

## Effects of 9 years of immunization with higher-valent pneumococcal conjugate vaccines on children in Germany and coverage of future vaccine formulations

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### BACKGROUND AND AIMS

A general recommendation for the pneumococcal conjugate vaccine (PCV) was issued for children  $\leq 2$  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 at the GNRCS using the Neufeld-Quellung reaction.

### RESULTS

The GNRCS has been collecting IPD isolates from children since 1997 (**Fig. 1**). From July 2017 to June 2018, the GNRCS received 94 IPD isolates from children  $< 2$  years, representing a reduction of 39% compared to 2005/2006 (before vaccination;  $n=154$ ), but an increase since 2011-2012 ( $n=75$ ) (**Fig. 2**).

Since the introduction of higher valent vaccination, case numbers have been fluctuating between 75 and 116. In the two older age groups a slight reduction in cases was observed. The proportion of cases caused by PCV13 serotypes has decreased from 88% before vaccine introduction to 69% at the introduction of higher-valent vaccines to 15% in 2018-2019 (**Fig. 3**).

The most prevalent residual PCV13 serotypes in 2018/2019 among children under 16 y. were 3 ( $n=7$ ), 19F ( $n=8$ ), 19A ( $n=9$ ) (**Fig. 4**).

Of 11 cases for which vaccination status could be ascertained, 7 (64%) were not or incompletely vaccinated (**Table 1**).

In 2018-2019, the most prevalent serotypes among IPD in children  $< 2$  years are 10A (13.9%), 23B (10.9%), 15B (7.3%) and 19A (6.8%) (**Table 2**).

In 2018-2019, among children  $< 2$  years, coverage of PCV13 was 15%. Future vaccines PCV15 (19%) and PCV20 (52%) would increase coverage considerably (**Fig. 5**). Among the serotypes not in these new formulations, 23B and 24F have been prevalent in the last four years (**Table 3**).

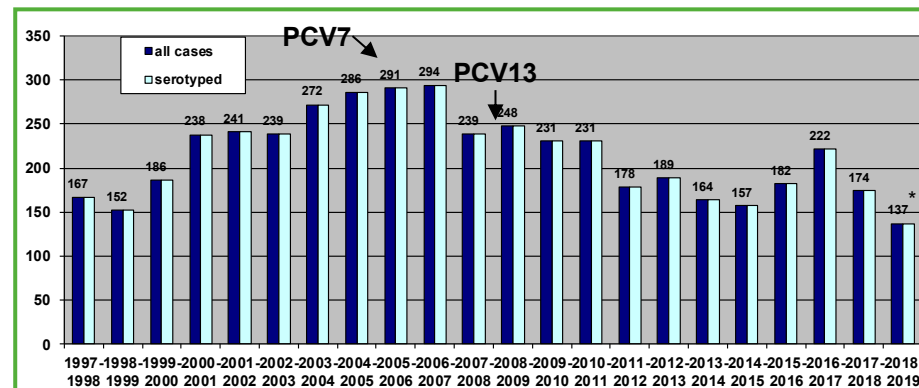


Fig. 1: Number of cases of IPD from children  $< 16$  years of age in Germany and number of serotyped cases per pneumococcal season (July to June in the following year). \* 2018-2019: incomplete season.

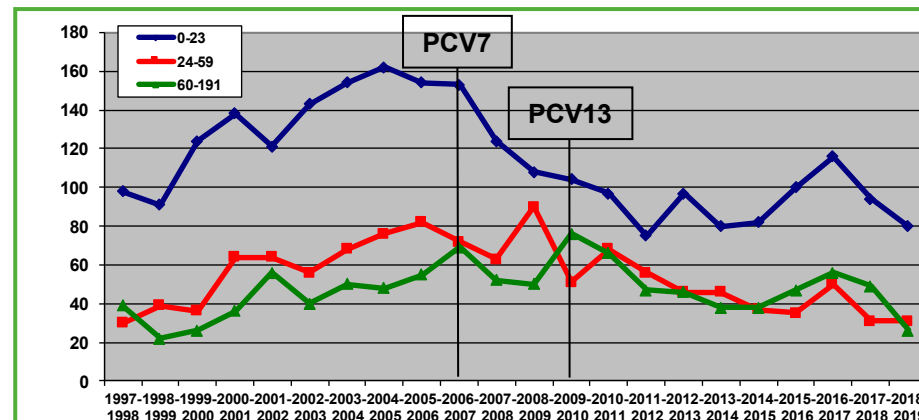


Fig. 2: Number of cases of IPD from children in Germany per pneumococcal season in three age groups: 0-1 year (blue), 2-4 years (red), 5-15 years (green). \* 2018-2019: incomplete season.

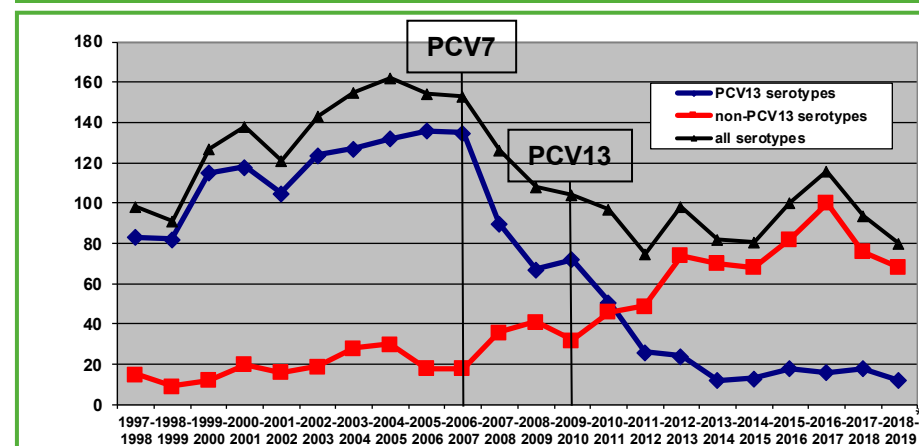


Fig. 3: Number of cases of IPD with PCV13- and non-PCV13 serotypes from children  $< 2$  years in Germany per pneumococcal season. \* 2017-2018: incomplete season.

Table 2: Serotype ranking among IPD in children  $< 16$  y. in Germany.

| Rank  | Serotype | average 1997-2006 | %    | Serotype | 2015-2016 | %     | Serotype | 2016-2017 | %     | Serotype | 2017-2018 | %     | Serotype | 2018-2019 | %     |
|-------|----------|-------------------|------|----------|-----------|-------|----------|-----------|-------|----------|-----------|-------|----------|-----------|-------|
| total | 231      | 100.0             |      | total    | 182       | 100.0 | total    | 222       | 100.0 | total    | 174       | 100.0 | total    | 137       | 100.0 |
| 1     | PCV13    | 201               | 87.0 | PCV13    | 108       | 59.3  | PCV13    | 122       | 55.0  | PCV13    | 104       | 59.8  | PCV13    | 83        | 60.6  |
| 2     | PCV10    | 195               | 84.4 | PCV10    | 38        | 20.9  | PCV10    | 43        | 19.5  | PCV10    | 24        | 13.8  | PCV10    | 27        | 19.7  |
| 3     | PCV7     | 174               | 75.3 | PCV7     | 29        | 11.0  | PCV7     | 11        | 5.0   | PCV7     | 10        | 5.7   | PCV7     | 11        | 8.0   |
| 4     | PCV13    | 142               | 61.5 | PCV13    | 13        | 7.1   | PCV13    | 9         | 4.1   | PCV13    | 5         | 2.9   | PCV13    | 11        | 8.0   |
| 5     | 14       | 49                | 21.2 | 10A      | 24        | 13.2  | 3        | 22        | 9.9   | 3        | 24        | 13.8  | 10A      | 19        | 13.9  |
| 6     | 9V       | 23                | 10.0 | 3        | 15        | 8.2   | 10A      | 20        | 9.0   | 10A      | 15        | 8.6   | 23B      | 15        | 10.9  |
| 7     | 19F      | 17                | 7.4  | 12F      | 15        | 8.2   | 15C      | 17        | 7.7   | 24F      | 14        | 8.0   | 15B      | 10        | 7.3   |
| 8     | 6B       | 17                | 7.4  | 24F      | 14        | 7.7   | 23B      | 17        | 7.7   | 23F      | 10        | 5.7   | 15A      | 9         | 6.6   |
| 9     | 1        | 17                | 7.4  | 15C      | 13        | 7.1   | 23F      | 16        | 7.2   | 10A      | 9         | 5.2   | 19F      | 8         | 5.8   |
| 10    | 23F      | 14                | 6.1  | 23B      | 12        | 6.6   | 24F      | 16        | 7.2   | 8        | 9         | 5.2   | 12F      | 8         | 5.8   |
| 11    | 7F       | 13                | 5.6  | 38       | 10        | 5.5   | 12F      | 12        | 5.4   | 38       | 8         | 4.6   | 3        | 7         | 5.1   |
| 12    | 3        | 13                | 5.6  | 23F      | 10        | 5.5   | 15B      | 9         | 4.1   | 12F      | 8         | 4.6   | 15C      | 6         | 4.4   |
| 13    | 15A      | 9                 | 3.9  | 19F      | 6         | 3.3   | 15A      | 7         | 3.2   | 15C      | 6         | 4.6   | 24F      | 5         | 3.6   |
| 14    | 24F      | 4                 | 1.7  | 14       | 3         | 1.6   | 39F      | 6         | 2.7   | 16F      | 4         | 2.3   | 8        | 3         | 2.2   |
| 15    | 9A       | 2                 | 0.9  | 19A      | 3         | 1.6   | 11A      | 5         | 2.3   | 17F      | 4         | 2.3   | 21       | 3         | 2.2   |
| 16    | 9V       | 2                 | 0.9  | 23A      | 3         | 1.6   | 23A      | 5         | 2.3   | 39F      | 4         | 2.3   | 17F      | 3         | 2.2   |
| 17    | 15A      | 2                 | 0.9  | 39B      | 3         | 1.6   | 35B      | 5         | 2.3   | 21       | 3         | 1.7   | 22F      | 3         | 2.2   |
| 18    | 5        | 2                 | 0.9  | 6C       | 3         | 1.6   | 9        | 4         | 1.8   | 27       | 3         | 1.7   | 23A      | 3         | 2.2   |
| 19    | 15B      | 2                 | 0.9  | 19C      | 2         | 1.1   | 9V       | 4         | 1.8   | 15B      | 3         | 1.7   | 9V       | 3         | 2.2   |
| 20    | 15C      | 2                 | 0.9  | 1        | 2         | 1.1   | 12A      | 3         | 1.4   | 23A      | 3         | 1.7   | 23F      | 2         | 1.5   |
| 21    | 18B      | 2                 | 0.9  | 20       | 2         | 1.1   | 16F      | 3         | 1.4   | 39F      | 3         | 1.7   | 15A      | 2         | 1.5   |
| 22    | 23F      | 2                 | 0.9  | 21       | 2         | 1.1   | 17F      | 3         | 1.4   | 20       | 2         | 1.1   | 39F      | 2         | 1.5   |
| 23    | 5        | 1                 | 0.4  | 31       | 2         | 1.1   | 20       | 2         | 0.9   | 31       | 2         | 1.1   | 14       | 1         | 0.7   |
| 24    | 38       | 1                 | 0.4  | 11A      | 2         | 1.1   | 27       | 2         | 0.9   | 34       | 2         | 1.1   | 20       | 1         | 0.7   |

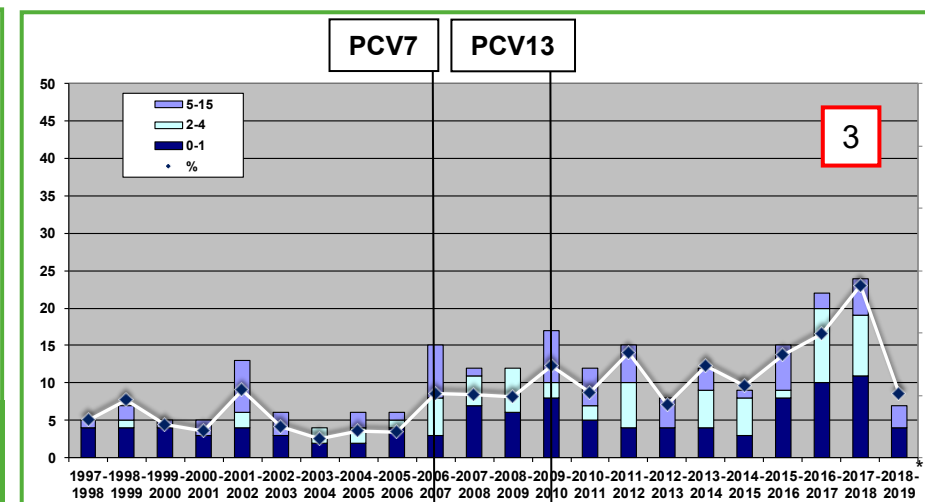


Fig. 4: Number of cases of IPD from children in Germany with serotypes 3, 19F and 19A per pneumococcal season (July to June in the following year). \* 2018-2019: incomplete season.

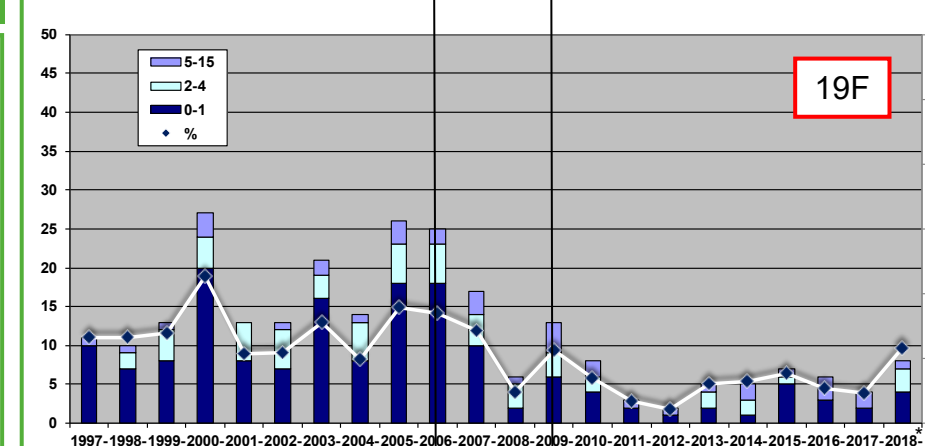


Fig. 4: Number of cases of IPD from children in Germany with serotypes 3, 19F and 19A per pneumococcal season (July to June in the following year). \* 2018-2019: incomplete season.

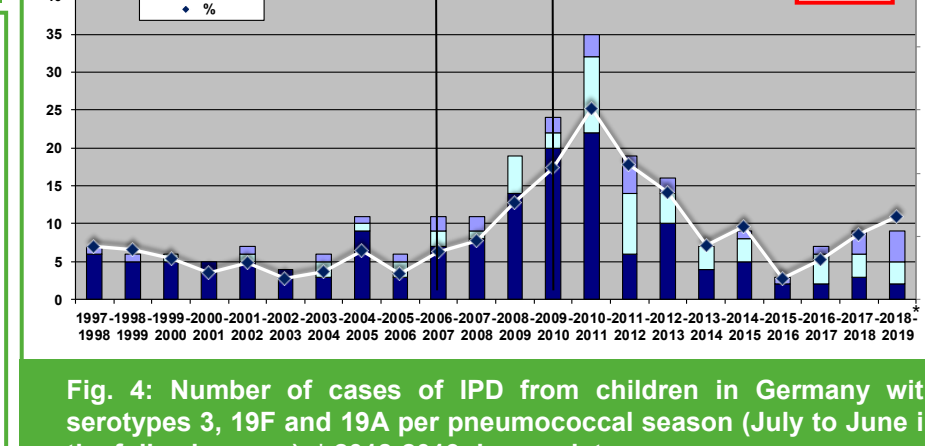


Fig. 4: Number of cases of IPD from children in Germany with serotypes 3, 19F and 19A per pneumococcal season (July to June in the following year). \* 2018-2019: incomplete season.

Table 1: Vaccination status of children 0-15 years of age with IPD caused by serotypes 3, 19F or 19A.

| Isolate | Diagnosis            | Age (months) | Serotype | Vaccination status | Conclusion                |
|---------|----------------------|--------------|----------|--------------------|---------------------------|
| 86418   |                      | 90           | 3        | unknown            |                           |
| 82828   | meningitis           | 79           | 3        | unknown            |                           |
| 85678   | meningitis           | 70           | 3        | unknown            |                           |
| 83498   | sepsis, otitis media | 16           | 3        | PCV13              | 2 doses, no booster       |
| 85519   | sepsis               | 0            | 3        | no                 |                           |
| 83918   |                      | 3            | 3        | unknown            |                           |
| 82760   | sepsis               | 11           | 3        | PCV13              | 3 doses, no booster       |
| 84687   | Pyelonephritis       | 3            | 19F      | PCV13              | acc. to age, 1 dose       |
| 83033   | meningitis           | 25           | 19F      | no                 |                           |
| 84463   | Mastoiditis          | 6            | 19F      | unknown            |                           |
| 84464   | Mastoiditis          | 34           | 19F      | unknown            |                           |
| 84515   | Sepsis               | 3            | 19F      | PCV13              | acc. to age, 1 dose       |
| 86421   | meningitis           | 12           | 19F      | unknown            |                           |
| 84918   |                      | 68           | 19F      | no                 |                           |
| 84472   |                      | 54           | 19F      | unknown            |                           |
| 84903   |                      | 56           | 19A      | PCV13              | acc. to age, 3+1 schedule |
| 85202   | meningitis           | 26           | 19A      | PCV13              | acc. to age, 2+1 schedule |
| 84077   |                      | 64           | 19A      | unknown            |                           |
| 85229   |                      | 1            | 19A      | unknown            |                           |
| 85538   |                      | 61           | 19A      | unknown            |                           |
| 83347   | Pneumonie            | 47           | 19A      | unknown            |                           |
| 83321   | sept. Arthritis      | 13           | 19A      | PCV13              | 2 doses, no booster       |
| 85650   | Sepsis, pneumonia    | 78           | 19A      | no                 |                           |
| 86308   | meningitis           | 169          | 19A      | unknown            |                           |

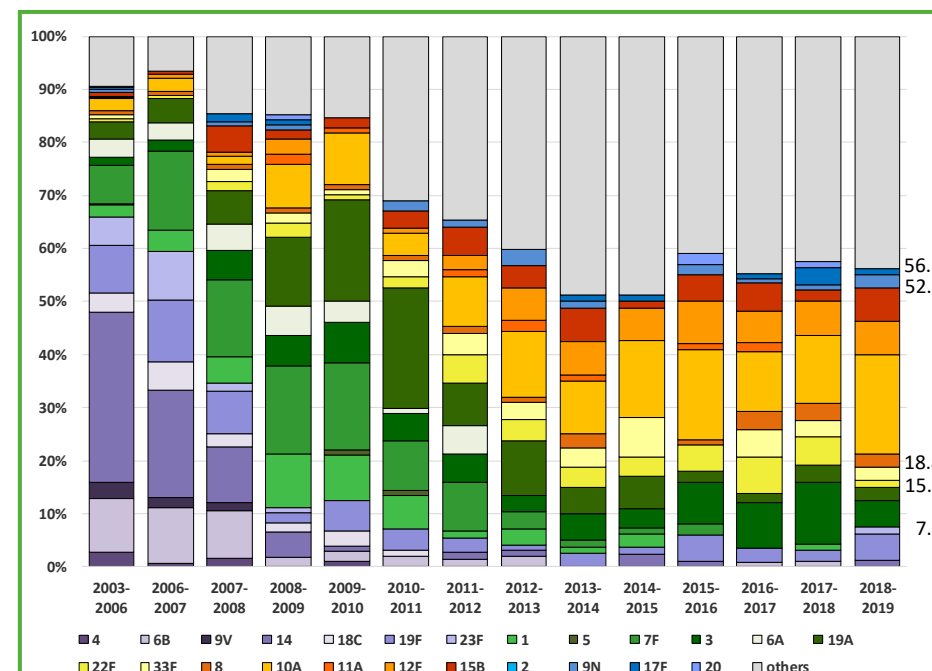


Fig. 5: Coverage of current and future vaccine formulations among children  $< 2$  years with IPD in Germany. PCV7 (purple), PCV13non7 (green), PCV15non13 (yellow) and PCV20non15 (orange). PPV23 serotypes not in PCV20 (blue), Serotype 6A (white).

Table 3: Serotype coverage of PCV13, additional serotypes in PCV15 and PCV20 and prevalent NVT.

|        | 2015-2016 | 2016-2017 | 2017-2018 | 2018-2019 |
|--------|-----------|-----------|-----------|-----------|
| PCV13  | 18,0      | 13,7      | 19,2      | 15,0      |
| 22F    | 5,0       | 6,9       | 5,3       | 1,3       |
| 33F    | 0,0       | 5,2       | 3,2       | 2,5       |
| 8      | 1,0       | 3,4       | 3,2       | 2,5       |
| 10A    | 17,0      | 11,2      | 12,8      | 18,8      |
| 11A    | 1,0       | 1,7       | 0,0       | 0,0       |
| 12F    | 8,0       | 6,0       | 6,4       | 6,3       |
| 15B    | 5,0       | 5,2       | 2,1       | 6,3       |
| 23B    | 6,0       | 8,6       | 2,1       | 12,5      |
| 24F    | 7,0       | 6,9       | 10,6      | 3,8       |
| others | 32,0      | 31,0      | 35,1      | 31,3      |

### CONCLUSIONS

- More than ten years after the introduction of higher-valent vaccines, PCV13 serotypes have been reduced among children, but serotypes 3, 19F and 19A persist.
- A large number of the remaining vaccine-type IPD cases occur in non- or incompletely vaccinated children ( $< 16$  years old).
- Currently, serotypes 10A, 23B, 15B and 19A are the most prevalent serotypes among children  $< 2$  years in Germany.
- Future vaccine formulation would considerably increase serotype coverage.