

Sérotypový replacement

MUDr. Milan Trojánek, Ph.D.

Katedra infekčního lékařství

Institut postgraduálního vzdělávání ve zdravotnictví

Klinika infekčních nemocí

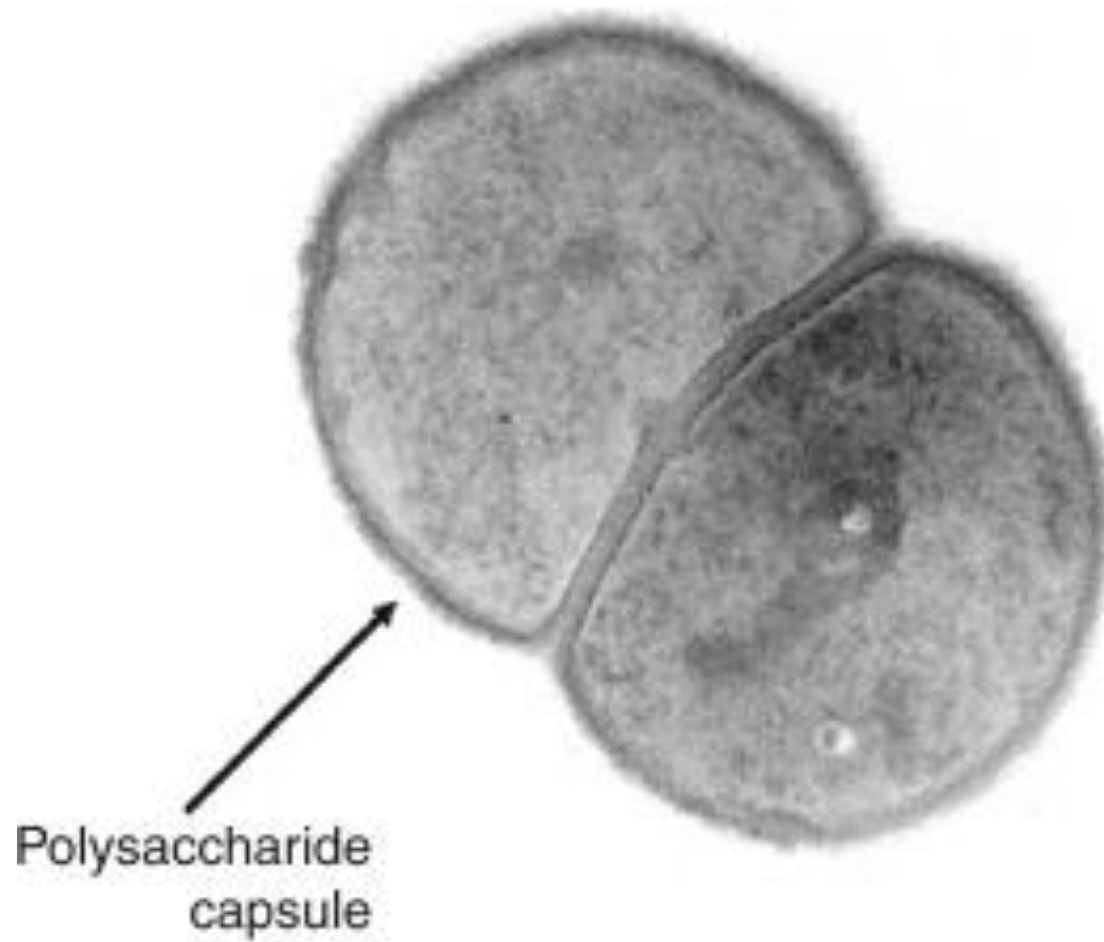
2. lékařská fakulta, Univerzita Karlova, Praha

Klinika infekčních, parazitárních a tropických nemocí

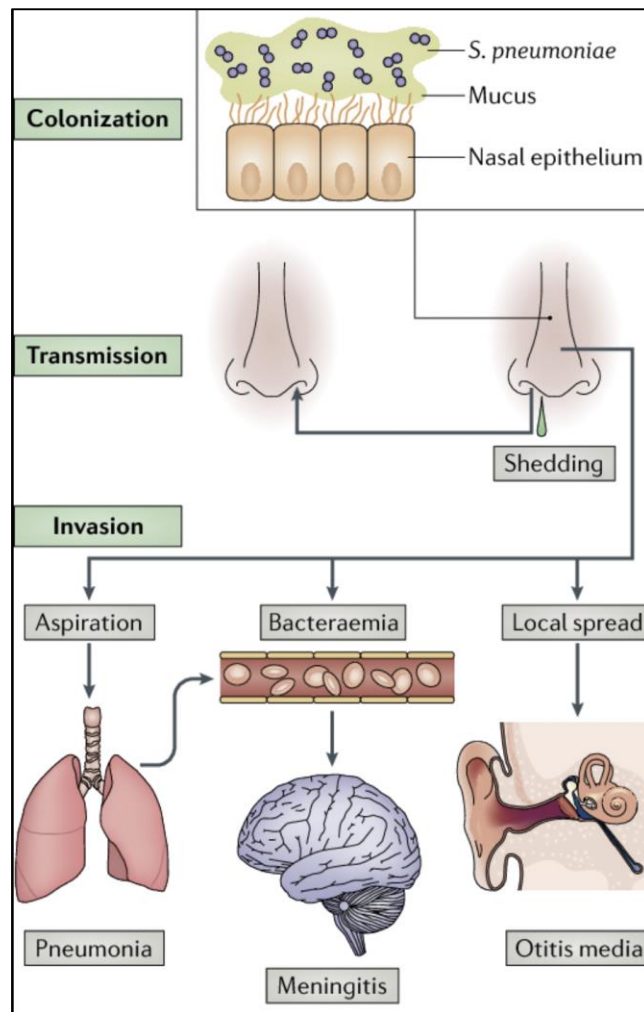
Fakultní nemocnice Bulovka, Praha



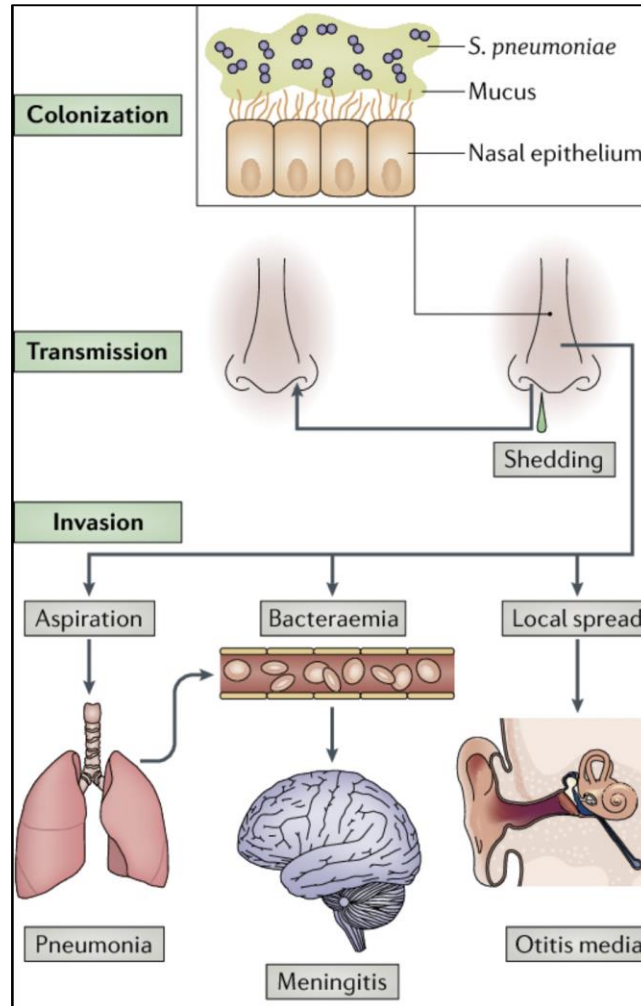
Pneumokoky



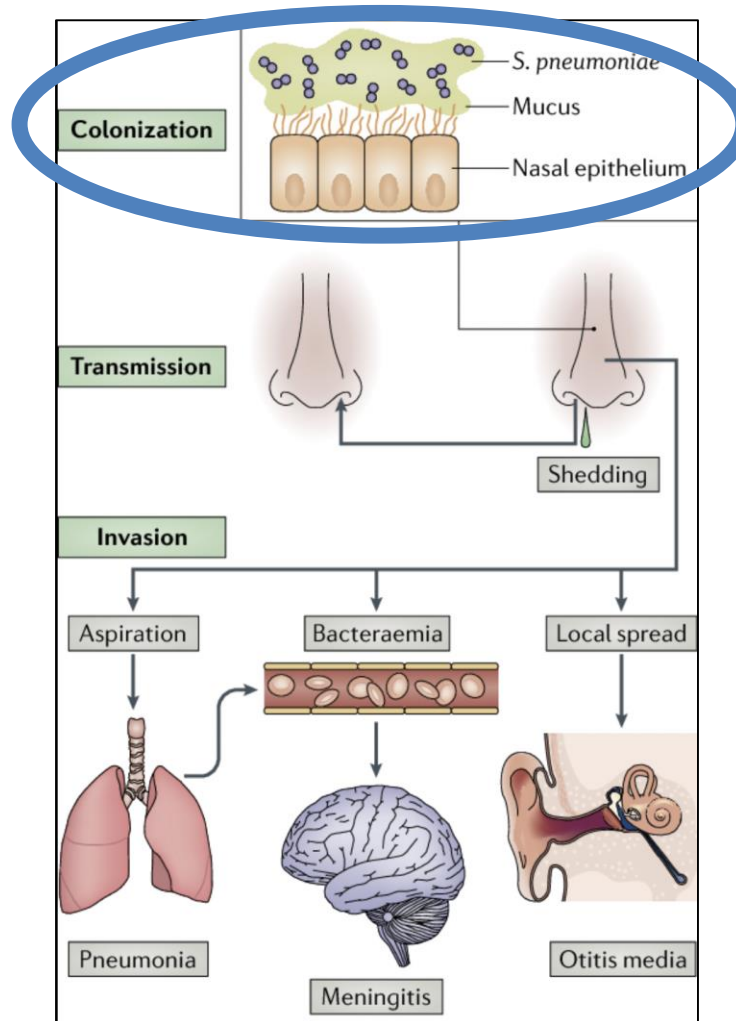
Pneumokoková onemocnění



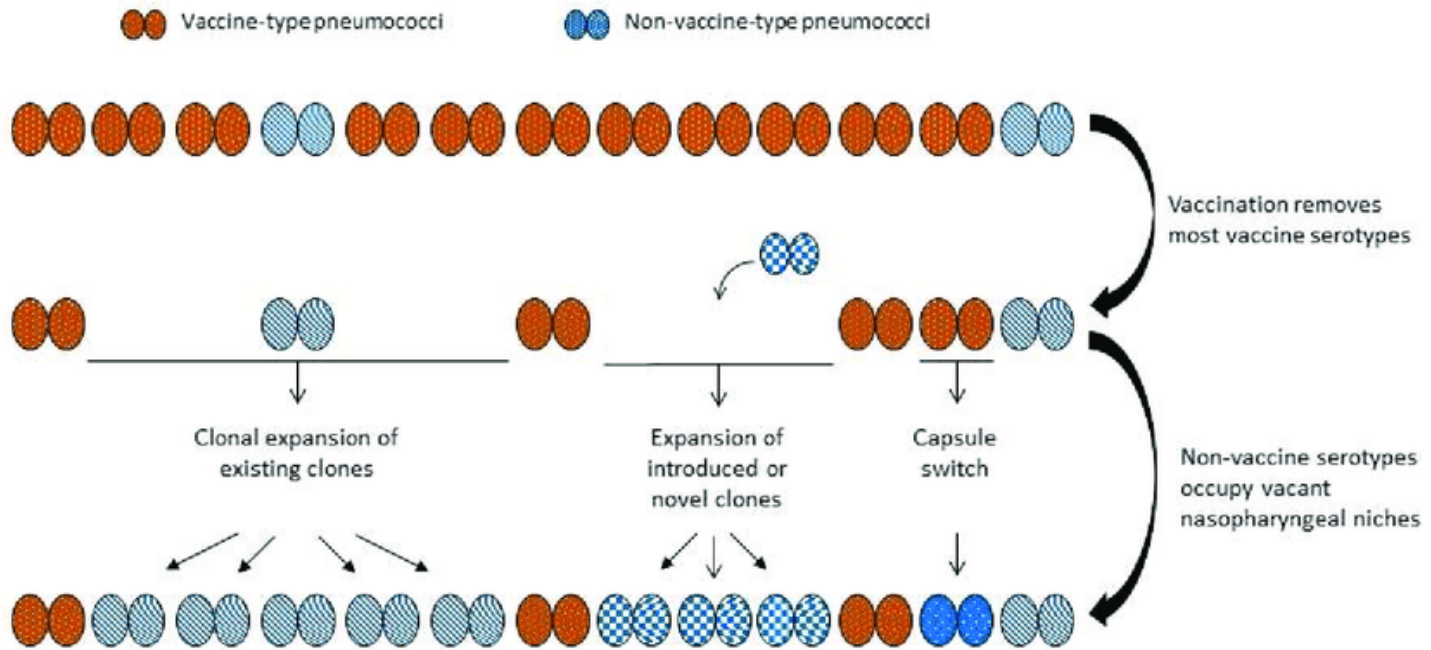
Replacement



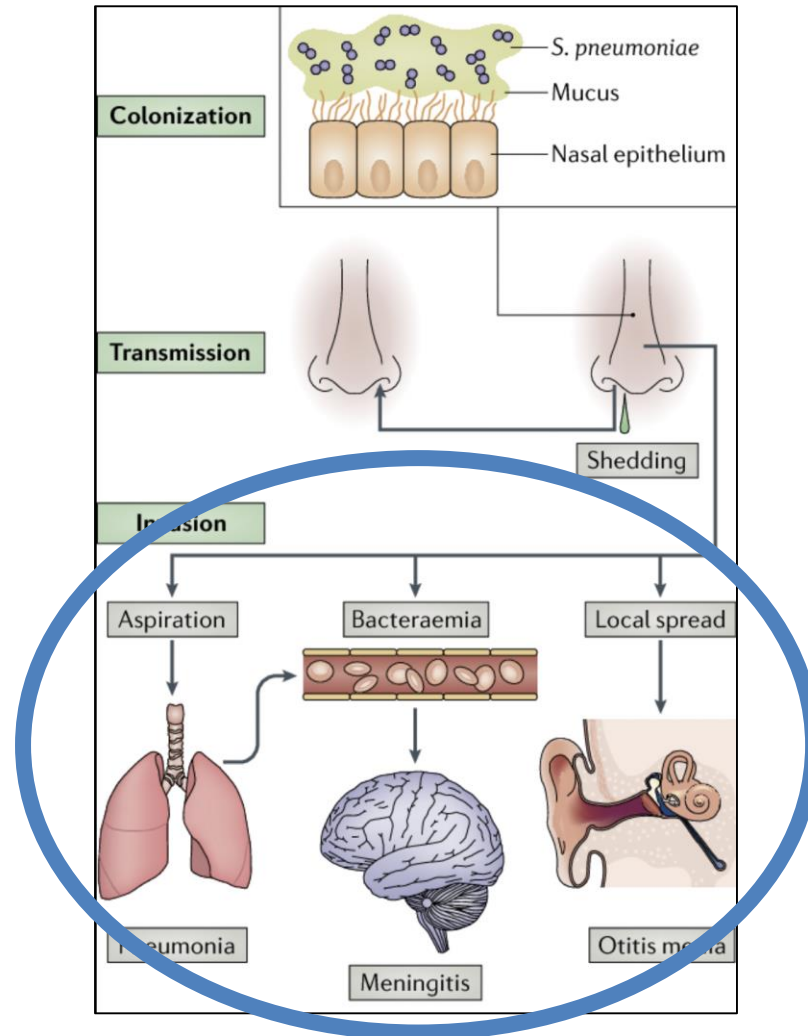
Replacement



Replacement

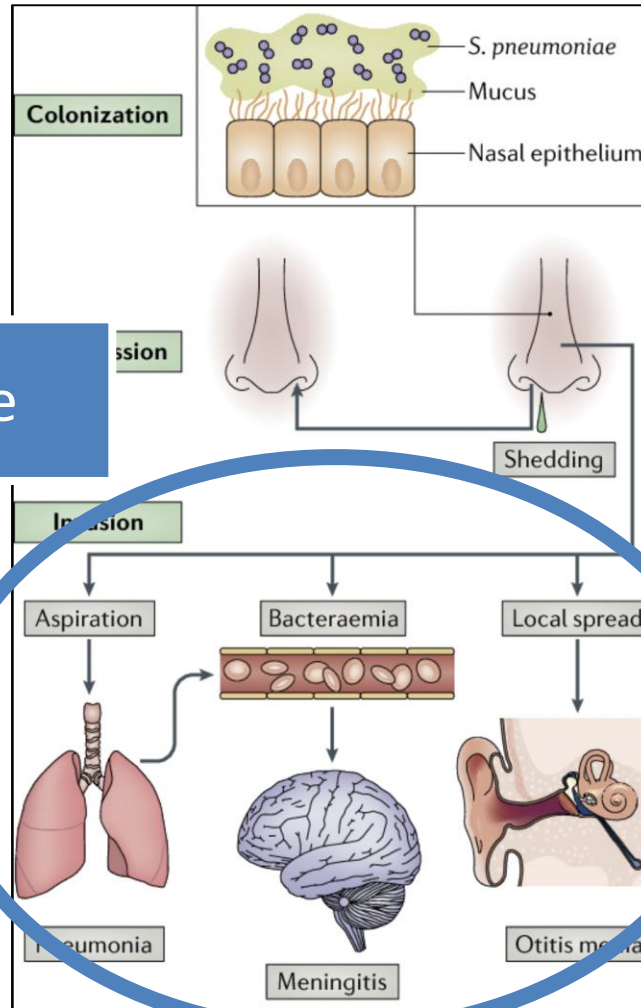


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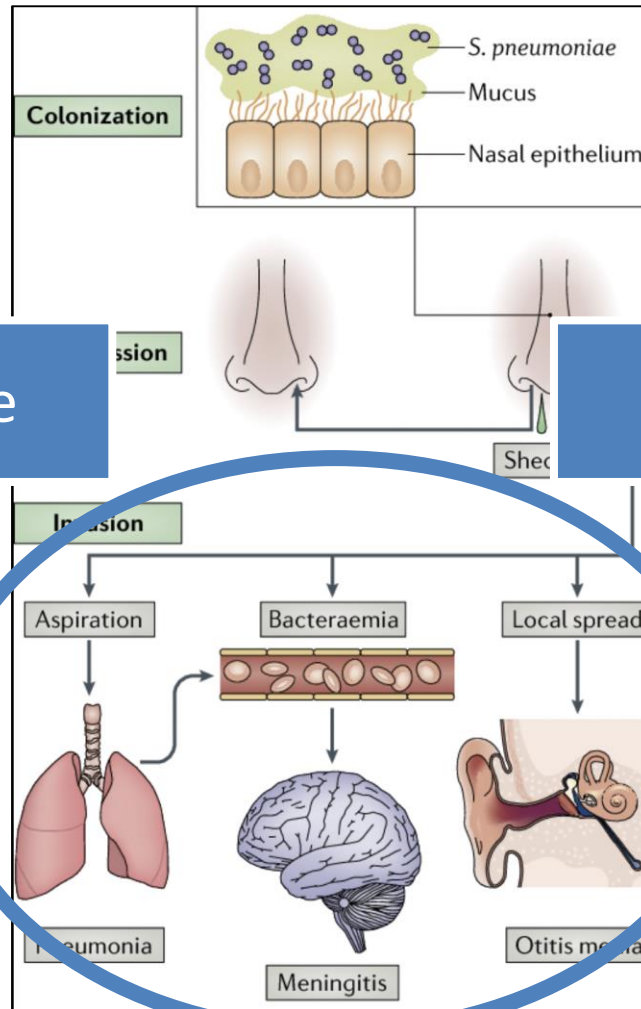


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Vlastnosti hostitele

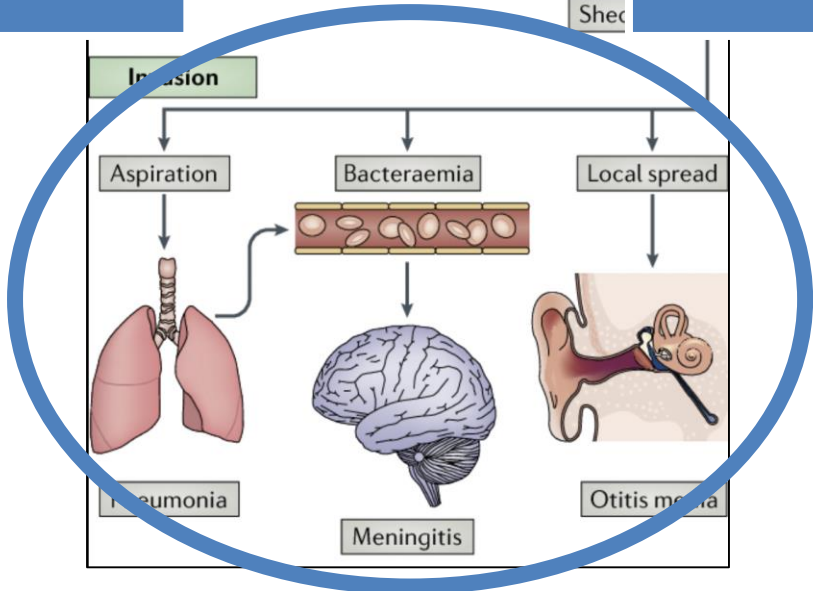


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Vlastnosti hostitele

Vlastnosti kmene



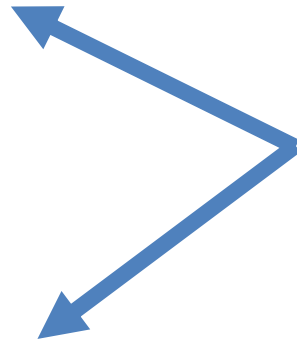
Replacement

Nízce invazivní sérotypy

Kolonizace nosohltanu
Onemocnění u rizikových pacientů
„Oportunní patogen“

Vysoce invazivní sérotypy

Invazivní onemocnění
Onemocnění i u zdravých jedinců
„Primární patogen“

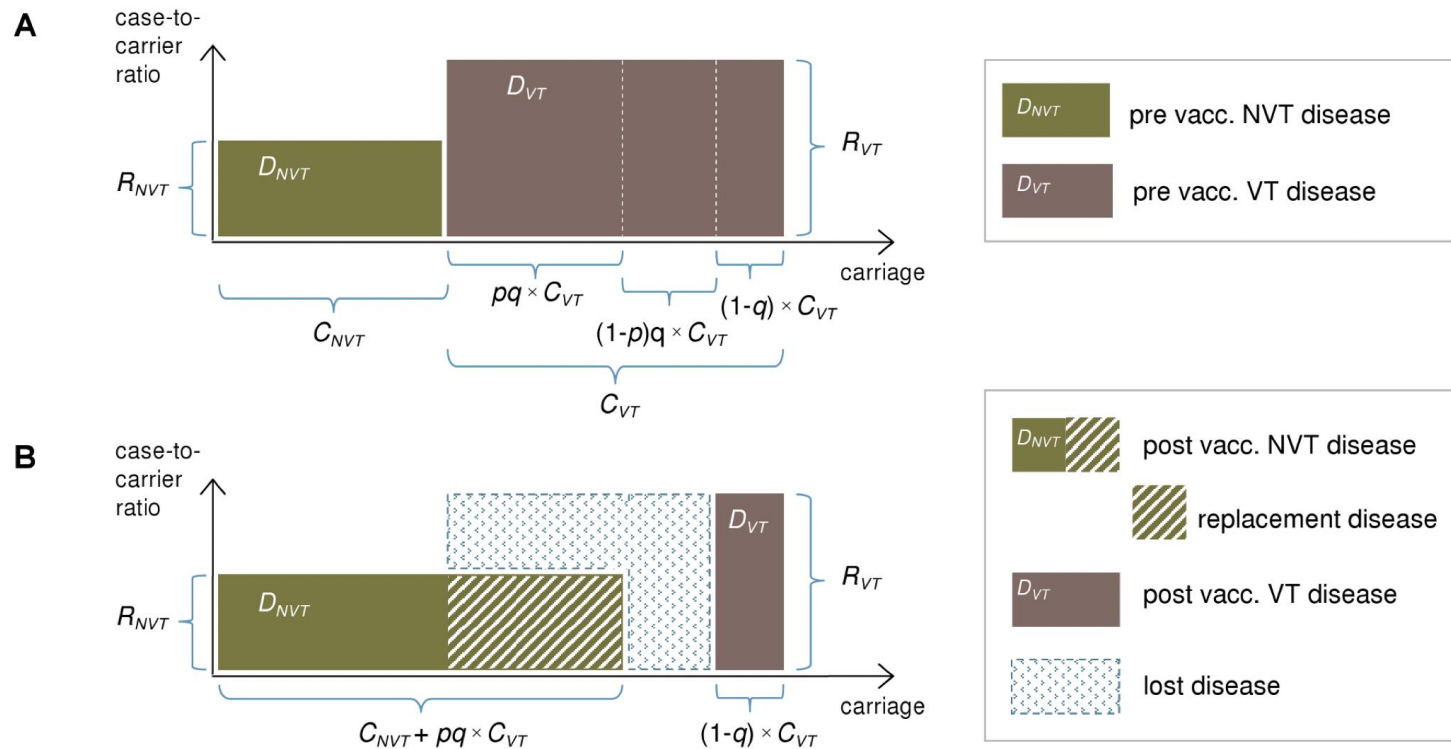


Vlastnosti kmene

Replacement

Optimal Serotype Compositions for Pneumococcal Conjugate Vaccination under Serotype Replacement

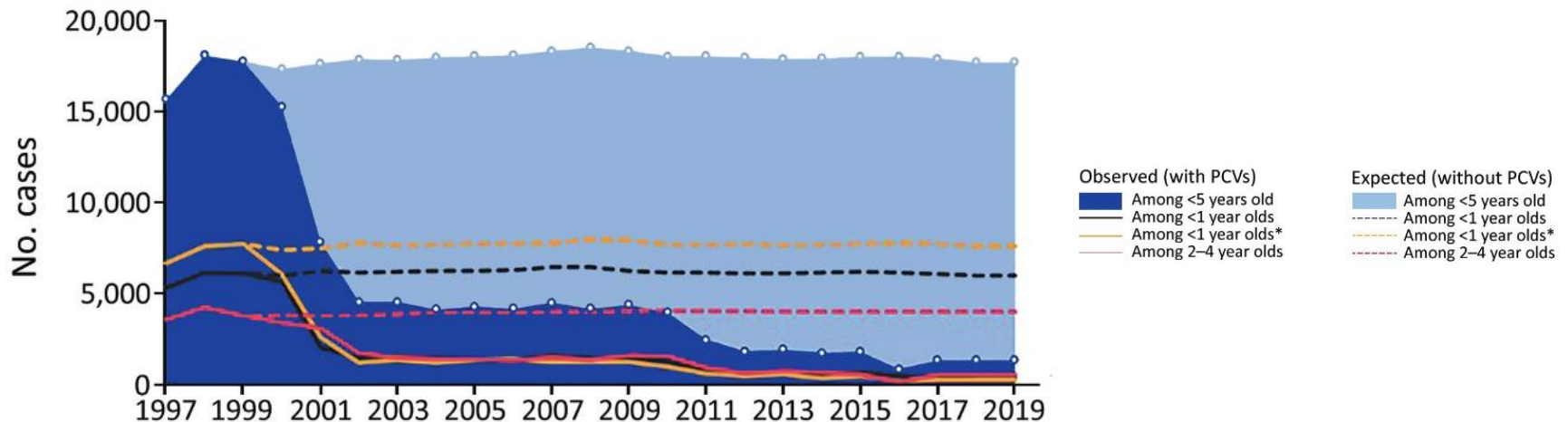
Markku Nurhonen*, Kari Auranen



IPO, USA, 1997-2019

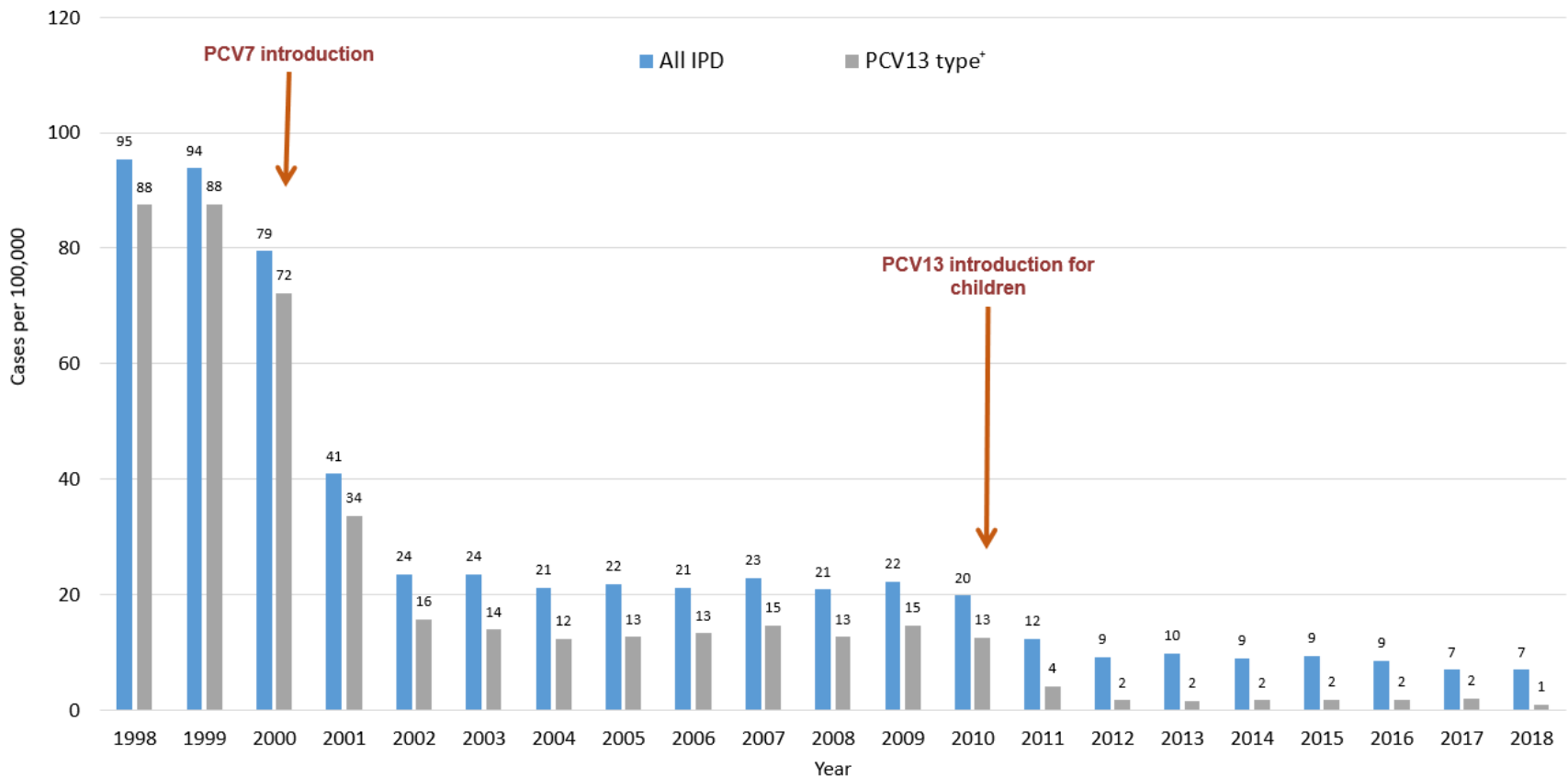
Twenty-Year Public Health Impact of 7- and 13-Valent Pneumococcal Conjugate Vaccines in US Children

Matt Wasserman, Ruth Chapman, Rotem Lapidot, Kelly Sutton, Desmond Dillon-Murphy, Shreeya Patel, Erica Chilson, Vincenza Snow, Raymond Farkouh, Stephen Pelton



IPO, USA, 1998-2018 (<5 let)

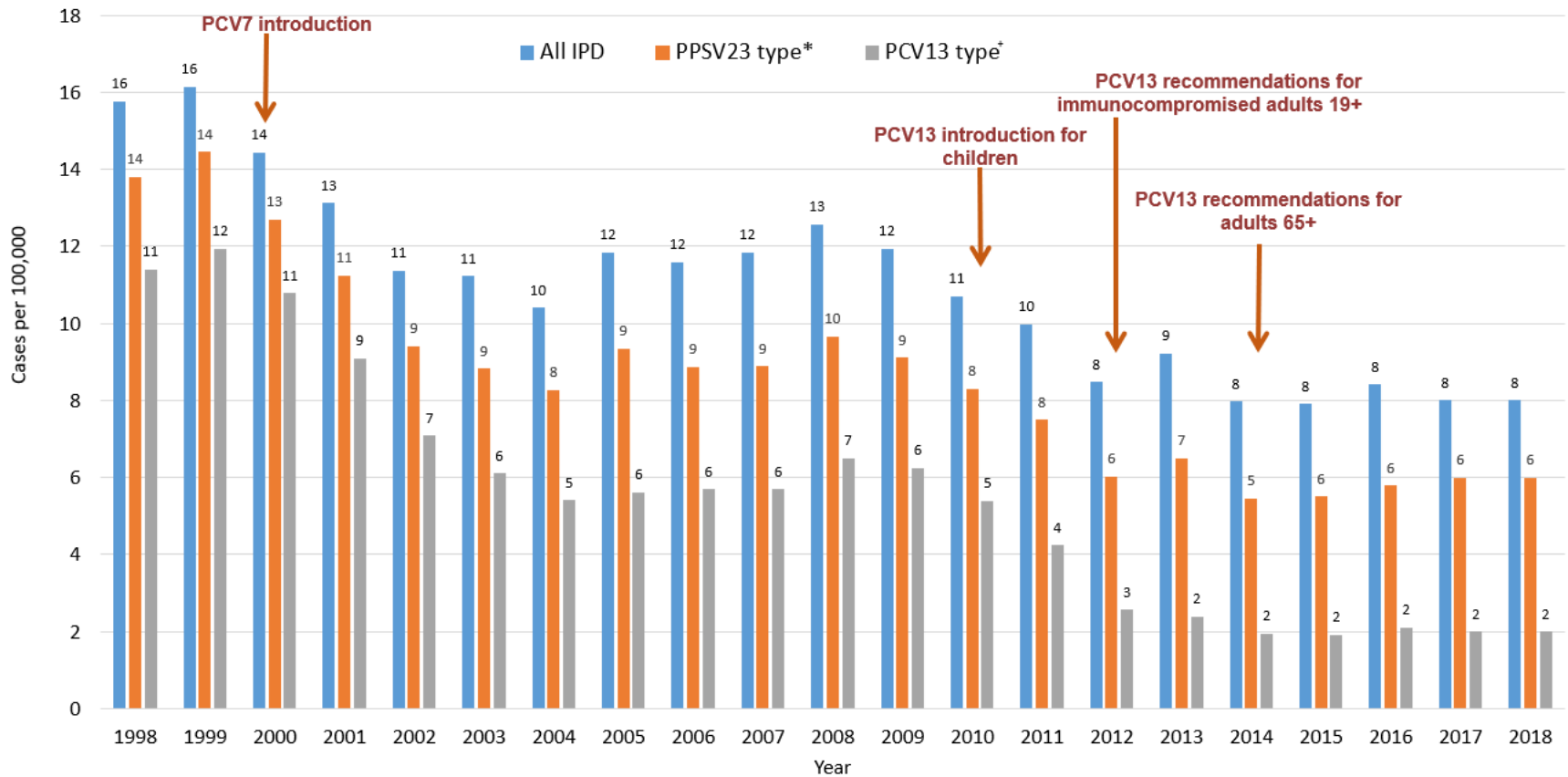
Trends in invasive pneumococcal disease among children aged <5 years old, 1998–2018



*PCV13 serotype: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

IPO, USA, 1998-2018 (19-64 let)

Trends in invasive pneumococcal disease among adults aged 19-64 years old, 1998–2018



*PPSV23 serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F

*PCV13 serotype: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

IPO, USA, 2008-2018 (KP)

Impact of the 13-Valent Pneumococcal Conjugate Vaccine on Invasive Pneumococcal Disease After Introduction Into Routine Pediatric Use

Roger Baxter,^{1,a} Laurie Aukes,¹ Stephen I. Pelton,^{2,3} Arnold Yee,¹ Nicola P. Klein,¹ William C. Gruber,⁴ Daniel A. Scott,⁵ and Kimberly J. Center⁵

¹Vaccine Study Center, Kaiser Permanente, Oakland, California, USA; ²Department of Pediatrics, Boston University School of Public Health, Boston, Massachusetts, USA;

³Department of Pediatrics, Boston Medical Center, Boston, Massachusetts, USA; ⁴Vaccine Clinical Research and Development, Pfizer Inc, Pearl River, New York, USA; and

⁵Vaccine Clinical Research and Development, Pfizer Inc, Collegeville, Pennsylvania, USA

Observační studie

Analýza laboratorních dat, kultivačně prokázané IPO

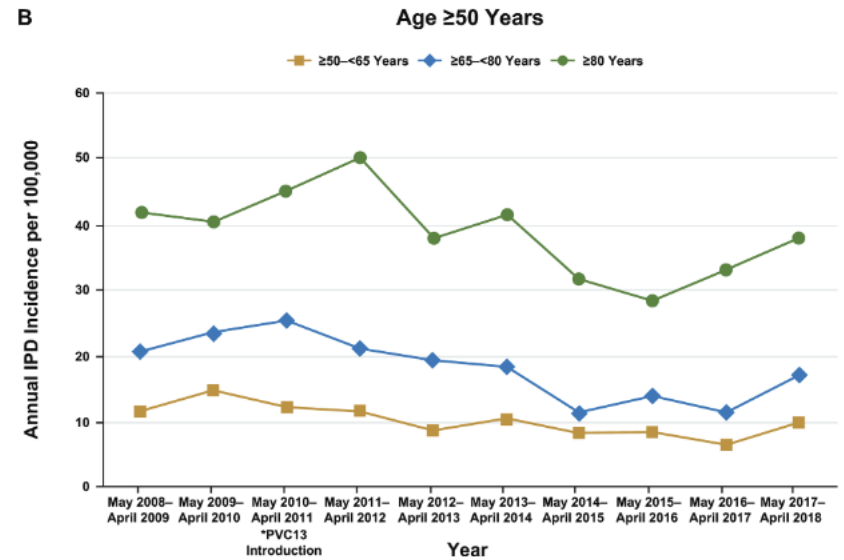
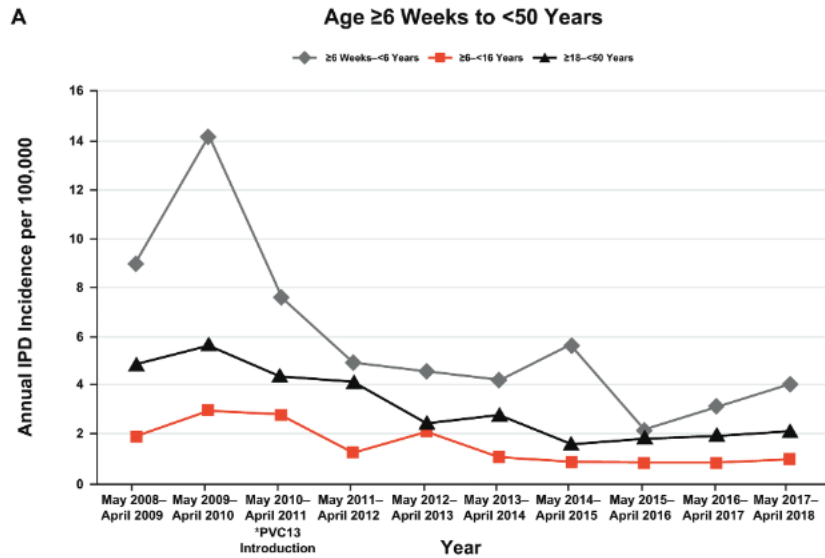
5/2008-4/2010 versus 5/2010-4/2018

IPO, USA, 2008-2018 (KP)

Serotype Category	Incidence ^a (per 100 000)			
	PCV7 Period	PCV13 Period	Rate Ratio (PCV13 Period/PCV7 Period)	
	May 2008–April 2010	May 2011–April 2018	95% Confidence Interval	
≥6 wk to <6 y				
All IPD	11.57	4.09	0.35	0.25–0.50
PCV13 ^b	5.12	0.84	0.16	0.09–0.30
PCV7 ^c	N/A	0.10	N/A	0.08–N/A
Cross-reactive ^d	0.19	0.79	4.15	0.74–88.17
PPSV23 ^e	5.50	1.89	0.34	0.21–0.56
Non-PCV13 ^f	1.71	2.52	1.47	0.75–3.19
NAS	4.74	0.73	0.15	0.08–0.30
≥6 wk				
All IPD	9.49	6.23	0.66	0.60–0.72
PCV13 ^b	4.67	1.89	0.40	0.35–0.46
PCV7 ^c	0.24	0.23	0.94	0.56–1.66
Cross-reactive ^d	0.96	1.01	1.06	0.81–1.39
PPSV23 ^e	5.99	3.16	0.53	0.47–0.59
Non-PCV13 ^f	3.34	3.35	1.00	0.87–1.16
NAS	1.48	0.99	0.67	0.54–0.85

^aCross-reactive serotypes include 6C, 7A, 7C, 9L, 9N, 19C, 23A, 23B.

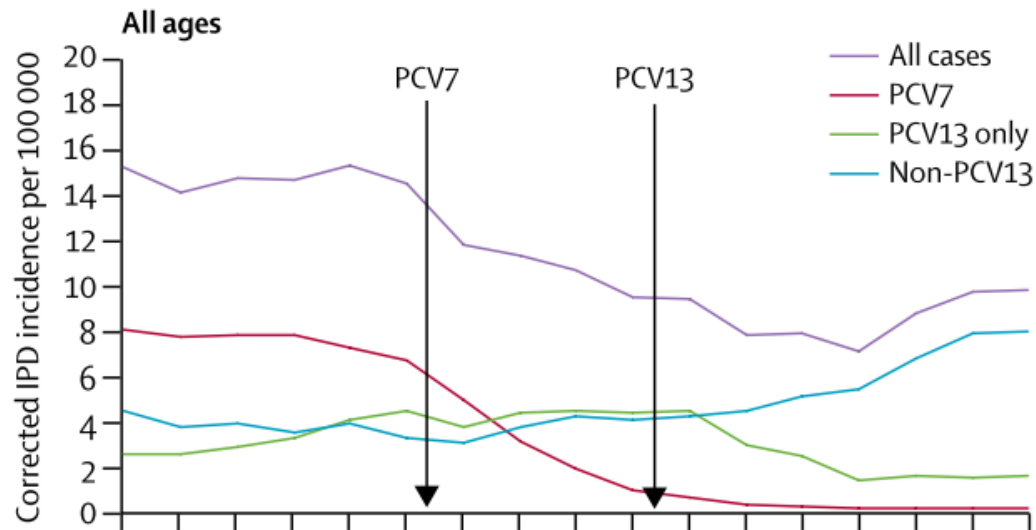
IPO, USA, 2008-2018 (KP)



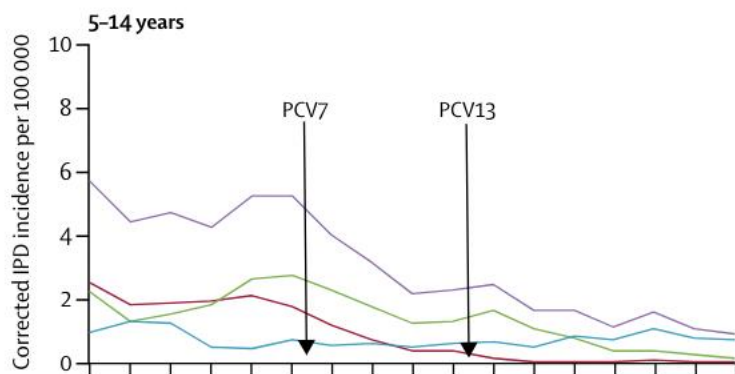
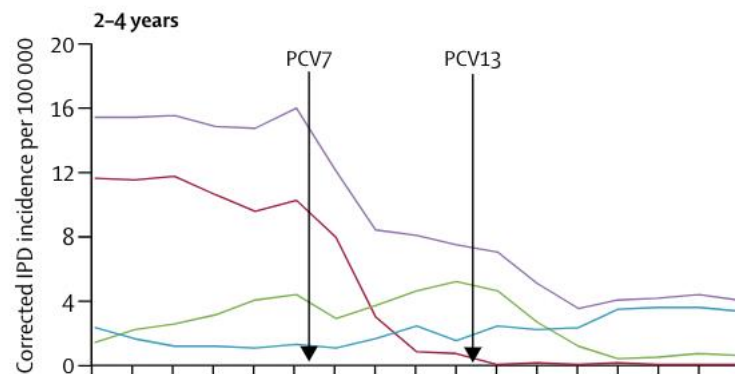
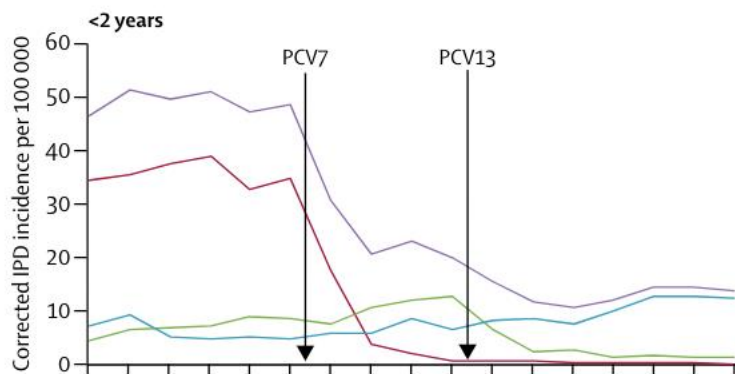
IPO, Velká Británie, 2000-2017

Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study

Shamez N Ladhani, Sarah Collins, Abdelmajid Djennad, Carmen L Sheppard, Ray Borrow, Norman K Fry, Nicholas J Andrews, Elizabeth Miller, Mary E Ramsay



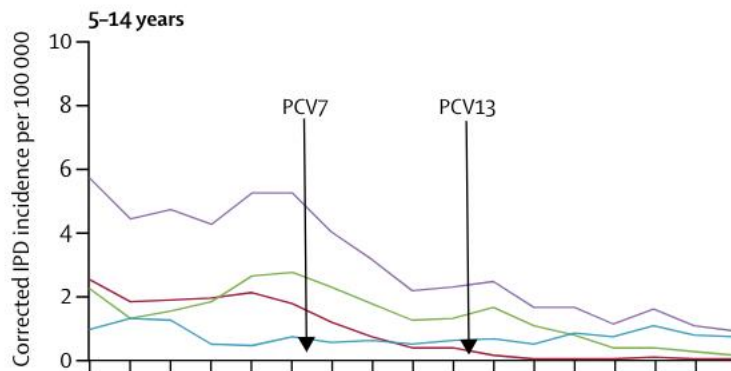
IPO, Velká Británie, 2000-2017



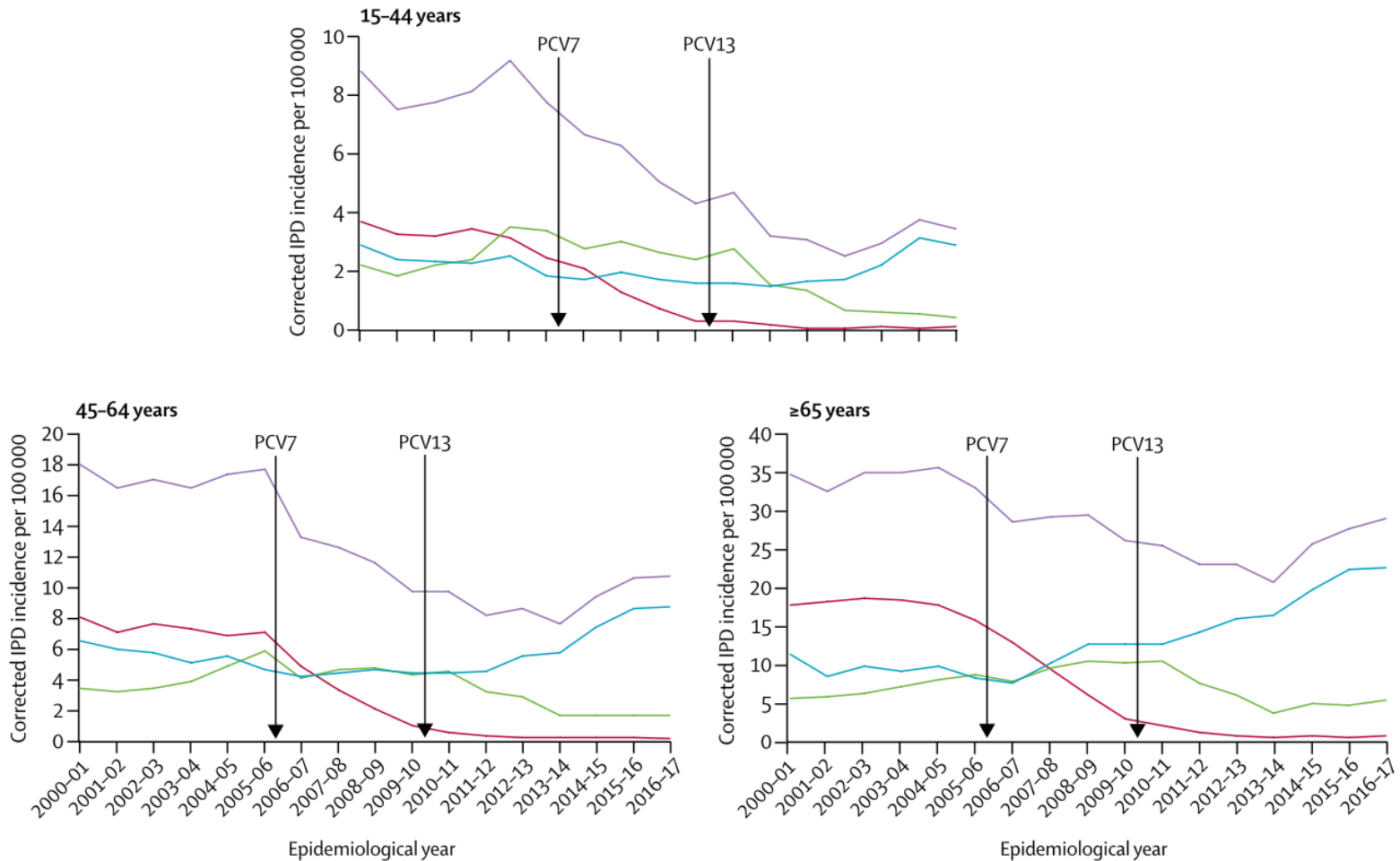
IPO, Velká Británie, 2000-2017



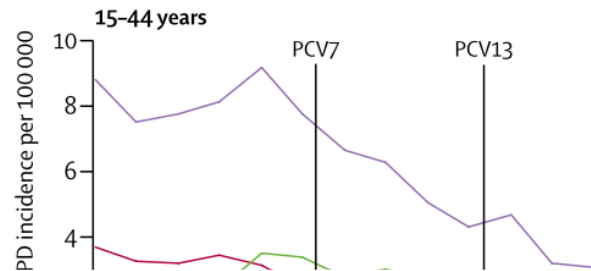
Vzestup nevakcinálních kmenů u dětí relativně nízký



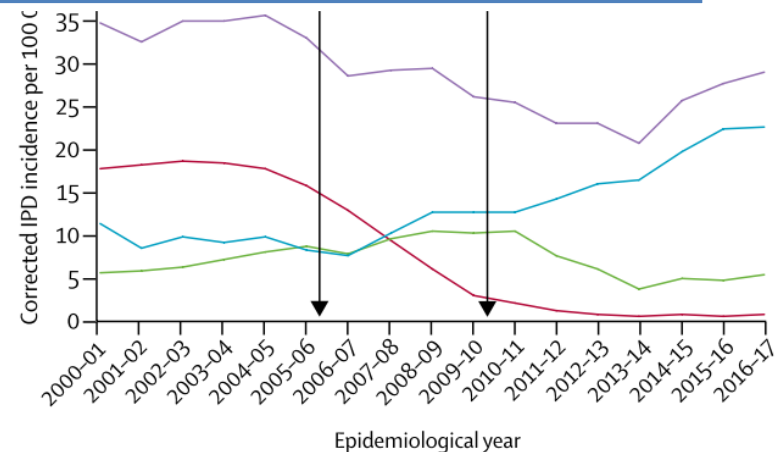
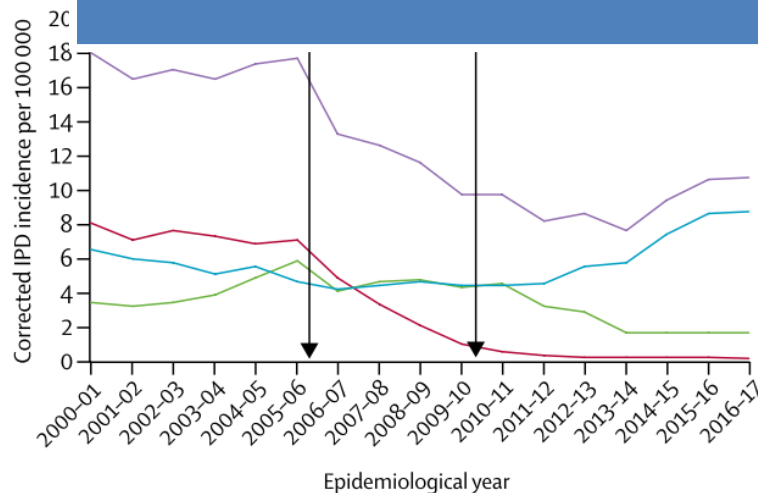
IPO, Velká Británie, 2000-2017



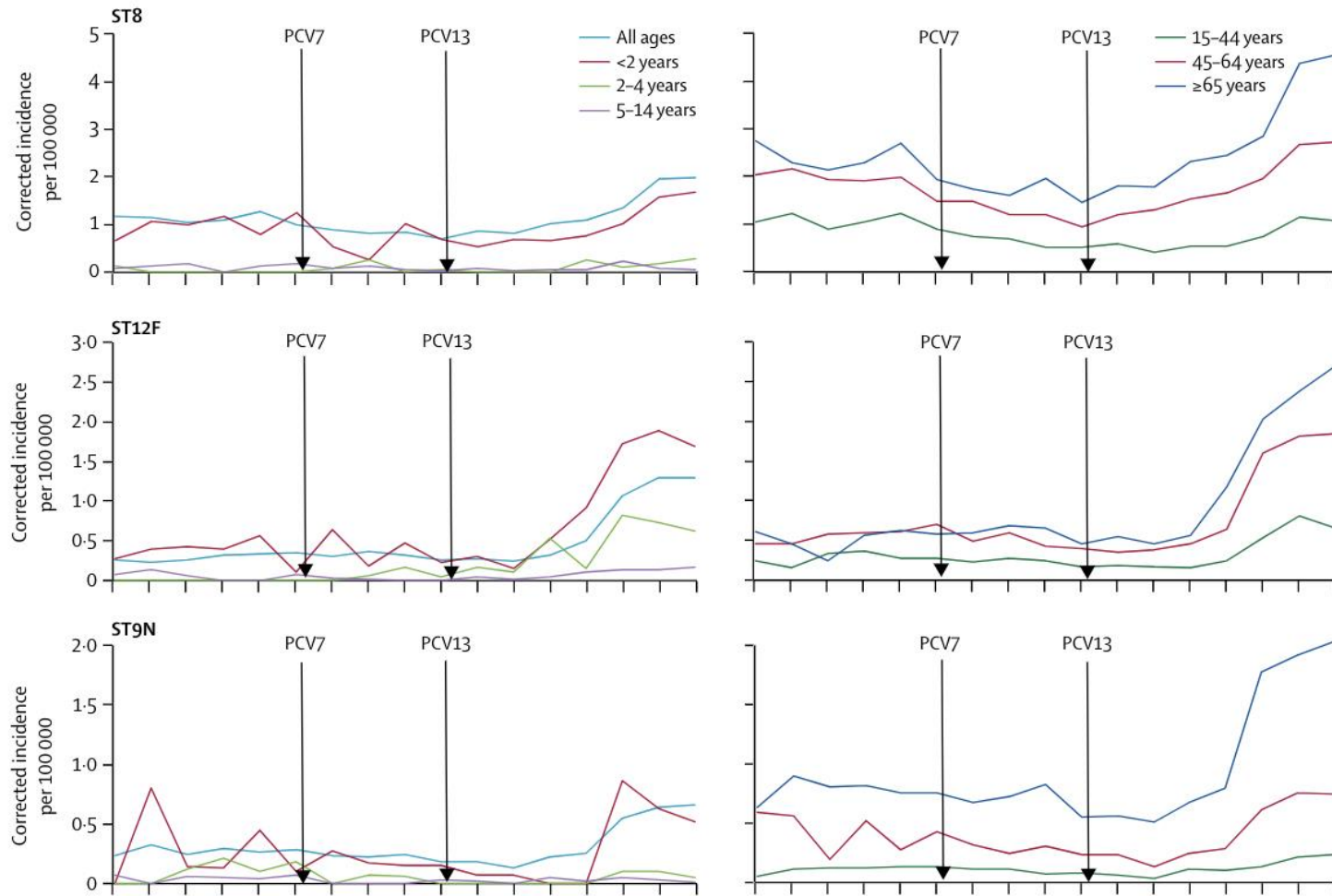
IPO, Velká Británie, 2000-2017



Replacement zejména ve věkových kohortách
45-64 let a > 65 let



IPO, Velká Británie, 2000-2017



IPO, Velká Británie, 2000-2017

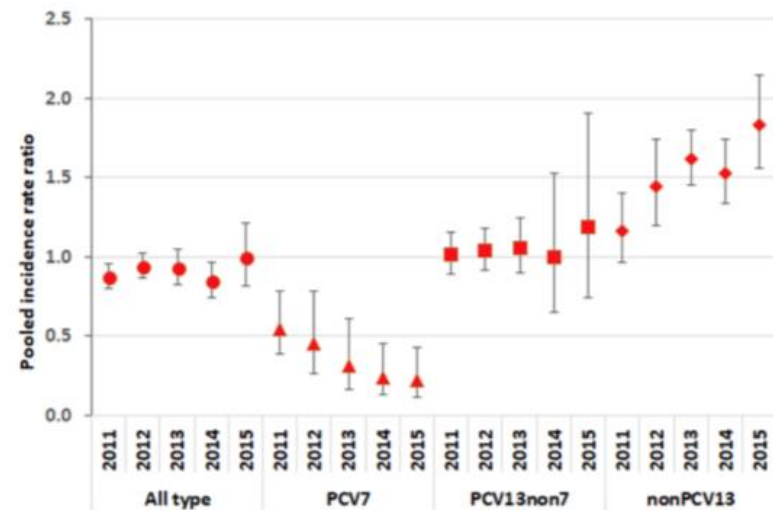
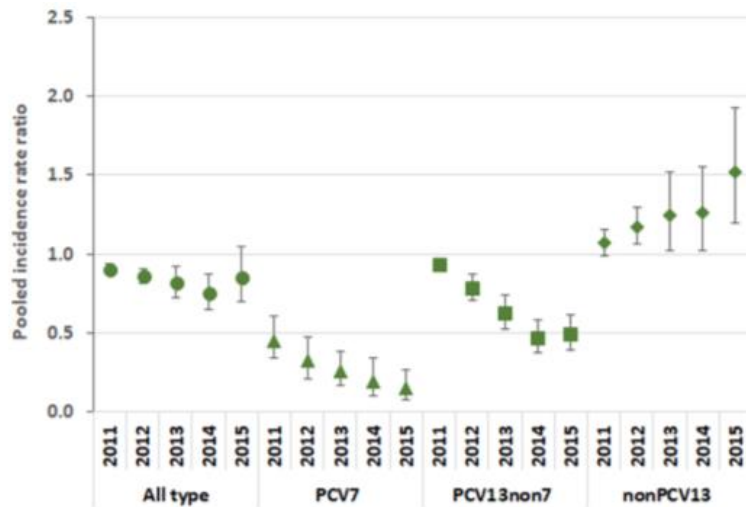
	<5 years	5-64 years	≥65 years	All ages*
8	33 (10.0%)	621 (27.2%)	463 (15.7%)	1120 (20.1%)
12F	47 (14.2%)	408 (17.9%)	275 (9.3%)	730 (13.1%)
3	23 (6.9%)	159 (7.0%)	340 (11.5%)	525 (9.4%)
9N	9 (2.7%)	159 (7.0%)	207 (7.0%)	375 (6.7%)
22F	17 (5.1%)	141 (6.2%)	216 (7.3%)	375 (6.7%)
19A	13 (3.9%)	119 (5.2%)	178 (6.0%)	310 (5.6%)
15A	18 (5.4%)	63 (2.8%)	152 (5.2%)	234 (4.2%)
33F	17 (5.1%)	57 (2.5%)	106 (3.6%)	180 (3.2%)
10A	27 (8.2%)	58 (2.5%)	90 (3.1%)	176 (3.2%)
23B	21 (6.3%)	43 (1.9%)	71 (2.4%)	135 (2.4%)
23A	3 (0.9%)	30 (1.3%)	89 (3.0%)	122 (2.2%)
11A	5 (1.5%)	36 (1.6%)	71 (2.4%)	112 (2.0%)
15B/C	26 (7.9%)	28 (1.2%)	45 (1.5%)	99 (1.8%)
16F	2 (0.6%)	32 (1.4%)	57 (1.9%)	91 (1.6%)
24F	11 (3.3%)	24 (1.1%)	55 (1.9%)	91 (1.6%)
7F	4 (1.2%)	45 (2.0%)	40 (1.4%)	89 (1.6%)
35B	9 (2.7%)	19 (0.8%)	59 (2.0%)	87 (1.6%)
Other	46 (13.9%)	241 (10.6%)	433 (14.7%)	720 (12.9%)
Total	331	2283	2947	5571

Replacement u IPO

ORIGINAL ARTICLE

Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination

Germaine Hanquet,^{1,2} Pavla Krizova,³ Palle Valentiner-Branth,⁴ Shamez N Ladhani,⁵



Replacement u IPO

Severovýchodní Anglie: Houseman C, Hughes GJ et al. Emerg Infect Dis 2017

Irsko: Corcoran M, Vickers I et al. Epidemiol Infect 2017

Norsko: Steens A, Bergsaker MA. Vaccine 2013

Francie: Lepoutre A, Varon E, Georges S et al. Vaccine 2015

Itálie: D'Ancona F, Caporali MG. Epidemiol Prev 2015

Španělsko: Camara J, Marimon JM et al. PloS One 2017

Kanada: Demczuk WHB, Martine I et al. Vaccine 2018

Austrálie: Jayasinghe S, Menzies R et al. Clin Infect Dis 2017

Replacement u IPO

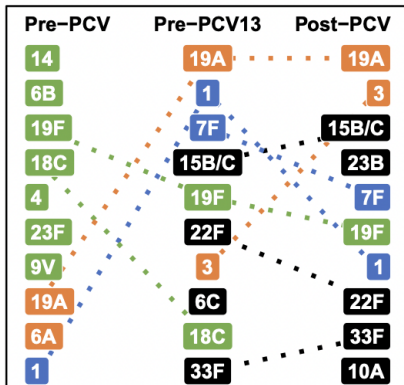
OPEN Divergent serotype replacement trends and increasing diversity in pneumococcal disease in high income settings reduce the benefit of expanding vaccine valency

Alessandra Løchen^{1,2}, Nicholas J. Croucher^{1,2,3} & Roy M. Anderson^{1,2,3}

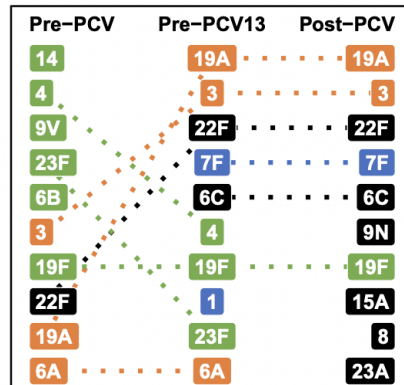
	PCV introduction	Vaccine doses	Surveillance data source	Years of vaccination data available	Serotyping
Australia	PCV7: 2005 PCV10: 2009 (some jurisdictions) PCV13: 2011	3 + 0	National Notifiable Disease Surveillance System (NNDSS)	Pre-PCV7: 1999–2005 Pre-PCV13: 2006–2011 Post: 2012–2016	Quellung reaction, molecular serotyping
Finland	PCV7: 2009 PCV10: 2010	2 + 1	National Institute for Health and Welfare (THL)	Pre-PCV10: 2004–2010 Post: 2011–2016	Quellung reaction
France	PCV7: 2006 PCV13: 2010	2 + 1	Centre National de References des Pneumocoques (CNRP)	Pre-PCV7: 2001–2006 Pre-PCV13: 2007–2010 Post: 2011–2016	Fourier transformation-infrared spectroscopy, multi locus sequence typing, genomic sequencing
Norway	PCV7: 2006 PCV13: 2011	2 + 1	Meldesystem for Smittsomme Sykdommer (MSIS)	Pre-PCV13: 2006–2011 Post: 2012–2016	Quellung reaction
USA	PCV7: 2000 PCV13: 2010	3 + 1	CDC's Emerging Infections Program/Active Bacterial Core Surveillance	Pre-PCV13: 2005–2010 Post: 2011–2013	Quellung reaction

Replacement u IPO

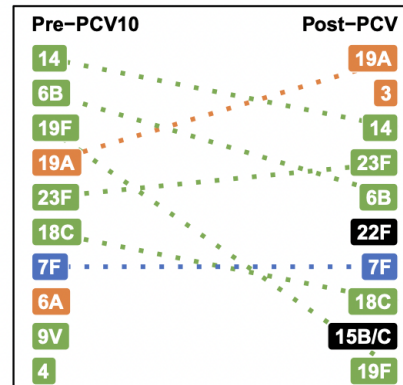
A Australia < 18 yrs



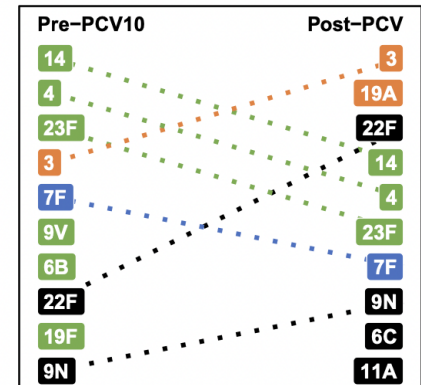
Australia > 18 yrs



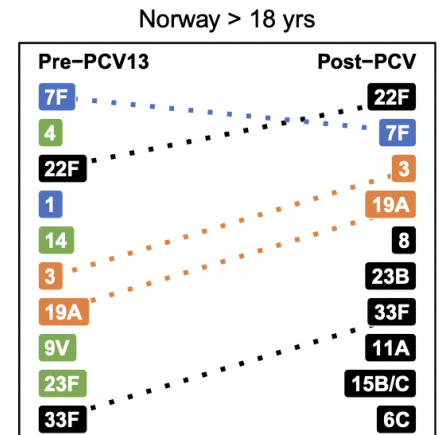
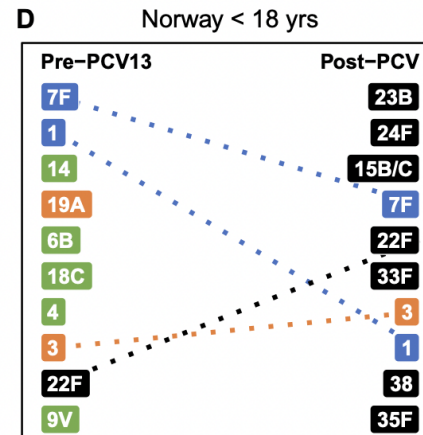
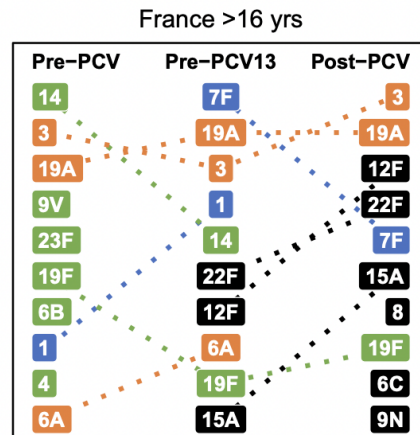
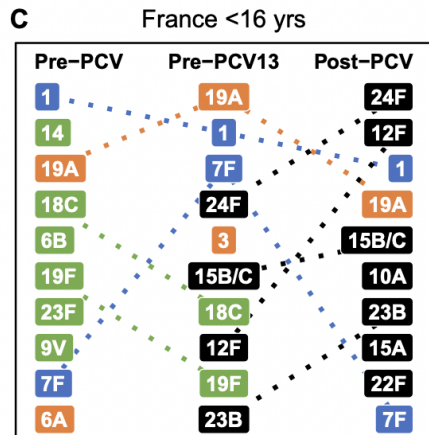
B Finland < 18 yrs



Finland > 18 yrs



Replacement u IPO



Jak lze vysvětlit rozdíl?

Making sense of differences in pneumococcal serotype replacement

Joseph A Lewnard, William P Hanage

Rozdíly v diagnostice a hlášení onemocnění

Odběry hemokultur (ambulantní versus hospitalizovaní)

Zařazení pacientů s okultní bakteriemií

Rozdíly mezi dětským a dospělým věkem

Jak lze vysvětlit rozdíl?

Making sense of differences in pneumococcal serotype replacement

Joseph A Lewnard, William P Hanage

Dynamika přenosu, věk, očkovací schéma, proočkovanosť

Schéma 2+1 versus 3+1 (+ užívané vakcíny)

- *Schéma 2+1 (72 %) versus 3+1 (38 %); Palmu AA 2017*

Celostátní data nezohledňují regionální rozdíly

Kontakt seniorů s dětmi (sociodemografické rozdíly)

Jak lze vysvětlit rozdíl?

Making sense of differences in pneumococcal serotype replacement

Joseph A Lewnard, William P Hanage

Prevalence rizikových faktorů v populaci

Sérotypová interakce, změny na molekulárně-biologické úrovni

Nosičství: 23A, 35B (USA) versus 21,22F (UK)

IPO (UK): 8, 9N, 12F, 15A

NonPCV13 sérotypy u pneumonií

13-Valent vaccine serotype pneumococcal community acquired pneumonia in adults in high clinical risk groups



Priya Daniel ^{a,*}, Chamira Rodrigo ^a, Thomas Bewick ^b, Carmen Sheppard ^c, Sonia Greenwood ^b, Tricia M. McKeever ^d, Caroline Trotter ^e, Wei Shen Lim ^a

^a Department of Respiratory Medicine, Nottingham University Hospitals NHS Trust, Nottingham NG5 1PB, UK

^b Department of Respiratory Medicine, Derby Teaching Hospitals NHS Foundation Trust, Derby DE22 3NE, UK

^c Respiratory and Vaccine Preventable Bacteria Reference Unit, Public Health England, Microbiology Services Division, Colindale Avenue, London NW9 5EQ, UK

^d Division of Epidemiology, University of Nottingham, Clinical Skills Building, Nottingham City Hospital Campus, Hucknall Road, Nottingham NG5 1PB, UK

^e Disease Dynamics Unit, Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge CB3 0ES, UK

Prospektivní kohortová studie, 2008-2013, Velká Británie

2224 pacientů s komunitní pneumonií:

Sérotyp zařazený v PCV13: 337 (15,2 %)

Sérotyp nezařazený v PCV13: 250 (11,2 %)

NonPCV13 sérotypy u pneumonií

Table 1

Distribution of co-morbid diseases in adults with pneumococcal CAP.

	16–64 years n = 266	≥65 years n = 377
Chronic heart disease	14 (5.3)	110 (29.2)
Chronic respiratory disease	23 (8.7)	107 (28.4)
Diabetes	26 (9.8)	56 (14.9)
Chronic kidney disease	4 (1.5)	44 (11.7)
Chronic liver disease	6 (2.3)	4 (1.1)
Immunosuppressed	8 (3.0)	10 (2.7)
Cancer	12 (4.5)	26 (6.9)
Dementia	0 (0.0)	19 (5.0)
Cerebrovascular disease	5 (1.9)	62 (16.5)

All values given as n (%).

16-64

Diabetes mellitus, chronické onemocnění dýchacího traktu

> 65

Chronické onemocnění srdce a cév, chronické onemocnění dýchacího traktu

NonPCV13 sérotypy u pneumonií

Table 3

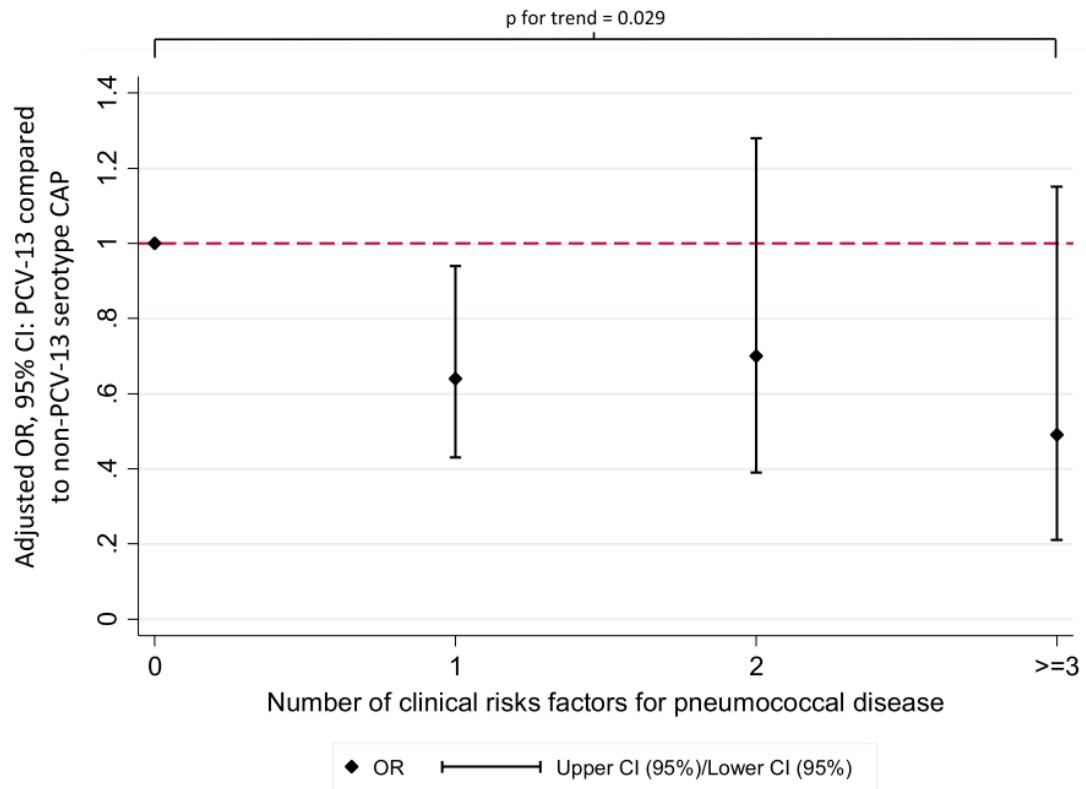
Association between clinical risk group and PCV-13 disease.

	aOR (95% CI)	p value
16–64 yrs with no clinical risk factor	Reference	–
16–64 yrs with clinical risk factor(s)	0.58 (0.32–1.06)	.077
≥65 yrs with no clinical risk factor	0.98 (0.61–1.55)	.915
≥65 yrs with clinical risk factor(s)	0.61 (0.41–0.92)	.018
Male gender	1.43 (1.02–1.99)	.037

Bold values indicate $p < 0.05$.

**Non-PCV13:
Pacienti starší 65 let s rizikovými faktory**

NonPCV13 sérotypy u pneumonií



Non-PCV13:
Pacienti mladší 65 let s vícečetnými komorbiditami

IPO, FN Bulovka, 2000-2019

	2000–2005		2006–2009		2010–2014		2015–2019		Celkem		P hodnota ³
	Počet	Procento	Počet	Procento	Počet	Procento	Počet	Procento	Počet	Procento	
Počet pacientů	67/304	22,0	75/304	24,7	88/304	28,9	74/304	24,3	304	100,0	-
Věk¹	52 (36-62)		58 (45-72)		61 (46-76)		60 (42-76)		58 (43-73)		0,009
Pneumonie	36/67	53,7	49/75	65,3	53/88	60,2	47/74	63,5	185/304	60,9	0,377
Meningitida	28/67	41,8	20/75	26,7	23/88	26,1	19/74	25,7	90/304	29,6	0,048
Ostatní	3/67	4,5	6/75	8,0	12/88	13,6	8/74	10,8	29/304	9,5	0,036
Intenzivní péče	39/62	62,9	35/70	50,0	46/88	52,3	37/73	50,7	157/293	53,6	0,225
Úmrtí	21/67	31,3	19/75	25,3	16/88	18,2	21/74	28,4	77/304	25,3	0,480
Závažný průběh²	49/65	75,4	48/75	64,0	63/88	71,6	51/74	68,9	211/302	69,9	0,687

IPO, FN Bulovka, 2000-2019

	2000-2005		2006-2009		2010-2014		2015-2019		Celkem		P hodnota ¹
	Počet	%	Počet	%	Počet	%	Počet	%	Počet	%	
PCV7	23/66	34,8	29/72	40,3	21/81	25,9	11/73	15,1	84/292	28,8	0,002
PCV10	33/66	50,0	38/72	52,8	39/81	48,1	17/73	23,3	127/292	43,5	0,001
PCV13	48/66	72,7	50/72	69,4	53/81	65,4	33/73	45,2	184/292	63,0	0,002
PCV15	49/66	74,2	50/72	69,4	62/81	76,5	38/73	52,1	199/292	68,2	0,018
PCV20	59/66	89,4	57/72	79,2	67/81	82,7	53/73	72,6	236/292	80,8	0,029
PPV23	57/66	86,4	59/72	81,9	69/81	85,2	55/73	75,3	240/292	82,2	0,149
Nevakcinální sérotyp (PCV13)	19/66	28,8	22/72	30,6	28/81	34,6	40/73	54,8	109/292	37,3	0,001
Celkem	66	100,0	72	100,0	81	100,0	73	100,0	292	100,0	-

IPO, FN Bulovka, 2000-2019

	2000-2005		2006-2009		2010-2014		2015-2019		Celkem		P hodnota ¹
	Počet	%	Počet	%	Počet	%	Počet	%	Počet	%	
PCV7	23/66	34,8	29/72	40,3	21/81	25,9	11/73	15,1	84/292	28,8	0,002
PCV10	3										0,001
PCV13	4										0,002
PCV15	4										0,018
PCV20	59/66	89,4	57/72	79,2	67/81	82,7	53/73	72,6	236/292	80,8	0,029
PPV23	57/66	86,4	59/72	81,9	69/81	85,2	55/73	75,3	240/292	82,2	0,149
Nevakcinální sérotyp (PCV13)	19/66	28,8	22/72	30,6	28/81	34,6	40/73	54,8	109/292	37,3	0,001
Celkem	66	100,0	72	100,0	81	100,0	73	100,0	292	100,0	-

Vzestup non-PCV13 sérotypů
28,8 % -> 54,8 %

IPO, FN Bulovka, 2000-2019

	2000-2005		2006-2009		2010-2014		2015-2019		Celkem		P hodnota ¹
	Počet	%	Počet	%	Počet	%	Počet	%	Počet	%	
PCV7	23/66	34,8	29/72	40,3	21/81	25,9	11/73	15,1	84/292	28,8	0,002
PCV10	3										0,001
PCV13	4										0,002
PCV15	4										0,018
PCV20	5										0,029
PPV23	5										0,149
Nevakcinální sérotyp (PCV13)	19/66	28,8	22/72	30,6	20/81	24,7	40/73	54,8	109/292	37,3	0,001
Celkem	66	100,0	72	100,0	81	100,0	73	100,0	292	100,0	-

Potenciální vícevalentní konjugované vakcíny mají relativně vysoké pokrytí

PCV20 (72,6 %) versus PPV23 (75,3 %)

IPO, FN Bulovka, 2000-2019

Sérotyp	Věk ¹	Délka hospitalizace ¹	Intenzivní péče		Úmrtí		Pneumonie		Meningitida		Ostatní		Počet pacientů
			Počet	%	Počet	%	Počet	%	Počet	%	Počet	%	
3	57 (46-65)	20 (13-34)	25/36	69,4	10/38	26,3	22/38	57,9	14/38	36,8	2/38	5,3	38
4	47 (36-60)	11 (8-17)	7/28	25,0	1/28	3,6	28/28	100,0	0/28	0,0	0/28	0,0	28
7F	55 (36-66)	16 (9-31)	11/23	47,8	5/24	20,8	13/24	54,2	8/24	33,3	3/24	12,5	24
8	49 (39-70)	13 (10-29)	9/19	47,4	2/21	9,5	14/21	66,7	7/21	33,3	0/21	0,0	21
1	38 (31-50)	12 (9-24)	4/17	23,5	1/18	5,6	16/18	88,9	2/18	11,1	0/18	0,0	18
P hodnota²	0,045	0,023	0,003		0,056		0,001						-

IPO, FN Bulovka, 2000-2019

Sérotyp	Věk ¹	Délka hospitalizace ¹	Intenzivní péče		Úmrtí		Pneumonie		Meningitida		Ostatní		Počet pacientů
			1	2	1	2	1	2	1	2	1	2	
3	57 (46-65)												38
4	47 (36-60)												28
7F	55 (36-66)												24
8	49 (39-70)	13 (10-29)	9/19	47,4	2/21	9,5	14/21	66,7	7/21	33,3	0/21	0,0	21
1	38 (31-50)	12 (9-24)	4/17	23,5	1/18	5,6	16/18	88,9	2/18	11,1	0/18	0,0	18
P hodnota²	0,045	0,023	0,003		0,056		0,001					-	

Rozdíl v klinické manifestaci a závažnosti onemocnění

Jaké je řešení?

PCV15

+ 22F, 33F

Merck Announces U.S. FDA Approval of VAXNEUVANCE™ (Pneumococcal 15-valent Conjugate Vaccine) for the Prevention of Invasive Pneumococcal Disease in Adults 18 Years and Older Caused by 15 Serotypes

PCV20

+ 8, 10A, 11A, 12F, 15B, 22F and 33F

U.S. FDA APPROVES PREVNAR 20™, PFIZER'S PNEUMOCOCCAL 20-VALENT CONJUGATE VACCINE FOR ADULTS AGES 18 YEARS OR OLDER

Závěr

Replacement představuje **problém**, který může limitovat nepřímou (i přímou) ochranu indukovanou očkováním

Závěr

Míra replacementu je závislá na řadě různých faktorů, roli hrají i **vlastnosti hostitele (susceptibilita k nízké invazivním patogenům)**

Závěr

Řešením není přestat očkovat, ale kontinuálně provádět kvalitní **surveillance** a případně optimalizovat užití dostupných a nových vakcín

Děkuji za pozornost

IPO, Kanada, 2010-2016

Serotype distribution of invasive *Streptococcus pneumoniae* in adults 65 years of age and over after the introduction of childhood 13-valent pneumococcal conjugate vaccination programs in Canada, 2010–2016



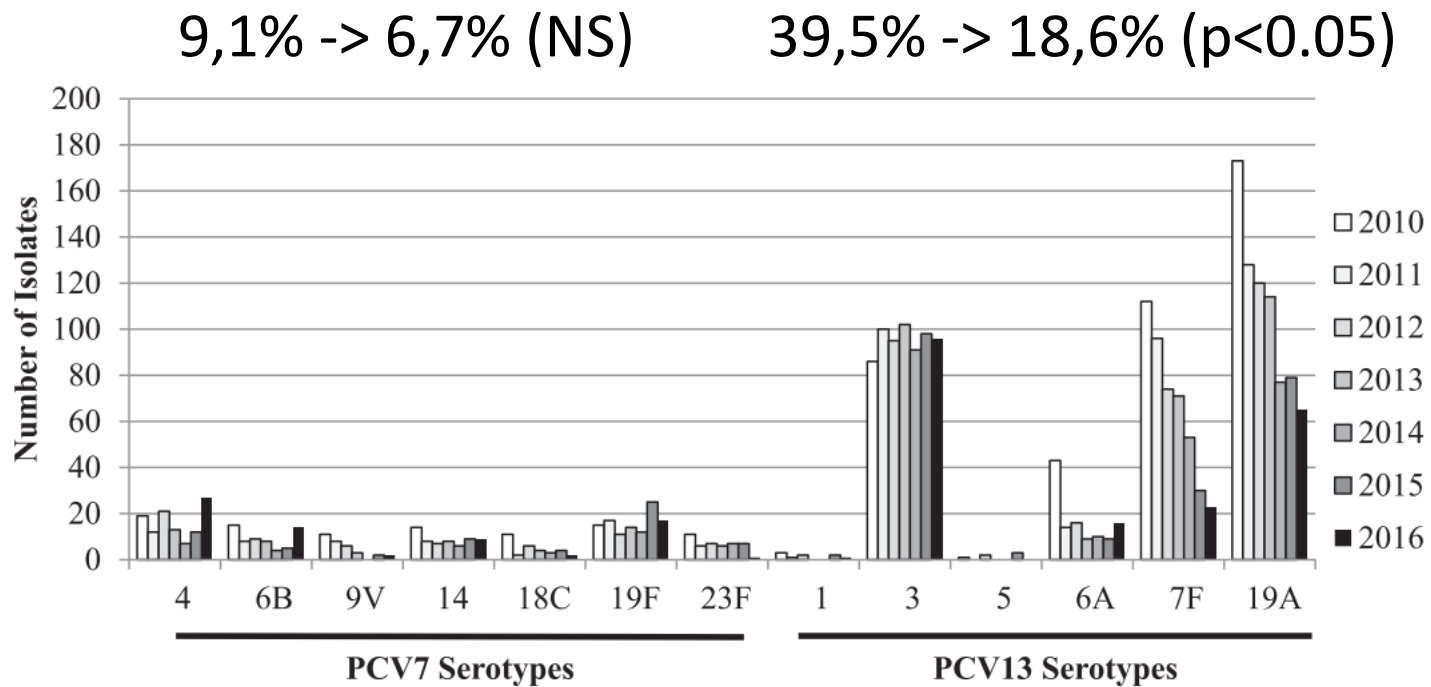
Walter H.B. Demczuk^a, Irene Martin^a, Shalini Desai^b, Averil Griffith^a, Laurence Caron-Poulin^b, Brigitte Lefebvre^c, Allison McGeer^d, Gregory J. Tyrrell^e, George G. Zhanel^f, Jonathan Gubbay^g, Linda Hoang^h, Paul N. Levettⁱ, Paul Van Caesele^j, Rita Raafat Gad^k, David Haldane^l, George Zahariadis^m, Gregory Germanⁿ, Jennifer Daley Bernier^o, Lori Strudwick^p, Michael R. Mulvey^{a,*}

2010-2016, Kanada

7282 případů u osob starších 65 let

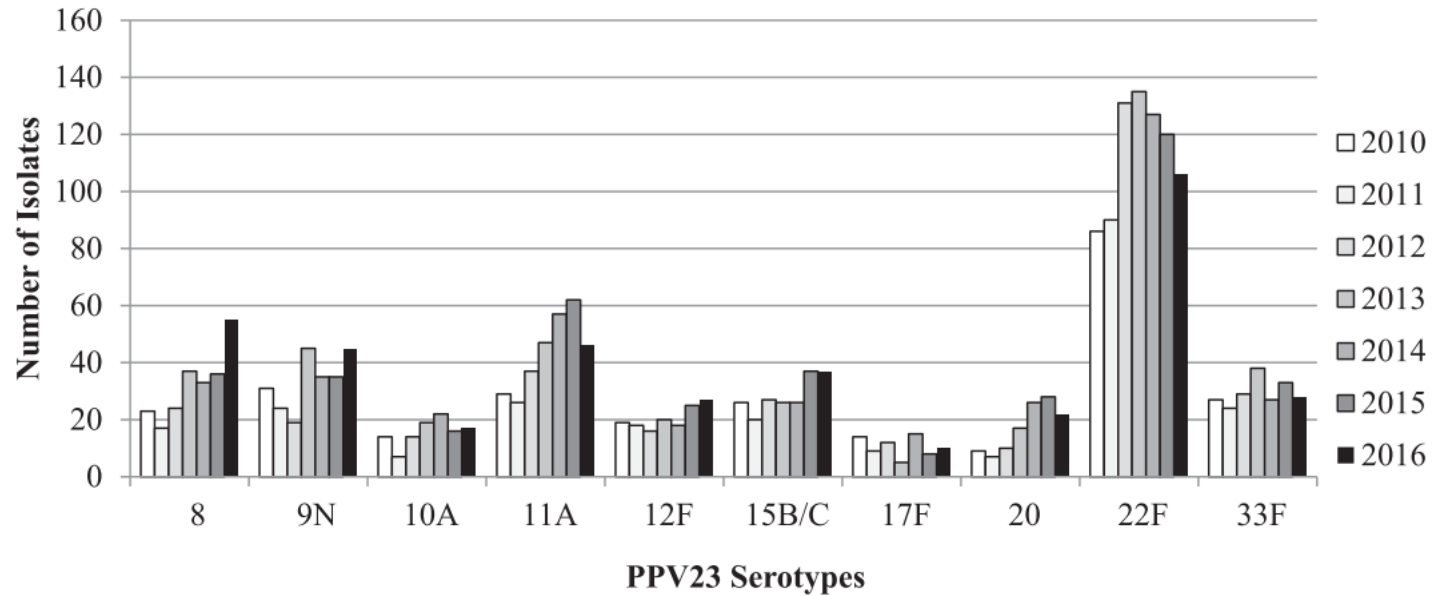
Signifikantní vzestup nonPCV13 sérotypů (25,1% -> 38,4%)

IPO, Kanada, 2010-2016



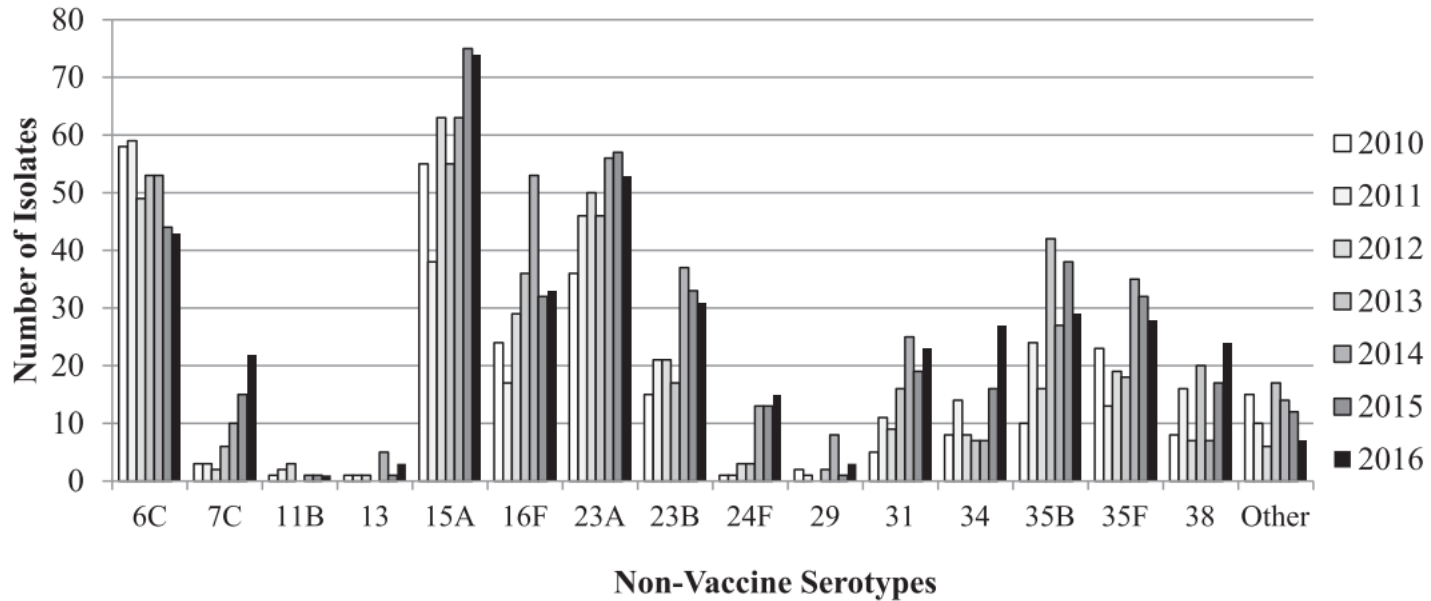
IPO, Kanada, 2010-2016

26,3% -> 36,2% (p<0,05)



IPO, Kanada, 2010-2016

25,1% -> 38,4% (p<0,05)



Pneumokokové vakcíny

