Evidence to Recommendations and GRADE for PCV13 Use Among Immunocompetent Adults ≥65 Years Old

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Advisory Committee on Immunization Practices
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Current Adult Pneumococcal Vaccine Recommendations

- In 2012 ACIP recommended PCV13 in series with PPSV23 for adults ≥19 years old with immunocompromising conditions
  - Not currently being re-evaluated
- In 2014 ACIP recommended PCV13 in series with PPSV23 for all PCV13-naïve adults ≥65 years old with the following considerations:
  - Short term use warranted because of the remaining PCV13-type disease burden
  - Long term utility may be limited due to anticipated indirect effects from pediatric PCV13 use
Policy Question

- Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in the context of indirect effects from pediatric PCV use experienced to date?
  - **Population**: Immunocompetent adults ≥65 years old, with and without chronic medical conditions
  - **Intervention**: PCV13 at ≥65 years old in series with PPSV23, in the context of indirect effects
  - **Comparison(s)**: PPSV23 alone at ≥65 years old, in the context of indirect effects
  - **Outcomes**: invasive pneumococcal disease (IPD), pneumonia, mortality, and PCV13 safety
ACIP Evidence to Recommendation (EtR) Framework

- Statement of problem
  - Public health priority
  - Burden of disease

- Benefits and harms
  - 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
Evidence to Recommendations

- **Statement of problem**
- Benefits and harms with GRADE
- Values and preferences of target population
- Acceptability to stakeholders
- Resource use
- Feasibility
Context: Indirect Effects from Pediatric PCV Use Experienced Among Adults ≥65 Years Old

- Nine-fold reduction in vaccine-type invasive pneumococcal disease (IPD) in the US since pediatric PCV (PCV7 and PCV13 combined) introduction¹
  - Indirect effects from PCV13 alone led to a 3 fold reduction (2010–2014)
  - Plateau in incidence since 2014 (combined direct and indirect effects)
- Similar reductions seen in IPD in Europe since pediatric PCV13 introduction²
  - Decline 77% in PCV7-type and 38% PCV13non7-type IPD (2009–2015)

¹Active Bacterial Core Surveillance, https://www.cdc.gov/abcs/reports-findings/surv-reports.html, comparing 2000 to 2014
²Hanquet et al. 2018
Context: Indirect Effects from Pediatric PCV Use Experienced Among Adults ≥65 Years Old

- Most studies demonstrate a reduction in all-cause pneumonia since introduction of PCVs for children in 2000¹
  - In the U.K. PCV7-type pneumonia declined by 88% and PCV13non7-type pneumonia declined by 30% (2008–2013)²
  - In the U.S. since pediatric PCV13 introduction, pneumococcal pneumonia hospitalizations have declined (2010–2014)³

¹Tsaban et al. 2017
²Rodrigo et al. 2015
³Lessa ACIP October 2018
Each enrollment period extends from September 19 of the first year through September 18 of the subsequent year, with the exception of the 2011-12 period, which ends on October 12, 2012, corresponding to the date of publication of the first recommendation for the use of 13-valent pneumococcal conjugate vaccine (PCV13) in series with 23-valent pneumococcal polysaccharide vaccine (PPSV23) in adults with certain immunocompromising conditions; denominators include all beneficiaries continuously enrolled in Medicare Parts A and B for the duration of the enrollment period.

https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/pcv13-medicare-beneficiaries.html
Summary: Vaccine-Preventable Disease Burden (PCV13)

- PCV13-type IPD incidence among adults ≥65 years in 2015–2017
  - Incidence plateaued at 5/100,000
  - PCV13 serotypes account for 20% of all IPD plus an addition 3% including 6C
  - Common PCV13 serotypes (% of PCV13-types): 3 (66%), 19A (13%), 7F (13%), 19F (12%)

- PCV13-type pneumonia incidence among adults ≥65 years in 2015–2016
  - Incidence estimates range across studies 17+ to 76/100,000
  - PCV13 serotypes account 3.7% of all-cause pneumonia
  - Common PCV13 serotypes (% of PCV13-types): 3 (37%), 19A (28%), 6A (12%), 5 (9%), 7F (7%)

*Estimated by applying the %PCV13-type IPD to the non-invasive pneumococcal pneumonia (NIPP) incidence estimate from the Surveillance for Non-invasive Pneumococcal Pneumonia (SNiPP)
# Remaining PCV13-type Disease Burden Compared to Other Vaccine-Preventable Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Outcome</th>
<th>Incidence per 100,000</th>
<th>Adult Vaccine Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal</td>
<td>Invasive and non-invasive PCV13-type pneumonia hospitalization among ≥65 years old</td>
<td>76</td>
<td>≥65 years old</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Herpes zoster cases among 50 year olds (incidence increases with age)</td>
<td>530</td>
<td>≥50 years old</td>
</tr>
<tr>
<td>Influenza</td>
<td>Laboratory confirmed influenza hospitalization among ≥65 years old in the 2017-2018 season</td>
<td>437</td>
<td>Universal, all adults</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Serogroup B meningococcal meningitis among 16–23 year olds</td>
<td>0.14</td>
<td>Individual clinical decision for healthy 16–23 year olds</td>
</tr>
</tbody>
</table>
Evidence to Recommendations

- **Statement of problem—Work Group Perspective**
- Benefits and harms with GRADE
- Values and preferences of target population
- Acceptability to stakeholders
- Resource use
- Feasibility
Burden of Disease

- PCV13-type disease reduced through indirect effects but burden still remains in older adults
- Uncertainty about the burden of PCV13-type pneumococcal pneumonia
- Since 2014 recommendation, at the population level, no further reductions in IPD, and inconsistent results from pneumonia impact studies
- Question: Is the PCV13-type disease burden still of public health importance?
- Judgement:
  - No
  - Probably no
  - Uncertain
  - Probably yes
  - Yes
ACIP EtR Framework Elements

- Statement of problem
- Benefits and harms with GRADE
- Values and preferences of target population
- Acceptability to stakeholders
- Resource use
- Feasibility
Policy Question

Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in the context of indirect effects from pediatric PCV use experienced to date?

- **Population**: Immunocompetent adults ≥65 years old, with and without chronic medical conditions
- **Intervention**: PCV13 at ≥65 years old in series with PPSV23, in the context of indirect effects
- **Comparison(s)**: PPSV23 alone at ≥65 years old, in the context of indirect effects
- **Outcomes**: invasive pneumococcal disease (IPD), pneumonia, mortality, and PCV13 safety
# Outcomes of Interest

<table>
<thead>
<tr>
<th>Type</th>
<th>Outcomes</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
<td><strong>PCV13-type IPD</strong></td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td><strong>PCV13-type non-bacteremic pneumococcal pneumonia (NIPP)</strong></td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td><strong>PCV13-type disease mortality</strong></td>
<td>Critical</td>
</tr>
<tr>
<td>Harms</td>
<td><strong>Serious adverse events associated with PCV13</strong></td>
<td>Critical</td>
</tr>
</tbody>
</table>

Measures of Effect Evaluated:

- Efficacy/effectiveness: individual-level effects associated with PCV13 use (PCV13 direct effects)
- Impact: population level changes in disease outcomes associated with PCV13 use (PCV13 direct and indirect effects)
Evidence Retrieval

- Systematic review of studies from Medline, Embase, CINAHL, Cochrane, and clinicaltrials.gov databases using search string:
  - (Pneumococcal Vaccin*) OR (pneumococcus vaccin*) OR (pneumonia* vaccin*) OR PCV13 OR pneumovax OR PPSV23 OR prevnar* OR pnu-immune AND senior* OR aged OR older adult* OR elderly OR (over 65) OR (older 65) OR >=65 OR =>65

- Dates January 1, 2014 to July 3, 2018

- Efforts made to obtain unpublished or other relevant data
  - Presentations to the work group from industry and independent researchers
Exclusion Criteria

- Observational studies
  - Low (<20%) PCV13 coverage in the population studied
  - Not applicable to the U.S. population (i.e. low pediatric vaccine coverage, no pediatric PCV13 program, low income country)

- Safety studies
  - PCV13 co-administered with other vaccines*
  - Randomized control trials (RCTs) with comparison groups other than PPSV23 or placebo

*included in the initial review process, but because SAEs could not be attributed to a single vaccine when vaccines were co-administered we excluded these studies from GRADE
Review Process

Unpublished data identified (n=8)

Title and abstract screening (n=2,239)

Full-text article screening (n=364)

Records excluded (n=1,883) (other population, outcomes, or vaccines)

Articles excluded (n=344) (other population, outcomes, or vaccines)

Studies included in GRADE analysis (n=20)
### PCV13 Efficacy, Effectiveness, and Impact on PCV13-type IPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Method</th>
<th>VE</th>
<th>(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonten [1]*</td>
<td>Dutch adults ≥65 years old</td>
<td>Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA) RCT (PCV13 vs placebo) (n=84,496)</td>
<td>75%</td>
<td>(41, 91)</td>
</tr>
<tr>
<td>Gessner [2]*</td>
<td>Dutch adults ≥65 years old</td>
<td>CAPiTA RCT (PCV13 vs placebo) (n=84,496) *</td>
<td>76%</td>
<td>(48, 89)*</td>
</tr>
<tr>
<td>Pilishvili [3]</td>
<td>US adults ≥65 years old</td>
<td>Case-control; Active Bacterial Core Surveillance (ABCs) IPD cases and age- and zip code matched population-based controls (n=1,530)</td>
<td>59%</td>
<td>(11, 81)</td>
</tr>
<tr>
<td>Pilishvili [4]</td>
<td>US adults ≥65 years old</td>
<td>Case-control; ABCs IPD cases enrolled in Medicare part B matched to controls on age group, census tract, and length of enrollment in part B (n=10,851)</td>
<td>47%</td>
<td>(4, 71)</td>
</tr>
<tr>
<td>Unpublished ABCs data [5]</td>
<td>US adults ≥65 years old</td>
<td>Pre-post analysis comparing incidence in 2013-14 vs 2016-17 (n=4,700,000)</td>
<td>-13%</td>
<td>(-26, 2)</td>
</tr>
</tbody>
</table>

*All episodes of PCV13-type IPD using modified intent-to-treat (mITT)

*Pfizer funded studies
Pneumonia Outcomes Included

- **PCV13-type pneumonia** – most specific outcome
  - Studies using Pfizer serotype specific urine antigen test (not commercially available)
  - Not able to detect the serotype for cases caused by non-invasive non-PCV13 types
- **All-cause pneumonia** – most sensitive, but least specific outcome
  - Expected measure of effect small due to smaller proportion of vaccine preventable disease
  - Replacement with non-PCV13-types can obscure impact on PCV13-type disease
# PCV13 Effectiveness and Impact on Pneumonia

— PCV13-type Pneumonia Including IPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Method</th>
<th>VE (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonten [1]*</td>
<td>Dutch adults ≥65 years old</td>
<td>CAPITA RCT (PCV13 vs placebo) (n=84,496)</td>
<td>45% (14, 65)</td>
</tr>
<tr>
<td>McLaughlin [7]*</td>
<td>U.S. adults ≥65 years old</td>
<td>Louisville cohort study [8] nested test negative design case-control; non-PCV13-type pneumonia as controls (n=2,034)</td>
<td>71% (6, 91) i</td>
</tr>
<tr>
<td>Prato [9]*</td>
<td>Italian adults ≥65 years old</td>
<td>Test-negative design case-control; non-PCV13-type pneumonia as controls (n=186)</td>
<td>38% (-131, 89) ii</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% change (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swerdlow [10]*</td>
</tr>
</tbody>
</table>

iIn the primary analysis, reported here, the controls were defined as all non-PCV13-type pneumonia. In a sensitivity analysis, where controls were defined as non-PCV13-type *pneumococcal* pneumonia, the VE was 69% (-47, 93).

ii*S. pneumoniae* confirmed in nasopharyngeal, sputum, bronchoalveolar-lavage, or sterile site on polymerase chain reaction (PCR) or culture

* Pfizer funded study
# PCV13 Effectiveness against Pneumonia — PCV13-type NIPP Exclusively

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Method</th>
<th>VE</th>
<th>(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webber [6]*</td>
<td>Dutch adults ≥65 years old</td>
<td>CAPiTA RCT (PCV13 vs placebo) (n=84,496)</td>
<td>43%</td>
<td>(12, 63)</td>
</tr>
<tr>
<td>McLaughlin [7]*</td>
<td>U.S. adults ≥65 years old</td>
<td>Louisville cohort study [8] nested test negative design case-control; non-PCV13-type pneumonia as controls (n=2,034)</td>
<td>68%</td>
<td>(-6, 90)</td>
</tr>
</tbody>
</table>
## PCV13 Impact on Pneumonia — NIPP

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Method</th>
<th>% Change (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gierke [11]</td>
<td>US adults ≥65 years old</td>
<td>Pre-post analysis comparing incidence in 2013-14 vs 2015-16 (n=1,948,275)</td>
<td>-35% (-14, -49) i</td>
</tr>
</tbody>
</table>

*i No change observed from 2014–2016 (most recent year of data), p=0.5.*
## PCV13 Effectiveness against Pneumonia — All-Cause Pneumonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Method</th>
<th>VE (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gessner [2]</td>
<td>Dutch adults ≥65 years old</td>
<td>CAPiTA RCT (PCV13 vs placebo) (n=84,496) +</td>
<td>8% (1, 15) +</td>
</tr>
<tr>
<td>Lessa [13]</td>
<td>U.S. adults ≥65 years old enrolled in Medicare part A/B</td>
<td>Cohort; discrete time survival model stratified by influenza vaccine receipt and influenza season (n=24,121,625)</td>
<td>6–11% (4, 14)</td>
</tr>
</tbody>
</table>

*All episodes of clinical pneumonia using modified intent-to-treat (mITT) and exact method

*Pfizer funded studies
### PCV13 Efficacy and Impact on Mortality

— PCV13-type Disease Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Method</th>
<th>Outcome</th>
<th>VE</th>
<th>(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonten [1]</td>
<td>Dutch adults ≥65 years old</td>
<td>RCT (PCV13 vs placebo) (n=84,496)</td>
<td>PCV13-type disease mortality</td>
<td>0%</td>
<td>(-1280, 93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All-cause mortality</td>
<td>-0.03%</td>
<td>(-5, 5)</td>
</tr>
<tr>
<td>Unpublished ABCs data [3]</td>
<td>US adults ≥65 years old</td>
<td>Pre-post analysis comparing incidence in 2013-14 vs 2016-17 (n=4,700,000)</td>
<td>PCV13-type IPD mortality</td>
<td>2%</td>
<td>(-30, 49)</td>
</tr>
</tbody>
</table>

*Pfizer funded studies
## Annual Number Needed to Vaccinate (NNV) among Adults ≥65 Years Old*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incidence per 100,000</th>
<th>Vaccine Effectiveness (VE)</th>
<th>(95%CI)</th>
<th>NNV (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13-type IPD</td>
<td>5^a</td>
<td>76%^b</td>
<td>(48, 89)</td>
<td>26,300</td>
</tr>
<tr>
<td>PCV13-type pneumonia, inpatient</td>
<td>17^c–76^d</td>
<td>43%^e</td>
<td>(12, 63)</td>
<td>3,000–14,000</td>
</tr>
<tr>
<td>PCV13-type pneumonia, outpatient</td>
<td>88^f</td>
<td>43%^e</td>
<td>(12, 63)</td>
<td>2,600</td>
</tr>
</tbody>
</table>

*Calculation: NNV= 1/(incidence rate*VE)

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^a Unpublished ABCs data [3]
^b Bonten [1]*
^c Gierke [11], estimated by applying the %PCV13-type IPD to the NIPP incidence estimate
^d Swerdlow [10]*
^e Webber [6]*
^f Nelson et al. 2008, estimated as 5.1% of all-cause outpatient pneumonia is PCV13-type
### Serious Adverse Events (SAEs) from RCTs — PCV13 Safety Critical Outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Study Design</th>
<th>Observation period</th>
<th>% SAE among PCV13 vaccinated</th>
<th>PCV13 (N)</th>
<th>% SAE among controls</th>
<th>Control (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonten [1]*</td>
<td>Dutch adults ≥65 years old</td>
<td>RCT (PCV13 vs placebo)</td>
<td>1 month</td>
<td>0.8%</td>
<td>42,237</td>
<td>0.7%</td>
<td>42,255</td>
</tr>
<tr>
<td>Jackson [14]</td>
<td>US adults 55-74 years old</td>
<td>RCT (PCV13 with and without prior PPSV23)</td>
<td>6 months</td>
<td>2.3%</td>
<td>883</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Juergens [15]*</td>
<td>South African adults ≥65 years old</td>
<td>RCT (PCV13 vs PPSV23)</td>
<td>43 days</td>
<td>0.6%</td>
<td>309</td>
<td>0.3%</td>
<td>301</td>
</tr>
<tr>
<td>Shiramoto [16]*</td>
<td>Japanese adults ≥65 years old</td>
<td>RCT (PCV13 vs PPSV23)</td>
<td>43 days</td>
<td>0.3%</td>
<td>382</td>
<td>0%</td>
<td>382</td>
</tr>
</tbody>
</table>

*Pfizer funded studies
### Serious Adverse Events (SAEs) from Observational Studies — PCV13 Safety Critical Outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Study Design</th>
<th>Observation period</th>
<th>% SAE among PCV13 vaccinated</th>
<th>PCV13 (N)</th>
<th>% SAE among controls</th>
<th>Control (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durando [18]*</td>
<td>Italian adults ≥70 years old</td>
<td>Cohort study</td>
<td>6 months</td>
<td>0.1%</td>
<td>871</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Haber [19]</td>
<td>US adults ≥65 years old</td>
<td>Cohort study (Vaccine Adverse Events Reporting System [VAERS])</td>
<td>--</td>
<td>&lt;0.01%</td>
<td>~9,269,000</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Shiramoto [20]*</td>
<td>Japanese adults ≥50 years old</td>
<td>Cohort study</td>
<td>1 month</td>
<td>0%</td>
<td>271</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tinoco [21]*</td>
<td>Mexican adults ≥65 years old</td>
<td>Cohort study</td>
<td>1 month</td>
<td>1.2%</td>
<td>161</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tseng [22]</td>
<td>US adults ≥65 years old</td>
<td>Cohort study (PCV13 vs PPSV23)</td>
<td>6 months</td>
<td>1.2%-5.8%</td>
<td>5,055</td>
<td>2.4%-5.5%</td>
<td>1,124</td>
</tr>
</tbody>
</table>

*Pfizer funded studies
# GRADE Summary

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Design</th>
<th># studies [references]</th>
<th>Initial Evidence Type</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Evidence Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PCV13-type invasive pneumococcal disease (IPD)</strong></td>
<td>RCT</td>
<td>1 — [1, 2]</td>
<td>1</td>
<td>Not serious</td>
<td>N/A</td>
<td>Serious</td>
<td>Not serious</td>
<td>2</td>
</tr>
<tr>
<td><strong>PCV13-type pneumonia</strong></td>
<td>RCT</td>
<td>1 — [1, 2, 6]</td>
<td>1</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>1</td>
</tr>
<tr>
<td><strong>Mortality from PCV13-type disease</strong></td>
<td></td>
<td>1 — [1]</td>
<td>1</td>
<td>Not serious</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very serious</td>
<td>2</td>
</tr>
<tr>
<td><strong>PCV13-type IPD</strong></td>
<td>Observational</td>
<td>4 — [3-5]</td>
<td>3</td>
<td>Serious</td>
<td>Not serious</td>
<td>Serious</td>
<td>Not serious</td>
<td>4</td>
</tr>
<tr>
<td><strong>PCV13-type pneumonia</strong></td>
<td>Observational</td>
<td>5 — [7, 9-12]</td>
<td>3</td>
<td>Very serious</td>
<td>Very serious</td>
<td>Serious</td>
<td>Very serious</td>
<td>4</td>
</tr>
<tr>
<td><strong>Mortality from PCV13-type disease</strong></td>
<td>Observational</td>
<td>1 — [5]</td>
<td>3</td>
<td>Serious</td>
<td>N/A</td>
<td>Serious</td>
<td>Very serious</td>
<td>4</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>RCT</td>
<td>4 — [1, 13-15]</td>
<td>1</td>
<td>Serious</td>
<td>Not Serious</td>
<td>Serious</td>
<td>N/A</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Observational</td>
<td>5 — [16-20]</td>
<td>3</td>
<td>Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>N/A</td>
<td>2</td>
</tr>
</tbody>
</table>
PCV13 Effects Among Adults ≥65 Years Old

- PCV13 is effective/efficacious in preventing:
  - PCV13-type IPD
  - PCV13-type NIPP, but the effectiveness data inconsistent across studies
- At the population level, no impact on IPD and inconsistent data across studies for impact on pneumonia observed since 2014
- No impact on mortality demonstrated
- No concerning safety signals detected
ACIP EtR Framework Elements

- Statement of problem
- Benefits and harms with GRADE — Work Group Perspective
- Values and preferences of target population
- Acceptability to stakeholders
- Resource use
- Feasibility
Anticipated Desirable Effects

- Summary: PCV13 effective in preventing disease among older adults, but the remaining disease burden low and predominated by serotype 3

- Question: How substantial are the desirable anticipated effects?
- Judgement: Minimal

- Question: What is the overall certainty of this evidence for the critical outcomes?
- Judgement: Low
Anticipated Undesirable Effects

- **Summary:** No concerning safety signals have been detected

- **Question:** How substantial are the undesirable anticipated effects?
  - **Judgement:** Minimal

- **Question:** What is the overall certainty of this evidence for the critical safety outcomes?
  - **Judgement:** 1

<table>
<thead>
<tr>
<th>No included studies</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Very low</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
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</table>

<table>
<thead>
<tr>
<th>Minimal</th>
<th>Small</th>
<th>Moderate</th>
<th>Large</th>
<th>Don’t know</th>
<th>Varies</th>
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</thead>
</table>
Balance of Benefits and Harms of PCV13 Use Among Adults ≥65 Years Old

- Summary: Benefits of continued PCV13 use relatively small, but outweighed the risks, which are also small
- Question: Do the desirable effects outweigh the undesirable effects before considering values, acceptability, recourses used and feasibility?
- Judgement: 
  - Favors intervention
  - Favors comparison
  - Favors both
  - Favors neither
  - Unclear
ACIP EtR Framework Elements

- Statement of problem
- Benefits and harms with GRADE
- **Values and preferences of target population**
- Acceptability to stakeholders
- Resource use
- Feasibility
Values and Preferences of Older Adults

- Evidence: very limited data available
  - Very few studies focus on older adult perceptions of PCV13 specifically
    - Pneumonia perceived as severe (more so than influenza), sometimes fatal illness\(^1\)\(^-\)\(^3\)
    - Low perceived personal susceptibility of pneumonia\(^1\)\(^-\)\(^2\)
- Work group perspective: Potential protection against pneumonia likely outweighs the side effects of PCV13 for older adults

\(^1\) Doshi et al. 2016
\(^2\) Brown et al. 2017 (PPSV23 only)
\(^3\) Kaljee et al. 2017
ACIP EtR Framework Elements

- Statement of problem
- Benefits and harms with GRADE
- **Values and preferences of target population — Work Group Perspective**
- Acceptability to stakeholders
- Resource use
- Feasibility
Values and Preferences of Older Adults

- Question: Do adults ≥65 years old feel that the desirable effects are large relative to the undesirable effects?
  - Judgement:

- Question: Is there important uncertainty about or variability in how much adults ≥65 years old value the main outcomes?
  - Judgement:
ACIP EtR Framework Elements

- Statement of problem
- Benefits and harms with GRADE
- Values and preferences of target population
- **Acceptability to stakeholders**
- Resource use
- Feasibility
Acceptability Evidence

- Limited studies assessing acceptability among stakeholders
- Three studies reviewed by the workgroup found:
  - Current recommendations are confusing for providers\(^1\)
  - Providers recommended continuing with current recommendation\(^2\)
  - Keeping the current recommendations maybe best programmatically if new conjugate vaccines available soon\(^3\)
  - Reimbursement for vaccine is still a programmatic issue\(^3\)

\(^1\) Hurley et al. 2018
\(^2\) Pfizer sponsored provider survey, unpublished, 2018
\(^3\) Association of Immunization Managers (AIM) survey, unpublished, 2018
ACIP EtR Framework Elements

- Statement of problem
- Benefits and harms with GRADE
- Values and preferences of target population
- **Acceptability to stakeholders — Work Group Perspective**
- Resource use
- Feasibility
Deliberations on the Acceptability of Continued PCV13 Use Among Adults ≥65 Years Old

- Considerations for discontinuing PCV13: overall impact on PCV13-type disease from vaccinating older adults is minimal in the context of indirect effects from pediatric PCV use

- Considerations for continuing PCV13
  - PCV13 can provide individual-level protection against remaining burden of disease
  - Frequent changes in recommendations may negatively impact the perceived importance of future adult vaccine recommendations and may present implementation challenges
Assessment Acceptability of Continued PCV13 Use Among Adults ≥65 Years Old

- Question: Is the intervention acceptable to key stakeholders?
- Judgement:

<table>
<thead>
<tr>
<th>No</th>
<th>Probably no</th>
<th>Uncertain</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
</tr>
</thead>
</table>
ACIP EtR Framework Elements

- Statement of problem
- Benefits and harms with GRADE
- Values and preferences of target population
- Acceptability to stakeholders
- **Resource use**
- Feasibility
VE-PPSV against PPSV-type pneumonia = 45%

VE-PCV against PCV-type pneumonia = 73%

Higher PCV-type pneumonia incidence
Higher PCV-type pneumonia CFR

Cost-effectiveness results
Ranges from one-way and multi-way sensitivity analyses

Note: Axis has changed from previous graphs of CERs to accommodate wider range in estimated CERs.

## Resources Used: Comparison of 2013 vs 2019

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>IPD Cases</td>
<td>-226</td>
<td>-163</td>
<td>-76</td>
<td>-84</td>
</tr>
<tr>
<td>Hospitalized Pneumonia Cases</td>
<td>-4,961</td>
<td>-1,858</td>
<td>-2,047</td>
<td>-5,262</td>
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<tr>
<td>Non-hospitalized Pneumonia Cases</td>
<td>-7,252</td>
<td>-2,715</td>
<td>-2,205</td>
<td>-5,611</td>
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<tr>
<td>Deaths due to IPD</td>
<td>-33</td>
<td>-24</td>
<td>-10</td>
<td>-11</td>
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<tr>
<td>Deaths due to Pneumonia</td>
<td>-332</td>
<td>-124</td>
<td>-79</td>
<td>-207</td>
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<tr>
<td>QALYs</td>
<td>3,053</td>
<td>990</td>
<td>709</td>
<td>1,624</td>
</tr>
<tr>
<td>Life-years</td>
<td>4,627</td>
<td>1,587</td>
<td>1,101</td>
<td>2,611</td>
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<tr>
<td>Total Cost</td>
<td>$199</td>
<td>$284</td>
<td>$398</td>
<td>$361</td>
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<tr>
<td>Medical Costs</td>
<td>-$139</td>
<td>-$54</td>
<td>-$25</td>
<td>-$63</td>
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<tr>
<td>Vaccine Costs</td>
<td>$338</td>
<td>$338</td>
<td>$423</td>
<td>$423</td>
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<tr>
<td><strong>Cost/QALY</strong></td>
<td><strong>$65,306</strong></td>
<td><strong>$286,855</strong></td>
<td><strong>$561,417</strong></td>
<td><strong>$222,132</strong></td>
</tr>
<tr>
<td><strong>Cost/Life-year</strong></td>
<td><strong>$43,087</strong></td>
<td><strong>$178,848</strong></td>
<td><strong>$361,367</strong></td>
<td><strong>$138,122</strong></td>
</tr>
</tbody>
</table>
ACIP EtR Framework Elements

- Statement of problem
- Benefits and harms with GRADE
- Values and preferences of target population
- Acceptability to stakeholders
- **Resource use — Work Group Perspective**
- Feasibility
Resources Used

- Summary: Estimated resources used higher now than in 2014
- Question: Is the intervention a reasonable and efficient use of resources?
- Judgment: 

<table>
<thead>
<tr>
<th>No</th>
<th>Probably no</th>
<th>Uncertain</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
</tr>
</thead>
</table>
ACIP EtR Framework Elements

- Statement of problem
- Benefits and harms with GRADE
- Values and preferences of target population
- Acceptability to stakeholders
- Resource use
- Feasibility — Work Group Perspective
Feasibility Considerations

- Current recommendations are complex, but have been integrated into many healthcare and public health systems.
- Universal age-based recommendations are easier to implement than risk-based recommendations.
- Medicare covers pneumococcal vaccination series (PCV13 and PPSV23) for adults $\geq 65$ years old.
  - If a change is made, CMS will review the new recommendation and the supporting evidence.
- Some state regulations that allow public health nurses and pharmacists to provide PCV13 are tied to ACIP recommendations.
- Effective communication strategies will be needed if policy changes are considered.
Feasibility

- Question: Is the current intervention feasible to continue?
- Judgement: Probably yes
ACIP EtR Framework Elements

- Statement of problem
- Benefits and harms with GRADE
- Values and preferences of target population
- Acceptability to stakeholders
- Resource use
- Feasibility
Type of Recommendation

- Options for consideration
  A. We do not recommend the intervention (PCV13 in series with PPSV23 no longer recommended for immunocompetent adults ≥65 years old)
  B. We recommend the intervention for individuals based on clinical decision-making (PCV13 in series with PPSV23 would be given to immunocompetent adults ≥65 years based on patient-provider judgement)
  C. We recommend the intervention (continue PCV13 in series with PPSV23 for immunocompetent adults ≥65 years old)
## Summary of Key Issues

<table>
<thead>
<tr>
<th>Reasons Raised in Favor of Continuing Routine PCV13 Use</th>
<th>Reasons Raised in Favor of Discontinuing Routine PCV13 Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PCV13 effective in preventing PCV13-type pneumococcal disease</td>
<td>• Overall impact on PCV13-type disease from vaccinating older adults is minimal in the context of indirect effects from pediatric PCV use</td>
</tr>
<tr>
<td>• PCV13-type disease has been reduced through indirect effects, but not eliminated</td>
<td>• Low remaining burden of PCV13-type disease limits the potential benefit from direct effects</td>
</tr>
<tr>
<td>• Easier to adhere to universal prevention strategies than to risk-based ones</td>
<td>• Lack of clear population-level impact on disease since 2014</td>
</tr>
<tr>
<td>• Frequent changes in recommendations may negatively impact the perceived importance of future adult vaccine recommendations and may present implementation challenges</td>
<td>• Judicious use of resources</td>
</tr>
<tr>
<td></td>
<td>• Simplification of the recommendations</td>
</tr>
</tbody>
</table>
Next Steps — June 2019

- Provide updated summary of the Evidence to Recommendations framework to ACIP including on studies being finalized:
  - Direct effects:
    1. Mathematical model estimating PCV13 direct and indirect effects against IPD using data from Active Bacterial Core Surveillance updated
    2. Case-control studies estimating PCV13 VE against IPD updated
  - Trends by serotype: Native American Adult Pneumonia Etiology Study updated
  - Acceptability and Feasibility: Adult and Child Consortium for Health Outcomes Research and Delivery Science, primary care provider survey
- Expected ACIP vote
Acknowledgements

- ACIP and the Pneumococcal Work Group
- Evidence Reviewers: Michelle Gaglia, Ryan Gierke, Jennifer Loo Farrar, Amara Fazal, Penina Haber, Miwako Kobayashi, Megan Light, Andrew Leidner, Jenny Milucky, Doug Outcalt-Campos, Asa Ohsaki, Nong Shang, Joanna Taliano, Wei Xing
Thank you!

For more information, contact CDC
1-800-CDC-INFO (232-4636)

cdc.gov/vaccines/pneumoapp

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
GRADE References


