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Nove vakcine protiv pneumokoka

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4. Dani vakcinacije

Novi Sad, 6. i 7. novembar 2024

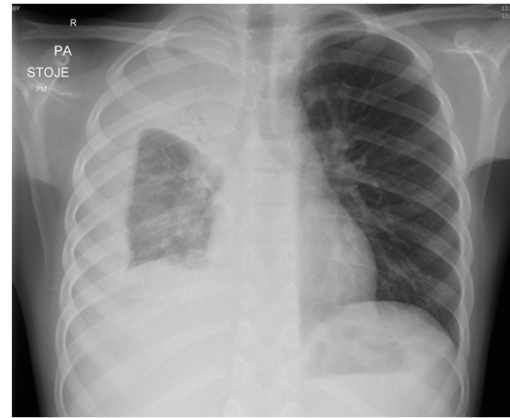


MF

UNIVERSITY OF LJUBLJANA
Faculty of Medicine

Streptococcus pneumoniae

- grampozitivni diplokok
- polisaharidna kapsula
- 101 serotip
- mali dio uzrokuje infekcije
- invazivne (sepsa, bakterijemija, meningitis, pneumonija, empijem, perikarditis, septički artritis, peritonitis,...)
- neinvazivne (otitis medija, sinuzitis, pneumonija)



THE LANCET, JANUARY 10, 1914.

Dobra stara vremena 1

- Witwaterstrand Native Labour Association, Južna Afrika
- oktobar 1911- april 1912
- 5963 vakcinisana i 5671 nevakcinisanih radnika u rudnicima zlata u Južnoj Africi
- inaktivirana pneumokokna vakcina

TABLE XII.—*Showing the Number of Pneumonia Cases and Deaths from Pneumonia which occurred in the W.N.L.A. Compound between the Date of the First Inoculation and the Departure of the Natives to the Mines.*

—	Number of men in the group.	Cases.		Deaths.	
		Number.	Per-centage.	Number.	Per-centage.
Inoculated	5963	147	2·6	50	0·83
Uninoculated	5671	198	3·5	87	1·53

Observations

ON

PROPHYLACTIC INOCULATION AGAINST PNEUMOCOCCUS INFECTIONS,

AND ON THE RESULTS WHICH HAVE BEEN ACHIEVED BY IT.¹

By SIR ALMROTH E. WRIGHT, M.D., F.R.S.,

IN CONJUNCTION WITH

W. PARRY MORGAN, M.B. CANTAB., L. COLEBROOK, M.B. LOND., AND R. W. DODGSON, M.D. LOND.

(Concluded from p. 10.)

Dobra stara vremena 2

- lečenje pneumokokne pneumonije protutelima
- u jesen 1920, New York
- priprema leka: konji u više navrata inokulirani pneumokokima tipa I, II i III, serum obrađen – na kraju obrade vodna otopina pneumokoknih protutela
- 1000 slučajeva pneumonije, 834 pneumokokne
- kod lečenih pacijenata sa tipom I, II i IV manje umrlih

TABLE 3.—COMPARISON OF DEATH RATE IN TREATED AND CONTROL SERIES

Type	Antibody Wards			Control Wards		
	Cases	Deaths	Rate %	Cases	Deaths	Rate %
Pneumococcus I.....	158	21	13.3	162	36	22.2
Pneumococcus II.....	83	23	27.7	67	27	40.3
Pneumococcus III.....	73	29	39.7	60	24	40.0
Pneumococcus IV.....	110	18	16.4	121	29	24.0
Total.....	424	91	21.4	410	116	28.3
Streptococcus, etc.	48	24	50.0	35	12	34.3
Unclassified.....	36	14	38.8	47	20	42.5

JAMA 1922;79: 343-349.

CLINICAL AND BACTERIOLOGIC STUDY OF ONE THOUSAND CASES OF LOBAR PNEUMONIA

WITH SPECIAL REFERENCE TO THE THERAPEUTIC
VALUE OF PNEUMOCOCCUS ANTIBODY SOLU-
TION: PRELIMINARY REPORT *

RUSSELL L. CECIL, M.D.

AND

NILS P. LARSEN, M.D.

NEW YORK

RESULTS OF TREATMENT WITH ANTIBODY

Antibody treatment was started as soon as the diagnosis of pneumonia was made. The solution was given intravenously in most cases, the technic being similar to that of serum administration. The dose was from 50 to 100 c.c. given once, sometimes twice, occasionally three times a day.

The reactions produced by this solution have been one of the most striking features of the study, and deserve especial attention. The typical reaction may be thus described: There is no immediate reaction. From twenty to forty minutes after the injection, the patient begins to shiver and is soon in the midst of a hard chill. The cyanosis and dyspnea become more marked, and the patient often shows extreme anxiety. The chill lasts from fifteen to thirty minutes. At its conclusion, the patient complains of fever, and the temperature may have risen to 106 F. or even to 108 or 109. In rare cases, the temperature may rise to 110. In one case, the rectal temperature was too high to be recorded on the thermometer. When the thermometer was removed, the bulb was missing, and a careful reading of the mercury column recorded 113.1! The patient was wildly delirious during this period of hyperpyrexia, but ice packs were followed by a rapid drop, and on the next morning he showed a normal temperature and made an uncomplicated recovery.

In a certain number of cases, morphin and atropin have been administered subcutaneously one-half hour before the injection of antibody, with the hope that such a procedure would mitigate the severity of the reactions. In general, it may be said that the reaction was somewhat less intense after morphin and atropin, but the effect was not striking. An effort was also

three times a day.

The reactions produced by this solution have been one of the most striking features of the study, and deserve especial attention. The typical reaction may be thus described: There is no immediate reaction. From twenty to forty minutes after the injection, the patient begins to shiver and is soon in the midst of a hard chill. The cyanosis and dyspnea become more marked, and the patient often shows extreme anxiety. The chill lasts from fifteen to thirty minutes. At its conclusion, the patient complains of fever, and the temperature may have risen to 106 F. or even to 108 or 109. In rare cases, the temperature may rise to 110. In one case, the rectal temperature was too high to be recorded on the thermometer. When the thermometer was removed, the bulb was missing, and a careful reading of the mercury column recorded 113.1! The patient was wildly delirious during this period of hyperpyrexia, but ice packs were followed by a rapid drop, and on the next morning he showed a normal temperature and made an uncomplicated recovery.

In a certain number of cases morphin and atropin

CLINICAL AND BACTERIOLOGIC STUDY
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106 F= 41 C
108 F= 42.2 C
109 F = 42.8 C
110 F = 43.3 C
113.1 F = 45.1 C

Dosadašnje vakcine proti pneumokoka

- 14-valentna polisaharidna (1977)
- 23-valentna polisaharidna (1983)

- 7-valentna konjugovana (2000)
- 10-valentna konjugovana (2009/10)
- 13-valentna konjugovana (2009/10)

Pregled vakcina

Vaccine	Serotypes Contained in the Vaccine	Efficacy	Limitation
<i>PPSV 23</i> (polysaccharide)	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F	Coverage of 23 serotypes. Effectiveness against IPD. Minimizing the severity of pneumonia.	Poor immunogenicity and effectiveness against pneumococcal pneumonia prevention.
<i>PCV 7 (conjugate)</i>	4, 6B, 9V, 14, 18C, 19F, and 23F	Reduced invasive disease. Reduced carriage. Protective herd effect.	Increase in 3 and 19A infections.
<i>PCV 10 (conjugate)</i>	1, 4 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	Reduced invasive disease. Reduced carriage.	Increase in 3 and 19A infections.
<i>PCV 13 (conjugate)</i>	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	Higher immunogenicity than PPV23. Effectiveness against pneumonia. Effectiveness against IPD.	Coverage of 13 serotypes only. High cost Increase in 35B infections.
<i>PCV15 (conjugate)</i>	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F	High immunogenicity. Effectiveness against pneumonia. Effectiveness against IPD.	Coverage of 15 serotypes only. High cost
<i>PCV 20 (conjugate)</i> (recently approved by FDA)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 10A, 11A, 12F, 15B, 22F and 33F	Substantial IgG production and functional bactericidal immune response.	Coverage of 20 serotypes. High-cost production.

7-valentna vakcina

- smanjila se incidencija invazivne bolesti uzrokovane vakcinalnim serotipovima
- pojavili su se zamenski serotipovi, među kojima najproblematičniji biva 19A

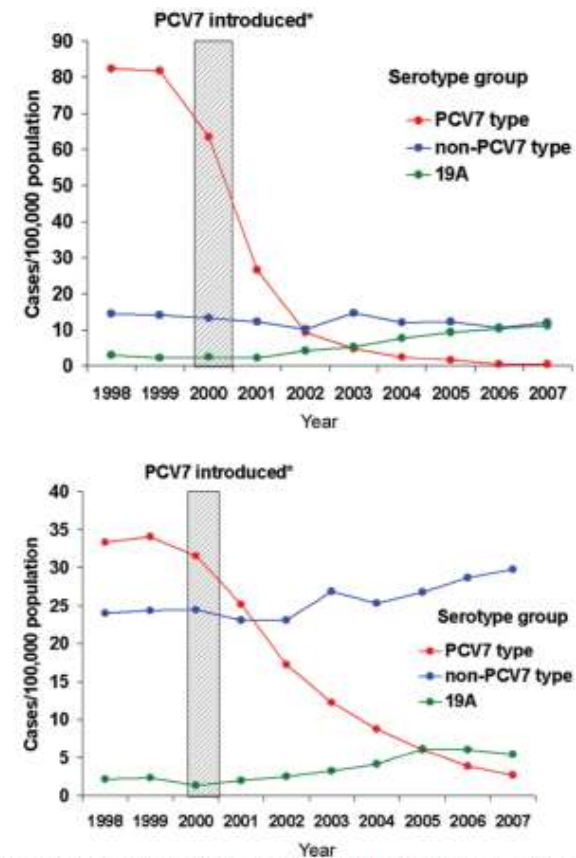


Fig. 1 Effect of PCV7 on IPD in children <5 years (direct effect; upper panel) and adults >65 years (herd effect; lower panel). Note increase in non-PCV7 types, especially 19A. * From reference [46], by permission of Oxford University Press.

Konjugovane pneumokokne vakcine

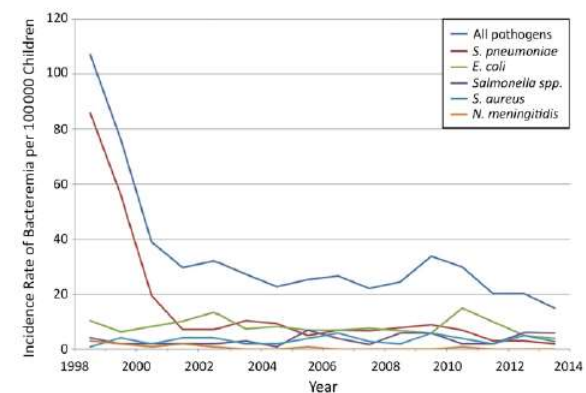
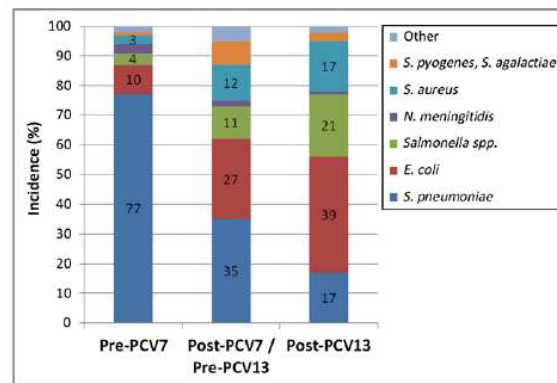
- vakcinacija značajno smanji incidenciju invazivnih infekcija vakcinalnim serotipovima
- u manjoj meri smanji se incidencija neinvazivnih infekcija vakcinalnim serotipovima
- smanji se nositeljstvo vakcinalnih serotipova
- pojava zamenskih serotipova smanji učinak vakcine

Šta se dogodi sa pneumokoknom bakterijemijom u dobro vakcinisanoj populaciji?

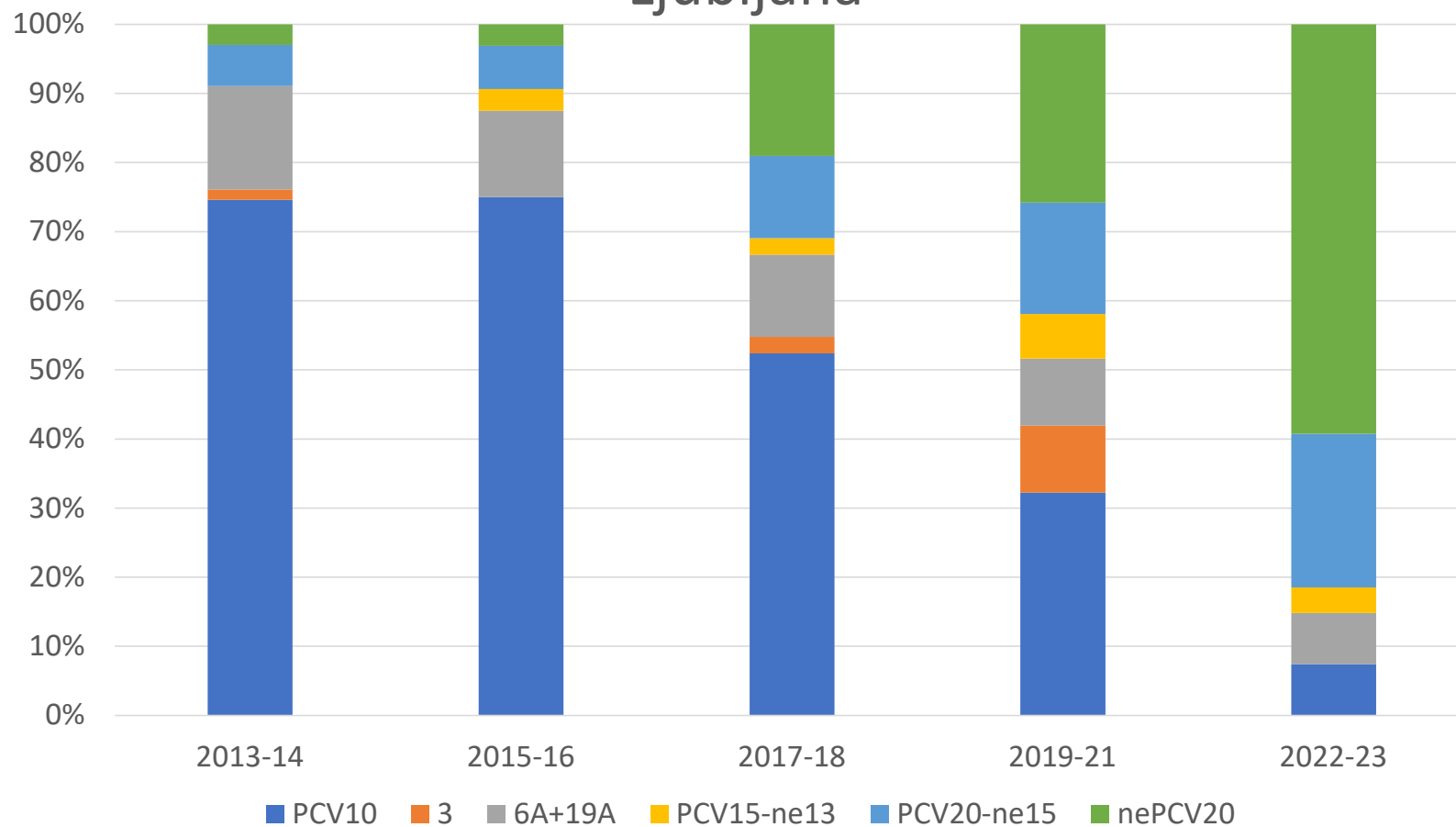
- retrospektivni pregled svih HK kod dece 3-36 m u NCKP od 1.9.1998 do 31.8.2014
- 57733 hemokultura
- 95.3% smanjenje broja pneumokoknih bakterijemija
- povećao se udeo drugih uzročnika: *E. coli*, *S. aureus*, *Salmonella* (ukupno 77%)
- okultna pneumokokna bakterijemija postala je retka
- potreban je novi pristup ambulantnom lečenju inače zdrave febrilne dece

TABLE 2 Incidence Rate of Bacteremia by Study Period

	Rate per 100 000 Children per Year (95% CI)			Rate per 10 000 Blood Cultures (95% CI)		
	Pre-PCV7	Post-PCV7/Pre-PCV13	Post-PCV13	Pre-PCV7	Post-PCV7/Pre-PCV13	Post-PCV13
All bacteremia	97 (79.4–117)	29 (20.4–38.9)	21 (13.5–30.3)	168 (144–195)	75 (59–94)	96 (78–117)
<i>S pneumoniae</i>	74.5 (59–93)	10 (5–18)	3.5 (1.1–8.7)	129 (108–153)	26 (17–38)	16 (9–26)
<i>E coli</i>	9.4 (4.8–17)	8.2 (4.1–15.7)	8.4 (4.1–15.7)	17 (10–27)	21 (13–32)	37 (26–51)
<i>Salmonella</i> spp	3.8 (1.1–8.7)	3.2 (1.1–8.7)	4.5 (1.6–10.2)	7 (3–14)	8 (3–16)	20 (12–31)
<i>S aureus</i>	3.1 (1.1–8.7)	4.6 (1.6–10.2)	3.5 (1.1–8.7)	6 (2–13)	9 (4–17)	16 (9–26)
<i>N meningitidis</i>	2.5 (0.6–7.2)	0.6 (0–3.7)	0.2 (0–3.7)	4.5 (2–10)	1.5 (0–6)	1 (0–6)
Contaminated blood culture	100 (82.1–120)	75.6 (60.3–93)	45 (33–59.8)	174 (151–199)	196 (172–222)	205 (180–231)



Evolucija udela serotipova 2013-2023, UKC Ljubljana



15-valentna vakcina

- dodana 2 nova serotipa: 22F i 33F
- 2 mcg svakog serotipa, 4 mcg 6B, konjugacija sa CRM-197
- NIP raspored vakcinacije: 2+1 ili 3+1
- neinferiorna imunogenost u usporedbi sa PCV13, bolja za 22F i 33F
- bolja imunogenost za serotip 3 od PCV13
- dobra bezbednost vakcine

20-valentna vakcina

- dodanih 7 novih serotipova: 8, 10A, 11A, 12F, 15B, 22F i 33F
- 2.2 mcg svakog serotipa, 4.4 mcg 6B, konjugacija sa CRM-197
- NIP raspored vakcinacije: 2+1 ili 3+1
- neinferiorna imunogenost u usporedbi sa PCV13, bolja za dodatnih 7 serotipova
- dobra bezbednost vakcine

Usporedba imunogenosti PCV15 vs. PCV20 3+1

- imunitet 1 m nakon bustera (12-15 m)
- za većinu ST niži titar protutela u usporedbi sa PCV13
- tako za PCV15 kao za PCV 20
- usporediva imunogenost PCV15 i PCV20

Table 1: Comparison of mean geometric opsonophagocytotic activity, titres one month after the toddler dose in trials using a 3+1 doses schedule (2, 4, 6 and 12–15 months)

Reference	Yeh et al., 2010			Lupinacci et al., 2023			Senders et al., 2021			Indirect comparisons		
Serotype	OPA PCV13	OPA PCV7	Ratio PCV13/PCV7	OPA PCV15	OPA PCV13	Ratio PCV15/PCV13	OPA PCV20	OPA PCV13	Ratio PCV20/PCV13	Ratio PCV15/PCV20	Ratio PCV15/PCV7	Ratio PCV20/PCV7
	A	B	C=A/B	D	E	F=D/E	G	H	I=G/H	J=F/I	K=Fx C	L=Ix C
1	N/A	N/A	N/A	138.5	228.6	0.61	50.4	92.9	0.54	1.12	N/A	N/A
3	N/A	N/A	N/A	389.1	455.9	0.85	93.0	109.3	0.85	1.00	N/A	N/A
4	1,180	1,492	0.79	2,558.3	3,492.6	0.73	490.3	662.5	0.74	0.99	0.58	0.59
5	N/A	N/A	N/A	1,062.9	1,538.8	0.69	78.7	112.8	0.70	0.99	N/A	N/A
6A	N/A	N/A	N/A	5,553.5	7,784.6	0.71	1,671.4	2,155.8	0.78	0.92	N/A	N/A
6B	3,100	4,066	0.76	4,641.8	5,897.0	0.79	1,354.9	1,808.1	0.75	1.05	0.60	0.57
7F	N/A	N/A	N/A	10,098.6	12,301.9	0.82	2,590.7	3,280.7	0.79	1.04	N/A	N/A
9V	11,856	18,032	0.66	1,714.5	4,237.1	0.40	1,280.2	2,030.0	0.63	0.64	0.27	0.41
14	2,002	2,366	0.85	4,558.1	3,010.5	1.51	938.8	1,127.9	0.83	1.82	1.28	0.70
18C	993	1,722	0.58	2,471.0	3,319.6	0.74	2,016.2	2,703.3	0.75	1.00	0.43	0.43
19A	N/A	N/A	N/A	3,370.4	5,584.6	0.60	651.3	874.8	0.74	0.81	N/A	N/A
19F	200	167	1.20	2,286.4	2,626.7	0.87	500.5	751.0	0.67	1.31	1.04	0.80
23F	2,723	4,982	0.55	6,098.6	13,677.9	0.45	693.1	1,253.9	0.55	0.81	0.24	0.30
Mean of ratios	N/A	N/A	0.77	N/A	N/A	0.75	N/A	N/A	0.72	1.04	0.63	0.54
Median of ratios	N/A	N/A	0.76	N/A	N/A	0.73	N/A	N/A	0.74	1.00	0.58	0.57

Abbreviations: N/A, not applicable; OPA, opsonophagocytotic activity; PCV7, 7-valent vaccine; PCV13, 13-valent vaccine; PCV15, 15-valent vaccine; PCV20, 20-valent vaccine

Usporedba imunogenosti PCV15 vs. PCV20 2+1

- imunitet 1 m nakon bustera (12-15 m)
- slični rezultati kao kod 3+1
- generalno usporediva imunogenost PCV15 i PCV20
- post-marketingške studije

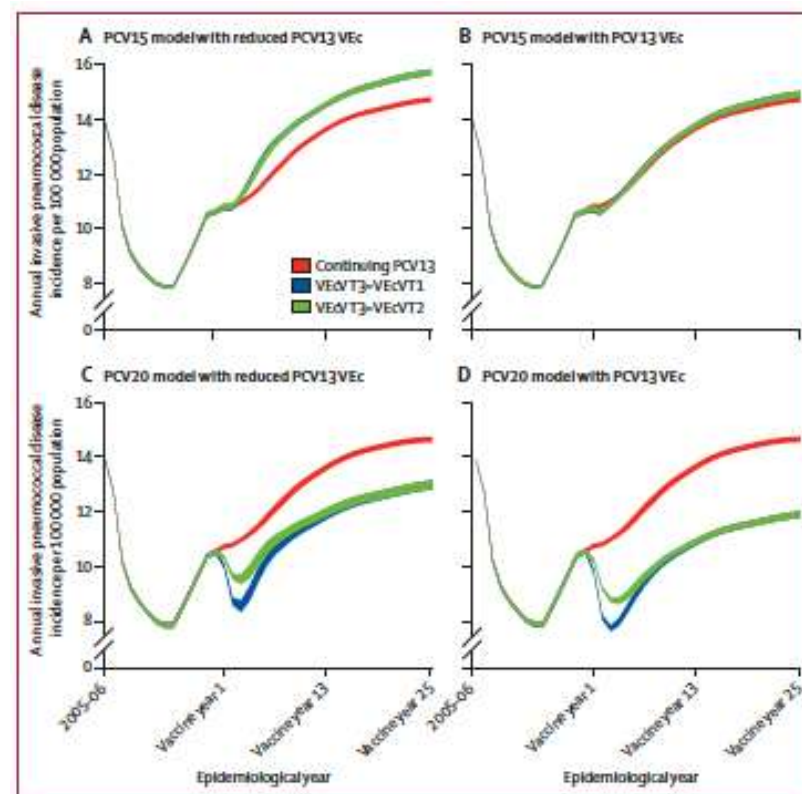
Table 2: Comparison of mean geometric opsonophagocytotic activity, titres one month after the toddler dose in trials using a 2+1 doses schedule (2, 4, and 11–15 months)

Reference	Martinon-Torres et al., 2023			Pfizer, NCT04546425 results, 2023			Ratio PCV15/PCV20
Serotype	OPA PCV15	OPA PCV13	Ratio PCV15/PCV13	OPA PCV20	OPA PCV13	Ratio PCV20/PCV13	
	A	B	C=A/B	D	E	F=D/A	G=C/F
1	136.8	164.6	0.83	54	101	0.53	1.55
3	321.5	303.0	1.06	99	129	0.77	1.38
4	2,231.7	3,206.4	0.70	904	992	0.91	0.76
5	791.6	947.9	0.84	60	82	0.73	1.14
6A	3,274.9	5,387.2	0.61	1,101	1,304	0.84	0.72
6B	2,439.9	3,182.4	0.77	537	864	0.62	1.23
7F	6,300.9	10,071.7	0.63	1,811	2,197	0.82	0.76
9V	1,904.4	2,616.6	0.73	3,254	4,544	0.72	1.02
14	2,638.8	2,682.1	0.98	738	920	0.80	1.23
18C	1,968.6	2,091.8	0.94	1,296	1,870	0.69	1.36
19A	2,995.6	4,254.3	0.70	754	707	1.07	0.66
19F	1,793.9	4,254.3	0.42	183	258	0.71	0.59
23F	4,517.8	7,987.6	0.57	697	975	0.71	0.79
Mean of ratios	N/A	N/A	0.75	N/A	N/A	0.76	1.02
Median of ratios	N/A	N/A	0.73	N/A	N/A	0.73	1.02

Abbreviations: N/A, not applicable; OPA, opsonophagocytotic activity; PCV13, 13-valent vaccine; PCV15, 15-valent vaccine; PCV20, 20-valent vaccine

Kakav bi mogao biti učinak nakon uvođenja u NIP u Engleskoj

- studija modeliranja koristeći realistične, starosno strukturirane i determinističke modele, koji su prilagođeni podacima o nositeljstvu i podacima o invazivnoj bolesti pre i posle uvođenja PCV7 i 13
- procena ključnih parametara: efikasnost PCV7 i PCV13 protiv nositeljstva VT i efikasnost PCV7 protiv invazivne bolesti – te isto tako za dodatne ST u PCV13, PCV15 i PCV20
- uključeno smanjenje učinka protiv starih VT zbog povećanja valencije vakcine
- Englezi imaju raspored 1+1
- ako bi PCV13 zamenili PCV20, došlo bi do smanjenja incidencije a prilikom zamene za PCV15 došlo bi do povećanja incidencije



Vakcina za decu vs. vakcina za odrasle

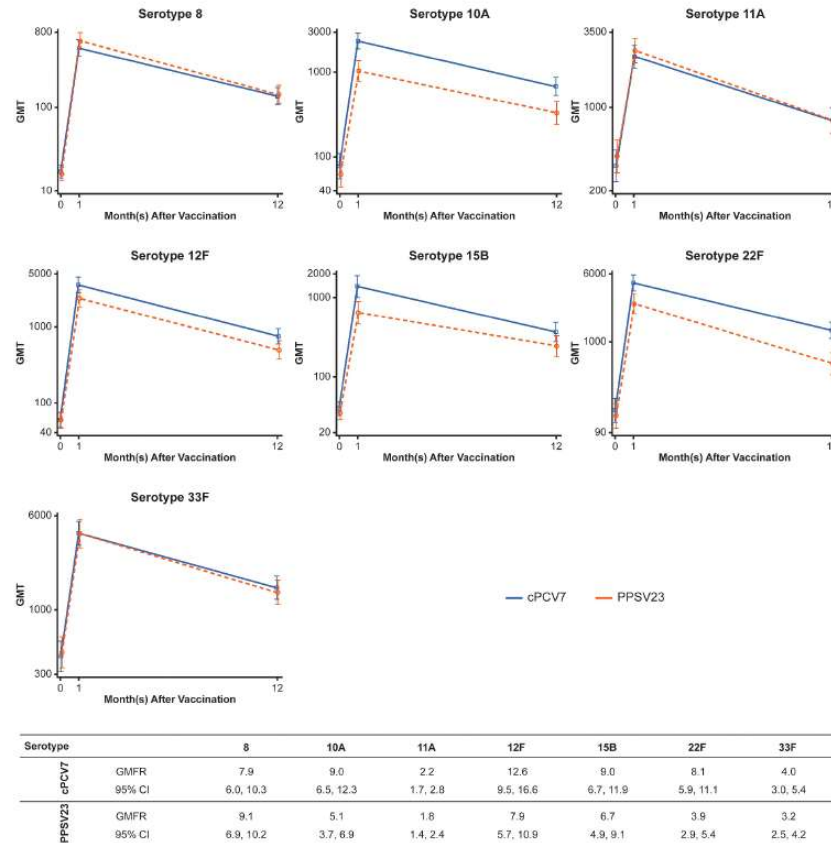
- univerzalnom vakcinacijom dece došlo je do smanjenja cirkulacije vakcinalnih serotipova
- vakcinacija dece zbog toga indirektno štiti ostali dio populacije od vakcinalnih serotipova
- ali s vremenom sve su više na meti zamenskih serotipova
- da li onda uopšte ima smisla istom vakcinom štititi odrasle?

Mogućnosti novih pneumokoknih vakcina

- proteinske vakcine: efikasne u mišjim modelima ali ne u humanim studijama
- konjugirane pneumokokne vakcine sa rekombinantnim pneumokoknim nositeljskim proteinima – imunogene ali neefikasne
- inaktivirane vakcine celih ćelija – imunogene
- žive atenuirane (modifikovane) vakcine
- modifikovan nosač - eCRM (manji efekt proteinskog nosača)
- MAPS

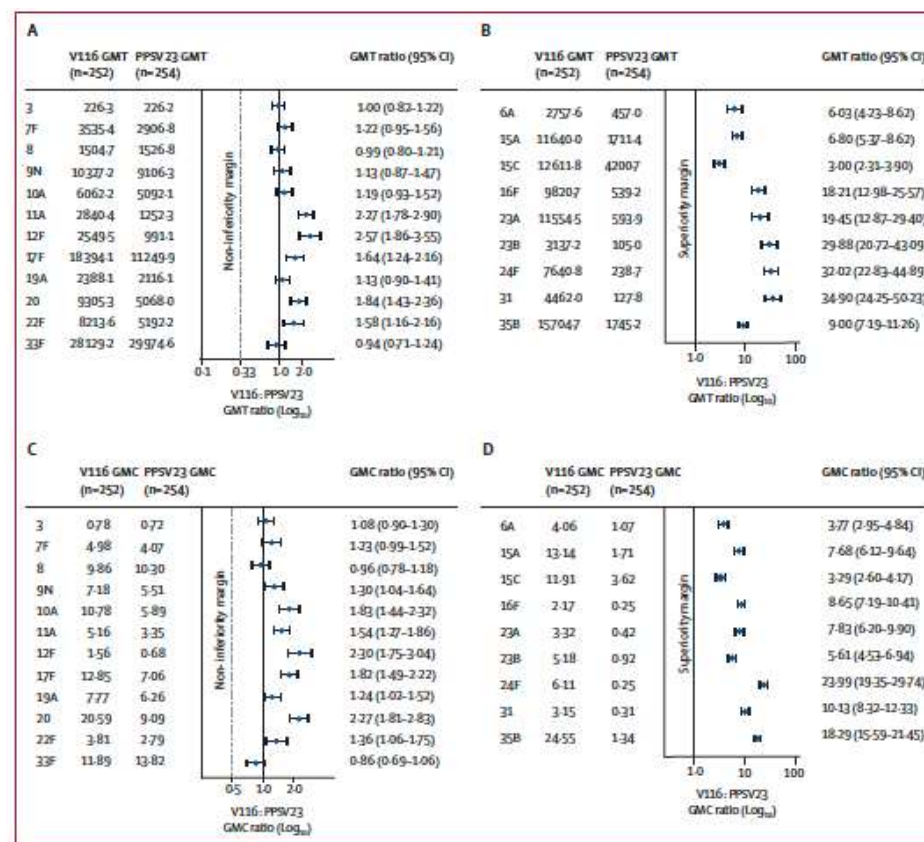
7-valentna konjugovana komplementarna vakcina

- komplementarna konjugovana vakcina za odrasle CRM197: ST 8, 10A, 11A, 12F, 15B, 22F, 33F
- faza I (50-64, n=60) g i faza II, odrasli (65-85 g, n=445)
- prethodno vakcinisani PCV13
- 1 doza cPCV7 vs PPS23
- bezbedna & imunogena



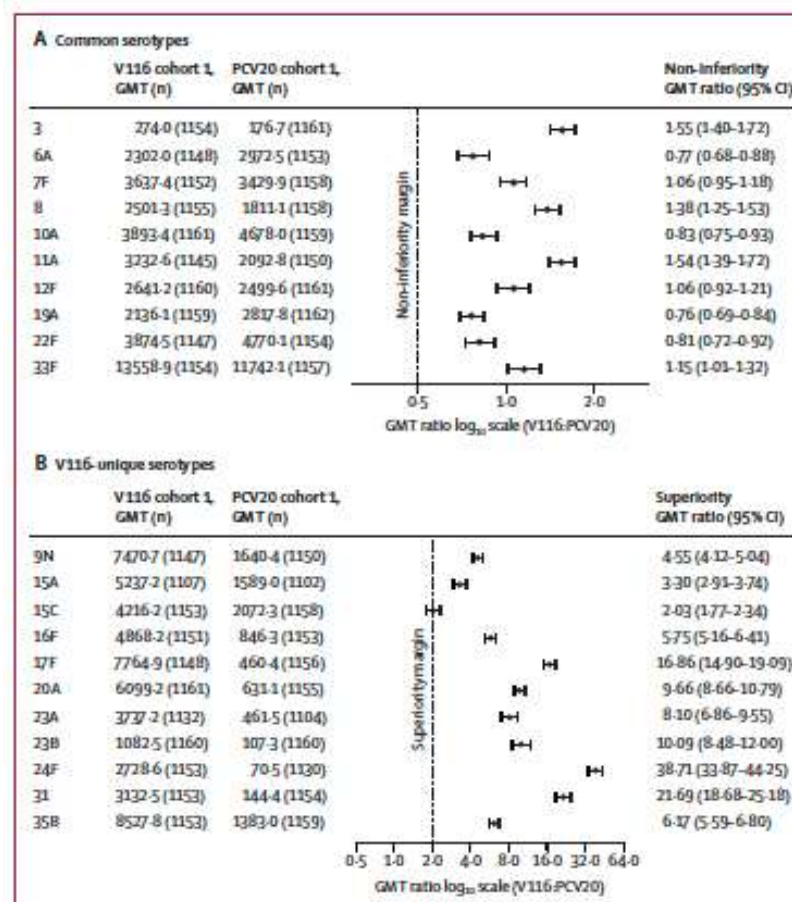
21-valentna konjugovana vakcina za odrasle

- CRM197: ST 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, **15A, 16F**, 17F, 19A, 20, 22F, **23A, 23B, 24F, 31, 33F, 35B** i deOac15B (**15C**)
- faza 1 (n=90, 18-49 god, 2 mcg vs. 4 mcg), faza 2 (n=510, 50+, 4 mcg)
- komparator PPV23
- usporedive nuspojave
- neinferiorna/bolja imunogenost



21-valentna konjugovana vakcina za odrasle

- CRM197: ST 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, **15A, 16F**, 17F, 19A, 20, 22F, **23A, 23B, 24F, 31, 33F, 35B** i deOac15B (**15C**)
- faza 3 2656 učesnika (18-49 god, 50+)
- komparator PCV20
- usporedive nuspojave
- neinferiorna za 10 zajedničkih ST, superiorna za 10/11 nezajedničkih ST (osim 15C)



24v pneumokokna konjugovana vakcina (VAX-24) kod odraslih

- protein eCRM+PS:1, **2**, 3, 4, 5, 6A, 6B, 7F, 8, **9N**, 9V, 10A, 11A, 12F, 14, 15B, **17F**, 18C, 19A, 19F, **20B**, 22F, 23F i 33F.
- faza 1 (n=64, 18-49 god) i faza 2 (n=771, 50-64 god), randomizacija 1:1:1:1
- PCV20 vs 1.1 mcg/2.2 mcg/2.2-4-4/mcg

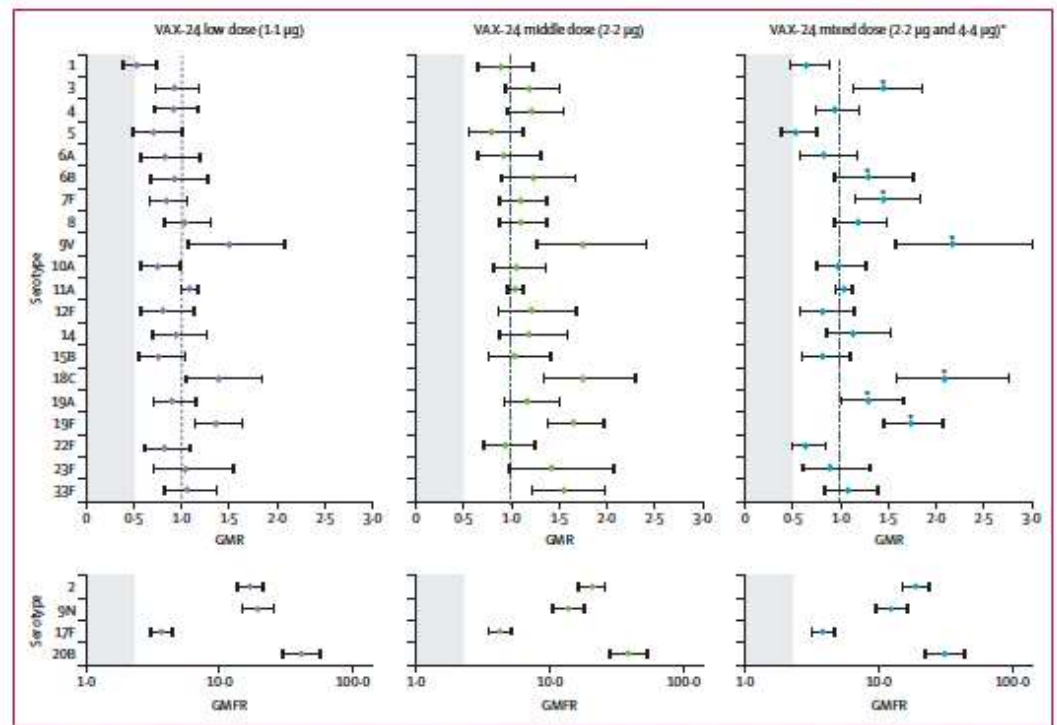


Figure 3: OPA Geometric mean titre ratio for each VAX-24 dose compared with PCV20 for shared serotypes and geometric mean fold rise for incremental serotypes at 28 days postvaccination

24v pneumokokna konjugovana vakcina (VAX-24) kod odraslih

- protein eCRM+PS:1, **2**, 3, 4, 5, 6A, 6B, 7F, 8, **9N**, 9V, 10A, 11A, 12F, 14, 15B, **17F**, 18C, 19A, 19F, **20B**, 22F, 23F i 33F.
- faza 2 (n=207, 65+ god), randomizacija 1:1:1:1
- PCV20 vs 1.1 mcg/2.2 mcg/2.2-4-4/mcg

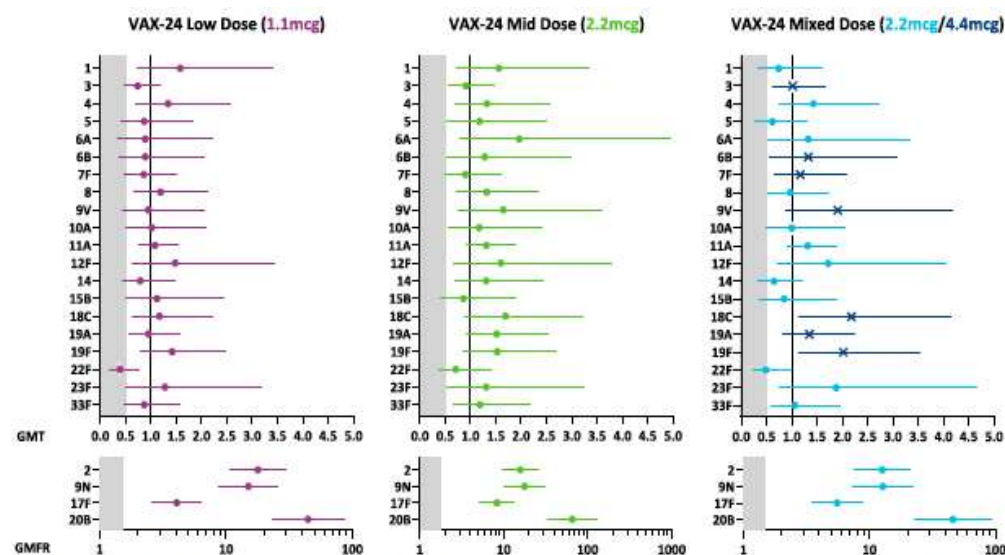


Fig. 3. Opaonophagocytic activity geometric mean titer (GMT) ratio for each VAX-24 dose compared with PCV20 for shared serotypes and geometric mean fold rise (GMFR) for incremental serotypes at 1 month post-vaccination (analysis of variance model, immunogenicity evaluable population). Error bars = 95 % CI.

MAPS-multiple antigen presenting system

A

- vakcine celih ćelija u proseku su efikasnije od komponentnih vakcina
- dosadašnji pristupi fokusirali su se na stimulaciju sinteze protutela
- efikasno kod Hib, pneumokoka, meningokoka
- manje efikasno kod stafilokoka, TB, gljiva i parazita
- stvaranje makromolekulnih MAPS kompleksa sa definisanim antigenskim, hemijskim i fizikalnim svojstvima
- pristup povezivanja zasnovan na afinitetima – nekovalentno vezivanje biotina i rizavidina
- ciljni proteini su genetski spojeni i sintetizovani u *E. coli*
- polisaharidi su biotinilovani
- nastali kompleks više liči na vakcinu celih ćelija i generira bolji imunitet (B i T limfociti)

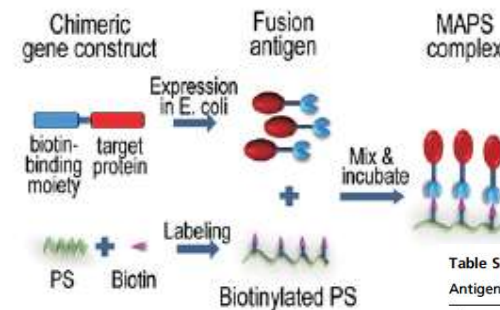
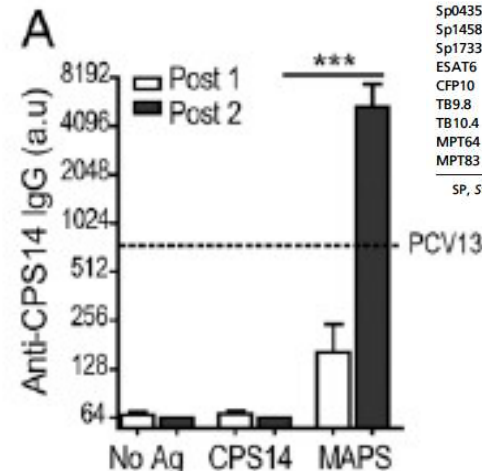


Table S1. Protein antigens used in this study

Antigen	Origin	Description
PdT	SP	Pneumolysin toxoid
PsaA	SP	Pneumococcal surface adhesin A
Sp1534	SP	Putative manganese-dependent inorganic pyrophosphatase
Sp0435	SP	Elongation factor P
Sp1458	SP	Thioredoxin reductase
Sp1733	SP	Putative phosphatase
ESAT6	MTB	6 -Da early secretory antigen
CFP10	MTB	10-kDa culture filtrate antigen
TB9.8	MTB	ESAT-6-like hypothetical protein
TB10.4	MTB	Low molecular weight protein antigen 7 (CFP7)
MPT64	MTB	Immunogenic protein
MPT83	MTB	Lipoprotein P23

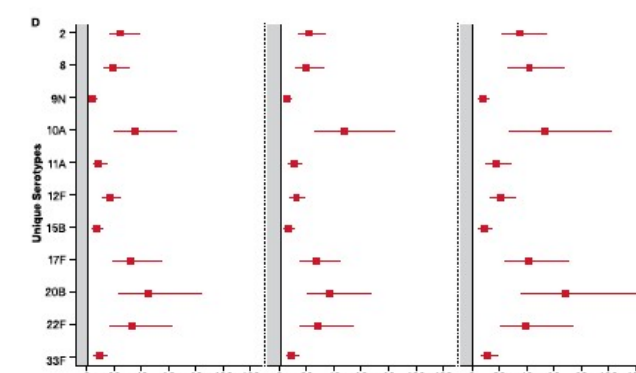
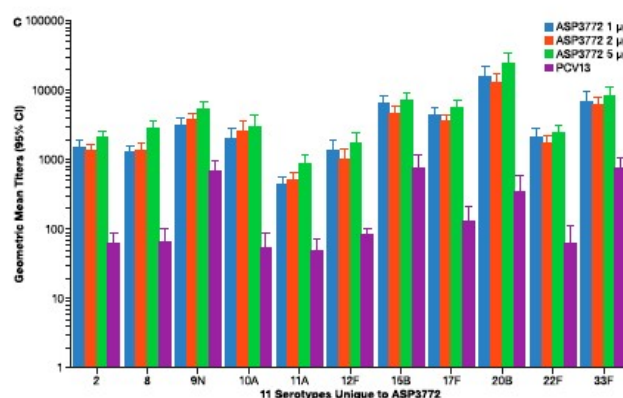
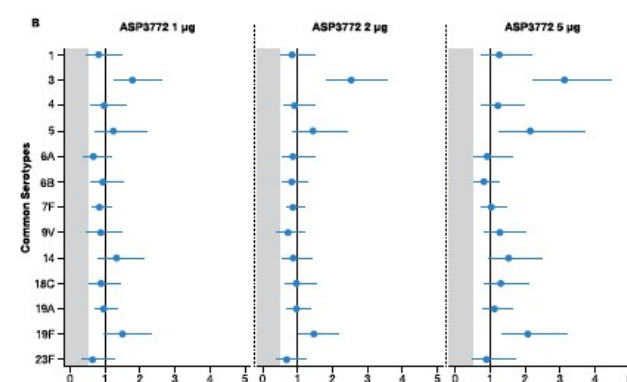
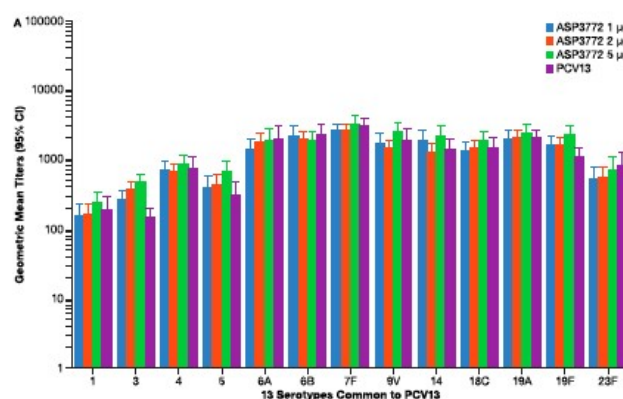
SP, *Streptococcus pneumoniae*; MTB, *Mycobacterium tuberculosis*.



PNAS 2013;110:13564-9.

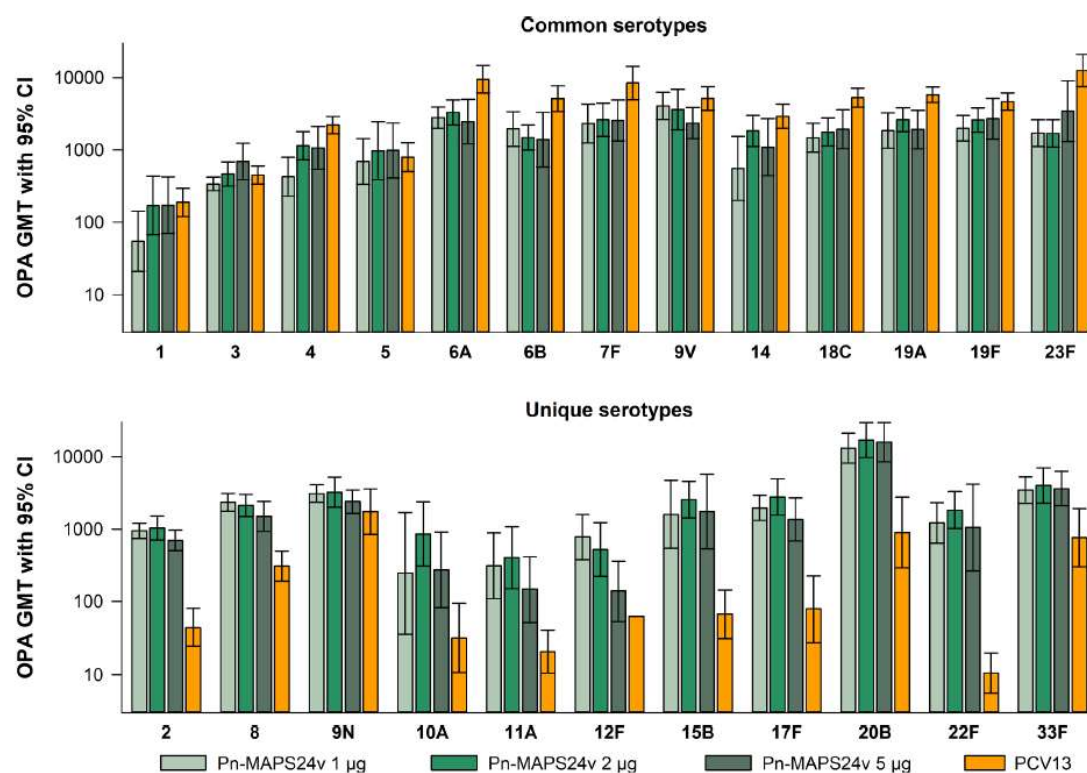
Pn-MAPS24v vakcina kod odraslih

- kapsularni polisaharidi:
1, 2, 3, 4, 5, 6A, 6B, 7F,
8, 9N, 9V, 10A, 11A,
12F, 14, 15B, 17F, 18C,
19A, 19F, 20B, 22F, 23F
i 33F.
- usporedba sa PCV13
- odrasli 18-85 godina (1,
2 i 5 mcg)
- nuspojave usporedive,
najčešće lokalna
reakcija
- odlična imunogenost



Pn-MAPS24v vakcina kod dece od 12-15 meseci

- kapsularni polisaharidi:
1, 2, 3, 4, 5, 6A, 6B, 7F,
8, 9N, 9V, 10A, 11A,
12F, 14, 15B, 17F, 18C,
19A, 19F, 20B, 22F, 23F
i 33F.
- usporedba sa PCV13
- deca 12-15 mes (1, 2 i 5
mcg)
- nuspojave usporedive,
najčešće lokalna
reakcija
- neinferiorna/bolja
imunogenost



Zaključak

- konjugovane vakcine dovele su do smanjenja incidencije pneumokoknih infekcija
- efekt je direktan i indirektan
- smanjuje se s vremenom zbog pojave zamenskih serotipova
- to iziskuje razvoj novih vakcina viših valencija
- ili drugačijeg inovativnog pristupa formulaciji vakcine
- imamo vakcine visokih valencija te inovativne vakcine u višim fazama kliničkog razvoja
- još uvek moramo stalno pratiti epidemiologiju pneumokoknih infekcija
- naš nazofarinks nikad neće biti sterilan