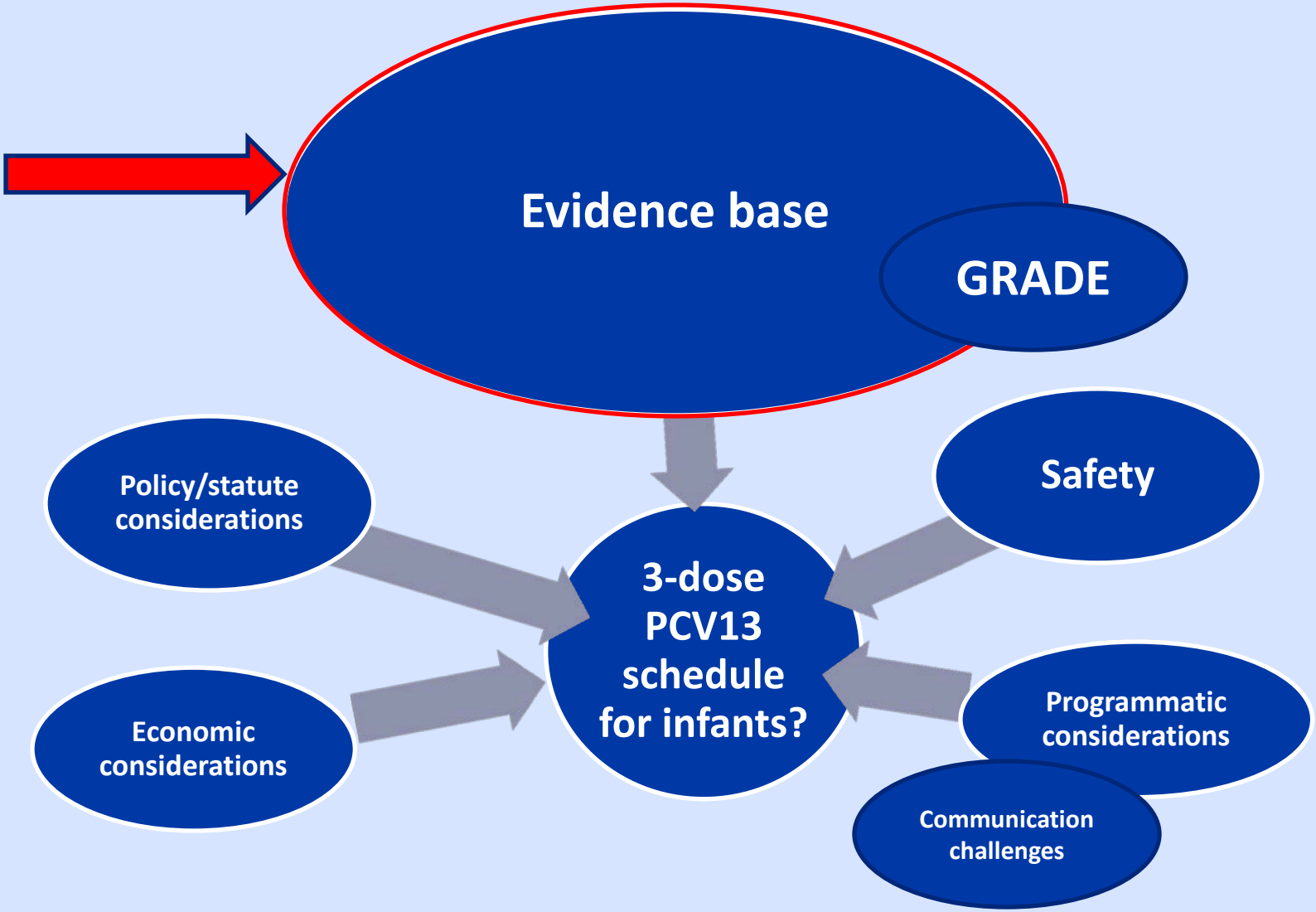
Considerations for a 3-dose PCV13 schedule for infants

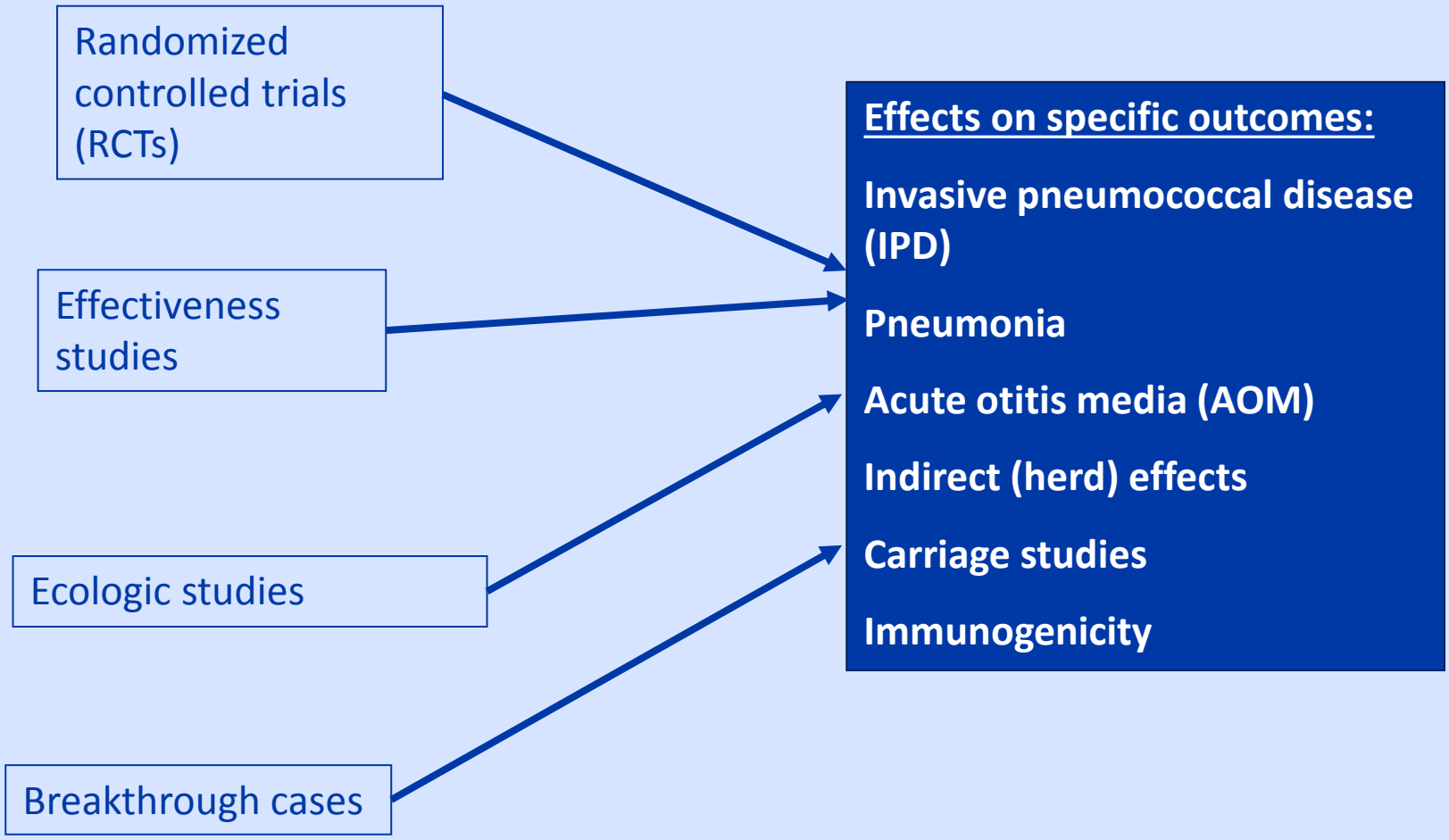
Tamara Pilishvili, MPH
Respiratory Diseases Branch
NCIRD, CDC
Advisory Committee on Immunization Practices
February 26, 2014

Considerations for a potential policy change

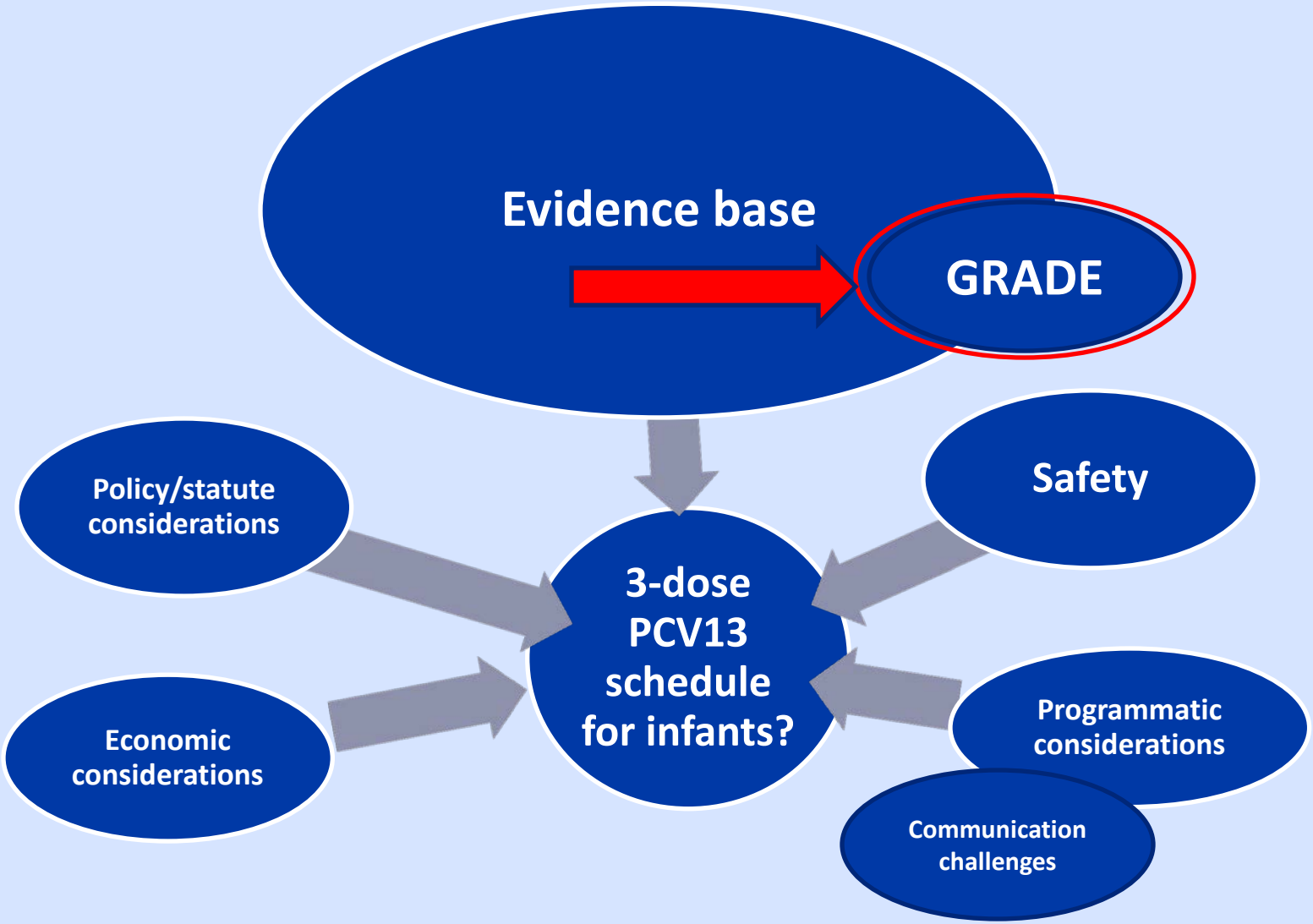


Reviewed evidence for 3-dose PCV schedules (presented Oct 2013)

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



Considerations for a potential policy change



GRADE summary

- Use of each schedule (3+1, 2+1, 3+0) as compared to no vaccination
  - GRADE conclusion: Strong (type 2) evidence and category A recommendation supporting use
- Schedules compared (2+1 vs 3+1 and 3+0 vs 3+1) using GRADE based on studies with direct comparisons
  - Three outcomes:
    - Immunogenicity (surrogate for IPD)
    - Pneumonia
    - AOM
  - GRADE conclusion: lower evidence quality (type 3) and category B recommendation

Key issues not covered by GRADE review

- Evidence not included in GRADE
  - Observational studies for IPD
  - Nasopharyngeal carriage
- Conclusions for each clinical outcome
- Summary of PCV13 breakthrough cases and failures
- Programmatic considerations for policy change
  - National Immunization Survey, PCV13 coverage data
  - Parental acceptance of vaccines and factors influencing refusals and delayed vaccination
- Work Group conclusions
- Next Steps

Evidence not accounted for by GRADE

- Observational studies for PCV impact on IPD

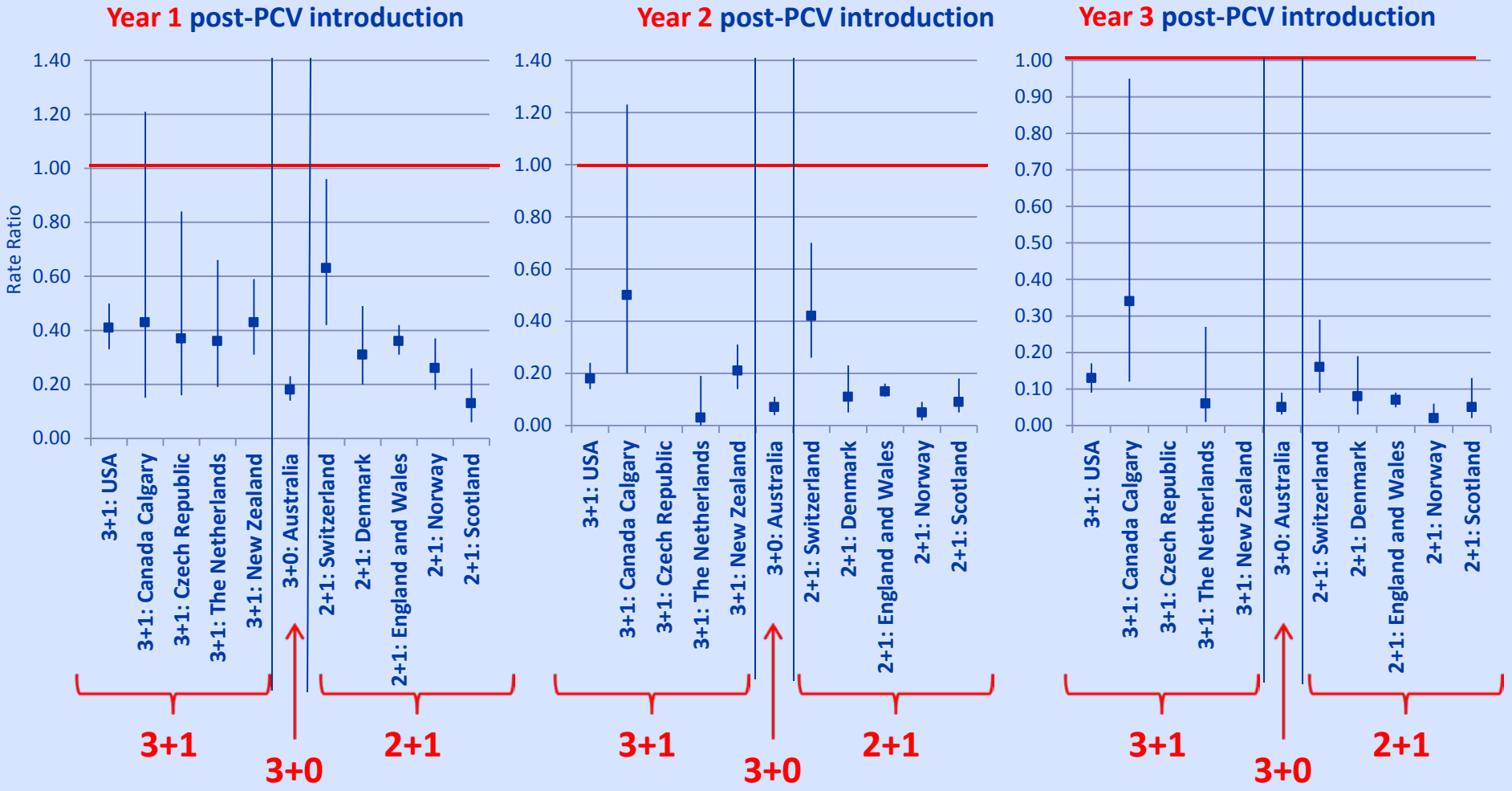
- Effects of reduced schedules on nasopharyngeal carriage

Observational studies evaluating PCV7 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 <5 years



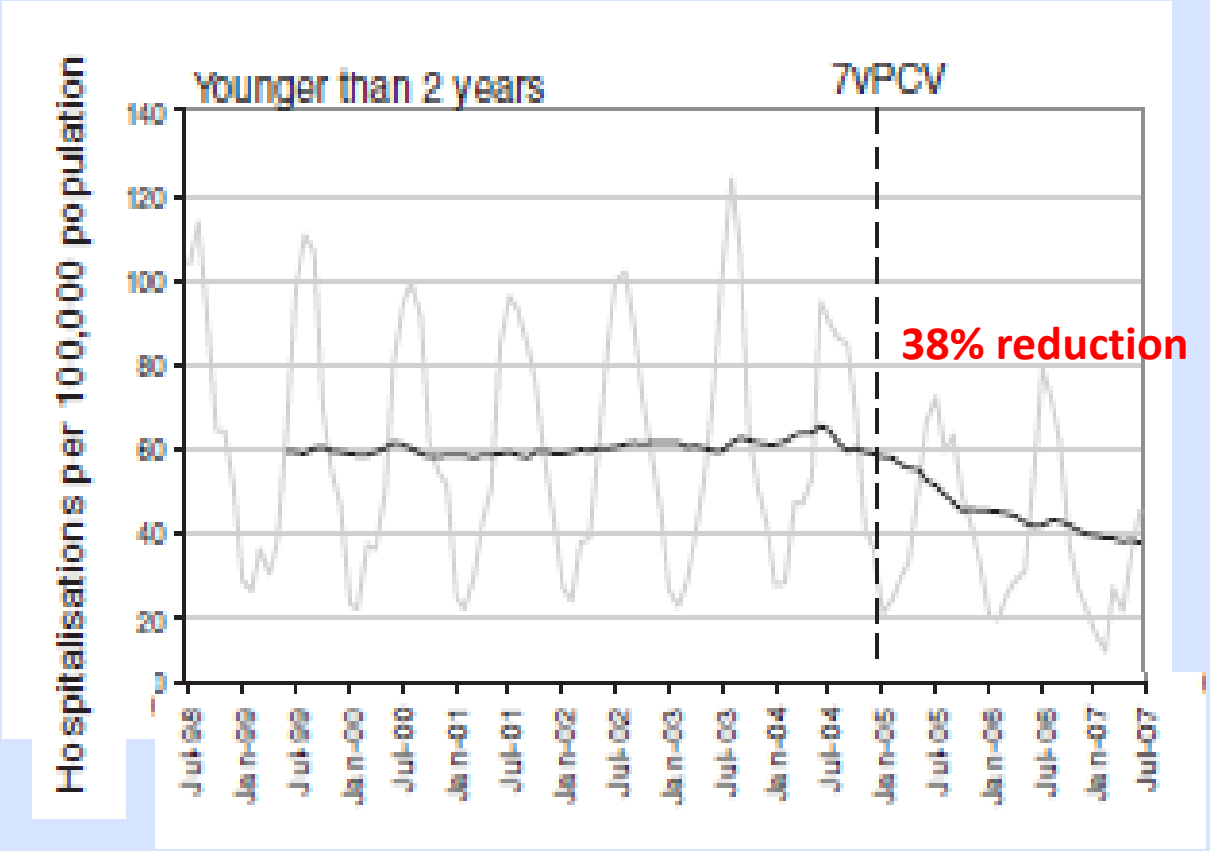
Feikin et al. *PLoS Medicine* 2013

Invasive disease conclusions

- Evidence from RCTs and observational studies suggests each schedule (3+1, 3+0 and 2+1) is highly effective at preventing IPD
- No studies designed to compare 3-dose schedules to 4-dose schedules head-to-head
- Direct comparisons across studies are not meaningful
  - Do not take into account differences in populations and methodology
  - Not powered to detect a difference between two highly effective schedules

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

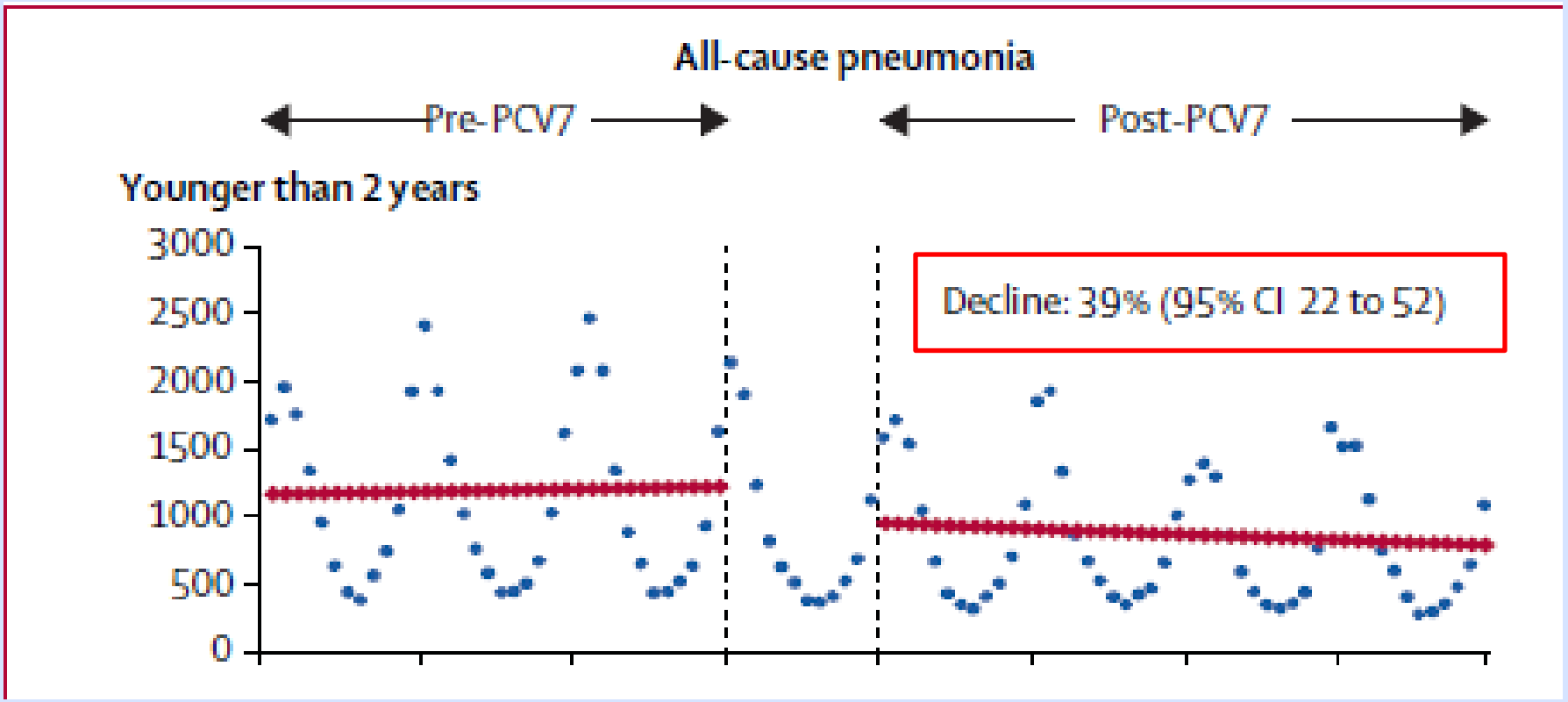
Monthly rates of hospitalization for all cause pneumonia per 100,000 population in Australia, July 1998 to June 2007



Jardine, PIDJ 2010

Observational studies: impact of PCV introduction on pneumonia, 3+1 schedule

Monthly admission rates for all cause pneumonia per 100,000 population in US, 1997-2004



Grijalva, Lancet 2007

Conclusions: Pneumonia

- Evidence from RCTs and observations studies shows that each schedule (3+1, 2+1, and 3+0) prevents pneumonia
- One observational study showed
  - 3-dose primary series is better than 2-dose primary series before booster dose against pneumonia early in US immunization program
  - no statistically significant differences observed post-booster or for later birth cohorts
- Schedule with 4-doses maybe more beneficial early post-introduction

Why is nasopharyngeal colonization data important to consider?

- NP colonization is necessary before infection can occur
- Reductions in vaccine-serotype colonization mean that those serotypes are less available to cause disease
- Provide direct evidence of reduced transmission expected with each schedule (in addition to evidence observed through indirect (herd) impact on IPD)

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

Russell et al 2010

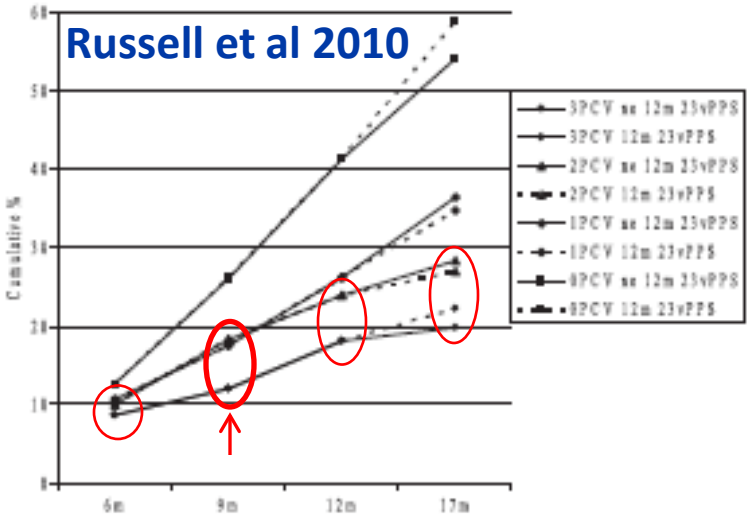
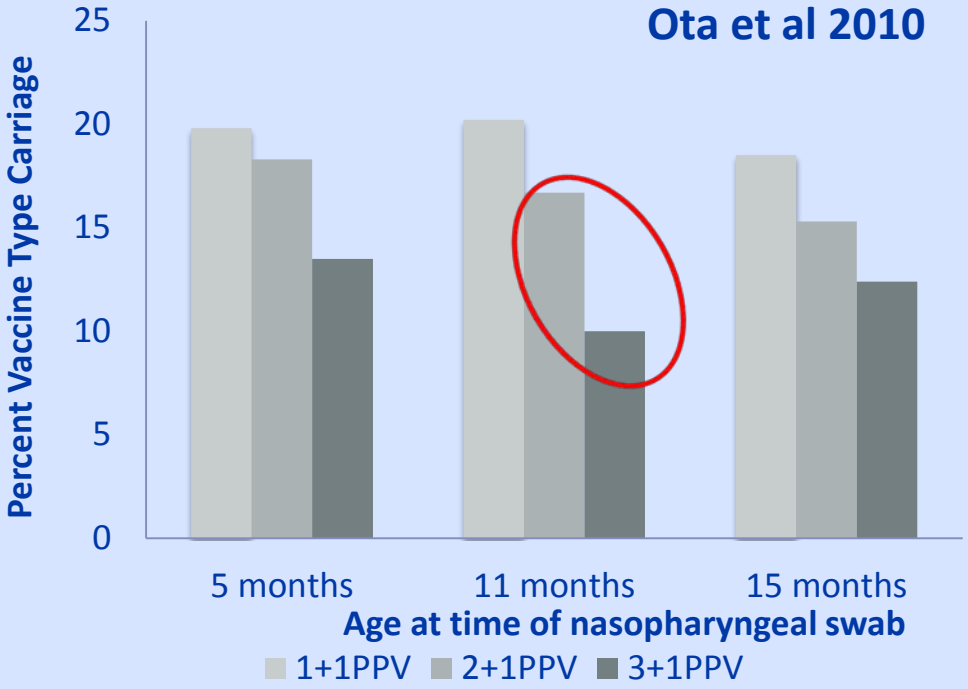


FIG. 1. Cumulative proportions of infants carrying a 7-valent pneumococcal conjugate vaccine (PCV) type at the ages of 6, 9, 12, and 17 months (m) by PCV and 23-valent pneumococcal polysaccharide vaccine (23vPPS) group allocation.

- 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

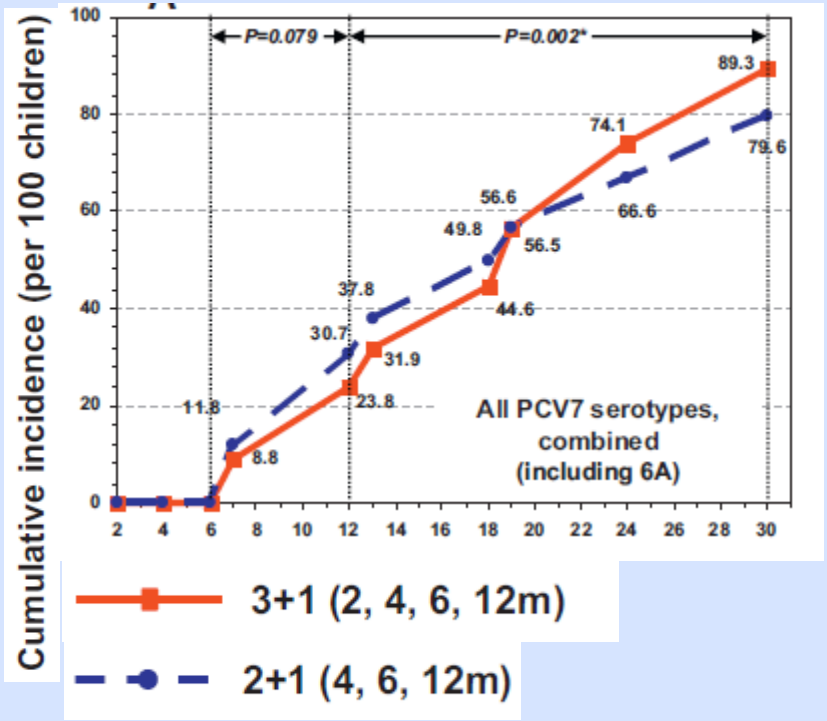
Ota et al 2010



- 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

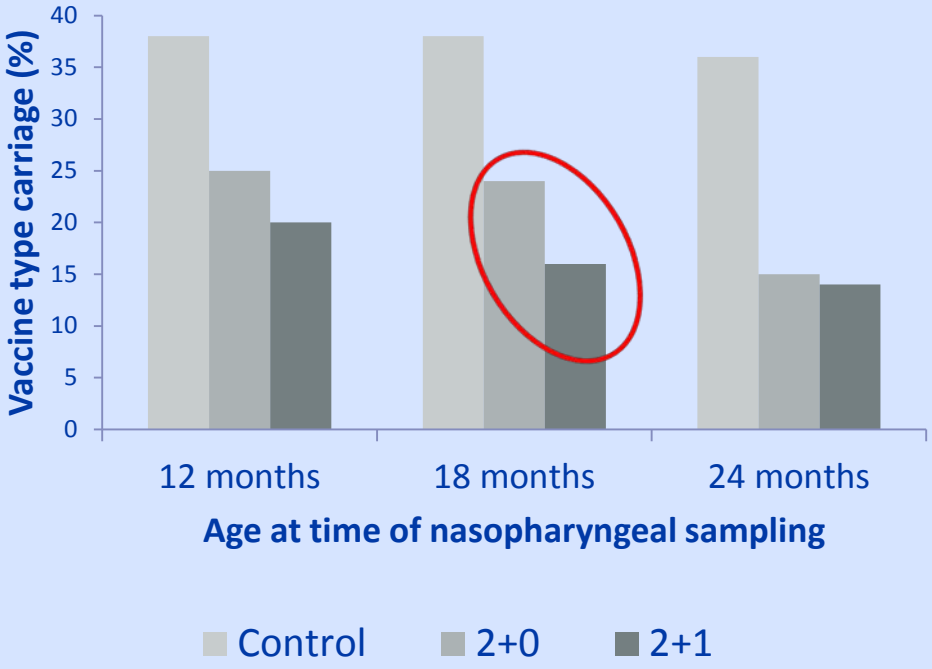
2+1 vs. 3+1



- 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

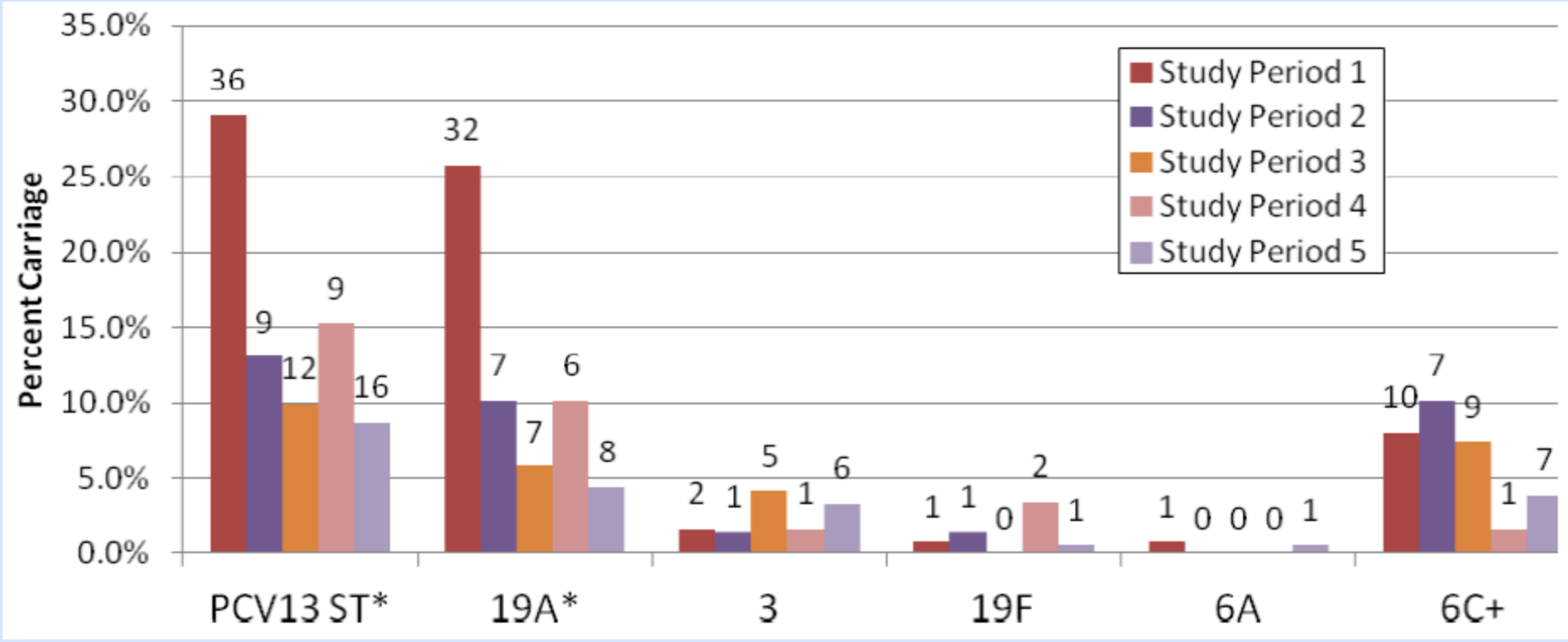
2+0 vs. 2+1



- 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

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 2014 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
- Post-PCV13 introduction US carriage data suggest PCV7 types are very rare and PCV13 type carriage is decreasing

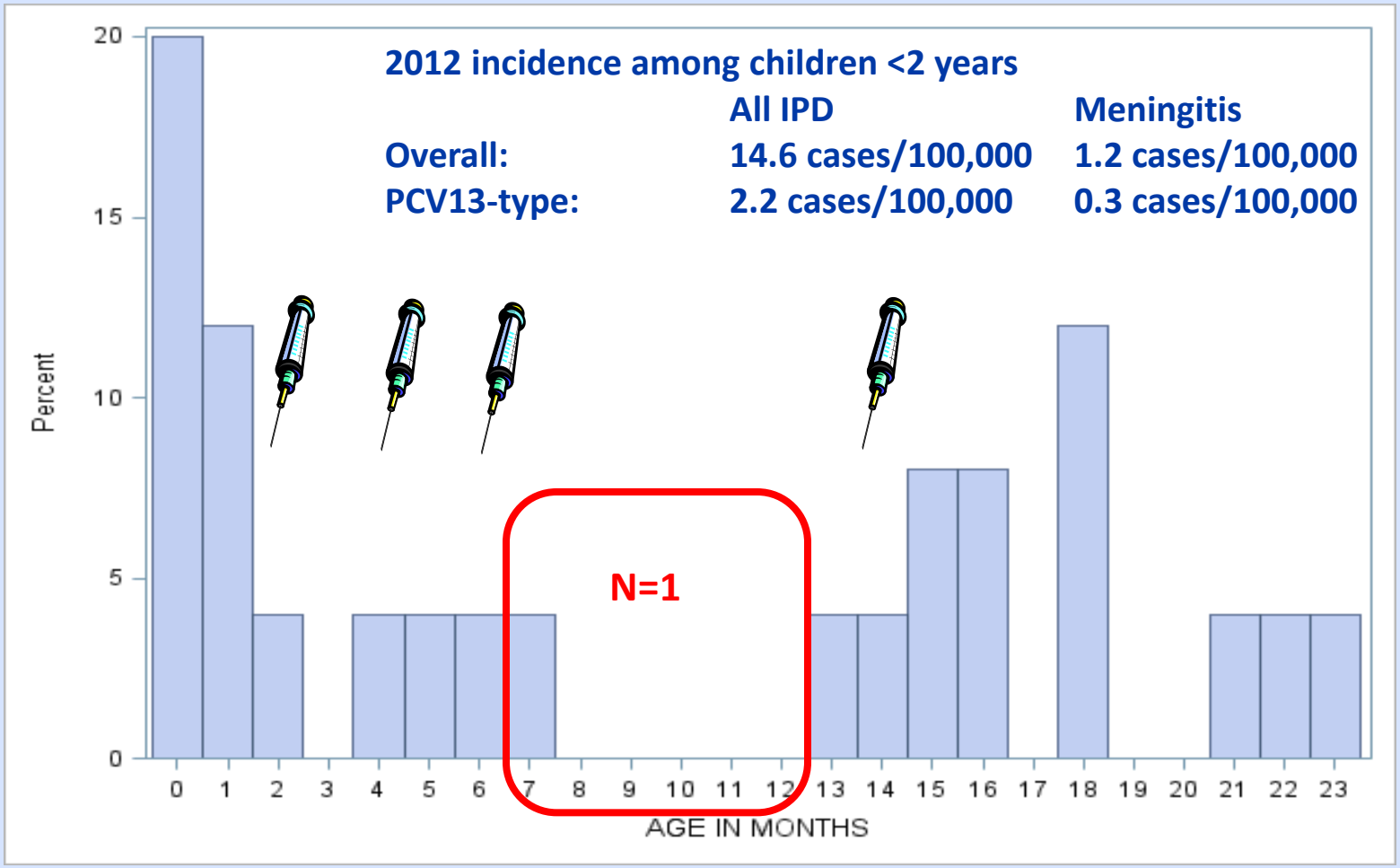
Evidence review: Conclusions

- 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

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

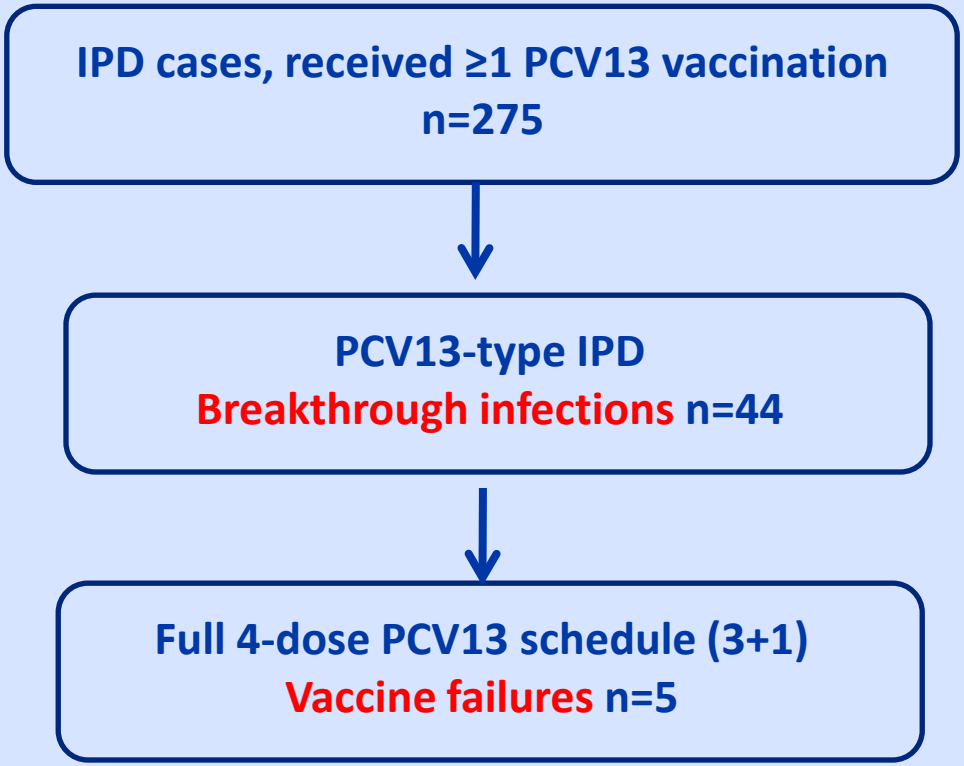
- Differences in antibody response between schedules may lead to differences in carriage and, potentially, in disease
- Differences may not be meaningful in a setting of strong national immunization program and already observed large direct and indirect benefits of PCV use
- PCV7 serotypes are very rare in the US, and therefore, less likely to cause disease
- Rates of PCV13 type IPD extremely low among children 6-11 months of age and continue to decline among all age groups
- Population level impact of 3-dose PCV programs (both direct and indirect effects) similar to the ones observed in the US

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



Active Bacterial Core surveillance, unpublished

PCV13 Breakthrough Infections, ABCs 2010–2013



Slide courtesy of Kim L. ABCs unpublished

PCV13 vaccine failures and breakthrough IPD cases, ABCs 2010-2013

Serotype	Number of cases (%) by PCV13 schedule					Total N (%)
	2+0	2+1	3+0	3+1 PCV13 failures	Other schedules*	
Total PCV13 type	5 (12%)	0 (0%)	5 (11%)	5 (12%)	29 (66%)	44
3	0	0	0	1	8	9 (22%)
7F	0	0	0	0	1	1 (2%)
19A	5	0	5	3	20	33 (74%)
19F	0	0	0	1**	0	1 (2%)

*Other category includes 1-dose (n=23), 2-dose (n=2), 3-dose (n=3), and 4-dose (n=1) PCV13 schedules

** 3 doses of PCV7 and a booster of PCV13

4 meningitis cases (2 type 19A, type 3, and 7F) and no deaths

Active Bacterial Core surveillance, unpublished

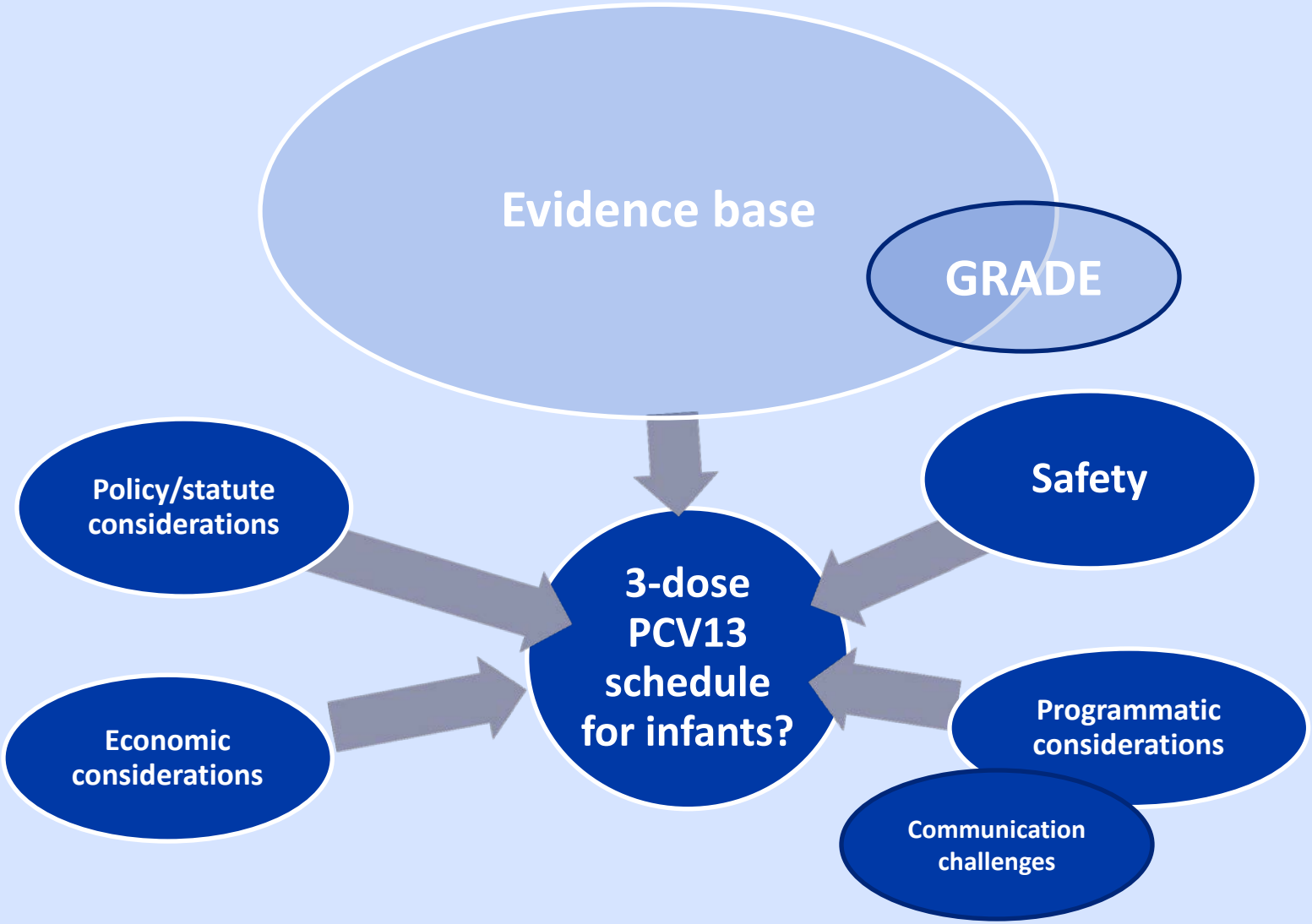
PCV13 vaccine failures and breakthrough IPD cases, by time post-last dose

Schedule	N	Ave. days (range)
1+0	6	60 (18-143)
2+0	5	74 (21-158)
3+0	5	81 (15-141)
2+1	0	-
3+1*	5	211 (120-399)

*Vaccine failures (a subset of breakthrough infections)

Active Bacterial Core surveillance 2010-2013, unpublished

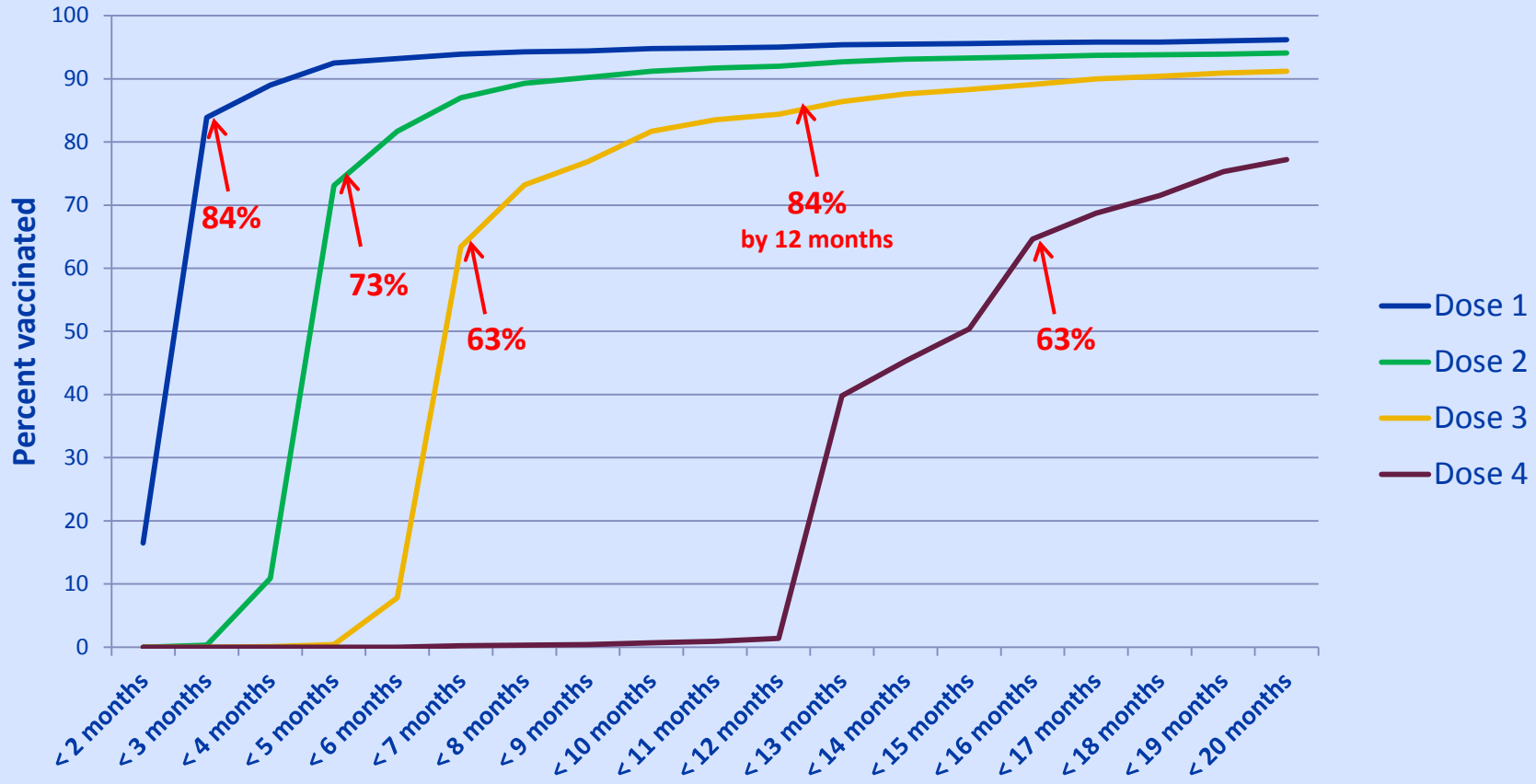
Considerations for a potential policy change



Programmatic considerations

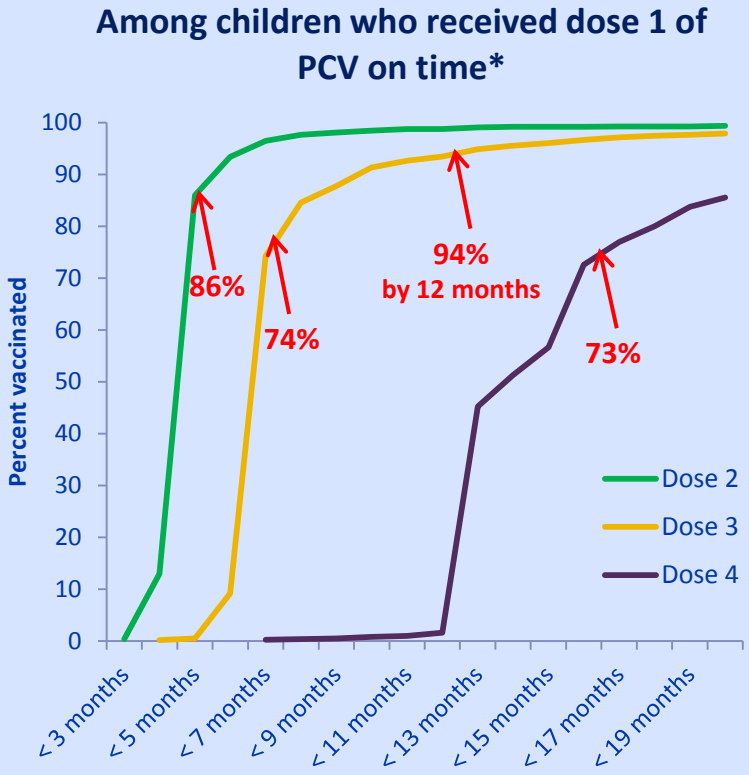
- Evaluate the performance of the vaccine program to deliver high coverage at each time point in the immunization schedule
  - Adherence to currently recommended schedule
  - Delay in timing of each dose and effects on completion of recommended schedule
- Evaluate the potential for non-adherence to introduce disparities in coverage
- Parental acceptance of the recommended vaccination schedule and factors contributing to delays and refusals

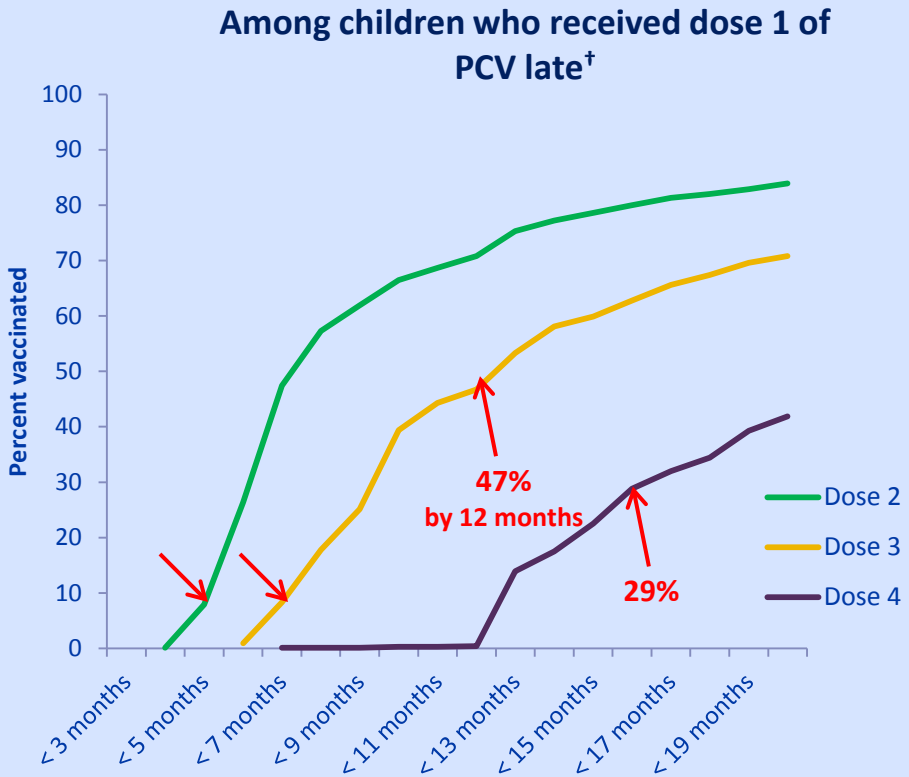
Cumulative percent vaccinated with each dose of PCV by month of age, 2012 NIS



Courtesy of Black C., Elam-Evans L. and Qian Li. CDC unpublished

Cumulative percent vaccinated with each dose of PCV by month of age and timeliness of dose 1, 2012 NIS



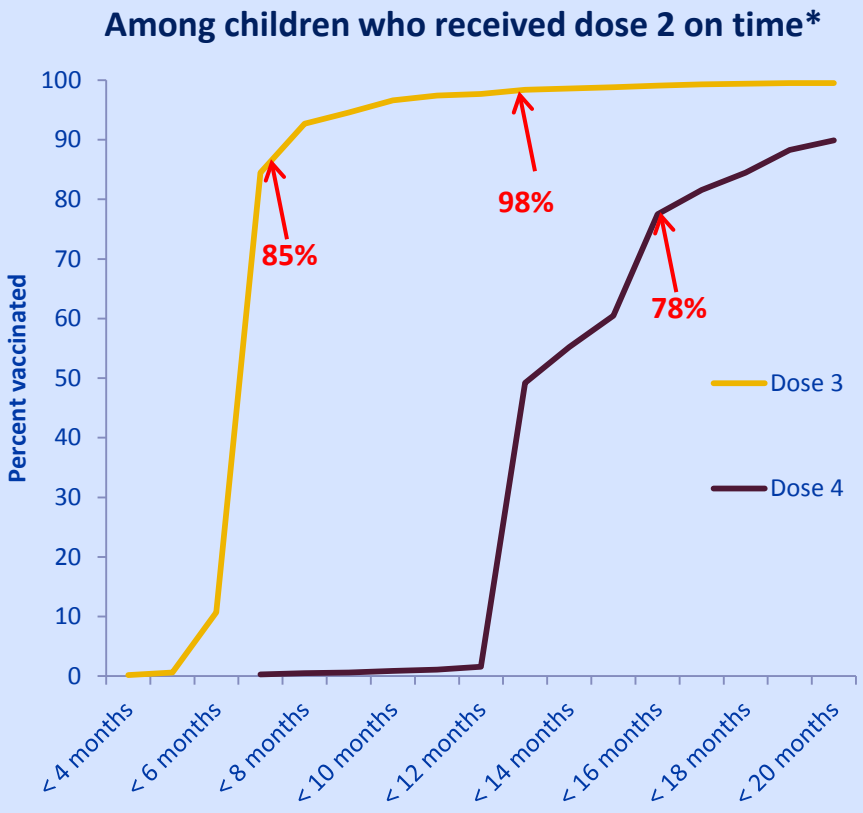


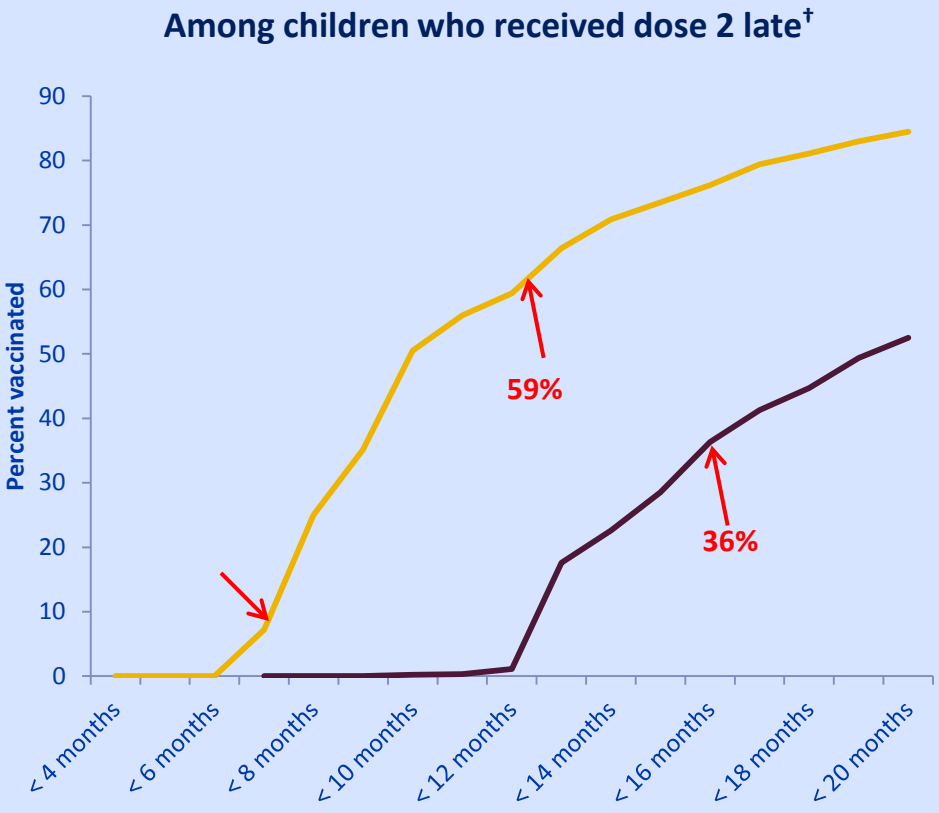
*Received 1st dose of PCV before 3 months of age

†Received 1st dose of PCV at ≥3 months. Excludes children who did not receive at least 1 dose of PCV

Courtesy of Black C., Elam-Evans L. and Qian Li. CDC unpublished

Cumulative percent vaccinated with each dose of PCV by month of age and timeliness of dose 2, 2012 NIS



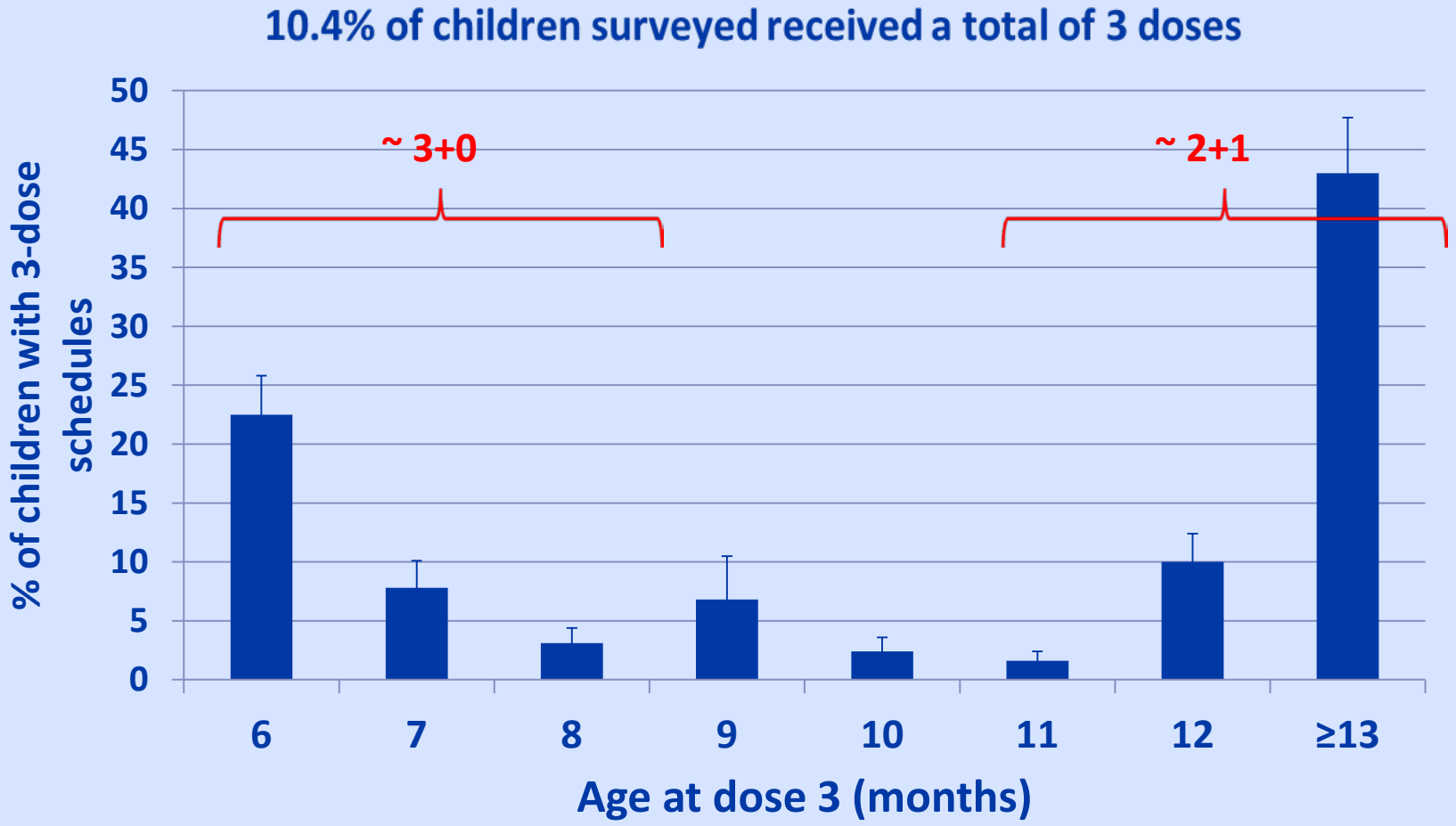


*Received 1st dose of PCV before 5 months of age

†Received 1st dose of PCV at ≥5 months. Excludes children who did not receive at least 2 dose of PCV

Courtesy of Black C., Elam-Evans L. and Qian Li. CDC unpublished

Age at 3rd dose among children receiving ONLY 3 PCV doses, NIS 2012



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

Courtesy of Black C. and Qian Li. CDC unpublished

PCV13 coverage by poverty level and schedule, 2012 NIS

	≥3 doses before 12 months		≥2 doses before 12 months and ≥1 dose at ≥12 months		≥3 doses before 12 months and ≥1 dose at ≥12 months	
	% vaccinated	95% CI	% vaccinated	95% CI	% vaccinated	95% CI
Total	84.4	83.3-85.5	85.9	84.9-86.9	79.2	78.0-80.4
Above Poverty >75,000	89.5	87.8-91.2	90.2	88.6-91.8	85.9	84.1-87.7
At or Above Poverty ≤ 75,000	85.2	83.6-86.8	86.6	85.1-88.1	80.5	78.8-82.2
Below Poverty	80.3	78.2-82.4	82.4	80.3-84.5	73.6	71.2-76.0
Unknown Poverty Status	83.4	78.5-88.3	84.6	79.9-89.3	78.7	73.4-84.0

Courtesy of Black C., Elam-Evans L. and Qian Li. CDC unpublished

Summary: PCV13 coverage in the US

- The vast majority of children receive PCV doses in the primary series on time
- The majority of children complete PCV primary series by 11 months of age; therefore, still eligible for a 4th (booster) dose in the 2nd year of life
- Among children for whom either dose 1 or dose 2 are delayed, a smaller proportion are eligible for and/or complete a 4-dose schedule
- Small proportion receive a total of 3 doses; difficult to identify which 3-dose schedule would be preferred
- The coverage decreases with increasing poverty level for all schedules; within each poverty strata, coverage is lowest for 3+1 schedule

Parental Delay or Refusal of Vaccine Doses, 2009 NIS

- N=11,206 parents of children 24–35 months old

- 25.8% (95%CI ±1.4%) delayed
- 8.2% (95%CI ± 0.9%) refused
- 5.8% (95% CI ± 0.7%) both delayed and refused

≥1 recommended vaccine doses

- Delays and refusals were associated with parental beliefs that
  - children receive too many vaccines (58.6% vs. 29.1%, $p<0.05$)
  - too many vaccines can overwhelm a child' immune system (48.6% vs. 28.3%, $p<0.05$)
  - vaccines have serious side effects (63.1% vs. 30.9%, $p<0.05$)
- Delays and refusals were more likely among
  - Parents with higher SES (income, education, healthcare coverage)
  - Children with lower coverage for all 10 recommended vaccines (e.g. PCV7 63.7% vs 82.6%)

Smith P. et al Public Health Rep. 2011

Parents' perceptions about vaccines

- N= 376 respondents of 2010 HealthStyles Survey who were the parent or guardian of one or more children ≤6 years

Vaccine Concerns Reported By Parents Of Children Age 6 Or Younger, 2010

Concern	Parents reporting concern (%)
It is painful for children to receive so many shots during one doctor's visit	38
My child is getting too many vaccines in one doctor's visit	36
Children get too many vaccines during the first two years of life	34
Vaccines may cause fevers in my child	32
Vaccines may cause learning disabilities, such as autism	30
The ingredients in vaccines are unsafe	26
Vaccines are not tested enough for safety	17
Vaccines may cause chronic disease	16
Vaccines are given to children to prevent diseases they are not likely to get	11
My child will not be vaccinated on time because there are not enough of some vaccines	9
Vaccines are given to children to prevent diseases that are not serious	8
No concerns	23

Kennedy et al Health Affairs 2011

Alternative Vaccination Schedule Preferences Among Parents of Young Children

- A cross-sectional, internet-based survey of a nationally representative sample of parents of children 6 months to 6 years of age
- More than 1 of 10 parents of young children currently use an alternative vaccination schedule
  - Non-black race and not having a regular provider associated with increased odds of alternative schedule
- A large proportion of parents currently following the recommended schedule seem to be “at risk” for switching to an alternative schedule
  - 28% believe delaying vaccine doses was safer than the schedule they used
  - 22% disagreed that the best schedule to follow is the one recommended by the experts

Dempsey et al Pediatrics 2011

Alternative Vaccination Schedule Preferences Among Parents of Young Children

Vaccine	Proportion of Parents, %[a]		
	Refused This Vaccine*	Delayed This Vaccine to Age Older Than Recommended**	Provided Doses of This Vaccine Over Prolonged Dosing Interval***
H1N1	86	34	13
Seasonal influenza	76	35	13
Varicella	46	44	22
Rotavirus	44	16	17
Pneumococcal conjugate	31	10	33
Hepatitis B	28	31	29
Measles-mumps-rubella	26	54	45
Hepatitis A	24	24	13
Haemophilus influenzae type b	15	17	21
Diphtheria-tetanus-acellular pertussis	6	24	43
Polio	6	16	32

[a] Weighted proportions. Parents could select >1 vaccine; therefore, responses do not sum to 100%.

* Among parents who reported refusing some vaccines (unweighted $N = 60$).

** Among parents who reported delaying some vaccines (unweighted $N = 63$).

*** Among parents who reported allowing a longer time interval between vaccine doses (unweighted $N = 36$).

Dempsey et al Pediatrics 2011

Parents With Concerns About Immunizations; NIS 2003-2004

- 13.4% delayed their child's vaccination; 8.9% accepted vaccination although doubted it was the best thing to do;, and 6.0% refused a vaccination for their child
- Delayed status
  - significantly associated with child's age (≤24 months), number of children (≥2) in the household, maternal marital status (not married), and concern that a vaccination might not be safe
  - "child was ill" was the most common reason for delaying any vaccine, including PCV
- Refused status
  - associated with child's age (>24 months), maternal race/ethnicity (white), and concern that a vaccination might not be safe
  - safety concerns were the most common reason for refusing vaccines, including PCV

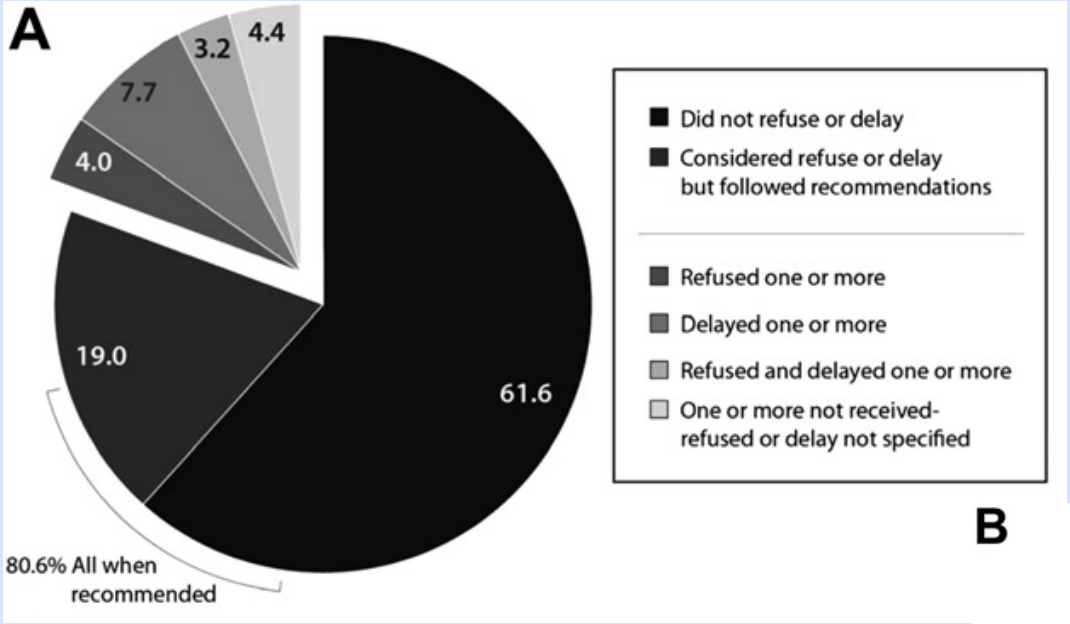
Gust et al Pediatrics 2011

Prevalence of Parental Concerns About Childhood Vaccines: The Experience of Primary Care Physicians

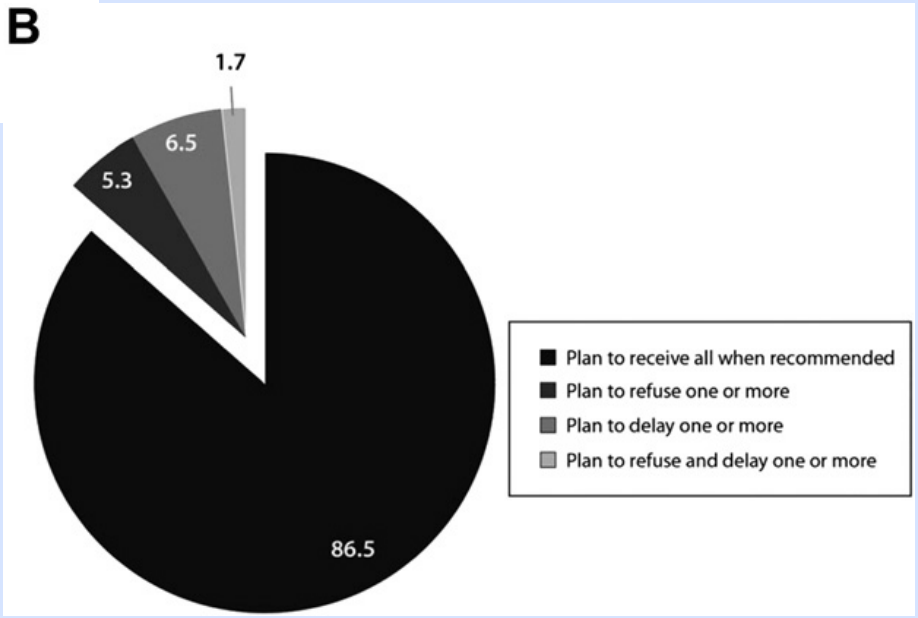
- Survey of nationally representative samples of pediatricians and family medicine physicians (N=696), February to May 2009
- 8% of physicians reported that ≥10% of parents refused a vaccine
- 20% reported that ≥10% of parents requested to spread out vaccines in a typical month
- 64% of all physicians would agree to spread out vaccines in the primary series at least sometimes

Kempe et al Amer J of Prevent. Med 2011

Vaccine Refusals or Delays: A National Telephone Survey of Parents of 6- Through 23-Month-Olds, 2010



Received ≥1 dose of recommended vaccines (N=1453, 96.6%)



- Among those who followed vaccine recommendations (n=1117), 94.9% were very or somewhat comfortable with the recommended number of childhood vaccines
- Among those who did not follow the recommendations (n=383), 54% were very or somewhat comfortable ($p<0.001$)

McCauley Academic Peds 2012

Summary: Parental Acceptance of Vaccines

- The majority of parents surveyed adhere to and do not have concerns about the recommended schedule
- Parent decisions do lead to delays (13%-25%) or refusals (6%-10%) for one or more recommended vaccine doses
- Parents who delay and refuse vaccine doses are more likely to have concerns about vaccine safety or multiple injections at each visit
- Parents who follow recommended schedule also report exhibiting doubts and have considered alternative schedules or refusing vaccine doses in the future
- Unclear whether removing a PCV dose at 6 months (i.e. 2+1) or 12-15 months (i.e. 3+0) will help reduce refusals or delays of other recommended vaccines

Work Group Conclusions

- GRADE review suggests that 3-dose schedules are likely equivalent to a 4-dose schedule
- Evidence from countries using 3-dose schedules is reassuring
- 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
- The Work Groups is not prepared to make a specific policy recommendation at this time:
  - Including a 3-dose PCV13 schedule for routine use among infants requires careful consideration of implementation issues
  - Further discussion is needed to define groups to be excluded from potential policy change and potential impact on non-adherence

Next steps: Groups to be excluded from potential policy change and rationale for exclusion

- American Indian/Alaska Native populations
  - health disparity from pneumococcal disease
  - history of ACIP recommendations specific to AI/AN people
  - discussion on what population groups to include
- Children with underlying medical conditions
  - Disparity in disease incidence
  - Lower PCV effectiveness or reduced immune response compared to healthy children
  - Discussion on what groups to exclude and clear communication strategies
  - Implementation issues related to timing of diagnosis and schedule selection

Next steps: Policy Options

The WG will give further consideration to the following policy options (in no particular order):

Option 1: 2+1 for routine use, 3+1 for high-risk groups (to be defined)

Option 2: 3+0 for routine use, 3+1 for high-risk groups (to be defined)

Option 3: 3-dose schedules (2+1 or 3+0) for routine use, 3+1 recommended at provider discretion for healthy infants, 3+1 for high-risk groups (to be defined)

Option 4: 3+1 for routine use, 3-dose schedules (2+1 or 3+0) optional for healthy infants, 3+1 for high risk groups

Option 5: Status quo

Discussion

- What are the gaps in information to consider including a 3-dose PCV13 schedule?
  - Provider/practice level issues
  - Public health program level issues
  - Parent considerations
- What specific concerns does the committee have about potentially including a 3-dose PCV13 schedule for routine use among infants?