Rethinking Number-Needed-to-Vaccinate for Adult Pneumococcal Conjugate Vaccine in the United States:

Accounting for long-term public health impact against community-acquired pneumonia

27th ECCMID, Vienna, Austria, April 25, 2017

John M. McLaughlin, PhD, David L. Swerdlow, MD, Raul E. Isturiz, MD
Pfizer Vaccines, Collegeville, PA, USA.

contact information: john.mclaughlin@pfizer.com

Disclosures:
all authors are employees and may be shareholders of Pfizer Inc

John McLaughlin, PhD

David Swerdlow, MD

Raul Isturiz, MD

Background & Rationale: NNV as a metric

- Number-needed-to-vaccinate (NNV) is increasingly used by vaccine technical committees and policymakers to inform decisions about vaccine use
  - e.g., public health impact, cost-effectiveness
- Generally speaking, lower NNVs correspond to more impactful and cost-effective interventions
- However, NNV is not always calculated uniformly
- Many current approaches tend to inflate NNV— in some cases these can be gross underestimations of vaccine impact

Background & Rationale: e.g., PCV13 in US Adults

- **In 2014, the US CDC estimated NNV with PCV13 to prevent one case of hospitalized CAP in adults aged ≥65**[1]
  - Part of evidence base for 2014 Advisory Committee on Immunization Practices (ACIP) deliberations about routine use of PCV13 in adults[1]
  - Used previous standard NNV formula put forth by Kelly et al (2004)[2]
  - Recommendations will be formally revisited by ACIP in 2018[3]
- **Kelly et al formula suited only for vaccines with duration of protection of ≤1 year, otherwise NNV is inflated**[4,5]
- **PCV13 has been shown to have duration of protection of at least 4 years in the CAPiTA study**[6,7]

Note: all references are listed on the last slide

Objectives

To compare two methodologies for calculating NNV with PCV13 to prevent one case of community-acquired pneumonia (CAP) among adults aged ≥65 years:

1. *Kelly et al NNV Formula (2004)*[2] *used by CDC in 2014*[1]*:* using annual (1-year) absolute *rate* difference
2. *NNV based on Original Number-needed-to-treat (NNT) (1995)*[8]*:* using absolute *risk* reduction over 5 years

Note: all references are listed on the last slide

What's the Difference Between an Incidence Rate and Cumulative Incidence?

- **Incidence Rate (IR)**
  - Number of new cases ("incidence") per unit of time ("rate")
  - Expressed as a rate (typically per 100k persons per year or person-years)
  - Almost always expressed annually
  - Difference between IRs is absolute *rate* difference

- **Cumulative Incidence (CI)**
  - Number of new cases during a defined time period divided by the number of persons at risk in the population at the study start
  - Expressed as a proportion or percentage
  - Difference in CIs is absolute *risk* difference

2 Approaches: NNV Based on Annual Incidence Rate *vs.* Cumulative Incidence Over Time

Criteria	Kelly et al NNV (2004)[2]	Original NNT (1995)[8]
Definition	number of people that need to be vaccinated to prevent one event attributed to disease <u>per year</u>	number of people that need to be treated to prevent one event attributed to disease <u>over a specified time period</u>

where, **NNT** is the number-needed to treat, **NNV** is the number-needed to vaccinate, **CI** is the cumulative incidence, **IR** is annual incidence rate, **0** represents the reference treatment or placebo, **1** the treatment under study, **VE** is vaccine effectiveness, **ARR** is absolute risk reduction

2 Approaches: NNV Based on Annual Incidence Rate *vs.* Cumulative Incidence Over Time

Criteria	Kelly et al NNV (2004)[2]	Original NNT (1995)[8]
Definition	number of people that need to be vaccinated to prevent one event attributed to disease <u>per year</u>	number of people that need to be treated to prevent one event attributed to disease <u>over a specified time period</u>
Formula	$NNV_{Kelly\ et\ al} = \frac{1}{IR_0 - IR_1} = \frac{1}{IR_0 * VE}$	$NNT = \frac{1}{CI_0 - CI_1} = \frac{1}{CI_0 * VE} = \frac{1}{ARR}$

where, **NNT** is the number-needed to treat, **NNV** is the number-needed to vaccinate, **CI** is the cumulative incidence, **IR** is annual incidence rate, **0** represents the reference treatment or placebo, **1** the treatment under study, **VE** is vaccine effectiveness, **ARR** is absolute risk reduction

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Components	annual (1-year) incidence rate, VE	cumulative incidence over time, VE

where, **NNT** is the number-needed to treat, **NNV** is the number-needed to vaccinate, **CI** is the cumulative incidence, **IR** is annual incidence rate, **0** represents the reference treatment or placebo, **1** the treatment under study, **VE** is vaccine effectiveness, **ARR** is absolute risk reduction

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Components	annual (1-year) incidence rate, VE	cumulative incidence over time, VE
1 / x	absolute *rate* reduction among treated/vaccinated	absolute *risk* reduction among treated/vaccinated

where, **NNT** is the number-needed to treat, **NNV** is the number-needed to vaccinate, **CI** is the cumulative incidence, **IR** is annual incidence rate, **0** represents the reference treatment or placebo, **1** the treatment under study, **VE** is vaccine effectiveness, **ARR** is absolute risk reduction

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Components	annual (1-year) incidence rate, VE	cumulative incidence over time, VE
1 / x	absolute *rate* reduction among treated/vaccinated	absolute *risk* reduction among treated/vaccinated
Inflates NNV when…	**vaccine provides protection for >1 year**	

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PCV13 in 65+: Standard NNV Methodology (Kelly et al.)

- In 2014, CDC calculated NNV to prevent one case of hospitalized CAP among adults aged ≥65 years as part of ACIP deliberations (GRADE)[1] using the formula from Kelly et al[2]

- **Assumed** (i) annual IR of hospitalized CAP was 1375 per 100,000[9]
  (ii) 10% of CAP was PCV13-type (ie, 137.5 per 100,000)[3]
  (iii) 45% PCV13 efficacy against PCV13-type CAP[6]

$$NNV_{Kelly\ et\ al} = \frac{1}{IR_0 - IR_1} = \frac{1}{IR_0 * VE} = \frac{1}{\left(\frac{137.5}{100{,}000}\right) * 0.45} = 1616 \approx \mathbf{1620}$$

- **BUT, Kelly et al formula ignores the cumulative effect of PCV13 in adults over time**

Note: all references are listed on the last slide

PCV13 in 65+: New (Cumulative) NNV Methodology

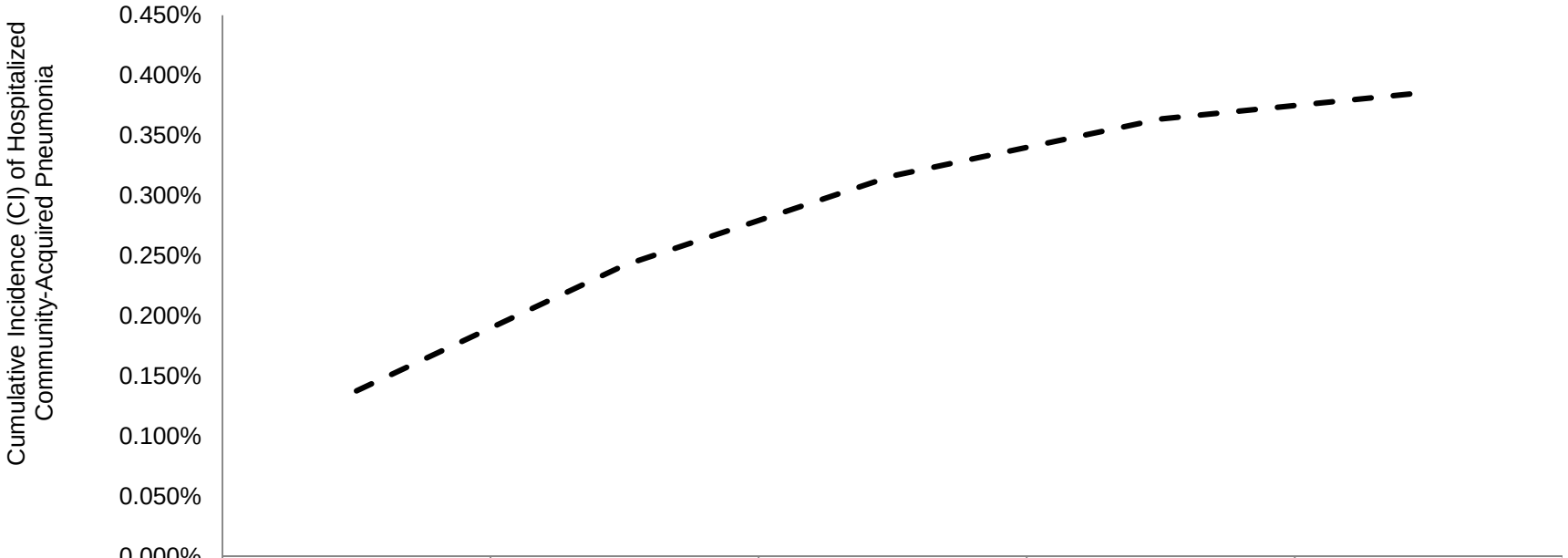
Assumptions to Model Cumulative PCV13 Effects in Adults ≥65 Over 5 Years

Model Input	Assumption	Reference
Cohort age group	65 years and older	n.a.
Vaccine cohorts	PCV13 vaccinated (n=100,000) Unvaccinated (n=100,000)	n.a.
Model time horizon	**5 years, Sept 2014 – Aug 2019**	n.a.
Annual mortality rate	**5 per 100 per year (5%)**	US Census[10]
IR of hospitalized CAP	1375 per 100,000 per year	Simonsen et al[9] ACIP 65+ GRADE[1]
% of CAP caused by PCV13 serotypes	**10, 8, 6, 4, and 2 in years 2014/15–2018/19, respectively**	Tomczyk et al[3] ACIP 65+ GRADE[1]
PCV13 VE against PCV13-type CAP	45% **for all 5 years** (ie, no waning)	CAPiTA[6,7]

= additional assumptions to account for cumulative impact of PCV13

Results

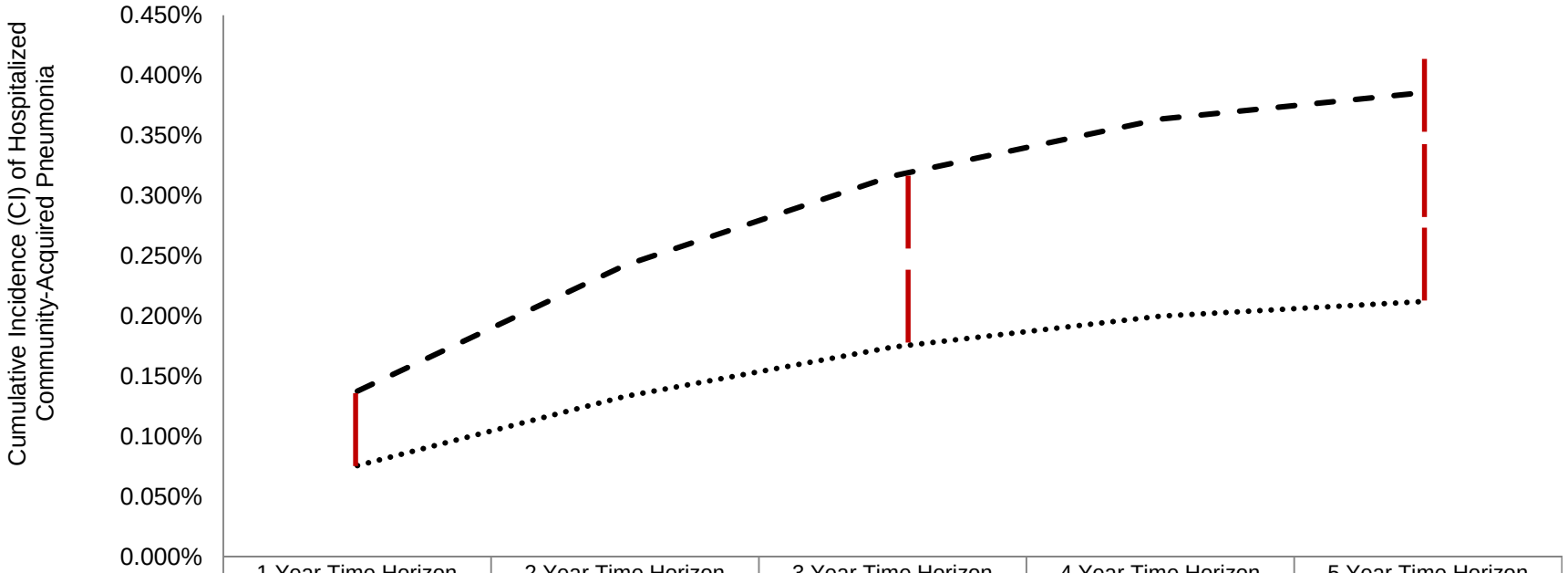
Cumulative Incidence of Hospitalized CAP Among Unvaccinated Adults ≥65 Over 5 Years (Sept 2014 − Aug 2019)



	1 Year Time Horizon Sept. 2014 − Aug. 2015	2 Year Time Horizon Sept. 2014 − Aug. 2016	3 Year Time Horizon Sept. 2014 − Aug. 2017	4 Year Time Horizon Sept. 2014 − Aug. 2018	5 Year Time Horizon Sept. 2014 − Aug. 2019
CI, No PCV13	0.138%	0.242%	0.316%	0.364%	0.386%

Results

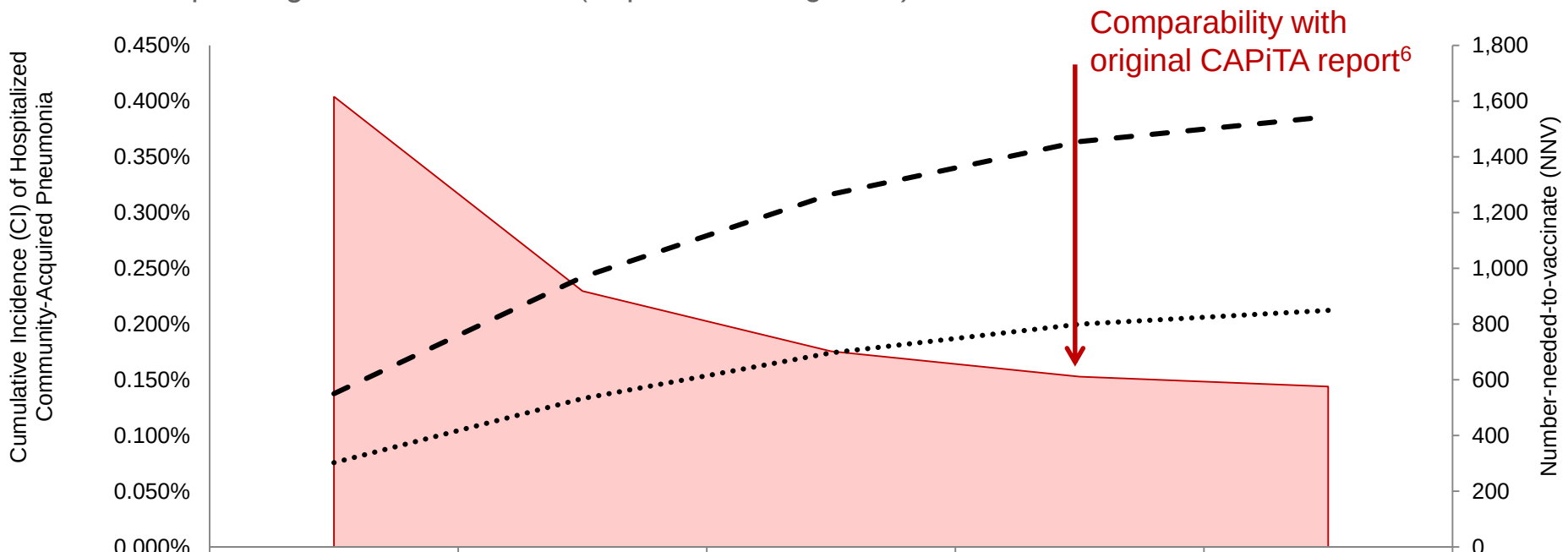
Cumulative Incidence of Hospitalized CAP Among Unvaccinated and PCV13-Vaccinated Adults ≥65 Over 5 Years (Sept 2014 − Aug 2019)



	1 Year Time Horizon Sept. 2014 − Aug. 2015	2 Year Time Horizon Sept. 2014 − Aug. 2016	3 Year Time Horizon Sept. 2014 − Aug. 2017	4 Year Time Horizon Sept. 2014 − Aug. 2018	5 Year Time Horizon Sept. 2014 − Aug. 2019
CI, No PCV13	0.138%	0.242%	0.316%	0.364%	0.386%
CI, PCV13	0.076%	0.133%	0.174%	0.200%	0.212%

Results

Cumulative Incidence of Hospitalized CAP Among Unvaccinated and PCV13-Vaccinated Adults ≥65 and Corresponding NNV Over 5 Years (Sept 2014 − Aug 2019)



	1 Year Time Horizon Sept. 2014 − Aug. 2015	2 Year Time Horizon Sept. 2014 − Aug. 2016	3 Year Time Horizon Sept. 2014 − Aug. 2017	4 Year Time Horizon Sept. 2014 − Aug. 2018	5 Year Time Horizon Sept. 2014 − Aug. 2019
NNV	1,616	918	702	611	576
CI, No PCV13	0.138%	0.242%	0.316%	0.364%	0.386%
CI, PCV13	0.076%	0.133%	0.174%	0.200%	0.212%

Our NNV Estimates in Perspective

Estimated NNV to prevent one case of CAP among adults aged ≥65 Years, by Study and Design

NNV Parameter	CDC 2014 ACIP GRADE 65+[1]
Time Horizon	1
Hosp. CAP IR based on	Simonsen et al.[9]
One case of hospitalized CAP	1620
One case of outpatient CAP	1110
One case of any CAP	656

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Estimated NNV to prevent one case of CAP among adults aged ≥65 Years, by Study and Design

NNV Parameter	CDC 2014 ACIP GRADE 65+[1]	Leo et al. NEJM Ed. 2015[11] (Unadj. for missed CAPiTA cases)
Time Horizon	1	3.97
Hosp. CAP IR based on	Simonsen et al.[9]	Bonten et al. CAPiTA[6]
One case of hospitalized CAP	1620	1030
One case of outpatient CAP	1110	n.a.
One case of any CAP	656	n.a.

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NNV Parameter	CDC 2014 ACIP GRADE 65+[1]	Leo et al. NEJM Ed. 2015[11] (Unadj. for missed CAPiTA cases)	van Werkhoven et al. J. Clin Epi 2015 (Unadj. for missed CAPiTA cases)[12]
Time Horizon	1	3.97	3.97
Hosp. CAP IR based on	Simonsen et al.[9]	Bonten et al. CAPiTA[6]	Bonten et al. CAPiTA[6]
One case of hospitalized CAP	1620	1030	1007
One case of outpatient CAP	1110	n.a.	n.a.
One case of any CAP	656	n.a.	n.a.

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Time Horizon	1	3.97	3.97	3.97
Hosp. CAP IR based on	Simonsen et al.[9]	Bonten et al. CAPiTA[6]	Bonten et al. CAPiTA[6]	Bonten et al. CAPiTA[6]
One case of hospitalized CAP	1620	1030	1007	**634**
One case of outpatient CAP	1110	n.a.	n.a.	n.a.
One case of any CAP	656	n.a.	n.a.	n.a.

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Our NNV Estimates in Perspective

Estimated NNV to prevent one case of CAP among adults aged ≥65 Years, by Study and Design

NNV Parameter	CDC 2014 ACIP GRADE 65+[1]	Leo et al. NEJM Ed. 2015[11] (Unadj. for missed CAPiTA cases)	van Werkhoven et al. J. Clin Epi 2015 (Unadj. for missed CAPiTA cases)[12]	van Werkhoven et al. J. Clin Epi 2015 (Adj. for missed CAPiTA cases)[12]	McLaughlin et al. 2017 ECCMID
Time Horizon	1	3.97	3.97	3.97	4 (5 – 3)
Hosp. CAP IR based on	Simonsen et al.[9]	Bonten et al. CAPiTA[6]	Bonten et al. CAPiTA[6]	Bonten et al. CAPiTA[6]	Simonsen et al.[9]
One case of hospitalized CAP	1620	1030	1007	**634**	**611** (576 – 702)
One case of outpatient CAP	1110	n.a.	n.a.	n.a.	418 (394 – 480)
One case of any CAP	656	n.a.	n.a.	n.a.	248 (234 – 285)

Note: all references are listed on the last slide

Conclusions

- PCV13 was recommended for all US adults aged ≥65 in 2014, but this recommendation will be revisited in 2018[3]
- When CDC originally estimated NNV to prevent CAP among adults aged ≥65,[1] the standard formula derived by Kelly et al (2004) was used[2]
- Kelly et al ignores any effect of vaccines beyond 1 year[2,4,5]
- PCV13 has demonstrated VE beyond 1 year in older adults[6,7]
- Revised NNV estimates that account for PCV13 duration of protection in adults were **approximately one-third of the original NNV** estimates calculated by CDC
  - Implying that PCV13 has nearly 3-times more value in adults than was originally estimated

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References

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Thank You