequate allocation concealment. The reported duration of follow-up varied from 1.6 to 3.2 years (11 studies did not clearly report duration of follow-up). Thus, the overall quality of studies was poor. The authors used the I-squared statistic to assess variability between studies, which was generally high. This isn't surprising given the variation in vac-

cines, settings (including Russia, New Guinea, and Uganda), and populations (including HIV patients, elderly, and healthy soldiers). When all available data are combined for the outcomes of presumptive pneumococcal pneumonia (11 studies, 56,564 participants), there was a benefit to vaccination (relative risk [RR] = 0.64; 95% CI, 0.43-0.96). The same was true for any pneumonia (19 studies, 82,665 participants; RR = 0.73; 0.56-0.94). However, there was no benefit in terms of death from pneumonia (odds ratio [OR] = 0.88; 0.62-1.25) or all-cause mortality (OR = 0.97; 0.87-1.09). Although outcomes were reported for bacteremia, definitive pneumococcal infection, and death due to pneumococcal infection, the numbers were small and confidence intervals were broad. Subgroup analyses only found benefit for the outcome of any pneumonia in those studies that were less well designed (no masking, placebo, or allocation concealment); those that studied generally healthy individuals, such as miners or soldiers; and those that were set outside Europe or North America.

Huss A, Scott P, Stuck AE, et al. Efficacy of pneumococcal vaccination in adults: a meta-analysis. *CMAJ*. 2009;180(1):48-58.

Oral corticosteroids not recommended for viral wheeze in younger children

Clinical question Do corticosteroids improve outcomes in young children with wheezing associated with a viral infection?

Bottom line Oral corticosteroids should not be routinely used for the treatment of children aged 10 months to 5 years who present with a suspected viral upper respiratory infection and wheezing. (Level of evidence = 1b)

Synopsis Although corticosteroids are of benefit in older children and adults with asthma triggered by a viral infection, their benefit in younger children is unclear. In this well-designed study, the researchers identified 687 children aged 10 to 60 months who presented

to 1 of 3 emergency departments with wheezing believed to be associated with a viral upper respiratory infection. Groups were balanced at the start of the study and analysis was by intention to treat. Children with severe disease or major comorbidities were excluded from the study. Only children who did not improve with the use of inhaled albuterol were included. Participants were then randomized to receive either an oral solution of prednisolone (10 mg if younger than 24 months, 20 mg if older than 24 months) or matching placebo. Severity scores (after albuterol) were measured by a pediatrician at baseline and at 4, 12, and 24 hours (if still in the hospital). Decisions about hospitalization and discharge were left to the treating physician. There was no significant difference between groups regarding length of stay, adverse events, albuterol use during the subsequent 7 days, or symptom scores at the end of 7 days. In a subgroup of 124 children at high risk for asthma in later childhood, there was no difference between treatment and placebo regarding clinical outcomes, and no difference between these and the other children in the study. In a second study in the same issue of this journal (*N Engl J Med*. 2009;360[4]:339-353), high-dose inhaled *fluticasone* given during a viral respiratory infection to children aged 1 to 6 years with moderate to severe wheezing reduced the need for systemic corticosteroids. However, the reduction was modest (8% vs 18%; number needed to treat = 10) and patients using preventive inhaled corticosteroids had less height and weight gains than control patients.

Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med*. 2009;360(4):329-338.

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Fluoroquinolones are effective for treatment of CAP

Clinical question Are fluoroquinolones more effective than the combination of a macrolide and beta-lactam in adults with community-acquired pneumonia (CAP)?

Bottom line Fluoroquinolones are as effective as the combination of a macrolide and beta-lactam in the treatment of CAP in outpatient adults, and may be more effective in hospitalized patients and in patients with severe pneumonia. (Level of evidence = 1a)

Synopsis The 2007 guidelines from the Infectious Diseases Society of America and the American Thoracic Society recommend either a respiratory fluoroquinolone (RF) or the combination of a macrolide and beta-lactam for adults with CAP. These researchers identified all published clinical trials that defined pneumonia as an abnormal chest radiograph in an adult with 4 or more of 14 clinical or laboratory abnormalities consistent with pneumonia (eg, fever, dyspnea, hypoxia, purulent sputum, leukocytosis). They used intention-to-treat data and the primary outcome was all-cause mortality. Of the 279 randomized controlled trials identified, 23 met their inclusion criteria. In the 18 trials with 7,020 patients that reported mortality data, there was no significant benefit to RFs over other antibiotics (odds ratio [OR] = 0.85; 95% CI, 0.65-1.12). Patients taking an RF showed a marginal benefit for the outcome of treatment success, defined as cure or improvement during the study period (OR = 1.17; 1.00-1.36). Benefit was greater in lower-quality trials. In particular, although double-blinded trials found no difference between RFs and other antibiotics regarding treatment success (OR = 1.13; 0.85-1.5), there was a significant benefit in open-label trials (OR = 1.35; 1.08-1.69). RFs were more effective than alternatives in hospitalized patients and in patients with severe pneumonia, but the defini-

tions of severity varied and the total number of patients was relatively small. Adverse effects were somewhat less common among patients taking an RF (OR = 0.86; 0.78-0.96), but the proportion who withdrew from trials because of adverse effects was similar between groups.

Vardakas KZ, Siempos II, Grammatikos A, et al. Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. *CMAJ*. 2008;179(12):1269-1277.

Elbow extension test rules out fracture

Clinical question Can the elbow extension test be used to rule out fracture in adults and children with an acute elbow injury?

Bottom line In a group of patients with acute elbow injury—31% were eventually found to have a fracture—the elbow extension test (described below) was effective in ruling out fracture without the need for radiography. But it was not as specific as it was sensitive; approximately half the patients who tested positive were fracture free. (Level of evidence = 1b)

Synopsis The investigators enrolled adults and children aged at least 3 years who presented to participating emergency departments within 72 hours of an elbow injury. All patients were examined using the elbow extension test, described below. Investigators enrolled 1,740 adults and children. Of the 958 adults, 33% were able to fully extend the elbow and thus avoided radiography. Adults with a positive test result underwent radiography; children underwent radiography at the discretion of their clinician. Patients who did undergo radiography were followed-up by telephone in 7 days to 10 days and were examined if they had any symptoms. The reference (gold standard) consisted of either radiographic findings, results of the telephone follow-up, or follow-up at an orthopedic clinic. The overall prevalence of fracture was 31%. The elbow extension test was

very effective in ruling out fracture, with an overall sensitivity of 96.8% (95% CI, 95.0-98.2) and a negative predictive value in this group of 97.2%. Approximately half the adults and children who failed the test actually had a fracture, giving the test a specificity of 48.5% (45.6-51.4) and a positive predictive value of 45.8%. The sensitivity of the test was better in adults, but the specificity was similar in all age groups. To perform the elbow extension test, the patient is seated with arms supinated. The patient is asked to flex their shoulders to 90° and then fully extend and lock both elbows. Injured and uninjured sides are compared visually.

Appelboam A, Reuben AD, Bengler JR, et al. Elbow extension test to rule out elbow fracture: multicentre, prospective validation and observational study of diagnostic accuracy in adults and children. *BMJ*. 2008;337:a2428.

Surgery is better than medical therapy for GERD

Clinical question Is surgery better than medical therapy in patients with severe gastroesophageal reflux disease (GERD)?

Bottom line Patients with significant and long-standing GERD who underwent surgical fundoplication as compared with medical therapy had significantly lower symptom scores at 1 year. This large study is consistent with other randomized trials. (Level of evidence = 1b)

Synopsis The researchers enrolled patients who required acid suppression for at least 12 months for symptom control of GERD or had endoscopic or pH-monitoring evidence of GERD. Half the 357 participants from 21 sites were treated for more than 30 months before enrollment. REFLUX quality of life scores (a measure of symptoms and also side effects and complications of therapy) ranged from an average of 55 to 78 of a possible 100, with 100 reflecting the fewest symptoms. The investigators identified a total of 810 patients eligible for the study; the first 357 of these patients were randomized, using

concealed allocation, to receive either laparoscopic fundoplication (the type was left to each surgeon) or best medical management as determined by their gastroenterologist. The other 453 patients were enrolled by preference; that is, they were asked which approach they preferred and were assigned to that treatment. In this aspect of the study, patients with more severe symptoms were more likely to select surgical treatment. Analysis was by intention to treat, which means patients were analyzed according to the group to which they were assigned. In the randomized portion, only 62% of patients randomized to surgery underwent fundoplication, whereas 84% of patients in the preference group had surgery. Nevertheless, at 1 year, 38% of patients randomized to surgery were taking reflux medication; only 14% of patients who actually received the surgery were taking medication. In the medical group, 90% of patients were still receiving treatment at 1 year (number needed to treat = 2, favoring surgery). REFLUX scores improved from 63.6 to 84.6 in the surgery group and from 66.8 to 73.4 in the medical group ($P < .001$). In the preference group, there was little difference with medical therapy, whereas the patients who selected surgery (those who had worse

symptom scores) improved from an average of 55.8 to 83.3.

Grant AM, Wileman SM, Ramsay CR, et al; REFLUX Trial Group. Minimal access surgery compared with medical management for chronic gastro-oesophageal reflux disease: UK collaborative randomised trial. *BMJ*. 2008;337:a2664.

Oophorectomy associated with decreased cancers in BRCA mutations

Clinical question How effective is prophylactic oophorectomy in preventing breast or ovarian cancer in women with *BRCA1* or *BRCA2* mutations?

Bottom line Prophylactic oophorectomy in women with *BRCA1* or *BRCA2* mutations is associated with a 50% reduction in the risk of developing breast cancer and an 80% reduction in the risk of developing ovarian cancer. (Level of evidence = 3a)

Synopsis These authors searched PubMed to find studies comparing *prophylactic oophorectomy* with *no oophorectomy* to prevent breast or ovarian cancer in women with mutations of *BRCA1* or *BRCA2* gene. They also contacted researchers and consortia to identify unpublished data. The authors don't report the following procedures associated with high-quality systematic reviews and meta-analyses: independent assessment of study eligibility, independent assessment of study quality, or inde-

pendent extraction of data. Not surprisingly, they identified no randomized trials. They found 10 studies (with more than 9,000 women) that included a comparison group: two case-control studies, four retrospective cohort studies, and four prospective cohort studies. Given this kind of methodologic heterogeneity, many researchers would have stopped and simply reported the findings as a systematic review. These authors, however, chose to pool the study results to get a "fruit salad" net effect. After pooling the results, these researchers estimated that prophylactic oophorectomy was associated with a 50% reduction in the risk of developing breast cancer and an 80% reduction in the risk of developing ovarian cancer. The ovarian cancers that develop in women after an oophorectomy are usually peritoneal cancers that are histologically the same as ovarian cancer. The reporting of results in this paper do not allow for estimating absolute rates of events.

Rebeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in *BRCA1* or *BRCA2* mutation carriers. *J Natl Cancer Inst*. 2009;101(2):80-87.

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