Considerations for Age-based Recommendations for Pneumococcal Conjugate Vaccine for Adults: GRADE of Evidence

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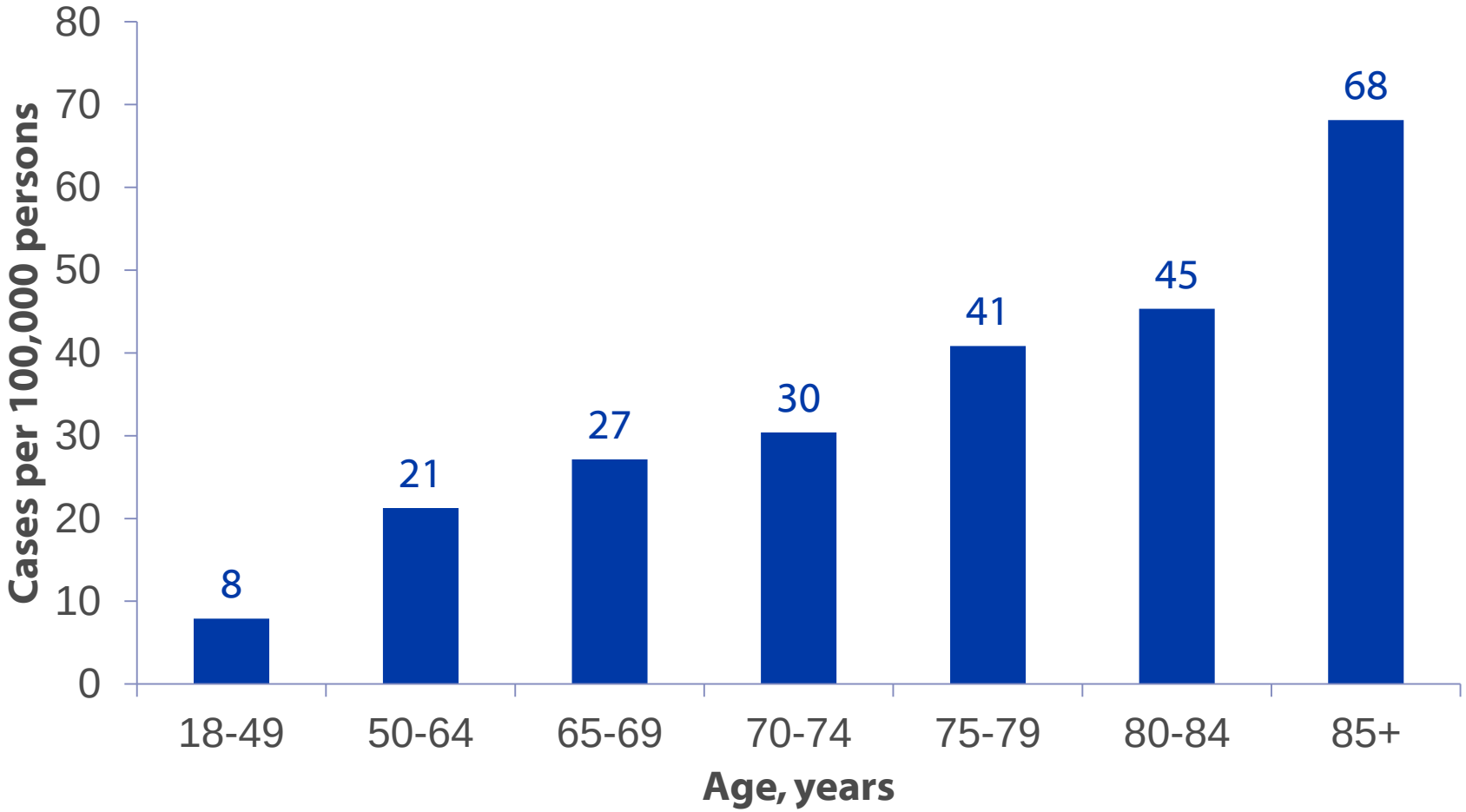
Incidence of Invasive Pneumococcal Disease among all adults, U.S., 2009



CDC, ABCs, unpublished, 2012

ACIP Recommendations for Use of Pneumococcal Polysaccharide Vaccine (PPSV23) in Adults

- All adults 65 yrs and older
- Adults 19-64 years old with the following conditions

Immunocompetent	Chronic Heart Disease Chronic Lung Disease Diabetes mellitus CSF Leaks Alcoholism Cigarette Smoking Asthma
Asplenia (functional/anatomic)	Sickle Cell Congenital or acquired asplenia
Immunocompromised	HIV Hematological Cancer Solid Cancer Transplant

Advisory Committee on Immunization Practices, MMWR 2010

GRADE Process Followed by the Work Group

1. Formulate specific policy question
2. Identify & rank relative importance of outcomes
3. Summarize relevant evidence for each outcome, including NNV (where possible)
4. Assess quality of evidence for each outcome
5. Summarize quality of evidence across outcomes
6. Review health economic data
7. Assess the balance of risks & benefits
8. Determine the recommendation category

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Step 1: Formulate the Policy Question

Should PCV13 be administered routinely to all adults 65 years of age or older?

- Population: Adults 65 years of age or older
- Intervention: 13-valent pneumococcal conjugate vaccine (PCV13) administered as a single dose injection
- Control: 23-valent pneumococcal polysaccharide vaccine (PPSV23)

Rationale for Considering PCV13 Use among Persons ≥65 Years Old

- Burden remains high among adults ≥65 years old
  - 1.4 million hospital days due to pneumococcal pneumonia *
  - 15,000 invasive pneumococcal disease cases and 2,600 deaths**
- ACIP universal recommendations for PPSV23 target this group
- Randomized controlled trial of PCV13 in the Netherlands targets this age group

* Huang et al . Vaccine 2011

**Active Bacterial Core Surveillance, 2010

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Step 2. Identify and Rank Relative Importance of Outcomes

- Which outcomes are important or critical for making a recommendation?
- How important is each outcome to prevent?
- Are data available to evaluate each outcome?
- Pneumococcal WG members queried and responses summarized

Step 2. Critical & Important Outcomes Identified by the Pneumococcal Work Group

Outcome	Importance	Include in Evidence Profile ?	Data available?
Invasive disease[a]	Critical	Yes	Yes
Pneumococcal pneumonia	Critical	Yes	No
Hospitalizations	Critical	Yes	No
Deaths	Critical	Yes	No
Serious adverse events	Critical	Yes	Yes
Systemic adverse events	Critical	Yes	Yes
Immunogenicity	Important	Yes	Yes
Office visits	Important	No	
Local reactions	Important	No	
Cost-effectiveness	Important	No	

[a]Sterile site isolation

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Step 3. Critical Outcome: Invasive Pneumococcal Disease (IPD)

- IPD = isolation of pneumococcus from a normally sterile site
- Double-blind, randomized, placebo-controlled
- Efficacy trial among HIV-Infected Adults in Malawi (N=496)
- All enrolled subjects had recovered from documented IPD
- 2 doses of PCV7 given 4 weeks apart

Endpoint	Vaccine Efficacy (95% CI)
PCV7-serotype IPD	74% (30%, 90%)

What effect might we expect among persons ≥65 years old in the US?

French N, et.al. *N Engl J Med* 2010;362:812-22.

How many persons ≥65 years old would need to be vaccinated to prevent a single case of PCV13-type IPD?

Number-needed-to vaccinate (NNV) =

$1 / (Rate_{unvaccinated} - Rate_{vaccinated})$

- $Rate_{unvaccinated}$ = 14 cases per 100,000 population[1]
- Assume efficacy against PCV13-type IPD = 74% (30%, 90%)[2]
- $Rate_{vaccinated}$ = 3.6 cases per 100,000 population (range 1.4-9.8)
- NNV = 9,653 (7,937-23,810)
- Caveat: NNV estimated based on efficacy vs. placebo. NNV would be higher if compared to PPSV23.

1. PCV13-type IPD rate among adults ≥65 years old in the US. CDC, ABCs, 2010
2. French N, et.al. *N Engl J Med* 2010;362:812-22.

Step 4. Assess Quality of Evidence for each Outcome

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

Step 4. Quality of Evidence for Invasive Pneumococcal Disease

Number of studies	Risk of bias	Inconsis-tency	Indirectness	Impreci-sion	Quality of evidence
RCT (1)	No serious	N/A	Very serious	No serious	3

Indirectness due to

1) Different population (immunocompromised, Malawi[1])
2) Different intervention (PCV7, 2 doses)
3) Different comparison group
   a. Placebo instead of PPSV
   b. PPSV efficacy against IPD among older adults = 50-80%[2]

1. French N, et.al. *N Engl J Med* 2010;362:812-22.
2. ACIP Recommendations for PPSV23, 2010

Outcomes for which data were not available

Outcome	Importance	Include in Evidence Profile ?	Data available?
Invasive disease	Critical	Yes	Yes
Pneumococcal pneumonia	Critical	Yes	No
Hospitalizations	Critical	Yes	No
Deaths	Critical	Yes	No
Serious adverse events	Critical	Yes	Yes
Systemic adverse events	Critical	Yes	Yes
Immunogenicity	Important	Yes	Yes
Office visits	Important	No	
Local reactions	Important	No	
Cost-effectiveness	Important	No	

Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults

E. Hak[1,2*], D.E. Grobbee[1], E.A.M. Sanders[2], T.J.M. Verheij[1], M. Bolkenbaas[1], S.M. Huijts[1], W.C. Gruber[3], S. Tansey[3], A. McDonough[3], B. Thoma[3], S. Patterson[3], A.J. van Alphen[4], M.J.M. Bonten[1,5]

- Randomized placebo-controlled trial (1:1)
- 85,000 community-dwelling, pneumococcal vaccine naïve adults ≥65 years
- Primary objective: efficacy against 1st episode of vaccine serotype community-acquired pneumonia (CAP)
- Secondary objectives: efficacy against non-bacteraemic VT CAP and VT IPD, all pneumococcal CAP, death
- Results expected in 2013

Step 3. Critical outcome: Serious Adverse Events

Outcome	No. of subjects (# studies)	Number of events (%)	Results
Overall SAE Deaths	6,000 (8)	0.2-1.1% 16/6000 (0.003%)	• No difference between the treatment groups • No deaths considered vaccine related

Phase III studies, presented at February 2011 ACIP

Step 3. Critical outcome: Systemic Adverse Events

Outcome	No. of studies	Incidence in PPSV23 vaccinated	Incidence in PCV13 vaccinated	Risk Difference per 1000 (95% CI)
1) Fatigue	RCT (3) PCV13 phase III	43.3%	34.0%	-9.3 (-16.4, -2.2)
2) Rash		16.4%	7.3%	-9.1 (-14.3, -4.0)
3) New generalized muscle pain		44.7%	36.8%	-7.9 (-15.2,-0.6)
4) Use of medications to treat fever		17.5%	8.6%	-8.9 (-16.6,-1.9)

Presented by Pfizer at February 2011 ACIP

Step 4. Quality of Evidence for Serious and Systemic Adverse Events

Outcome	Design (# studies)	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Quality of evidence
Serious and systemic adverse events	RCT (3)	No serious	No serious	No serious	No serious	**1**

Step 3. Important Outcome: Immunogenicity

- No established correlates of protection for adults
- Immunogenicity non-inferior to currently licensed vaccine (PCV vs. PPSV23)
- Studies utilize different assays (ELISA vs. OPA) and analytic methods
- Studies differ in populations studied by age group, presence of comorbidities, and previous vaccination status

Step 3. Immunogenicity: PCV13 phase III studies

Study #	*N*	Population	PCV13 vs. PPSV23 comparison (OPA)
004	740	60 to 64 years PPSV23 Naïve	• PCV13 > PPSV23 for 9/13 types • PCV13=PPSV23 for 4/13 types
3005	924	≥70 years PPSV23 >5 years	• PCV13>PPSV23 for 11/13 types • PCV13=PPSV23 for 2/13 types

Presented by Pfizer at February 2011 ACIP

Step 3. Immunogenicity: PCV7 published studies

Author	*N*	Population	PCV7 vs. PPSV23 comparison (ELISA)
Goldblatt, 2009	599	50 to 80 years No PPSV23 ≤5 years	• PCV7 = PPSV23 for 3/7 types • PCV7 > PPSV23 for 3/7 types • PCV7<PPSV23 for 1/7 types
De Roux, 2008	217	>70 years PPSV Naïve	• PCV7 = PPSV23 for 1 type • PCV7>PPSV23 for 6/7 types
Ridda, 2009	241	>60 years, frail PPSV Naïve	• PCV7 = PPSV23 for 4/4 types tested • Comparisons of other 3 types not done
Miernyk, 2009	203	55 to 70 years, Alaska Native PPSV Naïve	• PCV7 = PPSV23 for 4/4 types tested • Comparisons of other 3 types not done

Key point: Response to a single dose of PCV7 similar to that of PPSV23 in most studies, superior to PPSV23 for some studies.

Step 4. Quality of Evidence for Immunogenicity

Number of studies	Risk of bias	Indirectness	Quality of evidence
Phase III RCT (2)	No serious	Serious	2
PCV7 RCT (4)	No serious	Serious	2

Indirectness due to different outcome (antibody response without defined correlates of protection)

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Step 5. Summarize quality of evidence across outcomes

Comparison	Outcome	Study Design (# studies)	Findings	Quality of evidence	Overall evidence type
PCV7 vs. No vaccination	IPD	RCT (1)	Decreased risk among vaccinated	3	
PCV13 vs. PPSV23	Immunogenicity	RCT (2)	Response improved for PCV13 vs. PPSV23 or no difference	2	3
PCV7 vs. PPSV23	Immunogenicity	RCT (4)	Response improved for PCV7 vs. PPSV23 or no difference	2	
PCV13 vs. PPSV23	Serious and systemic adverse events	RCT (3)	No difference or decreased risk with PCV13	1	

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Step 6. Review health economic data

- Two independent models evaluating CE and public health impact of PCV13 for adults[1,2]
- The models show that PCV13 in adults could be highly cost-effective
- Both models rely heavily on assumptions about indirect effects of PCV13 on non-bacteremic pneumonia and PCV13 efficacy against pneumonia
- Current PPSV strategy is favored if PCV13 effectiveness is low against non-bacteremic pneumonia
- Results sensitive to assumptions regarding
  - PCV13 effectiveness against noninvasive pneumonia
  - PPSV effectiveness against IPD
  - Herd immunity effects on the likelihood of PCV13-type disease

[1]Smith et al. JAMA 2012 in press
[2]Weycker et al. Manuscript in preparation

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Step 7-8. Determine the Recommendation Category

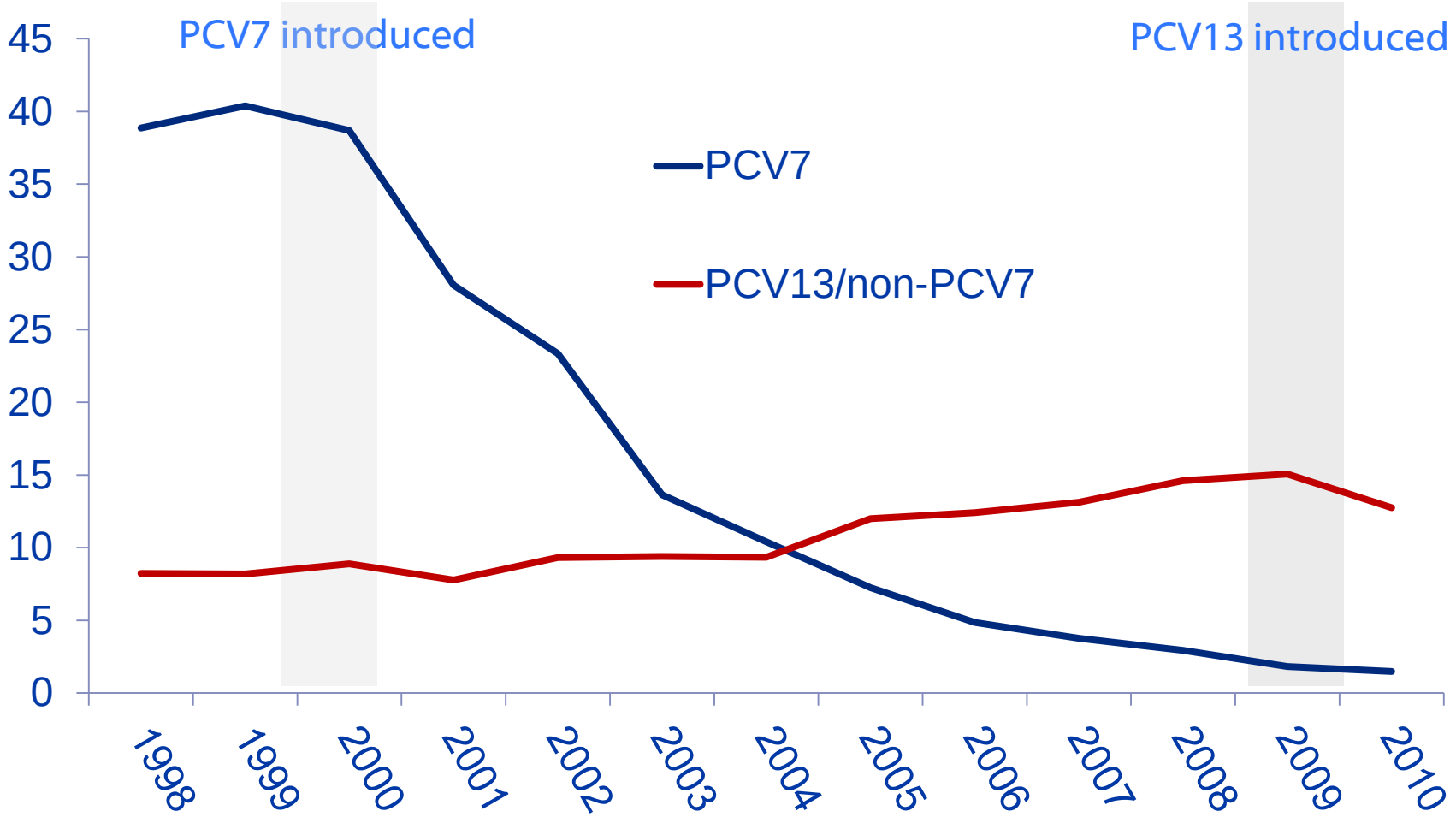
	Y/N	Comments
Is the evidence type/quality of evidence considered to be lower?	Y	- Limited data on efficacy against IPD (1 RCT in HIV+) - Missing data on 3 of 4 critical outcomes
Is there uncertainty about the balance of benefits versus harms and burdens?	Y	Uncertainty about the balance: 1) Indirect effects would reduce net benefits 2) Efficacy against pneumonia unknown
Is there high variability or uncertainty in relative importance assigned to outcomes?	N	- General consensus reached on which outcomes are critical - All critical outcomes assigned high values
Is there uncertainty about whether the net benefits are worth the costs?	Y	Uncertainty about whether the net benefits are worth the costs

WG decision: No recommendation at this time because critical data not yet available

Key factor not accounted for by GRADE process

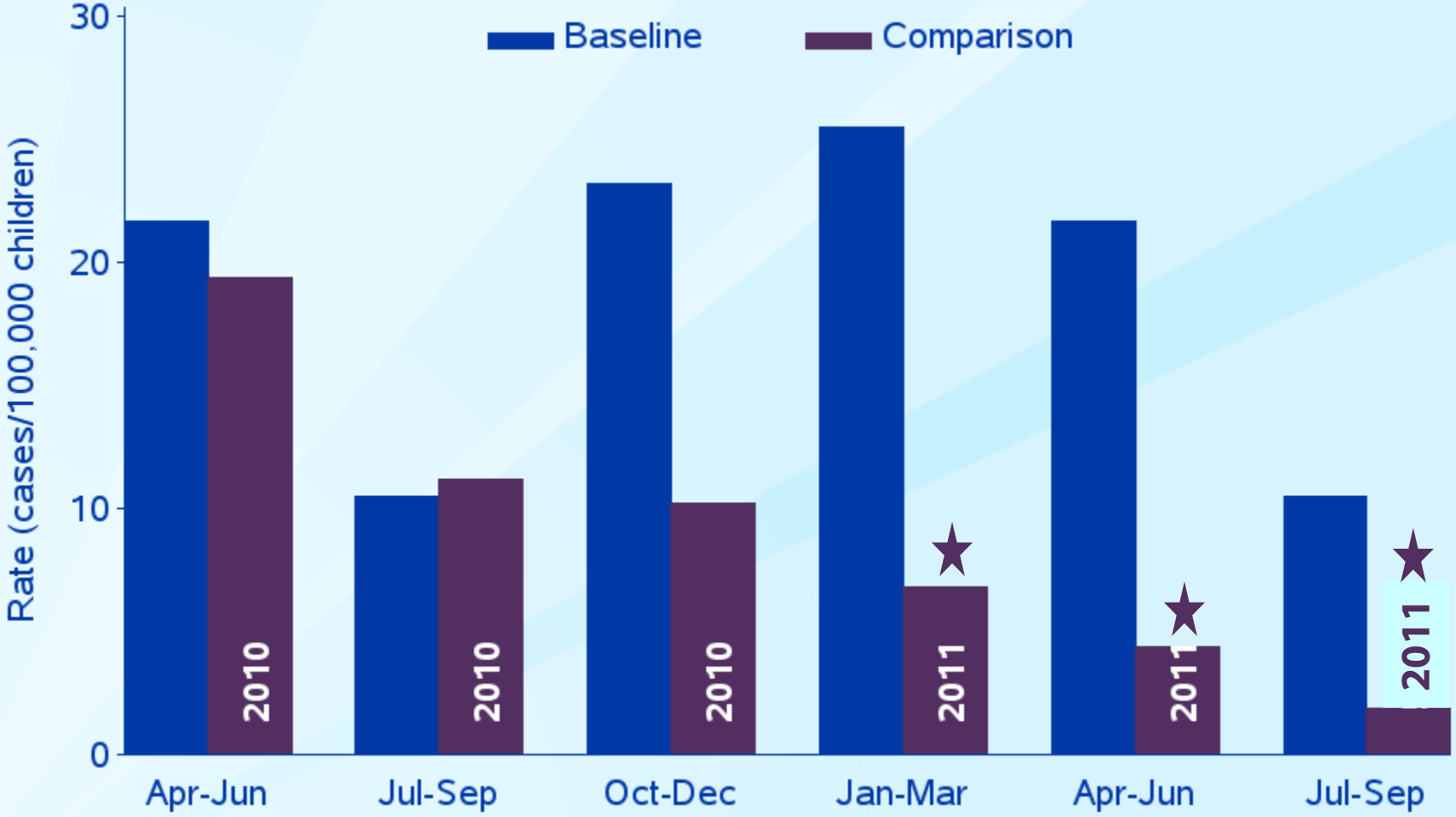
- Indirect effects of pediatric PCV13 program may reduce the proportion of adult IPD caused by PCV13 types
- The net benefits of PCV13 use among adults would be reduced

Incidence of Invasive Pneumococcal Disease Among Adults ≥65 Years by Serotype, 1998-2010



ABCs unpublished data, continuous sites

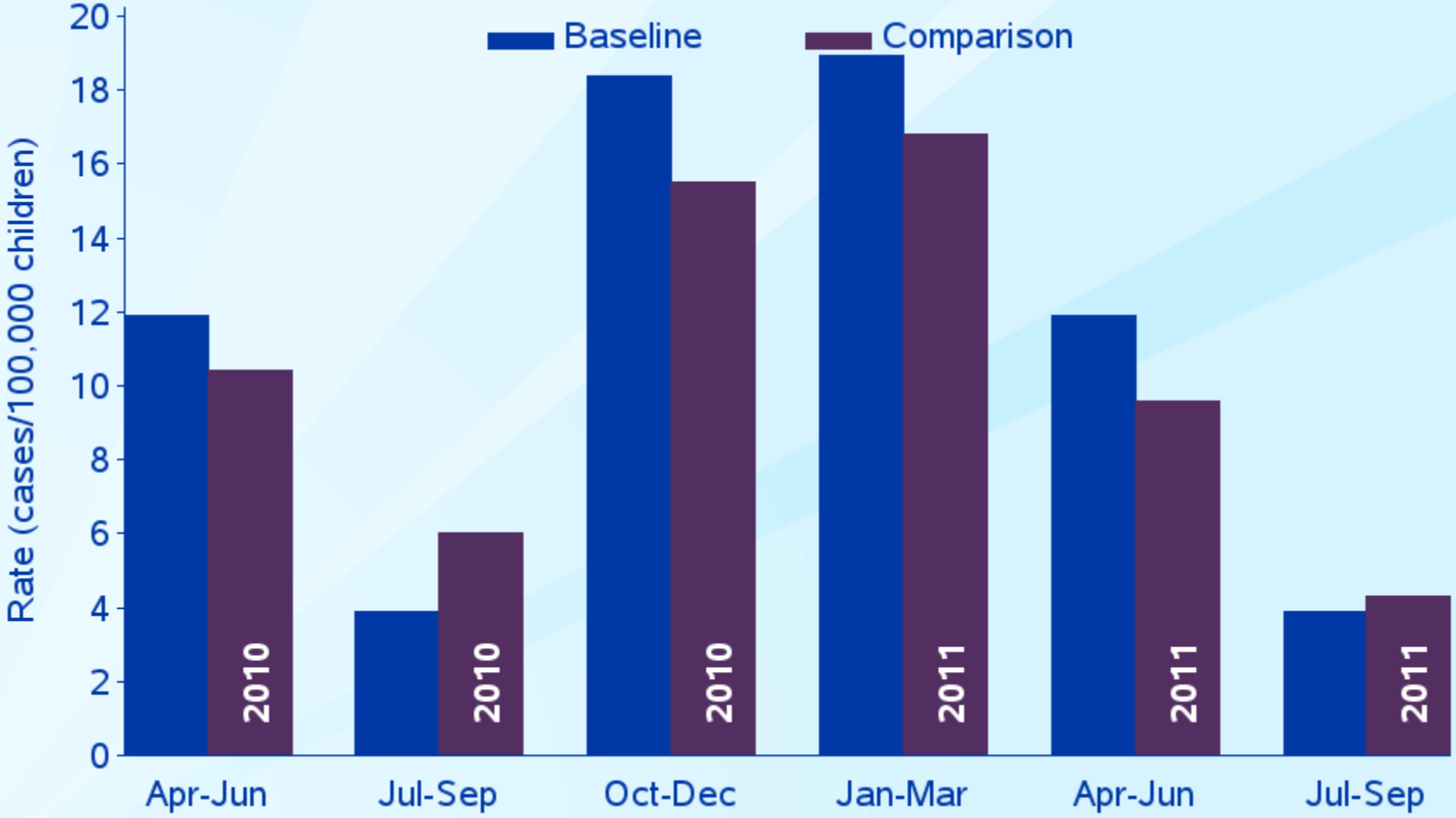
Rates of PCV13/non-PCV7 serotype IPD in children <2 years, 2006-2008 vs. 2010 and 2011, by quarter



Source: Active Bacterial Core surveillance (ABCs), unpublished

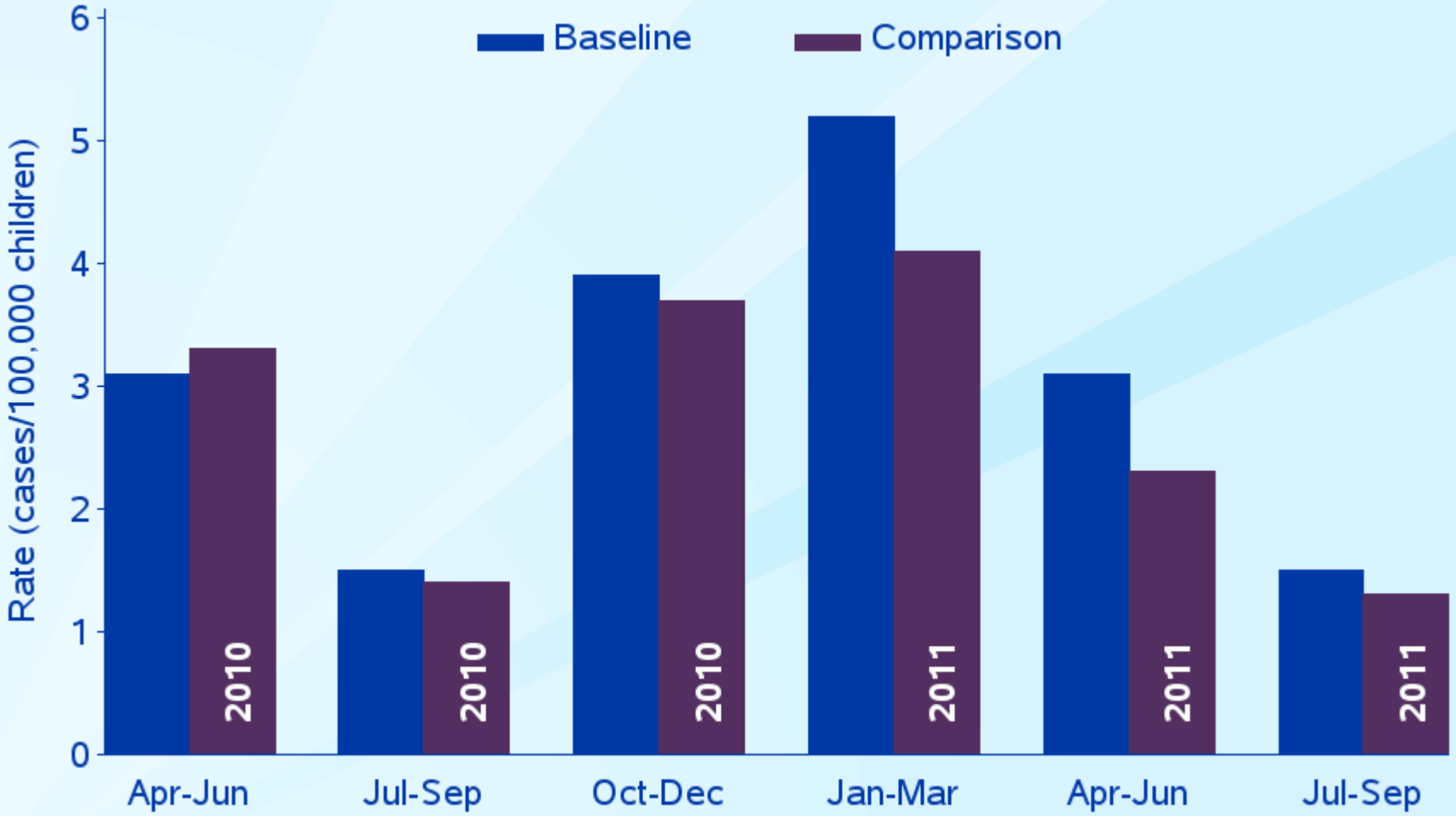
★ P<0.0001

Rates of PCV13/non-PCV7 serotype IPD in adults 65+ years old, 2006-2008 vs. 2010 and 2011, by quarter



Source: Active Bacterial Core surveillance (ABCs), unpublished

Rates of PCV13/non-PCV7 serotype IPD in adults 18-49, 2006-2008 vs. 2010 and 2011, by quarter



Source: Active Bacterial Core surveillance (ABCs), unpublished

Indirect Effects on Invasive Disease

- PCV7 introduction led to near elimination of PCV7-type IPD among adults of all age groups
- Significant declines in PCV13-type IPD in children within 1st year post-PCV13 introduction
- Possible early evidence of declines in PCV13-type IPD in adults
- Recent data show that PCV13 prevents colonization with PCV13 serotypes.[1,2]

Key point: Indirect effects of PCV13 on adult IPD are likely to be observed

1. R. Cohen, ICAAC 2011
2. A. Desai, ISPPD 2012

PCV13 age-based recommendations: Work Group consensus

At this time, the available evidence is insufficient to recommend routine use of PCV13 among older adults

- Critical data elements for the ACIP recommendation to be made are not available at this time
  - the indirect effects of PCV13 use in children on adult disease incidence
  - results from the CAPITA trial
- Clinical relevance of immunogenicity data unclear without defined correlate of protection
- Cost-effectiveness data relies heavily on assumptions of efficacy against pneumonia and potential indirect effects

Next steps

- Evaluating relevant new data as they become available
  - impact of pediatric PCV13 program on disease burden and serotype distribution among adults
  - efficacy trial against pneumonia (CAPITA)
- Update ACIP during upcoming meetings
- Publish MMWR
- Revisit age-based recommendations as additional data become available

Acknowledgements

ACIP members

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Thank you