OPTIMIZING PNEUMOCOCCAL CONJUGATE VACCINES (PCV) SCHEDULES FOR CHILDREN IN VARIOUS AREAS OF THE WORLD

What is the relative effect of administering PCV vaccines using a 3 primary doses (3p) versus 2 primary doses with a booster dose (2p+1) on key outcomes (i.e. disease, nasopharyngeal carriage of vaccine types and immunogenicity)?

Population: children (0-5 years of age)
Interventions: *(current WHO recommended schedule)*

- PCV vaccines (7, 10 and 13 valent vaccines),
  - three primary doses (3p) at 6, 10, 14 weeks or 2, 4, 6 months

Comparators:

- PCV vaccines (7, 10 and 13 valent vaccines),
  - two primary doses with a booster (2p+1) at 10 or 12 months of age,
  - no PCV

Outcomes:

- Disease: invasive pneumococcal disease, x ray confirmed pneumonia, meningitis, deaths
- Nasopharyngeal carriage of vaccine serotypes
- Immunogenicity: seropositivity and geometric mean antibody concentrations (GMCs),

SAGE has recommended that PCV should be added to the routine childhood immunization programme using a 3p schedule. SAGE also recommended that the WHO Secretariat give further consideration to the optimal timing and number of doses required to protect children. This document sets out the evidence on 2p+1 and 3p+1 PCV schedules and compares them to the 3 primary doses (3p).

The use of PCV vaccines versus no PCV is supported by strong evidence, including randomized controlled trials of efficacy against disease and carriage, immunogenicity studies, and observational data documenting impact on pneumonia and invasive disease following introduction into routine programs. The review of randomized clinical trials (RCTs) and observational studies found no definitive evidence that 3p schedule is superior to a 2p+1 schedule in its effect on clinical disease or carriage outcomes. The interpretation of differences found in immunological outcomes is limited because of uncertainty about their clinical relevance.

The choice of PCV schedule is likely to be informed by knowledge of the local epidemiology of pneumococcal disease (e.g. importance of serotype 1 in disease incidence in children) and by operational considerations (e.g. coverage achieved with various DTP doses and with measles vaccine, potential to reach children during the second year of life). Additional evidence from head-to-head comparisons about the relative benefits of different PCV schedules for PCV10 and PCV13 is needed to help inform decision-making on PCV schedules.

! THIS SUMMARY INCLUDES

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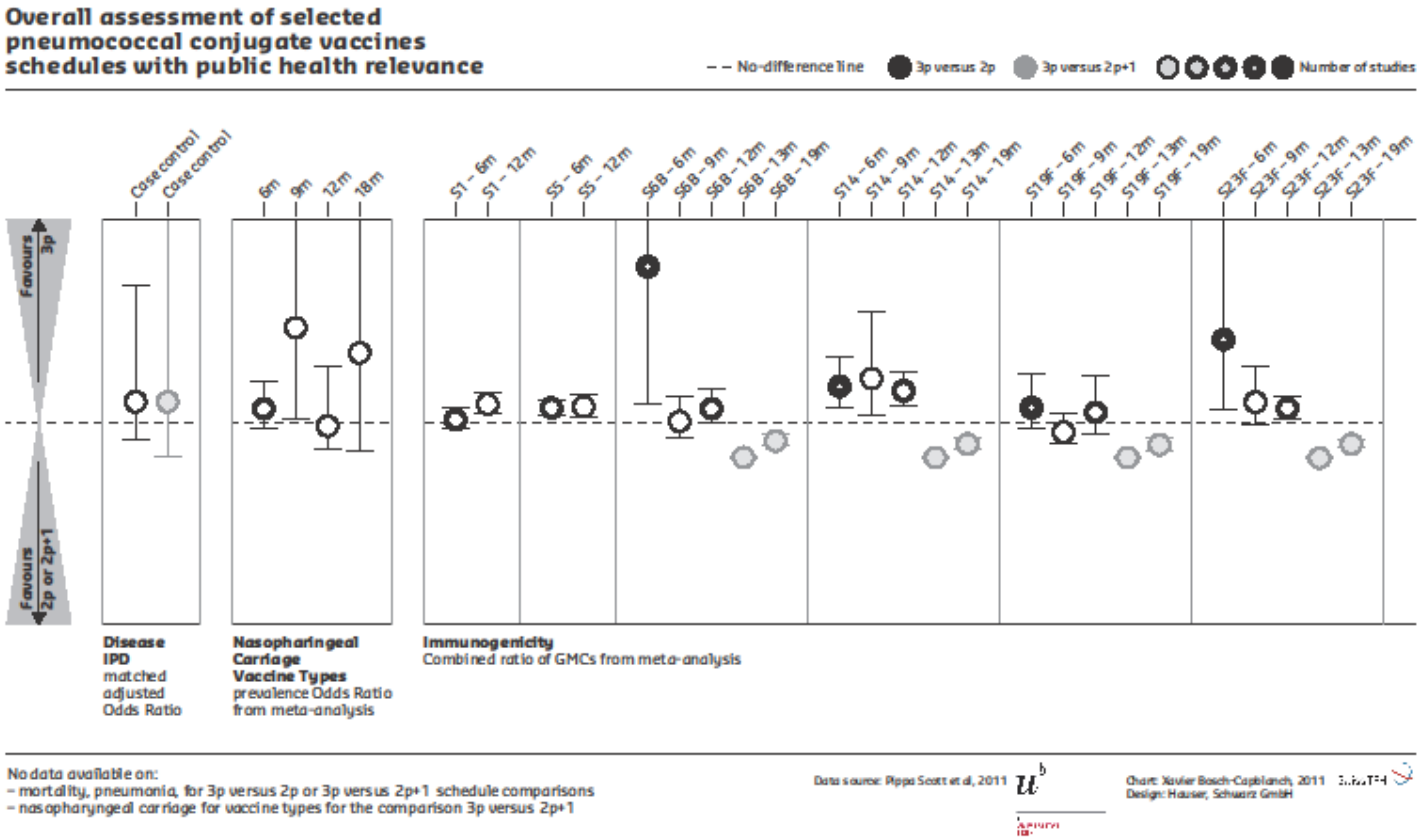
Adult vaccination, detailed logistics, or operational information

Assessment of selected pneumococcal conjugate vaccines schedules[1]



[1] This bubble chart is an overview of the comparative effects of selected pneumococcal vaccination schedules. The data presented here is from Scott P et al (2011) . In black colour 3p versus 2p and in gray colour 3p versus 2p+1. Each bubble represents the comparative effect in a study or pooled studies. The darkness of the bubble is an indication of the number of studies: light colour= 1 study, darker colour=5 studies). The labels indicate serotypes (S) and ages in months (m) of the estimates, and the vertical lines represent the 95% confidence intervals. When a bubble and its confidence intervals (vertical lines) is above the dotted line, the data favours 3p schedule, and vice-versa. The axis in the chart purposely has no scale on it, which allows to depicting data of different effect measures. However, the relative position of the bubbles faithfully reflects the estimated effects between schedules. All data used for this chart can be found in all details in the table in the following page.

Outcomes profile for selected schedule comparisons: 3p versus 2p and 3p versus 2p+1[2]

Outcome of interest	Type of study	# of studies	Country, PCV valency	age at outcome measurement, months	intended schedule months	type of outcome	estimate	95% CI lower limit	95% CI upper limit	I2 % heterogeneity test
3p versus 2p										
DISEASE										
Invasive pneumococcal disease (IPD)	Case control	1	USA 7V		3p <7 months vs. 2p< 7 months	OR matched adjusted	1.5	0.54	4.35	
NASOPHARYNGEAL CARRIAGE OF VACCINE TYPES										
Vaccine types carriage	RCT	2	Fiji 7v, Gambia 7v	6	1.5, 2.5, 3.5 vs. 1.5, 3.5	Combined OR from meta-analysis	1.32	0.85	2	
Vaccine types carriage	RCT	1	Fiji 7v	9	1.5, 2.5, 3.5 vs. 1.5, 3.5		3.33	1.09	10	
Vaccine types carriage	RCT	1	Fiji 7v	12	1.5, 2.5, 3.5 vs. 1.5, 3.5		0.89	0.33	2.38	
Vaccine types carriage	RCT	1	Fiji 7v	18	1.5, 2.5, 3.5 vs. 1.5, 3.5		2.7	0.28	25	
IMMUNOGENICITY										
Geometric mean antibody concentration (GMCs)										
SEROTYPE 1	RCT	2	Iceland 9V, Europe 10V	6	3, 4, 5 vs. 3, 5 / 2, 3, 4 vs 2, 4	Combined ratio of GMCs from meta analyses	1.05	0.82	1.35	70.1
SEROTYPE 5	RCT	2	Iceland 9V, Europe 10V	6	3, 4, 5 vs. 3, 5 / 2, 3, 4 vs 2, 4		1.34	1.16	1.54	0
SEROTYPE 6B	RCT	4	Fiji 7v, Iceland 9v, Gambia 7V, Europe 10V	6	1.5, 2.5, 3.5 vs. 1.5,3.5 / 3, 4, 5 vs. 3, 5 / 2 , 3, 4 vs 2, 3 / 2, 3, 4 vs 2, 4		4.83	1.45	16.14	97.6
SEROTYPE 14	RCT	4	Fiji 7v, Iceland 9v, Gambia 7V, Europe 10V	6	1.5, 2.5, 3.5 vs. 1.5,3.5 / 3, 4, 5 vs. 3, 5 / 2 , 3, 4 vs 2, 3 / 2, 3, 4 vs 2, 4		1.87	1.34	2.61	75.3
SEROTYPE 19F	RCT	4	Fiji 7v, Iceland 9v, Gambia 7V, Europe 10V	6	1.5, 2.5, 3.5 vs. 1.5,3.5 / 3, 4, 5 vs. 3, 5 / 2 , 3, 4 vs 2, 3 / 2, 3, 4 vs 2, 4		1.34	0.82	2.2	91.6
SEROTYPE 23F	RCT	4	Fiji 7v, Iceland 9v, Gambia 7V, Europe 10V	6	1.5, 2.5, 3.5 vs. 1.5,3.5 / 3, 4, 5 vs. 3, 5 / 2 , 3, 4 vs 2, 3 / 2, 3, 4 vs 2, 4		3.03	1.31	6.99	95.1
SEROTYPE 6B	RCT	1	Fiji 7v	9	1.5, 2.5, 3.5 vs. 1.5,3.5		1.01	0.63	1.63	
SEROTYPE 14	RCT	1	Fiji 7v	9	1.5, 2.5, 3.5 vs. 1.5,3.5		2.07	1.16	3.69	
SEROTYPE 19F	RCT	1	Fiji 7v	9	1.5, 2.5, 3.5 vs. 1.5,3.5		0.74	0.46	1.21	
SEROTYPE 23F	RCT	1	Fiji 7v	9	1.5, 2.5, 3.5 vs. 1.5,3.5		1.48	0.93	2.35	
SEROTYPE 1	RCT	1	Europe 10V	12	2, 3, 4 vs 2, 4		1.43	1.2	1.71	
SEROTYPE 5	RCT	1	Europe 10V	12	2, 3, 4 vs 2, 4		1.37	1.11	1.69	
SEROTYPE 6B	RCT	2	Fiji 7V, Europe 10V	12	1.5, 2.5, 3.5 vs. 1.5,3.5 / 2, 3, 4 vs 2, 4		1.32	0.96	1.83	63
SEROTYPE 14	RCT	2	Fiji 7V, Europe 10V	12	1.5, 2.5, 3.5 vs. 1.5,3.5 / 2, 3, 4 vs 2, 4		1.76	1.4	2.23	35.8
SEROTYPE 19F	RCT	2	Fiji 7V, Europe 10V	12	1.5, 2.5, 3.5 vs. 1.5,3.5 / 2, 3, 4 vs 2, 4		1.23	0.7	2.16	87.6
SEROTYPE 23F	RCT	2	Fiji 7V, Europe 10V	12	1.5, 2.5, 3.5 vs. 1.5,3.5 / 2, 3, 4 vs 2, 4		1.33	1.09	1.62	0
3p versus 2p+1										
DISEASE										
Invasive pneumococcal disease (IPD)	Case control	1	USA 7V	7	3 p ≤ 7m vs. 2 p ≤7m, + b12-16m	OR matched adjusted	1.5	0.15	14.6	
IMMUNOGENICITY										
Geometric mean antibody concentration (GMCs)										
SEROTYPE 6B	RCT	1	Israel 7V	13	2, 4, 6 vs. 4, 6 + b12	Combined ratio of GMCs from meta analyses	0.12	0.08	0.16	
SEROTYPE 14	RCT	1	Israel 7V	13	2, 4, 6 vs. 4, 6 + b12		0.11	0.09	0.15	
SEROTYPE 19F	RCT	1	Israel 7V	13	2, 4, 6 vs. 4, 6 + b12		0.11	0.08	0.15	
SEROTYPE 23F	RCT	1	Israel 7V	13	2, 4, 6 vs. 4, 6 + b12		0.1	0.08	0.13	
SEROTYPE 6B	RCT	1	Israel 7V	19	2, 4, 6 vs. 4, 6 + b12		0.52	0.4	0.68	
SEROTYPE 14	RCT	1	Israel 7V	19	2, 4, 6 vs. 4, 6 + b12		0.45	0.34	0.6	
SEROTYPE 19F	RCT	1	Israel 7V	19	2, 4, 6 vs. 4, 6 + b12		0.43	0.3	0.62	
SEROTYPE 23F	RCT	1	Israel 7V	19	2, 4, 6 vs. 4, 6 + b12		0.45	0.35	0.57	

[2] Source of data for this table: Scott P et al (2011), A systematic review of PCV schedules of data from randomized controlled trials and observational studies of childhood schedules using 7, 9, 10 and 13 valent vaccines.

Key findings on: number or primary doses, effects of booster dose, age at first dose and interval between doses.

The information in this table was extracted from:

(a) Scott P (1) et al (2011), Systematic review of PCV schedules;

(b) Conklin L (2) et al (2011) Landscape analysis of pneumococcal conjugate vaccine dosing schedules: A systematic review: Sub-report on the 3-dose schedules;

(c) key studies, available after the systematic searches for both reviews were concluded.

In each cell, the findings are reported in this order. Relevant findings are referred to only once. The overall conclusion is presented at the top of each cell in bold.

Outcome of interest	**Vaccination Schedules**	
	3p versus 2p	**3p versus 2p+1**
Mortality	**Limited data, conclusions can not be made** (a) Two RCTs (Iceland 9v (3) and Europe 10v (4)) collected mortality data as adverse events. One RCT (Gambia 7v (5)) reported it as a reason for loss to follow-up; no causes of death were supplied. No mortality data available from observational studies that directly compare 3p vs 2p. (b) No additional studies identified (c) No new studies identified	**No mortality data available for direct comparisons of 3p vs 2p+1** (a) No mortality data available from RCTs. No mortality data available from observational studies (b) No additional studies identified (c) No new studies identified
Vaccine type serotype (VT) invasive pneumococcal disease (IPD)	**Limited data suggest less IPD with the 3p schedule than with the 2p schedule, but the statistical evidence is not strong.** (a) No VT IPD data available from RCTs. One case–control study (USA 7v (6) reported data on VT IPD. The odds ratio favours 3p over 2p but the confidence intervals were wide and included 1[3]. (b) No additional studies identified (c) No new studies identified	**Limited data suggest less IPD with the 3p schedule than with the 2p+1 schedule, but the statistical evidence is not strong.** (a) No VT IPD data available from RCTs. One case–control study (USA 7v(6)) reported data on VT IPD. The odds ratio favour 3p over 2p+1 but the confidence intervals were wide and included 1[3]. (b) No additional studies identified (c) No new studies identified

[3] Potential biases include issues of control selection common to case-control studies. Other biases and confounding could also be present.

Outcome of interest	Vaccination Schedules	
	3p versus 2p	**3p versus 2p+1**
Pneumonia	**Limited data, conclusions can not be made** (a) One RCT (Europe 10v(4)) reported one case of bronchopneumonia in the 3p group (between1st dose and 30 days after 3rd dose). There was no reporting of pneumonia data in other RCTs with this comparison. A retrospective cohort (Pelton et al(7)), compared 2p vs. 3p of PCV7. The outcome was 'lower respiratory tract disease', including bronchitis, bronchiolitis, asthma or wheezing, and pneumonia due to pneumococcal infection or unspecified cause. Results showed fewer hospital admissions and outpatient visits for lower respiratory tract disease for children receiving 3 p before a booster dose was given. During the post-booster observation period outcomes did not differ[4]. (b) No additional studies identified (c) No new studies identified	**No pneumonia data available** (a) No pneumonia data available from RCTs. No pneumonia data available from observational studies (b) No additional studies identified (c) No new studies identified
Nasopharyngeal carriage vaccine type serotype (VT)	**Results for VT carriage tended to show less carriage with the 3p than with 2p schedule, but this was not consistent and the statistical evidence was not strong.** (a) There were 2 trials (Fiji 7v(8), Gambia 7v(5)) comparing carriage of vaccine pneumococcal serotypes. At 9 months of age, there was some statistical evidence of lower carriage in the 3p group than in the 2p group in one RCT that reported carriage at this time point. At other time points (i.e. 6, 12 or 18 months) there was no strong evidence that either schedule was superior. No VT nasopharyngeal carriage data from observational studies (b) One RCT from Israel (9) compared a 2p+1 schedule, given at 4, 6, and 12 months, to a 3p+1 schedule, given at 2, 4, 6, and 12 months. At 7 and 12 months, before the booster dose, the vaccine-type carriage in the 2p+1 group was 28.4% versus 22.6% in the 3p+1 group (information on 95% CI not available). However, at 13 and 18 months, after the booster dose, vaccine-type carriage was almost the same at	**Limited data available** (a) No RCTs identified No VT nasopharyngeal carriage data from observational studies. (b) One RCT from Israel (9) compared a 2p+1 schedule, given at 4, 6, and 12 months, to a 3p+1 schedule, given at 2, 4, 6, and 12 months. At 7 and 12 months, before the booster dose, the vaccine-type carriage in the 2p+1 group was 28.4% versus 22.6% in the 3p+1 group (information on 95% CI not available). However, at 13 and 18 months, after the booster dose, vaccine-type carriage was almost the same at

[4] These findings are difficult to compare with other studies in the Scott et al (2011) systematic review because of the different outcome definition.

Outcome of interest	Vaccination Schedules	
	3p versus 2p	**3p versus 2p+1**
Nasopharyngeal carriage vaccine type serotype (VT) (cont)	18.8% in the 3p+1 group and 19.1% in the 2+1 group. (c) No new studies identified	18.8% in the 3p+1 group and 19.1% in the 2+1 group. (c) No new studies identified
Immunogenicity	**Data show that both schedules induce high levels of seropositivity for most serotypes. Differences between 3p and 2p were generally small and mostly favoured the 3p.** (a) Data available from 5 trials (Fiji 7v(8), Gambia 7v(5), Israel 7v(10), Iceland 9v(3), Europe 10v(4)). At 6 months of age, the proportion seropositive was generally high in both 3p and 2p groups. Differences varied between studies and serotypes but small differences favoured the 3p, the largest differences were for serotypes 6B and 23F. By 12 months and by 17 months the proportions seropositive had dropped by varying degrees for all serotypes except 6B. At 6 months of age 3p tended to have higher GMC than 2p for all studies and serotypes. At 12 months of age, GMC values had dropped, but differences in GMC ratios tended to persist, with slightly lower pooled ratios than observed at 6 months of age. A cohort study (UK 9V(11) comparing 3p and 2p reported broadly similar results with both schedules at 5 months of age. At 12 months of age, there were more marked differences between the groups and overall levels of seropositivity had fallen for most serotypes The 3p had slightly higher levels of seropositivity at both cut-off points for all serotypes with exception of 19F at the 0.35µg/ml cut-off. No data from observational studies are available. (b) The 3p schedule produced higher post-primary GMC antibody response for all serotypes except for serotype 1 when compared to 2p in a model that analysed GMCs data from 61 studies and 119 study-arms. The model controlled for age at first dose, geographic region, PCV product, co administered vaccines, and laboratory methods[2]. GMCs for serotypes 6B, 23F, and 14 were significantly higher following 3p compared to 2p. The percent of children with titers above 0.35ug/ml (or 0.20ug/ml if studies used a GSK ELISA assay) tended to be a high	**Limited data, differences in seropositivity between 3p or 2p+1 were somewhat smaller after a booster dose favouring 2p+1.** (a) One RCT compared 3p and 2p+1 schedules (Israel 7v(11)). At 7 months, 1 month after the last primary dose in each group, there were modest differences in seropositivity (5 to 22%) between the groups for serotypes 6B, 14, 18C, 19F and 23F, which favoured the 3p schedule. At 13 months, 1 month after the booster dose in the 2p+1 schedule and 7 months after the last dose in the 3p schedule, antibody concentrations where much higher for the 2p+1 group for all serotypes; antibody levels had fallen back towards pre-vaccination levels in the 3p groups. At 19 months, antibody concentrations in the two groups were more similar. There was statistical evidence of differences favouring the 2p+1 schedule for all serotypes at 19 months when GMCs were compared. No data from observational studies are available. (b) Comparing the two 3p schedules in the 62 studies with GMC results, the post-booster antibody response (median age at blood draw = 14.8 months) of a 2p+1 schedule was significantly higher than the post-primary response (median age at blood draw = 6.3 months) of a 3+0 schedule for all serotypes. The post-booster median GMC response (in µg/ml) compared to the post-primary GMC response, ignoring confounders such as geographic region, DtaP verus DTwP as a co-administered vaccine and PCV product, was 8.3 v 2.7, 4.3 v 2.7, 6.7 v

Outcome of interest	Vaccination Schedules	
	3p versus 2p	**3p versus 2p+1**
Immunogenicity (cont)	for both schedules except for serotypes 6B and 23F, but those receiving a 3-dose primary schedule appeared slightly higher compared to those receiving a 2-dose primary schedule, although differences were small. (c) No new studies identified	1.3, 12.0 v 4.5, 8.1 v 3.8, and 4.5 v 1.7 for serotypes 1, 5, 6B, 14, 19F, and 23F respectively. (c) No new studies identified
Policy relevance of these findings	If incidence of disease is highest in the first year of life (or before the booster dose is given), a 2p or 2p+1 schedule might not offer optimal individual protection compared to 3p schedule. If there is substantial vaccine-induced herd immunity this difference may not be important.	

Outcome of interest	Vaccination Schedules	
	3p versus no PCV	**2p+1 versus no PCV**
Disease	**3 doses better than no PCV** (a) Clinical disease outcomes were reported in 2 RCTs (Gambia 9v(12), South Africa 9v(13)) and one case-control study([6]). For invasive pneumococcal disease caused by vaccine serotypes, the vaccine efficacy (VE) estimate when the analysis was restricted to those without HIV was 74% (95% CI 52, 86%, I2 0%, 2 RCTs). For radiologically confirmed pneumonia (first episode), estimated VE using intention to treat data was 24% (95% CI 9, 37%, I2 70% (2 RCTs) and heterogeneity was not explained by the inclusion of HIV-infected children. When restricted to those without HIV, The VE was 29 (95% CI 13, 42%, I2 64.3%, 2 RCTs). Mortality was reported as an outcome in 2 RCTs (Gambia (13) and South Africa (14)), with limited mortality data reported in 4 RCTs (China 7v (14), Gambia 9v pilot b (15), Ghana infants 9v (16), South Africa 9v pilot (17). VE against all-cause mortality was 16% (95% CI 3, 28%) in Gambia and 5% (95% CI -13, 21%) in South Africa.	**2p+1 better than no PCV** (a) No clinical data from RCTs or cohort studies were available. One non-randomized trial[31] found 65% (95% CI 47, 78%) fewer episodes of X-ray confirmed pneumonia among those choosing PCV compared to no PCV. One case-control study (Whitney et al (6)) reported vaccine effectiveness of 98% (95% CI 75, 100%) against vaccine serotype invasive pneumococcal disease for a 2p+1 schedule compared to no vaccination.

Disease	(b) There were additional nine RCTs using 7v vaccine that evaluated either a 3p (N=5) (Klugman 2003 (14), Cutts 2005(13), Lucero 2009(18), Madhi 2005(19), Richmond 2008(20) or a 3+1 (N=4) (Black 2002 (21), Hansen 2006(22), O'Brien 2002(), Adam 2008(23)) schedule. Almost all of these RCTs showed efficacy against clinical and/or radiologically confirmed pneumonia in general pediatric populations. In addition, two case-control studies and three indirect cohort analyses reported vaccine effectiveness of 95% (95% CI 88, 98%) and 90% (95% CI 24, 100%) and 76.6% (50.4, 88.9), 94.6% (69.7-99.5), and 98% (95-99) respectively, against vaccine serotype invasive pneumococcal disease for 3p doses compared to no vaccination. Two surveillance studies, (Roche 2008 (24), Lehman 2010(25)both from Australia, noted reductions of 89% and 90% in vaccine serotype IPD among children <2 years following routine introduction of a 3p schedule with a catch-up campaign for all children <2 years of age. Five observational studies evaluated a three dose primary series on clinical pneumonia- one study from Australia utilized a 3+0 schedule in non-indigenous populations (26) and four studies from the US evaluated a 3+1 schedule on general populations (Table 9) (Grijalva 2007 (27); Nelson 2008 (28); Simonsen 2011 (29) ;Zhou 2007 (30)). Almost all studies showed evidence of effectiveness of PCV use on the reduction of pneumonia rates (Figure 8). (c) In Australia (27) , a 38 %(95% CI 36-40%) reduction was seen in hospitalizations with a primary diagnosis of pneumonia among children <2 years of age in the 30 months following 7vPCV introduction on a 3p+0 schedule with catch-up for children <2 years.	(b) Three pre-/post-introduction analyses of pneumonia hospitalizations (De Wals 2008 (32); Ansaldi 2008 (33); Patrzalek 2010(34)) from administrative databases in countries using 2p+1 schedules found reductions ranging from 15% (95% CI 2.8, 26%) for all-cause pneumonia to 65% and 69%, respectively for X-ray-confirmed and lobar pneumonia, respectively. Studies of impact following vaccine introduction for 2p+1 are limited to a small number of countries, most with high vaccination coverage and use of a catch-up program; these findings were comparable to those seen with 3p or 3p+1 schedules. Seven observational surveillance/trend analysis studies (2) evaluated the effect of 2+1 (n=5) and 3+0 (n=2) schedules on vaccine-type IPD in children ⩽2 years of age (Figure 14). . Despite highly variable baseline incidence rates, all of these studies show a significant reduction in vaccine-type IPD after introduction of vaccine. Although impact can be seen early after introduction, the largest reduction can be seen in mature programs ⩾3 years after vaccine introduction. The paucity of data on the impact of these schedules in young children, particularly ⩾1 year after vaccine introduction, does not allow for a clear determination on which regimen is superior or inferior to the other. (c) No new studies identified
Nasopharyngeal carriage vaccine serotypes (VT)	**The 3p series resulted in less carriage of serotypes contained in the vaccine at 6, 9. 13 and 18 months than no PCV.** (a) Carriage data were reported in 6 RCTs (Fiji 7v (8), Gambia 9v pilot a (35), South Africa 9v (14) and South Africa 9v pilot (18) (3p vs 0 only in these). South Africa 9v data was 5 years after vaccination, Finland 7v (36)(and USA2 (37) (native americans) had data prior to booster). At around 6 months (3 RCTs), 9 months (3 RCTs), 12 months (2 RCTs) and 18 months of age (1 RCT), groups receiving 3p schedules were less likely to be carrying vaccine serotypes than groups that did not, but confidence intervals often crossed 1. The groups receiving PCV were more likely to be	**2p+1 better than no PCV.** (a) Carriage data were reported in 1 RCT(43). At 12, 18 and 24 months of age, the vaccinated group was less likely to be carrying vaccine serotypes(45).

Nasopharyngeal carriage vaccine serotypes (VT) (cont)	carrying non-vaccine serotypes at 6 and 9 months of age. This pattern was less pronounced at 12 months of age. (b) Additional 8 studies examined a 3p schedule (18, 36, 38, 39, 40, 41, 42, 45). Most 3-dose primary regimens reduced vaccine-type carriage, although statistical significance was not always reached. One study with a 3-dose primary regimen and a PCV7 product made by Merck showed a non-significant increase of vaccine-type carriage at 7 months of age (40). (c) No new studies identified	(b) As compared to unvaccinated controls, only two studies examined a 2-dose primary regimen (45, 44). All studies of 2-dose primary series revealed a reduction in vaccine-type carriage compared with the control group (no vaccination). (c) In an abstract from one observational study, carriage of vaccine serotypes dropped 35% among children <2 years of age with acute otitis media or pneumonia when assessed one year after vaccine introduction in Switzerland (45).
Immunogenicity	**3p better than no PCV.** (a) No data reported (b) Approximately 14 immunogenicity studies have demonstrated that a schedule of 3p doses induces a robust immune response compared to a control arm[2]. (c) No new studies identified	**No data available** (a) No immunogenicity studies have evaluated a schedule of 2p+1 doses compared to an unvaccinated control arm. (b) No new studies identified (c) No new studies identified
Policy relevance of these findings	These data strongly support the current WHO recommendation for the use of PCV vaccines worldwide on a 3p schedule.	The evidence supporting use of the 2p+1 schedule is more limited than for the 3p schedule because of the lack of RCTs with clinical outcomes. If incidence of IPD is highest in the first year of life (or before the booster dose is given), a 2p+1 schedule might not offer optimal individual protection compared to 3p schedule in the absence of population herd immunity.

Age at 1st dose and interval between doses	**Late start (3-6 months of age) vs. early start (1.5-2 months of age) schedules: insufficient data or data of inadequate quality to make conclusions.** (a) No clinical or carriage data from RCTs, cohort studies or case-control studies are available. Immunological data were reported in 4 RCTs (UK1 7v (46), USA3 7v (47), Canada1 7V primary (48), Germany 7v (49)). Antibody concentrations could be compared in 3 (UK1 7v, USA3 7v, Canada1 7V primary); results favoured the early start in 1 RCT (2 week difference between schedules in the age at first dose), the late start in 1 RCT (3 month difference) and showed no difference in 1 RCT (1 month difference). There were differences in terms of schedules and intervals between the last dose and immunological assessment both between comparison groups and between trials. **2-month vs. 1-month interval schedules: insufficient data or data of inadequate quality to make conclusions.** (a) No clinical data from RCTs or case-control studies are available that directly compare different intervals. Limited clinical data were reported in 2 cohort studies (International obs 10v, International obs7v. Only adverse event data so not relevant to compare efficacy of schedules). Immunological data were reported in 3 cohort studies. For PCV7, a 3p, 2-month interval schedule (2, 4, 6m) tended to result in similar or higher percentages seropositive 1 month after vaccination than a 3p, 1-month interval group (1.5, 2.5, 3.5m) but both groups were similar at 12-18 months of age (1 cohort study). A similar pattern was seen for a 2p 2-month interval schedule (2, 4m) vs. a 2p, 1 month interval schedule (2, 3m) except that differences persisted to 12 months (1 cohort study). For PCV10, the 3p, 2-month interval group tended to have similar or lower percentages seropositive 1 month after vaccination than 3p with a 1-month interval and this persisted at 12-18 months of age (1 cohort study). RCTs showed good VE for clinical outcomes for trials using 1 month interval, even though I month interval is thought to be potentially less good than 2 (i.e., more time between doses would allow the immune system to 'prime' for the next dose) **Longer interval vs. shorter interval between primary and booster schedules: No differences between intervals.** (a) Limited clinical data were reported in 1 RCT. No clinical data from cohort or case-control studies and no carriage data from RCTs, cohort or case-control studies were available that directly compare different intervals. Immunological data were reported in 2 RCTs. Seropositivity levels () ?) were very high (threshold 0.20µg/ml) with both booster schedules (1 RCT, 10-12 months vs. 8-10 months after last primary dose, 1.5 months after the booster dose). Late booster dose groups tended to have higher antibody concentrations than early booster groups but confidence intervals crossed 1 for all serotypes except 4 and 23F (2 RCTs Canada 7v booster (50), Finland 10V (51)), 10-12 months vs. 8-10 months after last primary dose (1.5 months after booster), and 11-12 months vs. 8-9 months after last primary dose (1 month after booster).
	(b) No new studies identified (c) No new studies identified

Assessment of the quality of evidence

GRADE table used to score the quality of evidence[5]

What is the effect administering PCV vaccines using a 3p versus 2p+1 schedule on key outcomes (i.e. disease, nasopharyngeal carriage of vaccine types and immunogenicity)?				
			Rating	Adjustment to score
Quality Assessment	No of studies/starting score		5 RCTs and 3 observational	4
	Factors decreasing confidence	Limitation in study design	serious	1
		Inconsistency	serious	1
		Indirectness	none serious	0
		Imprecision	serious	1
		Publication bias	none serious	0
	Factors increasing confidence	Strength of association	no	0
		Dose-response	yes	1
		Mitigated bias and confounding	no	0
	Final numerical score of quality of evidence			2
Summary of Findings	Statement on quality of evidence			Our confidence in the estimate of the effect on key outcomes is limited
	Conclusion			There is no definitive evidence that 3p schedule is superior to a 2p+1 schedule in its effect on clinical disease or carriage outcomes. The interpretation of differences found in immunological outcomes is limited because of uncertainty about their clinical relevance.

Summary of studies included in the GRADE assessment[6]

For the comparison 3p versus 2p (before the booster dose is given) the following studies contributed to the assessment: 3 RCTs and 2 observational studies (case control and retrospective cohort) with data on disease outcomes, 2 RCTs with data on nasopharyngeal carriage of vaccine types and; five RCTs and one observational study with data on immunological outcomes.
For the comparison 3p versus 2p+1 (after the booster dose is given) the following studies contributed to the assessment: one observational study with data on invasive pneumococcal disease (IPD) and one RCT with data on immunological outcomes

Iceland 9v (3)

RCT that assessed immunogenicity in infants with a pneumococcal–meningococcal conjugate vaccine in 2p versus 3p with a booster. Infants (N= 223) received 9vPnC–MnCC (CRM197-conjugated pneumococcal serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F and meningococcal C polysaccharides) either at 3 and 5 or 3, 4 and 5 months and a booster with either 9vPnC–MnCC or 23-valent pneumococcal-polysaccharide vaccine (23vPPS) and CRM197-MnCC, at 12 months. IgG measured at 3, 6, 12 and 13 months in all subjects and serum bactericidal activity (SBA) in half. One in the two-dose group had septicemia 7 days after the second dose, caused by S. pneumoniae serotype 7F.The 9vPnC–MnCC vaccine induced significant IgG to all components. Three doses induced higher antibody GMCs (geometric mean concentrations) at 6 months to seven of nine pneumococcal serotypes. This was most significant for 6B and 23F ($p < 0.001$), that also showed lower rate of responders >0.35 (6B, 23F) and >0.5┐ g/mL (6B). Antibody GMCs remained lower following

[5] The studies assessed in this table only include those identified by Scott P et al (2011), A systematic review of PCV schedules of data from randomized controlled trials and observational studies of childhood schedules using 7, 9, 10 and 13 valent vaccines. The additional studies identified by Conklin L et al (2011) Landscape analysis of pneumococcal conjugate vaccine dosing schedules: A systematic review: Sub-report on the 3-dose schedules were not included in this version due to time constraints but ,will be included in the final presentation to SAGE members in November 2011,
[6] The summary descriptions of the studies correspond to the information published by the authors. The methodological considerations were prepared by adjusting those reported by Scott P et al (2011). More detailed discussions can be found in this report.

9vPnC–MnCC booster in subjects primed with two doses although only significant for serotype 18C. Significant memory responses were observed 1 week after the 23vPPS toddler dose. MnCC–IgG GMC was lower after two doses, however with comparable SBA.
Methodological features: randomization sequence not described; concealment of allocation not described; outcome assessors blinded not mentioned. Disease outcomes reported as adverse events.

Europe 10v: (4)
RCT that evaluated the immunogenicity of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D-conjugate vaccine (PHiD-CV) using a simplified 2-dose priming and a 3-dose priming both followed by a booster dose. A total of 351 healthy subjects were primed with PHiD-CV at either 3 and 5 or 3, 4 and 5 months of age followed in all subjects by a booster dose at 11 to 12 months of age. Serotype-specific pneumococcal responses were measured 1 month following primary and booster vaccinations. Depending on the serotype, the percentages of subjects reaching the ELISA antibody threshold of 0.2 ug/mL were 92.8% to 98.0% following 2 primary doses and 96.1% to 100% following 3 primary doses except for serotype 6B (55.7% and 63.1%, respectively) and serotype 23F (69.3% and 77.6%, respectively). Opsonophagocytic activity (OPA) could be measured in 74.4% to 100% and 88.9% to 100% of the subjects after the 2-dose or 3-dose priming, respectively, except for serotype 1 (60.8% and 62.9%, respectively). In both groups, robust increases in ELISA antibodies and OPA titers were observed for all serotypes after the booster dose. Higher postprimary and postbooster ELISA antibody levels and OPA titers were observed for most serotypes following the 3 plus 1 schedule.
Methodological features: randomization sequence not described; concealment of allocation not described; outcome assessors blinded not mentioned. Disease outcomes reported as adverse events.

Fiji 7v (8)

RCT that evaluated the effect of a reduced-dose 7-valent pneumococcal conjugate vaccine (PCV) primary series followed by a 23-valent pneumococcal polysaccharide vaccine (23vPPS) booster on nasopharyngeal (NP) pneumococcal carriage. Infants aged 6 weeks were randomized to receive 0, 1, 2, or 3 PCV doses. Within each group, half received 23vPPS at 12 months. NP swabs were taken at 6, 9, 12, and 17 months. Isolates were serotyped by multiplex PCR and a reverse line blot assay. There were no significant differences in PCV vaccine type (VT) carriage between the 3- and 2-dose groups at 12 months. NP VT carriage was significantly higher (P, <0.01) in the unvaccinated group than in the 3-dose group at the age of 9 months. There appeared to be a PCV dose effect in the cumulative proportion of infants carrying the VT, with less VT carriage occurring with more doses of PCV. Non-PCV serotype (NVT) carriage rates were similar for all PCV groups. When groups were pooled by receipt or non receipt of 23vPPS at 12 months, there were no differences in pneumococcal, VT, or NVT carriage rates between the 2 groups at the age of 17 months. In conclusion, there appeared to be a PCV dose effect on VT carriage, with less VT carriage occurring with more doses of PCV. By the age of 17 months, NVT carriage rates were similar for all groups. 23vPPS had no impact on carriage, despite the substantial boosts in antibody levels.
Methodological features: randomization sequence adequate; concealment of allocation unclear, opaque envelope but not clear if linked to child before opening; outcome assessors blinded.

Gambia 7v (5)
The immunogenicity and impact on carriage of fewer doses of pneumococcal conjugate vaccine (PCV7) followed by booster with pneumococcal polysaccharide vaccine (PPV) were investigated. 684 infants were assigned randomly to one of the three groups that received one (A), two (B) or three (C) doses of PCV7 between 2 and 4 months of age, plus PPV at 10 months. Following primary vaccination protective antibody titers of >0.35 ug/ml against the PCV7 serotypes combined increased significantly with the number of PCV7 doses, 44% vs. 77% vs. 94% ($p < 0.001$), and correlated positively with the opsonophagocytic indices, but negatively with nasopharyngeal carriage of pneumococcus. The differences in antibody responses and pneumococcal carriage between the groups diminished following booster with PPV.
Methodological features: randomization sequence not described; concealment of allocation not described. Mortality was reported as reason of loss to follow up.

Israel 7v (10)
An open-label RCT evaluating two different schdeules: 3+1 (primary 2, 4, 6m [n=353]; booster 12m [n=163]); and 2+1 (primary 4, 6m [n=188]; booster 12m [n=169]). Nasopharyngeal cultures were obtained at 2, 4, 6, 7, 12, 13, 18, 19, 24, 30m (total=3798). Serum serotype-specific IgG ELISA was obtained at 2, 7, 13, 19m. At 7 months, antibody concentrations and % ≥0.35µg/ml were significantly lower in the 2+1 vs. 3+1 groups, mainly for serotypes 6B and 23F; this persisted after booster (age=12m). After ≥1 PCV7 dose, during 1st year, PCV7-serotype carriage was significantly higher in the 2+1 groups, mainly due to 6B and 6A carriage. However, this was reversed after booster, and thus for the entire period of 4-30m, no significant difference between the groups was observed. The effect of the 2+1 reduced-dose regimen on NP-Pnc-Carr was similar to that of the 3+1.
Methodological features: randomization sequence adequate; concealment of allocation unclear; outcome assessors blinded not reported.

USA 7v (6)
A case control study analysed data on invasive pneumococcal disease among children 3–59 months identified through the US Centers for Disease Control and Prevention's Active Bacterial Core surveillance. Three controls, matched for age and zip code were selected for each case. The matched odds ratio for vaccination were calculated using conditional logistic regression, controlling for underlying conditions. Vaccine effectiveness was calculated as one minus the adjusted matched odds ratio times 100%. The study included 782 cases and 2512 controls. Effectiveness of one or more doses against vaccine serotypes was 96% (95% CI 93–98) in healthy children and 81% (57–92) in those with coexisting disorders. It was 76% (63–85) against infections that were not susceptible to penicillin. Compared with no vaccine, point estimates for effectiveness of two, three, or four doses when given on an infant schedule were close to each other, with widely overlapping CI and were more effective than a single dose. Effectiveness of two, three, and four-dose schedules was similar up to 6 months after vaccination (97% [87–99] for 2 doses, 100% [96–100] for 3 doses, and 100% [58–100] for 4 doses) and 6 or more months following vaccination (95% [71–99] for 2 doses, 87% [64–95] for 3 doses, and 100% [93–100] for 4 doses). Vaccination prevented disease caused by all seven vaccine serotypes, and by vaccine-related serotype 6A. Several schedules were more protective than no vaccination; three infant doses with a booster were more protective against vaccine-type disease than were three infant doses alone (p=0·0323).
Methodological features: The case control have few vaccinated cases which limited statistical power. Therefore few potential confounders were included in analyzes comparing the schedules. This might result in residual confounding by factors such as socioeconomic status and those that might influence both vaccination and the risk of IPD. In general observational studies are more prone to bias. Results of case control studies can be biased by inappropriate selection of controls that are not representative of the population from which cases arose.

USA 7v cohort (7)
A retrospective matched-cohort study design and health insurance claims data, this study compared rates of lower respiratory tract infections (LRTD) between children who were born in 2002 and received 2 versus 3 PCV7 doses in the primary series, both before and after receipt of the booster dose.Two-dose and 3-dose children were matched (1:1) using propensity scoring. Cumulative rates of hospital admissions and outpatient visits for LRTD were tallied during the post-primary/pre-booster period and the post-booster period (to age 3 years), respectively.During the post-primary/pre-booster period, 3-dose children (n = 3293) had 7.8 (95% CI: 0.8 to 14.8) fewer LRTD-related hospital admissions (per 1000 children) and 57 (95% CI: −6 to 128) fewer LRTD-related outpatient visits (per 1000 children) than matched 2-dose subjects (n = 3293). During the post-booster period, the numbers of LRTD-related hospital admissions and outpatient visits did not differ significantly between 3-dose and 2-dose children.
Methodological features: In general observational studies are more prone to bias. In this study the outcome was 'lower respiratory tract disease', including bronchitis, bronchiolitis, asthma or wheezing, and pneumonia due to pneumococcal infection or unspecified cause.

UK 9v (11)

A cohort study in the U.K evaluated 2p or 3p schedules in infants (at 2 and 4 or 2/3/4 months of age) of a 9-valent pneumococcal conjugate vaccine (9VPCV) followed by boosting at 12 months of age. For infants, serotype-specific IgG geometric mean concentrations were similar post-primary immunization between the groups with both showing avidity maturation and similar booster responses. For toddlers, the primary response to 4 of the 9 serotypes was lower in the 1- compared with the 2-dose group (type 6B, 0.77 versus 7.1; type 14, 4.67 versus 14.98; type 19F, 5.05 versus 7.75; type 23F, 2.48 versus 5.05), although for all serotypes booster responses were similar between groups, and the post primary responses in the 1-dose group were at least as high as those after infant immunization. The 2-dose infant priming schedule of 9VPCV is comparable with the 3-dose schedule.

Methodological features: The comparison groups in this cohort study were different counties in the United kingdom and during different time periods (200-2001 or 2001-2003). This could have introduced bias if systematic differences existed between locations and time periods, such as recruitment processes or exposure to *S. pneumoniae*.

Key information on *Streptococcus pneumoniae* epidemiology

Burden of Disease (http://www.who.int/nuvi/pneumococcus/GBD_pneumococcus.pdf)

Key points

- ➔ In 2000, about 14·5 million episodes of serious pneumococcal disease (uncertainty range 11·1–18·0 million) were estimated to occur.
- ➔ Pneumococcal disease caused about 826 000 deaths (582 000–926 000) in children aged 1–59 months, of which 91 000 (63 000–102 000) were in HIV-positive and 735 000 (519 000–825 000) in HIV-negative children.
- ➔ Of the deaths in HIV-negative children, over 61% (449 000 [316 000–501 000]) occurred in ten African and Asian countries.
- ➔ *Streptococcus pneumoniae* causes around 11% (8–12%) of all deaths in children aged 1–59 months (excluding pneumococcal deaths in HIV-positive children). Achievement of the UN Millennium Development Goal 4 for child mortality reduction can be accelerated by prevention and treatment of pneumococcal disease, especially in regions of the world with the greatest burden.

Key clinical outcomes (http://www.who.int/immunization/SAGE_wg_detailedreview_pneumoVaccine.pdf)

Key points

- ➔ Important clinical syndromes include pneumonia, bloodstream infections, meningitis, and acute otitis media.
- ➔ Pneumonia with emphysema and/or bacteraemia, febrile bacteraemia and meningitis constitute the commonest manifestations of invasive pneumococcal disease.
- ➔ Pneumococci are a frequent cause of non-bacteraemic pneumonia. In developing countries, non-bacteraemic pneumonia causes the majority of pneumococcal deaths in children.
- ➔ Middle-ear infections, sinusitis and bronchitis represent non-invasive and less severe manifestations of pneumococcal infection, but they are considerably more common.
- ➔ Emerging antibiotic resistance increases the cost of treatment of pneumococcal infections and can result in treatment failures.

Age-specific distribution of key outcomes in children[7]

Key points

- ➔ Gambia/Kenya: Peaks in disease at 6-7 months of life. Neonatal disease burden remains somewhat unclear.Deaths have a similar age distribution as the cases. Higher proportion of meningitis in the younger kids (i..e < 6 mo) than in all IPD where the greater burden was in the second year of life.
- ➔ Meningitis belt data: Outside of major serogroup A meningococcal epidemics, pneumococcal meningitis incidence is as common as meningococcal meningitis in infants; about half that of meningococcal meningitis for ages 1 to 14 years; similar again from ages 15-29 years; and 2- to 4-fold more common than meningococcal meningitis for older ages. Depending on the age group, Sp meningitis incidence is 3.5 to 20-fold higher in the meningitis belt than the US or Europe. CFRs are 40-60% across all age groups (compared to 10-20% for Nm until age 50 years); consequently, Sp causes 2 to 15 times more common a cause of meningitis mortality than Nm. Approximately 60% of Sp meningitis cases and deaths in the meningitis belt occur from age 5-59 years. Among children age <5 years, there is a great serotype distribution; after age 5 years, serotype 1 causes 60-80% of Sp meningitis. Data on Sp pneumonia are lacking from the meningitis belt; applying data from children <2 years of age in the Gambian RCT to persons of all ages in the meningitis belt suggests a lifetime Sp pneumonia risk of 6-16%.
- ➔ Global review: Disease in the under 1 year of age strata is important, especially if death prevention is key.Very high variability in surveillance methods which confound the analyses, heterogeneity in surveillance needs to be accounted for in the analyses. Notable similarities between the analyses from various countries especially in the peaks of disease in finer age strata. Serotype 1, 3, 5 vaccine impact remains unknown and may be quite relevant. Impact on carriage, duration of colonization, duration of vaccine impact, and indirect effects. Serotype 1 epidemiology seems to be a bit different than other serotypes, without a peak at 3-18 months but with a more flat burden and so needs to be considered somewhat uniquely. This has a significant impact on the assessment of the need for a booster dose late in the first year or early in the second year of life.

[7] A global review is in progress. These are the main messages from the ad hoc expert consultation on Sept 12, 2011. A final report will be presented to SAGE members on Nov 2011.

PNEUMOCOCCAL CONJUGATE VACCINES: WHO Recommendations for Routine Immunization (2007) (http://www.who.int/wer/2007/wer8212.pdf)

The current WHO position statement (WER 2007) states: "… There are 2 schedules that have proven clinical efficacy: a 6 week–10 week–14 week series and a 2 month–4 month–6 month series; this latter series is followed by a booster dose at 12–15 months of age. Further information on the impact and the cost effectiveness of other potential schedules (for example, those using different numbers of doses or intervals between doses, and with and without boosters) may be important as low-income countries begin to implement vaccination with PCV-7 or review its use. Although administering a late dose (at around 12 months of age) may be challenging operationally for some national programmes, there may be suitable opportunities when a dose of PCV-7 could be given, such as at the time of measles vaccination. Countries should evaluate information on impact and scheduling once it is available and select the most appropriate schedule based on anticipated impact, cost effectiveness and programmatic feasibility. The risk of serious pneumococcal disease remains high throughout the first 24 months of life. When PCV-7 is first introduced into routine childhood immunization programmes, maximum individual and community-level protection can be achieved by also providing a single catch-up dose of the vaccine to previously unvaccinated children who are aged 12–24 months and to children aged 2–5 years who are considered to be at high risk……."

Recommended Routine Immunizations for Children
(http://www.who.int/immunization/policy/Immunization_routine_table2.pdf)

Antigen	Age at 1st dose	Doses in primary series	Interval between doses		Booster dose	Considerations (see below)
			1st to 2nd	2nd to 3rd		
Pneumococcal conjugate vaccine	6 weeks (min) with DTP1	3	4 weeks (min) with DTP2	4 weeks (min) with DTP3	(see below)	Single dose if 12-24 months of age Delayed/interrupted schedule Co-administration

Considerations:

- ➔ A three dose schedule compatible with DTP, Hepatitis B, Hib and OPV administration should be initiated before 6 months of age to maximize benefits of vaccination.
- ➔ Maximized individual and community-level protection at the time of introduction of the vaccine can be achieved by providing a single catch-up dose to unvaccinated children aged 12-24 months and to children aged 2-5 years who are at high risk.
- ➔ Booster - the additional benefit of administering an additional dose in the second year of life requires further investigation in developing country settings.
- ➔ Co-administration - may be administered concurrently with, though at a different injection site from, other vaccines in infant immunization programmes, including DTP, hepatitis B, *H. influenzae* type b and polio vaccines.
- ➔ Use of pneumococcal vaccine should be seen as complementary to the use of other pneumonia control measures, including appropriate case management and the reduction of exposure to know risk factors, such as indoor pollutants, tobacco smoke, premature weaning and nutritional deficiencies.

WHO Prequalified pneumococcal conjugate vaccines and approved schedules

(http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html)

Vaccine name	Composition - Containing serotypes													Vaccination schedule as indicated in the WHO prequalification leaflet			
	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	Infants	Previously unvaccinated, older infants and children		
															7-11 months	12-23 months	24 months and older
PCV 7 --- PREVENAR™ (for children 6 weeks to 9 years old)			x			x		x	x	x		x	x	**3p+1** ▪ 3 doses, 1st dose as early as 6 weeks of age, ▪ minimum 4 weeks between doses ▪ booster after 1st birthday	**2+1** ▪ 2 doses ▪ minimum 4 weeks between doses ▪ booster after 1st birthday and, at least 2 months after 2nd dose	**2p+0** ▪ 2 doses ▪ minimum 2 months between doses	**0p+1 (24 m-9 yr)** ▪ 1 dose
PCV 13 --- PREVENAR 13™ (for children 6 weeks to 5 years old)	x	x	x	x	x	x	x	x	x	x	x	x	x	**3p+1** ▪ 3 doses, 1st dose as early as 6 weeks of age, ▪ minimum 4 weeks between doses ▪ booster after 1st birthday	**2+1** ▪ 2 doses ▪ minimum 4 weeks between doses ▪ booster after 1st birthday &, at least 2 months after 2nd dose	**2p+0** ▪ 2 doses ▪ minimum 2 months between doses	**0p+1 (24 m- 5 yr)** ▪ 1 dose
PCV 10 --- Synflorix™ (for children 6 weeks to 2 years old)	x		x	x		x	x	x	x	x		x	x	**3p+1** ▪ 3 doses, 1st dose usually 2 months (as early as 6 weeks of age), ▪ minimum 4 weeks between doses ▪ booster at least 6 months after last priming dose	**2p+1** ▪ 2 doses, 1st dose usually 2 months (as early as 6 weeks of age), ▪ minimum 4 weeks between doses ▪ booster at least 6 months after last priming dose	**3p+1** ▪ 3 doses, 1st dose usually 2 months (as early as 6 weeks of age), ▪ minimum 4 weeks between doses ▪ need for booster not established	**Not applicable**

Interaction with other medicinal products and other forms of interaction as documented in the WHO prequalification package insert

PCV 10 --- Synflorix™ (for children 6 weeks to 2 years old)
(http://www.who.int/immunization_standards/vaccine_quality/Synflorix_WHO_leaflet_EN_May_2011.pdf**)**

- Synflorix™ can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib]: diphtheria-tetanus-acellular Pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), Haemophilus influenzae type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), **measles-mumps-rubella vaccine (MMR)**, varicella vaccine, meningococcal serogroup C conjugate vaccine (CRM197 and TT conjugates), oral polio vaccine (OPV) and rotavirus vaccine.
- Different injectable vaccines should always be given at different injections sites.
- Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 response, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). The clinical relevance of this observation is not known.
- No interference was observed with meningococcal conjugate vaccines irrespective of the carrier protein (CRM197 and TT conjugates).
- Enhancement of antibody response to Hib-TT conjugate, diphtheria and tetanus antigens was observed.
- As with other vaccines it may be expected that in patients receiving immunosuppressive treatment an adequate response may not be elicited.

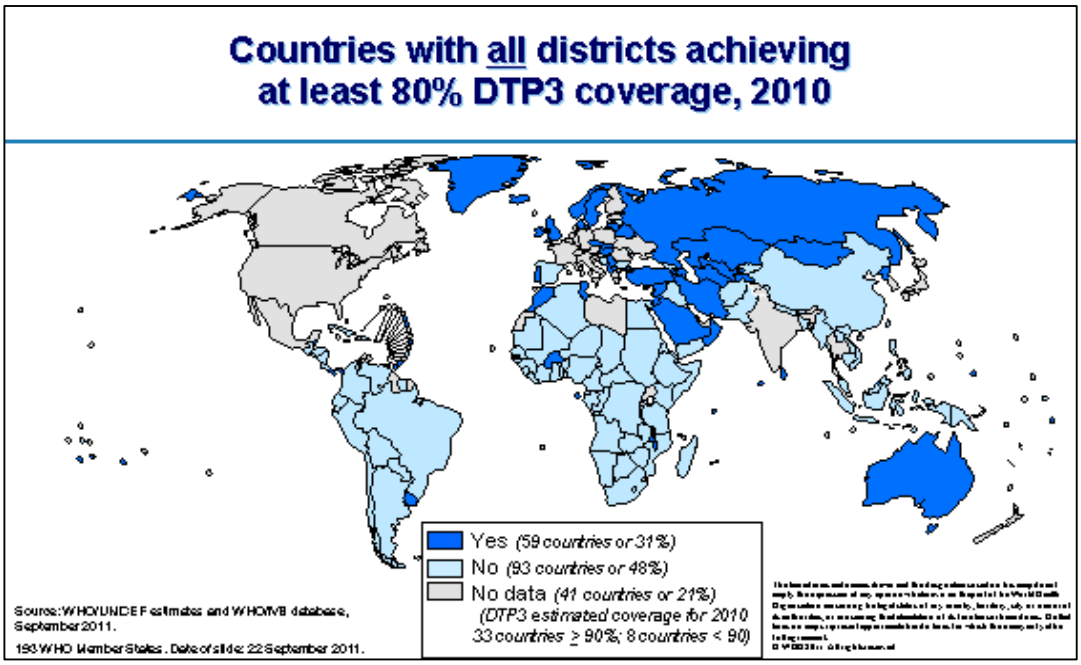
PCV 13 --- PREVENAR 13™ (for children 6 weeks to 5 years old)
(http://www.who.int/immunization_standards/vaccine_quality/prevenar13_pfizer_product_insert_nos.pdf)

- PREVENAR 13 may be given at the same time as diphtheria, tetanus, acellular or whole-cell pertussis, Haemophilus influenzae type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, **measles**, **mumps, rubella** and varicella vaccines.
- When rotavirus or hepatitis A vaccines were given with PREVENAR 13, the safety profiles were similar, but immunogenicity was not measured.

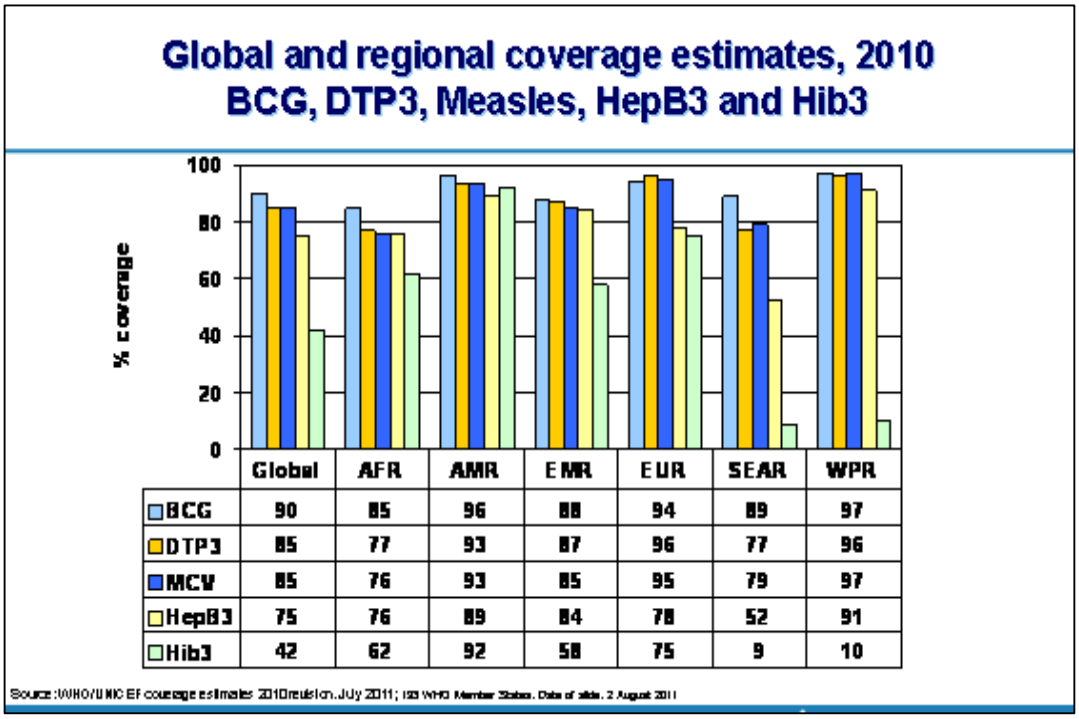
Key operational information of relevance for low and middle income countries

Below are selected graphs showing the coverage achieved by countries in 2010.
http://www.who.int/immunization_monitoring/routine/immunization_coverage/en/index4.html

Countries with all districts achieving at least 80% DTP3 coverage, 2010



Global and regional coverage estimates, BCG, DTP3, Measles, HepB3 and Hib3,2010



	Global	AFR	AMR	EMR	EUR	SEAR	WPR
BCG	90	85	96	88	94	89	97
DTP3	85	77	93	87	96	77	96
MCV	85	76	93	85	95	79	97
HepB3	75	76	89	84	78	52	91
Hib3	42	62	92	58	75	9	10

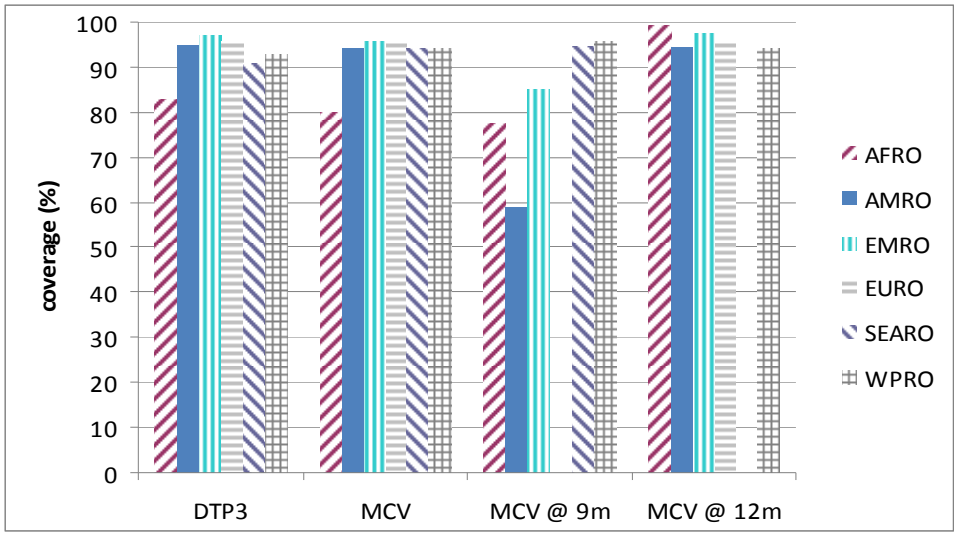
Analysis of DTP and MCV coverage based on country reports to WHO in 2010[8]

The table below was prepared using information on the coverage with Diphtheria Tetanus and Pertussis containing vaccines (DTP) and measles containing vaccines (MCV) as reported to WHO in 2010. These figures do not constitute official estimates of regional or country coverage. Official coverage reports data are available at (http://www.who.int/immunization_monitoring/routine/immunization_coverage/en/index4.html)

For example in EMRO, 11 countries recommend their MCV at 9 months and 10 countries recommend it at ≥12 months (labelled @ 12m). The 11 EMRO countries with MCV at 9 months have a median coverage of 85% (IQR 67.5 to94%)

WHO Region	Variables	DTP		Measles Containing Vaccine		
		DTP1	DTP3	overall coverage	for countries providing it at 9m	for countries giving it at 12m
AFRO	number of countries in this analysis	46	0	0	44	2
	Median	92.5	83	80	77.5	99
	u quartile	80	70	67	66.5	99
	l quartile	97.75	92.75	92.75	92	99
AMRO	number of countries in this analysis	35	0	0	1	34
	Median	98	95	94	59	94.5
	u quartile	96	89	90.5	59	92
	l quartile	99	97.5	98	59	98
EMRO	number of countries in this analysis	21	21	21	11	10
	Median	98	97	96	85	97.5
	u quartile	90	87	82	67.5	96.25
	l quartile	98	98	98	94	98.75
EURO	number of countries in this analysis	53	0	0	0	53
	Median	0	96	96		96
	u quartile	96	93	93		93
	l quartile	93	99	98		98
SEARO	number of countries in this analysis	11	0	0	10	0
	Median	94	91	94	94.5	
	u quartile	89	82.5	87	88.25	
	l quartile	97.5	95.5	97.5	97.75	
WPRO	number of countries in this analysis	27	0	0	7	19
	Median	98	93	94	96	94
	u quartile	93	87	82.5	90.5	82.5
	l quartile	99	97.5	97.5	97.5	97.5

Analysis of DTP and MCV coverage based on country reports to WHO in 2010



[8] These figures do not constitute official estimates of regional or country coverage. Official coverage reports data are available at (http://www.who.int/immunization_monitoring/routine/immunization_coverage/en/index4.html)

Cost and cost effectiveness: key considerations

Cost per dose UNICEF Supply Division (2010) (http://www.unicef.org/supply/files/11_05_23_PCV.pdf)

Presentation	Supplier name	Cost per dose (2010) US$
Pneumococcal (13 valent) in a single dose	Pfizer Inc	3.50
Pneumococcal (10 valent) in a two dose	Glaxo SmithKline Biological S.A.	3.50

Data shown awarded tail prices per dose (in US$) per product supplier per calendar year, based on contract commencement. Prices apply to GAVI eligible graduating countries as listed in GAVI website. It should be noted that vaccine supplier receive a subsidy from donors to the Advanced Market Commitment up to a price of US$ 7.00 for a certain portion of number of doses supplied. Prices displayed are in response to tenders with FCA incoterms, covering vaccines with VVMs. Last updated 23 May 2011.

Comparison of cost effectiveness tools for PCV vaccines (http://www.biomedcentral.com/1741-7015/9/53)
A review of cost effectiveness tools for PCV vaccines found that vaccine cost (dose price and number of doses), vaccine efficacy and epidemiology of critical endpoint (for example, incidence of pneumonia, distribution of serotypes causing pneumonia) were influential parameters in the models compared. Understanding the differences and similarities of such CE tools through regular comparisons could render decision-making processes in different countries more efficient, as well as providing guiding information for further clinical and epidemiological research. A tool comparison exercise using standardized data sets can help model developers to be more transparent about their model structure and assumptions and provide analysts and decision makers with a more in-depth view behind the disease dynamics. Adherence to the WHO guide of economic evaluations of immunization programs may also facilitate this process (http://www.ncbi.nlm.nih.gov/pubmed/19567247)

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