ACIP Evidence to Recommendations Framework

Questions: 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: Adults ≥65 years old, who do not have an immunocompromising condition**, cerebrospinal fluid (CSF) leak, or cochlear implant in the context of indirect effects from pediatric PCV use experienced to date
Intervention: PCV13 at ≥65 years old in series with PPSV23, in the context of indirect effects from pediatric PCV use experienced to date
Comparison(s): PPSV23 alone at ≥65 years old, in the context of indirect effects from pediatric PCV use experienced to date
Outcomes: Invasive pneumococcal disease (IPD), pneumonia, mortality, and PCV13 safety
*Immunocompetent defined in discussion as adults without an immunocompromising condition (chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies), CSF leak, or cochlear implant.
**Immunocompromising conditions include: chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, HIV, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies.

Background: On August 13, 2014, ACIP recommended routine use of 13-valent pneumococcal conjugate vaccine (PCV13) in series with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for adults aged ≥65 years. At the time, the recommendation was warranted because PCV13-type disease burden, in particular PCV13-type pneumonia, was determined to be an important public health problem. However, in the long-term ACIP recognized that continued indirect effects from pediatric PCV13 use could further reduce PCV13-preventable disease among adults and may limit the utility of the recommendation for routine PCV13 use among adults ≥65 years old. Therefore, ACIP proposed that the recommendation for routine PCV13 use among adults ≥65 years old be re-evaluated in 2018 and revised as needed.

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem of public health importance?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☒ *Yes* ☐ *Varies* ☐	**Among adults ≥65 years old:** **PCV13-type IPD incidence (2015–2017)[1]** • **Incidence plateaued at 5/100,000 (20% of all IPD)** • **Common PCV13 serotypes (ST, % of all IPD): 3 (15%), 19A (4%), and 19F (2%)** **PCV13-type pneumonia incidence (2015–2016)** • **Incidence estimates range across studies 17 to 76/100,000 (3.7% of all-cause pneumonia)[2, 3]** • **Common PCV13 serotypes (% of all-cause**	**Disparities in PCV13-type IPD incidence by age [1], ethnicity (Alaskan Natives and Navajos[5]), and presence of underlying medical conditions [6] have been reduced through indirect effects from pediatric PCV13 use but not eliminated.**

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			pneumonia): 3 (1.3%) and 19A (1%)[4]	
BENEFITS & HARMS	How substantial are the desirable anticipated effects?	*Minimal* ☐ *Small* ☒ *Moderate* ☐ *Large* ☐ *Don't know* ☐ *Varies* ☐	**Direct effects from PCV13 use among adults ≥65 years old:** • **PCV13 is effective/efficacious in preventing PCV13-type IPD and Non-Invasive Pneumococcal Pneumonia (NIPP) (See GRADE tables)** • **No effectiveness/efficacy for all-cause or PCV13-type mortality demonstrated (See GRADE tables)** • **Uncertainty about the benefits of PCV13 against ST3 disease; data indicates expected benefits are lower for ST3-type disease than for other PCV13-type disease [7]** • **Estimated cases averted:** o **781 (95%CI: -63, 1713) PCV13-type IPD cases among adults ≥65 years nationwide, Aug 2014–Mar 2018[1]** o **28,600 (95%CI: 21,000– 36,600) pneumonia cases among Medicare Part A/B beneficiaries, Sep 2014–Dec 2017[8]** • **Vaccinating a cohort of 65 year olds with PCV13 would prevent approximately 80 IPD and 4,000–10,000 pneumonia cases over the**	**Indirect effects from PCV use among children reduced pneumococcal disease among adults ≥65 years old** • **PCV13 IPD declined by nine fold [1]** • **All-cause pneumonia reductions observed in most studies [10, 11]** **PCV13 VE against PCV13-type IPD and pneumonia decreases with increasing age at vaccination[12]** • **65% (95%CI: 38, 81) at age 65 years** • **40% (95%CI: 17, 56) at age 75 years** • **Model did not converge at age 85 years**

*See EtR Guide for additional information.

** When no evidence is available, provide transparent reflection by guideline panel on the matter.

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			remaining lifetime of the cohort [9] **Population level impact since 2014 (combined direct and indirect effects)** • **No impact on PCV13-type IPD or mortality (plateau in rates)[1]** • **Inconsistent data across studies for impact on pneumonia[2, 3]**	
	CRITERIA	JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	How substantial are the undesirable anticipated effects?	*Minimal* ☒ *Small* ☐ *Moderate* ☐ *Large* ☐ *Don't know* ☐ *Varies* ☐	**No concerning safety signals seen in studies since the 2014 recommendations were made with at least 40% coverage among adults ≥65 years old. (See GRADE tables)**	**There is no evidence by subgroup within the adult population ≥65 years old of the harms of PCV13 use.**
	Do the desirable effects outweigh the undesirable effects?	*Favors intervention* ☒ *Favors comparison* ☐ *Favors both* ☐ *Favors neither* ☐ *Unclear* ☐	**Benefits of continued PCV13 use relatively small, but outweighed the risks, which are also small.**	

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ACIP Evidence to Recommendations Framework

	What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention No included studies ☐ | 4 Very low ☐ | 3 Low ☒ | 2 Moderate ☐ | 1 High ☐ Safety of the intervention No included studies ☐ | 4 Very low ☐ | 3 Low ☐ | 2 Moderate ☒ | 1 High ☐	**Please see GRADE Tables and Summary.**	**Indirect effects: studies consistently demonstrate large magnitude impacts from pediatric PCV use on disease among adults ≥65 years old.** **Direct effects: PCV13 consistently demonstrated to be effective in post licensure studies. Inconsistent results across studies on the impact on disease: no impact on PCV13-type IPD or pneumococcal pneumonia, but decreased PCV13-type pneumonia and all-cause pneumonia.** **Safety: PCV13 consistently demonstrated to be safe in post licensure studies.**
VALUES	Does the target population feel that the desirable effects are large relative to undesirable effects?	No ☐ | Probably no ☐ | Uncertain ☒ | Probably yes ☐ | Yes ☐ | Varies ☐	**Evidence: very limited data available [13-15]** • **Very few studies focus on older adult perceptions of PCV13 specifically** • **Pneumonia perceived as severe (more so than influenza), sometimes fatal illness** • **Low perceived personal susceptibility to pneumonia**	**Work group perspective:** **Most older adults would value the individual level protection from PCV13 vaccination above the side effects.**
	CRITERIA	JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability ☐ | Possibly important uncertainty or variability ☒ | Probably no important uncertainty or variability ☐ | No important uncertainty or variability ☐ | No known undesirable outcomes ☐	**No evidence identified for this domain.**	**Work group assessment:** **Uncertainty about how much adults ≥65 years old valued the main outcomes, but how important this uncertainty was could not be assessed further because of a lack of evidence.**

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<table>
<tr>
<td>ACCEPTABILITY</td>
<td>Is the intervention acceptable to key stakeholders?</td>
<td>No ☐ | Probably no ☐ | Uncertain ☐ | Probably yes ☐ | Yes ☐ | Varies ☒</td>
<td>Key findings from provider and immunization manager surveys [16-19]
• Current recommendations are confusing for providers
• Providers recommended continuing with current recommendation
• Keeping the current recommendations maybe best programmatically if new conjugate vaccines available soon
• Reimbursement for vaccine is still a programmatic issue</td>
<td>Frequent changes in recommendations may negatively impact the perceived importance of future adult vaccine recommendations. However, credibility comes from evidence-based recommendations.</td>
</tr>
<tr>
<td>RESOURCE USE</td>
<td>Is the intervention a reasonable and efficient allocation of resources?</td>
<td>No ☐ | Probably no ☒ | Uncertain ☐ | Probably yes ☐ | Yes ☐</td>
<td>
<table>
<tr><th>Model</th><th>Base case ($/QALY)</th><th>Range ($/QALY)</th></tr>
<tr><td>CDC</td><td>562,000*</td><td>112,000–2.3 million</td></tr>
<tr><td>Pfizer</td><td>199,000</td><td>46,000–650,000</td></tr>
<tr><td>Pitts-burgh</td><td>765,000</td><td>461,000–2.2 million</td></tr>
</table>
*CDC base case estimate, 222,000 when PCV13 VE for serotype (ST3) increased from 0% to 26% for ST3 IPD and 45% for ST3 pneumonia
</td>
<td>Greatest uncertainty in model inputs for:
• Pneumonia incidence
• PCV13 effectiveness against ST3 disease
• PPSV23 effectiveness against non-invasive pneumonia

Differences between models primarily due to:
• Vaccine effectiveness assumptions, especially PCV13 VE against ST3 pneumonia
• Other less important assumptions
o Case-fatality ratios
o Duration of indirect effects
o Utility assumptions

Reference [9]</td>
</tr>
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ACIP Evidence to Recommendations Framework

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☒ *Yes* ☐ *Varies* ☐	**Universal prevention strategies are easier to adhere to than to risk-based ones.** **Recommendations are complex, but integrated into many health care and public health systems.**	**Frequent changes to recommendations present implementation challenges.** **Change in recommendations could reduce access.** **Discontinuing PCV13 use among older adults would simplify the recommendations, potentially improving adherence.** **Effective communication strategies will be needed if a policy change occurs.**

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced* or *uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐	There is insufficient evidence to determine the balance of consequences ☐
	Opinion varies across the spectrum of this domain.					

Is there sufficient information to move forward with a recommendation?

Yes X

Type of recommendation	We do not recommend the intervention ☐	We recommend the intervention for individuals based on shared clinical decision-making ☐	We recommend the intervention ☐
	A majority of workgroup members proposed voting first on the policy to recommend PCV13 for all adults 65 years and older. This is the current policy and the framing of the policy question. However, when asked which of the three policy options workgroup members favored, the majority favored a change in the current policy. Most of those who favored a change thought that PCV13 should no longer be recommended for older adults.		

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ACIP Evidence to Recommendations Framework

Recommendation (text)	A. **Recommend PCV13**: "ACIP recommends PCV13 for all adults 65 years or older who have not previously received PCV13. PCV13 should be given first, followed by a dose of PPSV23." B. **Shared clinical decision making**: "ACIP recommends PCV13 based on shared clinical decision making for adults 65 years or older who do not have an immunocompromising condition**, cerebrospinal fluid (CSF) leak, or cochlear implant and who have not previously received PCV13. All adults 65 years or older should receive a dose of PPSV23." C. **No longer recommend PCV13**: "ACIP no longer recommends PCV13 for adults 65 years or older who do not have an immunocompromising condition**, cerebrospinal fluid (CSF) leak, or cochlear implant. All adults 65 years or older should receive a dose of PPSV23." **Immunocompromising conditions include: chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, HIV, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies.
Additional considerations (optional)	Reasons in favor of <u>discontinuing</u> routine PCV13 use: • Indirect effects from pediatric PCV use have reduced the burden of PCV13-type disease to historic lows • Overall impact on PCV13-type disease from vaccinating older adults observed to date is minimal; no impact on IPD and inconsistent findings across studies for impact on pneumonia • Benefits from continued PCV13 use are expected to be minimal • Credibility comes from evidence-based recommendations • Economic analyses results do not favor continued PCV13 use • Discontinuing PCV13 use among older adults would simplify the recommendations, potentially improving adherence Reasons in favor of <u>continuing</u> routine PCV13 use: • PCV13-type disease has been greatly reduced but not eliminated through indirect effects from pediatric PCV use • PCV13 is effective in preventing PCV13-type pneumococcal disease • A recommendation change would incur a cost to update electronic medical records, and decision support tools • Universal prevention strategies are easier to implement effectively than risk-based ones • Frequent changes in recommendations may negatively impact the perceived importance of future adult vaccine recommendations and may present implementation challenges

i This Evidence to Recommendation table is based on the GRADE Evidence to Decision framework developed through the *DECIDE* project. Further information is available at http://www.decide-collaboration.eu/evidence-decision-etd-framework

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ACIP Evidence to Recommendations Framework

Final deliberation and decision by the ACIP

Final ACIP recommendation	ACIP does not recommend the intervention ☐	ACIP recommends the intervention for individuals based on shared clinical decision-making ☒	ACIP recommends the intervention ☐
ACIP considerations	On June 26, 2019, ACIP voted to change the policy and recommended PCV13 based on shared clinical decision making for adults ≥65 years old who do not have an immunocompromising condition**, cerebrospinal fluid (CSF) leak, or cochlear implant and who have not previously received PCV13. All adults ≥65 years old should continue to receive one dose of PPSV23. If the decision is made to give PCV13, it should be given ≥1 year before PPSV23. A full description of the deliberations and votes that lead to this decision can be found in the MMWR policy note, Table 3. **Immunocompromising conditions include: chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, HIV, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies.		

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