Current Recommendations for Pneumococcal Polysaccharide Vaccine for Immunocompromised Adults: GRADE of Evidence

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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

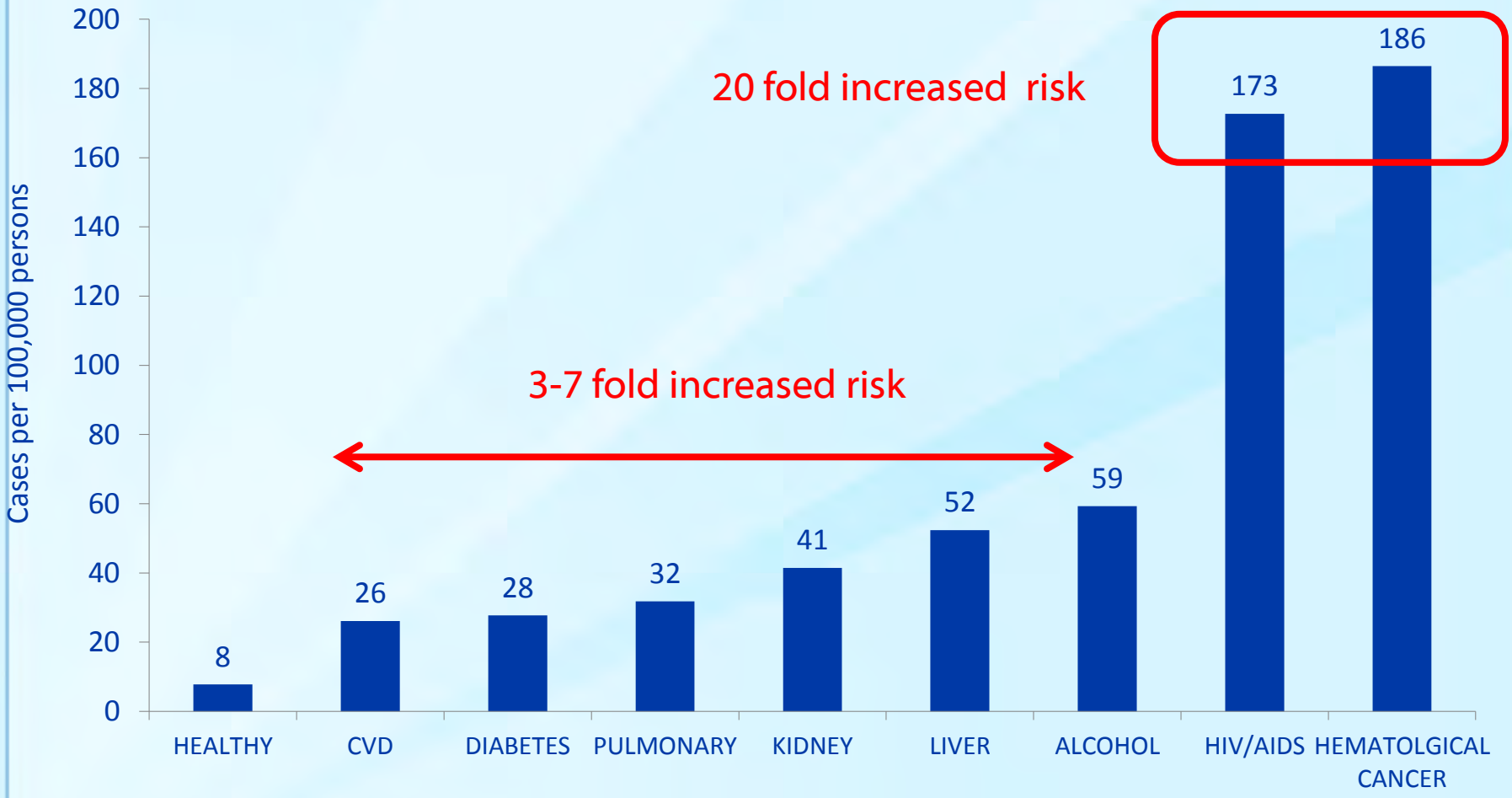
Immunocompetent	Chronic Heart Disease Chronic Lung Disease Diabetes mellitus CSF Leaks Alcoholism Cigarette Smoking Asthma
Asplenia (functional/anatomic)	Sickle Cell Congenital or acquired asplenia
Immunocompromised	HIV Hematological Cancer Solid Cancer Transplant

Advisory Committee on Immunization Practices, MMWR 2010

ACIP Recommendations for Revaccination with PPSV23

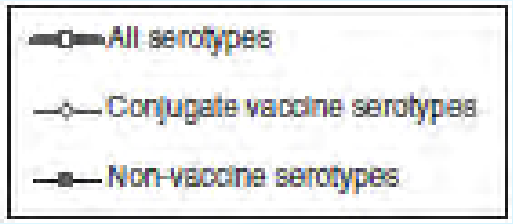
- Routine revaccination for most persons not recommended
- A second dose of PPSV23 is recommended 5 years after the first dose for persons aged 19–64 years with
  - Functional or anatomic asplenia
  - Immunocompromising conditions
    - Congenital or acquired immunodeficiencies
    - HIV infection
    - Chronic renal failure or nephrotic syndrome
    - Leukemias, lymphomas, Hodgkin disease
    - Generalized malignancy
    - Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids or radiation therapy
    - Solid organ transplantation
    - Multiple myeloma

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

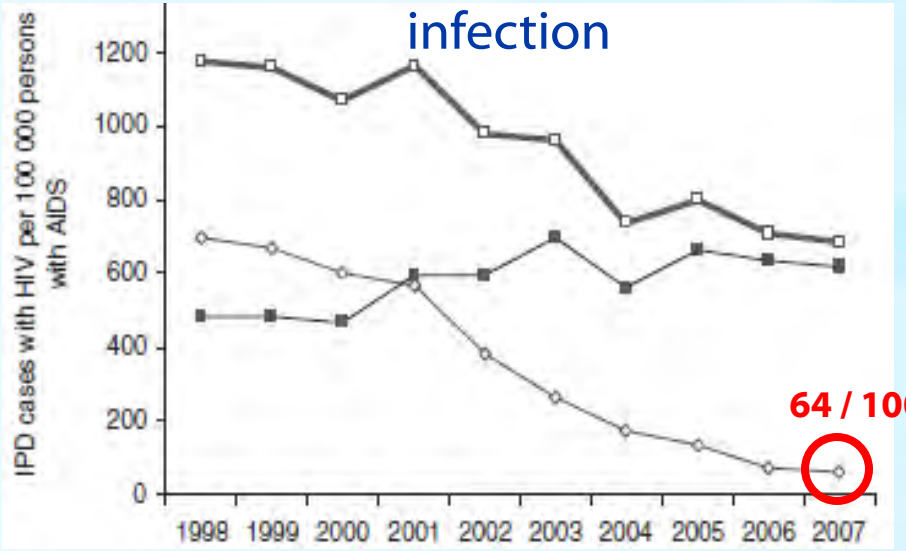


Kyaw, JID 2005;192:377-86

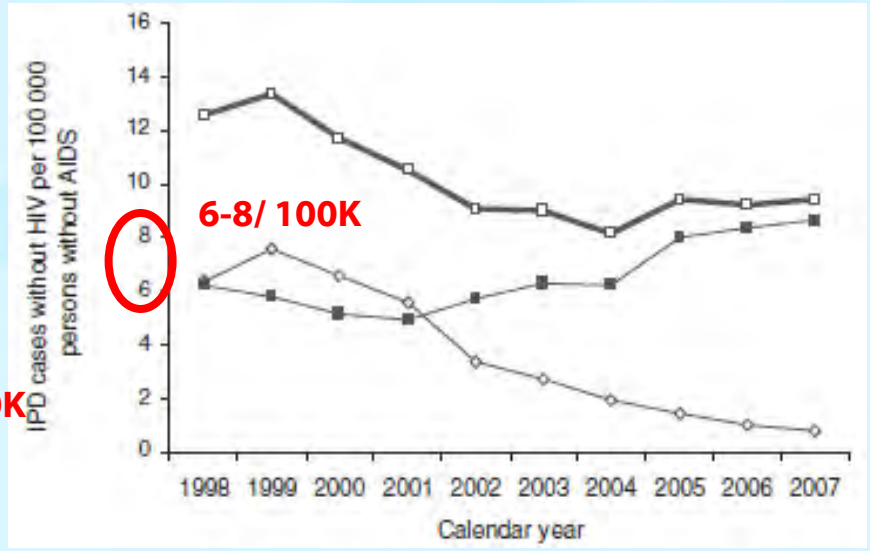
Trends in IPD rates among adults 18-64 yrs old with & without HIV-infection, before and after PCV7 introduction, 1998-2007



Adults with HIV infection



Adults without HIV infection



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

Why GRADE evidence for PPSV23 use among immunocompromised adults?

- PPSV23 is currently recommended for adults with immunocompromising conditions
- GRADE of evidence for PCV13 for immuocompromised adults compared PCV13 to PPSV23
- Demonstrated the need to systematically review and evaluate quality of evidence for PPSV23 use among immunocompromised adults

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

GRADE evaluation for current PPSV policy

Question of interest:

Should PPSV23 be administered routinely to **adults with immunocompromising conditions?**

Question formulated for GRADE:

Should PPSV23 be administered routinely **to adults with HIV?**

Rationale for GRADE of PPSV Use among Persons with HIV

- Chosen as a representative immunocompromising condition
- The majority of evidence from published studies available for adults with HIV
- The corresponding question for PCV13 use among immunocompromised adults was GRADEd for adults with HIV
- The risks of PPSV use would not be expected to be higher among adults with other immuocompromising conditions
- Limitation: The benefits may not be generalizable to all immunocompromised adults

Step 1: Formulate the Policy Question

Should PPSV23 be administered routinely to adults with HIV?

- Population: Adults 19 years of age or older with HIV
- Intervention: 23-valent pneumococcal polysaccharide vaccine (PPSV23) administered as a single dose injection
- Control: Placebo

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	Yes
Hospitalizations	Critical	Yes	No
Deaths	Critical	Yes	Yes
Serious adverse events	Critical	Yes	Yes
Systemic adverse events	Critical	Yes	Yes
Immunogenicity	Important	No	Yes
Office visits	Important	No	
Local reactions	Important	No	
Cost-effectiveness	Important	No	

[a]Sterile site isolation

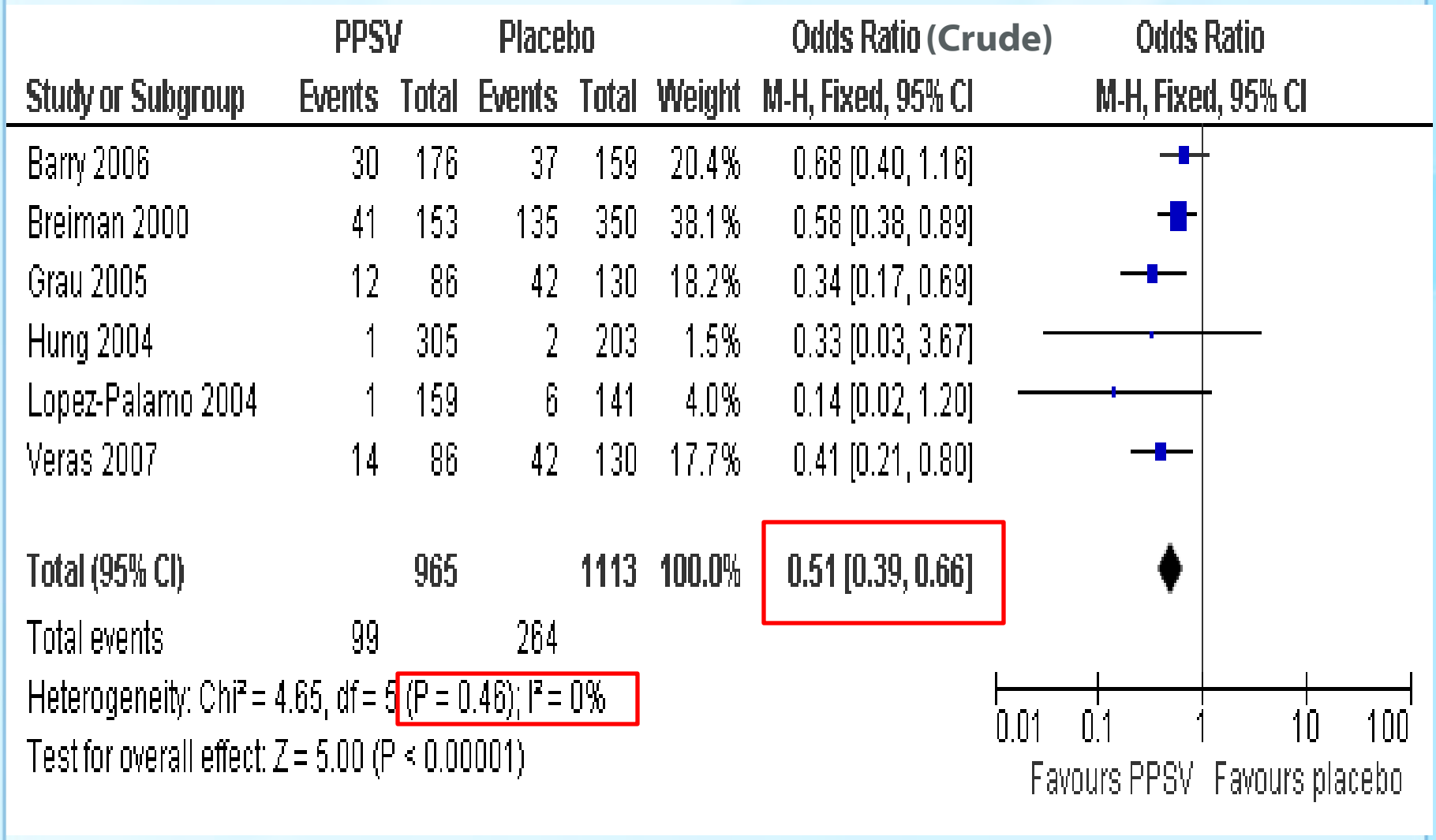
Step 3. Critical Outcome: Invasive Pneumococcal Disease (IPD)

- IPD = isolation of pneumococcus from a normally sterile site
- Double-blind, randomized, placebo-controlled trial
- Efficacy trial among HIV-Infected Adults in Uganda (N=1392)
- A single dose of PPSV23 or placebo given
- Follow up of the trial cohort; initial trial methods, blinding maintained

Endpoint=IPD	Vaccine Efficacy (95% CI)
Initial trial (French et al. 2000)	-48% (-232%, 35%)
Follow up (Watera et al. 2004)	-28% (-120%, 30%)

- PPSV NOT associated with decreased IPD risk
- Caveat: Generalizibility to US adults with HIV

Step 3. Critical Outcome: IPD Observational studies



How many HIV-positive adults 18 to 64 years old would need to be vaccinated to prevent a single case of IPD?

Number-needed-to vaccinate (NNV) =

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

- $Rate_{unvaccinated}$ = 155 cases per 100,000 population[1]
- Applied effectiveness against all IPD = 49% (34%, 61%)[2]
- $Rate_{vaccinated}$ = 79 cases per 100,000 population (range 53-95)
- **NNV = 1,316 (1,053-1,860)**
- Caveat: NNV based on vaccine effectiveness estimated from observational studies

1. IPD rate among adults HIV+ adults 18-64 years old in the US. CDC, ABCs, 2010
2. Summary estimate from 6 observational studies

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	Not serious	3
Observational (6)	Serious	No serious	No serious	No serious	4

Indirectness due to different population (highly immunocompromised, Uganda[1])

1. French N, et.al. 2000

Step 3. Critical Outcome: All-cause Pneumonia

- Pneumonia = acute (<28 days) respiratory illness with new pulmonary parenchymal shadowing on chest radiograph
- Double-blind, randomized, placebo-controlled trial
- Efficacy trial among HIV-Infected Adults in Uganda (N=1392)
- Follow up of the trial cohort; initial trial methods, blinding maintained

Endpoint=All-cause pneumonia	Vaccine Efficacy (95% CI)
Initial trial (French et al. 2000)	-102% (-245%, -19%)
Follow up (Watera et al. 2004)	-56% (-140%, 0%)

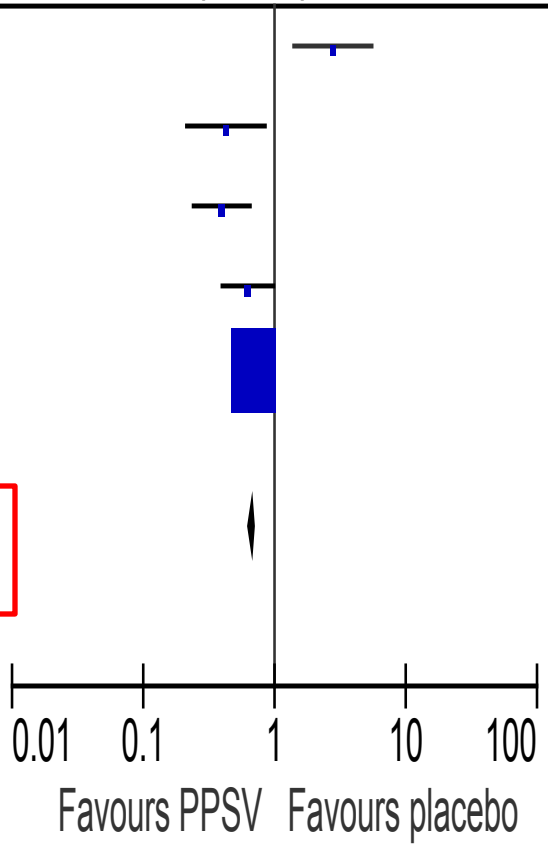
- PPSV NOT associated with decreased risk of pneumonia
- Caveat: Generalizibility to US adults with HIV

Step 3. Critical Outcome: All-cause pneumonia Observational studies

Study or Subgroup	PPSV Events	PPSV Total	Placebo Events	Placebo Total	Weight	Odds Ratio(Crude) M-H, Fixed, 95% CI
Hung 2004	42	305	11	203	0.5%	2.79 [1.40, 5.55]
Lopez-Palamo 2004	14	159	26	141	1.2%	0.43 [0.21, 0.86]
Penaranda 2007	20	151	162	583	2.7%	0.40 [0.24, 0.66]
Rodriguez-Barradas 2006	50	640	35	294	2.1%	0.63 [0.40, 0.99]
Teshale 2008	1650	11046	2485	12209	93.5%	0.69 [0.64, 0.74]
Total (95% CI)		**12301**		**13430**	**100.0%**	**0.69 [0.64, 0.73]**
Total events	1776		2719			

Heterogeneity: $Chi^2 = 22.36$, $df = 4$ ($P = 0.0002$); $I^2 = 82\%$

Test for overall effect: $Z = 11.16$ ($P < 0.00001$)



Step 4. Quality of Evidence for All-cause Pneumonia

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
Observational (5)	Serious	Serious	No serious	No serious	4

Indirectness due to different population (highly immunocompromised, Uganda[1])

1. French N, et.al. 2000

Step 3. Critical Outcome: Death

- Double-blind, randomized, placebo-controlled trial
- Efficacy trial among HIV-Infected Adults in Uganda (N=1392)
- Follow up of the trial cohort; initial trial methods, blinding maintained

Endpoint=Death	Vaccine Efficacy (95% CI)
Initial trial (French et al. 2000)	-8% (-33%, 13%)
Follow up (Watera et al. 2004)	16% (0%, 30%)

•PPSV associated with decreased risk of death ONLY on follow up study (Watera et al 2004); null findings for the initial trial (French et al 2000)

Step 4. Quality of Evidence for Death

Number of studies	Risk of bias	Inconsis-tency	Indirectness	Imprecision	Other considerations	Quality of evidence
RCT (1)	Not Serious	N/A	Serious	Not serious	Serious	3

- Indirectness due to different population (highly immunocompromised, Uganda[1])
- Other considerations: inconsistent findings on the follow up study; counter to biological plausibility

1. French N, et.al. 2000
2. Watera et al. 2004

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

- Post-licensure surveillance data
- No reports of severe febrile or anaphylactic reactions
- No neurologic disorders (e.g., Guillain-Barré syndrome) or deaths associated with PPSV
- Moderate systemic reactions (e.g., fever and myalgias) and severe local reactions (e.g., local induration) are rare

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

Step 5. Summarize quality of evidence across outcomes

Comparison	Outcome	Study Design (# studies)	Findings	Quality of evidence	Overall evidence type
PPSV23 vs. Placebo or No vaccination	IPD	RCT (1) Observational (6)	Negative VE among highly immunosuppressed; VE against all IPD 49% (34%, 61%) from observational studies	**3/4**	**3/4**
PPSV23 vs. Placebo or No vaccination	All-cause pneumonia	RCT (1) Observational (5)	Negative VE among highly immunosuppressed; VE 31% (27%, 36%) from observational studies	**3/4**	
PPSV23 vs. Placebo	Deaths	RCT (1)	Inconclusive data on efficacy against mortality	**3**	
PPSV23	SAE	Post-licensure surveillance	PPSV appears safe for use among adults with HIV	**3**	

Step 6. Review health economic data

- **CEA analysis in a setting of PCV use among children showed PPSV current policy (65 years or older and young adults with high-risk conditions) to be**
  - cost-effective (3,300/QALY) compared to no vaccination
  - Prevents IPD cases and deaths
- **Limitation: the model relies on assumptions regarding PPSV efficacy and post-PCV serotype distribution**
- **Uncertainty around cost effectiveness among immunocompromised adults**

Smith et al. Vaccine 2008

Step 7-8. Determine the Recommendation Category

	Y/N	Comments
Is the evidence type/quality of evidence considered to be lower?	Y	Inconsistent evidence for all-cause pneumonia; limited data from RCT not generalizable to the US HIV+ population
Is there uncertainty about the balance of benefits versus harms and burdens?	Y	Greater uncertainty about benefits; vaccine appears safe in this population
Is there high variability or uncertainty in relative importance assigned to outcomes?	N	WG consensus on which outcomes are important to prevent
Is there uncertainty about whether the net benefits are worth the costs?	Y	Cost-effectiveness in the general adult population demonstrated; uncertainty around the assumptions utilized in cost-effectiveness analyses

WG decision: Category B recommendation

Conclusions from the Pneumococcal Working Group

- High burden of disease among adults with immunocompromising conditions
- PPSV23 includes serotypes accounting for >70% of IPD in this group
- PPSV23 is effective against IPD in adults with HIV
- Inconsistent evidence for effectiveness against non-bacteremic pneumonia
- Vaccine is safe to use in these populations

Acknowledgements

ACIP members

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