# Population-adjusted effect of pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13) against invasive pneumococcal disease in children 6 years of age and younger in Germany

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## BACKGROUND AND AIMS

Two generations of PCVs have been used in Germany since the general vaccination recommendation from the standing commission of the Robert Koch Institute in 2006, initially PCV7, replaced (for the most part) with PCV13 and PCV10 in 2009. Few cases of vaccine-type IPD remain, particularly among children who adhered to the recommended 3+1 schedule (doses at 3, 4, and 5 months of life, and a booster dose after the first birthday). We sought population-level factors that impacted the likelihood of contracting vaccine-type IPD.

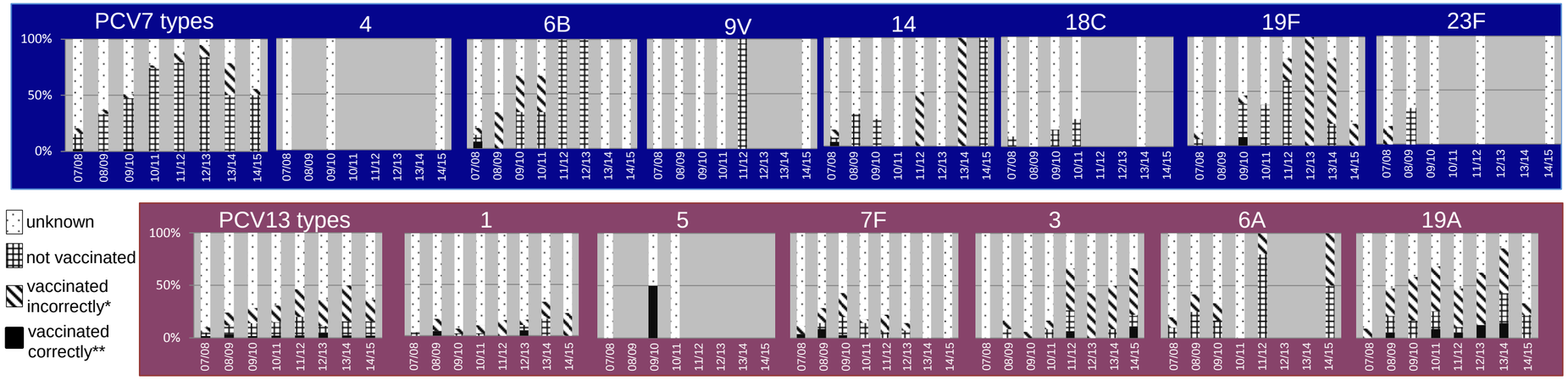
## METHODS

Pneumococcal isolates from children with IPD were serotyped at the GNRCS using the Neufeld-Quellung reaction. Vaccination status was defined as NO (no doses of vaccine), At All (AA, any dose of any vaccine) and Correct (CO14, appropriate number of doses received within 14 days of recommendations). Population demographic data were obtained from the German Federal Statistical Office, Destatis.

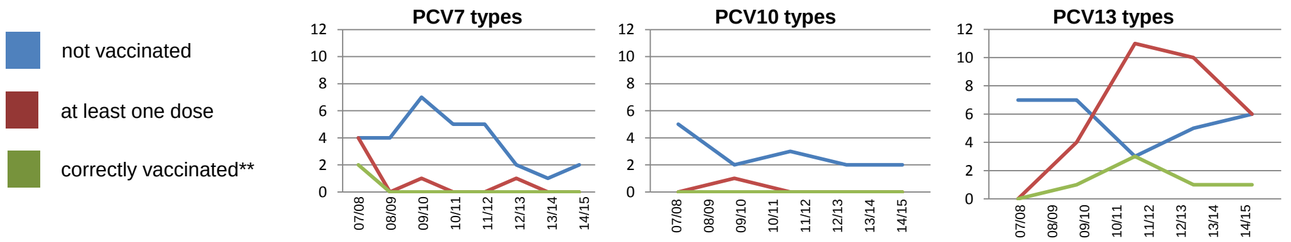
Multivariate Firth's bias-reduced logistic regression was used to show demographically- and regionally-adjusted impact of vaccination. Univariate regression models to predict vaccination status were constructed with federal state of residence, age of patient and season following vaccination for each IPD case and state-level averages for unemployment rate, household size, education, ratio of Germans to foreign nationals and single-parent households.

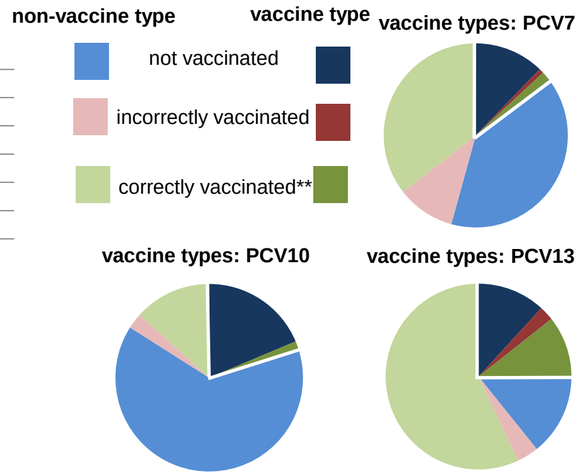
Univariate regression models to predict infection with selected serotypes were constructed with vaccination status, federal state of residence, age of patient and season following vaccination for each IPD case, and the same state-level averages as above. Predictor variables with p <0.2 were selected for inclusion in multivariate models, which were then refined with forward and backward stepwise selection using McFadden's Pseudo $R^2$ to assess goodness of fit.

Changes in pre-and post-vaccination serotype distribution were calculated with Fisher's exact test.




*= vaccinated with fewer doses than (or greater than 14 days after) recommended.
**= vaccinated with correct number of doses within 14 days of recommended timeframe.




## RESULTS

Comparing pre- and post- PCV7 seasons (2000-2006 vs. 2007-2015), IPD in vaccinated children significantly decreased in all vaccine serotypes, whereas in unvaccinated children IPD decreased in only three vaccine serotypes.

In the second-generation PCV seasons (2009-2015), unvaccinated children saw significant increases in the six additional serotypes, while IPD in vaccinated children decreased in all six serotypes.

PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) were over eight times more likely in unvaccinated children (OR= 8.13, 95%CI 1.30-9.06), adjusted for age, season of infection, and average household size.

PCV10 serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F) had no significant association with vaccination status, but were significantly associated with residence in Saxon-Anhalt (OR 2.53, 1.15-5.55) and season of infection.

PCV13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) were five times more likely in unvaccinated children (OR 5.09, 2.61-9.97), adjusted for residence in Berlin, Hesse, Rheinland-Pfalz, and season of infection.

Vaccination status was most strongly predicted by season of infection, followed by federal state of residence.

## CONCLUSIONS

- IPD in children in Germany has undergone a sea change in serotype distribution, strongly driven by the introduction of PCVs, despite lackadaisical adherence to the schedule recommendation.
- In children vaccinated with PCV7, 23% of IPD cases were in children that were correctly vaccinated (CO14). Only 2 cases of vaccine-type IPD (6B, 18C) were CO14.
- In children vaccinated with PCV10, 15% of IPD cases, none of which were vaccine-type, were CO14.
- In children vaccinated with PCV13, 31% of IPD cases, with 6 cases of vaccine-type IPD (19A x5, 3), were in CO14.