ISG
Influenza Specialist Group

Adult Vaccination and the role of polysaccharide and conjugate vaccines

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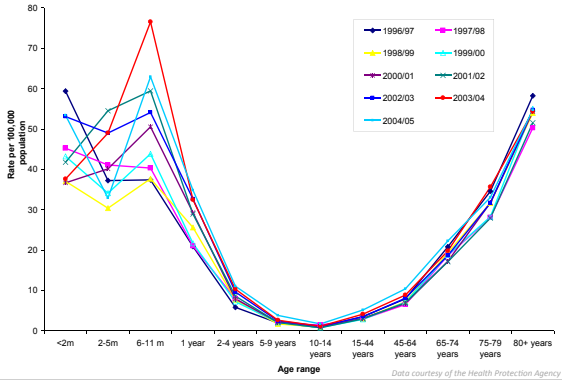
For Pneumococcal Serology

ISG
Influenza Specialist Group

- Pneumococcal Epidemiology and Vaccine development
- Efficacy of PPV23 in the elderly
- Efficacy of PCV13 against pneumonia in the elderly
- Recent US Policy decision re PCV13 in the elderly
- Current UK status of pneumococcal disease in the elderly and recent policy decisions

Invasive pneumococcal disease incidence rate per 100,000 population by age grouping England and Wales, 1996-2005



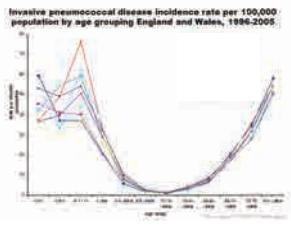
Data courtesy of the Health Protection Agency

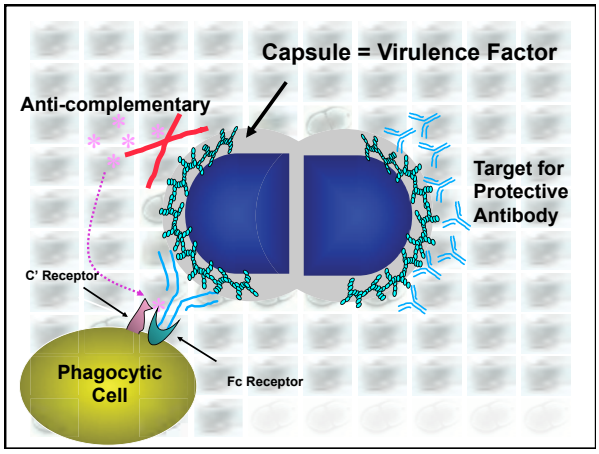
1977: Polysaccharide Vaccine (14 Valent)

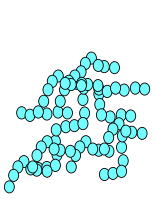
1983: Pneumovax® (23 Valent)

2000: Conjugate Vaccine (7 Valent)

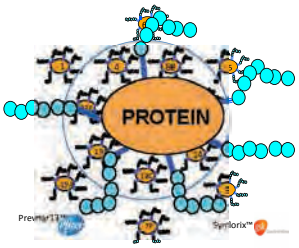
2009/10: Conjugate Vaccines (10 and 13 Valent)







Pneumovax® II, Merck
(23 serotypes)



Pure Polysaccharide Vaccine
T cell independent
Poor immunogenicity in young
No memory response
No impact on carriage

Protein-Polysaccharide Conjugate
T cell dependent
Immunogenic at all ages
Induces immune memory
Prevents acquistion of carriage

Vaccines for preventing pneumococcal infection in adults (Review)

Moberley S, Holden J, Tatham DP, Andrews RM

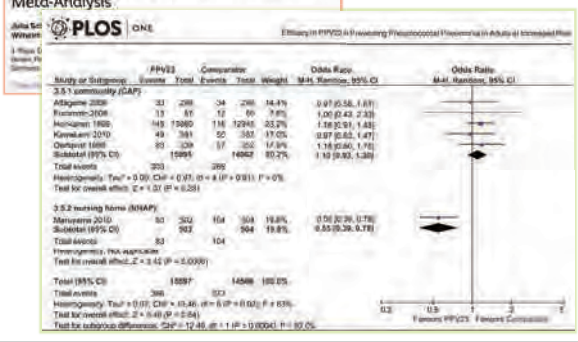
- Pneumococcal Polysaccharide Vaccine prevents IPD in healthy adults (protection wanes over time)
- RCT's less clear in chronic illness
- No evidence for pneumonia prevention or mortality reduction

THE COCHRANE COLLABORATION®

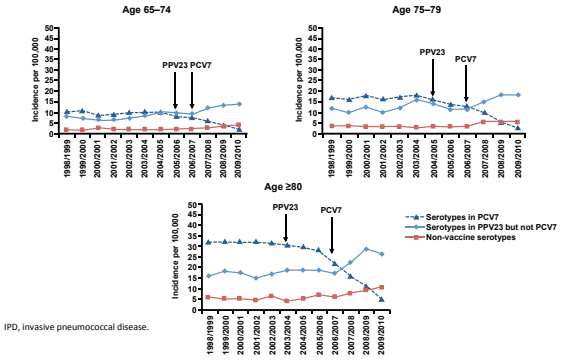
2008 and 2013

2016

Efficacy of PPV23 in Preventing Pneumococcal Pneumonia in Adults at Increased Risk – A Systematic Review and Meta-Analysis



IPD by Age Group and Serotypes, 1998/1999–2009/2010, England and Wales



IPD, invasive pneumococcal disease.

Andrews N et al. Vaccine. 2012: 6; 30(48): 6802-8

Estimation of 23v PPV vaccine effectiveness using the indirect cohort method in England and Wales.

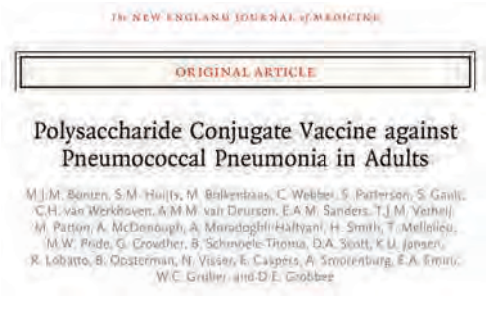
Updated analysis results May 24th 2011
Liz Miller/Nick Andrews, HPA

Time since vaccination	Risk group	Age 65-74	75-84	85+	All ages
0-1.99yrs	Non-risk	65 (23-84)	42 (-19-72)	-35 (-198-38)	35 (0-58)
	Risk1	69 (22-88)	70 (36-86)	42 (-57-78)	63 (40-78)
	Risk2	26 (-55-65)	54 (0-79)	34 (-103-79)	43 (9-65)
	All	**58 (32-73)**	**56 (32-71)**	**12 (-53-49)**	**48 (32-60)**
2-4.99yrs	Non-risk				(-64)
	Risk1	-13 (-151-49)	-3 (-91-45)	8 (-81-54)	0 (-50-33)
	Risk2	-92 (-252- -5)	48 (8-71)	42 (-20-72)	15 (-22-40)
	All	**4 (-42-35)**	**30 (2-50)**	**26 (-10-50)**	**21 (3-36)**
5yrs	Non-risk	28 (-72-70)	-94 (-102-42)	16 (-52-54)	18 (-20-44)
	Risk1	7 (-89-54)	14 (-45-49)	7 (-66-48)	12 (-48-33)
	Risk2	17 (-58-56)	17 (-23-57)	32 (-28-64)	20 (-11-43)
	All	**25 (-11-49)**	**8 (-24-32)**	**14 (-20-39)**	**15 (-3-30)**
Any time	Non-risk	56 (24-75)	27 (-16-54)	14 (-40-47)	34 (12-50)
	Risk1	21 (-46-57)	23 (-23-52)	11 (-51-48)	20 (-9-41)
	Risk2	-17 (-96-33)	38 (0-62)	35 (-15-64)	22 (-5-42)
	All	**28 (1-47)**	**25 (3-43)**	**18 (-11-39)**	**24 (10-36)**

* Risk 1: Heart, Diabetes, Lung (but none of risk 2)
** Risk 2: Renal, Immunosuppressed, Asplenia, Malignancy, Asthma (oral steroids)

Summary of Head to Head PCV vs PPV immunogenicity studies in healthy adults

Author	Country	Date	Population	*N*	Result of PCV vs PPSV comparison (ELISA)
Jackson		2007	70-79y	219	7vPCV=PPSV
De Roux		2008	>70y	219	7vPCV superior for 6/7 serotypes (not 19F)
Scott		2008	20-50y	15	13vPCV=PPSV
Goldblatt		2009	50-80y	599	7vPCV superior for 3/7 serotypes (4, 9V, 23F)
Ridda		2009	>60y	241	7vPCV=PPSV (4 serotypes analysed: 4, 6B, 18C, 23F)
Miernyk		2009	55-70y	203	7vPCV=PPSV (4 serotypes analysed: 4, 6B, 14, 19F)
Lazarus		2011	50-70	348	7vPCV superior for 4/7 serotypes (4, 9V, 18C, 23F)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

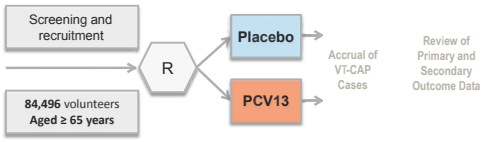
Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults

M.J.M. Bonten, S.M. Huijts, M. Bolkenbaas, C. Webber, S. Patterson, S. Gault, C.H. van Werkhoven, A.M.M. van Deursen, E.A.M. Sanders, T.J.M. Verheij, M. Patton, A. McDonough, A. Maradoghli-Hallyani, H. Smith, T. Mellelieu, M.W. Pride, G. Crowther, B. Schmoele-Thoma, D.A. Scott, K.U. Jansen, R. Lobanto, B. Oosterman, N. Visser, E. Caspers, A. Smorenburg, E.A. Emini, W.C. Gruber, and D.E. Grobbee

2015

CAPiTAClinical Trial Design

Excluded immunodeficient adults



CAPiTA was an event-driven trial dependent on accrual of sufficient number of cases of VT-CAP

Hak E, Grobbee DE, Sanders EAM, et al. Netherlands J Med. 2008;66:378-383.

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The Serotype-Specific Urinary Antigen Detection (UAD) Assay

- Developed by Pfizer specifically for the CAPiTA study
- A multiplex antigen-binding assay for detection of PCV13-type capsular polysaccharide
- Enables accurate testing of urine for the **presence of PCV13 serotypes:** 97% sensitivity and 100% specificity in adults with pneumonia

Pride MW et al. *Clin. Vaccine Immunol.* 2012;19(8):1131-1141
Huijts et al., *Eur Resp Journal.* 2013; 42(5):1283-90

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Primary and Secondary Objectives: Per Protocol

Efficacy Endpoint	Vaccine Group		VE (%)	95.2% CI	p-Value
	PCV13 (n=42,240)	Placebo (n=42,256)			
First episode of confirmed VT pneumococcal CAP	49	90	45.56	(21.82,62.49)	0.0006
First episode of confirmed NB/NI VT pneumococcal CAP	33	60	45.00	(14.21, 65.31)	0.0067
First episode of VT-IPD	7	28	75.00	(41.43, 90.78)*	0.0005

* 95% Confidence Intervals

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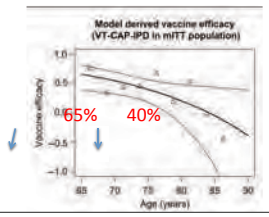
Primary and Secondary Objectives: mITT

Efficacy Endpoint	Vaccine Group		VE (%)	95% CI	p-Value
	PCV13 (n=42,240)	Placebo (n=42,256)			
First episode of confirmed VT pneumococcal CAP	66	106	37.74	(14.31, 55.05)	0.0028
Immunocompetent	51	93			
Immunodeficient/suppressed	14	11			



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Selected Exploratory Efficacy Endpoints

Efficacy Endpoint	Vaccine Group		VE (%)	95% CI	P-value
	Prevenar 13 (n=42,240)	Placebo (n=42,256)			
First episode of Confirmed Pneumococcal CAP (Per Protocol Population – VT, NVT & untypeable)	100	144	30.56	(9.75, 46.74)	0.0058
First episode of Confirmed NB/NI Pneumococcal CAP (Per Protocol Population – VT & NVT)	66	87	24.14	(-5.68, 45.76)	0.1056
First episode of IPD (Per Protocol Population – VT & NVT)	27	56	51.79	(22.38, 70.72)	0.0039
First episode of CAP (mITT Population – all cause CAP)	747	787	5.08	(-5.05, 14.24)	0.3194

VT = vaccine-type
NVT = nonvaccine-type
NB/NI = nonbacteremic/noninvasive
CAP = community acquired pneumonia
IPD = invasive pneumococcal disease

Safety

Safety Outcome	PCV 13 n=42,279	Placebo n=42,255	p-Value
Serious Adverse Events ≤28 days	327 (0.8%)	314 (0.7%)	0.606
Cardiac disorders	72 (0.2%)	74 (0.2%)	0.934
General disorders and administration site conditions	23 (0.1%%)	7 (<0.1%)	0.003
Deaths	3,006 (7.1%)	3,005 (7.1%)	0.979

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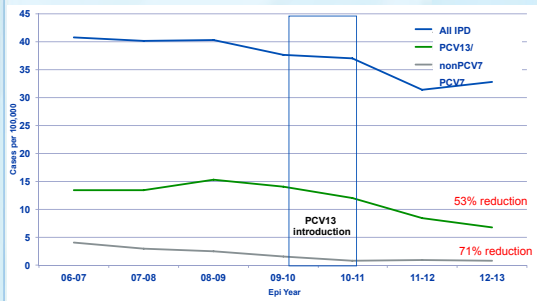
The US Perspective

Herd effects on IPD: Incidence of Invasive Pneumococcal Disease Among Adults >65 Years by Serotype, 1998-2013



Active Bacterial Core Surveillance, unpublished

Slides provided by Tamara Pilishvili, CDC

PCV13 herd effects on non-bacteremic pneumonia, 2011-2012

	All-cause pneumonia	Invasive pneumococcal disease	Non-invasive pneumococcal or lobar pneumonia	Empyema
<2 years	21% (14 to 28)*	64% (47 to 75)*	40% (14 to 59)*	50% (22 to 68)*
2–4 years	17% (7 to 27)*	55% (16 to 75)*	33% (–3 to 56)	46% (21 to 64)*
5–17 years	–3% (–20 to 11)	25% (–24 to 54)	51% (29 to 66)*	37% (13 to 54)*
18–39 years	12% (6 to 17)*	37% (20 to 51)*	32% (17 to 44)*	–8% (–25 to 6)
40–64 years	2% (–2 to 6)	13% (–1 to 26)	25% (16 to 33)*	–4% (–13 to 3)
≥65 years	3% (–1 to 6)	29% (16 to 40)*	34% (27 to 41)*	–1% (–10 to 7)

Data are percentage change (95% CI) according to our model. Assumes vaccine coverage at March, 2012 level.
*Significant reduction (p<0·05).

Table 3: Proportion of seasonal admissions to hospital averted by vaccination per season at coverage achieved in March, 2012

Simonsen et al Lancet Resp Med 2014

Slides provided by Tamara Pilishvili, CDC

Distribution of 13-Valent Pneumococcal Conjugate Vaccine *Streptococcus pneumoniae* Serotypes in US Adults Aged ≥50 Years With Community-Acquired Pneumonia

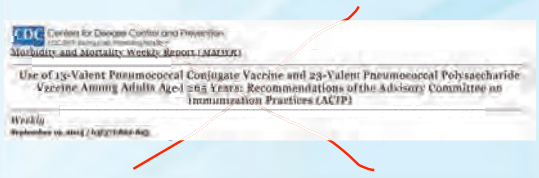
Robert L. Ellerson,[1] Shawna Gray,[2] Ruvika Alexander,[3] Paul C. McGovern,[4] Jay Graepel,[5] Michael W. Pride,[5] Jay Purdy,[5] Peter Paradise,[5] and Thomas M. File Jr[1,2]

- 781 subjects enrolled
- 710 CXR+ve pneumonia
- 708 Urinary Antigen Test
  - 78 Pneumococcal Positive (60% aged 50-64)
  - 21 PCV7 Serotype
    - *3% of the total CXR +ve Pneumonia*

J Infect Dis 2013

Policy options under consideration

- Add a dose of PCV13 at age ≥ 65 years to currently recommended PPSV23 regimen
  - PCV13 dose followed by a dose of PPSV23 at age ≥ 65 years
  - Risk-based recommendations for PCV13 and PPSV23 use remain unchanged


CDC Centers for Disease Control and Prevention
Morbidity and Mortality Weekly Report (MMWR)
Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine Among Adults Aged ≥65 Years: Recommendations of the Advisory Committee on Immunization Practices (ACIP)
Weekly

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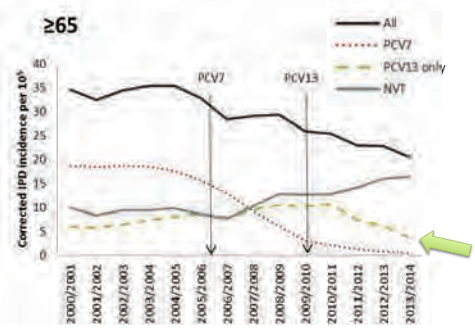
Slides provided by Tamara Pilishvili, CDC

Potential time-limited utility of routine PCV13 use among adults ≥65 years

- **ACIP should be routinely updated on the changes in vaccine-preventable disease burden among adults due to PCV13 direct and indirect effects during the next 3 years**
- **These data should inform revisions as needed to the proposed adult PCV13 recommendations in 2018**
  - Declining burden of PCV13-type disease among adults <65 years old due to indirect effect of vaccinating children may signal that PCV13 is no longer needed
  - Revised cost effectiveness evaluation incorporating changes in disease burden, uptake, and the cost of the vaccines will help align this recommendation with other adult vaccines in use

Slides provided by Tamara Pilishvili, CDC

Impact of PCV7 and PCV13 on IPD in 65+yr olds
(all PCV13 serotypes are in PPV23 apart from 6A)



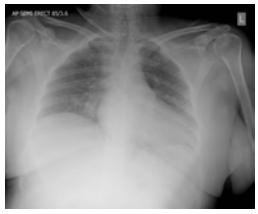
PCV13 only Serotypes: Will they continue to reduce to low levels?

ERJ Express. Published on March 18, 2015 as doi: 10.1183/09031936.00183614

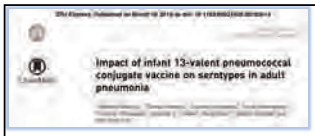
Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia

Chamira Rodrigo[1], Thomas Bewick[1], Carmen Sheppard[2], Sonia Greenwood[1], Tricia M. Mckeever[3], Caroline L. Trotter[4], Mary Slack[2], Robert George[2] and Wei Shen Lim[1]

Prospective cohort study of CAP admissions in ≥ 16 yr olds to two teaching hospitals in Nottingham over 5 years from September 2008 to August 2013



Eur Respir J. 2015 Jun;45(6):1632-41.



- Surveillance case definition: (similar to CAPiTA trial)
  - new infiltrates on CXR + clinical diagnosis CAP
  - Exclusion criteria: aspiration pneumonia, obstructive pneumonia from lung cancer, active TB, prior CAP admission within 10 days
- Lab confirmation of PCV13 type CAP (similar to CAPiTA trial)
  - Blood culture or PCV13 type identified in urine
- Participants: (more inclusive than CAPiTA trial)
  - 2702 eligible, 2321 consented, excluded 16 not CAP and 76 no urine sample, final # 2229 (82%)
  - Mean annual CAP incidence 79.9 per 10^5
  - Median age 71 years (IQR 55.1-80.5)
  - 653 (29%) lab confirmed as any pneumococcal CAP (566 non-invasive)
  - 30 day case fatality: pneumococcal cases 6.2%

Eur Respir J. 2015 Jun;45(6):1632-41.

Impact of PCV7 and PCV13 on VT CAP (from Rodrigo table 2) versus VT IPD (from Waight et al 2015)

Incidence per 100,000 of PCV13 attributable CAP

	2008/9	2012/13	IRR CAP	IRR-IPD > ≥65yrs
PCV7				
65-74	26.7	7.1	0.27	0.20
75-84	39.1	5.6	0.14	0.15
≥85	177.1	31.2	0.18	0.17
PCV13 only				
65-74	23.2	12.5	0.54	0.56
75-84	44.7	22.3	0.5	0.62
≥85	104.2	20.8	0.2	0.62

Slide Courtesy of Liz Miller, HPA

UK JCVI Interim statement 18th November 2015

- PPV23 should continue to be offered to those aged 65 years and over and the indicated risk groups. PCV13 should continue to be offered to those risk groups previously identified as being at particularly high risk* of, and high mortality from, IPD, but should not be offered more widely to other risk-groups or older adults.
- The epidemiology of pneumococcal disease is still evolving following the introduction of PCV13 into the childhood programme, and as such JCVI will keep the adult pneumococcal programme under review. It has been agreed that JCVI will consider the use of PPV23 again in three years, when it is anticipated that pneumococcal epidemiology in the UK may have achieved a steady state.

*Those indicated for PCV13 would include individuals who are clinically severely immunocompromised, for example: bone marrow transplant patients or those with acute and chronic leukaemias, multiple myeloma, or genetic disorders severely affecting the immune system (e.g. IRAK-4, NEMO, complement deficiency).

Summary and Conclusions

- Pneumococcal epidemiology is dynamic
- Simple tests to identify the bacterial cause of pneumonia remain elusive
- While different approaches to preventing adult disease have been taken in the US and UK, both approaches emphasise that decisions need to be reviewed soon in the light of changing epidemiology.
- Acknowledgments:
  - Professor Liz Miller, PHE
  - Tamara Pilishvili, CDC