Considerations for a 3-dose PCV13 schedule for infants

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Rationale for considering a 3-dose PCV13 schedule

- **Evidence supporting use of 3-dose PCV schedules emerging**
  - A 3-dose PCV13 schedule is approved by the European Medicines Agency (EMEA)
  - WHO recognizes a 3-dose schedule as an acceptable alternative to a 4-dose schedule*
  - At least 34 countries (21 high and 13 upper-middle income) have introduced PCV13 or PCV10 with 3 doses or have switched from 4- to 3-dose schedule

*Pneumococcal vaccines WHO position paper. Wkly Epidemiol Rec, 2012

Rationale for considering a 3-dose PCV13 schedule

- **Evidence supporting use of 3-dose PCV schedules emerging**

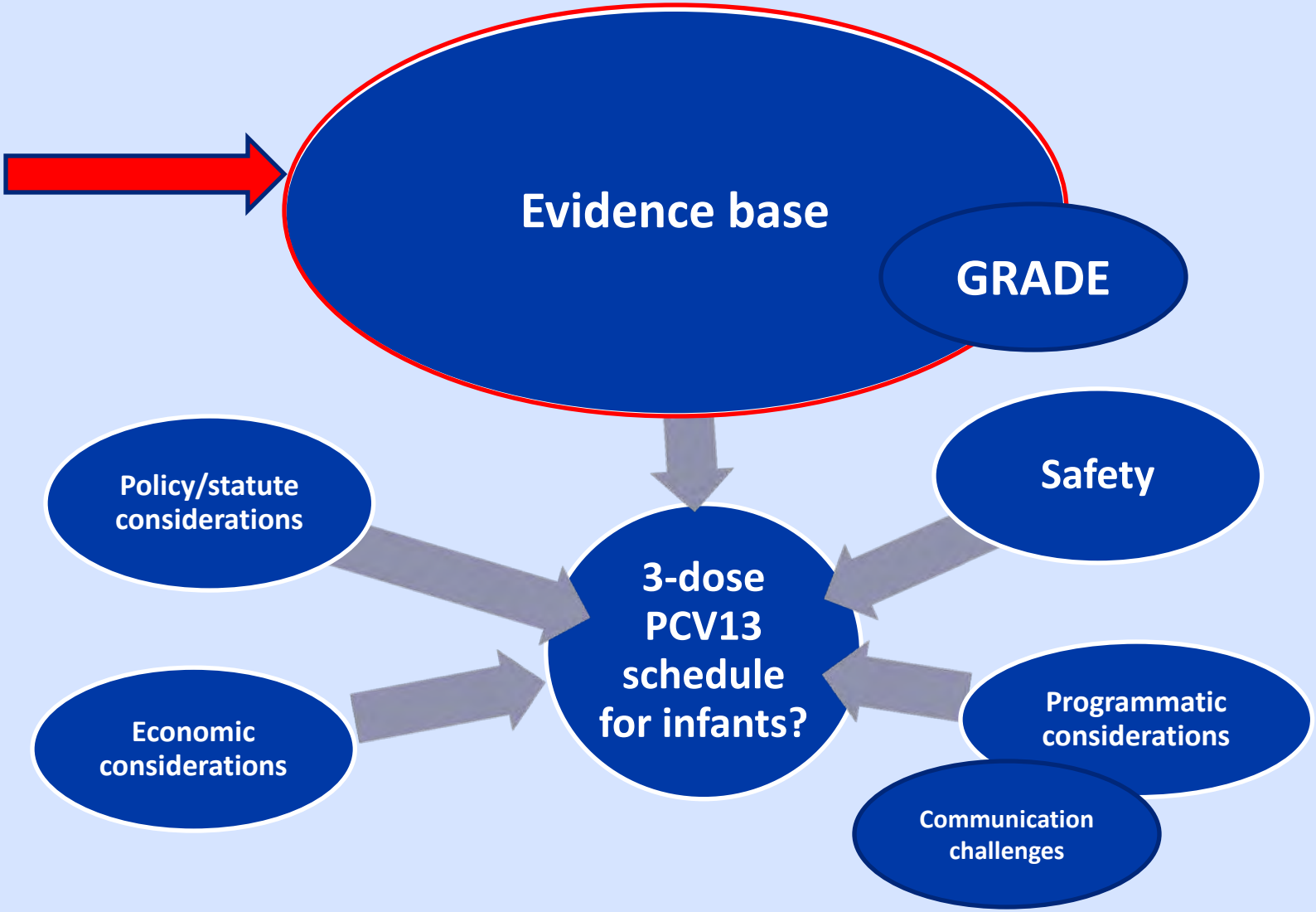
- **PCV7 use led to dramatic reductions in disease burden**
  - reductions in invasive pneumococcal disease (IPD) and pneumonia in children and adults; reductions in otitis media in children
  - PCV7 serotypes have virtually been eliminated from all age-groups
  - Disease due to PCV13 serotypes is rapidly declining

Rationale for considering a 3-dose PCV13 schedule

- Evidence supporting use of 3-dose PCV schedules emerging
- PCV7 use led to dramatic reductions in disease burden
- US now has a mature PCV program

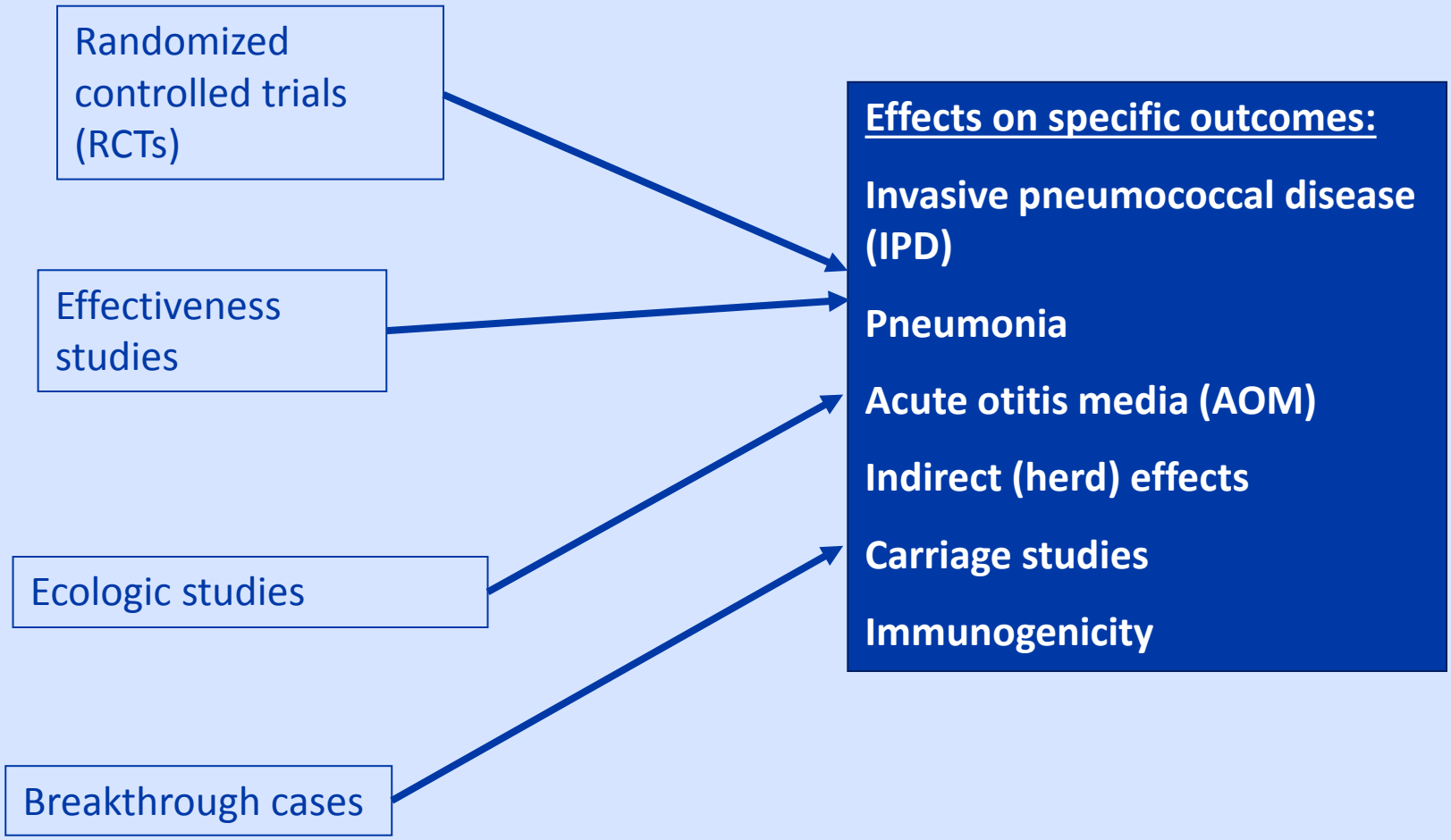
Can a 3-dose PCV13 schedule be included into a routine schedule for infants?

Considerations for a potential policy change



Framework for evaluating evidence for 3-dose PCV schedules

2-dose primary series followed by a booster (2+1)
3-dose primary series without a booster (3+0)



Controlled trials evaluating vaccine efficacy against vaccine-type IPD

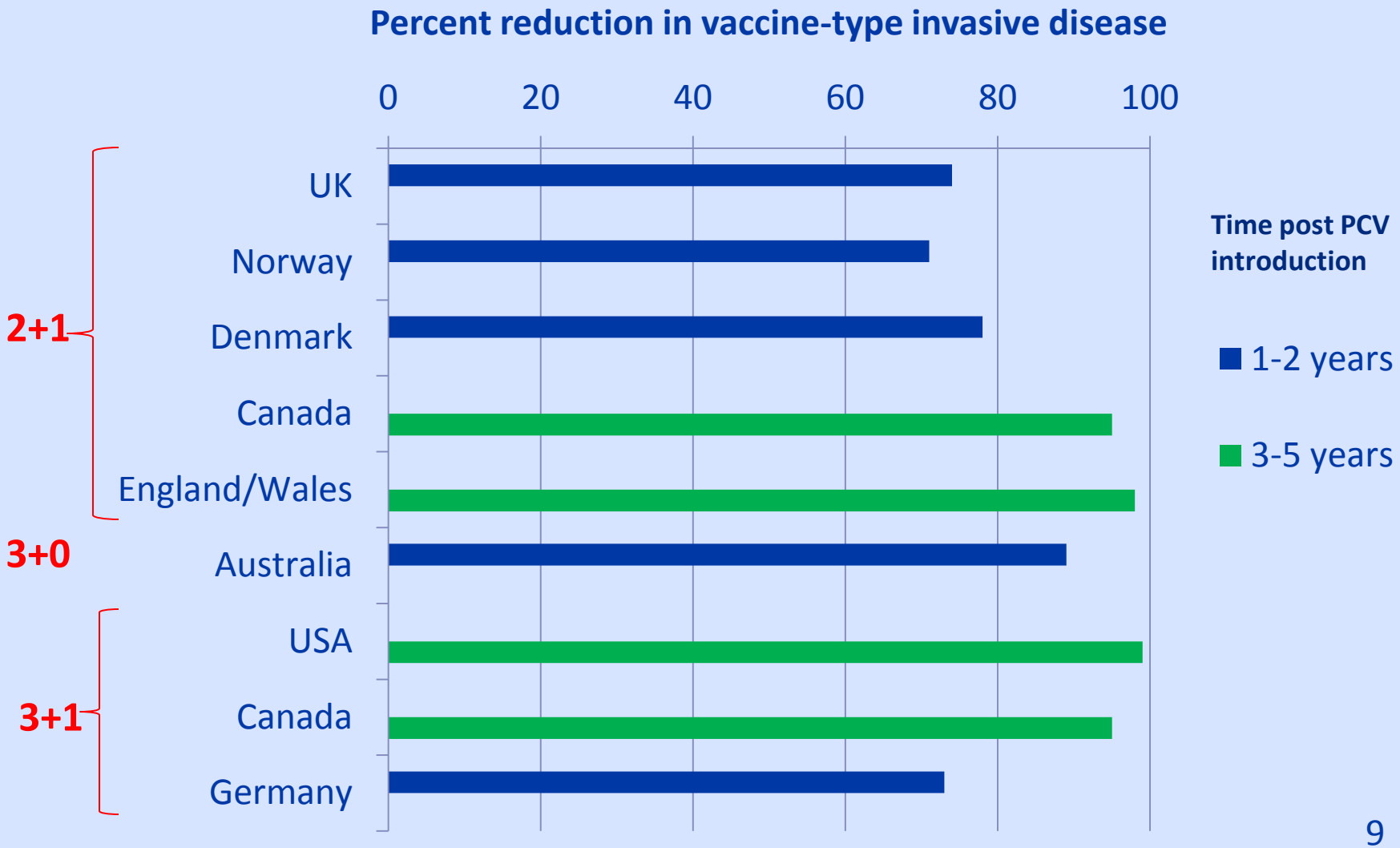
Country (Reference)	Schedule, Product, and Population	VE (95% CI) by schedule		
		2+1	3+0	3+1
Finland (Palmu 2013)	Age ≥6w & 2 doses at ≥4 w intervals, booster at ≥ 11 m (PCV10, GSK)	92% (58-100)		100% (83-100)
Gambia (Cutts 2005)	Age 6-51 w, 3 doses ≥25d apart (PCV9); General population		71% (46-86)	
South Africa (Klugman 2003)	6, 10, 14w (PCV9); HIV-uninfected		83% (39-97)	
USA (Black 2000)	2, 4, 6m, 12-15m (PCV7)			94% (80-99)
USA (O'Brien 2003)	2, 4, 6, 12-15m (PCV7); Native American			83% (21-96)

Observational studies evaluating effectiveness against vaccine-type IPD

Country	Design	Age group	VE (95% CI) by schedule			
			2+0	2+1	3+0	3+1
Canada (Deceuninck 2010)	Case-Control	2-59m	99% (90-100)	100% (15-100)	90% (24-100)	-
USA (Whitney 2006)	Case-Control	3-36m	96% (88-99)	98% (75-100)	95%* (88-98)	100%* (94-100%)
Spain (Barricarte 2007)	Case-control	<5 years	-	-	-	81% (-46-97)
USA (de Serres 2008)	Indirect cohort	3-59m	96% (93-98)	-	98% (95-99)	98% (95-99)
USA (Mahon 2006)	Indirect cohort	<5 years	70.5% (28.0, 87.9)	-	76.6% (50, 89)	90.5% (18, 99)
Germany (Ruckinger 2010)	Indirect cohort	3-59m	89.8%* (21-100)	-	95% (69.7-99.5)	94% (39.8-100)

*Study not powered to make direct comparisons of schedules; comparison of 3+1 to 3+0, odds ratio of 0 (0, 0.87)

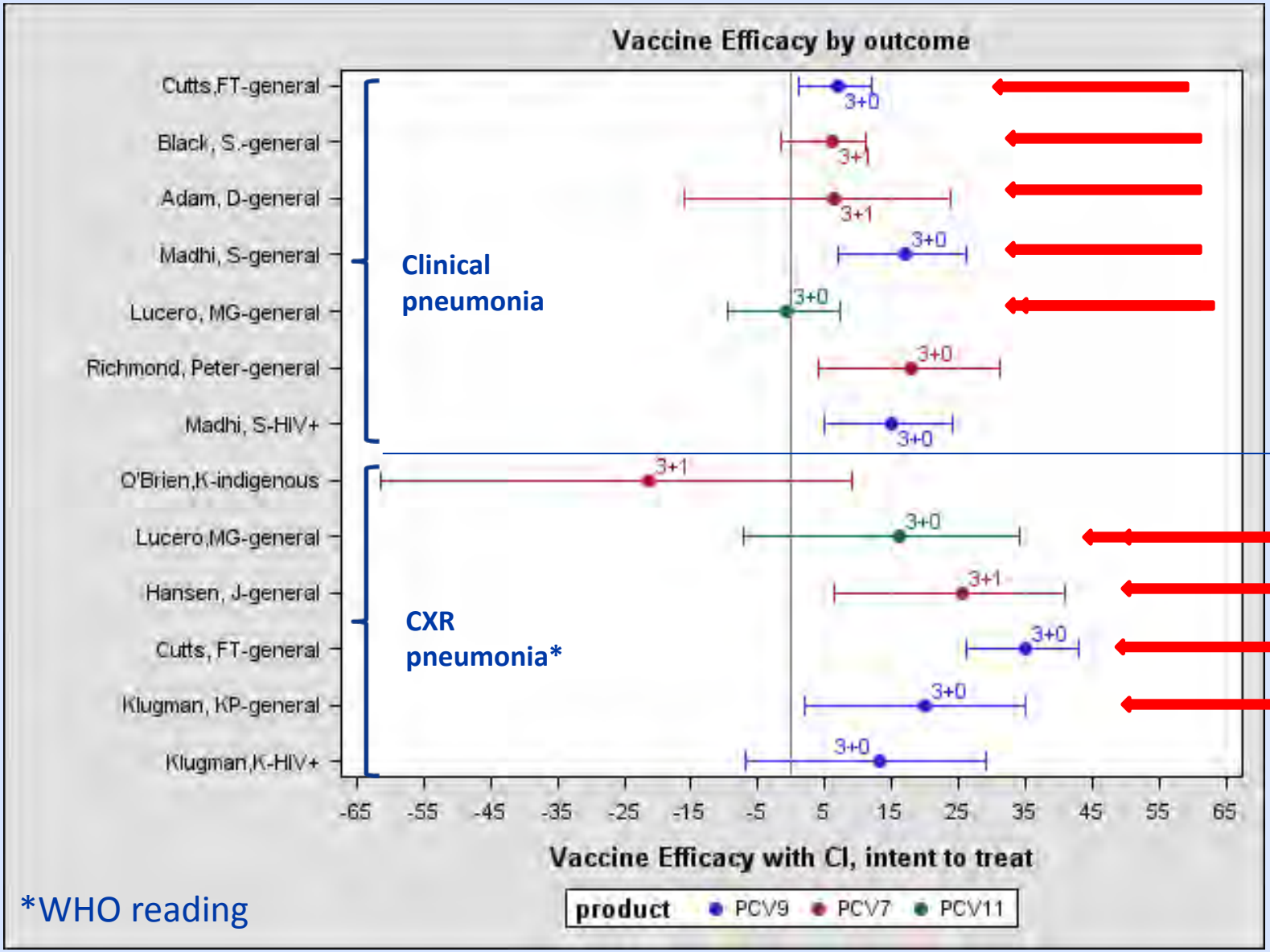
Population-level impact of PCV introduction on vaccine-type IPD among children



Invasive disease conclusions

- Both schedules (3+0 and 2+1) are highly effective at preventing IPD
- No studies designed to compare 3-dose schedules to 4-dose schedules head-to-head

RCTs evaluating efficacy against pneumonia



*WHO reading

Loo et al PIDJ 2013 In press

Observational studies: impact of PCV introduction on pneumonia, 2+1 schedule

Ansaldi, 2008	Hospitalizations per 10,000 person-years (95% CI)		
Outcome	Birth cohort 2000-2002	Birth cohort 2003-2005	Percent reduction (95%CI)
All-cause pneumonia	64.2 (58.4, 70.5)	54.4 (49.2, 60)	15.2 (2.8, 26.1)
Pneumococcal pneumonia	1.91 (1.07, 3.27)	0.56 (0.18, 1.36)	70.5 (9.7, 90.4)

Esposito, 2007	Episodes per 100 child-years		
Outcome	PCV7 group (n=811)	Control group (n=744)	Percent reduction (95%CI)
Radiologically-confirmed community-acquired pneumonia	1.7	4.8	65 (47-78)

Observational studies: impact of PCV introduction on pneumonia, 2+1 schedule

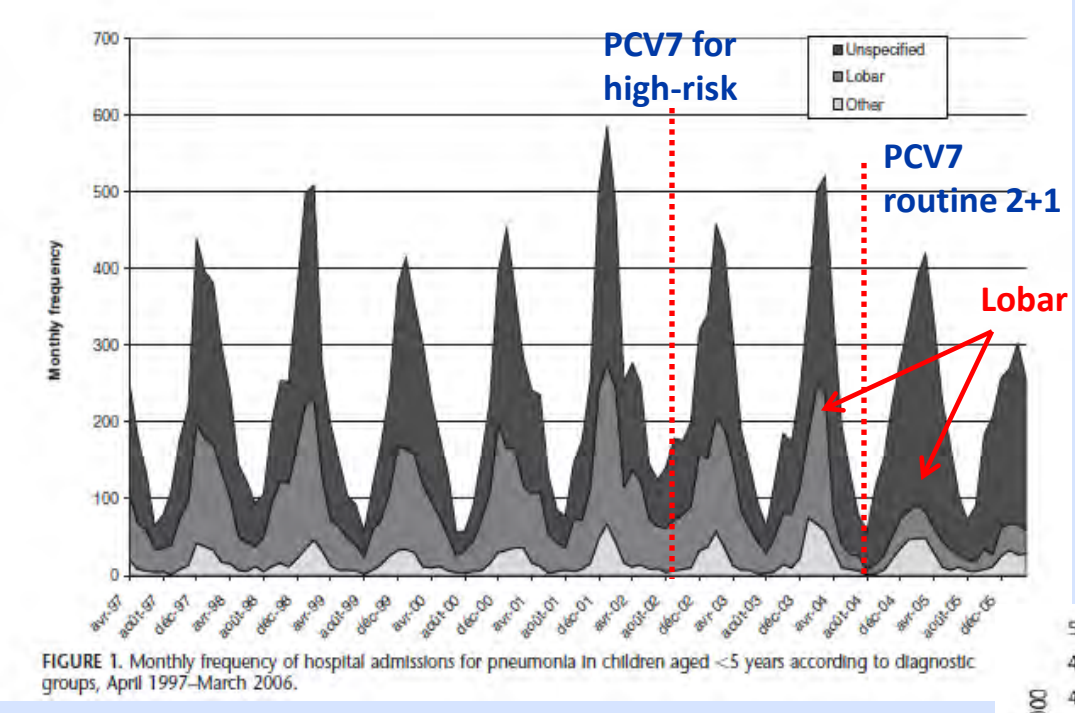


FIGURE 1. Monthly frequency of hospital admissions for pneumonia in children aged <5 years according to diagnostic groups, April 1997–March 2006.

Quebec (de Wals, 2008)
Clinical and CXR pneumonia

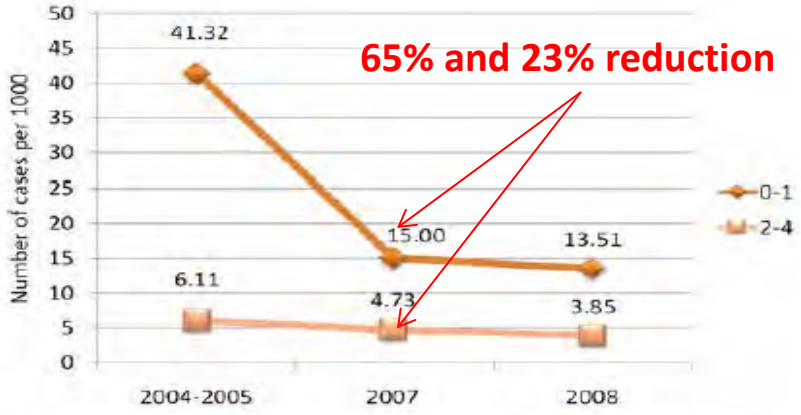
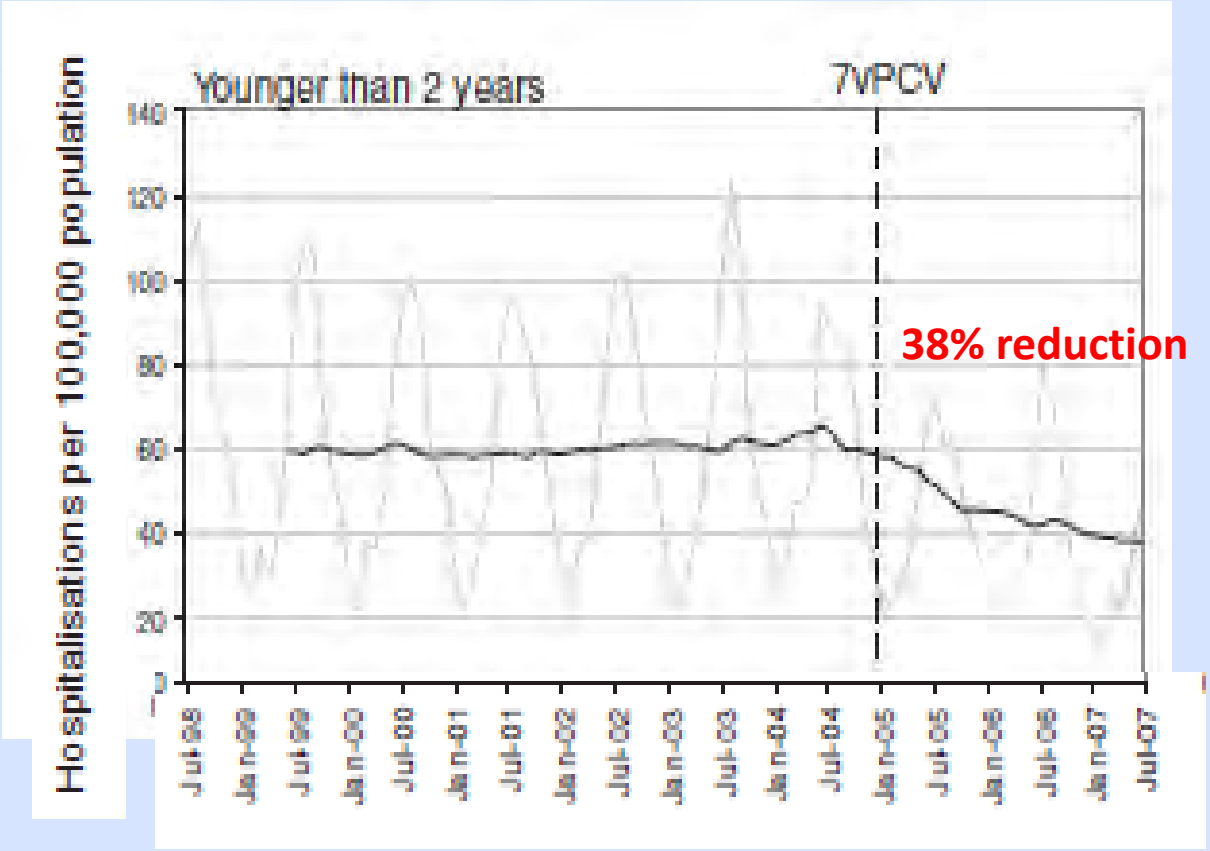


Fig. 1 Pneumonia hospitalization rates in age groups 0–1 and 2–4 years in Kielce before and after the introduction of pneumococcal vaccinations

Poland (Patrzalek, 2010)
CXR pneumonia

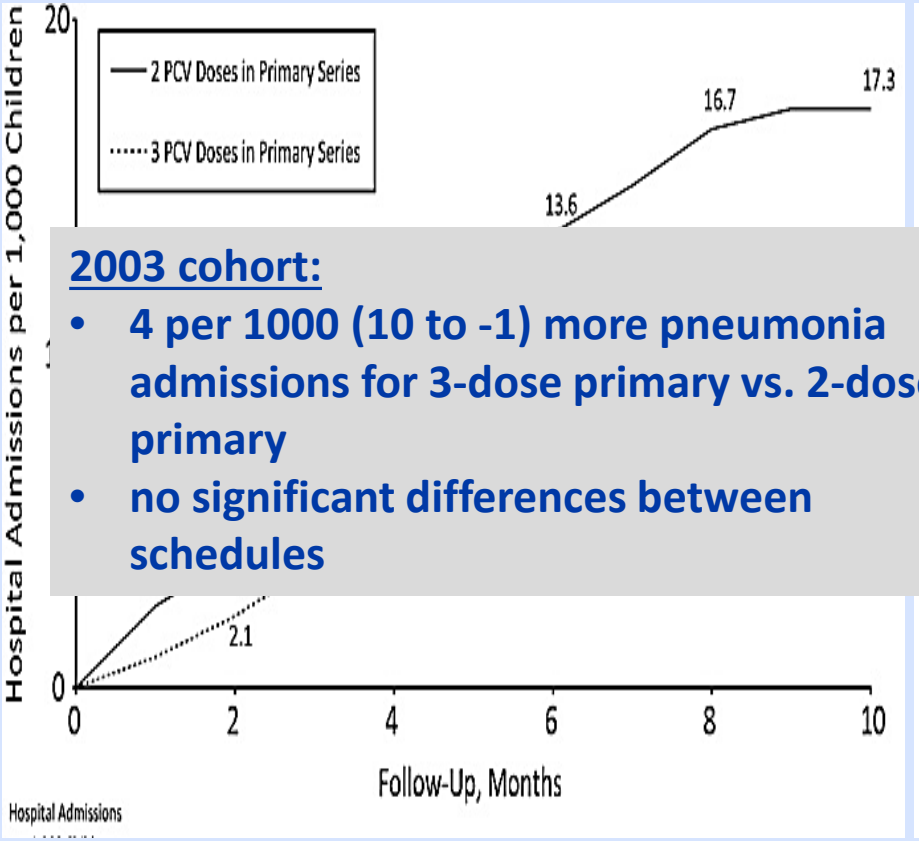
Observational studies: impact of PCV introduction on pneumonia, 3+0 schedule

Monthly rates of hospitalization for all cause pneumonia per 100,000 population in Australia, July 1998 to June 2007



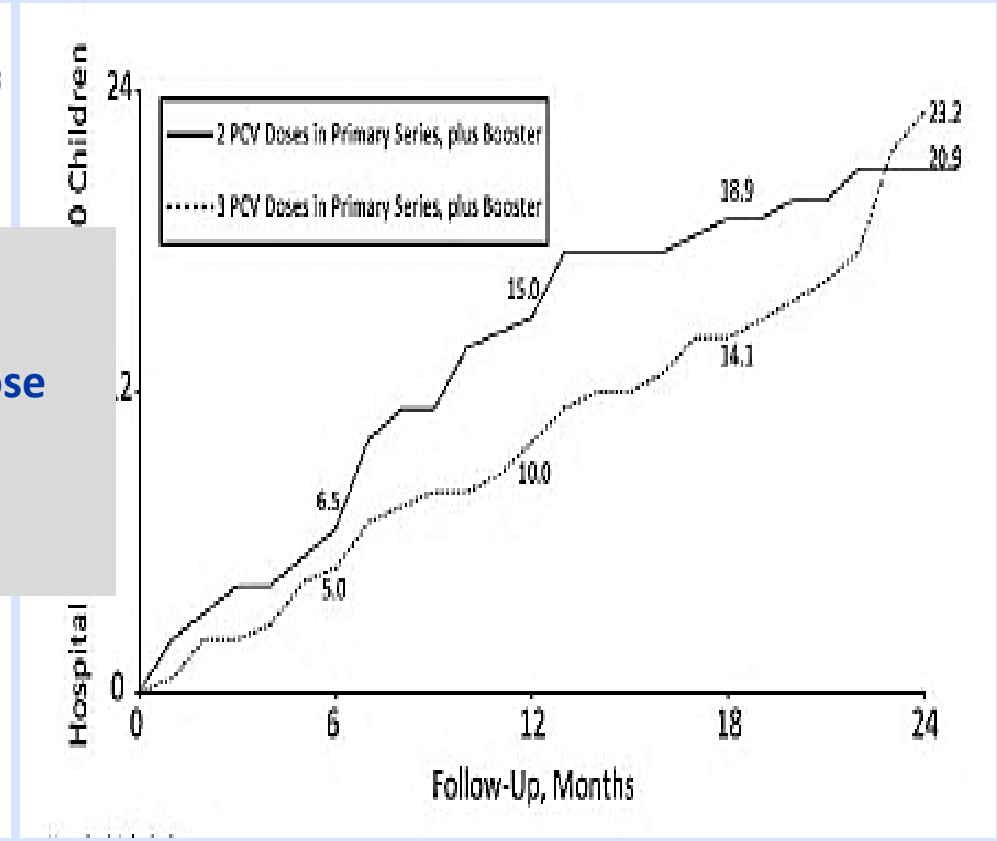
Jardine, PIDJ 2010

Observational study: comparison of 2+1 and 3+1 schedules before and after booster dose, 2002 cohort



2003 cohort:

- **4 per 1000 (10 to -1) more pneumonia admissions for 3-dose primary vs. 2-dose primary**
- **no significant differences between schedules**



- **Pre-booster: 7.8 per 1000 (0.8-14.8) fewer pneumonia admissions for 3-dose primary vs. 2-dose primary (2002 birth cohort)**
- **Post-booster: no significant differences between schedules**

Pelton et al. 2009

Conclusions: Pneumonia

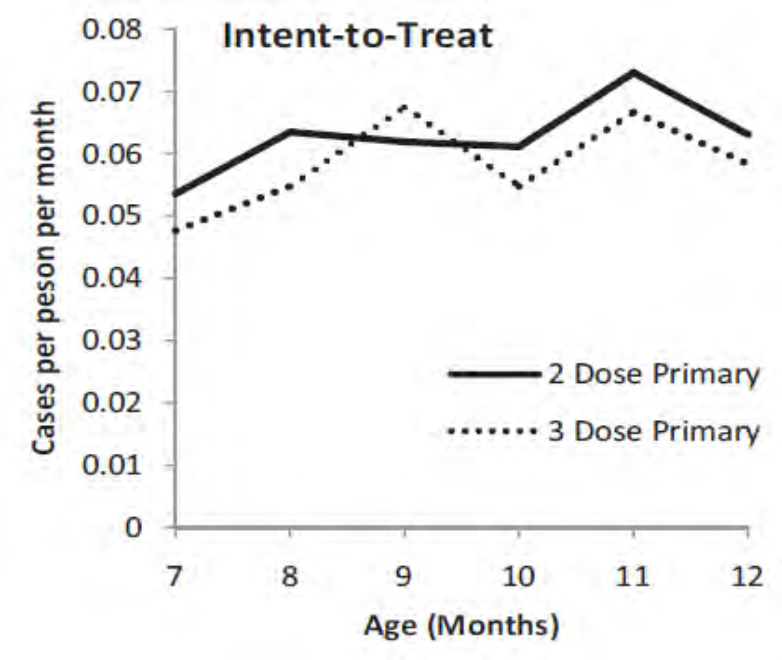
- Schedules with 3 PCV doses (2+1 and 3+0) prevent pneumonia
- One observational study showed that 3-dose primary series are better than 2-dose primary series before booster dose against pneumonia; no differences observed post-booster or for later birth cohorts
- Schedule with 4-doses maybe more beneficial early post-introduction

Observational studies: effectiveness of PCV against acute otitis media, 2+1 schedule

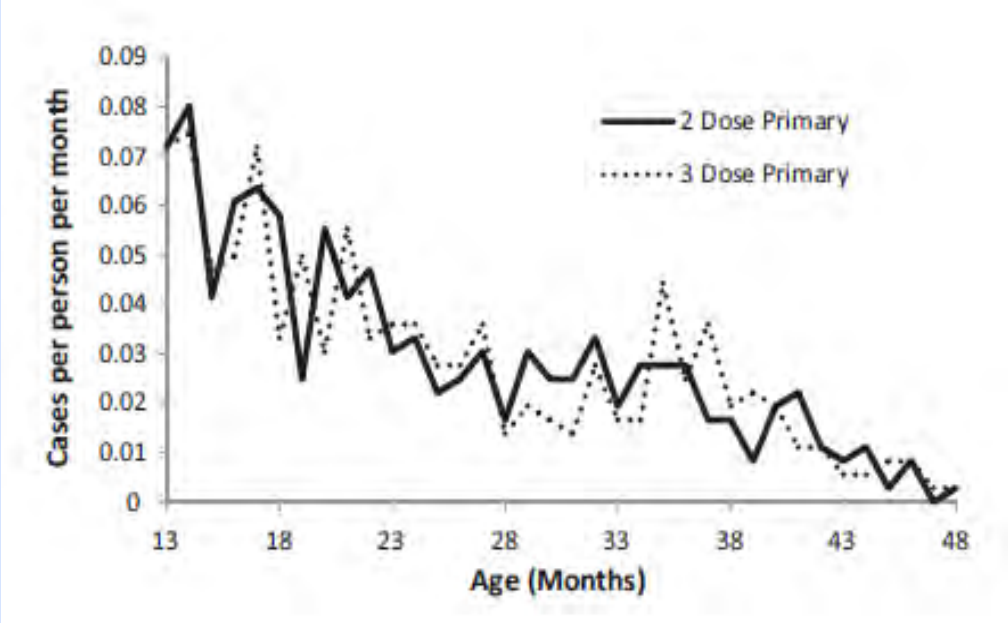
Country (Reference)	Methods and Outcome Measures	Schedule, Product, and Population	VE (95% CI)
Italy (Ansladi 2008)	Surveillance; ICD-9 codes	3, 5, and 11 m (PCV7)	36% (24-47)
Italy (Esposito 2007)	Prospective cohort; telephone interviews and physician confirmation of diagnosis	3, 5, and 11 m (PCV7)	17% (-0.02-39)
Canada (DeWals 2009)	Time-series analysis	2, 4, and 12m (PCV7)	13.2%

Acute otitis media monthly incidence in children receiving 2- or 3-dose PCV7 primary series, US 2002 birth cohort

Pre-booster



Post-booster



Pre-booster dose incidence (6 to 12 months):

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

Post-booster dose incidence (one to four years):

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

Stoecker et al Vaccine 2012

Conclusions: Acute Otitis Media

- No clinical efficacy data for 2+1 or 3+0
- Data from observational studies show reduction in AOM following PCV7 introduction on a 2+1 schedule
- No significant difference in AOM incidence for 2+1 vs. 3+1 before or after booster

Systematic review and meta-analysis of immunogenicity studies of PCV schedules: Bottom line

- 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
- In the second year of life (pre-booster and post-booster dose), little to no difference between those with 3-dose and 2-dose primary series; small but significant differences for some serotypes (6B and 23F)

Scott P et al Vaccine 2011
Rückinger et al Vaccine 2011
Knoll et al PIDJ 2013 In press

Original Investigation

Immunogenicity of 13-Valent Pneumococcal Conjugate Vaccine Administered According to 4 Different Primary Immunization Schedules in Infants

A Randomized Clinical Trial

Judith Spijkerman, MD; Reinier H. Veenhoven, MD, PhD; Alienke J. Wijmenga-Monsuur, PhD; Karin E. M. Elberse, PhD; Pieter G. M. van Gageldonk, BASc; Mirjam J. Knol, PhD; Hester E. de Melker, PhD; Elisabeth A. M. Sanders, MD, PhD; Leo M. Schouls, PhD; Guy A. M. Berbers, PhD

- PCV13 given on 4 different schedules: **2, 4, and 6m**; **2 and 4m**; 3 and 5m; 2, 3, and 4m; booster for all at 11.5m
- Comparisons relevant to the US schedule:
  - Post-primary series: 2, 4, and 6m primary better than 2 and 4m primary for 11 serotypes
  - Post-booster: 2,4, and 6m primary better than 2 and 4m primary for 3 serotypes (6B, 18C, and 23F)
- Confirmed findings of earlier studies

Spijkerman et al. JAMA 2013

Conclusions: Immunogenicity

- Both 3+0 and 2+1 schedules induce good antibody response
- After primary series, 3-dose primary better than 2-dose primary (types 6B and 23F); the difference no longer apparent in the second year of life (i.e. pre-booster)
- Little difference seen after booster between 2+1 and 3+1, except for types 6B and 23F
- Studies conducted outside national immunization program for PCV (no herd effects)
- Clinical significance of the aggregate GMC cut-off of 0.35 µg/ml is not well established for
  - Individual serotypes
  - Post-booster
  - Non-IPD endpoints (pneumonia, AOM, and carriage)

Carriage studies: clinical trials with direct comparisons of schedules with 2- vs. 3-dose primary series

Russell et al 2010

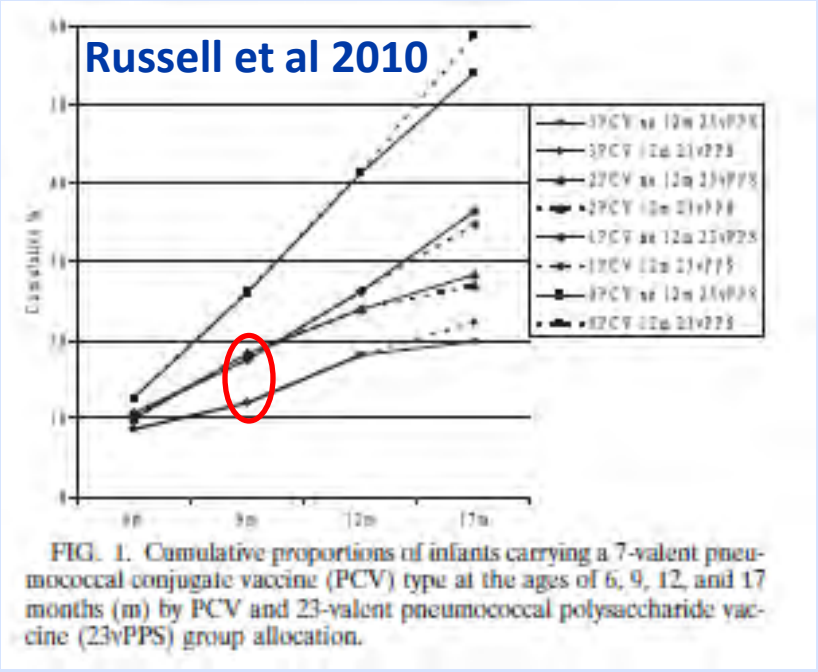
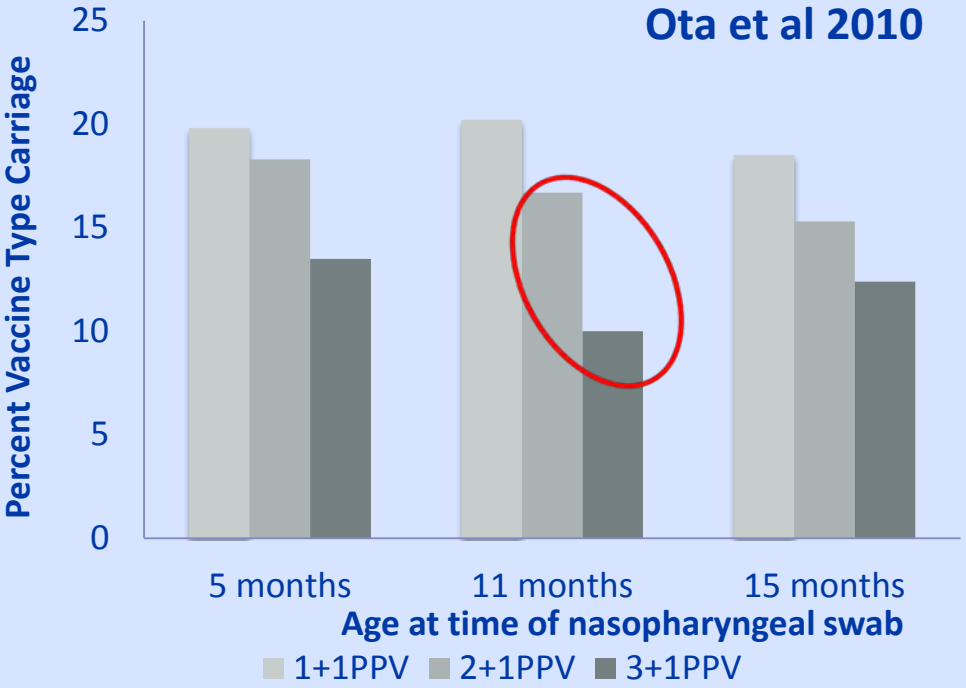


FIG. 1. Cumulative proportions of infants carrying a 7-valent pneumococcal conjugate vaccine (PCV) type at the ages of 6, 9, 12, and 17 months (m) by PCV and 23-valent pneumococcal polysaccharide vaccine (23vPPS) group allocation.

- Significantly less vaccine-type carriage in 3-dose group vs. 2-dose group at 9 months of age (odds ratio 0.30 (CI 0.09–0.9)
- No statistical differences at 6, 12, or 17 months

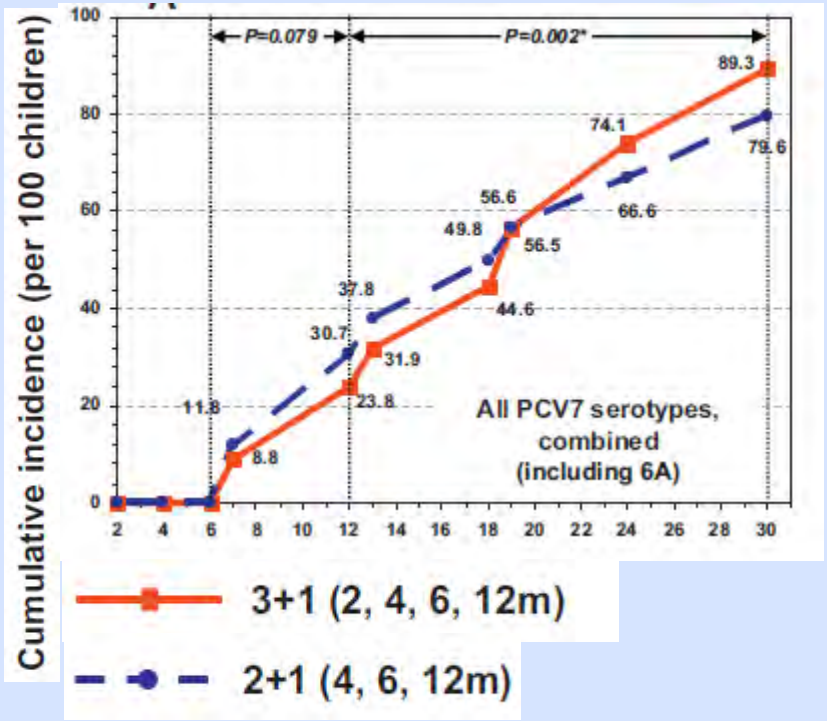
Ota et al 2010



- At 11 months, 3-dose group showed a borderline significant reduction in vaccine-type carriage compared to 2-dose group (10.0% v. 16.7%, p=0.056).
- No statistical differences seen at 5 and 15 months

Carriage studies: clinical trials with direct comparisons of schedules

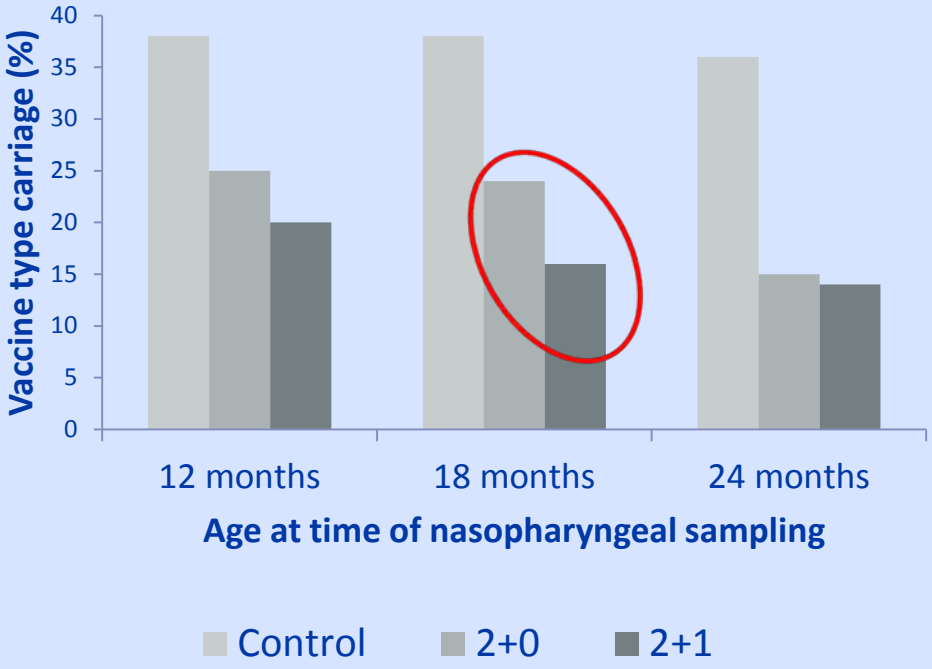
2+1 vs. 3+1



- Pre-booster (7-12 months of age), carriage rates for all PCV7 types non-significantly lower in the 3+1 group as compared to the 2+1 group (22.6% vs. 28.4%, p=0.089); differences significant for types 6A and 6B
- No statistical differences post-booster

Dagan et al 2012

2+0 vs. 2+1



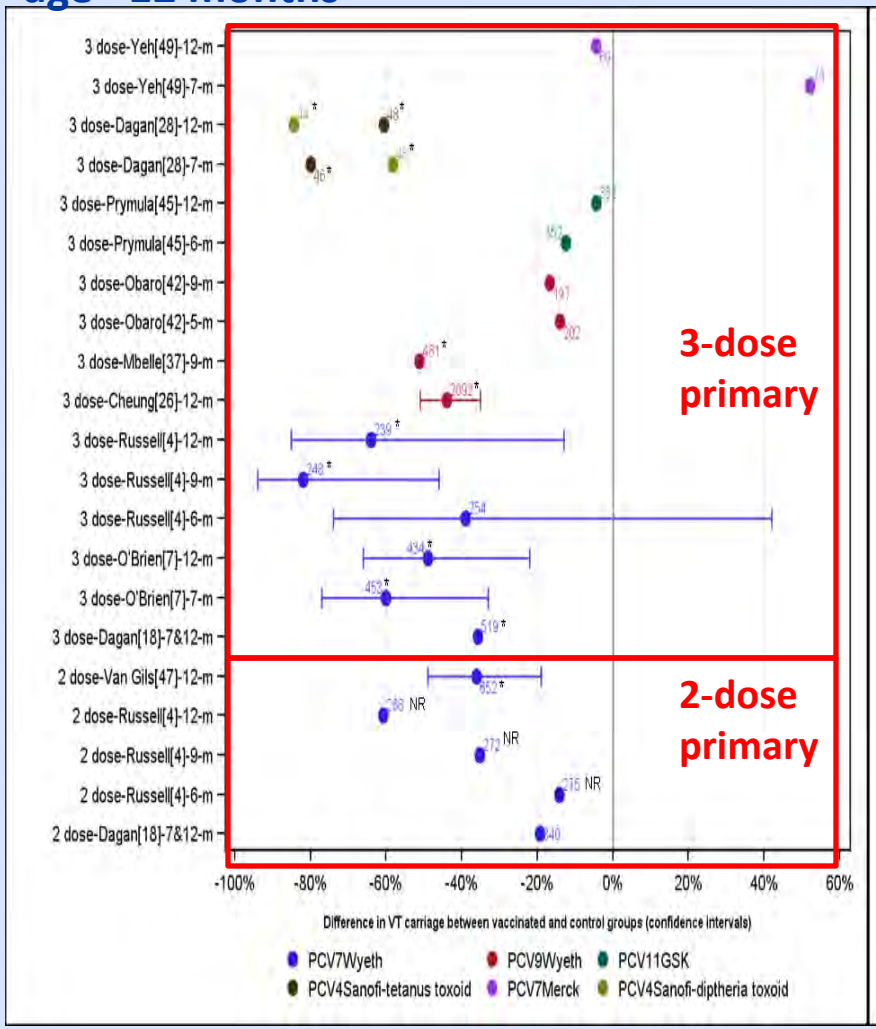
- Significantly lower prevalence of PCV7-type carriage at 18 months in the 2+1 group (16%) than the 2+0 group (24%, p=0.01)
- No statistical difference was found at 12 or 24 months

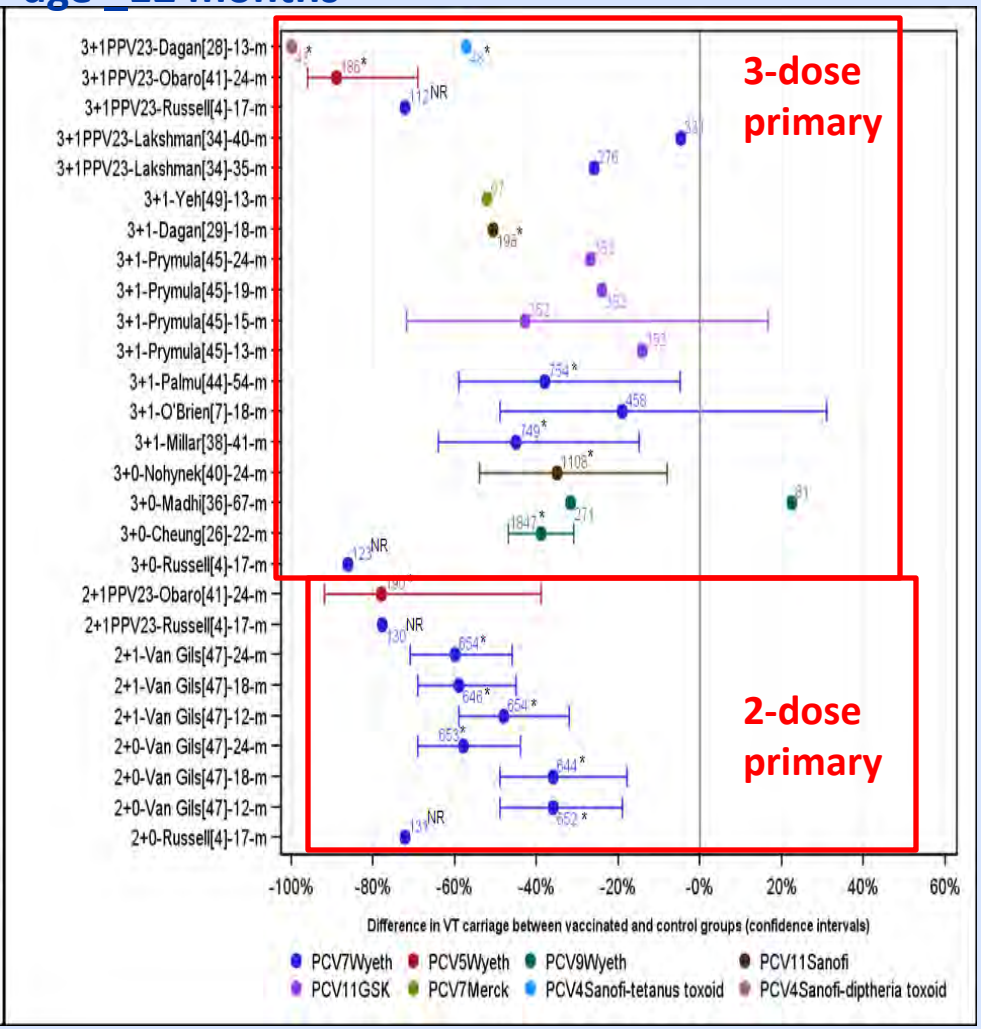
Van Gils et al 2009

Carriage of vaccine types in clinical trials by schedule compared to unvaccinated

2- or 3-dose series pre-booster, age <12 months

Schedules with or without a booster, age ≥12 months





Fleming-Dutra PIDJ 2013 In press

Carriage of vaccine types in clinical trials by schedule compared to unvaccinated

- 2- or 3-dose series pre-booster, age <12 months :
  - Ten clinical trials evaluated 2- and 3-dose primary regimens compared to control subjects (n=23 study arms)
  - Reductions in vaccine-type carriage seen in both 2-dose and 3-dose primary series arms
- 2- or 3-dose series with or without a booster, age ≥12 months:
  - Thirteen clinical trials with samples taken after the first year of life (n=29 study arms)
  - Reductions in vaccine-type carriage seen for 28/29 arms
- Differences between 2-dose and 3-dose primary series difficult to discern when comparing across studies.

Fleming-Dutra PIDJ 2013 In press

Conclusions: Nasopharyngeal Colonization

- All schedules (2+1, 3+0, and 3+1) reduce acquisition of colonization with vaccine serotypes compared with no PCV

- 3-dose primary better than 2-dose primary before booster dose at 1–7 months following the series; no differences at 12 months of age (before booster)

- No differences observed after booster dose

Conclusions: evidence review by outcome

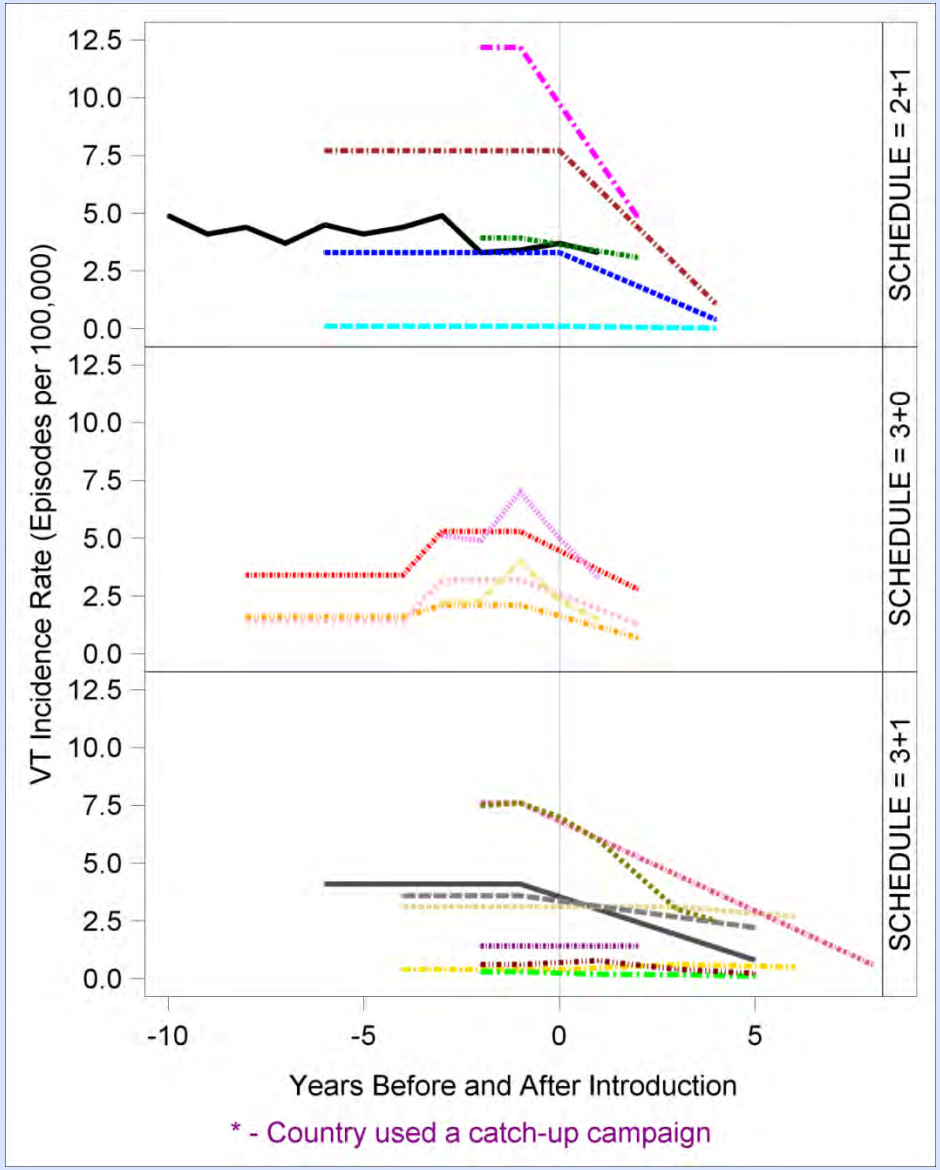
Outcome	IPD	Pneumonia	AOM	Immunogenicity	NP Colonization
Efficacy of 3-dose schedules evaluated in RCT?	Yes	Yes	No	Yes	Yes
Studies available with direct comparison between schedules?	No*	Yes	Yes	Yes	Yes
Studies show that a 3-dose schedule is different compared to 4-dose schedule?	No difference (based on comparisons across studies)	Yes, early post-introduction only	No difference (based on few studies)	Yes, for some serotypes, post-primary only No difference post-booster	Yes, for some serotypes, post-primary only No difference post-booster

*PCV10 trial evaluated 2+1 and 3+1; not powered for direct comparison

Interpreting the findings in the context of the US PCV13 program…

- Differences in antibody response between schedules may lead to differences in carriage and, potentially, in disease
- However,
  - Studies conducted outside of national immunization programs (no herd effects)
  - Serotypes in question are very rare in the US, and therefore, less likely to cause disease
  - Rates of PCV13 type IPD extremely low among children 6-11 months of age
  - Direct and indirect (herd) effects of 3-dose PCV programs at the population level similar to the ones observed in the US

Indirect effects of 3-dose PCV programs on IPD

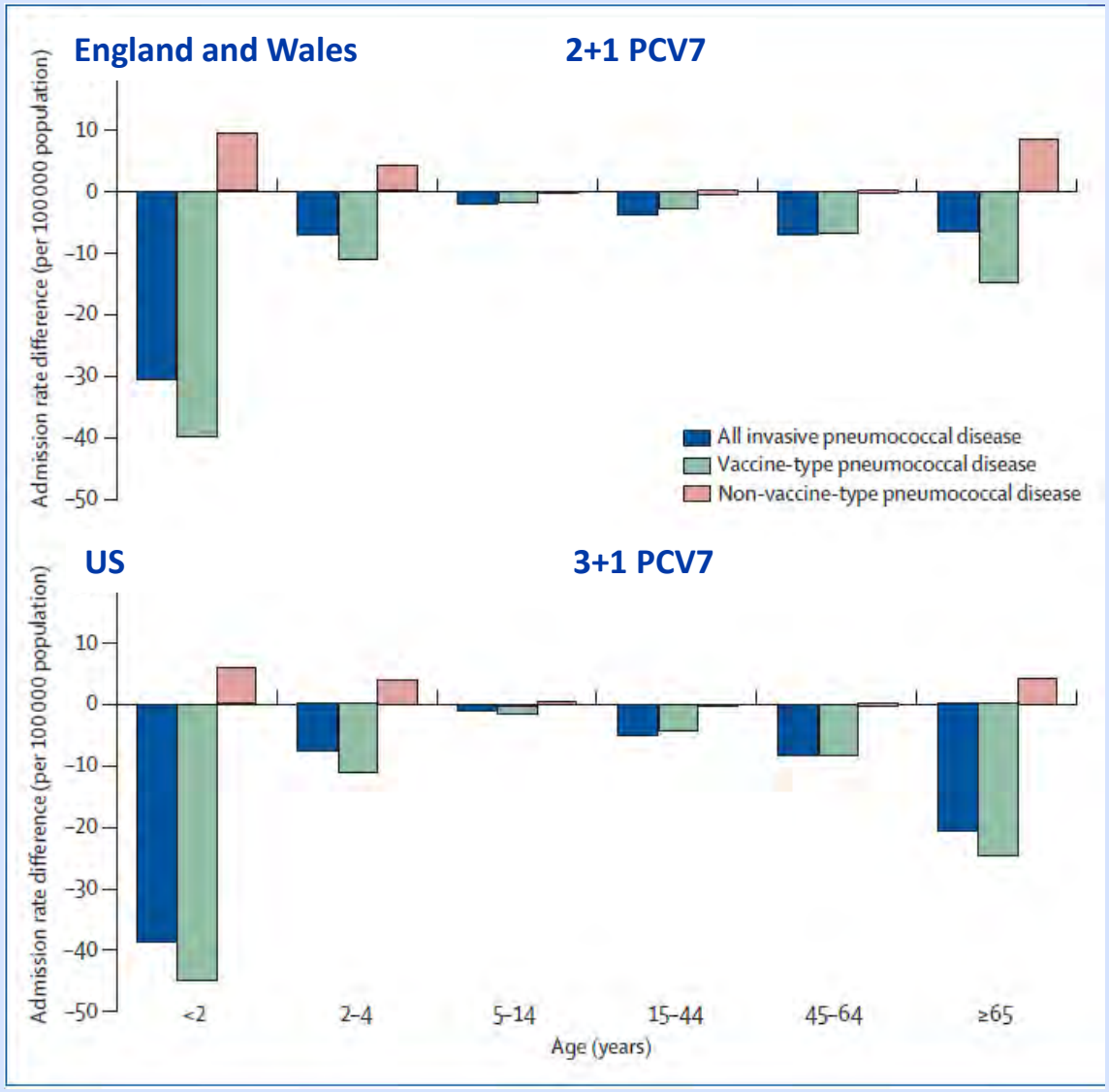


Country	Age group (years)	Number of years post introduction	Percent change in vaccine-type IPD
2+1			
UK	15-44	4	-88
	45-64	4	-86
UK	>=2	1	-22
Norway	20-39	2	-22
	40-64	2	-60
Scotland	5-64	3	-53
Denmark	5-65	2	-74
3+0			
Australia	15-29	2	-62
	30-49	2	-43
	50-64	2	-36
Australia	15-49	1	-35
	50-64	1	-35

Indirect effects of 3-dose PCV programs similar to the ones observed in the US

Loo et al. PIDJ 2013 In press

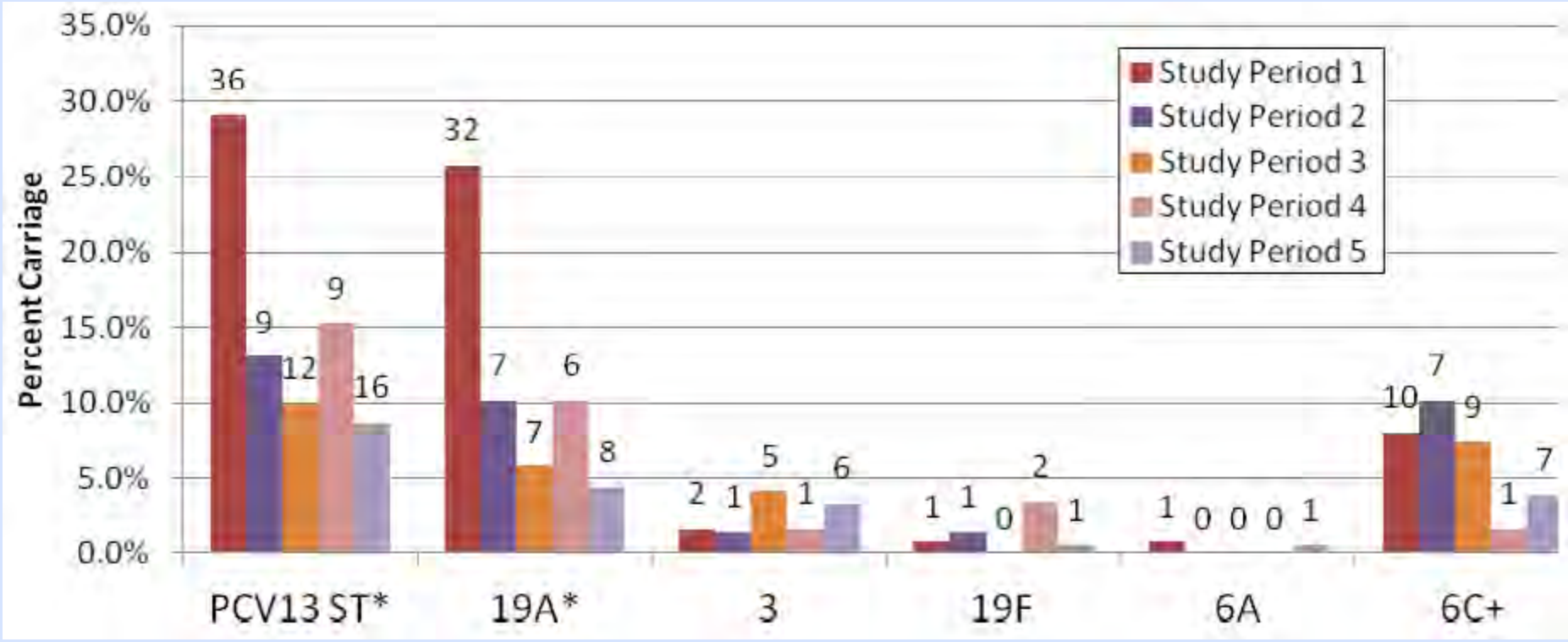
Comparison of indirect effects of PCV7 programs on hospitalized IPD in the US and England and Wales



- Incidence rates compared 4-years post-PCV7 introduction vs. pre-introduction
- Indirect effects of 3-dose PCV programs similar to the ones observed in the US
- **Key point:** absolute PCV7-type rate differences strikingly similar between two countries

Grijalva et al. Lancet 2011

Nasopharyngeal carriage of PCV13 serotypes in children, Atlanta 2010-2012



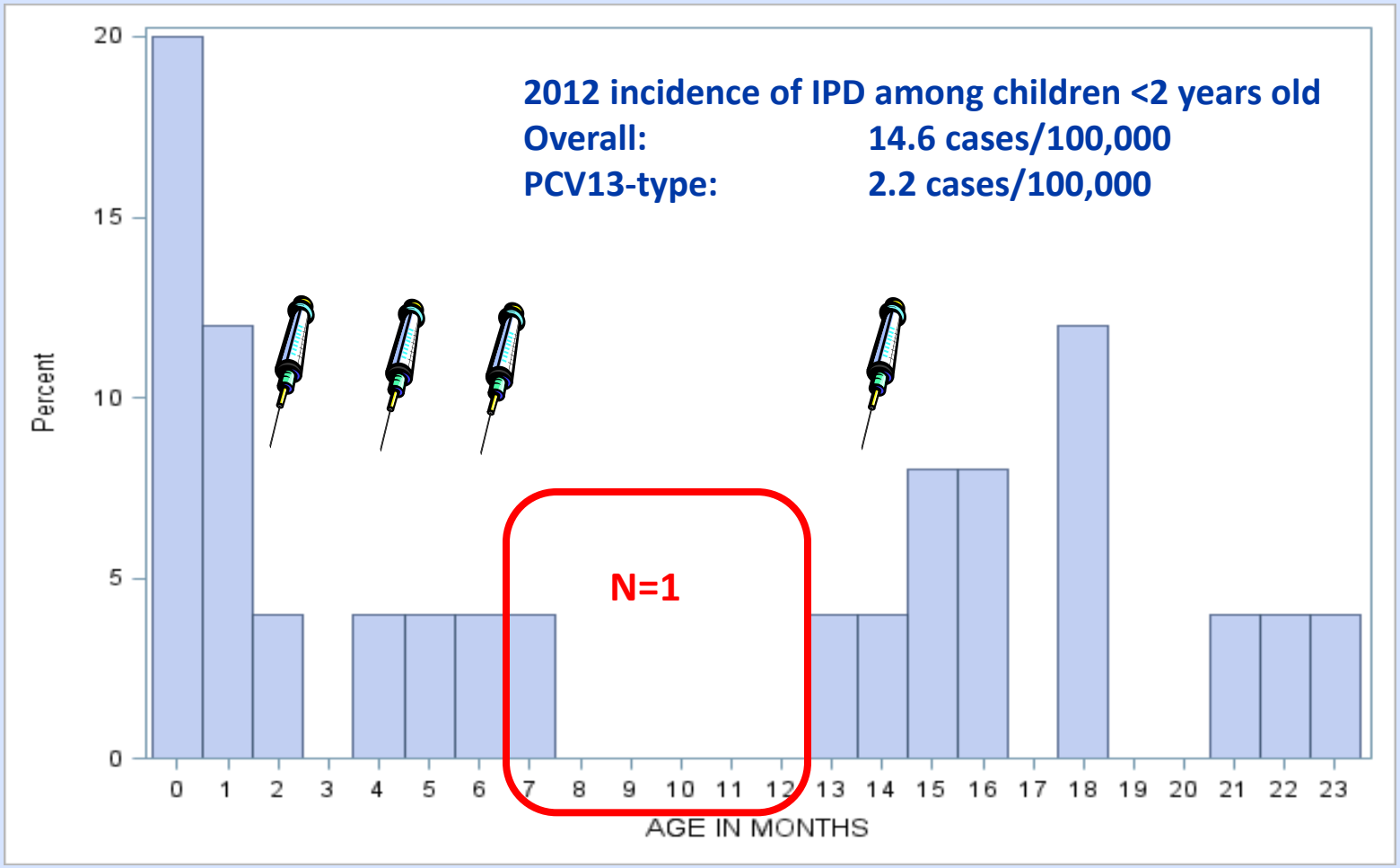
Serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, or 23F were not isolated in any study period

*** p<0.01 using Cochran-Armitage Trend Test**

+ 6C was included due to expected cross protection from PCV13 vaccination

Desai et al. PIDJ 2013 In press

Age distribution of PCV13-type IPD cases, children <2 years old, 2012-13 (N=25)



Active Bacterial Core surveillance, unpublished

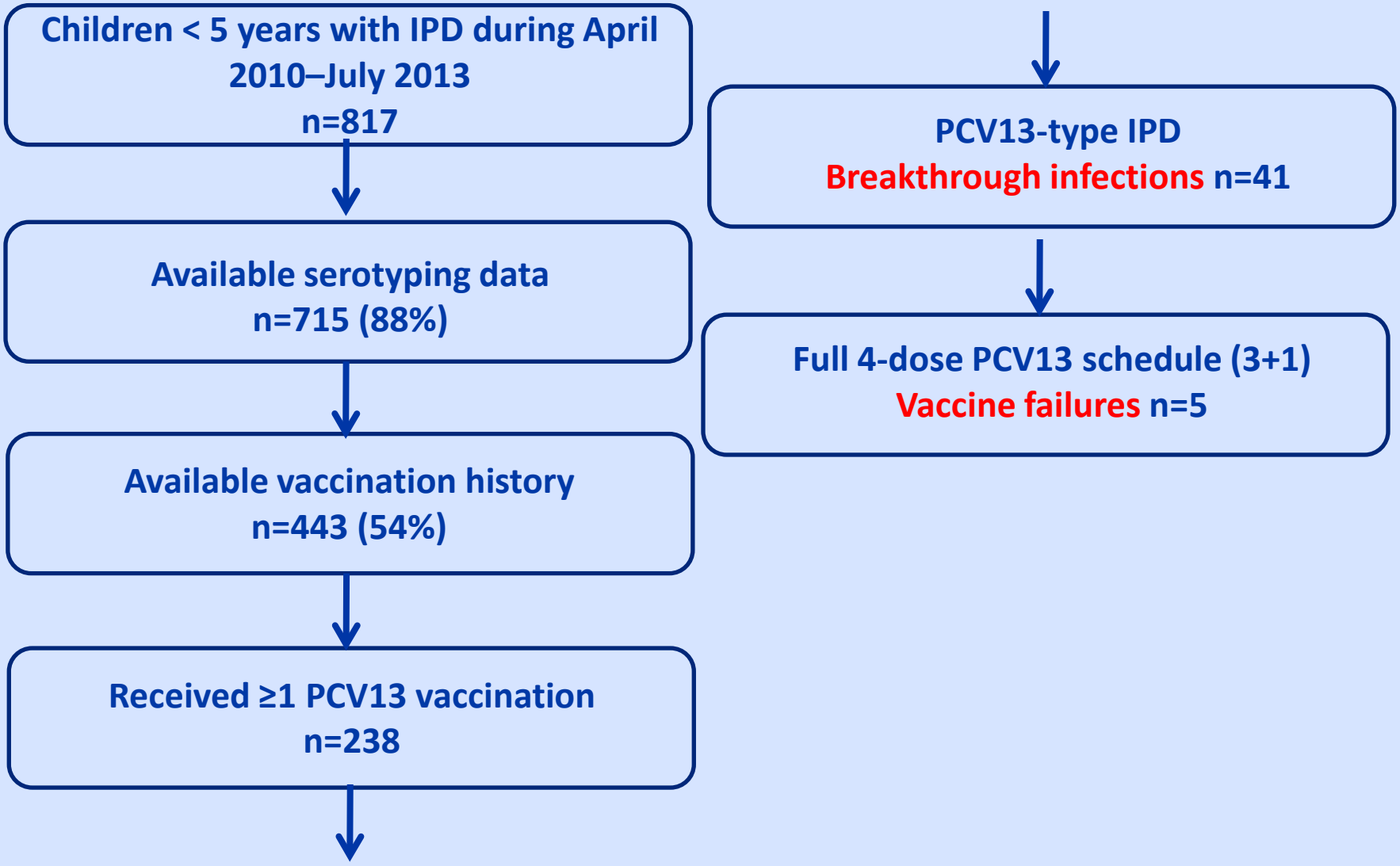
Age at 3rd dose among children receiving 3 PCV doses, National Immunization Survey 2012

Age at 3rd dose (months)	N (unweighted)	% vaccinated ± CI
6 to <7	414	22.5 ± 3.3
7 to <8	97	7.8 ± 2.3
8 to <9	49	3.1 ± 1.3
9 to <10	65	6.8 ± 3.7
10 to <11	29	2.4 ± 1.2
11 to <12	27	1.6 ± 0.8
12 to <13	167	10.0 ± 2.4
≥13 months	585	43.0 ± 4.7

NIS 2012 coverage for 3+ PCV 92.3% and 4+ PCV 81.9%

Courtesy of Black C. and Qian Li. CDC unpublished

PCV13 Breakthrough Infections, ABCs 2010–2013



Slide courtesy of Kim L. ABCs unpublished

PCV13 vaccine failures and breakthrough cases, ABCs 2010-2013

Serotype	Number of cases (%) by PCV13 schedule					Total N (%)
	2+0	2+1	3+0	3+1*	Other*	
Total PCV13 type	5 (12%)	2 (5%)	9 (22%)	5 (12%)	20 (49%)	41
3	0	1	1	1	6	9 (22%)
7F	0	0	0	0	1	1 (2%)
19A	5	1	8	4	11	30 (74%)
19F	0	0	0	0	1***	1 (2%)

*Vaccine failures (a subset of breakthrough infections)

** Other category includes 1-dose (n=16), 2-dose (n=1), 3-dose (n=2), and 4-dose (n=1) PCV13 schedules

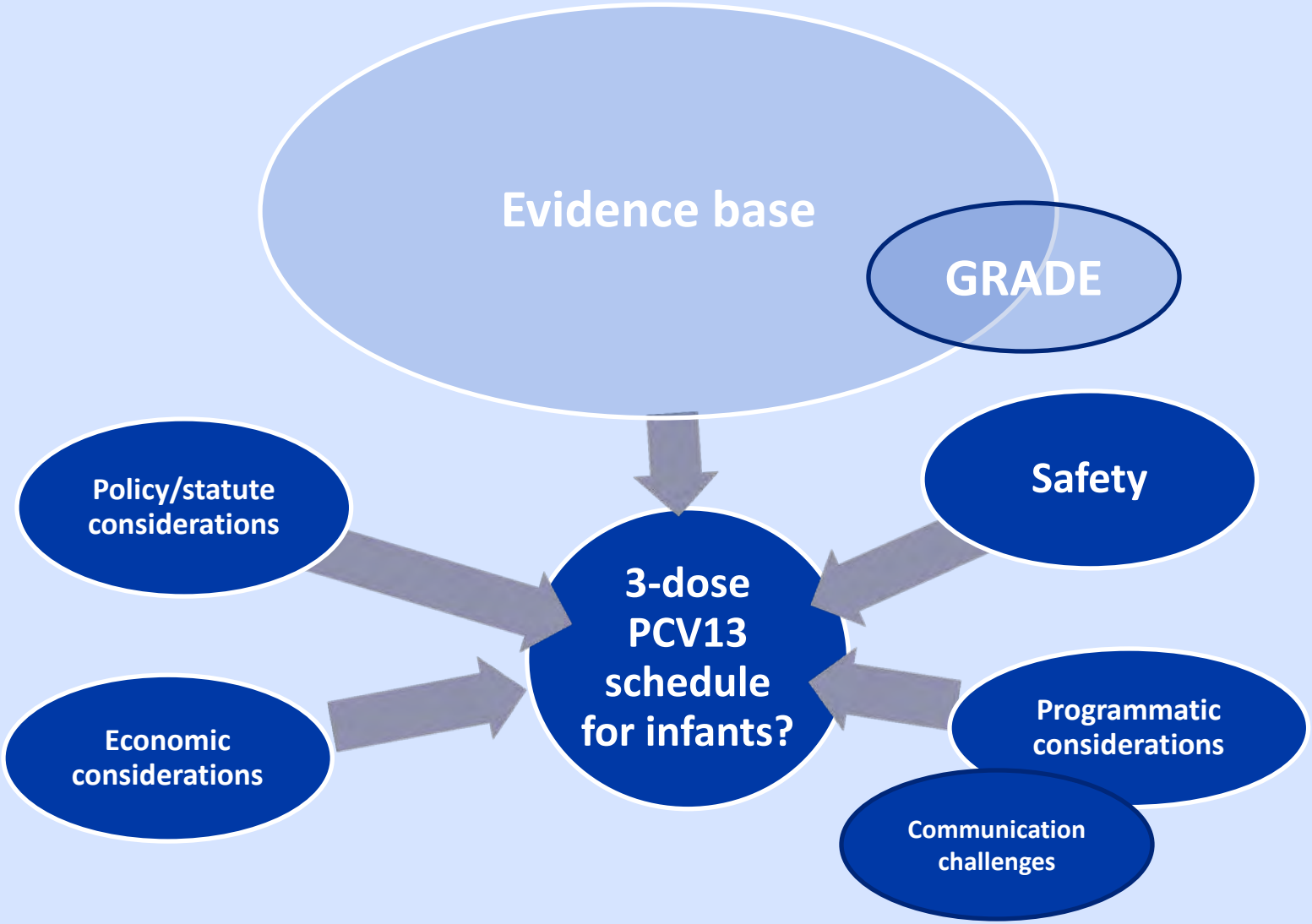
*** 3 doses of PCV7 and a booster of PCV13

ABCs unpublished

Conclusions

- Three-dose PCV schedules are effective against IPD, pneumonia, and otitis media
- Immunogenicity and carriage studies show that 3+1 schedule may be better than 2+1 before booster; no differences observed post-booster for most serotypes
- Strong direct and indirect (herd) effects observed in countries using 3-dose PCV schedules
- Differences between schedules may not be meaningful due to
  - PCV7 serotypes rarely cause disease in children and adults
  - PCV13 serotype disease rapidly declining
  - Herd effects similar, so no changes expected at the population level

Considerations for a potential policy change



Additional considerations

- Policy/statute issues
  - A 3-dose schedule is not approved by FDA and, therefore, this would be an off-label recommendation
  - Ensure that the wording of a potential recommendation allows for ACA coverage for insurance re-imbursement of the 4th dose
- Economic considerations
  - Cost-effectiveness analysis does not consider that the vaccine price may be adjusted
  - Ensure that the language of recommendations allows for no cost-sharing if providers choose to give a 4th dose
- Programmatic considerations
  - Evaluate the performance of the vaccine program to deliver high coverage at each time point in the immunization schedule
  - Acceptability of the various 3-dose schedule options and communication to providers and parents

Work Group Conclusions

- Including a 3-dose PCV13 schedule for routine use among infants would not adversely impact the individual protection against invasive pneumococcal disease, pneumonia, otitis media (fewer studies), or herd effects

- Acceptable schedule in the setting of a mature immunization program and strong herd effects may not need to be the same as that chosen at the time of licensure

- A 3-dose PCV13 schedule for infants is likely appropriate to maintain already observed benefits from 13 years of PCV use in the US

Next steps

- Input from ACIP, AAP, and AAFP
- Identify data gaps and collect information
- Review data
  - by timing of dose administration in primary series
  - comparing schedules with or without a booster
  - identify groups requiring separate consideration (e.g. immune compromised)
- GRADE process to evaluate the appropriate 3-dose schedules, considering effectiveness and safety data
- Present policy options at a future ACIP meeting

Discussion

- Is the available evidence adequate to consider including a 3-dose PCV13 schedule?
- If not, what are the gaps in information?
  - Supporting evidence/data
  - Provider/practice level issues
  - Public health program level issues
  - Parent considerations
- Does the committee have concerns about potentially including a 3-dose PCV13 schedule for routine use among infants?