Prevention of pneumococcal disease in Canadian adults – Old and New

Allison McGeer, MSc, MD, FRCPC

Mount Sinai Hospital

University of Toronto

Objectives

- Review epidemiology of pneumococcal disease in adults
- Discuss impact of current vaccination programs on the incidence of adult disease
- Ask what the benefit of new vaccines might be

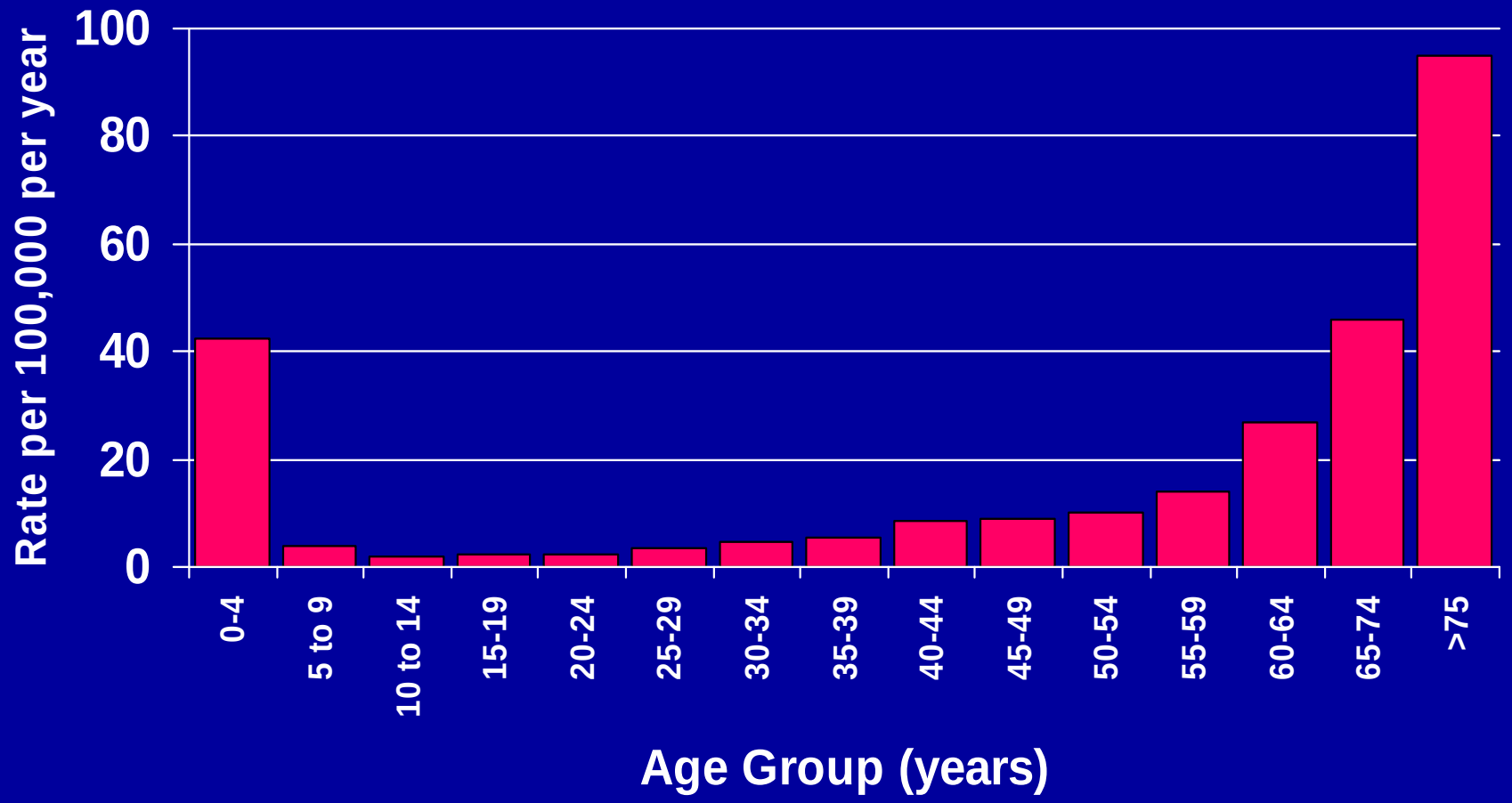
Annual rates of pneumococcal infection, Adults, developed world

Disease	Annual Rate	Case fatality
Pneumonia	15 per 10,000	5%
Bacteremia	1.5 per 10,000	15%
Meningitis	0.2 per 10,000	25%

Most common causes of death, Canada, 1995

Cause of death	Number of deaths
Cancer	56,000
Lung cancer	*19,900*
Breast cancer	*5,300*
Heart disease	43,000
Infections	20,000
Influenza	*4500*
S. aureus	*1500*
S. pneumoniae	*1500*

Age-Specific Incidence of Invasive Pneumococcal Disease, TIBDN, 1995



Introduction of pneumococcal vaccines Canada

- 1983 – PPV23 licensed
- 1996-9 – PPV23 programs for adults

Pneumococcal vaccination rates Eligible adults, Canada

Risk Group	Percent ever vaccinated		
	Canada 2001	Toronto 2002	BC 2008
>=65 years of age	42%	35-40%	34%
15-64 years of age with chronic condition	15%	12%	10%

Squires SG, CCDR 2001;27(10), Al-Sukhni, Vaccine 2007; NCS, 2008

How effective is pneumococcal vaccine?

- Against pneumococcal pneumonia
  - Effective in young healthy adults
  - In at risk adults, not effective, or effect <20% and not detectable
- Against invasive pneumococcal disease
  - CONTROVERSIAL
  - 8 meta-analyses; 2 Cochrane reviews

Preventive effect of pneumococcal vaccine in elderly subjects

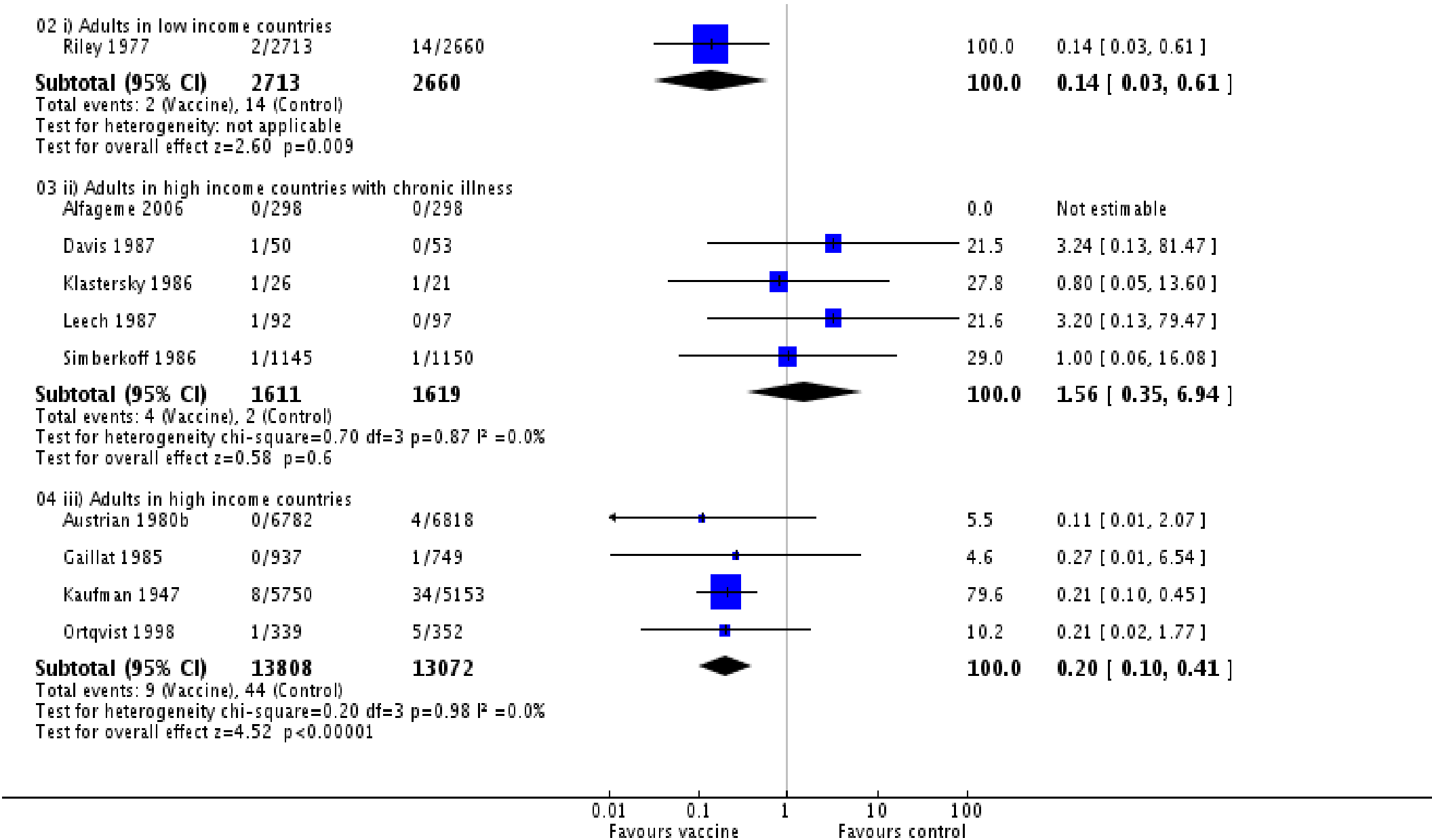
(Christenson, Eur Resp J 2004;23:363)

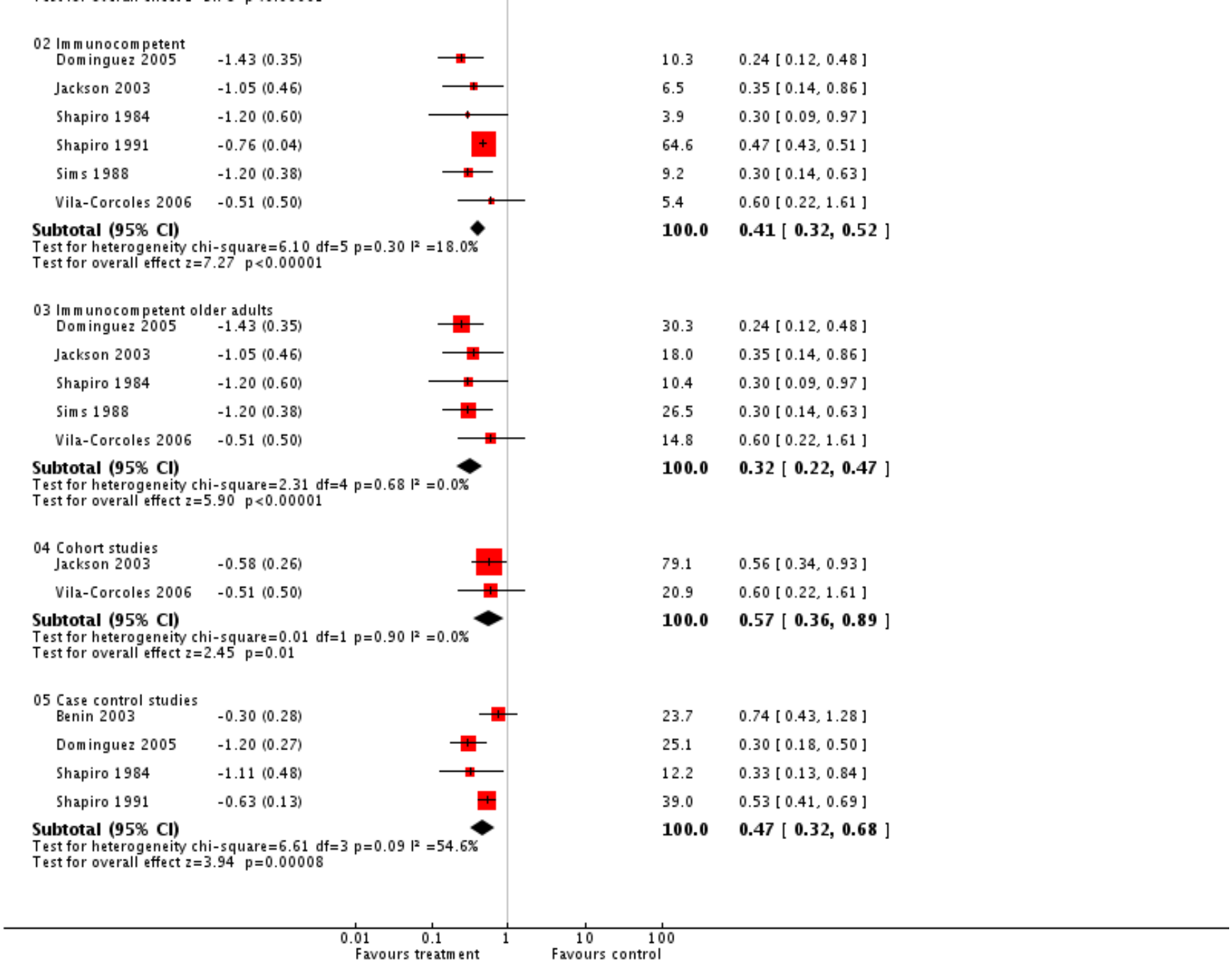
- Prospective cohort of 258,754 Finnish adults >65 years of age
- Offered pneumococcal and influenza vaccines, in 1998, flu again in 1999
- Pneumonia, hospitalization, mortality examined 12/1999 to 11/2000

Preventive effect of pneumococcal vaccine in elderly subjects

(Christenson, Eur Resp J 2004;23:363)

Outcome	Effect pneumococcal vaccine	Effect both vaccines
Hospital admission for pneumonia	0.91 (.82, 1.0)	0.71 (.65, .75)
Invasive pneumococcal disease	0.27 (.06, 1.14)	0.56 (.3, 1.05)
In-hospital mortality due to pneumonia	0.92 (.73, 1.19)	0.65 (.54, .78)


02 i) Adults in low income countries
Riley 1977 2/2713 14/2660 100.0 0.14 [0.03, 0.61]
Subtotal (95% CI) 2713 2660 100.0 0.14 [0.03, 0.61]
Total events: 2 (Vaccine), 14 (Control)
Test for heterogeneity: not applicable
Test for overall effect z=2.60 p=0.009
03 ii) Adults in high income countries with chronic illness
Alfageme 2006 0/298 0/298 0.0 Not estimable
Davis 1987 1/50 0/53 21.5 3.24 [0.13, 81.47]
Klastersky 1986 1/26 1/21 27.8 0.80 [0.05, 13.60]
Leech 1987 1/92 0/97 21.6 3.20 [0.13, 79.47]
Simberkoff 1986 1/1145 1/1150 29.0 1.00 [0.06, 16.08]
Subtotal (95% CI) 1611 1619 100.0 1.56 [0.35, 6.94]
Total events: 4 (Vaccine), 2 (Control)
Test for heterogeneity chi-square=0.70 df=3 p=0.87 I² =0.0%
Test for overall effect z=0.58 p=0.6
04 iii) Adults in high income countries
Austrian 1980b 0/6782 4/6818 5.5 0.11 [0.01, 2.07]
Gaillat 1985 0/937 1/749 4.6 0.27 [0.01, 6.54]
Kaufman 1947 8/5750 34/5153 79.6 0.21 [0.10, 0.45]
Ortqvist 1998 1/339 5/352 10.2 0.21 [0.02, 1.77]
Subtotal (95% CI) 13808 13072 100.0 0.20 [0.10, 0.41]
Total events: 9 (Vaccine), 44 (Control)
Test for heterogeneity chi-square=0.20 df=3 p=0.98 I² =0.0%
Test for overall effect z=4.52 p<0.00001
0.01
0.1
1
10
100
Favours vaccine
Favours control


02 Immunocompetent
Dominguez 2005 -1.43 (0.35) 10.3 0.24 [0.12, 0.48]
Jackson 2003 -1.05 (0.46) 6.5 0.35 [0.14, 0.86]
Shapiro 1984 -1.20 (0.60) 3.9 0.30 [0.09, 0.97]
Shapiro 1991 -0.76 (0.04) 64.6 0.47 [0.43, 0.51]
Sims 1988 -1.20 (0.38) 9.2 0.30 [0.14, 0.63]
Vila-Corcoles 2006 -0.51 (0.50) 5.4 0.60 [0.22, 1.61]
Subtotal (95% CI) 100.0 0.41 [0.32, 0.52]
Test for heterogeneity chi-square=6.10 df=5 p=0.30 I² =18.0%
Test for overall effect z=7.27 p<0.00001
03 Immunocompetent older adults
Dominguez 2005 -1.43 (0.35) 30.3 0.24 [0.12, 0.48]
Jackson 2003 -1.05 (0.46) 18.0 0.35 [0.14, 0.86]
Shapiro 1984 -1.20 (0.60) 10.4 0.30 [0.09, 0.97]
Sims 1988 -1.20 (0.38) 26.5 0.30 [0.14, 0.63]
Vila-Corcoles 2006 -0.51 (0.50) 14.8 0.60 [0.22, 1.61]
Subtotal (95% CI) 100.0 0.32 [0.22, 0.47]
Test for heterogeneity chi-square=2.31 df=4 p=0.68 I² =0.0%
Test for overall effect z=5.90 p<0.00001
04 Cohort studies
Jackson 2003 -0.58 (0.26) 79.1 0.56 [0.34, 0.93]
Vila-Corcoles 2006 -0.51 (0.50) 20.9 0.60 [0.22, 1.61]
Subtotal (95% CI) 100.0 0.57 [0.36, 0.89]
Test for heterogeneity chi-square=0.01 df=1 p=0.90 I² =0.0%
Test for overall effect z=2.45 p=0.01
05 Case control studies
Benin 2003 -0.30 (0.28) 23.7 0.74 [0.43, 1.28]
Dominguez 2005 -1.20 (0.27) 25.1 0.30 [0.18, 0.50]
Shapiro 1984 -1.11 (0.48) 12.2 0.33 [0.13, 0.84]
Shapiro 1991 -0.63 (0.13) 39.0 0.53 [0.41, 0.69]
Subtotal (95% CI) 100.0 0.47 [0.32, 0.68]
Test for heterogeneity chi-square=6.61 df=3 p=0.09 I² =54.6%
Test for overall effect z=3.94 p=0.00008
0.01 0.1 1 10 100
Favours treatment
Favours control

PPV23 efficacy against IPD
Indirect cohort analyses

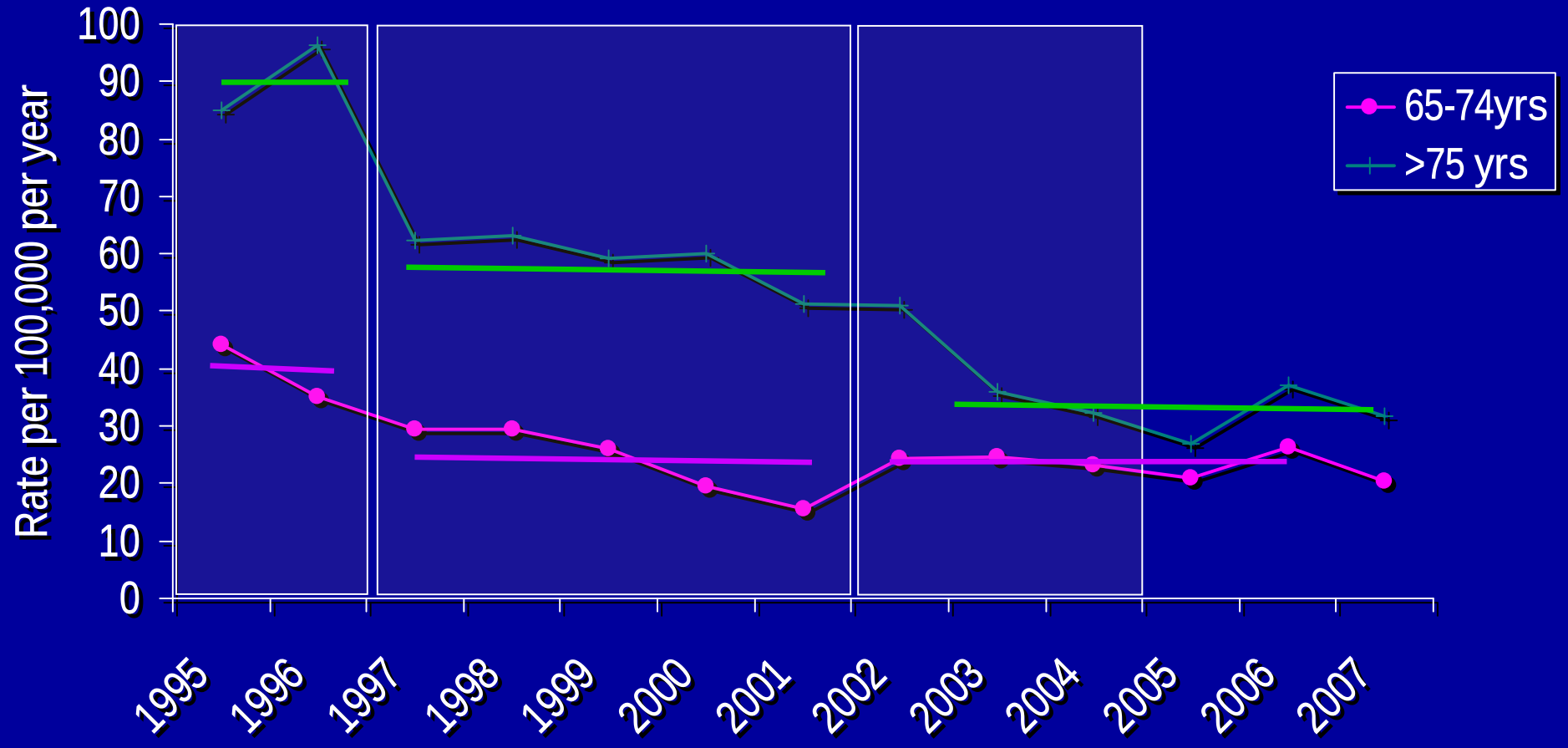
	Vaccine efficacy, eligible adults
US 1978-1992 (1)	57% (45,66)
Australia 1995-2002 (2)	79% (-14, 96)
Scotland 2003-4 (3)	51% (-278,94)
Ontario 1995-2006 (4)	49% (34,60)

1. Butler JC JAMA 1993; 270(15):1826-31. 2. Andrews Vaccine. 2004 Nov 25;23(2):132-8.
3. Mooney JD BMC Infect Dis. 2008 Apr 23;8:53. 4. Lui, CIC 2006

Rates of invasive pneumococcal disease, persons >=65 years of age

	Pre PPV program	Initial year of PPV program	Average post-PPV, pre PCV
TIBDN	58	44	38
Casper	-	53	33

Invasive pneumococcal disease, elderly Metropolitan Toronto, 1995-2007



But

- How is it possible that PPV prevents invasive pneumococcal disease, but not pneumonia?
- What is the duration of protection?
- Is hyporesponsiveness a clinically significant issue?

PPV23 efficacy against IPD
Indirect cohort analysis, TIBDN

	Vaccine efficacy
Healthy adults >=65 years	51% (33, 64)
Immunocompromised patients	38% (5, 59)
Against lab-confirmed pneumococcal pneumonia	31% (-18,60)

1. Butler JC JAMA 1993; 270(15):1826-31. 2. Andrews Vaccine. 2004 Nov 25;23(2):132-8.
3. Mooney JD BMC Infect Dis. 2008 Apr 23;8:53. 4. Lui, CIC 2006

Duration of effect

Butler et al.

Interval since vaccine:	Efficacy
<2 yrs	51%
2-4 yrs	54%
5-8 yrs	71%
9+ yrs	80%

Liu et al.

Interval since vaccine	Efficacy
<3 yrs	52%
3-5 yrs	47%
>5 yrs	46%

Is hyporesponsiveness clinically significant?

- Polysaccharide antigens can induce tolerance
  - Good evidence for meningococcal polysaccharide, some evidence for pneumococcal polysaccharide
- BUT
  - Data not as convincing in adults
  - Some evidence that hyporesponsiveness may be time-limited
  - Likely to be different for different serotypes

O'Brien K, Lancet Inf Dis 2007;7:597

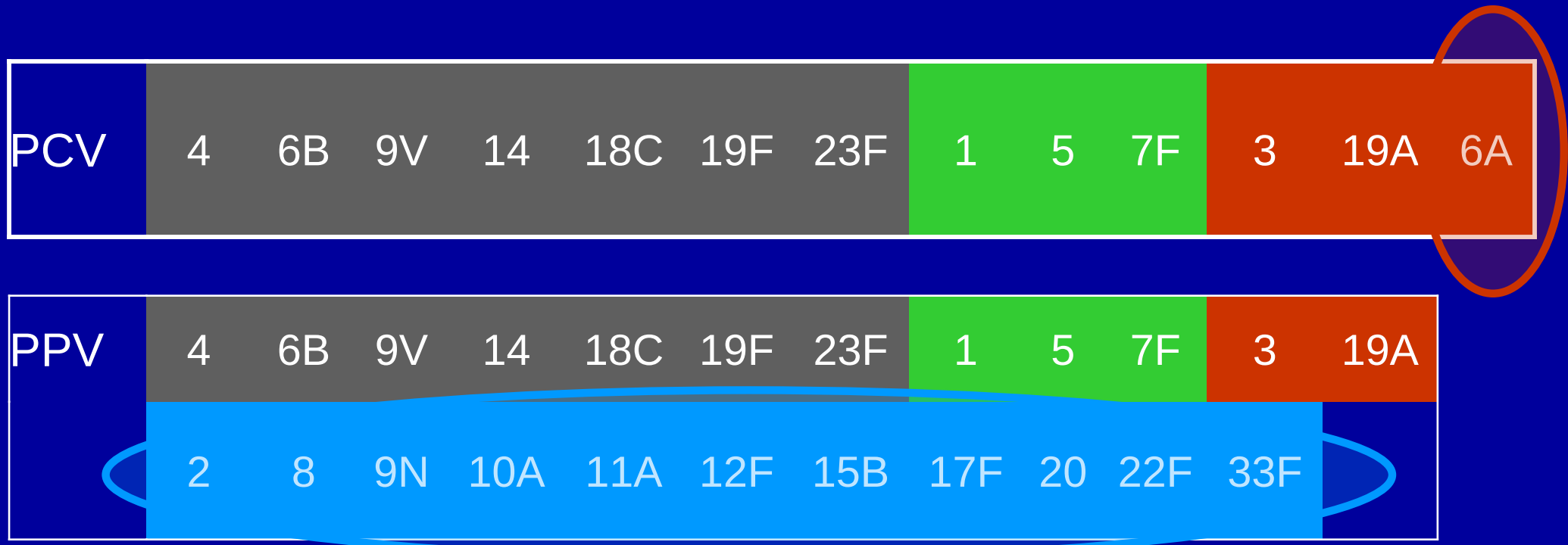
Introduction of conjugate pneumococcal vaccines, Canada

- 1983 – PPV23 licensed
- 1996-9 – PPV23 programs for adults
- **Dec 2001 – PCV7 licensed**
- **Sep 2002-Jan 2005 – PCV7 programs**
- **Dec 2008 - PCV10 licensed**
- **?2009 – PCV13 to be licensed**

Serotype composition of pneumococcal conjugate vaccines

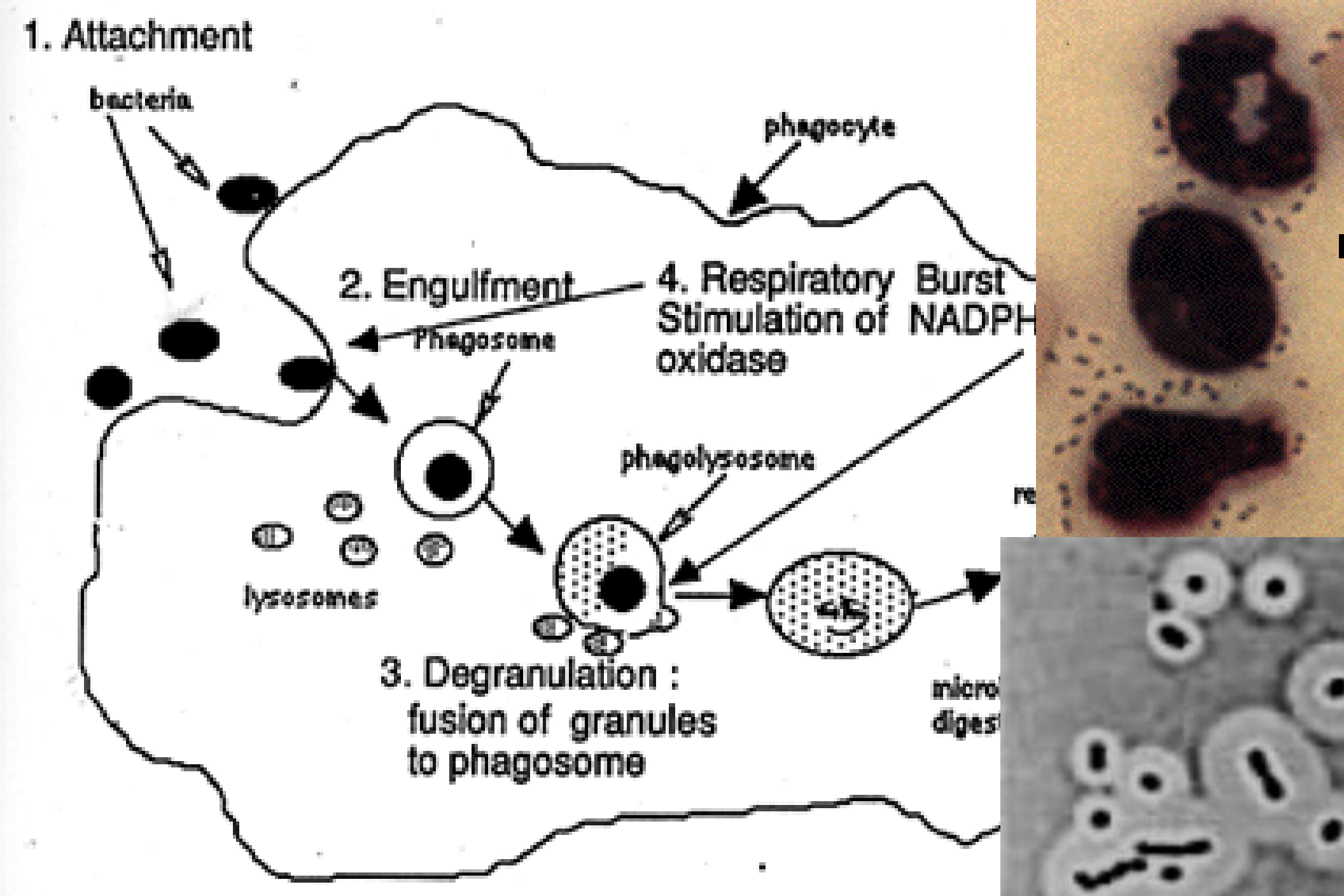
7-valent	10-valent	13-valent
4	4	4
6B	6B	6B
9V	9V	9V
14	14	14
18C	18C	18C
19F	19F	19F
23F	23F	23F
	1	1
	5	5
	7F	7F
		3
		6A
		19A

Serotype coverage
Conjugate vs. polysaccharide vaccines

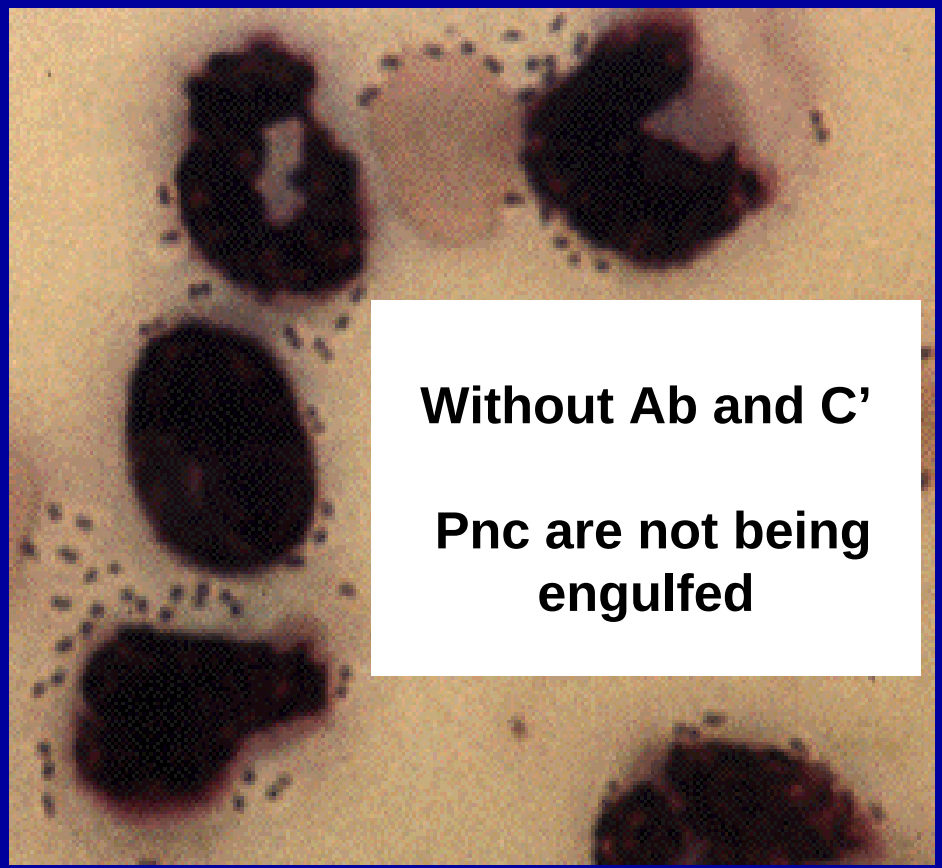


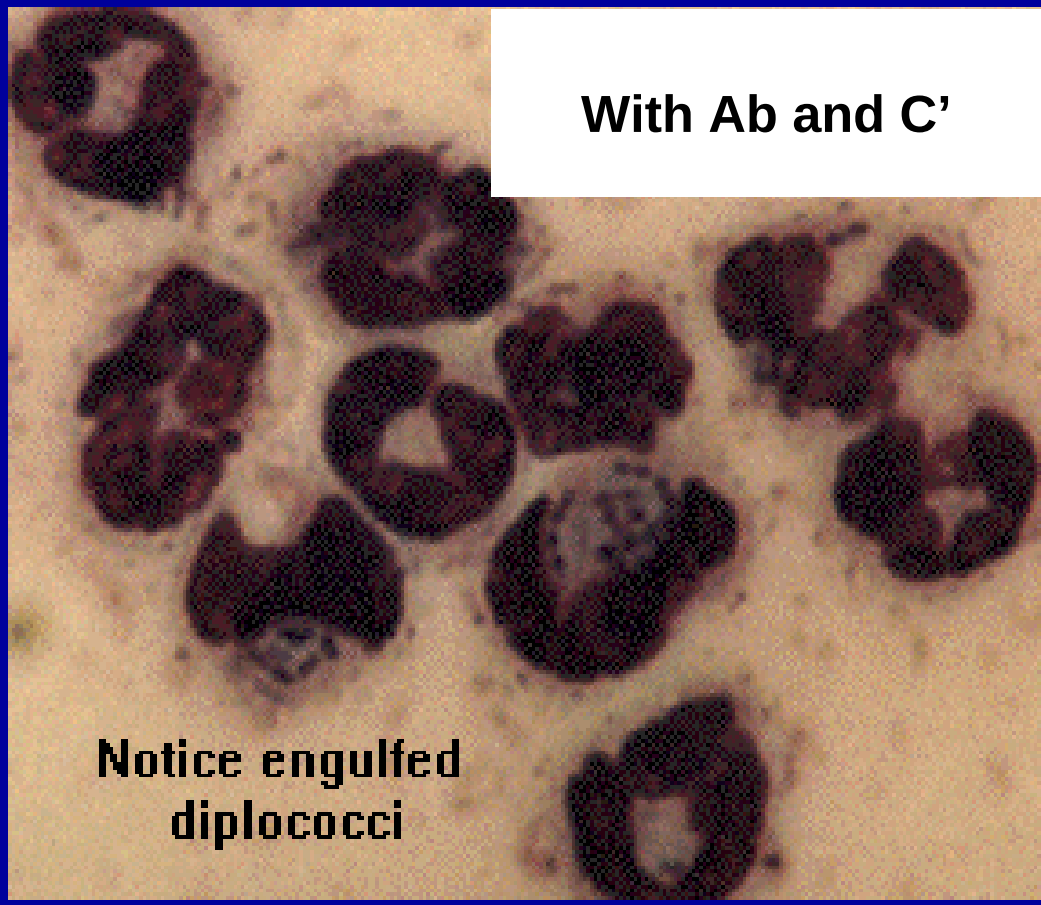
So, why not conjugate vaccines for adults?

- PC7 not great coverage in adults
  - 87% of pediatric IPD, but only 62% of adult IPD due to PCV7 serotypes (vs. >90% for PPV)
- PCV7 is more expensive, so perhaps not cost-effectiveness
- Adults are not large children
  - In immunogenicity studies, little difference between antibody response to PPV23 and PCV7 in adults
  - EIA titers are (a bit) higher, but OPA not different


1. Attachment
bacteria
phagocyte
2. Engulfment
Phagosome
4. Respiratory Burst
Stimulation of NADPH
oxidase
phagolysosome
lysosomes
3. Degranulation :
fusion of granules
to phagosome

Opsonophagocytic antibodies





Herd immunity from pediatric PCV7 programs

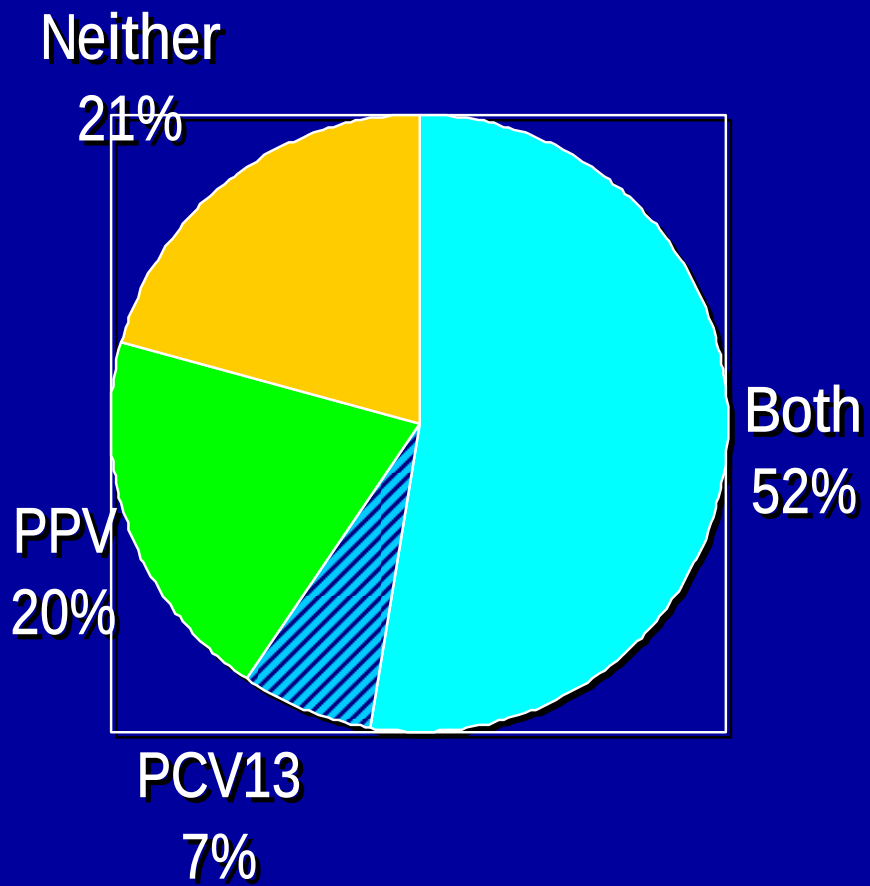
Decline in pneumonia admissions after routine childhood immunization with PCV7, USA

Grijalva, Nuorti et al. *Lancet 2007;369:1179*

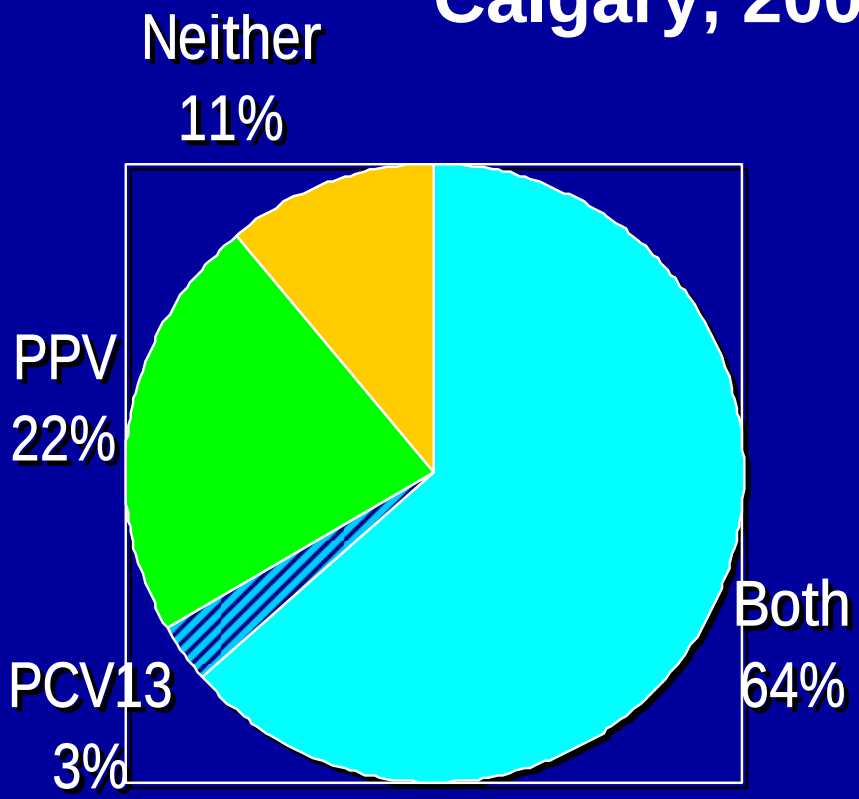
Age group	Decline in rate of hospital admission for pneumonia (95% CL)
<2 years	39% (22,52)
18-39 years	28% (4, 43)
40-64 years	19% (-3, 35)
>=65 years	15% (-2, 30)

Will PCV13 make a difference? – I
PCV13 vs. PPV coverage of adult IPD

Toronto, 2008



Calgary, 2007



What about pneumococcal pneumonia?

- Now occurs at a rate ~15-20 x higher than IPD, CFR 5% vs. 15% for IPD

- Will PCV13 protect adults against pneumococcal pneumonia?
  - EIA titers are higher……

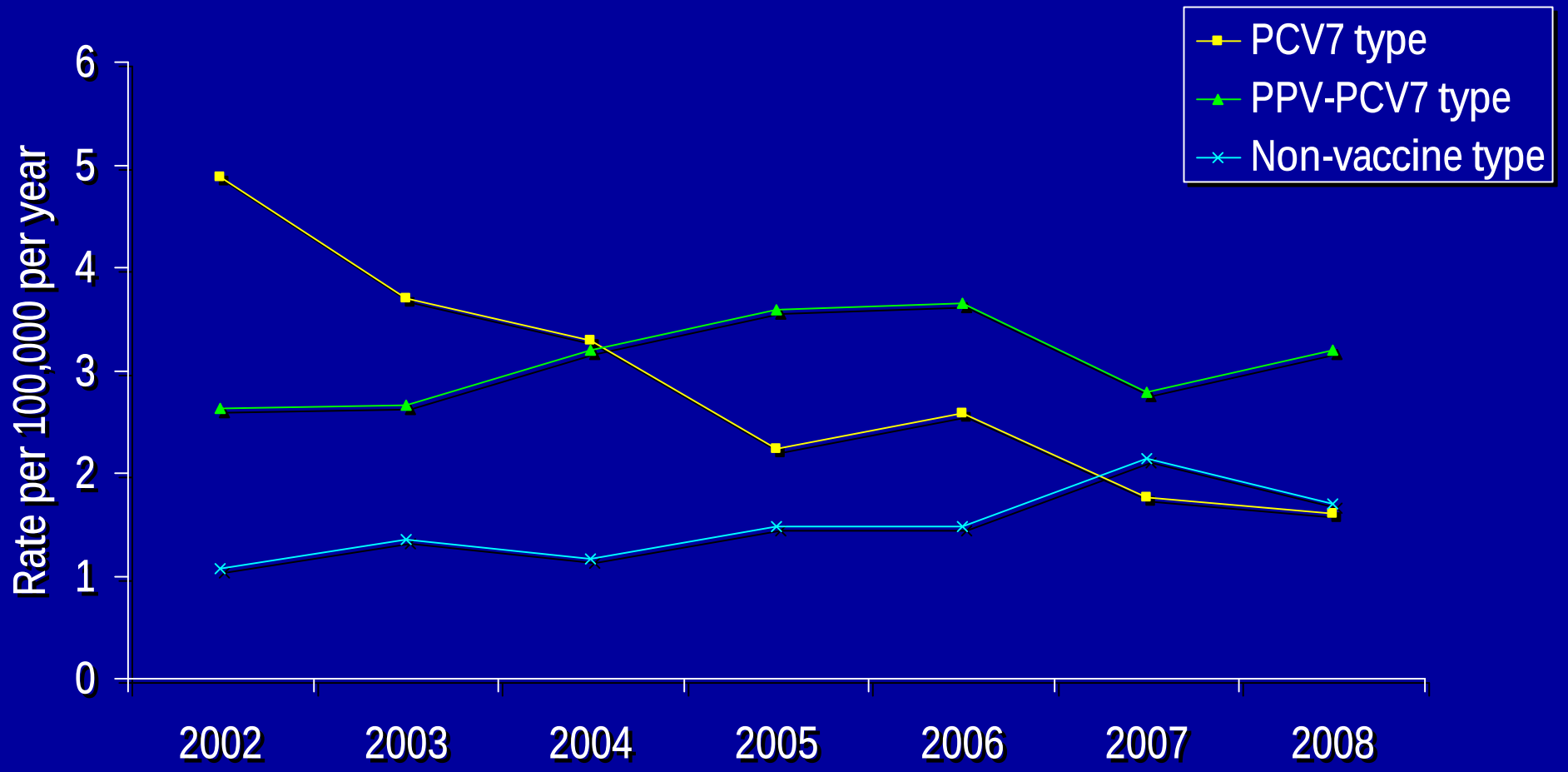
Questions - I

- Will the extended spectrum conjugate vaccines deliver?
- Can we really eradicate serotypes included in conjugate vaccines?
  - By pediatric vaccination alone?
  - More rapid effect with catch-up? Adult? four doses?
- Does PCV13 prevent pneumococcal pneumonia in adults?

Questions - II

- How extensive will serotype replacement be in adults?
  - Will it be with PPV23 serotypes or non-vaccine types?
- Is hyporesponsiveness with PPV23 a clinically significant issue?

Invasive pneumococcal disease
Adults
TIBDN, 2002-2008



What are the issues for Canadian adults?

- What is the interaction between influenza and pneumococcal pneumonia/invasive pneumococcal disease?