GRADE for 3-dose PCV13 schedules

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GRADE question

Should a 3-dose schedule of the 13-valent pneumococcal conjugate vaccine (PCV13) be recommended for generally healthy infants in the US?

PICO

PICO: Population, Intervention, Comparison, Outcome

Population (P):

Children 2-15 months of age with no underlying chronic medical conditions present

PICO – Intervention & comparison: Step One

GRADE all evidence for each schedule compared to no vaccine to assess the strength of evidence supporting each schedule

Intervention (I):

- 4 doses of PCV13: 2, 4, 6, and 12-15 months (3+1)
- 3 doses of PCV13: 2, 4, and 6 months (3+0)
- 3 doses of PCV13: 2, 4, and 12-15 months (2+1)

Comparison (C): No PCV13 given

PICO – Intervention & comparison: Step Two

GRADE only studies with direct comparisons of schedules

Intervention (I):

- 3 doses of PCV13: 2, 4, and 6 months (3+0)
- 3 doses of PCV13: 2, 4, and 12-15 months (2+1)

Comparison (C):

- 4 doses of PCV13 given at 2, 4, 6, and 12-15 months (3+1)

PICO - Outcomes

- A modified Delphi process was used to rank the importance of each possible outcome
  - *Total respondents* (N=48):
    - 4 Family practice (8%)
    - 3 Internal medicine (6%)
    - 14 Pediatrics (29%)
    - 3 Pediatric infectious disease (6%)
    - 21 Public health (44%)
    - 3 Other (6%)
- Results of rankings (1 through 9) used to select critical outcomes to be included in GRADE

PICO – Outcomes included: Step One

Outcome	Importance
Deaths from pneumococcal disease	8.6 (2-9)
Invasive pneumococcal disease (IPD): Sepsis, bacteremia, meningitis*	8.5 (6-9)
Pneumonia: Bacteremic and non-bacteremic	8 (5-9)
Serious adverse events: Potentially fatal or requiring hospitalization	7.7 (1-9)
Indirect effects on IPD: Prevent disease in unvaccinated by decreased transmission	6.6 (3-9)

*Pneumococcal meningitis and hospitalizations were also ranked but incorporated primarily in the IPD outcome.

PICO – Outcomes included: Step Two

Outcome	Importance
Immunogenicity: antibody responses to vaccine serotypes	6.5 (1-9)
Pneumonia/Lower respiratory tract infection	8 (5-9)
Acute otitis media	5.8 (2-9)

GRADE framework: Step One

- Summary of data and type of evidence by each schedule (3+1, 3+0, and 2+1) and outcome
  - IPD
  - Pneumonia
  - Indirect effects on IPD
  - Mortality
  - Serious adverse events
- Overall type of evidence for each schedule
- Values and preferences of each outcome
- Recommendation category for each schedule

GRADE framework: Step Two

- Summary of data and type of evidence for each comparison:
  - 3+0 vs 3+1
  - 2 vs. 3 primary doses (pre-booster)
  - 2+1 vs. 3+1
- And by outcome:
  - Immunogenicity (surrogate for IPD)
  - Lower respiratory tract infection (LRTI)
  - Acute otitis media (AOM)
- Overall type of evidence
- Values and preferences
- Recommendation category for schedule comparisons

Step One: GRADE the evidence for each schedule compared to no vaccine to assess strength of evidence supporting each schedule

Outcomes: Invasive disease and pneumonia PCV schedule 3+1 (RCTs)

Author, Year, Design	Participants	Intervention	VT IPD: VE (95%CI)	X-ray confirmed pneumonia: VE (95%CI)
Black 2000, 2002, RCT	Infants, USA	PCV7 3+1 at 2, 4, 6, 12-15 months	94 (80, 99)	20.5 (4-34)
O'Brien 2003, RCT	Infants, Navajo, USA	PCV7 3+1 at 2, 4, 6, 12-15 months	83 (21, 96)	-8 (-37, 15)
Palmu 2013, RCT	Infants, Finland	PCV10 3+1 (or 2+1 for <7 months & 2+1 for 7-11 months old)	100 (83, 100)	--
Tregnaghi 2011, RCT	Infants, Latin America	PCV10 3+1 at 2, 4, 6, 15-18 months	--	10 (2-18)

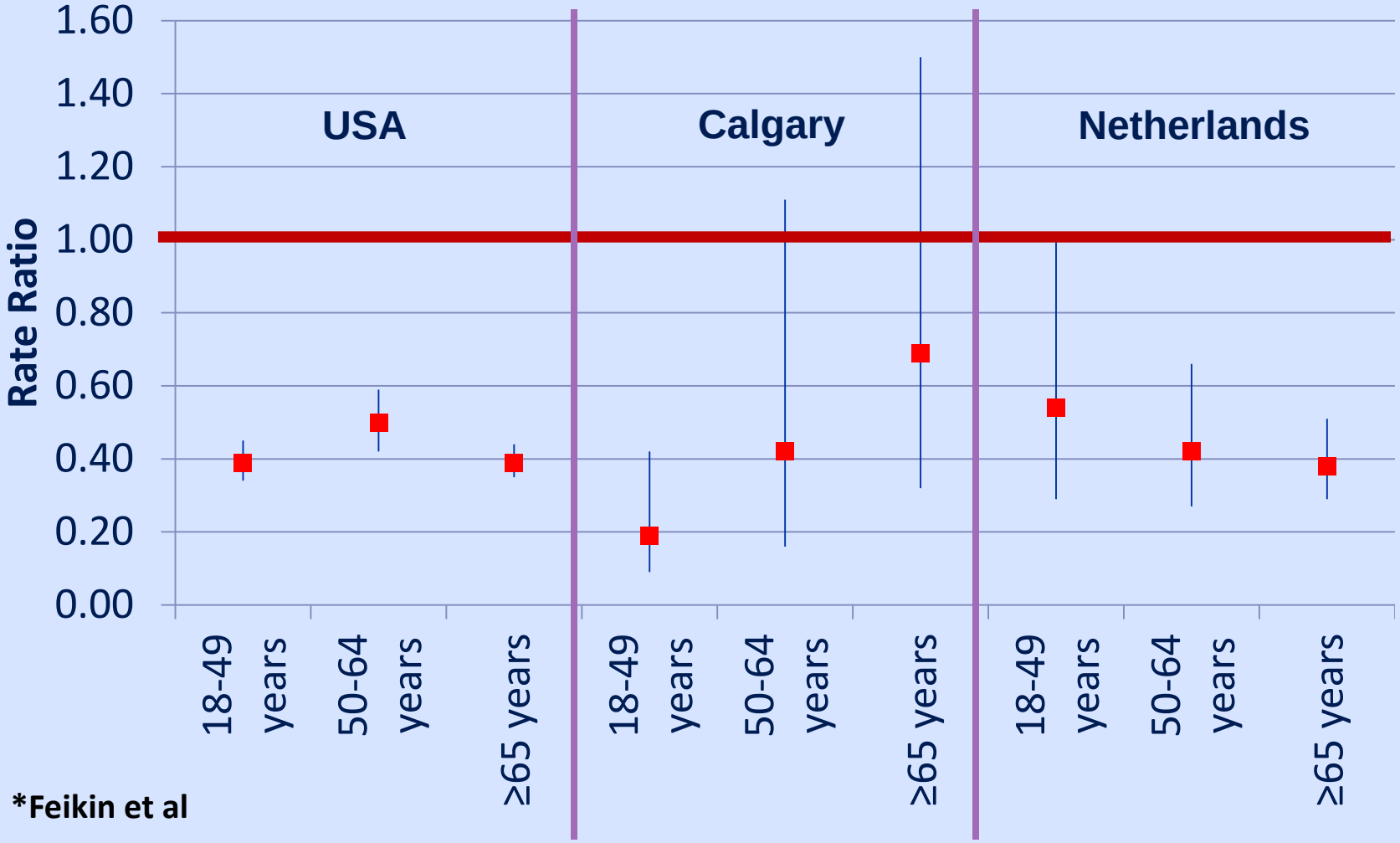
Outcomes: Invasive disease and pneumonia PCV schedule 3+1 (RCTs)

Outcome	# of subjects (studies)	Unvaccinated Incidence *	Vaccinated Incidence *	VE 95% CI	Absolute RD 95% CI*	NNT 95% CI*
IPD	43575 (3 RCTs)	173.5**	10.4	94 (64, 99)	0.0016 (0.0014, 0.0019)	613 (523, 726)
Pneumonia	62265 (3 RCTs)	1,026.5**	913.6	11 (-3, 23)	Not meaningful when VE not statistically significant	

***Vaccine-type incidence per 100,000 population among US children<2 years of age; NNT=Numbers needed to (treat) vaccinate; RD: Absolute risk difference per person**

****Pre-PCV7 rates of PCV13-type IPD from 1998-1999 in the US. Pre-PCV7 rates of all-cause pneumonia from 1996-1999 in the US.**

Outcomes: Indirect effects & PCV schedule 3+1
Rate ratios of vaccine type IPD among adults post-introduction year 3 (observational studies)



*Feikin et al

Assessing evidence type

GRADE	Description
1	Randomized controlled trials (RCTs), or overwhelming evidence from observational studies.
2	RCTs with important limitations, or exceptionally strong evidence from observational studies.
3	Observational studies or RCTs with notable limitations.
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations.

Assessing evidence type

GRADE CRITERIA: Risk of bias, inconsistency, indirectness, imprecision, and other considerations such as strength of association, dose-response, opposing plausible residual confounding or bias.

Downgraded	-1	If any of the GRADE criteria was determined to be serious.
	-2	If any of the GRADE criteria was determined to be very serious.
Upgraded	+1	If the strength of the association was large (RR>2) and there was no serious risk of bias.
	+2	If the strength of the association was very large (RR>5) and there was no serious risk of bias.

Type of evidence: PCV schedule 3+1

Outcome	Studies	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other consider-ations	Evidence type
IPD	3 RCTs	Not serious	Not serious	Not serious	Not serious	Not serious	1
Pneumonia	3 RCTs	Not serious	Not serious	Not serious	Not serious	Not serious	1
Indirect effects on IPD among adults	3 Obs.	Not serious	Not serious	Not serious	Not serious	Not serious +1 by strength of association	2

KEY POINT: There is high quality evidence which shows that PCV 3+1 schedule is effective against IPD and pneumonia; strong indirect effects demonstrated in countries using this schedule.

Outcomes: Invasive disease and pneumonia PCV schedule 3+0 (RCTs)

Author, Year, Design	Participants	Intervention	VT IPD: VE (95%CI)	X-ray confirmed pneumonia: VE (95%CI)
Klugman 2003, Madhi 2007, RCT	Infants (HIV +/-), South Africa	PCV9 3+0 at 6, 10, 14 weeks	83 (39, 97) after 2.3 years 79 (34, 93) after 6.2 years among HIV-uninfected	25 (4, 41) among HIV-uninfected
Cutts 2005, RCT	Infants, Gambia	PCV9 3+0 at 25 days apart	77 (51, 90)	37 (27, 45)
Lucero 2009, RCT	Infants, Philippines	PCV11 3+0 at 6, 10, 14 weeks	--	23 (-1, 41)

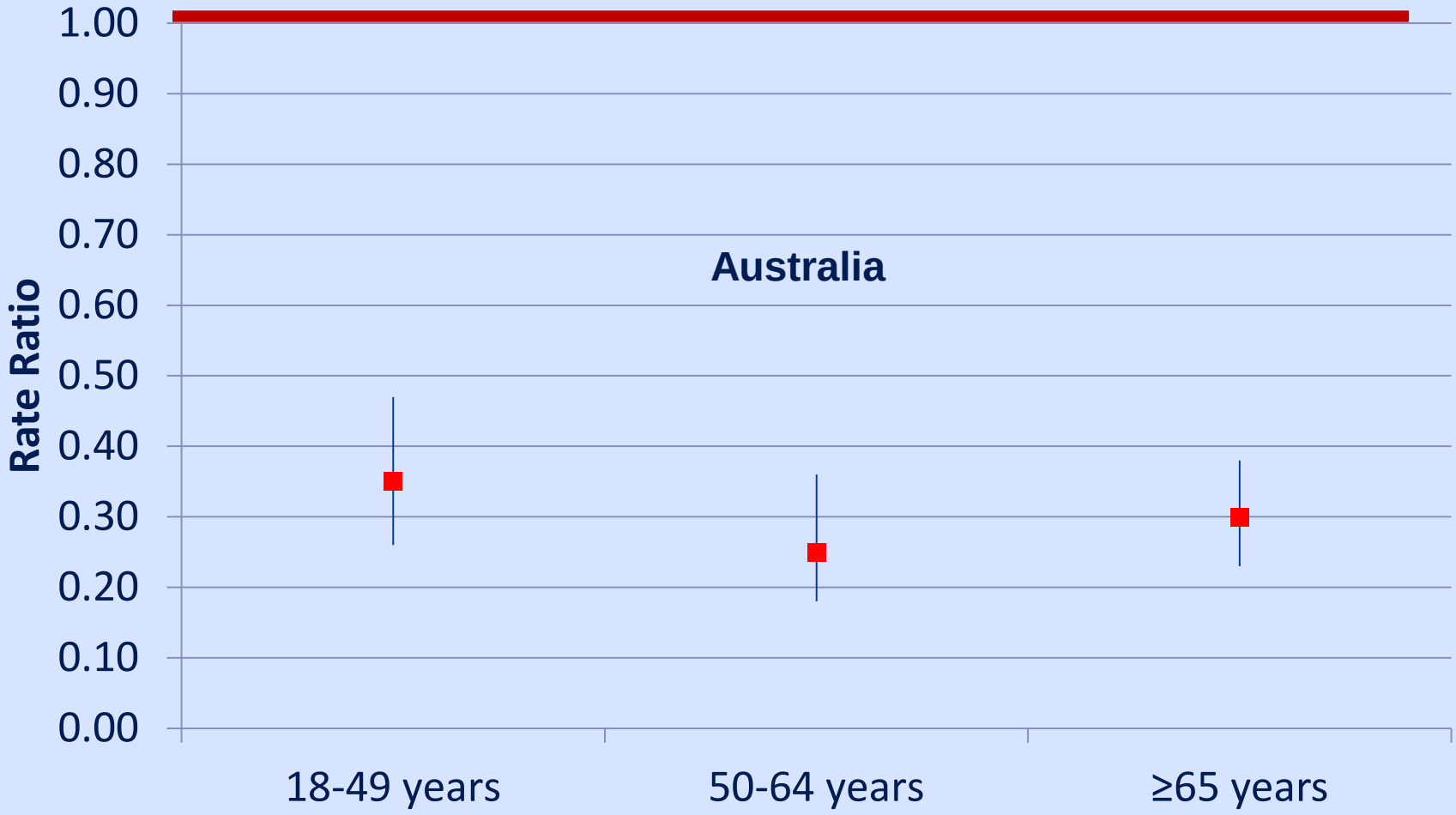
Outcomes: Invasive disease and pneumonia PCV schedule 3+0 (RCTs)

Outcome	# of subjects (studies)	Controls Incidence *	Vaccinated Incidence *	VE 95% CI	Absolute RD* 95% CI	NNT 95% CI*
IPD	56176 (2 RCTs)	173.5**	45.1	74 (58, 84)	0.0013 (0.0010, 0.0016)	779 (631, 1000)
Pneumonia	68207 (3 RCTs)	1,026.5**	759.6	26 (11, 38)	0.0027 (0.0011, 0.0039)	370 (256, 909)

***Vaccine-type incidence per 100,000 population among US children < 2 years of age; NNT=Numbers needed to (treat) vaccinate; RD: Absolute risk difference per person**

****Pre-PCV7 rates of PCV13-type IPD from 1998-1999 in the US. Pre-PCV7 rates of all-cause pneumonia from 1996-1999 in the US.**

Outcomes: Indirect effects & PCV schedule 3+0
Rate ratios of vaccine type IPD among adults post-introduction year 3 (observational studies)



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Type of evidence: PCV schedule 3+0

Outcome	Studies	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other consider-ations	Evidence type
IPD	2 RCTs	Not serious	Not serious	Not serious	Not serious	Not serious	1
Pneumonia	3 RCTs	Not serious	Not serious	Not serious	Not serious	Not serious	1
Indirect effects on IPD among adults	1 Obs.	Not serious	N/A	Not serious	Not serious	Not serious (upgrade +1 by strength of association)	2

KEY POINT: High quality evidence shows that PCV 3+0 schedule is effective against IPD and pneumonia; strong indirect effects demonstrated using this schedule.

Outcomes: Invasive disease
PCV schedule 2+1 (RCT)

Author, Year, Design	Participants	Intervention	VT IPD: VE (95%CI)
Palmu 2012, RCT	Infants, Finland	PCV10 2+1 at <7 months or 7-11 months old (or 3+1 or 2+0 for 12-18 months old)	92 (58, 100)

Outcomes: Pneumonia PCV schedule 2+1 (observational studies)

PCV7 and CXR-confirmed pneumonia

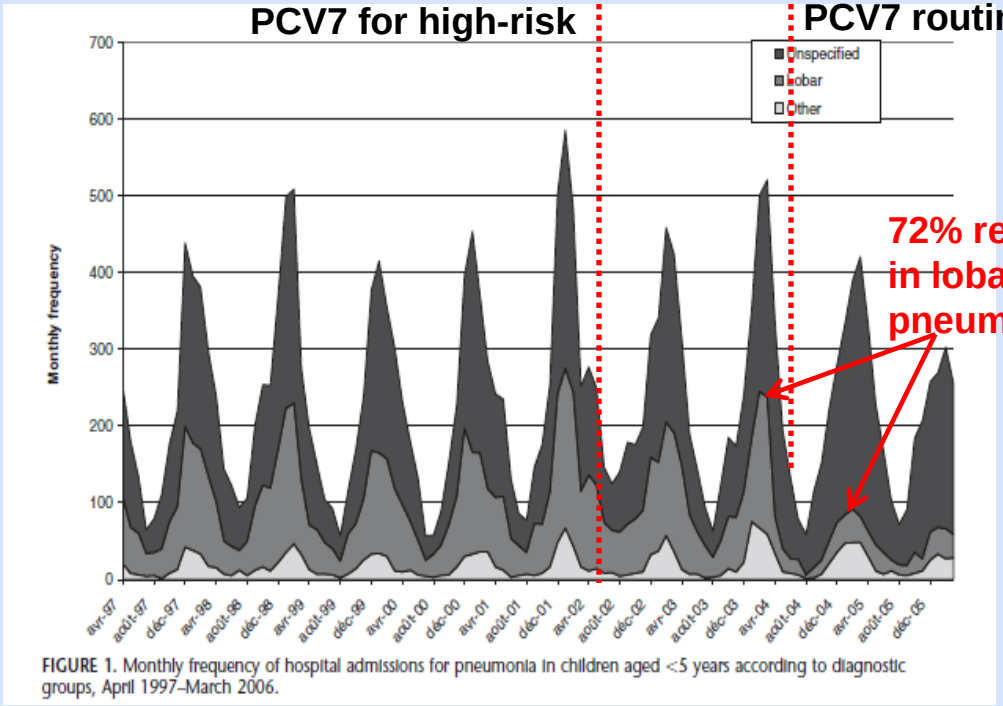


FIGURE 1. Monthly frequency of hospital admissions for pneumonia in children aged <5 years according to diagnostic groups, April 1997–March 2006.

1. Quebec (De Wals, 2008)

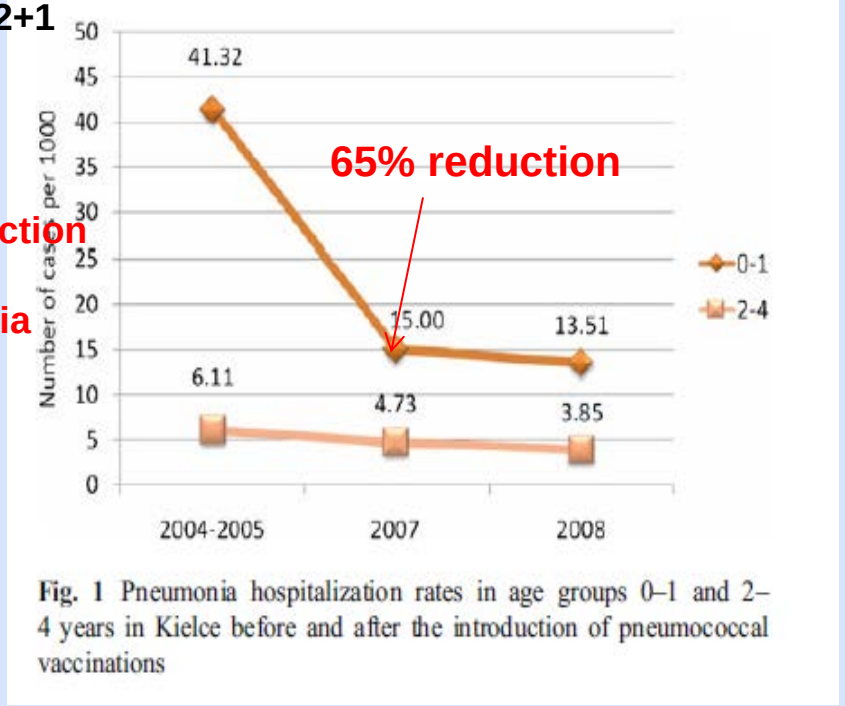


Fig. 1 Pneumonia hospitalization rates in age groups 0–1 and 2–4 years in Kielce before and after the introduction of pneumococcal vaccinations

2. Poland (Patrzalek, 2010)

3. Italy (Esposito, 2007) CXR pneumonia VE: 65 (95% CI: 47, 78)

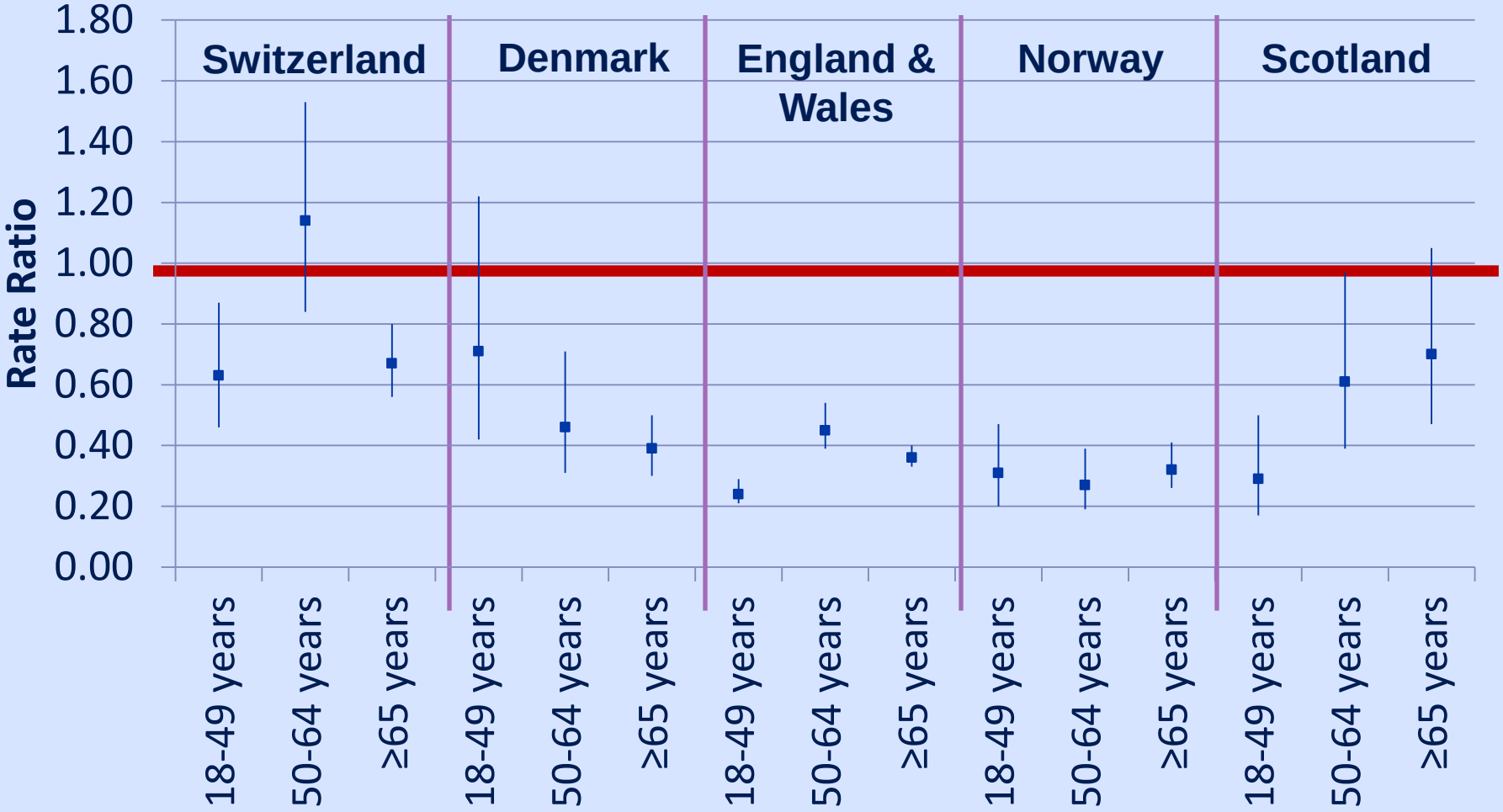
Outcomes: Invasive disease and pneumonia PCV schedule 2+1 (RCT and observational studies)

Outcome	# of subjects (studies)	Controls Incidence*	Vaccinated Incidence *	VE 95% CI	Absolute RD* 95% CI	NNT 95% CI*
IPD	15146 (1 RCT)	173.5**	6.9	96 (67, 99)	0.0017 (0.0014, 0.0019)	600 (514, 700)
Pneumonia	778465 (3 Obs.)	1,026.5**	305.0	70 (64, 74)	0.0072 (0.0066, 0.0076)	139 (132, 152)

***Vaccine-type incidence per 100,000 population among US children <2 years of age; NNT=Numbers needed to (treat) vaccinate; RD: Absolute risk difference per person**

****Pre-PCV7 rates of PCV13-type IPD from 1998-1999 in the US. Pre-PCV7 rates of all-cause pneumonia from 1996-1999 in the US.**

Outcomes: Indirect effects & PCV schedule 2+1
Rate ratios of vaccine type IPD among adults post-introduction year 3 (observational studies)



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Type of evidence: PCV schedule 2+1

Outcome	Studies	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other consideration	Evidence type
IPD	1 RCT	Not serious	N/A	Not serious	Not serious	Not serious	1
Pneumonia	3 Obs. studies	Not serious	Not serious	Not serious	Not serious	Not serious (upgrade +1 by strength of association)	2
Indirect effects on IPD among adults	5 Obs. Studies	Not serious	N/A	Not serious	Not serious	Not serious (upgrade +1 by strength of association)	2

KEY POINT: High quality evidence shows that 2+1 is effective against IPD and pneumonia; strong indirect effects on IPD observed in countries using PCV 2+1 schedule.

Outcomes: Mortality due to IPD in children post-PCV all schedules

Region	History or PCV	Data related to death
Ontario, Canada	2005: PCV7 (3+1) 2009: PCV10 (2+1) 2010: PCV13 (2+1) in 2010	2011 IPD rate: 12.4/100,000 & CFR 1.4% (didn't change pre-PCV7)
Denmark	2007: PCV7 (2+1)	2008 IPD rate 23/100,000 in <2years & CFR 0% (decreased from 2% pre-PCV7)
Australia	2005: PCV7 (3+0)	2006 IPD rate 21/100,000 CFR-3.7%
Belgium	2004: PCV7 (3+1) private sector 2007: PCV7 (2+1)	2008 IPD rate 61.1/100,000 & CFR<1%
United States	2000: PCV7 (3+1) 2010: PCV13 (3+1)	2007 IPD rate 23.6/100,000 & CFR-1.4% 2012 IPD rate-9.3/100,000 & CFR-1.5%

KEY POINT: Mortality rates due to IPD and case-fatality are low in high-income countries and, therefore, studies were not powered to evaluate the effect of any schedule on this outcome

Outcomes: Serious adverse events all schedules (RCTs and observational study)

Author, Year, Design	Participants	Intervention
Biologic licensure application for Prevnar13, 2009 (13 RCTs)	Children, US	PCV13 vs. PCV7
Black 2000, Black 2002 (1 RCT)	Infants, USA	PCV7 vs. Men-C
Tse 2012 (1 Obs.)	Children 6-59 months, US	Trivalent inactivated influenza vaccine (TIV) & PCV13

Outcomes: Serious adverse events by dose of PCV13 versus PCV7 (RCTs)

Outcome by Schedule		No. of subjects (# studies)	Incidence in PCV13 group	Incidence in PCV7 group	P
Deaths		13 RCTs	N=3 deaths*	N=1 death*	--
Overall SAEs+	Post-infant series	13 RCTs	0.4%	0.1%	0.049
	Dose 1		N=1	N=1	--
	Dose 2		N=4	N=1	
	Dose 3		N=2	N=3	
	Dose 4		N=0	N=1	

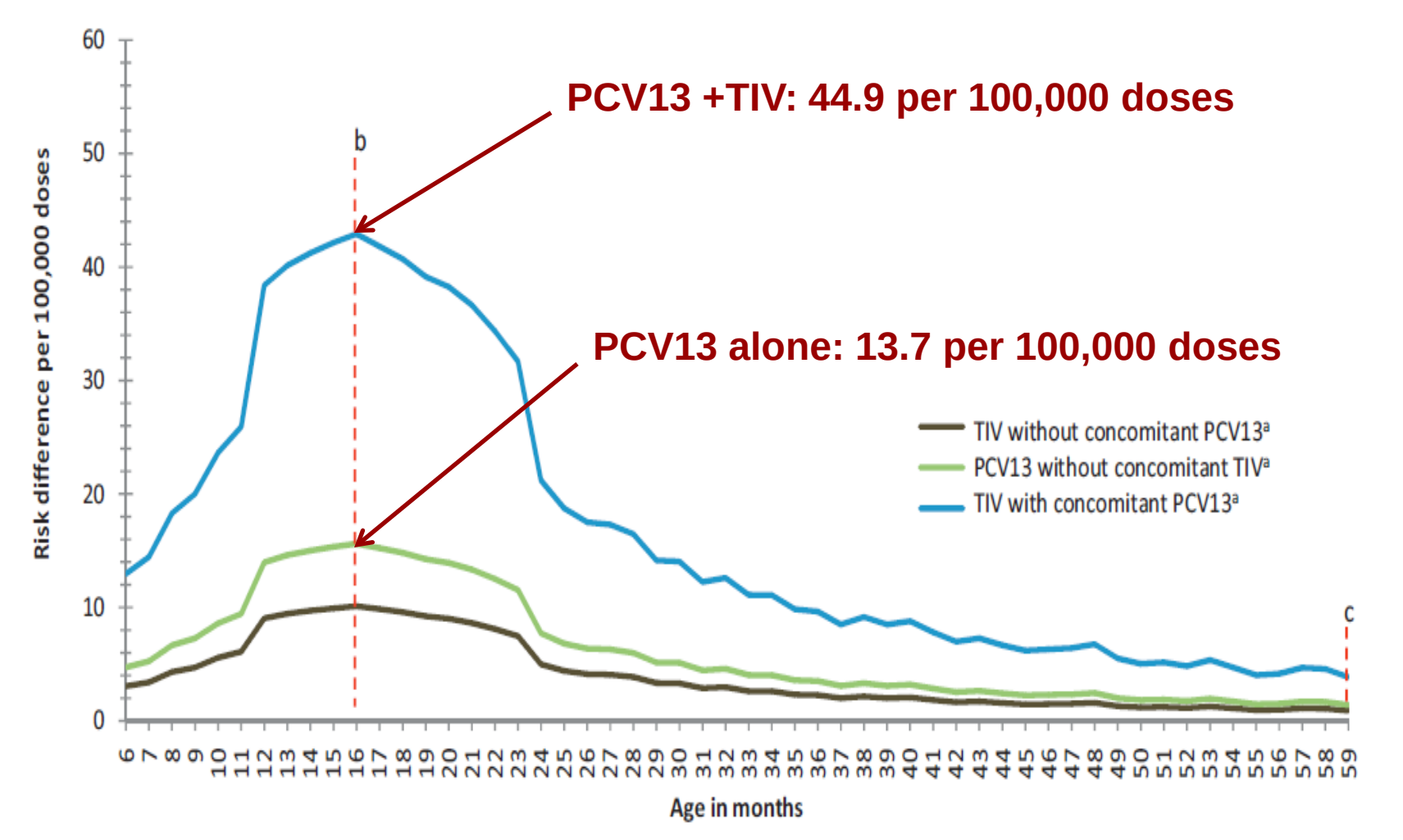
***PCV13: (3 days post-dose 1, 14 days post-dose 2, and 76 days post-dose 3)**
PCV7: (13 days post-dose 1)
+SAEs considered related to the vaccine by the investigator

Outcomes: Deaths in PCV7 versus Men-C+ (RCT)

Outcome by Schedule	No. of subjects (# studies)	Incidence in PCV7	Incidence in Controls/Men-C
Deaths	37868 (1 RCT)	0.2 cases/1000 children (n=4)	0.4 cases/1000 children (n=8)

+Investigators reported deaths as NOT related to the vaccine.

Outcomes: Risk differences data (per 100,000 doses) for febrile seizures in children after trivalent inactivated influenza vaccine)TIV and PCV13 (Vaccine Safety Datalink Project)



*Tse et al

Type of evidence: Serious adverse events

Outcome	Studies	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other consideration	Evidence type
SAEs	14 RCTs	Not serious	Not serious	Serious***	Not serious	Not serious	2

KEY POINT: PCV appears to be safe across all schedules.

Overall evidence type

	Schedule	Individual Evidence Types		Overall Evidence Types
Overall evidence type across all critical outcomes*	3+1	IPD	1	2
		Pneumonia	1	
		Indirect Effects	2	
		SAEs	2	
	3+0	IPD	1	2
		Pneumonia	1	
		Indirect Effects	2	
		SAEs	2	
	2+1	IPD	1	2
		Pneumonia	2	
		Indirect Effects	2	
		SAEs	2	

***The lowest evidence quality from critical outcomes assessed for each schedule**

Values and preferences

Values and preferences based on a priori outcomes rankings:

- IPD: High
- Pneumonia: High
- Serious adverse events: High
- Indirect Effects: Relatively lower value

Judgment of recommendation category

Considerations	3+1:	3+0:	2+1:	Explanation
Is the evidence quality low?	**NO**	**NO**	**NO**	Evidence quality type 2 for each schedule
Are the net benefits low or is there uncertainty about the balance of benefits vs.harms?	**NO**	**NO**	**NO**	No uncertainty about each schedule providing protection against critical outcomes
Is there variability or uncertainty in what outcomes are important to prevent?	**NO**	**NO**	**NO**	The WG reached consensus on which outcomes are important to prevent
Is there uncertainty about whether the net benefits are worth the costs?	**NO**	**NO**	**NO**	Intervention is cost-effective

Conclusions

Based on these judgments, the GRADE recommendation is:

Schedule	Recommendation Category
3+1	Category A
3+0	Category A
2+1	Category A

Step Two: GRADE only studies with direct schedule comparisons

Outcomes: Immunogenicity

The following data were extracted to measure antibody responses to each schedule:

1. IgG antibody concentrations measured following PCV administration
2. Proportion with concentration $\geq$ 0.35µg/ml

Comparisons between schedule made:

1. Risk ratios comparing % $\geq$ 0.35µg/ml between groups
2. Ratio comparing geometric mean concentrations (GMCs) in each group

Outcomes: Immunogenicity all direct schedule comparisons (RCTs)

Author, Year, Design	Participants	Intervention	Main outcomes
Givon-Lavi 2010, RCT	Infants; Israel	PCV7 3+1 or 2+1 or 3+0	GMC; % ≥0.35 and 1.0 µg/ml
Goldblatt 2006, RCT	Infants; UK	PCV9 2+1 or 3+1	GMC; % ≥0.2, 0.35 and 1.0 µg/ml
Silfverdal 2009, RCT	Infants; Denmark, Norway, Slovakia, Sweden	PHiD-CV10 2+1 or 3+1	GMC; % ≥0.2 and 0.35 µg/ml
Russell 2009, RCT	Infants; Fiji	PCV7 2 or 3 primary doses	GMC; % ≥0.35 and 1.0 µg/ml
Sigurdardottir 2008, RCT	Infants; Iceland	PCV9-MnCC 2 or 3 primary doses	GMC; % ≥0.35 µg/ml
Ota 2011, RCT	Infants; The Gambia	PCV7 2+1 or 3+1	GMC; % ≥0.35 µg/ml

Outcomes: Immunogenicity 3+0 versus 3+1 schedule (RCTs)

Outcome by schedule	No. of subjects (# studies)	3+0: % with antibodies ≥0.35µg/ml	3+1: % with antibodies ≥0.35µg/ml	Risk ratio (95% CI)	GMC ratios: 3+0 vs 3+1 (95% CI)
4	1940 (4 RCTs)	97	98	0.99 (0.97, 1.01)	**0.55 (0.43-0.70)**
6B	1940 (4 RCTs)	73	95	**0.77 (0.72, 0.82)**	**0.21 (0.11-0.39)**
9V	1940 (4 RCTs)	95	98	0.98 (0.95, 1.00)	**0.34 (0.26-0.44)**
14	1940 (4 RCTs)	95	95	1.00 (0.96, 1.03)	**0.48 (0.32-0.70)**
18C	1940 (4 RCTs)	96	98	0.98 (0.96, 1.01)	**0.49 (0.39-0.61)**
19F	1940 (4 RCTs)	95	95	1.00 (0.96, 1.03)	**0.57 (0.44-0.73)**
23F	1940 (4 RCTs)	77	94	**0.81 (0.76, 0.86)**	**0.21 (0.17-0.28)**
1	409 (2 RCTs)	91	97	**0.93 (0.88, 0.99)**	**0.59 (0.38-0.91)**
5	409 (2 RCTs)	99	99	1.00 (0.98, 1.02)	**0.41 (0.18-0.93)**

3+0: Measured post-primary (approx. 7 months)

3+1: Measured post-booster (approx. 13 months)

Outcomes: Immunogenicity post- 2 versus 3 primary doses (RCTs)

Outcome by schedule	No. of subjects (# studies)	2 dose-% with antibodies ≥0.35µg/ml	3 dose-% with antibodies ≥0.35µg/ml	Risk ratio (95% CI)	GMC ratios: 2 vs 3 doses (95% CI)
4	489 (2 RCTs)	0.99	0.99	1.00 (0.97, 1.02)	0.80 (0.95-1.63)
6B	489 (2 RCTs)	0.75	0.86	0.88 (0.72, 1.09)	**0.50 (0.28-0.90)**
9V	489 (2 RCTs)	0.96	0.99	0.97 (0.93, 1.01)	0.88 (0.52-1.49)
14	489 (2 RCTs)	0.93	0.99	0.95 (0.88, 1.02)	0.62 (0.10-3.71)
18C	489 (2 RCTs)	0.95	0.95	1.01 (0.97, 1.05)	0.82 (0.52-1.28)
19F	489 (2 RCTs)	0.98	0.99	0.99 (0.97, 1.01)	0.83 (0.26-2.63)
23F	489 (2 RCTs)	0.84	0.71	0.92 (0.85, 1.00)	**0.52 (0.28-0.97)**
1	218 (1 RCT)	1	0.99	1.00 (0.99, 1.02)	1.08 (0.40-2.92)
5	218 (1 RCT)	0.96	0.96	1.00 (0.94, 1.06)	0.79 (0.52-1.19)

Measured approx. one month-post last dose

Outcomes: Immunogenicity 2+1 versus 3+1 schedule (RCTs)

Outcome by schedule	No. of subjects (# studies)	2+1: % with antibodies ≥0.35µg/ml	3+1: % with antibodies ≥0.35µg/ml	Risk ratio (95% CI)	GMC ratios: 2+1 vs 3+1 (95% CI)
4	1858 (4 RCTs)	98	98	1.00 (0.98, 1.02)	1.05 (0.87-1.27)
6B	1858 (4 RCTs)	88	95	**0.92 (0.88, 0.97)**	**0.60 (0.44-0.82)**
9V	1858 (4 RCTs)	98	98	1.00 (0.98, 1.02)	0.94 (0.74-1.09)
14	1858 (4 RCTs)	95	95	1.00 (0.96, 1.03)	0.83 (0.65-1.03)
18C	1858 (4 RCTs)	96	97	0.99 (0.96, 1.01)	**0.75 (0.59-0.95)**
19F	1858 (4 RCTs)	95	94	1.00 (0.97, 1.04)	1.02 (0.79-1.31)
23F	1858 (4 RCTs)	93	94	0.98 (0.94, 1.02)	0.79 (0.62-1.03)
1	378 (2 RCTs)	96	97	0.98 (0.94, 1.02)	0.97 (0.72-1.31)
5	378 (2 RCTs)	99	99	0.99 (0.97, 1.02)	0.82 (0.63-1.08)

Measured post-booster (approx. 13 months)

Immunogenicity studies of PCV schedules: Key Point

- Proportions ≥0.35 µg/ml are high for schedules with 3- and 2-dose primary series
- Post-primary: 3-dose schedule better than 2-dose schedule for some serotypes (GMC ratios)
- In the second year of life (pre-booster and post-booster dose), small but significant differences for some serotypes (GMC ratios)
- The differences more pronounced after the primary series and when comparing GMC values (i.e. GMC ratios) rather than proportions ≥0.35 µg/ml

Immunogenicity studies: Endpoints and Caveats

- WHO determined a cut-off value that correlated with protection against IPD in several stages based on:
  - the results of US trial which showed a 0.2 µg/ml cut-off post dose 3 correlated with 97.3% VE
  - two RCTs, one in American Indian (1.0 µg/ml and 76.8% VE) and one in South African infants (0.68 µg/ml and 90%VE)
  - the aggregate cut-off value was raised to 0.35 µg/ml
- Children at higher risk for pneumococcal diseases may require higher antibody levels to achieve an equivalent protective efficacy

KEY POINT: The cut-off for IPD of 0.35 µg/ml likely higher than necessary for a US population of generally healthy infants

Immunogenicity studies: Endpoints and Caveats

- Clinical significance of the aggregate GMC cut-off of 0.35 µg/ml is not established for
  - Individual serotypes
  - Post-booster
  - Non-IPD endpoints (pneumonia, AOM, and carriage)
- GMC ratios do not take into account absolute values for groups compared (e.g. 2 µg/ml vs 4 µg/ml and 0.35 µg/ml vs 0.7 µg/ml have the same GMC ratios)

KEY POINT: It is important to interpret the differences with caution and look at both the % ≥ 0.35 µg/ml and absolute values.

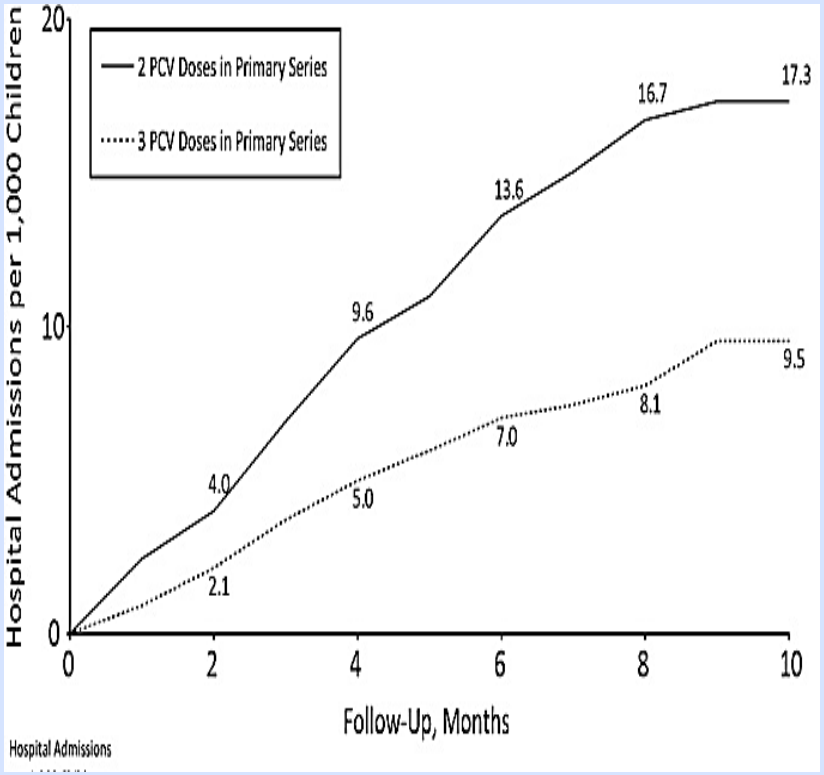
Type of evidence: Immunogenicity direct schedule comparisons (RCTs)

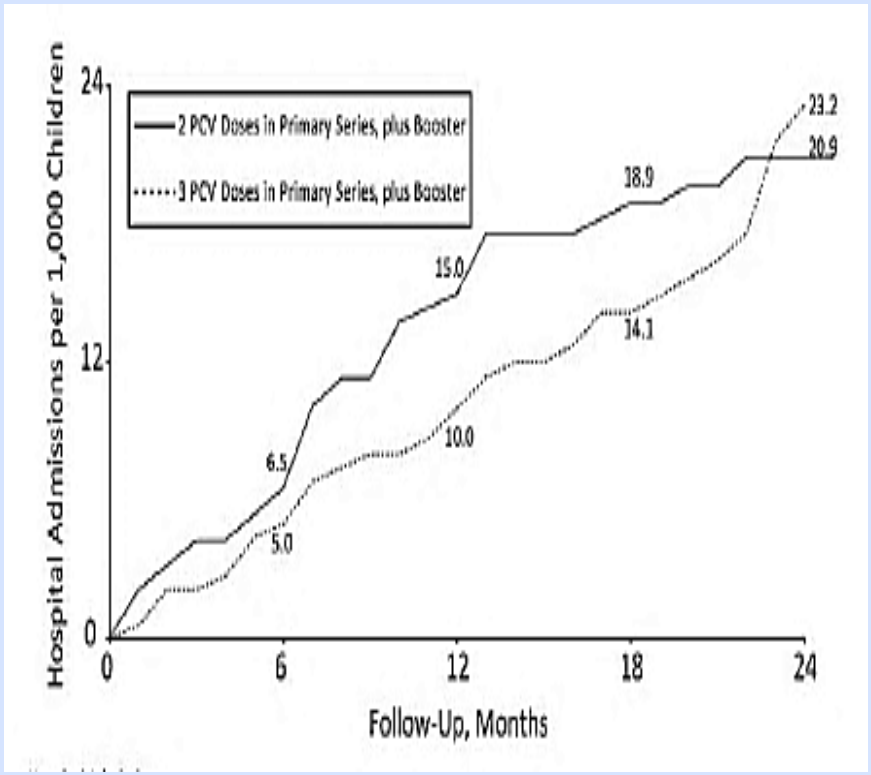
Outcome	Studies	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other consideration	Evidence type
Immuno-genecity 3+0/2+1 vs. 3+1	3 RCTs	Not serious	Not serious	Not serious	Not serious	Not serious	1
Immuno-genecity 2 vs. 3 doses	3 RCTs	Not serious	Not serious	Not serious	Not serious	Not serious	1

Outcomes: Pneumonia and AOM direct schedule comparisons (observational studies)

Author, Year, Design	Participants	Intervention	Main outcomes
Pelton 2010, Obs.	2002 Birth Cohort; USA	PCV7 2+1 (2, 4, 12-16 months) or 3+1 (2, 4, 6, 12-16 months)	Pneumonia/Lower respiratory tract infection (LRTI)
Stoecker 2012, Obs.	2002 Birth Cohort; USA	PCV7 2+1 (2, 4, 12-15 months) or 3+1 (2, 4, 6, 12-15 months)	Acute otitis media (AOM) by MarketScan Commercial Claims and Encounters Database

Outcomes: LRTI 2+1 vs 3+1 schedules before and after booster dose in US 2002 birth cohort (observational study)





Pre-booster: 7.8 per 1000 (0.8-14.8) fewer LRTI admissions for 3 vs 2 primary doses

Post-booster: No significant differences between schedules

Pelton et al. 2009

Outcomes: LRTI 2+1 vs 3+1 schedules before and after booster dose in US 2003 birth cohort (observational study)

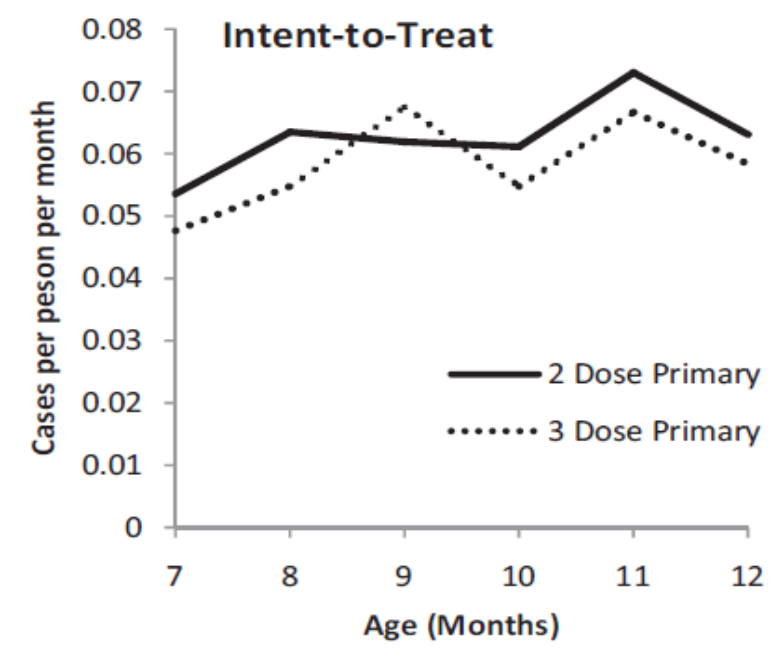
Outcome by schedule	No. of subjects (# studies)	2+1 group: Incidence+	3+1: Incidence+	Absolute rate difference+
Post-primary				
LRTI	14674 (1 Obs. – 2003 Cohort)	12.5	16.7	-4.2 (-10, 1)
Post-booster				
LRTI	7146 (1 Obs. – 2003 Cohort)	44.8	24.8	20 (-6, 36)

+Per 100,000 population: Lower respiratory tract infection (LRTI) and Acute Otitis Media (AOM)

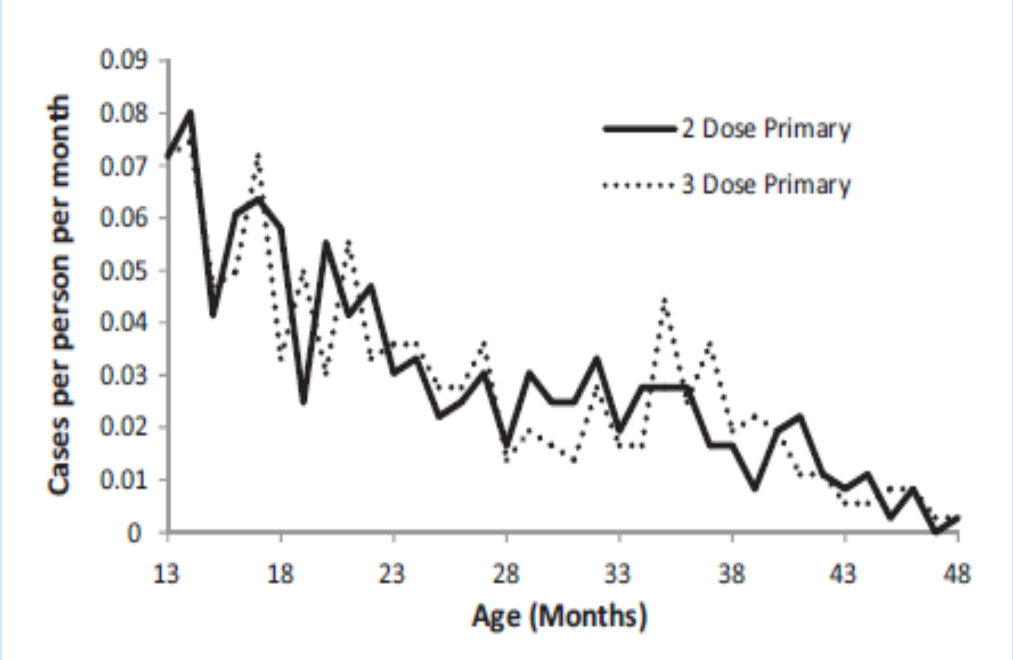
***Monthly incidence per person**

Outcomes: Acute otitis media 2 versus 3 primary doses, US 2002 birth cohort (observational study)

Pre-booster



Post-booster



Incidence (6 to 12 months):

- **0.38 cases/person for the 2 doses 0.35 cases/person for the 3 doses (not statistically different)**

Incidence (one to four years):

- **1.04 cases/person for the 2 doses**
- **1.03 cases/person for the 3 doses (not statistically different)**

KEY POINT: There were no differences between schedules with 2 versus 3 doses in primary series pre- or post-booster

Stoecker et al Vaccine 2012

Type of Evidence: Pneumonia and AOM, direct schedule comparisons

Outcome	Studies	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other consideration	Evidence type
LRTI 2+1 vs. 3+1	1 Obs.	Not serious	N/A	Not serious	Not serious	Not serious	3
AOM 2 vs. 3 doses	1 Obs.	Not serious	N/A	Not serious	Not serious	Not serious	3

KEY POINT: There are limited studies with direct head-to-head comparisons and clinical endpoints.

Overall Evidence Type

	Schedule	Individual Evidence Types		Overall Evidence Types
Overall evidence type across all critical outcomes*	2+1 vs 3+1	Immunogenicity	1	3
		LRTI	3	
		AOM	3	
	3+0 vs 3+1	Immunogenicity	1	3
		LRTI	3	
		AOM	3	

***The lowest evidence quality from critical outcomes assessed for each schedule**

Values and preferences

Based on a priori outcomes rankings:

- Pneumonia: High
- AOM: Relatively lower value
- Immunogenicity (as a surrogate for IPD): Relatively lower value

Judgment of recommendation category

Considerations	3+0 vs 3+1	2+1 vs 3+1	Explanation
Is the evidence quality low?	YES	YES	Head-to head comparisons not available for some critical outcomes; immunogenicity data used as a surrogate for IPD
Are the net benefits low or is there uncertainty about the balance of benefits vs. harms?	YES	YES	Uncertainty given differences observed for some serotypes and relevance for clinical outcomes
Is there variability or uncertainty in what outcomes are important to prevent?	NO	NO	No variability or uncertainty in which outcomes are important to prevent
Is there uncertainty about whether the net benefits are worth the costs?	NO	NO	Compared to a 2+1 schedule, the current 3+1 schedule is less cost-effective

GRADE Conclusion

- Step One: Strong evidence (type 2) supporting each schedule as compared to no vaccine
- Step Two: Limited evidence (type 3) supporting 3-dose schedules (2+1 and 3+0) as compared to the 4-dose schedule (3+1)
- GRADE supports Category B recommendation
- Next presentation: Discuss GRADE findings within a larger context for policy decision

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