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EDITORIAL

# Pneumococcal polysaccharide vaccines do not protect the elderly from pneumococcal infections

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The decision by the United States Food and Drug Administration (FDA) in 1977 to license a pneumococcal vaccine containing 14 of the 90 known serotypes of *Streptococcus pneumoniae* was based on little evidence.[1] The only published trials of this product then available involved healthy people with unusual risks of pneumococcal infection: South African gold miners and people living in the New Guinea highlands. In more industrialised countries, however, individuals at highest risk of pneumococcal infection are the elderly and those with certain chronic illnesses. Although the vaccine had not been studied in these populations, the government-sponsored group that formulates national immunisation guidelines in the United States, the Advisory Committee on Immunisation Practices (ACIP), recommended that they be vaccinated to prevent pneumococcal pneumonia. In doing so, they committed the grave scientific error of taking information obtained from certain populations and applying it to other, very different ones.

Subsequent prospective controlled and *blinded* trials of the 14-valent vaccine, or a later one containing 23 serotypes, included more than 100,000 patient-years of observation in trials in the USA, Finland and Sweden.[2-8] These investigations demonstrated that the ACIP's recommendations were unjustified: whether examined individually or in aggregate, these studies showed that the vaccine did not reduce pneumococcal pneumonias specifically, pneumonias from any cause, or overall mortality in the elderly or the chronically ill. In fact, combining the results of these trials shows that the frequency of each of these adverse outcomes was actually *higher* in those receiving the vaccine. At least seven meta-analyses (including two not cited by Assendelft *et al.*) in this issue have been published that collectively reviewed at least 16 randomised controlled trials – both blinded and unblinded – comprising almost 50,000 patients. The analyses have differed in their methods, the kinds of studies included, and their classification of the information.[9-15] Nevertheless, they agree in concluding that in industrialised nations the pneumococcal vaccine is ineffective in the elderly and the chronically ill. A recent large *retrospective* cohort study of the vaccine in the elderly in the USA (not available to Assendelft *et al.*) that evaluated 47,365 patients 65 years of age or older for three years also showed that it was ineffectual.[16,17] As with several other studies, the authors dwelled on the nonsignificant reduction in pneumococcal bacteraemias in the vaccine group, while downplaying the larger failure of the vaccine to prevent pneumonia or deaths.

The reasons that the polyvalent polysaccharide vaccine has failed to provide protection to those at greatest risk for pneumococcal pneumonia in industrialised countries are uncertain. They may relate to the inability of chronically ill or elderly patients to generate an adequate immunological response to the pneumococcal antigens, infection from serotypes not included in the vaccine, or a lower frequency of pneumococci as the cause of pneumonias in these populations than previously believed.[18] The most reasonable conclusion from the available evidence is that the vaccine may reduce the incidence of pneumococcal pneumonia among young, immunocompetent people in certain *epidemic* circumstances, such as gold miners in South Africa and New Guinea highlanders, or perhaps in military recruits, based on older studies with a different preparation. These groups have a high risk of acquiring infection because of close group living arrangements, and in some instances exposure to respiratory irritants, but because they are otherwise healthy they have a low risk of dying from it. The evidence is persuasive, however, that the vaccine lacks

effectiveness against *endemic* pneumococcal pneumonia, which tends to occur in the elderly and infirm. Unfortunately, it is among these persons that the mortality rate is substantial. Thus, the polysaccharide vaccine does not work in those who need it most. Perhaps the newer protein conjugated pneumococcal vaccine that has been effective in children[19] will be more immunogenic in high-risk adults, but only randomised controlled trials will provide this information.

Despite the disappointing studies of the polysaccharide vaccine, the ACIP (USA) continues to advise vaccination of the elderly and infirm, and is being urged to extend vaccination recommendations for those aged 50 to 64[20] and to smokers and Native and African Americans.[21] These recommendations are based on several retrospective studies using both standard and novel methods that suggested that the vaccine might be effective in preventing *invasive* pneumococcal disease (infections with positive cultures from normally sterile sites, primarily bacteraemia associated with pneumonia).[22] Retrospective case-control studies are inherently weaker forms of evidence than prospective controlled trials. Nevertheless, because these investigations suggest that immunisation *may* reduce the frequency of pneumococcal bacteraemia, the ACIP has shifted the justification for vaccination from preventing pneumococcal *pneumonia* to preventing *bacteraemia* from this organism.[22] Thus, what has been called the 'pneumonia shot' is no longer even recommended to prevent pneumonia! No evidence from prospective studies, however, indicates that a reduction in bacteraemia in patients with pneumococcal pneumonia will result in less frequent or shorter hospitalisations, decreased mortality, or reduced medical expenses. Moreover, studies suggesting that immunising the elderly is cost-effective for preventing bacteraemia depend on unreasonably high estimates of vaccine efficacy. The most widely cited cost-effectiveness analyses pertaining to American populations base their assumptions on a single retrospective study,[23] ignore the information from the prospective trials, and fail to acknowledge that the vaccine is ineffective in reducing the incidence of pneumococcal pneumonia.[20,24-26] A cost-benefit analysis from the Netherlands suggested that in the base case analysis the cost of preventing invasive pneumococcal disease ranged from 11,000-33,000 euros per quality-adjusted life year, but again used unreasonably high estimates of vaccine efficacy.[27]

The initially premature, and repeatedly promulgated recommendation by the ACIP and other authoritative agencies for the use of the polysaccharide pneumococcal vaccine among the elderly and the chronically ill thus rests on weak evidence based on retrospective studies. Their arguments do not adequately acknowledge the information from prospective, randomised, and blinded trials, nor do they address the concerns about the scientific validity of their recommendations that we first raised over 20 years ago.[8] It is therefore highly appropriate and admirable that authors from the Netherlands reviewed the available information to determine whether or not to recommend pneumococcal vaccination in the elderly in their country. Their careful and thoughtful analysis demonstrates the remarkable weakness of the information supporting vaccination and highlights the problem that the decision to encourage vaccination was formed before adequate studies became available. The authors are right to conclude that there is insufficient evidence to introduce pneumococcal vaccination of the elderly in the Netherlands. Rejecting the pressure to do so will ensure that at least the Netherlands will not contribute to 'the apparent conflict between evidence of effectiveness of pneumococcal polysaccharide vaccines and existing recommendations for their use'.[28]

## REFERENCES

1. Hirschmann JV, Lipsky BA. The pneumococcal vaccine after 15 years of use. Arch Intern Med 1994;154:373-7.
2. Dear K, Holden J, Andrews R, Tatham D. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev 2003:CD000422.
3. Simberkoff MS. Recently Published Controlled Trials of Pneumococcal Vaccine Efficacy in Adults. Curr Infect Dis Rep 1999;1:47-8.
4. Ortqvist A, Hedlund J, Burman LA, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish Pneumococcal Vaccination Study Group. Lancet 1998;351:399-403.
5. Honkanen PO, Keistinen T, Miettinen L, et al. Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. Vaccine 1999;17:2493-500.
6. Koivula I, Sten M, Leinonen M, Makela PH. Clinical efficacy of pneumococcal vaccine in the elderly: a randomized, single-blind population-based trial. Am J Med 1997;103:281-90.
7. Simberkoff MS, Cross AP, Al-Ibrahim M, et al. Efficacy of pneumococcal vaccine in high-risk patients. Results of a Veterans Administration Cooperative Study. N Engl J Med 1986;315:1318-27.
8. Hirschmann JV, Lipsky BA. Pneumococcal vaccine in the United States. A critical analysis. JAMA 1981;246:1428-32.
9. Fine MJ, Smith MA, Carson CA, et al. Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomized controlled trials. Arch Intern Med 1994;154:2666-77.
10. Hutchison BG, Oxman AD, Shannon HS, Lloyd S, Altmayer CA, Thomas K. Clinical effectiveness of pneumococcal vaccine. Meta-analysis. Can Fam Physician 1999;45:2381-93.
11. Moore RA, Wiffen PJ, Lipsky BA. Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials. BMC Fam Pract 2000;1:1.
12. 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;19:4780-90.

13. Watson L, Wilson BJ, Waugh N. Pneumococcal polysaccharide vaccine: a systematic review of clinical effectiveness in adults. Vaccine 2002;20:2166-73.
14. Puig-Barbera J, Belenguer Varea A, Goterris Pinto M, Brines Benlliure MJ. [Pneumococcal vaccine effectiveness in the elderly. Systematic review and meta-analysis]. Aten Primaria 2002;30:269-83.
15. 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;3:71-8.
16. Jackson LA, Neuzil KM, Yu O, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. N Engl J Med 2003;348:1747-55.
17. Hirschmann JV. Pneumococcal vaccination in older adults. N Engl J Med 2003;349:712-4.
18. Rubins JB, Janoff EN. Pneumococcal disease in the elderly: what is preventing vaccine efficacy? Drugs Aging 2001;18:305-11.
19. Edwards KM, Griffin MR. Great expectations for a new vaccine. N Engl J Med 2003;349:1312-4.
20. 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;138:960-8.
21. Gardner P. A need to update and revise the pneumococcal vaccine recommendations for adults. Ann Intern Med 2003;138:999-1000.
22. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1997;46:1-24.
23. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med 1991;325:1453-60.
24. Simberkoff MS. Pneumococcal vaccine in the prevention of community-acquired pneumonia: a skeptical view of cost-effectiveness. Semin Respir Infect 1993;8:294-9.
25. Sisk JE, Riegelman RK. Cost effectiveness of vaccination against pneumococcal pneumonia: an update. Ann Intern Med 1986;104:79-86.
26. Sisk JE, Moskowitz AJ, Whang W, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. JAMA 1997;278:1333-9.
27. Ament A, Baltussen R, Duru G, et al. Cost-effectiveness of pneumococcal vaccination of older people: a study in 5 western European countries. Clin Infect Dis 2000;31:444-50.
28. Jefferson T, Demicheli V. Polysaccharide pneumococcal vaccines. BMJ 2002;325:292-3.

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REVIEW

# Pneumococcal vaccination for the elderly in the Netherlands? Assessment of the quality and content of available comparative studies

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## ABSTRACT

**Background: A question that is currently topical in the Netherlands is whether it makes sense to introduce on a national scale vaccination against pneumococcal infections for elderly people who are at present receiving the influenza vaccination. We recently studied the scientific literature on the subject in an attempt to answer this question.**

**Methods: We searched for systematic reviews (SRs), randomised clinical trials (RCTs) and cohort studies in MEDLINE, EMBASE, the Cochrane Library, Current Controlled Trials and via Google (period 1966 to June 2002). The SRs and RCTs were assessed with a methodological checklist.**

**Results: We identified four SRs, two trials (of which one was pseudo-random) and one retrospective cohort study. The methodological quality of the SRs was reasonable and in this respect differed little among themselves. The SRs differed strongly with regard to subgroups, outcome measures, valency of vaccines, duration of follow-up and combination with influenza vaccination. The SRs showed that vaccination has more effect in low-risk groups, does not appear to be effective in high-risk patients and the elderly and is more effective in nonindustrialised countries. The outcomes based on the various outcome measures showed major differences. The three studies into the effectiveness of the pneumococcal vaccination in the elderly all showed major methodological shortcomings. For the majority of outcome measures the outcomes were negative.**

**Conclusion: There is insufficient convincing evidence in favour of the introduction of the pneumococcal vaccination as a supplement to influenza vaccination for the elderly. It seems as if (international) opinion had already been fully formed before published studies and systematic reviews become available in the last few years. It is perhaps worth considering setting up a prospective trial in the elderly Dutch population.**

## INTRODUCTION

A question that is currently topical in the Netherlands is whether it makes sense to introduce on a national scale vaccination against pneumococcal infections for elderly people who are at present receiving the influenza vaccination. We recently studied the scientific literature on the subject in an attempt to answer this question. At first sight it seemed difficult to give an unambiguous interpretation of the information uncovered, since a number of methodological problems were involved:

a) Most randomised clinical trials (RCTs) were performed on populations other than the target group under consideration here.[1,2]

b) Opinions on effectiveness were partly formulated before the RCTs focussing on elderly became available. And here, too, systematic reviews (SRs) played a part.
c) A great many different surrogate and end measures were applied in the RCTs.
d) The SRs available arrived at different conclusions and used a variety of methods.

This report gives a transparent analysis of systematic reviews currently available, RCTs and comparative cohort studies in order to investigate the extent to which these provide a valid and relevant answer to the question of whether the elderly in the Netherlands should receive the pneumococcal vaccination by way of supplement to the influenza vaccination.

## METHOD

### Literature search

The literature was searched and selected by the first author (period 1966 to June 2002). The search was conducted for the following.

*Published SRs*

Search carried out in MEDLINE and EMBASE [(Streptococcus infection (MeSH heading) or (pneumococc$ or streptococc$) (text word)] AND [vaccination (MeSH) or vaccin$ (text word)] in combination with the sensitive and specific search filter for SRs by Hunt and McKibbon;[3] Cochrane Database of Systematic Reviews;[4] Correspondence with authors.[5]

*Published randomised and nonrandomised clinical trials*

Search carried out in MEDLINE and EMBASE [(Streptococcus infection (MeSH heading) or (pneumococc$ or streptococc$) (text word)] AND [vaccination (MeSH) or vaccin$ (text word] in combination with the sensitive and specific search filter for RCTs from the Cochrane Collaboration.[6]
Search carried out in the Cochrane Controlled Trials Register.[7] Keywords as above.

*Unpublished RCTs*

Current Controlled Trials Register (http://www.controlled-trials.com).
General Internet browser (www.google.com). Keywords: pneumococcal vaccination.

### Assessing the literature

Assessment of the quality of the SRs and their relevance to the question was carried out with the aid of a standard assessment list[8] and an algorithm for conflicting SRs,[9] by two researchers doing the assessment independently of one another (RJPMS and MO). Assessment of the (R)CTs was carried out with the aid of a standard assessment list[10] by two researchers working independently of one another (RJPMS and MO).

## RESULTS

### Search

*Systematic reviews*

The MEDLINE and EMBASE search came up with four SRs.[11-15] In addition there was a second Cochrane protocol on the subject[16] which, however, gave no further information with regard to the subject and thus fell outside the present assessment.

*Clinical trials*

The search provided two RCTs on the effectiveness of vaccination in the elderly people.[1,2] And an Internet search using the Google search engine (www.google.com) with the keywords 'pneumococcal vaccination' led to nothing extra, apart from the hits already known. Finally a (non-randomised) retrospective cohort study was found in which pneumococcal vaccination (partly combined with influenza vaccination) was evaluated.[17,18]

### Systematic reviews

The methodological quality of the SRs was reasonable and in this respect differed little among themselves. Here it should be noted that the assessment list used mainly examines the correctness with which the various stages of an SR are implemented. But often there are several options for elaborating on a particular item. The four reviews therefore also differed from one another mainly with regard to method and outcomes. The algorithm of Jadad *et al.*[9] was used to investigate where the methodological differences between the SRs usually occur.

Clear differences were seen in the methods employed in the SRs. It is remarkable that three of the SRs were published within a relatively short period and that of the two trials in these SRs most relevant to our question, neither were,[12] both were[15] and only one[13,14] was included (*table 1*). The other (potentially) important differences between the SRs relate to the subgroups, outcomes, valency of the vaccines, duration of the follow-up in the trials and the combination with the influenza vaccination (*table 2*).

*Subgroups*

The subgroups formed differ greatly from review to review (*table 2*). In view of the question posed, there is a major issue here as to how aspects such as comorbidity and age are to be dealt with (>65 years sometimes not

**Table 1**
*Characteristics of (pseudo-)randomised studies*

| STUDY | PARTICIPANTS, PRINCIPAL EXCLUSIONS – LENGTH OF FOLLOW-UP | INTERVENTION/CONTROL | REVIEWS (REFERENCES) | | | |
|---|---|---|---|---|---|---|
| **Industrialised countries, high risk** | | | **11** | **12** | **13,14** | **15** |
| Klastersky 1986 | Bronchial carcinoma - unclear | 17-valent/placebo | + | + | + | + |
| Simberkoff 1986 | Chronic renal, hepatic, cardiac, pulmonary disease, alcoholism, diabetes. Excluded asplenia, recent hospitalisation, previous vaccination, haematological malignancy - 2.9 years | 14-valent/placebo | + | + | + | + |
| Davis 1987 | COPD. Excluded asthma, neoplasms, renal or hepatic impairment, sickle cell disease - 2 years | 14-valent/placebo | + | + | + | + |
| Leech 1987 | COPD. Excluded other lung disease, previous vaccination - 2 years | 14-valent plus influenza/ placebo plus influenza | + | + | + | + |
| **Industrialised countries, older age** | | | | | | |
| Koivula 1997 | Elderly, community - 3 years | 14-valent plus influenza/ influenza alone | | | + | + |
| Honkanen 1999 | Elderly, community. Excluded terminally ill - 3 years | 23-valent plus influenza/ influenza alone | | | O | + |
| **Industrialised countries, other** | | | | | | |
| McLeod 1945 | Young US military recruits | 4-valent/placebo | O | + | O | O |
| Kaufman 1947 | Long-term facility residents (80% aged >60 years) | 2,3-valent vaccine | O | + | O | O |
| Austrian 1980* | Health plan members aged >45 - 2 years | 12-valent/placebo | + | + | + | + |
| Austrian 1980* | Psychiatric inpatients - 3 years | 12-valent/placebo | + | + | + | + |
| Gaillet 1985 | Retirement home residents, geriatric inpatients. Excluded comorbidities, terminal illness, immunodeficiency - 2 years | 14-valent/no placebo | + | + | + | + |
| Ortqvist 1998 | Patients over 50 with previous pneumonia. Excluded immuno-suppression, low compliance - 4 years | 23-valent/placebo | | | + | + |
| **Less industrialised countries** | | | | | | |
| Austrian 1976* | Novice gold miners - 2 years | 6 or 13-valent/ meningococcal vaccine/placebo | + | + | + | + |
| Riley 1977 | Subsistence farmers - 3 years | 14-valent/placebo | + | + | + | + |
| Smit 1977* | Novice gold miners - 2 years | 6-valent/ meningococcal vaccine/placebo | + | + | + | + |
| Smit 1977* | Novice gold miners - 2 years | 12-valent/ meningococcal vaccine/placebo | + | + | + | + |

*Trials categorised according to Watson et al.[19] In the right-hand column inclusion of trial in question in the four systematic reviews. * Multiple trials presented in single report, + = trial included; o = trial excluded; blank = trial not available yet.*

specific as an inclusion criterion, while the average age is then quite high). To reach a conclusion it is important to determine whether a restriction should be imposed limiting the study to a particular trial dealing specifically with the question[1,2] or whether evidence from other trials (e.g. trials with a high average age of participants or trials with institutionalised patients with comorbidity) can be assessed as to its applicability to the question under examination.

*Outcome measures*
The outcome measures reported and analysed show major differences between the SRs. In addition, the conclusions of the various reviews contain a different hierarchy in the outcome measures.

*Valency of vaccines*
The vaccines used differ greatly in valency (*table 1*). None of the SRs pay any attention to this fact in separate subgroup analyses.

*Duration of follow-up*
This too differs greatly from trial to trial, which should not lead to any consequences if the relative risk/odds ratio remains constant over a shorter and longer period of follow-up. But in this area it is unclear as to whether such is the case.

*Combination with influenza vaccination*
Some studies report pneumococcal vaccination as being given supplementary to the influenza vaccination (as

**Table 2**
*Subgroups, outcome measures and account taken of vaccine valency in SRs*

| STUDY (REFERENCE) | SUBGROUPS | OUTCOME MEASURES | ACCOUNT TAKEN OF VACCINE VALENCY | ACCOUNT TAKEN OF RANDOMISATION IN TRIALS | ACCOUNT TAKEN OF COMBINATION WITH INFLUENZA VACCINE |
|---|---|---|---|---|---|
| 11 | 1. High risk: patients with comorbidity and institutionalised patients (n=5)<br>2. Low risk: miners, ambulant patients (n=7) | Confirmed pneumococcal pneumonia<br>Confirmed pneumococcal pneumonia, vaccine type<br>Possible pneumococcal pneumonia<br>Possible pneumococcal pneumonia, vaccine type<br>Pneumococcal disease<br>Not pooled, but described:<br>- Pneumonia (all causes)<br>- Bronchitis<br>- Mortality (all causes)<br>- Mortality (pneumonia)<br>- Mortality (pneumococcal infection) | No subgroup analysis with vaccines of different valencies | Restricted to genuine randomised studies | No |
| 12 | 1. Elderly (n=7)<br>2. Chronically ill (n=3)<br>3. Institutionalised (n=3) | Vaccine-type systemic pneumococcal infection<br>Systemic pneumococcal infection<br>Pneumococcal pneumonia<br>Non-vaccine type pneumococcal pneumonia | No subgroup analysis with vaccines of different valencies | Pseudo-random trials included | No |
| 13,14 | 1. Normal immune system: young, healthy (n=3)<br>2. Weakened immune system or elderly (n=10) | Pneumonia (all causes)<br>Pneumococcal pneumonia<br>Lower airway infections<br>Mortality (pneumonia)<br>Bacteriaemia | Yes, two older trials excluded<br>No subgroup analysis with vaccines of different valencies | Restricted to truly randomised studies; exclusion of pseudo-random trials: two older trials and one more recent one of the two specifically carried out on the elderly[2] | No |
| 15 | 1. Nonindustrialised (n=4)<br>2. Industrialised<br>a) All (n=10)<br>b) Patients with comorbidity/ high risk (n=4)<br>c) Elderly (>65 years) (n=2)<br>d) 'Other' (n=4) | Mortality (all causes)<br>Pneumonia (all causes)<br>Pneumonia (pneumococci)<br>Bacteraemia (pneumococci) | No subgroup analysis with vaccines of different valencies | Restricted to genuine randomised studies | No |

would be the case in the Netherlands) (*table 1*). However in other studies only the pneumococcal vaccination is administered. None of the SRs include this fact in their conclusions.

**Outcomes of systematic reviews**

*Table 3* shows the results of the four SRs in the same way as was presented in the original publications. It is immediately clear that subgroups, outcome measures and statistical heterogeneity have been dealt with in different ways.

The SRs deal with the 'elderly' category in different ways (*table 2*). In Fine *et al.*[11] the studies with a relatively large number of elderly people (often with comorbidity) come under the 'high-risk' category.

Hutchison *et al.*[12] deal separately with elderly people in the text of their SR. They state that seven of the 13 studies dealt predominantly with the elderly. In view of this numerical imbalance the authors believe that the results of overall poolings are also applicable to the elderly. It should be noted that this SR did not include the two studies carried out specifically on elderly people,[1,2] even though the SR appeared *after* publication of both studies, and that two major positively dated studies (from 1945 and 1947 respectively; with vaccine containing four and three pneumococcal types respectively) were included, whereas they had been omitted from the other SRs (*table 1*). In the SR by Moore *et al.*[13,14] the elderly are analysed together with the high-risk patients. Watson *et al.*[15] first separated the studies carried out in industrialised countries from

**Table 3**
*Outcomes of systematic reviews*

| REFERENCE | OUTCOME MEASURES (NUMBER OF STUDIES) | POOLED OUTCOMES [95% CI], STATISTICAL HETEROGENEITY |
|---|---|---|
| 11 | Confirmed pneumococcal pneumonia (n=8) | $OR_{fixed}$ 0.34 [0.24;0.48] $RD_{random}$ 4 [0;7]* |
| | Low risk (n=3) | $OR_{fixed}$ 0.32 [0.22;0.46] $RD_{random}$ 11 [2;19]* |
| | High risk (n=5) | $OR_{fixed}$ 1.23 [0.28;5.43] $RD_{random}$ 0 [-1;2] |
| | Vaccine-type confirmed pneumococcal pneumonia (n=3) | $OR_{fixed}$ 0.17 [0.09;0.33] $RD_{random}$ 8 [1;16]* |
| | Low risk (n=2) | $OR_{fixed}$ 0.16 [0.09;0.31] $RD_{random}$ 15 [-14;45]* |
| | High risk (n=1) | $OR_{fixed}$ 1.00 [0.06;16.06] $RD_{random}$ 0 [-2;2]@ |
| | Suspected pneumococcal pneumonia (n=4) | $OR_{fixed}$ 0.47 [0.35;0.63] $RD_{random}$ 13 [-21;47]* |
| | Low risk (n=1) | $OR_{fixed}$ 0.40 [0.29;0.56] $RD_{random}$ 41 [29;54]@ |
| | High risk (n=3) | $OR_{fixed}$ 0.98 [0.51;1.89] $RD_{random}$ -3 [-21;15] |
| | Vaccine-type suspected pneumococcal pneumonia (n=3) | $OR_{fixed}$ 0.39 [0.26;0.59] $RD_{random}$ 16 [-3; 35]* |
| | Low risk (n=2) | $OR_{fixed}$ 0.35 [0.23;0.55] $RD_{random}$ 25 [15;35] |
| | High risk (n=1) | $OR_{fixed}$ 0.86 [0.29;2.56] $RD_{random}$ 1 [-5;7]@ |
| | Pneumonia (all causes) (n=8) | $OR_{fixed}$ 0.90 [ 0.77;1.04] $RD_{random}$ 6 [-1;13] |
| | Low risk (n=5) | $OR_{fixed}$ 0.89 [0.76;1.05] $RD_{random}$ 6 [-2;14] |
| | High risk (n=3) | $OR_{fixed}$ 0.92 [0.63;1.35] $RD_{random}$ 5 [-16;26]* |
| | Bronchitis (n=3) | $OR_{fixed}$ 0.84 [0.69;1.02] $RD_{random}$ 8 [0;15] |
| | Low risk (n=3) | $OR_{fixed}$ 0.84 [0.69;1.02] $RD_{random}$ 8 [0;15] |
| | High risk (n=0) | - |
| | Mortality (all causes) (n=7) | $OR_{fixed}$ 1.02 [0.90;1.14] $RD_{random}$ 1 [-6;8] |
| | Low risk (n=3) | $OR_{fixed}$ 0.84 [0.70;1.01] $RD_{random}$ 2 [-2;7] |
| | High risk (n=4) | $OR_{fixed}$ 1.16 [1.00;1.35] $RD_{random}$ -18 [-47;11] |
| | Mortality (pneumonia) (n=4) | $OR_{fixed}$ 0.78 [0.57;1.06] $RD_{random}$ 2 [-2;5] |
| | Low risk (n=3) | $OR_{fixed}$ 0.79 [0.57;1.0] $RD_{random}$ 2 [-2;5] |
| | High risk (n=1) | $OR_{fixed}$ 0.51 [0.09;2.92] $RD_{random}$ 35 [-54;125]@ |
| | Mortality (pneumococcal pneumonia) (n=3) | $OR_{fixed}$ 4.59 [0.54;1.06] $RD_{random}$ -3 [-6;0] |
| | Low risk (n=0) | - |
| | High risk (n=3) | $OR_{fixed}$ 4.59 [0.54;38.81] $RD_{random}$ -3 [-6;0] |
| 12 | Systemic pneumococcal infection | |
| | Vaccine type (n=4) | OR 0.17 [0.09;0.31] |
| | All infections (n=6) | OR 0.27 [0.13;0.49] |
| | Vaccine-type pneumococcal pneumonia (n=9) | Range ORs 0.08-1.17* |
| | Pneumococcal pneumonia | Range ORs 0.24-8* |
| | Non-vaccine-type pneumococcal pneumonia | Range ORs 0.40-1.13* |
| 13,14 | Pneumonia (all causes) | |
| | Healthy, immunocompetent (n=3) | $RR_{fixed}$ 0.56 [0.47;0.66]§ NNT 29 [24;36] |
| | Elderly or high risk (n=5) | $RR_{fixed}$ 1.08 [0.92;1.27]§ |
| | Pneumococcal pneumonia | |
| | Healthy, immunocompetent (n=3) | $RR_{fixed}$ 0.16 [0.11;0.23]§ NNT 38 [33;45] |
| | Elderly or high risk (n=7) | $RR_{fixed}$ 0.88 [0.72;1.07]§ |
| | Lower airway infections | |
| | Healthy, immunocompetent (n=2) | $RR_{fixed}$ 0.85 [0.71;1.02]§ |
| | Elderly or high risk (n=3) | $RR_{fixed}$ 1.06 [0.97;1.16]§ |
| | Pneumonia-related mortality | |
| | Healthy, immunocompetent (n=1) | $RR_{fixed}$ 0.70 [0.50;0.96]§ NNT 213 [114;1660] |
| | Elderly or high risk (n=8) | $RR_{fixed}$ 0.93 [0.72;1.20]§ |
| | Pneumococcal bacteriaemia | |
| | Healthy, immunocompetent | $RR_{fixed}$ 0.18 [0.09;0.34]§ NNT 32 [26;44] |
| | Elderly or high-risk | $RR_{fixed}$ 0.53 [0.14;1.94]§ |
| 15 | Mortality (all causes) | |
| | Industrialised (n=8) | $RR_{fixed}$ 1.07 [0.97;1.18] $R_{random}$ 1.07 [0.97;1.18] |
| | High risk (n=3) | $RR_{fixed}$ 1.20 [1.00;1.42] $R_{random}$ 1.15 [0.87;1.52] |
| | Elderly (1) | $RR_{fixed}$ 0.99 [0.80;1.22] $R_{random}$ 0.99 [0.80;1.22] |
| | Nonindustrialised (n=1) | $RR_{fixed}$ 0.79 [0.63;0.99] $R_{random}$ 0.79 [0.63;0.99] |
| | Pneumonia (all causes) | |
| | Industrialised (n=9) | $RR_{fixed}$ 1.06 [0.97;1.17] $R_{random}$ 1.03 [0.86;1.25] |
| | High risk (n=3) | *$RR_{fixed}$ 1.17 [0.86;1.60] $R_{random}$ 1.13 [0.79;1.62] |
| | Elderly (n=2) | $RR_{fixed}$ 1.15 [0.95;1.40] $R_{random}$ 1.15 [0.95;1.40] |
| | Nonindustrialised (n=3) | $RR_{fixed}$ 0.67 [0.52;1.87] $R_{random}$ 0.67 [0.52;1.87] |

*Table continued on the next page.*

**Table 3 continued**
*Outcomes of systematic reviews*

| REFERENCE | OUTCOME MEASURES (NUMBER OF STUDIES) | POOLED OUTCOMES [95% CI], STATISTICAL HETEROGENEITY |
|---|---|---|
| 15 | Pneumococcal pneumonia | |
| | Industrialised (n=5) | $RR_{fixed}$ 1.06 [0.82;1.37] $R_{random}$ 1.06 [0.82;1.38] |
| | High risk (n=2) | $RR_{fixed}$ 1.07 [0.58;1.97] $R_{random}$ 0.91 [0.33;2.53]* |
| | Elderly (n=2) | *$RR_{fixed}$ 1.02 [0.75;1.40] $R_{random}$ 1.01 [0.69;1.49]* |
| | Nonindustrialised (n=0) | - |
| | Bacteriaemia (pneumococci) | |
| | Industrialised (n=6) | $RR_{fixed}$ 0.53 [0.22;1.29] $R_{random}$ 0.53 [0.20;1.43] |
| | High risk (n=1) | $RR_{fixed}$ 0.81 [0.05;12.16] $R_{random}$ 0.81 |
| | Nonindustrialised (n=1) | [0.05;12.16] $RR_{fixed}$ 0.14 [0.02;1.14] $R_{random}$ 0.14 [0.02;1.14] |

*OR = odds ratio; RR = relative risk; RD = risk difference (calculated as the difference in 'events' between intervention and control group per 1000 subjects); fixed = calculated according to the fixed effects model; random = calculated according to the random effects model.*
** statistical heterogeneity between the studies; @ fewer than two studies: statistical heterogeneity not tested by authors; ∫ because of limited sensitivity of fixed-effects model the authors do not report on statistical heterogeneity; everything pooled with fixed-effects model.*

those performed in nonindustrialised countries. Subsequently the high-risk patients and the elderly are presented separately in subgroups.

The following tendencies can be seen:
- Vaccination is more effective in low-risk groups.[11,13,15]
- Vaccination does not appear to be effective in high-risk patients and the elderly.[11,13,15]
- Vaccination is more effective in nonindustrialised countries.[15]
- The outcomes based on the various outcome measures can show major differences.[11-15]

**Randomised clinical trials and comparative cohort studies**
There are two trials involving elderly people in Western countries that investigate the effectiveness of the pneumococcal vaccination as complementary to the influenza vaccination.[1,2] In addition there is one recent (non-randomised) retrospective cohort study.[17,18]

These three studies appeared relatively recently and are not included in all the SRs. For this reason we discuss them separately here (*tables 4* and *5*).

It is remarkable that the trial carried out by Koivula *et al.*[1] was not published until 12 years after completion of the study. The study performed by Honkanen *et al.*[2] is not truly randomised. The patients were divided up according to date of birth. It is known that pseudo-randomisation of this type can lead to bias (generally because of overestimation of the effect).[19,20]
Both studies are so badly described that some items regarding quality assessment could not be completed.

The outcomes of the trial carried out by Honkanen *et al.*[2] all point to the lack of an effect. In the trial by Koivula *et al.*[1] a large number of subgroup analyses are used to identify a single subgroup that runs a 'greater risk' of pneumococcal pneumonia and the summary of the trial seems to indicate that the study has been positive. The subgroup (30% of the total population) consists of elderly persons with 'risk factor for pneumococcal pneumonia': aged ≥70 years, cardiac diseases, lung diseases, asthma, alcoholism, institutionalised life or bed-ridden. It is unclear whether this subgroup was defined beforehand or subsequently assembled on the basis of the results of the study. If the latter is the case (certainly in view of the large number of analyses carried out) the result is not very convincing.[21] In addition, account should be taken of the fact that for all the pneumonias together (including pneumococcal pneumonia) no protective effect was observed (see figures in *table 4*).

The retrospective cohort study done by Nichol *et al.*[17,18] involved a selected population, namely elderly people with a chronic lung disease. With regard to many methodological aspects the study was described in an insufficiently detailed manner to permit adequate assessment of the methodological quality (see *table 5*). The study is particularly interesting (account taken of the limitations imposed by the study design and the population selection) for the comparison with the Dutch situation with regard to the added value of the pneumococcal vaccination as a supplement to the influenza vaccination.
The study was retrospective in nature and thus sensitive to selection bias. And, indeed, there were some major differences as regards baseline between the various groups. Those administered pneumococcal vaccine were generally younger, healthier, had had pneumonia less often and had previously been vaccinated more often against influenza prior to the study. Interpretation of these figures uncorrected for the differences[18] is therefore

**Table 4**
*Trials carried out in the elderly in Western countries investigating the effectiveness of the pneumococcal vaccination as a supplement to the influenza vaccination*

| | REFERENCE 1 | REFERENCE 2 |
|---|---|---|
| **Study design** | | |
| Country | Finland | Finland |
| Period of trial | 1982-1985 | 1992-1994 |
| Inclusion | Elderly people ≥60 years | Elderly people ≥65 years |
| Exclusion | Not described | Acute febrile illnesses, terminal illnesses |
| Intervention | 14-valent pneumococcal vaccine plus influenza vaccine (valency not described) (n=1364) versus placebo and influenza vaccine (n=1473) | 23-valent pneumococcal vaccine plus 3-valent influenza vaccine (n=13,980) versus placebo and influenza vaccine (n=12,945) |
| Outcome measures | Pneumonia | Pneumococcal pneumonia |
| Pneumonia | Pneumococcal pneumonia | Pneumococcal bacteriaemia |
| Follow-up | 3 years | 3 years |
| **Methods** | | |
| Randomisation | Yes | Pseudo-random (allocation according to date of birth) |
| Allocation blinded | Yes | No |
| Complete follow-up | Information insufficiently detailed | Information insufficiently detailed |
| Intention-to-treat | Yes | Yes |
| Patients blinded | Yes | Information insufficiently detailed |
| Medical staff blinded | Yes | Information insufficiently detailed |
| Effect assessors blinded | Yes | Information insufficiently detailed |
| Comparability of groups at baseline | Yes | Yes |
| Prevention of co-interventions | Information insufficiently detailed | Information insufficiently detailed |
| **Outcomes** | | |
| | Pneumonia RR 1.16 [95% CI 0.83-1.62] | Pneumonia RR 1.2 [95% CI 0.9-1.5] |
| | Pneumococcal pneumonia RR 0.85 [95% CI 0.51-1.42] | Pneumococcal pneumonia RR 1.2 [95% CI 0.8-1.9] |
| | The only statistically significant outcome from 15 analyses is the RR for pneumococcal pneumonia for the 'higher-risk group': RR 0.42 [95% CI 0.19-0.94] | Pneumococcal bacteriaemia RR 0.4 [95% CI 0.1-1.9] |
| | For the same 'higher-risk group' for the all pneumonias (including pneumococcal pneumonia) outcome RR 0.99 [95% CI 0.63-1.57] | |

somewhat tricky. In the other article[17] baseline corrections were carried out. But correction is in no way a satisfactory solution to the problem of nonrandomisation[19] so that these figures should also be interpreted with caution. It is only in the article in which the baseline differences are corrected[17] that the added value of pneumococcal vaccination as a supplement to influenza vaccination is reported. But the reliability intervals are wide, making interpretation difficult.

## DISCUSSION

A question currently topical in the Netherlands is whether pneumococcal vaccination should be introduced for (all) elderly people as a supplement to the influenza vaccination. This report takes a critical look at the available comparative studies into the effectiveness of the pneumococcal vaccination.

To this end, the available SRs[11-15] were first assessed as to quality and investigated as to mutual differences. This showed that there are major differences between the systematic reviews with regard to the selection of studies, the distinction made in the valency of the vaccines, the division into subgroups and the choice of the outcome measures accorded the greatest value. It is remarkable that three of the SRs[12-15] were published within a relatively short period and two trials that best matched up to the research question[1,2] were sometimes included and sometimes not.

**Table 5**
*Comparative cohort studies in elderly people in Western countries investigating the effectiveness of pneumococcal vaccination as a supplement to influenza vaccination*

| | REFERENCE 17,18 |
|---|---|
| **Characteristics of study** | |
| Country | United States |
| Research period | 1993-1995 |
| Inclusion | Elderly patients ≥65 years with a chronic lung disease |
| Exclusion | Not described |
| Intervention | Pneumococcal vaccine, perhaps in combination with influenza vaccine; vaccinated with pneumococcal vaccine n=1280; not vaccinated with pneumococcal vaccine n=618 |
| Outcome measures | Admitted to hospital with pneumonia or influenza<br>Mortality |
| Follow-up | Two years |
| **Methods** | |
| Randomisation | No (retrospective cohort study 1993-1996) |
| Allocation blinded | No |
| Complete follow-up | Information insufficiently detailed |
| Intention-to-treat analysis | Information insufficiently detailed |
| Patients blinded | No |
| Medical staff blinded | No |
| Effect assessors blinded | Information insufficiently detailed |
| Comparability groups on baseline | No; insufficiently corrected for in analyses (see also text) |
| Prevention of co-interventions | Information insufficiently detailed |
| Outcomes | *Corrected for baseline differences*[17]<br>Admitted to hospital with pneumonia or influenza<br>$RR_{\text{pneumococcal vaccine}}$ RR 0.57 [95% CI 0.38-0.84]<br>$RR_{\text{pneumococcal and influenza vaccine}}$ RR 0.28 [95% CI 0.14-0.58]<br>Mortality<br>$RR_{\text{pneumococcal vaccine}}$ RR 0.71 [95% CI 0.56-0.91]<br>$OR_{\text{pneumococcal and influenza vaccine}}$ (unclear why suddenly OR) = 0.18 [95% CI 0.11-0.31] |
| | *Not corrected for baseline differences, pneumococcal and influenza vaccines reported on separately*[18]<br>Admitted to hospital with pneumonia or influenza<br>$RR_{\text{pneumococcal vaccine}}$ RR 0.73 [95% CI 0.48-1.13]<br>$RR_{\text{influenza vaccine}}$ RR 0.48 [95% CI 0.28-0.82]<br>$RR_{\text{pneumococcal and influenza vaccine}}$ RR 0.37 [95% CI 0.20-0.71]<br>Mortality<br>$RR_{\text{pneumococcal vaccine}}$ RR 0.66 [95% CI 0.48-194]<br>$RR_{\text{influenza vaccine}}$ RR 0.30 [95% CI 0.11-0.43]<br>$RR_{\text{pneumococcal and influenza vaccine}}$ RR 0.11 [95% CI 0.12-0.32] |

Analysis of the SRs shows that the pneumococcal vaccination has greater effect in low-risk groups, is not effective in high-risk patients and the elderly, is more effective in industrialised countries and that outcomes can differ greatly in the various outcome measures.

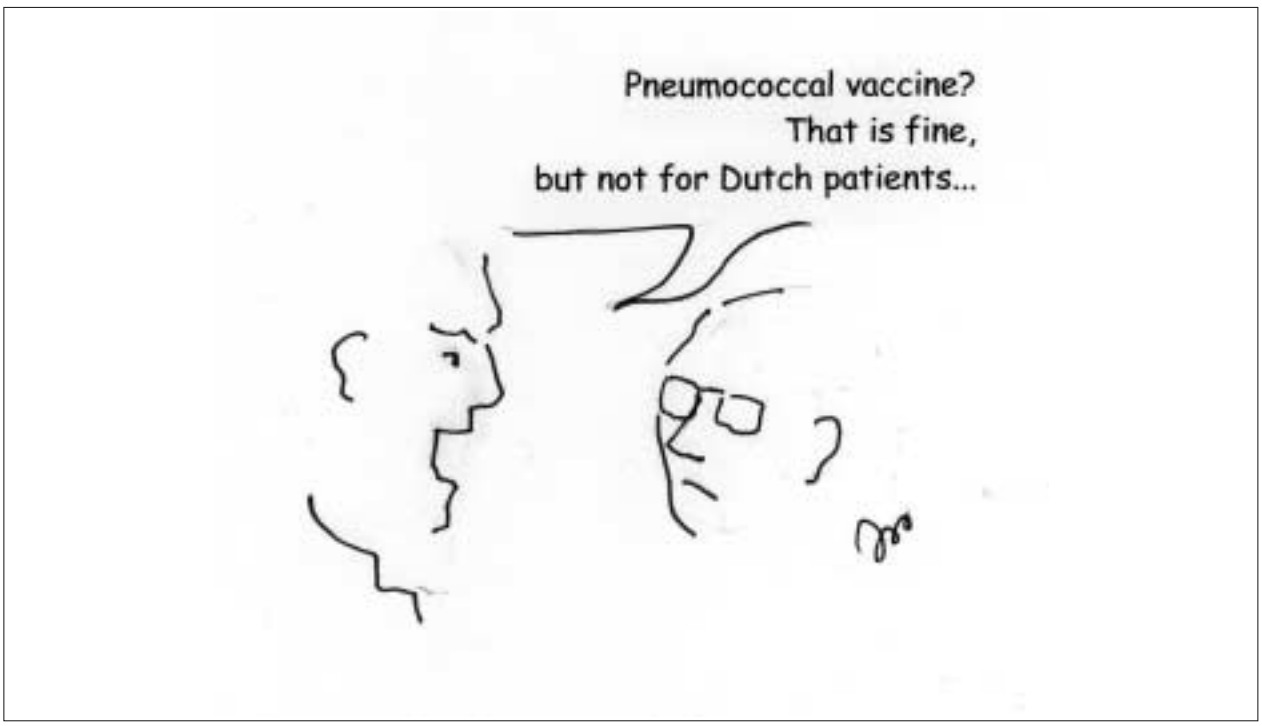
The studies into the effectiveness of the pneumococcal vaccination in the elderly (one RCT,[1] one pseudo-random study[2] and one retrospective study[17,18]) all showed major methodological shortcomings. For the majority of outcome measures the outcomes were negative.

It can be stated in conclusion that there is insufficient convincing evidence in favour of the introduction of the pneumococcal vaccination as a supplement to the influenza vaccination for the elderly. It seems as if (international) opinion had already been fully formed before published studies and systematic reviews became available in the last few years.

At present there is a lack of methodologically responsible randomised research into this specific indication. It is perhaps worth considering setting up a prospective trial in the elderly Dutch population. In calculating the size of the sample population required it should be realised that the above considerations indicate that the predicted effect will be limited. This applies in particular to the nonpneumococcal-related general outcomes such as 'all types of pneumonia' (thus not only pneumococcal-related), 'admission to hospital' and 'mortality'.

## REFERENCES


1. Koivula I, Sten M, Leinonen, Makela PJ. Clinical efficacy of pneumococcal vaccine in the elderly: a randomised, single blind population-based trial. Am J Med 1997;103:281-90.
2. Honkanen PO, Keistenen T, Miettenenen L, et al. Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. Vaccine 1999;17:2493-500.
3. Hunt DL, McKibbon KA. Locating and appraising systematic reviews. Ann Intern Med 1997;126:532-8.
4. Cochrane Database of Systematic Reviews. In: The Cochrane Library, Issue 1, 2001. Oxford: Update Software.
5. Holden J, Fine M, Jefferson T. Vaccines for preventing pneumococcal infection in adults (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 1, 2001. Oxford: Update Software.
6. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994;309:1286-91.
7. Cochrane Controlled Trials Register. In: The Cochrane Library, Issue 1, 2001. Oxford: Update Software.
8. Assendelft WJJ, Scholten RJPM, Hoving JL, Offringa M, Bouter LM. De praktijk van systematische reviews. XI. Zoeken en beoordelen van systematische reviews. Ned Tijdschr Geneeskd 2001;145:1625-31.
9. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. Can Med Assoc J 1997;156:1411-6.
10. Assendelft WJJ, Scholten RJPM, Eijck JThM van, Bouter LM. De praktijk van systematische reviews. III. Methodologische beoordeling van onderzoeken. Ned Tijdschr Geneeskd 1999;143:714-9.
11. Fine MJ, Smith MA, Carson CA, et al. Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomised controlled trials. Arch Intern Med 1994;134:2666-77.
12. Hutchison BG, Oxman AD, Shannon HS, et al. Clinical effectiveness of pneumococcal vaccine – meta-analysis. Can Fam Phys 1999;45:2381-93.
13. Moore AR, Wiffen PJ, Lipsky BA. Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials. Biomed Central (Family Practice) 2001 1:1 (http://biomedcentral.com/1471-2296/1/1).
14. Moore A, McQuay H (red). Are pneumococcal vaccines effective? Bandolier 2000;7(2):6-7.
15. Watson L, Wilson BJ, Waugh N. Pneumococcal polysaccharide vaccine: a systematic review of clinical effectiveness in adults. Vaccine 2002;20:2166-73.
16. Wood-Baker R, Poole PJ. Vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 1, 2001. Oxford: Update Software.
17. 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;159:2437-42.
18. Nichol KL. The additive benefits of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease. Vaccine 1999;17(suppl 1):S91-3.
19. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomized and non-randomized clinical trials. BMJ 1998;317:1185-90.
20. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological effects in controlled trials. JAMA 1995;273:408-12.
21. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. Ann Intern Med 1992;116:78-84.


Assendelft, et al. Pneumococcal vaccination for the elderly in the Netherlands.

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REVIEW

# Prevention of infections in hyposplenic and asplenic patients: an update

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## ABSTRACT

**Patients with functional or anatomic asplenia are at a significantly increased risk of overwhelming infection, particularly involving the encapsulated bacteria *Streptococcus pneumoniae* and *Haemophilus influenzae*. The risk is highest in infants and young children, but adults also have an increased risk of infection. Preventive strategies are very important and fall into three major categories: immunoprophylaxis, antibiotic prophylaxis and education. Studies have shown that many asplenic patients are unaware of their increased risk for serious infection and the appropriate health precautions that should be undertaken. In this article we emphasise the need for preventive measures in hyposplenic and asplenic patients. We discuss the value of newly developed conjugate vaccines and the need for revaccination. Finally we draw up a recommendation for the preventive management in functional and anatomical asplenic patients.**

## INTRODUCTION

Patients with functional or anatomic asplenia are at a significantly increased risk of overwhelming infection (postsplenectomy sepsis [PSS]), particularly involving the encapsulated bacteria *Streptococcus pneumoniae* and *Haemophilus influenzae*.[1-3] In 1919, Morris and Bullock recognised the importance of the spleen in resistance to infection in studying splenectomised rats.[4] The first reported case of postsplenectomy infection was by O'Donnel in 1929.[5] It was not until 1952 that attention focussed on the subject, when King and Shumacker reported five cases of severe infection in infants who had undergone splenectomy for spherocytosis.[6]

Preventive strategies against PSS fall into three major categories: immunoprophylaxis, antibiotic prophylaxis, and education. Different studies report a low adherence to these preventive measures in hyposplenic and asplenic patients.[1,7-10] Family practitioners and medical specialists should inform the patients at risk and make every effort to increase the coverage of recommended vaccines and chemoprophylaxis in this group.

Furthermore, the recent development of new conjugate vaccines has enhanced the options for preventive management in (functional) asplenic patients. This article calls attention to the importance of vaccination after splenectomy and reviews the recent developments with relation to immunisation, revaccination and other preventive measures.

## SPLENECTOMY AND HYPOSPLENISM

Surgical removal of the spleen is performed for several reasons, including trauma, immunological diseases, hypersplenism and malignancy.[2] In a major university hospital the most common reasons for performing splenectomy were haematological and immunological diseases (31%), while trauma accounted for only 16% (*table 1*). *Figure 1* shows the absolute incidence of splenectomy in the Netherlands from 1997 to 2002. Growing awareness of possible long-term complications has more recently led to an increasingly conservative approach toward resection and greater efforts to preserve splenic tissue.[1,2,11] In Hodgkin's disease, splenectomy is

**Table 1**
*Indication for splenectomy in the Erasmus University Medical Centre from 1998 to 2002 (Rotterdam, the Netherlands)**

| INDICATION OF SPLENECTOMY | NUMBER (%) |
|---|---|
| Haematological and immunological diseases | 73 (31%) |
| Abdominal malignancies | 54 (23%) |
| Trauma | 38 (16%) |
| Miscellaneous | 57 (24%) |
| Unknown | 13 (6%) |
| Total | 235 (100%) |

** Figures derived from the department of Medical Data Processing, Erasmus University Medical Centre.*

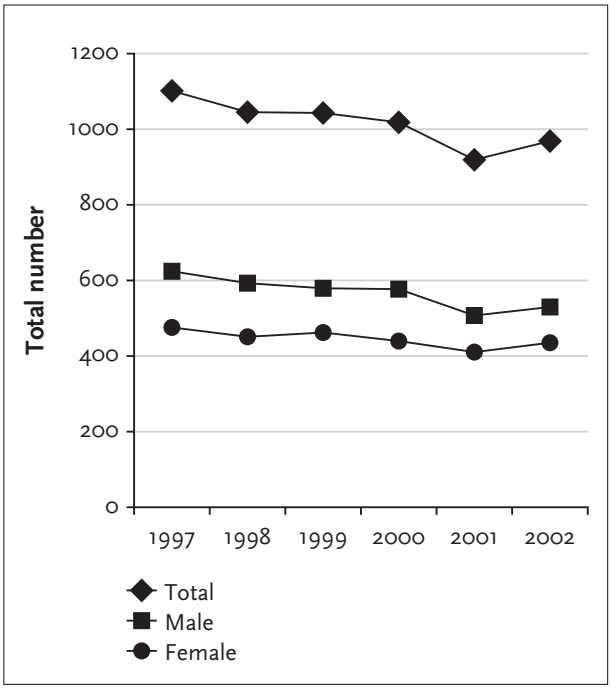


**Figure 1**
*Incidence of splenectomy in the Netherlands (total number)**

*** Figures derived from Prismant, Utrecht, the Netherlands.**

no longer a routine procedure.[12] However, the procedure remains important in the management of patients with hereditary haemolytic anaemias, spherocytosis in particular.[2]

Functional hyposplenism is associated with a wide variety of diseases, including several immunological and haematological diseases. In infants, asplenia is usually linked to serious organ malformations (Ivemark's syndrome), but isolated congenital asplenia diagnosed in adults can occur.[2] The true incidence of hyposplenism is unknown, mainly because the recognition requires a high index of suspicion.

The presence of Howell-Jolly bodies in the erythrocytes on a peripheral blood film is an important clue to the diagnosis of asplenia or functional hyposplenism. Howell-Jolly bodies are nuclear remnants normally removed by the spleen and may not occur with mild hyposplenism. Their presence in erythrocytes is thought to represent a risk for PSS.[1,7,13] The 'pocked erythrocyte count' (pit count) is a more sensitive indicator of splenic clearance and can be visualised by interference phase microscopy. Pocks are membrane vesicles removed only by the spleen, and the presence of more than 12% pocked red cells is indicative of asplenia.[1,14-16] A pocked erythrocyte count of less than 2% is expected in normal persons and a percentage of more than 3.5% is strongly correlated with functional hyposplenia.[15,16]

## POSTSPLENECTOMY SEPSIS

### Incidence

Singer[17] defined postsplenectomy sepsis (PSS) as septicaemia, meningitis, or pneumonia that is usually fulminant and occurs days to years after removal of the spleen.

Estimates of the incidence of postsplenectomy sepsis have frequency been fairly variable for many reasons, including different disease definitions, duration of follow-up, and stratification for age, splenectomy cause and underlying disease.[1,2]

The risk of PSS is highest in children, especially those under two years of age and during the first years after splenectomy.[1,3,17,18] There are, however, reported cases of fulminant sepsis 20 to 40 years after splenectomy, indicating that postsplenectomy patients carry a lifelong risk.[17,19-21]

The incidence of infection after splenectomy is usually quoted from the major collective review of Singer published in 1973, who evaluated 2795 patients with asplenia.[17] The incidence of PSS was 4.25% with a mortality rate of 2.52%. Singer concluded that death from postsplenectomy sepsis is 200 times as prevalent as death due to sepsis in the population at large. However, not all studies confirmed this considerably higher risk for sepsis after splenectomy.[3,22] Holdsworth *et al.* reported a collective review of the literature on PSS from 1952 to 1987.[3] In this study the incidence of infection after splenectomy in children under 16 years old was 4.4% with a mortality rate of 2.2%. The corresponding figures for adults were 0.9% and 0.8%. Walker prospectively observed 16 (2%) severe infections in 821 children undergoing splenectomy with a 70% five-year follow-up.[23]

The risk of PSS can also be stratified by underlying disease. The lowest risk is related to trauma, intermediate risk to spherocytosis, idiopathic thrombocytic purpura, or portal hypertension, and highest risk in thalassaemia or Hodgkin's disease.[2,17]

**Typical presentation and prognosis**

PSS may have a short prodrome of low-grade fever with chills, pharyngitis, muscle aches, vomiting, or diarrhoea. In a few hours this stage can rapidly evolve into severe septic shock with true rigors, hypotension and anuria. There is usually no clinical evidence of a local tissue infection. In children younger than five years of age, focal infections, particularly meningitis, are more common.[3] In severe cases rapid deterioration is often accompanied by disseminated intravascular coagulopathy (DIC) with adrenal haemorrhage (Waterhouse-Friderichsen syndrome). Other complications include purpura fulminans, extremity gangrene, convulsions and coma.[1,2,7]

The mortality rates of PSS range from 50 to 70%, despite appropriate antimicrobial therapy and intensive medical treatment.[3,24] Holdsworth *et al.* reported an overall fatality rate of 55.3% in 349 episodes.[3] The dramatic nature of the illness is further reflected by the time from initial symptoms to death, with 68% of the deaths occurring within 24 hours and 80% within 48 hours.[2,3] These data emphasise the importance of prevention of PSS.

**Microbiology of postsplenectomy sepsis**

*Streptococcus pneumoniae* is the most common organism involved in PSS and the causative agent in 50 to 90% of the cases.[1-3,17,24] A predominant polysaccharide serotype is not found, and there is no difference in serotype distribution involved in PSS from that in other forms of pneumococcal infection.[2]

*Haemophilus influenzae* type b is the second most common organism related to PSS.[1-3,24] Most cases occur in children younger than 15 years of age, 86% in one review.[3] Overall incidence of invasive disease decreased significantly with wide usage of conjugated *H. influenzae* type b vaccine and probably results in a decrease in the overall number of PSS cases associated with *H. influenzae*, with more of the remaining infection occurring in older, nonvaccinated persons.[2] Low virulent non-b capsular strains (a, c, d, e and f) may cause invasive infection, but are not relevant in PSS.[1]

*Neisseria meningitidis* has been cited as the third most common cause of PSS.[1-3] However, there is no evidence to suggest that meningococcaemia occurs more frequently or is more severe in asplenic or hyposplenic patients compared with healthy persons.[1,2]

*Capnocytophaga canimorsus* is a Gram-negative rod and part of the normal flora of dogs and cats. This bacillus can cause fulminant sepsis (purpura fulminans) following dog or cat bites and scratches.[1,2,25] Previous splenectomy, alcoholism, and glucocorticosteroid therapy are the most important risk factors for *C. canimorsus* sepsis. Approximately 35% of the cases of *C. canimorsus* septicaemia are associated with asplenia.[25,26]

*Salmonella* species have also been associated with PSS. *Salmonella* is a prominent pathogen in children with sickle cell anaemia and splenic dysfunction.[1,2,24,27,28]

Less common bacteria isolated from splenectomised patients include *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus* species, *Bacteroides* species, *Plesiomonas shigelloides, Eubacterium plautii* and *Pseudomonas pseudomallei*.[1,2,19]

Asplenic and hyposplenic patients appear to be more susceptible to serious infections with protozoans following tick bites (*Babesia microti* in North America and *Babesia bovis* in Europe).[1,2,7,29,30] These micro-organisms infect erythrocytes that are sequestered in the spleen. There is no consistent evidence that malaria follows a significantly more severe course in splenectomised patients.[1,2,29,31]

## PREVENTION OF INFECTIONS IN HYPOSPLENIC AND ASPLENIC PATIENTS

**Immunoprophylaxis**

*Pneumococcal-polysaccharide vaccine*

Pneumococcal immunisation with polyvalent capsular polysaccharide vaccine is uniformly recommended for asplenic and hyposplenic patients.[1,2,7,18,19,32,33] The currently available pneumococcal polysaccharide vaccine (PPV23) contains capsular polysaccharides from 23 serotypes, responsible for at least 85 to 90% of the serotypes that cause invasive pneumococcal infections among children and adults.[34] Bacterial capsular polysaccharides induce antibodies primarily by T-cell independent mechanisms. Therefore, antibody response to most pneumococcal capsular types is generally poor in children less than two years of age, whose immune systems are immature.[1,18,34,35] The antibody response is also decreased in children under the age of five years.

Healthy asplenic adults have been found to have normal or nearly normal antibody responses to polysaccharide antigens by most[36-40] but not all[41] investigators. Siber *et al.* compared the antibody response to pneumococcal capsular polysaccharide vaccine in patients with Hodgkin's disease, patients with asplenia due to other causes and in healthy adults. The antibody responses to immunisation were similar in these three groups. However, patients with Hodgkin's disease who started chemotherapy less than ten days after immunisation showed a significantly lower antibody response.[37] Impaired antibody response is related to underlying disease and the medical treatment of this disease. In Hodgkin's disease, antibody response improves as the time of immunisation after chemotherapy or radiation increases.[42]

Giebink *et al.* reported a normal antibody response in splenectomised children (mean age, 11.6 years) to pneumococcal polysaccharide vaccine.[36] Lee *et al.* concluded PPV23

to be safe and immunogenic in splenectomised children as well as healthy children above two years of age.[43] Several studies conclude polysaccharide pneumococcal vaccination to be efficacious in preventing PSS in hyposplenic and asplenic patients.[32,36,37,44-46] Konradsen *et al.* reported a considerable decrease of PSS in children since 1982, when antibiotic prophylaxis and pneumococcal vaccination were first recommended in splenectomised patients.[32]

The vaccine should be given a minimum of two weeks before elective splenectomy to ensure an optimal antibody response. After emergency splenectomy, patients should be immunised soon after surgical recovery or at time of discharge from the hospital.[1,2,7,18,33] Immunisation, however, should be delayed at least six months after immunosuppressive chemotherapy or radiotherapy.[18] To tide over this period, prophylactic antibiotics should be given. Hyposplenic patients should be immunised as soon as the diagnosis is made. Asplenic or hyposplenic children should be immunised with PPV23 after their second birthday (*table 2*).[35]

There is no consensus on the reimmunisation policy in hyposplenic and asplenic patients. Several studies advise revaccination with PPV23, because specific antibody levels decrease in high-risk patients as well as in healthy patients for a few years after first vaccination.[36,47-51] Weintrub *et al.* studied the duration of antibody response of pneumococcal polysaccharide vaccine and the effect of booster immunisation in patients with sickle cell anaemia.[50] They concluded that antibody levels had fallen by three to five years after first immunisation. Mean antibody levels after booster immunisation were significantly increased (which is not what one would expect from a thymus-independent vaccine), and no serious adverse events were noted. Giebink *et al.* reported in splenectomised patients a linear serum antibody concentration decline by 24 to 32% from the peak antibody level during the first year after vaccination.[36] These data suggest a need for revaccination after three to four years. Rutherford *et al.* advised revaccination between two and six years after splenectomy.[47]

Jackson *et al.* studied the safety of revaccination with the pneumococcal polysaccharide vaccine.[51] They demonstrated that self-limiting local injection site reactions occur more frequently following revaccination (11%) compared with first vaccination (3%). The risk of these local reactions was significantly correlated with prevaccination geometric mean antibody concentration. However, the risk of adverse events does not represent an absolute contradiction to revaccination with PPV23 for high-risk groups.[51]

The USA Centres for Disease Control (CDC) and Prevention Advisory Committee on Immunisation Practices (ACIP) recommend revaccination once with PPV23 in hyposplenic and asplenic patients after five years.[34] Revaccination after three years may be considered for children with functional or anatomic asplenia, who would be aged ≤10 years at the time of revaccination. Because data are insufficient concerning the safety of pneumococcal polysaccharide vaccine when administered three or more times, revaccination following a second dose is not routinely recommended.[34]

*Pneumococcal conjugate vaccine*

Recently, a protein-polysaccharide conjugate vaccine (PCV7) was licensed in the United States for use in infants and young children. In 2001, this vaccine was registered in the Netherlands. Conjugation of polysaccharides to proteins changes the nature of the antipolysaccharide response from T-lymphocyte independent to T-dependent. This antigen complex stimulates a T-helper cell response, leading to immunogenicity in early infants (>2 months of age), stimulation of high levels of IgG isotype antibodies and enhanced immunological memory responses.[35,52,53] The vaccine contains capsular polysaccharides from seven serotypes, each coupled with a nontoxic variant of diphtheria toxin.[52] These seven serotypes are responsible for approximately 64% of the invasive pneumococcal infections in children under the age of two years in the Netherlands.[35] PCV7 is safe and effective for use in the general population.[54,55] A large-scale efficacy trial in California (Kaiser Permanente Vaccine Study) concluded

**Table 2**

*Recommended schedule for PCV7 and PPV23 vaccination among infants and children with (functional) asplenia[35,52]**

| AGE AT FIRST DOSE | SCHEDULE FOR PCV7 | SCHEDULE FOR ADDITIONAL VACCINATION WITH PPV23 (AGE) |
|---|---|---|
| 2-6 months | 3 doses (4-8 weeks apart)<br>1 dose at age 12-15 months | 24 months |
| 7-11 months | 2 doses (6-8 weeks apart)<br>1 dose at age 12-15 months | 24 months |
| 12-23 months | 2 doses (8 weeks apart) | 24 months (≥2 months after last dose of PCV7) |
| 24-59 months | 2 doses (6-8 weeks apart) | ≥2 months after last dose of PCV7 |

* *Recommendations for adults with (functional) asplenia, see text.*

an efficacy of 97.4% in preventing invasive pneumococcal disease caused by vaccine serotypes in children with PCV7.[54] The CDC and ACIP (USA) recommend that the vaccine should be used in all children aged 2 to 23 months and in children aged 24 to 59 months who are at increased risk for pneumococcal disease, such as children with functional or anatomic asplenia.[52]

The Health Council of the Netherlands recommends introducing vaccination against pneumococci with PCV7 in the National Vaccination Programme as soon as combined administration of DKTP and Hib vaccines is possible. A combined vaccine for meningococcal C and pneumococcal infections will probably be available in early 2005. If research shows this combined vaccine to be safe, effective and efficient it would make sense to start using it on young infants.[56]

In expectation of the introduction of PCV7 in the National Vaccination Programme of the Netherlands, the vaccine should be administered to children less than five years of age who are at increased risk for pneumococcal infection.[35] Children with functional or anatomic asplenia who have completed the PCV7 vaccination series before the age of two years should receive one additional dose of PPV23 at two years of age (>2 months after the last dose of PCV7) to provide additional serotype coverage.[34,35,52] So, children with functional or anatomical asplenia between two and five years should be vaccinated with both vaccines (*table 2*). Of some concern are the results of a Dutch collaborative study showing that the combined vaccine strategy did not prevent infections in children with recurrent otitis media. A shift towards nasopharyngeal carriage of nonvaccine pneumococcal serotypes could be the explanation.[57] The need for reimmunisation is unclear.[52] Current data do not support a recommendation to replace PPV23 with PCV7 among older children (>5 years) and adults.[52] The proportion of invasive pneumococcal isolates covered by PCV7 is only 50 to 60% among older children and adults, in contrast with 80 to 90% coverage by PPV23 among this older group. Additional studies are needed to evaluate potential use of PCV7 in combination with PPV23 among adults at increased risk for pneumococcal infection.

*Haemophilus influenzae type b immunisation*

Although the efficacy and utility of vaccination against *H. influenzae* type b (Hib) in preventing PSS is less clear than pneumococcal vaccination, the Hib vaccine is being recommended for hyposplenic and asplenic individuals in the recent literature.[1,2,7,18,19,33]

In 1993, the Hib vaccine was introduced in the National Vaccination Programme in the Netherlands. Thus, most children up to 10 years of age have already been vaccinated. Many adults have acquired immunity against Hib through natural exposure, but this may not provide adequate protection in hyposplenic or asplenic patients.[1,2,18] The *H. influenzae* conjugate vaccine should be administered to all adults and children at risk who have not been vaccinated so far.[1,2,18,33,58] The vaccine has been shown to be immunogenic in patients with impaired splenic function.[58-61] The need for reimmunisation is unclear.[1,2,7,18,60]

*Meningococcal immunisation*

There are two meningococcal vaccines based on capsular polysaccharides: the bivalent meningococcal vaccine (serogroups A and C) and the quadrivalent meningococcal vaccine (serogroups A, C, W135 and Y). Ruben *et al.* concluded that bivalent meningococcal vaccine is immunogenic in asplenic persons, with the exception of those with lymphoma who had received prior chemotherapy and radiotherapy.[62] Because of the short duration of protection (two to three years) and the absence of protection against the most common serogroup B, these vaccines are not recommended routinely for asplenic patients.[1,2,7,18] However, it should be given to asplenic patients travelling to areas with increased risk of group A infection, such as sub-Saharan regions.[1,2,18]

The recently available meningococcal conjugate vaccine is composed of a serogroup C meningococcal polysaccharide conjugated to tetanus toxoid. In 2002 this vaccine was introduced in the National Vaccination Programme of the Netherlands. In contrast to the bivalent and quadrivalent meningococcal vaccines, this conjugated vaccine provides long-lasting immunity and is also effective in children under the age of two years. With the increasing number of infections by *Neisseria meningitidis* group C in Europe and the advantages of conjugated vaccines, patients with asplenia should receive this vaccine.[33] Travel to areas where other serogroups of meningococci are prevalent is an indication for revaccination with the bivalent or quadrivalent vaccine.[1,2,18,33] A meningococcal vaccine that covers serogroup B strains is still not available.

*Influenza immunisation*

Yearly administration of influenza vaccination is recommended, because it reduces the risk of secondary pneumococcal and *Haemophilus influenzae* infections.[1,2,7,18,19,33]

*Vaccine failure*

Sporadic cases of pneumococcal and other vaccine failures have been reported in immunised postsplenectomy patients.[63-68] So vaccination by itself should never allow a false sense of security. Furthermore, there are several other causative agents related to PSS which can not be vaccinated for.

**Prophylactic or empiric use of antibiotics**

Most authorities recommend antibiotic prophylaxis for asplenic or hyposplenic children, especially for the first two years after splenectomy.[19,20,32,69] Some investigators advocate continuing chemoprophylaxis until the age of 16 to 18 in children and for at least five years in adults.[18,20] Traditionally, a daily dose of oral penicillin or amoxicillin is the regime of choice.[1,2,18,20] Local resistance patterns or penicillin allergy may dictate the need to use other antibiotics.[18,33] Gaston *et al.* reported an 84% reduction in pneumococcal bacteraemia with the use of oral penicillin prophylaxis in children with sickle cell anaemia.[69] Whether (long-term) antibiotic prophylaxis in children is still necessary after the introduction of the pneumococcal conjugate vaccine has to be investigated.

The value of prophylactic antibiotics in older children or in adults has never been evaluated adequately in a clinical trial.[70,71] Long-term prophylaxis may be a risk factor for the selection of resistant strains, and efficacy may be reduced by noncompliance.[2,19,70,71] Therefore, long-term antibiotic prophylaxis in adults is not generally recommended.[24,70,71]

Access to 'stand-by' antibiotics is advised for asplenic patients in the current literature.[18,19,29,33,72] 'Stand-by' antibiotics should be taken at the first sign of infection (increase in body temperature, malaise or shivering) if the patient is unable to obtain prompt medical attention. However, in such situations medical help should still be sought without delay. A disadvantage of this strategy is the 'overtreatment' of many viral illnesses,[19] but to our opinion the benefits outweigh here.

**Patient education**

Patient education is an important and effective strategy in preventing PSS.[1,2,7,18,19] Studies have shown that up to 84% of postsplenectomy patients are unaware of their increased risk for serious infection and the appropriate health precautions that should be undertaken.[7-10] Patients should be informed about their increased susceptibility to certain infections, the potential seriousness of PSS and its possible very rapidly progressive and life-threatening course. They should be instructed to notify their physician of any acute febrile illness, especially if associated with rigors or systemic symptoms.[1,2,7,18,19,29] The different preventive strategies, as immunisation and the importance of re-vaccination, antibiotic prophylaxis and the need to carry 'stand-by' antibiotics, have to be discussed with the patients. Several investigators encourage patients to wear a medical alert bracelet or necklace and to carry a card documenting immunisation, any prophylactic antibiotics in use, and a plan for emergencies.[1,2,18,19,29,33] Patients should inform any new healthcare professionals, including dentists, of their asplenic or hyposplenic status.

Patients should be educated about the increased risk for travel-related infections, such as babesiosis. The importance of malarial prophylaxis and (simple) measures to reduce exposure to malaria parasites should be emphasised.[18,20] Asplenic patients travelling to sub-Saharan Africa, India and Nepal should receive the bivalent menigococcal (serogroups A and C) vaccine.[18] Patients should keep a therapeutic course of antibiotics with them during periods of travel, taking into account the regional resistance patterns of common pathogens.[1,18,20] Patients should be warned to seek prompt treatment of even a minor dog bite or other animal bite in view of the increased susceptibility to infection by *C. canimorsus*.[7,10,18,19,33]

## CONCLUSION AND RECOMMENDATIONS

Fulminant infection, such as postsplenectomy sepsis, is a major long-term risk in functional and anatomical asplenic patients. In consideration of the (recent) literature and the development of new vaccines we recommend a series of preventive measures for hyposplenic and asplenic patients. These are represented in *table 3*.

**Table 3**
*Recommendation for preventive measures in functional and anatomical asplenic patients*

| IMMUNISATION | AGE |
|---|---|
| Pneumococcal polysaccharide vaccine (PPV23)* | >2 years (*table 2*) |
| Pneumococcal conjugate vaccine (PCV7) | >2 months (*table 2*)<br><5 years |
| *Haemophilus influenzae* type b vaccine | >2 months |
| Meningococcal serogroup C conjugate vaccine | >2 months |
| Influenzae vaccine** | >6 months |
| **ANTIBIOTIC PROPHYLAXIS*** | |
| Daily antibiotic prophylaxis for the first two years after splenectomy in children | <18 years |
| 'Stand-by' antibiotics | All |
| **PATIENT EDUCATION** | All |

* *Revaccination: after five years (after three years for children <10 years of age at time of revaccination),* ** *revaccination: yearly,* *** *amoxicillin or claritromycin.*

## REFERENCES

1. Sumaraju V, Smith LG, Smith SM. Infectious complications in asplenic hosts. Infect Dis Clin North Am 2001;15(2):551-65.

2. Lutwick LI. Infections in asplenic patients. In: Principles and practice of infectious diseases. 5th edition. Mandell GL, Bennet JE, Dolin R (eds). Philadelphia: Churchchill Livingstone, 2000:3169-76.
3. Holdsworth RJ, Irving AD, Cushieri A. Postsplenectomy sepsis and mortality rate: Actual versus perceived risk. Br J Surg 1991;78:1031-8.
4. Morris DH, Bullock FD. The importance of the spleen in resistance to infection. Ann Surg 1919;70:513-21.
5. O'Donnel FJ. The value of splenectomy in Banti's disease. BMJ 1929;i:854.
6. King H, Schumaker HB jr. Splenic studies. I. Susceptibility to infection after splenectomy performed in infancy. Ann Surg 1952;136:239-42.
7. Brigden ML, Pattullo AL. Prevention and management of overwhelming postsplenectomy infection – An update. Crit Care Med 1999;27:836-42.
8. White KS, Covington D, Churchill P, Maxwell JG, Norman KS, Clancy TV. Patient awareness of health precautions after splenectomy. Am J Infect Control 1991;19(1):36-41.
9. Kinnersley P, Wilkinson CE, Srinivasan J. Pneumococcal vaccination after splenectomy: survey of hospital and primary care records. BMJ 1993;307(6916):1398-9.
10. Bridgen ML, Pattullo A, Brown G. Pneumococcal vaccine administration associated with splenectomy: The need for improved education, documentation, and the use of a practical checklist. Am J Hematol 2000;65:25-9.
11. Clancy TV, Ramshaw DG, Maxwell JG, et al. Management outcomes in splenic injury: A statewide trauma center review. Ann Surg 1997;226:17-24.
12. Jameson JS, Thomas WM, Dawson S, Wood JK, Johnstone JM. Splenectomy for haematological disease. J R Coll Surg Edinb 1996;41(5):307-11.
13. Corazza GR, Ginaldi L, Zoli G, et al. Howell-Jolly body counting as a measure of splenic function: A reassessment . Clin Lab Haematol 1990;12(3):269-75.
14. Hansen K, Singer DB. Asplenic-hyposplenic overwhelming sepsis: post-splenectomy sepsis revisited. Pediatr Dev Pathol 2001;4(2):105-21.
15. Pearson HA, Gallagher D, Chilcote R, et al. Developmental pattern of splenic dysfunction in sickle cell disorders. Pediatrics 1985;76(3):392-7.
16. Feder HM jr, Pearson HA. Assessment of splenic function in familial asplenia. N Engl J Med 1999;341:210-2.
17. Singer DB. Postsplenectomy sepsis. Perspective Paediatr Pathol 1973;1:285-311.
18. Working Party of the British Committee for Standards in Haematology Clinical Haematology Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. BMJ 1996;312:430-4.
19. Williams DN, Kaur B. Postsplenectomy care. Strategies to decrease the risk of infection. Postgrad Med 1996;100(1):195-8,201,205.
20. Lortan JE. Management of asplenic patients. Br J Haematol 1993;84:566-9.
21. Evans D. Post-splenectomy sepsis 10 years or more after operation. J Clin Path 1985;38:309-11.
22. Cullingford GL, Watkins DN, Watts AD, Mallon DF. Severe late post-splenectomy infection. Br J Surg 1991;78(6):716-21.
23. Walker W. Splenectomy in childhood: a review of cases in England and Wales 1960-4. Br J Surg 1976;63:36-43.
24. Styrt B. Infection associated with asplenia: Risks, mechanism, and prevention. Am J Med 1990;88(5N):33N-42N.
25. Kullberg BJ, Westendorp RG, Wout JW van 't, Meinders AE. Purpura fulminans and symmetrical peripheral gangrene caused by Capnocytophaga canimorsus (formerly DF-2) septicemia: A complication of dog bite. Medicine (Baltimore) 1991;70(5):287-92.
26. Zumla A, Lipscomb G, Corbett M, McCarthy M. Dysgonic Fermenter-type 2: an emerging zoonosis. Report of two cases and review. Q J Med 1988;68(257):741-52.
27. Workman MR, Philpott-Howard J, Bellingman AJ. Managing patients with an absent or dysfunctional spleen: Guidelines should highlight risk of Salmonella infection in sickle cell disease. BMJ 1996;312:1359-60.
28. Onwubalili JK. Sickle cell disease and infection. J Infect 1983;7:2-20.
29. Lynch AM, Kapila R. Overwhelming postsplenectomy infection. Infect Dis Clin North Am 1996;10(4):693-707.
30. Rosner F, Zarrabi MH, Benach JL, Habicht GS. Babesiosis in splenectomized adults. Review of 22 reported cases. Am J Med 1984;76(4):696-701.
31. Looareesuwan S, Suntharasamai P, Webster HK, Ho M. Malaria in splenectomized patients: report of four cases and review. Clin Infect Dis 1993;16(3):361-6.
32. Konradsen HB, Henrichsen J. Pneumococcal infections in splenectomized children are preventable. Acta Paediatr Scand 1991;80:423-7.
33. Davidson RN, Wall RA. Prevention and management of infections in patients without a spleen. Clin Microbiol Infect 2001;7:657-60.
34. ACIP. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1997;46(RR-8):1-24.
35. Haveman LM, Geelen SP, Sanders EA, Wolfs TF. Serious invasive pneumococcal disease in young children: the importance of vaccination. Ned Tijdschr Geneeskd 2002;146(41):1917-20.
36. Giebink GS, Le CT, Cosio FG, Spika JS, Schiffman G. Serum antibody responses of high-risk children an adults to vaccination with capsular polysaccharides of Streptococcus pneumoniae. Rev Infect Dis 1981;3(suppl):S168-78.
37. Siber GR, Gorham C, Martin P, Corkery JC, Schiffman G. Antibody response to pretreatment immunization and post-treatment boosting with bacterial polysaccharide vaccines in patients with Hodgkin's disease. Ann Intern Med 1986;104(4):467-75.
38. Sullivan JL, Ochs HD, Schiffman G, et al. Immune response after splenectomy. Lancet 1978;1(8057):178-81.
39. Pedersen FK, Nielsen JL, Ellegaard J. Antibody response to pneumococcal vaccine in splenectomized adults and adolescents. Acta Pathol Microbiol Immuno Scand 1982;90:257-63.
40. Caplan ES, Boltansky H, Schnyder MJ, et al. Response of traumatized splenectomized patients to immediate vaccination with polyvalent pneumococcal vaccine. J Trauma 1983;23(9):801-5.
41. Hosea SW, Burch CG, Brown EJ, Berg RA, Frank MM. Impaired immune response of splenectomised patients to polyvalent pneumococcal vaccine. Lancet 1981;1(8224):804-7.
42. Siber GR, Weitzman SA, Aisenberg AC, Weinstein HJ, Schiffman G. Impaired antibody response to pneumococcal vaccine after treatment for Hodgkin's disease. N Engl J Med 1978;299(9):422-8.

43. Lee HJ, Kang JH, Henrichsen J, et al. Immunogenity and safety of a 23-valent pneumococcal polysaccharide vaccine in healthy children and in children at increased risk of pneumococcal infection. Vaccine 1995;13(16):1533-8.
44. Ammann AJ, Addiego J, Wara DW, Lubin B, Smith WB, Mentzer WC. Polyvalent pneumococcal-polysaccharide immunisation of patients with sickle-cell anemia and patients with splenectomy. N Engl J Med 1977;297(17):897-900.
45. Foss Abrahamsen A, Hoiby EA, Hannisdal E, et al. Systemic pneumococcal disease after staging for Hodgkin's disease 1969-1980 without pneumococcal vaccine protection: A follow-up study 1994. Eur J Haematol 1997;58(2):73-7.
46. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy: an evaluation of current recommendations. JAMA 1993;270:1826-31.
47. Rutherford EJ, Livengood J, Higginbotham M, et al. Efficacy and safety of pneumococcal revaccination after splenectomy for trauma. J Trauma 1995;39(3):448-52.
48. Mufson MA. Antibody response of pneumococcal vaccine: need for booster dosing? Int J Antimicrob Agents 2000;14(2);107-12.
49. Nichol KL. Revaccination of high-risk adults with pneumococcal polysaccharide vaccine. JAMA 1999;281(3):280-1.
50. Weintrub PS, Schiffman G, Addiego JE jr, et al. Long-term follow-up and booster immunization with polyvalent pneumococcal polysaccharide in patients with sickle cell anemia. J Pediatr 1984;105(2):261-3.
51. Jackson LA, Benson P, Sneller VP, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. JAMA 1999;281(3):243-8.
52. ACIP. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2000;49(RR-9):1-35.
53. Eskola J. Immunogenicity of pneumococcal conjugate vaccines. Pediatr Infect Dis J 2000;19(4):388-93.
54. Black S, Shinefield H. Safety and efficacy of the seven-valent pneumococcal conjugate vaccine: evidence from Northern California. Eur J Pediatr 2002;161:S127-31.
55. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J 2000;19(3):187-95.
56. Health Council of the Netherlands. Universal vaccination against meningococcal serogroup C and pneumococcal disease. The Hague: Health Council of the Netherlands, 2001; publication no. 2001/27E.
57. Veenhoven R, Bogaert D, Uiterwaal C, et al. Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: a randomised study. Lancet 2003;361(9376):2189-95.
58. Ambrisono DM, Lee MY, Shamberger RC. Response to Haemophilus influenzae type B conjugate vaccination in children undergoing splenectomy. J Pediatr Surg 1992;27(8):1045-7.
59. Jakacki R, Luery N, McVerry P, Lange B. Haemophilus influenzae diphtheria protein conjugate immunization after therapy in splenectomized patients with Hodgkin Disease. Ann Intern Med 1990;112:143-4.
60. Cimaz R, Mensin C, D'Angelo E, et al. Safety and immunogenicity of a conjugate vaccine against Haemophilus influenzae type b in splenectomized and nonsplenectomized patients with Cooley anemia. J Infect Dis 2001;183(12):1819-21.
61. Rubin LG, Voulalas D, Carmody L. Immunogenicity of Haemophilus influenzae type b conjugate vaccine in children with sickle cell disease. Am J Dis Child 1992;146:340-2.
62. Ruben FL, Hankins WA, Zeigler Z, et al. Antibody response to meningococcal polysaccharide vaccine in adults without a spleen. Am J Med 1984;76:115-21.
63. Evans DI. Fatal post-splenectomy sepsis despite prophylaxis with penicillin and pneumococcal vaccine. Lancet 1984;1(8386):1124.
64. Brivet F, Herer B, Fremaux A, Dormont J, Tchernia G. Fatal post-splenectomy pneumococcal sepsis despite pneumococcal vaccine and penicillin prophylaxis. Lancet 1984;2(8398):356-7.
65. Koren A, Efrati Z, Algazi J, Katzuni E. Pneumococcal vaccine failure in a splenectomized child. Infect Control 1984;5(12):556.
66. Schlaeffer F, Rosenheck S, Baumgarten-Kleiner A, Greiff Z, Alkan M. Pneumococcal infections among immunised and splenectomised patients in Israel. J Infect 1985;10(1):38-42.
67. Klinge J, Hammersen G, Scharf J, Lutticken R, Reinert RR. Overwhelming postsplenectomy infection with vaccine-type Streptococcus pneumoniae in a 12-year-old girl despite vaccination and antibiotic prophylaxis. Infection 1997;25(6):368-71.
68. Shetty N, Aurora P, Rigway GL. Failure of anti-pneumococcal vaccine and prophylactic penicillin in a splenectomized patient. J Infect 1998;37(1):87-8.
69. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia: A randomized trial. N Engl J Med 1986;314:1593-9.
70. Makris M, Greaves M, Winfield DA, Preston FE, Lilleyman JS. Long-term management after splenectomy. Lifelong penicillin unproved in trials ... BMJ 1994;308(6921):131-2.
71. Finch RG, Read R. Long-term management after splenectomy. ... and may be ineffective. BMJ 1994;308(6921):132.
72. Bridgen ML. Detection, education and management of the asplenic or hyposplenic patient. Am Fam Physician 2001;63(3):499-506,508.

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ORIGINAL ARTICLE

# The StethoDop: a Doppler stethoscope attachment for investigation of arterial and venous insufficiency of the lower extremities

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## ABSTRACT

**Background: The aim of the current study was to investigate whether the StethoDop can serve as a valid and reproducible instrument for measuring the ankle-brachial index (ABI) and assessing venous reflux, even when used by inexperienced investigators, in comparison with the classic Doppler.**

**Methods: I) During four weeks, four ankle-brachial index (ABI) measurements were performed on 44 patients: one measurement with the classic Doppler by an experienced investigator, one with the classic Doppler by an inexperienced investigator and two measurements with the StethoDop by the inexperienced investigator. II) 36 patients were screened for venous insufficiency by detecting venous reflux with the StethoDop and classic Doppler at the saphenofemoral and saphenopoplitial junctions by an inexperienced investigator. The results were compared with the results of the duplex as gold standard and with the results of the examination by an experienced dermatologist with the classic Doppler.**

**Results: I) The confidence interval of ABI measurement for both the classic Doppler and the StethoDop by the inexperienced investigator was within an acceptable +/-0.21 interval of significant change. II) For venous reflux determination, the overall sensitivity and specificity of the StethoDop were comparable with the sensitivity and specificity of the classic Doppler: sensitivity 76.0 and 75.0%, specificity 94.8 and 94.2%, respectively. The positive predictive value of the StethoDop, compared with the duplex, was 87.5%; the negative predictive value was 90.0%.**

**Conclusion: I) For ABI measurement, the StethoDop is a valid instrument with reproducible results, even when used by inexperienced investigators. II) For venous reflux determination, the StethoDop is a valid screening instrument for venous insufficiency. However, as with determination with the classic Doppler, the reflux assessment by StethoDop gives no information about the deep veins and may miss up to 24% of apparent reflux.**

## INTRODUCTION

Doppler ultrasound is a simple and quick method to evaluate arterial and venous disease in a noninvasive manner. The ability of the Doppler ultrasound to study blood flow transcutaneously has been widely used. Recently a new Doppler device, called the StethoDop, became available. It is a compact 5 MHz Doppler, which can easily be attached to most standard stethoscopes. In addition to its small size, the StethoDop probe has a large surface and its crystals are placed at an optimal angle in the probe, which makes the StethoDop easy to use. The manufacturer claims that even inexperienced investigators can achieve valid and reproducible measurements.

The ankle-to-brachial index (ABI), the ratio of the ankle-to-arm systolic pressure, is widely used as a simple, noninvasive and objective measure of the severity of atherosclerotic peripheral arterial disease,[1] and used as a marker of cardiovascular disease.[2] The ABI is a valid, reproducible measurement, when performed with a

**Th. Thien was not involved in the handling and review process of this paper.

standard handheld Doppler device by experienced investigators;[3] however, small changes in time are not always clinically relevant. Previous studies have shown that an ABI can range from at least 0.15 to 0.21[4-7] before it should be considered as a clinically relevant and significant change. Doppler ultrasound is also a simple and quick way to noninvasively evaluate venous disease.[8,9] The handheld Doppler is routinely used in outpatient clinics of dermatology departments to confirm the presence of reflux at both the saphenofemoral and saphenopopliteal junctions. For this, the duplex (echo Doppler) investigation is considered to be the gold standard.[10] In previous studies the sensitivity of venous reflux in the saphenofemoral and saphenopopliteal veins, measured by handheld Doppler, varied between 54 and 92% and the specificity between 72 and 93%, respectively.[8,9,11]

The aim of this study was to investigate whether the StethoDop can perform as a valid instrument with reproducible results for measuring the ABI and assessing venous reflux by inexperienced investigators, in comparison with the gold standard for these determinations.

## METHODS

### Ankle-to-brachial index

Forty-four patients who were referred to the vascular laboratory of the University Hospital of Nijmegen for ABI measurement during one month participated in the study. ABI measurements were performed four times in each patient on the same day. The first measurement was performed with an 8 MHz (Imexdop CT+, USA) Doppler by an inexperienced investigator. This investigator only had one week of training at the vascular laboratory, performing ten ABI measurements supervised by an experienced vascular technician. Two measurements were performed with the StethoDop by the same inexperienced investigator. Another measurement was performed with the classic 8 MHz Doppler by an experienced vascular technician.
The ABI measurements were carried out in the vascular laboratory under identical standardised circumstances with one of two identical sets of equipment. The two investigators were unaware of each other's results. The patient was positioned supine for ten minutes before testing. During this time the symptoms of intermittent claudication, cardiovascular risk factors and medical history were evaluated using a questionnaire. A physical examination was performed for peripheral oedema and palpation of the arterial pulses.
The left and right brachial systolic blood pressure and the systolic blood pressure of the posterior tibial artery and the dorsal pedal artery at the left and right ankle were measured with a sphygmomanometer. The ABI for each limb was calculated as the higher of the two pedal artery systolic pressures divided by the higher brachial artery systolic blood pressure.

### Venous reflux

Altogether, 36 patients with symptoms of venous insufficiency participated in the study. These patients were all referred to the vascular laboratory or the outpatient clinic of the dermatology department of the University Medical Centre of Nijmegen (UMCN) in an eight-week period.
The clinical symptoms (varicosis, oedema, painful or tired legs) and medical history were evaluated using a questionnaire. The Doppler assessment of venous reflux was done with the patient in standing position. Venous reflux was determined at the saphenofemoral junction in the groins, medial to the femoral artery pinching the quadriceps. In addition, venous reflux was assessed at the saphenopopliteal junction in the back of the knee, lateral to the popliteal artery pinching and releasing the calf. An audible flow signal lasting for more than one second after releasing the muscle was used as the threshold for diagnosing significant reflux.
At the outpatient clinic of the dermatology department of the UMCN three measurements were performed: one assessment of venous reflux with a classic 8 MHz Doppler (Hadeco Minidop ES-100 VX, Japan) by an inexperienced investigator, one assessment of venous reflux with the 5 MHz StethoDop by the same inexperienced investigator, and one assessment of venous reflux with the classic 8 MHz Doppler by an experienced dermatologist. The investigators were unaware of each other's results. At the vascular laboratory the reflux was assessed by the inexperienced investigator with the StethoDop and these results were compared with the duplex, which was performed by an experienced vascular technician.

### Statistical methods

The mean difference and the 95% confidence interval of the difference between the ABI measurements were calculated and plotted according to the methods of Bland and Altman. With the duplex and reflux assessment performed by the experienced dermatologist with the classic Doppler as the gold standard, the sensitivity and specificity of the venous reflux assessments performed by the inexperienced investigator using the StethoDop and the classic Doppler were determined.

## RESULTS

### Ankle-brachial index

Of the 44 evaluated patients, 66% were male. The mean age was 61 years, range 40 to 83 years. Thirty-

three patients were referred with symptoms of intermittent claudication, eight patients were referred for postoperative control. The remaining three patients were referred for screening for atherosclerosis without symptoms. The prevalence of risk factors in the investigated population was smoking n=18 (41%), hypertension n=18 (41%), hypercholesterolaemia n=14 (32%) and diabetes mellitus n=6 (14%). For one patient, the ABI was measurable in just one leg, because the dorsal pedal artery was not compressible and the signal of the tibial posterior artery was not audible. The mean ABI measured by the vascular technicians was 0.87 (range 0.28-1.47).

The difference in ABI did not vary with mean ABI (*figures 1* and *2*). The mean difference between the measurements of the vascular technicians with the classic Doppler and those of the inexperienced investigator with the same classic Doppler was 0.013 with a 95% confidence interval of -0.17 to 0.20.

The mean difference between the measurements of the vascular technicians with the classic Doppler and those of the inexperienced investigator with the StethoDop was 0.020 with a 95% confidence interval of -0.16 to 0.20.

The mean difference between the two measurements of the inexperienced investigator with the StethoDop was -0.0077 with a 95% confidence interval of -0.16 to 0.15.

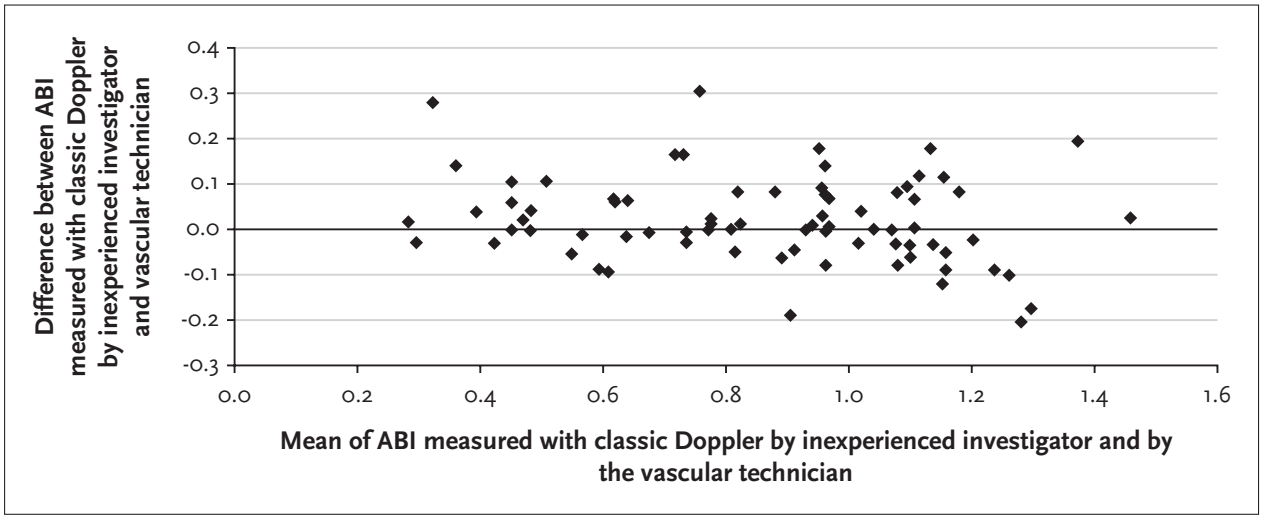


**Figure 1**

*Mean of ABI measured with the classic Doppler by the inexperienced investigator and by the vascular technician, plotted against the difference*

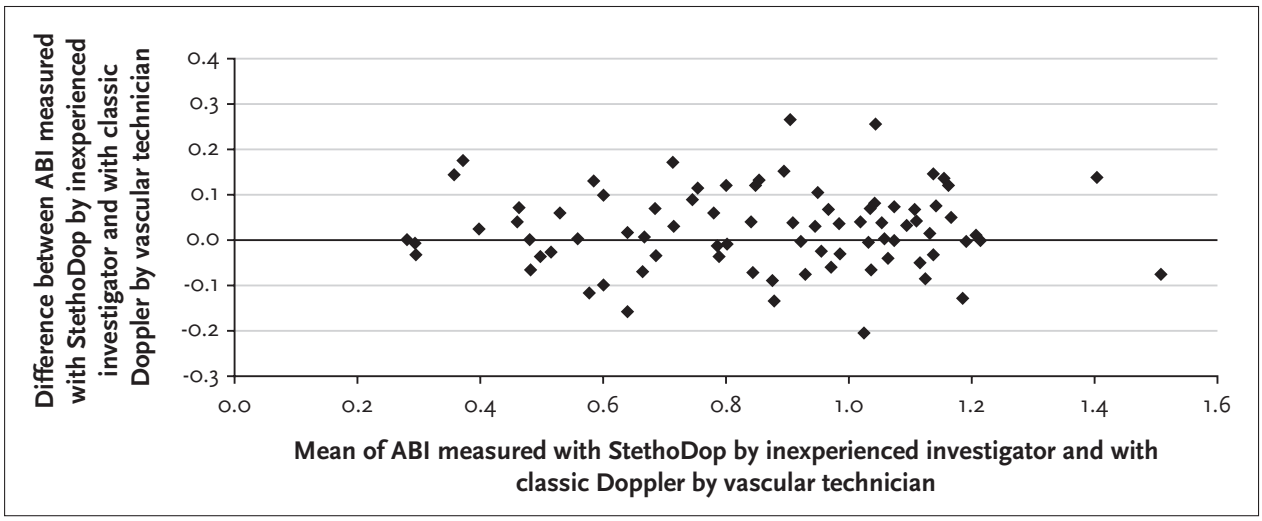


**Figure 2**

*Mean of ABI measured with StethoDop by inexperienced investigator and with classic Doppler by vascular technicians, plotted against the difference*

There was no relationship between the body mass index (BMI) and the difference in the measurements of the vascular technicians and the measurements with StethoDop or Doppler by the inexperienced investigator (r=0.139/0.180 right/left for StethoDop; r=0.113/0.186 right/left for Doppler).
Eight patients had peripheral oedema. Of these patients, in four measurements the difference between the ABI measured by vascular technicians and the ABI measured with Doppler by the inexperienced investigator was more than 0.15, where none of the StethoDop measurements differed more than 0.15.

**Venous reflux**
A total of 36 patients were evaluated: 27 female (75%) and 9 male (25%). The mean age was 49 years (range 23 to 82 years). Thirty-five patients had symptoms of venous insufficiency, 11 had suffered a deep venous thrombosis in the last five years. The reflux of all patients was examined with the StethoDop by the inexperienced investigator. In 18 patients the reflux was assessed with the classic Doppler by the inexperienced investigator and in 14 patients also by the dermatologist. Of 22 patients a duplex is done in one or both legs, depending on clinical presentation.

*Table 1* shows the sensitivity and specificity of the measurements by the inexperienced investigator with the StethoDop and classic Doppler (the measurements of the dermatologist or the duplex as gold standard), separated in the reflux assessments of the saphenofemoral and saphenopopliteal junctions. Overall, the sensitivity of the StethoDop was 76.0%, the specificity 94.8%. The overall sensitivity of the classic Doppler was 75.0%, the specificity 94.2%. The positive predictive value of the StethoDop, compared with the duplex, was 87.5%; the negative predictive value 90.0%.

## DISCUSSION

In the current study, we evaluated the clinical usability of a new Doppler instrument, the StethoDop. This study demonstrates that the StethoDop performed well for ABI measurements and for detecting venous reflux in the lower extremity and that it was easy to use.
Previous studies have shown that an ABI must change at least 0.15 to 0.21[4-7] before this change may be considered to be significant. In our study the mean difference between the measurements of the inexperienced investigator with the StethoDop and those of the vascular technicians with the classic Doppler was 0.020 and the 95% CI was -0.16 to 0.20. This confidence interval does not exceed the +/-0.21 interval of significant change. Therefore, the ABI measurements obtained with the StethoDop are not significantly different, even when performed by inexperienced investigators. However, the measurements of the inexperienced investigator with the classic Doppler are not significantly different either, since the 95% CI was -0.17 to 0.20. These results are even better than those in the study by Ray *et al.*, showing that ABI measurements by inexperienced investigators were not comparable with those of an experienced investigator. Furthermore, the StethoDop measurements are reproducible because the 95% CI of the two measurements with the StethoDop [-0.16 to 0.15] does not exceed the +/- 0.21 interval of significant change.
Therefore, it can be concluded that the StethoDop is validated for ABI measurement with reproducible results, even when obtained by inexperienced investigators. It can be used as an initial screening instrument for atherosclerotic peripheral arterial disease, although referral to a vascular laboratory is often necessary for an additional exercise test (walking test) or for determining the localisation of the obstruction.

**Table 1**
*Sensitivity and specificity of StethoDop and classic Doppler*

| LOCALISATION | DEVICE | CLASSIC DOPPLER, PERFORMED BY EXPERIENCED DERMATOLOGIST | DUPLEX, PERFORMED BY VASCULAR TECHNICIAN | OVERALL |
|---|---|---|---|---|
| Sapheno-femoral | StethoDop | Sensitivity: 66.7%<br>Specificity: 91.7% | Sensitivity: 69.2%<br>Specificity: 100% | Sensitivity: 68.8%<br>Specificity: 95.5% |
| Sapheno-femoral | Doppler | Sensitivity: 50.0%<br>Specificity: 82.4% | Sensitivity: 75.0%<br>Specificity: 100% | Sensitivity: 70.0%<br>Specificity: 87.5% |
| Sapheno-popliteal | StethoDop | Sensitivity: 100%<br>Specificity: 96.0% | Sensitivity: 83.3%<br>Specificity: 92.6% | Sensitivity: 88.9%<br>Specificity: 94.2% |
| Sapheno-popliteal | Doppler | Sensitivity: 66.7%<br>Specificity: 100% | Sensitivity: 100%<br>Specificity: 100% | Sensitivity: 83.3%<br>Specificity: 100% |
| Overall | StethoDop | Sensitivity: 83.3%<br>Specificity: 93.9% | Sensitivity: 73.7%<br>Specificity: 95.7% | Sensitivity: 76.0%<br>Specificity: 94.8% |
| Overall | Doppler | Sensitivity: 60.0%<br>Specificity: 91.2% | Sensitivity: 81.8%<br>Specificity: 100% | Sensitivity: 75.0%<br>Specificity: 94.2% |

Previous studies have shown a sensitivity of the reflux assessment by Doppler of 54 to 92%, which is frequently higher at the saphenopopliteal junction than at the saphenofemoral junction. The specificity was 72 to 93%. The results in this study with the StethoDop are comparable, with a varying sensitivity from 69.2% at the saphenopopliteal junction to 83.3% at the saphenofemoral junction. The specificity in our study was 100% at the saphenofemoral junction and 92.6% at the saphenopopliteal junction. The overall sensitivity and specificity of the StethoDop was similar to the sensitivity and specificity of the handheld Doppler device: sensitivity 76.0 and 75.0%, specificity 94.8 and 94.2%, respectively. The positive predictive value of the StethoDop compared with the duplex as the gold standard was 100% for the saphenofemoral junction and 71.4% for the saphenopopliteal junction. These values were calculated with a small number of patients, due to the low prevalence of reflux in our group of patients. The negative predictive value is more reliable, being calculated with a higher number of patients: 83.3% for the saphenofemoral junction and 96.2% for the saphenopopliteal junction.

These are acceptable results for a simple, noninvasive examination as the StethoDop reflux assessment. Moreover, the StethoDop has shown to be easy to use because of its small size, the big surface of the probe and the Doppler crystals already placed at an optimal angle. Therefore, the StethoDop seems to be suitable as a screening instrument for venous insufficiency. However, just as the classic Doppler, the reflux assessment by StethoDop gives no information about abnormalities of the deep veins. Furthermore, one may miss up to 24% of apparent reflux. Considering this, the duplex remains the reference measurement for venous reflux, although it may miss apparent refluxes.

In conclusion, in this study the StethoDop appeared to be a convenient instrument with valid and reproducible results for measuring the ABI and assessing venous reflux. Further studies in larger groups may strengthen the current results.

## REFERENCES

1. Yao ST, Hobbs JT, Irvine WT. Ankle systolic pressure measurements in arterial disease affecting the lower extremities. Br J Surg 1969;56:676-9.
2. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the cardiovascular health study. Circulation 1993;88:837-45.
3. Ray SA, Srodon PD, Taylor RS, Dormandy JA. Reliability of ankle: brachial pressure index measurement by junior doctors. Br J Surg 1994;81:188-90.
4. Baker JD, Dix D. Variability of doppler ankle pressures with arterial occlusive disease: an evaluation of ankle index and brachial-ankle pressure gradient. Surgery 1981;89:134-7.
5. Fowkes FGR, Hously E, Macintyre CCA, Prescott RJ, Ruckley CV. Variability of ankle and brachial systolic pressures in the measurement of atherosclerotic peripheral arterial disease. J Epidemiol Community Health 1988;42:128-33.
6. Stoffers HEJH, Kaiser V, Kester A, Schouten H, Knottnerus A. Peripheral arterial occlusive disease in general practice: the reproducibility of the ankle-arm systolic pressure ratio. Scan J Prim Health Care 1991;9:109-14.
7. Fisher CM, Burnett A, Makeham V, Kidd J, Glasson M, Harris JP. Variation in measurement of ankle-brachial pressure index clinical practice. J Vasc Surg 1996;24:871-5.
8. Campbell WB, Niblett PG, Ridler BMF, Peters AS, Thompson JF. Hand-held doppler as a screening test in primary varicose veins. Br J Surg 1997;84:1541-3.
9. Raju S, Fredericks R. Evaluation of methods for detecting venous reflux. Arch Surg 1990;125:1463-7.
10. Baker SR, Burnand KG, Sommerville KM, Lea Thomas M, Wilson NM, Browse NL. Comparison of venous reflux assessed by duplex scanning and descending phlebography in chronic venous disease. Lancet 1993;341:400-3.
11. Mercer KG, Scott DJA, Berridge DC, Weston M. Outpatient varicose vein assessment: hand-held doppler or duplex scanning? Br J Surg 1996;83:556-70.

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# Bluish-grey pigmentation of fingernails, gingiva, teeth and peri-oral region

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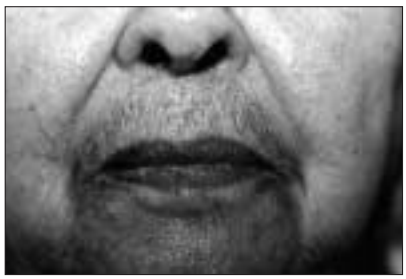
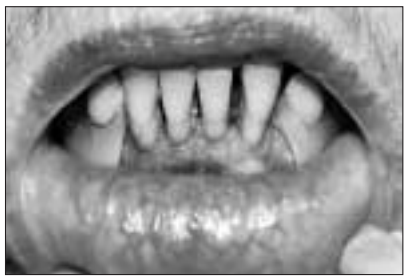
## CASE REPORT

A 70-year-old woman was evaluated because of a bluish-grey pigmentation around her mouth and fingernails. She had a medical history of rheumatoid arthritis and was treated parenterally with gold for one year in 1992 and with oral minocycline between 1997 and 2002. In the past she had smoked heavily. She stopped smoking in 1999. She did not have much sun exposure. The bluish-grey discoloration was first noticed in 1999 on her fingernails.
On physical examination she had a diffuse bluish-grey pigmentation of the nail bed of her fingers, the peri-oral region, the gingiva and at the proximal side of her four own teeth (*figures*).

## WHAT IS YOUR DIAGNOSIS?

See page 65 for the answer to this photo quiz.





**A colour version of this photo quiz can be found on our website www.njmonline.nl.**

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CASE REPORT

# Chylous ascites and chylothorax due to constrictive pericarditis in a patient undergoing haemodialysis

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## ABSTRACT

**Chylous ascites and chylothorax are rare clinical entities and usually caused by neoplasms, particularly lymphomas, liver cirrhosis, superior vena cava thrombosis, nephrotic syndrome, and some cardiac events such as dilated cardiomyopathy or right heart failure. Constrictive pericarditis is an extremely rare cause of this clinical state. We report a 41-year-old male patient undergoing haemodialysis who presented with chylous ascites and chylothorax. Echocardiography and heart catheterisation revealed constrictive pericarditis. He underwent pericardiectomy and after the operation the ascites and pleural effusion resolved rapidly. We suggest that constrictive pericarditis should be considered in the differential diagnosis of chylous ascites and chylothorax.**

## INTRODUCTION

Chylous ascites and chylothorax are rare clinical findings. Constrictive pericarditis rarely causes chylous ascites and chylothorax. To our knowledge there are only five cases in the literature presenting with chylous ascites due to constrictive pericarditis,[1-5] and only one presenting with chylothorax and recent-onset chylous ascites following thoracic band ligation.[6] We report a patient undergoing haemodialysis who developed chylous ascites and chylothorax, secondary to constrictive pericarditis.

## CASE REPORT

A 41-year-old male patient was admitted to our clinic with the symptoms of abdominal distension and dyspnoea continuing for seven months. He had been undergoing haemodialysis three times a week for two years. The cause of his chronic renal failure was chronic glomerulonephritis. Six months ago he was admitted to another clinic because of these symptoms and at that time chylous ascites and chylothorax were detected. He was given empirical antituberculosis therapy for six months without any response. On physical examination, his blood pressure was 75/40 mmHg, pulse 96 beats/min, and temperature 37°C. Jugular venous pressure was high. On pulmonary auscultation, respiratory sounds were decreased in bilateral lower lung fields. Heart sounds were also difficult to hear. Ascites was detected in the abdomen. Laboratory findings were as follows: Hb 8.5 g/dl, htc 25.4%, WBC 5000/mm$^3$, platelets 207,000/mm$^3$, C- reactive protein 0.96 mg/dl (N: 0-0.81), erythrocyte sedimentation rate 72 mm /h, urea 111 mg/dl, creatinine 6.50 mg/dl, AST 25U/l, ALT 32 U/l, lactate dehydrogenase (LDH) 265 U/l (N 225-450), glucose 102 mg /dl, total protein 7.4 g/dl, albumin 3.6 g/dl, amylase 75 U/l (N 25-125), cholesterol 176 mg/dl and triglycerides 83 mg/dl. The other laboratory findings were in normal ranges.

Abdominal ultrasonography (USG) and computerised tomography (CT) showed bilateral atrophic kidneys and massive intraperitoneal effusion. Thorax CT revealed bilateral pleural effusions, thickness of the pericardium with calcification (*figure 1*). No lymphadenopathy or mass was visible on abdominal and thorax CT.

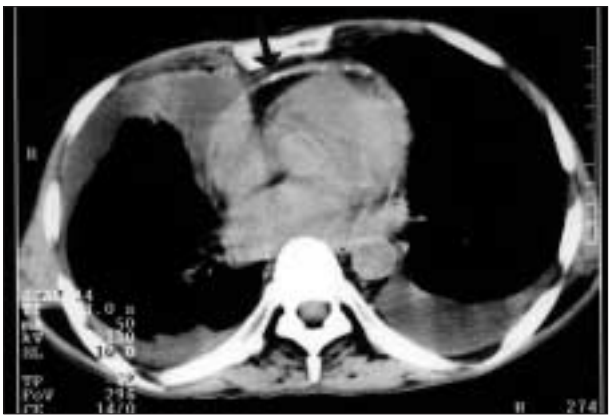

**Figure 1**
*A thorax computerised tomography imagination revealing bilateral pleural effusion, localised pleural effusion at the right paracardiac region, pericardial thickness and calcification (arrow), costal pleural thickness*

Paracentesis yielded a milky fluid with the following biochemical composition: triglycerides 405 mg/dl, cholesterol 85 mg/dl, total protein 4.7 g/dl, albumin 2. 7 g/dl, glucose 72 mg/dl and LDH 121 U/l. Cell count of the fluid was 600/mm$^3$. Thoracentesis also disclosed a milky fluid and laboratory studies were as follows: triglycerides 395mg/dl, cholesterol 95mg/dl, LDH 185 U/l, total protein 6.4 g/dl, albumin 2.56 g/dl, glucose 65 mg/dl and a count of cell 550/mm$^3$. Cytology and cultures, including mycobacterial, from peritoneal and pleural fluid were negative.
Transoesophageal echocardiography showed the thickness of the pericardium, pericardial effusion localised behind the right atrium and spontaneous echo contrast in the right atrium and ventricle. Ejection fraction was 60%. Right and left heart catheterisation revealed normal coronary arteries and left ventricular function. Haemodynamic findings were consistent with constrictive pericarditis.
The patient underwent pericardiectomy. Postoperatively ascites and pleural effusion gradually resolved over a three-week period, and his blood pressure returned to normal ranges. He felt well and no longer complained of dyspnoea and abdominal distension. The histopathological examination of the pericardial material revealed exudation of fibrin, lypomatosis, hyalinisation and calcification which shows chronic nonspecific inflammation. There were no granulomas or malignant infiltration. Cultures of pericardial fluid for mycobacterium and other agents were sterile. A specific cause for pericarditis could not be documented.

## DISCUSSION

Chylothorax and chylous ascites are rare clinical findings and characterised by milky peritoneal and pleural fluid from elevated triglycerides, which are most commonly caused by obstruction and disruption of the thoracic duct or one of its major divisions as a result of a malignant tumour, trauma or inflammation.[1,2,6] A milky appearance and a triglyceride level of more than 110 mg/dl generally confirm the diagnosis.[1,7] Neoplasms, particularly lymphoma, are the most common causes.[1,2] Liver cirrhosis, superior vena cava thrombosis, nephrotic syndrome and Behcet's disease have also been reported as the causes of chylous ascites.[1] Any cardiac cause of elevated right-sided venous pressure such as dilated cardiomyopathy, severe tricuspid regurgitation, constrictive pericarditis and right heart failure may also cause chylous ascites.[2,8] Abdominal and thoracic CT and fluid examination must be carried out to exclude a malignancy or inflammation in the fluid. Also a lymphangiogram can be done to demonstrate the site of obstruction of lymphatic flow.[1]
Constrictive pericarditis can rarely cause chylous ascites and chylothorax. To our knowledge, there are only five cases in the literature presenting with chylous ascites.[1-5] One of these cases also had liver cirrhosis.[4] And as we know, it is possible to develop chylous ascites and chylothorax with cirrhosis without constrictive pericarditis. In the English literature there is only one case of constrictive pericarditis presenting with chylothorax and chylous ascites following thoracic band ligation.[6] In this case, it is unclear whether the cause of the chylous ascites was thoracic duct ligation or constrictive pericarditis.[6]
The potential mechanisms for the development of chylous ascites and chylothorax resulting from constrictive pericarditis are the increasing effective capillary filtration secondary to central venous hypertension and reduced lymphatic drainage due to the high pressure in the left subclavian vein. Increased capillary filtration may result in excessive lymph formation.[1-3]
In our case, the patient presented with both chylous ascites and chylothorax and we detected constrictive pericarditis by thorax CT and echocardiography. The diagnosis was confirmed by left and right heart catheterisation. We could not show any other cause (malignancy, cirrhosis, thrombosis of superior or inferior vena cava, dilated cardiomyopathy and right heart failure) of the chylous ascites and chylothorax. Finally, following the pericardiectomy the rapid resolve of the ascites and pleural effusion made us conclude that the chylothorax and chylous ascites were secondary to constrictive pericarditis. Since the fluid resolved after the operation and the CT scans of abdomen and thorax did not reveal any masses that may cause lymphatic obstruction, a lymphatic scintigraphy and/or lymphangiography were not performed.
Constrictive pericarditis may occur when the healing of an acute fibrinous or serofibrinous pericarditis or a chronic pericardial effusion is followed by obliteration of the pericardial cavity with the formation of granulation

tissue.[9] The aetiology of constrictive pericarditis is usually unclear. Marta *et al*. reported this ratio as 42%.[10]
Tuberculosis is the most common known cause of this disorder. Also purulent infections, trauma, cardiac operation, mediastinal irradiation, histoplasmosis, neoplastic disease, acute viral or idiopathic pericarditis, rheumatoid arthritis, SLE, and chronic renal failure treated by chronic dialysis may result in constrictive pericarditis.[9]
The aetiology of constrictive pericarditis is unclear in patients with chylous ascites, except for the case reported by England *et al*. [2] In that patient, the author reported that pericarditis developed after cardiac surgery.
In our case the patient was first treated with antitubercular drugs for six months, but he did not respond to the therapy. Also histopathological examination of the pericardium revealed no granulomas. So, we could exclude tuberculosis as the cause of the pericarditis. The patient also had chronic renal failure and we know that it may be the main cause of this condition. Pericardial involvement in end-stage renal failure commonly manifests as an acute uraemic or dialysis pericarditis and less commonly as chronic constrictive pericarditis.[11] The clinical presentation of constrictive pericarditis in uraemic patients is similar to those observed in nonuraemic patients with less frequent chest pain in uraemics than nonuraemics.[11]
So, constrictive pericarditis should be considered in the differential diagnosis of chylous ascites and/or chylothorax.

## NOTE

In memory of a beloved friend and a perfect doctor, Sinan Auşar.

## REFERENCES

1. Guneri S, Nazlı C, Kinay O, Kirimli O, Mermut C, Hazan H. Chylous ascites due to constrictive pericarditis. Int J Card Imaging 2000;16:49-54.
2. England RW, Grathwohl KW, Powell GE. Constrictive pericarditis presenting as chylous ascites. J Clin Gastroenterol 2002;35:104-5.
3. Savage MP, Munoz SJ, Herman WM, Kusiak VM. Chylous ascites caused by constrictive pericarditis. Am J Gastroenterol 1987;82:1088-90.
4. Williams AT, Schneider RP. Chylous ascites should suggest constrictive pericarditis even in a patient with cirrhosis. J Clin Gastroenterol 1990;12:581-4.
5. Marshall JB, Pola L. Chylous ascites secondary to constrictive pericarditis. A discussion of pathophysiologic mechanism. Dig Dis Sci 1982;27:84-7.
6. Motta G, Vianello F, Pietrogrande F. Chylothorax as the first manifestation of constrictive pericarditis. Am J Med 2003;114:772-3.
7. Romero S. Nontraumatic chylothorax. Curr Opin Pulm Med 2000;6:287-91.
8. Villena V, Pablo A de, Martin-Escribano P. Chylothorax and chylous ascites due to heart failure. Eur Respir J 1995;8:1235-6.
9. Braunwald E. Pericardial disease. In: Fauci AS, Braunwald E, Isselbacher KJ, et al (eds). Harrison's Principles of Internal Medicine. International Edition. Mc Graw-Hill, 1998;1:1334-40.
10. Marta MJ, Oliviera A, Varela MG, Saavedra JA, Ravara L. Constrictive tuberculous pericarditis: case report and review of the literature. Rev Port Cardiol 2003;22:391-405.
11. Alpert MA, Ravenscraft MD. Pericardial involvement in end-stage renal disease. Am J Med Sci 2003;325(4):228-36.

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CASE REPORT

# Interstitial pneumonia and hepatitis caused by minocycline

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## ABSTRACT

**A 28-year-old patient is described who presented with progressive dyspnoea and jaundice due to interstitial pneumonia and hepatitis. The most likely cause is a drug-related reaction to minocycline. We discuss the different kinds of drug-related reactions that are most likely involved.**

## INTRODUCTION

Minocycline is a semisynthetic tetracycline widely used for the treatment of acne vulgaris and for treatment of infections. A variety of mild adverse reactions have been described. Among these, light-headedness in women is most prominent. In addition, photosensitivity, various rashes, fever, hyperpigmentation, nausea and weakness have been reported.
More serious immunological adverse reactions include serum sickness-like syndrome and other hypersensitivity reactions, drug-induced lupus, autoimmune hepatitis, pneumonitis and vasculitis.[1-4]
We describe a patient who developed hepatitis and severe dyspnoea while on treatment with minocycline for severe acne vulgaris.

## CASE REPORT

A 28-year-old Caucasian man was admitted to our hospital because of progressive dyspnoea and jaundice. He had a six-week history of abdominal symptoms after a flu-like episode with gradual onset of jaundice. After one week, progressive dyspnoea developed. He complained of severe exertional dyspnoea and orthopnoea. He suffered from a weight loss of 16 kg in a six-week period. There was no history of fever, rash or arthralgia. The patient denied intravenous drug abuse, although he admitted to occasionally using speed, cocaine and XTC. There was no history of changing sexual contacts, nor had he received a blood transfusion. He had lived in the Caribbean for three years, until five years ago. There was no history of recent travel. The medical history revealed an infectious mononucleosis years ago and acne vulgaris, for which the patient had been taking minocycline 100 mg once a day for the last two years.
On examination we saw an ill-looking, weakened and deeply jaundiced patient with a respiratory rate of 40-45/min, temperature 37.8°C, pulse rate of 72 beats/min and BP 110/80 mmHg. Chest auscultation revealed crackles over the lower lung fields. There were no palpable masses in the abdomen. A chest radiograph revealed diffuse small sized consolidations in both lungs (*figure 1*). Abdominal ultrasonography revealed a normal liver with no signs of portal thrombosis; the spleen was slightly enlarged at a length of 12 cm.
Laboratory evaluation showed a WBC of 7.4 x $10^9$/l with 0.2 x $10^9$/l eosinophils. Liver function tests were abnormal: alanine transaminase 523 U/l (normal <25); aspartate transaminase 311 U/l (normal <20); γ-glutamyl transferase 109 U/l (normal <45); alkaline phosphatase 156 U/l (normal 30-90); total bilirubin 161 umol/l (normal <16); conjugated bilirubin 123 umol/l (normal <4.5). The prothrombin time (PT) and activated partial thromboplastin time

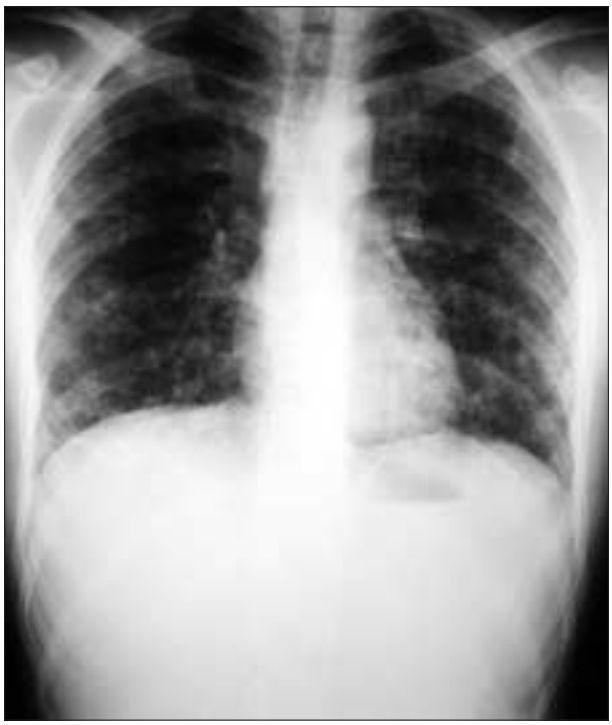

**Figure 1**
*Chest radiograph on admission with diffuse small sized consolidations in both lungs*

(APTT) were normal. The erythrocyte sedimentation rate was 22 mm/h with a C-reactive protein of 12 mg/l. The kidney function was normal. The test for antinuclear antibody (ANA) was negative. The antineutrophil cytoplasmatic autoantibody (ANCA) test showed an atypical pattern with no antibodies against proteinase 3 and myeloperoxidase. Complement studies showed a normal C3 and slightly increased C4 of 489 (normal 120-360 mg/l). There were negative serological test results for hepatitis A, B, C, EBV and CMV. The HIV status was negative. Serological tests against *Legionella* species, influenza virus, parainfluenza virus, RS virus, *Mycoplasma pneumoniae*, adenovirus, coxsackie B5, *Chlamydia psittaci* and *Coxiella burnetii* were also negative.
On admission arterial blood gas analysis without oxygen showed a $pO_2$ of 57 mmHg, $pCO_2$ of 35 mmHg, pH of 7.45, $HCO_3$ of 24 mmol/l, a base excess of 1.1 and an oxygen saturation of 91%. Because of the unclear diagnosis and the severe clinical condition of the patient, we decided to perform an open lung biopsy under anaesthesia; thereafter, the patient was transferred to the intensive care unit for further ventilatory support for six days. Cultures from the lung biopsy material were negative for viruses, including CMV, and bacteria, including *Mycobacterium tuberculosis*, *Legionella* species, *Mycoplasma* and *Pneumocystis carinii*. Histology revealed a diffuse interstitial dense infiltration with lymphocytes, but no eosinophils, with thickening of

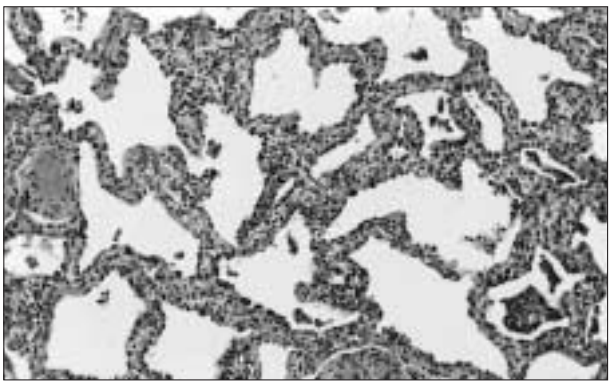

**Figure 2**
*Histology of lung biopsy: interstitial infiltration of lymphocytes with thickening of the alveolar septa*

the alveolar septa by oedema. Some fibroblast plugs, macrophages and foam cells were observed. No granulomas were seen. Furthermore there were some signs of organising pneumonia, as can be seen in association with a bronchiolitis obliterans organising pneumonia (BOOP) (*figure 2*).
After having excluded a variety of infectious causes, we concluded that the most likely diagnosis was a hypersensitivity reaction possibly related to the minocycline. There were no signs of malignancy, nor was another toxic agent likely to be responsible. The drug was stopped on admission. The patient was treated with prednisolone 60 mg iv once a day and was switched to prednisolone 60 mg orally once a day after three weeks. Within one month there was a gradual recovery with resolving of the dyspnoea and normalisation of the liver tests and arterial blood gas analysis. The chest radiograph was unchanged with interstitial infiltrates still present. On discharge the prednisolone dose was 40 mg daily and was thereafter slowly tapered. During his stay on the ward the patient suffered from hallucinations for a short period of time, which recovered after medication prescribed by the psychiatrist.

## DISCUSSION

Serious adverse effects, as in this patient, have been described with minocycline. These usually concern young, otherwise healthy people to whom minocycline is prescribed because of acne vulgaris. Our patient suffered from hepatitis and severe dyspnoea due to pulmonary infiltrates.

Various forms of minocycline-induced hepatic injury have been described. One form is a direct dose-related hepatotoxic effect, also described with tetracycline.[5] On liver biopsy, it looks like microvesicular steatosis. A second

form is fulminant hepatic failure as part of an allergic idiosyncratic reaction, requiring liver transplantation.[6] A third form is considered an autoimmune hepatitis, which is characterised by fever, arthralgia, rash, elevated transaminases, positive ANA antibodies and elevated immunoglobulins. Liver biopsy shows chronic active hepatitis.[7-9] Our patient did not have a history of rash or arthralgia, nor did he have positive ANA antibodies. Although a direct hepatotoxic effect is possible, resolution of the damage with glucocorticoid therapy would not be expected. A liver biopsy would have made the diagnosis more accurate, but was not performed.
Hepatic injury due to minocycline has also been described due to a hypersensitivity reaction, which usually occurs two to four weeks after the start of minocycline treatment. It is characterised by fever, rash and internal organ involvement, usually hepatic injury, although pulmonary, haematological, or renal impairment may occur. This reaction may be life-threatening and is thought to be caused by a reactive metabolite of minocycline.[1,4,10]

Severe dyspnoea and bilateral pulmonary infiltrates may also occur as part of the same hypersensitivity reaction. It is accompanied by blood eosinophilia and/or pulmonary eosinophilia, although in some cases as our patient, the eosinophilia is absent. In most cases there is also an elevated IgE level. On chest radiography it typically gives biapical subpleural opacities, but infiltration can develop anywhere.[11-15] T lymphocytes are thought to play an important role in the pathogenesis of drug-induced hypersensitivity pneumonitis.[16] Alternatively, pulmonary infiltrates can be caused by minocycline-induced lupus, but in our patient there were no antinuclear antibodies.[17,18]

Our patient was on treatment with minocycline for two years when he first developed jaundice followed by severe progressive dyspnoea. It is tempting to speculate about an immunological pathogenesis of the hepatitis and pulmonary infiltrates. The prolonged exposure to minocycline or a metabolite may have been the trigger. The patient did not fulfil the criteria of drug-induced lupus and it is unclear whether there was a response to steroids. The combination of liver and pulmonary involvement would fit a hypersensitivity reaction. This is more commonly seen after a short period of minocycline treatment, although reactions have developed after a more prolonged period.[14]
Severe drug-related reactions may pose a difficult diagnostic problem especially in patients under treatment for a longer period of time. Recognition of the drug-related reaction and adequate management are essential for such a potentially life-threatening event.

## REFERENCES

1. Elkayam O, Yaron M, Caspi D. Minocycline-induced autoimmune syndromes: an overview. Semin Arthritis Rheum 1999;28:392-7.
2. Elkayam O, Levartovysky D, Brauthar C, et al. Clinical and immunological study of 7 patients with minocycline-induced auto-immune phenomena. Am J Med 1998;105:484-7.
3. Hoefnagel JJ, Leeuwen RL van, Mattie H, Bastiaens MT. Bijwerkingen van minocycline in de behandeling van of acne vulgaris. Ned Tijdschr Geneeskd 1997;141(29):1424-7.
4. Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by Minocycline. Report of 13 patients and review of the literature. Arch Dermatology 1996;132:934-9.
5. Burette A, Finet C, Prigogine T, Roy G de, Deltenre M. Acute hepatic injury associated with Minocycline. Arch Intern Med 1984;144:1491-2.
6. Pohle T, Menzel J, Domschke W. Minocycline and fulminant hepatic failure necessitating liver transplantation. Am J Gastroenterol 2000;95(2):560-1.
7. Gough A, Chapman S, Wagstaff K, Emery P, Elias E. Minocycline induced auto-immune hepatitis and systemic lupus erythematosus-like syndrome. BMJ 1996;312:169-72.
8. Teitelbaum JE, Perez-Atayde AR, Cohen M, Bousvaros A, Jonas MM. Minocycline-related autoimmune hepatitis: case series and literature review. Arch Pediatr Adolesc Med 1998;152:1132-6.
9. Tomer G, Shneider BL. Minocycline-induced hepatitis. J Pediatr Gastroenterol Nutr 2000;30:105-6.
10. Angulo JM, Sigal LH, Espinoza LR. Coexistent Minocycline-induced systemic lupus erythematosus and autoimmune hepatitis. Semin Arthritis Rheum 1998;28:187-92.
11. Bridges AJ. Minocycline-induced pneumonia. Ann Intern Med 1993;118:749-50.
12. Dykhuizen RS, Zaidi AM, Godden DJ, Jegarajah S, Legge JS. Lesson of the week: Minocycline and pulmonary eosinophilia. BMJ 1995;310:1520-1.
13. Horikx PE, Gooszen HCh. Minocycline als oorzaak van acute eosinofiel pneumonie. Ned Tijdschr Geneeskd 1992;136:530-2.
14. Sigmann P. Minocycline-induced pneumonia. Ann Intern Med 1993;118:750.
15. Sitbon O, Bidel N, Dussopt C, et al. Minocycline pneumonitis and eosinophilia; a report on eight patients (Evaluation). Arch Intern Med 1994;154:1633-8.
16. Guillon J-M, Joly P, Autran B, et al. Minocycline-induced cell-mediated hypersensitivity pneumonitis. Ann Intern Med 1992;117:476-81.
17. Ghristodoulou CS, Emmanuel P, Ray RA, Good RA, Schnapf BM, Cawkwell GD. Respiratory distress due to Minocycline-induced pulmonary lupus. Chest 1999;115:1471-3.
18. Matsuura T, Shimizu Y, Fujimoto H, Miyazaki T, Kano S. Minocycline-relates lupus. Lancet 1992;340:1553.

## ANSWER TO PHOTO QUIZ (ON PAGE 58)

## BLUISH-GREY PIGMENTATION OF FINGERNAILS, GINGIVA, TEETH AND PERI-ORAL REGION

### DIAGNOSIS

The bluish-grey hyperpigmentation was caused by minocycline. Patients undergoing minocycline therapy may develop a blue-grey appearance in sun-exposed areas in addition to pigmentation of the mucous membranes, teeth, nails, bones and thyroid. The diffuse hyperpigmentation results from complexes containing melanin or hemosiderin and minocycline and does not appear to be dose-dependent. The mechanism is still unclear. Hyperpigmentation of the skin and oral mucosa usually resolves within months to years after discontinuation of therapy. The hyperpigmentation is often permanent when other sites (such as adult teeth) are involved. Although minocycline-induced hyperpigmentation is not harmful, the drug should be discontinued when this adverse effect is recognised.[1]

This bluish-grey hyperpigmentation is to be distinguished from the skin discoloration that can be seen by treatment with gold, called chrysiasis. In such cases, it is characteristic that initially the peri-orbital region is affected by a mauve appearance that intensifies and deepens into a blue-grey colour, while extending to involve the face, neck and upper limbs. The hyperpigmentation is permanent. It is accentuated in sun-exposed areas and by smoking and caused by deposits of gold in the dermis.[2,3]

### REFERENCES

1. Morrow GL, Abbott RL. Minocycline-induced scleral, dental and dermal pigmentation. Am J Ophtalmol 1998;125(3):396-7.
2. Miller ML, Harford RR, Yeager JK, Johnson F. A case of chrysiasis. Cutis 1997;59(5):256-8.
3. Smith RW, Leppard B, Barnett NL, Millward-Sadler GH, Mc Crae F, Cawley ML. Chrysiasis revisited: a clinical and pathological study. Br J Dermatol 1995;133(5):671-8.

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# Pneumococcal vaccination for healthy elderly: a comment

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## INTRODUCTION

**In contrast to many other Western countries there is still a debate in the Netherlands about whether pneumococcal vaccination is of benefit for healthy elderly people. In 1982 the Health Council of the Netherlands issued a report on this subject and concluded that there was no scientific background for vaccinating people only based on age over 65 years.[1] In the meantime pneumococcal vaccination for the elderly has been introduced in a number of Western countries and this was the reason for preparing a new report within the Health Council.[2]**

Pneumococcal vaccination was introduced before the Second World War.[3] Vaccination has been very successful in younger populations with healthy individuals living in special conditions with a high incidence of pneumococcal disease, such as young miners in South Africa and people living in the highlands of New Guinea.[4] Later on, there appeared to be more difficulties in elderly people and people with conditions influencing their immune status. Early vaccine was based on 2-4 pneumococcal serotypes. Later 6-13 and 14-valent vaccines were developed. At this moment, 23-valent polysaccharide vaccines are mainly used. For children a special vaccine has been developed with an antigen conjugated to protein. A 7-valent conjugate vaccine is currently being used. It will probably not be possible to develop a more than 10-valent vaccine in the near future.
After vaccination, protection against infection starts after two to three weeks. The duration of the protection is uncertain. In healthy adults, antibody is present up to five years after vaccination.

Local erythema and pain at the site of injection occur frequently.[5] Systematic reactions are rare. These side effects are more frequent in patients who have had a pneumococcal vaccination with an earlier vaccination within three years and in patients with a history of a pneumococcal infection during the three years before the vaccination.[6]

Pneumococcal vaccination is often combined with vaccination against influenza. The latter is given each year, pneumococcal vaccination every five years. There is no problem in giving both vaccinations at the same time if different injection sites are used.
It could be that adding pneumococcal vaccination to the regular vaccination against influenza in the Netherlands would lower the adherence to the influenza vaccination programme. Opstelten and colleagues did a pilot study in Dutch general practices and found no significant decline in the number of older patients coming for their yearly flu vaccinations.[7]

## SPECIAL INDICATIONS FOR PNEUMOCOCCAL VACCINATION

A small but important group of patients that is at high risk for serious pneumococcal disease is the group of patients without a (functional) spleen.[8] The number of asplenic patients in the Netherlands is unknown, but every year approximately 1000 splenectomies are performed after a trauma or due to disease. One out of 20 asplenic patients will have a life-threatening infection once in

their lives. More than 50% of these patients will die due to these infections within two days after the first symptoms.[9]
In the earlier advice of the Dutch Health Council in 1982 pneumococcal vaccination was pressingly recommended for asplenic patients. Revaccination should take place every five years. Besides pneumococcal vaccinations these patients should have antibiotics available to take in cases of fever.[8]
Pneumococcal vaccination is also recommended for patients with sickle-cell anaemia who can have afunctional spleen function due to multiple spleen infarctions and patients with leakage of cerebrospinal fluid.
Vaccinations should be considered for patients with Hodgkin's and non-Hodgkin's lymphoma disease, patients with HIV, myeloma, chronic lymphatic leukaemia, auto-immune disease, renal disease, alcoholism, cirrhosis and patients receiving immunosuppressants or recipients of transplants of organs or bone marrow.

## IMPLEMENTATION OF INFLUENZA VACCINATION IN THE ELDERLY

In the Netherlands, vaccination against influenza has been implemented successfully. Before 1994, influenza vaccination was only recommended for patients at high risk. Vaccination was carried out in patients with chronic lung disease, diabetes and chronic heart disease. Most vaccinations were given by GPs. However, there was no structured programme to identify all patients at risk and to invite them to receive their vaccinations. In 1994 the Minister of Health advised vaccinating all persons of 65 years and older. A national programme was introduced to help GPs to identify patients at risk using their computer systems. A reasonable imbursement was given to all GPs involved. In the following years, the vaccination rate increased to up to 76% of the patients at risk in 2000.[10] In that year 17.1% of the total population in the Netherlands was vaccinated.

## EVIDENCE FOR THE EFFICACY OF PNEUMOCOCCAL VACCINATION

The ideal way to prove that pneumococcal vaccination gives protection against death or serious morbidity due to pneumococcal disease would be the randomised clinical trial (RCT). To address the question as to whether pneumococcal vaccination should be introduced in the Netherlands for otherwise healthy persons of 65 years and older together with a vaccination against influenza, there is only one RCT that can be used for this special population.[11] In this study only a subgroup of patients with other related risk factors had benefit from pneumococcal vaccination. Assendelft and co-workers of the Dutch Cochrane Centre performed an assessment of the available literature. In this issue of this journal they report their results with their conclusions that there is insufficient convincing evidence in favour of the introduction of the pneumococcus vaccination as a supplement to the influenza vaccination for healthy persons 65 years of age or older.[12]
This does not mean that it is proven that pneumococcal vaccinations have no benefit. There still is circumstantial evidence that there are benefits. In a recent large retrospective cohort study with almost 50,000 patients there was a reduction in the risk of pneumococcal bacteraemia (hazard ratio 0.56 (0.33 - 0.93)) although there was a small increase in the number of patients who needed hospitalisation for pneumonia.[13] Only a large randomised controlled trial in this special population using the right endpoints can be conclusive.
Now discussion becomes a question of belief. Do we harm a number of people when we do not vaccinate them or are we using our energy and money for the wrong purpose?
In many countries there are official recommendations for pneumococcal vaccination of the elderly.[14] Therefore in these countries placebo-controlled studies are hardly possible due to ethical considerations.
In the United States an 18% decline in the number of cases of invasive pneumococcal disease in people older than 65 years of age has recently been reported.[15] This might be due to the introduction of the conjugate pneumococcal vaccine for children (herd immunity), but these ideas are not based on data.[16]

## THE HEALTH COUNCIL REPORT 2003

Based on the results of the meta-analysis of the Dutch Cochrane Centre and after numerous and extensive deliberations the Health Council of the Netherlands decided that there is no conclusive evidence for the effectiveness of pneumococcal vaccination in addition to influenza vaccination in healthy persons 65 years or older.[2] The council recommended starting a prospective study in the Netherlands with healthy elderly vaccinated for influenza who are randomised to receive an additional pneumococcal vaccination. The results of this study or comparable studies could provide the argument to make new recommendations.
The success of the influenza vaccination programme in the Netherlands performed in general practice shows that if enough evidence does become available for pneumococcal vaccination in the future, general practice will be the best place to execute this additional vaccination programme.

## NOTE

Professor Van den Bosch was a member of the Committee of the Health Council of the Netherlands that prepared the recent report on pneumococcal vaccination.[2]

## REFERENCES

1. Gezondheidsraad. Advies inzake pneumococcen-immunisatie. The Hague 1082/14.
2. Gezondheidsraad. Vaccinatie tegen pneumokokken bij ouderen en risicogroepen (Pneumococcal vaccination for elderly and people at risk). The Hague 2003/10.
3. Kaufman P. Pneumonia in old age; active immunization against pneumonia with Pneumococcus Polysaccharide; results of a 6-year study. Arch Intern Med 1947;79:518-31.
4. Austrian R, Douglas RM, Schiffman, G, et al. Prevention of pneumococcal pneumonia by vaccination. Trans Assoc Am Physicians 1976;89:184-94.
5. Anonymous. Prevention of pneumococcal disease. Recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep 1997;46(RR08):1-24.
6. Sankilampi U, Honkanen PO, Pyhälä R, et al. Association of pre-vaccination antibody levels with adverse reaction to pneumococcal and influenza vaccines administered simultaneously in the elderly. Vaccine 1997;15:1133-7.
7. Opstelten W, Hak E, Verheij TJ, Essen GA van. Introducing a pneumococcal vaccine to an existing influenza immunization program: vaccination rates and predictors of noncompliance. Am J Med 2001;111:474-9.
8. Melles DC, Marie S de. Prevention of infections in hyposplenic patients: an update. Neth J Med 2004;62:45-52.
9. Lynch AM, Kapila R. Overwhelming postsplenectomy infection. Infect Dis Clin North Am 1996;10:693.
10. Koivula I, Sten M, Leinonen M, et al. Clinical efficacy of pneumococcal vaccine in the elderly: a randomized, single blind population-based trial. Am J Med 1997;103:281-90.
11. Assendelft WJJ, Scholten RJPM, Offringa M. Pneumococcal vaccination for the elderly in the Netherlands: assessment of the quality and content of available comparative studies. Neth J Med 2004;62:36-44.
11. Tacken M. LINH data. Influenza vaccination 2000. Huisarts Wet 2002;45:5.
12. Jackson JA, Neuzil KM, Onchee YU, et al. Effectiveness of pneumococcal polysaccaride vaccine in older adults. New Engl J Med 2003;348:1747-55.
13. Whitney CG. Preventing pneumococcal disease. ACIP recommends pneumococcal polysaccharide vaccine for all adult age > or = 65. Geriatrics 2003;58:20-2.
14. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. New Engl J Med 2003;348:1737-46.
15. Edwards KM, Griffin MR. Great expectations for a new vaccine. New Engl J Med 2003;349:1312-4.

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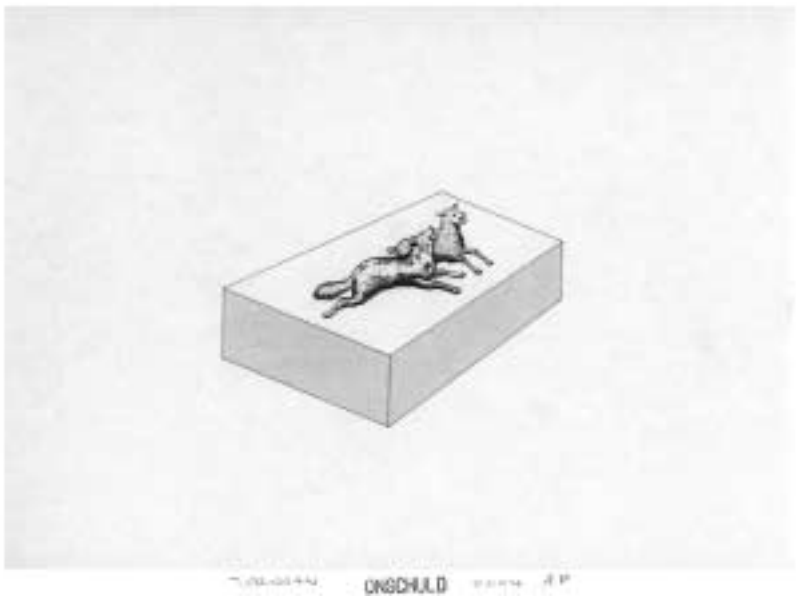
# 'Onschuld'

**Peter Jordaan**




'Onschuld' is a silk-screen printing made by Peter Jordaan, who lives and works in Arnhem. As designing artist, Peter Jordaan (1954) works in the fields of drawing and graphic art. His work is a mixture of recognition and severity. Identifiable in imagination and severe in emptiness and use of colours.

The artist is currently showing his work together with Ad Gerritsen, Rinke Nijburg and Cees Andriessen at the Henriette Polak Museum in Zutphen in an exposition entitled 'G schrijft vreemde brieven'. This exposition is part of a series of group exhibitions being held in Germany, Denmark and Norway. Besides his work as an artist, he has just finished a study in partnership with Marjolein de Groen on the feasibility of a centre for artists in Gelderland where art can meet science.

A limited edition (20) of this original silk-screen print, size 22 x 30 cm, is available at a price of € 150.

The prints are all numbered and signed. You can order the print at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands, by e-mail: galerie-unita@planet.nl or see the internet site: www.galerie-unita.com.

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