PRIME Study:
PCV Review of Impact Evidence

SAGE

10/18/2017

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on behalf of the PRIME Study Team

PCV Review of Impact Evidence (PRIME):

Objective

Provide up-to-date summary of evidence on:
PCV immune response, **effectiveness** and **impact**

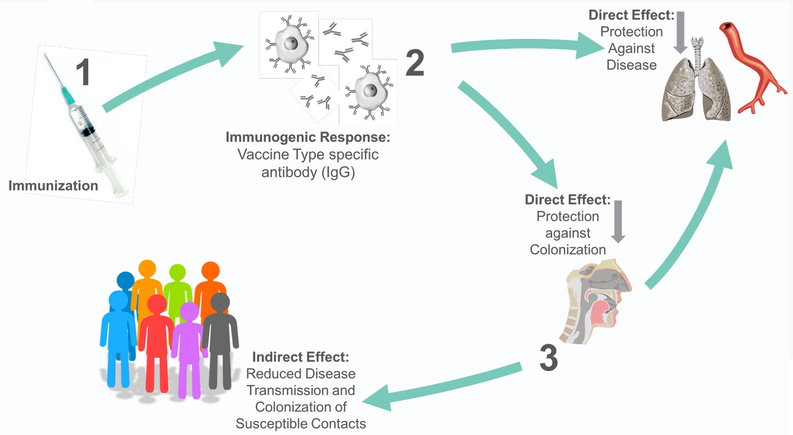
METHODS:

- Systematic review published 1994-2017
- Clinical trials and observational studies of routine use
- 3-dose schedule (2+1 and 3+0)
- PCV10 and PCV13

OUTCOMES:

PCV effectiveness and impact on:

- Immunogenicity
- Nasopharyngeal carriage
- Invasive disease (**IPD**)
- *Pneumonia*
- *Mortality*



ANALYSES:

- Meta-analyses for immunogenicity
- Descriptive summary for other outcomes due to differences in methods and epidemiologic settings
- Considered:
  - previous PCV7 use,
  - age (<5 years and >5),
  - dosing schedule,
  - time since introduction,
  - catch-up program

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PRIME Inclusion/Exclusion Criteria:

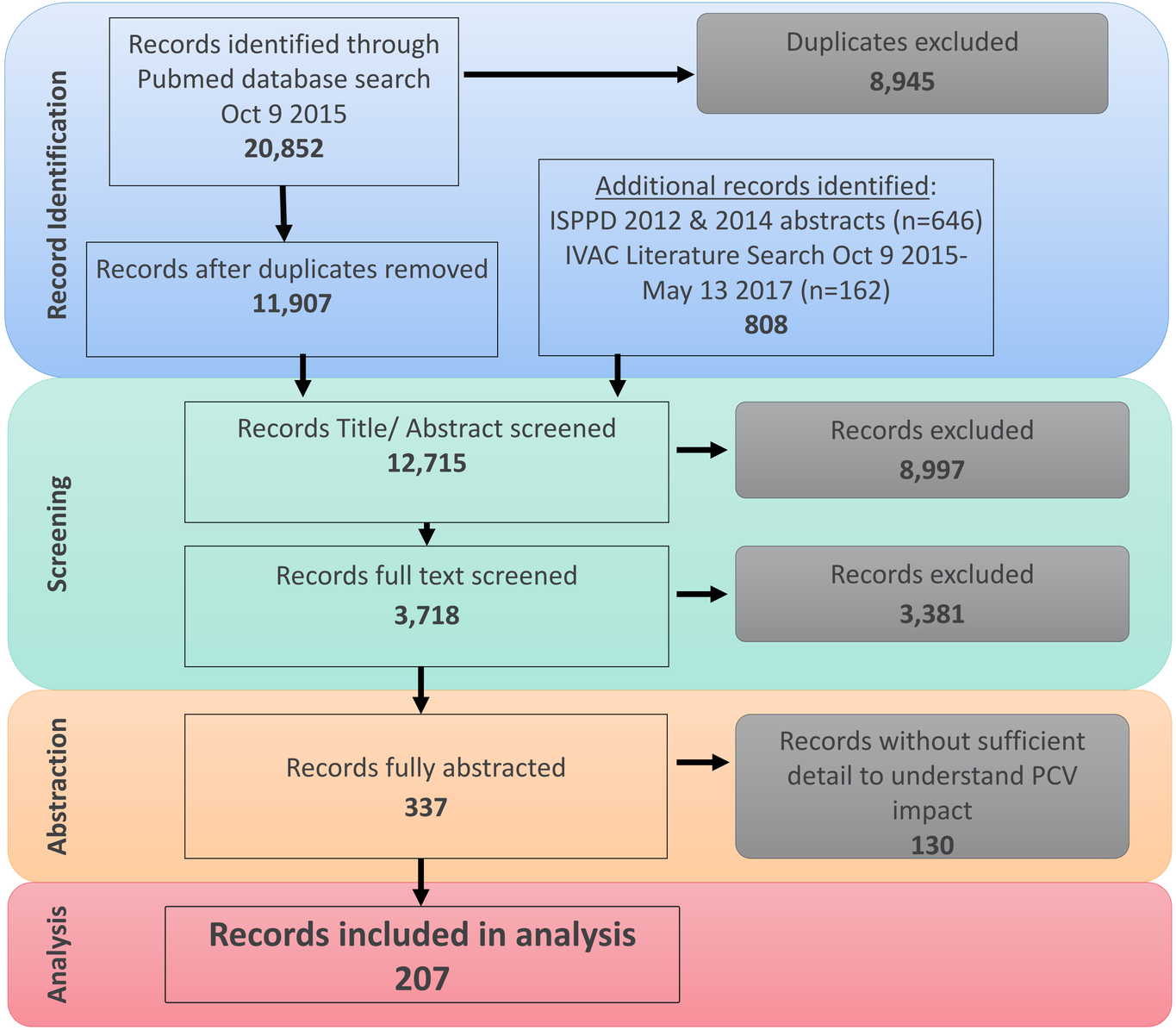
Included:

- Product: PCV10 or PCV13
- Dosing Schedule: 3+0 or 2+1
  - 2+0 and 3+1 included where technically relevant
- Outcomes:
  - vaccine-type immunogenicity (IgG GMC, % Responders),
  - vaccine-type nasopharyngeal carriage,
  - vaccine-type invasive pneumococcal disease (**IPD**)
- Study types: clinical trials, observational studies reporting pre- and post-vaccine introduction incidence rates for disease outcomes or prevalence for carriage

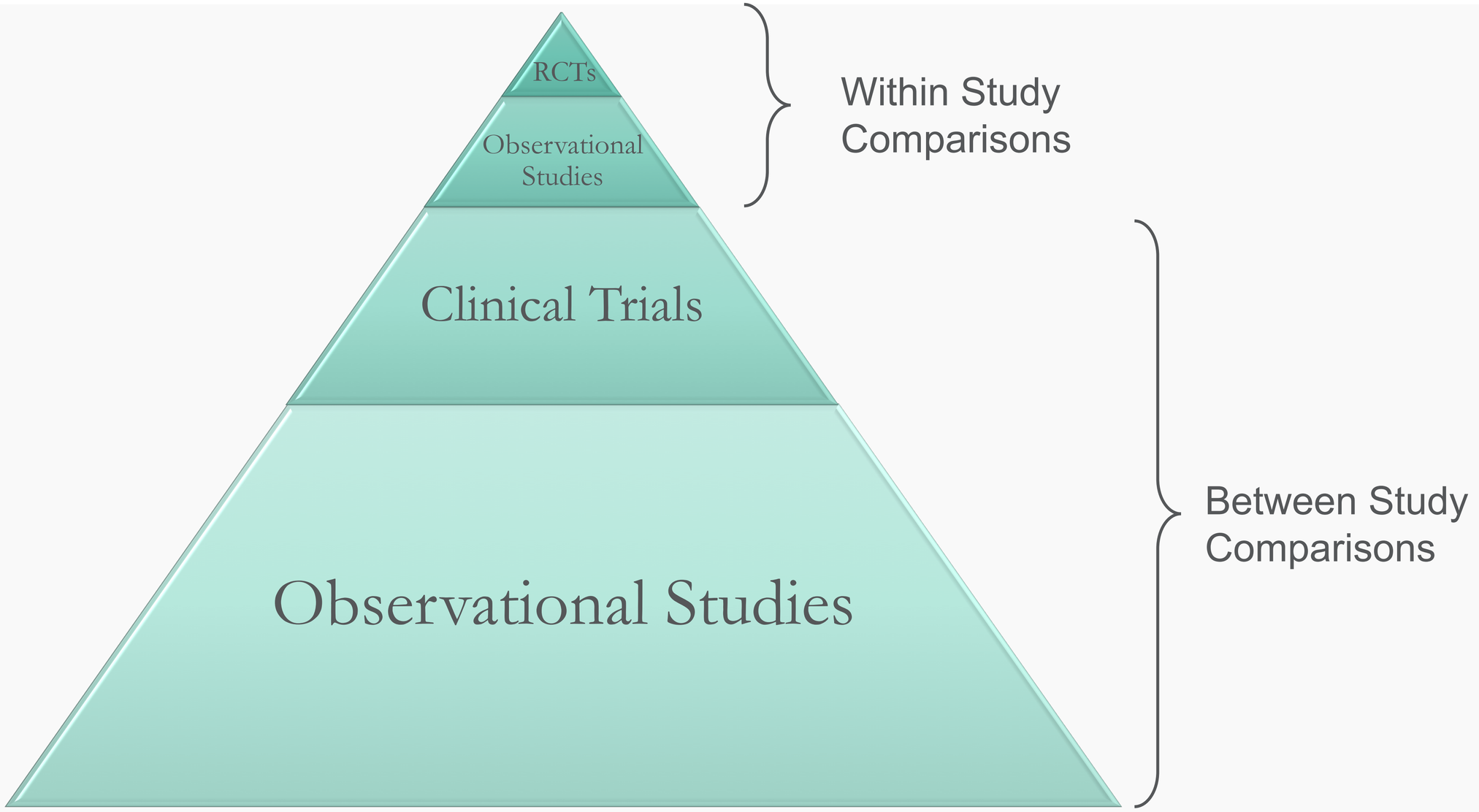
Excluded:

- Outcomes: otitis media, immunogenicity measured by opsonophagocytic activity or avidity
- Study types: Post-only disease incidence data; case-series data for disease outcomes (i.e., no denominator)
- Indirect effects: studies with less than 3 years of PCV10/13 use

PRISMA: Inclusion/Exclusion Report



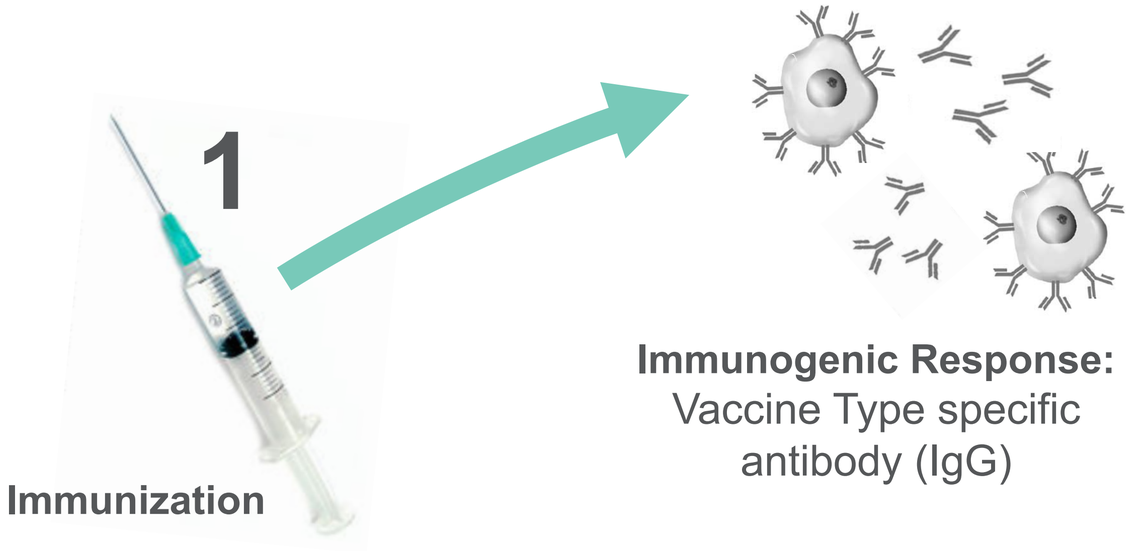
Data Hierarchy: Available Evidence



PICO Question 1: Schedule Comparison

Intervention	**2p+1 vs. 3p+0 schedule**
Population	• Vaccinated children (direct effects) • Unvaccinated older children and adults (indirect effects)
Outcomes	• Immunogenicity • NP carriage • IPD

PCV Modes of Action

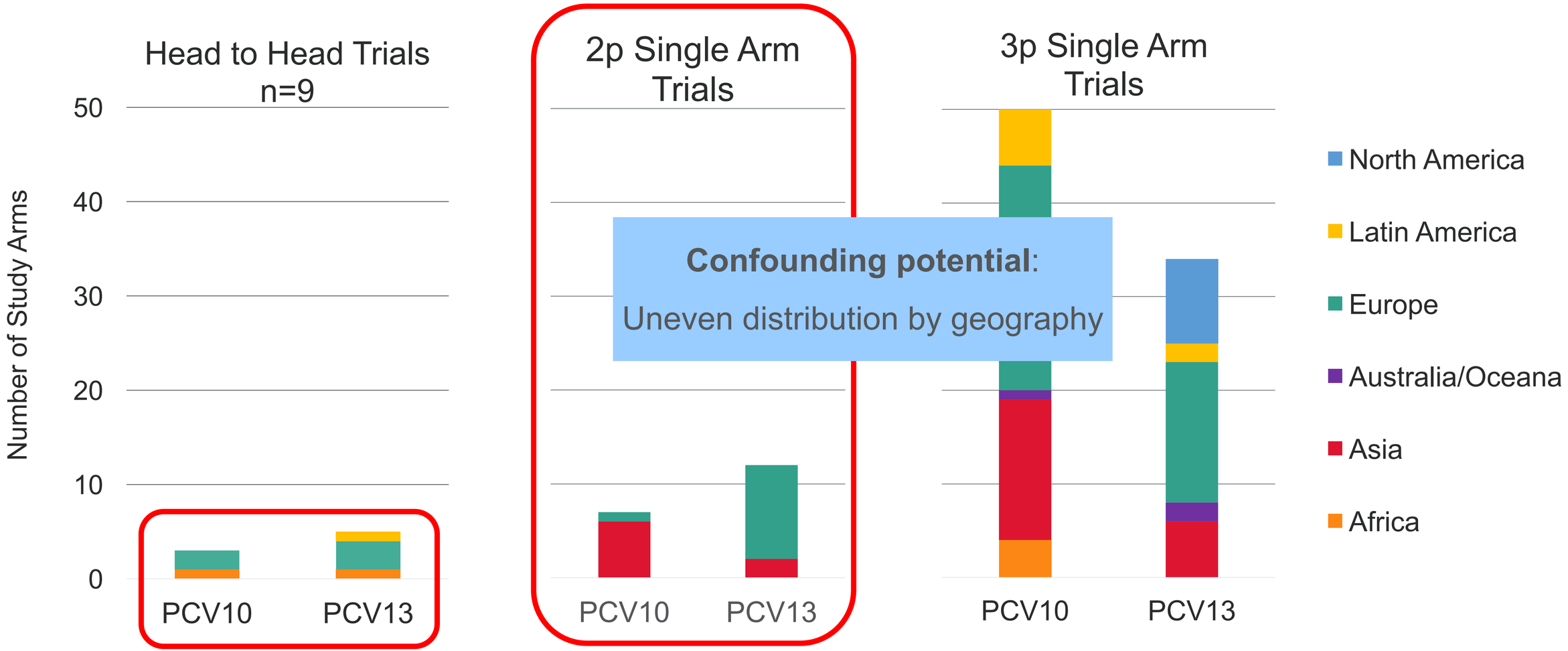


Immunogenic Response:
Vaccine Type specific antibody (IgG)

Immunogenicity

Schedule Comparison Results: Immunogenicity

Included Study Arms by Dosing Schedule, PCV Product and Region:



2p = 2 Primary Doses; 3p = 3 Primary Doses

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Schedule Comparison Results: Immunogenicity

Head to Head Comparison of Schedules: IgG geometric mean concentration (GMC)

Analysis: meta-analysis of 9 randomized clinical trials

Post Primary (i.e. 2 vs 3 doses):

Results	Serotype
GMC: Similar	3 19F
GMC: Favors 3p	1 5 7F 14 19A
	6A 6B 23F

Post-Dose 3 (i.e., at age 4m vs. 15m):

Results	Serotype
GMC: Similar	3 19A
GMC: Favors 2+1	1 5 6A 7F 14 19F 23F
	6B

- GMC reflects amount of antibody, not necessarily *protection*
- Higher GMC does not necessarily correlate to better protection if there is a threshold for protection

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Schedule Comparison Results: Immunogenicity

Head to Head Comparison of Schedule: Percent Response (above correlate of protection)

Post Primary (i.e. 2 vs 3 doses):

Results	Serotype
GMC: Similar **%Response: Similar**	3 19F
GMC: Favors 3p **%Response: Similar**	1 5 7F 14 19A
GMC: Favors 3p **%Response: Favors 3p**	6A 6B 23F

Post-Dose 3 (i.e., at age 4m vs. 15m):

Results	Serotype
GMC: Similar **%Response: Similar**	3 19A
GMC: Favors 2+1 **%Response: Similar**	1 5 6A 7F 14 19F 23F
GMC: Favors 2+1 **%Response: Favors 2+1**	6B

Results: Similar % Response between schedules for most STs;
-- Favors 3+0 in the primary series for 6A, 6B, 23F
-- Favors 2+1 for 6B

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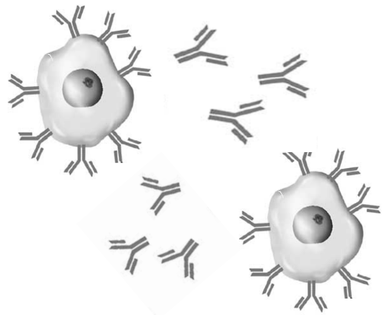
PCV Modes of Action

1

Immunization



Immunogenic Response:
Vaccine Type specific antibody (IgG)

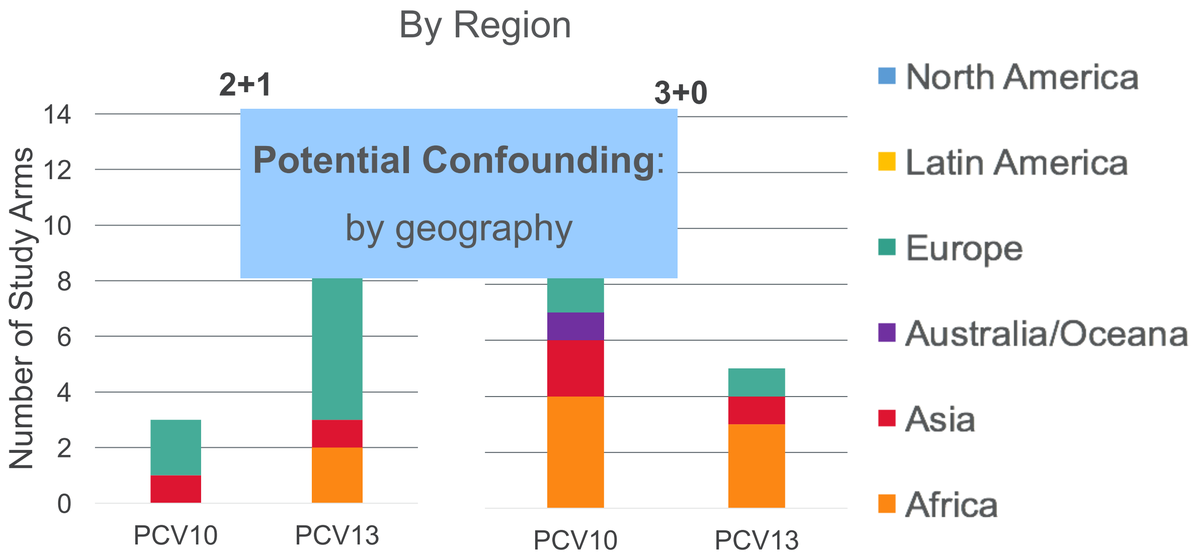
2

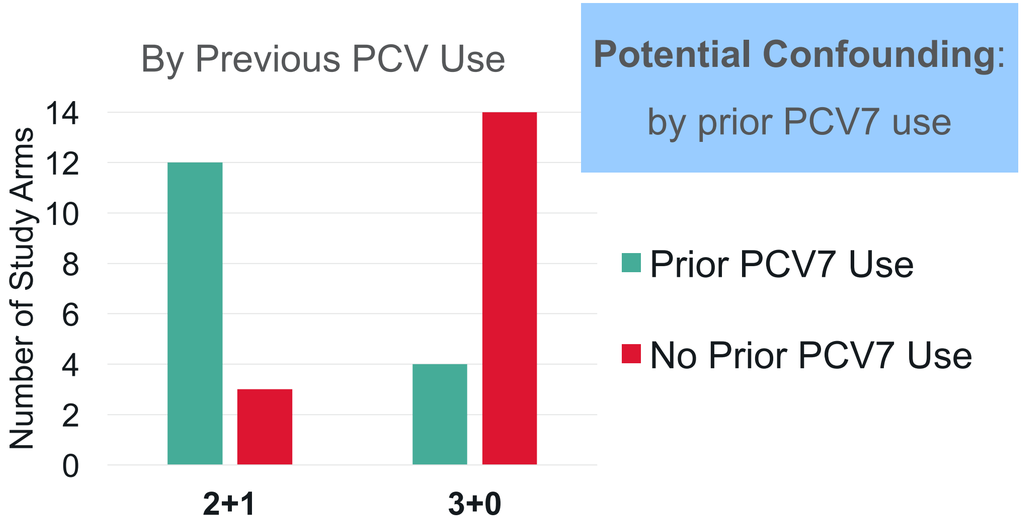
Nasopharyngeal Carriage

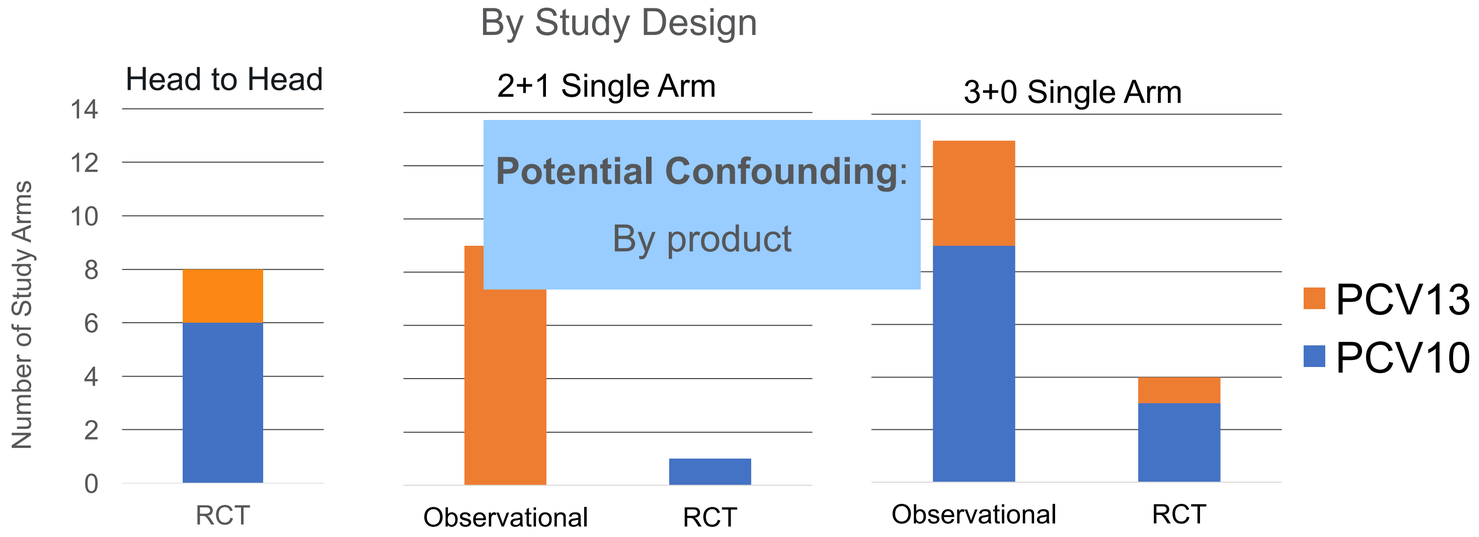
Direct Protection Against Colonization

Schedule Comparison Results: NP Carriage

Included Studies in NPC Analysis by Product and Schedule:







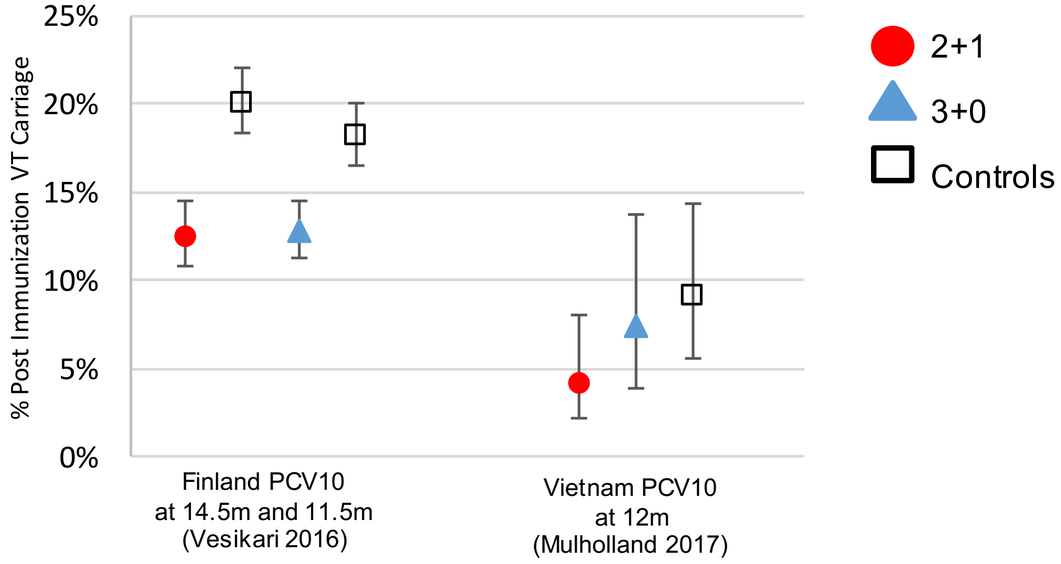
Schedule Comparison Results: NP Carriage

Vaccine Type Carriage: 2+1 (Red) vs 3+0 (Blue)

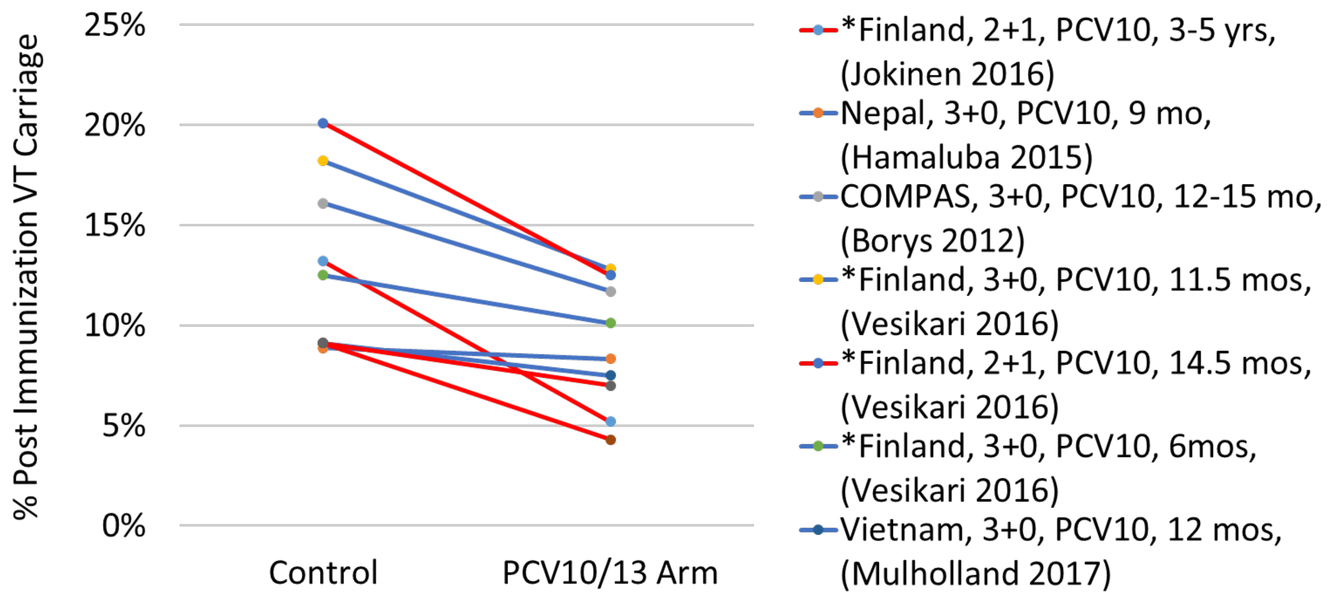
Analysis: Head to head trials, comparison of schedules between trials, and between-study comparisons of observational studies

Results: Head to head trials and single-schedule trials: directionally favoring 2+1 (red)

a) Head to Head RCTs:



b) H2H & Single-Schedule RCTs:



Schedule Comparison Results: NP Carriage

Vaccine Type Carriage: 2+1 (Red) vs 3+0 (Blue)

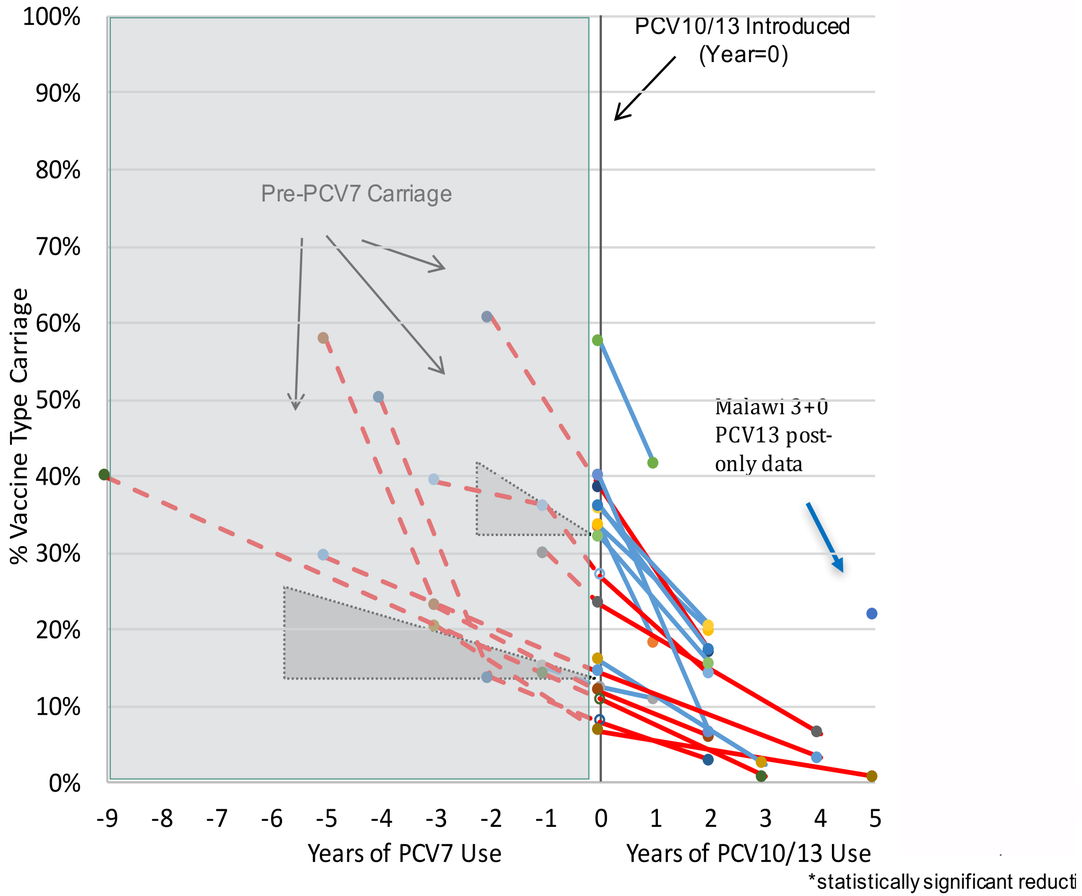
Results: Between-study comparisons of observation studies suggest similar impact, but potential confounding

Results: Between-study comparisons suggest similar impact.

But confounding due to:

- Prior PCV7 use
- Current product
- Pneumococcal carriage prevalence

c) NP Carriage before and after PCV introduction



*statistically significant reducti

**Grey triangles represent prior use of PCV7, but no pre-PCV7 carriage data are available so the slope of the line is unknown. The triangle's left edge extends to the year of PCV7 intro.

- *Gambia 3+0 PCV13 <1yrs (Roca, 2015)
- Australia 3+0 PCV13 <3y Aboriginal (Wigger, 2014)
- *Burkina Faso 3+0 PCV13 <5y (Moisi, 2016)
- Malawi 3+0 CU PCV13 3-5y (Swarthout, 2016)
- *Cambodia 3+0 PCV13 0-11m (SuyKuong, 2016)
- *France 2+1 PCV13 <2yrs (Dunais, 2015)
- *Norway 2+1 PCV13 <2 yrs (Steens, 2016)
- *Israel 2+1 CU PCV13 <5 yrs (Danino; Ben Shimol, 2016)
- UK 2+1 PCV13 <5 <4yrs (Devine; Jones, 2016)
- *So.Af. 2+1 PCV13 <2yrs (Nzenze, 2016)
- *UK 2+1 CU PCV13 <5yrs (Van Hoek)
- So.Af. 2+1 CU PCV13 <2yrs (Nzenze, 2015)
- *Mozambique 3+0 PCV10 <2y (Sigaque, 2016)
- *Kenya 3+0 CU PCV10 <2y (Hammitt, 2016)
- *Kenya 3+0 PCV10 <5y (Kim, 2016)
- *Kenya 3+0 CU PCV10 <5y (Kim, 2016)
- Fiji 3+0 PCV10 <2y (Dunne, 2016)
- Sweden 2+1 PCV13 <6 (Galanis, 2016)

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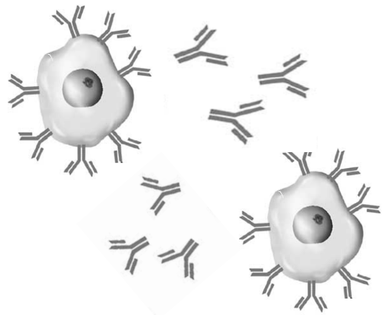
PCV Modes of Action

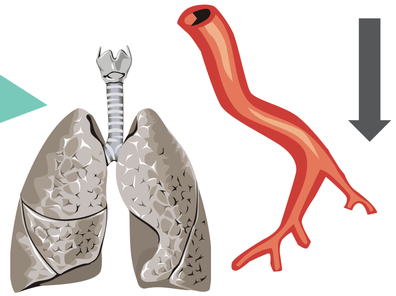
Immunization

1



Immunogenic Response:
Vaccine Type specific antibody (IgG)

2



Direct Protection Against Disease

Direct Protection Against Colonization

Invasive Disease

Schedule Comparison Results: Invasive Disease

Included Studies in IPD Analysis by Product and Schedule:

Inclusion Criteria:

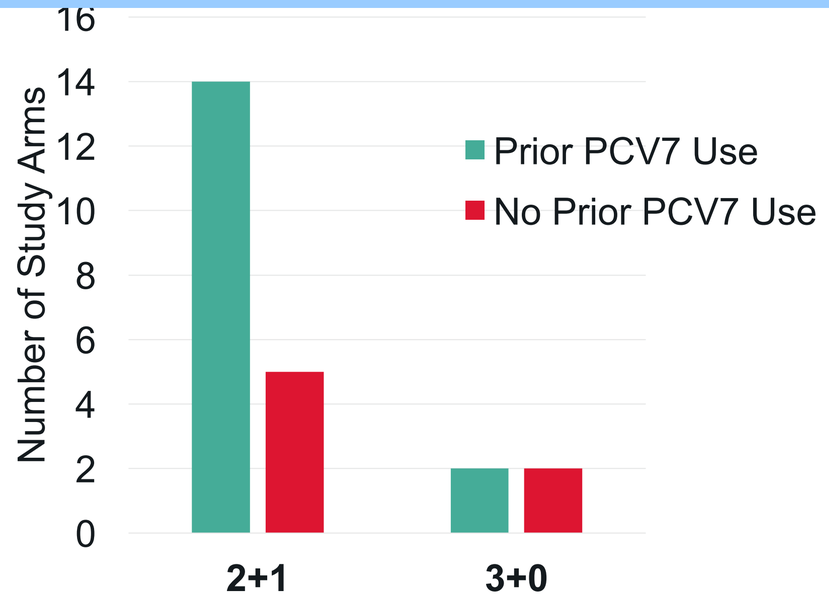
- VT IPD reported as a group or serotype-specific
- RCTs, case-control, and pre-post vaccination incidence
- Meningitis, bacteremic pneumonia

Exclusion Criteria:

- Immunocompromised or special populations
- Number of cases only (i.e., no incidence)

Confounding potential:

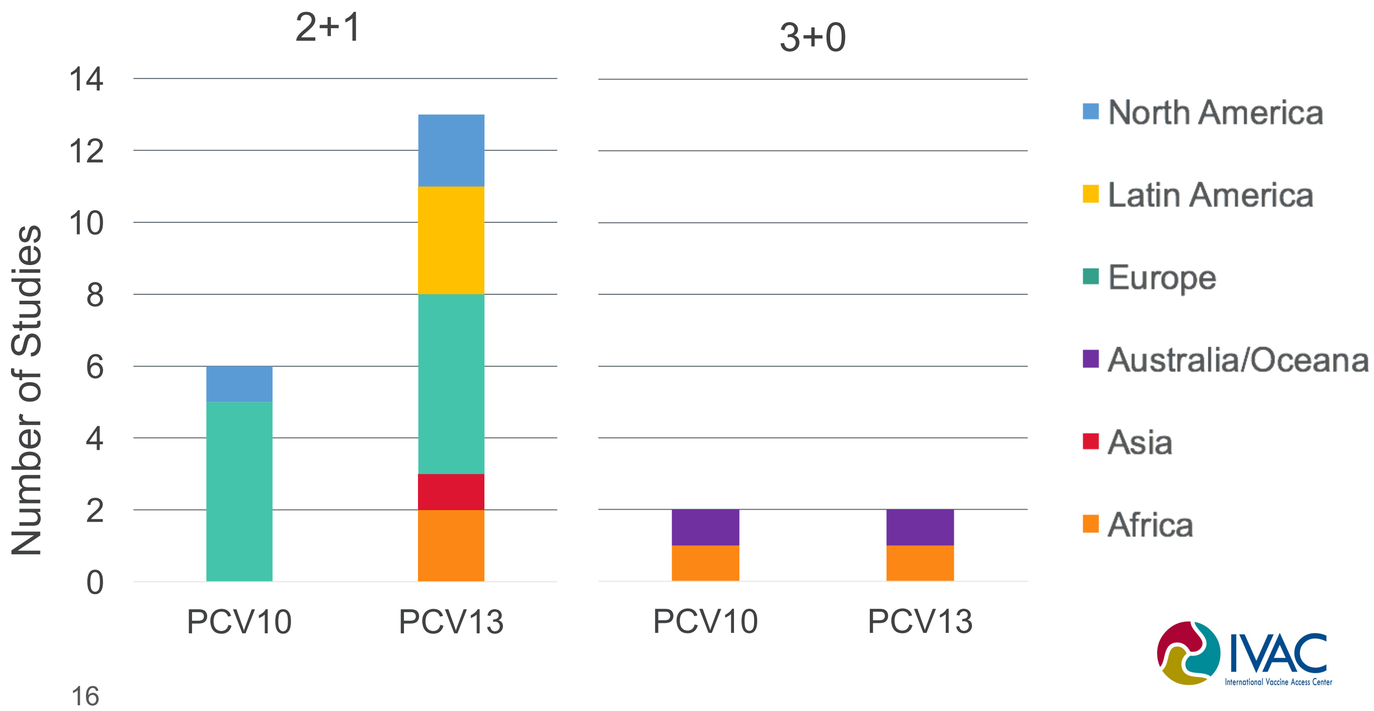
Most studies in the context of prior PCV7 use



Confounding potential:

Differential distribution by region and product

Incl… Region:



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Schedule Comparison Results: Vaccine Type IPD

Vaccine Impact on PCV10/13-Type Disease by Schedule and Previous PCV7 Use:

Results: Both schedules reduce the burden of Vaccine-Type IPD; Similar impact seen between schedules

2+1 Schedule: (n=14)

Prior PCV7 Use	Number of Studies:	Range of Point Estimates (% reduction)
No	n=3	82 to 93%
Yes	n=11	70 to 100%

3+0 Schedule: (n=4)

Prior PCV7 Use	Number of Studies	Range of Point Estimates (% reduction)
No	n=2	92% to 92%
Yes	n=2	70 to 82%

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Schedule Comparison Results: Invasive Disease

ST1 is a special vaccine type

Vaccine efficacy and impact

- Pre-licensure 3+0 trials in Africa show no impact on ST1 IPD (however, small N)
- Recent outbreaks in PCV-using countries raised concerns whether 3+0 produces long-lasting protection

Epidemiology

- Creates outbreaks
- Dominant IPD serotype in Africa and Asia
- Differentially occurs in older children

Schedule Comparison Results: Serotype 1 IPD

Vaccine Impact on ST 1 Disease by Schedule:

Results: Evidence that both schedules impact burden of ST1 IPD; substantial data paucity on 3+0

2+1 Schedule:

2+1:	Range of Point Estimates (% reduction)
n=7 *(all PCV13)*	0 to 98%
• Impact (n=4)	88 to 98%
• No Impact (n=1)	0% (NS)
• Inconclusive (n=2)*	--
n=1 Case Control	84%

*Few ST1 IPD isolates pre-PCV13

NS = not statistically significant

3+0 Schedule:

3+0:	Range of Point Estimates (% reduction)
n=4*	90%
• Impact (n=2)**	90%
• Inconclusive (n=2)***	--

*Includes two unpublished studies that were available to the SAGE working group after the PRIME analysis
**One unpublished study: no impact reported
**Few ST1 IPD isolates pre-PCV10/13

Schedule Comparison: Overall Conclusions

Outcome	Vaccine Type (VT) Disease
Immunogenicity	Antibody concentration (GMC): **- 3 primary doses more immunogenic than 2 primary doses** **- 2+1 more immunogenic after 3rd dose** % Responders: Schedules showed **similar impact except for 6A, 6B and 23F**
NP Carriage	Schedules showed **similar impact**
IPD	VT: Both schedules showed **similar impact**; Limited 3+0 data ST1: Clear evidence of 2+1 impact; evidence of 3+0 impact but limited data
Overall	**Both schedules are effective** in reducing VT Carriage and Disease

PICO Question 2: Product Comparison

Intervention	**PCV10 vs PCV13**
Population	• Vaccinated children (direct effects) • Unvaccinated older children and adults (indirect effects)
Outcomes	• Immunogenicity • NP carriage • IPD

PICO II Question: Product Comparison

Both products were licensed and pre-qualified on the basis of immunogenicity and non-inferiority to PCV7, which was licensed on the basis of demonstrated efficacy against invasive pneumococcal disease

PCV10 – Synflorix:

- Carrier Proteins: protein D from non-typeable Haemophilus influenzae (PD) (NTHi), Tetanus Toxoid (TT), Diphtheria Toxoid (DT)

PCV13 – Prevenar-13:

- Carrier Protein: CRM197 a non-toxic mutant of diphtheria toxin (CRM)

Product	Serotype & Carrier Protein												
	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
PCV10	1µg PD		3µg PD	1µg PD		1µg PD	1µg PD	1µg PD	1µg PD	3µg TT		3µg DT	1µg PD
PCV13	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	4.4 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM

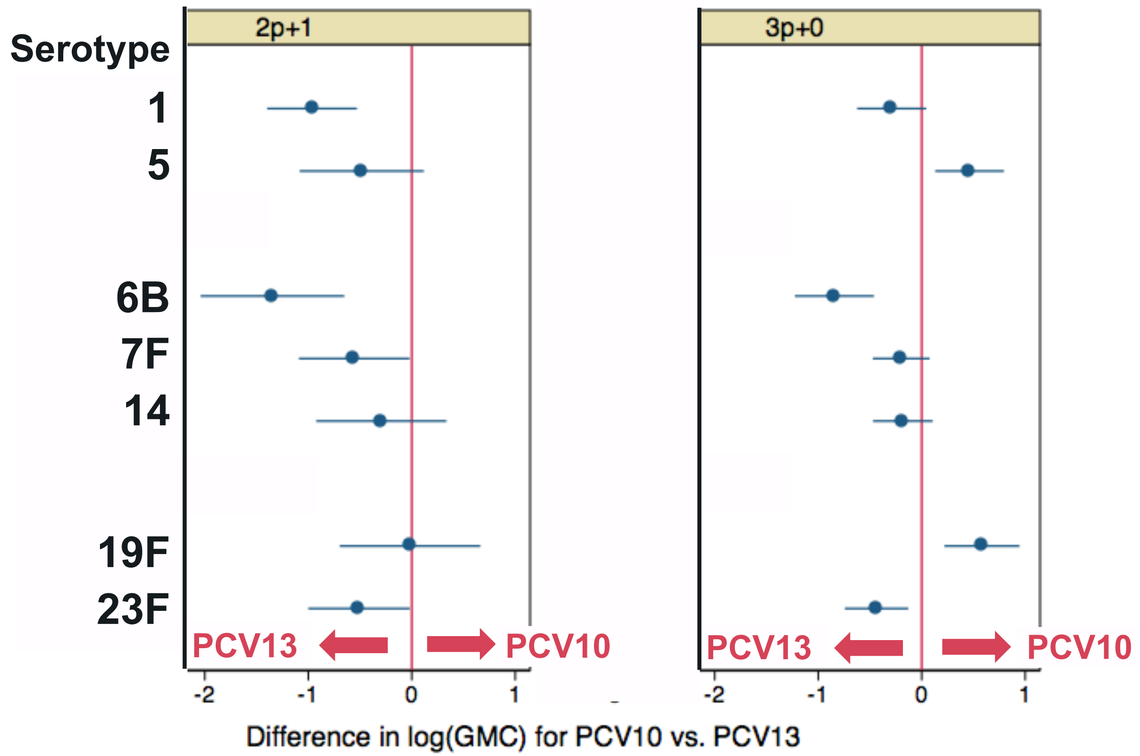
Product Comparison Results: Immunogenicity

Analysis: Between-study meta-analysis comparison at the post-dose 3 time point (all n≥14)

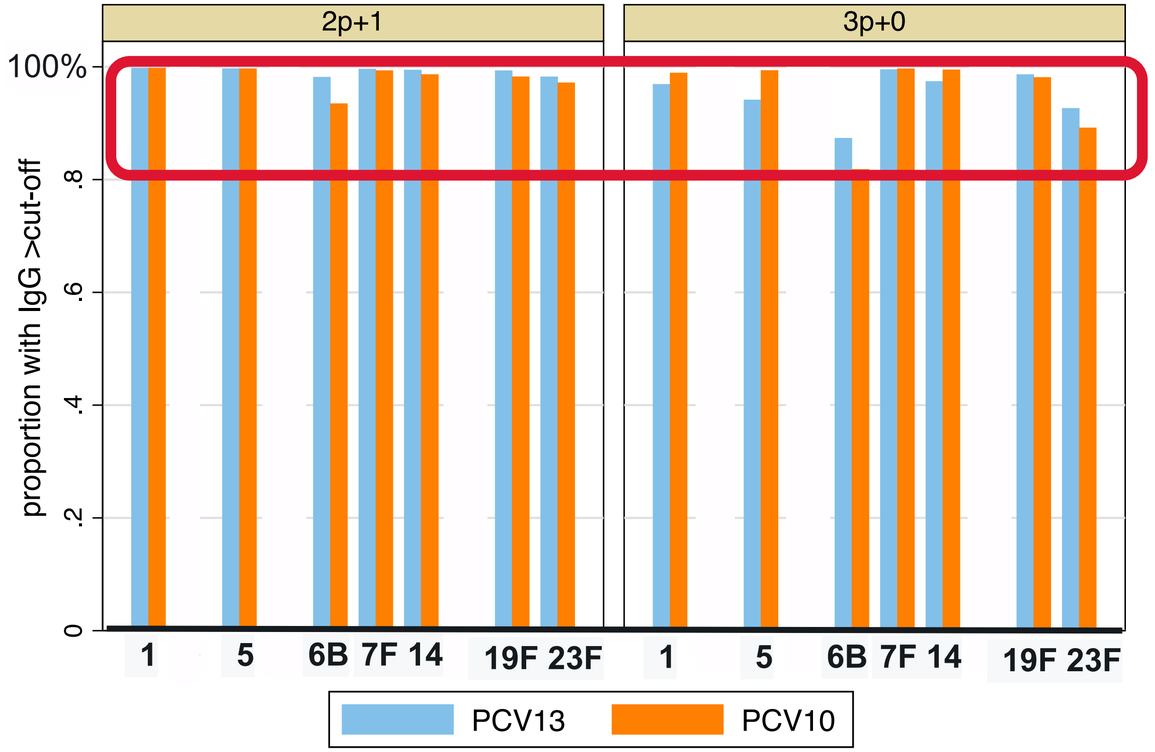
- 7 representative serotypes of the 10 in common were analyzed

Results: **For serotypes in common**: GMC: more STs favored PCV13
%Responder: PCV10 and PCV13 were comparable

Immunogenicity (log GMC) after Dose 3



Percent Reaching Correlate of Protection after Dose 3



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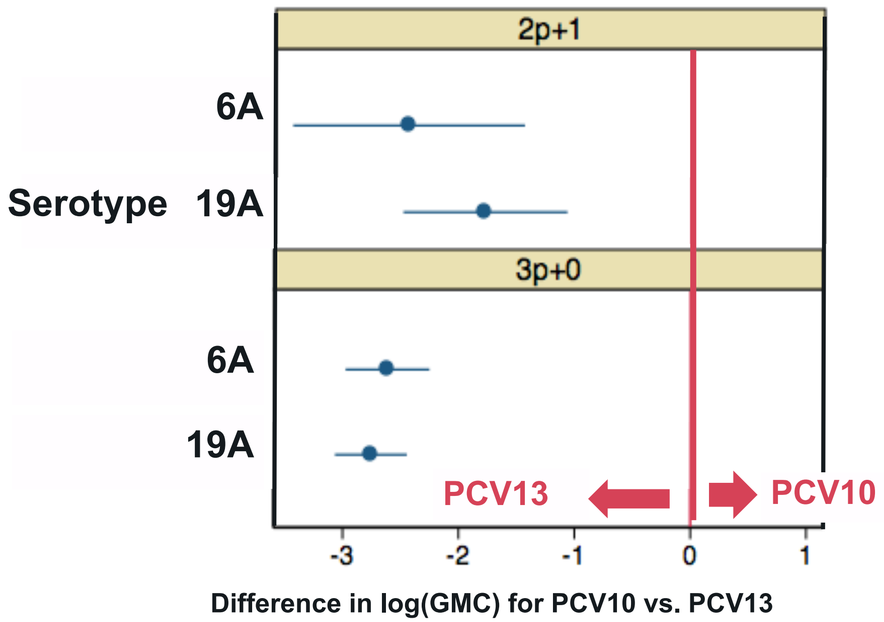
Product Comparison Results: Immunogenicity

Analysis: Between-study meta-analysis comparisons at the post-dose 3 time point (all n≥14 except ST3 PCV10 n=1))

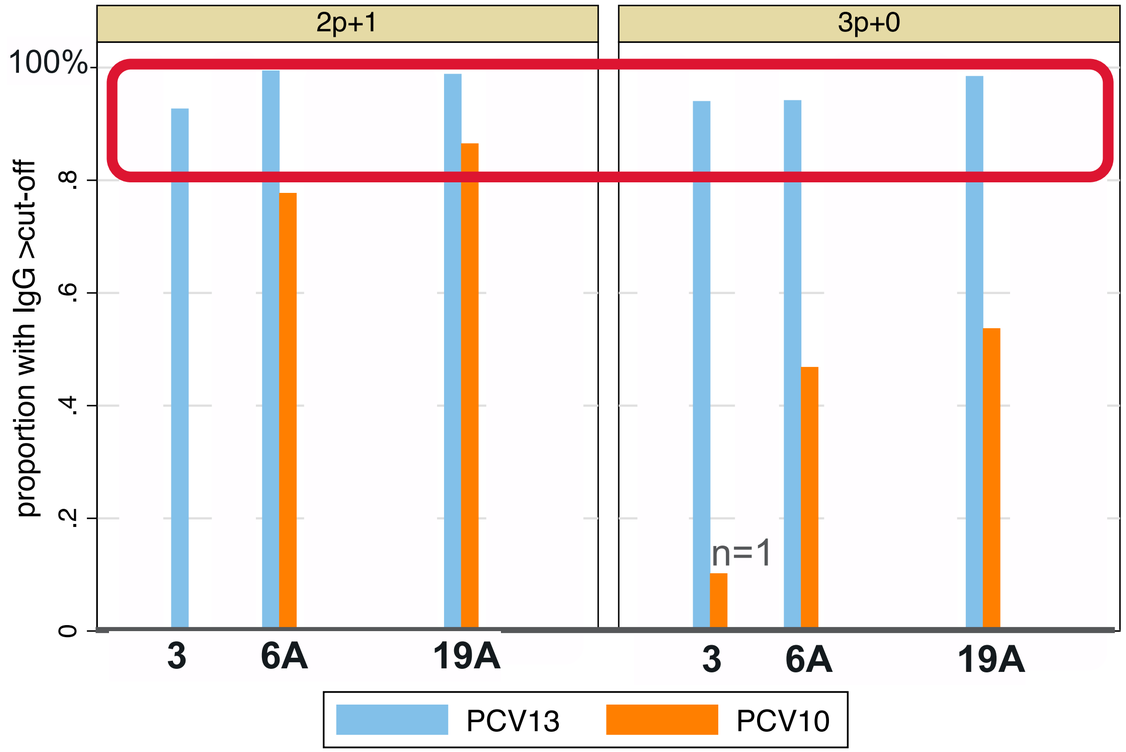
Results: **For serotypes 3, 6A and 19A** in PCV13 but not in PCV10:

- PCV13 is more immunogenic than PCV10; limited evidence to evaluate ST3 in PCV10
- PCV10 is immunogenic against STs 6A and 19A, but only with 2+1 schedule
  - Fewer than 60% of PCV10-vaccinated infants reached correlate of protection with 3p+0

Immunogenicity (log GMC) after Dose 3



Percent Reaching Correlate of Protection after Dose 3

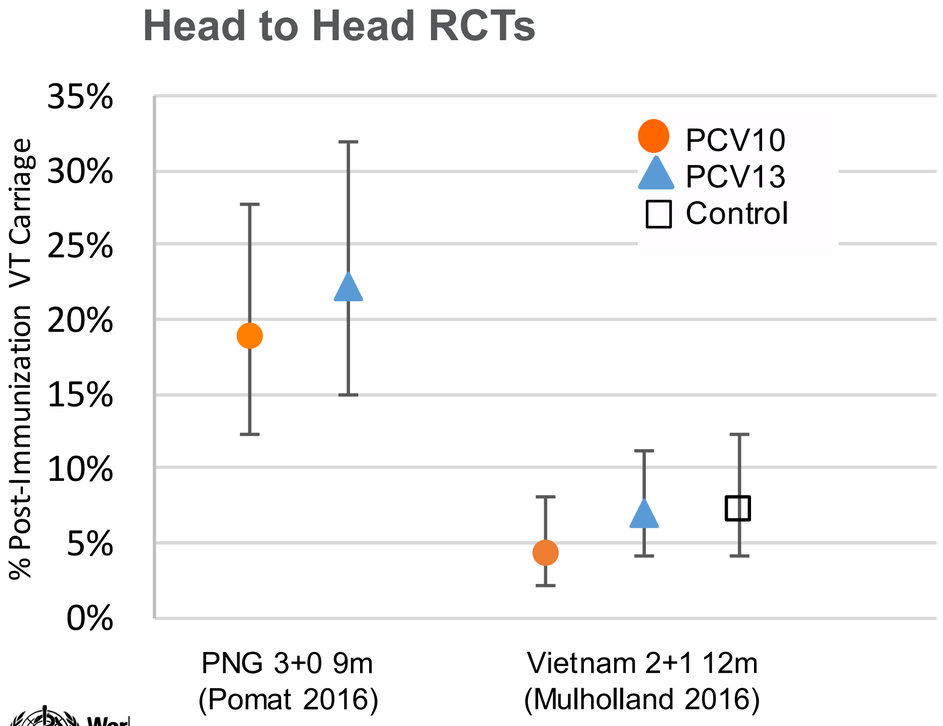


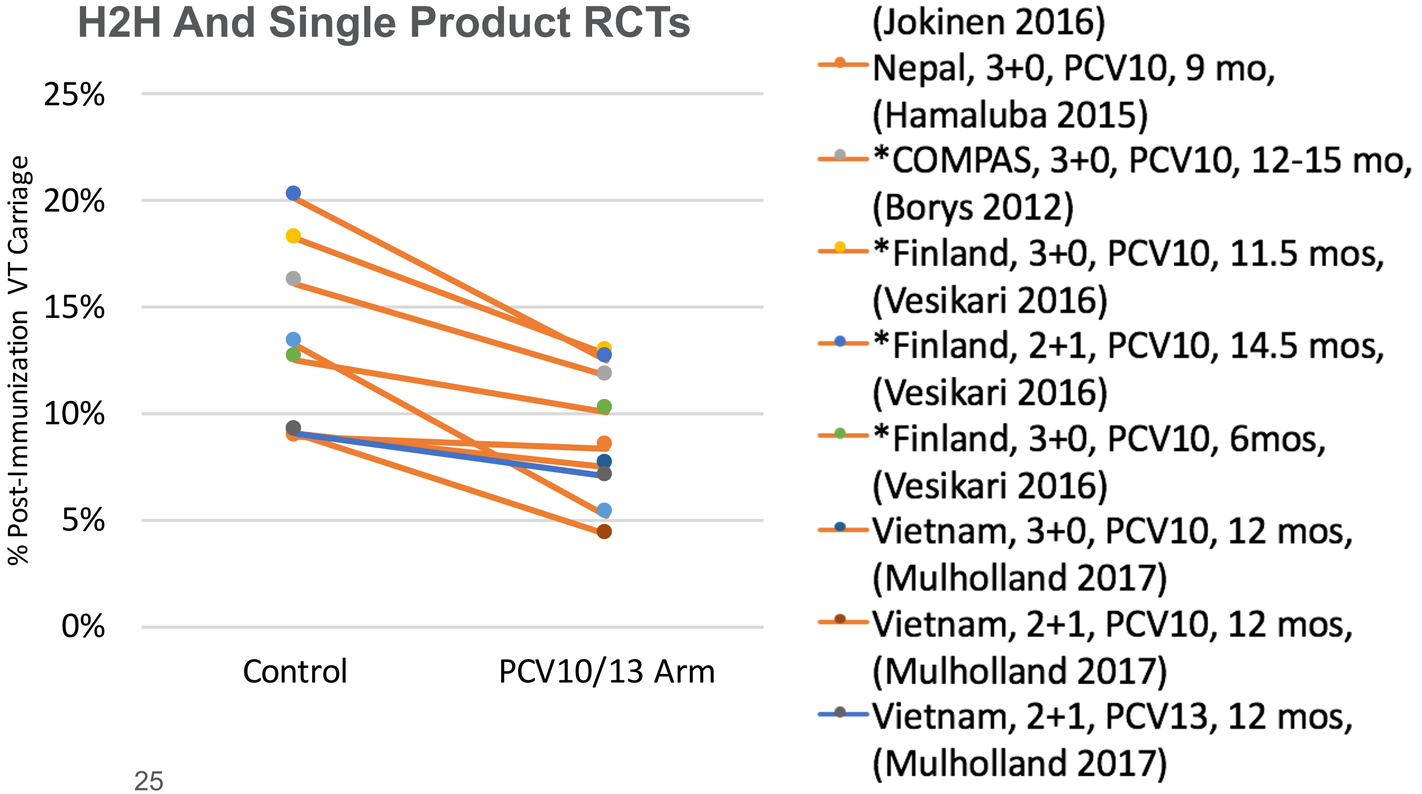
Product Comparison Results: NP Carriage VT

Vaccine Type Carriage: PCV10 (Orange) vs PCV13 (Blue)

Analysis: Head to head trials, between-trial comparisons of single product trials, and between-study comparison of observational studies of routine use

Results: Both products are effective against their respective serotypes; Similar impact seen between products





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Product Comparison Results: NP Carriage VT

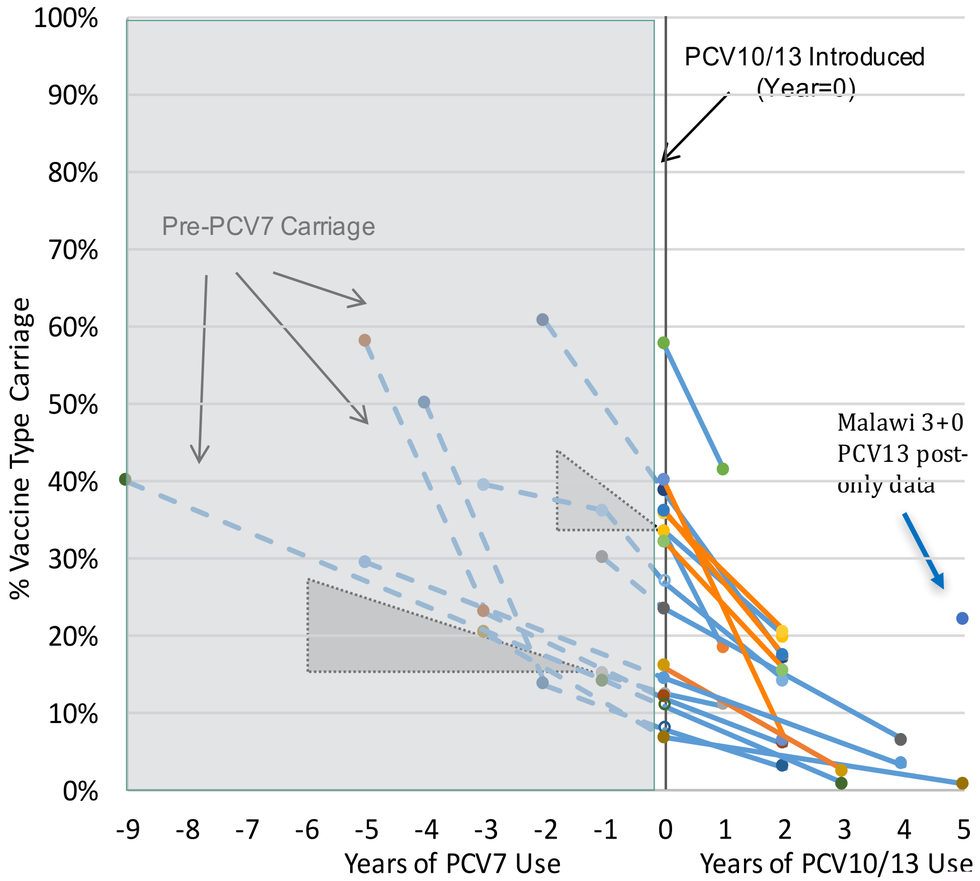
Vaccine Type Carriage: PCV10 (Orange) vs PCV13 (Blue)

Observational studies of NP Carriage before and after PCV introduction

Results:

- Similar declines for both PCV10 and PCV13 when adjusted for starting value

- Considerable confounding:
  - schedule (all PCV10 are 3+0)
  - previous use of PCV7 (~all PCV13 previously used PCV7)



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- Australia 3+0 PCV13 <3y Aboriginal (Wigger, 2014)
- *Burkina Faso 3+0 PCV13 <5y (Moisi, 2016)
- Malawi 3+0 CU PCV13 3-5y (Swarthout, 2016)
- *Cambodia 3+0 PCV13 0-11m (SuyKuong, 2016)
- *France 2+1 PCV13 <2yrs (Dunais, 2015)
- *Norway 2+1 PCV13 <2 yrs (Steens, 2016)
- *Israel 2+1 CU PCV13 <5 yrs (Danino; Ben Shimol, 2016)
- UK 2+1 PCV13 <5 <4yrs (Devine; Jones, 2016)
- *So.Af. 2+1 PCV13 <2yrs (Nzenze, 2016)
- *UK 2+1 CU PCV13 <5yrs (Van Hoek)
- So.Af. 2+1 CU PCV13 <2yrs (Nzenze, 2015)
- *Mozambique 3+0 PCV10 <2y (Sigaque, 2016)
- *Kenya 3+0 CU PCV10 <2y (Hammitt, 2016)
- *Kenya 3+0 PCV10 <5y (Kim, 2016)
- *Kenya 3+0 CU PCV10 <5y (Kim, 2016)
- Fiji 3+0 PCV10 <2y (Dunne, 2016)
- Sweden 2+1 PCV13 <6 (Galanis, 2016)

*p<0.05

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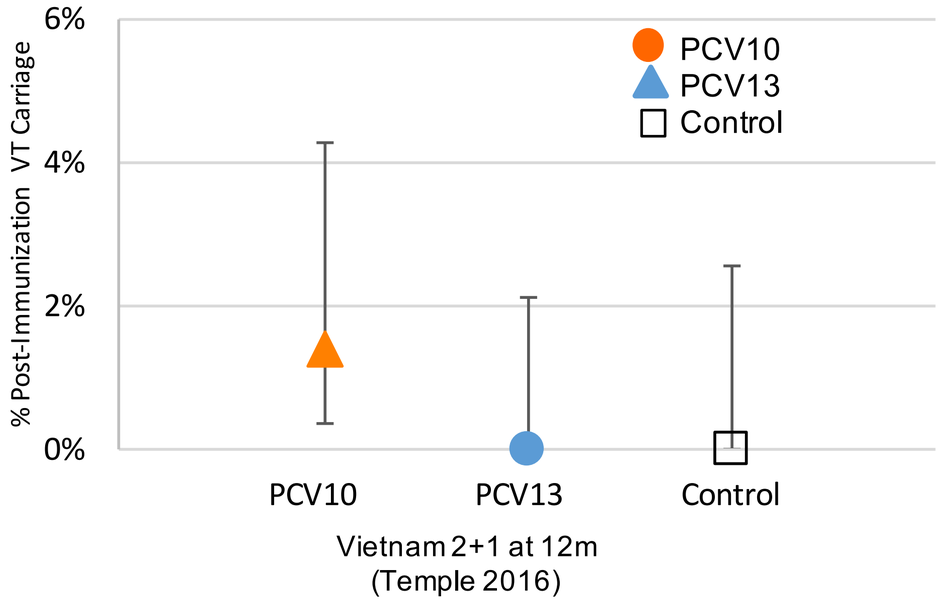
Product Comparison Results: NP Carriage ST3

Serotype 3 Carriage: PCV10 (Orange) vs PCV13 (Blue)

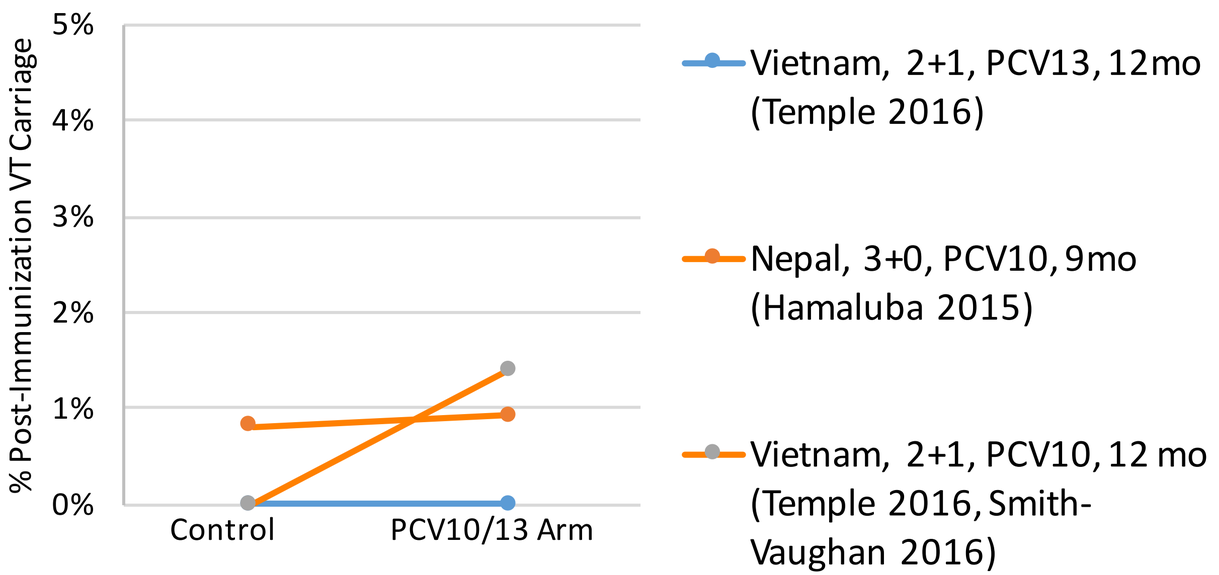
Results:

- Limited trial data available
- No evidence PCV10 impacted ST3 carriage

Head to Head RCTs



H2H And Single Product RCTs



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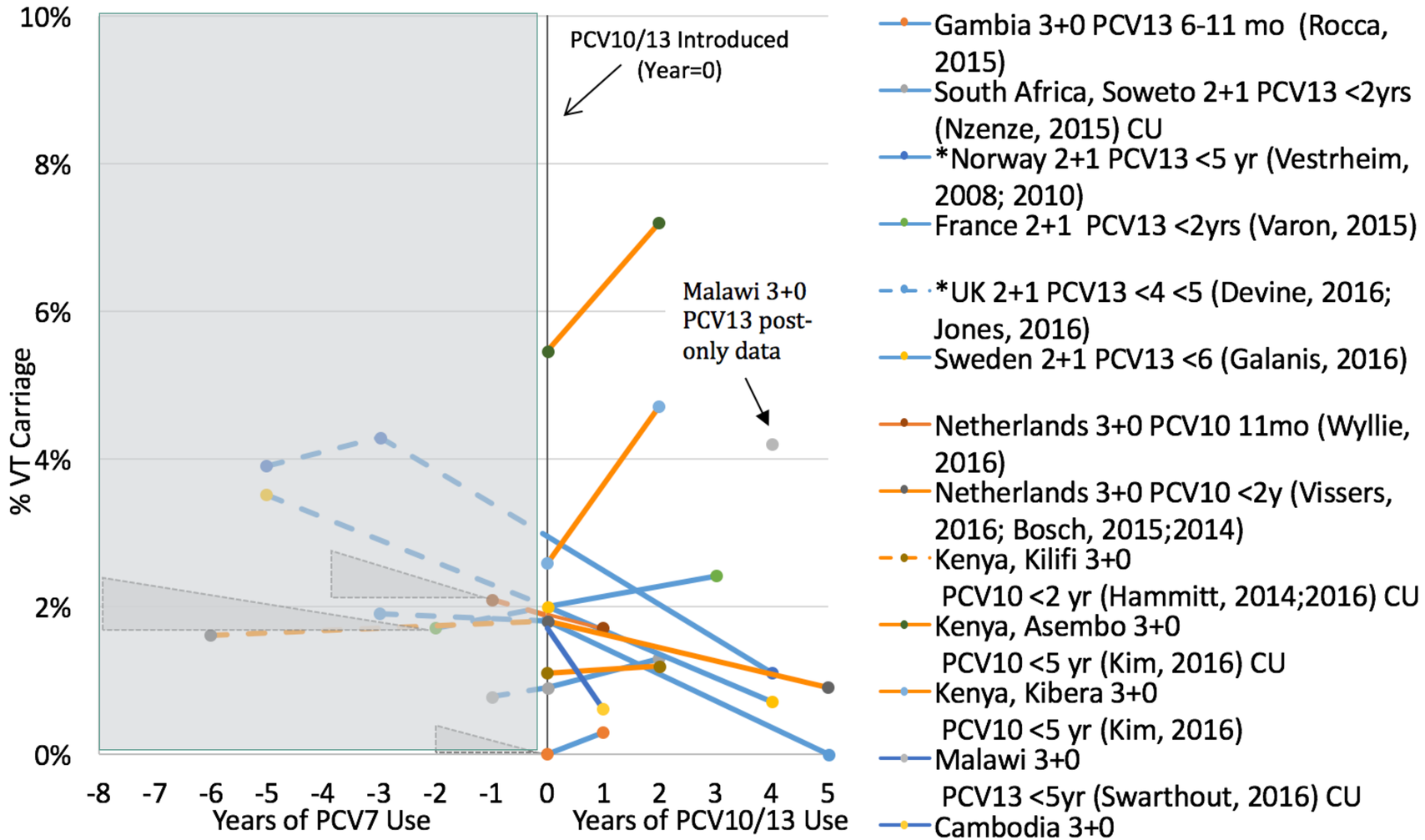
Product Comparison Results: NP Carriage ST3

Serotype 3 Carriage: PCV10 (Orange) vs PCV13 (Blue)

Results:

- No impact seen with either product
- Equal number of studies showed increases and decreases in carriage

Observational studies of NP Carriage before and after PCV introduction



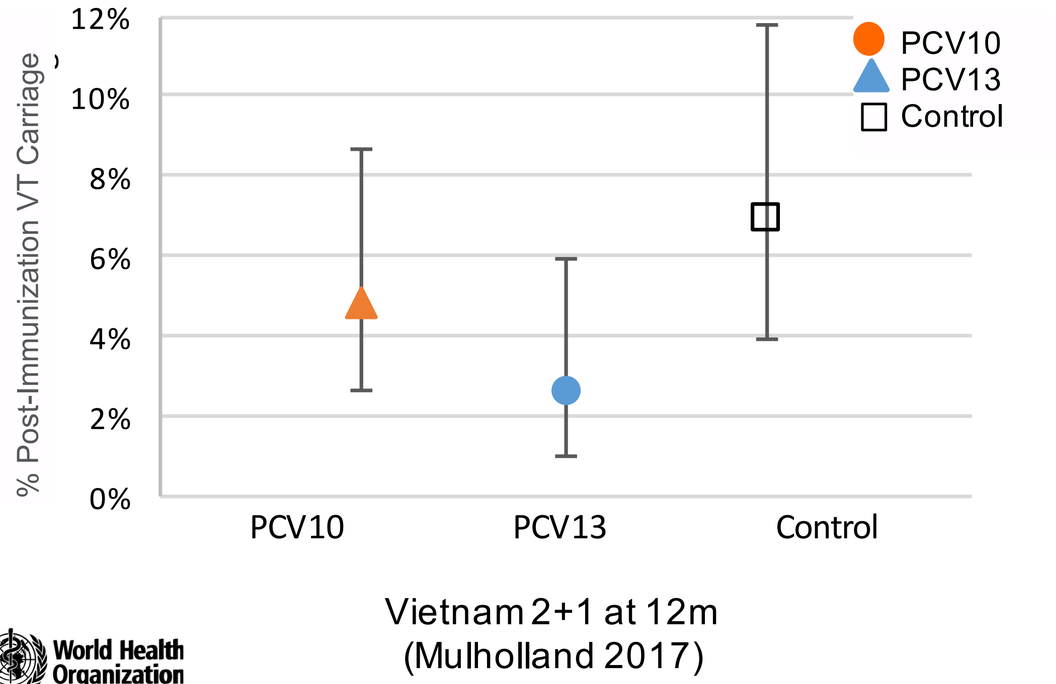
Product Comparison Results: NP Carriage ST6A

Serotype 6A Carriage: PCV10 (Orange) vs PCV13 (Blue)

Results:

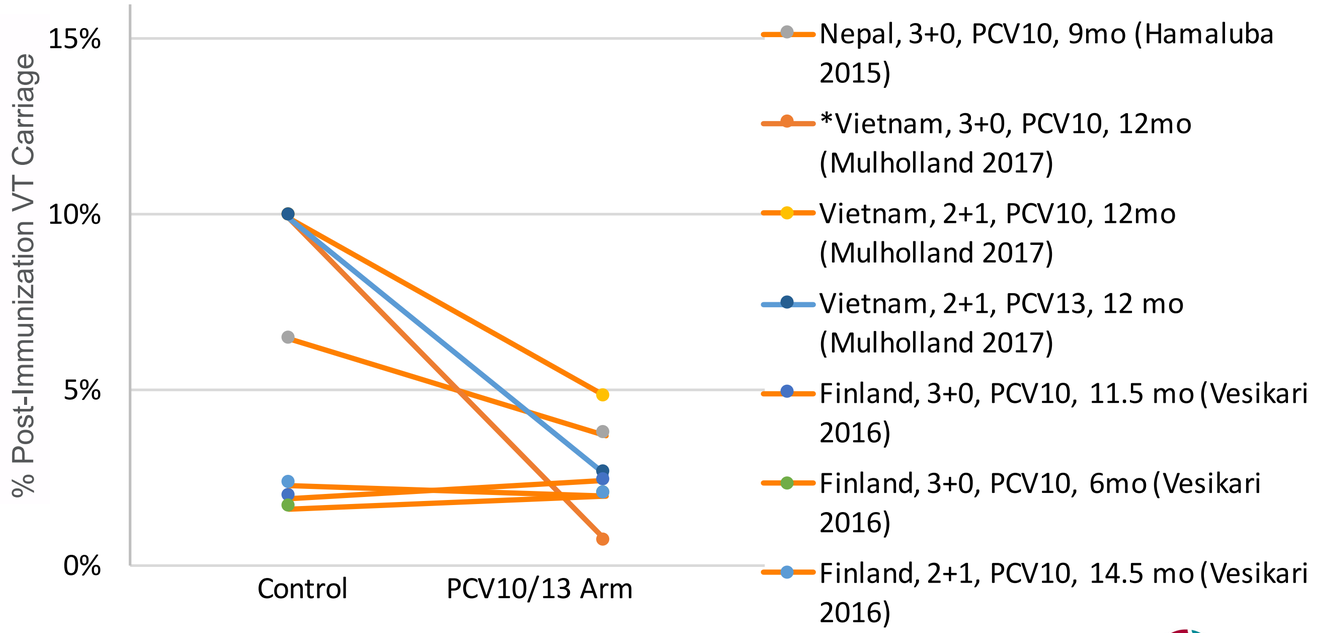
- Reductions seen for both products
- Some evidence favoring PCV13
  - Head to head trial favored PCV13 although non-significant; PCV10 trial (Finland) showed no reduction but had very low baseline carriage (<2.5%)
  - Declines in ST 6A more pronounced with PCV13 in routine use studies

Head to Head RCTs



Vietnam 2+1 at 12m
(Mulholland 2017)

H2H And Single Product RCTs



World Health Organization

IVAC International Vaccine Access Center

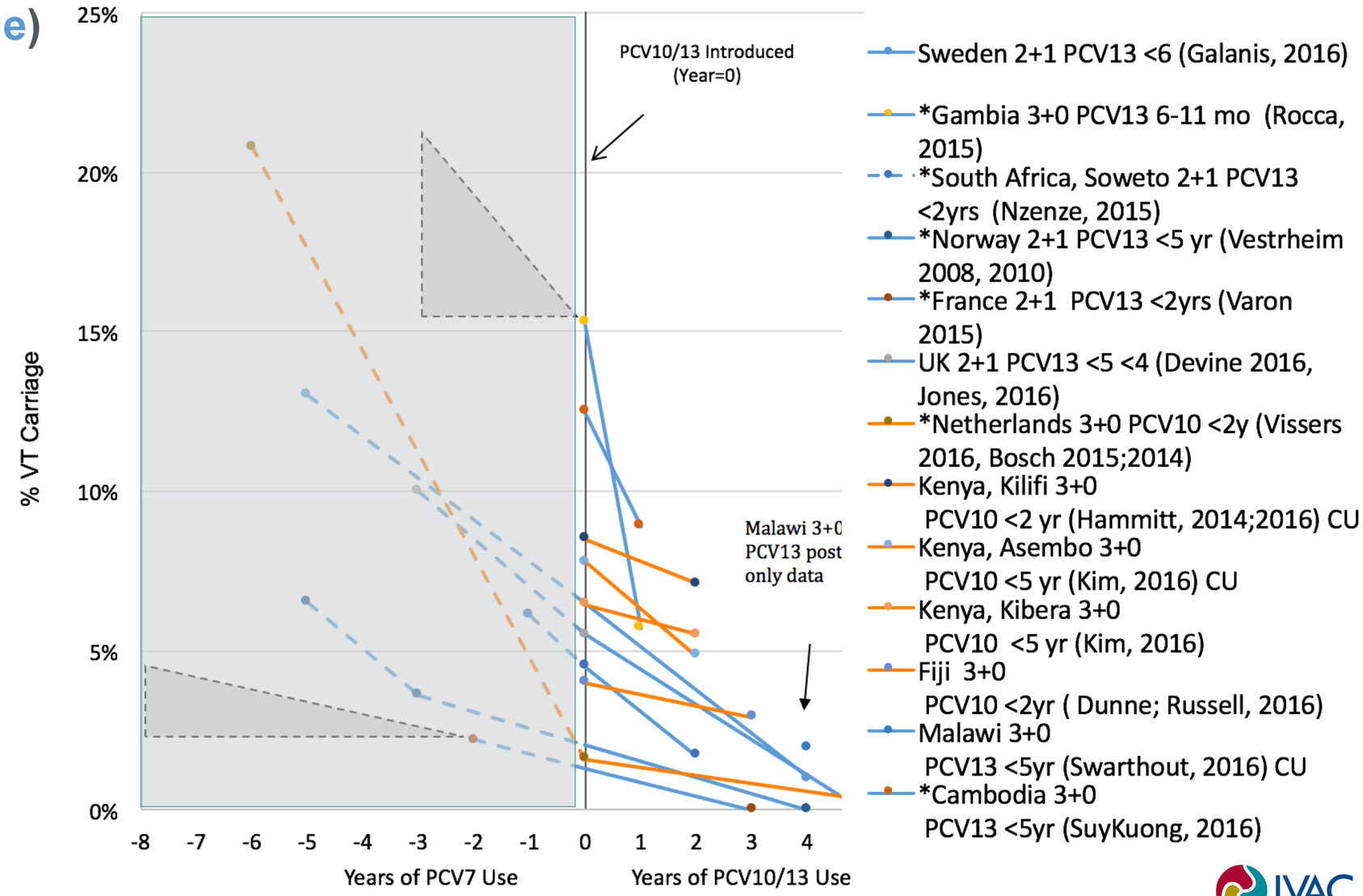
Product Comparison Results: NP Carriage ST6A

Serotype 6A Carriage: PCV10 (Orange) vs PCV13 (Blue)

Results:

- Declines in ST 6A more pronounced with PCV13

Observational studies of NP Carriage before and after PCV introduction



World Health Organization

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Product Comparison Results: NP Carriage ST6C

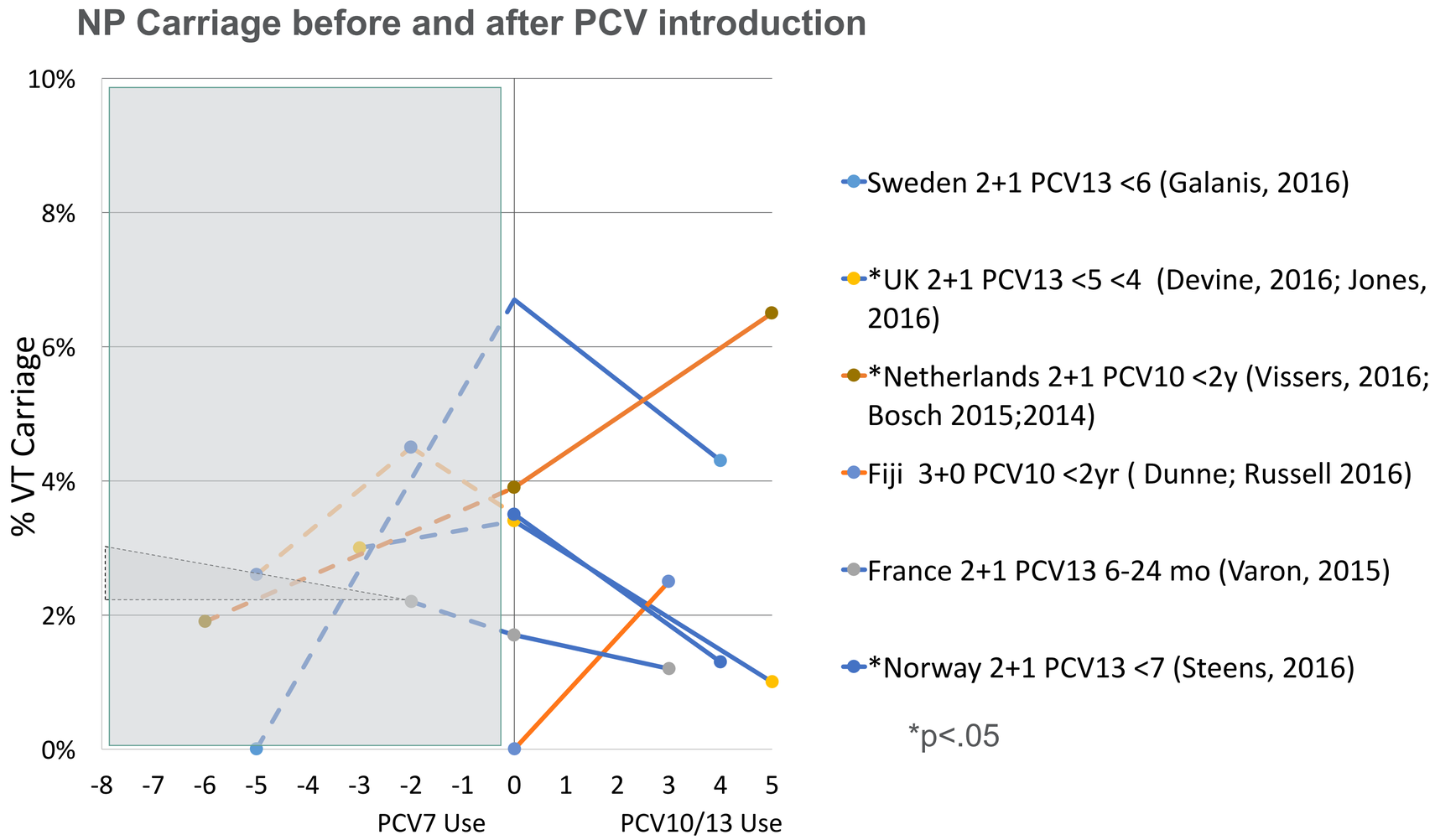
Serotype 6C Carriage: PCV10 (Orange) vs PCV13 (Blue)

Analysis: Between study comparisons of observational studies only

- No trial data available

Results:

- PCV13 shows reduction while PCV10 showed increase



*p<.05

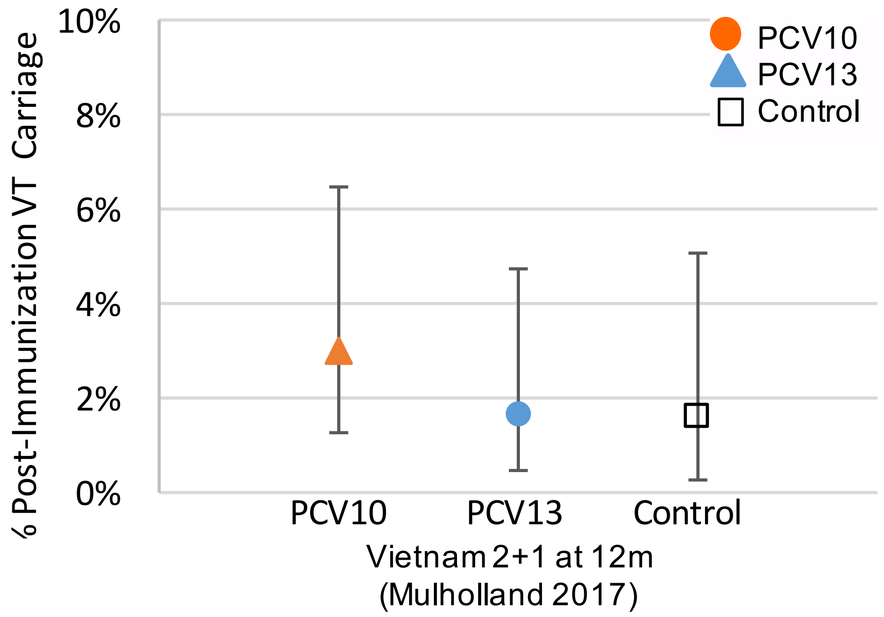
Product Comparison Results: NP Carriage ST19A

Serotype 19A Carriage: PCV10 (Orange) vs PCV13 (Blue)

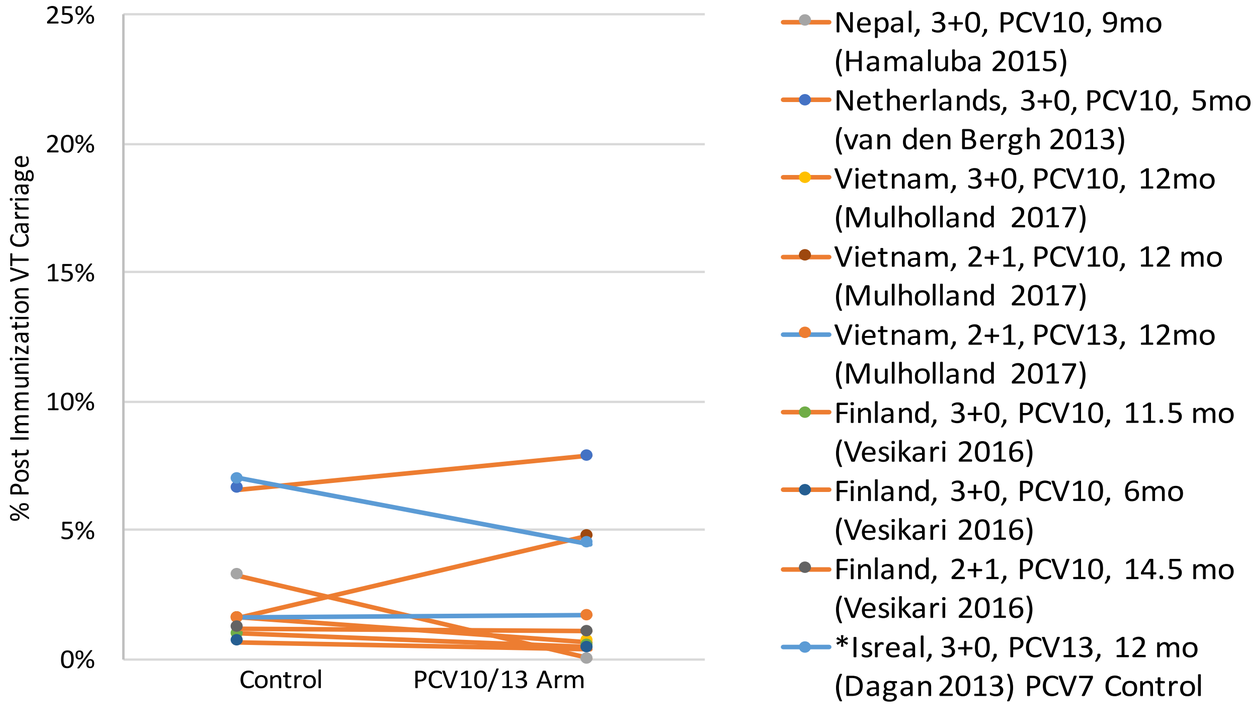
Results:

- Evidence favors PCV13
  - Head to head trial showed greater impact with PCV13 though non-significant
  - Some increases seen in PCV10 single arm trials
  - Routine use of PCV13 showed reduction in carriage while PCV10 showed some increases

Head to Head RCTs



H2H And Single Product RCTs



*p<.05

World Health Organization

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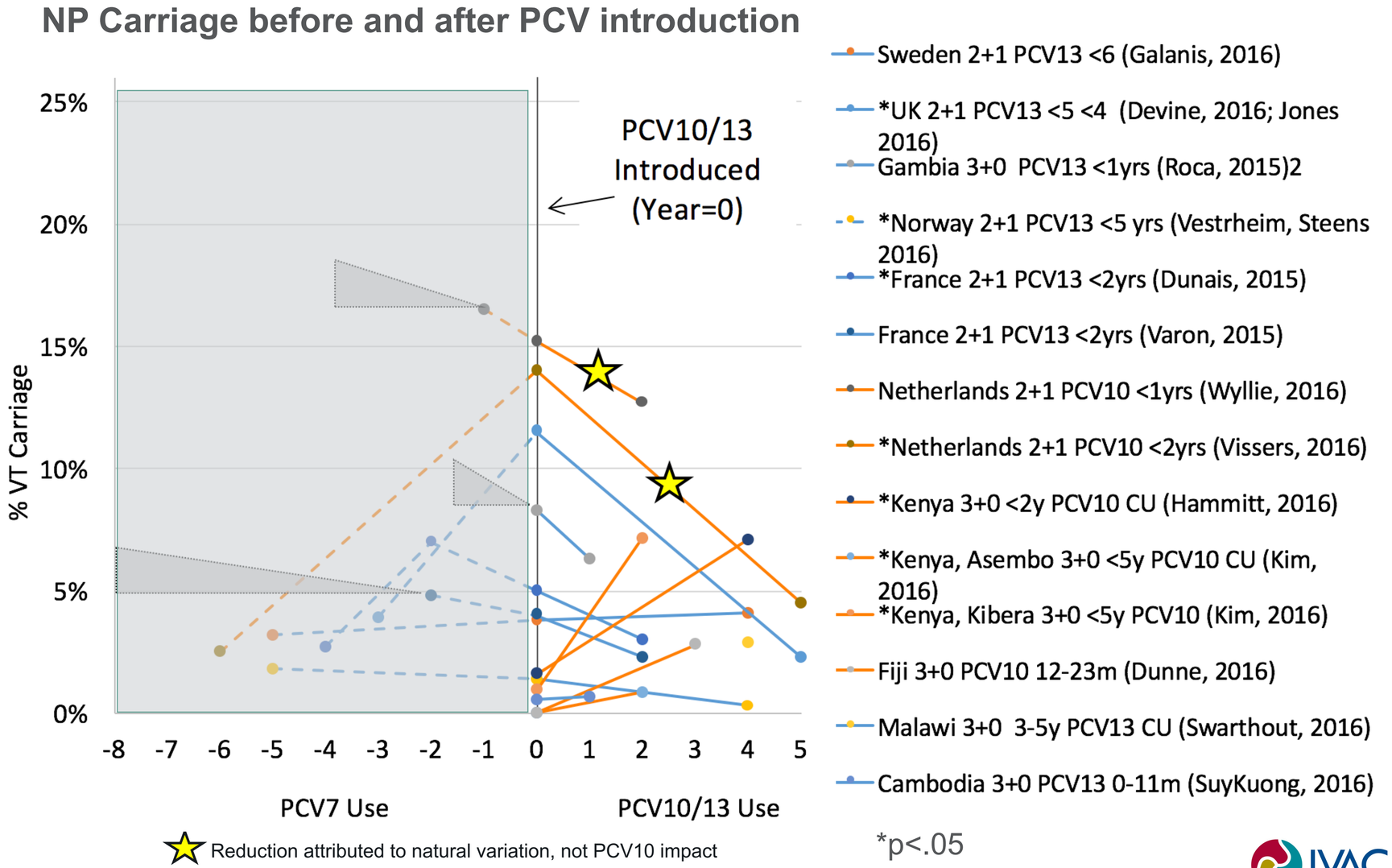
Product Comparison Results: NP Carriage ST19A

Serotype 19A Carriage: PCV10 (Orange) vs PCV13 (Blue)

Results:

- PCV13 showed consistent reductions while PCV10 showed some increases



*p<.05

Product Comparison Results: NP Carriage

In Summary: products had similar results except ST19A and perhaps ST6A (favored PCV13)

Vaccine Serotypes in Common	Serotypes in PCV13 and not in PCV10			ST6C
	ST3	ST6A	ST19A	
Similar impact with both products	No Impact with either product	Impact with both products; **Declines more pronounced with PCV13**	**Impact with PCV13** but not PCV10	Limited data for both products

Product Comparison Results: Vaccine Type IPD

Vaccine Impact on PCV10/13-Type Disease by Product and Previous PCV7 Use:

Results:

- Both products similarly reduced (directly and indirectly) IPD caused by the serotypes within each vaccine

PCV10: (n=6)

Prior PCV7 Use	Number of Studies:	Range of Point Estimates
No	N=4	87 to 93%
Yes	N=2	77 to 96%

PCV13: (n=10)

Prior PCV7 Use	Number of Studies	Range of Point Estimates
No	N=1	82%
Yes	N=9	65 to 100%

Product Comparison Results: ST3 IPD

Vaccine Impact on ST3 Disease by Product and Previous PCV7 Use:

Results:

- PCV10 showed no impact on ST3 (not included in the vaccine), but limited data
- PCV13 had inconclusive results

PCV10:

Number of Studies:	Range of Point Estimates
N=3	-354 to 29%
• No or low Impact (n=1) • Increase (n=2)*	29% (NS) -194 to -354%
N=1 Case Control**	8% (NS)

*Both Finland
**Ineligible 4-dose study that was reviewed by SAGE WG (Brazil, Domingues 2014)

PCV13:

Number of Studies	Range of Point Estimates
N=7	-35 to 85%
• Impact (n=2) • No or low Impact (n=5)	68 to 85% -35 to 41% (NS)
N=2 Case Control*	0 to 26% (NS)

*Includes n=1 ineligible 4-dose study that was reviewed by SAGE WG (Germany, Weinnberger 2016)

World Health Organization

IVAC International Vaccine Access Center

Product Comparison Results: ST6A IPD

Vaccine Impact on ST6A Disease by Product:

Results:

- Data for both products limited, but supportive of direct effect
- PCV13 studies were in context of prior PCV7 use with low burden of ST6A remaining; reductions seen in both vaccinated and unvaccinated cohorts

PCV10:

Number of Studies:	Range of Point Estimates
N=2	56 to 89%
• Impact (n=1) • Non-Significant Impact (n=1)	89% 56% (NS)
N=2 Case Control*	15 to 62% (NS)

*Impact of ≥1 dose

PCV13:

Number of Studies	Range of Point Estimates
N=6	36(NS) to 100%
• Impact (n=2) • Inconclusive (n=4)*	100% --
N=1 Case Control**	98%

*Few ST6A IPD isolates remaining post PCV7
**Impact of ≥2 doses

Product Comparison Results: ST6C IPD

Vaccine Impact on ST6C Disease by Product:

Results:

- PCV10: no data available
- PCV13: non-significant impact in vaccinated cohorts
  - Indirect Effects: Impact seen in >65y cohort (n=1)

PCV10:

Number of Studies:	Range of Point Estimates
No Available Evidence	

PCV13:

Number of Studies	Range of Point Estimates
Non-Significant Impact (n=3)	36 to 63% (NS)
• 3+1 schedule (n=1)*	100%

*Ineligible 4-dose study that was reviewed by SAGE WG; 69% (95%CI 55 – 78) among unvaccinated cohorts (Pilishvili et al. IDWeek 2017)

Product Comparison Results: ST19A IPD

Vaccine Impact on ST19A-Type Disease by Product:

Results:

- PCV10: only effectiveness (i.e., case-control) studies indicate some protective direct effects
  - Indirect effects studies suggest no change or increase in 19A disease
- PCV13: all studies showed protective effects (both direct and indirect)

PCV10:

Number of Studies:	Range of Point Estimates
N=2	-54% to no change
• No or low impact (n=2)	-54% to no change
N=5 Case Control*	29 to 82%

*n=1 ≥2 doses, n=4 ≥1 dose; Includes indirect cohort studies

PCV13:

Number of Studies	Range of Point Estimates
N=8	68 to 100%
• Impact (n=8)	68 to 100%
N=6 Case Control*	67 to 94%

*n=3 ≥2 doses, n=3 ≥1 dose; includes indirect cohort studies

Product Comparison Results: IPD

In Summary: products had similar results except ST19A favors PCV13; unknown for ST6C

Vaccine Serotypes in Common	Serotypes in PCV13 and not in PCV10			ST6C
	ST3	ST6A	ST19A	
Similar impact with both products	Impact not demonstrated for either product	Impact with both products; data limited	Limited data but **favors PCV13**	No data for PCV10; Some impact with PCV13 but data limited

Product Comparison: Overall Conclusions

Outcome	Vaccine Serotypes in Common	Serotypes in PCV13 and not in PCV10			ST6C
		ST3	ST6A	ST19A	
Immunogenicity	Impact with both products	Favors **PCV13**	Impact with both products but Favors **PCV13**	Impact with both products but Favors **PCV13**	Evidence not available
NPC	Impact with both products	No Impact with either product	Impact with both products; Declines more pronounced with **PCV13**	PCV10 Impact not demonstrated. Favors **PCV13**	Limited data for both products
IPD	Similar impact with both products	Impact not demonstrated for either product	Impact with both products; data limited	Limited data but Favors **PCV13**	Some impact with PCV13 but data limited; No data for PCV10
Overall	**Impact with both products**	Impact not demonstrated for either product	**Impact with both products**	Limited data but Favors **PCV13**	Insufficient evidence to compare products

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