Effectiveness of pneumococcal conjugate vaccines (PCV7, PCV10 and PCV13) against invasive pneumococcal disease among children under two years of age in Germany

M. van der Linden, G. Falkenhorst, S. Perniciaro and M. Imöhl
National Reference Center for Streptococci (GNRCS) and Institute of Medical Microbiology, RWTH-Aachen, Germany

Mark van der Linden
University Hospital RWTH Aachen
Institute of Medical Microbiology
National Reference Center for Streptococci
Pauwelsstrasse 30, 52074 Aachen, Germany
Email: mlinden@ukaachen.de

OBJECTIVES

A general recommendation for vaccination with pneumococcal conjugate vaccine (PCV) with a 3+1 schedule was issued for German children ≤2 years in 2006. As of 2009, PCV7 was replaced by higher-valent PCVs, mostly PCV13. We calculated vaccine effectiveness (VE) of PCVs using the indirect cohort method.

METHODS

Pneumococcal isolates from children with IPD were serotyped at the GNRCS using the Neufeld-Quellung reaction. Vaccine Effectiveness (VE) was calculated using the indirect cohort method as described by Broome et al. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using Firth's bias-reduced logistic regression as described by Heinze. VE was adjusted for age and season following the issue of the vaccination recommendation. All calculations were performed using R (version 3.1.1, The R Foundation for Statistical Computing, Vienna, Austria).

Only children with complete information on vaccination status, i.e. date of vaccination and type of vaccine, were included in the analysis. To reflect the conjugate vaccine introduction in Germany, the analysis was split in two periods. From July 2006 until June 2010, children vaccinated with PCV7 were analysed. From July 2010 until June 2015, vaccinations with PCV13 were assessed. For PCV10 only data from July 2009 until June 2010 were used, due to the very low use of this vaccine after June 2010.

To assess the timeliness of pneumococcal conjugate vaccination in Germany, the actual age at vaccination was compared to the scheduled age (first dose: 60-89 days of age, second dose: 90-119 days, third dose: 120-149 days, booster: 330-449 days). The analysis was performed for PCV7 and PCV13.

RESULTS

For 618 children (67.1%), the vaccination status at the time of infection could be accurately determined. Of these, 379 (61.3%) were vaccinated and 239 (38.7%) were not vaccinated. Among the vaccinated children, 125 (33.0%) were vaccinated with PCV7, 32 (8.4%) with PCV10 and 221 (58.3%) were vaccinated with PCV13 at the time of infection. One child had received a primary series of PCV10 and a booster with PCV13 and this case was excluded from further analysis. The percentage of children vaccinated with at least one dose of any PCV at the time of infection gradually increased from 25.6% in 2006-2007 to 83.8% in 2014-2015 (**Fig. 1**).

For PCV7, the adjusted VE against all 7 serotypes + 6A was 80% for at least one dose, 97% after three primary doses and 95% post booster dose (**Table 1**).

VEs for PCV10 +6A+19A was 90% for at least one dose, 98% after three primary doses. In the post booster cohort there were no vaccinated cases or controls (**Table 2**).

For PCV13, the adjusted VE was 86% for at least one dose, 85% post primary, and 91% post booster. For the additional serotypes included in PCV13, VEs were 82%, 80% and 90% respectively. VE (at least one dose) for serotype 1 was 83%, serotype 3: 74%, 6A: 96%, 7F: 84%, 19A: 77%. During the analysis period, no cases with serotype 5 were reported (**Table 3**).

Vaccination rates increased from 26% in 2006-2007 to 84% in 2014-2015, but there was considerable delay in administration of doses (**Fig. 2, Fig. 3**).

Over 90% of vaccine serotype cases were in non- or incompletely- vaccinated children.

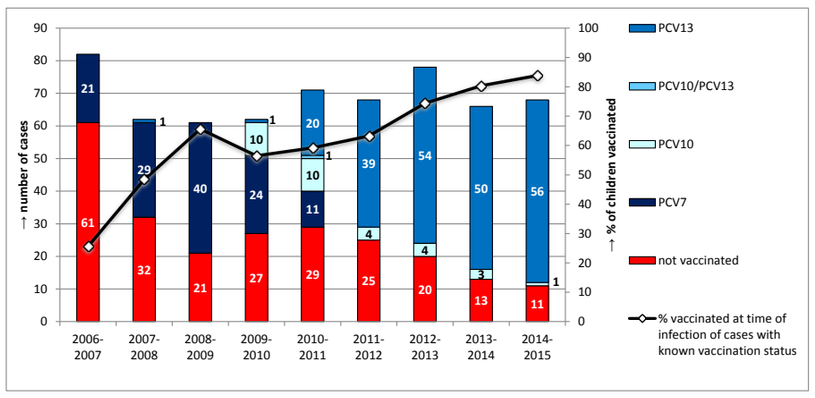

Fig 1: Vaccination status at time of infection of 618 children with IPD reported to the GNRCS from July 2006 – June 2015. Red: not vaccinated, dark blue: vaccinated with PCV7, light blue: vaccinated with PCV10, blue: vaccinated with PCV13. The black line represents the percentage of children vaccinated at the time of infection among the cases for which the vaccination status could be ascertained.

Table 1: Vaccine effectiveness of PCV7+6A (2006-2010) for IPD in children <2 years of age in Germany.

2006-2010		cases vaccinated: unvaccinated	controls vaccinated: unvaccinated	crude vaccine effectiveness (95% CI)	adjusted vaccine effectiveness (95% CI)
PCV7 serotypes + 6A					
	at least one dose	20:94	94:60	**84% (72 to 91)**	**80% (63 to 89)**
	post primary	1:49	38:27	**98% (91 to 100)**	**97% (89 to 100)**
	post booster	0:44	11:19	**98% (84 to 100)**	**95% (57 to 100)**
Serotype 4					
	at least one dose	0:1	94:60	79% (-307 to 100)	70% (-636 to 100)
	post primary	0:1	38:27	76% (-364 to 100)	51% (-1088 to 100)
	post booster	0:1	11:19	44% (-1054 to 100)	-86% (-50978 to 99)¶
Serotype 6B					
	at least one dose	2:20	94:60	**92% (74 to 98)**	**90% (66 to 98)**
	post primary	0:15	38:27	**98% (82 to 100)**	**97% (72 to 100)**
	post booster	0:14	11:19	**94% (48 to 100)**	85% (-89 to 100)
Serotype 9V					
	at least one dose	0:4	94:60	**93% (32 to 100)**	89% (-13 to 100)
	post primary	0:2	38:27	86% (-85 to 100)	83% (-158 to 100)
	post booster	0:2	11:19	66% (-367 to 100)	-16% (-18054 to 99)¶
Serotype 14					
	at least one dose	2:24	94:60	**93% (79 to 99)**	**90% (68 to 98)**
	post primary	0:12	38:27	**97% (77 to 100)**	**97% (71 to 100)**
	post booster	0:15	11:19	**95% (52 to 100)**	89% (-20 to 100)
Serotype 18C					
	at least one dose	4:6	94:60	56% (-52 to 88)	8% (-239 to 76)
	post primary	0:3	38:27	90% (-11 to 100)	79% (-137 to 100)
	post booster	0:4	11:19	81% (-103 to 100)	66% (-635 to 100)
Serotype 19F					
	at least one dose	5:11	94:60	**69% (14 to 90)**	55% (-34 to 87)
	post primary	1:6	38:27	**84% (15 to 98)**	73% (-44 to 97)
	post booster	0:4	11:19	81% (-103 to 100)	72% (-301 to 100)
Serotype 23F					
	at least one dose	3:8	94:60	**74% (11 to 94)**	61% (-62 to 92)
	post primary	0:6	38:27	**95% (50 to 100)**	89% (-23 to 100)
	post booster	0:3	11:19	76% (-184 to 100)	33% (-9761to 100)
Serotype 6A					
	at least one dose	4:7	94:60	62% (-26 to 90)	**73% (1 to 93)**
	post primary	0:4	38:27	**92% (21 to 100)**	**91% (8 to 100)**
	post booster	0:1	11:19	43% (-1054 to 100)	74% (-478 to 100)

Table 2: Vaccine effectiveness of PCV10+6A+19A (2009-2010) for IPD in children <2 years of age in Germany.

2009-2010		cases vaccinated: unvaccinated	controls vaccinated: unvaccinated	crude vaccine effectiveness (95% CI)	adjusted vaccine effectiveness (95% CI)
PCV10 serotypes +6A+19A					
	at least one dose	3:23	7:4	**91% (58 to 98)**	**90% (54 to 98)**
	post primary	1:12	5:1	**97% (72 to 100)**	**98% (73 to 100)**
	post booster	0:4	0:2		
PCV10-non-PCV7 serotypes					
	at least one dose	1:15	7:4	**97% (64 to 100)**	**97% (59 to 100)**
	post primary	0:8	5:1	**97% (47 to 100)**	**97% (43 to 100)**
	post booster	0:2	0:2		
PCV7 serotypes in PCV10					
	at least one dose	2:8	7:4	**82% (0 to 98)**	**86% (12 to 99)**
	post primary	1:5	5:1	**93% (24 to 100)**	**95% (31 to 100)**
	post booster	0:2	0:2		
Serotype 1					
	at least one dose	0:2	7:4	88% (-93 to 100)	62% (-811 to 100)
	post primary	0:0	5:1		
	post booster	0:0	0:2		
Serotype 5					
	at least one dose	0:0	7:4		
	post primary	0:0	5:1		
	post booster	0:0	0:2		
Serotype 7F					
	at least one dose	0:7	7:4	**96% (53 to 100)**	**97% (54 to 100)**
	post primary	0:4	5:1	**97% (47 to 100)**	**61% (43 to 100)**
	post booster	0:1	0:2		
Serotype 6A					
	at least one dose	0:2	7:4	88% (-93 to 100)	72% (-372 to 100)
	post primary	0:1	5:1	91% (-163 to 100)	80% (-575 to 100)
	post booster	0:0	0:2		
Serotype 19A					
	at least one dose	1:4	7:4	80% (-55 to 98)	79% (-76 to 99)
	post primary	0:3	5:1	96% (28 to 100)	94% (-23 to 100)
	post booster	0:1	0:2		

Table 3: Vaccine effectiveness of PCV13 (2006-2010) for IPD in children <2 years of age in Germany.

2010-2015		cases vaccinated: unvaccinated	controls vaccinated: unvaccinated	crude vaccine effectiveness (95% CI)	adjusted vaccine effectiveness (95% CI)
PCV13 serotypes					
	at least one dose	25:55	194:43	**90% (82 to 94)**	**86% (74 to 93)**
	post primary	10:22	74:20	**87% (70 to 95)**	**85% (62 to 94)**
	post booster	2:13	33:16	**91% (65 to 98)**	**91% (61 to 99)**
PCV13-non-PCV7 serotypes					
	at least one dose	23:43	194:43	**88% (78 to 93)**	**82% (66 to 91)**
	post primary	10:16	74:20	**82% (57 to 93)**	**80% (46 to 93)**
	post booster	2:12	33:16	**90% (62 to 98)**	**90% (54 to 98)**
PCV7 serotypes in PCV13					
	at least one dose	2:12	194:43	**96% (84 to 99)**	**94% (78 to 99)**
	post primary	0:6	74:20	**98% (81 to 100)**	**99% (80 to 100)**
	post booster	0:1	33:16	84% (-225 to 100)	83% (-240 to 100)
Serotype 1					
	at least one dose	2:5	194:43	**90% (56 to 98)**	**83% (15 to 97)**
	post primary	1:2	74:20	84% (-31 to 99)	49% (-614 to 96)
	post booster	0:1	33:16	84% (-225 to 100)	82% (-328 to 100)
Serotype 3					
	at least one dose	6:5	194:43	**74% (10 to 92)**	**74% (2 to 93)**
	post primary	1:2	74:20	84% (-31 to 99)	80% (-68 to 98)
	post booster	1:2	33:16	70% (-140 to 97)	63% (-393 to 97)
Serotype 5					
	at least one dose	0:0	194:43		
	post primary	0:0	74:20		
	post booster	0:0	33:16		
Serotype 6A					
	at least one dose	0:4	194:43	**95% (55 to 100)**	**96% (56 to 100)**
	post primary	0:1	74:20	91% (-78 to 100)	84% (-214 to 100)
	post booster	0:2	33:16	90% (-30 to 100)	84% (-224 to 100)
Serotype 7F					
	at least one dose	1:12	194:43	**97% (88 to 100)**	**84% (18 to 98)**
	post primary	0:2	74:20	**95% (29 to 100)**	86% (-116 to 100)
	post booster	0:0	33:16	51% (-9185 to 100)	32% (-8066 to 99)
Serotype 19A					
	at least one dose	14:17	194:43	**81% (60 to 92)**	**77% (47 to 90)**
	post primary	8:9	74:20	**75% (30 to 92)**	**73% (18 to 92)**
	post booster	1:7	33:16	**90% (49 to 99)**	**88% (25 to 99)**

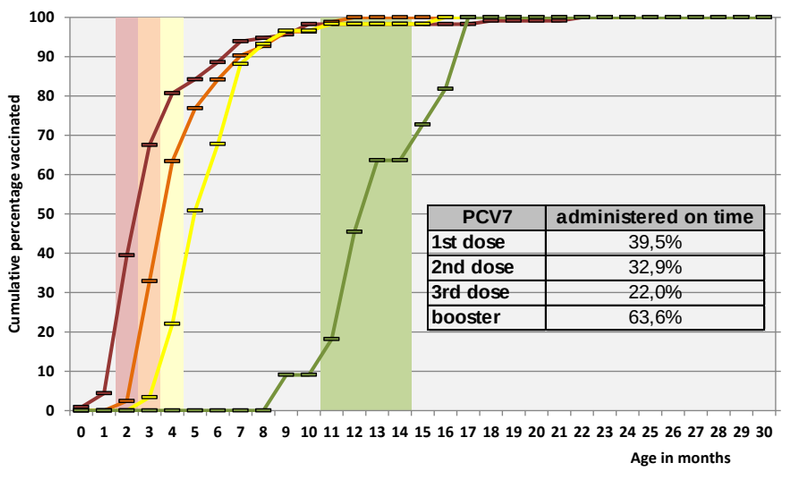

Fig 2: Timeliness of pneumococcal conjugate vaccination (PCV7) of children under two years of age with IPD in Germany (July 2006 – June 2010). Bars indicate scheduled vaccination times, lines indicate cumulative actual vaccination rates in percentage (red: 1st dose, orange: 2nd dose, yellow: 3rd dose, green: booster dose). Only doses given before the time of infection were taken into consideration.

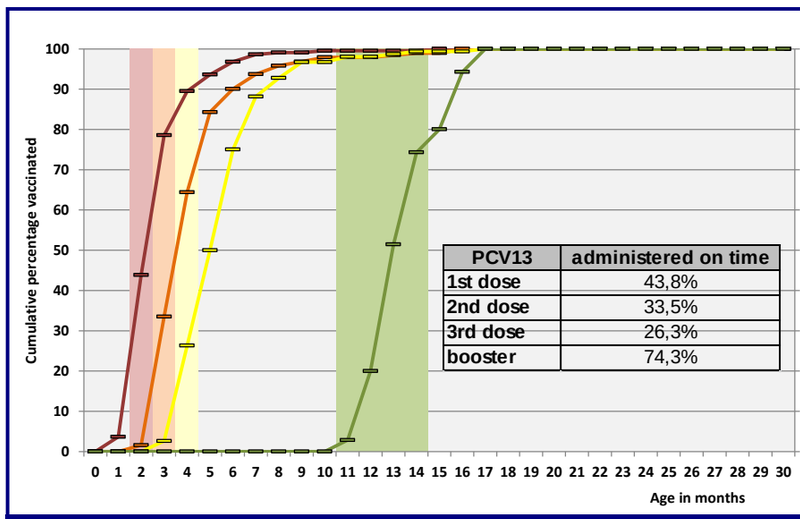

Fig 3: Timeliness of pneumococcal conjugate vaccination (PCV13) of children under two years of age with IPD in Germany (July 2010 – June 2015). Bars indicate scheduled vaccination times, lines indicate cumulative actual vaccination rates in percentage (red: 1st dose, orange: 2nd dose, yellow: 3rd dose, green: booster dose). Only doses given before the time of infection were taken into consideration.

CONCLUSIONS

- Our data show high a VE for PCV7 for all included serotypes and 6A. The VE for each single serotype is high but for 6A CIs are wide and include zero.
- Our data show high a VE for PCV10 for all included serotypes, 6A and 19A. The VE for serotype 7F is high, but for serotypes 1, 6A and 19A CIs are wide and include zero.
- Our data show high a VE for PCV13 for all included serotypes. The VE for each single serotype is high, including for serotype 3.
- A disturbing finding is the considerable delay in administration of vaccine doses among children with IPD.
- About 90% of the remaining vaccine type IPD cases in children <2 years could have been prevented by timely vaccination.