

Pneumococcal Vaccines: GRADE Tables and Summary

Introduction

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 among adults was assessed to be an important public health problem. However, in the long-term ACIP recognized that continued reductions in PCV13-type disease due to indirect effects from pediatric PCV13 use might limit the utility of this recommendation. Therefore, ACIP proposed that the recommendation for routine PCV13 use among adults ≥65 years old be re-evaluated in 2018 and revised as needed. As part of ACIP's process, a systematic review and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) of the evidence for PCV13 use among adults ≥65 years old was conducted. The policy question was "Should PCV13 be administered routinely to all immunocompetentⁱ adults aged ≥65 years in the context of indirect effects from pediatric PCV use experienced to date?"

Methods

Evidence of benefits and harms for the routine use of PCV13 among adults aged ≥65 years old was reviewed based on the GRADE approach. GRADE was adopted by ACIP in 2010 as the framework for evaluating the scientific evidence that informs recommendations for vaccine use (<https://www.cdc.gov/vaccines/acip/recs/grade/about-grade.html>). The benefits and harms considered as critical outcomes in GRADE are listed in Table 1. The evidence type for each critical outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, and imprecision.

The population was adults aged 65 years and older who do not have an immunocompromising conditionⁱⁱ cerebrospinal fluid (CSF) leak, or cochlear implant; the intervention was PCV13 in series with PPSV23 versus PPSV23 alone, in the context of indirect effects; and the outcomes were prevention of invasive pneumococcal disease (IPD), pneumonia, mortality, and PCV13 safety.

Scientific literature was searched in Medline, Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Cochrane, and clinicaltrials.gov between January 1, 2014 and July 3, 2018. Search terms are listed in the Appendix. This search identified 6,788 references.

The primary reviewer screened title and abstracts. Articles were included if they provided data on vaccination with PCV13 and included primary data on outcomes of interest among ≥65 years old who do not have an immunocompromising conditionⁱⁱ. Efforts were made to obtain additional published studies by cross-referencing included studies' reference lists. Additionally, unpublished studies were sought out by consulting with vaccine manufacturers and subject matter experts. After title and abstract screening, 364 studies were identified for in-depth review. Of these, 344 were among other populations, did not use PCV13, or did not evaluate an outcome of interest. Additionally, observational studies were excluded if the coverage in the population was <20% or if the indirect effects were dissimilar to those experienced in the U.S. (i.e. low pediatric vaccine coverage, no pediatric PCV13 program, low-income country). Randomized control trials (RCT) that examined the safety

ⁱ 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.

ⁱⁱ 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.

outcome were excluded if PCV13 was co-administered with another vaccine, because SAEs could not be attributed to PCV13, and if there was no PPSV23 or placebo comparison group. This left 20 studies for the GRADE analysis [1-20].

Table 1: Critical Outcomes Included in GRADE

Outcomes	Importance	Type
PCV13 efficacy, effectiveness, and impact on PCV13-type IPD	Critical	Benefits
PCV13 efficacy, effectiveness, and impact on PCV13-type non-bacteremic pneumococcal pneumonia (NIPP)	Critical	
PCV13 efficacy, effectiveness, and impact on mortality associated with PCV13-type disease	Critical	
Serious adverse events including deaths associated with PCV13	Critical	Harms

Results

Table 2: PCV13 efficacy, effectiveness, and impact on PCV13-type IPD (critical outcomes)

Study	Population	Method	Outcome	VE	(95%CI)
Bonten [1]*	Dutch adults ≥65 years old	Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA) RCT (PCV13 vs placebo) (n=84,496)	1 st episode of PCV13-type IPD	75%	(41, 91)
Gessner [2]*	Dutch adults ≥65 years old	CAPiTA RCT (PCV13 vs placebo) (n=84,496)	All episodes of PCV13-type IPD using modified intent-to-treat (mITT)	76%	(48, 89)
Pilishvili [3]	US adults ≥65 years old	Case-control; Active Bacterial Core Surveillance (ABCs) IPD cases and age- and zip code matched population-based controls (n=1,530)	PCV13-type IPD	59%	(11, 81)
Pilishvili [4]	US adults ≥65 years old	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)	PCV13-type IPD	47%	(4, 71)
				% change	(95%CI)
Pilishvili [5]	US adults ≥65 years old	Pre-post analysis comparing incidence in 2013-14 vs 2016-17	PCV13-type IPD	-13%	(-26, 2)

*Pfizer funded studies

Table 3: PCV13 efficacy, effectiveness, and impact on pneumonia (critical outcomes)

Study	Population	Method	Outcome	VE	(95%CI)
Bonten [1]* Webber [6]* Gessner [2]*	Dutch adults ≥65 years old	CAPiTA RCT (PCV13 vs placebo) (n=84,496)	1 st episode of PCV13-type pneumonia	45%	(14, 65)
			All episodes PCV13-type pneumonia excluding IPD	43%	(12, 63)
			All episodes clinically confirmed pneumonia	8%	(1, 15)
McLaughlin [7]*	U.S. adults ≥65 years old	Louisville cohort study [8] nested test negative design case-control; non-PCV13-type pneumonia as controls (n=2,034)	PCV13-type pneumonia	71%	(6, 91) ⁱⁱⁱ
			PCV13-type pneumonia excluding IPD	70%	(4, 91)
Prato [9]*	Italian adults ≥65 years old	Test-negative design case-control; non-PCV13-type pneumonia as controls ^{iv} (n=186)	PCV13-type pneumonia	38%	(-131, 89)
Lessa [10]	U.S. adults ≥65 years old enrolled in Medicare part A/B	Cohort; discrete time survival model stratified by influenza vaccine receipt and influenza season (n=24,121,625)	All-cause pneumonia defined by ICD codes	6–11%	(4, 8; 9, 13)
				% change	(95%CI)
Swerdlow [11]*	U.S. adults ≥65 years old	Louisville cohort study [8] pre-post analysis comparing incidence in June 2014-May 2015 vs June 2015-May 2016	PCV13-type pneumonia	-32%	(-8, -49)
Gierke [12]	US adults ≥65 years old	Surveillance for Non-Invasive Pneumococcal Pneumonia (SNiPP) pre-post analysis comparing incidence in 2013-14 vs 2015-16	Non-Invasive Pneumococcal Pneumonia	-35%	(-14, -49) ^v

*Pfizer funded studies

ⁱⁱⁱ In the primary analysis, the controls were defined as all non-PCV13-type pneumonia. In a sensitivity analysis, controls were defined as non-PCV13-type pneumococcal pneumonia (VE 69% [-47, 93]).^{iv} *S. pneumoniae* confirmed in nasopharyngeal, sputum, bronchoalveolar-lavage, or sterile site on polymerase chain reaction (PCR) or culture^v No change observed from 2014–2016 (most recent year of data), p=0.5.

Table 4: PCV13 efficacy, effectiveness, and impact on mortality (critical outcomes)

Study	Population	Method	Outcome	VE	(95%CI)
CAPiTA [1]*	Dutch adults ≥65 years old	RCT (PCV13 vs placebo) (n=84,496)	PCV13-type disease mortality	0%	(-1280, 93)
			All-cause mortality during 4 year follow up period	-0.03%	(-5, 5)
				% change	(95%CI)
Pilishvili [5]	US adults ≥65 years old	Pre-post analysis comparing incidence in 2013-14 vs 2016-17	Death during hospitalization for PCV13-type IPD	2%	(-30, 49)

*Pfizer funded studies

Table 5: PCV13 Safety — serious adverse events (SAEs) reported in randomized control trials (RCT)

Study	Population	Study Design	Observation period	% SAE reported among PCV13 only group	# vaccinated with PCV13	% SAE reported among control group (placebo or PPSV23)	# in the control group
Bonten [1] ^{vi*}	Dutch adults ≥65 years old	RCT (PCV13 vs placebo)	1 month	0.8%	42,237	0.7% ^{vii}	42,255
Juergens [13]*	South African adults ≥65 years old	RCT (PCV13 vs PCV13 without aluminum phosphate vs PPSV23) open-label ^{viii}	43 days	0.6% ^{ix}	309	0.3%	301
Shiramoto [14]*	Japanese adults ≥65 years old	RCT (PCV13 vs PPSV23)	43 days	0.3% ^x	382	0%	382

*Pfizer funded studies

^{vi} Safety sub-study (n=2,011) groups followed for 6 months after vaccination: SAE among PCV13 7% vs placebo 6%, p=0.41

^{vii} No statistically significant difference in all SAEs combined, p=0.61. Safety difference noted were: 23 patients who received PCV13 vs 7 patients who received placebo had general disorders and administration site conditions (p=0.003); 12 patients who received PCV13 vs 2 patients who received placebo had non-cardiac chest pain and 5 patients who received PCV13 vs 1 patients who received placebo had "events of chest pain" though overall 72 patients who received PCV13 v 74 patients who received placebo had cardiac disorders (p=0.9)

^{viii} Additional doses of PCV13 given to those who were part of the initial group who received PCV13; among those who received PCV13 again 1 year later (n=136) SAE 2.2% including 1 death, SAEs deemed not related to the vaccine; among those who received PCV13 again (2 years after previous PCV13 and 1 year after PPSV23) (n=105) SAE 1.9% including 1 death, SAEs deemed not related to the vaccine.

^{ix} All SAEs deemed not related to the vaccine

^x 1 SAE which was deemed not related to the vaccine

Table 6: PCV13 Safety — serious adverse events (SAEs) reported in observational studies

Study	Population	Study Design	Observation period	% SAE among PCV13 only group	# vaccinated with PCV13	% SAE among control group (placebo or PPSV23)	# in the control group
Durando [15]*	Italian adults ≥70 years old	Cohort study (voluntary enrollment after PCV13 vaccination)	6 months	0.1% ^{xi}	871	NA	NA
Haber [16]	US adults ≥65 years old	Passive surveillance through the Vaccine Adverse Events Reporting System (VAERS)	--	<0.01% ^{xii}	~9,269,000 ^{xiii}	NA	NA
Jackson [17]	US adults 55-74 years old	Observational cohort for PCV13 SAE (designed as RCT with varying number of PCV13 doses)	6 months	2.3% ^{xiv}	883	NA	NA
Shiramoto [18]*	Japanese adults ≥50 years old	Cohort study, open-label	1 month	0%	271	NA	NA
Tinoco [19]*	Mexican adults ≥65 years old	Cohort study, open-label	1 month	1.2% ^{xv}	161	NA	NA
Tseng [20]	US adults ≥65 years old	Cohort comparing PCV13 vs PPSV23	6 months	1.2%-5.8%	5,055	2.4%-5.5%	1,124

*Pfizer funded studies

^{xi} 2 SAEs, 1 of which occurred at 29 days post vaccination and was deemed to be possibly related to PCV13. Less than 40% completed 6 month safety follow-up.^{xii} 14 deaths and 138 other SAEs, percentage calculated as 152/9,269,000=0.00164%^{xiii} Approximate denominator calculated using Pfizer reported 23% PCV13 coverage among adults ≥65 years old at the end of this study (December 2015)*40,300,000 ≥65 years old population from the 2010 U.S. Census=9,269,000^{xiv} Overall 27 SAEs among 25 patients; all of which researches deemed not to be vaccine related. Among 883 patients, 1,117 doses of PCV13 so SAE rate=27/1,117=2.3%^{xv} 2 SAEs which were both deemed not related to the vaccine

GRADE Summary

Outcome	Design	# studies — [references]	Initial Evidence Type ^{xvi}	Risk of Bias	Inconsistency	Indirectness	Imprecision	Evidence Type ^{xvi}
Benefits								
PCV13-type invasive pneumococcal disease (IPD)	RCT	1 — [1, 2]	1	Not serious	N/A	Serious ^{xvii}	Serious	3
PCV13-type pneumonia		1 — [1, 2, 6]	1	Not serious	N/A	Serious ^{xvii}	Serious	3
Mortality from PCV13-type disease		1 — [1] ^{xviii}	1	Not serious	N/A	Serious ^{xvii}	Very serious	4
PCV13-type IPD	Observational	3 — [3-5]	3	Serious ^{xix}	Not serious	Not serious	Very serious	4
PCV13-type pneumonia		5 — [7, 9-12]	3	Very serious ^{xx}	Very serious	Serious ^{xxi}	Very serious	4
Mortality from PCV13-type disease		1 — [5]	3	Serious ^{xxii}	N/A	Not serious	Very serious	4
Harms								
Serious adverse events	RCT	3 — [1, 13, 14]	1	Serious ^{xxiii}	Not Serious	Serious ^{xvii}	---	3
	Observational	6 — [15-20]	3	Serious ^{xxiv}	Not Serious	Not Serious	---	3 ^{xxv}

^{xvi} Evidence levels: 1) High, 2) Moderate, 3) Low, 4) Very Low

^{xvii} Downgraded since the RCT (CAPiTA) was among a population with low PCV13 indirect effects from pediatric PCV13 use and low PPSV23 coverage

^{xviii} Mortality was not a primary end-point in this RCT, and there were very few deaths caused by PCV13-type disease

^{xix} Potential unmeasured confounding, misclassification of vaccine status, and indirectness for impact studies that examined the population level impact

^{xx} In addition to the risk of bias for the IPD outcome, the pneumonia outcome studies also had short observation periods and used non-specific outcomes

^{xxi} Two studies did not measure specific outcome of interest (i.e. PCV13-type pneumococcal pneumonia)

^{xxii} Active Bacterial Core surveillance only captures inpatient mortality or in the outpatient setting, deaths that occur very proximally to the diagnosis of IPD

^{xxiii} Modified blinding procedures, open label, and short follow up period

^{xxiv} Inadequate or no control/comparison group

^{xxv} Upgraded since multiple observational studies with consistent results

Summary

In 2014, the GRADE conclusion was that PCV13 was efficacious in preventing PCV13-type disease in aged ≥65 years with an overall moderate level of evidence. Since 2014, there have been 16 studies (2 RCTs and 14 observational) added to the body of evidence. Observational studies are a lower evidence type in GRADE. However, the updated evidence continues to support that PCV13 is efficacious and effective for preventing invasive and non-invasive PCV13-type disease among adults aged ≥65 years. Additionally, there have been no concerning safety signals detected. In addition to safety and efficacy, the current policy question is “in the context of indirect effects from pediatric PCV13 use.” The indirect effects from pediatric PCV used reduced PCV13-type disease in older adults to all-time lows prior to 2014. Since 2014, PCV13 coverage among adults ≥65 years old steadily risen to 40% in 2017 [21]. Since the introduction of PCV13 for all adults aged ≥65 years, no impact on PCV13-type IPD at the population-level has been observed [5] and the data across studies that measure the impact on pneumonia have been inconsistent [11, 12].

At the June 2019 meeting, after reviewing the Evidence to Recommendation Framework (<https://www.cdc.gov/vaccines/acip/recs/grade/PCV13-etr.html>) including the GRADE analysis, 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 conditionⁱⁱ, cerebrospinal fluid (CSF) leak, or cochlear implant and who have not previously received PCV13. For more information see 2019 policy note: Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine Among Adults ≥65 Years Old: Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP) [21].

APPENDIX: Search Methods

Database	Strategy	Run Date	Records
Medline (OVID) 1946-	(Pneumococcal ADJ5 Vaccin*) OR (pneumococcus ADJ5 vaccin*) OR (pneumonia* ADJ5 vaccin*) OR PCV13 OR pneumovax OR PPSV23 OR prevnar* OR pnu-immune AND senior* OR aged OR older adult* OR elderly OR (over ADJ2 65) OR (older ADJ2 65) OR >=65 OR =>65	7/3/2018	4407
Embase (OVID) 1947-	(Pneumococcal ADJ5 Vaccin*) OR (pneumococcus ADJ5 vaccin*) OR (pneumonia* ADJ5 vaccin*) OR PCV13 OR pneumovax OR PPSV23 OR prevnar* OR pnu-immune AND senior* OR aged OR older adult* OR elderly OR (over ADJ2 65) OR (older ADJ2 65) OR >=65 OR =>65 NOT Pubmed/medline	7/3/2018	4822 -2707 duplicates =2115 unique items
CINAHL (Ebsco)	(Pneumococcal N5 Vaccin*) OR (pneumococcus N5 vaccin*) OR (pneumonia* N5 vaccin*) OR PCV13 OR pneumovax OR PPSV23 OR prevnar* OR pnu-immune AND senior* OR aged OR older adult* OR elderly OR (over N2 65) OR (older N2 65) OR >=65 OR =>65 exclude Medline records	7/3/2018	122 -26 duplicates =96 unique items
Cochrane Library	(Pneumococcal NEAR/5 Vaccin*) OR (pneumococcus NEAR/5 vaccin*) OR (pneumonia* NEAR/5 vaccin*) OR PCV13 OR pneumovax OR PPSV23 OR prevnar* OR pnu-immune AND senior* OR aged OR older adult* OR elderly OR (over NEAR/2 65) OR (older NEAR/2 65) OR >=65 OR =>65 NOT	7/3/2018	198 -109 duplicates =89

	PubMed:so		unique items
Clinicaltrials.gov	Pneumococcal Conjugate Vaccine OR pneumococcal polysaccharide vaccine OR PCV13 OR pneumovax OR PPSV23 OR prevnar* OR pne-immune	7/3/2018	181

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