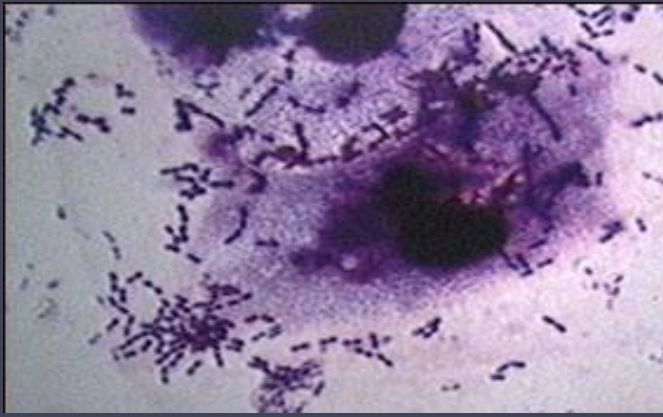


## Serviço de Infecçiology

Diretora de Serviço: Dra. Patrícia Pacheco



# VACINAÇÃO ANTIPNEUMOCÓCICA

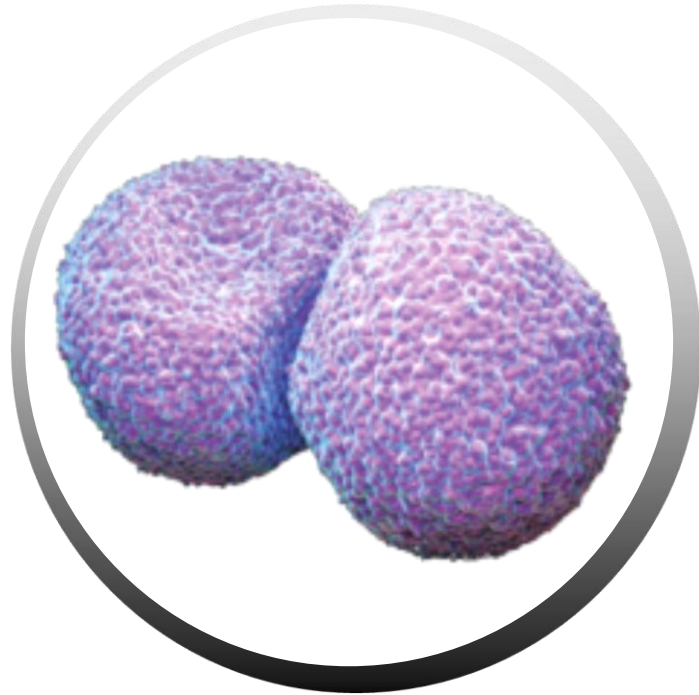


Preletores: Joana Batista, Luís Duque

Preletor convidado: Dr. Filipe Froes

21 de Janeiro de 2016

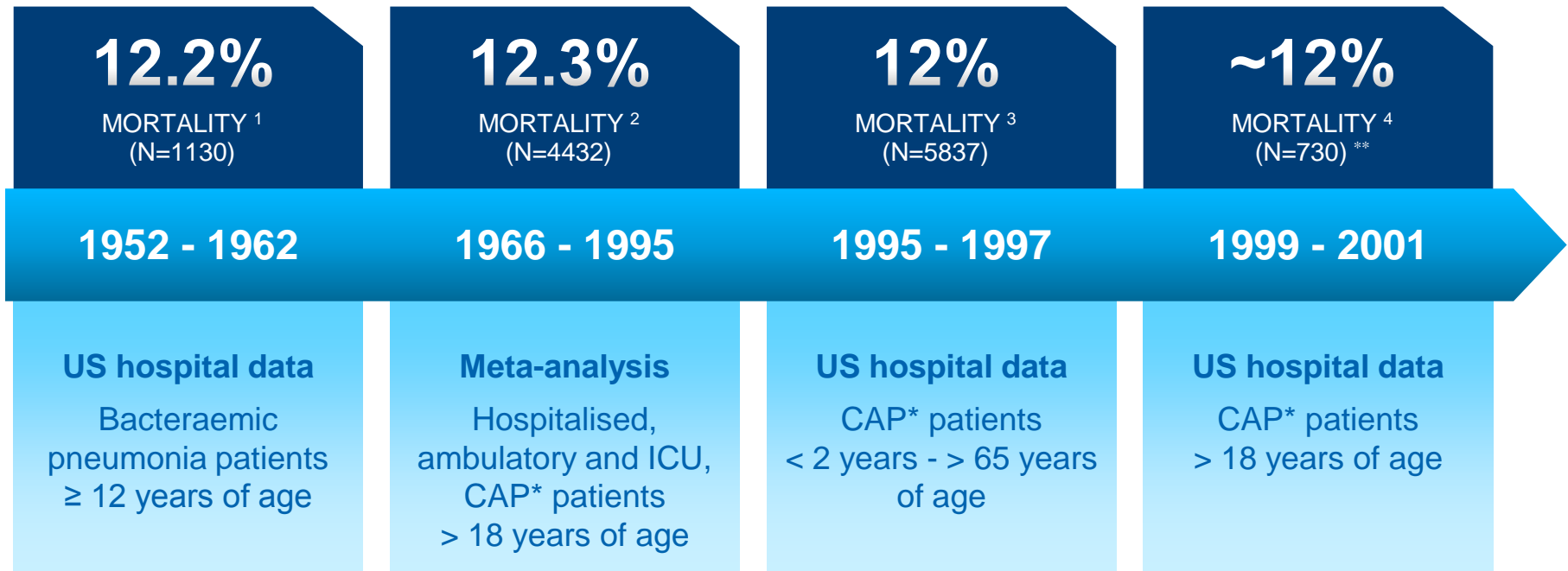
# Agente da doença pneumocócica



- *Streptococcus pneumoniae*<sup>1</sup>
  - ▣ Diplococcus Gram positivo
  - ▣ Cápsula polissacárida
  - ▣ > 90 serotipos capsulares
- Cápsula polissacárida<sup>1</sup>
  - ▣ Determinante antigénico
  - ▣ Fator de virulência

# Doença pneumocócica como entidade clínica potencialmente grave

Mortality rates for hospitalised patients with IPD and CAP\* have remained constant over time <sup>1-4</sup>



***Streptococcus pneumoniae* can be resistant to antibiotics which makes prevention even more important <sup>5-7</sup>**

\* CAP = Community-Acquired Pneumonia.

\*\* Average of 30-day and 90-day mortality in ICU vs ward patients, with average of 2 rates ~12%.

1. Austrian R *et al.* Ann Intern Med. 1964;60:759-776. 2. Fine MJ *et al.* JAMA. 1996;274:134-141. 3. Feikin DR *et al.* Am J Pub Health. 2000;90:223-229.

4. Restrepo MI *et al.* Chest. 2008;133:610-617. 5. ECDC report. Antimicrobial resistance surveillance in Europe 2010. 6. Liñares J *et al.* Clin Microbiol Infect. 2010;16:402-410. 7. Kyaw MH *et al.* N Engl J Med. 2006;354:1455-1463.

# Incidência da doença pneumocócica invasiva é maior nos extremos etários

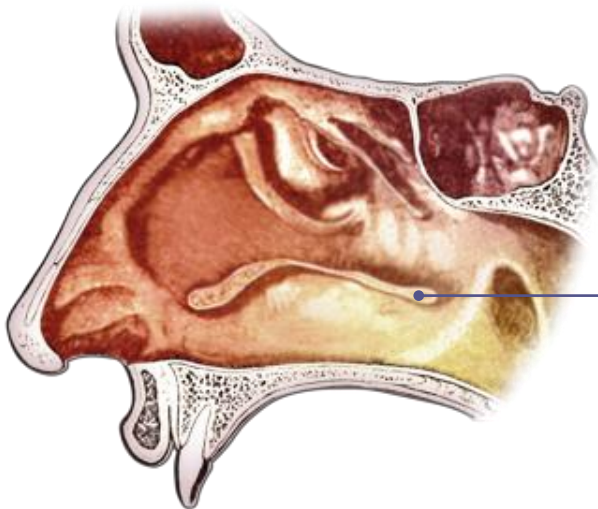
**Incidence and mortality rates of invasive pneumococcal disease in the United States, 2010 – Active Bacterial Core Surveillance (ABCs) report, Emerging Infections Program Network**

| Age (years)   | Cases       |               | Deaths     |               |
|---------------|-------------|---------------|------------|---------------|
|               | Number      | (Rate*)       | Number     | (Rate*)       |
| <1            | 142         | (34.2)        | 1          | (0.24)        |
| 1             | 112         | (26.6)        | 1          | (0.24)        |
| 2 to 4        | 171         | (13.1)        | 1          | (0.08)        |
| 5 to 17       | 111         | (2.2)         | 1          | (0.02)        |
| 18 to 34      | 260         | (3.8)         | 18         | (0.26)        |
| 35 to 49      | 670         | (10.5)        | 43         | (0.68)        |
| 50 to 64      | 1064        | (18.8)        | 103        | (1.82)        |
| ≥65           | 1292        | (36.4)        | 199        | (5.61)        |
| <b>Total:</b> | <b>3822</b> | <b>(12.8)</b> | <b>367</b> | <b>(1.23)</b> |

\* Cases or deaths per 100,000 population for ABCs areas, which represent nearly 30,000,000 persons in certain counties in 10 states in the United States.

# Nasofaringe: reservatório para *Streptococcus pneumoniae*

- ***Streptococcus pneumoniae* pode fazer parte da flora da nasofaringe** <sup>1</sup>
- **Taxas de colonização nasofaríngea por *Streptococcus pneumoniae*:**
  - 9%–87.2% em crianças de idade <5 anos <sup>2,3</sup>
  - 4%–45% em adultos <sup>3,4</sup>



**Colonização nasofaríngea é geralmente pré-requisito para doença pneumocócica mucosa e invasiva** <sup>2,4,5</sup>

Image redrawn from: <http://www.1911encyclopedia.org/images/f/f4/Olfactorysystem-2.jpg>.

# *Streptococcus pneumoniae*



- O polissacárido capsular de superfície do *Streptococcus pneumoniae* é a principal defesa contra as células fagocíticas do sistema imunitário (SI)
- Os Acs anti-capsulares facilitam a fagocitose e morte das bactérias
- As vacinas disponíveis contêm polissacáridos dos serotipos mais frequentemente implicados na doença humana invasiva

# 2 tipos de vacina pneumocócica disponíveis para a população adulta

|               | Vacina             | Serotipos  | Serotipos Adicionais                            |
|---------------|--------------------|--|---|
| Conjugada     | VPC13 <sup>1</sup> | 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, 19A |   |
| Polissacárida | VPP <sup>2</sup>   | = (excepto 6A)                                     | 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F |

PCV13, 13-valent pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine.

1. Prevenar13® Summary of Product Characteristics. 2. Pneumo 23 Summary of Product Characteristics.

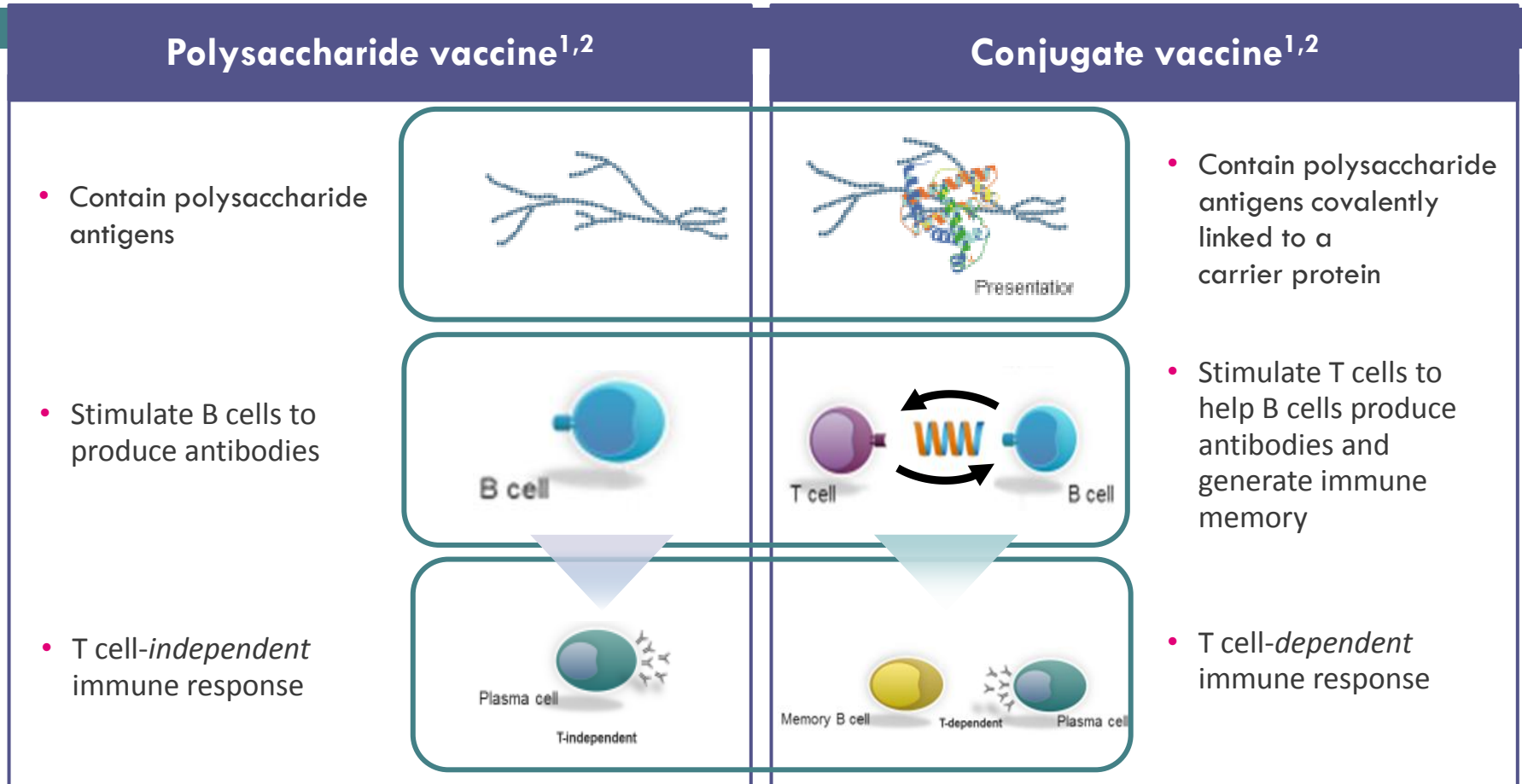
# Vacina pneumocócica polissacárida (VPP)

- Pneumo 23®
- Contém material capsular de 23 serotipos de pneumococo
  - Esta vacina não é imunogénica se idade inferior a 2 anos, dado que os polissacáridos não conjugados não induzem imunidade

# Vacina pneumocócica conjugada (VPC)

- Prevenar 13®
  - Composta por 13 tipos dos polissacáridos capsulares mais comumente associados a doença, com ligação covalente a uma proteína semelhante à toxina diftérica.

# Rationale for conjugation



Memory B-cell production has not been studied with PCV13 in adults

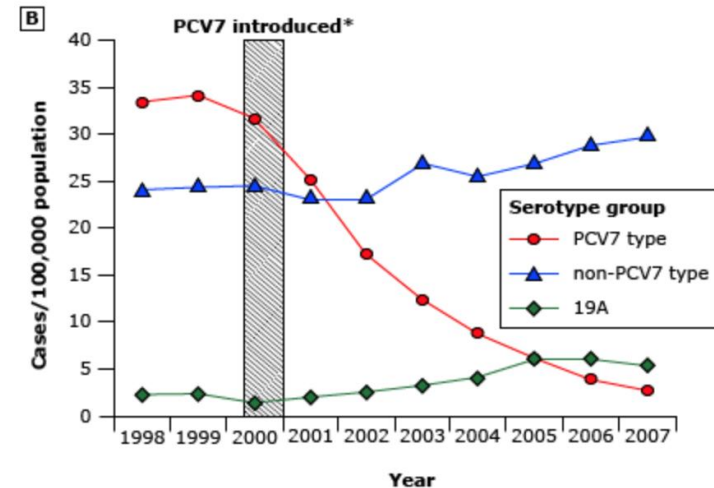
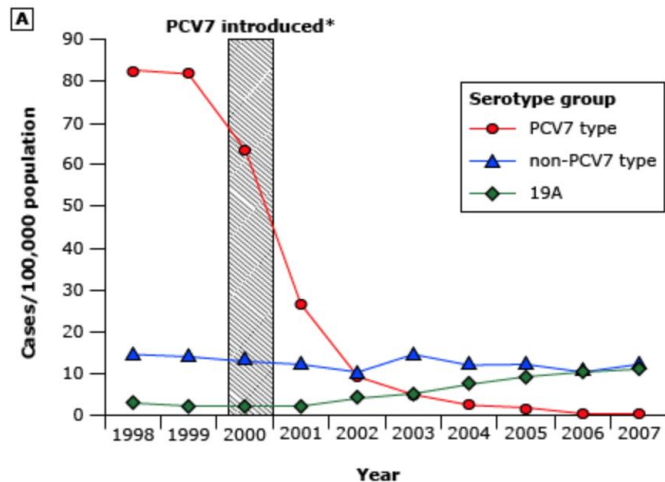
PCV13, 13-valent pneumococcal conjugate vaccine.

1. Siegrist CA. In: Plotkin, et al., eds. Vaccines, 5th edn. 2008:17–36. 2. Pollard AJ, et al. Nat Rev Immunol 2009;9:213–20.

# Vacina pneumocócica conjugada (VPC)

- ▣ **Esta proteína torna estes polissacáridos antigénicos em crianças mais jovens**
- ▣ Indução de **resposta glicoproteínica**
- ▣ Atuam no estado de portador **antígeno** e **consequentemente poderão conferir imunidade** o indirecta a **os** vacinados

# Doença invasiva pneumocócica na era da vacina pneumocócica conjugada



Alterações na incidência de DIP por serotipo em crianças com idade <5 anos (A) e adultos com idade igual ou > 65 anos(B), nos **EUA** após a introdução da VPC no calendário vacinal pediátrico em 2000.

# Composition of PCV-7 vs PCV-10 vs PCV-13

## PCV-7<sup>[a]</sup>


|     |
|-----|
| 4   |
| 6B  |
| 9V  |
| 14  |
| 18C |
| 19F |
| 23F |

## PCV-10<sup>[b]</sup>

|     |           |
|-----|-----------|
| 4   | 3 µg- PrD |
| 6B  | 1 µg- PrD |
| 9V  | 1 µg- PrD |
| 14  | 1 µg- PrD |
| 18C | 3 µg- TT  |
| 19F | 3 µg- DT  |
| 23F | 1 µg- PrD |
| 1   | 1 µg- PrD |
| 5   | 1 µg- PrD |
| 7F  | 1 µg- PrD |

## PCV-13<sup>[c]</sup>

|     |            |
|-----|------------|
| 4   | 2.2 µg-CRM |
| 6B  | 4.4 µg-CRM |
| 9V  | 2.2 µg-CRM |
| 14  | 2.2 µg-CRM |
| 18C | 2.2 µg-CRM |
| 19F | 2.2 µg-CRM |
| 23F | 2.2 µg-CRM |
| 1   | 2.2 µg-CRM |
| 5   | 2.2 µg-CRM |
| 7F  | 2.2 µg-CRM |
| 3   | 2.2 µg-CRM |
| 6A  | 2.2 µg-CRM |
| 19A | 2.2 µg-CRM |

*Haemophilus influenzae* derived Protein D 

a. WHO website bulletin. 2015.

b. eMC website (22743). 2015.

c. eMC website (22689). 2015.

# Ensaio CAPiTA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults

M.J.M. Bonten, S.M. Huijts, M. Bolkenbaas, C. Webber, S. Patterson, S. Gault, C.H. van Werkhoven, A.M.M. van Deursen, E.A.M. Sanders, T.J.M. Verheij, M. Patton, A. McDonough, A. Moradoghli-Haftvani, H. Smith, T. Mellelieu, M.W. Pride, G. Crowther, B. Schmoele-Thoma, D.A. Scott, K.U. Jansen, R. Lobatto, B. Oosterman, N. Visser, E. Caspers, A. Smorenburg, E.A. Emini, W.C. Gruber, and D.E. Grobbee

### BACKGROUND

Pneumococcal polysaccharide conjugate vaccines prevent pneumococcal disease in infants, but their efficacy against pneumococcal community-acquired pneumonia in adults 65 years of age or older is unknown.

### METHODS

In a randomized, double-blind, placebo-controlled trial involving 84,496 adults 65 years of age or older, we evaluated the efficacy of 13-valent polysaccharide conjugate vaccine (PCV13) in preventing first episodes of vaccine-type strains of pneumococcal community-acquired pneumonia, nonbacteremic and noninvasive pneumococcal community-acquired pneumonia, and invasive pneumococcal disease. Standard laboratory methods and a serotype-specific urinary antigen detection assay were used to identify community-acquired pneumonia and invasive pneumococcal disease.

### RESULTS

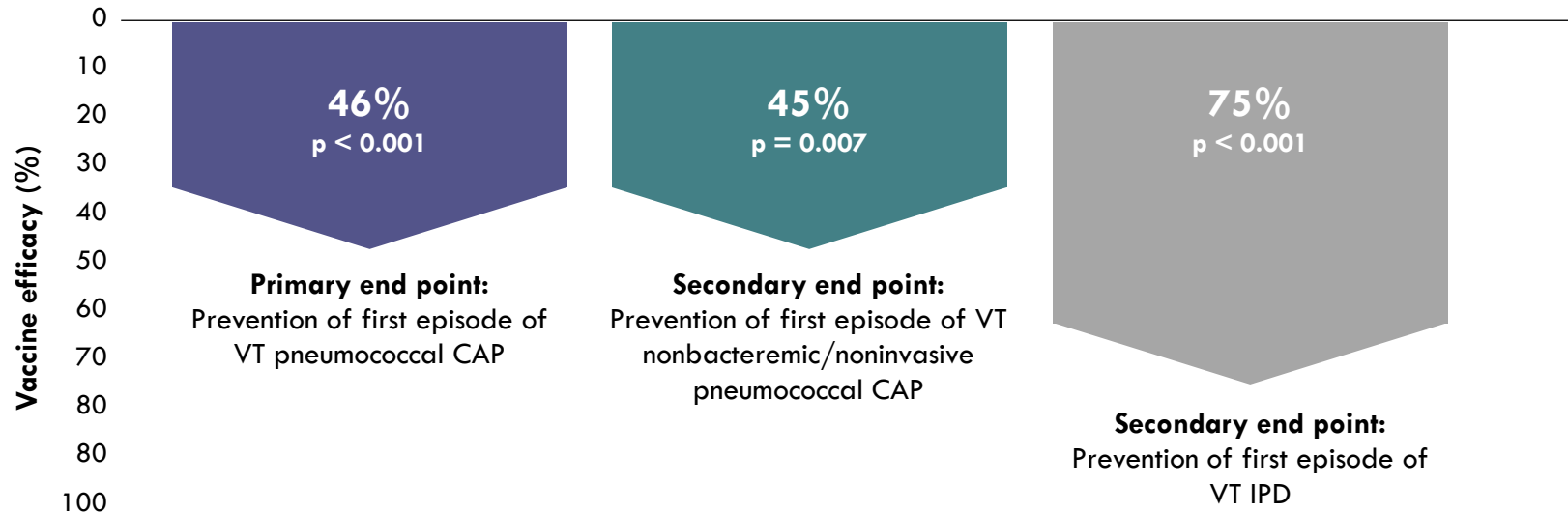
In the per-protocol analysis of first episodes of infections due to vaccine-type strains, community-acquired pneumonia occurred in 49 persons in the PCV13 group and 90 persons in the placebo group (vaccine efficacy, 45.6%; 95.2% confidence interval [CI], 21.8 to 62.5), nonbacteremic and noninvasive community-acquired pneumonia occurred in 33 persons in the PCV13 group and 60 persons in the placebo group (vaccine efficacy, 45.0%; 95.2% CI, 14.2 to 65.3), and invasive pneumococcal disease occurred in 7 persons in the PCV13 group and 28 persons in the placebo group (vaccine efficacy, 75.0%; 95% CI, 41.4 to 90.8). Efficacy persisted throughout the trial (mean follow-up, 3.97 years). In the modified intention-to-treat analysis, similar efficacy was observed (vaccine efficacy, 37.7%, 41.1%, and 75.8%, respectively), and community-acquired pneumonia occurred in 747 persons in the PCV13 group and 787 persons in placebo group (vaccine efficacy, 5.1%; 95% CI, -5.1 to 14.2). Numbers of serious adverse events and deaths were similar in the two groups, but there were more local reactions in the PCV13 group.

### CONCLUSIONS

Among older adults, PCV13 was effective in preventing vaccine-type pneumococcal, bacteremic, and nonbacteremic community-acquired pneumonia and vaccine-type invasive pneumococcal disease but not in preventing community-acquired pneumonia from any cause. (Funded by Pfizer; CAPiTA ClinicalTrials.gov number NCT00744263.)

# Primary and secondary objectives, per-protocol population

## Reduction in pneumococcal disease with PCV13



## Statistically significant reductions in first episode of VT pneumococcal CAP with PCV13<sup>1</sup>

Overall, adverse event profile was consistent with that of prior studies in adults<sup>1</sup>

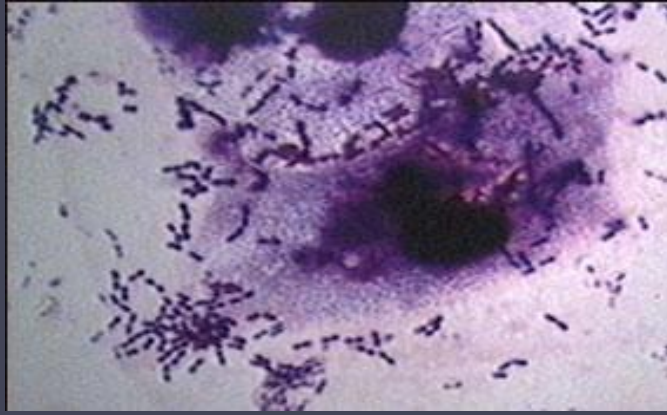
PCV13, n = 42,240; Placebo, n = 42,256.

CAP, community-acquired pneumonia; CI, confidence interval; IPD, invasive pneumococcal disease; NB, non-bacteremic; NI, non-invasive; PCV13, 13-valent pneumococcal conjugate vaccine; VE, vaccine efficacy; VT, vaccine type.

Figure created using data from: 1. Bonten MJM, et al. N Engl J Med 2015;372:1114–25.

# Imunização Recomendada

- Crianças
- Adultos com risco aumentado de pneumonia e doença pneumocócica invasiva
- Adultos com  $> 65$  anos



***BACK UP SLIDES***



21 de Janeiro de 2016

# Programa Nacional Vacinação (2015)

| Vacinas contra:                                  | Idades      |         |         |         |         |         |          |          |          |             |                        |
|--|-------------|---------|---------|---------|---------|---------|----------|----------|----------|-------------|------------------------|
|  | Nasci-mento | 2 Meses | 3 meses | 4 meses | 5 meses | 6 meses | 12 meses | 18 meses | 5-6 anos | 10-13 anos  | Toda a vida 10/10 anos |
| Tuberculose                                      | BCG         |         |         |         |         |         |          |          |          |             |                        |
| Hepatite B                                       | VHB 1       | VHB 2   |         |         |         | VHB 3   |          |          |          |             |                        |
| Infeções por <i>Haemophilus influenzae b</i>     |             | Hib 1   |         | Hib 2   |         | Hib 3   |          | Hib 4    |          |             |                        |
| Difteria-Tétano-Tosse convulsa                   |             | DTPa 1  |         | DTPa 2  |         | DTPa 3  |          | DTPa 4   | DTPa 5   | Td          | Td                     |
| Poliomielite                                     |             | VIP 1   |         | VIP 2   |         | VIP 3   |          |          | VIP 4    |             |                        |
| Infeções por <i>Streptococcus pneumoniae</i> (a) |             | Pn13 1  |         | Pn13 2  |         |         | Pn13 3   |          |          |             |                        |
| Infeções por <i>Neisseria meningitidis</i> C     |             |         |         |         |         |         | MenC     |          |          |             |                        |
| Sarampo-Parotidite epidémica-Rubéola             |             |         |         |         |         |         | VASPR 1  |          | VASPR 2  |             |                        |
| Infeções por vírus do Papiloma humano (b)        |             |         |         |         |         |         |          |          |          | HPV 1,2 (b) |                        |

(a) Pn13: aplicável às crianças nascidas a partir de 1 de janeiro de 2015.

(b) HPV: aplicável apenas a raparigas. Esquema de vacinação: 0, 6 meses.

# Imunização gratuita pelo SNS

**Quadro II** - Grupos com risco acrescido para DIP. Adultos ( $\geq 18$  anos de idade).

**Vacinação recomendada e gratuita contra infeções por *S. pneumoniae* (Pn13)**

| <b>A - Imunocompetentes</b>                   |   |
|---|---|
| <b>Condição:</b>                              | <b>Situações abrangidas:</b>  |
| Fístulas de LCR                               |   |
| Implantes cocleares (candidatos e portadores) |   |
| <b>B - Imunocomprometidos</b>                 |   |
| <b>Condição:</b>                              | <b>Situações abrangidas:</b>  |
| Asplenia ou disfunção esplénica               | - Asplenia congénita ou adquirida<br>- Doença de células falciformes      |
| Imunodeficiências primárias <sup>(a)</sup>    |   |
| Infeção por VIH                               | Com valores de linfócitos T CD4 <sup>+</sup> <500 células/mm <sup>3</sup> |
| Recetor de transplante                        | - Células precursoras hematopoiéticas<br>- Órgãos sólidos                 |
| Doença neoplásica ativa                       | - Leucemias<br>- Linfomas<br>- Mieloma múltiplo                           |
| Síndrome nefrótico                            |   |

(a) Exclui défice isolado de IgA e doentes em terapêutica de substituição com imunoglobulinas sem função B residual.

# Indicação para administração de VPC13 e/ou VPP23 em adultos (EUA)

Indications for the administration of the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for adults in the United States

| Risk group  | Underlying condition                                 | PCV13       | PPSV23      |                |
|---|--|-------------|-------------|----------------|
|   |  | Recommended | Recommended | Revaccination  |
| <b>Immunocompetent persons</b>                      | Chronic heart disease*                               |             | X           |                |
|   | Chronic lung disease <sup>¶</sup>                    |             | X           |                |
|   | Diabetes mellitus                                    |             | X           |                |
|   | Cerebrospinal fluid leak                             | X           | X           |                |
|   | Cochlear implant                                     | X           | X           |                |
|   | Alcoholism   |             | X           |                |
|   | Chronic liver disease, cirrhosis                     |             | X           |                |
|   | Cigarette smoking                                    |             | X           |                |
|   | Age ≥65  | X           | X           | Δ              |
| <b>Persons with functional or anatomic asplenia</b> | Sickle cell disease/other hemoglobinopathy           | X           | X           | X <sup>◊</sup> |
|   | Congenital or acquired asplenia                      | X           | X           | X <sup>◊</sup> |
| <b>Immunocompromised persons</b>                    | Congenital or acquired immunodeficiency <sup>§</sup> | X           | X           | X <sup>◊</sup> |
|   | Human immunodeficiency virus infection               | X           | X           | X <sup>◊</sup> |
|   | Chronic renal failure                                | X           | X           | X <sup>◊</sup> |
|   | Nephrotic syndrome                                   | X           | X           | X <sup>◊</sup> |
|   | Leukemia   | X           | X           | X <sup>◊</sup> |
|   | Lymphoma   | X           | X           | X <sup>◊</sup> |
|   | Hodgkin disease                                      | X           | X           | X <sup>◊</sup> |
|   | Generalized malignancy                               | X           | X           | X <sup>◊</sup> |
|   | Iatrogenic immunosuppression <sup>‡</sup>            | X           | X           | X <sup>◊</sup> |
|   | Solid organ transplant                               | X           | X           | X <sup>◊</sup> |
|   | Multiple myeloma                                     | X           | X           | X <sup>◊</sup> |

\* Including congestive heart failure and cardiomyopathies, excluding hypertension.

¶ Including chronic obstructive pulmonary disease, emphysema, and asthma.

Δ All adults aged ≥65 years should receive a dose of PPSV23 even if they were vaccinated when they were less than 65 years of age; however, a minimum interval of five years between PPSV23 doses should be maintained. Those who are receiving PPSV23 for the first time at or after age 65 should receive only a single dose (and do not require revaccination).

◊ Patients <65 years of age who have functional or anatomic asplenia or who are immunocompromised should be revaccinated one time five years after the initial dose, and again at or after age 65 (and at least five years after the previous dose).

§ Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).

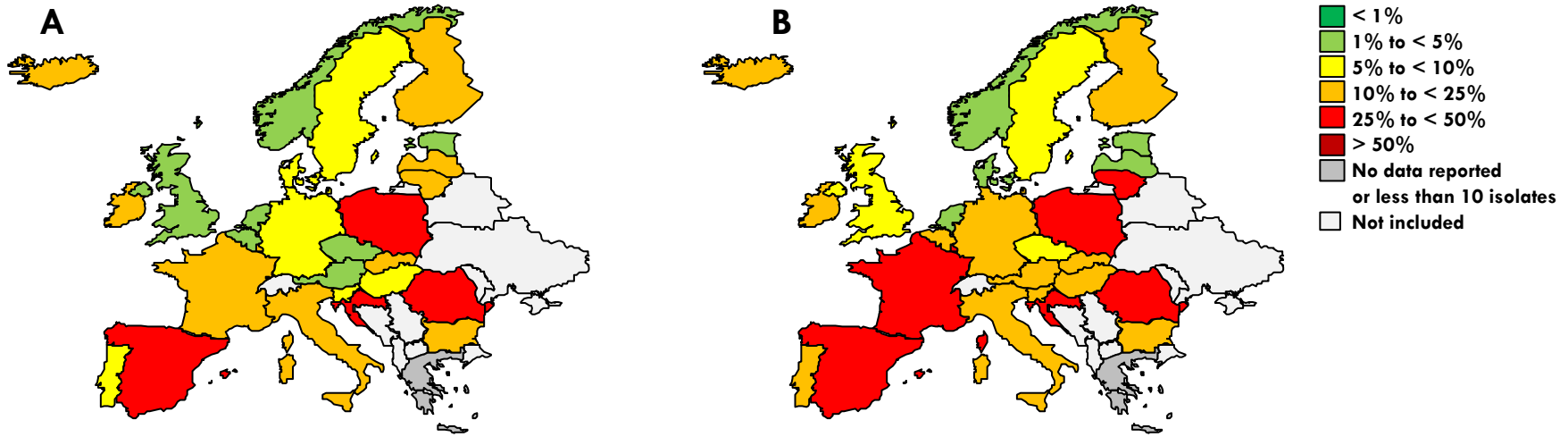
‡ Diseases requiring treatment with immunosuppressive drugs, including long-term systemic glucocorticoids and radiation therapy.

Adapted from:

- Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2014; 63:822.
- Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2012; 61:816.
- Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR Morb Mortal Wkly Rep* 2010; 59:1102.
- Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant* 2009; 15:1143.

# Pneumococcal antimicrobial resistance is an ongoing concern

*Streptococcus pneumoniae* isolates (%) in Europe that are intermediate or resistant to A) penicillin and B) macrolides, 2013<sup>1</sup>



- Antibiotic-resistant *S. pneumoniae* is a global problem<sup>2</sup>
- Throughout Europe there were large inter-country variations in the susceptibility of *S. pneumoniae* to penicillin or macrolides, ranging from 1% to 40%<sup>3</sup>
  - For serogroup 19, 52% of isolates had decreased susceptibility to penicillins and/or macrolides<sup>3</sup>

1. European Centre for Disease Prevention and Control. Proportion of penicillins resistant (R + I) *Streptococcus pneumoniae* in participating countries in 2013. [http://www.ecdc.europa.eu/en/healthtopics/antimicrobial\\_resistance/database/Pages/map\\_reports.aspx](http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx). Accessed April 2015. 2. Song JH, et al. Vaccine 2012;30:2728–37. 3. ECDC. Antimicrobial resistance surveillance in Europe 2013. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm, Sweden: ECDC; 2014.

# Vacina pneumocócica conjugada (VPC)

- Vacinas não incluídas no PNV até 2014
- Desde 2001, a imunização com VPC7 (extra-SNS), ocorreu de forma progressiva, estimando-se a cobertura vacinal em cerca de 75% em 2008 (população pediátrica)
- 2009: VPC 10
- 2010: VPC 13
- 2015: VPC 13 PNV (Norma 008/2015)

