



Expanded Use of PCV13 & PPV23

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Objectives

- Explain the differences between the conjugate and polysaccharide vaccines and why these are important in considerations of their use in different populations
- Evaluate the potential benefit of expanded use of PPV23 and PCV13 and prospects for additional valencies

Outline

- Describe current pneumococcal vaccines in Canada and their differences
- Review evidence for benefit of PPV23 & PCV13 in adults
- Describe current national recommendations for use of pneumococcal vaccines in adults
- Describe prospects for new pneumococcal vaccines

Current Pneumococcal Vaccines in Canada

– Pneumococcal conjugate vaccines

- Second generation vaccines

- 10-valent (**PHiD-CV**, Synflorix™) – 2008

- (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F)

- » Also active vs NTHi (protein D conjugate)

- 13-valent (**PCV13**, Prevnar 13™) – 2010

- (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A)

– Pneumococcal plain polysaccharide vaccine

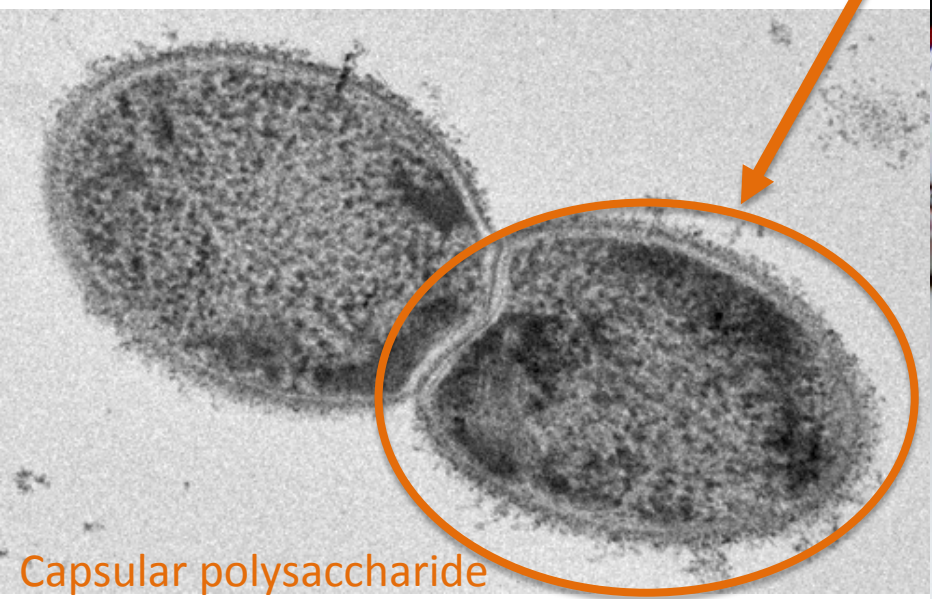
- 23-valent (**PPSV23**, Pneumovax 23) – 1983

- (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 19A, 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F)

- Includes all PCV13 serotypes except 6A

The pneumococcus & beer nuts

Both are sugar coated!



Capsular polysaccharide

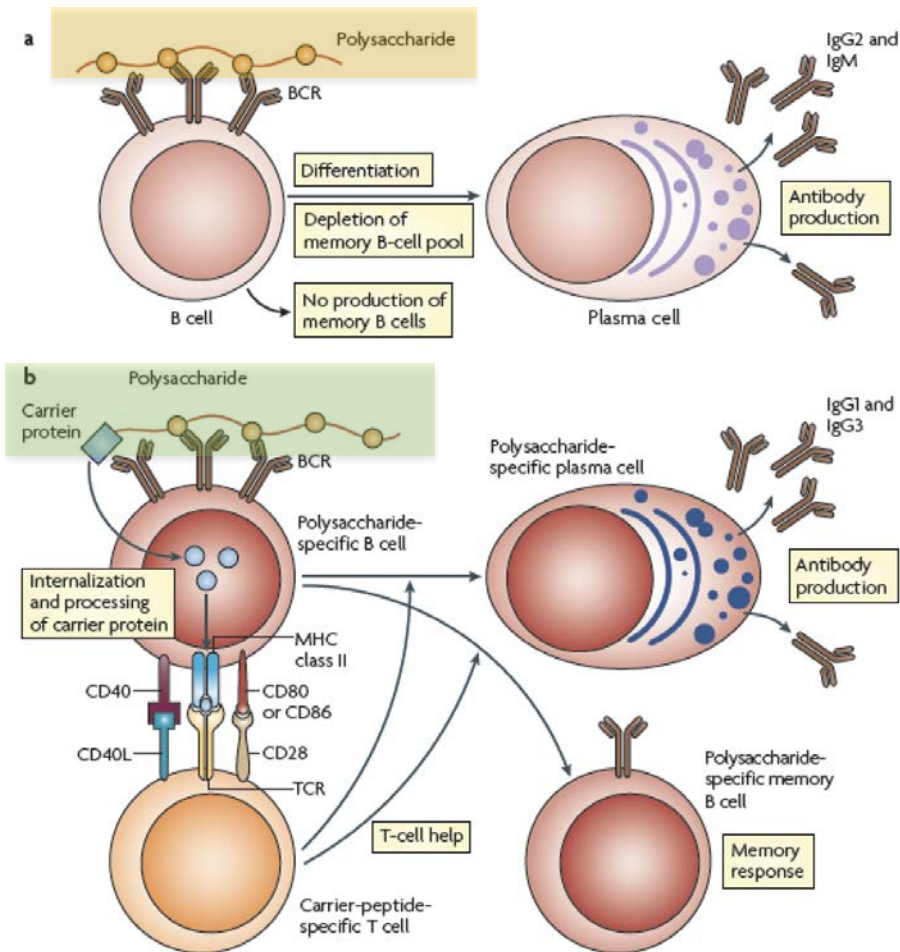


Table sugar

Pneumococcal Capsular Polysaccharide (CPS)

- “Sugar coating” is capsular polysaccharide (CPS)
- CPS is main virulence factor of pneumococcus
 - Effective at evading innate and adaptive immune system
- Each unique CPS determines the “serotype”
 - 97 known serotypes in 46 serogroups
- All current vaccines act against multiple serotypes

Immune response to polysaccharide & protein-polysaccharide conjugate vaccines



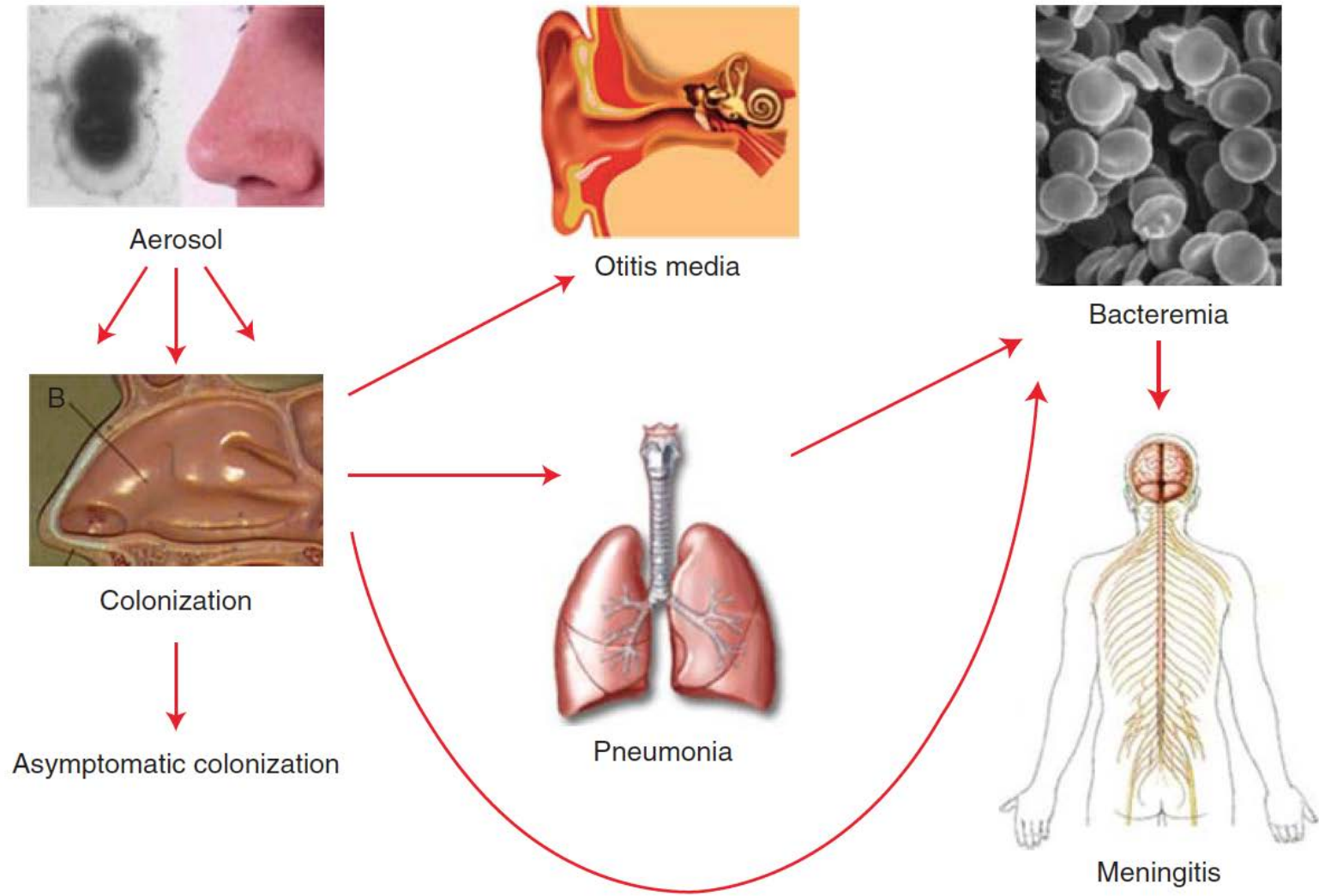
- Polysaccharide vaccines less effective

- T-cell independent Ag
- Short lived Ab response, not boostable
- B-cells depleted (future hyporesponsiveness)

- Protein-polysaccharide conjugate vaccines

- T-cell dependent Ag
- Memory B-cells produced – boostable
- However, duration & magnitude of protection is variable

Progression of Pneumococcal Disease

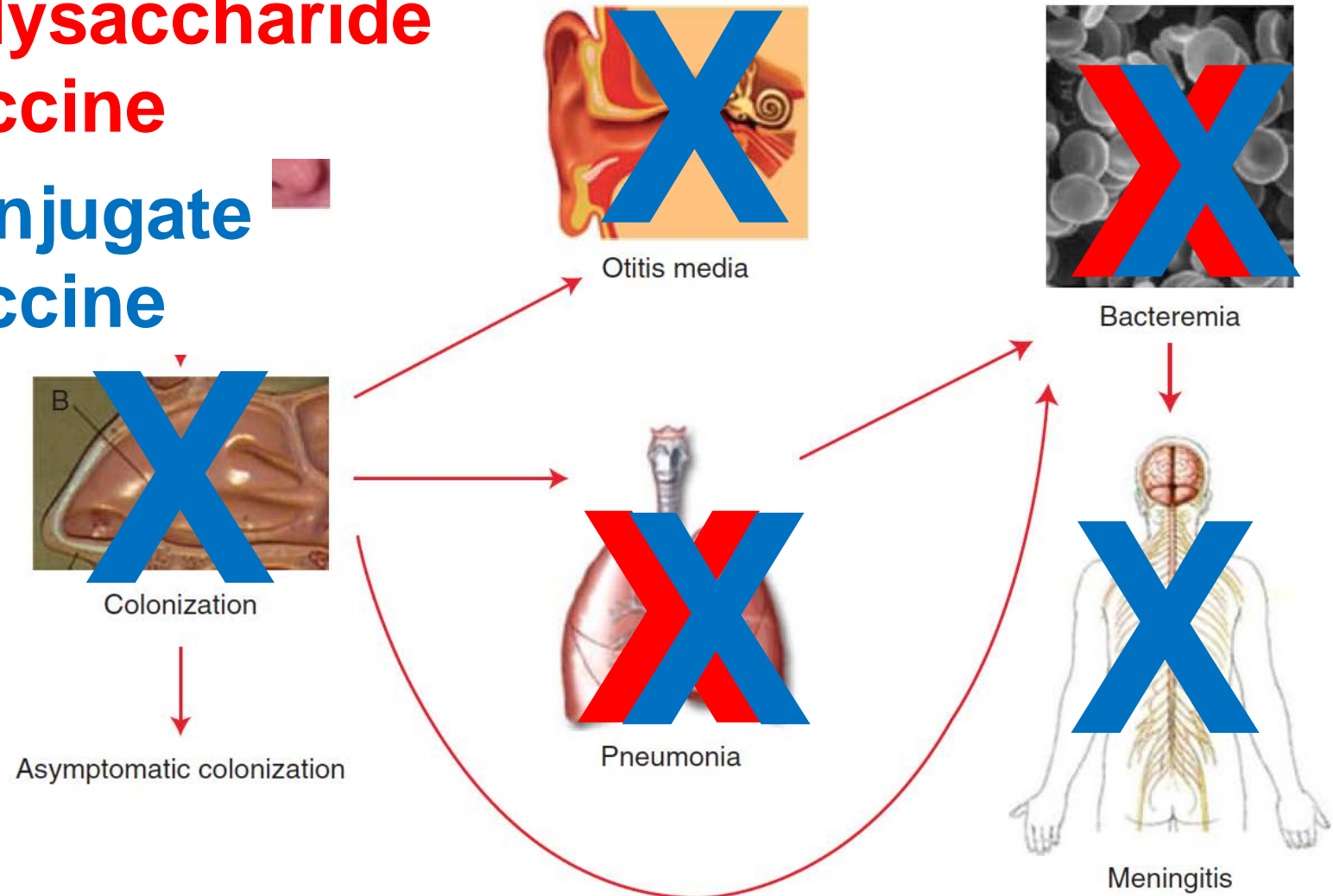


From: Henriques-Normark & Tuonamen. *Cold Spring Harb Perspect Med* 2013;3:a010215

Targets of Pneumococcal Vaccines

**Polysaccharide
Vaccine**

**Conjugate
Vaccine**



PPV23 Vaccine Effectiveness (VE) in Adults >50 Yrs: Systematic Review & Meta-Analysis of 32 Studies

| Pooled Results | Vaccine Effectiveness (VE) | 95% CI |
|--------------------------------------|-----------------------------------|-------------------|
| Invasive Pneumococcal Disease | | |
| Clinical Trials | - | - |
| Cohort Studies | 50% | (21%, 69%) |
| Case-Control Studies | 54% | (32%, 69%) |
| | | |
| Community Acquired Pneumonia | | |
| Clinical Trials | -10% | (-36%, 12%) |
| Cohort Studies | 17% | (-26%, 45%) |
| Case-Control Studies | 7% | (-10%, 21%) |

PPV23 Vaccine Effectiveness (VE) in Adults >50 Yrs: Systematic Review & Meta-Analysis of 32 Studies

| Effect Estimates Stratified by Time since Vaccination* | Vaccine Effectiveness (VE) | 95% CI |
|---|----------------------------|-------------------|
| Invasive Pneumococcal Disease | | |
| Cohort vaccinated <5 yrs | 74% | (56%, 85%) |
| Cohort vaccinated any time | 24% | (4%, 40%) |
| Community Acquired Pneumonia | | |
| Cohort vaccinated <5 yrs | 24% | (-32%, 59%) |
| Cohort vaccinated any time | 5% | (-14%, 21%) |

*Data from case-control studies described counterintuitive increased VE if vaccinated >5 years before case

PCV13 Vaccine – CAPiTA Trial

- Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA)
- Placebo-controlled RCT, Netherlands, ~85,000 healthy adults ≥ 65 yrs, 1 dose PCV13
- Outcomes
 - Primary: VT-Pneumococcal CAP
 - Secondary: Invasive VT-Pneumococcal CAP and Non-Invasive VT-Pneumococcal CAP
- Novel measure
 - Luminex technology urinary antigen detection of PCV13 serotypes

PCV13 Vaccine Efficacy in Adults ≥65 Yrs: CAPiTA Trial (CAP immunization Trial in Adults)

| Randomised Clinical Trial Results | Vaccine Efficacy (VE) | 95% CI |
|--|-----------------------|-------------------|
| Invasive Pneumococcal Disease | | |
| 1 st episode vaccine type (VT) IPD | 75% | (41%, 91%) |
| | | |
| Community Acquired Pneumonia | | |
| 1 st episode any CAP | 5% | (-5, 14%) |
| 1 st episode VT pneumococcal CAP | 46%* | (22%, 62%) |
| 1 st episode non-invasive (NI) VT pneumococcal CAP | 45%* | (14%, 65%) |
| Mortality pneumococcal CAP or IPD | 15% | (-198%, 76%) |

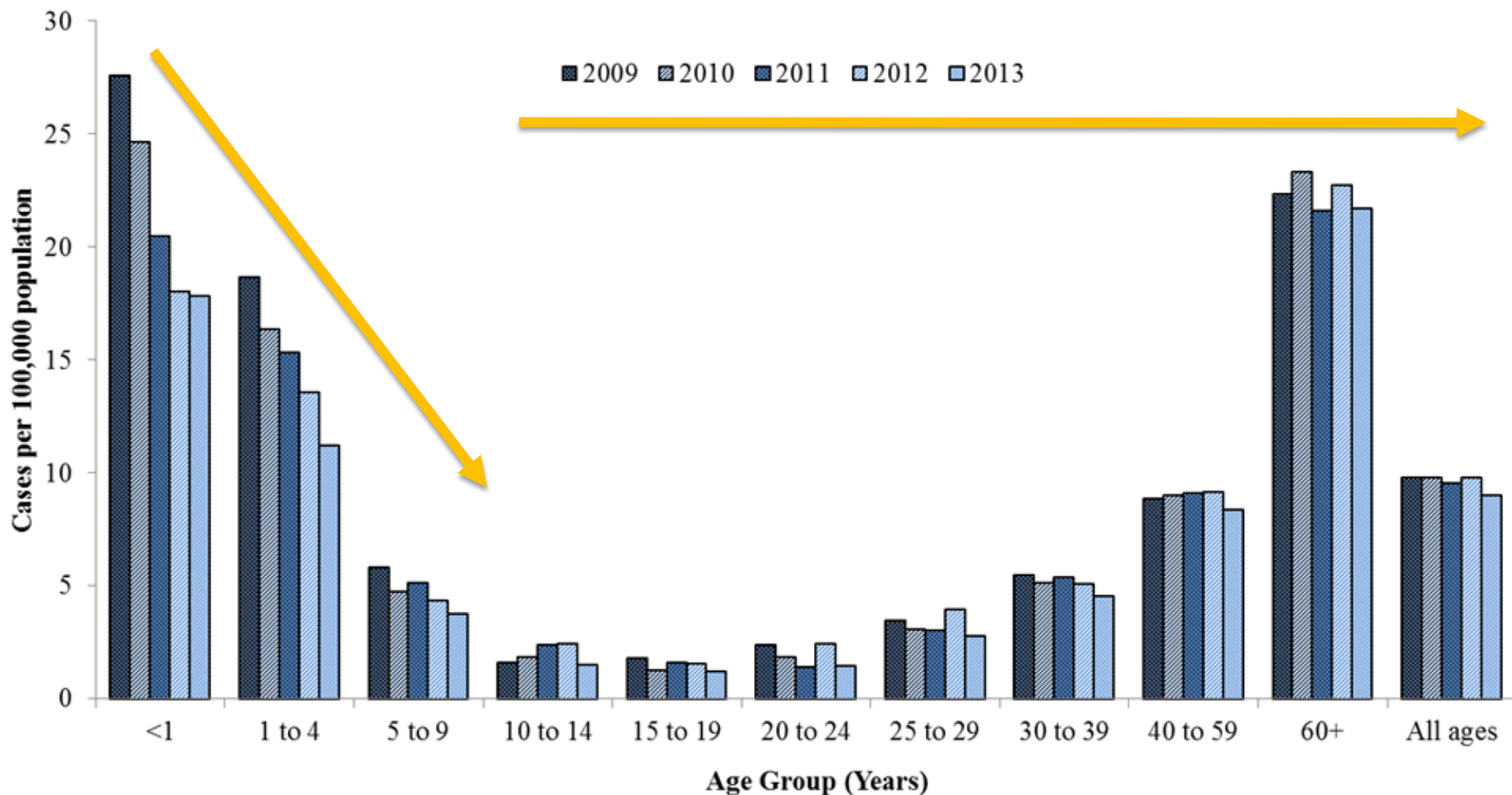
*Benefit lasts 4 or more years

So...

- Neither PPV23 nor PCV13 is a perfect vaccine for older adults
 - But both vaccines do protect against IPD
 - Neither vaccine has significant impact on overall CAP but PCV13 does protect against VT CAP
- Both vaccines have indications in younger adults
- Many unanswered questions!

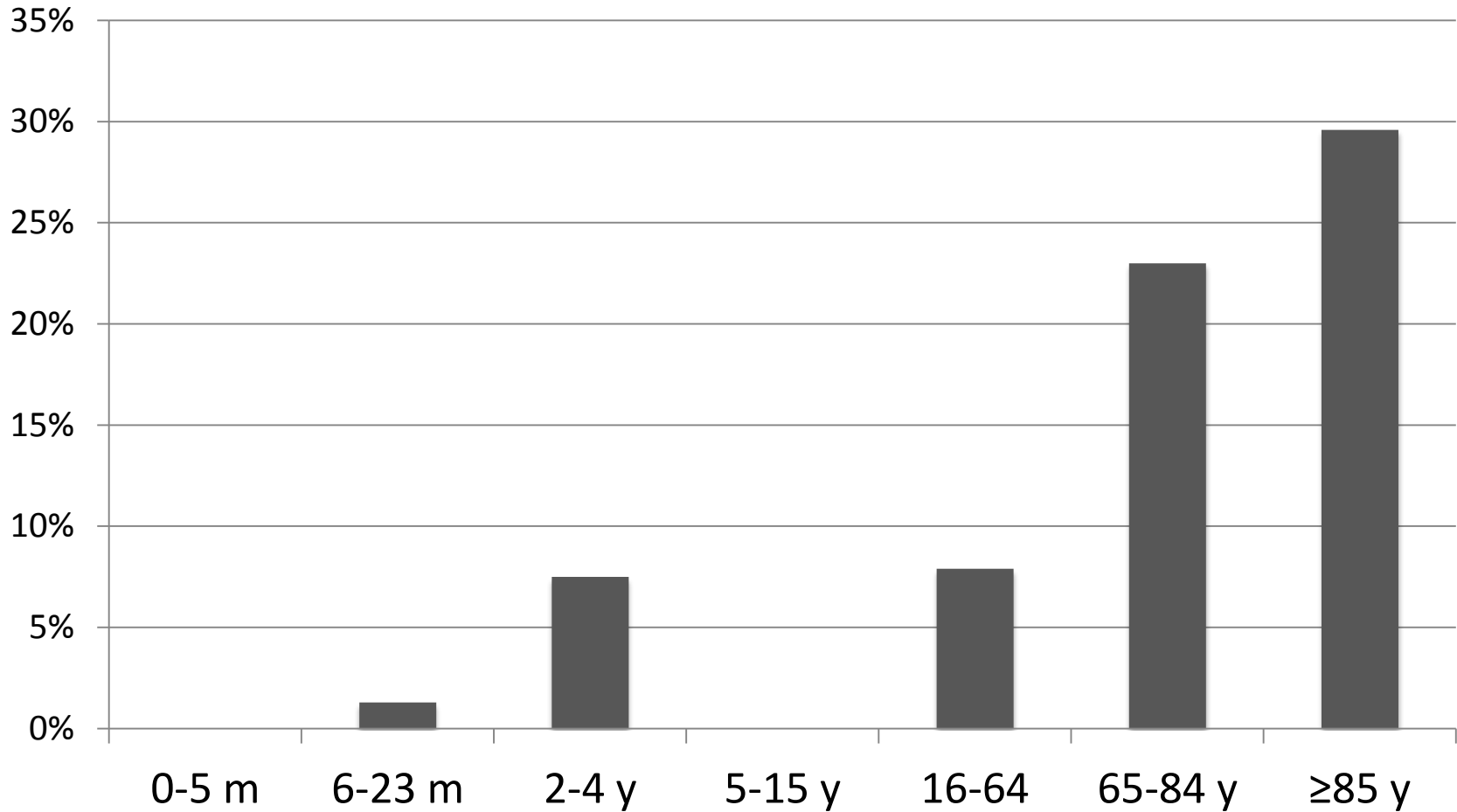
Hasn't PCV13 for children eliminated
PCV13 ST disease in adults?

IPD in Canada, All Ages, 2009-2013



IPD in Calgary

30 Day Mortality by Age Groups

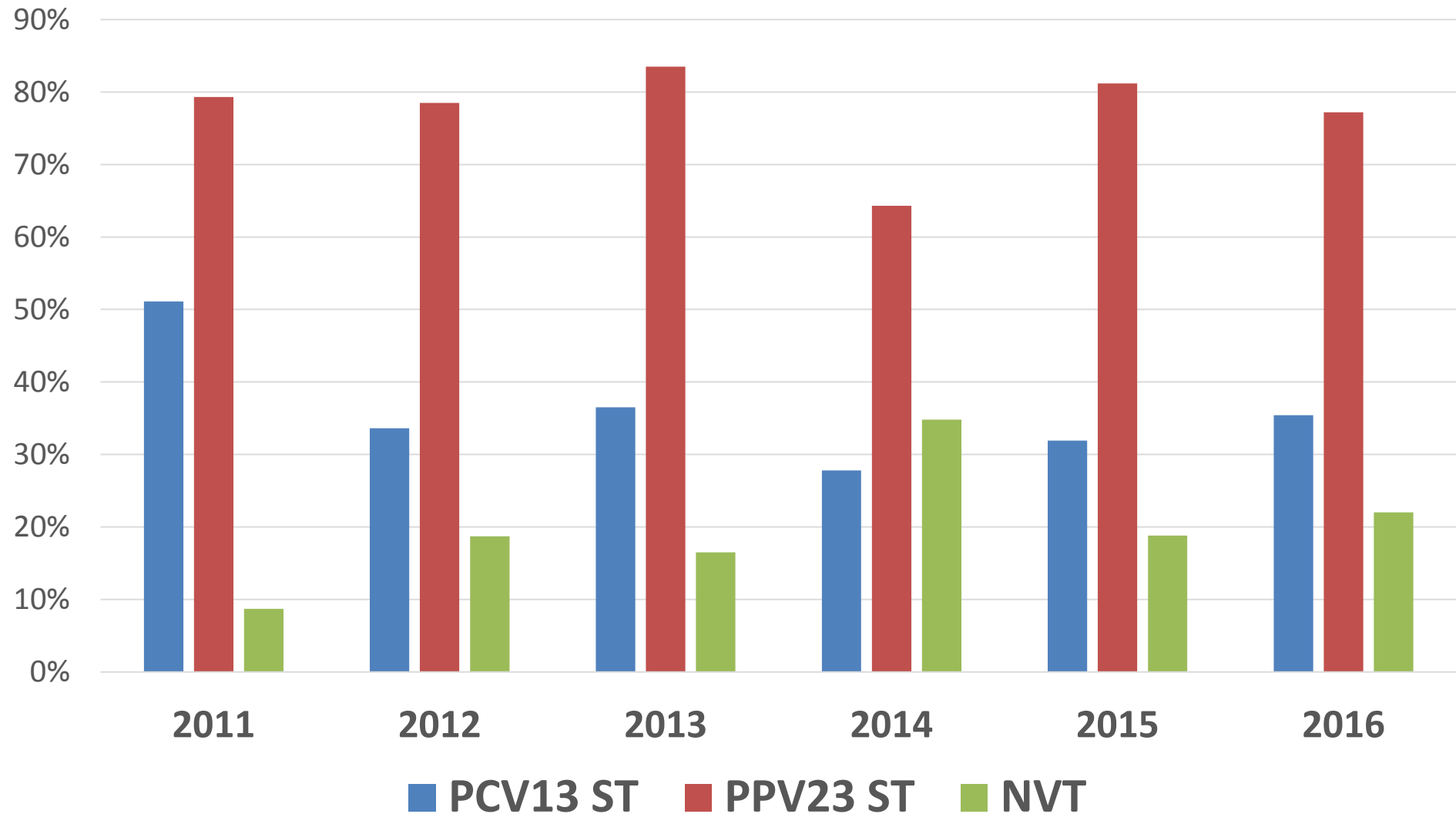


Updated from Ricketson et al. 10th Canadian Immunization Conference, Vancouver 2012.

CASPER IPD Study & Leal et al. *PIDJ* 2012;31(9):e169

Adult IPD Calgary

% of Cases in Vaccine Groups



National Recommendations: NACI and Canadian Immunization Guide

- Four new NACI statements since 2013
- Canadian Immunization Guide currently updated
- Note:
 - PNEU-C-13 = PCV13
 - PNEU-P-23 = PPV23

Risk factors for IPD

- Age – very young & elderly
- High risk conditions
 - Non-immunocompromising
 - Immunocompromising
- Day care centre attendance under 5 years of age
- Smoking
- Alcoholism
- Homeless persons
- Illicit drug users

Use of PCV13 +/- PPV23 in Adults (NACI 2013, 2016)

- **NACI (2016)**

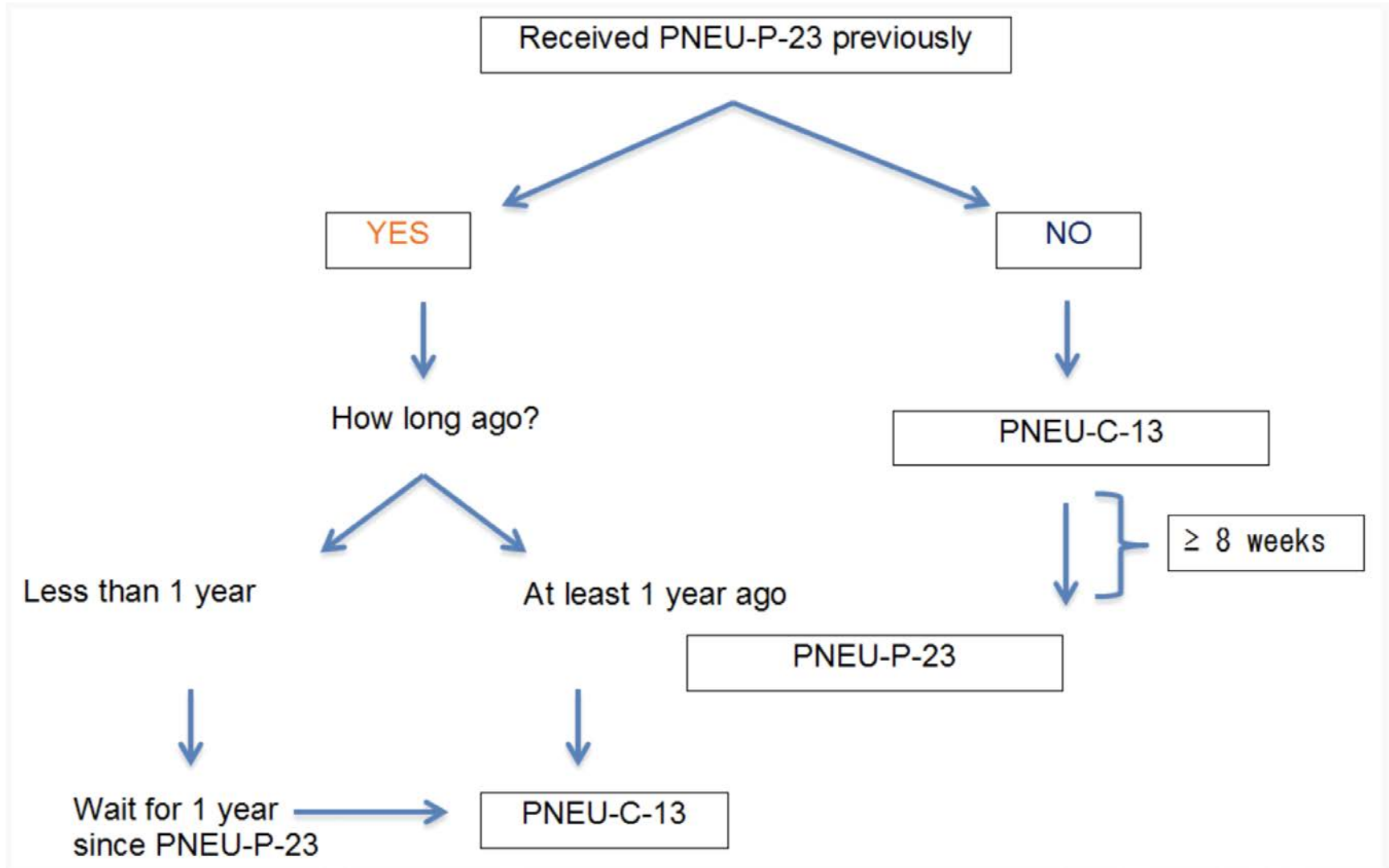
- ... there is **good evidence**, on an individual basis, to recommend in **immunocompetent adults aged 65 years and older not previously immunized against pneumococcal disease, the use of PCV13 vaccine followed by PPV23, for the prevention of CAP and IPD** caused by the 13 pneumococcal serotypes included in the conjugate vaccine. (NACI recommendation grade A).
Superseded 2013 recommendation
- ... based on circulating serotypes, there is **fair evidence to recommend the use of PPV23 vaccine in routine immunization programs** for adults aged 65 years and older. (NACI recommendation Grade B)

Use of PCV13 +/- PPV23 in Adults (NACI 2013, 2016)

- **NACI (2013)**

- ... **good evidence** for HSCT recipients (3 doses PCV13) & HIV (1 dose PCV13 + PPV23)
- ... **fair evidence** for asplenia, sickle cell disease or other hemoglobinopathies, congenital immunodeficiencies, immunosuppressive therapy (corticosteroids, chemotherapy, radiation therapy, post-organ-transplant therapy, biologic and non-biologic immunosuppressive therapies), malignancies (1 dose PCV13 + PPV23)
- ... **insufficient evidence** for PCV13 for chronic conditions without immunosuppression including chronic CSF leak, cochlear implants, chronic neurologic condition, chronic cardiac or pulmonary disease, diabetes mellitus, chronic kidney disease, chronic liver disease

Sequencing of PCV13 & PPV23



Re-Immunization with PPV23 (NACI 2015)

- Immunity following PPV23 declines rapidly
- Re-vaccination of those at highest risk of IPD disease provides a “boost” in immune response
- Little evidence that hypo-responsiveness occurs with 1 additional dose of PPV23
- Recommendations:
 - High-risk, >2 yrs old, prior PCV13 & PPV23, should receive 2nd dose PPV23 5 yrs after 1st dose
 - Insufficient evidence for further PPV23 doses
 - All persons should receive a dose of PPV23 at age ≥ 65 yr

Addition of Asthma as High-Risk Condition (NACI 2014)

- ... **good** evidence to recommend the addition of asthma - with or without prolonged use of systemic corticosteroid or associated with COPD - as a high-risk condition warranting vaccination to prevent IPD. (NACI recommendation A)
- If... required a medical attention for asthma in the past 12 months should be vaccinated ... Asthma is not considered an immunocompromising condition in and of itself but rather a medical condition with a higher risk of IPD.
- In Summary:
 - Children 2 – 18 yrs should receive PCV13 as appropriate for their age group and a additional dose of PPV23 at least 8 weeks after
 - Adults with asthma should receive one dose of PPV23 as other adults with chronic conditions increasing the risk of IPD, without immune suppression.
 - At this time further booster doses of PCV13 or PPV23 are not recommended

Canadian Immunization Guide (Updated 2016-12-22)

- Some differences from NACI recommendations
- Healthy adults ≥ 18 yr
 - 1 dose PPV23 for all ≥ 65 yr for all
 - 1 dose PCV13 for all ≥ 65 yr may be considered..., followed by 1 dose PPV23
- PCV13 (+PPV23) recommended for
 - Nephrotic syndrome

Prospects for New Pneumococcal Vaccines

- Current vaccines imperfect – need for new vaccines
 - Protection not universal
 - Serotype replacement
 - Expensive to produce
- Prospects
 - PCVs with increased serotypes – PCV15 (+22F, 33F)
 - PCVs with less expensive technologies
 - Pneumococcal protein vaccine
 - PspA failed (2004) due to homology with cardiac myosin
 - Several others in development e.g., pneumolysin
 - Killed whole cell vaccine (unencapsulated)

Conclusions

- PPV23 and PCV13 both protect against invasive pneumococcal disease (IPD) in adults
- PCV13 protects against pneumococcal community acquired pneumonia (CAP) and protection lasts 4 or more years
- Neither vaccine reduces overall CAP
- There are numerous indications to give both vaccines in sequence (PCV13 followed by PPV23) to adults
- There are no data to direct providing multiple repeated doses in adulthood



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Medical conditions resulting in high-risk of IPD

- **Non-immunocompromising conditions**
 - Chronic cerebrospinal fluid (CSF) leak
 - Chronic neurologic condition that may impair clearance of oral secretions
 - Cochlear implants, including children and adults who are to receive implants
 - Chronic heart disease
 - Diabetes mellitus
 - Chronic kidney disease
 - Chronic liver disease, including hepatic cirrhosis due to any cause
 - Chronic lung disease, including asthma requiring medical care in the preceding 12 months
- **Immunocompromising conditions**
 - Sickle cell disease, congenital or acquired asplenia, or splenic dysfunction
 - Congenital immunodeficiencies involving any part of the immune system, including B-lymphocyte (humoral) immunity, T-lymphocyte (cell) mediated immunity, complement system (properdin, or factor D deficiencies), or phagocytic functions
 - Immunocompromising therapy, including use of long-term corticosteroids, chemotherapy, radiation therapy, and post-organ transplant therapy
 - HIV infection
 - Hematopoietic stem cell transplant (recipient)
 - Malignant neoplasms, including leukemia and lymphoma
 - Nephrotic syndrome
 - Solid organ or islet transplant (candidate or recipient)