13-valent Pneumococcal Conjugate Vaccine Use in Adults with Immunocompromising Conditions: GRADE of Evidence

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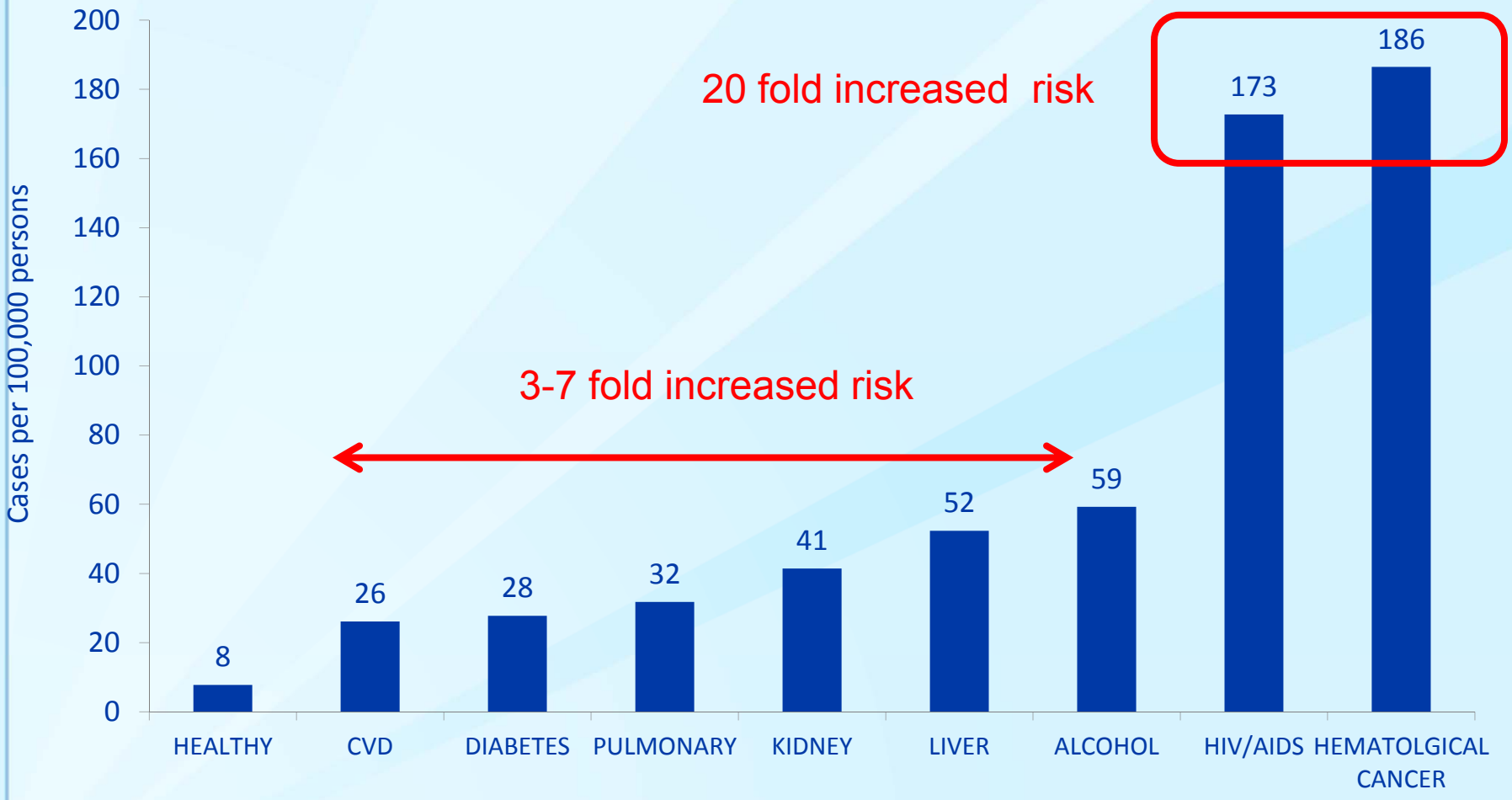
Policy question considered by Pneumococcal Working Group:

Should ACIP recommend PCV13 for immunocompromised adults?

Incidence of IPD in adults aged 18--64 years with selected underlying conditions, United States, 2009



Kyaw, JID 2005;192:377-86

Questions for the ACIP

- Does ACIP agree with the Working Group's GRADE evaluation of the evidence supporting a recommendation for use of PCV13 in immunocompromised adults?

- What additional issues should the Working Group consider before bringing a recommendation for a vote?

GRADE Process Followed by the Work Group

1. Formulate specific policy question
2. Identify & rank relative importance of outcomes
3. Summarize all evidence for critical & important outcomes 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 specific policy question

"Should PCV13 be administered routinely to adults with immunocompromising conditions?"

- Population: Adults ≥18 years-old with immunocompromising conditions
- Intervention: Pneumococcal conjugate vaccine (PCV13) administered as a single dose injection
- Control: Pneumococcal polysaccharide vaccine (PPSV23)
- Outcomes: See Step 2

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

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	

*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
- All enrolled subjects (n=496) had recovered from documented IPD
- 2 doses of PCV7 given 4 weeks apart

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

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

What effect might we expect among HIV-infected adults in the U.S.*?*

Number-Needed-to Vaccinate=

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

- $Rate_{unvaccinated}$ = 64 cases per 100,000[1]
- Efficacy PCV13-type IPD = **74**% (30%--90%)[2]
- $Rate_{vaccinated}$ = 17 per 100,000 (6.4--44.8)

NNV = 2,011 (1,736--5,208)

1. Cohen, AIDS 2010;24(14):2253-62
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

Outcome	Design (# studies)	Risk of bias	Inconsis-tency	Indirectness	Impreci-sion	Quality of Evidence
IPD	RCT (1)	No serious	N/A	Very serious	No serious	**2/3**

Indirectness due to

1) different population (Malawi, IPD survivors, limited ARVs[1])
2) different intervention (PCV7, 2 doses)

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

Step 3. Critical Outcome: Serious Adverse Events

Outcome	No. of subjects (# studies)	Number of events (%)	Results
Overall SAE	6,000	0.2%--1.1%	• No difference between the treatment groups
Deaths	(8)	16/6000 (0.003%)	• 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	3 (RCT 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 2011 ACIP

Step 3. Critical outcome: Systemic Adverse Events

Outcome	No. of studies	Incidence in PPSV23 vaccinated	Incidence in PCV7 vaccinated	Results
Mild, self- limited secondary effects	3 (Penaranda Lesprit Feikin)	20%	34%	No serious adverse events No differences in SAEs reported p=0.07

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 & systemic adverse events	RCT (6)	No serious	No serious	Serious	No serious	**2**

Indirectness due to

1) Different population in Phase III (not immunocompromised)
2) Different intervention (PCV7)

Step 3: Immunogenicity: PCV7 Published Studies

Author	N	Population	PCV7 vs. PPSV23 comparison (ELISA)
Feikin 2004, USA	67	CD4 ≥ 200	PCV = PPSV (4/5) PCV > PPSV (1/5) at 8 wks
Lesprit 2007,France	208	CD4=200-500 Stable ARV	PCV = PPSV (6/9) at 8 wks
Penaranda 2010, Spain	220	CD4=200-400	PCV= PPSV at 4wks
Crum 2010, USA	204	Pre PPSV CD4 U 533	PCV> PPSV at 4wks PCV= PPSV at 26wks

Key point: Response to a single dose of PCV7
Non inferior or superior to that of PPSV23

Step 3: Immunogenicity: PCV13 Phase III Studies

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

Presented by Pfizer at February 2011 ACIP

Step 4. Quality of Evidence for Immunogenicity

Outcome	Design (# studies)	Risk of bias	Indirectness	Quality of Evidence
Immuno-genicity	PCV7 RCT (4)	No serious	Serious	**2**
Immuno-genicity	PCV13 RCT (2) (Phase III)	No serious	Very Serious	**3**

Indirectness due to

1) different outcome (antibody response without defined correlates of protection)
2) different population in Phase III (not immunocompromised)

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Step 5. Summarize quality of evidence across outcomes

Comparison	Outcome	Study Design	Findings	Quality of Evidence	Overall Quality of Evidence
PCV7 vs. No vaccination	IPD	RCT (1)	Decreased risk among vaccinated	**2/3**	**2/3**
PCV13 vs. PPSV23	Serious & Systemic adverse events	RCT (6)	No difference; Significantly fewer systemic for PCV13	**2**	
PCV13 vs. PPSV23	Immunogenicity	RCT (2)	Response similar for some types, superior with PCV13 for others	**3**	
PCV7 vs. PPSV23	Immunogenicity	RCT (4)	Response similar for some types, superior with PCV7 for others	**2**	

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Step 7&8. Determine Recommendation Category

Question	Response	
Is the evidence level/quality “Lower“?	**Yes**	Indirectness & lack of evidence for 3 of 4 critical disease outcomes
Is there uncertainty about the balance of benefits versus harms & burdens?	**No**	Very high burden of disease in immunocompromised
Is there variability or uncertainty in what is important?	**No**	WG Consensus on critical outcomes
Is there uncertainty about whether the net benefits are worth the costs?	**Yes**	Uncertainty regarding costs/benefits relative to PPSV23

Category B

Conclusions from the Pneumococcal Working Group

- Extremely high burden of disease among immunocompromised adults
- GRADE process led to conclusion that PCV13 is effective in this group & that benefits likely outweigh harms
- No additional data expected to influence GRADE conclusions for immunocompromised group
- Indirect effects of PCV13 use in children unlikely to eliminate PCV13 serotypes from immunocompromised adults

Working Group Next Steps

- Additional GRADE question: PCV13+PPSV23 vs. PPSV23
- Timing & Interval
- Sequence
- Reach consensus on conditions considered to be "Immunocompromising"
- Draft recommendation language for ACIP
- Possible vote June 2012

Questions for the ACIP

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- What additional issues should the Working Group consider before bringing a recommendation for a vote?

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