Bundesgesundheitsbl 2016 · 59:1623–1657
DOI 10.1007/s00103-016-2466-9

G. Falkenhorst[1] • C. Remschmidt[1] • T. Harder[1] • O. Wichmann[1] • S. Glodny[1] • E. Hummers-Pradier[2] • T. Ledig[3] • C. Bogdan[4]

[1]Immunization Unit, Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany

[2]Department of General Practice, University Medical Center Göttingen, Göttingen, Germany

[3]Medical Practice, Ditzingen, Germany

[4]Mikrobiologisches Institut – Klinische Mikrobiologie, Immunologie und Hygiene, Friedrich Alexander Universität (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany

Background paper to the updated pneumococcal vaccination recommendation for older adults in Germany

In consideration of new data and the availability of an additional vaccine for adults, the German Standing Committee on Vaccination (STIKO) has updated its recommendation for the routine vaccination of older adults against pneumococcal diseases.

Updated recommendation

Routine vaccination is recommended for all adults from the age of 60 years. Vaccination shall be given with a vaccine of the greatest possible efficacy against the pneumococcal serotypes currently causing disease in the target group; this is currently the 23-valent polysaccharide vaccine (PPSV23).

In principle, because of the limited duration of protection provided by the vaccine, STIKO considers repeated vaccinations with PPSV23 useful from a medico-epidemiological perspective. The current prescribing information specifies that "healthy adults should not routinely be re-vaccinated", i. e. routine re-vaccination is not covered by the market authorization. However, according to the prescribing information "re-vaccination may be considered for persons at increased risk for severe pneumococcal disease". In this case STIKO recommends a minimum interval of 6 years between vaccine doses.

Seniors who belong to one of the risk groups listed in table 2 of the STIKO recommendations because of a chronic condition (category "I") or because of occupational exposure (category "B") should be vaccinated according to the specific recommendations for these groups.

Seniors who have already been vaccinated with the 13-valent conjugate vaccine (PCV13) should receive a follow-up vaccination with PPSV23 6–12 months after PCV13 to expand serotype coverage.

The objective of the vaccination recommendation is to reduce the number of cases of invasive pneumococcal disease and pneumococcal pneumonia and their consequences, such as hospitalization, disability, and death among older adults in Germany.

This report is a translation of the original publication in German language in Epidemiologisches Bulletin 36/2016, available at http://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2016/36/Art_01.html

Eva Hummers-Pradier, Thomas Ledig, Christian Bogdan are members of the German Standing Committee on Vaccination (STIKO).

Summary

Background and objective
The incidence of pneumococcal diseases among adults increases with age. Therefore, Germany's Standing Committee on Vaccination (Ständige Impfkommission, STIKO) has since 1998 recommended vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for all people aged ≥60 years. PPSV23 has been the only pneumococcal vaccine licensed for adults until few years ago. Universal pneumococcal vaccination of infants, using a conjugate vaccine, has been recommended by STIKO since 2006. Since then, pneumococcal serotypes contained in conjugate vaccines have declined among cases of pneumococcal disease not only in children, but – through herd protection – also in older adults. The 13-valent pneumococcal conjugate vaccine (PCV13), currently used for most infants in Germany, has now been approved for use in adults as well. Data on the efficacy of PCV13 against clinical endpoints in older adults was published in 2015. For that reason, STIKO investigated whether one of the two vaccines (or the combination of both) should be preferred in order to reduce the burden of pneumococcal diseases in older adults, and at what age the vaccine should be given.

Efficacy against invasive pneumococcal diseases
Pooled data from 4 randomised controlled trials (RCTs) of PPSV23 in older adults show an efficacy of 73 % against invasive pneumococcal disease (IPD) caused by any serotype (95 % confidence interval [CI], 10–92 %). The IPD cases in these studies were mostly caused by one of the 23 serotypes contained in the vaccine. The efficacy of PCV13 in older adults was investigated in one RCT. Efficacy against IPD by any serotype was 49 % (95 % CI, 21–67 %, modified-intention-to-treat analysis). Efficacy against IPD by the 13 serotypes contained in the vaccine (VT-IPD) was 76 % (95 % CI, 47–90 %).

Efficacy against pneumococcal pneumonia
After exclusion of 2 RCTs with a high risk of bias, pooled efficacy of PPSV23 against pneumococcal pneumonia (PP) caused by any serotype in the remaining 2 RCTs was 64 % (95 % CI, 35–80 %). In the included observational studies, pooled efficacy ranged from 37 % to 53 %, with broadly overlapping CIs, depending on study type. The efficacy of PCV13 against PP caused by any serotype was 22 % (95 % CI, 2–39 %), and against VT-PP it was 38 % (95 % CI, 14–55 %).

Anticipated epidemiological and health economic effects
The above-mentioned studies do not provide clear evidence of a difference between the two vaccines regarding efficacy against clinical endpoints (IPD, PP) caused by the serotypes contained in the respective vaccine. In the 2015-'16 season, 70 % of IPD cases in people aged ≥60 years were caused by PPSV23 serotypes, but only 30 % by PCV13 serotypes. Because PPSV23 contains all the serotypes in PCV13 (except for serotype 6A), vaccination with PPSV23 confers broader serotype coverage and can thereby prevent considerably more cases.
The estimated effects of various vaccination strategies were compared using a dynamic transmission model. Because the protection the vaccines provide is limited to a few years, the effects of a one-time vaccination (e. g. at age 60) are minor. Administering a one-time vaccination with PPSV23 to 30 % (which is the current vaccination uptake in Germany) of people turning 60 in 2016–2020 could prevent a cumulative estimate of 2,253 hospitalisations and 270 deaths from pneumococcal diseases in the remaining lifespan (about 25 years). A one-time vaccination with PCV13 alone, however, would prevent only 725 hospitalisations and 101 deaths. Compared with vaccination with PPSV23 only, sequential vaccination with PCV13 and PPSV23 could prevent an additional 296 hospitalisations and 47 deaths in this period (about 25 years). Observing a longer period of time for this vaccination strategy (e. g. people who turn 60 in 2016–2030) would further diminish the benefit of the additional PCV13 vaccination because the model predicts a continued marked reduction in PCV13 serotypes over the coming years.
A vaccination strategy with repeated PPSV23 vaccinations every 6 years leads to markedly better results. Vaccinating 30 % of people turning 60 in 2016–2020, with initial and re-vaccinations with PPSV23, could prevent a cumulative estimate of 22,169 hospitalisations and 4,272 deaths over those people's lifetimes. Initial vaccination with PCV13 and PPSV23 (with re-vaccinations with PPSV23 only), would further prevent an additional 72 hospitalisations and 10 deaths only over this time span.
For a one-time vaccination with PPSV23, the number needed to vaccinate (NNV) is 801 to prevent a hospitalisation and 6,609 to prevent a death. For a sequential vaccination strategy, the NNV of PCV13 in addition to PPSV23 is 6,072 to prevent an additional hospitalisation and 38,024 to prevent an additional death. For the vaccination strategy with initial and re-vaccinations every 6 years with PPSV23, the NNV is considerably lower than for a one-time vaccination (398 per hospitalisation prevented and 2,064 per death prevented) because the disease incidence rises with age. If the initial vaccination is sequential (PCV13 + PPSV23) and the re-vaccinations are with PPSV23, an additional 25,000 older adults must be vaccinated with PCV13 to prevent an additional hospitalisation and 167,000 to prevent an additional death.
The costs of the vaccination strategy with initial and re-vaccinations with PPSV23 alone are € 12,800 per quality-adjusted life year (QALY) gained and € 6,700 per hospitalisation prevented. If the initial vaccination is sequential (PCV13 + PPSV23), the costs are about € 2,800,000 per QALY gained and € 1,500,000 per additional hospitalisation prevented (**Table 11**).

Conclusion
Based on these findings, STIKO continues to recommend vaccination with PPSV23 for all adults at age 60 years. STIKO also considers re-vaccinations in intervals of ≥6 years to renew vaccine protection useful for medical and epidemiological reasons.
According to the market authorisation of PPSV23 repeated vaccinations are only indicated for "persons with an elevated risk for severe pneumococcal diseases". Therefore, the indication for re-vaccination should be assessed on an individual basis. Patients should be counselled not only on the increased reactogenicity of re-vaccinations compared with first-time vaccinations, but also about the risk of losing protection without re-vaccination.
Sequential vaccination with PCV13 and PPSV23 is not recommended as a standard vaccination for older adults because of the low number of additional preventable cases and the very high NNV.
People with certain underlying diseases, in particular immunocompromising conditions, can benefit from a sequential vaccination (PCV13 followed by PPSV23). For more information, please see the STIKO recommendation on indication-based vaccination against pneumococci in Epidemiologisches Bulletin 37/2016 at www.rki.de (in German).

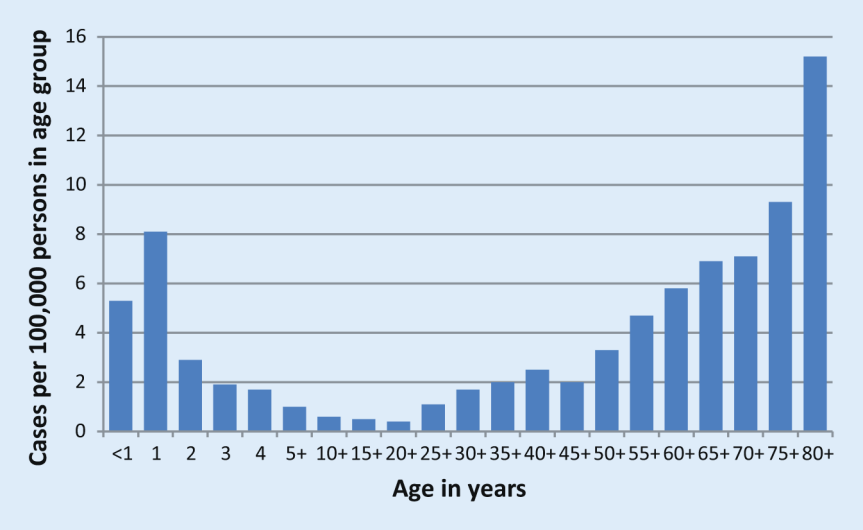

Fig. 1 ▲ Incidences of invasive pneumococcal diseases (IPD) reported in the German federal states of Brandenburg, Saxony, Saxony-Anhalt, and Mecklenburg-Vorpommern, average of the years 2011–2015, by age
Source: Mandatory case reporting according to State Regulations. Data from Thuringia not included because the reported incidence is only about one tenth of that in the other states, which certainly does not reflect the real situation

Scientific rationale

1. Pathogen and clinical presentation

Pneumococci *(Streptococcus pneumoniae)* are gram-positive encapsulated bacteria. The polysaccharide capsule is a critical virulence factor because it prevents phagocytosis of the pathogen. The antigenic properties of the capsule polysaccharides allow over 90 serotypes to be distinguished, while even more serotypes are still being discovered [1]. Related serotypes are clustered into serogroups. Some serogroups exhibit cross-immunity among the various serotypes belonging to the same serogroup; these include serogroup 6 with the epidemiologically important serotypes 6A and 6B. But there are also serogroups with no cross-immunity of mention between serotypes; e. g. between serotypes 19A and 19F [2, 3].

Pneumococci colonise the human nasopharynx, usually without causing symptoms. However, through local spread they can cause diseases of the upper (sinusitis, middle ear inflammation) and lower (pneumonia) respiratory tract [4]. Invasive pneumococcal diseases (IPDs) are particularly serious. They are defined as the isolation of pneumococci from normally sterile body fluids. The most common forms of IPD are bacteraemia (verified by blood culture) and meningitis (detection in cerebrospinal fluid). Far less often are pneumococci found in pleural, joint, or ascites taps. Different serotypes exhibit different levels of ability to cause invasive diseases [5].

The most common forms of pneumococcal (Pnc) diseases in adults are community-acquired pneumonia (CAP) and IPD. In adults, IPD manifests mostly as pneumococcal pneumonia with concomitant bacteraemia. A clear delineation between the two manifestation forms is not possible. Presumably, many IPD cases are misssed because often no blood cultures are performed during the diagnostic work-up of a CAP case, or because they show up false negative; e. g. in patients who have already started antibiotic treatment [4].

2. Epidemiology

Pneumococci are transmitted by droplet infection from person to person. Small children with asymptomatic nasopharyngeal colonisation are the epidemiologically most important pathogen reservoir. No representative data are available on the prevalence of nasopharyngeal (NP) carriers in Germany. A cross-sectional study conducted in England in 2012–'13, 6 years after universal vaccination of infants with pneumococcal conjugate vaccine (PCV) was introduced, found the prevalence of NP carriers to be 48 % among children aged <5 years, 22 % among ages 5–20 years, and 3 % among ages >20 years. Although the overall prevalence of NP carriers was similar to that in 2001–'02 (before universal vaccination of infants was introduced), the percentage of carriers of the serotypes contained in the currently used PCV13 vaccine dropped from over 75 % to around 5 % in that period [6].

Incidence of IPD

In Germany there is *no nationwide mandatory reporting* of pneumococcal diseases. The states of Saxony-Anhalt, Saxony, Mecklenburg-Vorpommern, Brandenburg, and Thuringia each have a statewide reporting obligation for IPD. Higher incidence is reported among children aged <2 years, and older adults (**Fig. 1**). No conclusions on actual IPD incidence can be drawn from these reporting data because the extent of underreporting is unknown. Reasons for underreporting are insufficient diagnostics (blood cultures) and possible noncompliance with reporting obligations.

Since 1997, the Robert Koch Institute (RKI) in Berlin has been conducting voluntary, laboratory-based *sentinel surveillance for IPD cases*. Until 2006, only IPD cases in children were recorded. In connection with the recommendation for universal vaccination of children, this surveillance was expanded with the online PneumoWeb (www.rki.de/pneumoweb) in 2007 to include people of all ages. The primary aim of PneumoWeb is to monitor the effects of vaccination on serotype distribution in IPD cases in all age groups (see Sect. 4). In addition to the anticipated reduction in vaccine serotypes, the extent of a potential serotype replacement should also be tracked. Serotype replacement is understood as an increase in serotypes not contained in the vaccine that fill the gap left by the reduction in vaccine serotypes. Consequently, the vaccination's effect on the overall incidence of IPD can be lower than what could be anticipated, based on

the vaccine's efficacy against the serotypes contained within [7].

The actual incidence of IPDs cannot be determined from PneumoWeb data because only some of the clinical microbiological laboratories in Germany participate voluntarily in the surveillance. Furthermore, the size of the catchment population of the participating laboratories and the clinics they serve is not known. Assuming that nearly all IPD cases are treated on an inpatient basis, *hospital diagnosis statistics* offer a better indication of the incidence of IPD cases *diagnosed* in Germany (see Sect. 6.1, **Table 1**).

Incidence of pneumococcal pneumonia

Germany has no surveillance system in place that allows estimation of the incidence of pneumococcal pneumonia. We therefore conducted an exploratory literature search of reviews of studies on the incidence of pneumococcal pneumonia in Europe, and linked the findings to data from the German CAPNETZ study [8] and official hospital diagnosis statistics (www.gbe-bund.de) (see Sect. 6.1).

3. Pneumococcal vaccines

As early as the 1930s, Kaufman proved in a major clinical trial, with around 11,000 participants, that humans can be immunised against a pneumococcal infection through an injection of polysaccharide components of the pneumococcal capsule [9]. Industrially produced vaccines against pneumococci have been available since the 1970s, initially in the form of a 14-valent pure pneumococcal polysaccharide vaccine (PPSV14) with 50 µg of capsule polysaccharide per serotype [2]. This was replaced in 1983 by the 23-valent polysaccharide vaccine (PPSV23), which is still on the market. PPSV23 consists of 25-µg capsule polysaccharides of each of the serotypes that were epidemiologically most important at that time (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F), and contains no adjuvant [4].

Unlike in adults, polysaccharide vaccines exhibit low immunogenicity in children aged <2 years, a group with high incidence of IPD [4]. This led to development of pneumococcal conjugate vaccines (PCVs), in which the polysaccharide antigens are bonded to a carrier protein, resulting in a marked improvement in immunogenicity in infants and young children. But the production process is more complex; therefore, the first licensed conjugate vaccine (PCV7) contained only the antigens of the seven most common serotypes at that time: 4, 6B, 9V, 14, 18C, 19F, and 23F. In February 2001, PCV7 was licensed in the European Union for children aged ≤5 years.

In late 2009, PCV7 was replaced by PCV13, which contains the additional serotypes 1, 3, 5, 6A, 7F, and 19A. In subsequent years, market authorisation was gradually expanded to include older age groups, and in July 2013, PCV13 was authorised for all age groups ≥6 weeks. Since 2009, an additional 10-valent conjugate vaccine (PCV10, Synflorix®) has been available for children aged ≤5 years. It contains serotypes 1, 5, and 7F, in addition to the PCV7 serotypes. The conjugate vaccines contain 1–3 µg (PCV10) or 2.2–4.4 µg (PCV7, PCV13) polysaccharide of each serotype, and aluminium phosphate as an adjuvant.

All serotypes in PCV13 are also present in PPSV23, with the exception of 6A. However, PPSV23 likely provides partial protection against serotype 6A because of cross-immunity with serotype 6B, which the vaccine contains [2, 3, 10].

Protection from nasopharyngeal colonisation with pneumococci of the serotypes contained in a PCV vaccine has been credibly documented. Therefore, routine PCV vaccination in childhood results in herd protection. Regarding PPSV, however, a review article from 2012 reported that this vaccine led to a reduction in nasopharyngeal colonisation with serotypes contained in the vaccine in only one of four studies cited [10, 11].

4. Current STIKO recommendations for pneumococcal vaccination

In 1998, STIKO first recommended pneumococcal vaccination with a polysaccharide vaccine for people aged ≥60 years (called *"senior vaccination"*), with repeat vaccination after 6 years [12]. In 2009, the recommendation for repeat vaccinations was restricted to certain risk groups; with a one-time vaccination recommended as the standard for older adults. A number of reports of severe local reactions, and contradictory evidence in the medical literature regarding poorer antibody responses after repeat vaccinations, were the reasons for this change [13]. Since then, several further studies have been published, necessitating a reassessment of these issues.

In addition, STIKO recommends pneumococcal vaccination *for children, adolescents, and adults at increased risk* because of an underlying disease (table 2 in the STIKO recommendations). Since 2006, STIKO has additionally recommended *universal vaccination* with pneumococcal conjugate vaccine *for all infants*.

The primary aim of universal vaccination during infancy is reducing the burden of invasive pneumococcal disease including complications, such as hospitalisation, disability, and death, in this age group. Furthermore, a reduction in asymptomatic nasopharyngeal colonisation in vaccinated children, and an associated reduction in the IPD disease burden in (unvaccinated) people in higher age groups through herd protection were also anticipated [14]. STIKO had not defined an explicit objective for the senior vaccination; that is part of this update.

Implementation

The vaccination status of adults was recorded as part of the "Study of the Health of Adults in Germany" (*Studie zur Gesundheit Erwachsener in Deutschland, DEGS*), conducted by the RKI from 2008 to 2011 [15]. Pneumococcal vaccination uptake among participants aged 65–79 years was 31.4 % (95 % CI, 28.1–34.9 %); slightly higher in women (33.2 %) than in men (29.3 %). Vaccination uptake was significantly higher in the former East Germany, both in women (57.9 %) and men (49.7 %), than in the former West Germany (women, 27.2 %; men, 24.6 %).

Serotype distribution since introduction of universal infant vaccination

PneumoWeb data (**Fig. 2 and 3**) show that the percentage of serotypes contained in the conjugate vaccines among all IPD cases has dropped substantially since the

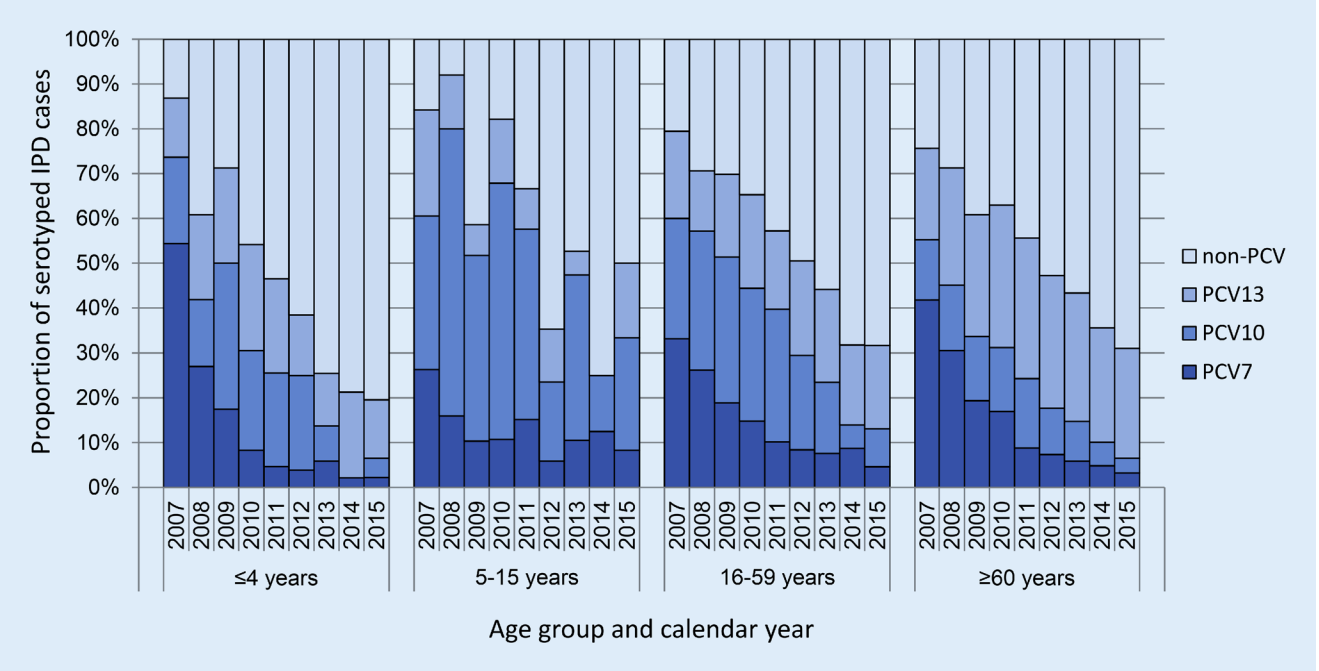

Fig. 2 ▲ Relative distribution of serotypes contained in the different pneumococcal conjugate vaccines of the IPD cases recorded in PneumoWeb, by age group and year of disease
PCV7 = serotypes contained in the 7-valent pneumococcal conjugate vaccine, PCV10 = serotypes additionally contained in the 10-valent pneumococcal conjugate vaccine, PCV13 = serotypes additionally contained in the 13-valent pneumococcal conjugate vaccine
Since 2012, fewer than 20 isolates have been available for serotyping in the age group 5 – 15 years due to very low incidence. Thus the percentages shown for serotype distribution in this age group are subject to a high degree of uncertainty

recommendation of universal infant vaccination. That drop applies not only to the target age group of young children, but to all age groups; in other words, the anticipated herd protection has occurred. Among ≥60 year olds, the percentage of PCV13 serotypes among IPD cases dropped from about 75 % when universal infant vaccination was introduced in 2007 to 30 % in the 2015–'16 season. To the contrary, the percentage of IPD cases caused by PPSV23 serotypes was about 70 % in 2015–'16. **Fig. 2** shows the relative percentage of the respective vaccine serotypes. **Fig. 3** shows the absolute case numbers for people aged ≥60 years.

Serotype (ST) 3 is a special case; it belongs to the six additional serotypes contained in PCV13 that are not included in PCV7. While the case numbers of the other PCV13 serotypes have steadily decreased since 2007, cases by ST 3 have increased. In the last two seasons, ST 3 was by far the most common serotype, causing almost 20 % of all IPD cases in people aged ≥60 years (**Fig. 3**). Unlike the other five additional serotypes in PCV13, its percentage among IPD cases in Germany did not drop after the switch from PCV7 to PCV13, in either children or older adults (see **Fig. 4** and [16]). A similar phenomenon has been observed in other countries [17–19].

PCV13 thus appears to provide little or no protection from ST 3 for children, and therefore no, or only limited, herd protection can be expected in other age groups. In an analysis of IPD cases among children in the United Kingdom [20], the serotype-specific efficacy of PCV13 against ST 3 was by far the lowest; it was the only serotype with a statistically insignificant vaccine efficacy of 26 % (95 % CI, –69 to 68 %). At the same time, the efficacy against the other serotypes in PCV13 (ST 5 was not calculated because of low case numbers) was 82 % (95 % CI, 68–89 %).

It is difficult to assess whether vaccination of adults with PCV13 or PPSV23 can provide protection from illness caused by ST 3 because the number of ST 3 cases is too low in published studies with clinical endpoints or because information on the serotype is missing (see Sect. 6.2). In an evaluation of British IPD surveillance data according to the Broome method, the efficacy of PPSV23 against IPD caused by ST 3 (along with the much rarer ST 1) in older adults was significantly lower than for the other PPSV23 serotypes investigated [21].

The only randomised controlled trial (RCT) on the efficacy of PCV13 against clinical endpoints in older adults (CAPITA study [22]) showed statistically non-significant efficacy of 56 % (95 % CI, –6 to 82 %) against PP caused by ST 3 [23]. The efficacy against PP by all 13 vaccine serotypes was 46 % (95 % CI, 23–62 %). These findings align with the assumption that PCV13 has an efficacy against ST 3 comparable with that against the other 12 serotypes, as well as with the assumption that it is significantly less effective against ST 3 – as in children – than against the other serotypes.

A biological explanation could be that the chemical bonding of the capsule polysaccharides in *S. pneumoniae* serotype 3 (and the epidemiologically insignificant ST 37) to the cell wall is weaker than that of all other serotypes. That trait allows ST 3 to separate its capsule polysaccharides more easily and thus neutralise circulat-

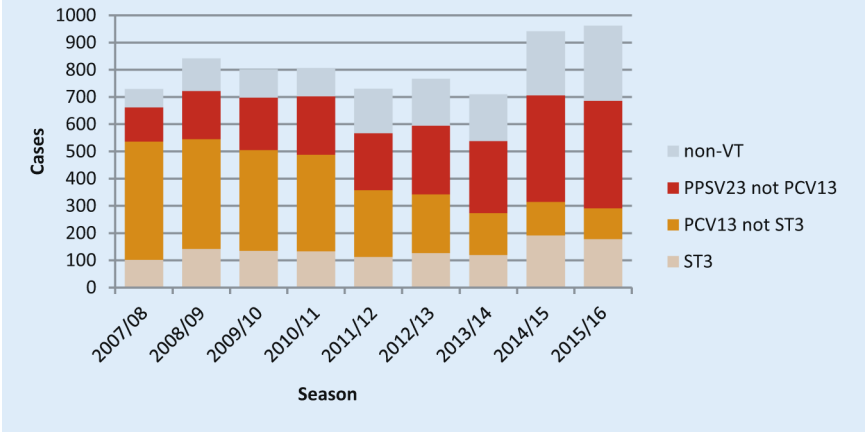

Fig. 3 ▲ Serotype distribution of the IPD cases recorded on PneumoWeb in seniors 60 years and over, absolute case numbers
ST3 = serotype 3, *non-VT* = serotypes not contained in any vaccine
Seasonal variations of case numbers may reflect real differences in incidence, but may also result from surveillance artefacts, e. g. changing numbers of laboratories participating in PneumoWeb

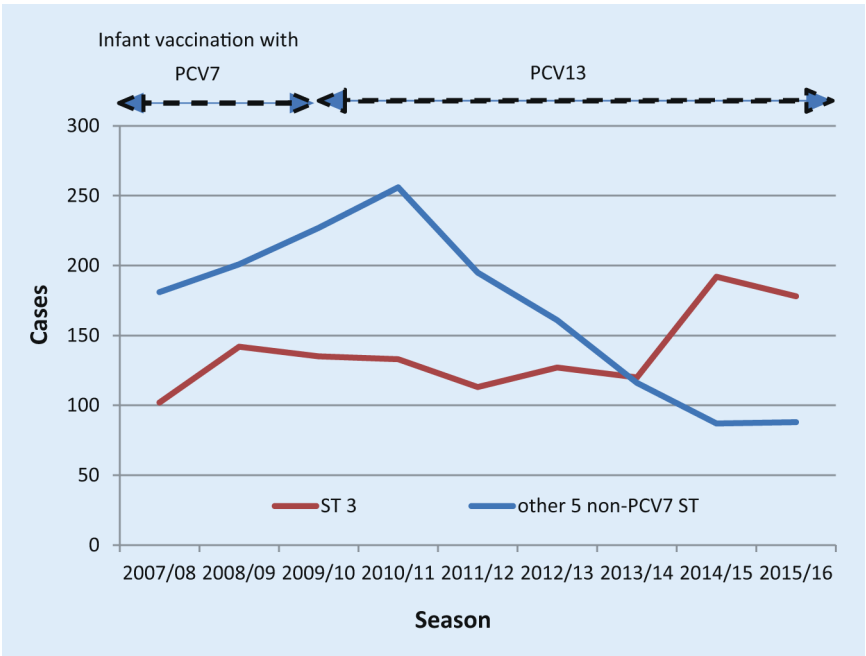

Fig. 4 ▲ IPD cases in people aged ≥60 years, caused by the 6 serotypes (1, 3, 5, 6A, 7F, 19A) included in PCV13 but not PCV7

ing serum antibodies against ST 3, thereby preventing opsonisation which is necessary for phagocytosis of the encapsulated pneumococci [24]. Immunogenicity studies in adults have also shown significantly weaker immune response to ST 3 than to other serotypes for both PCV13 and PPSV23 [25–28]. In modelling the epidemiological effects of the vaccination (see Sect. 6.5), the base case rested on the assumption that both PPSV23 and PCV13 are only half as effective against ST 3 as against the other serotypes contained in the respective vaccine. One sensitivity analysis in favour of PCV13 tested the implications of the assumption that PCV13 is as effective against ST 3 as against the vaccine serotypes, yet PPSV23 is only half as effective.

5. Approach for evaluating the current vaccination recommendation

STIKO took the expansion of the market authorisation of PCV13 to include all age groups, along with finalisation of a major RCT on the efficacy of PCV13 in older adults (CAPITA study, see below), as an occasion to re-examine its current recommendation on the standard vaccination of adults aged ≥60 years ("senior vaccination"). This re-examination focused on:

a) Whether older adults should receive one particular vaccine (PPSV23 or PCV13) or both sequentially, in consideration of the changes in serotype distribution since introduction of universal infant vaccination
b) At what age the vaccination should be administered
c) Whether follow-up vaccinations are beneficial

The aim of the vaccination was defined as a reduction in the number of invasive pneumococcal diseases and pneumococcal pneumonia cases and their consequences, such as hospitalisation, disability, and death, among older adults in Germany.

The following approach was taken to answer the three issues above:

1. Exploratory literature research on the disease burden of pneumococcal diseases among older people in Germany, in consideration of hospital diagnosis statistics
2. Systematic literature research on the efficacy of PPSV23 and PCV13 in older adults against clinical endpoints
3. Systematic literature research on the reactogenicity and safety of a one-time vaccination with PPSV23 or PCV13
4. Systematic literature research on the immunogenicity, reactogenicity, and safety of follow-up vaccinations with PPSV23
5. Comparison of the anticipated epidemiological and health economic effects of different vaccination strategies (vaccine and age at vaccination) using transmission modelling and a health economic evaluation

Table 1 Case numbers extracted from hospital diagnosis statistics for Germany, by age, mean values of the years 2010–2013

ICD10 code	Cases, 20 to <60 years	Cases, ≥60 years	Cases, ≥65 years	Deaths, 20 to <60 years	Deaths, ≥60 years	Deaths, ≥65 years
IPD						
A40.3 – Sepsis with *S. pneumoniae*	589	1,446	1,253	58	255	235
G00.1 -Pneumococcal meningitis	184	207	160	12	25.5	24
Sum IPD	772	1,653	1,413	70	280	259
Incidence IPD	1.7/100,000	7.6/100,000	8.4/100,000	0.2/100,000	1.3/100,000	1.5/100,000
Pneumonia						
J13 – Pneumonia caused by *S. pneumoniae*	710	1,703	1,486	33	205	191
J15.9 – Bacterial pneumonia, unspecified	1,762	8,255	7,683	–	–	–
J18 – Pneumonia, pathogen unspecified	35,068	159,775	148,607	–	–	–
J12-J18 total (all codes for pneumonia)	44,293	192,138	178,022	–	–	–
Estimated case numbers or deaths due to pneumococcal pneumonia*	8,859	38,428	35,604	420	5,162	4,984
	Incidence			*Mortality*		
*Estimated incidence or mortality due to pneumococcal pneumonia**	20/100,000	178/100,000	213/100,000	1/100,000	24/100,000	30/100,000

* Assumptions: 20 % of the cases coded as J12-J18 are caused by pneumococci; the lethality of pneumococcal pneumonia equals the ratio (J13 deaths)/(J13 cases)*100

Members of RKI's Immunisation Unit carried out points 1–4. Work package 5 was set out for public tender and awarded to the Center for Health Economics Research (CHERH) of the University of Hannover. Specifics of the approaches to each task were determined in consultation with STIKO's pneumococci workgroup.

The findings of the studies identified for points 2 and 3 were summarised in *meta-analyses* based on random effects models, using Review Manager 5.2 software [29]. The quality of the evidence was assessed in line with the methods of the Grading of Recommendations Assessment, Development and Evaluation (*GRADE*) Working Group [30]. According to GRADE, evidence quality is a measure of trust in the accuracy of the effect estimate. The quality assessment is judged separately for each investigated endpoint in four levels (high – moderate – low – very low). Results of RCTs are ranked a priori as "high" quality in GRADE; results of observational studies are ranked as "low" because of the inherently higher risk of bias of this study type. Based on certain criteria defined in the GRADE method, the evidence is examined to determine if it justifies a downgrade or upgrade of the quality level.

6. Methods and findings regarding the various aspects

6.1 Burden of pneumococcal diseases among older adults in Germany

It is difficult to estimate the incidence of pneumococcal pneumonia (PP) because a microbiological diagnosis is confirmed in only a fraction of community-acquired pneumonia (CAP) patients. One reason for this is that in many cases the patient receives a calculated antibiotic therapy without any effort to establish the pathogen; that is the rule in CAP cases treated on an outpatient basis. Another reason is that the viability of pneumococci outside the human body is limited. This reduces the sensitivity of microbiological cultures from blood or sputum samples under routine conditions, often with long transport times to the laboratory. Microbiological cultures are also usually negative in patients who have begun antibiotic treatment. The widespread urine antigen test BinaxNOW® *S. pneumoniae* (Alere GmbH, Cologne, Germany) has a sensitivity of only 63–82 %, with a specificity of 78–100 % [31], depending on the study.

An exploratory literature search in MEDLINE, and a survey of experts in the STIKO pneumococci workgroup, failed to produce any studies that provided a direct estimate of the incidence of PP in Germany. It can be assumed that the vast majority of PP cases are community-acquired [4]. For that reason, we estimated the incidence of PP by multiplying the incidence of all CAP by the percentage of CAP cases caused by pneumococci as determined in other studies.

The *CAPNETZ study* [8, 32] is the largest prospective study on the microbiologi-

cal aetiology of CAP cases in adult patients in Germany. From 2002 to 2009, a total of 7,800 patients with CAP were included in the study, of whom about two-thirds received inpatient treatment. A pathogen was identified in 24.5 % of the 3,720 patients aged ≥65 years. The most frequently identified pathogen was pneumococci, at 330 cases, comprising 9 % of all CAP cases and 33 % of all patients in whom any pathogen was identified [8]. The percentage of cases caused by pneumococci among cases with no detected pathogen is difficult to estimate.

Two recent review articles summarised the findings of studies on the CAP pathogen spectrum in various European countries [33, 34]. The percentage of PP among all CAP cases in the included studies ranged from 0–67 % [33] and 12–85 % [34]. The causes of this gaping difference are more likely differences in the diagnostic tests conducted, case definitions, and patient collectives, rather than real differences between countries or studies [33]. Based on a meta-analysis (random effects model) of 77 individual studies, with a total of 24,410 CAP patients, Rozenbaum et al. [33] estimate the percentage of PP as 19.3 % (no CI is given) of all CAP cases in which a pathogen was detected.

A study of adults in Finland aged ≥65 years [35], which was published after the review by Rozenbaum et al., found a higher percentage of PP (30 %; 56 of 187 CAP cases with pathogen detection), but the PP diagnosis was sometimes confirmed serologically (antibodies against *pneumococcal surface adhesin A* or *choline-binding protein A*). The percentage of PP among all CAP cases in the placebo arm of the CAPITA trial was only 22 % (174 of 787 CAP cases), although a specially developed, highly sensitive urine antigen test was used to detect PCV13 serotypes. There is no information in the publication [22] on the number of CAP cases with detection of any pathogen.

Table 1 shows case numbers from the hospital diagnosis statistics for Germany (www.gbe-bund.de). Less than 1 % of all pneumonia cases were coded as PP (ICD10 code J13); most certainly a significant underestimation of the actual percentage. Based on the data reported by Rozenbaum et al. [33] and from the CAPITA study, we estimate that pneumococci caused roughly 20 % of all cases coded with any ICD10 code for pneumonia (J12–J18). At the time of our analysis, the most recent figures available were from 2013. To compensate for inter-seasonal fluctuations, we calculated the mean value for 2010–2013: 38,428 PP cases in people aged ≥60 years. This corresponds to an annual population-based *incidence of 178 cases of pneumococcal pneumonia treated on an inpatient basis per 100,000 people aged ≥60 years*. The incidence rose slightly from 2010 (167/100,000) to 2013 (196/100,000). The number of cases coded as invasive pneumococcal disease (ICD10 codes A40.3 and G00.1) was <5 % of the estimated PP cases (**Table 1**), which very likely results from underdiagnosis, as discussed above.

We estimated the number of deaths due to PP by calculating the case fatality of PP as a ratio (J13 deaths/J13 cases)*100 and multiplying it by the estimated total number of CAP cases caused by pneumococci. That resulted in a case fatality of 12 %, equalling *5,162 deaths caused by PP per year in people aged ≥60 years*. Additionally, 280 deaths caused by invasive pneumococcal diseases (ICD10 codes A40.3 and G00.1) were recorded, equalling an *annual mortality of 25/100,000* as a result of pneumococcal diseases in those aged ≥60 years.

This statistic includes only those deaths that occurred during hospitalisation; the actual mortality is likely higher. In the CAPNETZ study, the 30-day case fatality of PP cases in people aged ≥60 years was somewhat lower, at 7.7 % (32 of 418 cases). Notably, this number includes outpatient PP cases, which are probably less lethal than inpatient cases. There is also a selection bias in CAPNETZ in favour of those less severely ill, because only patients capable of giving consent were included in the study (Mathias Pletz, personal message, 12. 2. 2015).

6.2 Efficacy of one-time vaccination with PPSV23 or PCV13 against clinical endpoints in older people

Authors GF and CR conducted a *systematic literature search* for studies on the efficacy of pneumococcal vaccines against clinical endpoints. A two-stage strategy was used to identify relevant studies. First, original works published in or before 2011 were identified using the broad-based Cochrane review "Vaccines for Preventing Pneumococcal Infection in Adults," from 2013 [36], scrutinising the lists of both included and excluded studies. Studies published after 2011 were then identified using a search strategy adapted to the Cochrane review in the databases MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials, on 3 July 2015 (Flowchart see **Fig. A1** in the Appendix). An updated search on 15 July 2016 yielded no additional hits. The systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [37].

Study selection was based on PICO questions defined by STIKO (**Table 2**). In addition to RCTs, observational studies (cohort and case-control studies, including case-case studies using the Broome method [56]) were included as long as results were adjusted for relevant confounders (e. g. age, comorbidities). Risk of bias of included studies was assessed using the Cochrane Risk of Bias Tool [57] for RCTs and the Newcastle–Ottawa Scale [58] for observational studies.

No evaluation was conducted on the endpoints "all-cause CAP" and "all-cause mortality" because the sizes of the individual studies were insufficient to determine or rule out an effect on these endpoints with adequate statistical power. See also the discussion in [43] and the calculations in [59].

Direct comparison PPSV23 vs. PCV13

Only one study with a direct comparison of the efficacy of PPSV23 and PCV7 against clinical endpoints in older adults was found [60]. In this randomised, non-blinded study, chronic obstructive pulmonary disease (COPD) patients aged ≥40 years (mean, 63.5 years) were vaccinated with PPSV23 or PCV7. The primary endpoint of the study was immunogenicity data. Of the endpoints defined in our PICO questions, only overall mortality was reported. Among 80 participants in each of the two groups

Table 2 Inclusion criteria for the systematic literature review (PICO questions)

Population	– Persons 60 years and over, healthy or with age-typical underlying diseases – Countries/populations with living conditions comparable to those in Germany	
Intervention	– Vaccination with PPSV23 – Vaccination with PCV13 *If no studies with PCV13 available:* vaccination with PCV7	
Comparator intervention	– No vaccination or placebo *or* – Direct comparison PPSV23 vs. PCV13 (or PCV7)	
Endpoints	– Invasive pneumococcal disease (IPD) *If data are available: By vaccine serotypes (VT-IPD)* – CAP caused by pneumococci (PP), inpatient treatment *If data are available: By vaccine serotypes (VT-PP)*	CRITICAL
	– CAP caused by pneumococci, outpatient treatment *If data are available: Limited to vaccine serotypes* – All-aetiology CAP – All-cause mortality	IMPORTANT

CAP community-acquired pneumonia

monitored over 2 years, 4 participants in the PCV7 group and 7 in the PPSV23 group died (odds ratio [OR] = 0.55; 95 % CI, 0.15–1.95). The extremely wide CI, which also includes the value 1, does not permit a comparative assessment of the two vaccines.

PPSV23

The efficacy of polysaccharide vaccines was investigated in numerous RCTs already summarised in several meta-analyses. At the time of our own literature searches, the Cochrane review by Moberley et al. [36] and a review by Huss et al. [61] were the most recent ones. Because different studies were included or excluded, the findings of those two reviews are contradictory in some points; see also the correspondence between the authors [62, 63]. Problematic about the two reviews (and other older reviews) is that they pool data from RCTs of adults of various age groups, with various polysaccharide vaccines (different valencies, different quantities of antigen), inconsistent case definitions, and of populations with highly varying base risk of pneumococcal diseases [59].

For that reason, we conducted our own meta-analysis, including only those RCTs that meet the criteria set forth in the PICO questions (**Table 2**)–a total of 4 RCTs. In light of the low case numbers in these RCTs and the resulting broad CIs of the pooled estimates, we also analysed observational studies (**Table 3**).

Evidence from RCTs. **Fig. 5** shows the pooled effect estimates of the RCTs as forest plots. Using the formula vaccine efficacy (VE) = (1-RR)*100, *the pooled vaccine efficacy of PPSV23 against IPD is 73 %*. The CI is very wide due to low case numbers (95 % CI, 10–92 %). The IPD cases that occurred in the studies by Honkanen et al. and Örtqvist et al. were all caused by vaccine serotypes. Maruyama et al. provide no information on serotype.

After exclusion of two trials with a high risk of bias, the pooled *vaccine efficacy of PPSV23 against pneumococcal pneumonia is 64 %*, with a moderately wide CI (95 % CI, 35–80 %). Because many cases were diagnosed using a urine antigen test, there are no data on VE against PP caused by vaccine serotypes.

In modelling the various vaccination strategies, the VE estimates were interpreted as efficacy against IPD or PP *caused by vaccine serotypes*, thus providing a conservative assessment of PPSV23.

The meta-analysis for the endpoint IPD showed no heterogeneity. Regarding PP, the meta-analysis of all 4 RCTs showed considerable heterogeneity ($I^2 = 78\,\%$), which disappeared after exclusion of the 2 RCTs with a high risk of bias ($I^2 = 0\,\%$).

Considerations for inclusion and exclusion of individual RCTs. 1. The results of the previously published meta-analyses by Moberley et al. [36] and Huss et al. [61] were greatly influenced by the trials by Honkanen et al. [41] and Örtqvist et al. [40]. We included these two trials for the endpoint IPD, but not for the endpoint PP because in a large number of cases in both studies, the PP diagnosis was based on detection of pneumolysin IgG in serum [54] or in circulating immune complexes in serum [55], using poorly validated *in-house* ELISAs. Serum samples from both studies were tested at the same laboratory in Finland where the *in-house* ELISAs had also been developed. It later became evident that their specificity was insufficient for vaccination efficacy studies.

(a) In the original publication by Jalonen et al. [54], pneumolysin IgG was measured in paired serum samples of 159 patients (range, 16–95 years old; mean, 63 years) with radiologically confirmed pneumonia. Paired serum samples of 27 patients with bacteraemia caused by other pathogens, and one-time serum samples from 29 healthy blood donors (mean age, 50 years) served as controls. A "positive" result was defined as an antibody concentration exceeding the 99th percentile of healthy controls in at least one of the paired serum samples, or a ≥ 2-fold titre increase. For an ELISA, this cut-off is unusually low (a 4-fold or greater increase is common) because a 2-fold increase can often be observed even in repeated measurements of the same serum sample, as a result of measurement inaccuracies. The sensitivity of the test is reported

Table 3 Studies included for the efficacy/effectiveness of PPSV23

Publication	Study type	Country	Study population	Number vaccinated/unvaccinated	Period of follow-up observation	Sponsor	Risk of bias	Inclusion for endpoints IPD/PP
Alfageme 2006 [38]	RCT	Spain	COPD patients, aged 61–73 years	298/298	2.7 years	Spanish Pneumology Society and Andalusian Health Service	Low	Y/Y
Maruyama 2010 [39]	RCT	Japan	Residents of retirement homes, aged 55–105 years	502/504	2.3 years	Japanese Ministry of Education, Culture, Sport, Science, and Technology	Low	Y/Y
Örtqvist 1998 [40]	RCT	Sweden	Former CAP patients, aged 50–85 years	339/352	2.4 years	MSD, Swedish Heart/Lung Foundation, Karolinska Institute	Low [a]	Y/N[a]
Honkanen 1999 [41]	(RCT)[b]	Finland	Resident population, aged ≥65	13,980/12,945	1.4 years	Academy of Finland, Pasteur-Mérieux	Unclear[a]	Y/N[a]
Hechter 2012 [42]	Cohort study	USA	Participants in the *California Men's Health Study*	7,718/9,232 at study begin	Variable	Kaiser Permanente Southern California	High	Y/N[c]
Jackson 2003 [43]	Cohort study	USA	Resident population, aged ≥65 years	42,977/84,203 (PY)	Variable (81 % 5–8 years)	CDC (USA)	Low	Y/N[c]
Ochoa-Gondar 2014 [44]	Cohort study	Spain	Resident population, aged ≥60 years	29,065/46,968 (PY)	up to 5 years	Spanish Health Ministry	Low	Y/Y
Tsai 2015 [45]	Cohort study	Taiwan	Resident population, aged ≥75 years	229,181/229,181	1 year	Taiwan CDC	High	Y/N[c]
Vila-Corcoles 2006 [46]	Cohort study	Spain	Resident population, aged ≥65 years	17,401/16,504 (PY)	Variable (87 % 2–5 years)	Spanish Health Ministry	Low	Y/Y
				Cases/Controls				
Dominguez 2005 [47]	CaCo	Spain	IPD cases ≥65 y + matched controls	149/447	2–3 years	Catalonian Health Authority	Low	Y/N[d]
Leventer-Roberts 2015 [48]	CaCo	Israel	IPD cases ≥65 y + matched controls	212/848	up to 5 years	Pfizer	Low	Y/N[d]
Vila-Corcoles 2009 [49]	CaCo	Spain	IPD and PP cases ≥50 y (74 % ≥65 y) + matched controls	IPD: 94/188 PP: 304/608	up to 7.5 years	Spanish Health Ministry	Low	Y/Y
Andrews 2012 [21]	Broome	England & Wales	IPD cases ≥65 y	564/551 [e]	up to 5 years	Health Protection Agency	Low	Y/N[d]
Gutiérrez 2014 [50]	Broome	Spain	IPD cases ≥60 y	588/211 [e]	up to 5 years	no information	Low	Y/N[d]
Rudnick 2013 [51]	Broome	Canada	IPD cases ≥65 y	1,138/240 [e]	up to 5 years	Canadian Institutes for Health Research, CDC USA, Ontario Thoracic Society, Fig.tt Laboratories, Bayer Healthcare, GlaxoSmithKline, Pfizer	Low	Y/N[d]
Wright 2013 [52]	Broome	England	IPD cases ≥65 y	374/73 [e]	up to 9 years	Health Protection Agency, Sanofi Pasteur MSD	Low	Y/N[d]
Wiemken 2014 [53]	Case-case	USA, Europe	CAP cases ≥65 y	279/2,409 [f]	No information	No financing	High	N/Y

CaCo case control study, *PY* person years follow-up, *Y* yes, *N* no, *PP* pneumococcal pneumonia

[a]Excluded for endpoint PP because a large number of the reported PP cases were diagnosed using inadequately validated tests for pneumolysin antibodies [54, 55] (see comments in the text), [b]Pseudo randomization by birth year (even/uneven), [c]Endpoint PP not reported, [d]Only IPD cases were included in the study, [e]IPD cases caused by vaccine serotypes/IPD cases caused by non-vaccine serotypes, [f]CAP cases caused by pneumococci/CAP cases without detection of pneumococci

as 82 %. The publication provides no specificity estimate. In general, it is difficult to determine the specificity because there is no "gold standard" test to reliably distinguish PP cases from pneumonia cases by other pathogens.

(b) In the original work by Leinonen et al. [55] on measuring pneumolysin antibodies in circulating immune complexes (ply-IC), 2 to 3 consecutive serum samples from 129 patients (range, 15–93 years old; mean age, 61 years) with radiologically confirmed pneumonia were tested, along with one-time serum samples from 109 healthy children and adolescents (range, 6 months to 18 years old) and 11 young adults (range, 20–30 years old) as controls. The sensitivity of this method is reported as 97.8 %, with a specificity of 83.4 %. Doubts regarding the validity of this calculation owe to the fact that the direct measurement of pneumolysin IgG in serum [54] described above and even the ply-IC test itself were used as part of the definition of a "real" case of PP, and to the considerable age difference between cases and controls.

(c) In a later study by Scott et al., co-authored by Leinonen [64], serum samples from 129 adolescent or adult PP patients in Kenya (mean age, 32 years; 50 % HIV-positive) were examined using the ply-IC ELISA. PP was diagnosed by cultivating pneumococci from blood cultures or lung aspirate, or through urine antigen testing. Ninety-seven patients (mean age, 35 years; 31 % HIV-positive) with other diagnoses and from the same hospital served as controls.
Up to 3 serum samples were taken from the cases (about 6, 11, and 33 days after disease onset), but only one sample was taken from each control. Only the highest score from each patient was used in the calculations, creating a bias in favour of higher values in patients. The sensitivity and specificity of the ply-IC test were calculated for various cut-off values. At a specificity of 95 % (90 %), sensitivity was only 22 % (30 %). In contrast to the original publication by Leinonen et al. [55], pneumolysin produced from genetically altered *Bacillus subtilis* and *Escherichia coli* was used as the antigen in this study, instead of pneumolysin from *S. pneumoniae* cultures. Both antigens produced broadly consistent results. Of note, Jalonen et al. [65] had already shown that the ELISA with pneumolysin from *S. pneumoniae* and *B. subtilis* as the antigen delivers comparable results, and it can therefore be assumed that these three different methods of pneumolysin production lack any noteworthy impact on the ELISA results.
The authors concluded that *measurement of pneumolysin antibodies in circulating immune complexes was not a clinically viable test for diagnosing PP* in their study population because of *insufficient sensitivity and specificity.* Furthermore, the test was able to exceed the sensitivity of blood cultures as a diagnostic method only at the expense of a loss of specificity so great that it renders the test *useless for vaccine efficacy studies* [64].

(d) Musher et al. [66] attempted an external validation of the ply-IC method in the United States. Serum samples were examined from 16 patients with bacteraemic pneumonia, 15 with non-bacteraemic pneumonia, 16 with pneumococcal colonisation with no signs of pneumonia or other acute bacterial infection, 16 stable COPD patients, and 40 healthy control subjects. The authors followed the laboratory protocol of Leinonen et al. [55], using pneumolysin from *E. coli* as the antigen. They found pneumolysin antibodies in circulating immune complexes in 60 % of the patients with non-bacteraemic PP, 63 % of the healthy patients with pneumococcal colonisation, 44 % of the stable COPD patients, and 23 % of the healthy controls (aged 50–64 years). In bacteraemic patients antibody concentrations in the acute phase were lower than, and the reconvalescence phase similar to those in non-bacteraemic pneumococcal pneumonia patients and subjects with pneumococcal colonisation. The authors conclude that the ply-IC test does not allow a distinction between pneumococcal disease and colonisation, and is therefore unsuitable as a method for estimating disease burden caused by pneumococci or diagnosing pneumococcal pneumonia in vaccine efficacy studies [66].

2. After completion of our meta-analysis, two further meta-analyses of the efficacy of PPSV23 in older adults were published in 2016 [67, 68].

(a) The meta-analysis by Schiffner-Rohe [67] was commissioned by Pfizer and all authors were employees of the company or a consulting firm working for it. Because Pfizer is the manufacturer of the competing product PCV13, the authors have a strong conflict of interest.
The authors only considered RCTs. They argue that the RCT by Maruyama et al. [39] should not be considered. They state that the study population was not representative of the STIKO recommendation's target group because it consisted of retirement home residents, and because the study was conducted in Japan, not Europe. However, following this argument, the RCT by Örtqvist et al. [40], which Schiffner-Rohe included, should also have been excluded because all study participants had been treated for pneumonia as inpatients and were later vaccinated with PPSV23 or placebo. This population is also not representative of the target group of the STIKO recommendation.

(b) Kraicer-Melamed et al. [68] meta-analysed the efficacy of PPSV23 against IPD, all-cause CAP, and PP in RCTs and observational studies. They used "living in retirement homes" as an exclusion criterion for the literature search, without further justification. Thereby they excluded the Maruyama et al. RCT but included the RCTs by Örtqvist et al. and Honkanen et al. [41]. Nevertheless, the authors concluded that the available data indicated efficacy of PPSV23 against IPD and did not exclude efficacy of PPSV23 against all-cause CAP.

The participants in the RCT by Maruyama et al. were in fact older, and probably had more comorbidities than the av-

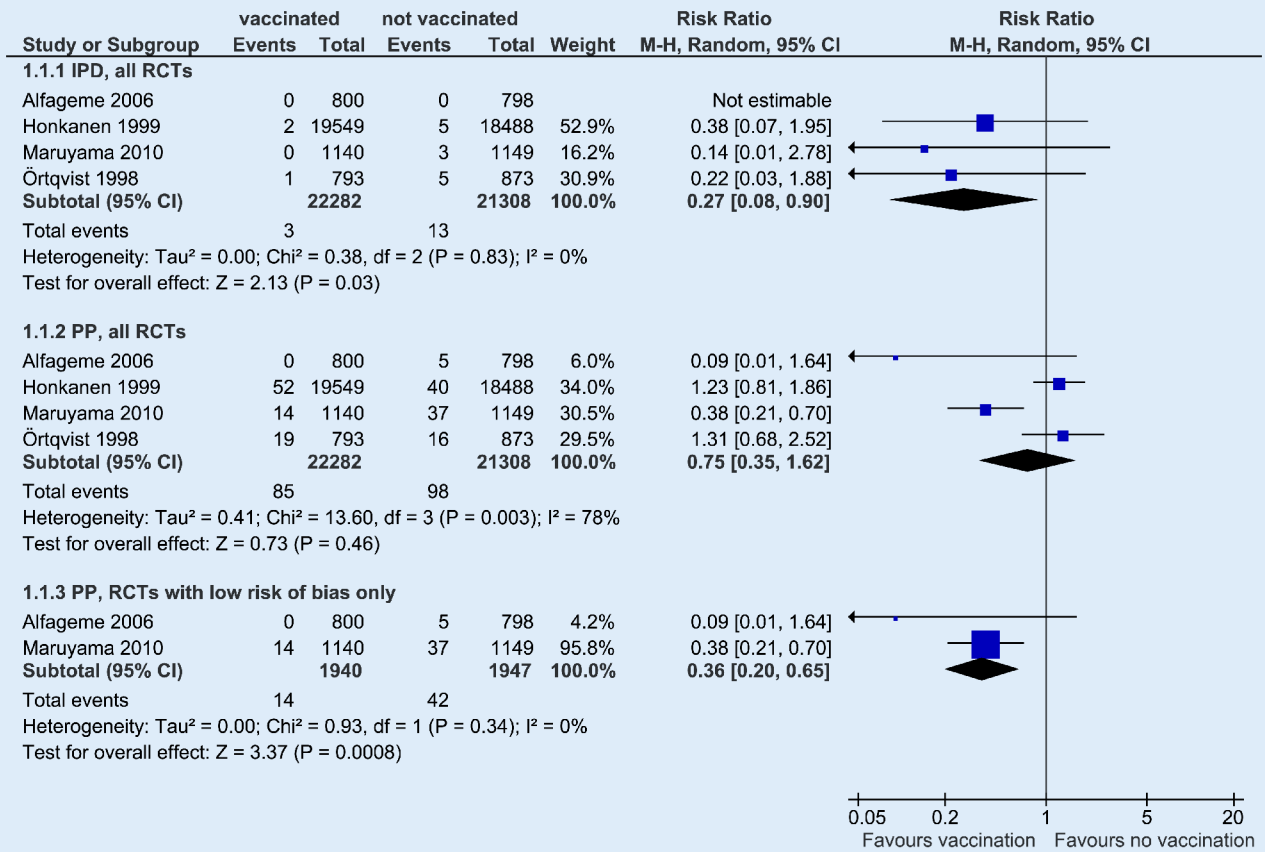

Fig. 5 ▲ Efficacy of PPSV23 against invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP) caused by any serotype, results of RCTs
The person-years of the follow-up are shown as Total

erage person aged ≥60 years in Germany. It is not clear whether that had any impact on the observed vaccine efficacy. In STIKO's opinion there is no plausible biological reason why PPSV23 should be more effective in this study population than in healthier people or the younger of older adults. Thus, the efficacy achievable with PPSV23 in the target group of the STIKO recommendation is more likely to be *under*estimated than overestimated through inclusion of the Maruyama study. The same applies to the RCT by Örtqvist et al., which we included in our meta-analysis for the endpoint IPD. Its exclusion for the endpoint PP was not due to any questionable representativeness of the study population, but rather, as explained above, because of its use of the pneumolysin antibody test with doubtful specificity for the diagnosis of PP. For the same reason, we did not consider the Honkanen et al. study [41] for the endpoint PP in our meta-analysis.

Evidence from observational studies. One essential problem of observational studies is that the respective groups of vaccinated and unvaccinated people frequently differ with regard to underlying diseases and other health-related factors (e. g. lifestyle). Correspondingly, the basic risk of pneumococcal disease can be different in the two groups, even without vaccination. That can lead to a distortion of the observed relative risks (i. e. confounding). For that reason, we included only studies in which important confounders (at least age and comorbidities) were recorded and taken into account in an adjusted statistical analysis.

Three registry-based cohort studies [43, 44, 46], 3 matched case-control studies [47–49], and 4 "case-case studies" using the Broome method [21, 50–52] fulfilled this condition. Efficacy against PP was also investigated in a study with a similar case-case design, in which pneumonia cases caused by other pathogens or with no identified pathogen were used as the control group [53]. A large registry-based cohort study from Sweden [69] was excluded because it did not take confounders into account. Not all publications reported findings on all endpoints of interest to us.

We used the adjusted odds ratios (OR) for the meta-analyses (**Fig. 6**). In the cohort studies (**Fig. 6a**), the pooled point estimates of the *vaccine effectiveness against IPD by any serotype was 45 %, and 48 % against PP.* This is lower than the corresponding figures in the RCTs, though the CIs overlap widely. The pooled vaccine effectiveness against IPD (by any serotype) in the case-control studies (**Fig. 6b**) was 59 %; this figure falls between the results of the RCTs and the cohort studies. Effectiveness was lower in the most recent study, conducted by Leventer-Roberts et al. [48]. That may be because the percentage of IPD cases caused by serotypes contained in PPSV23 had al-

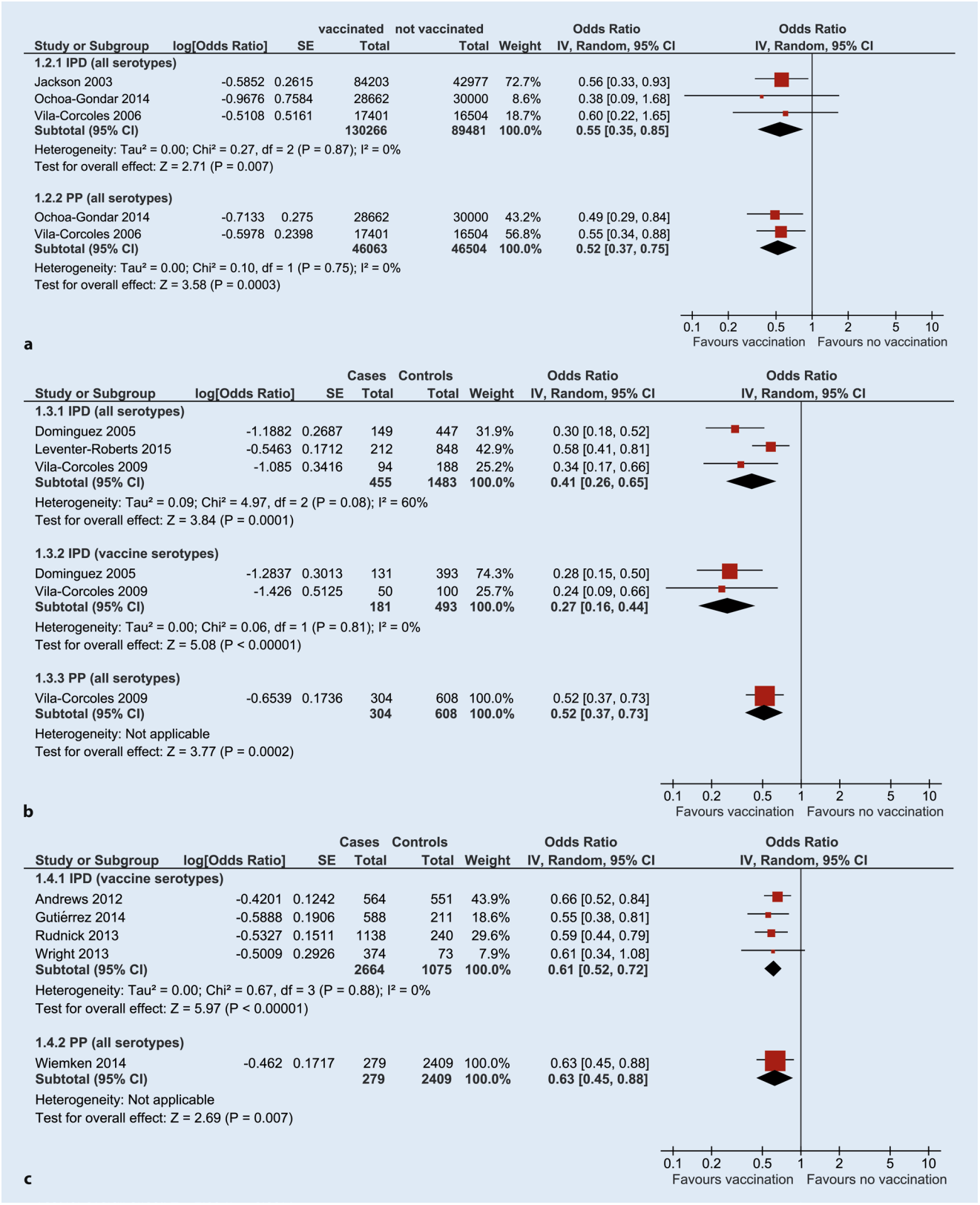

Fig. 6 ◀ Effectiveness of PPSV23 against invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP), results of observational studies. **a** Registry-based cohort studies. The person years of the follow-up are shown as Total. The adjusted odds ratios are shown. The data for the Ochoa-Gondar et al. study refer to people who have been vaccinated with PPSV23 within the past five years compared to those who are unvaccinated. **b** Case control studies. **c** Case-case studies. We calculated the odds ratio for the Andrews et al. study based on the data in Table 3 of the publication for the combined group of ≥65-year-olds vaccinated in the past 0-<2 or 2-<5 years, excluding the immunocompromised group

ready dropped because of infant vaccination with PCV7 when the study was conducted in 2008–2010. Correspondingly, the effectiveness against IPD caused by vaccine serotypes (VT-IPD) in the older case-control studies was only slightly higher than that against IPD caused by any serotype, because the percentage of non-PPSV23 serotypes was low at the time these studies were conducted. The pooled effectiveness against VT-IPD in the case-case studies using the Broome method (**Fig. 6c**) was lower, at 39 %. The reason for this is not apparent.

The pooled vaccine effectiveness against pneumococcal pneumonia caused by any serotype was similar across all study types: 48 % in cohort studies, 48 % in one case-control study, and 37 % in one case-case study, with broadly overlapping CIs. Because many of the cases were diagnosed using urine antigen test, there is no separate information on the efficacy against PP caused by vaccine serotypes.

PCV13

The efficacy of PCV13 against clinical endpoints in people aged ≥65 years was investigated in a large placebo-controlled RCT (CAPITA trial) in the Netherlands, where there is, to date, no general recommendation of pneumococcal vaccination for older adults. The results were reported in March 2015 in a peer-reviewed publication [22]. Additional information on the study design can be found in [70].

The study participants were recruited between September 2008 and January 2010 among residents of the Netherlands aged ≥65 years (mean, 72.8 years). Exclusion criteria included immunodeficiency, immunosuppression, earlier vaccination against pneumococci, or residence in a retirement home [70]. Approximately 42,000 participants were vaccinated with PCV13 and around 42,000 with placebo, and followed-up for a mean of 4 years. In addition to the usual methods for diagnosing PP, a specially developed urine antigen test was used. This assay selectively detects antigens of the pneumococcal serotypes contained in PCV13 [71]. That allowed cases caused by vaccine serotypes (VT-PP) to be distinguished from those caused by non-vaccine serotypes, even in non-invasive pneumococcal pneumonia.

In the per-protocol study population, 7 cases of VT-IPD occurred in the vaccinated group and 28 in the placebo group, equalling a vaccine efficacy of 75 % (95 % CI, 41–91 %) against VT-IPD. Thirty-three cases of non-invasive VT-PP occurred in the vaccinated group and 60 in the placebo group, equalling a vaccine efficacy of 45 % (95.2 % CI, 14–65 %) against non-invasive VT-PP. The efficacy of PCV13 against IPD caused by any serotype was 52 % (95 % CI, 22–71 %); against non-invasive PP by any serotype it was 24 % (95 % CI, –6 to 46 %).

Case patients who were immuno*competent* at the time of vaccination, but who later developed immunodeficiency, were excluded from the per-protocol population. These individuals were included in the *"modified intention-to-treat analysis"*. This analysis, which reflects the real life situation better than the per-protocol analysis, showed a vaccine efficacy of 76 % (95 % CI, 47–90 %) against VT-IPD and 41 % (95.2 % CI, 13–61 %) against non-invasive VT-PP. The vaccine efficacy against IPD caused by any serotype was 49 % (95 % CI, 21–67 %); against non-invasive PP caused by any serotype it was 17 % (95.2 % CI, –10 to 38 %) see **Fig. 7**.

The group of excluded participants, i. e. those who developed immunodeficiency in the period between vaccination and disease, exhibited no statistically significant vaccine efficacy of PCV13. This may have been due to the small number of cases (4 cases of VT-IPD, 17 cases of non-invasive VT-PP). Arithmetically vaccine efficacy against non-invasive VT-PP in this group was 30 % (95 % CI, –105 to 78 %) [23].

The CAPITA trial demonstrated a statistically significant vaccine efficacy of PCV13 against IPD (VT and any serotype) and against non-invasive PP *by vaccine serotypes*. However, no significant efficacy was observed against non-invasive PP by any serotype. This holds true for both the per-protocol and the modified-intention-to-treat analysis.

Quality of evidence based on GRADE criteria

Regarding *PPSV23*, we ranked the quality of the evidence for both endpoints (IPD, PP) at the second-highest level, "moderate". RCTs are primarily classified as high-quality evidence in GRADE. The downgrade owed to the wide CIs of the efficacy against IPD and a study population that deviates from the PICO question (indirectness) for the endpoint PP (see GRADE profile **Table A1** in the Appendix). That results in a degree of uncertainty regarding the actual level of the efficacy of PPSV23.

Regarding *PCV13*, we ranked the quality of evidence as "high" for the endpoint VT-IPD, and as "moderate" for the endpoint VT-PP, because of the wide CI (see GRADE profile **Table A2** in the Appendix). We did not assess the quality of evidence for the endpoints IPD and PP caused by any serotype because the observed efficacies were largely determined by the local serotype mix at the time of the study. Because infants in the Netherlands were vaccinated with PCV7 or PCV10 at the time of the CAPITA study, the serotype mix is not comparable to the current situation in Germany, where herd protection by universal infant vaccination with PCV13 since 2010 has led to a significant drop in PCV13 serotypes (except ST 3) in all age groups.

Comparative assessment of efficacy data for PPSV23 and PCV13

The point estimates from RCTs for efficacy against IPD caused by serotypes contained in the respective vaccine are nearly identical: 73 % for PPSV23 and 76 % for PCV13 (*modified intention-to-treat* analysis). The efficacy of PPSV23 against PP *caused by any serotype* was significantly higher (64 % in RCTs and 48 % in cohort studies) than that of PCV13 (17 %), and similar to the efficacy of PCV13 against *vaccine-type* PP (41 %). However, the CIs are so wide that a *comparative* assessment of the two vaccines is scarcely possible. Thus, it cannot be ruled out with certainty that one of the two vaccines may have a greater or lower efficacy to a relevant degree.

With regard to the endpoint PP, the data on vaccine efficacy from RCTs are based on only one RCT with PCV13 (CAPITA study) and only 2 RCTs with PPSV23. Furthermore, the pooled vaccine efficacy of PPSV23 is largely determined by the Maruyama et al. RCT. None of the 3 RCTs investigated a study population completely representative of the

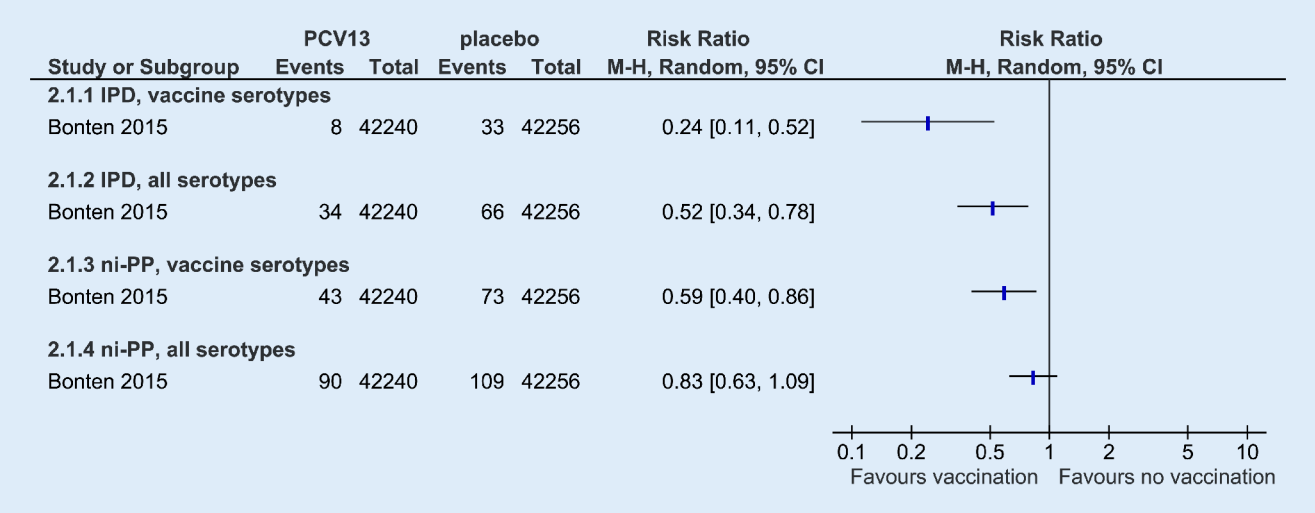

Fig. 7 ▲ Efficacy of PCV13 against invasive pneumococcal diseases (IPD) and non-invasive pneumococcal pneumonia (ni-PP), CAPITA RCT, modified intention-to-treat analysis
This graph was created using the Review Manager software. In some cases, the boundaries of the confidence intervals (CI) deviate slightly (by 0.01 to 0.02) from the figures in the publication, where a different statistical procedure was used to calculate the CI, and in some cases a 95.2 % CI was given

STIKO recommendation target group. On average, the participants in the trials by Maruyama et al. and Alfageme et al. were older and/or (probably) had more comorbidities, which may lead to underestimation of the vaccine efficacy achievable by PPSV23 among older adults in Germany. Conversely, the efficacy of PCV13 among older adults in Germany is probably lower than that recorded in the CAPITA trial because CAPITA only included people without immunodeficiency or immunosuppression.

It is often claimed that the protection offered by the pure (non-conjugate) polysaccharide vaccine against PP has not been proved (e. g. [22, 61]). However, the current Cochrane review from 2013 [36] shows a pooled efficacy of 28 % (95 % CI, 7–44 %) against *all-cause pneumonia*. This means that efficacy against PP must be higher, because only a fraction of all CAP cases is caused by pneumococci. Studies of very different populations (i. e. young and old, developed and developing countries) were included in that meta-analysis, leading to a large heterogeneity of the results. Polysaccharide vaccines demonstrated high efficacy against PP in several classic RCTs conducted in the 1970s among young South African goldminers, who had a very high risk of pneumococcal pneumonia. In this population, highly significant vaccine efficacies of 76–92 % against VT-PP have been observed for various experimental 6-, 12-, and 13-valent PPSVs [72, 73]. Even though these findings cannot be applied quantitatively to people aged ≥60 years, or to the current PPSV23 vaccine, they do impressively demonstrate the proof of principle that pure polysaccharide vaccines can provide protection from PP.

From a pathophysiological perspective, it appears implausible that protection from non-bacteraemic pneumonia should solely depend on prevention of pneumococcal colonisation of the upper respiratory tract through mucosal antibodies. When a colonised person aspirates pneumococci it leads to a local inflammatory reaction with the exudation of plasma (oedema fluid) into the alveoli. The emergent plasma antibodies and complement components cause opsonisation of the pneumococci in the alveoli and, thus, induce their phagocytosis and killing [74]. Thereby, plasma antibodies also contribute to preventing clinical manifestation of pneumonia. The result of the Maruyama et al. [39] RCT, in which an efficacy of 62 % (95 % CI, 30–79 %) of PPSV23 against PP by any serotype was observed in retirement home residents, underscores this view.

With regard to the *population-based impact achievable by the two vaccines*, it must be noted that the serotypes contained in PCV13 have regressed considerably since the use of PCV7 and PCV13 for infant vaccination. In the 2015–'16 season they caused only 30 % of the IPD cases in people aged ≥60 years in Germany. In contrast, serotypes contained in PPSV23 caused 70 % of the IPD cases in this age group (**Fig. 3**). The consequence is that vaccination with PPSV23 can prevent more IPD cases at the population level than PCV13, even if the efficacy of PPSV23 were only half that of PCV13.

No recent data are available on *serotype distribution in non-invasive PP* cases in Germany because, in these cases, often no pathogens are cultivated (e. g. from sputum) and the diagnosis is based on a positive BinaxNOW® urine antigen test, which does not allow for serotype differentiation. Presumably serotype distribution is influenced by herd protection through infant vaccination in a similar manner as in IPD cases. In Denmark, serotype distribution in PP cases in adults was investigated in 2011, 1 year after the switch from PCV7 to PCV13 in the infant vaccination programme [75]. In PP cases *with* bacteraemia (i. e. IPD cases), the proportion of PCV13 serotypes was 59 % (95 % CI, 48–70 %), and that of PPSV23 serotypes was 87 % (95 % CI, 74–100 %). A similar relative distribution, though at a lower level, was found among non-bacteraemic PP cases (pathogen cultivation from sputum, pleural punctate, or bron-

chial lavage); 34 % (95 % CI, 25–43 %) of which were caused by PCV13 serotypes and 57 % (95 % CI, 48–66 %) by PPSV23 serotypes.

Rodrigo et al. [76] studied the serotype distribution among mostly non-bacteraemic PP cases in adults (median age, 71 years) in England. Over 5 years (September 2008 to August 2013) 2,229 in-patients with CAP at two major hospitals in Nottingham were included. In 653 (29 %) of these patients, PP was diagnosed, thereof 87 (13 %) with bacteraemia. In April 2010, approximately half way through the study, the infant vaccination programme in England switched from PCV7 to PCV13. Compared with the study period before the switch to PCV13, a reduction in PP cases caused by PCV13 of approximately 40 % occurred thereafter. The greatest reduction was in serotypes also contained in PCV7 (–88 %); while the six extra serotypes contained in PCV13 dropped by 30 %. It is not surprising that the six extra serotypes dropped less, because only the first 3 years after the switch to PCV13 in the infant vaccination programme were investigated, and it can take several years for herd protection effects to accumulate [77].

Duration of vaccine protection

The duration of protection provided by *PPSV23* can be roughly estimated through an overall assessment of the findings of our meta-analyses. The vaccine efficacy of PPSV23 observed in the RCTs applies to a follow-up period of 2–3 years after vaccination. In contrast, a variable – on average longer – period following vaccination was investigated in the cohort studies because many of the participants had already been vaccinated several years before recruitment. This probably explains why the observed vaccine effectiveness in the cohort studies was lower.

The effectiveness for PPSV23 of 48 % against PP and 62 % against IPD cited for the cohort studies by Ochoa-Gondar et al. [44] in this report apply to people who had been vaccinated in the previous 5 years, compared with people never vaccinated against pneumococci. People who had "ever [been] vaccinated" (i. e. including vaccinations >5 years ago) did not have a significantly lower illness rate than those never vaccinated. That means that no significant protection was detectable for the period exceeding 5 years after vaccination.

Andrews et al. [21] arrived at similar results in their calculation of PPSV23 effectiveness using the Broome method. For people aged 65–74 years, effectiveness against VT-IPD was 65 % (95 % CI, 23–84 %) within <2 years after vaccination and 62 % (95 % CI, 21–82 %) in the period 2–5 years after vaccination. More than 5 years after vaccination, a significantly lower, and statistically no longer significant, effectiveness of 28 % (95 % CI, –72 to 70 %) was found (Table 4 in [21]).

These data suggest that vaccine efficacy after a one-time vaccination with PPSV23 declines continuously from a relatively high level shortly after vaccination. As soon as 5 years after vaccination a large portion of those vaccinated may no longer be protected.

Regarding duration of protection after *vaccination with PCV13* of older adults, the CAPITA study [22] provides the only available data. No significant reduction in vaccine efficacy was detected during the 4-year follow-up period in this RCT. However, the case number in the fourth year was so low that an onset of reduction cannot be ruled out. Data from children's vaccination suggest that the duration of protection provided by a one-time vaccination with PCV13 is limited [78].

6.3 Reactogenicity and safety of a one-time vaccination with PPSV23 or PCV13

Authors SG and TH identified studies on the reactogenicity and safety ("safety aspects") of PPSV23 and PCV13 in older adults by using a systematic literature search based on the PICO questions in **Table 4**. See **Fig. A2** in the Appendix for the search strategy and flow chart.

Three studies (two RCTs and one cohort study) on safety aspects were found for PPSV23, and two RCTs for PCV13. Inactivated influenza vaccine (IIV) was administered at the same time to both the intervention and control groups. Data on safety aspects from the CAPITA study (RCT PCV13 vs. placebo) available in the form of a *supplementary appendix* [23] since March 2015 were taken into account retroactively. Safety aspects in a direct comparison between PPSV23 and PCV13 were investigated in three RCTs (**Table 5**).

Table 6 lists the results of the studies on PPSV23 or PCV13. The publication by Grilli et al. [79] contained no evaluable data. Information on the endpoint "unplanned medical visits" was found only in D'Alessandro et al. [81]. A total of 305 people (1 % of the study population) had an unplanned medical examination, 1.3 % in the intervention group and 0.9 % in the control group. Four people – all vaccinated with PPSV23 and IIV – were hospitalised because of dyspnoea with malaise, long-lasting fever, bronchopneumonia, or circulatory collapse, though it is unclear whether there was a causal relationship with the vaccination.

PPSV23 + inactivated influenza vaccine (IIV) vs. IIV alone

The assessment was based on the studies by Honkanen et al. [80] and D'Alessandro et al. [81] Unplanned medical visits, muscle pain, joint pain, local reactions, and/or malaise/fatigue occurred significantly more frequently among those vaccinated with PPSV23 than in the control group. There was no significant difference in frequency of fever and headache. The GRADE-ing of the best available evidence resulted in "very low" to "low" quality of the evidence for the investigated endpoints (see GRADE profile **Table A3** in the Appendix).

PCV13 (+IIV) vs. placebo (+IIV)

In the three evaluated RCTs [23, 82, 83], those vaccinated with PCV13 reported muscle pain and local pain significantly more often (GRADE: "moderate" quality of evidence). Fever, malaise, headache, muscle and joint pain occurred more frequently among those vaccinated with PCV13, but the differences were not (or not in all three studies) significant (GRADE: "low" and "moderate" quality of evidence, respectively. See GRADE profile **Table A4** in the Appendix)

PPSV23 vs. PCV13

In the direct comparison of the two vaccines (**Table 7**) there was a consistently higher percentage of muscle pain among

Table 4 Inclusion criteria for the literature research on safety aspects in older adults (PICO questions)

Population	– Persons 60 years and over, healthy or with age-typical underlying disease (expanded search for adults age ≥50 years, depending on data available) – Countries/populations with living conditions comparable to those in Germany
Intervention	– first vaccination with PPSV23 (no follow-up vaccination) – first vaccination with PCV13 (no follow-up vaccination)
Comparator intervention	– No vaccination or placebo *or* – Direct comparison PPSV23 vs. PCV13
Endpoints	– Fever >38°C (>100°F) ≤14 days after vaccination – Unplanned medical visits ≤14 days after vaccination
	– Systemic effects: headache, malaise, muscle and/or joint pain – Severe local reactions: pain

Table 5 Studies included on safety aspects of the vaccination with PPSV23 or PCV13 in older adults

Publication	Study type	Country	Study population	Intervention	Control
Grilli 1997 [79]	RCT	Italy	Retirement home residents, age: 78 years (range: 41–94 y)	**PPSV23 + IIV** *n* = 50	**IIV** *n* = 42
Honkanen 1996 [80]	RCT	Finland	Resident population, age ≥65 years	**PPSV23 + IIV** *n* = 4,755	**IIV** *n* = 4,581
D'Alessandro 2004 [81]	CS	Italy	Vaccination of seniors ≥65 years by general practitioners	**PPSV23 + IIV** *n* = 12,485	**IIV** *n* = 16,601
Frenck 2012 [82]	RCT	USA	Healthy adults 50–59 years; phase 3 study	**PCV13 + IIV** *n* = 551	**Placebo + IIV** *n* = 560
Schwarz 2011 [83]	RCT	Germany	Healthy adults ≥65 years	**PCV13 + IIV** *n* = 576	**Placebo + IIV** *n* = 575
Bonten 2015 [23]	RCT	Nether-lands	Healthy adults ≥65 years	**PCV13** *n* = 918	**Placebo** *n* = 907
Greenberg 2014 [84]	RCT	USA	Seniors 60–64 years	**PPSV23** *n* = 238	**PCV13** *n* = 482
Jackson 2013 [85]	RCT	USA	Seniors 60–64 years	**PPSV23** *n* = 414	**PCV13** *n* = 417
Juergens 2014 [86]	RCT	South Africa	Healthy seniors ≥65 years	**PPSV23** *n* = 301	**PCV13** *n* = 309

CS cohort study, *IIV* inactivated influenza vaccine, *RCT* Randomized controlled trial

PPSV23 recipients across all evaluated studies. Only slight differences were detected for the other investigated safety endpoints, without a clear trend in favour of either vaccine. Only percentages were reported in the three RCTs. It is not possible to translate these back into absolute numbers. For that reason, an assessment based on GRADE could not be conducted.

Summary and assessment of the safety aspects

For the most part, more adverse events occurred in the intervention groups than in the control groups, regardless of the vaccine being PPSV23 or PCV13. The quality of evidence is in the area of "very low" to "moderate". Frequency of side effects must not be compared across studies with PPSV23 + IIV and PCV13 + IIV because of the different follow-up periods and recording methods.

In the direct comparison of PPSV23 and PCV13, muscle pain was observed more frequently after PPSV23, but the difference was significant in only one of the three studies. The other investigated endpoints appear to occur with similar frequency after both vaccines, but there are some major differences in the reported frequency of individual endpoints (e. g. fever) between studies. The presentation of the data in the publications does not allow meta-analysis.

Based on the limited data available, *no important differences in reactogenicity between PPSV23 and PCV13 could be detected*. However, there are no studies on possible side effects that occur >14 days after vaccination, and the sizes of the identified studies are insufficient to detect rare potentially serious side effects.

6.4 Efficacy and reactogenicity of repeated vaccination with PPSV23

Approach

To assess this question, authors CR, TH, and GF on 26 June 2015 conducted a systematic literature research based on the PICO questions in **Table 8** in the data-

Table 6 Reactogenicity of the vaccination with PPSV23 or PCV13 in older adults

	Honkanen 1996	D'Alessandro 2004	Frenck 2012	Schwarz 2011	Bonten 2015 (CAPITA study)
Follow up	*4 days*	*3 days*	*14 days*	*14 days*	*7 days*
I	PPSV23 + IIV	PPSV23 + IIV	PCV13 + IIV	PCV13 + IIV	PCV13 [a]
C	IIV	IIV	Placebo + IIV	Placebo + IIV	Placebo [a]
Endpoint					
Fever ≥38°C					
I	9/4755 (0.2 %)	329/12,485 (2.6 %)[b]	9/261 (3.4 %)	18/431 (4.2 %)	**26/885 (2.9 %)**
C	5/4581 (0.1 %)	185/16,601 (1.1 %)[b]	4/257 (1.6 %)	14/433 (3.2 %)	**11/860 (1.3 %)**
Unplanned medical visits					
I	n.i.	**163/12,485 (1.3 %)**	n.i.	n.i.	n.i.
C	n.i.	**142/16,601 (0.9 %)**	n.i.	n.i.	n.i.
New muscle pain					
I	n.i.	**135/12,485 (1.1 %)**[c]	**252/385 (65.5 %)**	**126/468 (26.9 %)**	**165/896 (18.4 %)**
C	n.i.	**52/16,601 (0.3 %)**[c]	**123/326 (37.7 %)**	**76/456 (16.7 %)**	**73/868 (8.4 %)**
Any aggravated muscle pain					
I	n.i.		**109/314 (34.7 %)**	85/454 (18.7 %)	**81/889 (9.1 %)**
C	n.i.		**71/294 (24.1 %)**	63/449 (14.0 %)	**38/866 (4.4 %)**
New joint pain					
I	n.i.	**128/12,485 (1.0 %)**[c]	102/309 (33.0 %)	73/452 (15.7 %)	66/886 (7.4 %)
C	n.i.	**55/16,601 (0.3 %)**[c]	73/296 (24.7 %)	59/451 (13.0 %)	47/866 (5.4 %)
Any aggravated joint pain					
I	n.i.		62/292 (21.2 %)	71/452 (15.7 %)	46/884 (5.2 %)
C	n.i.		51/284 (18.0 %)	58/447 (13.0 %)	36/865 (4.2 %)
Local pain					
I	**441/4,755 (9.3 %)**[d]	**902/12,485 (7.2 %)**	**407/469 (86.8 %)**	n.i.	**330/914 (36.1 %)**
C	**284/4581 (6.2 %)**[d]	**555/16,601 (3.3 %)**	**119/321 (37.1 %)**	n.i.	**53/863 (6.1 %)**
Headache					
I	n.i.	74/12,485 (0.6 %)	**263/399 (65.9 %)**	154/472 (32.6 %)	142/892 (15.9 %)
C	n.i.	75/16,601 (0.5 %)	**216/382 (56.5 %)**	139/468 (29.7 %)	130/878 (14.8 %)
Malaise/fatigue					
I	n.i.	**323/12,485 (2.6 %)**	226/389 (58.1 %)	178/476 (37.4 %)	**168/895 (18.8 %)**
C	n.i.	**222/16,601 (1.3 %)**	188/359 (52.4 %)	154/483 (31.9 %)	**130/876 (14.8 %)**

Significantly different values in ***bold***.
I intervention arm, ***C*** control arm, ***IIV*** inactivated influenza vaccine, ***n. i.*** no information
[a]The majority of subjects in both study arms were also vaccinated against influenza. In the safety population the influenza vaccination was administered at least 7 days before or after the PCV13 or placebo vaccination, [b]Fever >37.8°C, [c]No distinction between newly occurring pain and aggravation of existing pain, [d]Local reactions of all types (pain, swelling, redness); pain not reported separately

bases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. A search was also conducted in the reference lists of the studies included, as well as the registry of clinical trials, Clinicaltrials.gov. We followed the PRISMA directives [37] in conducting the systematic literature review. A detailed report of our review has been accepted for publication in BMC Infectious Diseases (Remschmidt et al.).

The literature search resulted in 1,162 returns, of which only 14 studies [26, 27, 60, 87–97] met the inclusion criteria (see **Table 9**). We excluded studies that examined only immunosuppressed patients (e. g. HIV-positive patients or kidney transplant patients), in which a different vaccine formulation (e. g. PPSV14) was used, or in which the repeat vaccination was administered within 1 year of the initial vaccination. Data on clinical endpoints were not reported in any of the included studies. Nine studies reported immunogenicity data, and 10 reported data on safety and reactogenicity.

Immunogenicity

Immunogenicity data were reported in 9 studies [26, 27, 88–90, 92, 93, 96, 97]. IgG

Table 7 Reactogenicity of the vaccination with PPSV23 or PCV13 in direct comparison

	Greenberg 2014 [a]	Jackson 2013	Juergens 2014 [b]
Follow up	*14 days*	*14 days*	*14 days*
Endpoint			
Fever ≥38°C			
PPSV23	1.6%	1.1%	9.6%
PCV13	4.2%	4.0%	8.3%
Unplanned medical visits			
PPSV23	n.i.	n.i.	n.i.
PCV13	n.i.	n.i.	n.i.
New general muscle pain			
PPSV23	51.5%	57.8%	25.1%
PCV13	46.9%	56.2%	24.6%
Aggravated muscle pain			
PPSV23	**32.5%**	37.3%	16.0%
PCV13	**22.0%**	32.6%	13.0%
New joint pain			
PPSV23	23.8%	30.1%	13.0%
PCV13	15.5%	24.4%	10.7%
Aggravated joint pain			
PPSV23	21.1%	21.4%	10.4%
PCV13	14.0%	24.9%	9.2%
Local pain			
PPSV23	0.8% [c]	**8.6%**	2.1% [c]
PCV13	2.3% [c]	**1.7%**	3.0% [c]
Headache			
PPSV23	46.1%	54.4%	30.7%
PCV13	49.7%	54.0%	30.6%
Malaise/fatigue			
PPSV23	49.1%	61.5%	34.8%
PCV13	50.5%	63.2%	28.1%

Significantly different values in *bold*; ***n. i.*** no information

[a]For the endpoint "severe local reactions", the percentages refer to a study size of 127 to 180 persons in the PPSV23 group and 258 to 374 in the PCV13 group. For all other endpoints the study size was 127 to 202 persons in the PPSV23 group and 258 to 383 persons in the PCV13 group, [b]The percentages refer to a study size of 235 to 264 persons in the PPSV23 group and 234 to 271 persons in the PCV13 group. No *p*-values are given in the publication, [c]Severe local pain

levels were measured in 8 studies with different ELISA assays; the consensus ELISA recommended by WHO was used in only 2 studies. Five studies used an opsonophagocytic activity (OPA) assay.

We did not pool the data because the antibody (AB) levels are not comparable across studies (different laboratory assays, AB against different serotypes measured, different populations, different time intervals between vaccination and blood sampling). To compare the results of AB levels across studies, we calculated within each individual study the ratio of the AB level at identical time points after (or before) the second and first dose of PPSV23. This dimensionless ratio allows comparison of the results of the various studies. A ratio of >1 means that the AB level was higher at the same point in time after the second dose than after the first.

In general, the AB levels before the second dose (3–10 years after the first dose) were higher than in PPSV23-naive individuals before the first dose. At 1 and 2 months after vaccination, the ratio was mostly between 0.7 and 1; i. e. shortly after the second dose the rise in AB levels was less marked than after the first dose (**Fig. 8**). Only two studies measured AB levels 1 or 2 years after vaccination. The ratio for most serotypes was close to 1 in Dransfield et al. [60]. In Musher et al. [27] the ratio was >1 after 2 years; i. e. AB levels were higher on average after the second PPSV23 dose. In all four studies in which the AB levels were measured 5–10 years after the second dose, they were consistently higher than, or at least as high as, 5–10 years after the first dose (ratio ≥1).

Musher et al. [27] also examined AB levels after a third dose administered 10 years after the second. One month after the third dose, the AB levels were somewhat lower than 1 month after the second dose, but it must be taken into account that the study participants were 10 years older at the time of the third vaccination.

These results refute a sustained hyporesponsiveness after follow-up PPSV23 vaccinations in adults. They concur with comparative analyses in older adults (aged 50–80 years), who exhibited similar quantities of anti-PPS antibody producing plasma cells and memory B cells in peripheral blood (measured by ELISPOT without or with restimulation) 1 week or 2 years after vaccination with PPSV23 or PCV7 [98, 99]. The reduced frequency of memory B cells in peripheral blood through PPSV23, described but mechanistically not yet defined by a different workgroup, was mostly limited to a period of 4 weeks after vaccination. After 6 months, the number of peripheral memory B cells in the PCV7 and PPSV23 groups had fallen to a similar level [100].

As T-cell-independent antigens, pneumococcal polysaccharides (PPS) do not trigger a stronger immune response after repeated immunisation. However, various studies have shown that PPS induce efficient activation of IgM^+ memory B cells ($IgM^+IgD^+CD27^+$) and generation of long-lived plasma cells ($CD38^+CD20^{low}$). This is accompanied by the generation and persistence of IgM and IgG antibodies against PPS [101–108]. IgM^+ memory B cells circulating in the blood are the peripheral correlates of the marginal zone B cells of the spleen. They develop within

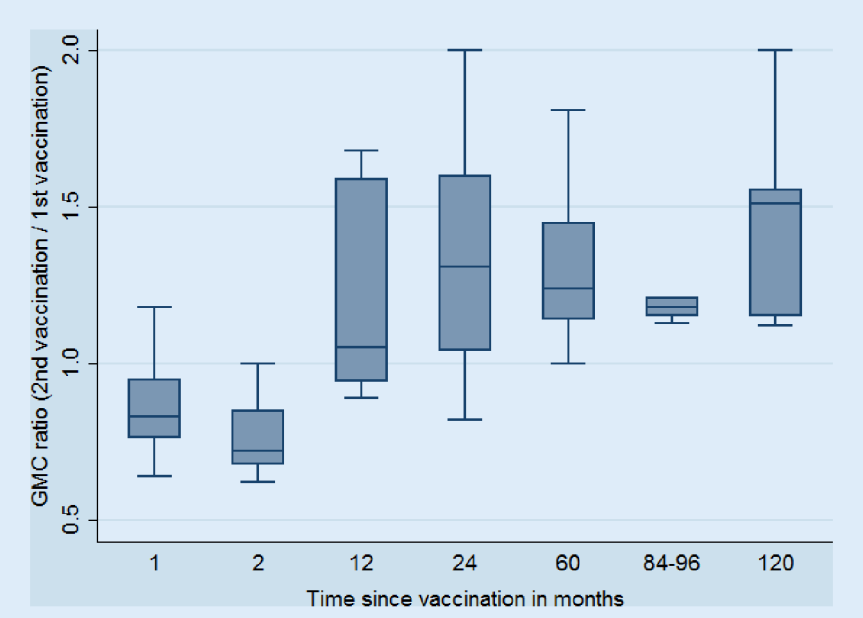

Fig. 8 ▲ Ratios of immunoglobulin G (IgG) concentration
This figure summarizes the ratios of the geometric mean IgG concentrations (GMC) for all serotypes and times after vaccination reported in all 8 included studies. The boxes indicate the 25th and 75th percentile of the GMC ratios; the horizontal line within the box is the median ratio. A ratio of >1 means that the GMC was higher at the same point in time after the 2nd dose than after the 1st dose

the first 2 years of life as part of the marginal zone's maturation. They are absent in asplenic patients [103, 105, 108]. With increasing age, the number of $IgM^+IgD^+CD27^+$ memory B cells in the blood drops substantially, as do, to a lesser degree, the numbers of plasma cells and $IgM^-IgD^-CD27^+$ switched memory B cells. This causes a lower anti-PPS IgM response after PPSV23 vaccination, while the anti-PPS IgG response (as is the opsonisation activity of the serum) is preserved by stimulation of switched memory B cells [109–112]. Although the lower IgM response may negatively influence vaccine efficacy, these findings, on the whole, indicate that PPSV23 is immunogenic also in older adults.

Reactogenicity and safety of re-vaccinations

We identified 10 studies that compared the frequency of adverse drug reactions (ADRs) after a first and second vaccination with PPSV23. Five [27, 88–90, 93] were prospective studies in which the participants recorded ADRs in a diary for 14 days after vaccination. Four studies [91, 94, 95, 97] used large databases to identify unplanned medical visits (i. e. emergency room, hospitalisation) 1–30 days after the respective vaccination. In one study [87] vaccinated people were asked retrospectively by telephone about ADRs. As these interviews did not take place until 8 months after the vaccination, there are considerable doubts about the accuracy of the answers. For that reason, we have excluded this study from further analyses.

Results

Across studies, fever (0–9 % after first dose, 0–10 % after second dose) and unplanned medical visits (0.3–2.2 % in total) were reported with similar frequency. For other ADRs there were marked differences across studies; for example, headache was reported by 2–61 % of the vaccinees after the first dose, and in 13–57 % after the second dose.

Depending on the endpoint, 1–3 studies reported significantly more unplanned medical visits, headache, general malaise, muscle pain, joint pain, severe local pain, and/or limitations in arm movement after the re-vaccination than after the initial vaccination. No significant differences were found with regard to fever or severe ADRs.

In a stratified analysis, two studies [27, 94] found significant differences in the rate of ADRs only if the interval between the first and second dose was <5 years. If the interval was >5 years [94] or 10 years [27], the difference was described as no longer statistically significant. In participants who received a second dose of PPSV23 5–13 years after the initial vaccination, Jackson et al. [89] found no statistically significant dependence of the ADR frequency on the interval between the vaccinations. However, there was a significant correlation of ADR frequency to AB levels shortly before the second dose.

Some studies also reported ADRs after further (third and fourth) PPSV23 vaccinations. No additional increase of ADRs could be clearly observed.

In summary, *the rate of non-severe ADRs was higher after re-vaccination than after the initial vaccination*. Data indicate that an interval of <5 years between the first and second vaccine dose is associated with higher ADR frequency. Additional vaccinations (third or fourth) do not appear to lead to increased ADR frequency.

6.5 Transmission model and health economic evaluation

The epidemiological modelling of pneumococcal diseases (IPD and PP) and health economic evaluation of various vaccination strategies were conducted by the Center for Health Economics Research (CHERH) at the University of Hannover. Here, the main assumptions and results of the modelling are described. The full project report (in German) is available from the RKI website: www.rki.de/impfen > Forschungsprojekte.

Model structure

As mentioned, herd protection through childhood vaccination with PCV13 strongly influences serotype distribution of pneumococcal diseases in all age groups, including the target group of people aged ≥60 years. Two circumstances are decisive:

1. Children are the main source of pneumococcal infection for older people, because children are much more frequently nasopharyngeal carriers of

Table 8 Selection criteria for studies on the efficacy and reactogenicity of repeated vaccination with PPSV23

Population	– Persons 60 years and over, healthy or with age-typical underlying disease (expanded search for adults age ≥50 years, depending on data available) – Countries/populations with living conditions comparable to those in Germany
Intervention	– Repeat vaccination with PPSV23
Comparator intervention	– First time vaccination with PPSV23
Endpoints	– Clinical endpoints: Invasive pneumococcal diseases (IPD), Pneumococcal pneumonia (with inpatient treatment) – Immunogenicity – Mean ELISA antibody levels (*geometric mean concentrations*, GMCs), opsonophagocytic indices – Safety/reactogenicity – Fever >38°C (>100°F) ≤14 days after the vaccination, unplanned medical visits ≤14 days after the vaccination, headache, malaise, muscle and/or joint pain, severe local reactions: pain, impaired arm movement

pneumococci than are older adults [113].

2. The pneumococcal conjugate vaccines used to vaccinate infants provide selective protection from nasopharyngeal colonisation with *vaccine serotypes*. Therefore, they influence the serotype mix in colonised children and, thus, the serotype mix in disease cases in all age groups as well.

To take this phenomenon into account, a dynamic transmission model was developed. Pneumococcal serotypes were divided into five groups: PCV7 serotypes, additional serotypes in PCV13 except serotype (ST) 3, ST 3, additional serotypes in PPSV23 (minus ST 6A), and non-vaccine serotypes. ST 3 is a special case because vaccination efficacy against this serotype is questionable (see Sect. 4). In the base case, it is assumed that PPSV23 and PCV13 are half as effective against ST 3 as against the other serotypes contained in the respective vaccine.

The transmission parameters that determine nasopharyngeal colonisation were calibrated based on the effects observed in Germany since introduction of universal infant vaccination and – under the assumption of stable vaccine uptake in infants – used to predict future development of case numbers and serotype mix in disease cases (IPD, PP) among older adults. Data on the varying invasiveness of different serotypes were taken into account [114, 115].

As the next step, the epidemiological and health economic effects of the following vaccination strategies were examined:

- one-time vaccination with PPSV23
- one-time vaccination with PCV13
- sequential vaccination with PCV13 + PPSV23
- repeated vaccinations with PPSV23 after initial vaccination with PPSV23
- repeated vaccinations with PPSV23 after sequential initial vaccination with PCV13 + PPSV23

In the base case, modelling was based on the assumptions listed in **Table 10**, which were varied in several sensitivity analyses.

Assessment of epidemiological effects

The model predicts a continued marked reduction in the percentage of PCV13 serotypes in pneumococcal disease cases among older adults, resulting from herd protection through infant vaccination. Therefore, in the coming years, the share of pneumococcal disease episodes preventable by vaccination of older adults with PCV13 would be limited to <30 % of all cases, even with a theoretical vaccine efficacy of 100 % and vaccine uptake of 100 %.

The main epidemiological and health economic results of the model are summarised in **Table 11 and 12.** The numbers of preventable cases etc. shown apply to the remaining lifespan of people reaching the respective vaccination age (60, 65, or 70 years) in 2016–2020, which is about 25 years with initial vaccination at age 60. Vaccine uptake of 30 % was assumed based on the situation in Germany as of the time of writing.

Table 11 shows the results for the base case. **Table 12a** shows the results of a sensitivity analysis on the assumption of 0 % efficacy of PPSV23 against PP (with PCV13 efficacy unchanged). **Table 12b and c** show the results for these two scenarios on the additional assumption that PCV13 is as effective against ST 3 as against the other vaccine serotypes, while PPSV23 is half as effective against ST 3 (in **Table 12c**, only against IPD).

Results of vaccination strategies with one-time vaccination

The results show that the vaccination of older adults with PPSV23 can, on the whole, prevent more cases, and the numbers needed to vaccinate (NNV) to prevent hospitalisation or death are lower than for vaccination with PCV13. *Therefore, PPSV23 is the superior choice for a vaccination strategy with one vaccine only.*

One-time vaccination with PPSV23 results in NNVs to prevent one hospitalisation with IPD or PP in the range of 648–801, depending on age at vaccination. NNVs to prevent one death range from 4,247 to 6,690. Few additional cases could be prevented by sequential vaccination with PCV13 + PPSV23. In the base case, depending on age at vaccination, about 3,500–6,100 older adults must be vaccinated with PCV13 in addition to PPSV23 to prevent one additional hospitalisation, and 18,000–38,000 to prevent one additional death. In contrast, doubling the PPSV23 vaccine uptake in older adults from the current c. 30 % to 60 % could roughly double the number of prevented cases.

Results of vaccination strategies with repeated vaccinations

Because of the limited duration of protection provided by PPSV23, and the lack of a booster effect, repeating the vaccination at regular intervals appears plausible. The duration of protection and the frequency and severity of side effects must be taken

Table 9 Studies included for endpoints immunogenicity, safety and reactogenicity of repeated vaccinations with PPSV23

Author, year	Study design	Country	Study population[a]	Participants (n) receiving 1st/2nd vaccine dose	Time span between vaccinations	Reported endpoints	Funding
Dransfield, 2012[b]	Prosp. cohort	USA	COPD patients, 64 (± 10) yrs	42/48	mean 8.4 (± 3.5) yrs	WHO-ELISA OPA	National Heart, Lung, and Blood Institute
Hammit, 2011	Prosp. cohort	USA	Alaska native population, 55–74 yrs	123/121 (2nd dose) and 71 (3rd or 4th dose)	6–22 yrs	non-WHO-ELISA OPA	US Department of Health and Human Services – National Vaccine Program Office
Jackson, 1999	Prosp. cohort	USA	Resident population, 50–74 yrs	901/513	5–13 yrs (median 6 yrs)	non-WHO-ELISA; OPA	Centers for Disease Control and Prevention and Lederle Laboratories
Jackson, 2006	Register-based cohort	USA	Resident population, 50–80+ yrs	279,504/36,888 (2nd dose) and 603 (3rd dose)	1–9+ yrs, after 2nd dose: mean 7 (± 3) yrs	Safety only (ICD-9 codes)	not reported
Jackson, 2013	Prosp. cohort	USA	Resident population with stable pre-existing underlying chronic conditions, 60–64 yrs	157–181 (longitudinal cohort)[c]	3,5–4 yrs	OPA; Safety (diary)	Wyeth Vaccine Research/ Pfizer
Manoff, 2010[d]	Prosp. cohort	USA	Resident population, 65–88 yrs	60/60	3–5 yrs	Merck-ELISA OPA	Funded in part by Merck & Co
Musher, 2010	Prosp. cohort	USA	Resident population ≥50 yrs	221/395[e]	3–5 yrs	Merck-ELISA	Merck & Co
Musher, 2011[f]	Prosp. cohort	USA	Resident population 60–93 yrs	67 (2nd dose)/67 (3rd dose)	10 yrs	Merck-ELISA	Merck & Co
Oshima, 2014	Prosp. cohort	Japan	COPD patients, 65–80+ yrs	40 (longitudinal cohort)	8–9 yrs	WHO-ELISA OPA	Ministry of Health, Labour, and Welfare of Japan
Shih, 2002	Register-based cohort	USA	Resident population, 65–80+ yrs	96,327/23,663	6 mo-9 yrs (43 % >5 yrs)	Safety only (ICD-9 codes)	Centers for Medicare & Medicaid Services
Snow, 1995	Register-based cohort	USA	Resident population ≥65 yrs	66,256/1,099	not reported clearly, <1 to >3 yrs	Safety only (hospital admission data, ICD-9 codes)	not reported
Törling, 2013	Prosp. cohort	Sweden	Patients with history of CAP, 50–88 yrs	61 (longitudinal cohort)	4–7 yrs (mean 5.3)	non-WHO-ELISA	not reported
Walker, 2005	Register-based cohort	USA	Alaska native population, 72 % ≥60 yrs	144/35 (2nd dose) and 179 (≥3rd dose)	45 % ≥6 yrs, 55 % <6 yrs	Safety only (ICD-9 codes, chart review)	Funded in part by Association of Schools of Public Health

CAP community acquired pneumonia, *COPD* chronic obstructive pulmonary disease, *ELISA* Enzyme-Linked Immunosorbent Assay, *OPA* Opsonophagocytic Activity assay; *Prosp.* prospective, *WHO* World Health Organization, *WHO-ELISA* ELISA according to WHO consensus protocol

a: In some studies, some analyses (e. g. safety) were conducted in a smaller subpopulation.

b: Published as randomized controlled trial but treated as cohort study here.

c: Not all patients were considered for all endpoints.

d: Sub-study of Musher, 2010

e: Number of participants at 5 yrs: 159/181. Only the results for the sub-group of ≥ 65 year olds were considered for this analysis.

f: Extension study of Musher, 2010

into account in defining the vaccination interval. Intervals <6 years were not modelled because more side effects are to be expected with shorter intervals.

The calculations in **Table 11 and 12**. are based on the assumption that re-vaccinations have the same efficacy as the initial vaccination, and that all people who receive the initial vaccination (30 % of each age cohort) receive re-vaccinations at the defined intervals for the rest of their lives.

Because the risk of falling ill with a pneumococcal infection increases with age, both the individual and epidemiological benefits of vaccination increase with age. Thus, the sum of re-vaccinations can prevent far more cases than one-time vaccination, and the NNVs are markedly lower. That also applies to a sensitivity analysis on the assumption that repeat vaccinations are only 75 % as effective as the initial vaccination (data not shown).

Table 10 Assumptions for modelling (base case)

Parameter	Value assumed	Based on
Vaccine uptake among seniors	30 %	DEGS study [15]
Efficacy of PPSV23		
– against VT-PP	66.5 %*	Own meta-analysis of RCTs (**Fig. 5**)
– against VT-IPD	75.0 %*	Own meta-analysis of RCTs (**Fig. 5**)
– duration of protection **	IPD: 4.7 years CAP: 3.8 years	Modelled based on the results of RCTs and cohort studies
– against serotype 3	Half efficacy	see Sect. 4
Efficacy of PCV13		
– against VT-PP	45.9 %*	CAPITA study [22]
– against VT-IPD	76.6 %*	CAPITA study [22]
– duration of protection **	8.2 years	CAPITA study and English data on the duration of protection in children [78]
– against serotype 3	Half efficacy	see Sect. 4
Incidence of IPD	Age-dependent	Result of the dynamic transmission model for Pnc carriers in consideration of infant vaccination since 2006, based on German data on IPD incidence before the introduction of infant vaccination [116, 117]
Incidence of PP	Age-dependent	Incidence data from federal health reports and IMS-Health, estimated percentage of PP among all CAP cases 20 % [33]
Case fatality	Age-dependent	Based on serotype-specific English data [118], adjusted to serotype mix and age structure in Germany
Serotype mix	Dependent on calendar year	Result of dynamic transmission model, serotyping results of the National Reference Centre for streptococci
Disease costs per case		
– IPD	€ 8,581	DRG browser 2012/2014
– CAP, inpatient treatment	€ 3,178	DRG browser 2012/2014
Vaccine prices (per dose, pack of 10)		
– PPSV23	€ 29.08	Lauer scale of charges 15 October 2015
– PCV13	€ 60.24	Lauer scale of charges 15 October 2015
– Vaccination fees	€ 7.19	Average of vaccination agreements
Discounting	3 %	

* Initial vaccination efficacy, reduction over time was taken into account in the model. Values for PPSV23 apply to cases caused by any serotype, but were used in the model as efficacy against cases caused by vaccine serotypes (VT) to provide a conservative model.
** The period of protection shown is an arithmetical mean that takes the waning of protection over time into account.

The effects resulting from an initial sequential vaccination with PCV13 and PPSV23, instead of PPSV23 alone, were also modelled. In the base case and in scenarios shown in **Table 12a and b**, sequential vaccination can prevent only around 2–20 additional hospitalisations and 1–3 additional deaths per year, with very high NNVs and costs per quality-adjusted life year (QALY). Only in the scenario in **Table 12c**, sequential vaccination leads to noteworthy numbers of additional prevented hospitalisations and deaths, with reasonable NNVs and costs of <€ 100,000 per QALY. This scenario assumes a lack of efficacy of PPSV23 against non-bacteraemic PP and lower efficacy against ST 3 for PPSV23, but not for PCV13. STIKO considers this scenario highly improbable for the reasons given in Sect. 4 and 6.2. The scenario was modelled to get an impression of how drastic the assumptions in favour of PCV13 need to be to achieve reasonable NNVs and costs per QALY for the sequential vaccination.

Health economic evaluation

Assuming a vaccine uptake of 30 % of each cohort reaching age 60 (or 65 or 70) in 2016–2020, and taking into account the direct and indirect costs (work lost), the various vaccination strategies result in the figures shown in **Table 11 and 12**.

In the base case (**Table 11**), the costs for a one-time vaccination with PPSV23, depending on age at vaccination, are about € 17,100–18,800 per hospitalisation prevented, and € 14,400–15,700 per QALY gained. The vaccination strategy with PPSV23 dominates PCV13; i. e. *one-time vaccination with PPSV23 prevents more hospitalisations and deaths at lower costs than one-time vaccination with PCV13*. That is true even if lacking efficacy of PPSV23 against PP is assumed (**Table 12a**).

The costs of sequential vaccination with PCV13 + PPSV23 are very high: in the base case € 216,000–375,000 per additional prevented hospitalisation and € 306,000–366,000 per additional QALY gained. In the scenario that assumes no efficacy of PPSV23 against PP (**Table 12a**), the costs of sequential vaccination per additional prevented hospitalisation and QALY gained are still around 2–4.5 times higher than those of vaccination with PPSV23 alone.

In the *vaccination strategies with repeated PPSV23 vaccinations*, the differences between the two strategies (initial vaccination with PPSV23 alone vs. initial sequential vaccination) are even greater. In the base case, vaccination with PPSV23 alone would incur costs of about € 6,700–6,900 per hospitalisation prevented, and € 12,000–13,000 per QALY gained. The costs of sequential vaccination, however, are extremely high: € 426,000 to € 2.8 million per additional hospitalisation prevented and QALY gained, respectively.

Table 11 Preventable cases, NNV and costs of various vaccination strategies. Vaccination of persons who will reach vaccination age (60, 65, or 70 years) in 2016–2020. Base case

	Cases prevented (Cumulative for the remaining lifespan of individuals vaccinated)			**NNV to prevent one**		**Cost per hospitalization prevented (PP or IPD)**	**Costs per QALY gained**
Vaccine/ vaccination age	PP, hospitalized	IPD	Deaths	Hospitalization (PP or IPD)	Death		
PPSV23 alone (one-time)							
60 years	1,505	748	270	801	6,690	€ 18,838	€ 14,383
65 years	1,440	700	298	725	5,208	€ 19,634	€ 15,670
70 years	1,357	627	303	648	4,247	€ 17,056	€ 15,436
PCV13 alone (one-time)							
60 years	454	271	101	2,490	17,931	€ 149,338	€ 112,606
65 years	463	265	119	2,134	13,026	€ 129,327	€ 100,829
70 years	519	236	137	1,703	9,411	€ 102,370	€ 96,372
Sequential vaccination (one-time PCV13 + PPSV23) *additional* preventable cases and *additional* necessary vaccinations with PCV13, compared to vaccination with PPSV23 alone							
60 years	186	110	47	6,072	38,024	€ 375,498	€ 366,499
65 years	212	113	56	4,762	27,438	€ 293,721	€ 318,812
70 years	273	90	71	3,521	17,960	€ 216,506	€ 306,411
Initial vaccination with PPSV23 at age 60 years and re-vaccinations with PPSV23 (compared to no vaccination)							
every 6 years	17,898	4,271	4,272	398	2,064	€ 6,690	€ 12,839
every 8 years	13,734	3,424	3,267	396	2,077	€ 6,685	€ 12,294
every 10 years	11,026	2,826	2,650	403	2,104	€ 6,880	€ 12,195
Sequential vaccination at age 60 years and re-vaccinations with PPSV23 *additional* preventable cases and *additional* necessary vaccinations with PCV13, compared to vaccination with PPSV23 alone							
every 6 years	47	24	11	25,038	167,139	€ 1,561,736	€ 2,810,187
every 8 years	120	70	29	9,471	61,333	€ 587,983	€ 598,592
every 10 years	160	95	40	7,052	45,011	€ 436,714	€ 425,785

NNV Number needed to vaccinate, *QALY* quality-adjusted life year

7. Conclusions

STIKO examined its existing recommendation for pneumococcal vaccination of older adults with regard to the question which of the possible vaccination strategies (vaccination with PPSV23, vaccination with PCV13, sequential vaccination PCV13 + PPSV23) is preferable, or whether an infant vaccination programme alone (without vaccination of older adults) is sufficient from an epidemiological perspective. STIKO also investigated whether the vaccination age should be raised from the current 60 years, and whether repeated vaccinations should be recommended.

There is no evidence available from a direct comparison of the efficacy of the two available vaccines. Data from RCTs and observational studies in which either PPSV23 or PCV13 were investigated in comparison with no vaccination or placebo indicate *no significant differences in efficacy between the two vaccines in the protection they provide against IPD and pneumococcal pneumonia caused by the serotypes contained in the respective vaccine.*

However, the confidence intervals of the efficacy estimates against IPD are so wide that a clinically relevant efficacy difference between PCV13 and PPSV23 against vaccine serotype disease cannot be ruled out with certainty. With regard to reactogenicity, RCTs with a direct comparison of the two vaccines did not show any significant differences either, except for a slightly higher occurrence of muscle pain after PPSV23.

Crucial to the choice of the most effective vaccination strategy is the fact that the proportion of PCV13 serotypes in disease cases in all age groups has dropped significantly through herd protection provided by PCV13 vaccination of infants. *In the 2015–'16 season, only 30 % of IPD cases in people aged ≥60 years were caused by PCV13 serotypes, while 70 % were caused by PPSV23 serotypes.* In light of this serotype distribution, the protection from invasive pneumococcal diseases achievable through vaccination with PCV13 – regardless of the vaccination's efficacy – is greatly limited from the outset. Hardly any data on serotype distribution of PP without bacteraemia in adults are available. A Danish study suggests the percentage of both PCV13 and PPSV23 serotypes may

Table 12a Sensitivity analysis with 0 % efficacy of PPSV23 against PP

	Cases prevented (Cumulative for the remaining lifespan of individuals vaccinated)			NNV to prevent one		Cost per hospitalization prevented (PP or IPD)	Costs per QALY gained
Vaccine/ vaccination age	PP, hospitalized	IPD	Deaths	Hospitalization (PP or IPD)	Death		
PPSV23 alone (one-time)							
60 years	0	748	128	2,413	14,063	€ 72,085	€ 37,746
65 years	0	700	146	2,217	10,627	€ 67,244	€ 36,344
70 years	0	627	144	2,051	8,903	€ 61,403	€ 37,549
PCV13 alone (one-time)							
60 years	454	271	101	2,490	17,931	€ 149,338	€ 112,606
65 years	463	265	119	2,134	13,026	€ 129,327	€ 100,829
70 years	519	236	137	1,703	9,411	€ 102,370	€ 96,372
Sequential vaccination (one-time PCV13 + PPSV23) *additional* preventable cases and *additional* necessary vaccinations with PCV13, compared to vaccination with PPSV23 alone							
60 years	454	110	72	3,187	24,889	€ 192,859	€ 178,595
65 years	463	113	83	2,684	18,681	€ 163,898	€ 163,370
70 years	519	90	99	2,098	12,854	€ 127,421	€ 153,893
Initial vaccination with PPSV23 at age 60 years and re-vaccinations with PPSV23 (compared to no vaccination)							
every 6 years	0	4,271	1,359	2,064	6,485	€ 43,657	€ 40,730
every 8 years	0	3,424	1,076	1,982	6,308	€ 42,600	€ 38,642
every 10 years	0	2,826	868	1,974	6,426	€ 43,186	€ 38,338
Sequential vaccination at age 60 years and re-vaccinations with PPSV23 *additional* preventable cases and *additional* necessary vaccinations with PCV13, compared to vaccination with PPSV23 alone							
every 6 years	454	24	66	3,761	27,087	€ 234,936	€ 247,730
every 8 years	454	70	77	3,433	23,262	€ 213,880	€ 207,647
every 10 years	454	95	84	3,275	21,472	€ 203,719	€ 191,253

NNV Number needed to vaccinate, *QALY* quality-adjusted life year

be lower than in IPD cases, with a similar ratio between the two serotype groups.

In light of the above, the epidemiological effects of various vaccination strategies (PPSV23, PCV13, and sequential vaccination) were examined in a dynamic transmission model. This showed that in the base case, *considerably more cases of IPD and PP can be prevented through vaccination with PPSV23 than through vaccination with PCV13. Sequential vaccination with PCV13 + PPSV23 prevents only very few additional cases at very high costs.*

If in the 5-year period of 2016–2020, according to the current vaccine uptake, 30 % of people who reach 60 years are vaccinated with a single dose of PPSV23, an estimated cumulative total of 2,253 hospitalisations and 270 deaths from pneumococcal diseases can be prevented in their lifetimes, compared to no vaccination (NNV: 801 per hospitalisation, 6,690 per death). If the vaccine uptake were doubled, the number of hospitalisations and deaths prevented would also roughly double, while the NNV would remain the same. Additional vaccination with a single dose of PCV13 would prevent a cumulative total of only 296 further hospitalisations and 47 further deaths; i. e. around 5–7 times more vaccinations with PCV13 than with PPSV23 were needed to prevent one additional hospitalisation or one additional death.

A significant limitation of the efficacy of pneumococcal vaccination is the limited duration of protection. For that reason, STIKO also analysed the evidence on efficacy and reactogenicity of re-vaccinations with PPSV23. In the first 2 months after a second vaccination with PPSV23, antibody levels were lower than in the first 2 months after the initial vaccination. However, 1–10 years after re-vaccination antibody levels were as high or even higher than 1–10 years after the initial vaccination. That might mean that re-vaccination provides somewhat lower protection than the initial vaccination. To our knowledge, there are no studies with clinical endpoints examining this question.

Because the risk of contracting a pneumococcal infection increases with age, both the individual and epidemiological benefit of vaccination increase with age. That leads to lower NNVs and costs per case prevented for re-vaccinations, even if a 25 % lower efficacy than for the initial vaccination is assumed.

The costs of a vaccination strategy consisting of initial and re-vaccinations with

Table 12b Sensitivity analysis with half efficacy of PPSV23 against ST 3 and full efficacy of PCV13 against ST 3

	Cases prevented (Cumulative for the remaining lifespan of individuals vaccinated)			NNV to prevent one		Cost per hospitalization prevented (PP or IPD)	Costs per QALY gained
Vaccine/ vaccination age	PP, hospitalized	IPD	Deaths	Hospitalization (PP or IPD)	Death		
PPSV23 alone (one-time) vs. no vaccination							
60 years	1,505	748	270	801	6,690	€ 18,838	€ 14,383
65 years	1,440	700	298	725	5,208	€ 19,634	€ 15,670
70 years	1,357	627	303	648	4,247	€ 17,056	€ 15,436
PCV13 alone (one-time) vs. no vaccination							
60 years	813	485	188	1,391	9,613	€ 80,499	€ 59,102
65 years	841	480	221	1,175	7,029	€ 69,128	€ 53,717
70 years	962	430	256	924	5,014	€ 53,584	€ 50,582
Sequential vaccination (one-time PCV13 + PPSV23) *additional* preventable cases and *additional* necessary vaccinations with PCV13, compared to vaccination with PPSV23 alone							
60 years	502	324	130	2,175	13,788	€ 130,323	€ 101,032
65 years	546	327	153	1,768	10,077	€ 106,065	€ 90,647
70 years	672	284	186	1,335	6,870	€ 79,447	€ 85,310
Initial vaccination with PPSV23 at age 60 years and re-vaccinations with PPSV23 (compared to no vaccination)							
every 6 years	17,898	4,271	4,272	398	2,064	€ 6,690	€ 12,839
every 8 years	13,734	3,424	3,267	396	2,077	€ 6,685	€ 12,294
every 10 years	11,026	2,826	2,650	403	2,104	€ 6,880	€ 12,195
Sequential vaccination with PPSV23 at age 60 years and re-vaccinations with PPSV23 *additional* preventable cases and *additional* necessary vaccinations with PCV13, compared to vaccination with PPSV23 alone							
every 6 years	246	183	66	4,191	27,101	€ 255,020	€ 179,637
every 8 years	372	246	95	2,910	18,913	€ 175,743	€ 129,773
every 10 years	450	294	116	2,415	15,533	€ 145,118	€ 109,942

NNV Number needed to vaccinate, *QALY* quality-adjusted life year

PPSV23 alone and a sequential strategy (initial vaccination with PCV13 + PPSV23, re-vaccinations with PPSV23) were compared. In both strategies, initial vaccination is assumed to occur at age 60 years. In the base case, the costs of the PPSV23-only strategy were € 6,700 per hospitalisation prevented, and € 12,800 per QALY gained. Thus, vaccination of older adults with PPSV23 (applied to costs per QALY) is clearly more cost-effective than, for example, rotavirus vaccination of infants (about € 120,000 per QALY [119]). The strategy of sequential initial vaccination would incur extremely high additional costs of about € 1.5 million per hospitalisation prevented, and € 2.8 million per QALY gained.

Based on these findings and considerations, STIKO continues to recommend vaccination with PPSV23 for all adults at age 60 years. Additionally, *STIKO considers re-vaccinations with PPSV23 with an interval of ≥6 years useful from a medico-epidemiological perspective to maintain vaccine protection.* The current prescribing information of PPSV23 limits re-vaccination to "persons at increased risk of severe pneumococcal disease." The indication for re-vaccination of healthy older adults should therefore be evaluated individually. Sequential vaccination with PCV13 and PPSV23 is not recommended as a standard vaccination for older adults because of the low number of additional preventable cases, very high NNV, and high additional costs.

Acceptance of PPSV23, in particular of re-vaccinations, could be impaired by the known reactogenicity of the vaccine. Based on the available data, reactions to the vaccination (e. g. painful local swelling, headache, pain in the limbs) appear to occur more frequently after re-vaccinations than after the initial vaccination. Vaccinees must be informed of this. *Stronger reactogenicity* was observed *especially at intervals of <5 years between vaccinations*. At intervals of >5 years, time between vaccinations appears to not further influence the frequency and severity of adverse events. Furthermore, these reactions mostly appear to last only 2–3 days, as controlled studies have shown.

In STIKO's opinion the balance of benefits (protection from a severe disease with considerable case fatality) and risks of vaccination (painful side effects of limited duration) clearly favours repeated vaccinations. STIKO advocates accompanying implementation of this vaccination recommendation with a reactogenicity study

Table 12c Sensitivity analysis with 0 % efficacy of PPSV23 against PP and half efficacy against IPD caused by ST 3, with full efficacy of PCV13 against ST 3

	Cases prevented (Cumulative for the remaining lifespan of individuals vaccinated)			NNV to prevent one		Cost per hospitalization prevented (PP or IPD)	Costs per QALY gained
Vaccine/ vaccination age	PP, hospitalized	IPD	Deaths	Hospitalization (PP or IPD)	Death		
PPSV23 alone (one-time) vs. no vaccination							
60 years	0	748	128	2,413	14,063	€ 72,085	€ 37,746
65 years	0	700	146	2,217	10,627	€ 67,244	€ 36,344
70 years	0	627	144	2,051	8,903	€ 61,403	€ 37,549
PCV13 alone (one-time) vs. no vaccination							
60 years	813	485	188	1,391	9,613	€ 80,499	€ 59,102
65 years	841	480	221	1,175	7,029	€ 69,128	€ 53,717
70 years	962	430	256	924	5,014	€ 53,584	€ 50,582
Sequential vaccination (one-time PCV13 + PPSV23) *additional* preventable cases and *additional* necessary vaccinations with PCV13, compared to vaccination with PPSV23 alone							
60 years	813	324	159	1,582	11,287	€ 92,372	€ 74,203
65 years	841	327	184	1,321	8,379	€ 78,315	€ 68,106
70 years	962	284	219	1,024	5,824	€ 60,081	€ 63,604
Initial vaccination with PPSV23 at age 60 years and re-vaccinations with PPSV23 (compared to no vaccination)							
every 6 years	0	4,271	1,359	2,064	6,485	€ 43,657	€ 40,730
every 8 years	0	3,424	1,076	1,982	6,308	€ 42,600	€ 38,642
every 10 years	0	2,826	868	1,974	6,426	€ 43,186	€ 38,338
Sequential vaccination at age 60 years and re-vaccinations with PPSV23 *additional* preventable cases and *additional* necessary vaccinations with PCV13, compared to vaccination with PPSV23 alone							
every 6 years	813	183	123	1,806	14,642	€ 106,436	€ 91,544
every 8 years	813	246	138	1,699	13,000	€ 99,677	€ 82,488
every 10 years	813	294	151	1,625	11,927	€ 95,051	€ 76,977

NNV Number needed to vaccinate, *QALY* quality-adjusted life year

to examine whether the frequency and severity of the reactions after re-vaccinations in practice are in the same range as expected based on published data.

To enhance the epidemiological effects of the PPSV23 vaccination recommendation, a significant increase in vaccine uptake among older adults from the current 30 % is desirable. To address this, the reasons for the low vaccine uptake especially in the states of the former West Germany should be established, and acceptance of the vaccination should be increased through customised measures. Vaccine uptake in the target group needs to be tracked regularly to evaluate such measures. Furthermore, there is urgent need to continue laboratory-based surveillance of serotype distribution in IPD cases, and expand it to include studies of serotype distribution in non-bacteraemic pneumococcal pneumonia. Understanding the serotype distribution is an indispensable prerequisite for effectively assessing various vaccination strategies, also with regard to the higher-valent pneumococcal conjugate vaccines expected in the future.

STIKO recommendations on risk-based vaccination of people with certain underlying diseases were not part of this evaluation. Updated STIKO recommendations for risk-based vaccination against pneumococci can be found in the revised table 2 of the STIKO recommendations. The scientific rationale for these recommendations has been published separately (in Epid Bull 37/2016, in German).

Compliance with ethical guidelines

Conflict of interest. The authors declare that they have no conflicts of interest.

References

1. Oliver MB, van der Linden MP, Kuntzel SA, Saad JS, Nahm MH (2013) Discovery of Streptococcus pneumoniae serotype 6 variants with glycosyltransferases synthesizing two differing repeating units. J Biol Chem 288:25976–25985
2. Robbins JB, Austrian R, Lee CJ et al (1983) Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. J Infect Dis 148:1136–1159
3. Lee H, Nahm MH, Burton R, Kim KH (2009) Immune response in infants to the heptavalent pneumococcal conjugate vaccine against

vaccine-related serotypes 6 A and 19 A. Clin Vaccine Immunol 16:376–381
4. Jackson LA (2013) Pneumococcal polysaccharide vaccines. In: Vaccines (Hrsg) Plotkin S, Orenstein W, Offit P. Elsevier Saunders, Philadelphia
5. Hausdorff WP, Feikin DR, Klugman KP (2005) Epidemiological differences among pneumococcal serotypes. Lancet Infect Dis 5:83–93
6. van Hoek AJ, Sheppard CL, Andrews NJ et al (2014) Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England. Vaccine 32:4349–4355
7. Weinberger DM, Malley R, Lipsitch M (2011) Serotype replacement in disease after pneumococcal vaccination. Lancet 378:1962–1973
8. Klapdor B, Ewig S, Pletz MW et al (2012) Community-acquired pneumonia in younger patients is an entity on its own. Eur Respir J 39:1156–1161
9. Kaufman P (1947) Pneumonia in old age; active immunization against pneumonia with pneumonococcus polysaccharide; results of a six year study. Arch Intern Med (Chic) 79:518–531
10. Klugman KP (2013) Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In: Vaccines (Hrsg) Plotkin S, Orenstein W, Offit P. Elsevier Saunders, Philadelphia
11. Simell B, Auranen K, Kayhty H, Goldblatt D, Dagan R, O'Brien KL (2012) The fundamental link between pneumococcal carriage and disease. Expert Rev Vaccines 11:841–855
12. Robert Koch Institut (1998) Impfempfehlungen der Ständigen Impfkommission (STIKO) am Robert Koch-Institut. Epid Bull (15):101–114
13. Ständige Impfkommission (2009) Pneumokokken-Polysaccharid-Impfung – Anpassung der Empfehlung und Begründung. Epid Bull (32):337–338
14. Ständige Impfkommission (2006) Begründung der STIKO-Empfehlungen zur Impfung gegen Pneumokokken und Meningokokken vom Juli 2006. Epid Bull (31):255–260
15. Poethko-Muller C, Schmitz R (2013) Impfstatus von Erwachsenen in Deutschland: Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 56:845–857
16. van der Linden M, Falkenhorst G, Perniciaro S, Imöhl M (2015) Effects of infant pneumococcal conjugate vaccination on serotype distribution in invasive pneumococcal disease (IPD) among children and adults in Germany. PLOS ONE 10:e0131494
17. Harboe ZB, Dalby T, Weinberger DM et al (2014) Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. Clin Infect Dis 59:1066–1073
18. Richter SS, Diekema DJ, Heilmann KP, Dohrn CL, Riahi F, Doern GV (2014) Changes in pneumococcal serotypes and antimicrobial resistance after introduction of the 13-valent conjugate vaccine in the United States. Antimicrob Agents Chemother 58:6484–6489
19. Garcia Gabarrot G, Lopez Vega M, Giffoni PG et al (2014) Effect of pneumococcal conjugate vaccination in Uruguay, a middle-income country. PLOS ONE 9:e112337
20. Andrews NJ, Waight PA, Burbidge P et al (2014) Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. Lancet Infect Dis 14:839–846
21. Andrews NJ, Waight PA, George RC, Slack MP, Miller E (2012) Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine 30:6802–6808
22. Bonten MJ, Huijts SM, Bolkenbaas M et al (2015) Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults. N Engl J Med 372:1114–1125
23. Bonten MJ, Huijts SM, Bolkenbaas M et al (2015) Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults. Supplementary appendix. N Engl J Med 372:1114–1125. doi:10.056/NEJMoa1408544
24. Choi EH, Zhang F, Lu YJ, Malley R (2015) Capsular Polysaccharide (CPS) Release by Serotype 3 Pneumococcal Strains Reduces the Protective Effect of Anti-Type 3 CPS Antibodies. Clin Vaccine Immunol 23:162–167
25. Jackson LA, Gurtman A, van Cleeff M et al (2013) Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults. Vaccine 31:3577–3584
26. Musher DM, Manof SB, Liss C et al (2010) Safety and antibody response, including antibody persistence for 5 years, after primary vaccination or revaccination with pneumococcal polysaccharide vaccine in middle-aged and older adults. J Infect Dis 201:516–524
27. Musher DM, Manoff SB, McFetridge RD et al (2011) Antibody persistence ten years after first and second doses of 23-valent pneumococcal polysaccharide vaccine, and immunogenicity and safety of second and third doses in older adults. Hum Vaccin 7:919–928
28. Simonsen V, Brandao AP, Brandileone MC et al (2005) Immunogenicity of a 23-valent pneumococcal polysaccharide vaccine in Brazilian elderly. Braz J Med Biol Res 38:251–260
29. The Nordic Cochrane Centre, The Cochrane Collaboration: Review Manager (RevMan). Copenhagen2014.
30. Guyatt G, Oxman AD, Akl EA et al (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64:383–394
31. Sinclair A, Xie X, Teltscher M, Dendukuri N (2013) Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by Streptococcus pneumoniae. J Clin Microbiol 51:2303–2310
32. Pletz MW, von Baum H, van der Linden M et al (2012) The burden of pneumococcal pneumonia - experience of the German competence network CAPNETZ. Pneumologie 66:470–475
33. Rozenbaum MH, Pechlivanoglou P, van der Werf TS, Lo-Ten-Foe JR, Postma MJ, Hak E (2013) The role of Streptococcus pneumoniae in community-acquired pneumonia among adults in Europe: a meta-analysis. Eur J Clin Microbiol Infect Dis 32:305–316
34. Torres A, Blasi F, Peetermans WE, Viegi G, Welte T (2014) The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. Eur J Clin Microbiol Infect Dis 33:1065–1079
35. Palmu AA, Saukkoriipi A, Snellman M et al (2014) Incidence and etiology of community-acquired pneumonia in the elderly in a prospective population-based study. Scand J Infect Dis 46:250–259
36. Moberley S, Holden J, Tatham DP, Andrews RM (2013) Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev 1:Cd000422
37. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Plos Med 6:e1000097
38. Alfageme I, Vazquez R, Reyes N et al (2006) Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax 61:189–195
39. Maruyama T, Taguchi O, Niederman MS et al (2010) Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. BMJ 340:c1004
40. Örtqvist A, Hedlund J, Burman LA et al (1998) 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 351:399–403
41. Honkanen PO, Keistinen T, Miettinen L et al (1999) Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. Vaccine 17:2493–2500
42. Hechter RC, Chao C, Jacobsen SJ et al (2012) Clinical effectiveness of pneumococcal polysaccharide vaccine in men: California Men's Health Study. Vaccine 30:5625–5630
43. Jackson LA, Neuzil KM, Yu O et al (2003) Effectiveness of pneumococcal polysaccharide vaccine in older adults. N Engl J Med 348:1747–1755
44. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T et al (2014) Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged >/= 60 years: 3 years of follow-up in the CAPAMIS study. Clin Infect Dis 58:909–917
45. Tsai YH, Hsieh MJ, Chang CJ et al (2015) The 23-valent pneumococcal polysaccharide vaccine is effective in elderly adults over 75 years old-Taiwan's PPV vaccination program. Vaccine 33:2897–2902
46. Vila-Corcoles A, Ochoa-Gondar O, Hospital I et al (2006) Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. Clin Infect Dis 43:860–868
47. Dominguez A, Salleras L, Fedson DS et al (2005) Effectiveness of pneumococcal vaccination for elderly people in Catalonia, Spain: a case-control study. Clin Infect Dis 40:1250–1257
48. Leventer-Roberts M, Feldman BS, Brufman I, Cohen-Stavi CJ, Hoshen M, Balicer RD (2015) Effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive disease and hospital-treated pneumonia among people aged >/=65 years: a retrospective case-control study. Clin Infect Dis 60:1472–1480
49. Vila-Corcoles A, Salsench E, Rodriguez-Blanco T et al (2009) Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in middle-aged and older adults: a matched case-control study. Vaccine 27:1504–1510

50. Gutierrez Rodriguez MA, Ordobas GMA, Garcia-Comas L et al (2014) Effectiveness of 23-valent pneumococcal polysaccharide vaccine in adults aged 60 years and over in the Region of Madrid, Spain, 2008-2011. Euro Surveill 19:20922
51. Rudnick W, Liu Z, Shigayeva A et al (2013) Pneumococcal vaccination programs and the burden of invasive pneumococcal disease in Ontario, Canada, 1995-2011. Vaccine 31:5863–5871
52. Wright LB, Hughes GJ, Chapman KE, Gorton R, Wilson D (2013) Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in people aged 65 years and over in the North East of England, April 2006–July 2012. Trials Vaccinol 2:45–48
53. Wiemken TL, Carrico RM, Klein SL et al (2014) The effectiveness of the polysaccharide pneumococcal vaccine for the prevention of hospitalizations due to Streptococcus pneumoniae community-acquired pneumonia in the elderly differs between the sexes: results from the Community-Acquired Pneumonia Organization (CAPO) international cohort study. Vaccine 32:2198–2203
54. Jalonen E, Paton JC, Koskela M, Kerttula Y, Leinonen M (1989) Measurement of antibody responses to pneumolysin--a promising method for the presumptive aetiological diagnosis of pneumococcal pneumonia. J Infect 19:127–134
55. Leinonen M, Syrjälä H, Jalonen E, Kujala P, Herva E (1990) Demonstration of pneumolysin antibodies in circulating immune complexes—a new diagnostic method for pneumococcal pneumonia. Serodiagn Immunother Infect Dis 4:451–458
56. Broome CV, Facklam RR, Fraser DW (1980) Pneumococcal disease after pneumococcal vaccination: an alternative method to estimate the efficacy of pneumococcal vaccine. N Engl J Med 303:549–552
57. Higgins JP, Altman DG, Gotzsche PC et al (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928
58. Wells GA, Shea B, O'Connell D et al (2015) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Zugegriffen: 10. Juli 2015
59. Fedson DS, Liss C (2004) Precise answers to the wrong question: prospective clinical trials and the meta-analyses of pneumococcal vaccine in elderly and high-risk adults. Vaccine 22:927–946
60. Dransfield MT, Harnden S, Burton RL et al (2012) Long-term comparative immunogenicity of protein conjugate and free polysaccharide pneumococcal vaccines in chronic obstructive pulmonary disease. Clin Infect Dis 55:e35–44
61. Huss A, Scott P, Stuck AE, Trotter C, Egger M (2009) Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ 180:48–58
62. Andrews R, Moberley SA (2009) The controversy over the efficacy of pneumococcal vaccine. CMAJ 180:18–19
63. Scott P, Huss A, Stuck AE, Trotter C, Egger M (2009) Efficacy of pneumococcal polysaccharide vaccine. CMAJ 180(5):1134–1135
64. Scott JA, Hall AJ, Leinonen M (2000) Validation of immune-complex enzyme immunoassays for diagnosis of pneumococcal pneumonia among adults in Kenya. Clin Diagn Lab Immunol 7:64–67
65. Jalonen E, Taira S, Paton JC, Kerttula Y, Suomalainen P, Leinonen M (1990) Pneumolysin, produced in Bacillus subtilis as antigen in enzyme immunoassay for etiological diagnosis of pneumococcal pneumonia. Serodiagn Immunother Infect Dis 4:459–468
66. Musher DM, Mediwala R, Phan HM, Chen G, Baughn RE (2001) Nonspecificity of assaying for IgG antibody to pneumolysin in circulating immune complexes as a means to diagnose pneumococcal pneumonia. Clin Infect Dis 32:534–538
67. Schiffner-Rohe J, Witt A, Hemmerling J, von Eiff C, Leverkus FW (2016) Efficacy of PPV23 in preventing pneumococcal pneumonia in adults at increased risk - A systematic review and Meta-analysis. PLOS ONE 11:e0146338
68. Kraicer-Melamed H, O'Donnell S, Quach C (2016) The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. Vaccine 34:1540–1550
69. Christenson B, Hedlund J, Lundbergh P, Ortqvist A (2004) Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. Eur Respir J 23:363–368
70. Hak E, Grobbee DE, Sanders EA et al (2008) Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults. Neth J Med 66:378–383
71. Pride MW, Huijts SM, Wu K et al (2012) Validation of an immunodiagnostic assay for detection of 13 Streptococcus pneumoniae serotype-specific polysaccharides in human urine. Clin Vaccine Immunol 19:1131–1141
72. Austrian R, Douglas RM, Schiffman G et al (1976) Prevention of pneumococcal pneumonia by vaccination. Trans Assoc Am Physicians 89:184–194
73. Smit P, Oberholzer D, Hayden-Smith S, Koornhof HJ, Hilleman MR (1977) Protective efficacy of pneumococcal polysaccharide vaccines. JAMA 238:2613–2616
74. MacPherson G, Austyn J (2012) Exploring Immunology – Concepts and Evidence. Wiley-Blackwell, Weinheim
75. Benfield T, Skovgaard M, Schonheyder HC et al (2013) Serotype distribution in non-bacteremic pneumococcal pneumonia: association with disease severity and implications for pneumococcal conjugate vaccines. PLOS ONE 8:e72743
76. Rodrigo C, Bewick T, Sheppard C et al (2015) Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. Eur Respir J 45:1632–1641
77. Pilishvili T, Lexau C, Farley MM et al (2010) Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 201:32–41
78. Melegaro A, Choi YH, George R, Edmunds WJ, Miller E, Gay NJ (2010) Dynamic models of pneumococcal carriage and the impact of the Heptavalent Pneumococcal Conjugate Vaccine on invasive pneumococcal disease. Bmc Infect Dis 10:90
79. Grilli G, Fuiano L, Biasio LR et al (1997) Simultaneous influenza and pneumococcal vaccination in elderly individuals. Eur J Epidemiol 13:287–291
80. Honkanen PO, Keistinen T, Kivela SL (1996) Reactions following administration of influenza vaccine alone or with pneumococcal vaccine to the elderly. Arch Intern Med 156:205–208
81. D'Alessandro D, Ciriminna S, Rossini A, Bossa MC, Fara GM (2004) Requests of medical examinations after pneumococcal & influenza vaccination in the elderly. Indian J Med Res 119(Suppl):108–114
82. Frenck RW Jr., Gurtman A, Rubino J et al (2012) Randomized, controlled trial of a 13-valent pneumococcal conjugate vaccine administered concomitantly with an influenza vaccine in healthy adults. Clin Vaccine Immunol 19:1296–1303
83. Schwarz TF, Flamaing J, Rumke HC et al (2011) A randomized, double-blind trial to evaluate immunogenicity and safety of 13-valent pneumococcal conjugate vaccine given concomitantly with trivalent influenza vaccine in adults aged >/=65 years. Vaccine 29:5195–5202
84. Greenberg RN, Gurtman A, Frenck RW et al (2014) Sequential administration of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults 60-64 years of age. Vaccine 32:2364–2374
85. Jackson LA, Gurtman A, Rice K et al (2013) Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine 31:3585–3593
86. Juergens C, De Villiers PJT, Moodley K et al (2014) Safety and immunogenicity of 13-valent pneumococcal conjugate vaccine formulations with and without aluminum phosphate and comparison of the formulation of choice with 23-valent pneumococcal polysaccharide vaccine in elderly adults: A randomized open-label trial. Hum Vaccines Immunother 10:1343–1353
87. D'Heilly S, Bauman WL, Nichol KL (2002) Safety and acceptability of pneumococcal vaccinations administered in nontraditional settings. Am J Infect Control 30:261–268
88. Hammitt LL, Bulkow LR, Singleton RJ et al (2011) Repeat revaccination with 23-valent pneumococcal polysaccharide vaccine among adults aged 55-74 years living in Alaska: no evidence of hyporesponsiveness. Vaccine 29:2287–2295
89. Jackson LA, Benson P, Sneller VP et al (1999) Safety of revaccination with pneumococcal polysaccharide vaccine. JAMA 281:243–248
90. Jackson LA, Gurtman A, van Cleeff M et al (2013) Influence of initial vaccination with 13-valent pneumococcal conjugate vaccine or 23-valent pneumococcal polysaccharide vaccine on anti-pneumococcal responses following subsequent pneumococcal vaccination in adults 50 years and older. Vaccine 31:3594–3602
91. Jackson LA, Nelson JC, Whitney CG et al (2006) Assessment of the safety of a third dose of pneumococcal polysaccharide vaccine in the Vaccine Safety Datalink population. Vaccine 24:151–156
92. Manoff SB, Liss C, Caulfield MJ et al (2010) Revaccination with a 23-valent pneumococcal polysaccharide vaccine induces elevated and persistent functional antibody responses in adults aged 65 > or = years. J Infect Dis 201:525–533
93. Ohshima N, Nagai H, Matsui H et al (2014) Sustained functional serotype-specific antibody after primary and secondary vaccinations with a pneumococcal polysaccharide vaccine in elderly patients with chronic lung disease. Vaccine 32:1181–1186

94. Shih A, Quinley J, Lee TK, Messina CR (2002) Assessing pneumococcal revaccination safety among New York State Medicare beneficiaries. Public Health Rep 117:164–173
95. Snow R, Babish JD, McBean AM (1995) Is there any connection between a second pneumonia shot and hospitalization among Medicare beneficiaries? Public Health Rep 110:720–725
96. Törling J, Hedlund J, Konradsen HB, Ortqvist A (2003) Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. Vaccine 22:96–103
97. Walker FJ, Singleton RJ, Bulkow LR, Strikas RA, Butler JC (2005) Reactions after 3 or more doses of pneumococcal polysaccharide vaccine in adults in Alaska. Clin Infect Dis 40:1730–1735
98. Baxendale HE, Johnson M, Keating SM et al (2010) Circulating pneumococcal specific plasma and memory B cells in the elderly two years after pneumococcal conjugate versus polysaccharide vaccination. Vaccine 28:6915–6922
99. Baxendale HE, Keating SM, Johnson M, Southern J, Miller E, Goldblatt D (2010) The early kinetics of circulating pneumococcal-specific memory B cells following pneumococcal conjugate and plain polysaccharide vaccines in the elderly. Vaccine 28:4763–4770
100. Clutterbuck EA, Lazarus R, Yu LM et al (2012) Pneumococcal conjugate and plain polysaccharide vaccines have divergent effects on antigen-specific B cells. J Infect Dis 205:1408–1416
101. Capolunghi F, Cascioli S, Giorda E et al (2008) CpG drives human transitional B cells to terminal differentiation and production of natural antibodies. J Immunol 180:800–808
102. Khaskhely N, Mosakowski J, Thompson RS, Khuder S, Smithson SL, Westerink MA (2012) Phenotypic analysis of pneumococcal polysaccharide-specific B cells. J Immunol 188:2455–2463
103. Kruetzmann S, Rosado MM, Weber H et al (2003) Human immunoglobulin M memory B cells controlling Streptococcus pneumoniae infections are generated in the spleen. J Exp Med 197:939–945
104. Moens L, Wuyts M, Meyts I, De Boeck K, Bossuyt X (2008) Human memory B lymphocyte subsets fulfill distinct roles in the anti-polysaccharide and anti-protein immune response. J Immunol 181:5306–5312
105. Rosado MM, Gesualdo F, Marcellini V et al (2013) Preserved antibody levels and loss of memory B cells against pneumococcus and tetanus after splenectomy: tailoring better vaccination strategies. Eur J Immunol 43:2659–2670
106. Taillardet M, Haffar G, Mondiere P et al (2009) The thymus-independent immunity conferred by a pneumococcal polysaccharide is mediated by long-lived plasma cells. Blood 114:4432–4440
107. Takizawa M, Sugane K, Agematsu K (2006) Role of tonsillar IgD+CD27+ memory B cells in humoral immunity against pneumococcal infection. Hum Immunol 67:966–975
108. Weller S, Braun MC, Tan BK et al (2004) Human blood IgM "memory" B cells are circulating splenic marginal zone B cells harboring a prediversified immunoglobulin repertoire. Blood 104:3647–3654
109. Powers DC, Anderson EL, Lottenbach K, Mink CM (1996) Reactogenicity and immunogenicity of a protein-conjugated pneumococcal oligosaccharide vaccine in older adults. J Infect Dis 173:1014–1018
110. Shi Y, Yamazaki T, Okubo Y, Uehara Y, Sugane K, Agematsu K (2005) Regulation of aged humoral immune defense against pneumococcal bacteria by IgM memory B cell. J Immunol 175:3262–3267
111. Tangye SG, Good KL (2007) Human IgM+CD27+ B cells: memory B cells or "memory" B cells? J Immunol 179:13–19
112. Leggat DJ, Thompson RS, Khaskhely NM, Iyer AS, Westerink MA (2013) The immune response to pneumococcal polysaccharides 14 and 23 F among elderly individuals consists predominantly of switched memory B cells. J Infect Dis 208:101–108
113. Hussain M, Melegaro A, Pebody RG et al (2005) A longitudinal household study of Streptococcus pneumoniae nasopharyngeal carriage in a UK setting. Epidemiol Infect 133:891–898
114. Brueggemann AB, Peto TE, Crook DW, Butler JC, Kristinsson KG, Spratt BG (2004) Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. J Infect Dis 190:1203–1211
115. Choi YH, Jit M, Flasche S, Gay N, Miller E (2012) Mathematical modelling long-term effects of replacing Prevnar7 with Prevnar13 on invasive pneumococcal diseases in England and Wales. PLOS ONE 7:e39927
116. Reinert RR, Haupts S, van der Linden M et al (2005) Invasive pneumococcal disease in adults in North-Rhine Westphalia, Germany, 2001-2003. Clin Microbiol Infect (11):985–991
117. von Kries R, Toschke M, Siedler A, Reinert RR (2004) Population-based Nationwide Study on Invasive Pneumococcal Infections among Children in Germany (1997–2003)
118. van Hoek AJ, Andrews N, Waight PA, George R, Miller E (2012) Effect of serotype on focus and mortality of invasive pneumococcal disease: coverage of different vaccines and insight into non-vaccine serotypes. PLOS ONE 7:e39150
119. Aidelsburger P, Grabein K, Bohm K et al (2014) Cost-effectiveness of childhood rotavirus vaccination in Germany. Vaccine 32:1964–1974

Appendix

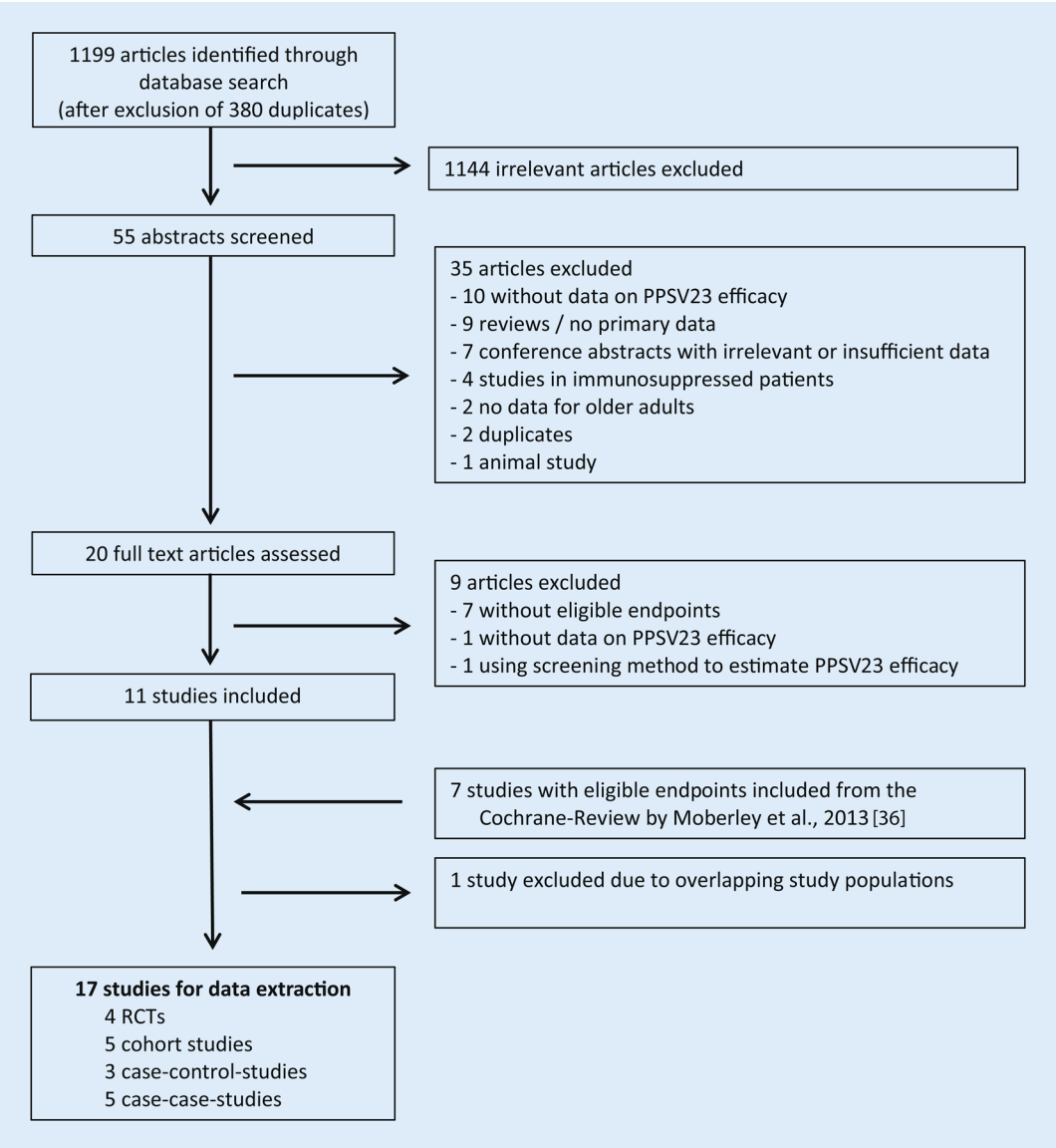

Fig. A1 ◄ Flow chart for the systematic literature search on the efficacy/effectiveness of a one-time vaccination with PPSV23

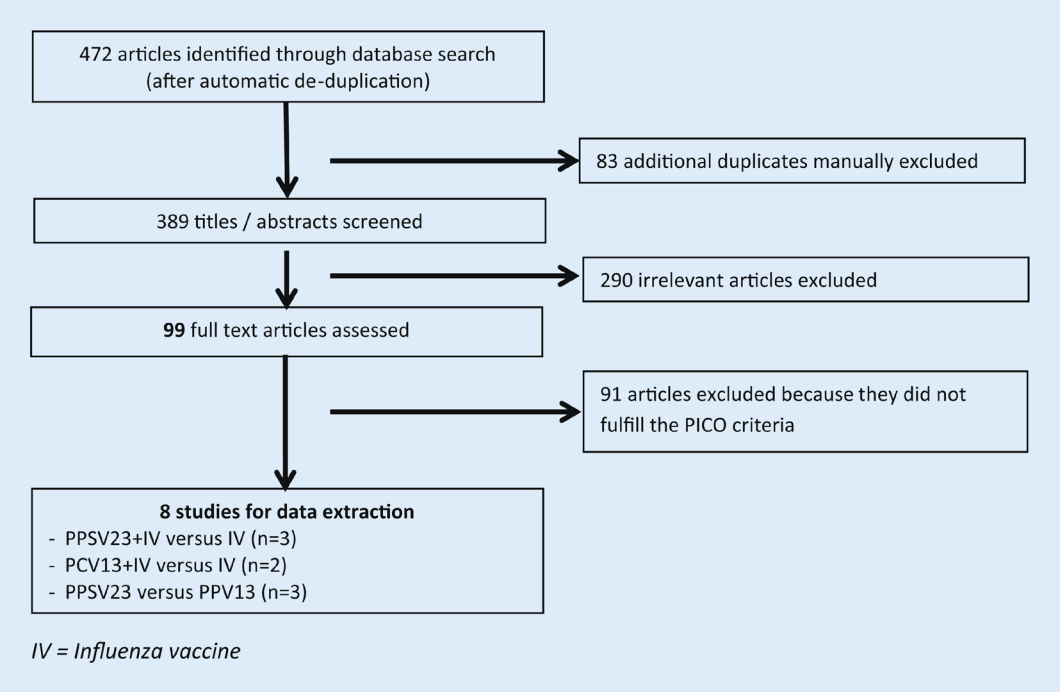

Fig. A2 ◄ Flow chart for the systematic literature search on the safety and reactogenicity of PPSV23 and PCV13

Search strategy

Search in PubMed:
(elderly OR adult* OR (old*adult*)) AND (pneumococc*[title/abstract] AND vaccin*[title/abstract] NOT (10-valent[title/abstract])) AND (safety[title/abstract] OR reactogenicity[title/abstract] OR (adverse event*[title/abstract])) NOT pediatr*[title/abstract]

Search in Embase, Cochrane Central Register of Controlled Trials (CCTR), *Cochrane Database of Systematic Reviews* (CDSR), Current Contents Medizin (German language publications), MEDLINE

via DIMDI:
SBAS EM10; CCTR93; CDSR93; CCMed; ME10
find ft = (elderly OR adult? OR (old-?,adult?))
find ft = (pneumococc? AND vaccin?)
find ft = (safety OR reactogenicity OR (adverse event*))
Find 2 AND 3 AND 4
Find 5 AND LA = (GERM;ENGL;ITAL;-FREN;SPAN)
CH dup (automatic removal of duplicates)

Table A1 GRADE profile for efficacy of PPSV23

Quality assessment							Study size (cases/person-years)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PPSV23	no vaccination	Relative (95 % CI)	Absolute		
IPD all serotypes (follow-up 2–3 years)												
4	RCT	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/22282 (0.01 %)	13/21308 (0.06 %)	RR 0.27 (0.08 to 0.9)	445 fewer per 1,000,000 (from 61 fewer to 561 fewer)	+++ MODERATE	CRITICAL
Pneumococcal pneumonia (follow-up 2–3 years)												
2	RCT	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	14/1940 (0.72 %)	42/1947 (2.2 %)	RR 0.36 (0.2 to 0.65)	13806 fewer per 1,000,000 (from 7550 fewer to 17257 fewer)	+++ MODERATE	CRITICAL

Question: Should PPSV23 vs. no vaccination be used to prevent IPD and pneumococcal pneumonia in people ≥60 years?
Setting: Industrialized countries
[1]Pseudo-randomization by birth year and lack of blinding in the trial by Honkanen et al., but this is not expected to have any major impact on the observed incidence of IPD.
[2]Wide confidence interval (CI), number of preventable cases at the boundaries of the CI varies by a factor of 9.
[3]Indirect in so far as the study by Maruyama et al., which contributes more than 95 % to the pooled efficacy estimate, was conducted among retirement home residents in Japan, and not in the general population. Vaccine efficacy (VE) possibly deviates from VE in people of the same age in the general population in Germany.

Table A2 GRADE profile for efficacy of PCV13

Quality assessment							Study size (ca ses/persons)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13	no vaccination	Relative (95 % CI)	Absolute		
Vaccine type IPD (follow-up mean 4 years)												
1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/42240 (0.02 %)	28/42256 (0.07 %)	RR 0.25 (0.11 to 0.57)	497 fewer per 1,000,000 (from 285 fewer to 590 fewer)	++++ HIGH	CRITICAL
Vaccinetype pneumococcal pneumonia (follow-up mean 4 years)												
1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	33/42240 (0.08 %)	60/42256 (0.14 %)	RR 0.55 (0.36 to 0.84)	639 fewer per 1,000,000 (from 227 fewer to 909 fewer)	+++ MODERATE	CRITICAL

Question: Should PCV13 vs. no vaccination be used to prevent IPD and pneumococcal pneumonia in people ≥60 years?
Setting: Industrialized countries
[1]Wide confidence interval (CI), number of preventable cases at the boundaries of the CI varies by a factor of 4.

Table A3 GRADE profile for safety aspects of PPSV23

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccination with PPSV23	Control	Relative (95 % CI)	Absolute		
Fever (follow-up 4 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	9/4755 (0.19 %)	5/4581 (0.11 %)	RR 1.73 (0.58 to 5.17)	1 more per 1000 (from 0 fewer to 5 more)	+ VERY LOW	IMPORTANT
Unplanned medical visits (follow-up 3 days)												
1	observational studies	serious[4]	no serious inconsistency	serious[2]	no serious imprecision	none	163/12485 (1.3 %)	142/16601 (0.86 %)	RR 1.53 (1.22 to 1.91)	5 more per 1000 (from 2 more to 8 more)	+ VERY LOW	IMPORTANT
Headache (follow-up 3 days)												
1	observational studies	serious[4]	no serious inconsistency	serious[2]	no serious imprecision	none	74/12485 (0.59 %)	75/16601 (0.45 %)	RR 1.31 (0.95 to 1.81)	1 more per 1000 (from 0 fewer to 4 more)	+ VERY LOW	IMPORTANT
Myalgia (follow-up 3 days)												
1	observational studies	serious[4]	no serious inconsistency	serious[2]	no serious imprecision	none	135/12485 (1.1 %)	52/16601 (0.31 %)	RR 3.45 (2.51 to 4.75)	8 more per 1000 (from 5 more to 12 more)	+ VERY LOW	IMPORTANT
Joint pain (follow-up 3 days)												
1	observational studies	serious[4]	no serious inconsistency	serious[2]	no serious imprecision	none	128/12485 (1 %)	55/16.601 (0.33 %)	RR 3.09 (2.26 to 4.24)	7 more per 1000 (from 4 more to 11 more)	+ VERY LOW	IMPORTANT
Severe local reaction (follow-up 4 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	83/4755 (1.7 %)	37/4581 (0.81 %)	RR 2.16 (1.47 to 3.18)	9 more per 1000 (from 4 more to 18 more)	++ LOW	IMPORTANT

Question: Should PPSV23 vs. no vaccination be used to prevent IPD and pneumococcal pneumonia in people ≥60 years?
Setting: Industrialized countries
[1]Staff and participants were not blinded.
[2]Simultaneous vaccination with inactivated influenza vaccine.
[3]Wide confidence interval.
[4]Confounding by indication likely; no adjusted RRs are reported.

Table A4 GRADE profile for safety aspects of PCV13

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccination with PCV13	Placebo	Relative (95 % CI)	Absolute		
Fever (follow-up 14 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	27/692 (3.9 %)	18/690 (2.6 %)	RR 1.5 (0.83 to 2.7)	13 more per 1000 (from 4 fewer to 44 more)	++ LOW	IMPORTANT
Headache (follow-up 14 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	417/871 (47.9 %)	355/850 (41.8 %)	RR 1.14 (1.03 to 1.26)	58 more per 1000 (from 13 more to 109 more)	+++ MODERATE	IMPORTANT
Muscle Pain (follow-up 14 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	194/768 (25.3 %)	134/743 (18 %)	RR 1.39 (1.15 to 1.69)	70 more per 1000 (from 27 more to 124 more)	+++ MODERATE	IMPORTANT
Joint pain (follow-up 14 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	133/744 (17.9 %)	109/731 (14.9 %)	RR 1.2 (0.95 to 1.51)	30 more per 1000 (from 7 fewer to 76 more)	+++ MODERATE	IMPORTANT
Local pain (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	407/469 (86.8 %)	119/321 (37.1 %)	RR 2.34 (2.02 to 2.71)	497 more per 1000 (from 378 more to 634 more)	+++ MODERATE	IMPORTANT

Question: Should PCV13 vs. no vaccination be used to prevent IPD and pneumococcal pneumonia in people ≥60 years?
Setting: Industrialized countries
[1]Age group in one study (Frenck et al. 2012) 50–59 years; in both studies simultaneous vaccination with inactivated influenza vaccine.
[2]Wide confidence interval which includes the value 1.