Pertussis Vaccine Effectiveness in a Frequency-Matched Population-Based Case-Control Canadian Immunization Research Network Study in Ontario, Canada 2009-2015

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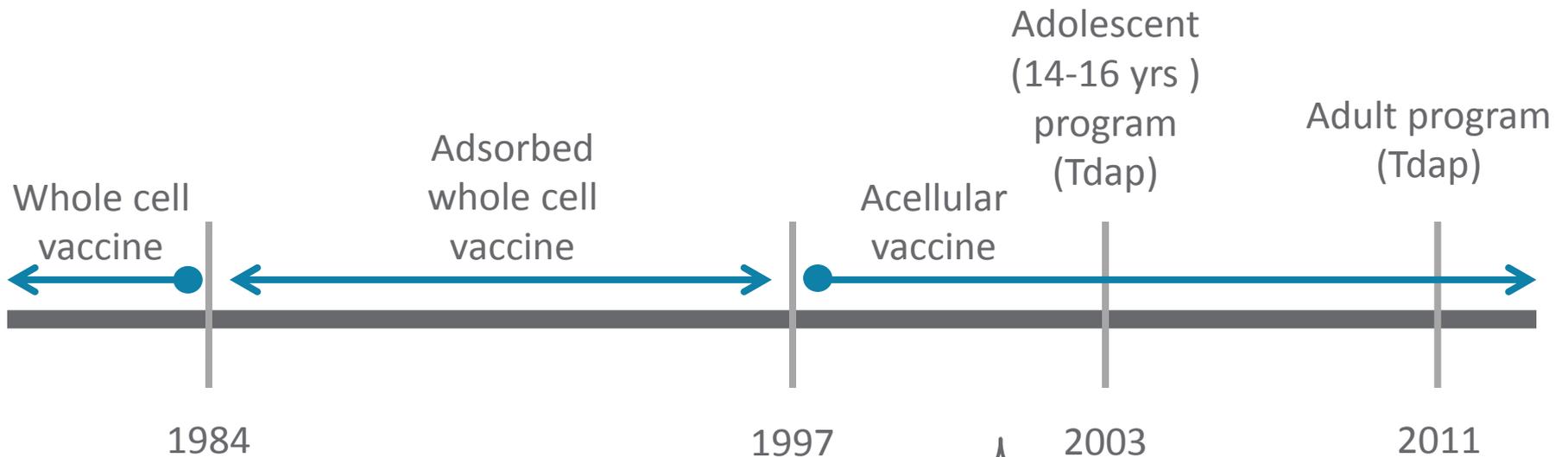Canadian Immunization Conference

Disclosure Statement

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

Background

- The greatest challenge facing pertussis control is waning protection from acellular pertussis vaccines

- Systematic review of acellular pertussis vaccine, within 3 years, at least 3 components: efficacy **84%** (81-87%)[1]

- Trial of 5-component vaccine with up to 2 years follow-up: efficacy **94% against culture-confirmed pertussis, 85% against typical disease, 78% against mild and atypical** [2]

- Follow up is short in clinical trials: field evaluation is required to assess vaccine effectiveness (VE)

[1]Gustafsson et al, NEJM 1996 Feb 8;334(6):349-56; [2]Fulton et al, CID. 2016 Feb 7;62(9):1100-1110

Pertussis Immunization Program in Ontario

Whole cell vaccine

Adsorbed whole cell vaccine

Acellular vaccine

Adolescent (14-16 yrs) program (Tdap)

Adult program (Tdap)

1984

1997

2003

2011

- Primary series (DTaP-IPV-Hib)
  - 2, 4, 6 months
- Booster doses
  - 18 months (DTaP-IPV-Hib)
  - 4-6 years (DTaP-IPV / Tdap-IPV since May 2012)

Frequency-Matched Case-Control Study Design (FMD)

- **Cases**: Mandatory reports of confirmed and probable pertussis cases to the integrated Public Health Information System (iPHIS) in 2009-15

  - Strict case definitions, requiring typical/severe symptoms

- **Controls**: Randomly selected from Ontario Health Insurance Plan billing database (OHIP), frequency matched on primary care provider, age group, and year of pertussis diagnosis

- **Cases and Controls**: Born since 1992

Linkage and Data Sources

- iPHIS data linkage
  - Deterministic using health card number, or probabilistic linkage using first and last name, birthdate, sex, postal code

- Sources of data:
  - **Sex, socioeconomic status and rural residence**: Ontario's Registered Person's Database
  - **Chronic conditions**: Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)
  - **Health care use**: Ontario Health Insurance Plan (OHIP), CIHI National Ambulatory Care Reporting System (NACRS) and DAD.
  - **Vaccination status**: Vaccine billing codes

FMD Controls 1:4 Frequency Match

Total number of cases

n = 1,335

Pool of potential controls from same physicians

n = 1,017,783

Frequency matched on age, year of diagnosis.
4 controls per case: simple random sampling without replacement
N = 5,340

VE (up-to-date) and time since last vaccination

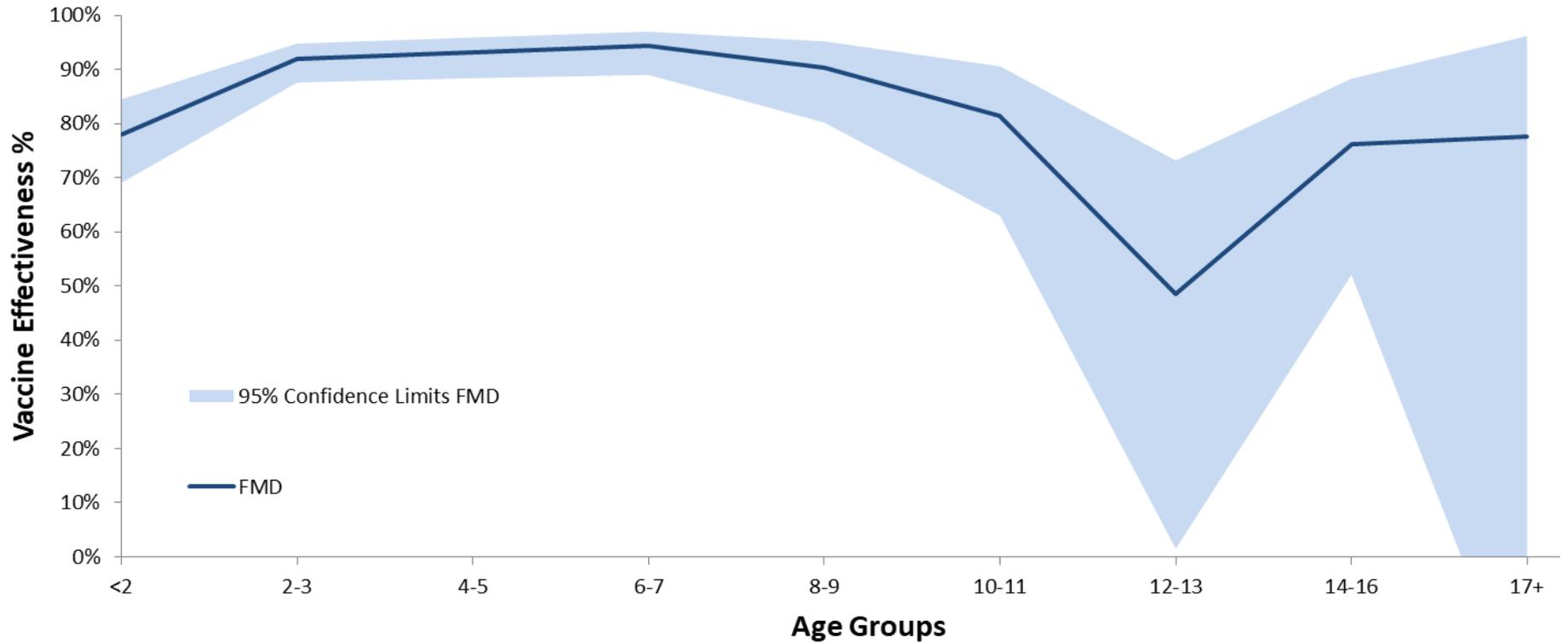| Age	Time since last vaccination	Adjusted† VE % (95%CI)
6-18 months	15-364 days	85.7 (76.3 – 91.3)
18 months-4 years	15-364 days	91.7 (86.4 – 94.9)
	1-3 years	89.0 (82.9 – 92.9)
4-14 years	15-364 days	92.8 (86.4 – 96.1)
	1-3 years	90.4 (86.5 – 93.1)
	4-7 years	84.0 (78.4 – 88.2)
	≥ 8 years	80.4 (71.3 – 86.6)
14-22 years	15-364 days	92.5 (74.1 – 97.8)
	1-3 years	82.8 (57.3 – 93.1)
	4-7 years	78.3 (40.8 – 87.1)
	≥ 8 years	66.5 (35.3 – 82.7)

† Adjusted for sex, socioeconomic status, rurality, healthcare utilization and comorbidity

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Pertussis VE by Age Group

Estimates of Pertussis VE for those up-to-date by time since last vaccination - <u>ignoring age</u>

Time since last vaccination	Crude % VE (95% CI)	Adjusted % VE†(95% CI)
15-364 days	88 (86, 91)	87 (84, 90)
1-3 years	89 (86, 91)	88 (85, 91)
4-7 years	81 (77,85)	77 (69, 82)
≥ 8 years	78 (72, 83)	74 (63, 82)

† Adjusted for sex, socioeconomic status, rurality, healthcare utilization and comorbidity

Pertussis Vaccine Effectiveness in Ontario:
Comparing Frequency-Matched with Test-Negative Design
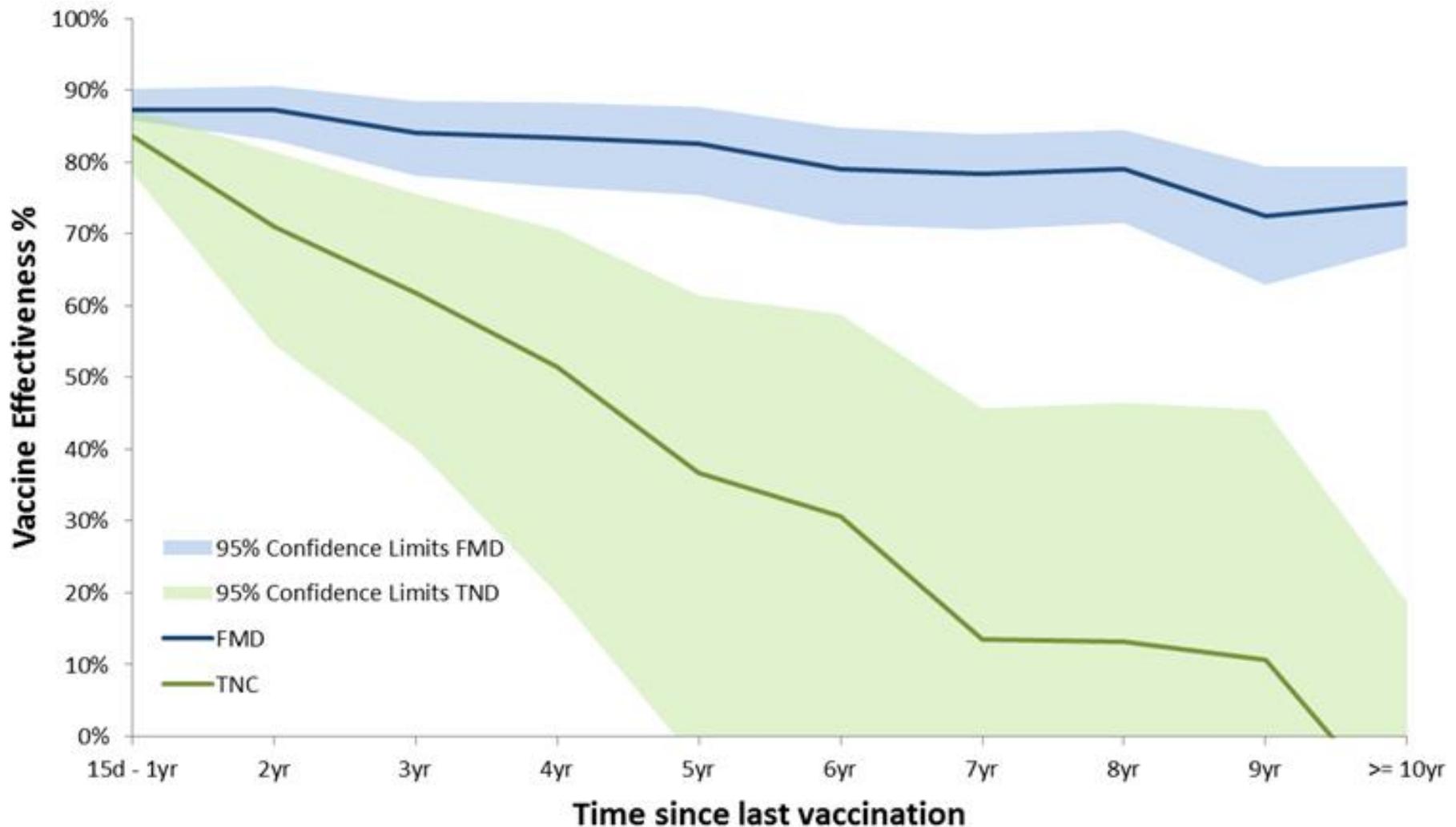
Conclusions

- For young children, vaccine effectiveness against Ontario strict/typical confirmed and probable case definitions is high

- During adolescence effectiveness falls to 80% before the booster. Afterwards, it falls from 93% to 83% within 3 years, consistent with current epidemiology

- Additional action may still be needed to protect infants, including immunization in pregnancy

https://www.ontario.ca/page/vaccines

Thank you!

Acknowledgments

Investigators

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Funding

Additional slides

Main Exposure: Vaccine Status

Up-to date vaccination status

Age	Number of Doses						
	0	1	2	3	4	5	6
0-2 months	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3-4 months	UN	UTD	N/A	N/A	N/A	N/A	N/A
5-6 months	UN	INC P	UTD	N/A	N/A	N/A	N/A
7-18 months	UN	INC P	INC P	UTD	N/A	N/A	N/A
19 months - 6 years	UN	INC P	INC P	INC P	UTD	N/A	N/A
7-16 years	UN	INC P	INC P	INC P	COM P M1	UTD	N/A
17 years +	UN	INC P	INC P	INC P	COM P M2	COM P B1 M1	UTD

Unvaccinated

Incomplete for primary vaccinations

Complete primary vaccinations, missing one (M1) or two (M2) boosters

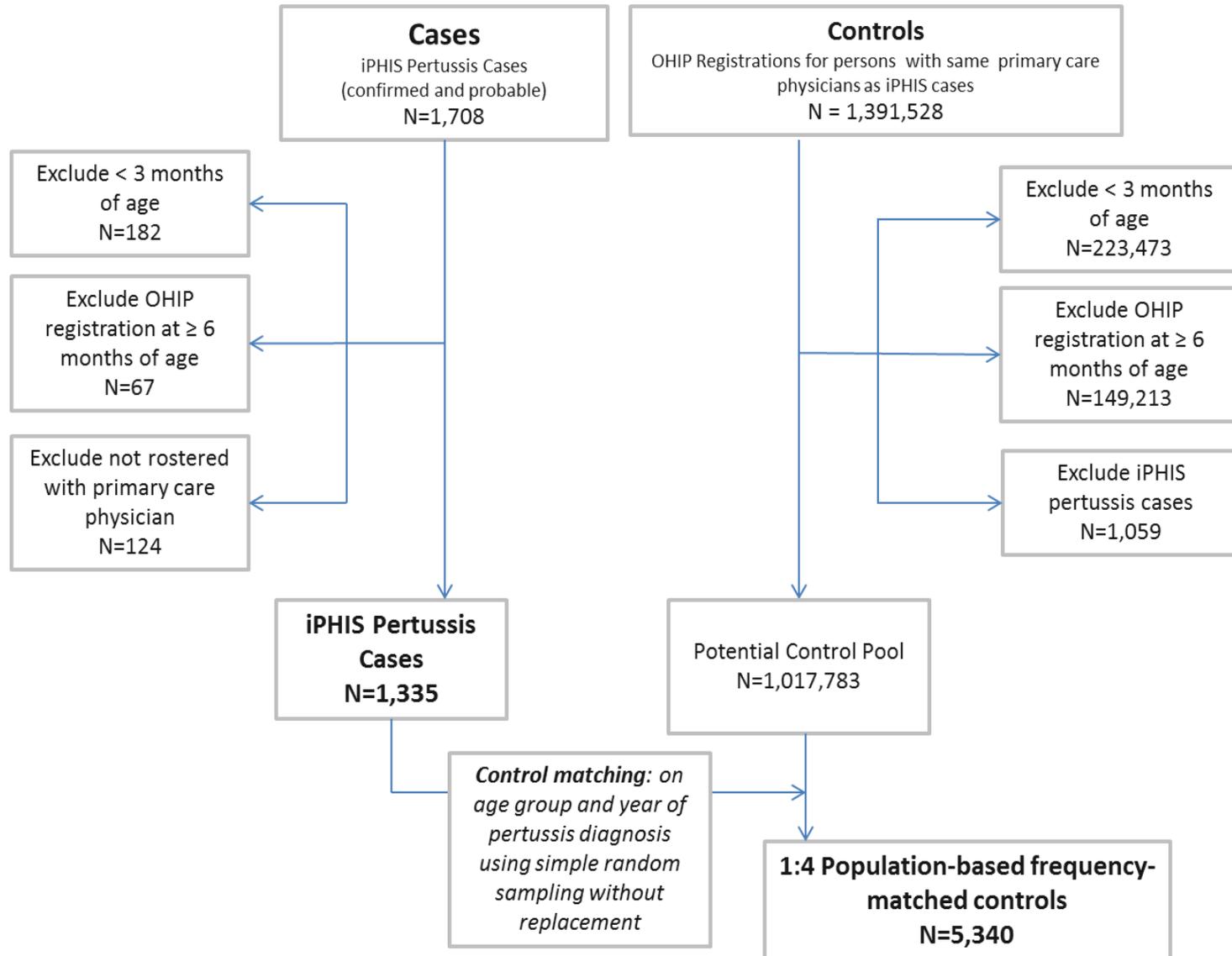Complete primary vaccinations with one booster, missing one booster

Ontario iPHIS confirmed case definition

- **Laboratory confirmation** of infection **AND** one or more of the following:
  - cough lasting 2 weeks or longer/ paroxysmal cough of any duration/cough with inspiratory "whoop"/cough ending in vomiting or gagging, or associated with apnea

- **OR Epidemiologic link** to a laboratory-confirmed case **AND** one or more of the following <u>for which there is no other known cause</u>:
  - paroxysmal cough of any duration/cough with inspiratory "whoop"/cough ending in vomiting or gagging, or associated with apnea

FMD: Ontario iPHIS probable case definition

- Cough lasting 2 weeks or longer in the absence of appropriate laboratory tests and <u>not epidemiologically linked</u> to a laboratory-confirmed case for which there is no other known cause **AND** one or more of the following, with no other known cause:

  - paroxysmal cough of any duration/cough with inspiratory "whoop"/cough ending in vomiting or gagging, or associated with apnea

FMD: Case and control selection

Cases
iPHIS Pertussis Cases
(confirmed and probable)
N=1,708

Controls
OHIP Registrations for persons with same primary care
physicians as iPHIS cases
N = 1,391,528

Exclude < 3 months
of age
N=182

Exclude < 3 months
of age
N=223,473

Exclude OHIP
registration at ≥ 6
months of age
N=67

Exclude OHIP
registration at ≥ 6
months of age
N=149,213

Exclude not rostered
with primary care
physician
N=124

Exclude iPHIS
pertussis cases
N=1,059

**iPHIS Pertussis
Cases
N=1,335**

Potential Control Pool
N=1,017,783

*Control matching: on
age group and year of
pertussis diagnosis
using simple random
sampling without
replacement*

**1:4 Population-based frequency-
matched controls
N=5,340**

Vaccination for Pertussis

OHIP Billing Codes	Code	Description	Frequency	Percent
Pertussis-specific	G840	Quadrivalent vaccine (DTaP-IPV)	163	0.20
	G841	Pentavalent vaccine (DTaP-IPV-Hib)	1060	1.31
	G847	DTaP vaccine	95	0.12
Immunization, generic	G538	Immunization with visit	76109	93.78
	G539	Immunization only	3726	4.59

# FMD: Vaccine effectiveness in 2009-15 and excluding 2012 outbreak
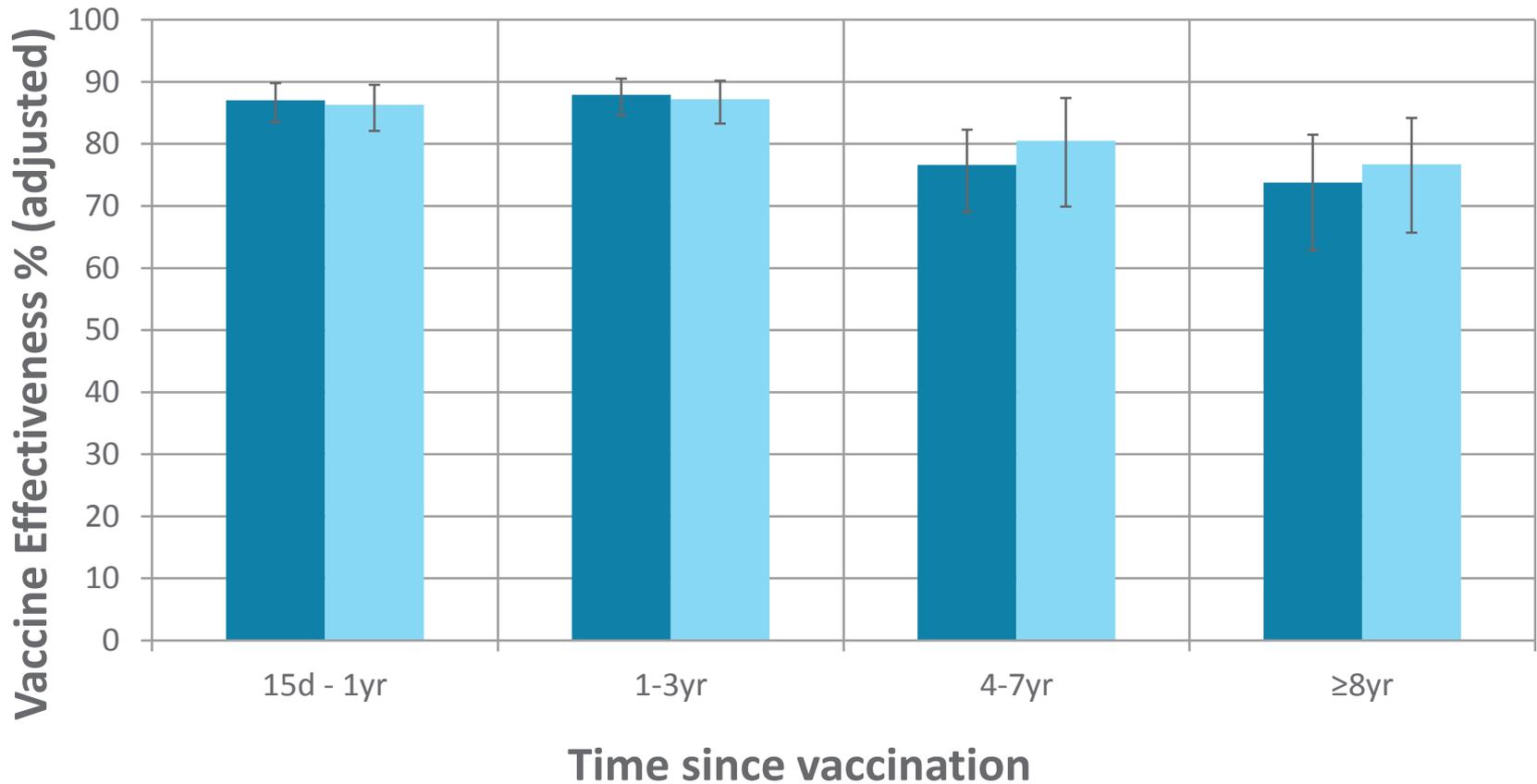
VE and time period since last vaccination stratified by age for children and adolescents who are up-to-date for immunizations

† Adjusted for sex, socioeconomic status, rurality, healthcare utilization and comorbidity

Age	Time since last vaccination	Crude VE % (95%CI)	Adjusted† VE % (95%CI)
6-18 months	15-364 days	84.9 (77.4 – 89.9)	85.7 (76.3 – 91.3)
18 months – 4 years	15-364 days	93.2 (89.4 – 95.7)	91.7 (86.4 – 94.9)
	1-3 years	90.0 (85.1 – 93.3)	89.0 (82.9 – 92.9)
4 years -14 years	15-364 days	94.3 (89.6 – 96.9)	92.8 (86.4 – 96.1)
	1-3 years	91.8 (88.8 – 94.1)	90.4 (86.5 – 93.1)
	4-7 years	86.0 (81.4 – 89.4)	84.0 (78.4 – 88.2)
	≥ 8 years	85.3 (79.1 – 89.7)	80.4 (71.3 – 86.6)
14 years – 22 years	15-364 days	87.9 (67.1 – 95.5)	92.5 (74.1 – 97.8)
	1-3 years	76.8 (48.9 – 89.4)	82.8 (57.3 – 93.1)
	4-7 years	63.3 (38.9 – 83.8)	78.3 (40.8 – 87.1)
	≥ 8 years	59.3 (23.7 – 78.3)	66.5 (35.3 – 82.7)

Pertussis Vaccine Effectiveness in Ontario:
Comparing TND with FMD, by time since last vaccination
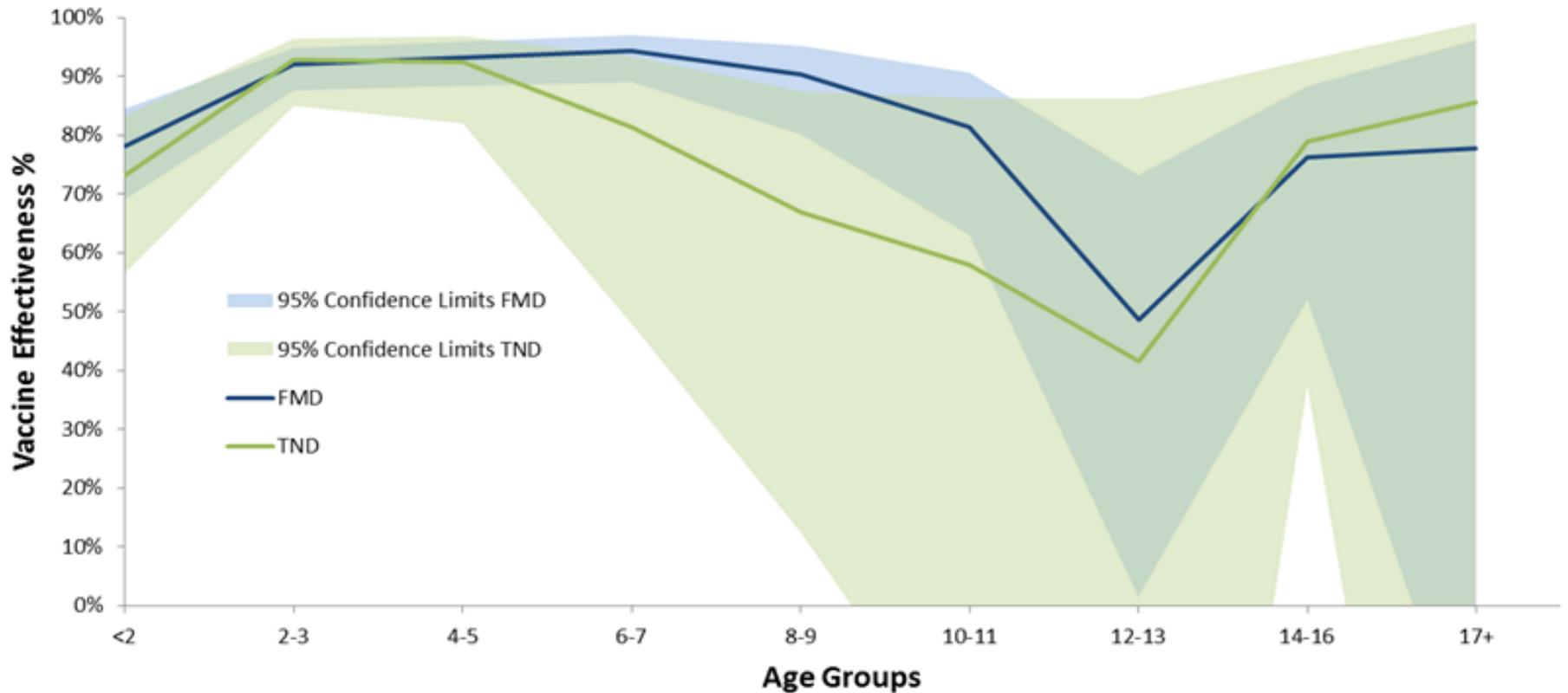
Potential source of bias: Are test-negative controls less likely to be tested if vaccinated?

- Test-negative design controls:
  - **14.6%** of 5381 controls were unvaccinated

- Frequency-matched controls:
  - **8%** of 5340 controls were unvaccinated

- TND controls are significantly more likely to be unvaccinated than FMD controls P<0.0001

- Testing bias could lead to VE being under-estimated

VE differs by case definition and study design

- Both designs may **over-estimate VE and waning** if milder cases are undetected and these increase with age.

- Both designs may **under-estimate VE** if controls are over-matched with cases

- FMD may **over-estimate VE** because of strict case definition

- TND may **over-estimate VE** if vaccinated cases less likely to be tested, but testing bias may decline with increasing age/time since vaccination

- TND may **under-estimate VE** if:
  - Vaccinated controls are less likely to be tested
  - Controls are false-negative cases