
Pneumococcal Vaccination in Patients with Pulmonary Disease

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Comorbidities Can Increase IPD Incidence in Adults of All Ages

Age	2–15 Years		16–64 Years		≥65 Years	
	IR	OR	IR	OR	IR	OR
No Risk Group	3.9	1.0	5.2	1.0	17.9	1.0
Asplenia / Splenic Dysfunction	19.0	4.7	12.0	2.3	13.0	0.7
Chronic Respiratory Disease	50.0	12.7	91.0	16.8	91.0	5.1
Chronic Heart Disease	16.0	4.1	36.0	6.9	54.0	3.0
Chronic Kidney Disease	46.0	11.7	34.0	6.5	16.0	0.9
Chronic Liver Disease	117.0	29.6	172.0	33.3	129.0	7.2
Diabetes	15.0	3.8	24.0	4.6	41.0	2.3
Immunosuppression	162.0	41.0	88.0	17.1	209.0	11.7
HIV Infection	398.0	100.0	316.0	61.2	95.0	5.3

IR = Incidence Rate
OR = Odds Ratio

IPD Risk group	Condition
Chronic heart disease	congestive heart failure, cardiomyopathy
Chronic lung disease	Asthma, COPD, Cystic Fibrosis, Bronchiectasis, Idiopathic pulmonary fibrosis, and Pneumoconiosis
Diabetes mellitus	
Cerebrospinal fluid leaks	
Cochlear implant	
functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies Congenital or acquired asplenia, or splenic dysfunction
Chronic renal disease	chronic renal failure from any cause and Nephrotic syndrome
Chronic liver disease	primary biliary cirrhosis, primary sclerosing cholangitis, sarcoid, hepatitis B or C virus, alcoholic cirrhosis, cryptogenic cirrhosis, autoimmune hepatitis, and hemochromatosis
Acquired Immunodeficiency	HIV, immunosuppressive therapy, long-term steroid use, and radiation
Congenital immunodeficiency	B or T lymphocyte deficiency, complement C1, C2, C3, and C4 deficiencies
Malignancy	leukemia, lymphoma, Hodgkins, multiple myeloma, and disseminated malignancies
Solid organ transplantation	heart, liver, kidney, and other
Splenectomy	due to any cause

Factors associated with increased risk of *pneumococcal* disease in adults

- Socioeconomic
 - ▣ Poverty
 - ▣ Crowding
- Environmental
 - ▣ Preceding viral respiratory illness
 - ▣ **High air pollution levels**
 - ▣ **Winter season**
 - ▣ Residence in an institution
- Behavioral
 - ▣ **Smoking**
 - ▣ Heavy alcohol use



Chronic Respiratory Diseases and *Pneumococcal* Infections

Potential Physiologic Associations Between Respiratory Diseases and Bacterial Infections

Multifactorial explanations for increased risk of pneumococcal disease in persons with chronic respiratory diseases^{1,2}

- Decreased lung function increases the risk of bacterial respiratory infections²
- Deficient non-immunologic host responses (e.g. gag and cough reflexes) in persons with chronic disorders contribute to risk of pneumococcal disease¹

- Viral infections early in life have been linked with the development of asthma²

- Bacterial and viral infections can cause exacerbations of asthma²

1. Fedson D. *Vaccines*. 4th ed. 2003.

2. Guilbert TW, Denlinger LC. *Expert Rev Respir Med*. 2010;4:71-83.

***Streptococcus pneumoniae* and COPD**

Bacterial infection is a factor in 70 - 75% of exacerbations

- up to 60% caused by *S.pneumoniae*, *H. influenzae* or *M. catarrhalis*¹

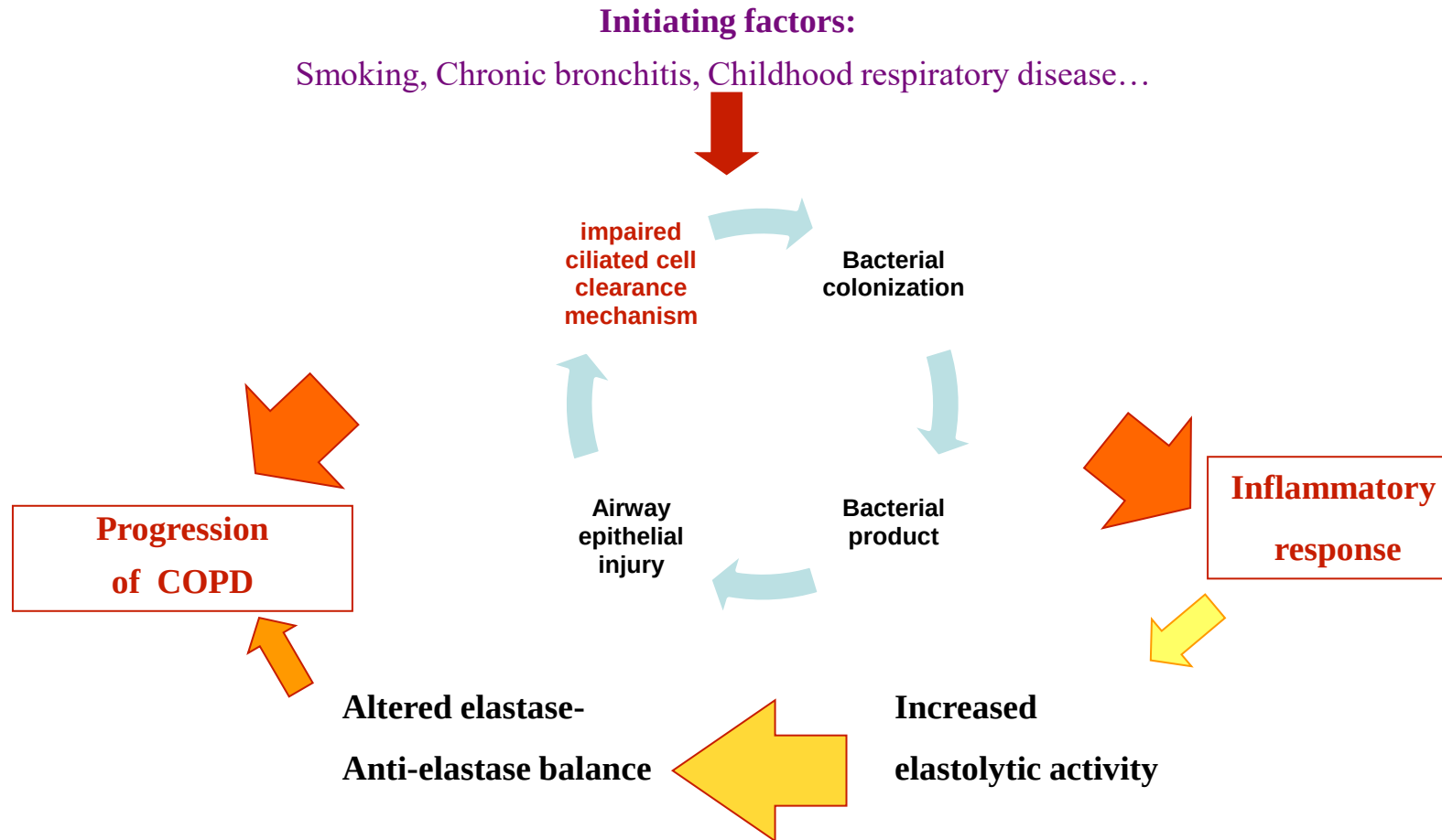
The presence of an upper respiratory tract infection leads to:

- more severe exacerbation
- longer symptom recovery time at exacerbation²

¹ Garcia-Vidal C, et al. Clin Microbiol Infect 2009; 15: 1033–8.

² Domenech et al. J Antimicrob Chemother 2011; 66: 487–493

COPD patients enter into a vicious circle



Schematic diagram of the vicious circle hypothesis of the role of bacterial colonization in the progression of COPD.

Adapted from Sanjay, 2000

Association between *pneumococcal* infections and the presence of asthma

Asthma is associated to a doubled risk of *pneumococcal* infection after adjusting for the other risk factors of *pneumococcal* infection¹

The presence of asthma is an independent factor of invasive pneumococcal infections. The risk is higher in patients with a poorly controlled asthma but remained very significant in patients presenting with mild asthma²

¹ Talbot TR, et al. *N Engl J Med*.2005;352:2082-2090.

² Klemets P, et al. *Thorax* 2010;65:698–702.

IPD and Asthma in Persons 2 - 49 Years of Age, US

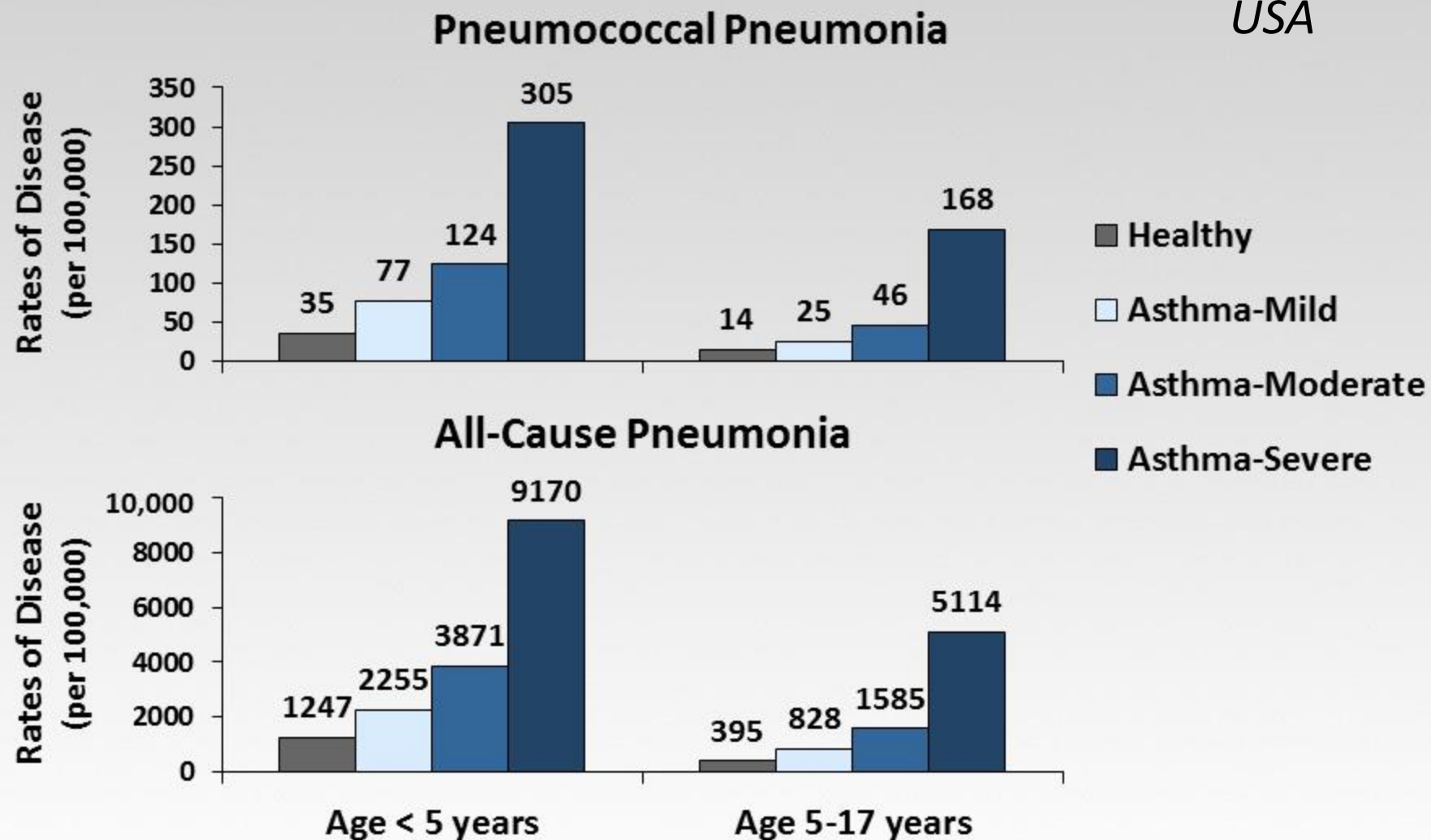
Association Between the Presence of Asthma and the Risk of IPD

Age (yrs)	Adjusted odds ratio (OR) for IPD (95% CI) in persons with asthma
2-4	2.3 (1.4-4.0)
5-17	4.0 (1.5-10.7)
18-49	2.4 (1.8-3.3)

- Among children 5-17 years of age, the presence of asthma resulted in a 4x higher risk of IPD
- The cumulative excess risk of IPD over 10 years in persons with asthma is 10-30 cases per 10,000 persons

Results by Severity of Asthma

USA

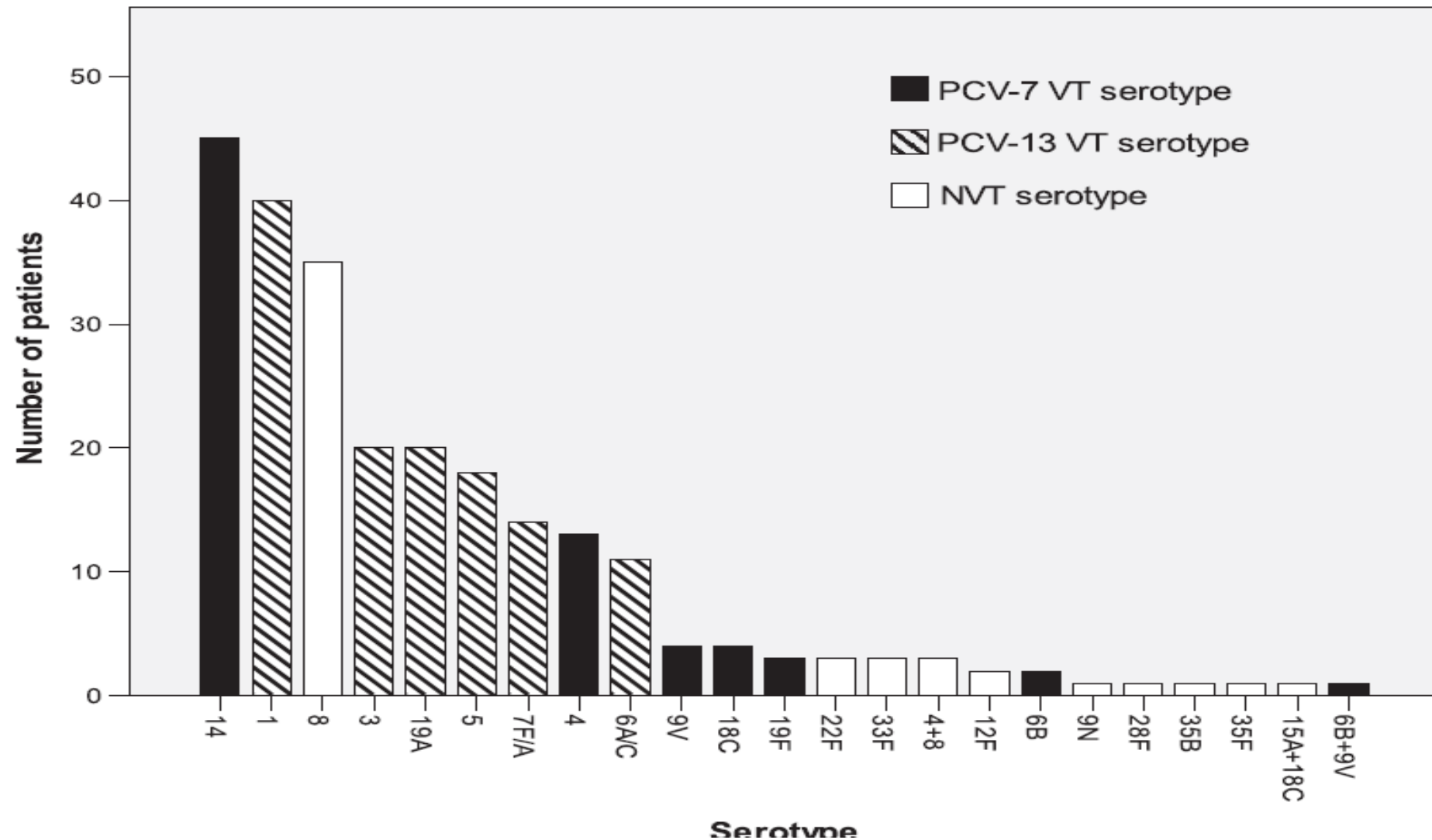


**Distribution of serotypes of
S. pneumoniae in Patients with Respiratory
Infections**

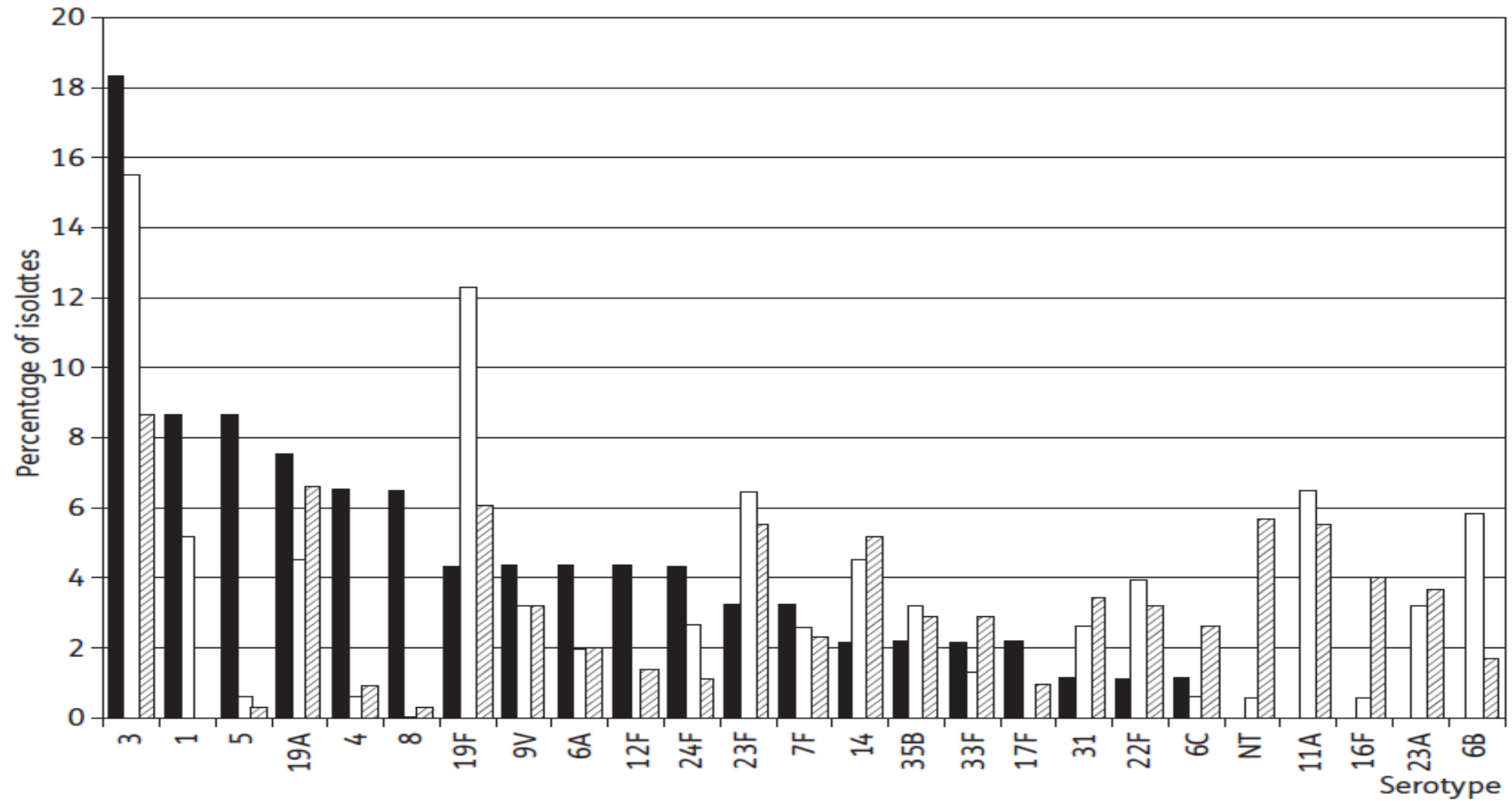
Most Invasive Pneumococcal Serotypes

- Top five capsular serotypes causing *Pneumococcal* septicaemia and meningitis were **14, 19F, 6B, 23F and 18C**, yet 80-90% of cases of *Pneumococcal* empyema are caused by **serotypes 1, 3, 7F and 19A**.
- Studies show that serotypes **9V and 19F** were associated with relapses, suggesting that serotype could play an important role in the persistence of pneumococcal isolates
- In Spain, Serotypes **1, 3, and 7F** were more frequent in pneumonia.

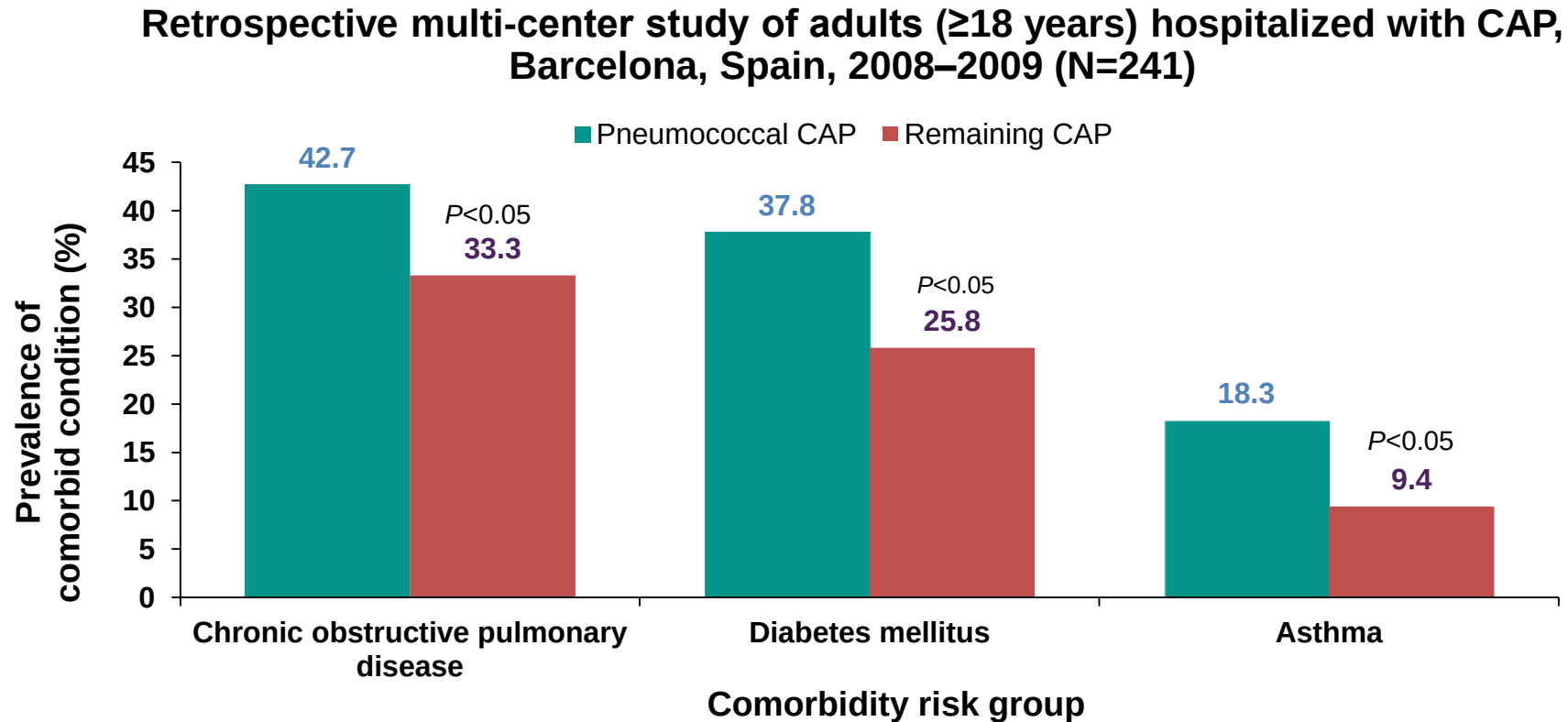
Serotype prevalence in adults hospitalized with pneumococcal non-invasive community-acquired pneumonia



Distribution of serotypes of pneumonia and AECOPD *S. pneumoniae* isolates isolated from adult patients with COPD

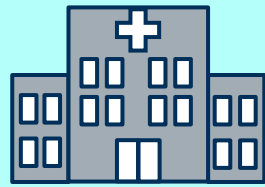


Chronic Medical Conditions Are Significantly More Frequent in Patients With Pneumococcal CAP Compared With Patients With CAP Due to Other Causes



- *Streptococcus pneumoniae* was the most frequently detected etiologic agent. Pneumococcal CAP was identified in 34% of in-patients

Pneumonia Can Have a Substantial Impact in Patients With COPD



COPD patients with pneumonia are
9x more likely to be hospitalized

for any cause in the next 12 months¹

Adjusted OR 9.2 (95% CI 8.9–9.4); $P < 0.0001$; $n = 84,130$ per cohort



First-time COPDAE patients with pneumonia have
50% higher 30-day mortality rates

than COPDAE patients without pneumonia^{2*}

12.1% vs 8.3%; aHR=1.20 (95% CI 1.17–1.24)

*For COPDAEs requiring hospitalization.

aHR=adjusted hazard ratio; CI=confidence interval; COPD=chronic obstructive pulmonary disease; COPDAE=acute exacerbation of COPD; OR=odds ratio.

1. Lin J, et al. *Clinicoecon Outcomes Res.* 2014;6:349-356. 2. Sogaard M, et al. *Int J Chron Obstruct Pulmon Dis.* 2016;11:455-465.

Patients With CAP, Including Pneumococcal Pneumonia, Report Worsening of Comorbid Conditions

Prevalence of health condition worsened by pneumonia*

Health condition	Reported worsening (%)
Asthma	22.0
COPD	24.4
Chronic bronchitis	12.2
Chronic emphysema	8.6
High blood pressure	20.1
Heart disease	5.9
Diabetes	9.8
Other	8.5

*Self-reported during CAP burden of illness questionnaire (CAP-BIQ), US adults aged 50 years and older, 2011.

CAP=community-acquired pneumonia; COPD=chronic obstructive pulmonary disease.

Wvrvich KW. et al. *Patient*. 2013;6(2):125-134.

Antibiotic-resistant *pneumococci* and COPD

- Antibiotic-resistant pneumococci have been associated with patients with underlying diseases including COPD ^{1,2}
- Pneumococcal causing Acute Exacerbation COPD showed higher rates of resistance than those causing pneumonia ³
- Worryingly, recent reports show that more than half of *pneumococcal* isolates are now resistant to Penicillin. Many penicillin-resistant *pneumococci* be resistant to other antimicrobial drugs²

¹Yezli S, et al. J Chemother 2012;24:125-36.

²Shibl AM, et al. Vaccine 2012;30 Suppl 6:G32-6.

³Pe´rez-Trallero et al. AAC, 2011, p. 2729–2734

❖ **PPSV23** has **limited efficacy** in children <2 years, nonbacteremic *pneumococcal* pneumonia, otitis media, **exacerbations of COPD**, multiple myeloma, lymphoma, and chronic alcoholism ^{1,2}

❖ The 13 serotypes of PCV13 account for about 81% to 91% of the *pneumococcal* isolates that cause serious infection ^{1, 2}

¹Vila-Corcoles A, et al. Vaccine 2009;27:1504-10.

²Jackson LA, et al. N Engl J Med 2003;348:1747-55.

Comparative Immunogenicity of Conjugate and Polysaccharide Pneumococcal Vaccines in COPD Patients

✓ PCV13 induces a greater functional antibody response than PPSV23 in patients with **COPD** that persists for 2 years after vaccination.

Due to the high burden of Community Acquired Pneumonia caused by serotypes included in the two available vaccines, wider protection may be provided **using both vaccines** in certain situations ¹

Interestingly, the immune response to include serotypes is higher in the elderly who receive **PCV13 followed by PPSV23** ¹

³¹Jackson LA, *et al.* Vaccine 2013;31:3594-602.

Benefits of PCV13 in Adults aged ≥ 65 years, IPD and CAP- CAPITA trial

Outcome	No. of subjects	Vaccine efficacy (95% CI)
PCV13-serotype Invasive Pneumococcal disease	85,000 adults	74%(30-90%)
Inpatient CAP	85,000 adults	45%(14-65%)
Outpatient CAP	85,000 adults	45%(14-65%)

Bonten M, Bolkenbaas M, Huigts S, et al. CAPITA abstract #0541

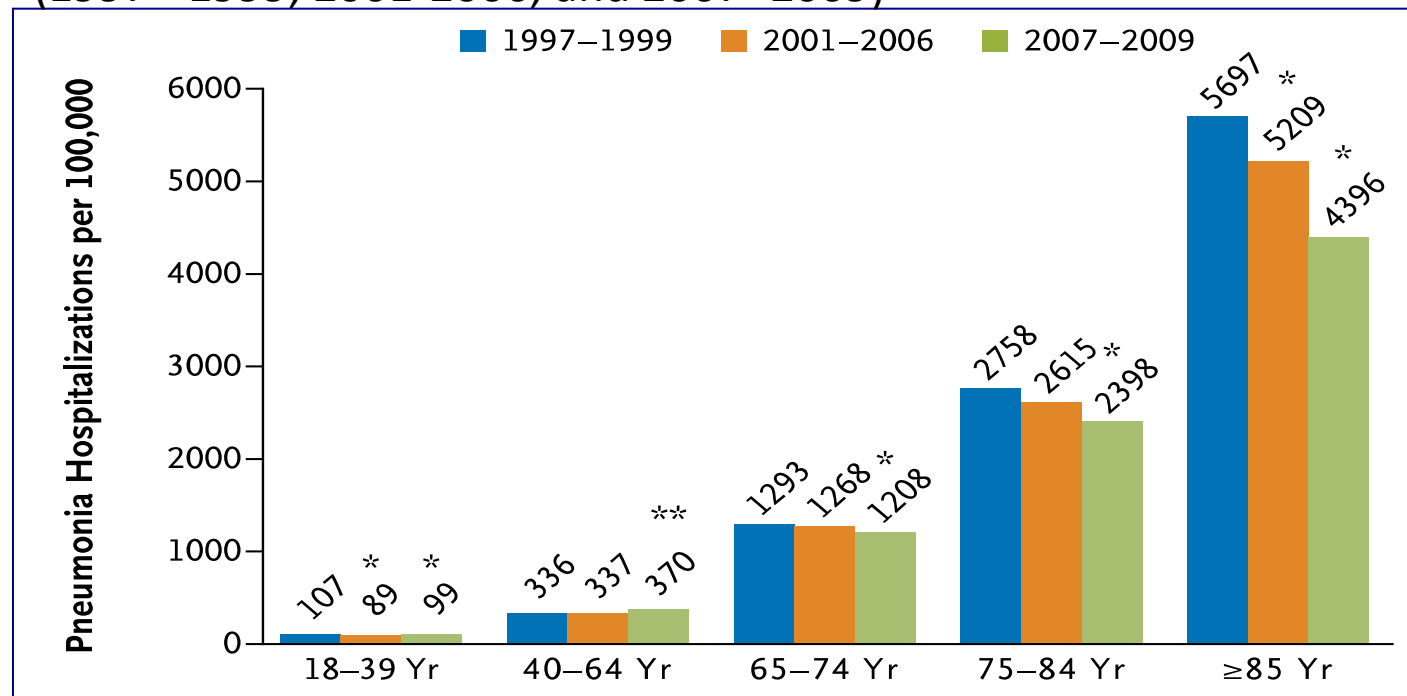
<http://www.cdc.gov/vaccines/acip/recs/GRADE/pneumo-vac-adult.pdf>

PCV impact on hospitalization for pneumonia

Adult & Elderly indirect impact

USA 1997-2009 (pre- and PCV7 era)

Average annual rates of hospitalization for pneumonia in adults
(1997 - 1999, 2001-2006, and 2007 -2009)



*: *p* significant

Cost Effectiveness of Pneumococcal Conjugate Vaccination in COPD Patients

- The administration of 13-valent pneumococcal conjugate vaccine (PCV13) in a **≥ 50 years of age COPD would have higher health benefits** than the current vaccination policy with polysaccharide vaccine in Spain.
- The incremental costs of this vaccination strategy are counterbalanced in part by savings from averted pneumococcal disease cases.
- Vaccination with PCV13 in COPD patients aged ≥ 50 years was a cost-effective strategy in Spain.¹



Pneumococcal Vaccination: Guidelines and Recommendations

ACIP Recommendations for Use of Prevenar 13 in Adults

ACIP Voted to Recommend the Use of Prevenar 13 for Adults 19 Years of Age and Older with Immunocompromising Conditions

- **Recommendation for PPSV23-naïve adults:**
 - We recommend adults 19 years of age or older with immunocompromising conditions*, functional or anatomic asplenia, CSF leaks or cochlear implants, and who have not previously received Prevenar 13 or PPSV23 **receive a single dose of Prevenar 13 followed by a dose of PPSV23 at least 8 weeks later**
- **Recommendation for adults previously vaccinated with PPSV23:**
 - We recommend adults 19 years of age or older with immunocompromising conditions*, functional or anatomic asplenia, CSF leaks or cochlear implants, and who have previously received one or more doses of PPSV23, **receive a dose of Prevenar 13, 1 or more years after the last PPSV23 dose was received**
 - For those that require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after Prevenar 13 and at least 5 years since the most recent dose of PPSV23

* ACIP defines immunocompromising conditions as: congenital or acquired immunodeficiencies; HIV infection; chronic renal failure or nephrotic syndrome; leukemias, lymphomas, Hodgkins disease; generalized malignancy; diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids or radiation therapy; solid organ transplantation; and multiple myeloma.

ACIP, Advisory Committee on Immunization Practices; PPSV, pneumococcal polysaccharide vaccine; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

Table 3.2. Vaccination for stable COPD

- Influenza vaccination reduces serious illness and death in COPD patients (**Evidence B**).
- The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been shown to reduce the incidence of community-acquired pneumonia in COPD patients aged < 65 years with an FEV₁ < 40% predicted and in those with comorbidities (**Evidence B**).
- In the general population of adults ≥ 65 years the 13-valent conjugated pneumococcal vaccine (PCV13) has demonstrated significant efficacy in reducing bacteremia and serious invasive pneumococcal disease (**Evidence B**).

Pneumococcal vaccine

Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all patients ≥ 65 years of age (**Table 3.2**). The PPSV23 is also recommended for younger COPD patients with significant comorbid conditions including chronic heart or lung disease.³⁴ Specific data on the effects of PPSV and PCV in COPD patients are limited and contradictory.³⁵ A systematic review of injectable vaccines in COPD patients identified seven studies for inclusion (two trials of a 14-valent vaccine and 5 trials of a 23-valent injectable vaccine) and observed reductions in the incidence of pneumonia and acute exacerbations that did not reach statistical significance.³⁶ PPSV23 has been shown to reduce the incidence of community-acquired pneumonia in COPD patients < 65 years, with an FEV₁ < 40% predicted, or comorbidities (especially cardiac comorbidities).³⁷ The PCV13 has been shown to exhibit at least the same or greater immunogenicity than the PPSV23 up to two years after vaccination in COPD patients.³⁸ In a large RCT PCV13 demonstrated significant efficacy for the prevention of vaccine-type community-acquired pneumonia (45.6%) and vaccine-type invasive pneumococcal disease (75%) among adults ≥ 65 years and the efficacy persisted for at least 4 years.³⁹

efficacy for the prevention of vaccine-type community-acquired pneumonia (45.6%) and vaccine-type invasive pneumococcal disease (75%) among adults ≥ 65 years and the efficacy persisted for at least 4 years.³⁹

Conclusion

- *Pneumococci* are among the **most frequently** responsible microorganisms for COPD exacerbations
- Pneumococcal causing AECOPD showed **higher rates of resistance** than those causing pneumonia
- PCV13 is **effective** in preventing vaccine-serotype pneumococcal among adults, bacteremic and nonbacteremic CAP, and IPD (Capita trial)
- **PCV13 reduce the rate of the pneumococcal disease**, especially those caused by drug resistant strains due to the protective action of the vaccine against serotypes responsible for drug resistance
- **PCV13 should be given first** in previously non-immunized individuals. Immune response to include serotypes is higher in the elderly who receive **PCV13 followed by PPSV23**