

Effects of 8 years of immunization with higher-valent pneumococcal conjugate vaccines among children in Germany

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BACKGROUND AND AIMS

A general recommendation for the pneumococcal conjugate vaccine (PCV) was issued for children ≤ 2 years in Germany in 2006. In 2009, two higher-valent PCVs (PCV10, PCV13) were licensed. Here, we present data on invasive pneumococcal disease (IPD) cases following PCV program onset.

METHODS

Pneumococcal isolates from children with IPD were serotyped (Quellung reaction) and tested for antibiotic resistance (MIC).

RESULTS

The GNRCS has been collecting IPD isolates from children since 1997 (**Fig. 1**). From July 2016 to June 2017, the GNRCS received 116 IPD isolates from children < 2 years (**Fig. 2**). The 116 isolates represent a reduction of 25% ($n=154$) compared to 2005/2006 (before vaccination), but an increase since 2011-2012 ($n=75$). , of which 15 had PCV13 serotypes (**Fig. 3**). Nine of these were from unvaccinated children. From July 2017 - April 2018, 140 cases were reported from children < 16 years of age, 30 with PCV13 serotypes , of which only 5 with PCV13 and in a correct schedule. For 14 the vaccination status could not yet be evaluated (**Table 1**).

The 116 isolates from 2016-2017 represent a reduction of 25% ($n=154$) compared to 2005/2006 (before vaccination), but an increase since 2011-2012 ($n=75$). The total amount of cases has increased, but the PCV13 proportion has decreased from 88% before vaccine introduction to 69% at the introduction of higher-valent vaccines to 14% in 2016/2017.

Among PCV13-non-PCV7 serotypes (**Fig. 4**), reductions were observed for children ≤ 2 years in serotypes 1 (-100%), 6A (-100%), 7F (-100%) and 19A (-90%). Serotype 3 showed no reduction, and serotype 5 remains rare in Germany. Compared to 2009/2010, reductions in children 2-4 years and 5-16 years were observed for serotype 1 (-89% and -100%) and serotype 7F (-100%, -90%), whereas cases of serotypes 5, 6A and 19A were rare. Serotype 3 decreased among 2-4 year old children from 2 cases to 1 and from 7 cases to 2 in 5-15 year olds.

In non-vaccine serotypes, 15A/B/C, 10A, 23B, 22F, 24F and 12F were most prevalent (**Table 2**).

Serotypes of penicillin non-susceptible and macrolide resistant isolates have changed after the start of childhood vaccination. Macrolide resistance levels have dropped substantially (**Fig. 5**).

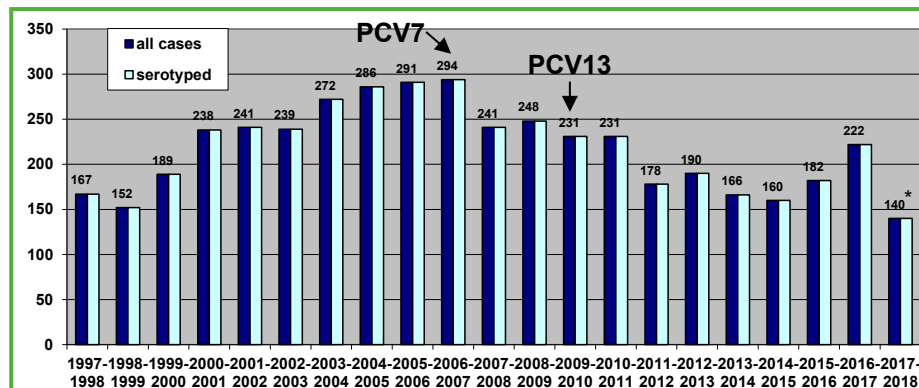


Fig. 1: Number of cases of IPD from children < 16 years of age in Germany and number of serotyped cases per pneumococcal season (July to June in the following year). * 2017-2018: incomplete season.

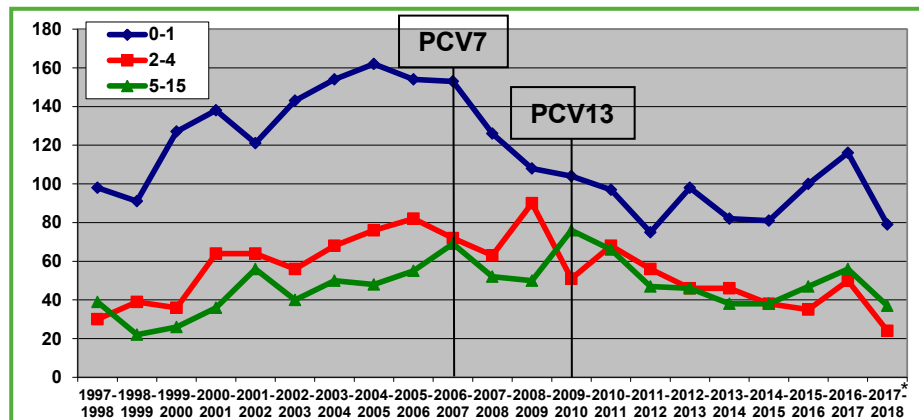


Fig. 2: Number of cases of IPD from children in Germany per pneumococcal season in three age groups: 0-1 year (blue), 2-4 years (red), 5-15 years (green). * 2017-2018: incomplete season.

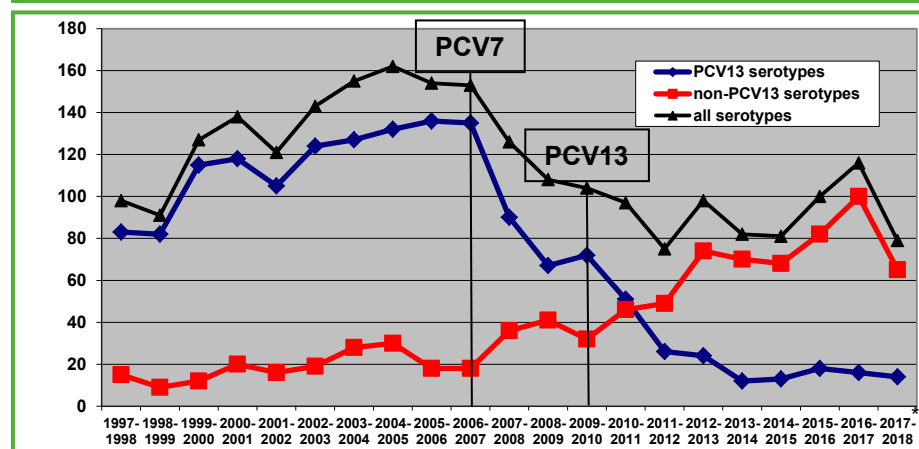


Fig. 3: Number of cases of IPD with PCV13- and non-PCV13 serotypes from children < 2 years in Germany per pneumococcal season. * 2017-2018: incomplete season.

Table 2: Serotype ranking among IPD in children in Germany.

Rank	Serotype	average 1997-2006	%	Serotype	2014-2015	%	Serotype	2015-2016	%	Serotype	2016-2017	%	Serotype	2017-2018	%
	total	231	100.0	total	159	100.0	total	182	100.0	total	222	100.0	total	140	100.0
1	PCV13	201	87.0	PCV13	86	54.1	PPV23	108	59.3	PCV13	122	55.0	PCV13	82	58.6
2	PCV13	198	84.4	PCV13	44	27.7	PCV13	38	20.9	PCV13	42	19.0	PCV13	38	27.1
3	PCV18	174	75.3	PCV10	23	14.5	PCV10	20	11.0	PCV18	11	5.0	PCV10	7	5.0
4	PCV17	142	61.5	PCV17	10	6.3	PCV17	13	7.1	PCV17	9	4.1	PCV17	2	1.4
1	14	49	21.2	24F	19	11.9	10A	24	13.2	3	22	9.9	3	18	12.9
2	9V	23	10.0	10A	15	9.4	3	15	8.2	10A	20	9.0	24F	13	9.3
3	19F	17	7.4	10A	10	6.3	15	8.2	15C	17	7.7	10A	12	8.6	
4	6B	17	7.4	1	9	5.7	24F	14	7.7	23B	17	7.7	22F	9	6.4
5	1	17	7.4	3	9	5.7	15C	13	7.1	22F	16	7.2	8	5.7	
6	23F	14	6.1	12F	8	5.0	23B	12	6.6	24F	16	7.2	15C	7	5.0
7	7F	13	5.6	15A	7	4.4	3	10	5.5	10F	12	5.4	15A	6	4.3
8	19C	13	5.6	15C	7	4.4	23F	10	5.5	15B	9	4.1	15F	6	4.3
9	4	9	3.9	33F	7	4.4	19F	6	3.3	10A	7	3.2	23B	6	4.3
10	6A	8	3.5	38	6	3.8	15B	6	3.3	15A	7	3.2	1	5	3.6
11	10A	6	2.6	23A	6	3.8	7C	5	2.7	35F	7	3.2	38	4	2.9
12	3	6	2.6	22F	5	3.1	5	5	2.7	10F	6	2.7	17F	4	2.9
13	10A	4	1.7	23B	5	3.1	9N	4	2.2	38	6	2.7	33F	4	2.9
14	24F	4	1.7	35F	5	3.1	14	3	1.6	35F	6	2.7	21	3	2.1
15	9A	2	0.9	7F	4	2.5	10A	3	1.6	11A	5	2.3	27	3	2.1
16	9N	2	0.9	35B	4	2.5	23A	3	1.6	23A	5	2.3	15B	3	2.1
17	15A	2	0.9	19F	3	1.9	35B	3	1.6	35B	5	2.3	16F	3	2.1
18	8	2	0.9	14	2	1.3	6C	3	1.6	8	4	1.8	35F	3	2.1
19	15B	2	0.9	15C	2	1.3	15C	2	1.1	9N	4	1.8	19F	2	1.4
20	15C	2	0.9	6A	2	1.3	1	2	1.1	12A	3	1.4	20	2	1.4
21	18B	2	0.9	21	2	1.3	20	2	1.1	10F	3	1.4	31	2	1.4
22	22F	2	0.9	21	2	1.3	21	2	1.1	10F	3	1.4	34	2	1.4
23	5	1	0.4	34	2	1.3	31	2	1.1	20	2	0.9	11A	2	1.4
24	38	1	0.4	11A	2	1.3	11A	2	1.1	27	2	0.9	15A	2	1.4

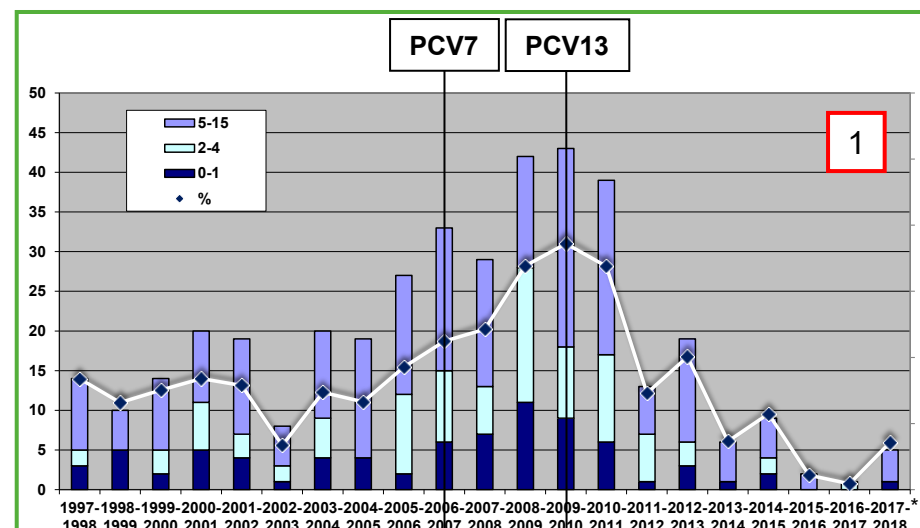


Fig. 4: Number of cases of IPD from children in Germany with serotypes 1, 3, 7F and 19A per pneumococcal season (July to June in the following year). * 2017-2018: incomplete season.

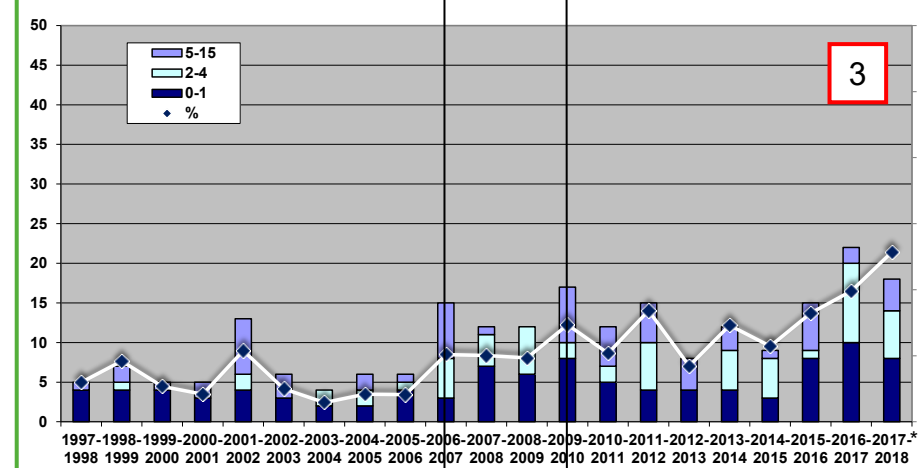


Fig. 5: Serotypes of penicillin non-susceptible and macrolide resistant isolates from children and adults with IPD in Germany.

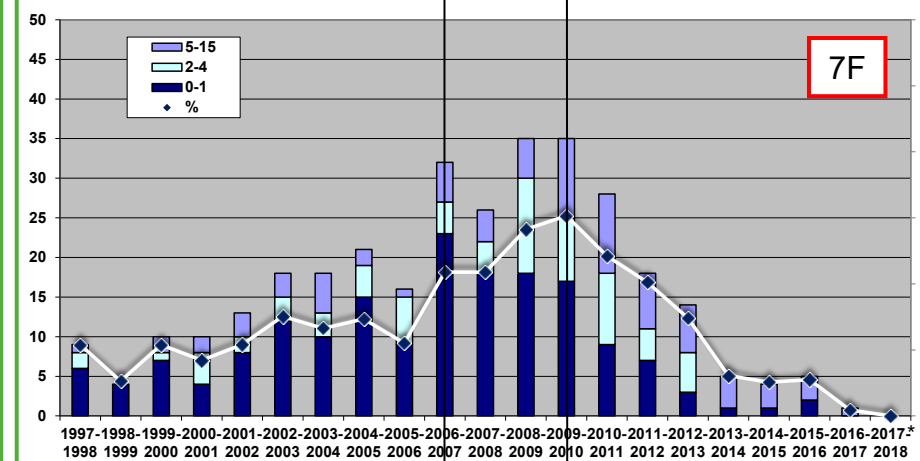


Fig. 6: Serotypes of penicillin non-susceptible and macrolide resistant isolates from children and adults with IPD in Germany.

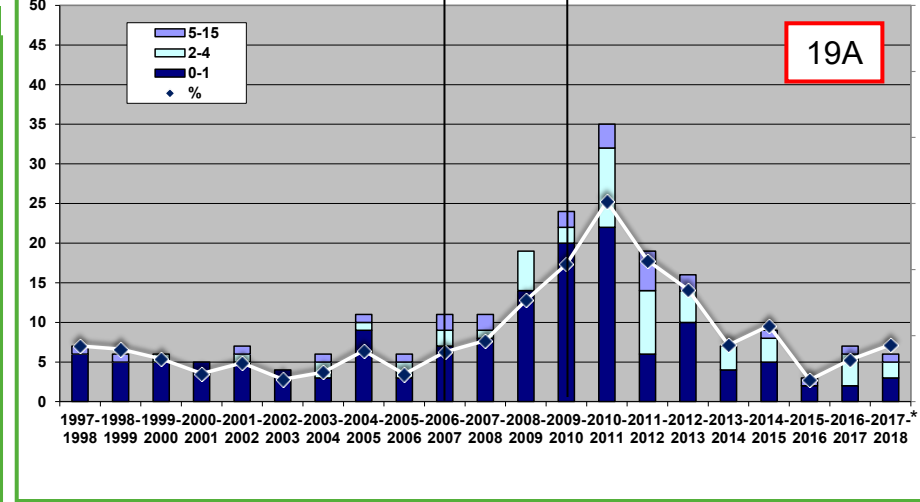


Fig. 7: Serotypes of penicillin non-susceptible and macrolide resistant isolates from children and adults with IPD in Germany.

Table 1: Vaccination status of children 0-15 years of age with IPD caused by a PCV13 serotype.

Isolate	Age (mo)	Diagnosis	Vaccination status	Serotype
80901	0	sepsis	no	1
77989	3	meningitis	no	3
78245	8	sepsis	no	3
80099	4	mastoiditis	PCV13, 1 dose 6 days before onset of disease	3
80163	18	sepsis, pneumonia	PCV13, according to age, 2+1 schedule	3
78793	19	sepsis	unknown	3
79110	5	sepsis	unknown	3
80795	2	mastoiditis, otitis media	unknown	3
81706	6	pneumonia	PCV13, 1 dose 7 days before onset of disease	19A
80778	3	sepsis	unknown	19F
78392	18	no data	unknown	19A
78762	1	sepsis	unknown	19A
78915	1	meningitis	PCV13, exact vaccination dates unknown	19F
79026	4	no data	PCV13, exact vaccination dates unknown	19A
children 2-4 years of age				
78911	39	meningitis, OM, mastoiditis	PCV10, according to age, 2+1 schedule	3
79952	32	no data	unknown	3
80128	43	pleuraempyema	unknown	3
80993	42	meningitis	unknown	3
81027	24	pneumonia	unknown	3
81323	29	sepsis	PCV13, according to age, 2+1 schedule	3
77679	25	sepsis, otitis media	PCV13, according to age, 2+1 schedule	19A
79790	38	sepsis, pneumonia, pleuraempyema	PCV13, acc. to age, 3+1, booster 21 mo.	19A
children 5-15 years of age				
78728	96	no data	no	1
79718	151	sepsis	unknown	1
81206	149	no data	unknown	1
78302	114	no data	acc. to age: PCV7 (3x prim), PCV13 booster at 36 mo.	3
79293	114	meningitis, sepsis	acc. to age: PCV7 (3x prim), PCV10 booster	3
80540	111	pneumonia	unknown	3
80917	86	sepsis	unknown	3
81668	92	meningitis	PCV13, according to age, 3+1 schedule	19A

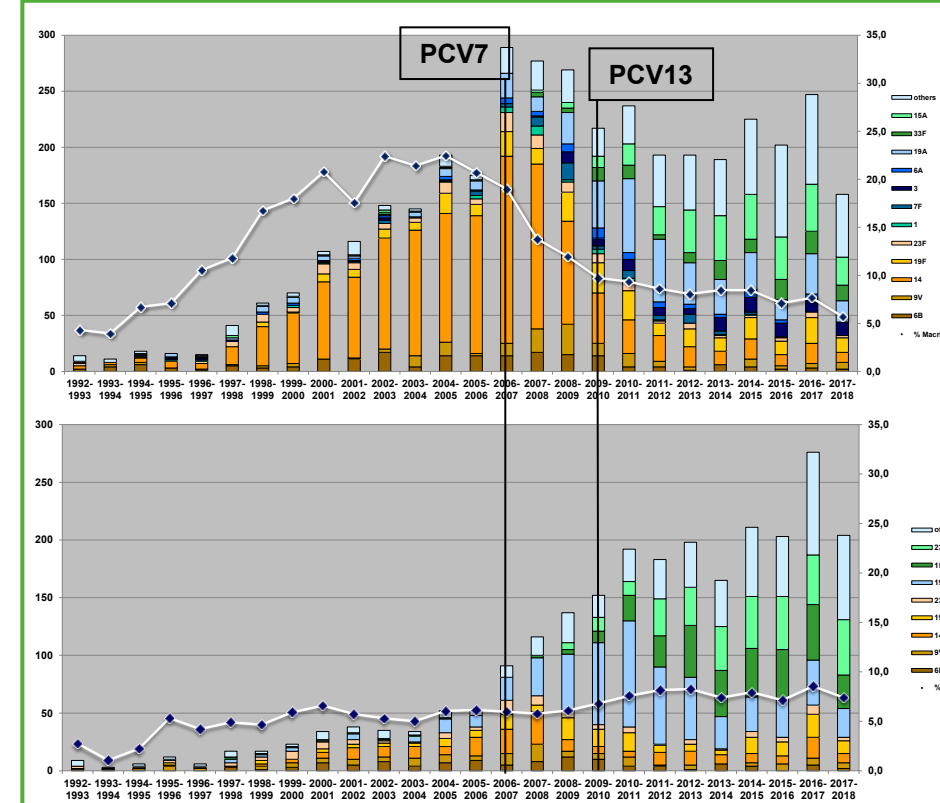


Fig. 8: Serotypes of penicillin non-susceptible and macrolide resistant isolates from children and adults with IPD in Germany.

CONCLUSIONS

- A large number of the remaining vaccine-type IPD cases occur in non-vaccinated children (< 16 years old).
- Currently, serotypes 3, 10A, 15A/B/C, 22F, and 24F are the most prevalent serotypes among children < 16 years in Germany.
- Serotypes responsible for penicillin and macrolide resistance have changed.