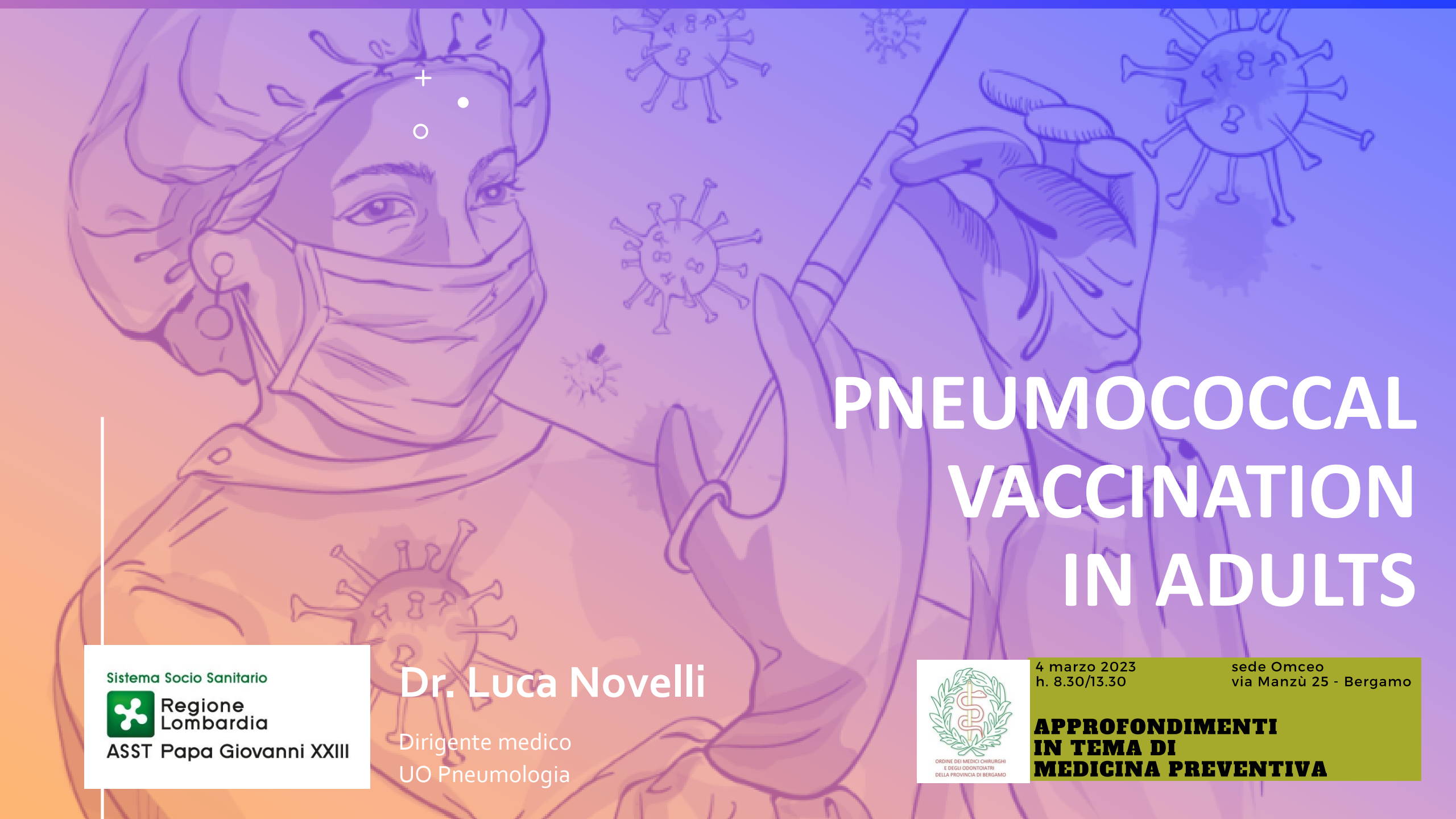

PNEUMOCOCCAL VACCINATION IN ADULTS

Sistema Socio Sanitario
Regione Lombardia
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UO Pneumologia

ORDINE DEI MEDICI CHIRURGHI E DEGLI ODONTOIATRI DELLA PROVINCIA DI BERGAMO

4 marzo 2023
h. 8.30/13.30

sede Omceo
via Manzù 25 - Bergamo

APPROFONDIMENTI IN TEMA DI MEDICINA PREVENTIVA

HISTORY

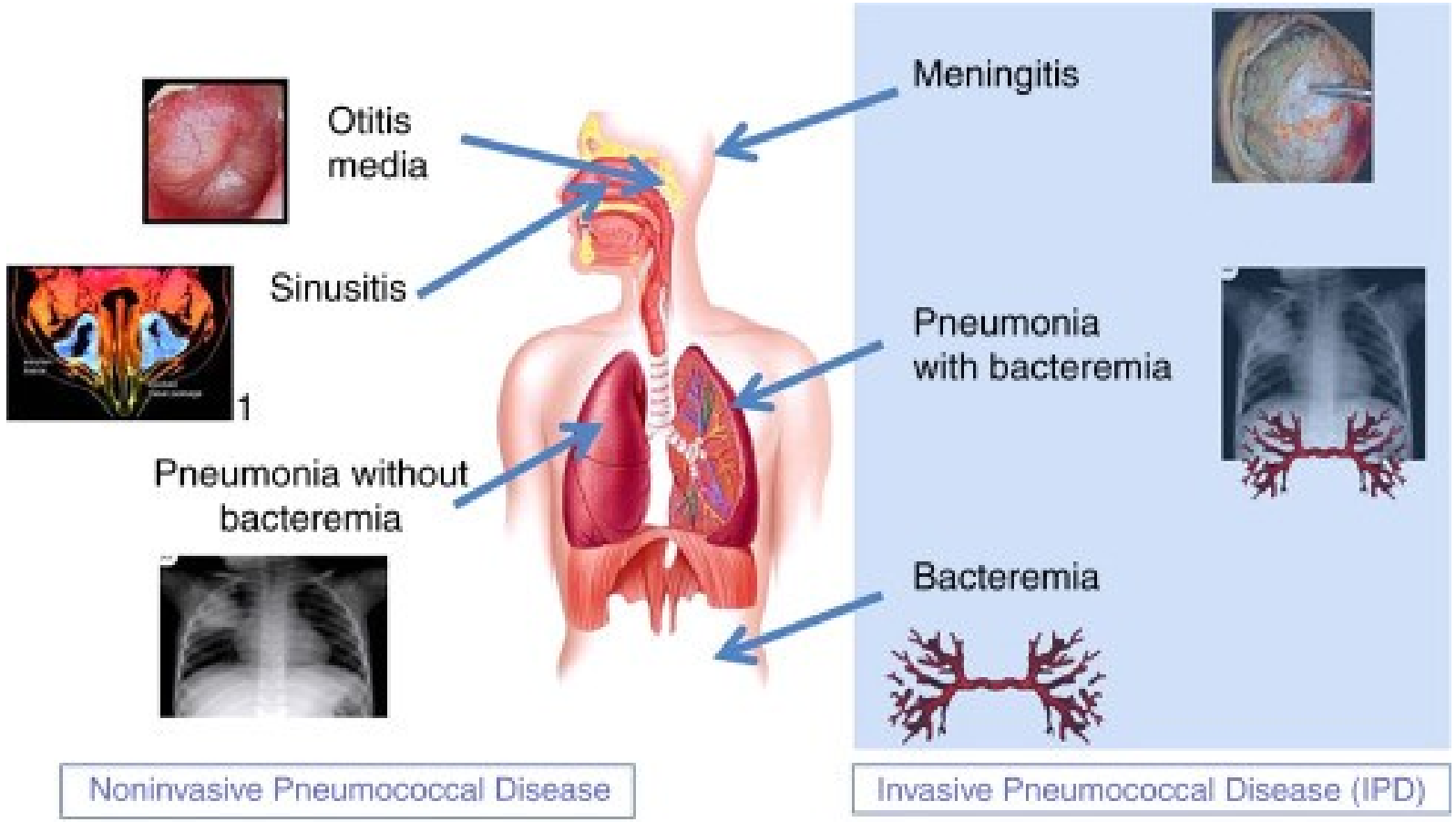
- 1881 → S. Pneumoniae first isolated by Pasteaur
- 1883 → Association between pneumococcus and lobar pneumonia
- 1911 → efforts to develop effective pneumococcal vaccines
- 1915-1945 → the chemical structure and antigenicity of pneumococcal capsular polysaccharide, its association with virulence, and the role of bacterial polysaccharides in human disease were described (1940, 80 serotypes)
- 1930 → W. Tillet e T. Francis identified C-reactive protein in Pneumoccal positive serum
- 1940 → advent of penicillin, interest in vaccination declined
- 1977 → first pneumococcal polysaccharide vaccine (14-valent) was licensed for use in USA
- 1983 → PPSV23
- 2000 → first conjugate pneumococcal vaccine (PCV7)

RATIONALE FOR VACCINATION

Burden of disease — *S. pneumoniae* is the leading bacterial cause of pneumonia worldwide. Other manifestations of pneumococcal infection include meningitis, bacteremia of undetermined source, acute purulent sinusitis, and otitis media. These pneumococcal infections cause substantial morbidity and mortality.

Immunogenicity — Both the PPSV23 and PCV are immunogenic in adults. The response to pneumococcal vaccine in adults is measured by the rise in antibody levels and/or serum opsonic (phagocytic) activity after vaccine administration. Antibody responses may be reported as mean immunoglobulin (Ig)G levels or opsonophagocytic titers (the dilution at which serum shows an opsonizing [phagocytic] effect).

Invasive Pneumococcal Disease (IPD)



[1]image from WebMD 2014

IPD

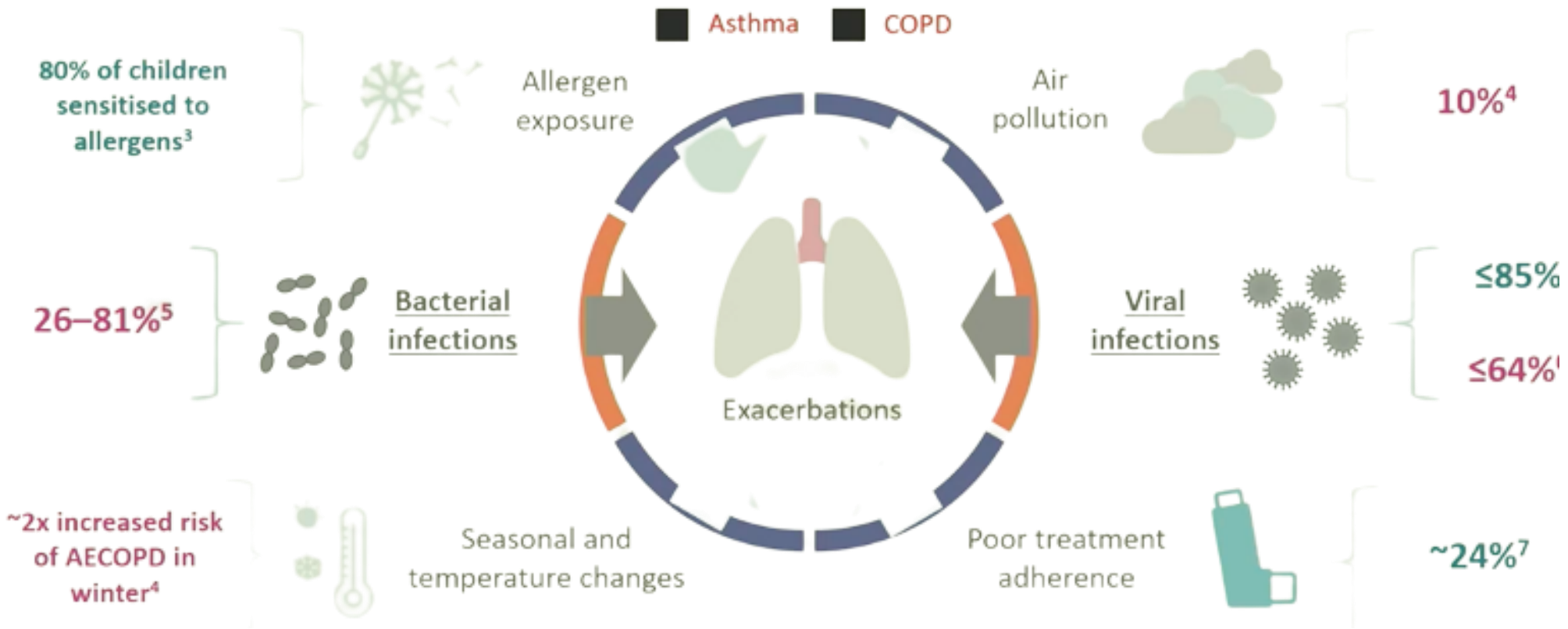
- *Streptococcus pneumoniae* is a leading cause of community-acquired bacterial invasive disease and a major cause of morbidity and mortality globally

- more than 300 000 deaths each year attributable to *S pneumoniae* in children younger than 5 years worldwide,1 and more than 690000 deaths in adults older than 70 years in 195 countries in 2015

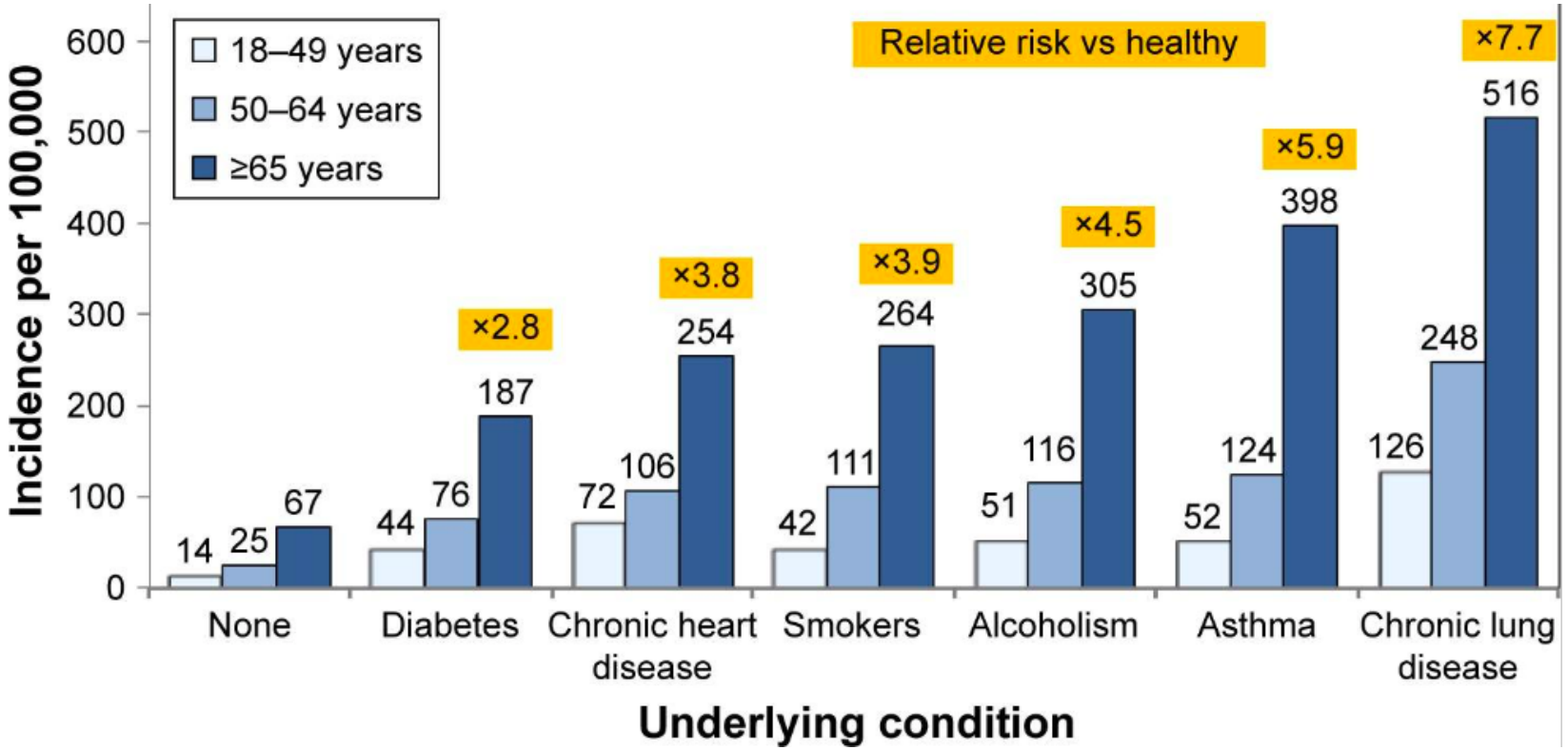
Ouldali N et al. Lancet Infect Dis 2020; 21: 137–47

Not only IPD...

Infections are among the most common contributors to respiratory disease exacerbations



Pneumococcal pneumonia in adults in UK (2007-2010)



Froes F, Roche N, Blasi F. Pneumococcal vaccination and chronic respiratory diseases. *Int J Chron Obstruct Pulmon Dis*. 2017;12:3457-3468. Published 2017 Dec 5. doi:10.2147/COPD.S140378

VACCINE TYPES

Polysaccharide vaccines — PPSV is composed of partially purified pneumococcal capsular polysaccharides. The only available formulation contains 23 pneumococcal polysaccharides (PPSV23) from the 23 serotypes that were the most common cause of pneumococcal disease in adults in the 1980s;

Conjugate vaccines — PCV consist of pneumococcal capsular polysaccharides covalently linked to a protein. Since these were first developed for pediatric use, earlier formulations included serotypes that caused the most disease in children. More recent formulations have selected serotypes that commonly cause disease in adults (Different **carrier proteins** have been used for conjugation, the most common being CRM197, a **nontoxic variant of diphtheria toxin**.

PCV FORMULATIONS

7-valent PCV (PCV7; Prevnar 7)¶

10-valent PCV (PCV10; Synflorix)¶

13-valent PCV (PCV13; Prevnar 13)*

15-valent PCV (PCV15; Vaxneuvance)*

20-valent PCV (PCV20; Prevnar 20/Apexxnar)^

*For Children and Adults

¶developed for Children at the beginning

^Only adult (at now)

PCV20

- **Prevnar** 20 is a vaccine indicated for active immunization for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older.

- **DOSAGE AND ADMINISTRATION:** Adults 18 years of age and older: a single dose

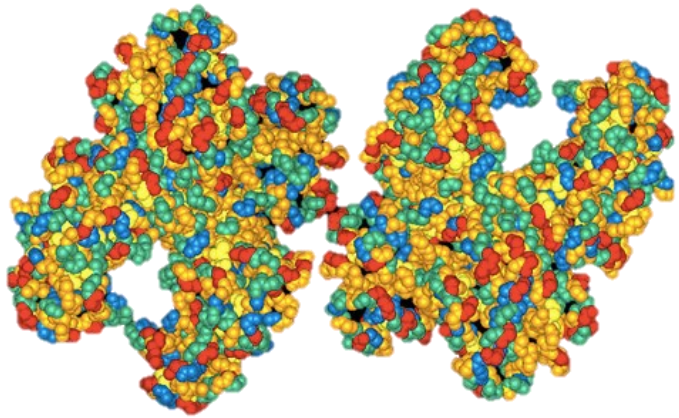
- **DOSAGE FORMS AND STRENGTHS:** 0.5 mL suspension for intramuscular injection

- **ADVERSE REACTIONS:** the most commonly reported solicited adverse reactions >10% were pain at the injection site (>70%), muscle pain (>50%), fatigue (>40%), headache (>30%), and arthralgia and injection site swelling (>10%).

- **CLINICAL CONSIDERATIONS:** Based on PCV13, with the addition of polysaccharide conjugates of seven more S. pneumoniae serotypes; Elicits robust immune responses to all 20 S. pneumoniae serotypes covered by the vaccine; Well tolerated, with a tolerability and safety profle similar to that for PCV13.

CONTRAINDICATIONS

Severe allergic reaction (anaphylaxis) to any component of Prevnar 20 or to **diphtheria toxoid**



CRM197 is an enzymatically inactive and nontoxic form of diphtheria toxin that contains a single amino acid substitution (G52E). Being naturally nontoxic, CRM197 is an ideal carrier protein for conjugate vaccines against encapsulated bacteria.

- CONJUGATION CLEARLY IMPROVES THE QUALITY AND DURATION OF THE IMMUNE RESPONSE

CRM197 mutant diphtheria toxin crystal structure 4AE1 as visualized using DNASTAR's Lasergene Protean 3D

Comparison of serotypes in pneumococcal vaccines

Conjugate vaccines					Polysaccharide vaccine
PCV7 (Prevnar 7)	PCV10* (Synflorix)	PCV13 (Prevnar 13)	PCV15 (Vaxneuvance)	PCV20 (Prevnar 20)	PPSV23 (Pneumovax 23)
–	1	1	1	1	1
–	–	–	–	–	2
–	–	3	3	3	3
4	4	4	4	4	4
–	5	5	5	5	5
–	–	6A	6A	6A	–
6B	6B	6B	6B	6B	6B
–	7F	7F	7F	7F	7F
–	–	–	–	8	8
–	–	–	–	–	9N
9V	9V	9V	9V	9V	9V
–	–	–	–	10A	10A
–	–	–	–	11A	11A
–	–	–	–	12F	12F
14	14	14	14	14	14
–	–	–	–	15B	15B
–	–	–	–	–	17F
18C	18C	18C	18C	18C	18C
–	–	19A	19A	19A	19A
19F	19F	19F	19F	19F	19F
–	–	–	–	–	20
–	–	–	22F	22F	22F
23F	23F	23F	23F	23F	23F
–	–	–	33F	33F	33F

→ Serotypes covered by PCV20 but not by PCV13 are responsible for a signifcant proportion (approximately 30% or more) of IPD cases in adults

→ Serotypes 8, 12F and 22F were the most emerging after PCV13

Ouldali N et al. Lancet Infect Dis 2020; 21: 137–47

Comparison between:

PPSV	PCV
POOR PRIMING EFFECT	GOOD PRIMING EFFECT
SHORT-DURATION ANTIBODY RESPONSE	LONG-LASTING ANTIBODY RESPONSE
POOR SWITCH IgM-IgG	GOOD SWITCH IgM-IgG
IgG2 RESPONSE	HIGH IgG1 RESPONSE
POOR BOOSTER EFFECT	VALID BOOSTER EFFECT

Comparison of properties of the pneumococcal polysaccharide and conjugate vaccines

	Polysaccharide vaccine	Conjugate polysaccharide vaccine
Stimulates antibodies in infants and toddlers	No	Yes
Stimulates antibodies in healthy adults	Yes	Yes
Stimulates antibodies in immunocompromised adults	+/-	+/-
Antibodies are long-lasting	+/-	+/-
Primes immunologically for enhanced responses	No	Possibly
Stimulates mucosal immunity, resulting in decreased colonization	No	Yes
Exhibits herd effect (secondary protection of unvaccinated individuals)	No	Yes
Use is associated with replacement strains	No	Yes

MUCOSAL IMMUNITY leads to two population-level effects:

INDIRECT (HERD) IMMUNITY:

the PCV owes its success to its ability directly to prevent infection in vaccinated individuals and indirectly to reduce contagion in the population by reducing nasopharyngeal colonization rates

EMERGENCE OF REPLACEMENT STRAINS: vaccination with PCV and the subsequent reduction in nasal carriage of PCV serotypes appears to create an **ecologic niche** for nonvaccine serotypes, mostly among children. The widespread use of pneumococcal conjugate vaccines has caused the emergence of "replacement strains," a term used to describe nonvaccine pneumococcal serotypes that have appeared as colonizers of the nasopharynx and as a cause of pneumococcal disease

Vaccination and replacement serotypes effect

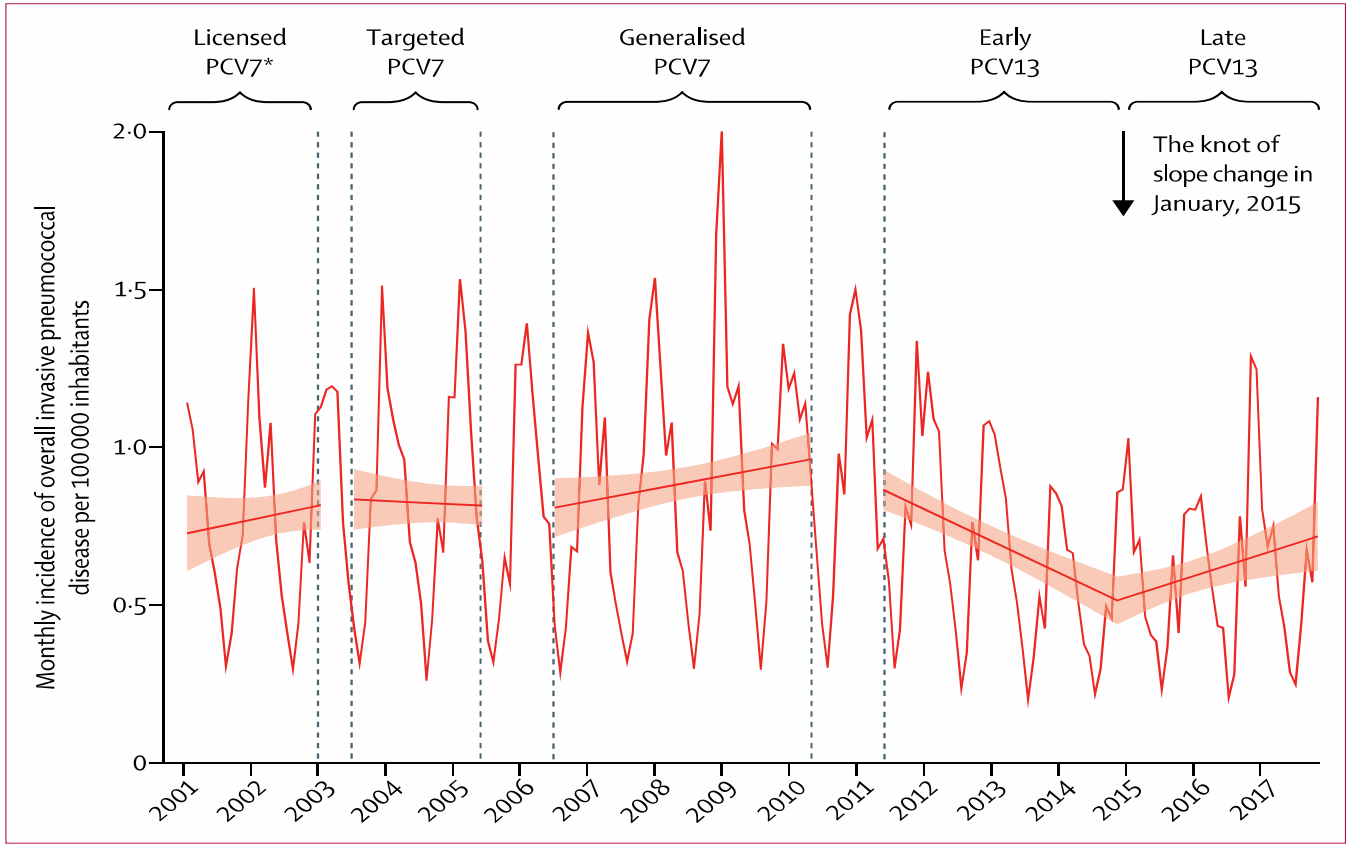


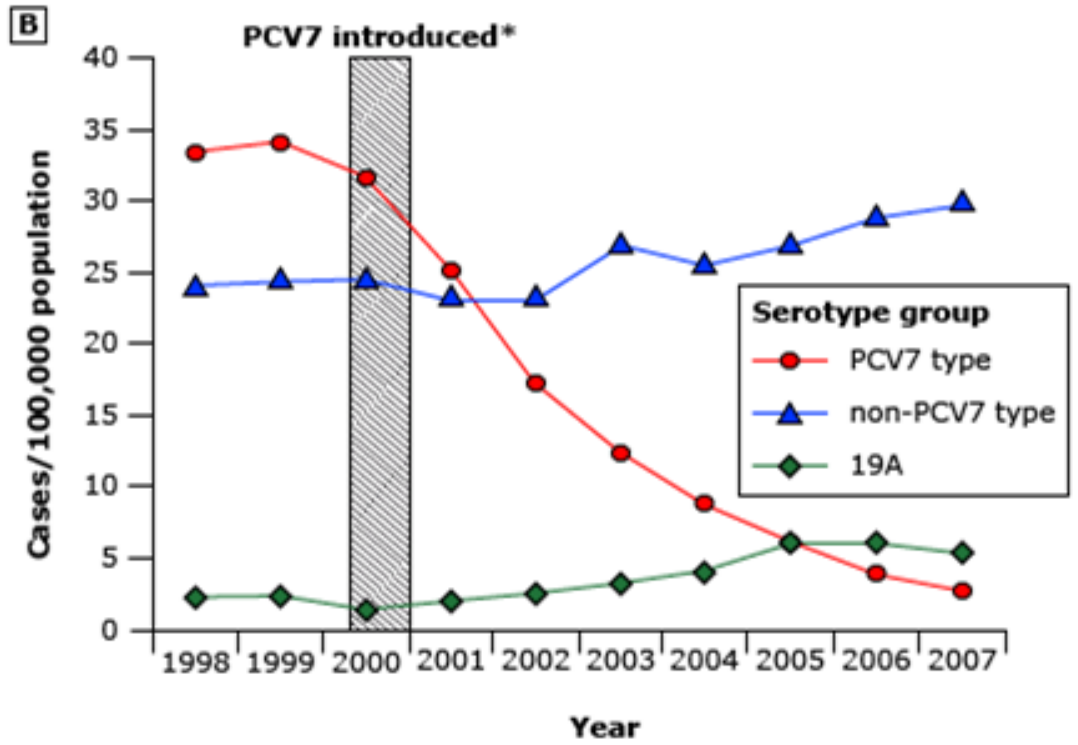
Figure 1: **Time-series analysis of invasive pneumococcal disease incidence over 17 years**

These findings should drive the development of next-generation PCVs

Ouldali N et al. Lancet Infect Dis 2020; 21: 137–47

Changes in IPD in the era of the conjugate vaccine

S. pneumoniae type 19A (not included in PCV7) emerged as the most common cause of pneumococcal disease in children and adults a few years after universal vaccination with PCV7 began in the United States. Several other serotypes have greatly increased in prevalence since the introduction of PCV13.



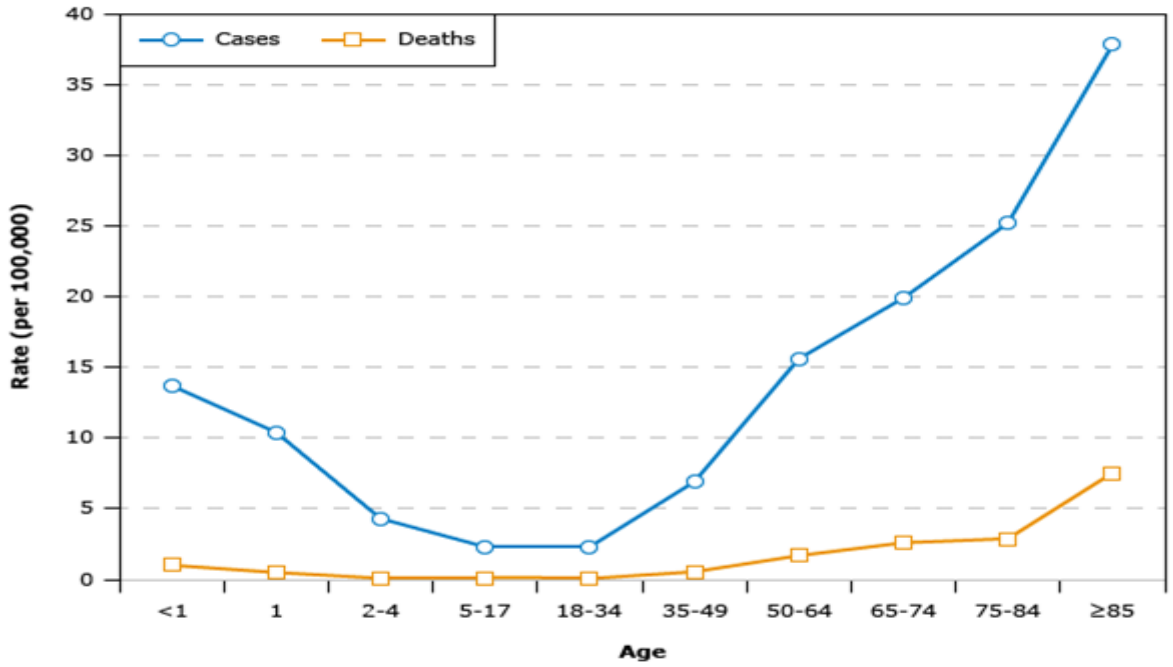
Indications for vaccination

All adults ≥65 years of age
Adults 19-64 years of age with any of the following:
Predisposing medical conditions: ▪ Alcohol use disorder ▪ Chronic heart disease* ▪ Chronic lung disease¶ ▪ Chronic liver disease ▪ Diabetes Mellitus ▪ Sickle cell disease or other hemoglobinopathies ▪ Current cigarette smoking
Increased risk of meningitis: ▪ Cerebrospinal fluid leak ▪ Cochlear implant
Immunocompromising conditions and other conditions associated with altered immunocompetence△: ▪ Congenital or acquired immunodeficiency◇ ▪ Generalized active malignancy ▪ Human immunodeficiency virus infection§ ▪ Iatrogenic immunosuppression¥ ▪ Hodgkin disease ▪ Leukemia ▪ Lymphoma ▪ Multiple myeloma ▪ Solid organ transplant ▪ Chronic kidney disease‡ and nephrotic syndrome ▪ Functional or anatomic asplenia
History of invasive pneumococcal disease†

These populations are at increased risk of developing IPD and/or are at higher risk of significant morbidity and mortality from IPD. In 2018, approximately **43 percent of IPD occurred in those over the age of 65** and another **48 percent in adults <65 years** of age with predisposing conditions.

Incidence and mortality rates of IPD in the United States (2019)

Vaccination is not recommended for healthy adults less than 65 years of age. Although the risk for pneumococcal disease starts to increase at age 50 analyses have suggested initiating vaccination at that age would not be cost-effective.



Case and death rate per 100,000 for invasive pneumococcal disease from Active Bacterial Core (ABC) Surveillance areas.

Data from: Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae, 2019. Centers for Disease Control and Prevention. Available at: www.cdc.gov/abcs/downloads/SPN_Surveillance_Report_2019.pdf (Accessed on June 13, 2022).

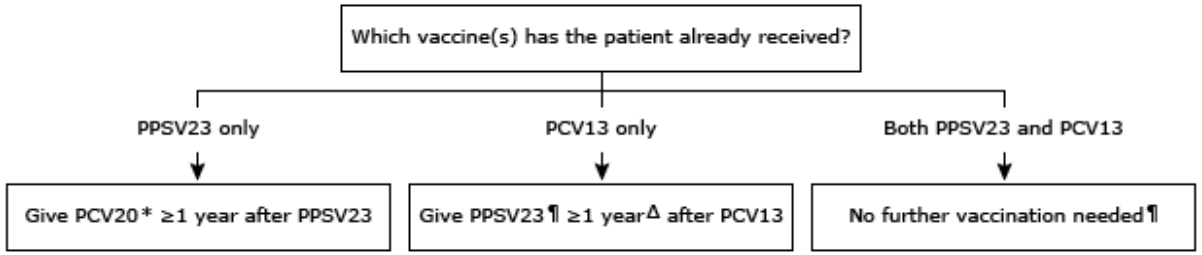
Approach to vaccine selection

Recommendations for adults who have never received a pneumococcal conjugate vaccine, by underlying medical condition or other risk factor and age group

Underlying medical condition or other risk factor	19 through 64 years old	≥ 65 years old
None	Not recommended	Administer 1 dose of PCV20 OR 1 dose of PCV15 followed by 1 dose of PPSV23 at least 1 year later
Alcoholism Chronic heart disease Chronic liver disease Chronic lung disease Cigarette smoking Diabetes mellitus Cochlear implant Cerebrospinal fluid leak Chronic renal failure Congenital or acquired asplenia Congenital or acquired immunodeficiency Generalized malignancy HIV infection Hodgkin disease" Iatrogenic immunosuppression Leukemia Lymphoma Multiple myeloma Nephrotic syndrome Sickle cell disease/other hemoglobinopathies Solid organ transplant	Administer 1 dose of PCV20 OR 1 dose of PCV15 followed by 1 dose of PPSV23 at least 1 year later *The minimum interval (8 weeks) can be considered in adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak.*	Administer 1 dose of PCV20 OR 1 dose of PCV15 followed by 1 dose of PPSV23 at least 1 year later *The minimum interval (8 weeks) can be considered in adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak.* *Reminder: No additional doses are indicated at this age if PCV15 or PCV20 were administered at a younger age.*

Kobayashi M. et al. MMWR 2022;71:109

UpToDate recommendations for pneumococcal vaccination in recipients of previous pneumococcal vaccines



The ACIP updated its pneumococcal vaccine recommendations in 2022. This algorithm provides guidance to clinicians for adults who have already initiated or completed a primary pneumococcal vaccine series with older pneumococcal vaccine formulations. Refer to the UpToDate text on pneumococcal vaccination in adults for additional information.

PCV20: 20-valent pneumococcal conjugate vaccine; PPSV23: 23-valent pneumococcal polysaccharide vaccine; PCV13: 13-valent pneumococcal conjugate vaccine; ACIP: United States Centers for Disease Control and Preventions Advisory Committee on Immunization Practices; PCV15: 15-valent pneumococcal conjugate vaccine.

* If PCV20 is not available, PCV15 is a recommended alternative.

¶ Some experts favor revaccination with PPSV23 for select individuals. Refer to the UpToDate text on pneumococcal vaccination in adults for additional information.

Δ In high-risk individuals (eg, immunocompromising conditions, cochlear implant, or cerebrospinal fluid leak), a shorter interval of ≥8 weeks may be used to maximize protection more quickly.

UpToDate®

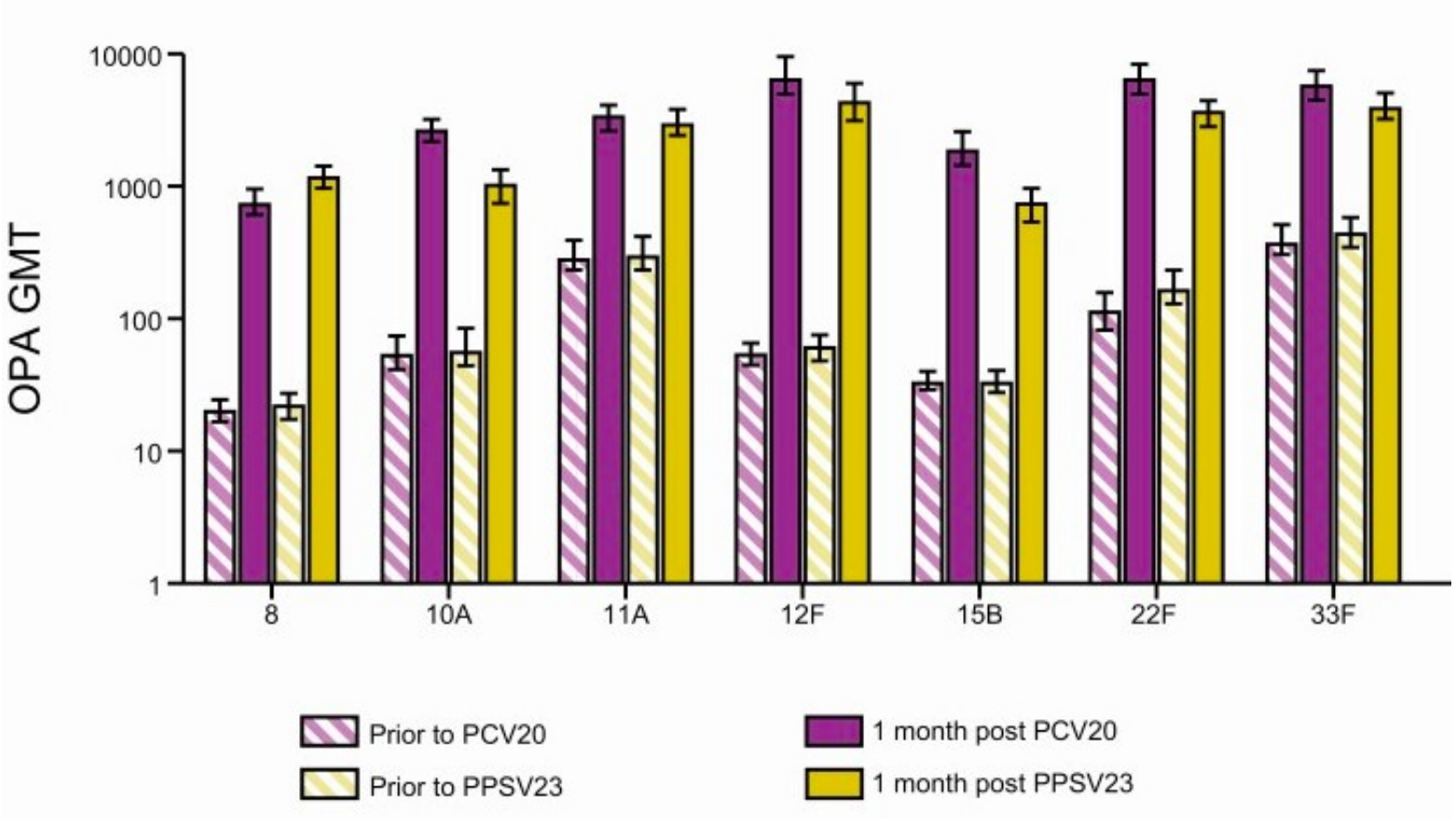
The immunogenicity of PCV20 in adults has been established over a number of double-blind and open label randomised, controlled clinical trials , with the pivotal trial (B7471007) evaluating the immunological non-inferiority of PCV20 to PCV13 (for the 13 matched S. pneumoniae serotypes in PCV13) and PPSV23 (for the seven additional S. pneumoniae serotypes.

Table 1 Key trials in the 20-valent pneumococcal conjugate vaccine clinical development program in adults

Trial identifier(s) (locations)	Trial description[a]	Cohorts/groups (no. of subjects)
B7471007; NCT03760146 (Sweden, USA) [34]	Pivotal randomised, double-blind phase III trial in 3902 vaccine-naïve adults aged ≥ 18 years to evaluate non-inferiority of PCV20 to PCV13 (13 common serotypes) and to PPSV23 (7 additional serotypes) in subjects aged ≥ 60 years, with immunobridging in subjects aged 18–49 years and 50–59 years to subjects aged ≥ 60 years	Subjects aged ≥60 years: PCV20/saline (1514); PCV13/PPSV23 (1495) Subjects aged 50–59 years: PCV20 (334); PCV13 (111) Subjects aged 18–49 years: PCV20 (336); PCV13 (112)
B7471006; NCT03835975 (Sweden, USA) [37]	Randomised, open-label phase III trial in 875 adults aged ≥ 65 years to evaluate PCV20 immunogenicity in subjects with prior pneumococcal vaccination	With prior PPSV23[b]: PCV20 (253); PCV13 (122) With prior PCV13[c]: PCV20 (248); PCV13 (127) With prior PCV13 and PPSV23[d]: PCV20 (125)
B7471004; NCT04526574 (USA) [35]	Randomised, double-blind phase III trial in 1796 subjects aged ≥ 65 years to investigate the co-administration of PCV20 with a QIV (Fluad Quadrivalent)	QIV and PVC20 administered concomitantly (898); QIV and PVC20 administered 1 month apart (898)
B7471026; NCT04887948 (USA) [36]	Randomised, double-blind phase III trial in 570 subjects aged ≥ 65 years to investigate the co-administration of PCV20 with a booster dose of the RNA-based SARS-CoV-2 (COVID-19) vaccine BNT162b2	PCV20 alone (187); BNT162b2 alone (185); PCV20 and BNT162b2 administered concomitantly (187)[e]
B7471008; NCT03828617 (USA) [32]	Randomised, double-blind phase III trial in 1710 vaccine-naïve adults aged 18–49 years to compare the immunogenicity of three different lots of PCV20	PCV20: Lot 1 (489); Lot 2 (490); Lot 3 (485) PCV13 (245)
B7471002; NCT03313037 (USA) [31, 40]	Randomised, double-blind phase II trial in 444 vaccine-naïve adults aged 60–64 years	PCV20/saline (222); PCV13/PPSV23 (222)
B7471005; NCT03642847 (USA) [33]	Randomised, double-blind phase Ib trial (to support PCV20 clinical development in Japan) in 104 vaccine-naïve Japanese adults aged 18–49 years residing in the USA for ≤5 years	PCV20 (35); cPCV7[f] (34); PCV13 (35)
B7471001; NCT02955160 (USA) [27]	Randomised, double-blind, first-in-human phase I trial in 66 vaccine-naïve adults aged 18–49 years	PCV20 (33); Tdap (33)

Shirley, Matt. "20-Valent Pneumococcal Conjugate Vaccine: A Review of Its Use in Adults." *Drugs* vol. 82,9 (2022): 989-999. doi:10.1007/s40265-022-01733-z

OPA GMFRs from baseline to 1 month after PCV20 or PPSV23 vaccination for the 7 serotypes unique to PCV20 and PPSV23



For 6 of these 7 serotypes, OPA GMFRs were higher in the PCV20 group compared with PPSV23.

Hurley, Donald et al. "Safety, Tolerability, and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine (PCV20) in Adults 60 to 64 Years of Age." *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* vol. 73,7 (2021): e1489-e1497. doi:10.1093/cid/ciaa1045

Cost-Effectiveness of Vaccination with PCV20 in the Italian Adult Population

Table 2. Share of cases by serotype.

Disease	PCV13	PCV15	PCV20
IPD [3]	31.6%	39.1%	69.6%
P-NBP [21]	25.0%	33.6%	57.2%

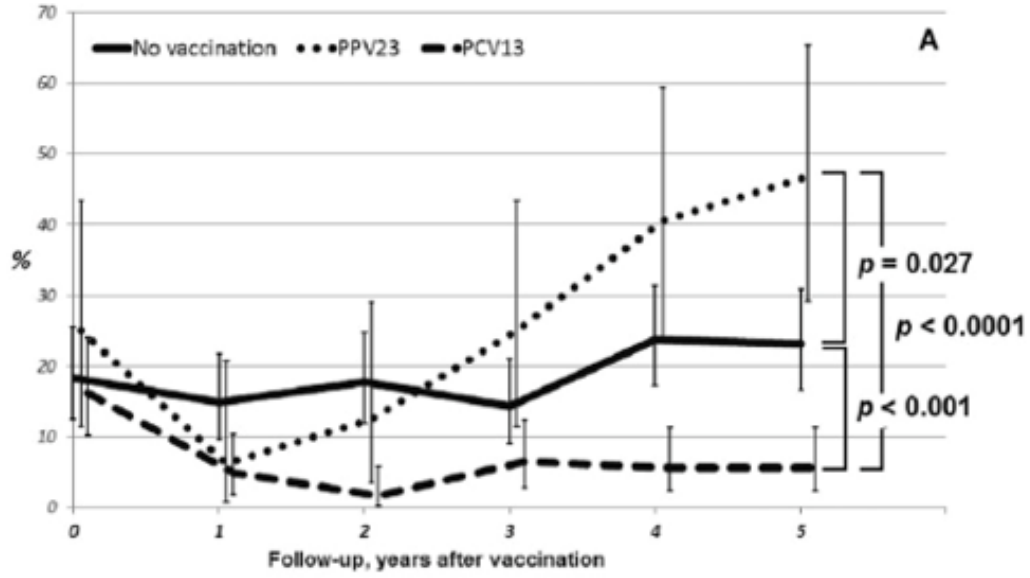
Polistena B, Icardi G, Orsi A, Spandonaro F, Di Virgilio R, d'Angela D. Cost-Effectiveness of Vaccination with the 20-Valent Pneumococcal Conjugate Vaccine in the Italian Adult Population. *Vaccines*. 2022; 10(12):2032. https://doi.org/10.3390/vaccines10122032

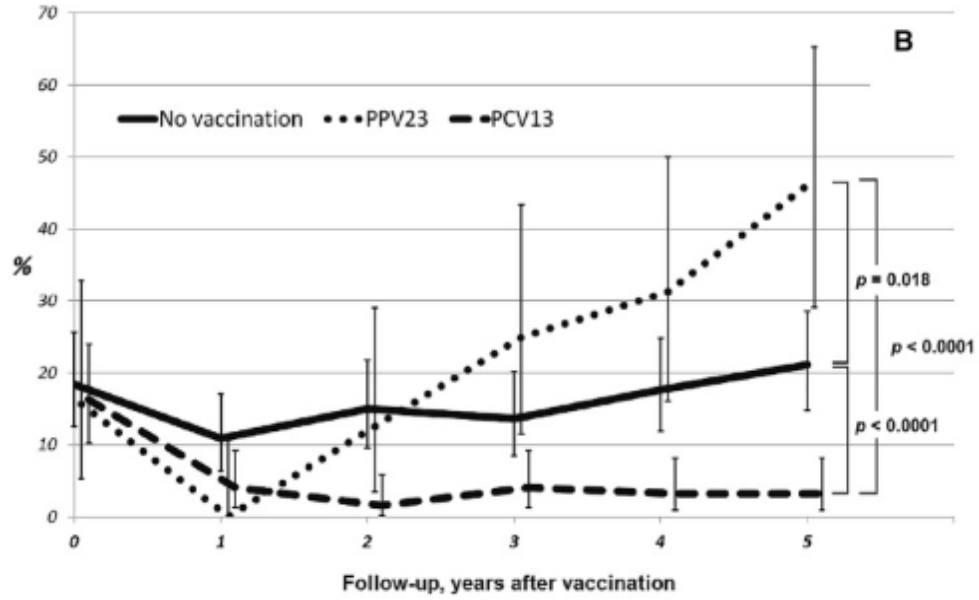
Vaccine	PCV13	PCV15	PCV20	PCV20 vs. PCV13	PCV20 vs. PCV15
			Disease cases		
Bacteraemia (excluding meningitis)	4982	4751	3811	-1171	-940
Meningitis	965	921	738	-227	-183
Hospitalised NBP cases	771,594	770,098	761,748	-9845	-8350
Non-hospitalised NBP cases	1,651,431	1,648,231	1,630,373	-21,058	-17,858
			Outcomes		
Deaths (from IPD and NBP)	99,715	99,516	98,506	-1208	-1009
Life years (LY) (x1000)	75,044.2	75,042.2	75,050.7	+6.6	+5.5
QALY (x1.000)	52,687.2	52,688.0	52,692.0	+4.7	+4.0
			Costs		
Vaccination costs (x EUR 1000)	EUR 448,495	EUR 448,495	EUR 489,063	EUR +40,568	EUR +40,568
Other health costs (x EUR 1000)	EUR 2,523,553	EUR 2,515,726	EUR 2,475,521	EUR 48,032	EUR -40,205
Total health costs (x EUR 1000)	EUR 2,972,047	EUR 2,964,220	EUR 2,964,584	EUR -7464	EUR -0.364
			ICER		
ICER for LY gained (EUR)				Dominant	66
ICER for QALY gained (EUR)				Dominant	91

Polistena B, Icardi G, Orsi A, Spandonaro F, Di Virgilio R, d'Angela D. Cost-Effectiveness of Vaccination with the 20-Valent Pneumococcal Conjugate Vaccine in the Italian Adult Population. *Vaccines*. 2022; 10(12):2032. https://doi.org/10.3390/vaccines10122032

Effectiveness of vaccination in preventing pneumonia

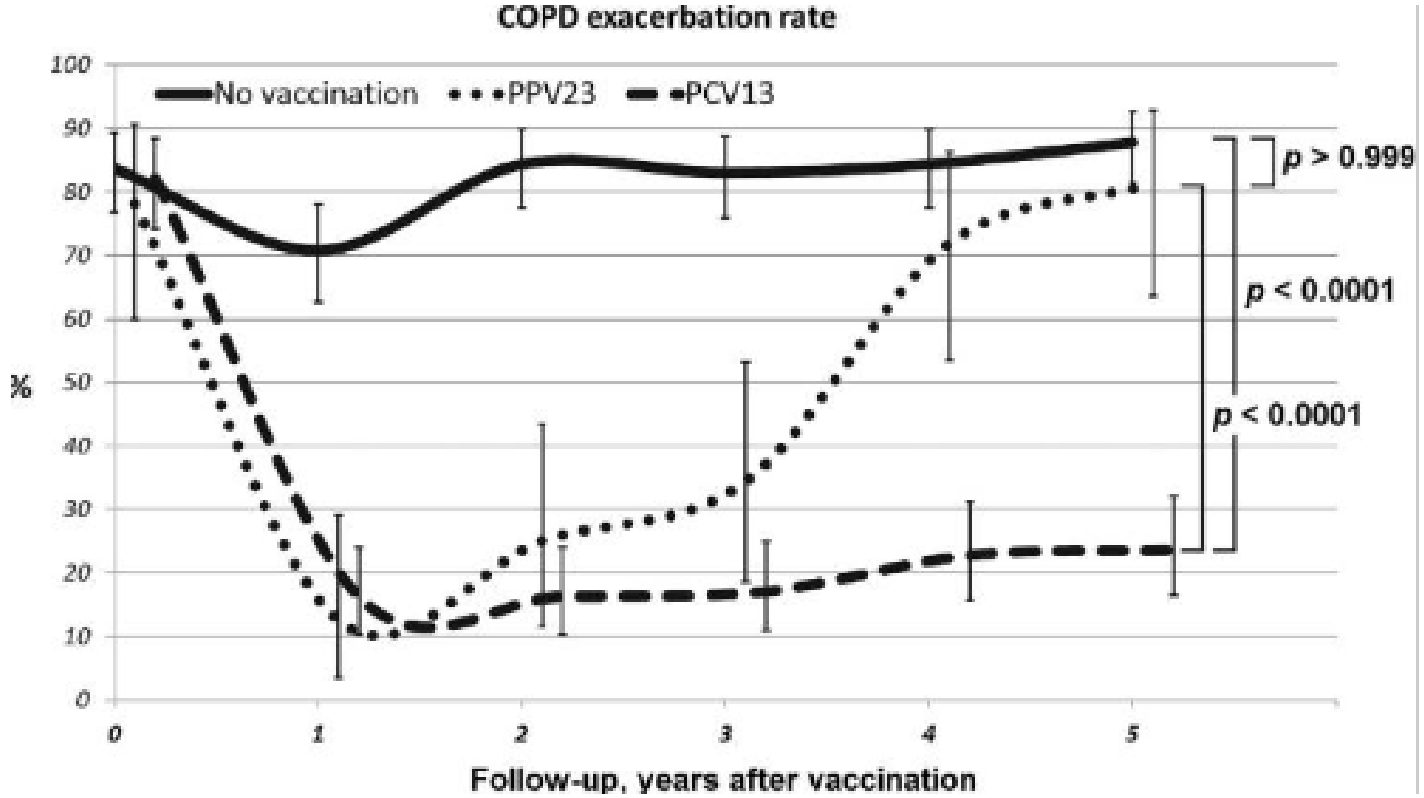
Dynamis of total pneumonia rate (A) and rate of hospitalizations with pneumonia (B) in the study groups.





Ignatova, G.L., Avdeev, S.N. & Antonov, V.N. Comparative effectiveness of pneumococcal vaccination with PPV23 and PCV13 in COPD patients over a 5-year follow-up cohort study. *Sci Rep* **11**, 15948 (2021). https://doi.org/10.1038/s41598-021-95129-w

Effectiveness of vaccination for reducing the rate of COPD exacerbations



Ignatova, G.L., Avdeev, S.N. & Antonov, V.N. Comparative effectiveness of pneumococcal vaccination with PPV23 and PCV13 in COPD patients over a 5-year follow-up cohort study. *Sci Rep* **11**, 15948 (2021). https://doi.org/10.1038/s41598-021-95129-w

PCV-13 Vaccination and ABR

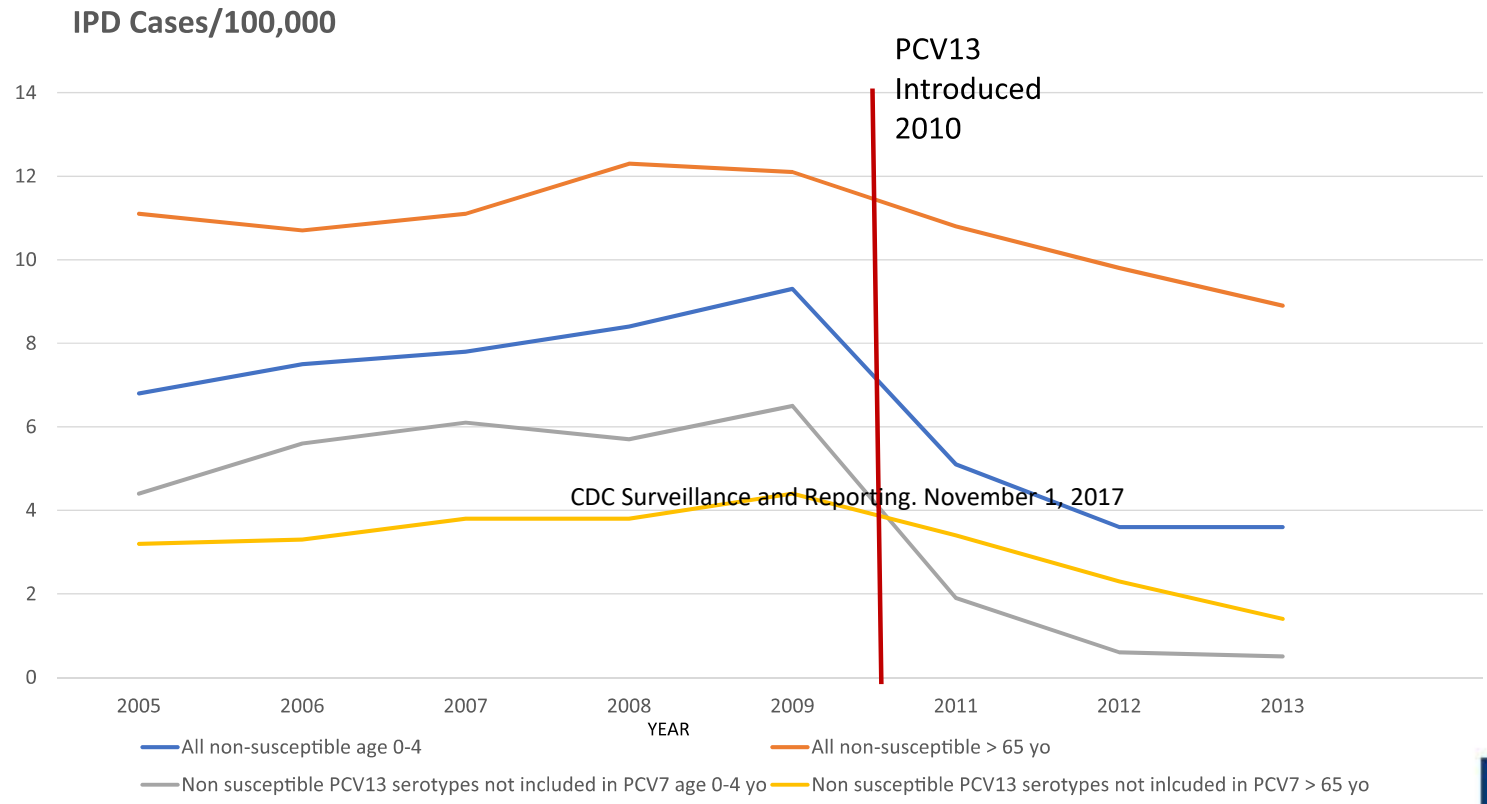
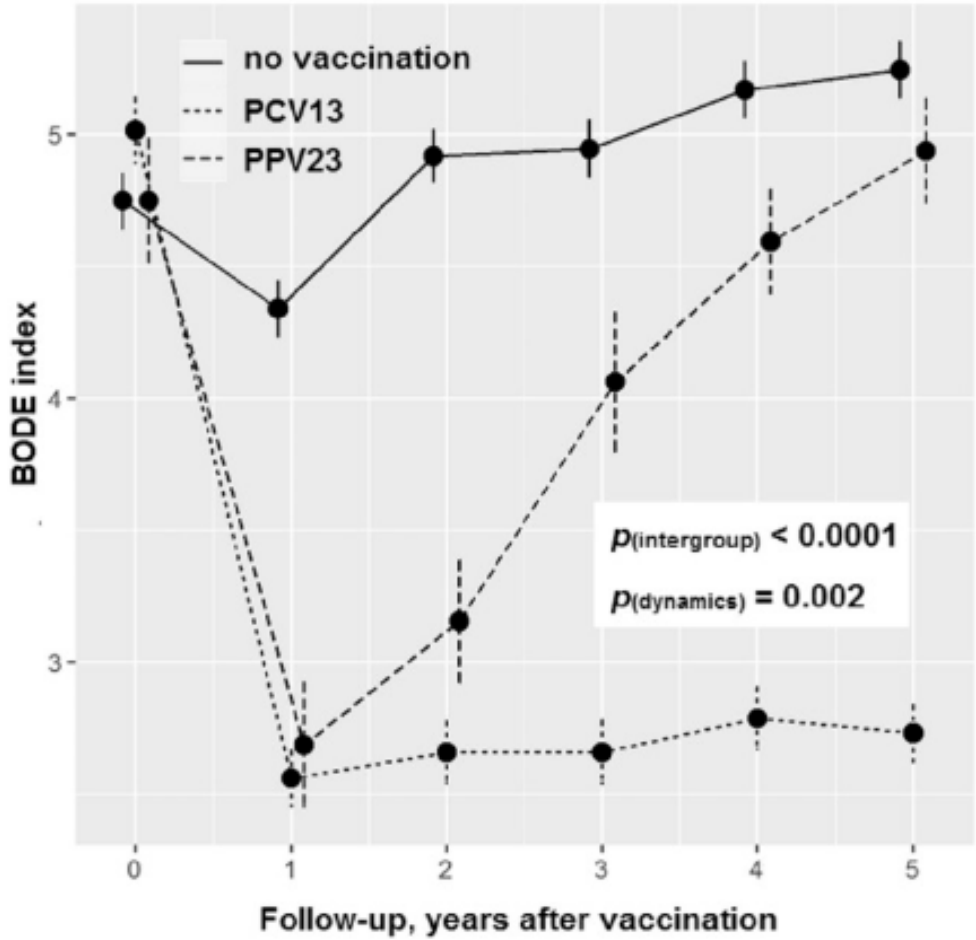


Fig. 2. US trends in invasive non–penicillin-susceptible pneumococcal disease 2005–2013.

Introduction of PCV13 demosntrated a reduction od non-penicillin-susceptible IPD in US

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Effectiveness of vaccination for improving patients' quality of life and respiratory function parameters



Ignatova, G.L., Avdeev, S.N. & Antonov, V.N. Comparative effectiveness of pneumococcal vaccination with PPV23 and PCV13 in COPD patients over a 5-year follow-up cohort study. *Sci Rep* **11**, 15948 (2021). https://doi.org/10.1038/s41598-021-95129-w

BODE index and COPD

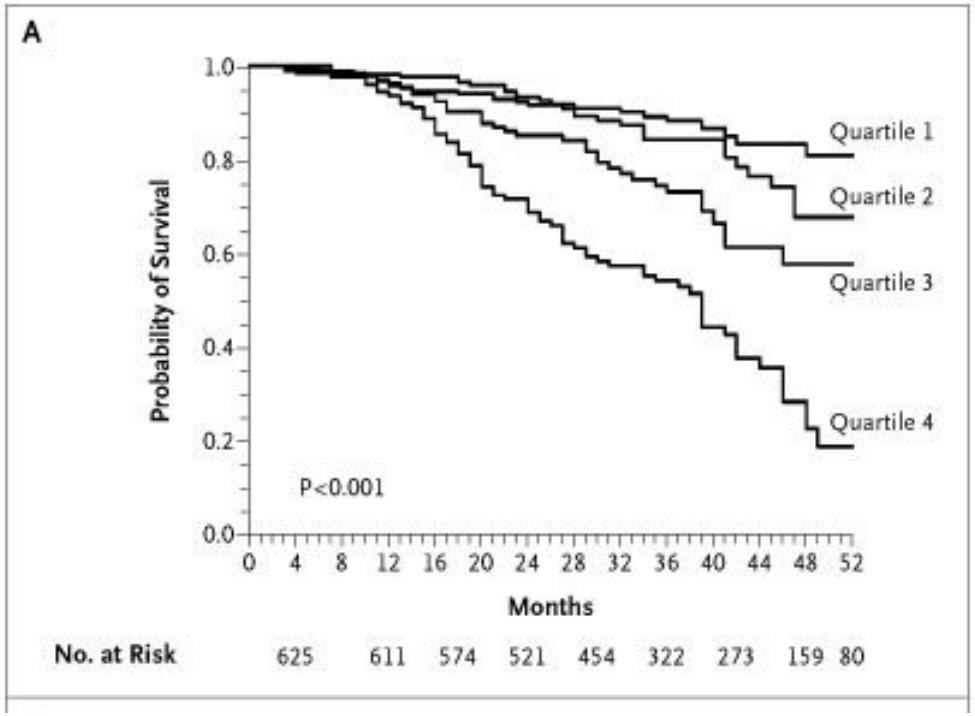


Table 2. Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index.*

Variable	Points on BODE Index			
	0	1	2	3
FEV_1 (% of predicted)†	≥65	50–64	36–49	≤35
Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale‡	0–1	2	3	4
Body-mass index§	>21	≤21		

* The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. FEV_1 denotes forced expiratory volume in one second.

† The FEV_1 categories are based on stages identified by the American Thoracic Society.

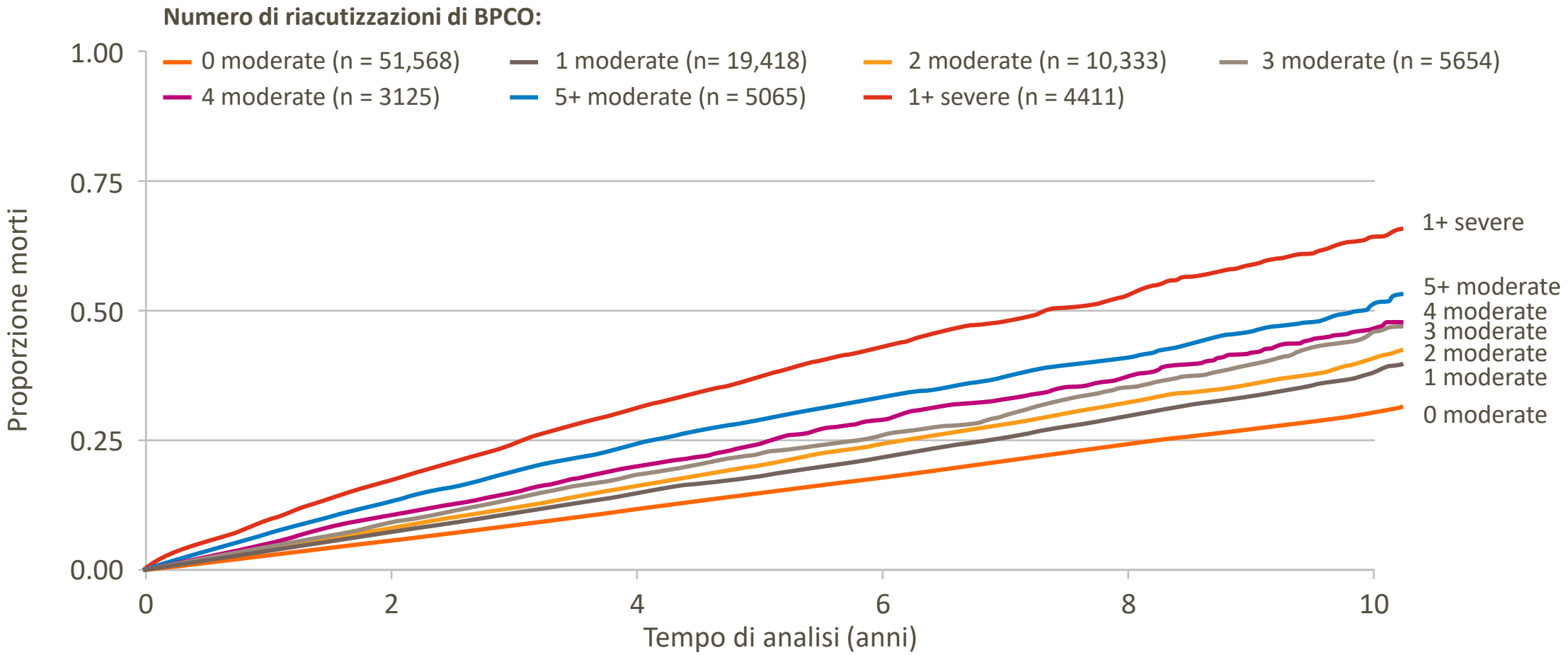
‡ Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

§ The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

Celli BR et al. N Engl J Med 2004; 350:1005-1012

Effetto sulla mortalità: la proporzione di morti aumenta con l'aumento di frequenza e severità delle riacutizzazioni

I pazienti a maggior rischio di morte sono quello con ≥1 riacutizzazione severa



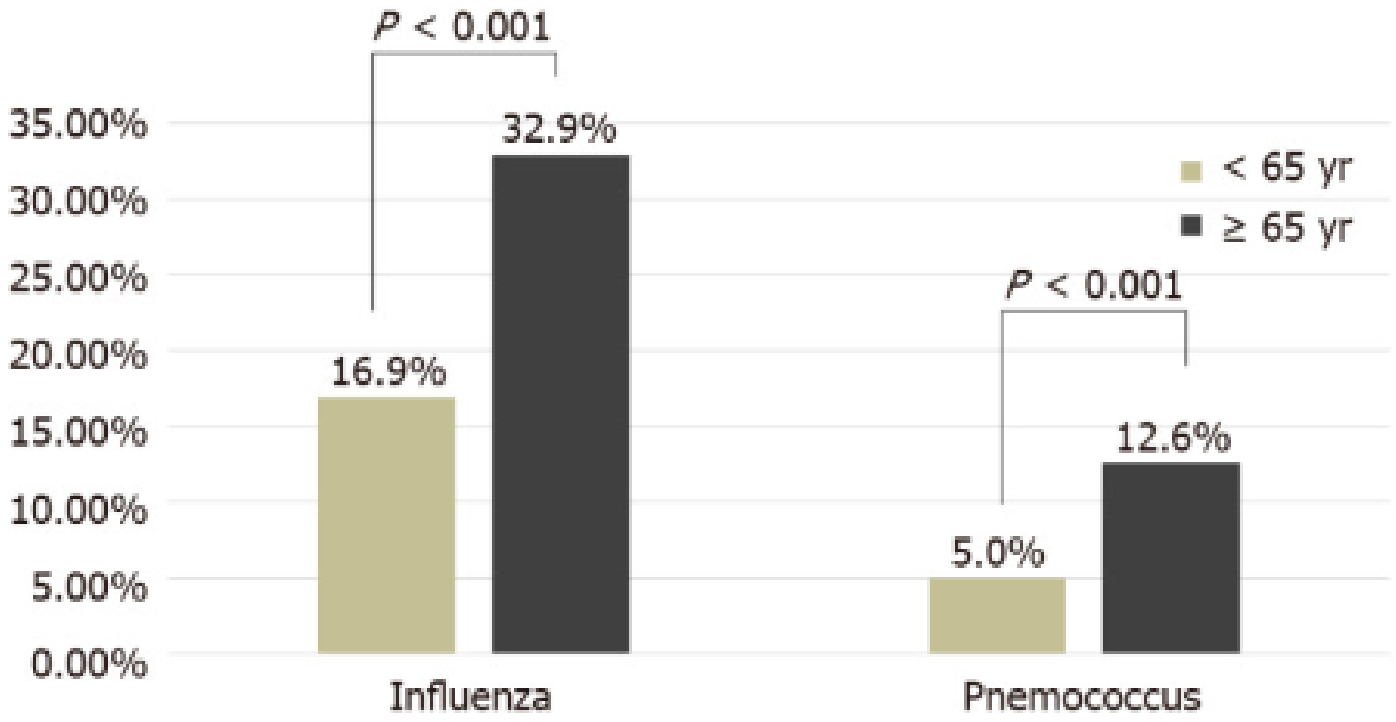
Population-based study of 99,574 patients with COPD from the UK Clinical Practice Research Datalink, 1 January 2004–31 March 2015.
Time to death assessed using a Cox proportional hazards model.

COPD, chronic obstructive pulmonary disease.

Rothnie KJ et al. Am J Resp Crit Care Med, 2018

The comparison of the vaccination rates in patients with type 2 diabetes mellitus (according to age): Turkish study

Prevention of influenza and pneumococcal infections with routine vaccination decreased mortality and morbidity and the hospitalization rates in patients with diabetes.



Demirci I, Haymana C, Salman S, et al. Rates and associates of influenza and pneumococcus vaccination in diabetes mellitus: A nationwide cross-sectional study (TEMD vaccination study). *World J Diabetes*. 2021;12(12):2107-2118. doi:10.4239/wjd.v12.i12.2107

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