대한결핵 및 호흡기학회

제125차 춘계학술대회

Pneumococcal Vaccination in Chronic Respiratory Diseases

PCV vs. PPSV

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Chung-Ang University

Study Goals:
Guideline, Evidence, Programs

- What is evidence of vaccine efficacy for pneumonia and AECOPD?
- pneumococcal vaccine coverage and awareness are low and need to be improved.
- Respiratory physicians need to communicate the benefits of vaccination more effectively to their patients with chronic respiratory diseases.

SECTION I.

진료지침

Case study

- 58 y/o, male
- 55 pack-years
- Dyspnea on Exertion: Borg 5
- CAT 14, m-MRC 3
- FEV1/FVC 65%, FEV1 35%

- No history of previous pneumococcal vaccination
- No exacerbation within previous one year
- No comorbid diseases

Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]

Group C

LAMA + LABA
LABA + ICS
Further exacerbation(s)
LAMA

Group D

Consider roflumilast if FEV_1 < 50% pred. and patient has chronic bronchitis
Consider macrolide (in former smokers)
Further exacerbation(s)
LAMA + LABA + ICS
Persistent symptoms/further exacerbation(s)
Further exacerbation(s)
LAMA
LAMA + LABA
LABA + ICS

Group A

Continue, stop or try alternative class of bronchodilator
evaluate effect
A bronchodilator

Group B

LAMA + LABA
Persistent symptoms
A long-acting bronchodilator (LABA or LAMA)

Preferred treatment =

In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

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Non-Pharmacologic Treatment

- Education and self-management
- Physical activity
- Pulmonary rehabilitation programs
- Exercise training
- Self-management education
- End of life and palliative care
- Nutritional support
- Vaccination
- Oxygen therapy

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Non-Pharmacologic Treatment - Summary

Table 4.9. Key points for the use of non-pharmacological treatments
Education, self-management and pulmonary rehabilitation
• Education is needed to change patient's knowledge but there is no evidence that used alone it will change patient behavior.
• Education self-management with the support of a case manager with or without the use of a written action plan is recommended for the prevention of exacerbation complications such as hospital admissions **(Evidence B)**.
• Rehabilitation is indicated in all patients with relevant symptoms and/or a high risk for exacerbation **(Evidence A)**.
• Physical activity is a strong predictor of mortality **(Evidence A)**. Patients should be encouraged to increase the level of physical activity although we still don't know how to best insure the likelihood of success.
Vaccination
• Influenza vaccination is recommended for all patients with COPD **(Evidence A)**.
• Pneumococcal vaccination: the PCV13 and PPSV23 are recommended for all patients > 65 years of age, and in younger patients with significant comorbid conditions including chronic heart or lung disease **(Evidence B)**.
Nutrition
• Nutritional supplementation should be considered in malnourished patients with COPD **(Evidence B)**.
End of life and palliative care
• All clinicians managing patients with COPD should be aware of the effectiveness of palliative approaches to symptom control and use these in their practice **(Evidence D)**.
• End of life care should include discussions with patients and their families about their views on resuscitation, advance directives and place of death preferences **(Evidence D)**.

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Management of Exacerbations

Table 5.8. Interventions that reduce the frequency of COPD exacerbations	
Intervention class	**Intervention**
Bronchodilators	LABAs LAMAs LABA + LAMA
Corticosteroid-containing regimens	LABA + ICS LABA + LAMA + ICS
Anti-inflammatory (non-steroid)	Roflumilast
Anti-infectives	Vaccines Long term macrolides
Mucoregulators	N-acetylcysteine Carbocysteine
Various others	Smoking cessation Rehabilitation Lung volume reduction

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COPD 급성악화로 인한 입원 치료 후에는 추가 악화를 예방하기 위해서 적절한 조치가 시작되어야 한다. COPD 급성악화 위험과 빈도를 줄일 수 있는 것으로 알려진 방법들은 다음과 같다.

표 4-8. 급성악화 예방을 위한 약물 또는 비약물적 치료

기관지확장제	흡입지속성베타작용제 흡입지속성항콜린제 흡입지속성베타작용제 및 흡입지속성항콜린제의 병합
스테로이드 포함 약제	흡입지속성베타작용제 및 흡입스테로이드 병합 흡입지속성베타작용제 및 흡입지속성항콜린제 및 흡입스테로이드제 병합
항염증약제	Roflumilast[90]
감염 예방	예방접종 장기간의 macrolides
Mucoregulators	N-acetylcysteine Carbocysteine
기타	금연 호흡재활[84] 폐용적 축소술

2018개정 **COPD 진료지침**

Chronic Obstructive Pulmonary Disease

1) 예방접종

모든 COPD 환자에게 인플루엔자 백신 접종을 권장한다[109]. COPD 환자에서 인플루엔자 백신은 입원이 필요한 하기도 감염과 사망을 감소시키며[110-113] 고령의 환자에서 더 효과적이다[114]. 고령의 COPD 환자가 인플루엔자 백신 접종을 받으면 허혈성심질환의 위험이 감소한다[115].

65세 이상의 모든 COPD 환자에게 폐렴구균 백신 접종을 권장한다. 23가 폐렴구균 다당질백신(PPSV23)은 FEV_1 40% 미만 혹은 동반질환(특히, 심장질환)들을 지닌 65세 미만 COPD 환자들의 지역사회획득 폐렴 발생이 감소한다[116]. 폐렴구균 단백결합 백신(PCV 13)은 접종 후 2년까지 PPSV23보다 동등하거나 우월한 면역성을 보인다[117]. 한 연구에서 PCV 13은 65세 이상의 성인에서 백신형 지역사회획득 폐렴과 침습성 폐렴구균질환의 예방에 유의한 효과가 있었으며, 이 효과는 최소 4년 이상 지속되었다[118].

대한결핵 및 호흡기학회

COPD 진료지침 개정위원회

Better to prevent than to fight pneumococcal disease with antibiotics

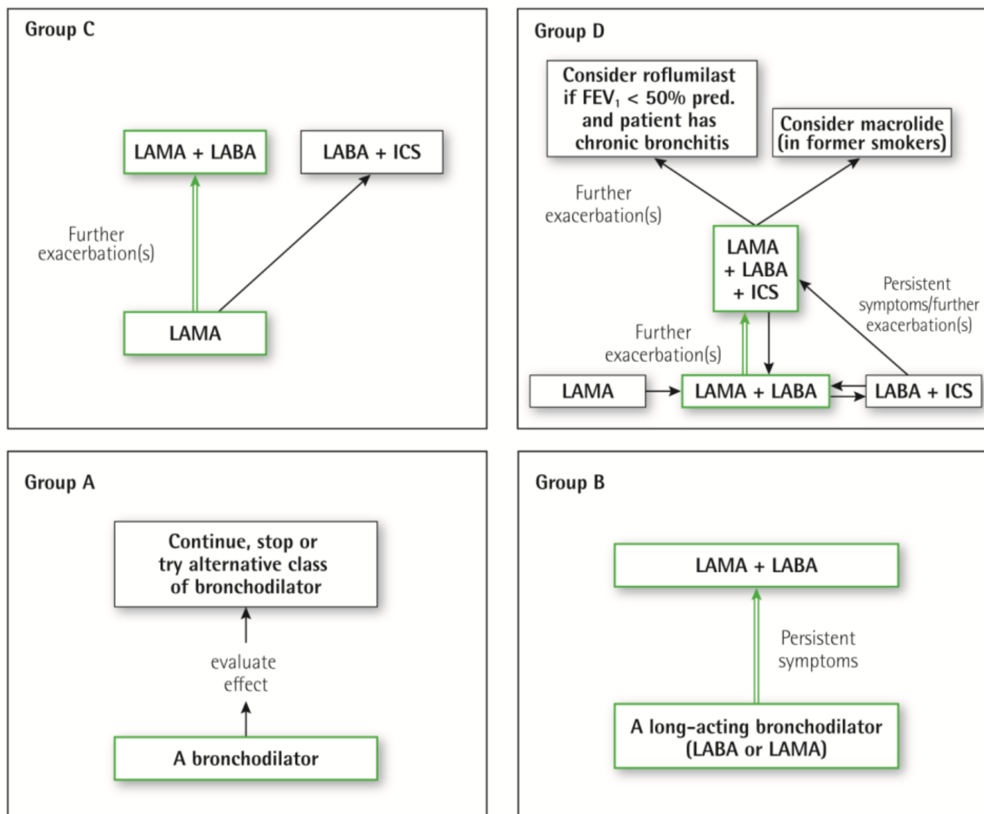
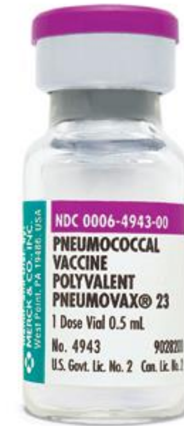
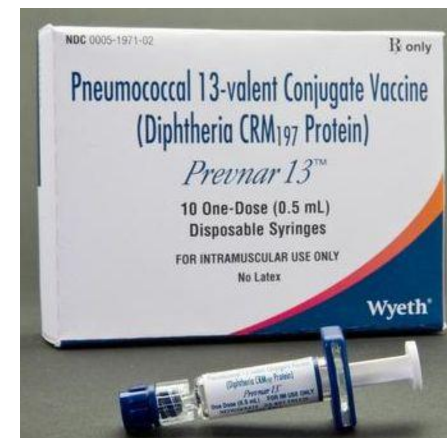


Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]





국내 학회 진료지침서 내 폐렴구균접종 권장

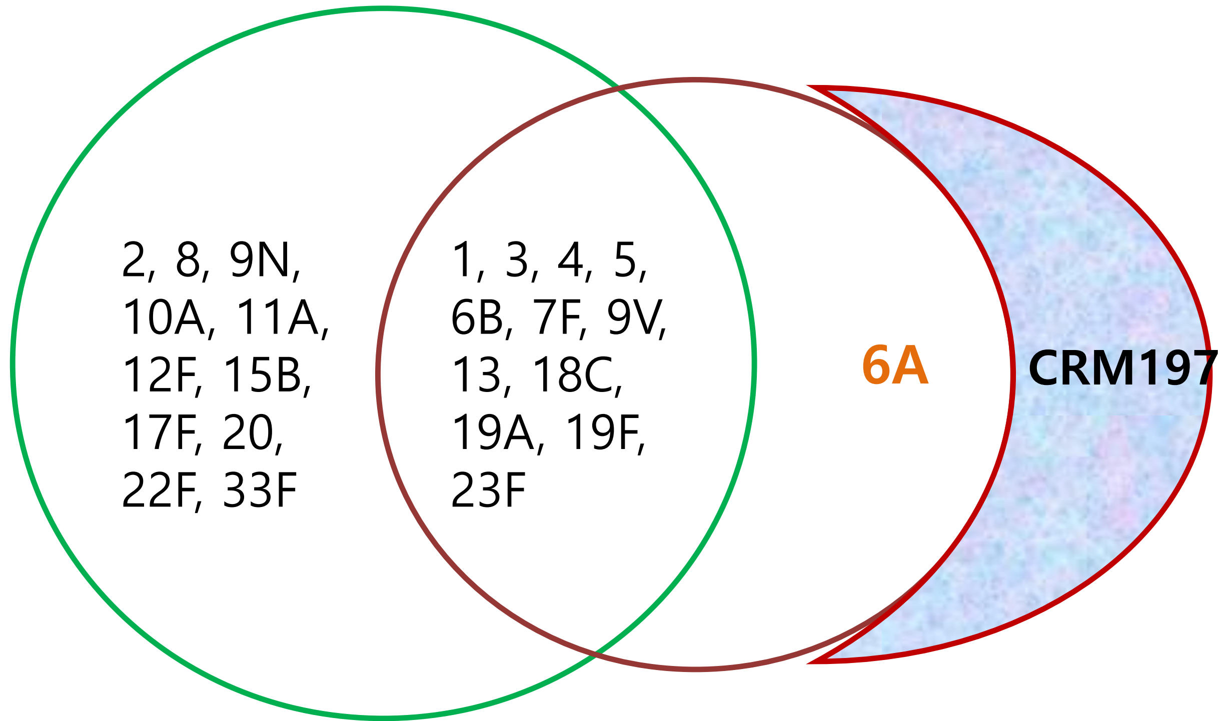
학회, 지침서	만성호흡기질환자 대상	방법
2018 COPD 진료지침	65세이상의 COPD 모두.	폐렴구균백신
2017 금연진료지침	장기간의 흡연력	폐렴구균백신
2017 성인지역사회획득폐렴항생제사용지침	고령, 위험인자	PCV, PPSV 병용
2014 천식진료지침	근거 부족	
2015한국천식진료지침	소아, 노인, 중증천식. 고려(근거수준D/ 권고수준: 높음)	
2014감염학회 성인예방접종. 성인 지역사회획득 폐렴 항생제사용지침. 2018년.	만성호흡기질환	폐렴사슬알균백신. PCV, PPSV병용. 구체적 방법. PCV13 → PPSV23

PspA Dimer
coiled coil α-helix
proline-rich
choline-binding
PspC Dimer
PsaA
Neuraminidase
F-antigen
IgA1 protease
Capsular Polysaccharide
Pneumolysin
Autolysin
C-polysaccharide
Cell Membrane
Cell Wall

J Bacteriol. 1975;122:1339-50.

Clin Microbiol Rev. 1998;11(4):645-57.

PPSV23 PCV13



Polysaccharide vaccines

3 → 4 → 6 → 12 →

PPV14(1977), PPSV23(1988)

Conjugate Vaccines

7 → 9 → 11 → 13

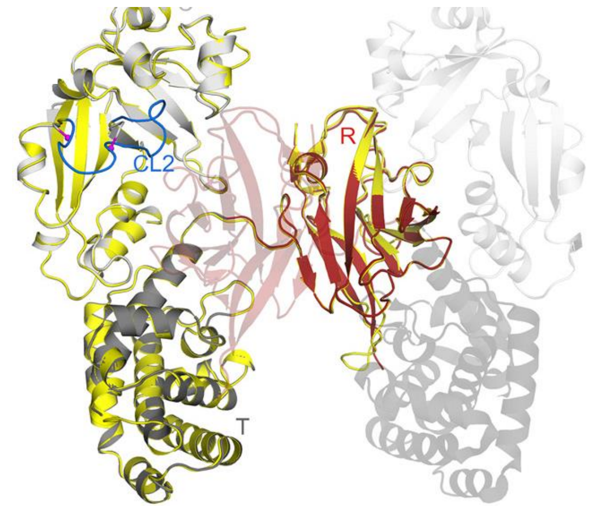
PCV7(2000), PCV13(2010)

CRM197
Cross Reacting Material

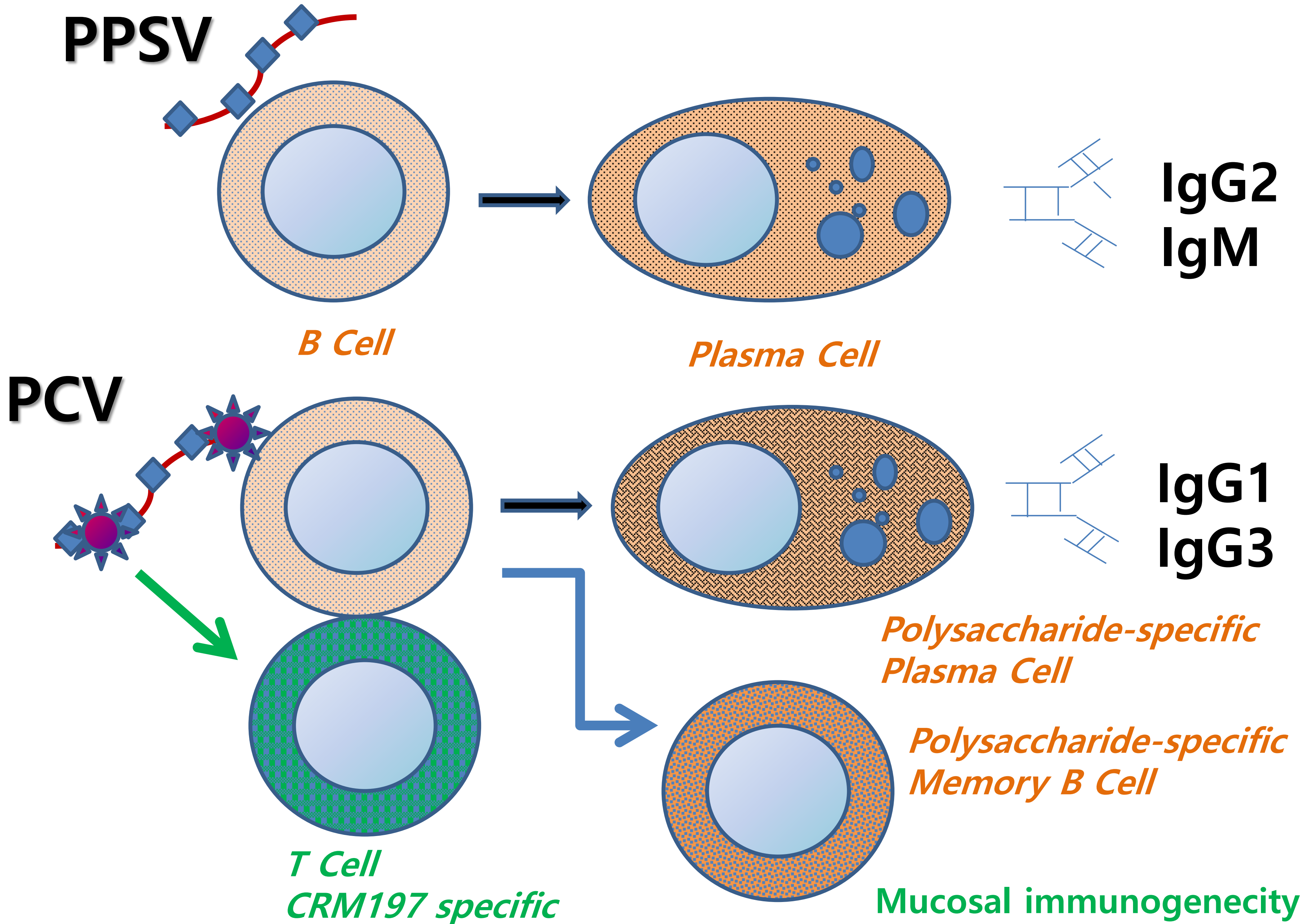
- Diphtheria toxoid:
  Detoxified; ▲G52E: ADP Ribosyltransferase
- Mucosal immunogenecity
- Haptens

- Interference effect
  Influenza vaccine: no
  Zoster vaccine: mild in elderly

- Complex with HB-EGF
  anti-cancer(prostate, ovary, etc.)

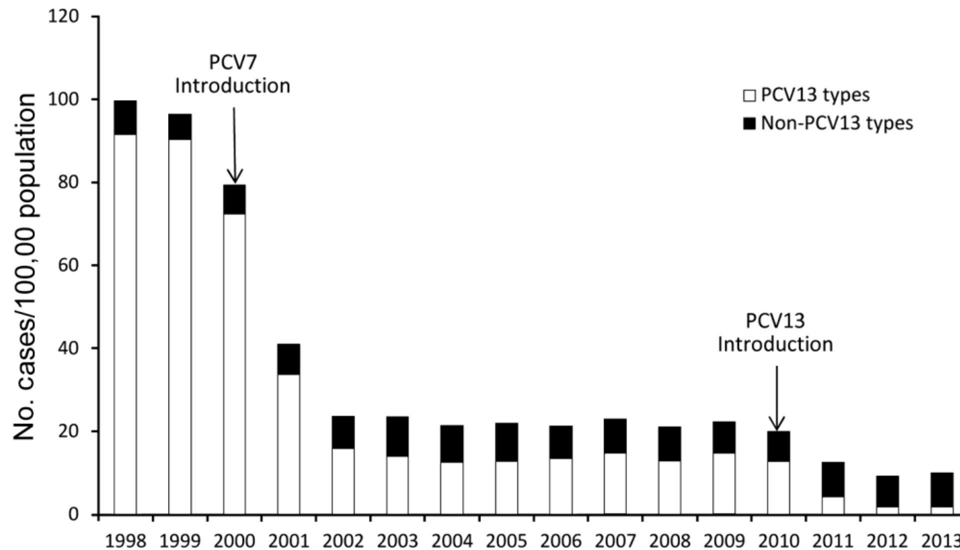


PNAS. 2012;109:5229-34

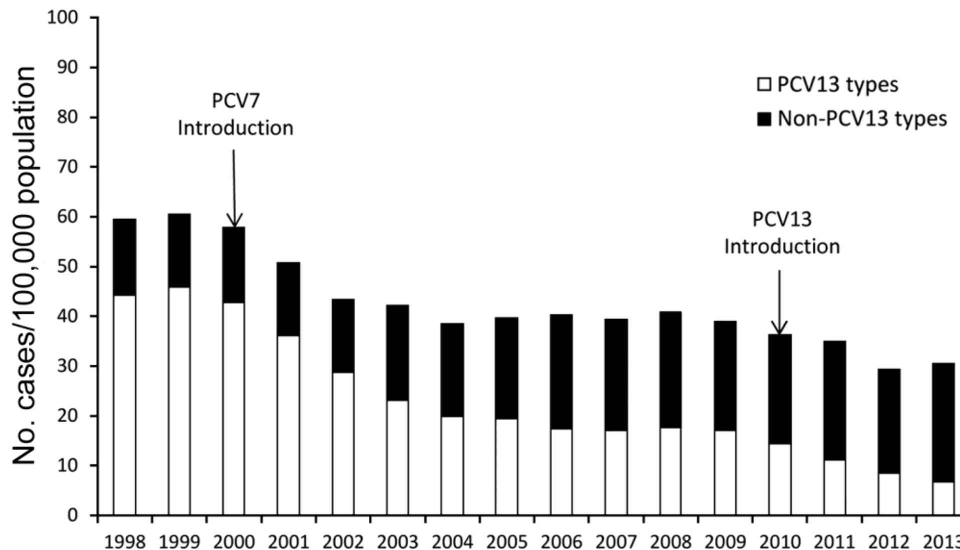

PPSV
IgG2
IgM
B Cell
Plasma Cell
PCV
IgG1
IgG3
Polysaccharide-specific
Plasma Cell
Polysaccharide-specific
Memory B Cell
T Cell
CRM197 specific
Mucosal immunogenecity

Incidence of Invasive Pneumococcal Disease with PCV with PCV(USA)

AGE < 5 YR

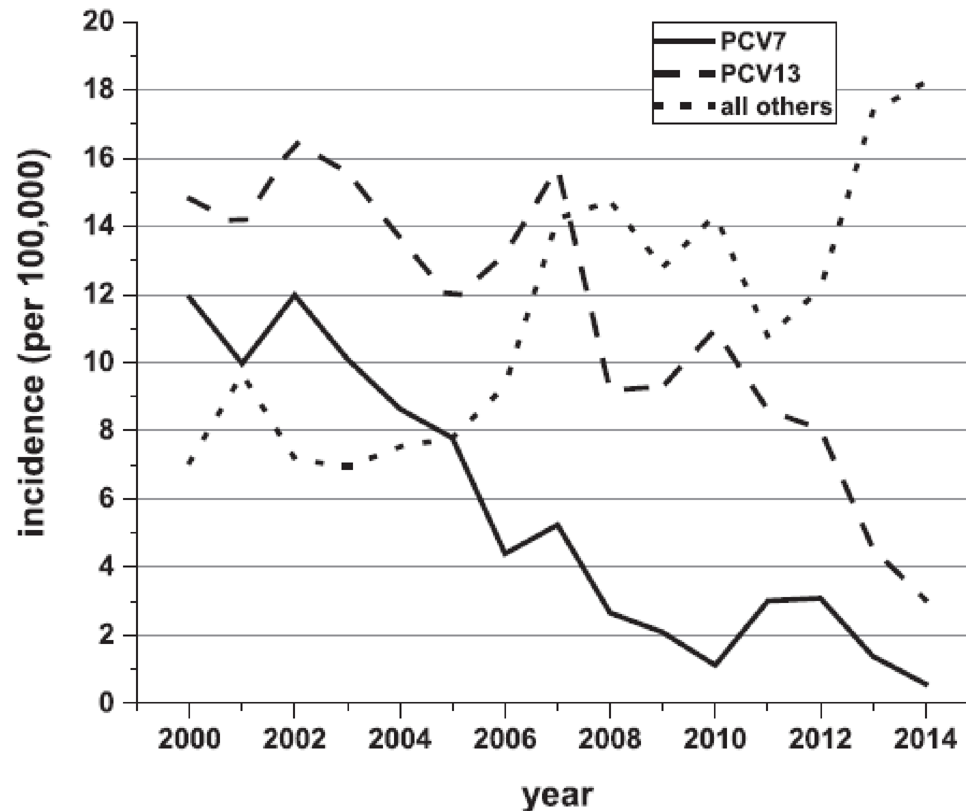


AGE> 65 YR



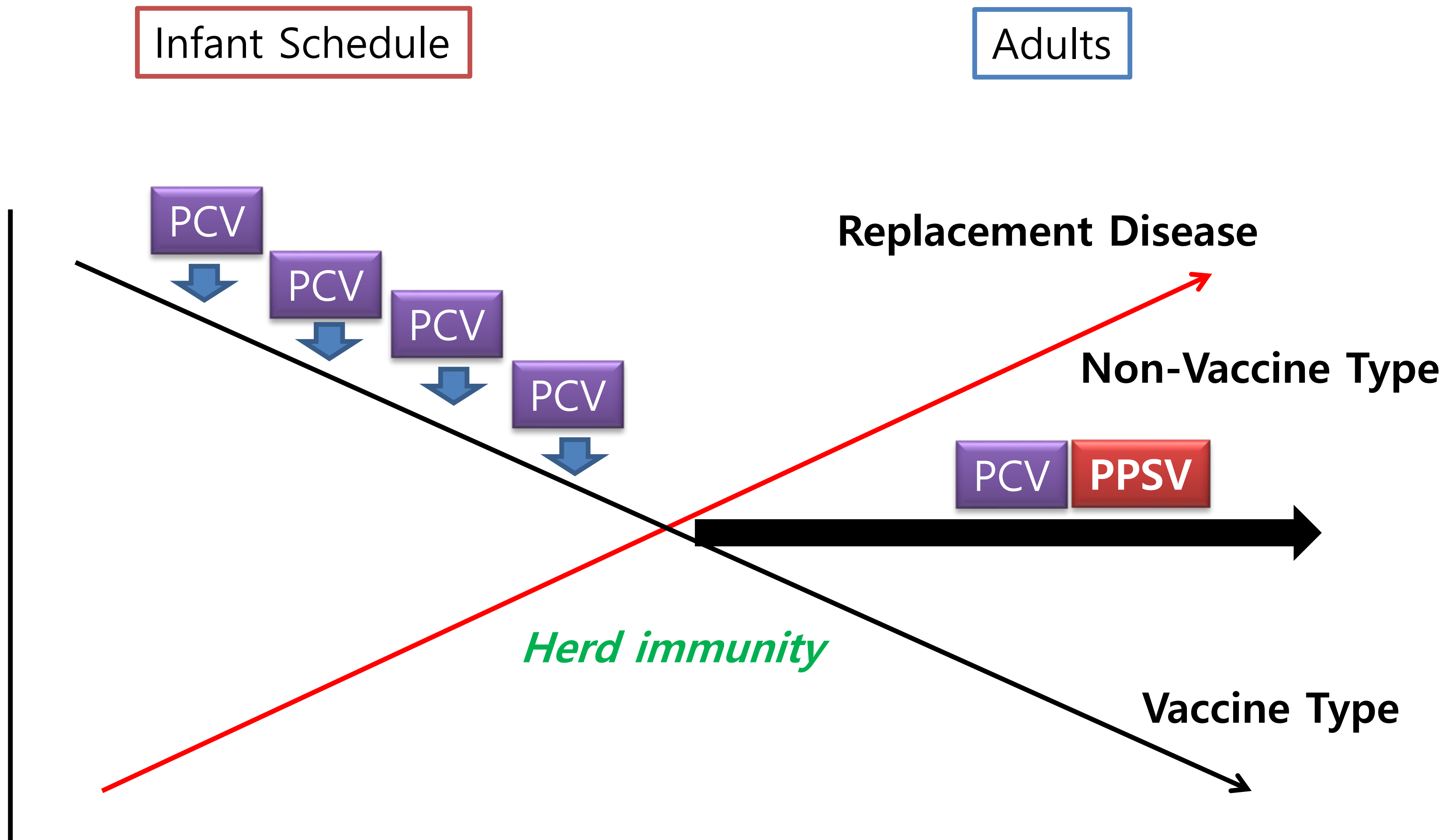
EMERGING INFECT DIS. 2015;21(9):1551-6.

Incidence of invasive pneumococcal disease

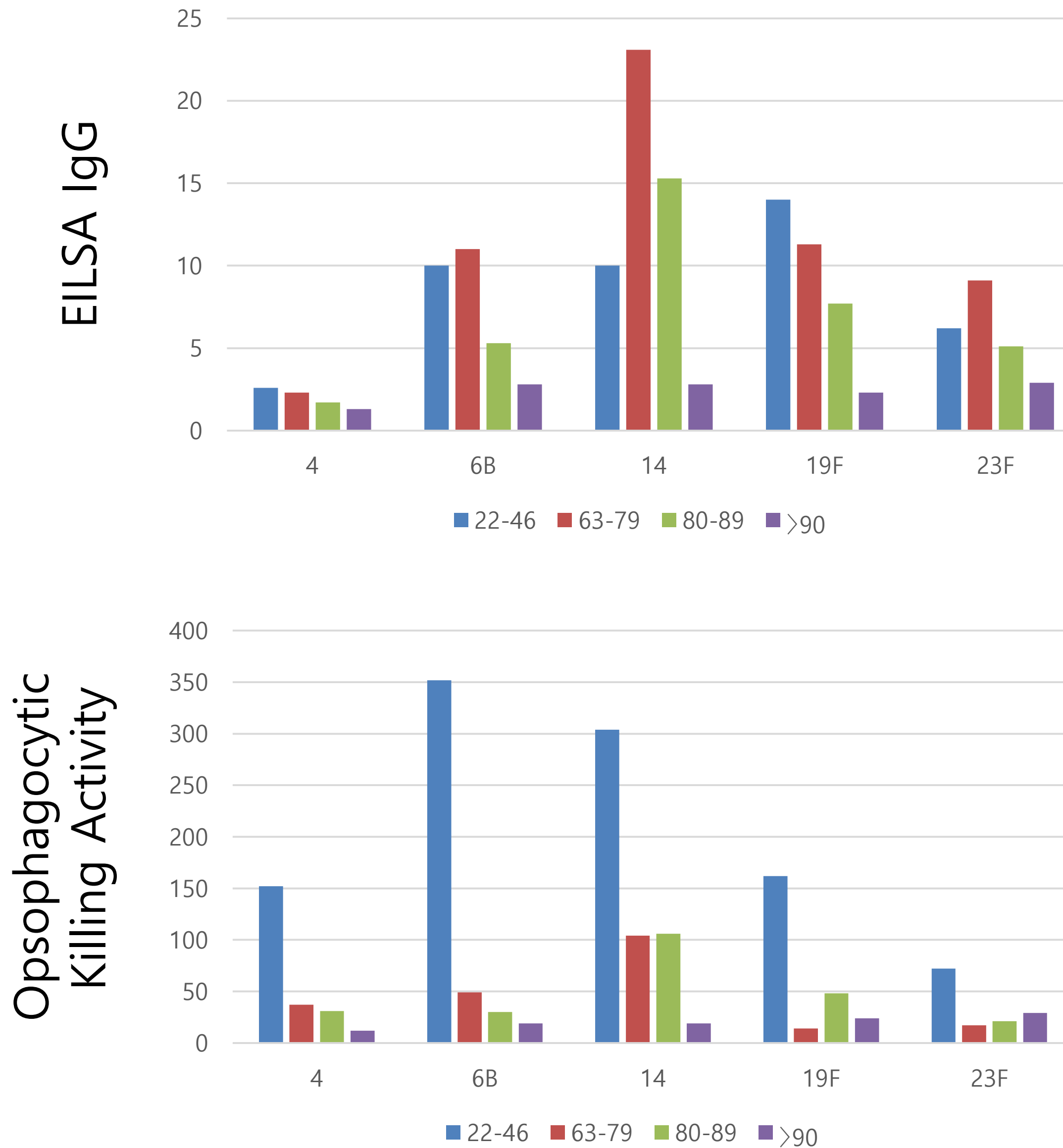


The American Journal of Medicine (2018) 131, 100.e1–100.e7

Serotype Replacement



ANTIBODY TITER AFTER PPSV23



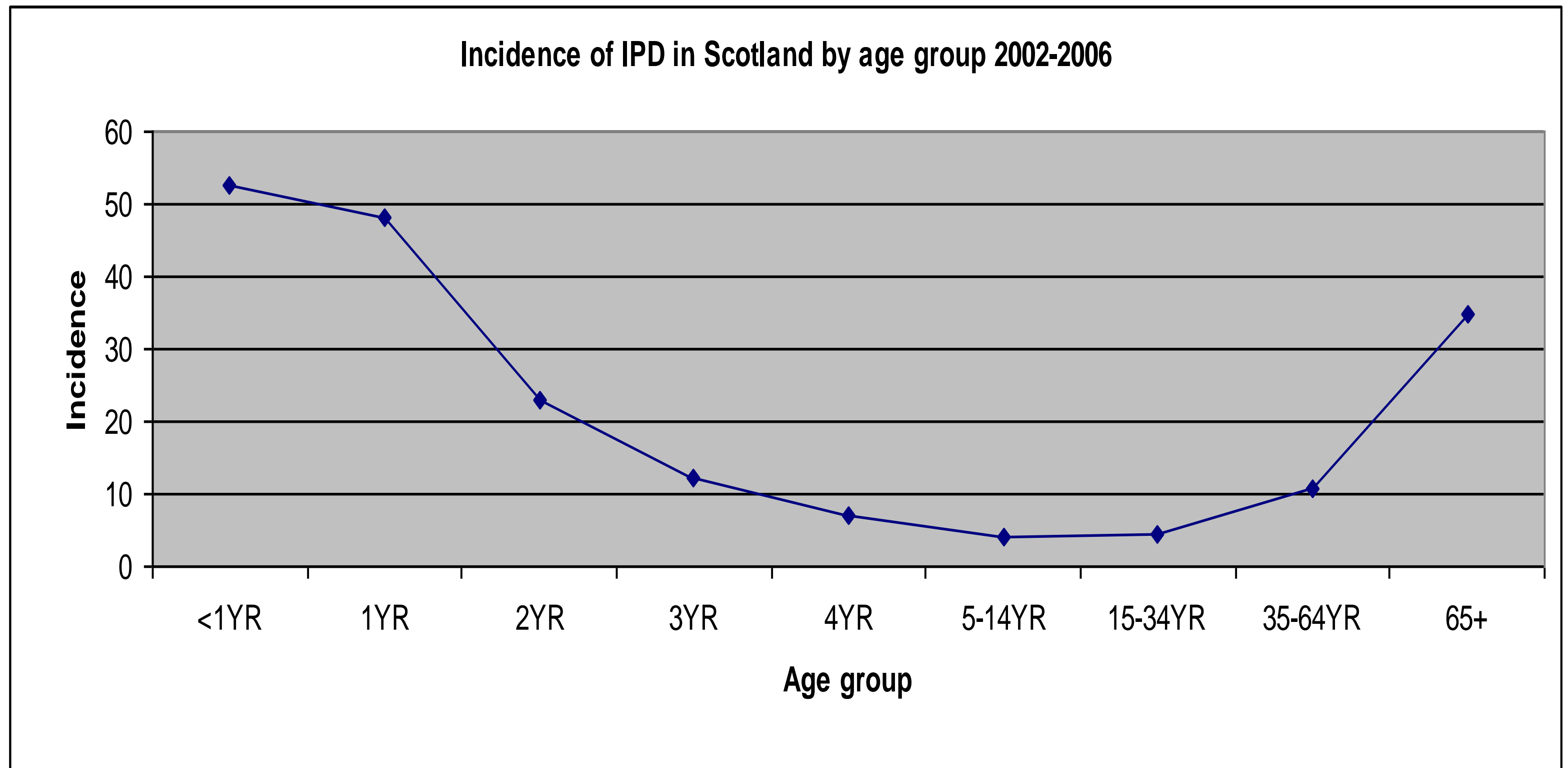
CID. 1999;29:281-8.

DURABILITY OF PPSV VACCINE EFFECTIVENESS %(95% CI)

AGE(YR)	<3YR	3-5YR	>5YR
<55	93 (82;97)	89 (74;96)	85 (62;94)
55-64	88 (70;95)	82 (57;93)	75 (38;90)
65-74	80 (51;92)	71 (30;88)	58 (-2;83)
75-84	67 (20;87)	53 (-15;81)	32 (-67;72)
>85	46 (-31;78)	22 (-90;68)	-13 (-174;54)

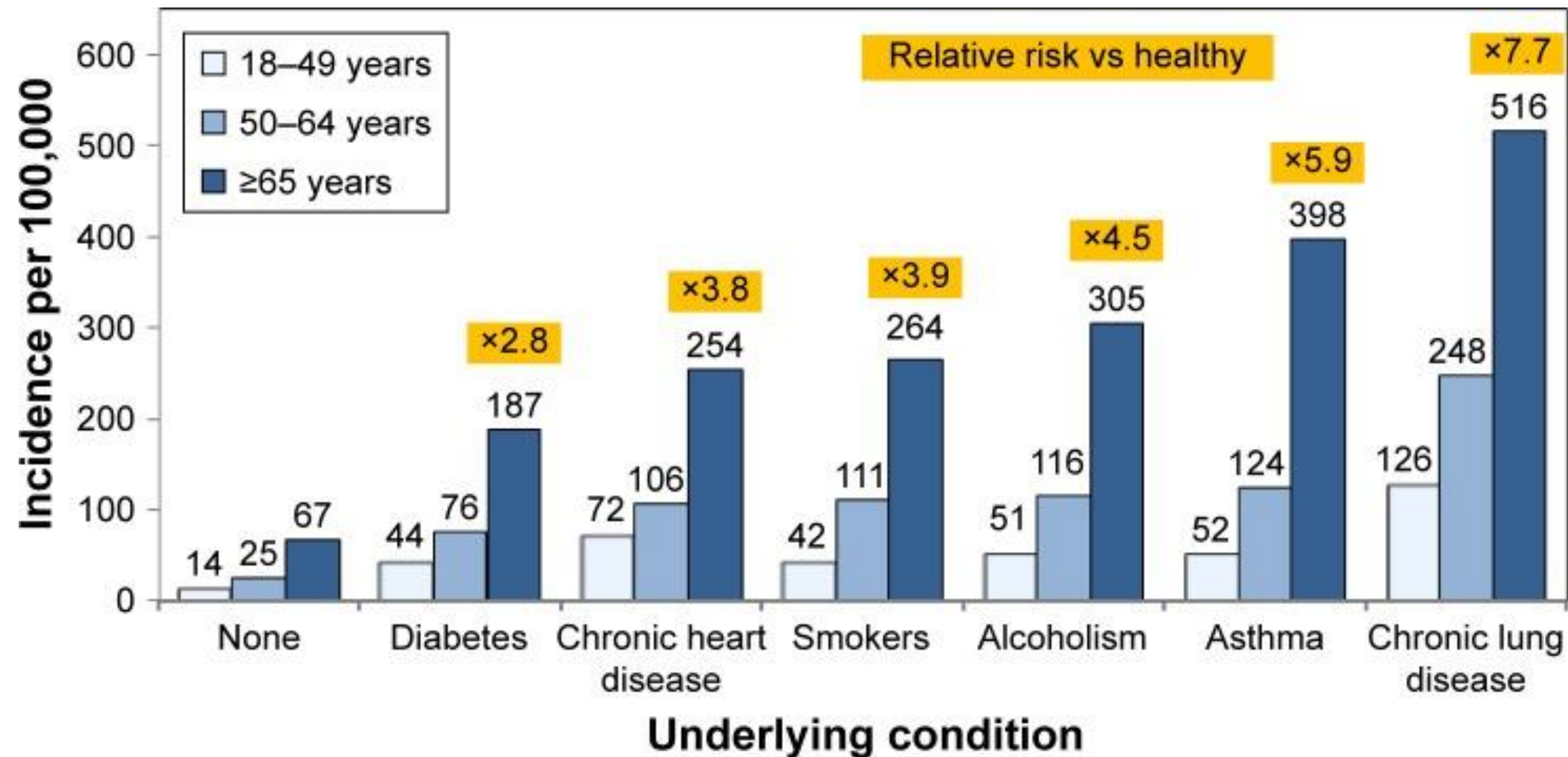
NEJM. 1991;325:1453-60.

Incidence



Mean incidence 13.4 per 100,000

Highest in < 1year (52.6) 1 year (48.1) and >65s (34.8)



International Journal of COPD 2017:12:3458-

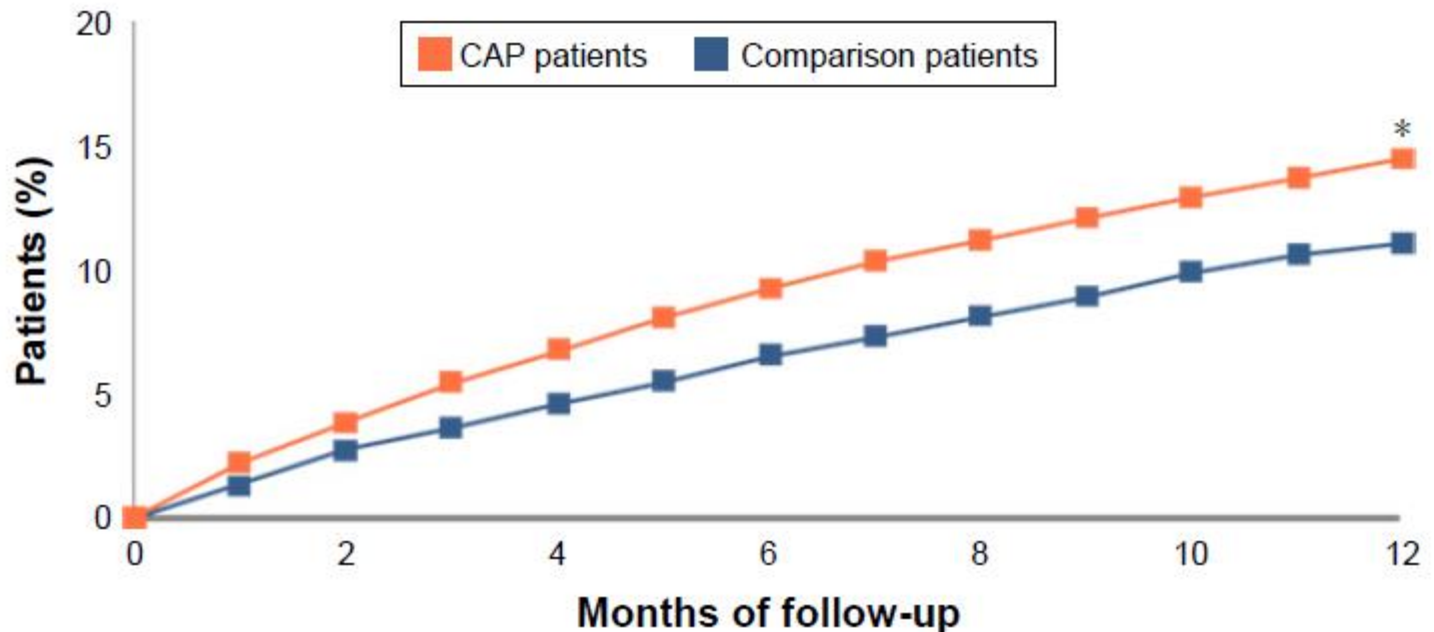
Relative Risk of Invasive Pneumococcal Diseases(IPD) in Chronic Respiratory Diseases

	OR(95% CI)			
	18-59 yrs	60-79 yrs	≥ 80 yrs	All
COPD	10.3 (5.8-18.0)	6.3(5.1-7.8)	4.0(3.0-4.8)	4.7(4.0-5.6)
Asthma	4.9(3.0-7.8)	1.9(1.3-2.9)	1.5(0.9-2.7)	2.0(1.5-2.6)
Sarcoidosis	1.0(0.8-20.6)	2.5(0.7-8.8)	-	2.0(0.7-6.2)
Pneumoconiosis	-	2.0(0.2-17.1)	-	1.9(0.2-16.1)
Fibrosis	6.5(1.1 -39.1)	11.6(3.9-34.4)	4.4(1.5-12.6)	5.1(2.5-10.4)
Bronchiectasis	9.9(3.4-28.3)	2.5(0.5-11.8)	-	1.9(0.7-5.2)
Hypersensitivity pneumonitis	9.5(0.6-151.8)	-	-	0.9(0.2-16.5)

- IPD in COPD: n = 248(25, 147, 76 in each age group)
- IPD in asthma: n= 71 (26, 31, 14 in each age group)

Clin Microbiol Infect 2013;19:1148-54

Community-acquired pneumonia (CAP) and occurrence of subsequent AE-COPD (USA, 2010)



Number of patients at risk							
CAP patients	8,274	7,493	6,891	6,384	5,908	5,412	4,984
Comparison patients	8,274	7,715	7,273	6,847	6,372	5,889	5,460
Percentage with a subsequent exacerbation							
CAP patients	–	3.9%	6.8%	9.3%	11.2%	12.9%	14.6%
Comparison patients	–	2.8%	4.7%	6.6%	8.1%	9.9%	11.2%

*$P < 0.001$

International Journal of COPD 2017:12:3458-

SECTION II.

접종 스케쥴

19세, 기저질환+

(대한 감염학회, 미국예방접종자문위원회)

immunity		PCV13	PPV23(1st)	PPV23(2nd)
competent	Chronic lung diseases	+	+	
	smoking	+/-	+	
compromised	steroid	++	++	+

- PCV13 First, only one.

  PCV augments PSV, but PSV inhibits PCV.

- Interval

  PCV13 → PPV23: ≥ 8 weeks

  PPV23 → PCV13: ≥ 1 year (6 mos.)

  PPV23 → PPV23: ≥ 5year

국내 권장 (2018)

	≥ 65 세			< 64 세	
	건강인	고위험		고위험	
		면역저하	만성질환	면역저하	만성질환
예산지원	PPV23	PPV23	PPV23	-	-
질병관리본부	PPV23	PCV13 → PPV23	PPV23	PCV13 → PPV23	PPV23
대한감염학회	PCV13 or PPV23	PCV13 → PPV23	PCV13 → PPV23	PCV13 → PPV23	PCV13 → PPV23

연령별 폐렴구균백신 접종 가이드(18세 이상)

65세 이상의 건강한 고령자

☑ PCV13 또는 PPV23 접종

과거 접종력

접종 권고

18~64세 (만성 호흡기질환)*

☑ **PCV13 우선 접종**

→ PCV13을 접종 할 수 없다면 PPV23 접종

65세 이상 만성 호흡기 질환자*

- 과거에 폐렴사슬알균 백신 접종을 받지 않은 경우

PCV13 접종 → PPV23 접종

6-12개월 간격 (최소 8 주간격)

- 과거에 PCV13 접종을 받은 경우

PCV13 접종 → PPV23 접종

6-12개월 간격 (최소 8 주간격)

- 65세 이전에 PPV23 접종을 받은 경우

65세 이전 PPV23 접종 → PCV13 접종 → PPV23 접종

1년 이상 간격 **6-12개월 간격** (최소 8 주간격)

5년 이상 간격

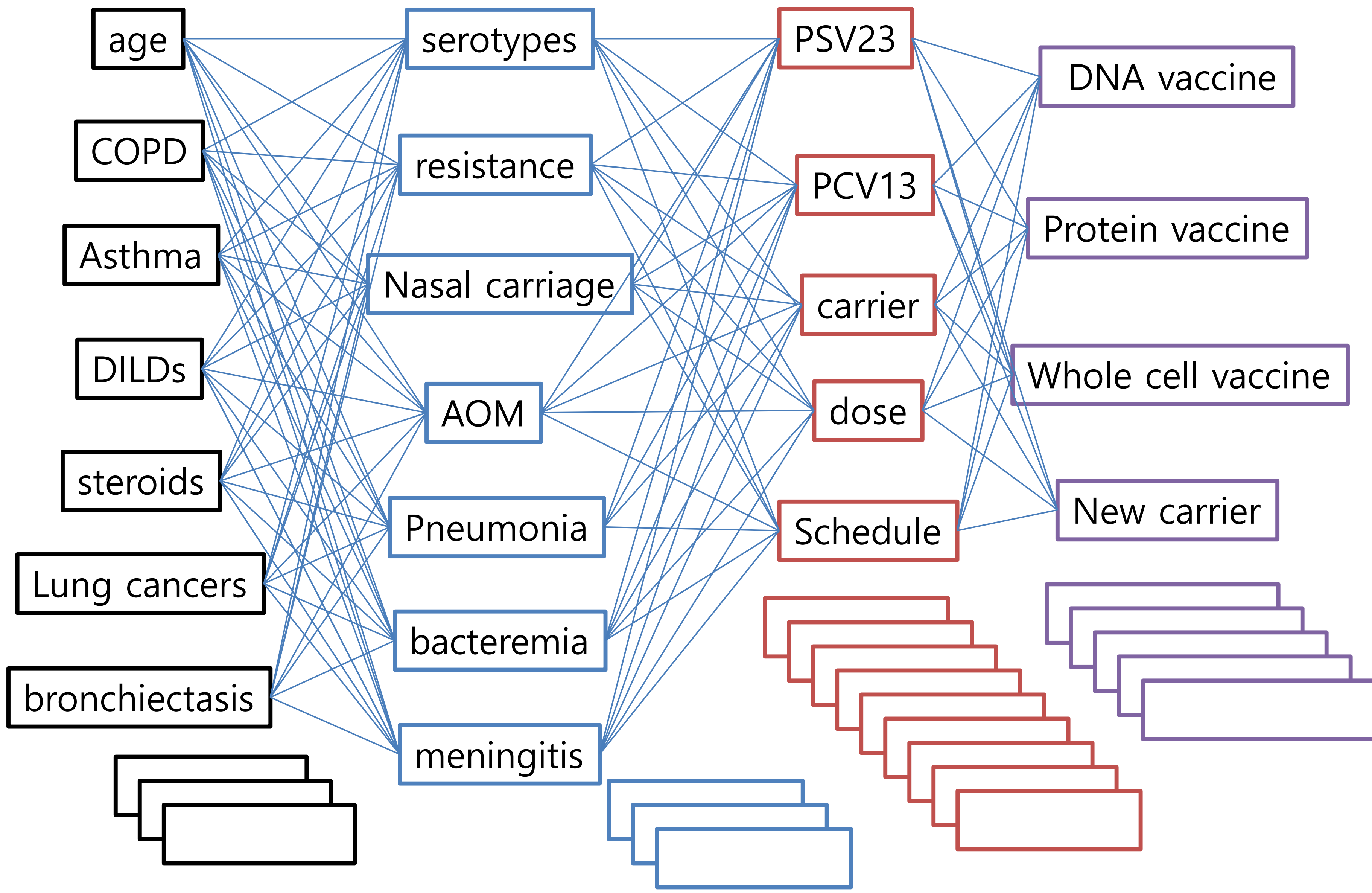
- 65세 이후에 PPV23 접종을 받은 경우

65세 이후 PPV23 접종 PCV13 접종

1년 이상 간격

대한감염학회

Vaccination in Precision Medicine Era



患者의容態에관한문제。

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診斷 0·1

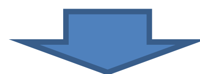
26·10·1931

以上　責任醫師　李箱

SECTION III.

근거 자료

	Carrier Protein	Polysaccharide content	Vaccine Efficacy	Duration of antibody	KFDA
PPV23	none	All Serotypes: 25 mcg	IPD: 50-80%(healthy), none in ≥75 yr, chronic dis	5 yrs; Shorter in chronic dis.	Adults≥ 50Yrs, children (≥2 yr) with high risk
PCV13	CRM_{197}: 32mcg	ST 6B: 4.4 mcg Others: 2.2 mcg	Mucosal immunity; Nasal carriage	4yrs. (at least)	Infants, Children and adults (≥6 wk)



	50-64 y/o (004 trial)		≥70y/o, ≥ 5yr PPV23 (3005 trial)	
	superior	similar	superior	similar
PCV13 > PPSV23	1,4,6B,7F, 9V, 18C, 19A, 23F	3,5,14, 19F	1,4,5, 6B, 7F, 9V, 18C, 19F, 19A, 23F	3, 14

Vaccine effectiveness (Meta-analysis)

- Randomized clinical trials;
  Extremely difficult - Large sample size, Herd immunity by pediatric immunization

- PCV:
  65% (65 – 74 yrs) → 40% (≥70 yrs)

Clin Infect Dis 2015;61:1835-8

- PPV: ≥60 yrs (Any serotypes)
  48-64% against CAP
  45-73% against IPD

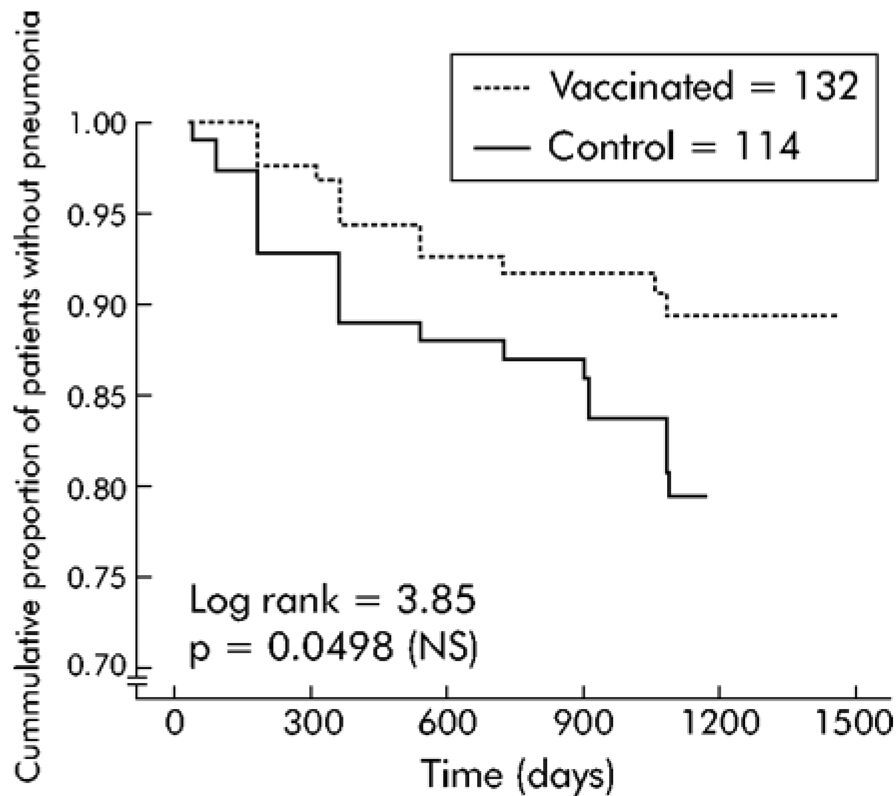
Vaccine. 2016;34:1540-50
PLoS One. 2017;12:e0169368

PPSV23 for preventing pneumonia in COPD

- Cochrane Reviews: total of 12 RCTs involving 2171 participants with COPD
- Major COPD guidelines (COPDX 2016; ERS 2014; GOLD 2016; NICE 2010)

	Odds Ratio	95% CI	P value
Community Acquired Pneumonia(≥1)	**0.61**	**0.42 , 0.89**	**0.01**
Exacerbation of COPD(≥1)	**0.60**	**0.39 , 0.93**	**0.02**

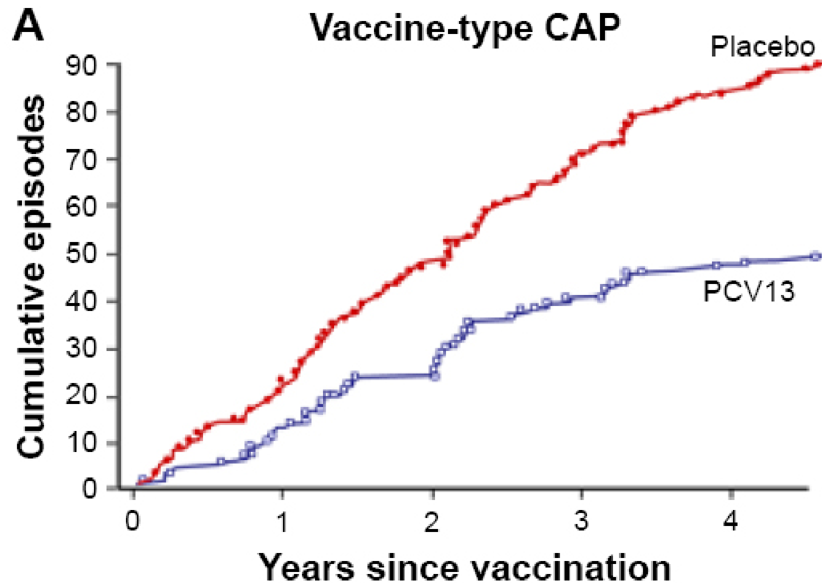
Cumulative Proportion of Patients with Severe COPD Without Pneumonia Over the Follow-up Period



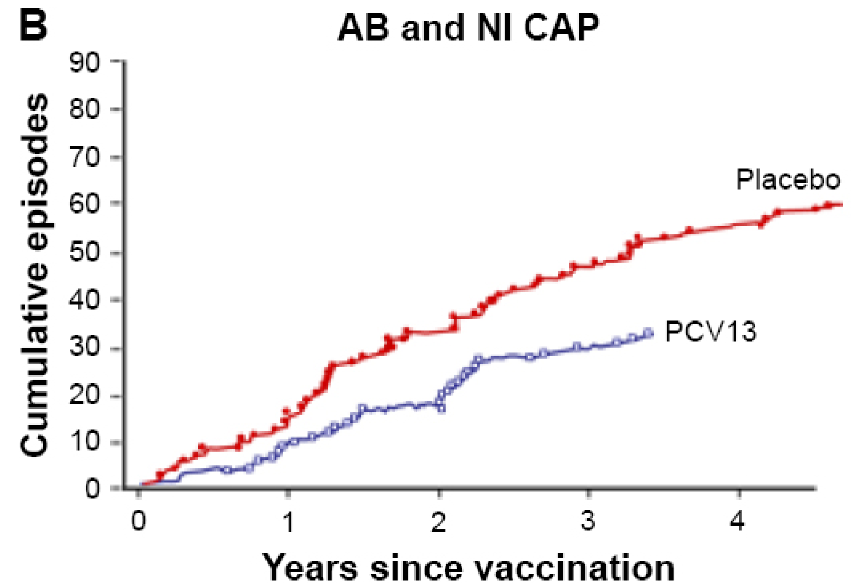
Alfageme, *et al.* Thorax. 61(3):189-95, 2006

Efficacy of PCV13 in older adults (CAPiTA)

abacteremic (AB)
noninvasive (NI)



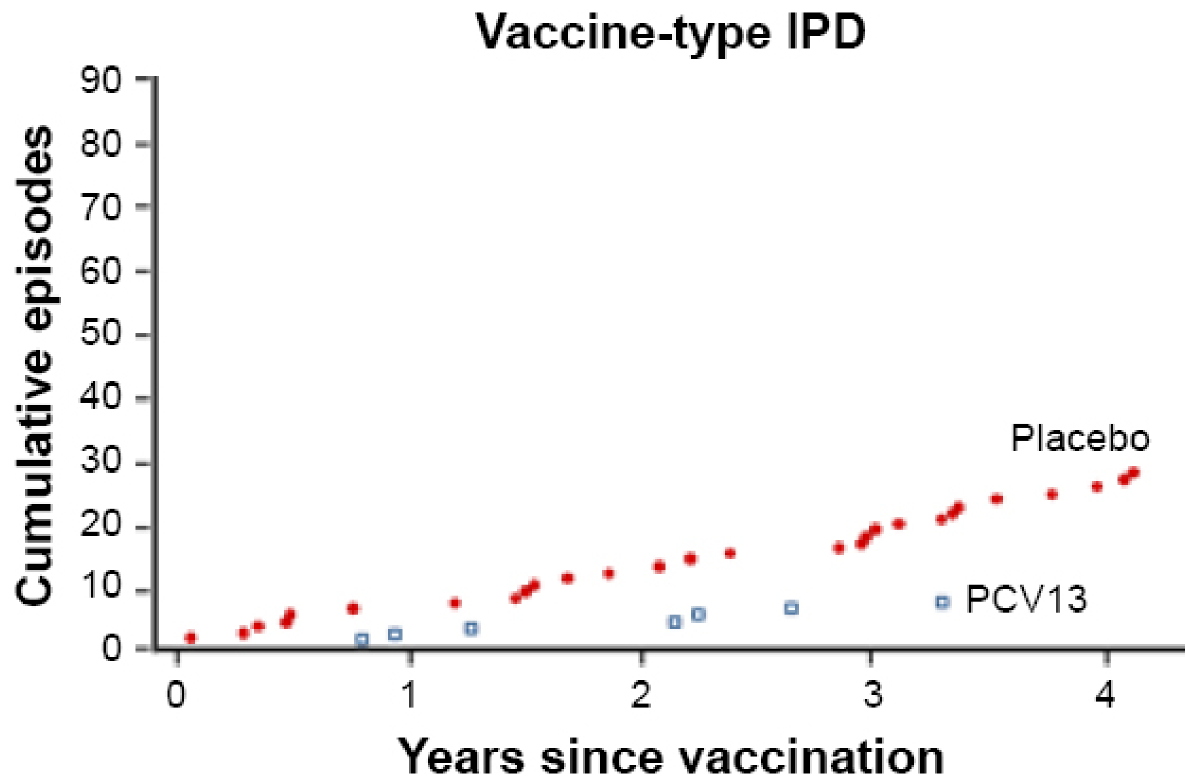
Vaccine efficacy:
45.6% (95.2% CI: 21.8%–62.5%)
P<0.001



Vaccine efficacy:
45% (95.2% CI: 14.2%–65.3%)
P=0.007

Bonten et al. *N Engl J Med*. 372:1114–25.

First episodes of vaccine-type IPD from vaccination to 5-year follow-up



Vaccine efficacy:
75% (95% CI: 41.4%–90.8%)
P<0.001

Bonten et al. *N Engl J Med*. 372:1114–25.

Post hoc PCV13 VE for VT CAP in at-risk older adults

	At risk (n = 41,385)		Without known risk (n = 42,679)		All (N = 84,064)
	PCV13 (n = 20,680)	Placebo (n = 20,705)	PCV13 (n = 21,339)	Placebo (n = 21,340)	
Sex, n (%)					
Female	8313 (40.2)	8095 (39.1)	10,400 (48.7)	10,292 (48.2)	37,100 (44.1)
Male	12,367 (59.8)	12,610 (60.9)	10,939 (51.3)	11,048 (51.8)	46,964 (55.9)
Age at enrolment, y					
Median	72.0	72.0	71.2	71.1	71.6
<75, n (%)	13,678 (66.1)	13,654 (65.9)	15,202 (71.2)	15,277 (71.6)	57,811 (68.8)
75–<85, n (%)	6200 (30.0)	6275 (30.3)	5452 (25.5)	5412 (25.4)	23,339 (27.8)
≥85, n (%)	802 (3.9)	776 (3.7)	685 (3.2)	651 (3.1)	2914 (3.5)
Asthma	**2008 (9.7)**	**2094 (10.1)**	0 (0)	0 (0)	4102 (4.9)
Lung disease	**4224 (20.4)**	**4324 (20.9)**	0 (0)	0 (0)	8548 (10.2)
Smoking	**5175 (25.0)**	**5147 (24.9)**	0 (0)	0 (0)	10,322(12.3)

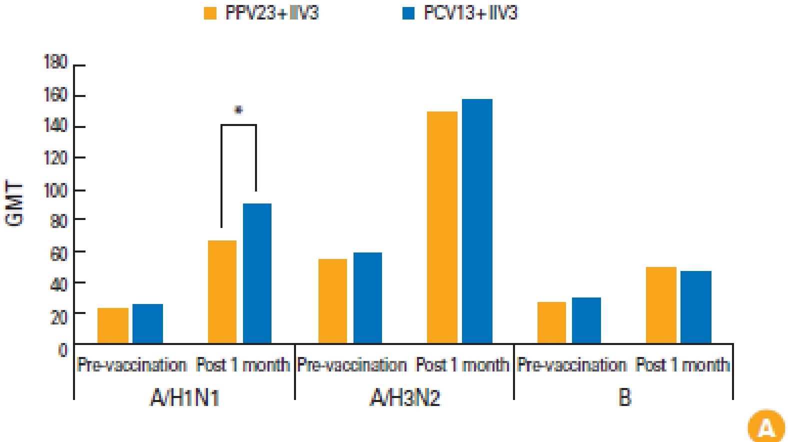
Vaccine, 2018;36(11):1477-1483

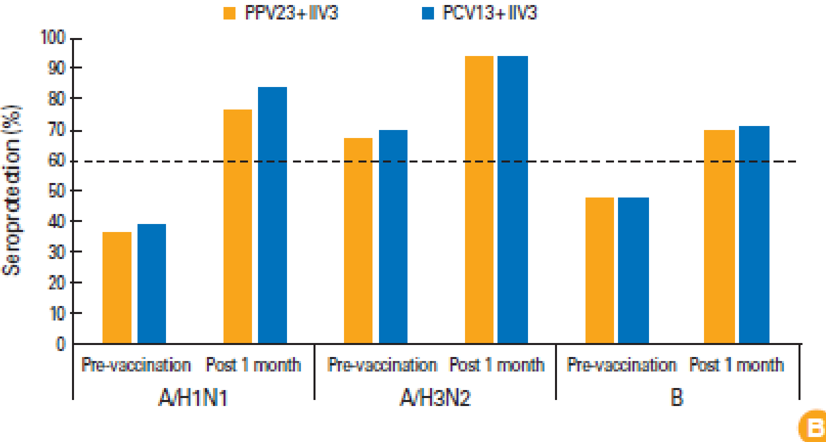
Post hoc PCV13 VE for VT CAP in at-risk older adults

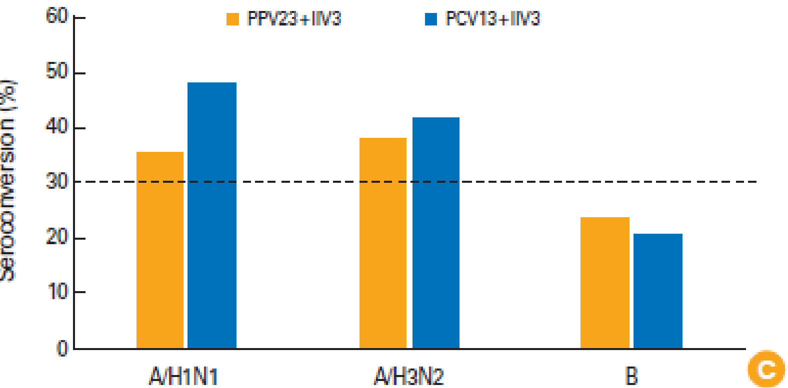
	At risk (n = 41,385)		Without known risk (n = 42,679)		All (N = 84,064)	
	PCV13 (n = 20,680)	Placebo (n = 20,705)	PCV13 (n = 21,339)	Placebo (n = 21,340)	PCV13 (n = 42,019)	Placebo (n = 42,045)
PY	81,676	81,668	85,408	85,318	167,084	166,985
Mean follow-up, y	3.95	3.94	4.00	4.00	3.98	3.97
Per protocol analysis						
PCV13 VE *	40.3 [11.4, 60.2]		66.7 [11.8, 89.3]		45.6 [21.9, 62.5]	
All episodes of VT-CAP	47	74	6	18	53	92
PCV13 VE *	36.5 [6.9, 57.1]		66.7 [11.8, 89.3]		42.4 [18.2, 59.9]	
Modified intention-to-treat analysis						
PCV13 VE *	32.5 [3.9, 53.0]		63.7 [14.7, 86.1]		39.1 [15.9, 56.2]	
All episodes of VT-CAP ‡	60	88	8	23	68	111
PCV13 VE *	31.8 [4.0, 51.9]		65.3 [19.0, 86.7]		38.8 [16.2, 55.5]	

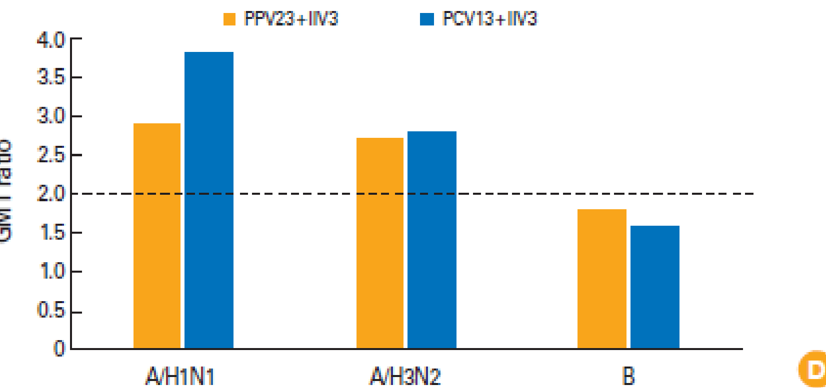
Vaccine, 2018;36(11):1477-1483

Immunogenicity and safety of Influenza vaccine + PCV13 / PPSV23 in the elderly









Clin Exp Vaccine Res. 2017; 6(1): 38–44.

Real-life Vaccine Coverage

Nation	Rate	Target Population(age)	Year
UK	70%	≥65	2014 - 2015
Spain	76%	≥60	2010
Ireland	36%	≥65	2013
Norway	15 - 30%	≥65	2014 - 2015
Germany	15%	High risk adults	2014
France	~5%	≥65	2010 - 2011

https://www.versorgungsatlas.de/themen/alle-analysen-nach-datum-sortiert/?tab=6&uid=74. Accessed October 11, 2017.
Int J Tuberc Lung Dis. 2015;19(6):735–741.
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http://invs.santepubliquefrance.fr/Publications-et-outils/Rapports-et-syntheses/Maladies-infectieuses/2011/Enquete-nationale-de-couverture-vaccinale-France-janvier-2011. Accessed October 1, 2017.
Epidemics. 2015;11:24–31.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/448406/hpr2615_ppv.pdf. Accessed October 1, 2017.

Conclusion

- Guideline for Pneumococcal Vaccination in Chronic Respiratory Diseases will be continuously evolving.
- Polysaccharide conjugate vaccine:

  Higher immunogenecity and vaccine efficacy for vaccine type invasive pneumococcal pneumonia and AECOPD.
- Polysaccharide vaccine:

  Still important in elderly and chronic respiratory diseases.

  Serotype replacement disease.
- New vaccines with more serotypes or targeting other bacterial antigens will be mandatory.
- ***Physician's concerns: most important!***