13-valent pneumococcal conjugate vaccine (PCV13) effects on disease caused by serotype 3

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Rationale

- Serotype 3 (ST3) causes most of the remaining PCV13-type disease burden in the US and countries using PCV13
- Evidence on PCV13 effectiveness against ST3 disease not consistent across settings/studies
- Assumptions around PCV13 effects on ST3 disease influence estimates of expected vaccine impact and results of economic analyses

Background

- ST3 pneumococcal strains:
  - Unique genetic, phenotypic, physiologic characteristics associated with invasiveness and disease severity
  - Temporal variations in incidence potentially unrelated to vaccine introduction
- Various mechanisms by which reduced effectiveness against ST3 explained
  - mucoid ST3 capsule was shown to release free polysaccharides (animal model study)[1]
  - interferes with antibody-mediated bacterial killing and protection
  - reduced opsonophagocytosis due to increased thickness/density of polysaccharide capsule[2]

[1]Choi et al. Clin Vaccine Immunol. 2016

[2]Poolman et al. Vaccine 2009

Serotype specific immune response and effectiveness against IPD[1]

	Vaccine effectiveness (95% CI)	Predicted vaccine effectiveness at 0·35 µg/mL ELISA cutoff*	Calculated correlate of protection in µg/ml for ELISA* (95% CI)
PCV13			
1	84% (54 to 95)	96%	0·78 (0·47 to 1·68)
3	26% (–69 to 68)	97%	2·83 (1·16 to ∞)
6A†	98% (64 to 99·8)	90%	0·16 (0·08 to 1·05)
7F	91% (70 to 98)	98%	0·87 (0·40 to 1·80)
19A	67% (33 to 84)	95%	1·00 (0·60 to 2·47)
5	..	89%	..

Key points:

- **Estimated threshold of protection was higher for ST3 IPD, compared with other PCV13 types[1]**
- **Thresholds for protection against acquisition of nasopharyngeal carriage are much higher than those for IPD**
- **No evidence to suggest PCV13 impacts ST3 carriage[2]**
- **Therefore, no herd effect from childhood PCV13 programs could be expected**

[1]Andrews et al. Lancet ID 2014

[2]Summary of systematic review for WHO SAGE Position paper. February 2019 (https://www.who.int/immunization/documents/positionpapers/en/)

PCV13 effects on IPD caused by serotype 3

- Effectiveness in children
- Population-level impact in children and adults (indirect effects)
- Effectiveness in adults

Effectiveness of PCV13 against ST3 IPD in children

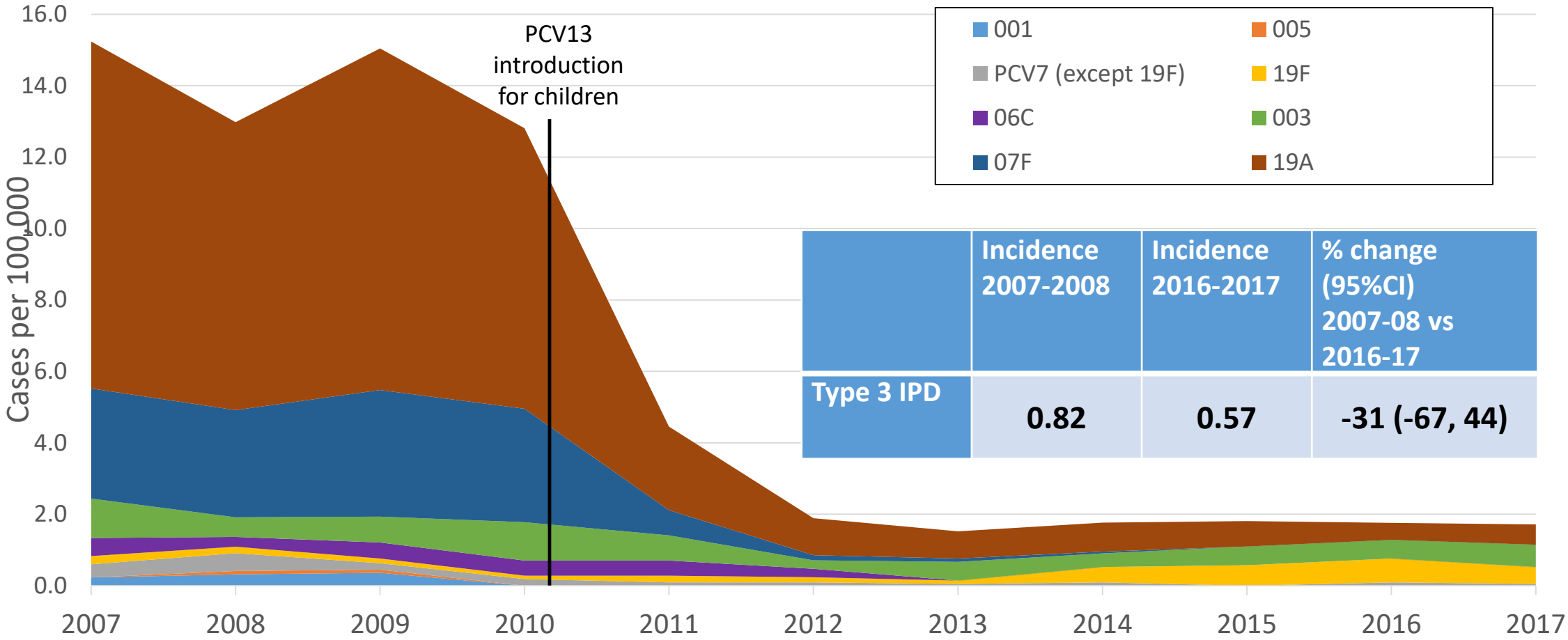
Country	Age group and schedule	VE (95% CI)
Canada (Deceuninck 2018)	≥1 dose at 2-59 months	20% (-265% to 82%)
USA (Moore 2016)	≥1 dose at 2-59 months	80% (30% to 95%)
Germany (VanderLinden 2016)	≥1 dose at 2-23 months	74% (2% to 93%)
Germany (Weinberger 2016)	≥2 doses before 12 months of age and 1 dose at 12 months or later	0% (-791 to 89%)
UK (Andrews 2014)	≥2 doses before 12 months of age and 1 dose at 12 months or later	26% (-69% to 68%)
Spain (Dominguez 2016)	≥1 doses at 7-59 months of age	26% (-65% to 67%)

- WHO position statement based on systematic review of primary evidence on immunogenicity and effectiveness against IPD, pneumonia, and NP carriage for PCV10 and PCV13 in children
- "Despite immunogenicity data, evidence for a direct or indirect reduction in IPD due to serotype 3 after administration of PCV13 was inconclusive, although most studies showed no effect."
- PCV10 does NOT contain types 3, 19A, and 6A

Product choice

Both PCV10 and PCV13 have substantial impacts against pneumonia, vaccine-type IPD and NP carriage…PCV13 may have an additional benefit **in settings where disease attributable to serotype 19A or serotype 6C is significant.**

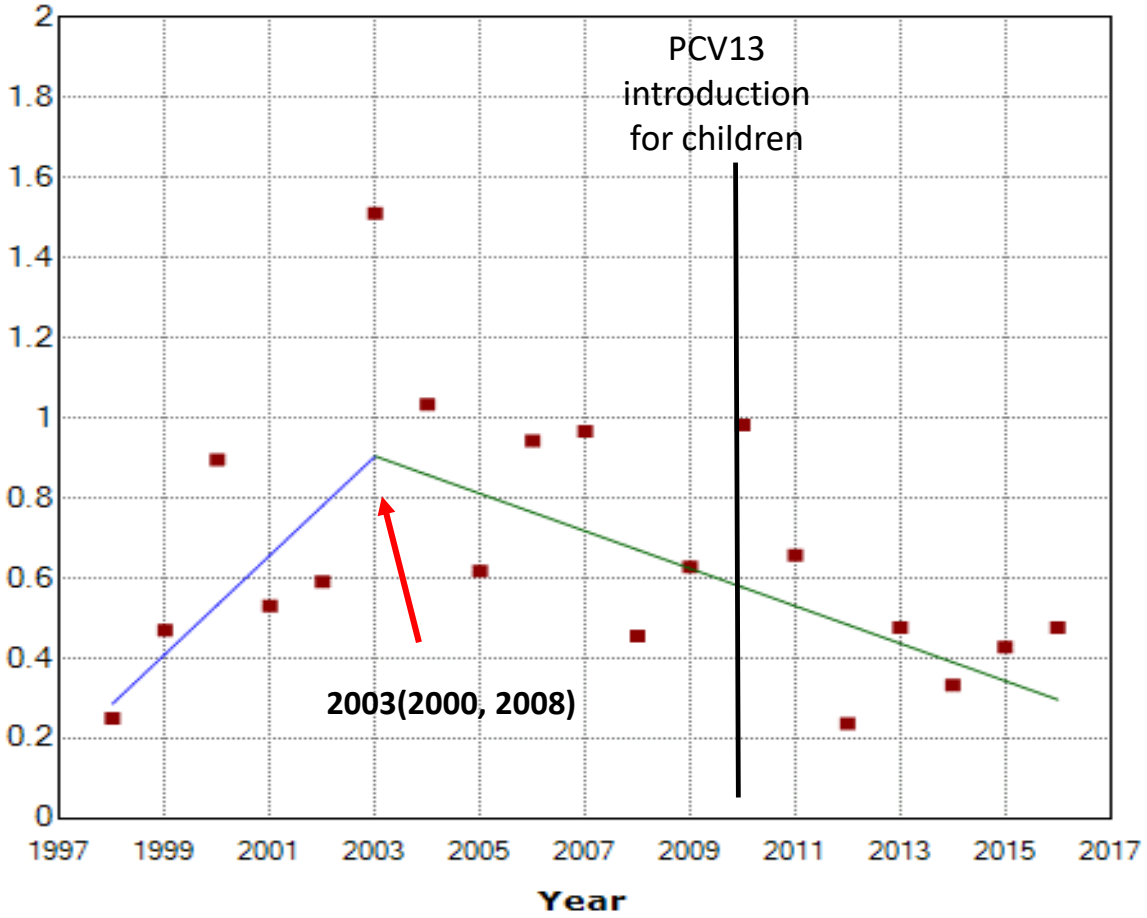
PCV13-type IPD rates among children < 5 years old by serotype, 2007 –2017



	Incidence 2007-2008	Incidence 2016-2017	% change (95%CI) 2007-08 vs 2016-17
Type 3 IPD	0.82	0.57	-31 (-67, 44)

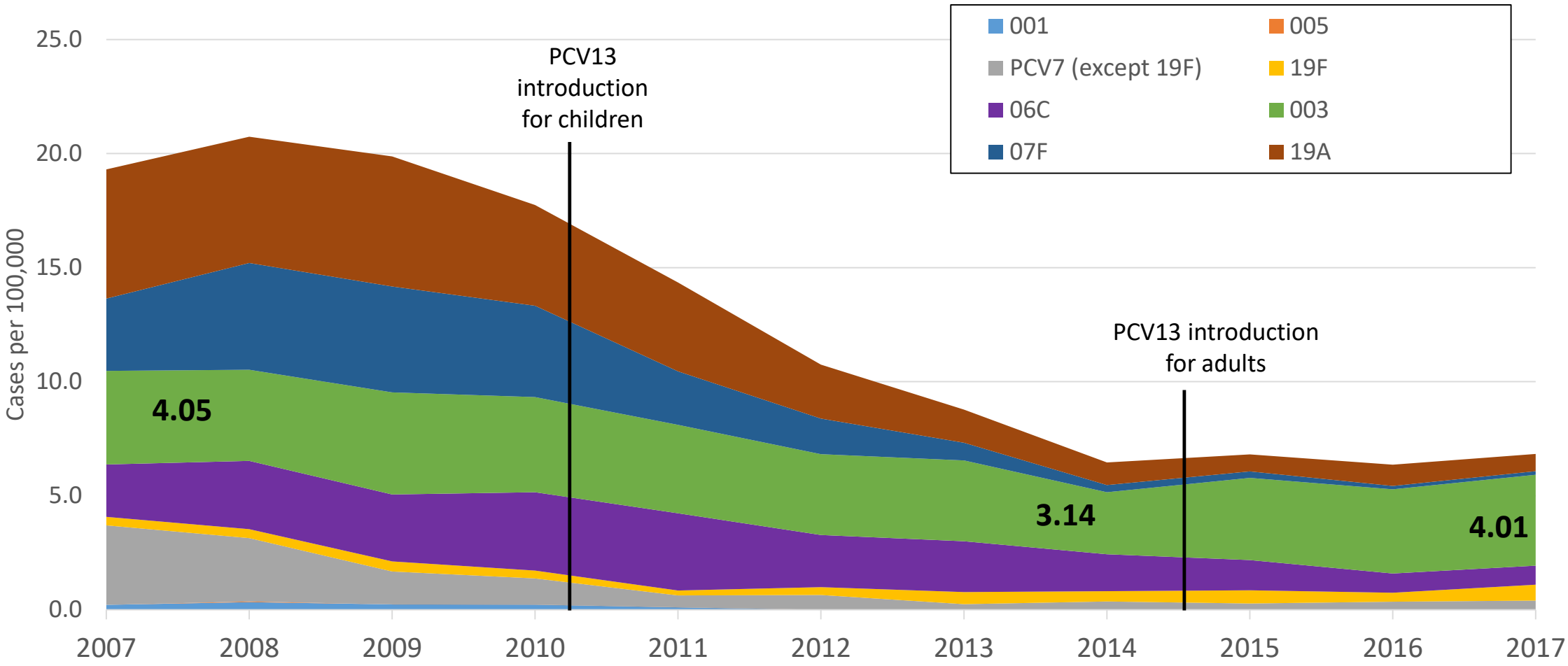
Changes in serotype 3 IPD incidence, 1998–2017

Children <5 years



Active Bacterial Core Surveillance, CDC unpublished data

PCV13-type IPD rates among adults ≥65 years old by serotype, 2007 – 2017



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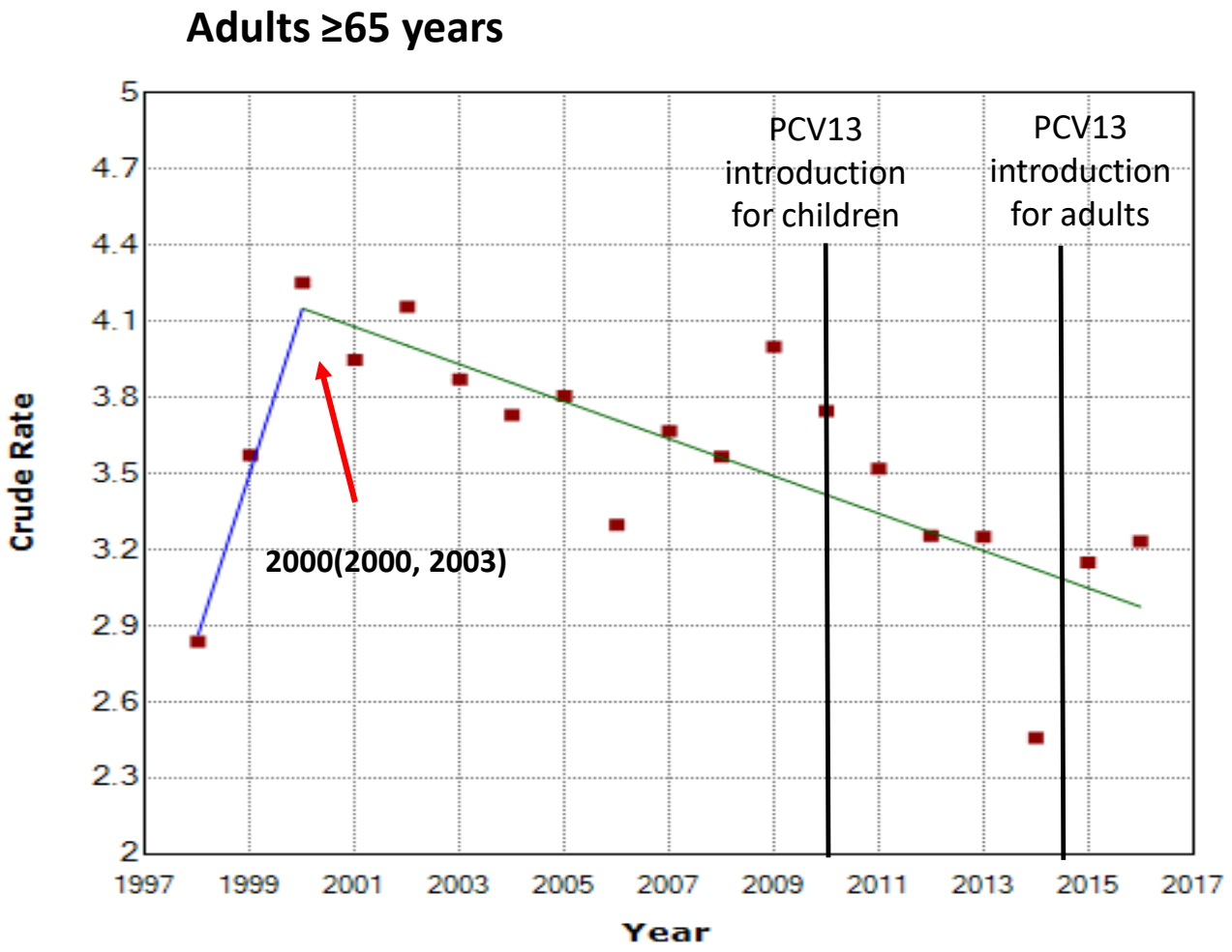
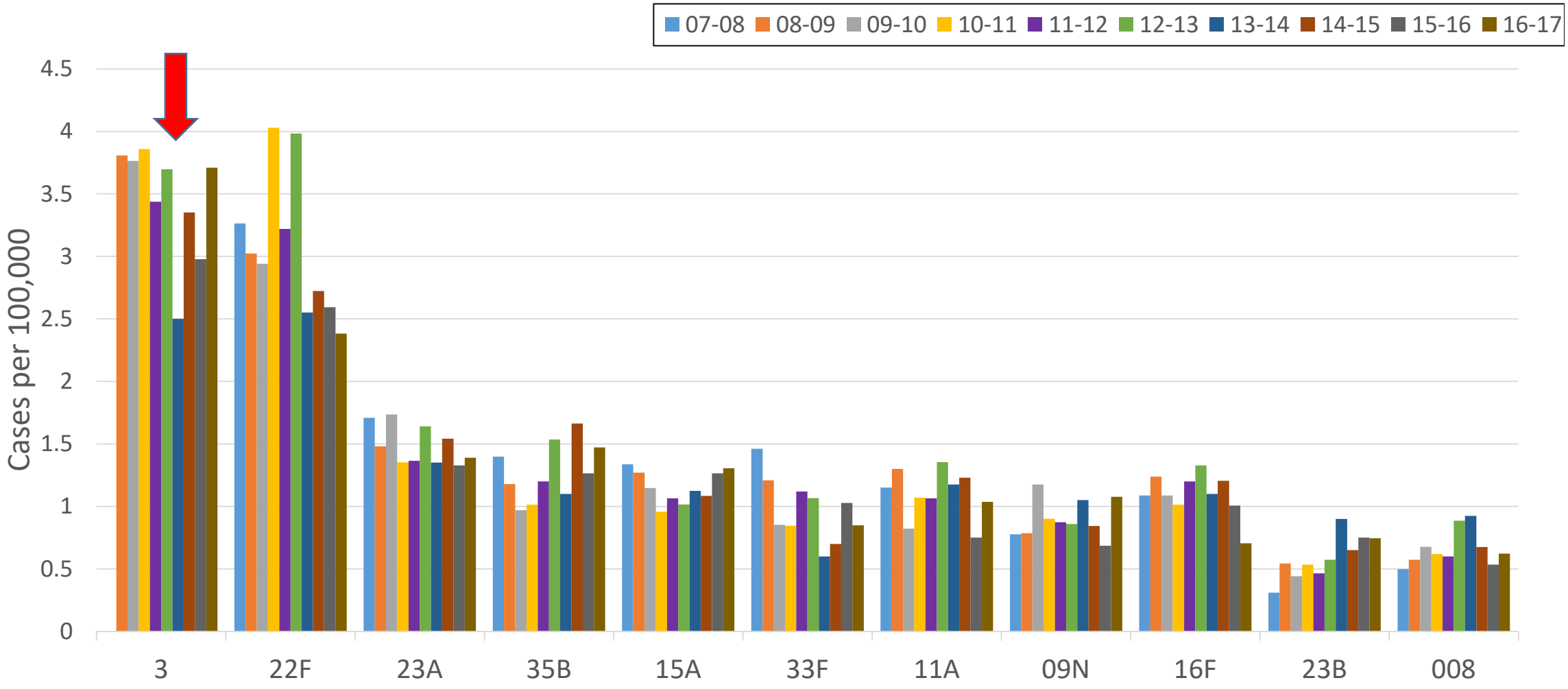


Active Bacterial Core Surveillance, CDC unpublished data

IPD rates among adults ≥65 years old, July 2007 – June 2017, top serotypes 2015-2017



Active Bacterial Core Surveillance, CDC unpublished data

Cumulative estimated number of PCV13-type IPD cases prevented through administration of PCV13 to adults ≥65 years (direct effects) 8/2014–5/2017

	Observed (A)	Predicted, if no PCV13 use in adults (B)	Cases prevented through PCV13 direct effects	
			ABCs cases	US cases
PCV13-type (+6C) cases	907	924 (860, 990)	17 (-47, 83)	190 (-470, 870)
PCV13-type (+6C) cases (excluding type 3)	416	472 (427, 520)	56 (12, 104)	580 (120, 1080)

(B)-(A): Total number of PCV13-type IPD cases prevented in adults ≥65 years through PCV13 direct effects based on (observed IPD cases) minus (estimated cases in a setting of indirect effects only)

Active Bacterial Core Surveillance, CDC unpublished data

Case-control study evaluating PCV13 effectiveness among US Medicare beneficiaries 65 year or older by vaccine serotype group

	N discordant sets	Unadjusted model		Adjusted model*	
All IPD	320	14%	(-11, 33)	**24%**	**(2, 41)**
PCV13-type	62	30%	(-27, 62)	36%	(-18, 65)
PCV13-type + 06C	71	**44%**	**(0, 69)**	**47%**	**(4, 71)**
PCV13-type+6C (no 3)	34	**64%**	**(6, 86)**	**67%**	**(11, 88)**
Type 3	37	22%	(-64, 63)	26%	(-58, 65)
Non-Vaccine types	103	4%	(-47, 37)	13%	(-36, 44)

*Adjusted for gender, presence of chronic and immunocompromising conditions

CDC's Active Bacterial Core Surveillance and CMS collaboration, unpublished data

PCV13 Effectiveness against ST3 IPD

Study	Population	Method	VE (95%CI)
CAPiTA [1, 2] *	Dutch adults ≥65 years old (n=84,496)	Post-hoc analysis (0 cases in PCV13 arm, 4 cases in control arm)	100% (-52, 100)

*Pfizer funded study

1.Bonten MJM, et al. *NEJM*. 2015

2. Gessner et al. In press

PCV13 effects on **pneumonia** caused by serotype 3

Pneumonia caused by serotype 3

- Limited studies available evaluating serotype-specific pneumonia burden and vaccine effectiveness
- No commercially available tests to detect pneumococcal serotypes causing non-bacteremic pneumonia
- Studies utilizing Pfizer-developed serotype-specific urine antigen test (SSUAD)

PCV13 Effectiveness against ST3 Pneumonia

Study	Population	Method	VE (95%CI)
CAPiTA [1, 2] *	Dutch adults ≥65 years old (n=84,496)	RCT (PCV13 vs placebo), 1st episode	
		Per protocol	56.3% (-12, 85)
		mITT	60.0% (5, 85)
		Post-hoc analysis, all clinical CAP, 1st episode	61.5% (18, 83)
Louisville cohort study [3]*	U.S. adults ≥65 years old	Nested test negative design case-control; non-PCV13-type pneumonia as controls (n=2,034)	52.8% (-100, 89)

*Pfizer funded study

1.Bonten MJM, et al. *NEJM*. 2015

2. Gessner et al. In press

3.McLaughlin JM, et al. *Clin Infect Dis.* 2019

Population-level impact on ST3 pneumonia
Pfizer-supported Louisville Pneumonia Study

	Year 1 Jun 2014 – May 2015	Year 2 Jun 2015 – May 2016	Absolute Difference	% Relative Reduction
	Incidence Rate per 100,000 per year (95% Confidence Interval*)			
≥65y All	**PCV13 coverage, May 2015† = 11.1%**	**PCV13 coverage, May 2016† = 35.6%**		
All-cause CAP	2412 (2317, 2511)	2080 (1992, 2172)	332	13.8 (8.5, 18.7)
PCV13-type CAP	112 (93, 135)	76 (61, 96)	36	31.5 (8.3, 48.9)

*95% confidence interval is based on Poisson distribution.
†Uptake estimates are specific to Louisville (Jefferson County) Kentucky and were based on IQVIA administrative claims (numerator) and US Census data (denominator).
CAP=community-acquired pneumonia; PCV13=13-valent pneumococcal conjugate vaccine; SSUAD=PCV13 serotype-specific urinary antigen detection assay.

[1] Swerdlow et al June 2018 ACIP pneumococcal session presentation

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	Oct 2014-Sep 2015	Oct 2015-Sep 2016		
% of CAP Caused by ST3 [2]	0.78%	1.26%		
	Incidence Rate per 100,000 per year			
ST3 CAP[3]	18.8	26.2	+7.4	

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Expected incidence through direct effects in 2016 = (Incidence at baseline) x (VE) x (Coverage)

= 18.8 x 61.5% (VE) x 35.6% (Coverage) ≈ **14.7**

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[2] Courtesy of Pfizer, unpublished data
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Summary

In children

- **PCV13 effectiveness against ST3 IPD:**
  - Inconsistent findings with most studies showing no effectiveness
  - Duration of protection likely short (EU network study)
  - VE higher for toddler doses (US vs UK, Germany)

- **No population-level impact on ST3 IPD demonstrated in the US and countries using PCV13**

Summary

In adults

- **PCV13 effectiveness against ST3 IPD in adults**:
  - Non-statistically significant VE in CAPiTA post-hoc analysis (not powered)
  - Low (and not significant) effectiveness in one case-control study
- **No population-level impact on ST3 IPD demonstrated in the US and countries using PCV13 among adults (indirect or direct)**
- **PCV13 effectiveness against ST3 pneumonia in adults:**
  - Moderate (not significant) effectiveness against ST3 CAP among adults in 2 Pfizer supported studies (CAPiTA and Louisville TND)
  - Effectiveness demonstrated in a post-hoc and mITT analysis of CAPiTA
- **Limited data on population-level impact on ST3 pneumonia; no evidence of impact in one cohort study by 2016 (~36% coverage)**

Conclusions

- PCV13 may provide some level of direct protection against IPD and pneumonia caused by serotype 3
  - Inconsistent findings across studies and populations
  - Effectiveness is lower as compared to other PCV13-types (IPD)
- Given VE and PCV13 coverage to date (~40%), population-level impact is expected
- No evidence of population-level impact on type 3 disease to date
  - Limited duration of protection
  - No impact on carriage = continued circulation and exposure of susceptible individuals
- High-level of uncertainty remains on the expected benefits of PCV13 against type 3 disease
- Assumptions around inputs for VE vs ST3 disease for models estimating expected public health benefits from PCV13 use in adults should consider a range of values
  - No effectiveness (VE=0%) to account for studies with 95% CI for VE cross the null value
  - Point estimates for VE against ST3 IPD and pneumonia

Thank you!

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