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EFFECTIVENESS OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE ESTIMATED WITH THREE PARALLEL STUDY DESIGNS AMONG VACCINE-ELIGIBLE CHILDREN IN FINLAND

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ABSTRACT

Background

Ten-valent pneumococcal conjugate vaccine (PCV10) was introduced into the Finnish National Vaccination Programme (NVP) in 9/2010. We estimated the individual-level effectiveness (VE) of PCV10 in children during eight years of vaccine implementation.

Methods

Data on invasive pneumococcal disease (IPD) were collected from national, population-based surveillance, and vaccination status from the vaccination register. Vaccine-eligible children were followed from six months of age until end of 2018 (born 6/2010 or later, ages 6–102 months). VE was estimated with three parallel approaches: full cohort, nested case-control and indirect cohort designs adjusting with age-group, sex and calendar year.

Results

VE against PCV10 serotype IPD was estimated at 93% (95% credible interval 87–97%), 98% (90–100%) and 100% (98–100%), and against PCV10-related serotypes at 46% (-13–72%), 51% (-24–79%), and 78% (-7–97%), with the full cohort, nested case-control, and indirect cohort designs, respectively.

The estimated VE against non-PCV10-related (neither PCV10 nor PCV10-related) serotypes was negative but included zero effectiveness (full cohort VE -67%, -711–52%; nested case-control VE -77%, -929–59%). VE against all IPD was estimated with these two methods at 54% (24–71%) and 61% (26–79%). Over time, VE against PCV10 IPD remained stable but VE against all IPD decreased.

Discussion

All designs provided estimates that were concordant with each other, but those with the full cohort design were usually the most precise. PCV10 offered sustained high VE against PCV10-serotype IPD on vaccinated children during the first decade after introduction into the programme.

1 INTRODUCTION

Pneumococcal conjugate vaccines (PCVs) have been successful in providing direct protection for vaccinated children as well as herd protection for all members of the population against pneumococcal diseases caused by the serotypes included in the vaccines. Replacement in carriage and disease by serotypes not included in the vaccines has partially reduced the overall impact of conjugate vaccines, although less in child populations compared with adults [1].

The population-level impact of a pneumococcal vaccination programme can be assessed with a before-after design [2]. To assess the impact, time series data from a long enough pre-introduction period are needed to reliably estimate the baseline incidence of IPD and to control secular trends in serotype-specific rates.

During wide-scale use, the direct protective effect of the vaccine on the vaccinated (vaccine effectiveness, VE) can be estimated by comparing the incidence of disease in the vaccinated and unvaccinated parts of the population in parallel [3]. Both the vaccinated and unvaccinated experience the indirect effects of the vaccination programme but unvaccinated individuals are used as the comparator group.

Although information on vaccination status is often available for specific subpopulations, this is rare for the entire population. Several parallel study designs, e.g. the indirect cohort, screening, and case-control designs have been used for VE estimation in certain subpopulations [4-10]. VE of 13-valent pneumococcal conjugate vaccine has also been estimated for the whole child population of New South Wales and Western Australia [11]. The indirect cohort and case-control designs have been compared in VE estimation of PCVs e.g. in the US [5, 12] and Brazil [13, 14].

In Finland, surveillance of IPD dates back to 1995, with comprehensive linkage of cases to the national population register and serotyping data since 2004, long before the implementation of universal infant vaccination with ten-valent pneumococcal conjugate vaccine (PCV10) in 2010. The PCV10 vaccination programme has shown very high impact in reducing the incidence of all IPD in vaccine-eligible children, driven by a marked decrease in IPD by PCV10 serotypes together with slow replacement in children by IPD caused by non-PCV10 serotypes [15, 16]. A national vaccination register covering all infant vaccinations has

been in place since 2009 [17], allowing the estimation of VE within entire cohorts of vaccine-eligible children.

The aim of this work was to estimate VE of PCV10 in children 6–102 months of age eight years after the programme implementation, and to compare different estimation methods and their congruence in the Finnish setting characterised by high vaccine uptake.

2 METHODS

2.1 Vaccination programme

PCV10 was introduced after a public tendering process into the Finnish national vaccination programme (NVP) without catch-up vaccinations in September 2010. All children born on or after June 1, 2010, have been eligible for vaccination with a 2+1 schedule at 3, 5 and 12 months of age. Vaccination coverage rose quickly above 90% and the uptake of at least one dose of PCV10 was estimated at 95.5% in the birth cohort of 2015 [18]. Prior to PCV10 vaccinations in the FinIP trial [19] and NVP, 7-valent pneumococcal conjugate was recommended for certain risk groups, but pneumococcal vaccines were not routinely used and the vaccine uptake was minimal (<2%).

Influenza vaccine was introduced into the NVP in the beginning of the influenza season 2007/2008 for children aged 6 to 36 months. The uptake of influenza vaccine in this age group has been estimated to vary between 15 and 40% [17].

2.2 Data sources and case definition

The study cohort was defined based on the Finnish Population Information System as all vaccine-eligible children (born between 6/2010 and 6/2018 and followed from 1/2011 through 12/2018, from 6 months up to 102 months of age, Figure 1). The vaccination status of each individual child in the cohort was retrieved from the National Vaccination Register. The child was defined as vaccinated if at least one dose of PCV10 was registered. Based on this definition, vaccination coverage was 91.7% in the cohort. The individual follow-up started at the age of six months to ensure that the majority (95.3%) of the vaccinated study subjects had received 2 doses of PCV10 before their first birthday. Some 0.3% of children had received the 13-valent conjugate vaccine; in the analysis they were considered as vaccinated with PCV10. Children whose vaccinations were incompletely covered by the National Vaccination Register (altogether 14%, 71882 out of 508734 vaccine-eligible children) were excluded from the analysis. Reasons for incomplete

vaccination information were related to either the child's health care center not providing complete data, or to the child itself having moved to another municipality or abroad [17].

Cases of invasive pneumococcal disease (IPD) were identified from the National Infectious Diseases Register (NIDR), a population-based electronic laboratory surveillance system maintained by the Finnish Institute for Health and Welfare (THL). The IPD surveillance in Finland and the THL laboratory methods have been described earlier [20, 15]. There have been no major changes in care seeking practices or detection methods during the study period.

The cases, defined as isolations of *Streptococcus pneumoniae* from blood or cerebrospinal fluid, were categorised according to the causative serotype into three mutually exclusive groups: PCV10 serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F), PCV10-related serotypes that belong to the same serogroups as the PCV10 serotypes, and non-PCV10-related serotypes. All register-based information was linked by using the unique national personal identity code.

2.3 Vaccine effectiveness

VE was defined as one minus the relative rate of IPD in vaccinated compared with unvaccinated in the study cohort (Figure 1). VE was estimated against the three serotype groups, and separately against the PCV10-related serotype 19A and against all IPD. Five vaccinated cases without serotype data were included only in the analysis of VE against all IPD.

Three study designs were used to estimate VE. In the full cohort design all children in the study cohort were included and followed until IPD, death or end of study period. VE was estimated with Poisson regression adjusted by age group (6–23, 24–47, 48–102 months), sex and calendar year. In the nested case-control design, five controls for each IPD case were selected from the case's risk set, matching with age, sex and calendar year. Case's risk set included all children in the study cohort who were at risk of IPD at the time of case occurrence. Conditional logistic regression was used to estimate VE. In the indirect cohort design, VE was estimated as the odds of vaccination in IPD cases of the target serotype or serotype group compared to

the odds of vaccination in non-PCV10-related cases. VE was estimated with logistic regression adjusted by age group, sex and calendar year. To assess any time trends in serotype-specific incidence rates or VE, the study period was split into two parts: years 2010–2014 (early period) and 2015–2018 (latter period).

Statistical inferences were performed within the Bayesian framework. Uninformative prior distributions were used: normal distribution with mean 0 and variance 10^6 for predictor parameters and Gamma distribution with mean 1 and intensity 10^5 for precision. All analyses were carried out with R (version 3.4.4) and the INLA library. Results are presented as point estimates (posterior mean) and 95% posterior probability (credible) intervals (CI).

2.4 Ethical approval

The authorisation for research use of surveillance data was granted by THL, the regulatory agency with jurisdiction over national health registry data (THL/1090/6.02.00/2013). The THL Institutional Review Board approved the study.

3 RESULTS

Table 1 presents VE against IPD in vaccine-eligible children estimated with three parallel study designs. There were altogether 150 IPD cases: 15 caused by PCV10, 78 by PCV10-related, and 52 by non-PCV10-related serotypes. Serotypes 14 (7 cases) and 19F (4 cases) were the most common PCV10 serotypes. Serotype 19A was the most common PCV10-related serotype with 60 cases, followed by 23B, 23A and 6A with 6, 4 and 3 cases, respectively. All three 6A cases had been vaccinated. Serotypes 3 (21 cases), 22F (10 cases), and 15B/C (6 cases) were the most common non-PCV10-related serotypes.

VE against PCV10-serotype IPD was estimated at 93% (95% credible interval 87–97%), 98% (90–100%) and 100% (98–100%) with the full cohort, nested case-control and indirect cohort designs, respectively. VE against PCV10-related IPD was estimated respectively at 46% (-13–72%), 51% (-24–79%) and 78% (-7–97%). The majority of PCV10-related IPD cases were caused by serotype 19A. Therefore, the estimates of VE against 19A IPD under the three designs were close to that of the whole PCV10-related IPD group (50%, -19–78%; 45%, -54–79%; 66%, -76–95%).

VE against non-PCV10-related IPD was estimated at -67% (-711–52%) and -77% (-929–59%) with the full cohort and nested case-control designs, respectively. VE against all IPD was estimated at 54% (24–71%) with the full cohort and 61% (26–79%) with the nested case-control design. Of note, VE against non-PCV10-related IPD or all IPD could not be estimated with the indirect cohort design since IPD cases of non-PCV10-related serotypes were used as controls in the analysis.

When the follow-up was split into two sub-periods, some trends in VE were discerned (Table 2). The estimates of VE against PCV10 IPD remained the same as for the entire study period, but the credible intervals were wider due to smaller case counts, especially in 2015–2018. Towards the end of the latter period (2015–2018), vaccine-type disease had practically been eliminated as there was only one case of serotype 19F in 2017 in an unvaccinated child and no cases caused by PCV10 serotypes in 2018.

The incidence of 19A disease increased from 0 to 8.7/100 000 person-years in unvaccinated and from 2 to 3.8/100 000 person-years in vaccinated children from the early (2010–2014) to the latter (2015–2018) period. Based on the full cohort design, VE against 19A was 59% (4–81%) during the latter period.

The point estimate of VE against non-PCV10-related IPD decreased from -32% to -105% with the full cohort design in 2015–2018. However, the credible intervals were wide and included zero effectiveness (-1860–63% in 2015–2018). The incidence of non-PCV10-related IPD was low throughout the study period. However, vaccinated children generally had higher non-PCV10-related IPD incidence than unvaccinated children. VE against all IPD decreased from the early period (70%; 35–85%) to the latter period (39%; -24–67%), as estimated with the full cohort design.

4 DISCUSSION

We estimated the direct effectiveness (VE) of the ten-valent pneumococcal conjugate vaccine (PCV10) against IPD in young children in Finland using nationwide register data of vaccination and invasive disease outcomes and three alternative study designs. The full cohort, nested case-control and indirect cohort designs provided estimates that were broadly in agreement with each other. Based on the full cohort design, VE against PCV10-serotype IPD was very high (93%, 95% credible interval 87–97%). Although the point estimate of VE against non-PCV10-related IPD was negative (-67%; -711–52%), the credible interval was wide and included zero effectiveness. VE against PCV10-related IPD was 46% (-13–72%) and that against all IPD 54% (24–71%).

To gain more insight into the performance of the vaccination programme over time, the study period was split into two shorter periods (the early period 2010–2014 and the latter period 2015–2018). Throughout the study period, the incidence of PCV10 serotypes decreased substantially [15, 16], and eight years after vaccine implementation no cases by PCV10 serotypes were detected. Nonetheless, the effectiveness against PCV10 IPD remained consistently high indicating vaccine-induced protection under decreasing exposure to circulating PCV10 serotypes.

The incidence of IPD due to non-PCV10-related serotypes remained at a very low level throughout the study period, although the incidence was higher compared with the pre-PCV10 period [16]. The rate was higher in vaccinated than in unvaccinated children most likely due to replacement carriage [21]. The point estimates of VE were negative during both time periods and decreased during the latter period compared with the early period, but the credible intervals were very wide and included zero effectiveness. Eventually, VE against non-PCV10-related IPD should approach zero when vaccine-type carriage has been replaced by non-vaccine-type carriage and non-vaccine serotypes transmit equally in the vaccinated and unvaccinated parts of the population.

The incidence of PCV10-related IPD increased during the study period mainly due to increase in serotype 19A that accounted for the majority of PCV10-related IPD. After a substantial secular decline in the

incidence before PCV10 introduction, 19A has been the main replacing serotype in Finnish children as well as in the older, unvaccinated population [16, 22]. Interestingly, the incidence of 19A IPD was more than two-fold among unvaccinated as compared to vaccinated children in the years 2015–2018, resulting in a clearly positive VE (59%; 4–81%). We have reported that the 19A cases in the vaccine-eligible cohort tended to be older than those of the reference cohort in the pre-vaccine period [16]. The distribution of circulating 19A clones has also changed in Finland after PCV10 introduction [23].

VE against all IPD decreased from the early period (70%; 35–85%) to the latter period (39%; -24–67%). Based on a similar reasoning as in the case of non-PCV10-related serotypes, VE against all IPD could be expected to decrease to zero in a new equilibrium. Our situation does not entirely correspond to this as non-PCV10-related IPD was detected generally more often in vaccinated than in unvaccinated children although PCV10 IPD had practically been eliminated in the end of study period. In addition, the higher incidence of 19A IPD in unvaccinated children contributed to the finding that VE against all IPD remained positive.

In any of the three parallel study designs employed in this study, VE is estimated by comparing the incidence of IPD in vaccinated and unvaccinated children simultaneously during the same follow-up time. In practice, several factors affect the estimation. To ensure the best possible comparability between the study designs, all analyses in our study were adjusted or matched with age group, sex and calendar year.

However, the indirect cohort and nested case-control designs usually allow for better adjustment than the full cohort design as data are often more easily available for small subsets of the population. If a case was matched to a sample of those who were at risk at the time of case occurrence, it should allow adjusting for changes in e.g. vaccination coverage and age distribution. Nevertheless, the full cohort design is optimal in utilising the entire follow-up of the underlying cohorts. In our study this was demonstrated by the better precision of the full cohort design in the sense that the estimated credible intervals were narrower than with the other designs.

A strength of the indirect cohort design over other parallel designs derives from it allowing matching of controls to cases in terms of e.g. underlying chronic diseases [4, 24]. The estimates, however, may be biased due to disproportionate NVT replacement between the vaccinated and unvaccinated [25]. According to our results, VE against PCV10 and PCV10-related serotype IPD were estimated somewhat higher with the indirect cohort design when compared with the two other approaches, as expected according to Andrews et al [25]. In Brazil, VE against PCV10-serotype IPD was estimated somewhat higher with the matched case-control design than with the indirect cohort design (84%; 66–92% versus 73%; 44–87%) [13, 14]. In the US, the estimates of VE against PCV13 serotype IPD were almost equal with the two designs (96%; 93–98% versus 97%; 94–98%) [5, 12]. With the indirect cohort design, VE against non-PCV10-related IPD or all IPD are not estimable because cases of non-PCV10-related IPD are used as controls in the analysis.

A strength of our study is that the nation-wide health registers can be linked with unique personal identity codes, allowing the estimation of VE in the whole vaccine-eligible cohort. From the perspective of estimation, the high vaccination coverage of 92% is a limitation as it leads to very small numbers of unvaccinated cases and high uncertainty in VE estimates.

We consider the outcome data of our study, i.e. laboratory confirmed IPD cases, specific and comprehensively registered. By contrast, it is possible that data on exposure to PCV vaccination are inaccurate or partly missing. If controls are incorrectly assigned as unvaccinated, VE will be underestimated. We mitigated this problem by excluding those individuals whose vaccinations were incompletely covered by the National Vaccination Register and by starting the follow-up only at the age of six months.

In summary, our study shows that PCV10-vaccinated children were highly protected against PCV10-serotype IPD almost a decade into the programme. At the same time, PCV10-serotype IPD was practically eliminated and the serotype distribution changed dramatically among vaccine-eligible children. The remaining burden of invasive pneumococcal disease was distributed more evenly between vaccinated and unvaccinated children towards the end of the study period, as indicated by the decreasing trend in vaccine effectiveness against all IPD.

Authorship contributions

HR-K coordinated the data collection, carried out the analyses, interpreted the data and drafted the manuscript; KA, AAP, JPN, and HN designed the study, interpreted the data and reviewed and revised the manuscript; MT, and LS supervised the microbiological data quality and reviewed and revised the manuscript; all authors approved the final manuscript as submitted. All authors attest they meet the ICMJE criteria for authorship.

Conflict of Interest Statement for all authors

The Finnish Institute for Health and Welfare has received research funding from GlaxoSmithKline Vaccines for the conduct of a nationwide effectiveness trial of the 10-valent pneumococcal conjugate vaccine, and from Pfizer, Inc. and Sanofi Pasteur, Inc. for non-pneumococcal research. HR-K, AAP, MT, and LS are co-investigators in these studies. The other authors have no conflicts to disclose. The current study was entirely publicly funded.

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Table and Figure legends

Table 1. Vaccine effectiveness against IPD in PCV10 vaccinated children, estimated with three parallel study designs (full cohort; nested case-control; indirect cohort) Finland, September 2010 – December 2018.

Footnote: [a] PCV10 serotypes in the data: 6B, 7F, 14, 19F, 23F; [b] PCV10-related serotypes in the data: 6A, 6C, 6D, 7C, 9N, 19A, 23A, 23B; [c] non-PCV10-related serotypes in the data: 3, 11A, 12F, 15A, 15B/C, 22F, 24F, 33F, 34, 35F, 38.

Table 2. Vaccine effectiveness against IPD in PCV10 vaccinated children, estimated with three parallel study designs (full cohort; nested case-control; indirect cohort). Finland, September 2010 – December 2014 and January 2015 – December 2018.

Figure 1. IPD cases and their vaccination status in the study cohort of PCV10 eligible children in Finland. The dashed vertical line represents the split of the study period into two sub-periods in which VE was estimated separately (early period 2010–2014; latter period 2015–2018). [PLEASE USE COLOR IN PRINT]

Table 1. Vaccine effectiveness against IPD in PCV10 vaccinated children, estimated with three parallel study designs (full cohort; nested case-control; indirect cohort) Finland, September 2010 – December 2018.

Design/Serotype group	**Unvaccinated**		**Vaccinated**		**Vaccine effectiveness (%)**	
					Estimate	**95% crebile interval**
2010-2018						
Full cohort design	**Cases**	**Follow-up years**	**Cases**	**Follow-up years**	**Adjusted with age group, sex and calendar year**	
PCV10 serotypes [a]	8	114440	7	1580743	93.4	87.2-96.6
PCV10-related serotypes [b]	9	114440	69	1580743	46.2	-13.2-71.9
19A	7	114440	53	1580743	50.1	-19.2-78.2
Non-PCV10-related serotypes [c]	2	114440	50	1580743	-66.7	-711.4-52.1
All IPD	19	114440	131	1580743	54.1	23.7-71.1
Nested case-control design	**Cases**	**Controls**	**Cases**	**Controls**	**Matched with age, sex and calendar year**	
PCV10 serotypes	8	9	7	66	98.0	89.9-99.7
PCV10-related serotypes	9	29	69	361	50.5	-23.6-79.2
19A	7	24	53	276	45.2	-53.8-79.2
Non-PCV10-related serotypes	2	15	50	245	-76.6	-928.8-58.9
All IPD	19	54	131	696	61.1	25.6-79.3
Indirect cohort design	**Cases**		**Cases**		**Adjusted with age group, sex and calendar year**	
PCV10 serotypes	8		7		99.9	98.4-100
PCV10-related serotypes	9		69		78.3	-6.8-96.7
19A	7		53		65.7	-75.7-94.9
Non-PCV10-related serotypes	2		50		Reference	-
All IPD	19		131		-	-

Footnote: [a] PCV10 serotypes in the data: 6B, 7F, 14, 19F, 23F; [b] PCV10-related serotypes in the data: 6A, 6C, 6D, 7C, 9N, 19A, 23A, 23B; [c] non-PCV10-related serotypes in the data: 3, 11A, 12F, 15A, 15B/C, 22F, 24F, 33F, 34, 35F, 38.

Table 2. Vaccine effectiveness against IPD in PCV10 vaccinated children, estimated with three parallel study designs (full cohort; nested case-control; indirect cohort). Finland, September 2010 – December 2014 and January 2015 – December 2018.

Period/Design/ Serotype group	Unvaccinated		Vaccinated		Vaccine effectiveness (%) Estimate	95% crebile interval
2010-2014						
Full cohort design	**Cases**	**Follow-up years**	**Cases**	**Follow-up years**	**Adjusted with age group and sex**	
PCV10 serotypes	6	33678	5	400907	93.0	77.3-97.9
PCV10-related serotypes	2	33678	11	400907	54.1	-143.6-88.1
19A	0	33678	8	400907	NA	NA
Non-PCV10-related serotypes	1	33678	16	400907	-32.1	-1203.7-76.7
All IPD	9	33678	32	400907	70.4	35.2-85.3
Nested case-control design	**Cases**	**Controls**	**Cases**	**Controls**	**Matched with age, sex and calendar year**	
PCV10 serotypes	6	7	5	48	98.3	88.5-99.8
PCV10-related serotypes	2	5	11	60	67.6	-154.5-95.2
19A	0	3	8	37	NA	NA
Non-PCV10-related serotypes	1	6	16	79	-30.3	-1666.3-84.1
All IPD	9	18	32	187	82.3	48.4-94.0
Indirect cohort design	**Cases**		**Cases**		**Adjusted with age group and sex**	
PCV10 serotypes	6		5		99.2	88.1-100
PCV10-related serotypes	2		11		88.1	-255.4-99.7
19A	0		8		NA	NA
Non-PCV10-related serotypes	1		16		Reference	-
All IPD	9		32		-	-
2015-2018						
Full cohort design	**Cases**	**Follow-up years**	**Cases**	**Follow-up years**	**Adjusted with age group and sex**	
PCV10 serotypes	2	80761	2	1179836	93.6	54.1-99.1
PCV10-related serotypes	7	80761	58	1179836	43.3	-36.5-72.2
19A	7	80761	45	1179836	59.4	4.3-80.7
Non-PCV10-related serotypes	1	80761	34	1179836	-104.8	-1860.1-62.6
All IPD	10	80761	99	1179836	38.5	-23.5-66.6
Nested case-control design	**Cases**	**Controls**	**Cases**	**Controls**	**Matched with age, sex and calendar year**	
PCV10 serotypes	2	2	2	18	96.9	51.7-99.9
PCV10-related serotypes	7	24	58	301	45.2	-53.9-79.2
19A	7	21	45	239	56.8	-25.1-84.3
Non-PCV10-related serotypes	1	9	34	166	-123.4	-2576.7-68.3
All IPD	10	36	99	509	40.3	-39.4-73.1
Indirect cohort design	**Cases**		**Cases**		**Adjusted with age group and sex**	
PCV10 serotypes	2		2		100.0	NA
PCV10-related serotypes	7		58		76.5	-70.3-98.1
19A	7		45		80.2	-39.8-98.4
Non-PCV10-related serotypes	1		34		Reference	-
All IPD	10		99		-	-

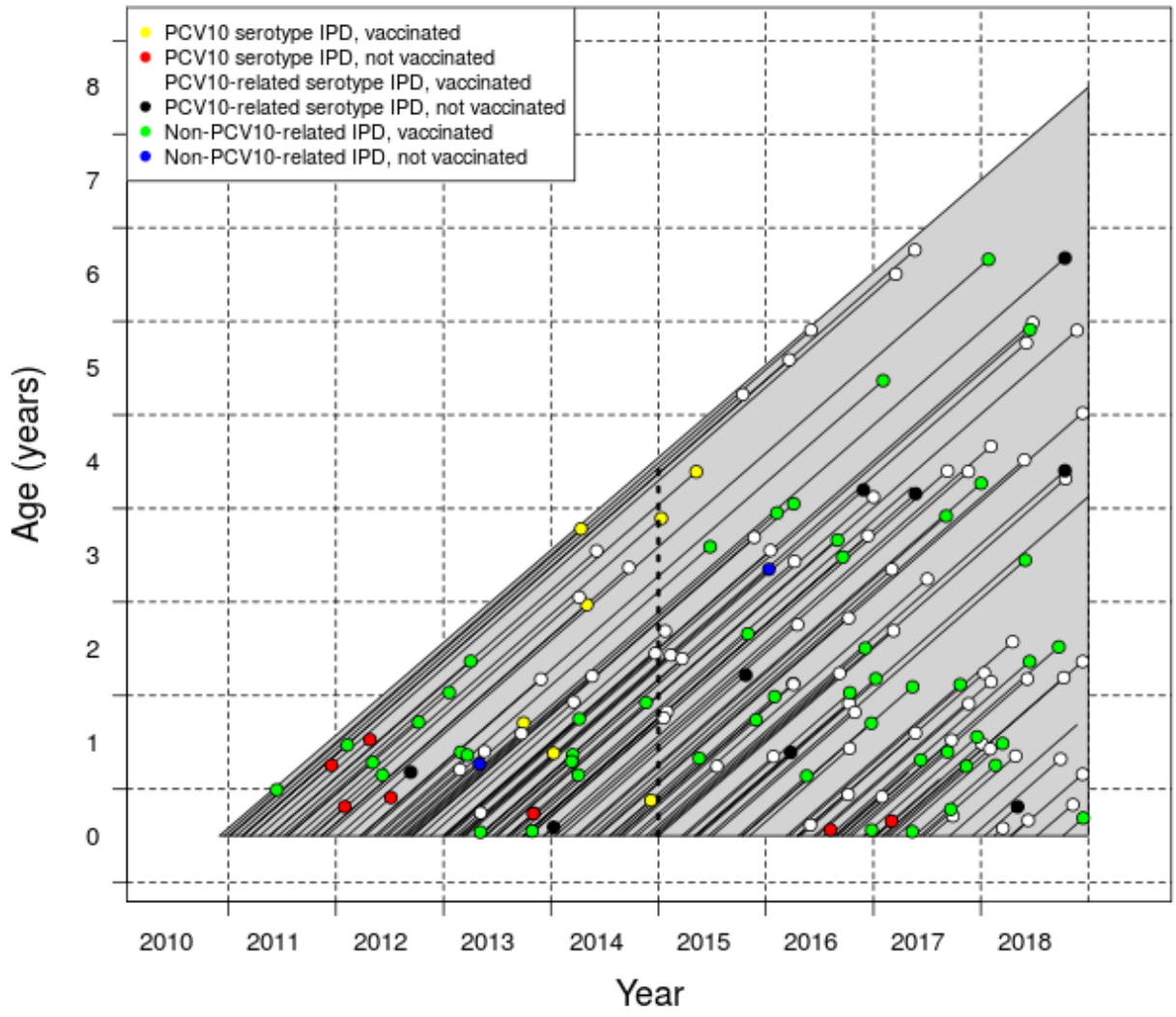
PCV10 serotype IPD, vaccinated
PCV10 serotype IPD, not vaccinated
PCV10-related serotype IPD, vaccinated
PCV10-related serotype IPD, not vaccinated
Non-PCV10-related IPD, vaccinated
Non-PCV10-related IPD, not vaccinated
Age (years)
0
1
2
3
4
5
6
7
8
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year

Figure 1