Effectiveness of three pneumococcal conjugate vaccines to prevent invasive pneumococcal disease in Quebec, Canada.

- Geneviève Deceuninck [1], Gaston De Serres [1-3] , Nicole Boulianne [1-2], Brigitte Lefebvre [4], Philippe De Wals [1-3].

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Disclosure Statement

- I have no affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization.

Implementation of PCV Program in Quebec

October 2002:

- PCV-7 offered to high-risk infants and childen<5yrs old (4 doses)

December 2004:

- PCV-7 offered to low-risk infants (3 doses, + catch-up < 5 year-old)

June-August 2009:

- switch from PCV-7 to PCV10 (PHiD-CV) (no catch-up)

January 2011:

- switch from PCV10 to PCV-13 (no catch-up)

PCV coverage (2 years of age)[1]

- At least 1 dose : 97%
- 3 doses : 84% (2006) to 93% (2012)

[1]Boulianne et al, INSPQ, 2013

Objective

Evaluation of the effectiveness of the three PCVs sequentially used in the context of a 2+1 doses recommendation during the period 2005-2013

Methods

- **Frequency matched case-control study**
  - Province of Québec, Nunavik excluded, 2005-2013
  - Children 2 months to 4 years old
  - Phone survey
    - Tobacco exposure, day care, breastfeeding, season, influenza immunization, asthma, high risk medical conditions (= indications for a 4th dose), number of children and adults in the household, mother's education, household income, ethnicity, region
  - + immunization records check in medical files with parent's written authorization

- **Cases :**
  - IPD confirmed by culture/PCR from normaly sterile site sample
  - Notified and recruited by Public Health authorities (IPD = reportable disease)
  - Reference date = date of sampling for culture.

- **Controls**
  - Random age and year-stratified sample of the Quebec Health Insurance Registry (RAMQ) database
    - Monthly fixed number of participants,
    - ≈ 4 participants for each expected case
  - Reference date = date of interview (or the 15th of the month).

Vaccine effectiveness = $(1\text{-}OR_{immunization})*100\%$

With $OR_{immunization}$

- Computed by logistic regression
- Weighted for sample fractions of controls
- Adjusted for age, year, season and any medical risk factor (indication of 4 doses/asthma/severe prematurity)

(other variables were not confounding the association between immunisation and IPD were discarded from the model in order to keep optimal power)

Results

- 889 eligible IPD cases 2005-2013
  - 689 recruited by public health authorities
  - 667 interviewed
  - 516 (58% of those eligible) returned written authorization to check immunization records
- 3,356 randomly selected controls.
  - 2,613 interviewed
  - 1,767 (53% of those eligible) returned written authorization to check immunization records

Vaccine effectiveness (≥1 dose)

IPD Serotypes	Cases number	PCV-7	PCV-10	PCV-13
Any serotype	Total 516 V+ cases VE V- 83 95%CI	305 **50%** 29 to 64%	34 **72%** 46 to 85%	44 **66%** 29 to 83%
PCV7 included + 6A (4,6B,9V,14,18C,19F,23F)	Total 73 V+ cases VE V- 49 95%CI	23 **90%** 82 to 95%	1 **96%** 50 to 100%	0 **ND**
PCV10 incl. + 6A (+1,5F,7F)	Total 118 V+ cases VE V- 54 95%CI	60 **78%** 63 to 86%	2 **97%** 84 to 99%	0 **ND**
PCV13 included (+3,6A,19A)	Total 310 V+ cases VE V- 71 95%CI	193 **63%** 45 to 74%	17 **84%** 65 to 93%	10 **86%** 62 to 95%

VE computed by logistic regression model weighted for sampling fraction of controls and adjusted for age, year, season and underlying medical conditions including asthma and severe prematurity.

ND = Not Determined as no case was observed in vaccinated children and no controls vaccinated in the same strata.

Vaccine effectiveness (≥1 dose)

IPD Serotypes	Cases number			PCV-7	PCV-10	PCV-13
Serotype 19A	Total	167	V+ cases	113	13	9
	V-	16	VE	**42%**	**71%**	**74%**
			95%CI	-9 to 69%	24 to 89%	11 to 92%
Serotype 7F	Total	38	V+ cases	30	1	0
	V-	5	VE	**15%**	**93%**	**ND**
			95%CI	-161 to 72	23 to 99%	

VE computed by logistic regression model weighted for sampling fraction of controls and adjusted for age, year, season and underlying medical conditions including asthma and severe prematurity.

ND = Not Determined as no case was observed in vaccinated children and no controls vaccinated in the same strata.

VPC10, VPC13 and MIXED SCHEDULE, ≥2 doses

IPD Serotypes	Cases number			PCV-10	PCV-10/13	PCV-13
Any serotype	Total	516	V+ cases	26	16	41
	V-	83	VE	75%	66%	65%
			95%CI	51 to 87%	23 to 85%	29 to 83%
Serotype 19A	Total	167	V+ cases	11	3	9
	V-	16	VE	71%	78%	68%
			95%CI	16 to 90%	2 to 95%	-13 to 91%
PCV13 included	Total	310	V+ cases	12	3	9
	V-	71	VE	85%	89%	85%
			95%CI	66 to 94%	58 to 97%	55 to 94%

VE computed by logistic regression model weighted for sampling fraction of controls and adjusted for age, year, season and underlying medical conditions including asthma and severe prematurity.

- No vaccine/mix showed effectiveness against all non PCV13 included serotypes
  - VE negative, all confidence intervals span zero

19A cases in children immunized with PCV10 or PCV13 in Quebec

- PCV10: 13 cases (2009-2012)
  - in children without any risk factor
  - after 1st dose : 2 cases, age 3 and 4 months
  - after 2nd dose : 7 cases, age 5 to 13 months old
  - after 3rd dose : 4 cases, age 16 to 32 months

- PCV13: 9 cases (2011-2013)
  - in children without any risk factor
  - after 2nd dose : 9 cases, at age 9 to 12 month-old
    - before the booster dose could be administered

PCVs effectiveness comparison in other studies

Comparison of 3 PCVs effectiveness against all IPD (VE ≥1 dose)			
Vaccine	Serotype	Quebec (2+1)	Others (3+1)
PCV-7	all	**50% (29 to 64)**	**72% (65 to 78)[1]**
PCV-10	all	**72% (46 to 85)**	**65% (11 to 86)[3]**
PCV-13	all	**66% (29 to 83)**	**59% (49-70)[6]**

Ref : [1] Whithney, [2]Tregnaghi2014, [3]Moore 2014

PCVs effectiveness comparison in other studies

Comparison of 3 PCVs effectiveness against included serotypes (VE ≥1 dose)				
Vaccine	Serotype	Quebec 2+1	Others 2+/1	Others 3+1
PCV-7	7 incl.	**90%(82-100)**		**96%(93-98)/ /81%(57-92) [1]**
PCV-10	10 incl.	**97%(84-99)**	**92% (58-100) [2]**	**100 %(83-100) [2] 84 %(66-92) [4] 100% (74-100) [3]**
PCV-13	13 incl.	**86% (62 -95)**	**75% (58-84) [5]**	**89 %(79-94) [6]**

Ref : [1] Whithney, [2] Palmu 2013, [3]Tregnaghi2014, [4]Domingues2014 , [5]Andrews2014, [6]Moore 2014

Comparison of 3 PCVs effectiveness against 19A serotype in different studies (VE ≥1 dose)				
Vaccine	Serotype	Quebec 2+1	Others 2+/1	Others 3+1
PCV-7	19A	**42%(-9-69)**		**26%(-45-62)[1]**
PCV-10	19A	**71%(24-89)**		**82% (11-96)[4]**
PCV-13	19A	**74%(11-92)**	**67 %(33-84) [5]**	**90% (76-96)[6]**

Ref : [1] Whithney, [2] Palmu 2013, [3]Tregnaghi2014, [4]Domingues2014 , [5]Andrews2014, [6]Moore 2014

- Mixed schedule PCV10/PCV13
  - Similar protection as compared with a PCV10-only or a PCV13-only schedule
  - May be a promising cost-effective avenue

Limitations

- Case-control study
  - Baseline IPD risk may be different in vaccinated and unvaccinated children.
  - Unmeasured confounders / residual confounding
  - Only 58% of eligible IPD cases fully participated

- Limited power
  - Population : ≈ 80,000 births per year
  - Truncation of the observation on December 31st 2013
    - » Long-term VE estimates unavalaible yet for PCV13

Conclusion

- PCV10 and PCV13 seem to be more effective than PCV7
- Cross-protection against 19A ensured by PCV10
- No difference in protection was seen between a PCV10-only, a PCV13-only, or a mixed PCV10+PCV13 schedule.