

Pneumococcal Vaccines for Older Adults: What is the right approach?

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Senior Subject Matter Expert, IHRC Inc.

My background and funding

- ❑ US Centers for Disease Control and Prevention (CDC), retired July 1
- ❑ Current funding:
 - IHRC, Inc.: consultant for CDC
 - Limited-time consulting: Guidepoint, SutroVax, Inc

Pneumococcal vaccines for older adults

What is the right approach?

- ❑ Background -- why the need for vaccines for adults
- ❑ Considerations and reconsiderations for using conjugate vaccine-- the US experience
- ❑ What do we want from a pneumococcal vaccine for adults?

Colonization, Mucosal Disease, Invasive Disease

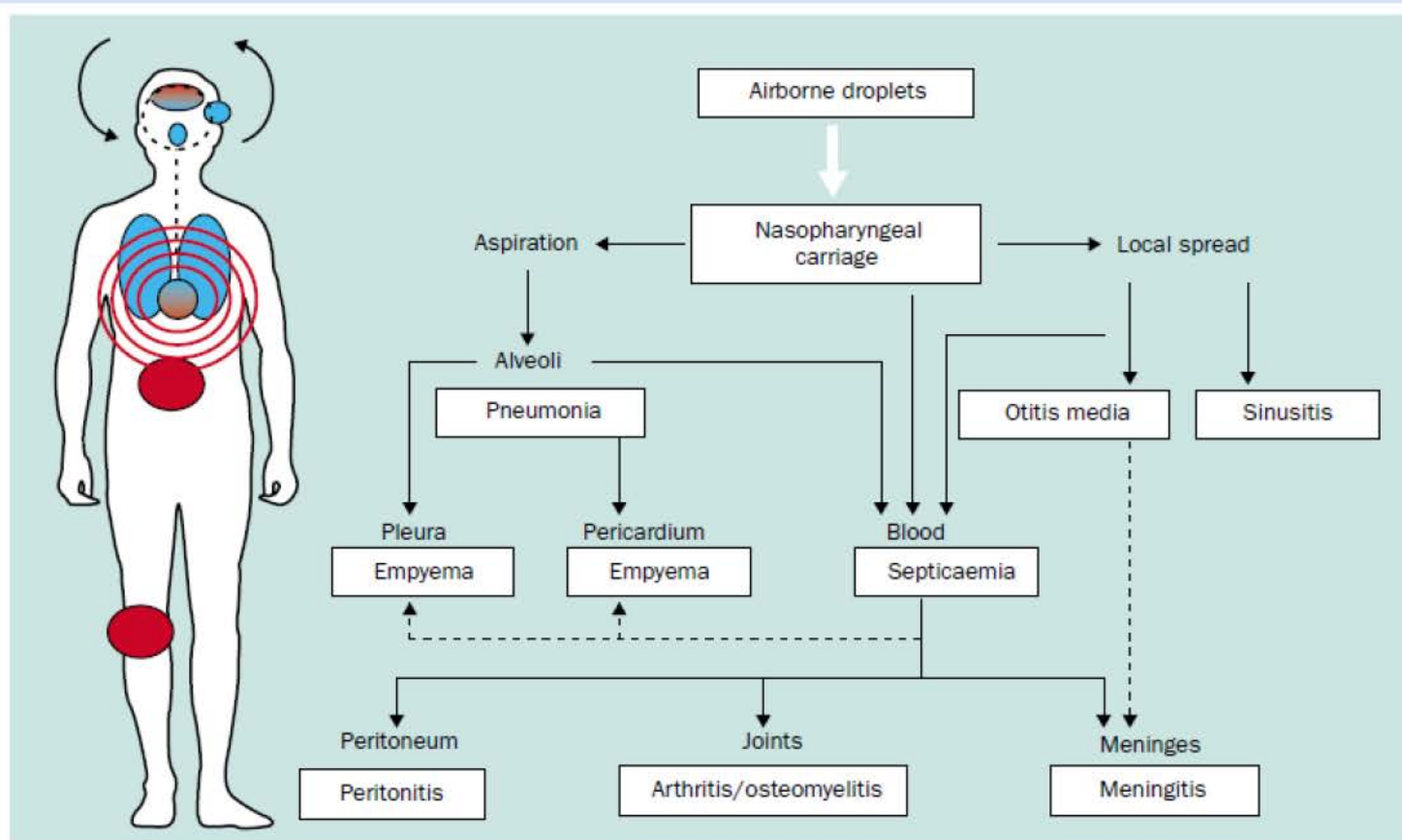


Figure 1. Pathogenic route for *S. pneumoniae* infection. Redrawn from reference 2. Organs infected through the airborne and haematogenous routes are depicted in blue and red, respectively.

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Bogaert, Lancet Infect Dis 2004;4:144-54

Colonization, Mucosal Disease, Invasive Disease

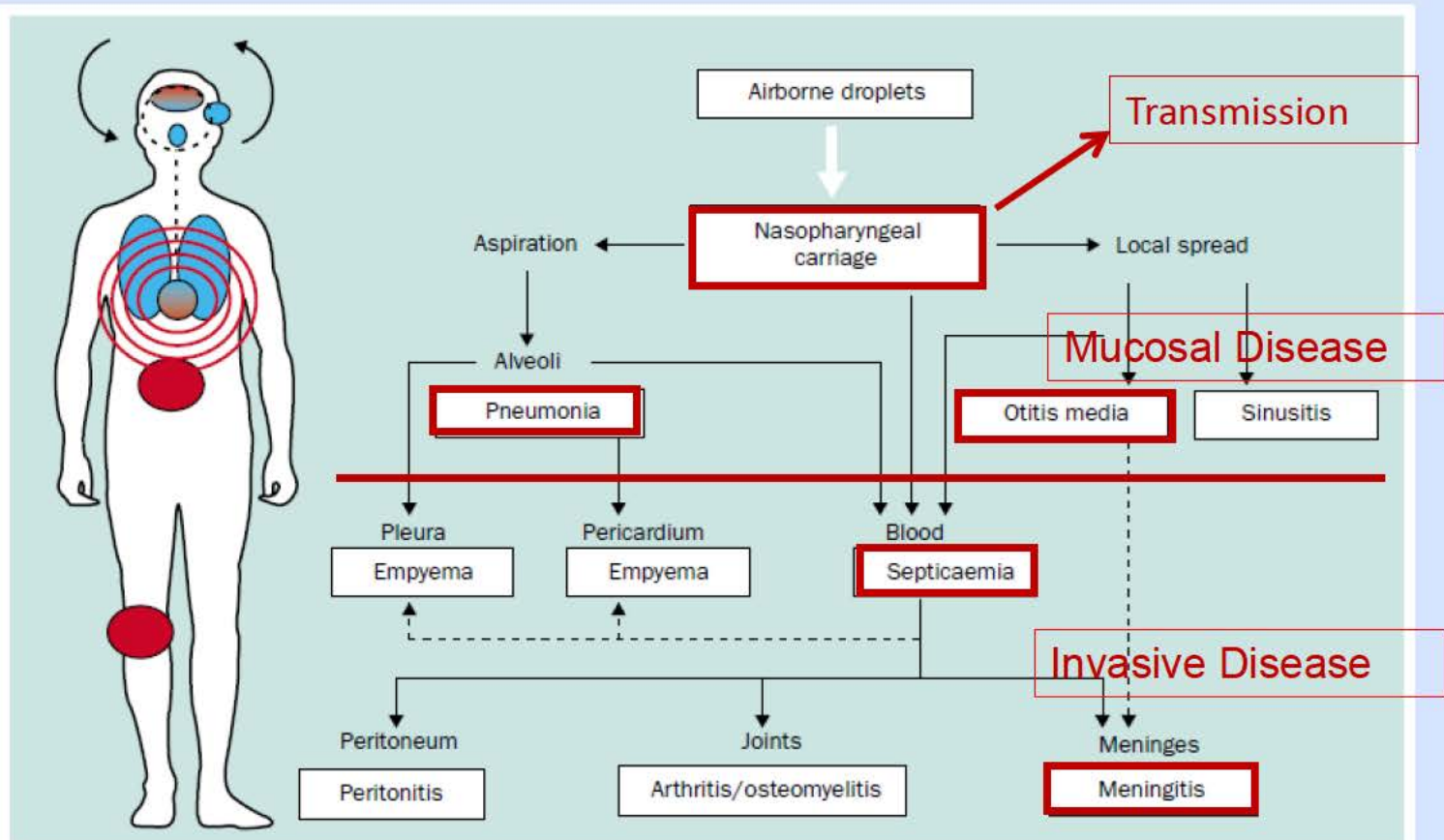


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Bogaert, Lancet Infect Dis 2004;4:144-54

Age-Specific Incidence of Invasive Pneumococcal Disease, US, 1998



Robinson, JAMA 2001;285:1729-35

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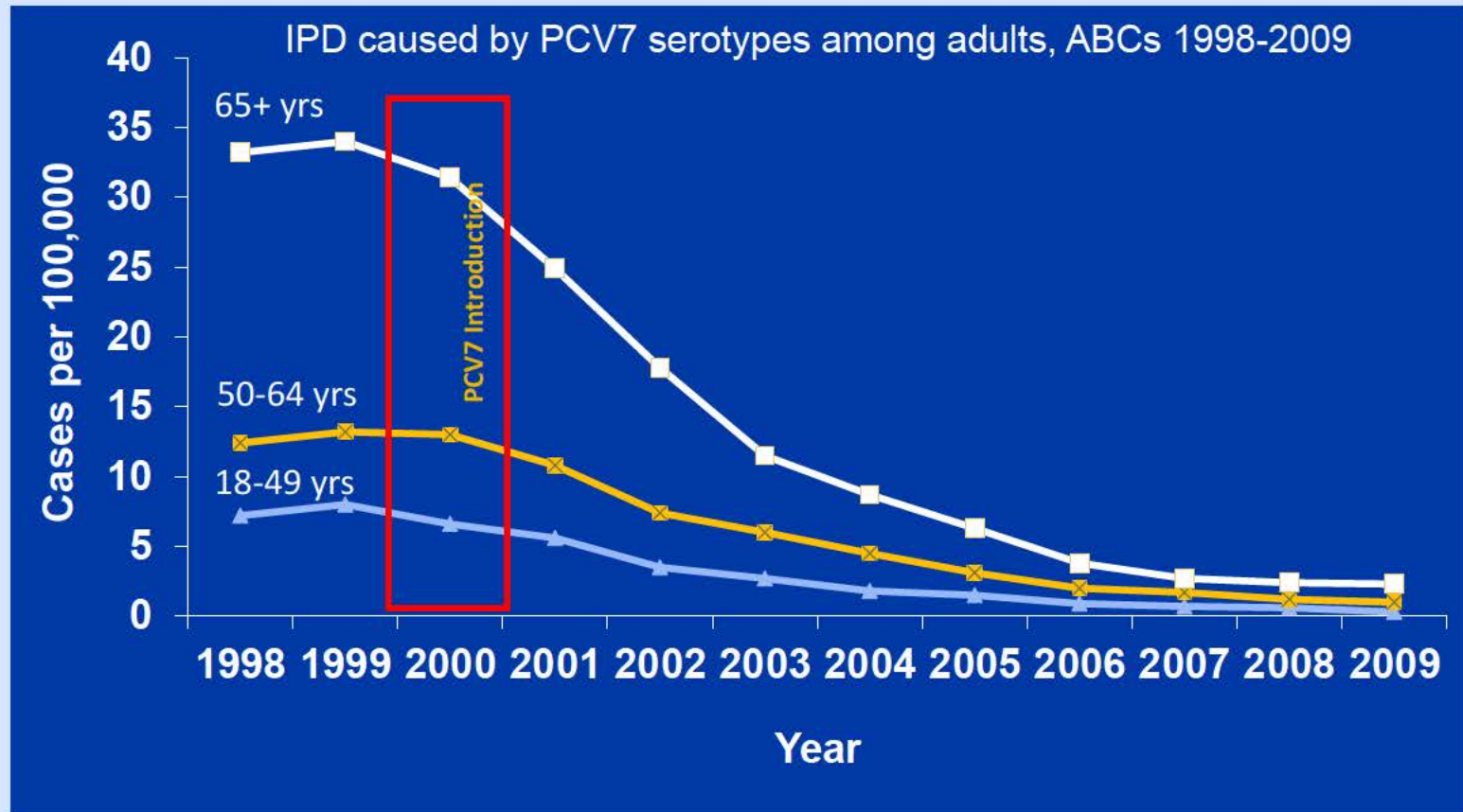
Vaccines to Preserve Health

- ❑ People age 65+ years a large and growing segment of the population
- ❑ Many are healthy, active, engaged
- ❑ Immunizations a simple way to preserve health



Photo source: dailymail.co.uk from Reddit

Vaccinating children highly effective for preventing disease in adults



Moore, IDSA, 2009

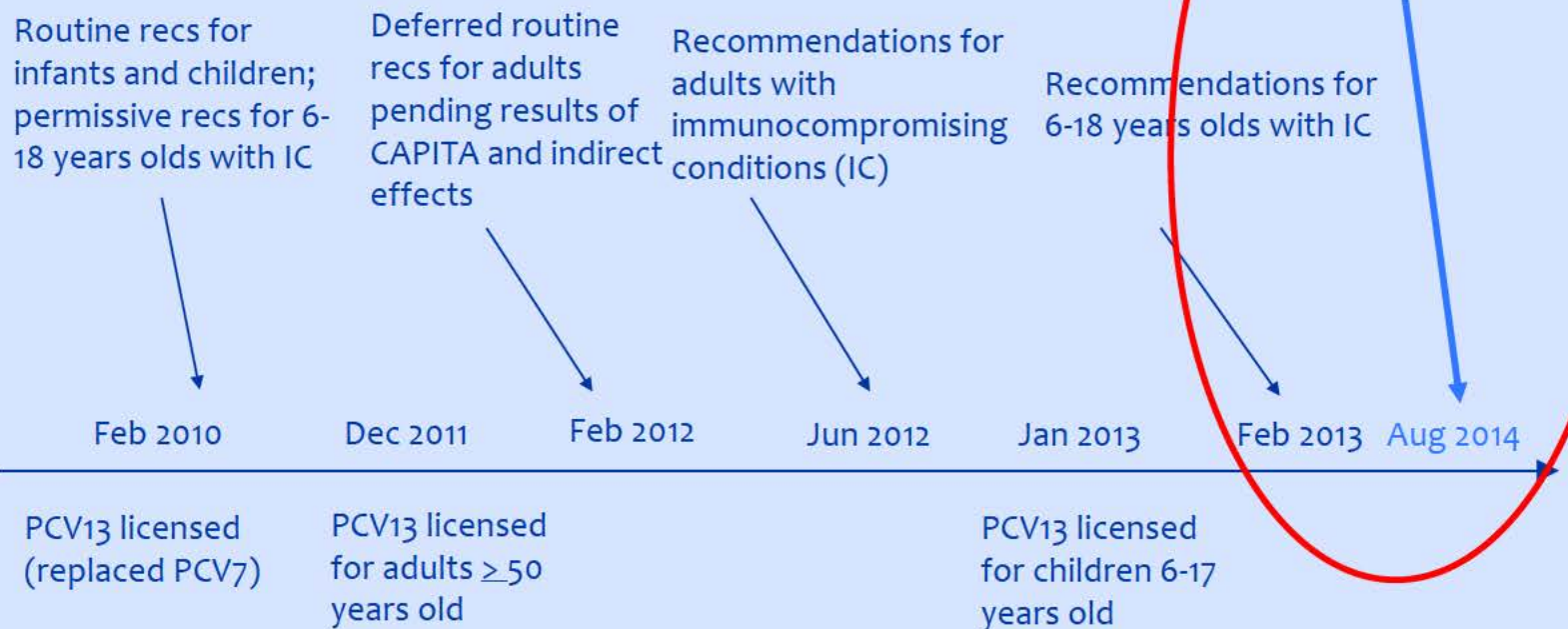
Need better prevention measures for pneumonia in older adults

- Prevention measures targeting respiratory infections
 - Indirect effects from pediatric PCV program
 - 23-valent pneumococcal polysaccharide vaccine (PPSV23) used in US since 1983
 - Expanded flu vaccine recommendations and improved coverage
 - Smoking cessation and prevention program; second-hand smoke restricted in public areas
- In spite of these measures:
 - Pneumonia/influenza still 8th leading cause of death in US
 - >57,000 deaths in 2015 CDC.gov

Polysaccharide & Conjugate Vaccines: A Comparison

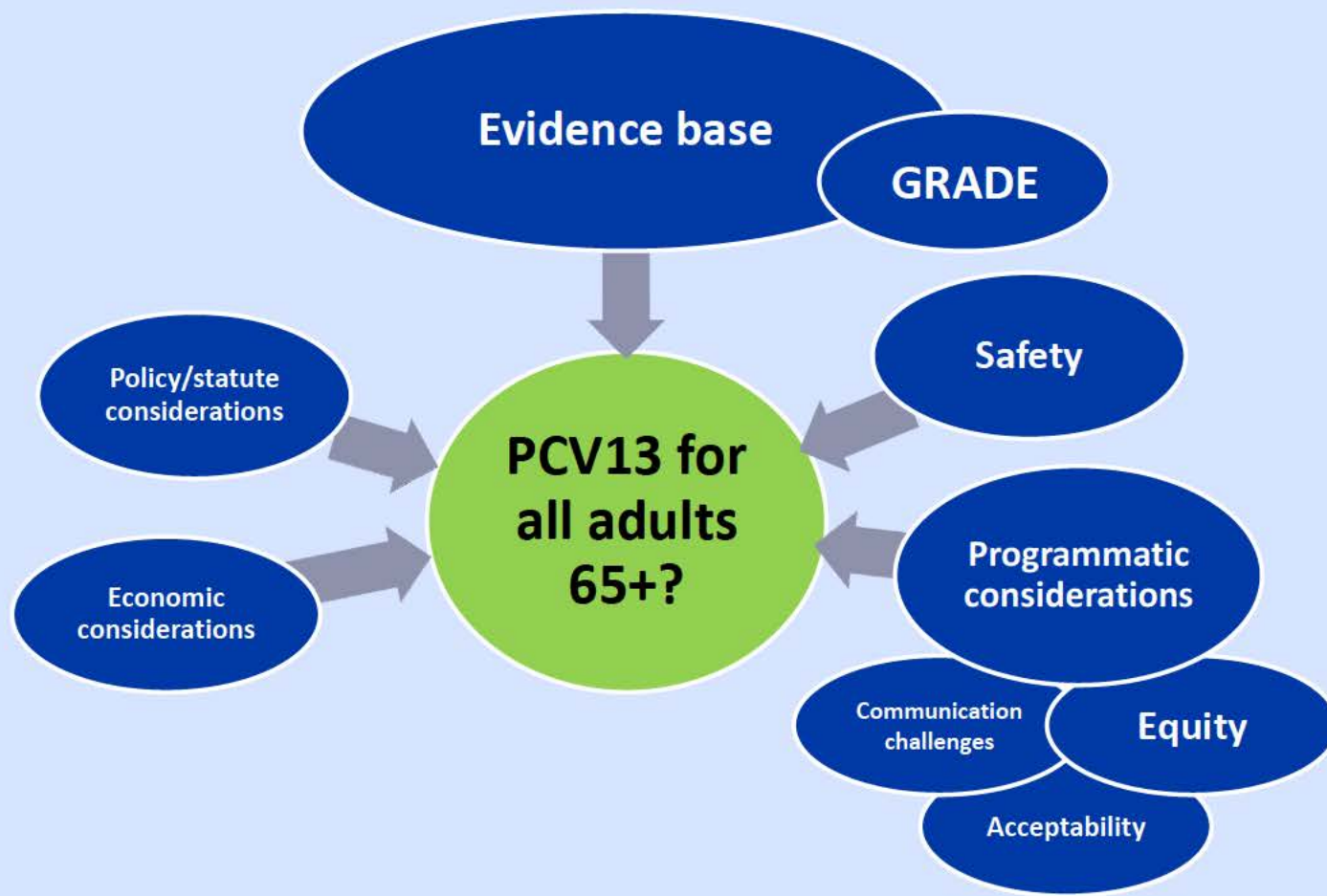
Characteristic	Polysaccharide	Conjugate
Components	Purified polysaccharide	Purified polysaccharide covalently bound to carrier protein
Immunogenic?	Only among >2 year-olds	All ages (T-dependant pathway)
First year available	1918→1977→1983	2000→2009→2010
Number of serotypes	4→14→23	7→10→13
Effect against bacteremia	Substantial	Substantial
Effect against carriage	None	Substantial
Effect against non-bacteremic pneumonia	No consensus	Moderate
Schedule	≤3 doses after age 2 years	4 doses <age 2 years; possibly 1 after
Cost	US \$55	US \$124
Examples	23-valent Pneumococcal Polysaccharide Vaccine (PPSV23)	13-Valent Pneumococcal Conjugate Vaccines (PCV13)

ACIP Pneumococcal Work Group Activities 2010-2014



IC = with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants

Considerations for changing vaccine policy



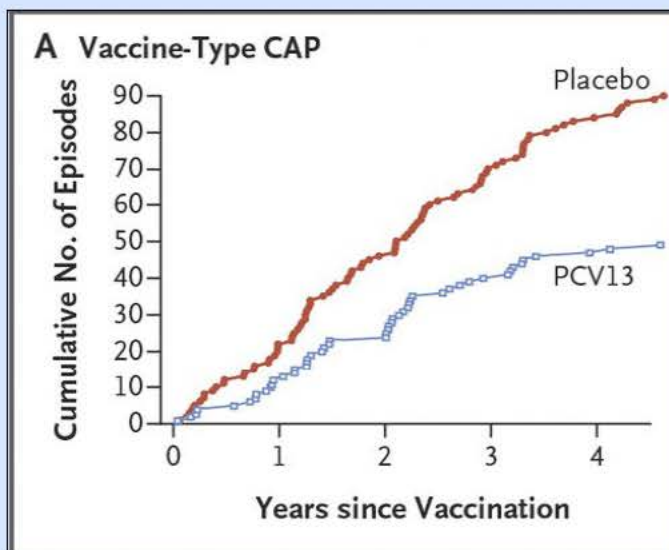
Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults

E. Hak^{1,2*}, D.E. Grobbee¹, E.A.M. Sanders², T.J.M. Verheij¹, M. Bolkenbaas¹, S.M. Huijts¹, W.C. Gruber³,
S. Tansey³, A. McDonough³, B. Thoma³, S. Patterson³, A.J. van Alphen⁴, M.J.M. Bonten^{1,5}

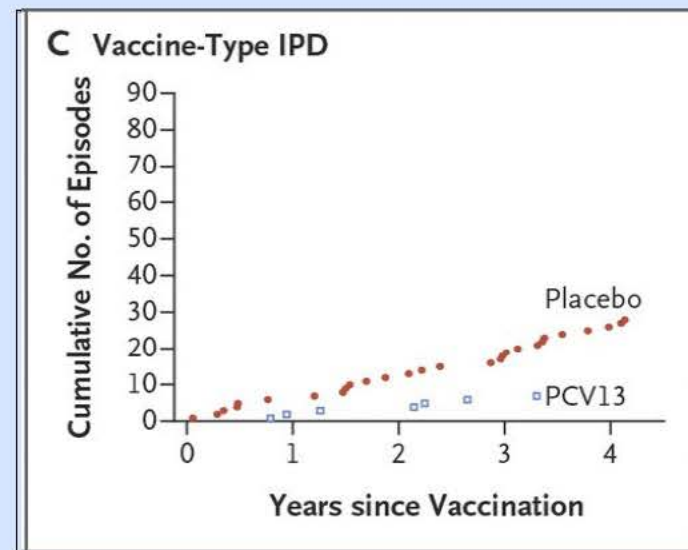
¹Julius Center for Health Sciences and Primary Care, Departments of ²Pediatric Immunology and Infectious Diseases, and ³Medical Microbiology, University Medical Center Utrecht, the Netherlands, ³Wyeth Vaccines Research, Wyeth, Pearl River New York, USA, ⁴Netherlands Vaccine Institute, Bilthoven, the Netherlands, *corresponding author: tel.: +31 (0)88-756 82 14, fax: +31 (0)88-76 80 99, e-mail: e.hak@umcutrecht.nl

- Randomized, placebo-controlled trial of 84,496 adults ≥ 65 yrs of age in the Netherlands
- Primary endpoint
 - Vaccine-type community-acquired pneumonia
 - Measured using serotype-specific urine antigen assay

CAPiTA: Cumulative Episodes of Efficacy End Points in the Per-Protocol Population



CAP vaccine efficacy 46% (22%, 63%)



IPD vaccine efficacy 75% (41%, 91%)

Bonten MJ et al. N Engl J Med 2015;372:1114-1125.

PCV in Older Adults: Quality of evidence (GRADE)

Comparison	Outcome	Study Design (# studies)	Findings	Quality of evidence	Overall evidence type
PCV13 vs. no vaccination	IPD	RCT (1)	Decreased risk among vaccinated	2	
PCV13 vs. no vaccination	Pneumonia	RCT (1)	Decreased risk among vaccinated	1	2
PCV7 or PCV13 vs. PPSV23	Immunogenicity	RCT (6)	Response improved for PCV vs. PPSV23 or no difference	2	
PCV13 vs. PPSV23	Serious and systemic adverse events	RCT (3)	No difference or decreased risk with PCV13	1	

PCV in Older Adults: Quality of evidence (GRADE)

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PCV13 vs. no vaccination	HIGH QUALITY EVIDENCE (I.e., this vaccine works)				2
PCV7 or PPSV23 vs. PPSV23			difference		
PCV13 vs. PPSV23	Serious and systemic adverse events	RCT (3)	No difference or decreased risk with PCV13	1	

OK, the vaccine works...

...but do we need it?

“We don’t need PCV13 because vaccinating children has taken care of virtually all the disease.”

Q: Disease rates have gone down...but have they gone down so far that vaccinating adults is pointless?

A: Need to do the math!

Modeling expected public health impact and cost-effectiveness of PCV13 for older adults in the U.S.

- ❑ Various strategies considered:
 - Vaccination at ages 50, 60, and 65 years
 - PCV13 instead of PPSV23
 - PCV13 in sequence with PPSV23
- ❑ Took into account:
 - Anticipated reductions in vaccine-serotype disease over time because of pediatric program (used PCV7 experience)
 - A guess at how quickly coverage would increase
 - Waning immunity over time after vaccination
 - Disease occurring only in nonimmunosuppressed persons
 - A lot of other stuff

Stoecker C et al. ACIP 2014 and J Gen Intern Med. 2016 Aug; 31(8): 901–908.

Expected public health impact and cost-effectiveness in the U.S.

- ❑ Adding PCV13 at age 65 years to existing PPSV23 recommendations likely the optimal strategy
 - PPSV23's extended serotype range helps with IPD; PCV13 helps with pneumonia
- ❑ Health benefits for cohort of 65-yo's vaccinated
 - 5000 fewer pneumonia hospitalizations
 - 7300 fewer outpatient pneumonias
- ❑ Cost-effectiveness comparable to other accepted adult interventions (base case: \$62,000/QALY)
- ❑ But, cost-effectiveness likely to decrease over time
 - For 2019 cohort, \$273,000/QALY

Stoecker C et al. ACIP 2014 and J Gen Intern Med. 2016 Aug; 31(8): 901–908.

Expected public health impact and cost-effectiveness in the U.S.

- Adding PCV13 at age 65 years to existing PPSV23

Math supported giving PCV

- Health benefits for cohort of 65-yo's vaccinated

- 5000 fewer pneumonia hospitalizations
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- Cost-effectiveness compared to no vaccination (base case: \$62,000/QALY)

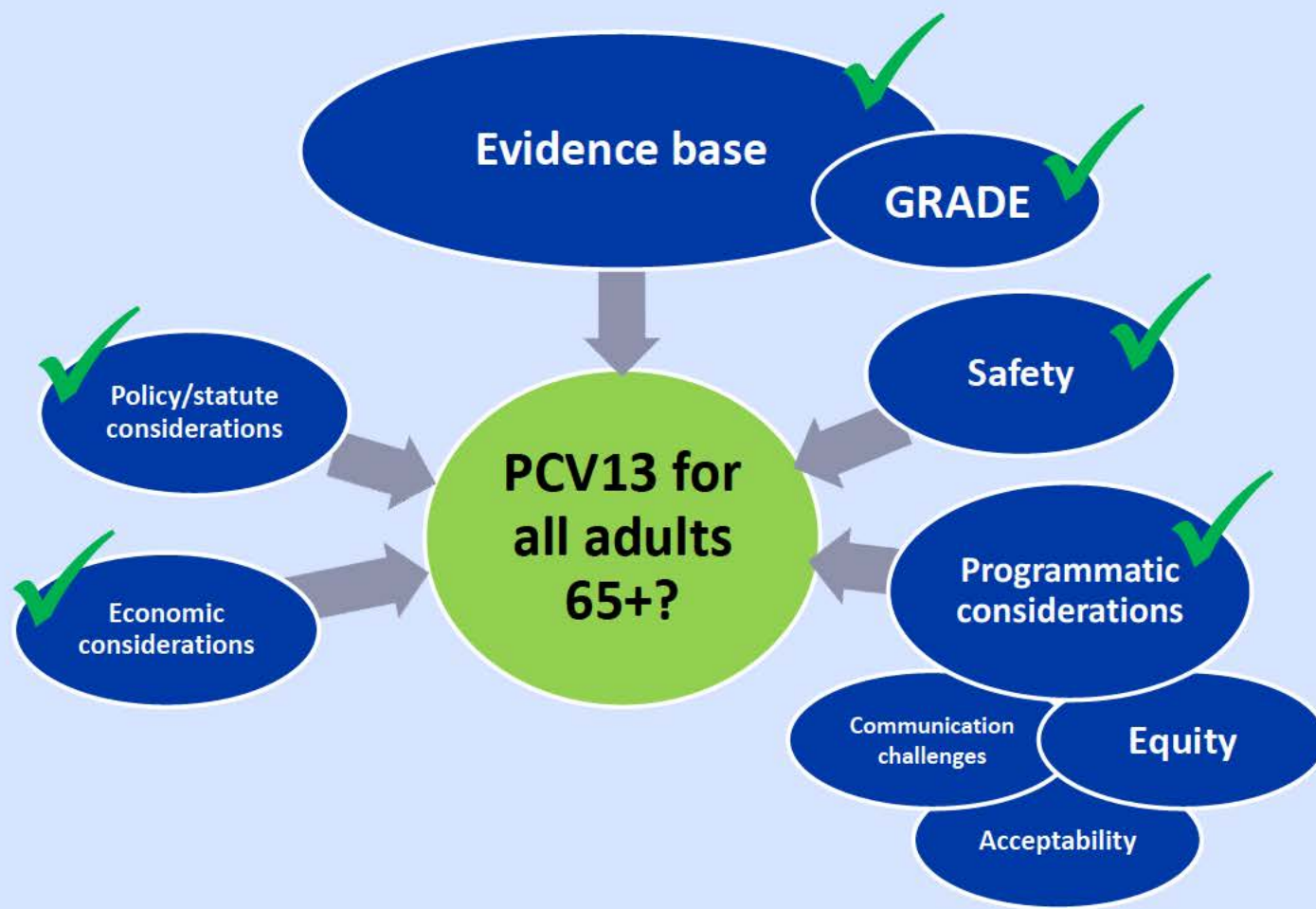
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Caveats:

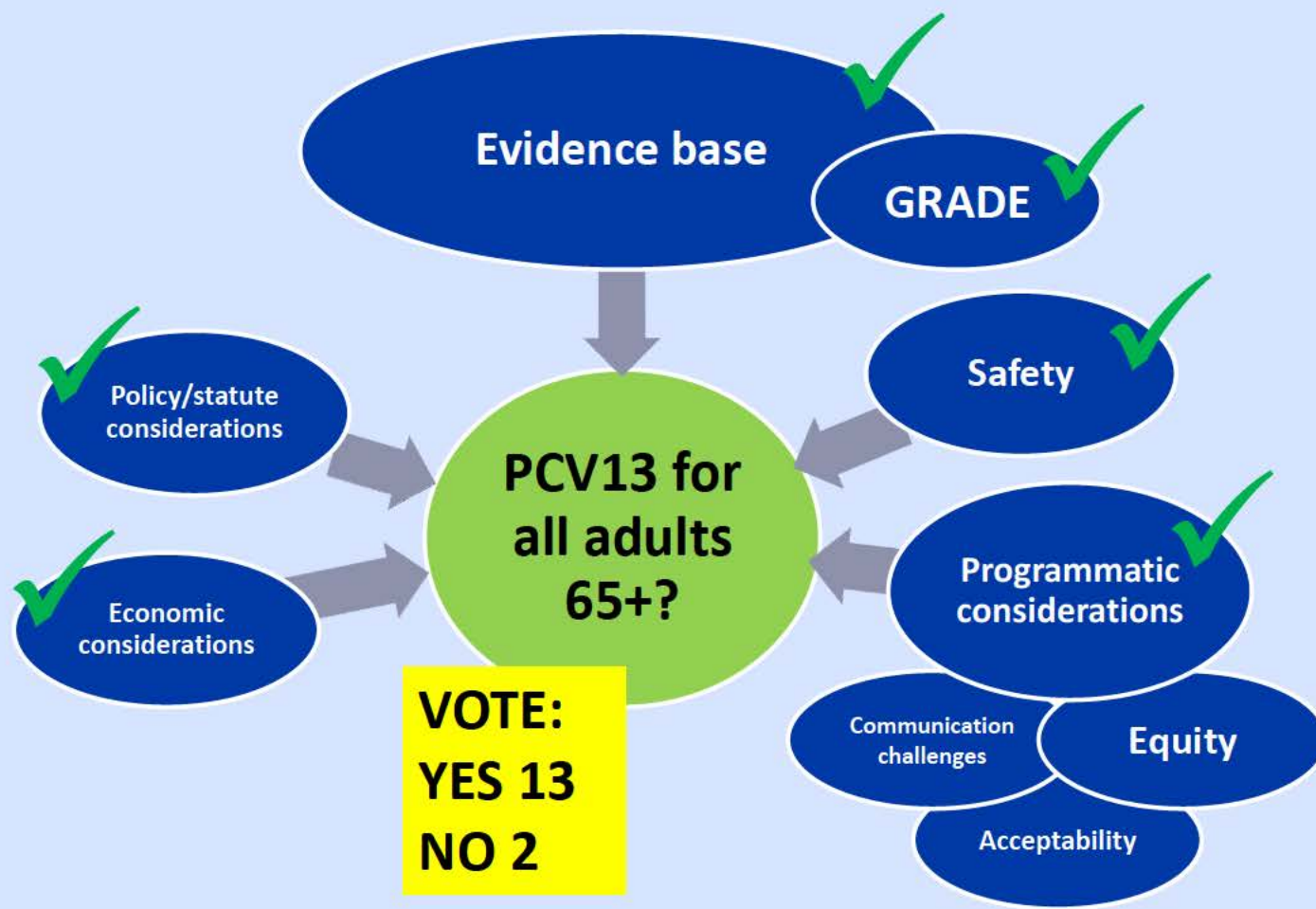
- Need for PCV likely to drop over time
- US situation may not be applicable elsewhere

Stoecker C et al. ACIP 2014 and J Gen Intern Med. 2016 Aug; 31(8): 901–908.

Considerations for changing vaccine policy



Considerations for changing vaccine policy



❑ **2014 Advisory Committee on Immunization Practices (ACIP)**

- Both PCV13 and PPSV23 should be routinely administered in series to all adults aged ≥ 65 years.
- When possible, PCV13 given first followed by PPSV23 later
- The recommendations for routine PCV13 use among adults aged ≥ 65 years will be reevaluated in 2018 and revised as needed.



- ## ❑ **2015 update:** interval between PCV13 and PPSV doses should be ≥ 1 year (regardless of order)

Tomczyk S et al. MMWR September 19, 2014 / 63(37);822-825

Kobayashi M et al. MMWR September 4, 2015 / 64(34);944-947

2018 ACIP Pneumococcal Vaccine Work Group

Mandate to:

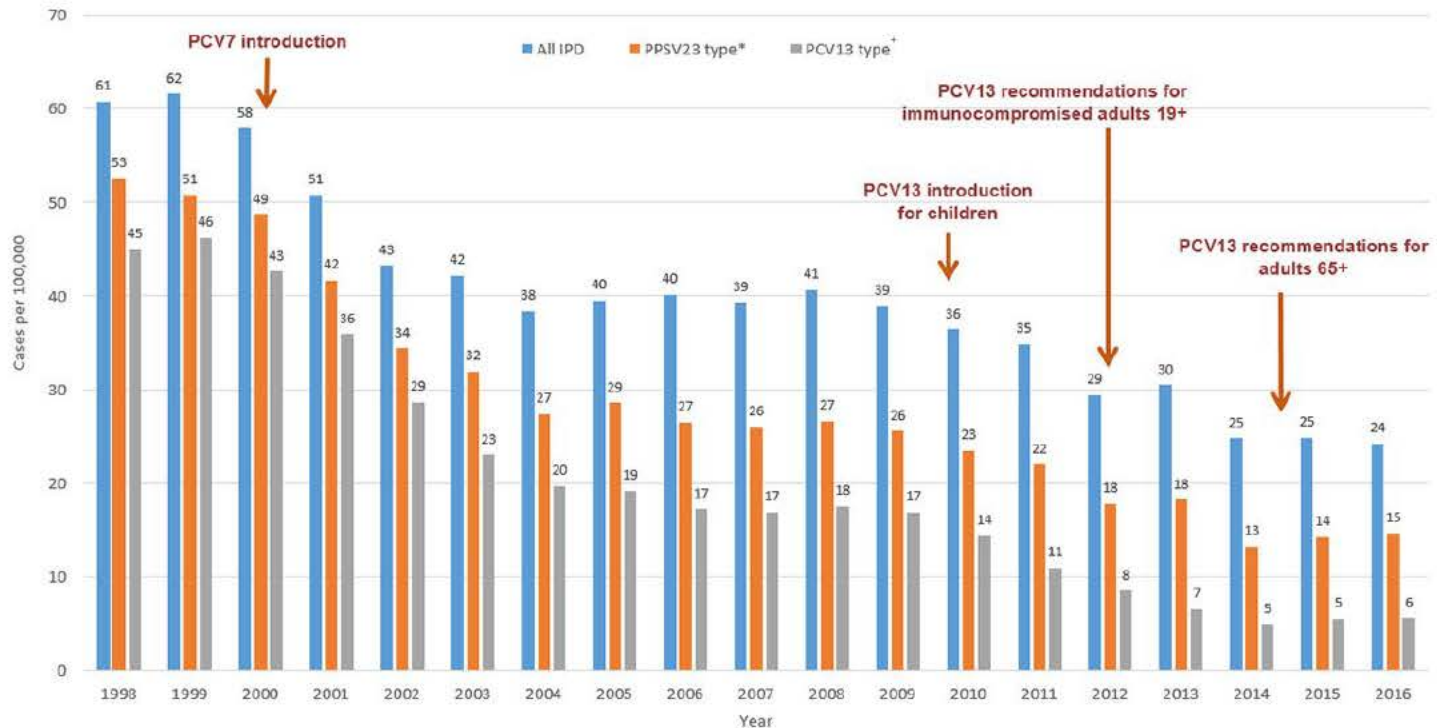
- Review current data on efficacy, effectiveness, immunogenicity, and cost-effectiveness of pneumococcal vaccines
- Assess recommendations considering up-to-date evidence and evidence strength
- Revise or update recommendations for pneumococcal vaccine use, as needed

Setting:

- PCV13 coverage modest
 - Increased to ~40% through 2017 among adults 65+ yrs
 - Lower among those 19-64 yrs with vaccine indications
- Safety assessment good
 - VAERS: mostly injection site reactions, no unexpected reports or patterns
 - VSDL: no increased risk of reactions compared to PPSV23

Invasive pneumococcal disease trends, adults 65+ Active Bacterial Core surveillance (ABCs)

Trends in invasive pneumococcal disease among adults aged ≥ 65 years old, 1998–2016



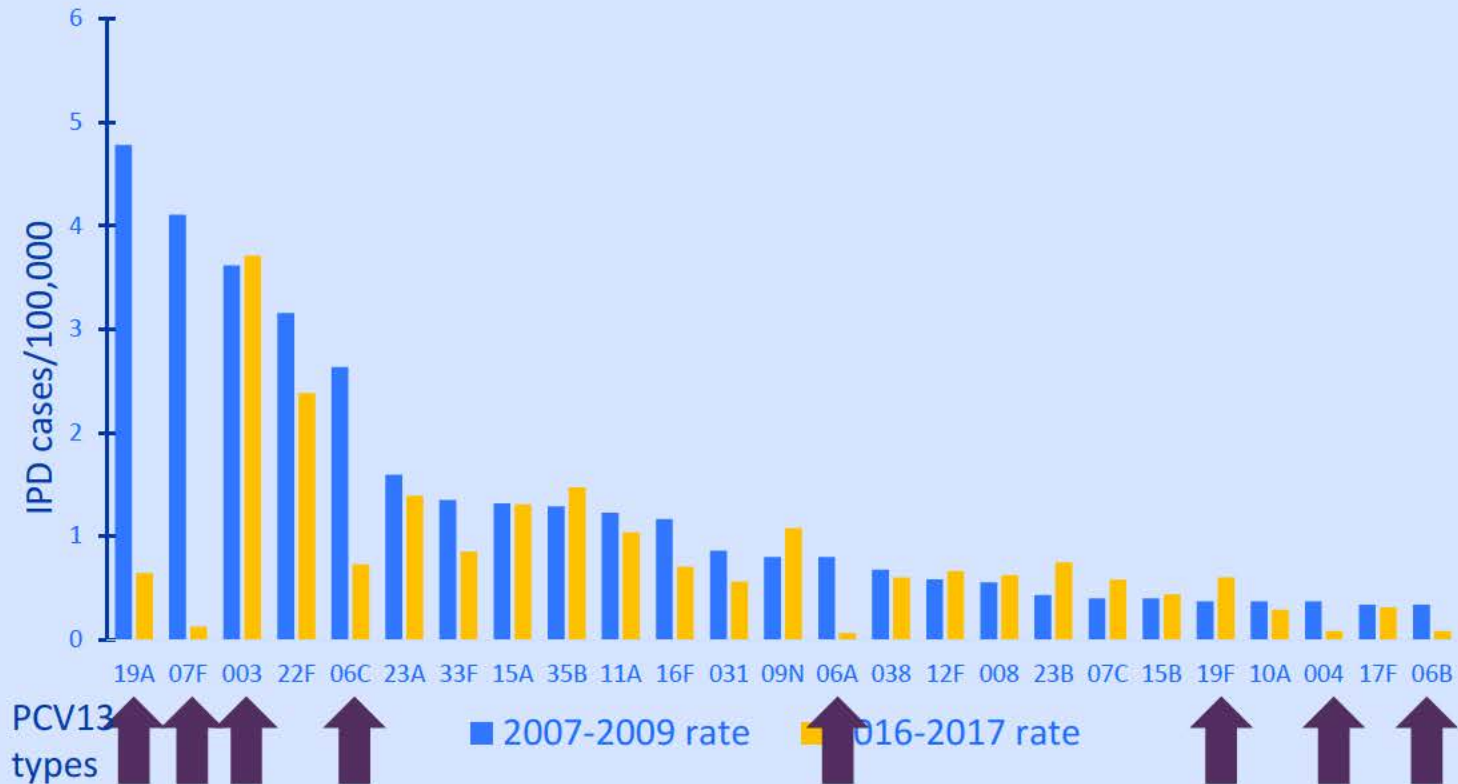
*PPSV23 serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F

+PCV13 serotype: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

www.cdc.gov/abcs

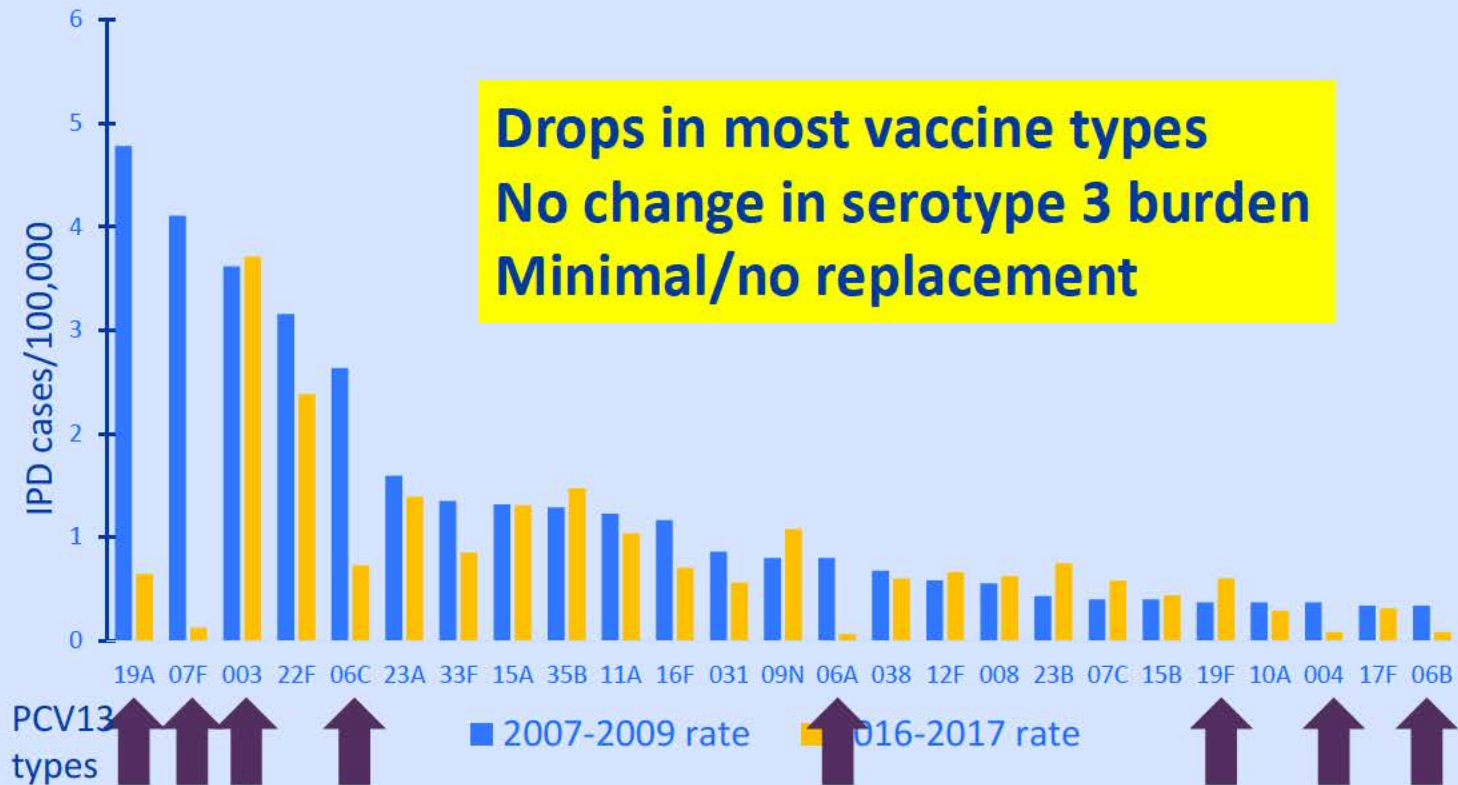
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Top serotypes causing IPD in US adults 65+, 2007-2009 and 2016-2017



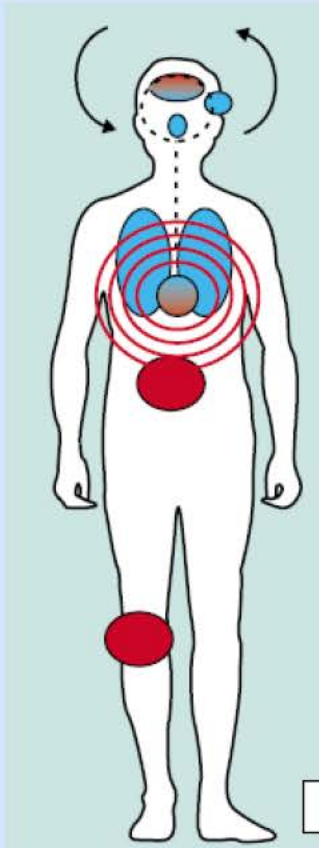
Source: US Centers for Disease Control and Prevention, Active Bacterial Core surveillance

Top serotypes causing IPD in US adults 65+, 2007-2009 and 2016-2017



Source: US Centers for Disease Control and Prevention, Active Bacterial Core surveillance

Evidence for ACIP's assessment of Adult PCV13 policy: Invasive disease

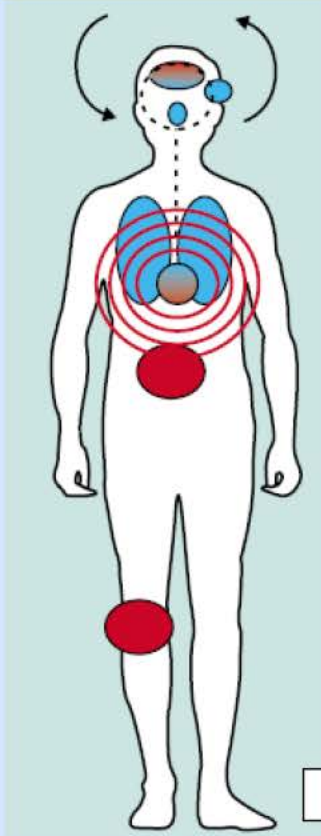


- PCV13-type IPD incidence in US adults ≥ 65 years old declined 68% after pediatric PCV13 began in 2010; no change from 2014 to 2016
 - PCV13 serotype 3 most common serotype
 - Low PCV13 disease rates among Alaska Natives and Navajo before implementation of adult program (indirect effects); no change after
- Mathematical model estimated direct PCV13 effects on observed IPD trends in IPD among adults ≥ 65 years old
 - Between 80-760 IPD cases prevented since 2014 among U.S adults ≥ 65 years; benefits decreasing over time
- PCV13 effectiveness against PCV13-type IPD 47% (95%CI 4–71%) to 65% (95%CI 19–85%) in 2 case-control studies
 - Confidence intervals overlap with the CAPiTA PCV13

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

Pillishvili, ACIP meeting Feb 2018; Hammitt, ACIP June 2018

Evidence for ACIP's assessment of Adult PCV13 policy: Invasive disease

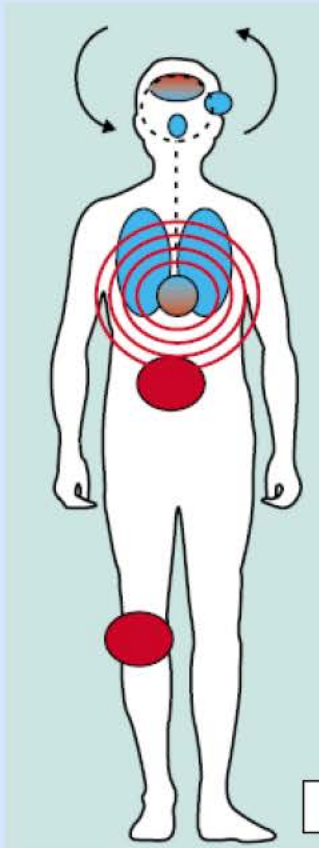


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 - Mathematical model estimated direct PCV13 effects on observed IPD trends in IPD among adults ≥ 65 years old
 - Between 80-760 IPD cases prevented since 2014 among
- **PCV13 effective in older adults (serotype 3?)**
 - **Direct benefit of adult program small in most recent years**

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

Pillishvili, ACIP meeting Feb 2018; Hammitt, ACIP June 2018

Evidence for ACIP's assessment of Adult PCV13 policy: Pneumonia

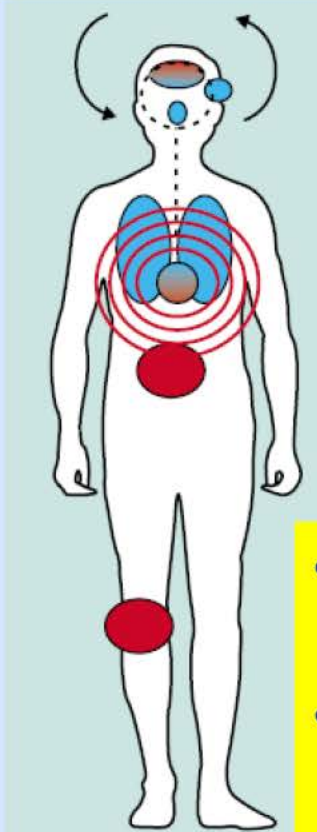


- PCV13 effectiveness against PCV13-type pneumonia 73% (95% CI 13–92) demonstrated in a test negative case-control study design
 - Confidence intervals overlap with CAPiTA PCV13 efficacy estimates of 45% (95%CI 14–65%) against PCV13-type pneumonia
- Among American Indians in the southwest US, 26% of chest x-ray confirmed pneumonia had pneumococcal diagnosis; of these, 31% PCV13-types by SSUAD, mostly serotype 3

McLaughlin, ACIP Feb 2018; Hammitt, ACIP June 2019

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

Evidence for ACIP's assessment of Adult PCV13 policy: **Pneumonia**



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- **PCV13 effective against pneumonia (serotype 3?)**
- **Remaining pneumonia mostly nonvaccine types or serotype 3**

McLaughlin, ACIP Feb 2018; Hammitt, ACIP June 2019

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

Evidence for ACIP's assessment of Adult PCV13 policy: Nasopharyngeal Carriage

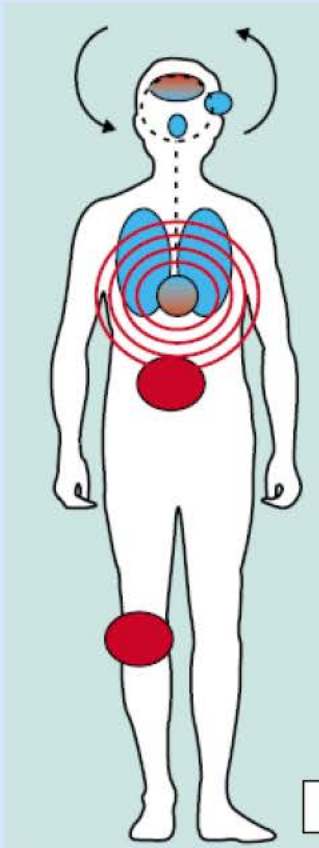
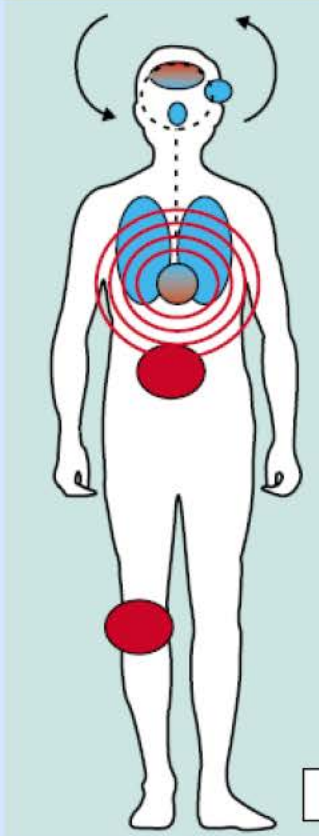


Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

- Nasopharyngeal carriage before and after PCV13 introduction in adults ≥ 65 in Atlanta
 - Children < 5 years:
 - PCV13-serotype carriage declined from 8% in 2011 to $< 1\%$ in 2017
 - Total *S. pneumoniae* carriage remained the same ($\sim 30\%$)
 - Adults ≥ 65 years:
 - PCV13-serotype carriage 0.2% in 2015-16
 - Total *S. pneumoniae* carriage also low (1.8%)

Thomas, ACIP meeting Oct 2017; Lessa, ACIP meeting Oct 2017

Evidence for ACIP's assessment of Adult PCV13 policy: Nasopharyngeal Carriage



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Older adults rarely exposed to PCV13 serotypes

Figure: Bogaert, Lancet Infect Dis 2004;4:144-54

ACIP Meetings coming soon

- October 2018: Discussion and data review
 - PCV13 impact on IPD and serotype distribution for the remaining disease burden
 - U.S. trends in US pneumonia hospitalizations, noninvasive pneumococcal pneumonia in ABCs sites for older adults
 - Cost effectiveness of PCV13 for adults ≥ 65 year old
 - Preliminary EtR and GRADE
- February 2019: Tentative vote
 - Should PCV13 be administered routinely to all adults aged ≥ 65 years in a setting of sustained PCV13 indirect effects?

ACIP Evidence to Recommendation (EtR)

Goal: develop a uniform approach to evaluation and use of the evidence base for ACIP recommendations

Framework:

- Statement of problem
 - Public health priority
 - Burden of disease
- Benefits and harms (GRADE)
 - Balance of desirable and undesirable effects
 - Certainty in evidence
 - Values and preferences of target population
- Acceptability to stakeholders
- Resource use
 - Health economic analyses
- Feasibility
 - Implementation considerations

ACIP PCV13 recommendations for adults: To drop or not to drop?

- DROP PCV13 FOR OLDER ADULTS
 - Disease caused by vaccine types now uncommon, except serotype 3
 - Preliminary evidence suggests herd effects from children drive low rates in adults, not direct effects
 - Vaccination is a lot of time and expense for low likelihood of benefit
- DON'T DROP
 - Vaccine is safe and effective
 - Communication/acceptability challenges, i.e. “Drop the more effective vaccine?”
 - Logistics/systems challenges: If new vaccines around the corner, why not wait to change and avoid rapid program shifts?

What serotypes would we include in the ideal adult pneumococcal conjugate vaccine?

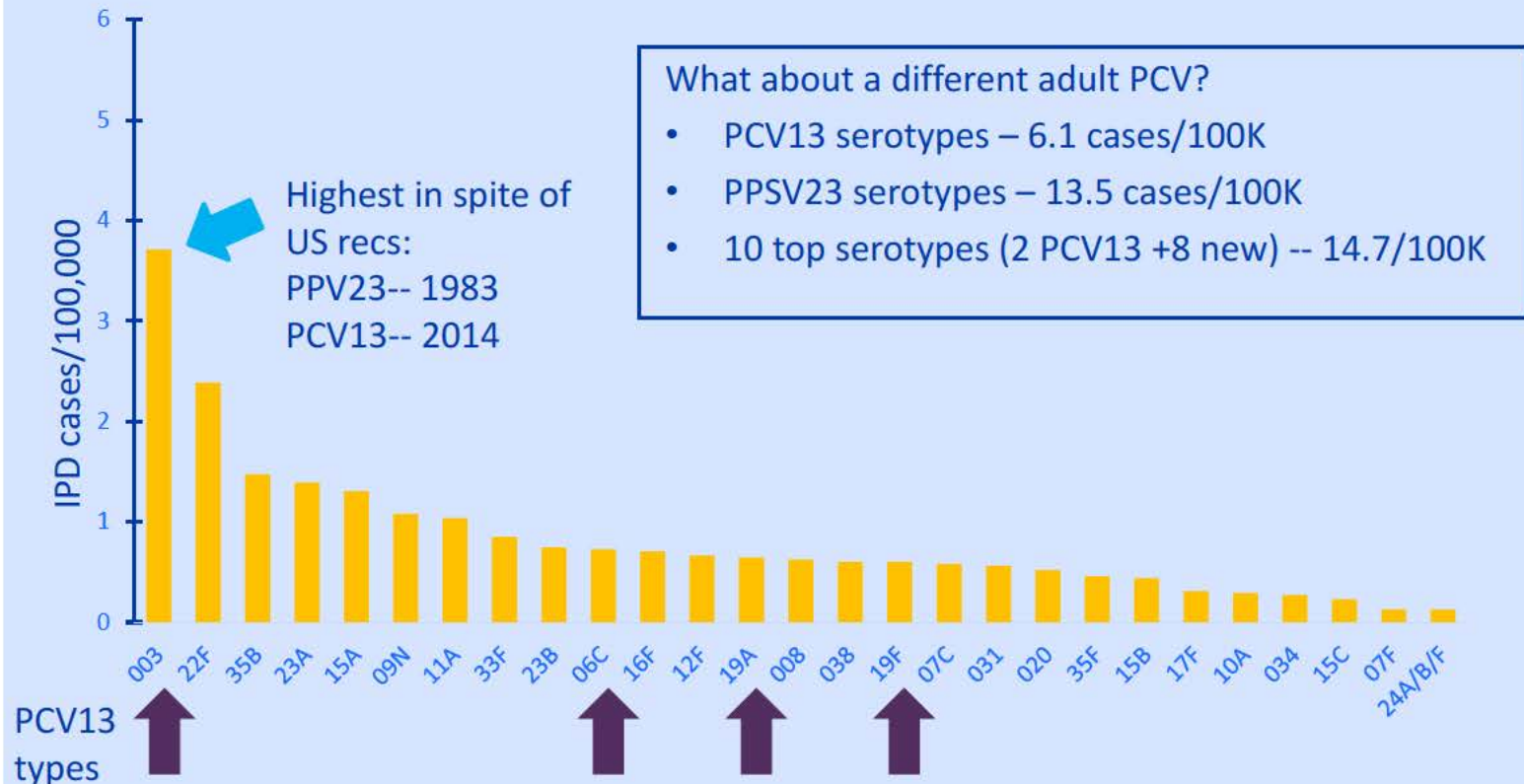


**"Have no fear of perfection,
you'll never reach it"**

- Salvador Dali

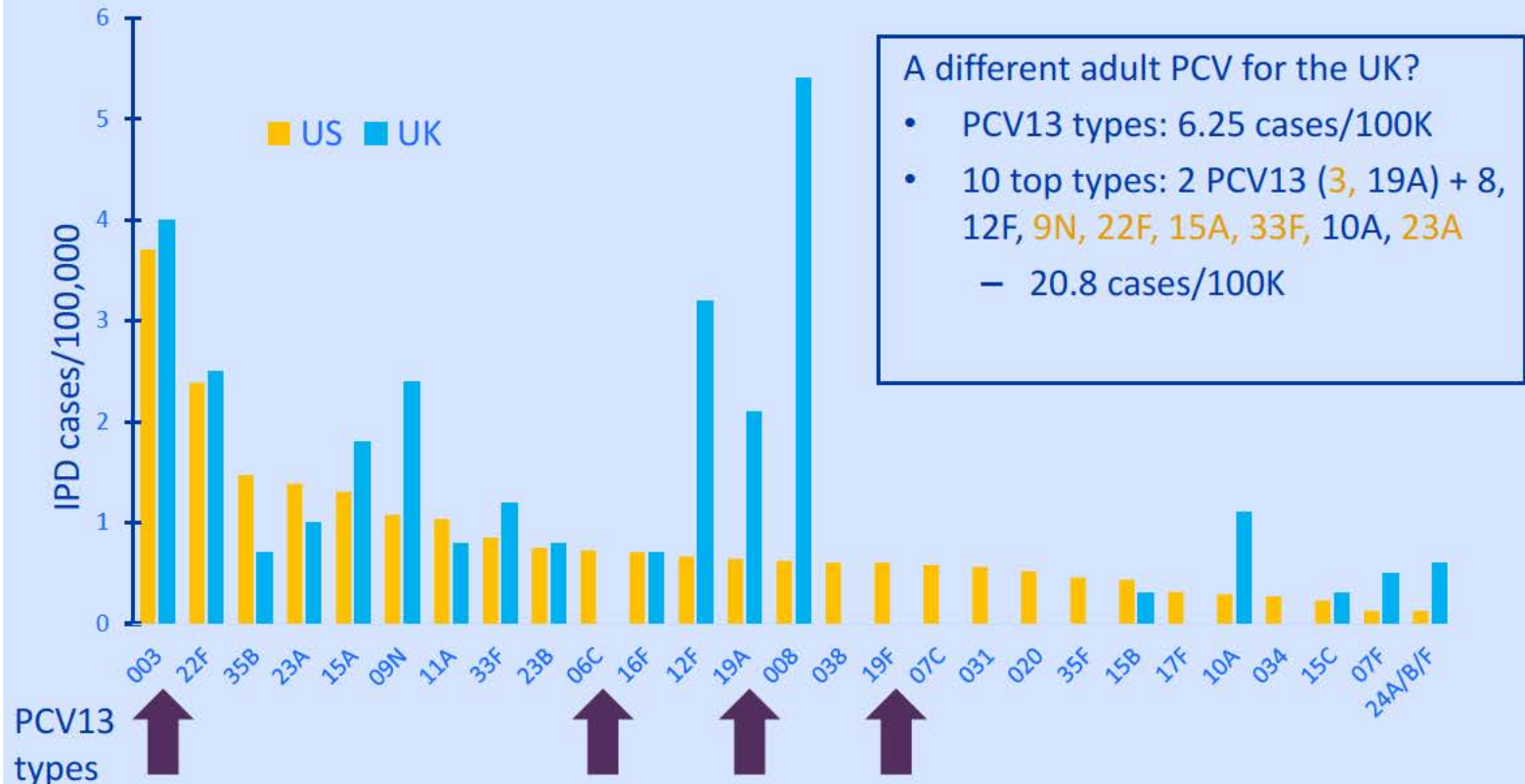
TwistedSifter.com

Top serotypes causing IPD in US adults 65+ years, 2016/17



Source: US Centers for Disease Control and Prevention, Active Bacterial Core surveillance

Top serotypes causing IPD in US and UK adults 65+ years, 2016/17



Sources: US CDC Active Bacterial Core surveillance; Ladhani et al Lancet Infect Dis 2018

Considerations for designing an adult vaccine

- Serotype 3 remains common, even with recs for PCV13 (U.S.) and PPV23; differs from other PCV antigens. Is a better serotype 3 component possible?
- In push to cover more serotypes, potentially to replace PPSV23, will individual components interfere with each other's ability to elicit an immune response?
- Given herd effects, should adult vaccines target different serotypes than those in the pediatric formulation? Or would production/licensing issues preclude this option?
- Will costs permit use in low- and middle-income countries?
- How to choose best serotypes to include, given differences between countries? 8-10 antigens likely to target substantial burden

Questions

What should ACIP do about the adult recommendation?

What/how many serotypes should an adult vaccine have?



Photo source: nowthatsnifty.blogspot.com

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