Medische avond Infectiologie

Online - 2021

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- Vaccinatie tegen zona – D. Ommeslag
- Update pneumokokken vaccinatie – F Triest
- Meningokokken en vaccinatie – T Vercruysse

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Pneumokokkenvaccinatie

Een terugblik en stand van zaken

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- **Pneumokokkenziekte**
- Epidemiologie en risicofactoren
- Pneumokokken vaccinatie
- Aanbevelingen in België
- Vaccinatie in bijzondere omstandigheden
- Kernboodschappen

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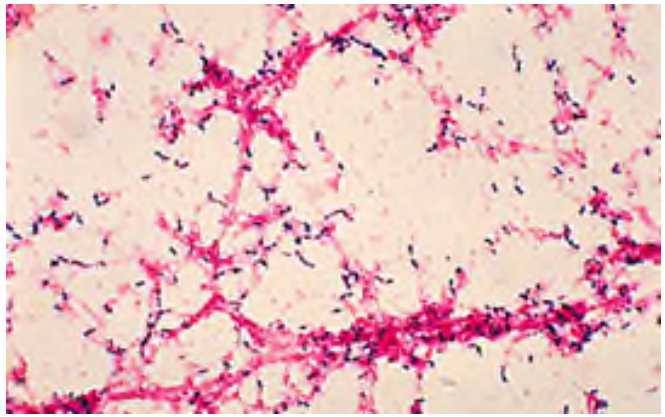
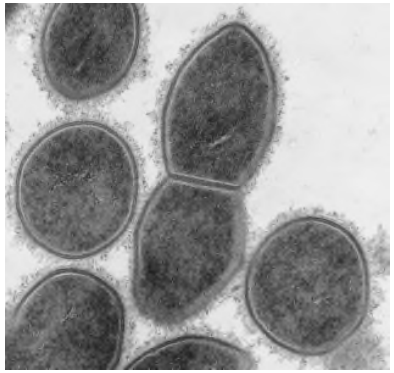
Geschiedenis

- 1881 Pasteur (Fr. ‘Micrococcus pasteuri’), Sternberg (US)
- 1883 Associatie pneumococcus en lobaire pneumonie
- 1884 Gramkleuring
- 1926 Diplococcus
  - *NB facultatief anaeroob gram-positief lancetvormig, typisch in paren*



- 1915 – 1945 structuur pn. polysaccaridekapsel
  - Associatie virulentie
  - 1940 > 80 serotypes
- S. pneumoniae
- 2020 > 100 serotypes



https://www.cdc.gov/vaccines/pubs/pinkbook/pneumo.html

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Kolonisatie en ziekte

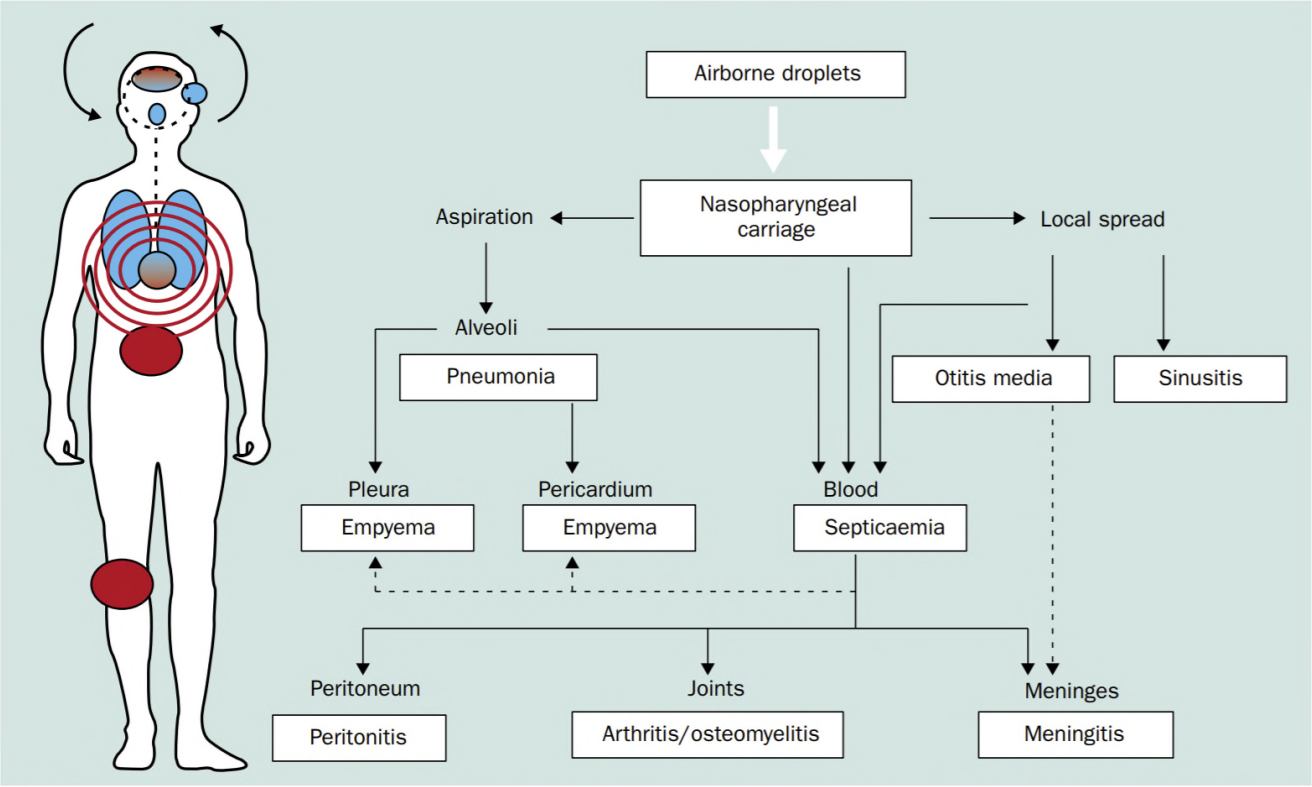

Figure 1. Pathogenic route for S pneumoniae *infection. Redrawn from reference 2. Organs infected through the airborne and haematogenic routes are depicted in blue and red, respectively.*

- Commensale flora BLW
  - Kinderen
    - Belangrijkste bron voor verspreiden
- Infecties
  - Wanneer ?
    - Afweer verzwakt
    - Tijdens virale LWI
    - Recente aqcquistie nieuw serotype
  - Voorkomen :
    - Doorgaans geïsoleerd
    - Clusters in kindercentra, verpleeghuizen
- Kapsel
  - Belangrijkste virulentiefactor
  - ≠ Types → ≠
    - Resistentie tegen fagocytose
    - Complementremming
    - Invasieve kenmerken

Bogaert et al. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *The Lancet. Infectious diseases*, *2004*
https://lci.rivm.nl/sites/default/files/entity_print_pdf/597/Pneumokokkenziekte.pdf

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- Pneumokokkenziekte
- **Epidemiologie en risicofactoren**
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- Kernboodschappen

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Epidemiologie – verspreiding

- Over hele wereld
- Voornamelijk winter en voorjaar in landen met gematigd klimaat
- Risicogroepen overdracht
  - Kinderen tot 3 jaar
  - ≥ 3 dagen per week opvang
  - Kinderen uit grote gezinnen
  - Tieners die vaak samen zijn (‘crowding’)

- Advies 9562: Vaccinatie tegen pneumokokken. Hoge Gezondheidsraad. Juli 2020.
- https://www.zorg-en-gezondheid.be/sites/default/files/atoms/files/34%20Pneumokokkose%20%E2%80%93%20invasieve%20pneumokokkenziekte.pdf

Epidemiologie – invasieve pneumokokkenziekte EU

Figure 1. Distribution of confirmed invasive pneumococcal disease cases per 100 000 population by country, EU/EEA, 2018

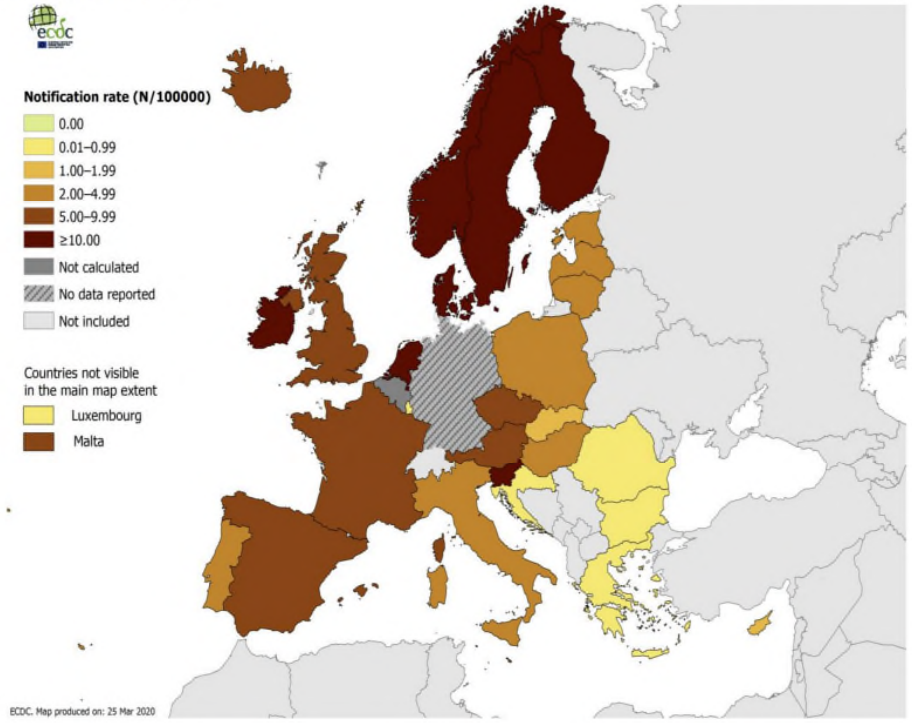


Figure 2. Distribution of confirmed invasive pneumococcal disease cases per 100 000 population, by age and gender, EU/EEA, 2018

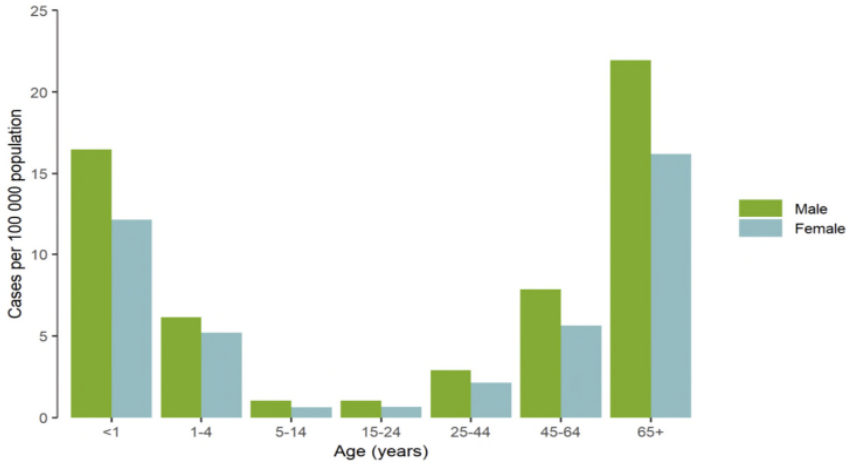
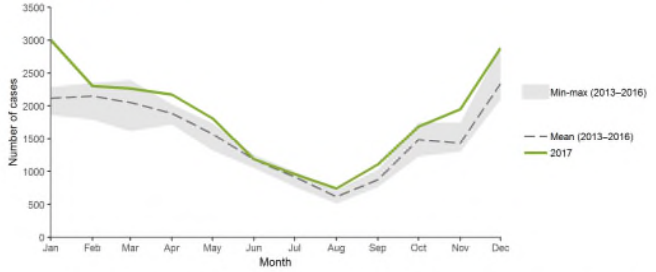


Figure 3. Distribution of confirmed invasive pneumococcal disease cases by month, EU/EEA, 2013–2016 and 2017



Source: Country reports from Austria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

- https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2018_IPD.pdf

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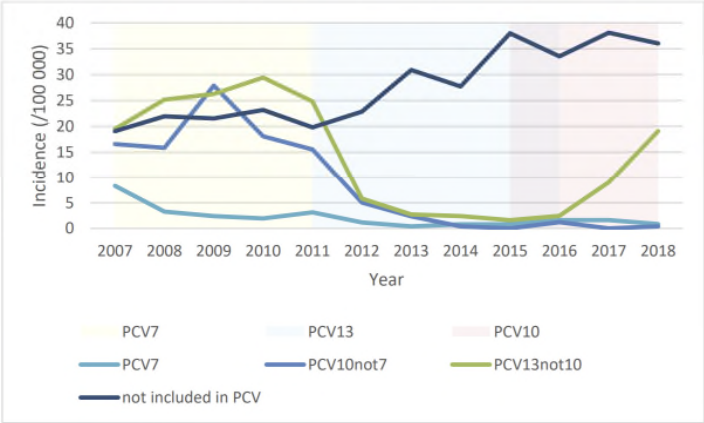
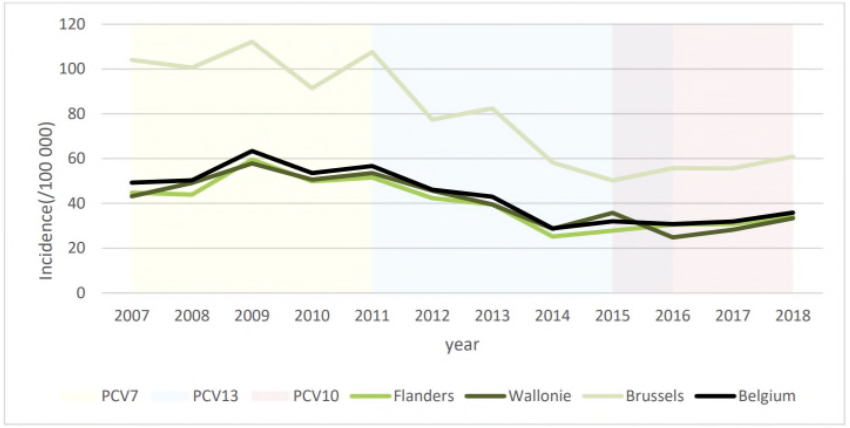
Epidemiologie – invasieve pneumokokkenziekte België

Figuur 4: Incidentie van invasieve pneumokokkeninfecties (/100,000) voor kinderen jonger dan 2 jaar voor vaccin-serotypes PCV7, PCV10-serotypes niet in PCV7 (PCV10not7) en PCV13-serotypes niet in PCV10 (PCV13not10), 2007-2018, België (Bron: NRC voor *S. pneumoniae*, UZ Leuven)



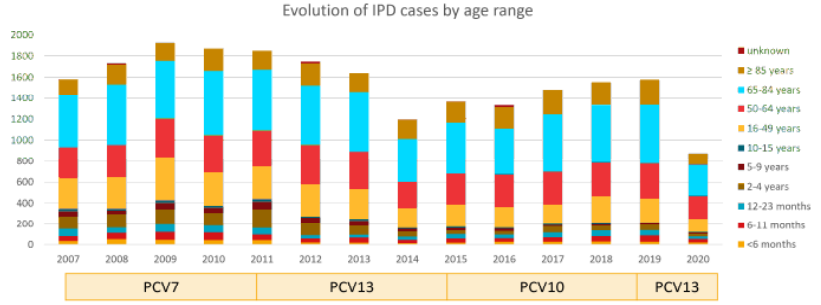
Figuur 4: Incidentie van invasieve pneumokokkeninfecties (/100,000) voor personen ouder dan 50 jaar per regio, 2007-2018, België (Bron: NRC voor *S. pneumoniae*, UZ Leuven)



2004 PCV7
2011 PCV13
2015 (V) PCV10
2016 (W) PCV10
2017 PCV13

- **Trends**
  - 2007: daling IPP incidentie bij kinderen jonder dan 2 jaar
  - 2011 – 2015 daling in alle leeftijdsgroepen
  - 2016 opnieuw stijging in alle leeftijdsgroepen
    (onder niveau pre-vaccinatie)
- **PVC13-exclusieve serotypes**
  - 3, 6A, 19A
    - **19A: 2016 2% -> 2018 27% van invasieve infecties**
  - 2007 – 2011: lichte stijging
  - 2011 – 2012: daling
  - 2016 stijging

IPD by year and by age range – Surveillance in Belgium

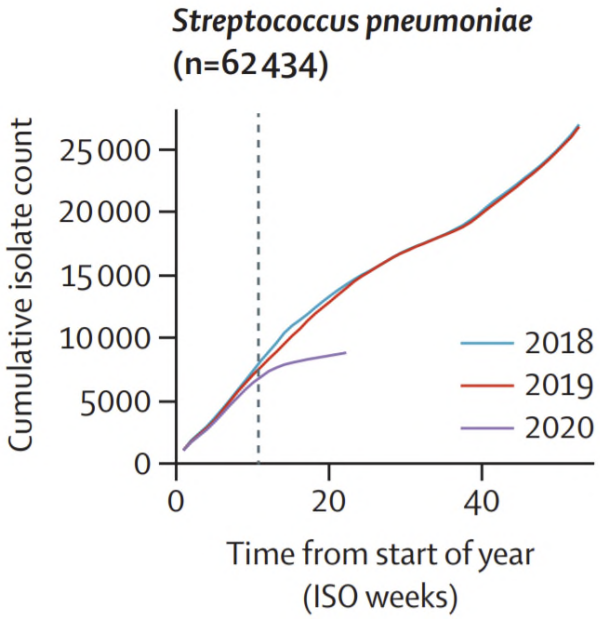


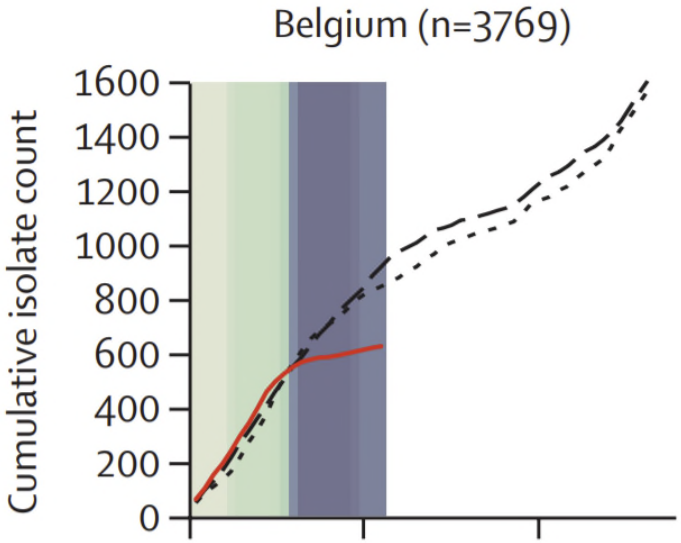
Based on data from table 3 (sum of bacteremia and pleuritis and meningitis cases)

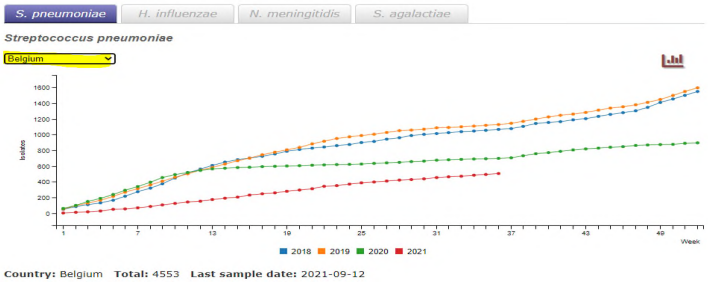
- https://www.sciensano.be/sites/default/files/rapport_ipd_2018_nl_web2.pdf
- https://nrchm.wiv-isp.be/nl/ref_centra_labo/streptococcus_pneumoniae_invasive/Rapporten/Rapport%20Streptococcus%20pneumoniae%202020.pdf

	Prik 1 (merknaam vaccin)	Prik 2 (merknaam vaccin)	extra vaccin
8 weken	IPV-DTPa-Hib-HBV (Hexyon)	Pnc-13 (Prevenar 13)	Rota[2,3]
12 weken	IPV-DTPa-Hib-HBV (Hexyon)		Rota[2,3]
16 weken	IPV-DTPa-Hib-HBV (Hexyon)	Pnc-13 (Prevenar 13)	Rota[2,3]
12 maanden	MBR (MMR VAX Pro)	Pnc-13 (Prevenar 13)	
15 maanden	IPV-DTPa-Hib-HBV (Hexyon)	MenC (NeisVac-C)	
6 jaar	IPV-DTPa (Tetravac)		
10 jaar	MBR (MMR VAX Pro)		
12 jaar	HPV (Gardasil 9)[1]		
14 jaar	dTpa (Triaxis)		

Impact van strikte isolatie en hygiënische maatregelentijdens de COVID pandemie







Interpretation The introduction of COVID-19 containment policies and public information campaigns likely reduced transmission of *S pneumoniae*, *H influenzae*, and *N meningitidis*, leading to a significant reduction in life-threatening invasive diseases in many countries worldwide.

Brueggemann et al. Changes in the incidence of invasive disease due to Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative. *The Lancet. Digital health*, *2021*

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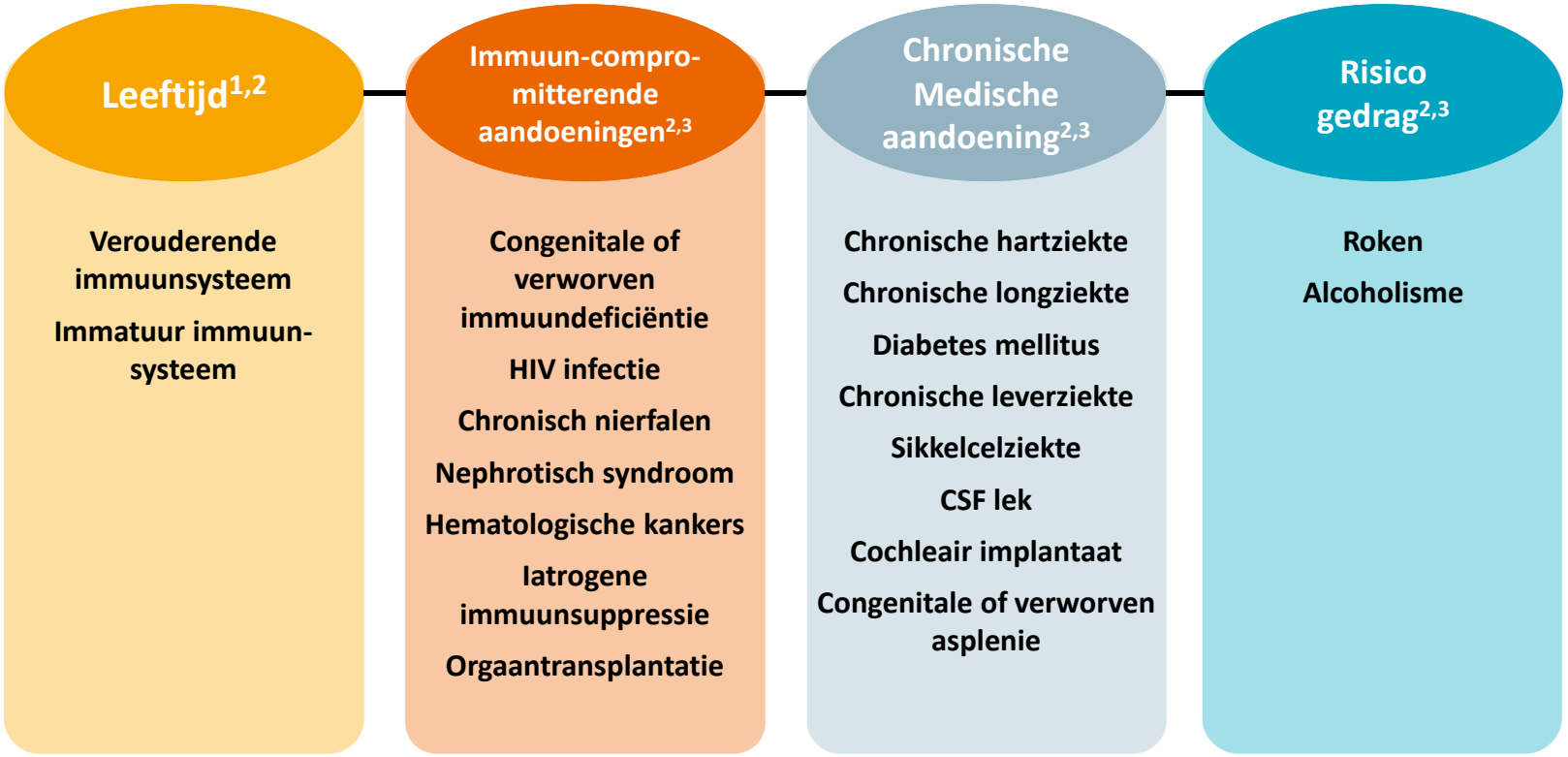
Risicofactoren voor pneumokokkenziekte



CSF=cerebrospinal fluid; HIV=human immunodeficiency virus.

1. Centers for Disease Control and Prevention. Active Bacterial Core surveillance (ABCs) report. Emerging Infections Program Network: *Streptococcus pneumoniae*, 2014. http://www.cdc.gov/abcs/reports-findings/survreports/spneu14.pdf. Accessed April 11, 2017. **2.** Kobayashi M, et al. *MMWR Morb Mortal Wkly Rep*. 2015;64(34):944-947. **3.** Centers for Disease Control and Prevention. Pneumococcal disease. In: Hamborsky J, Kroger A, Wolfe S, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases.* 13th ed. Washington, DC: Public Health Foundation; 2015:279-296.

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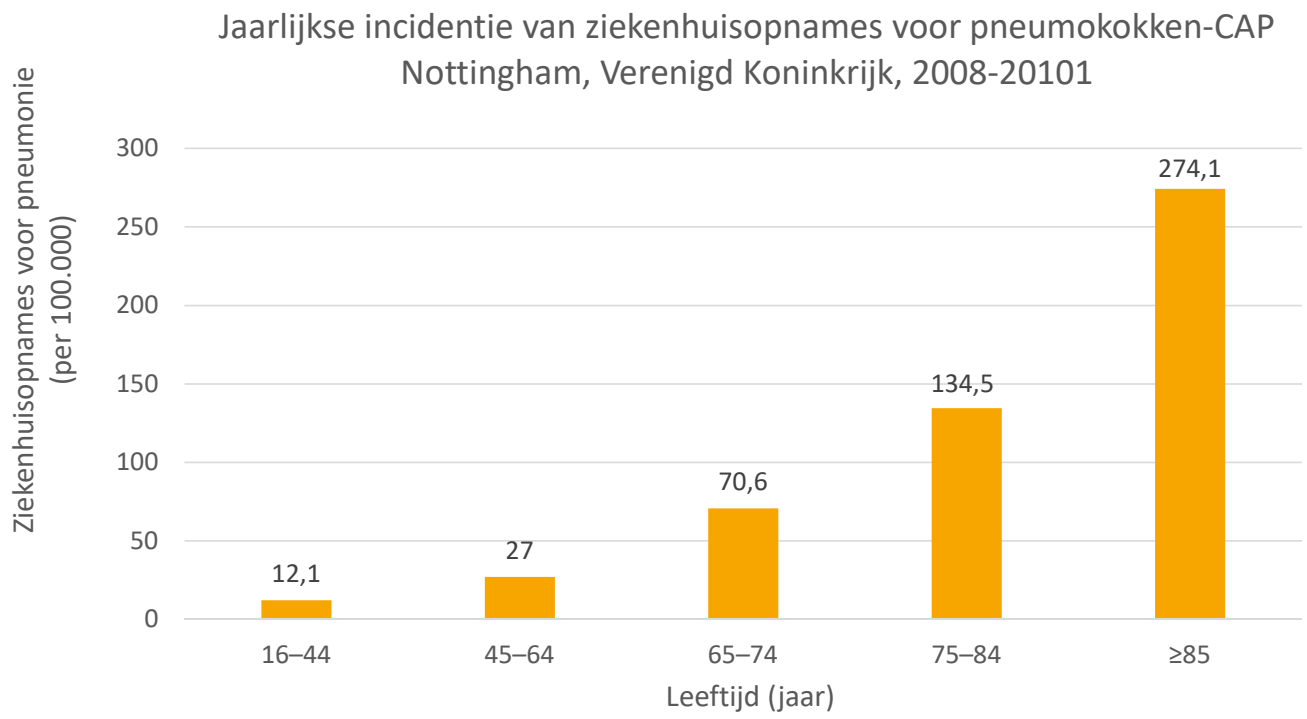
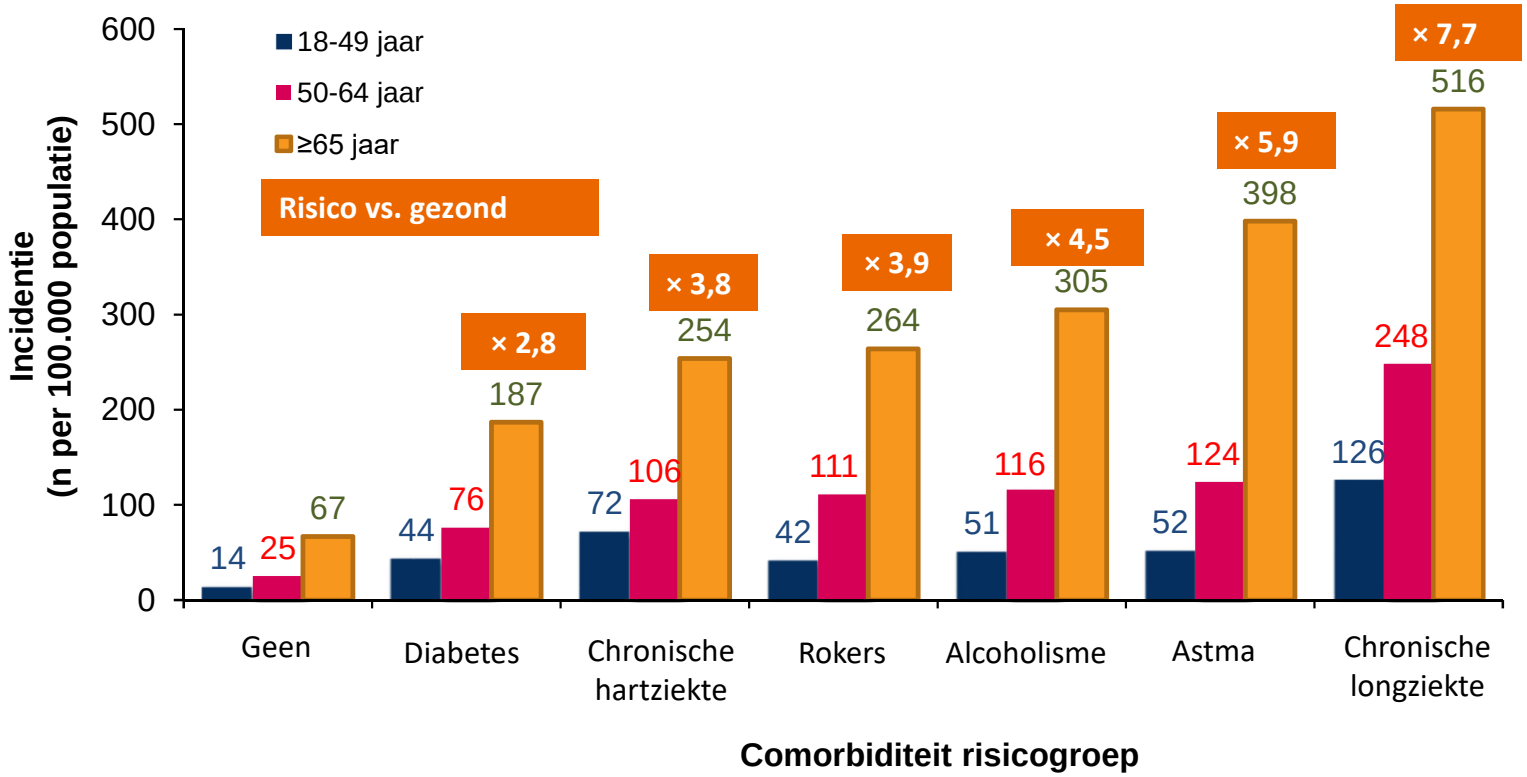
Risico voor opname wegens pneumokokken pneumonie stijgt met de leeftijd



Prospectief, observationeel cohortonderzoek gedurende 2 jaar in een grote groep van opleidingsziekenhuizen in het VK.

1. Bewick T, et al. Thorax 2012;67:540–45.

Comorbiditeiten en ‘risico gedrag’ verhogen het risico op pneumokokkenpneumonie



Gegevens van een retrospectief cohortonderzoek uit 3 grote, longitudinale, Amerikaanse gezondheidszorgdatabanken van de medische en poliklinische verkoop van geneesmiddelen van 2007 tot 2010

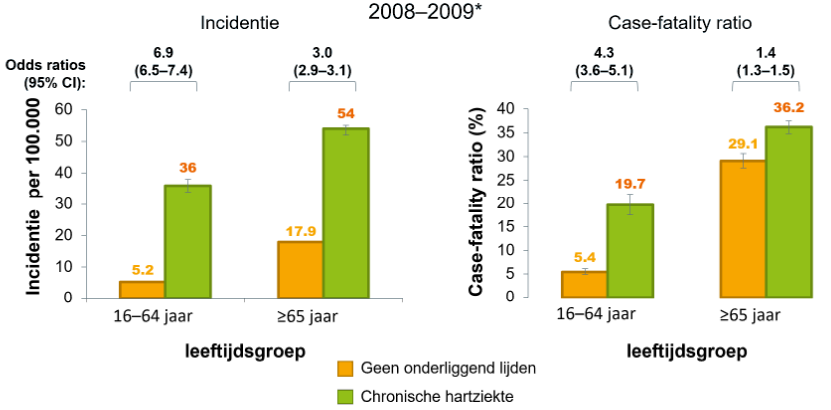
*Personen in de leeftijd van 18-49 jaar, 50-64 jaar en ≥65 jaar droegen bij aan een totaal van respectievelijk 49,3 miljoen, 30,6 miljoen en 11,7 miljoen persoonsjaren van observatie.

Shea KM, et al. Open Forum Infect Dis. Published online May 8, 2014. doi:10.1093/ofid/ofu024.

Comorbiditeiten verhogen het risico op en van invasieve pneumokokkenziekte (mortaliteit)

Hogere incidentie en mortaliteit van invasieve pneumokokkenziekte bij volwassenen met chronische hart- ziekten*

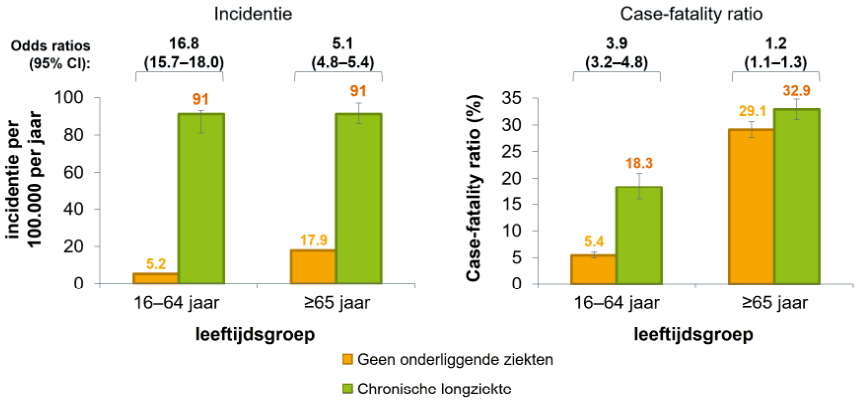
Geschatte jaarlijkse incidentie en de case-fatality ratio van invasieve pneumokokkenziekte in Engeland bij personen met chronische hartziekte, per leeftijd, 2008–2009*



* Een populatie van 1213 volwassenen van 16-64 jaar en 4841 volwassenen van ≥65 jaar met ischemische hartziekte die behandeling vereist, congenitale hartaandoening, hypertensie met hartcomplicaties of chronisch hartfalen nodig hebben, Engeland, 2008-2009.CI = betrouwbaarheidsinterval.van Hoek AJ, et al. J Infect. 2012; 65 (1): 17-24.

Hogere incidentie en mortaliteit van invasieve pneumokokkenziekte bij volwassenen met chronische longziekten

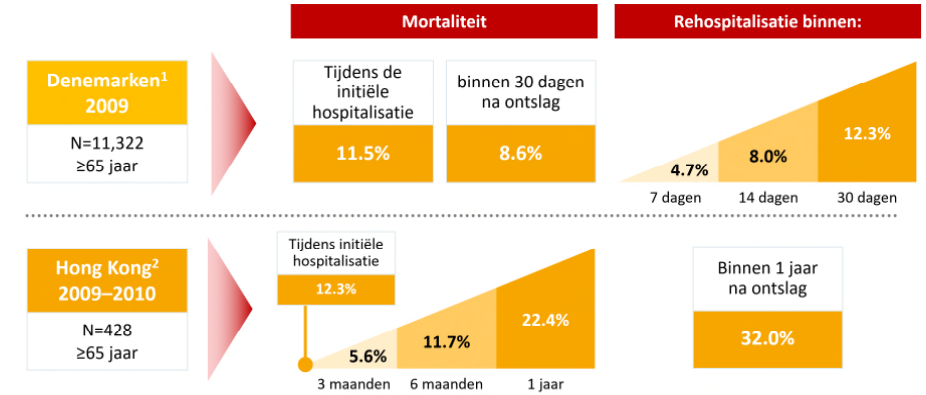
Geschatte jaarlijkse incidentie en de case-fatality ratio van IPZ in Engeland bij personen met chronische longziekte, per leeftijd, 2008–2009*



* Een populatie van 938 patiënten van 16-64 jaar en 2364 patiënten van 65+ jaar met chronische obstructieve longziekte, chronische bronchitis en emfyseem (exclusief astma), Engeland, 2008-2009.
CI = betrouwbaarheidsinterval.
van Hoek AJ, et al. J Infect. 2012; 65 (1): 17-24.

Mortaliteit en morbiditeit bij pneumonie

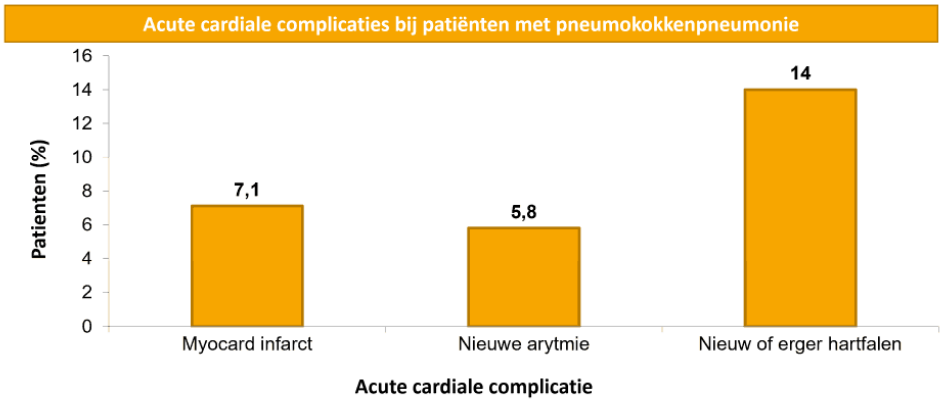
Optreden van een pneumonie is geassocieerd met rehospitalisaties en mortaliteit bij 65+'ers



Rehospitalisatie voor pneumonie was de meest significante risico factor voor mortaliteit

Klausen HH, et al. *Respir Med*. 2012;106:1778-1787. **2.** Ma HM, et al. *Intern Med J*. 2013;43:1210-1215.

Hospitalisatie voor pneumokokken-pneumonie = verhoogd risico op majeure cardiale complicaties



Musher DM, et al. *Clin Infect Dis*. 2007;45(2):158-165.

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Geschiedenis

Sir Almroth Wright coordinated the first trial of a whole-cell pneumococcal vaccine in South Africa from 1911 to 1912.

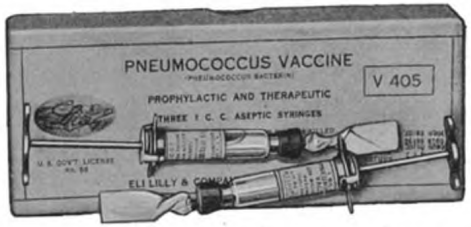
Pneumococcus Vaccine, Prophylactic and Therapeutic (Pneumococcus Bacterin).

Used for the prophylaxis and treatment of pneumonia.

DOSAGE: Initial dose in treatment, 50 million. Subsequent doses, given at intervals of twenty-four hours, should be increased rapidly.

In case of epidemics of pneumonia, the advisability of preventive inoculations of the vaccine should be considered. Wright, after his extensive work among the natives of South Africa, decided that a dose of 1,000 million killed pneumococci was productive of the most satisfactory results, and that the incidence of pneumonia was materially reduced in the three months following inoculation. Lister's more recent work on both animals and man has established certain important facts as to the value of this method of preventing pneumonia. He recommends three subcutaneous injections at seven-day intervals consisting of 2,000 million killed pneumococci of the types against which immunization is desired.

The most recent work is that of Cecil and Austin at Camp Upton, New York. These workers vaccinated 12,519 men against Types I, II and III of the pneumococcus and arrived at the conclusion that prophylactic vaccination against these organisms is practical and apparently gives protection against the pneumonias produced by these types of the pneumococcus.



1,000 million killed pneumococci in each c. c.

V 396 Two 1 c. c. ampoule vials.
V 398 One 5 c. c. ampoule vial.
V 399 One 20 c. c. vial.
V 401 One 1 c. c. aseptic syringe.

V 404 Three 1 c. c. ampoule vials, one each of 250, 500 and 1,000 million.
V 405 Three 1 c. c. aseptic syringes, one each of 250, 500 and 1,000 million.

TABLE I. Pneumococcal vaccines distributed since 1977

Manufacturers (trade names)	Valence: serotypes included	Date introduced, initial region
Pneumococcal polysaccharide vaccines		
Merck Sharp & Dohme (MSD) (Pneumovax™)	14-valent: 1, 2, 3, 4, 5, 6A, 7F, 8, 9N, 12F, 18C, 19F, 23F, 25F	November 1977, USA
Lederle Laboratories (Pnu-Imune™)		August 1979, USA
Institut Mérieux (Imovax Pneumo 14™)		February 1981, France
SmithKline Beecham (Moniarix™)	17-valent: 1, 2, 3, 4, 6A, 7F, 8, 9N, 11A, 12F, 14, 15F, 17F, 18C, 19F, 23F, 25	1980s, Europe
Merck Sharp & Dohme (MSD) (Pneumovax™ 23)	23-valent: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	July 1983, USA
Lederle Laboratories (Pnu-Imune™ 23)		July 1983, USA
Institut Mérieux (Pneumo 23™)		1987, Europe
Chengdu Institute of Biological Products		2005, China
Pneumococcal conjugate vaccines		
Wyeth Laboratories (Prevnar™ or Prevenar™)	7-valent: 4, 6B, 9V, 14, 18C, 19F, 23F	February 2000 for infants, USA and Europe
GlaxoSmithKline (Synflorix™)	10-valent: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	March 2009 for infants: Europe
Wyeth Laboratories (Prevnar™ 13 or Prevenar™ 13)	13-valent: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	February 2010 for infants, late 2011 for adults, Europe, Australia, USA

J.D. Grabenstein, K.P. Klugman. A century of pneumococcal vaccination research in humans. Clinical Microbiology and Infection, 2012

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Overzicht serotypes in pneumokokkenvaccins

	Vaccin	Serotypes	Extra serotypes
Conjugaat	PCV13[1]	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, 19A	tav PCV10: 3, 6A, 19A
Conjugaat	PCV10[3]	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	
Polysaccharide	PPSV[2]	Opgenomen (behalve 6A)	2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F

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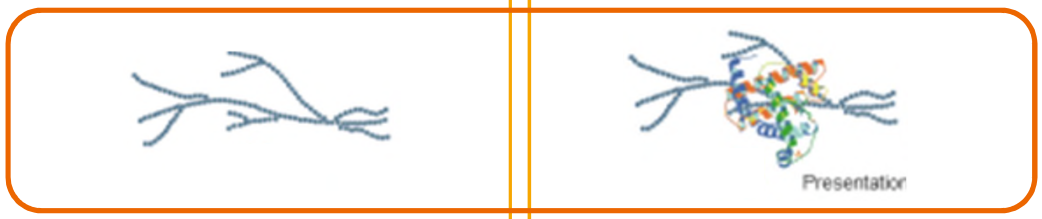
Geconjugeerde vaccins

Polysaccharide Vaccine		Conjugate Vaccine
• Contain polysaccharide antigens		• Contain polysaccharide antigens covalently linked to a carrier protein
• Stimulate B cells to produce antibodies		• Stimulate T cells to help B cells produce antibodies and generate immune memory
• T-cell–*independent* immune response that cannot be boosted		• T-cell–*dependent* immune response and booster response with revaccination

Conjugation allows for stimulation of the T-cell–dependent immune response necessary for immune memory

1Siegrist CA. In: Plotkin et al, eds. *Vaccines.* 5th ed. Philadelphia, PA: Saunders Elsevier; 2008:17-36. **2.** Pollard AJ, et al. *Nat Rev Immunol*. 2009;9(3):213-220. **3.** Clutterbuck EA, et al. *Immunology.* 2006;119(3):328-337.
de Roux A, et al. *Clin Infect Dis.* 2008;46(7):1015-1023.

Winje BA, Berild JD, Vestrheim DF, Denison E, Lepp T, Roth A, Valentiner-Branth P, Slotved HC, Storsæter J
Efficacy and effectiveness of pneumococcal vaccination in adults – an update of the literature". Report 2019. Oslo: Norwegian Institute of Public Health, 2019.

PPV23 – invasieve pneumokokkenziekte

Figure 1. Forest plot for the comparison of PPV23 vs no vaccine for the prevention of invasive pneumococcal disease, all serotypes (any IPD) – RCTs

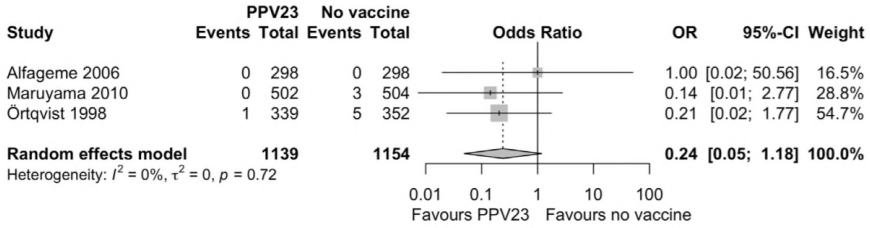
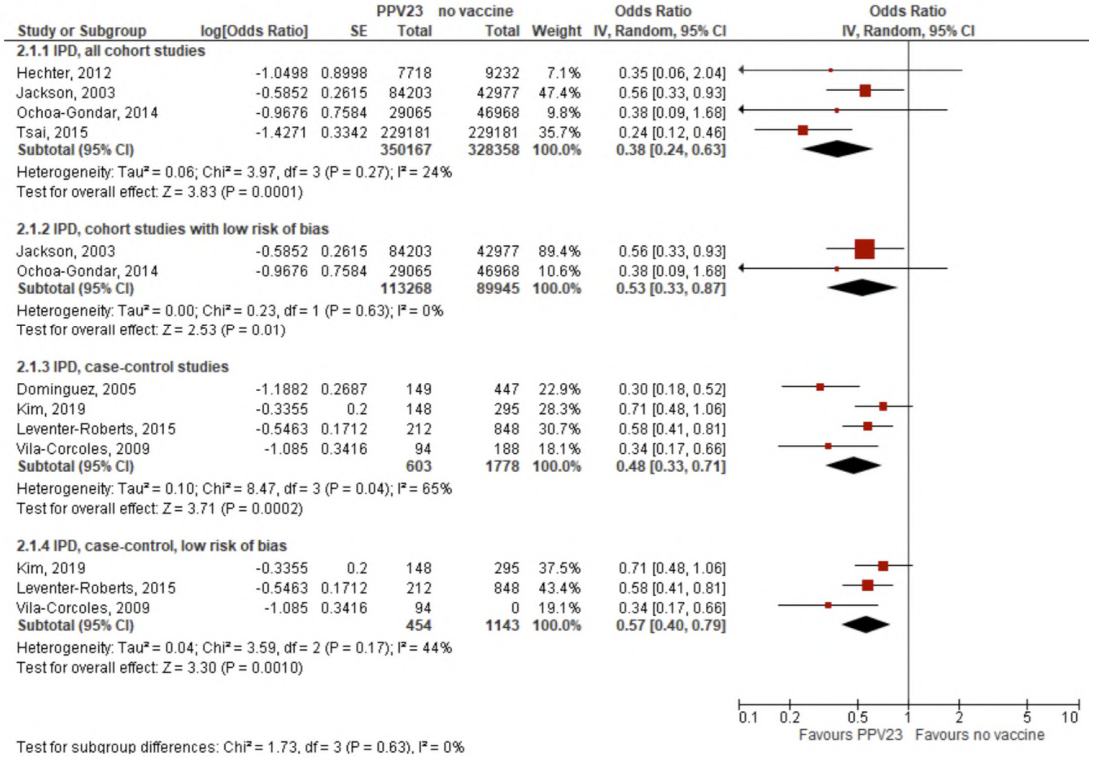


Figure 2, Forest plot for the comparison of PPV23 vs no vaccine for the prevention of invasive pneumococcal disease, all serotypes (any IPD) – observational studies[1]



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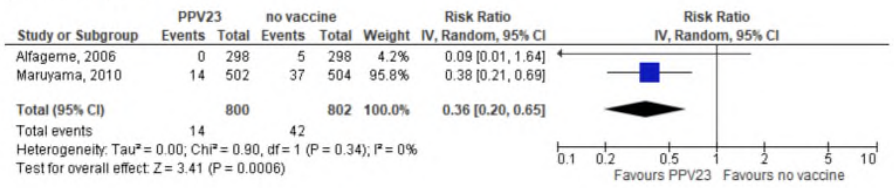
PPV23 – pneumonie

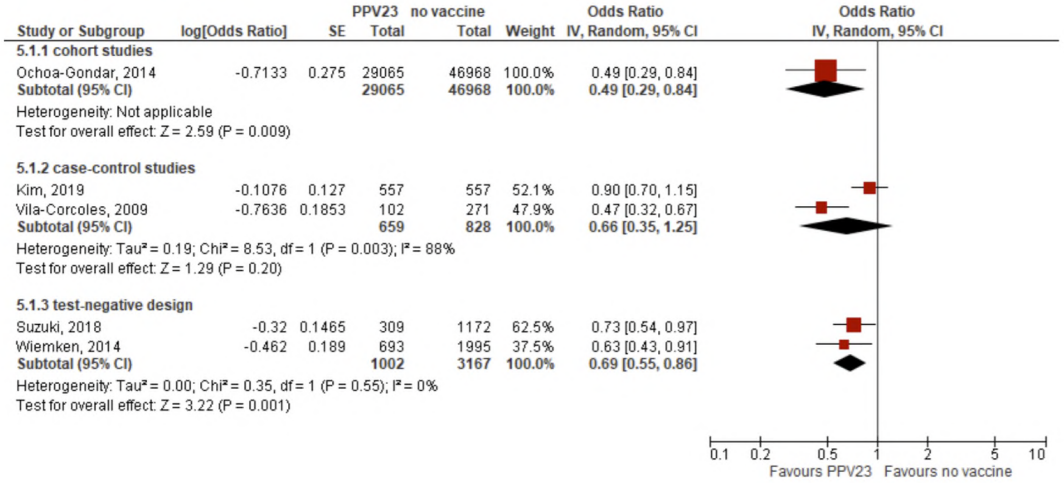
Figure 4, Forest plot for the comparison of PPV23 vs no vaccine for the prevention of pneumococcal pneumonia (PnPn) – RCTs



Study or Subgroup	PPV23 Events	PPV23 Total	no vaccine Events	no vaccine Total	Weight	Risk Ratio IV, Random, 95% CI
Alfageme, 2006	0	298	5	298	4.2%	0.09 [0.01, 1.64]
Maruyama, 2010	14	502	37	504	95.8%	0.38 [0.21, 0.69]
Total (95% CI)		**800**		**802**	**100.0%**	**0.36 [0.20, 0.65]**
Total events	14		42			

Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 3.41 (P = 0.0006)

Figure 5, Forest plot for the comparison of PPV23 vs no vaccine for the prevention pneumococcal pneumonia (PnPn) - observational studies



Study or Subgroup	log[Odds Ratio]	SE	PPV23 Total	no vaccine Total	Weight	Odds Ratio IV, Random, 95% CI
5.1.1 cohort studies						
Ochoa-Gondar, 2014	-0.7133	0.275	29065	46968	100.0%	0.49 [0.29, 0.84]
Subtotal (95% CI)			**29065**	**46968**	**100.0%**	**0.49 [0.29, 0.84]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.59 (P = 0.009)						
5.1.2 case-control studies						
Kim, 2019	-0.1076	0.127	557	557	52.1%	0.90 [0.70, 1.15]
Vila-Corcoles, 2009	-0.7636	0.1853	102	271	47.9%	0.47 [0.32, 0.67]
Subtotal (95% CI)			**659**	**828**	**100.0%**	**0.66 [0.35, 1.25]**
Heterogeneity: Tau² = 0.19; Chi² = 8.53, df = 1 (P = 0.003); I² = 88%						
Test for overall effect: Z = 1.29 (P = 0.20)						
5.1.3 test-negative design						
Suzuki, 2018	-0.32	0.1465	309	1172	62.5%	0.73 [0.54, 0.97]
Wiemken, 2014	-0.462	0.189	693	1995	37.5%	0.63 [0.43, 0.91]
Subtotal (95% CI)			**1002**	**3167**	**100.0%**	**0.69 [0.55, 0.86]**
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 3.22 (P = 0.001)						

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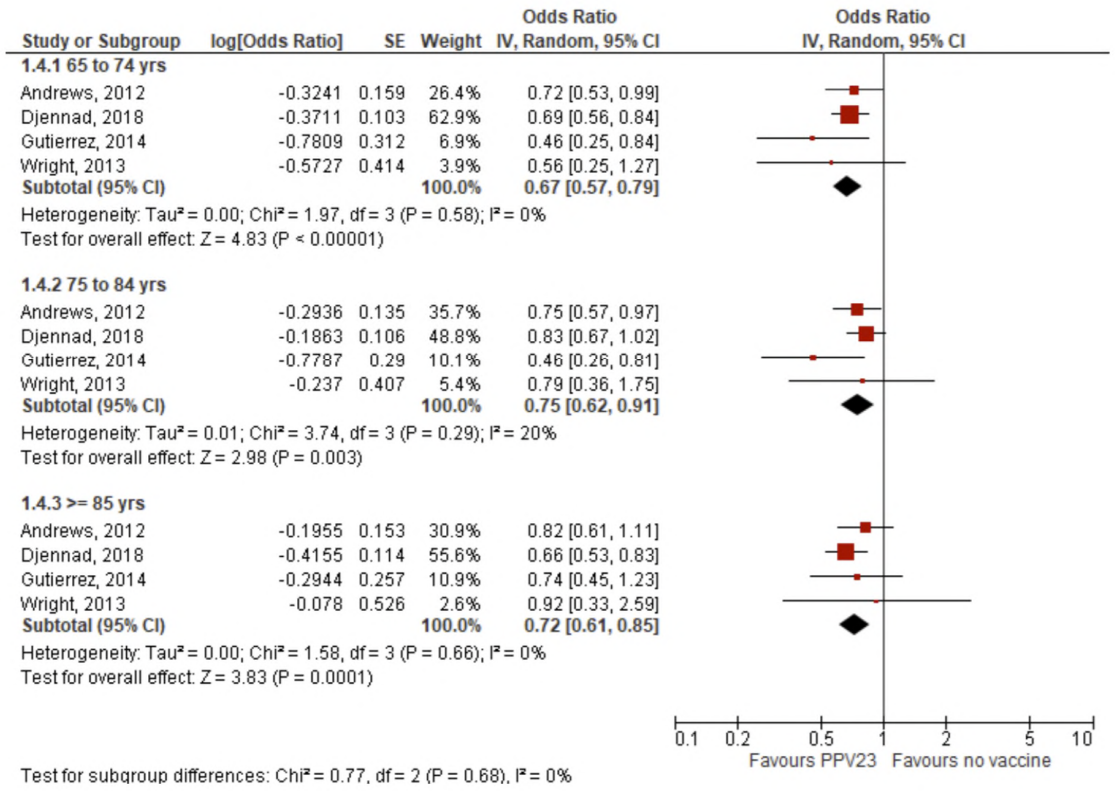
PPV23 – invasieve pneumokokkenziekte – effect van leeftijd

Appendix 6: PPV23 VE for the prevention of VT-IPD by age, indirect cohort studies



PPV23 – effect van tijd

Table 13, Vaccine effectiveness (VE % [95% CI]) against pneumococcal disease outcomes by time since vaccination for PPV23

Author (y)	Outcome	VE by time since vaccination (y)			
		< 2 y	2 to < 5 y	5 to < 10 y	>= 10 y
Suzuki, 2017	PnPn	32 (2 to 51)	26 (-12 to 51)	0.2 (-77 to 27)	
	VT-PnPn	38 (5 to 59)	35 (-7 to 60)	26 (-56 to 65)	
Andrews, 2012	VT-IPD	48 (32 to 60)	21 (3 to 60)	15 (-3 to 30)	
Djennad, 2019	VT-IPD	41 (23 to 54)	34 (16 to 48)	23 (12 to 32)	
Gutierrez, 2014*	VT-IPD	45 (19 to 62)		33 (-6 to 57)	
Rudnick, 2013	VT-IPD	41 (20 to 57)		34 (6 to 54)	
Wright, 2013	VT-IPD	-9 (-119 to 43)		38 (-6 to 64)	-21 (-137 to 35)

*included individuals >= 60 years

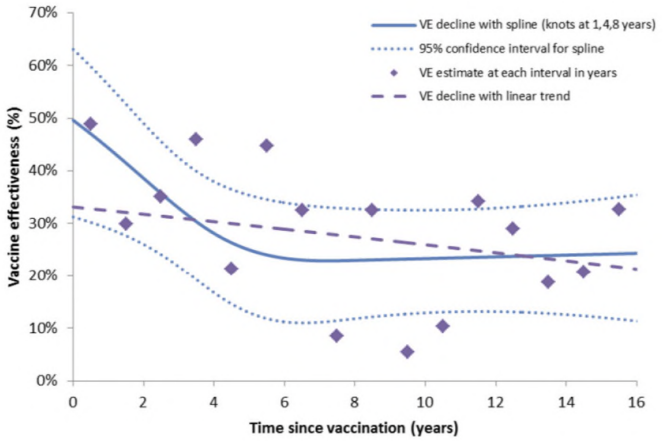


Fig. 1. Vaccine effectiveness by time since vaccination using the spline model and a linear decline. Individual estimates for each year are also shown but are based on small numbers within each year.

- Djennad et al A, *EClinicalMedicine*, *2019*

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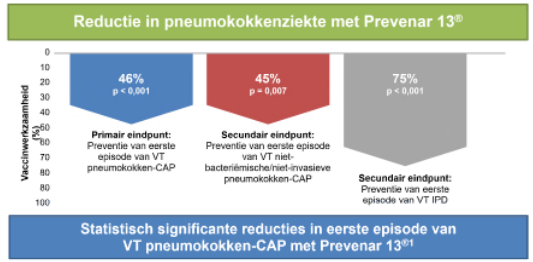
PCV13

Table 6, Overview of publications in CAPITA (clinical endpoints), amended from KCE report

Study characteristics, CAPITA	Community-Acquired Immunization Trial in Adults				
Region, country	The Netherlands				
Design	Parallel-group, double blind, randomized, placebo-controlled trial				
Study period	2008-2013, enrollment 2008-2010				
Population	Adults ≥65 years with no previous pneumococcal vaccination, no immunosuppression or immunodeficiency, no known hypersensitivity to vaccination and not living in nursing homes or other long-term care facilities. Included 84 496 participants, mean age 72.8, ± 5.7 years				
Intervention	PCV13				
Comparator	Placebo				
Outcome	Primary and secondary outcomes: First episode of VT-CAP, NI NB VT-CAP and VT-IPD Post-hoc analyses on pre-specified exploratory outcomes				
Primary and secondary outcomes	Per protocol (PP)		modified Intention To Treat (mITT)		Author, year
	vacc/non-vacc	VE % (95% CI)	vacc/non-vacc	VE % (95% CI)	
Or first episode of disease					
Any IPD	27/56	52 (22 to 71)	34/66	49 (21 to 67)	Bonten et al., 2015
VT-IPD	7/28	75 (41 to 91)	8/33	76 (47 to 90)	
All cause CAP[I]	-	-	747/787[I]	5 (-5 to 14)	
PnCAP	100/144	31 (10 to 47)	135/174	22 (2 to 39)	
VT-CAP	49/90	46 (22 to 63)	66/106	38 (14 to 55)	
NI NB CAP	66/87	24 (-6 to 46)	90/109	17 (-10 to 38)	
NI NB VT-CAP	33/60	45 (14 to 65)	43/73	41 (13 to 61)	
For any episode of disease					
VT-CAP	53/92	42 (18 to 60)	70/112	38 (15 to 54)	Bonten et al., 2015
Post-hoc analyses (pre-specified, exploratory outcomes)					
Clinical PnCAP (all episodes)[II]	-	-	1375/1495	8 (1 to 15)	Gessner et al., 2018
Culture confirmed PnCAP[III]	20/41	51 (15 to 73)	24/48	50 (17 to 71)	Webber et al., 2017
Culture confirmed VT-CAP[III]	5/20	75 (31 to 93)	5/23	74 (34 to 91)	
Culture confirmed nonVT-CAP[III]	50/53	6 (-42 to 37)	60/67	-3 (-46 to 28)	

Primaire en secundaire doelstellingen, per-protocol populatie



VE: vaccine efficacy; CAP: community acquired pneumonia: Pn: pneumococcal; VT: vaccine serotypes; nonVT: non-vaccine serotypes; NI: non-invasive; NB: non-bacteremic

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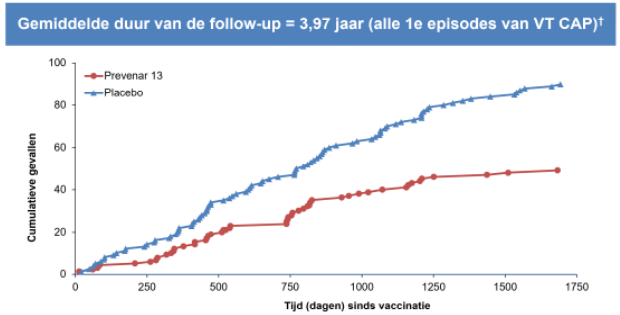
PCV13 – effect van tijd

De beschermende werkzaamheid bleef het gehele 4 jaar durende onderzoek aanhouden[1]



†Post-hocanalyse.
VT CAP, vaccintype niet-nosocomiale pneumonie
Figuur bewerkt naar: 1. Bonten MJM, et al. N Engl J Med 2015;372:1114-25.

3.7.2 Vaccine effectiveness by time since vaccination, PCV13

In CAPITA post-hoc analyses,[69, 71] in which they plotted the cumulative number of disease episodes against the time from vaccination, the authors concluded that efficacy occurred soon after vaccination and persisted throughout the duration of the trial (almost 4 years). However, case-numbers the fourth year was low and potentially insufficient to demonstrate a waning effect. CAPITA has not reported non-cumulative VE by time since vaccination, i.e. < 2 years, 2 to < 5 years.

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Key messages

- *S. pneumonia* is a major cause of morbidity and mortality, specifically at the extremes of age and in individuals with immunocompromising medical conditions. Two different vaccines, a 23-valent polysaccharide vaccine (PPV23) and a 13-valent pneumococcal conjugate vaccine (PCV13) are available to prevent pneumococcal disease in adults.
- No studies compare vaccine effectiveness of PPV23 and PCV13 head-to-head.
- Direct comparison between the two vaccines are difficult due to differences in populations, time since vaccination and study designs.
- Whereas the evidence for PCV13 is dominated by one large trial with overall healthy elderly, the evidence for PPV23 VE is based on several trials of moderate quality and several observational studies.
- Results obtained from RCTs and those obtained from various observational designs are inconsistent, making it difficult to summarize available evidence into single quantitative measures.
- Higher vaccine effectiveness seen in clinical trials may reflect shorter follow-up time compared with observational studies, where waning immunity is likely to play a role.
- Both PPV23 and PCV13 are comparably effective for the prevention of all-type invasive pneumococcal disease (IPD) in the broader adult population, across study designs and settings.
- PCV13 seems to provide better protection than PPV23 against vaccine type IPD (for serotypes common to PCV13 and PPV23).
- The overall body of evidence shows PPV23 VE at a level comparable to PCV13.
- Both vaccines showed generally lower VE with increasing age, but data are limited for PCV13.
- Both vaccines showed generally lower VE in groups with comorbidities compared with groups without known risk.
- With one exception from a case-control study with overall high VE estimates, both vaccines failed to show significant VE in immunocompromised groups.

Clinical Infectious Diseases

MAJOR ARTICLE

Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Hospitalization for Community-Acquired Pneumonia in Older US Adults: A Test-Negative Design

John M. McLaughlin,[1] Qin Jiang,[1] Raul E. Isturiz,[1] Heather L. Sings,[1] David L. Swerdlow,[1] Bradford D. Gessner,[1] Ruth M. Carrico,[2] Paula Peyrani,[2] Timothy L. Wiemken,[3] William A. Mattingly,[2] Julio A. Ramirez,[2] and Luis Jodar[1]

[1]Pfizer Vaccines, Collegeville, Pennsylvania; and [2]Department of Medicine, Division of Infectious Diseases, School of Medicine and [3]Department of Epidemiology and Population Health, School of Public Health and Information Sciences, University of Louisville, Kentucky

Background. Following universal recommendation for use of 13-valent pneumococcal conjugate vaccine (PCV13) in US adults aged ≥65 years in September 2014, we conducted the first real-world evaluation of PCV13 vaccine effectiveness (VE) against hospitalized vaccine-type community-acquired pneumonia (CAP) in this population.

Methods. Using a test-negative design, we identified cases and controls from a population-based surveillance study of adults in Louisville, Kentucky, who were hospitalized with CAP. We analyzed a subset of CAP patients enrolled 1 April 2015 through 30 April 2016 who were aged ≥65 years and consented to have their pneumococcal vaccination history confirmed by health insurance records. Cases were defined as hospitalized CAP patients with PCV13 serotypes identified via culture or serotype-specific urinary antigen detection assay. Remaining CAP patients served as test-negative controls.

Results. Of 2034 CAP hospitalizations, we identified PCV13 serotypes in 68 (3.3%) participants (ie, cases), of whom 6 of 68 (8.8%) had a positive blood culture. Cases were less likely to be immunocompromised (29.4% vs 46.4%, $P = .02$) and overweight or obese (41.2% vs 58.6%, $P = .01$) compared to controls, but were otherwise similar. Cases were less likely to have received PCV13 than controls (3/68 [4.4%] vs 285/1966 [14.5%]; unadjusted VE, 72.8% [95% confidence interval, 12.8%–91.5%]). No confounding was observed during adjustment for patient characteristics, including immunocompromised status, body mass index, and history of influenza and pneumococcal polysaccharide vaccination (adjusted VE range, 71.1%–73.3%).

Conclusions. Our study is the first to demonstrate real-world effectiveness of PCV13 against vaccine-type CAP in adults aged ≥65 years following introduction into a national immunization program.

Keywords. PCV13; vaccine effectiveness; community-acquired pneumonia; test-negative; adult.

PLOS ONE

RESEARCH ARTICLE

Pneumococcal Conjugated Vaccine Reduces the High Mortality for Community-Acquired Pneumonia in the Elderly: an Italian Regional Experience

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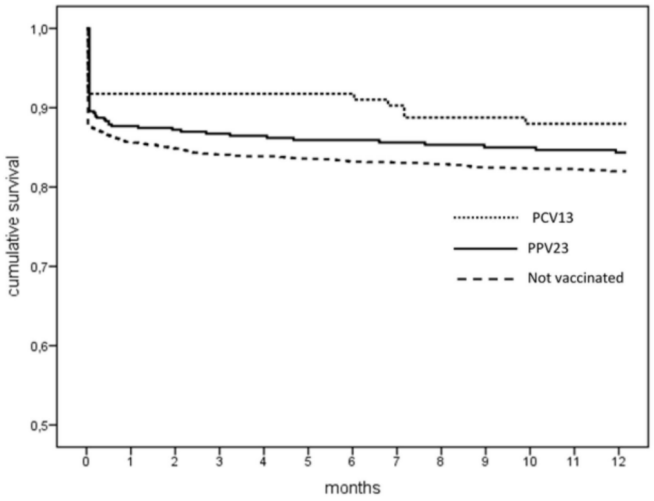
1 Department of Cardiac, Thoracic, and Vascular Sciences, Hygiene and Public Health Unit, University of Padua, Padua, Italy, **2** EuroHealth Net, Friuli Venezia Giulia Region Health Directorate, Udine, Italy



Background: Community-acquired pneumonia (CAP) is an important cause of illness and death worldwide, particularly among the elderly. Previous studies on the factors associated with mortality in patients hospitalized for CAP revealed a direct association between the type of microorganism involved, the characteristics of the patient and mortality. Vaccination status against pneumococcal disease was not considered. We conducted a retrospective analysis on the mortality rates after a first hospitalization for CAP in north-east Italy with a view to examining especially the role of anti-pneumococcal vaccination as a factor associated with pneumonia-related mortality at one year.

Method: Between 2012-2013, patients aged 65+ hospitalized with a primary diagnosis of CAP, identified based on International Classification of Diseases, Ninth Revision, Clinical Modification codes 481-486, were enrolled in the study only once. Patients were divided into three groups by pneumococcal vaccination status: 1) 13-valent pneumococcal conjugate vaccine (PCV13) prior to their hospitalization; 2) 23-valent pneumococcal polysaccharide vaccine (PPV23) within 5 years before hospitalization and 3) unvaccinated or PPV23 more than 5 years prior to admission. Gender, age, length of hospital stay and influenza vaccination were considered. Comorbidities were ascertained by means of a properly coded diagnosis. Every patient was followed up for 1 year and the outcome investigated was mortality for any cause and for pneumonia.

Results: A total of 4,030 patient were included in the study; mean age at the time of admission to hospital was 84.3±7.7; 50.9% were female. 74.2% of subjects had at least one comorbidity; 73.7% has been vaccinated against influenza. Regard to pneumococcal vaccine, 80.4% of patients were not vaccinated, 14.5% vaccinated with PPV23 and 5.1% with PCV13. The 1-year survival rates after hospitalization for pneumonia were 83.6%, 85.9% and 89.3% in the unvaccinated, PPV23 and PCV13 groups, respectively. Regression analysis indicated that the risk of death due to pneumonia increased significantly with age (adjusted OR: 1.073; 1.061-1.085), shorter hospital stay (adjusted OR: 0.981; 0.971-0.990), and male gender (adjusted OR: 1.372; 1.165-1.616). The model also confirmed the pneumococcal 13-valent conjugated vaccine as an independent protective factor for mortality-related pneumonia (adjusted OR: 0.599; 0.390-0.921).

Conclusion: The main finding of our observational cohort study is a high mortality rate among elderly patients admitted to hospital for pneumonia. The present study suggests a protective role for PCV13 vaccination.

- Pneumokokkenziekte
- Epidemiologie en risicofactoren
- Pneumokokken vaccinatie
- **Aanbevelingen in België**
- Vaccinatie in bijzondere omstandigheden
- Kernboodschappen

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Adviezen Hoge Gezondheidsraad

Volwassenen 65–85 jaar oud

Niet eerder gevaccineerd	PCV13	≥8 weken	PPV23	
Eerder gevaccineerd	eerder PPV23	≥1 jaar	PCV13	

Volwassenen 50–85 jaar oud met chronische long-, hart-, lever-, nierziekte, rokers, alcoholisme

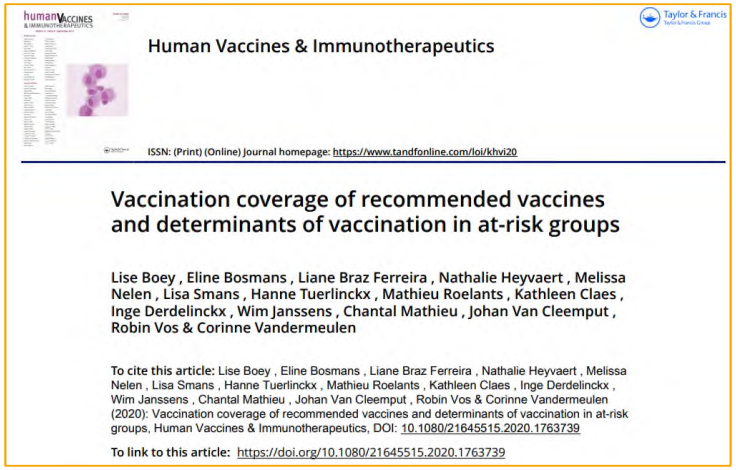
Niet eerder gevaccineerd	PCV13	≥8 weken	PPV23	Elke 5 jaar	PPV23	
Eerder gevaccineerd	eerder PPV23	≥1 jaar	PCV13	Elke 5 jaar	PPV23	

Moet overwogen worden bij ernstige comorbiditeit..

Volwassenen 16–85 jaar oud met immuunstoornissen (incl HIV, kanker, orgaantransplantatie, IMID, ...), asplenia, sikkelcel anemie, CSV lek, cochleair implantaat

Nier eerder gevaccineerd	PCV13	≥8 weken	PPV23	Elke 5 jaar	PPV23	
Eerder gevaccineerd	eerder PPV23	≥1 jaar	PCV13	Elke 5 jaar	PPV23	

Vaccination coverage in risk groups is low
Informing the patient is important



Human Vaccines & Immunotherapeutics

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Vaccination coverage of recommended vaccines and determinants of vaccination in at-risk groups

Lise Boey , Eline Bosmans , Liane Braz Ferreira , Nathalie Heyvaert , Melissa Nelen , Lisa Smans , Hanne Tuerlinckx , Mathieu Roelants , Kathleen Claes , Inge Derdelinckx , Wim Janssens , Chantal Mathieu , Johan Van Cleemput , Robin Vos & Corinne Vandermeulen

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To link to this article: https://doi.org/10.1080/21645515.2020.1763739

Table 2. Documented vaccination coverage in adult risk patients.

	Diphtheria-Tetanus		Pertussis		Influenza		Pneumococcus		Hepatitis B	
n = 1331	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
All patients (n = 1331)	387	29.1 (26.7–31.6)	136	10.2 (8.7–12.0)	584	43.9 (41.2–46.6)	429	32.2 (29.7–34.8)		NA
DM type 1 (n = 173)	45	26.0 (19.8–33.3)	22	12.7 (8.3–18.8)	39	22.5 (16.7–29.6)	7	4.0 (1.8–8.5)		NA
DM type 2 (n = 177)	54	30.5 (23.9–37.9)	29	16.4 (11.4–22.9)	85	48.0 (40.5–55.6)	43	24.3 (18.3–31.4)		NA
CKD (n = 138)	33	23.9 (17.2–32.1	7	5.1 (2.2–10.6)	39	28.3 (21.1–36.7)	32	23.2 (16.6–31.3)	43	31.2 (23.7–39.7)
COPD (n = 187)	65	34.8 (28.1–42.1)	23	12.3 (8.1–18.1)	121	64.7 (57.4–71.4)	75	40.1 (33.1–47.5)		NA
Heart failure (n = 200)	58	29.0 (22.9–35.9)	17	8.5 (5.2–13.5)	77	38.5 (31.8–45.7)	40	20.0 (14.8–26.4)		NA
HIV (n = 201)	61	30.3 (24.2–37.3)	7	3.5 (1.5–7.3)	88	43.8 (36.9–50.9)	146	72.6 (65.8–78.6)	49	24.4 (18.7–31.0)
SOT (n = 255)	71	27.7 (22.5–33.8)	31	12.2 (8.5-17.0)	135	52.9 (46.6–59.2)	86	33.7 (28.0–39.9)		NA

NA: not available, CI: confidence interval, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, DM: Diabetes mellitus, SOT: solid organ transplantation.

Table 4. Reasons for non-vaccination.

	Diphtheria-tetanus (n = 86)	Influenza (n = 157)	Pneumococcus (n = 138)
N = 367	n(%)	n(%)	n(%)
Concerns and doubts			
Concerns about safety	1 (1.2)	20 (12.7)	1 (0.1)
Doubts about necessity of vaccination	8 (9.3)	10 (6.4)	2 (1.4)
Doubts about effectiveness of vaccination	-	10 (6.4)	-
Opposition to vaccination	-	14 (8.9)	5 (3.6)
Afraid of needle	-	1 (0.6)	-
Does already take a lot of medication	-	1 (0.6)	-
Information			
Not aware of the recommendation	33 (38,4)	4 (2.5)	111 (80.4)
Discouraged by physician	-	4 (2.5)	-
Assumed not to be necessary since absence of injuries	4 (4.6)	-	-
Practical reasons			
Having forgotten to get the vaccine	25 (29.1)	1 (0.6)	3 (2.2)
I have not received vaccine yet, but will get it in the future	-	64 (40.7)	2 (1.4)
Vaccine is too expensive	-	-	1 (0.7)
Not given due to medical condition/treatment	-	3 (1.9)	-
Lack of time	-	1 (0.6)	-
No reason	12 (14.0)	23 (14.6)	13 (9.4)

: Lise Boey , Eline Bosmans , Liane Braz Ferreira , Nathalie Heyvaert , Melissa Nelen , Lisa Smans , Hanne Tuerlinckx , Mathieu Roelants , Kathleen Claes , Inge Derdelinckx ,Wim Janssens , Chantal Mathieu , Johan Van Cleemput , Robin Vos , Corinne Vandermeulen (2020): Vaccination coverage of recommended vaccines and determinants of vaccination in at-risk groups, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2020.1763739

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- Kernboodschappen

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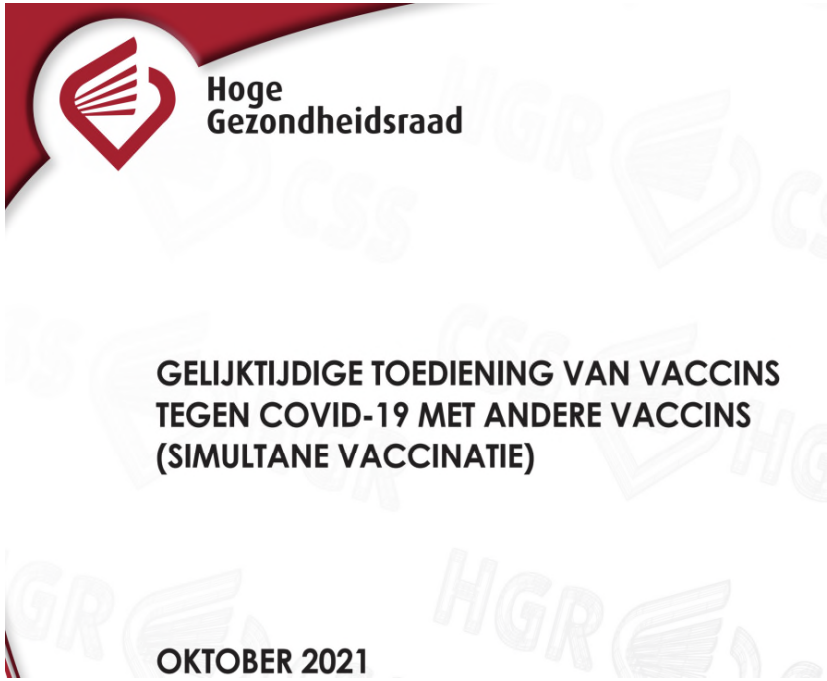
Simultaan met COVID-19 vaccinatie



Coadministration of COVID-19 vaccines with other vaccines

COVID-19 vaccines **may be administered without regard to timing of other vaccines**. This includes simultaneous administration of COVID-19 vaccine and other vaccines on the same day.

If multiple vaccines are administered at a single visit, administer each injection in a different injection site. For people ≥11 years, the deltoid muscle can be used for more than one intramuscular injection administered at different sites in the muscle. For children (5–10 years), if more than two vaccines are injected in a single limb, the vastus lateralis muscle of the anterolateral thigh is the preferred site because of greater muscle mass.

Best practices for multiple injections include:

- Label each syringe with the name and the dosage (amount) of the vaccine, lot number, the initials of the preparer, and the exact beyond-use time, if applicable.
- Separate injection sites by 1 inch or more, if possible.
- **Administer the COVID-19 vaccine and vaccines that may be more likely to cause a local reaction in different limbs, if possible.**

- HGR NR. 9675
- https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#Coadministration

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Tijdens de zwangerschap

Pneumokokken	Pneumovax 23® Prevenar 13 ®	Polysaccharide niet geconjugeerd Polysaccharide geconjugeerd	Gebruik indien nodig

Aanbevelingen:

I. In het geval dat een vrouw niet/nooit is ingeënt met een vaccin tegen (onder andere) tetanus, dienen tijdens de zwangerschap 2 dosissen van het tetanusvaccin toegediend te worden, waarvan er één een component tegen kinkhoest bevat, en een derde dosis dient toegediend te worden tijdens het post partum.

II. Alle zwangere vrouwen zouden tijdens het griepseizoen gevaccineerd moeten worden tegen de seizoensgriep, zoals voorgeschreven in het advies met betrekking tot griep, ongeacht het stadium van de zwangerschap op het moment van de vaccinatie.

III. Alle zwangere vrouwen zouden gevaccineerd moeten worden tegen kinkhoest, bij voorkeur tussen week 24 en 32 van de zwangerschap, en bij elke nieuwe zwangerschap.

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Immuniteitsnazicht (humoraal)

TABLE IV. Summary of PPV23-deficient response phenotypes

Phenotype*	PPV23 response, age >6 y	PPV23 response, age <6 y	Notes
Severe	≤2 protective titers (≥1.3 μg/mL)	≤2 protective titers (≥1.3 μg/mL)	Protective titers present are low
Moderate	<70% of serotypes are protective (≥1.3 μg/mL)	<50% of serotypes are protective (≥1.3 μg/mL)	Protective titers present to ≥3 serotypes
Mild	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 70% of serotypes	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 50% of serotypes	2-Fold increases assume a prevaccination titer of less than cutoff values in Summary Statement 26
Memory	Loss of response within 6 mo	Loss of response within 6 mo	Adequate initial response to ≥50% of serotypes in children <6 y of age and ≥70% in those >6 y of age

Orange, J. S., Ballow, M., Stiehm, E. R., Ballas, Z. K., Chinen, J., De La Morena, M., Kumararatne, D., Harville, T. O., Hesterberg, P., Koleilat, M., McGhee, S., Perez, E. E., Raasch, J., Scherzer, R., Schroeder, H., Seroogy, C., Huissoon, A., Sorensen, R. U., & Katial, R. (2012). Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. *The Journal of allergy and clinical immunology*, *130*(3 Suppl), S1–S24. https://doi.org/10.1016/j.jaci.2012.07.002

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Nederland

Extra medische risicogroep

De Gezondheidsraad adviseert om mensen die longschade hebben opgelopen door COVID-19 en hiervan chronische klachten ondervinden voorlopig ook te benoemen als medische risicogroep. De longarts stelt hiervoor de indicatie. Wie de prik geeft hangt af van lokale afspraken tussen de long- en huisarts.

Pneumokokkenvaccinatie en chemotherapie

Voor mensen die chemotherapie krijgen gelden aanvullende adviezen voor toediening van het pneumokokkenvaccin. Deze adviezen zijn anders dan bij toediening van het griepvaccin.

Griep (influenza) komt vooral in de wintermaanden voor en de samenstelling van het griepvaccin verandert jaarlijks. De griepvaccinatie wordt in het najaar gegeven en biedt alleen bescherming in het aansluitende winterseizoen. Pneumokokkeninfecties komen het hele jaar voor. Het pneumokokkenvaccin verandert niet van samenstelling en is beschermend voor 5 jaar. Mede daarom worden bij de griepvaccinatie tijdens chemotherapie andere afwegingen gemaakt dan bij een pneumokokkenvaccinatie tijdens chemotherapie. Er zijn veel verschillende vormen van chemotherapie die allemaal een ander effect hebben op de immuunrespons, dit is dus een hele heterogene groep. Het algemene advies bij chemotherapie en vaccinatie is om de vaccinatie minimaal 3 maanden na de laatste kuur of minimaal 2 weken voor de start van chemotherapie te geven. Voor een patiënt waarvan bekend is dat hij bijna klaar is met chemotherapie of waarbij de kuur net is afgelopen kan het pneumokokkenvaccin op de huisartsenpraktijk of in de zorginstelling bewaard worden om deze op een later moment toe te dienen. Voor patiënten die nog midden in hun chemotherapie zitten kan de behandelend specialist een individuele afweging maken of er tijdens de chemotherapie gevaccineerd kan worden en welk moment dan het beste is. Voor hematologische tumoren is een richtlijn in ontwikkeling.

https://www.rivm.nl/pneumokokken/professionals/uitvoerders-nppv

- Pneumokokkenziekte
- Epidemiologie en risicofactoren
- Pneumokokken vaccinatie
- Aanbevelingen in België
- Vaccinatie in bijzondere omstandigheden
- **Kernboodschappen**

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Kernboodschappen

- Vaccineer voor pneumokokken volgens HGR richtlijnen
  - ‘Nog ruimte voor verbetering’
  - Breder geheel van (seizoensgebonden) impact ‘respiratoire infecties’

- Kies voor de beste bescherming
  - PCV13 + PPV23 !
  - Indien bij gezonde personen tussen 65 en 85 jaar gekozen zou worden om slechts 1 pneumokokkenvaccin te gebruiken: gebruik dan PPV23 om de breedste bescherming te bieden

- Bij vermoeden stoornis humorale immuniteit (niet secundair aan medicatie)
  - Koppelen aan bepalen vaccinatie respons

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