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Association Between Pediatric Vaccination Rates And Patterns Of Pneumococcal Disease In Adults In The Pcv7 And Pcv13 Eras

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Association between pediatric vaccination rates and patterns of pneumococcal disease in adults in the PCV7 and PCV13 eras

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ABSTRACT

BACKGROUND: Pneumococcal conjugate vaccine (PCV) is now recommended for use in adults in the United States. Because vaccination of children with PCVs protects adults from the targeted serotypes, local variations in PCV uptake among children could influence the effectiveness of direct immunization of adults. The effect of variations in PCV7 and PCV13 uptake in children will be compared to assess the possible effectiveness of PCV vaccination in adults.

METHODS: We obtained ZIP Code-level invasive pneumococcal disease (IPD) data from an active population-based surveillance system in Connecticut (1998-2013) and ZIP Code-level data on immunization with 3+ or 4+ doses of PCV from the state immunization registry. To estimate the decline in PCV serotypes in each age group during the PCV7 and PCV13 eras, we fit logistic regression models to estimate the proportion of IPD cases in a month caused by a vaccine serotype. To determine whether SES factors and/or vaccine uptake was associated with adult IPD cases we fit logistic regression models to estimate the proportion of IPD cases among adults >40 years that was caused by PCV-targeted serotypes. Covariates included ZIP Code-level socioeconomic indicators (e.g. percent black, income), percent of the population that received at least 3 (3+) or at least 4 (4+) doses of PCV (mean centered), and a linear spline to control for the average rate of decline across all ZIP Codes. The data were split into the 2000-2009 PCV7 era and the 2010-2013 PCV13 era to compare the effect of the two vaccines. In the PCV7 era we selected the best model for estimating the proportion of IPD cases among adults >40 years that was caused by PCV7-targeted serotypes by ranking the models by AIC score. In the PCV13 era we conducted AIC based model averaging to estimate the proportion of IPD cases among adults >40 years that was caused by PCV13-targeted serotypes.

RESULTS AND SIGNIFICANCE: The PCV7 serotypes declined rapidly as causes of IPD in children while the decline was slower and delayed in adults. A similar pattern was seen in the PCV13 serotype decline. ZIP Codes that had a higher proportion of children that did not complete the four-dose PCV7 series had a higher proportion of adult IPD cases caused by PCV7 serotypes. This trend is not yet evident in adults during the PCV13 era. Local variations in PCV uptake might influence the effectiveness of PCVs in preventing pneumococcal disease in adults.

INTRODUCTION

Pneumococcal conjugate vaccines (PCVs) have been used in children in the United States for over a decade. Introduction of the original conjugate vaccine (PCV7) was associated with rapid declines in invasive pneumococcal disease (IPD) caused by the PCV7-targeted serotypes among both children (who received the vaccine) and adults (who did not receive the vaccine) [1-4]. After introduction of the PCV7 vaccine in 2000, increases in the number of IPD cases caused by some nonvaccine pneumococcal serotypes was noted. A 13-valent vaccine (PCV13) was introduced in February 2010, which included the seven original serotypes plus six additional serotypes responsible for 63% of IPD cases in children during the post-PCV7 era [5, 6]. The new 13-valent vaccine was predicted to prevent 106,000 IPD cases and save $11.6 billion compared to PCV7 over a 10-year period in the United States [7].

There are still important questions about how to best protect adults from pneumococcal disease. Recently, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of PCV13 among adults aged ≥65 years in the United States [8]. However, because adults are indirectly protected when children receive PCVs, the fraction of IPD cases in adults that can be prevented declines over time, and it is not clear whether direct immunization of adults with the same vaccine would be effective [9, 10].

Little is known about how vaccine uptake rates with 3+ or 4+ doses, transmission intensity, and serotype distributions vary between communities. It is possible that in high population density settings, adults maintain transmission of PCV-targeted serotypes due to decreased exposure to young vaccinated children. Previous studies have found that low PCV7 uptake is associated with being black or Hispanic, receiving vaccinations from public health providers, and low household income [11, 12]. Variations in these factors could result in geographic pockets that have a higher or lower fraction of IPD cases caused by vaccine-targeted serotypes. In the pre-vaccine period, IPD

incidence has been shown to be higher in census tracts with more poverty, and greater numbers of blacks [13-15]. The serotype distribution is also different for census tracts with greater poverty and higher percentage black [13]. The pre-existing IPD trends and trends in vaccine uptake could influence the impact of direct immunization of adults with PCVs.

We tested the hypothesis that in the years following vaccine introduction, PCV-targeted serotypes caused a disproportionate fraction of IPD cases among adults living in communities with a lower socioeconomic status (SES) or lower uptake of PCVs among children. We evaluated this hypothesis using state-wide data from Connecticut on IPD incidence among children and adults and data on PCV7 and PCV13 uptake among children.

METHODS

All analyses were split by the PCV era for comparison. We assumed that the PCV7 era encompassed data from 2000-2009, while the PCV13 era covered 2010-2013.

Data Sources

Data on invasive pneumococcal cases were collected from the Active Bacterial Core surveillance system for the state of Connecticut for the period from 1998 to 2013 [4]. For each case, we had data on the month and year of sampling, the serotype, and the age group (<5, 5 to 17, 18 to 39, 40 to 64, and over 65 years). IPD case data for 2014 was not yet available at the time of this analysis.

Data on PCV uptake by ZIP Code were obtained from the Connecticut Immunization Registry and Tracking System (CIRTS). CIRTS is a mandatory, opt-out registry used to keep permanent records of the vaccination of children up through the age of two years. Approximately

10% of families opt out of the registry, and the other missing data constitute loss to follow-up (e.g. move out of state) or incomplete records. The data were aggregated by birth cohort and ZIP Code, and we obtained the total number of children in the registry in each strata and the number of children who received 3+ or 4+ doses of PCV. To estimate the total coverage of PCV in each month and ZIP Code among children 12-59 months of age, we used a cohort approach similar to Nuorti et al [11]. We assumed that the birth rate was constant over the year and that all children who received 3+ or 4+ doses of vaccine by age 2 were vaccinated according to schedule.

The CIRTS database cannot distinguish PCV7 doses from PCV13 doses in the years immediately after the implementation of PCV13. We estimated the switch over from PCV7 to PCV13 in 2010 using U.S.-wide calculations from Schuck-Paim et al [16]. Schuck-Paim calculated the switch over from PCV7 to PCV13 using physicians' office claims data from January 2008 to May 2012. We multiplied the number of children in CIRTS receiving 3+ or 4+ doses of PCV vaccine by the PCV13 uptake estimate in Schuck-Paim et al. We filled in the PCV13 vaccine uptake estimates from June 2012 to December 2013 using May 2012 uptake estimates, therefore assuming that the rest of the PCV13 era's vaccine uptake was equal to May 2012.

Because we wanted to focus on the importance of variations in vaccine uptake between ZIP Codes, we mean centered the vaccine uptake variables—for each date, we subtracted the mean uptake of 3+ or 4+ doses of PCV for the state of Connecticut from the uptake of 3+ or 4+ doses in each ZIP Code. These new mean-centered variables are centered around 0 at each date (**Figure S1, S2**). To quantify the additional benefit of completing the full 4 dose series, we subtracted the 4+ dose uptake variable from the 3+ dose uptake variable and then subtracted the mean at each date from this variable. Thus, this variable indicates whether the percent of children in a ZIP Code that received 3 doses but did not receive a 4^{th} dose differed from the state average.

Demographic data for each ZIP Code tabulation area (ZCTA) in Connecticut were obtained from the U.S. Census Bureau. We collected information on SES indicators such as the percentage of the population that was black, white, or Hispanic, income per capita, population density, and population size in each ZIP Code.

The Human Investigation Committees at Yale School of Medicine and the Connecticut Department of Public Health approved this study.

Estimating the rate of decline of vaccine serotypes in the PCV7 era and the PCV 13 era

We estimated the overall rate of decline of vaccine serotypes in each age group. To estimate the decline in PCV7 serotypes, we fit separate logistic regression models where the outcome was the proportion of cases of IPD in a given month caused by a vaccine serotype. The typical approach would be to fit a trend line to these data to estimate this decline over time. However there is uncertainty about exactly when this decline should begin, and the time of the decline might vary between age groups. To capture the uncertainty, we used a linear spline, where the location of the spline knot (the change point) was unknown. This provides a robust estimate for the rate of the decline and an estimate for when the decline begins in each age group. The potential covariates for the PCV7 logistic regression were a series of linear splines that had a value of 0 prior to a change point and then changed (log)-linearly after the change point. We fit 144 separate regressions, each of which had a single spline with the knot in a different month between 1998 and 2009.

In the PCV13 era we used the linear spline method from the PCV7 era (which estimated the change in slope over time), as well as another statistical method that measured if there was an immediate change in mean. The linear spline method modeled a series of linear splines that had a value of 0 prior to a change point and then changed (log)-linearly after the change point. This

models a constant rate of decline that occurs over a longer time period. However, because in the PCV13 era uptake of PCV13 occurred more rapidly than in the PCV7 era **(Figure 2**), we anticipated that the gradual spline method might not fit the data well in the PCV13 era. Therefore, we decided to include another method that accounted for an immediate decline in PCV13 serotypes. The immediate decline method uses a dummy variable to test for an immediate change in mean. We also created a new variable to account for pre-existing time trends before PCV13 vaccine introduction.

This meant that we had four different logistic regression model types to test the rate of decline of vaccine serotypes in the PCV13 era (Mean Change without Secular Trent, Mean Change with Secular Trend, Slope Change without Secular Trend, and Slope Change with Secular Trend). The fifth type of logistic regression we used was a null model that modeled the odds that there was no change in vaccine serotypes in the PCV13 era (Null Model).

To estimate the decline in PCV13 serotypes in the PCV13 era for each age group, we tested the five different types of logistic regressions, which modeled the odds that an IPD case in a given month was caused by a PCV13 vaccine serotype. We fit 96 separate regressions for each model type, in order to test a single spline with the knot in a different month between 2006 and 2013. This was repeated for each of the five age groups resulting in a total of 2,400 logistic regressions (480 per age group).

The fit of each of the models in the PCV7 and PCV13 era was evaluated using the Akaike Information Criterion (AIC). The AICs were used to generate a weight for each model (better-fitting models had higher weights) and to estimate the probability of the decline beginning in any given month [17, 18]. This provides a distribution of likely values for the change point, and the mean and 2.5^{th} and 97.5^{th} percentiles of this distribution gives the credible interval for the most

likely change point for each age group. The rate of decline per year from each of the models was estimated as 100*(exp(Coeff_trend*12)-1). To get an estimate of the rate of decline per age group and the 95% credible intervals in the PCV7 era, this value was averaged across the all candidate models in the PCV7 era, with the weight determined by the AIC score [19]. In the PCV13 era, we summed the weights of each model type (determined by AIC score) for each age group to find which model type best described the decline in vaccine serotypes for that age group in the PCV13 era (**Table 7**). To get an estimate of the rate of decline per age group and the 95% credible intervals in the PCV13 era, this value was averaged across the all the 96 different spline models from the best model type with the weights determined by the AIC score.

Factors associated with PCV uptake in children

To evaluate factors associated with variations in vaccine uptake, we fit a logistic regression model. The outcome variable in this univariable analysis was the proportion of children in the CIRTS registry within a given ZIP Code that received 3+ doses, 4+ doses, or only 3 doses of PCV divided by the total number of children in the CIRTS registry for that ZIP Code. The covariates were ZIP Code-level SES factors, including proportion of the population in the ZIP Code that was black or Hispanic, proportion under the age of 5, logarithm of income per capita, and logarithm of population density (overall, and under age 5). This particular analysis used vaccine uptake data from a single date (January 1, 2006 for PCV7 era, and Jan 1, 2012 for PCV13 era), with the assumption that the relative differences in uptake between ZIP Codes was consistent over time. This date was chosen for the PCV7 era because the vaccine program had "matured" by this point (i.e. the entire <5 year old cohort should have been vaccinated according to schedule). The PCV13 date was chosen as it was the center point in time for the four years of data. A significant coefficient

value ($p<0.05$) for the SES variable was taken as evidence that vaccine uptake differed by SES characteristic in a ZIP Code.

Exploratory analysis for relationship between vaccine uptake and serotype distribution

To evaluate the link between vaccine uptake and the proportion of IPD cases caused by a PCV serotype, we divided ZIP Codes into five groups for each year (quintiles) based on uptake of 4+ doses. We then compared the average uptake of PCV for each of these quintiles in each year and the observed proportion of IPD cases caused by PCV serotypes in each of these quintiles.

Factors associated with variations in proportion of IPD cases in adults caused by PCV7 serotypes

To determine whether PCV7 uptake or SES factors were associated with the proportion of disease cases caused by PCV-targeted serotypes, we fit a logistic regression. The outcome variable was the proportion of IPD cases at a given date and ZIP Code that was caused by a PCV7 serotype. For this analysis, we focused only on adults >40 years of age (40-64 and 65+ age groups). Based on the results of the change point analyses, all models in the PCV7 era included a linear spline (with a knot in June 2001 for PCV7) to capture the average decline in PCV serotypes across all ZIP Codes. The model with the lowest AIC score was considered the model with the best fit to the IPD data in adults.

Factors associated with variations in proportion of IPD cases in adults caused by PCV13 serotypes

In the PCV13 era, we tested all linear splines from January 2006 to December 2013. We decided to test all linear spline since the 95% CIs for the change points in the adult age groups were

very wide, indicating much less certainty in the change points than in the PCV7 era. We tested the 40-64 and 65+ age groups together and separately **(Tables 4-6)**, as the change point analysis indicated that the 65+ age group experienced a slightly quicker decline in PCV13 serotypes. The ZIP Code-level covariates were uptake of 3+ doses of the vaccine (mean-centered for each date), uptake of 4+ doses of the vaccine (mean-centered for each date), and only 3 doses of the vaccine (mean-centered for each date), proportion of the population of the population that was black, and logarithm of population density (overall, and over age 65). We chose these covariates as they were the best predictors of IPD cases in the PCV7 era. We fit 16 models with different combinations of covariates and splines. Because there was uncertainty about which SES variables to include, and how to model the change in IPD cases over time we averaged all our models together in a Bayesian model averaging approach.

To summarize the beta estimates for each covariate in the model, we averaged all 16 regression models across the model types using the covariate weights calculated from the AIC scores. We assumed that there was a 0.5 prior probability that there was no change point in the data (null model), and set the prior probability for the models with a change point to be 0.5/16. All of the models tested and their associated AIC can be found in **Table S1-S5**.

Evaluating fit of models identified in the PCV7 and PCV13 eras to determine factors associated with variations in proportion of IPD cases in adults caused by PCV13 serotypes

To evaluate the fit of the best model/averaged model in PCV7 and PCV13 eras, we divided the ZIP Codes into five groups (quintiles) in each year by the predicted proportion of IPD cases caused by PCV serotypes. Within each quintile, we estimated the mean predicted value and the

observed proportion of IPD cases caused by PCV serotypes for that year. The observed and expected values of these quintiles should be similar in all years if the model fits well.

All models were fit using PROC GENMOD (SAS V9.3, Cary, NC)

Sensitivity analysis for factors associated with variations in proportion of IPD cases in adults caused by PCV13 serotypes

The PCV7 era had a significant advantage when testing factors associated with variations in proportion of IPD cases in adults caused by PCV7 serotypes, as there was 10 years of post-vaccine data to analyze. 2000 and 2010 are considered transition years in the data as they are vaccine introduction years, and both years have very low vaccine coverage levels. This means that these years are not very useful for analysis. Therefore, the PCV13 era only had three years of post-vaccine data to analyze while the PCV7 era had nine years of post-vaccine data. As a result we are less confident in the analyses from the PCV13 era than the PCV7 era. Our results from the logistic regressions that tested the factors associated with variations in proportion of IPD cases in adults caused by PCV13 serotypes, were different from the factors associated in the PCV7 era. In the PCV7 era we found that failure to complete all 4 doses of PCV7 was a predictor of adult PCV7-targted serotype cases. However this was not evident in the PCV13 data, but perhaps this was due to lack of vaccine uptake data. In order to determine when we would have been able to detect the effect of PCV7 vaccination, we restricted the years of PCV7 vaccine uptake and IPD data sequentially. We retested the logistic regression model beginning with only one year of PCV7 data, and worked back up to 7 years. This provided an estimate for how many years of data were needed before PCV13 uptake is an important predictor.

RESULTS

Characteristics of IPD and vaccine data

From 2000 to 2009 during the PCV7 era, there were 5,838 cases of IPD captured in our database. Of these cases, 709 occurred among <5 year old children, 226 among 5-17 year olds, 581 among 18-39 year olds, 1,947 among 40-64 year olds, and 2,375 among those 65+. Across all 12 years of data collection in the PCV7 era, 3,525 cases were caused by non-PCV7 serotypes, while 2,313 cases were caused by PCV7 serotypes. From 2010 to 2013 during the PCV13 era there were 1,258 cases of IPD captured in the database. Of these PCV13 era cases, 69 occurred in the <5 year old children, 35 among the 5-17 year olds, 94 among the 18-39 year olds, 476 among the 40-64 year olds, and 585 among the 65+ age group. Of these 1,258 total cases, 846 cases were caused by non-PCV13 serotypes and 412 cases were caused by PCV13 serotypes.

By December 2009 (end of the PCV7 era), 94.7% of the children in the vaccine registry were vaccinated with 3+ doses of PCV7, and 88.4% were vaccinated with 4+ doses of PCV7. These estimates from CIRTS are similar to coverage estimates from the National Immunization Survey [20]. Using the U.S. estimated coverage for PCV13 [16], we estimated that 89.6% of children were vaccinated with 3+ doses of PCV13, and 81.83% with 4+ doses of PCV13 vaccine by May 2012. According to NIS, 94.8% of children in Connecticut were vaccinated with 3+ doses of a PCV and 91.1% were vaccinated with 4+ doses of a PCV by December 2012. The NIS database does not distinguish between PCV7 and PCV13, so we would expect the NIS coverage estimates to be higher than our PCV13 calculations since the NIS database includes both PCVs in estimated coverage. After comparing the NIS estimated coverage and our calculated PCV13 coverage, we can see that the switch over to PCV13 almost complete by 2012.

Changes in the proportion of IPD cases caused by PCV7 and PCV13 serotypes

After PCV7 was introduced in 2000, the proportion of IPD cases caused by the seven targeted serotypes declined in all age groups (**Figure 1A**). This decline was evident among children <5 years in early 2000, while the decline was delayed by ~17 months among adults 40-64 and 65+ years of age (**Figure 1B**). The decline among children aged 5-17 was further delayed, until late 2002. The rate of decline of the PCV7 serotypes among the <5 year olds was significantly more rapid than among the adults. The rate of decline among children under 5 was -62.7% per year (95% CI: -55.4, -68.8%) compared with -36.2% (95% CI: -32.0, -40.3%) and -37.0% (95% CI: -32.7, -40.98%) per year among 40-64 and 65+ year olds, respectively. By 2008, <8% of IPD cases in adults ages 40+ were caused by PCV7 serotypes

A similar pattern of PCV13 serotype decline was seen after the introduction of PCV13 in February 2010. We estimated the percent decline in PCV13 serotypes in each age group using the model type with the highest weight as calculated from AIC score (**Table 7**). The decline in children <5 started in May 2010, and was best described by the Mean Change without Secular Trend model (immediate change with a constant percent decline across all years). The PCV13 serotypes declined -81.7% (95% CI: -88.8, -69.8%) during the PCV13 era for those <5 years old. The decline in the 40-64 age group started in January 2011, and was best described by the Slope Change without Secular Trend model (linear percent decline per year). The decline among adults 40-64 years old was -36.1% per year (95% CI: -58.3, -1.9%). The decline in the 65+ age group was slightly earlier than the 40-64 year olds, starting in August 2010, and was also best described by the Slope Change without Secular Trend model. The decline among adults 65+ was -28.9% per year (95% CI: -43.7, -10.11%) (**Figure 1C, D**).

Variations in PCV uptake by ZIP Code

Uptake of 3+ and 4+ doses of PCV7 varied substantially between ZIP Codes (**Figure 2B**). These differences in uptake were minimized during the PCV13 period (**Figure 2D**). In univariable analyses, ZIP Codes with lower uptake of 3+ or 4+ doses of PCV7 and PCV13 were significantly more likely to have a higher percentage of the population that was black or Hispanic, a higher percentage of the population that was under 5 years of age, and a higher overall population density and population density of children <5 years of age (**Table 1**). ZIP Codes with lower uptake of 3+ or 4+ doses of PCV13 were also significantly more likely to have a lower per capita income. This association with per capita income was not seen in the PCV7 era.

Factors associated with variations in proportion of IPD cases in adults caused by PCV7 serotypes

ZIP Codes with lower-than-average PCV7 uptake (3+ or 4+ doses) at a given date tended to have a higher proportion of IPD cases caused by PCV7 serotypes (**Figure 3A, Table 3)**. Variables associated with lower SES (e.g. population density) were not significantly associated with the serotype distribution (**Table 3, S1**). In the best-fit multivariable model (**Table 3)**, having a higher proportion of IPD caused by PCV7 serotypes was associated with a higher-than-average percent of children failing to receive the 4^{th} dose after having received 3 doses of PCV7. As the gap between 3 and 4 dose coverage increased by 10%, the odds of IPD caused by a PCV7 serotype case increased by 54.3% (95% CI: 20.2%, 98.2%). There was also a non-significant association between uptake of 3+ doses of PCV7 and serotype distribution (**Table 3**). Additionally, the 40-64 year old category had a 15.1% lower odds (95% CI: -33.17%, 6.30%) of IPD caused by a PCV7 serotype compared to the 65+ age category. This model accurately captured variations in the proportion of IPD cases caused by PCV7 serotypes for all years (**Figure 4**). Four years after vaccine introduction, the model

predicted that 16-25% of cases would be caused by PCV7 serotypes. By 2009, the model predicted that just 3-5% of cases would be caused by PCV7 serotypes. Several other models also fit the data well (i.e. AIC score within 2 points of best model). All of these models included age group, uptake of 3+ doses of PCV7 (mean centered), and either uptake of 4+ doses of PCV7 (mean centered) or uptake of only 3 doses PCV7 (mean centered). Population density (log-transformed) was also included in several of the best-fit models (**Table 3**, **Table S1**), but did not affect the estimates of the importance of vaccine uptake (**Table 3)**.

Factors associated with variations in proportion of IPD cases in adults caused by PCV13 serotypes

There was no discernible relationship between PCV13 uptake and proportion of IPD cases in adults caused by PCV13 serotypes (**Figure 3B**). By December 2010, only 35% of Connecticut had switched to PCV13 from PCV7, and it was not until late 2011 that high levels of PCV13 coverage were achieved. Most of the variables associated with lower SES were not significantly associated with the serotype distribution for any of the model types, except for percentage black in a ZIP Code. (**Table 4, 5**). There was no association between PCV13 uptake and serotype distribution across all age category models (**Table 4-6**). The only significant predictor of adult PCV13 serotype cases was percentage black in a ZIP Code, and this variable was significant for the 40-64 age category models, and the combined age category models but not for 65+ age category models. For every 10% increase in the percentage black in a ZIP Code, the odds of a PCV13-targeted IPD case in the 40-64 age group decreased by -22.11% (95% CI: -28.99, -14.53), while the odds for the 65+ age group decreased by -2.79% (95% CI: -11.24, 6.46). In the combined age group model, the odds decreased by -17.64 (95% CI: -23.37, -11.49).

These models accurately captured the decline in proportion of IPD cases caused by PCV13 serotypes over time (**Figure 5**), but did not accurately estimate variations in the proportion of IPD cases within a given year. For the PCV13 era we used PROC CORR to find the Pearson Correlation Coefficient between the observed proportion of IPD cases caused by PCV13 serotypes, and the predicted mean value. The 40-64 age category models and the combined age category models had the best fit to the data of the 3 age category models. The 40-64 year old age category models had a correlation coefficient of 0.77, the 65+ age category models had a correlation coefficient of 0.63, and the combined age group models had a correlation coefficient of 0.78. All the correlation coefficients were significant at the $p<0.05$ level. The decline in proportion PCV13 cases over time is clear, but there is a little separation between the quintiles of data. The correlation coefficients indicate that the 65+ age group was not as well described by the logistic regression models as the 40-64 years olds, and the combined age groups.

Sensitivity analysis for factors associated with variations in proportion of IPD cases caused by PCV7 serotypes

After sequentially restricting the data in the PCV7 era, we determined that it took 6 years before PCV7 vaccine uptake was a significant predictor of adult PCV7-targeted IPD cases. In the early years after vaccine introduction, demographic variables (in particular percentage black) were better predictors than vaccine uptake. The best fit model identified using the 2000-2009 data range was not the lowest AIC scored model until testing data from 2000-2006. Vaccine uptake is not a significant predictor in any model until after 2002.

DISCUSSION

PCVs are now in use among children around the world, and many countries are considering whether adults should also receive the same vaccine. Adults receive strong indirect protection in settings with high uptake of PCVs among children. In our data, only a small fraction of IPD cases in adults were caused by PCV7 serotypes after a decade of vaccine use in children. In such settings, immunizing adults with the same vaccine as children might not be justified. However, our data suggest that local variations in vaccine uptake among children might allow PCV7-targeted serotypes to persist as causes of disease in adults when the uptake levels are not maximal. In locations where vaccine uptake is less complete, either due to vaccine refusals or deficiencies in the public health system, local variations in PCV7 uptake in children might influence the serotype distribution in adults and could factor into decisions about whether to also immunize adults with PCVs.

In the PCV13 era we saw that demographic variables such as percentage black were better predictors of pockets of adult IPD PCV13-targeted cases. When looking at the results of the sensitivity analysis for factors associated with variations in proportion of IPD cases caused by PCV7 serotypes, we can see that in the early years after PCV7 introduction demographic variables were better predictors than vaccine uptake until about 2006. In the PCV13 era the only significant predictor of IPD PCV13-targeted case was percentage black in a ZIP Code. Percentage black in a ZIP Code was significant predictor for the 40-64 and combined age groups, but not the 65+ age group **(Table 4, Table 5**). There is a 3-22% decrease in adult PCV13-targeted IPD cases for every 10% increase in percentage black in a ZIP Code, for the adult age groups. This negative association may be due to serotype replacement effects from the PCV7 era. After the introduction of PCV7, blacks experienced higher levels of serotype replacement, and had increases in the non-PCV7

serotypes beyond that of whites. By 2009, a higher proportion of IPD in whites was caused by PCV13-targeted serotype than in blacks [14, 21]. Therefore, serotype replacement may have affected the racial groups differently, and serotype distribution may differ for low SES groups as a result. PCV13 may not be ideally designed to eliminate the most common serotypes in blacks, and may be better suited to the serotype distributions in whites.

The sensitivity analysis for identifying how soon PCV7 uptake becomes an important predictor in PCV7 period also supports the idea that racial composition of a ZIP Code is important in the early years of vaccine introduction. We found that in the first 4 years of PCV7 introduction, the percent black in a ZIP Code was an important predictor of adult PCV7-targeted IPD cases. These results support the idea that we may see the same association between local variations in vaccine uptake in children and the persistence of PCV13-targeted serotypes among adults as in the PCV7 era. We may be capturing the early association where race is an important early predictor of persistence of PCV13-targeted serotypes among adults.

Uptake of PCVs in children in Connecticut has been high overall, with ~95% of children in the CIRTS registry having received at least 3 doses of PCV7. Similarly, 89.6% of children in the CIRTS registry received at least 3 doses of PCV13 in 2013. Uptake of PCV13 across Connecticut was faster and overall there was less difference in uptake between the ZIP Codes compared to the PCV7 era (**Figure 2D**). Uptake of 4 doses of PCV lagged behind in some ZIP Codes in Connecticut. In particular, areas with lower SES indicators tended to have lower uptake of PCV7 and PCV13. Outreach to low income communities may be needed to improve 4+ dose vaccination rates in these areas.

Given the costs associated with PCVs, there is substantial interest in considering alternative dosing or reduced-dose schedules for PCVs. Because much of the benefit derived from PCVs

results from indirect protection, it is important to consider how dosing schedules might influence such indirect effects. A systematic review of dosing schedules on rates of carriage and disease [22, 23] suggested that a variety of dosing schedules can indirectly protect adults. The review suggested that in the first year of life, 3 doses of PCV had a greater effect on the risk of colonization than 2 doses. There were not clear differences between dosing schedules on the magnitude of the indirect effect against IPD or pneumonia. Our results suggest that the 4th dose of PCV7 might have an additional benefit beyond that provided by 3 doses of vaccine in indirectly protecting adults against IPD. Our study has the advantage of being able to examine this question in the context of a single study population over time. We found that ZIP Codes with a high percentage of children that failed to complete the 4-dose PCV7 series had a significantly higher proportion of IPD cases in adults caused by PCV7 serotypes. This association persisted after controlling for demographic characteristics, which are themselves associated with variations in PCV uptake. This type of analysis will need to be repeated in an independent setting to evaluate the potential impact of this 4th dose on protecting adults from IPD. The relationship between PCV uptake in children and disease rates in adults may or may not translate to the post-PCV13 period. Our sensitivity analysis indicates that at least six years of data are needed before the impact of PCV uptake on the proportion of IPD cases caused by the vaccine serotypes in adults can be assessed; thus, there may not be enough data available yet in the PCV13 era to compare the two periods. So far, the best model describing the decline in PCV7 serotypes has not been a good fit for the PCV13 data. In particular, the 65+ age category is not well described by this best model from the PCV7 era. More data are needed to determine if the 4th dose of PCV13 provides additional protection over the 3rd dose, as in the PC7 era.

Our results have some limitations. This is an observational study with ecological data. As a result, associations between vaccine uptake and serotype distribution at the ZIP Code level should be interpreted with caution. While we control for demographic characteristics in our multivariate model, we cannot exclude the possibility that other unmeasured confounders impact serotype distribution at the ZIP-Code level. For instance, it is possible that higher rates of co-morbidities in some communities might increase the risk for developing vaccine-serotype disease. Our approach of analyzing the proportion of disease cases caused by vaccine serotypes, rather than incidence, partly controls for this issue by implicitly adjusting for differences in overall disease risk between communities. This assumes that the factors that lead to persistence of vaccine serotypes are the same factors that influence the risk for disease caused by non-vaccine serotypes. The model averaging approach used to determine the best models in the PCV13 era is more robust than the calculations from the PCV7 period, which does not have the additional averaged data. However when setting up our prior probabilities for the 16 models with a change point, we assumed that the prior probability was the same for all these models. This may not have been the case, and some models should have been weighted more or less heavily.

There were several important limitations regarding the CIRTS data. It was difficult to estimate the switch over from PCV7 to PCV13 as the CIRTS database does not distinguish between PCV7 and PCV13, so we do not have exact data on ZIP-Code level uptake of PCV13. Furthermore, the switch over period in Connecticut may not be perfectly described by the national data used to estimate it, as the uptake pattern in Connecticut may have been different. Not every child in Connecticut is represented in the CIRTS immunizations registry. The vaccination status of ~15% of the children is unknown, so our vaccine uptake estimates may overestimate the true coverage level in the ZIP Codes if the children not included in CIRTS are less likely to have been vaccinated with

PCV. Additionally, the CIRTS registry primarily follows children through age 2, so if the 4th dose of PCV is delayed beyond age 2, it will not be captured in the registry. If some populations are more likely to delay the 4th dose, this could impact the interpretation of our results. We also only had 4 years of data to analyze for the PCV13 period, as the 2014 vaccine uptake data were not yet available.

In conclusion, we found that vaccine uptake varies with SES factors [24] and that pediatric vaccination affects serotype patterns in adults [25-27]. Our findings are unique in that after controlling for SES factors and the overall trend associated with vaccine introduction, we identified an association between local variations in vaccine uptake in children and the persistence of PCV7-targeted serotypes among adults. This underscores the importance of maintaining high coverage of vaccines among the pediatric population for protecting individuals of all ages. It remains to be seen if this association is mirrored in the PCV13 era, as more data are needed to analyze this association.

Table 1. Factors associated with higher percent vaccinated with 3+ or 4+ doses of PCV7 in Connecticut.

Univariable Model	Variables[†]	Odds Ratio	95% CI
Uptake 3+ Doses	Percent Black[†]	0.55	0.50, 0.60
	Percent Hispanic[†]	0.82	0.74, 0.91
	Percent Under 5[†]	0.17	0.08, 0.37
	Log Density[*]	0.48	0.42, 0.54
	Log Density Under 5[*]	0.55	0.50, 0.61
	Log Income[*]	1.09	0.92, 1.30
Uptake 4+ Doses	Percent Black[†]	0.80	0.74, 0.85
	Percent Hispanic[†]	0.86	0.81, 0.91
	Percent Under 5[†]	0.27	0.17, 0.50
	Log Density[*]	0.73	0.68, 0.80
	Log Density Under 5[*]	0.76	0.71, 0.82
	Log Income[*]	1.19	1.04, 1.34
Uptake Only 3 Doses	Percent Black[†]	0.95	0.90, 1.01
	Percent Hispanic[†]	1.03	0.96, 1.10
	Percent Under 5[†]	1.49	0.82, 2.71
	Log Density[*]	0.96	0.88, 1.05
	Log Density Under 5[*]	0.98	0.90, 1.05
	Log Income[*]	0.86	0.76, 0.99

[†]Change in odds per 10-percentage point change in socioeconomic variable

[*]Change in odds per 1 log change in socioeconomic variable

Table 2. Factors associated with higher percent vaccinated with 3+ or 4+ doses of PCV13 in Connecticut.

Univariable Model	Variables	Odds Ratio	95% CI
Uptake 3+ Doses	Percent Black†	0.98	0.97, 0.99
	Percent Hispanic†	1.05	1.01, 1.07
	Percent Under 5†	0.64	0.55, 0.73
	Log Density*	1.03	1.01, 1.03
	Log Density Under 5*	1.02	1.01, 1.03
	Log Income*	1.17	1.12, 1.23
Uptake 4+ Doses	Percent Black†	0.93	0.92, 0.94
	Percent Hispanic†	0.93	0.90, 0.95
	Percent Under 5†	0.46	0.40, 0.52
	Log Density*	0.95	0.94, 0.97
	Log Density Under 5*	0.95	0.94, 0.96
	Log Income*	1.34	1.29, 1.39
Uptake Only 3 Doses	Percent Black†	1.14	1.13, 1.16
	Percent Hispanic†	1.32	1.28, 1.27
	Percent Under 5†	3.31	2.72, 4.01
	Log Density*	1.19	1.16, 1.21
	Log Density Under 5*	1.18	1.16, 1.21
	Log Income*	0.61	0.57, 0.65

†Change in odds per 10-percentage point change in socioeconomic variable

*Change in odds per 1 log change in socioeconomic variable

Table 3. Factors associated with having a higher proportion of invasive pneumococcal disease cases caused by a PCV7-targeted serotype.

Model	Variables	Percent change[***]	95% CI
Best Model			
	Only 3 Doses (Mean Centered)[†]	54.30	20.20, 98.20
	3+ Doses (Mean centered)[†]	-15.70	-33.24, 6.30
	Age Category[*]	-1.60	-3.10, -0.20
	Linear Trend [**]	-36.16	-38.12, -30.23
Alternative models			
Bivariable	Linear Trend [**]	-36.16	-38.12, -30.23
	Only 3 Doses (Mean Centered)[†]	46.96	14.91, 87.95
Bivariable	Linear Trend [**]	-36.16	-38.12, -30.23
	Age Category[*]	-1.19	-2.76, 0.10
	Linear Trend [**]	-36.16	-38.12, -30.23
	3+ Doses (Mean Centered)[†]	-9.70	-27.96, 13.20
Bivariable	Linear Trend [**]	-36.16	-38.12, -30.23
	Log-population density[***]	5.01	-1.64, 12.11
Multivariable	Only 3 Doses (Mean Centered)[†]	50.23	16.07, 94.45
	3+ Doses (Mean centered)[†]	-14.36	-32.36, 8.55
	Age Category[*]	-1.69	-3.15, -0.02
	Linear Trend[**]	-36.16	-38.12, -30.23
	Log-population density[***]	2.81	-4.04, 10.14

For the full list of models tested and their AIC scores, see Table S1

[†] Change in odds per 10-percentage point change in PCV7 uptake

[*] Odds of a 40-65 year old compared to the odds of a 65+ year old

[**] Change in odds per year after June 2001

Table 4. Factors associated with having a higher proportion of invasive pneumococcal disease cases caused by a PCV13-targeted serotype in ages 40-64 and 65+ combined (Model Averaged).

Variables	Percent Change***	95% CI
***Change in odds per 1 log change in socioeconomic variable		
Age Category*	53.83	(-35.20, 265.18)
3+ Doses (Mean Centered) †	0.00	(-0.57, 0.57)
4+ Doses (Mean Centered) †	0.00	(-0.02, 0.02)
Only 3 Doses (Mean Centered) †	31.76	(-37.68, 178.59)
Log of Population Density**	0.00	(-0.46, 0.46)
Log of Population Density > age 65**	0.00	(-0.20, 0.20)
Percent Black†	-17.64	(-23.37, -11.49)

For the full list of models tested and their AIC scores, see Table S4

† Change in odds per 10-percentage point change in PCV7 uptake

* Odds of a 40-65 year old compared to the odds of a 65+ year old

** Change in odds per 1 log change in socioeconomic variable

*** ((Odds Ratio)-1)*100

Table 5. Factors associated with having a higher proportion of invasive pneumococcal disease cases caused by a PCV13-targeted serotype in ages 40-64 (Model Averaged).

Variables	Percent Change[***]	95% CI
Age Category[*]	-	-
3+ Doses (Mean Centered) [†]	0.00	(-0.57, 0.57)
4+ Doses (Mean Centered) [†]	0.00	(-0.02, 0.02)
Only 3 Doses (Mean Centered) [†]	30.94	(-51.12, 250.77)
Log of Population Density[**]	0.00	(-0.51, 0.51)
Log of Population Density > age 65[**]	0.00	(-0.23, 0.23)
Percent Black[†]	22.11	(-28.99, -14.53)

For the full list of models tested and their AIC scores, see Table S2

[†] Change in odds per 10-percentage point change in PCV7 uptake

[*] Odds of a 40-65 year old compared to the odds of a 65+ year old

[**] Change in odds per 1 log change in socioeconomic variable

[***] ((Odds Ratio)-1)*100

Table 6. Factors associated with having a higher proportion of invasive pneumococcal disease cases caused by a PCV13-targeted serotype in ages 65+ (Model Averaged).

Variables	Percent Change[***]	95% CI
Age Category[*]	-	-
3+ Doses (Mean Centered)[†]	1.57	(-18.41, 26.45)
4+ Doses (Mean Centered)[†]	0.88	(-12.90, 0.02)
Only 3 Doses (Mean Centered)[†]	1.17	(-34.45, 56.16)
Log of Population Density[**]	-1.51	(-8.92, 6.51)
Log of Population Density > age 65[**]	-1.26	(-7.97, 5.93)
Percent Black[†]	-2.79	(-11.24, 6.46)

For the full list of models tested and their AIC scores, see Table S3

[†] Change in odds per 10-percentage point change in PCV7 uptake

[*] Odds of a 40-65 year old compared to the odds of a 65+ year old

[**] Change in odds per 1 log change in socioeconomic variable

[***] ((Odds Ratio)-1)*100

Table 7. Best model type by age group as determined by weight calculated from AIC score

Age Category	Model Type	Weight
	Null	0.0005
	Mean Change without Secular Trend	0.3956
<5	Mean Change with Secular Trend	0.1861
	Slope Change without Secular Trend	0.2831
	Slope Change with Secular Trend	0.1348
	Null	0.7486
	Mean Change without Secular Trend	0.0928
5-17	Mean Change with Secular Trend	0.0444
	Slope Change without Secular Trend	0.0818
	Slope Change with Secular Trend	0.0325
	Null	0.0006
	Mean Change without Secular Trend	0.1221
18-39	Mean Change with Secular Trend	0.0523
	Slope Change without Secular Trend	0.5952
	Slope Change with Secular Trend	0.2298
	Null	0.0005
	Mean Change without Secular Trend	0.0575
40-64	Mean Change with Secular Trend	0.1269
	Slope Change without Secular Trend	0.5488
	Slope Change with Secular Trend	0.2662
	Null	0.0003
	Mean Change without Secular Trend	0.2039
65+	Mean Change with Secular Trend	0.1824
	Slope Change without Secular Trend	0.3533
	Slope Change with Secular Trend	0.2599

FIGURES

FIGURE 1. Decline in PCV7 and PCV13 serotypes in Connecticut over time. (A) The proportion of invasive pneumococcal disease cases caused by PCV7 serotypes in each month and year by age group, 1998-2009. (B) The probability that the PCV7-associated decline begins in any given month. These distributions can be compared to estimate how long it takes the indirect effect to reach unvaccinated age groups. (C) The proportion of invasive pneumococcal disease cases caused by PCV13 serotypes in each month and year by age group, 2006-2013. (D) The probability that the PCV13-associated decline begins in any given month. These distributions can be compared to estimate how long it takes the indirect effect to reach unvaccinated age groups. The best model type (Mean Change without Secular Trend, Mean Change with Secular Trend, Slope Change without Secular Trend, Slope Change with Secular Trend) for each age group was used to calculate the probability.

FIGURE 2: Uptake of PCV7 among children 12-59 months of age in Connecticut. (A) Average uptake of 3+ doses (blue) and 4+ doses (red) of PCV7. (B) Uptake of 4+ doses of PCV7 by ZIP Code for all ZIP Codes with at least 20 children per birth cohort. (C) Average uptake of 3+ doses (blue) and 4+ doses (red) of PCV13. (D) Uptake of 4+ doses of PCV13 by ZIP Code for all ZIP Codes with at least 20 children between 12 and 59 months.

FIGURE 3: (A) Association between uptake of 4+ doses of PCV7 and proportion of IPD cases caused by PCV7 serotypes, 2001-2009. (B) Association between uptake of 4+ doses of PCV13 and proportion of disease cases caused by PCV13 serotypes, 2010-2013. Each color indicates a different

calendar year. The bubbles represent quintiles of PCV7 uptake by ZIP Code in each year. The size of the bubble is proportional to the number of IPD cases in that strata.

FIGURE 4: Comparison of proportion of IPD cases among 40+ year old adults in a ZIP Code and year predicted to be caused by a PCV7 serotype (broken into quintiles by predicted proportion of IPD PCV7-targeted adult cases in each year) and the observed proportion in the corresponding group. The solid diagonal line denotes where observed=expected.

FIGURE 5: Comparison of proportion of disease cases among 40-64 age group, 65+ age group, and combined age group in a ZIP Code and year predicted to be caused by a PCV13 serotype (broken into quintiles by predicted proportion of IPD PCV7-targeted adult cases in each year) and the observed proportion in the corresponding group. The solid diagonal line denotes where observed=expected.

FIGURE S1: Mean-centered uptake of PCV7 among children 12-59 months of age in Connecticut, by ZIP Code. For each date, the mean value across all ZIP Codes was taken and subtracted from the observed uptake value. (A) Mean-centered average uptake of 3+ doses of PCV7. (B) Mean-centered uptake of 4+ doses of PCV7. (C) Mean-centered uptake of only 3 doses of PCV7. All ZIP Codes with at least 20 children between 12 and 59 months are shown.

FIGURE S2: Mean-centered uptake of PCV13 among children 12-59 months of age in Connecticut, by ZIP Code. For each date, the mean value across all ZIP Codes was taken and subtracted from the

observed uptake value. (A) Mean-centered average uptake of 3+ doses of PCV13. (B) Mean-centered uptake of 4+ doses of PCV13. (C) Mean-centered uptake of only 3 doses of PCV13. All ZIP Codes with at least 20 children between 12 and 59 months are shown.

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Figure 1

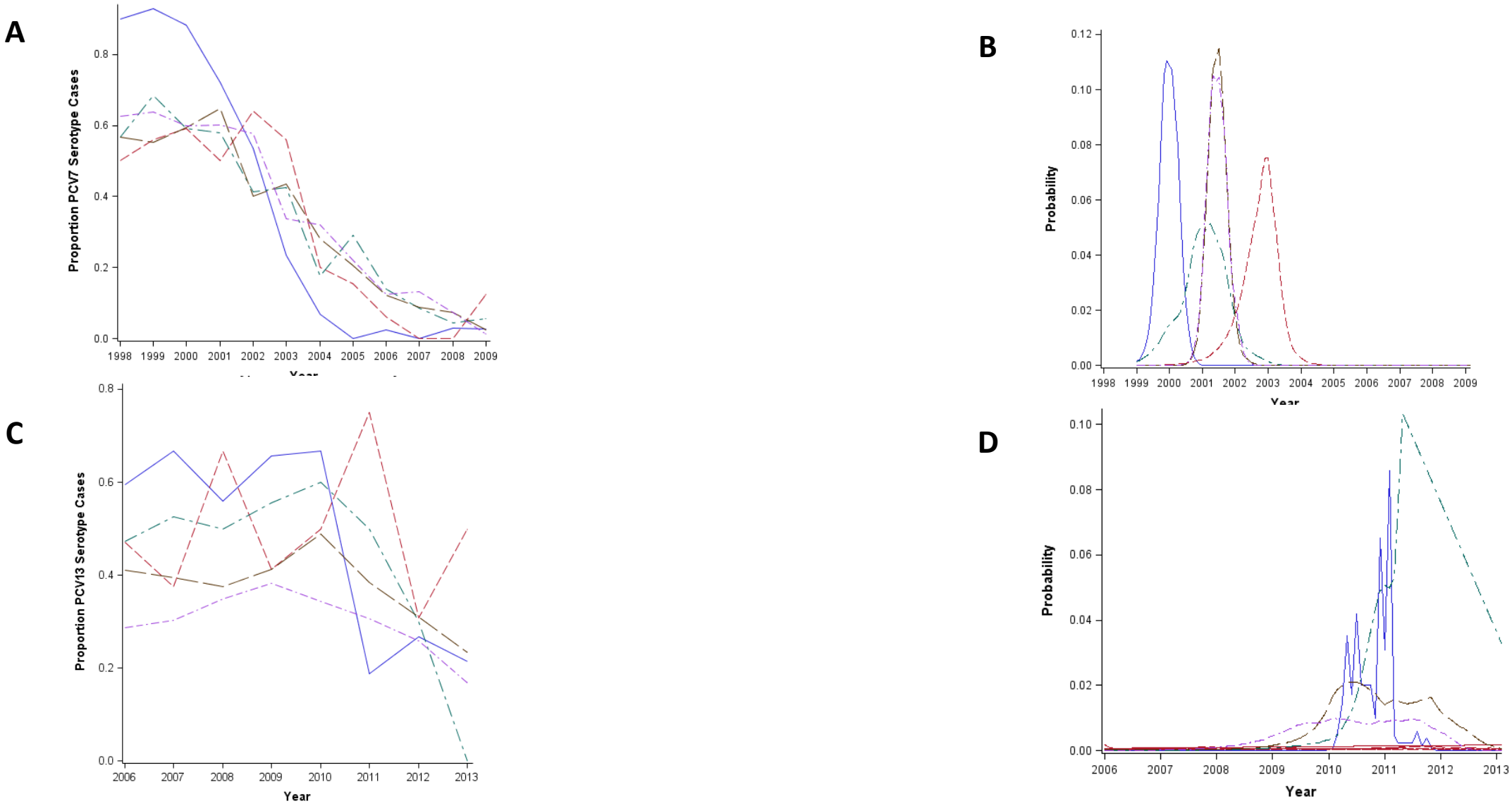
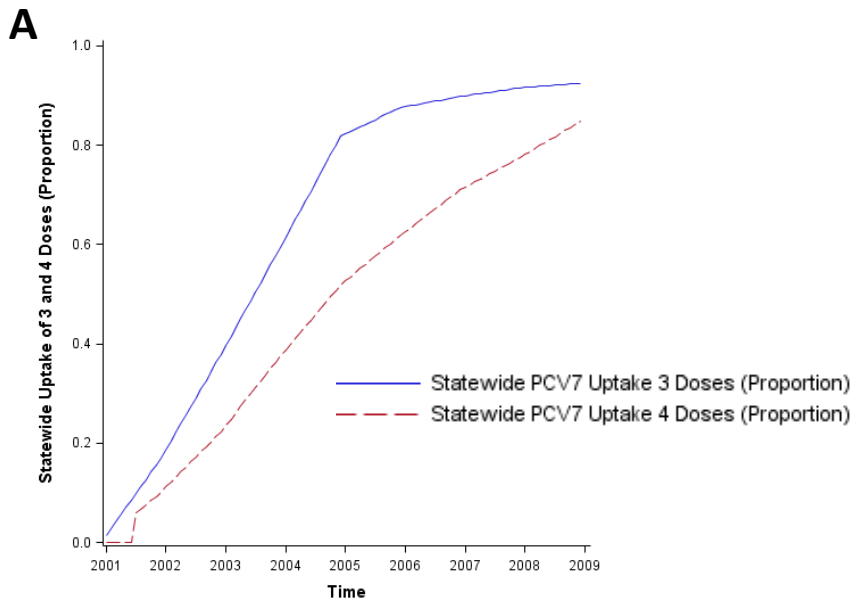
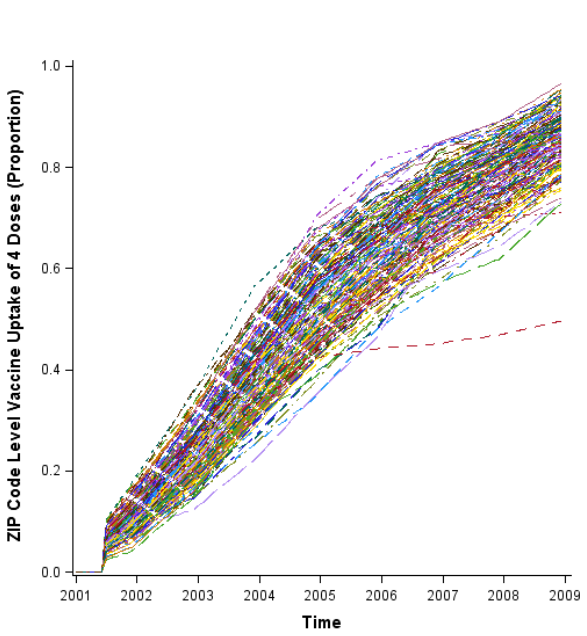
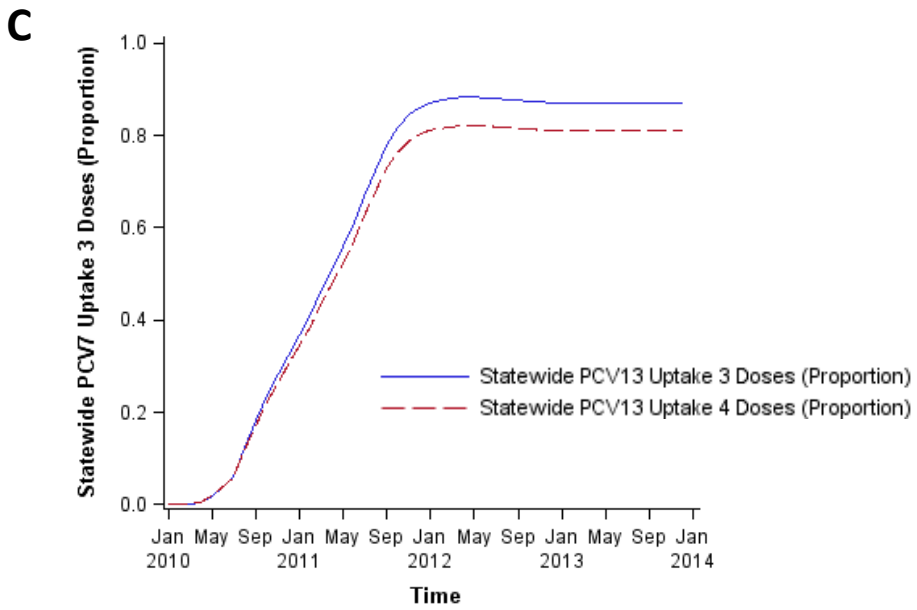

A
Proportion PCV7 Serotype Cases
0.0
0.2
0.4
0.6
0.8
1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
B
Probability
0.00
0.02
0.04
0.06
0.08
0.10
0.12
1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
Year
C
Proportion PCV13 Serotype Cases
0.0
0.2
0.4
0.6
0.8
2006 2007 2008 2009 2010 2011 2012 2013
Year
D
Probability
0.00
0.02
0.04
0.06
0.08
0.10
2006 2007 2008 2009 2010 2011 2012 2013
Year
Age Category
<5
5-17
18-39
40-64
65+

Figure 2


A
Statewide Uptake of 3 and 4 Doses (Proportion)
1.0
0.8
0.6
0.4
0.2
0.0
2001
2002
2003
2004
2005
2006
2007
2008
2009
Time
Statewide PCV7 Uptake 3 Doses (Proportion)
Statewide PCV7 Uptake 4 Doses (Proportion)


B
ZIP Code Level Vaccine Uptake of 4 Doses (Proportion)
1.0
0.8
0.6
0.4
0.2
0.0
2001
2002
2003
2004
2005
2006
2007
2008
2009
Time


C
Statewide PCV7 Uptake 3 Doses (Proportion)
1.0
0.8
0.6
0.4
0.2
0.0
Jan
May
Sep
Jan
May
Sep
Jan
May
Sep
Jan
May
Sep
Jan
2010
2011
2012
2013
2014
Time
Statewide PCV13 Uptake 3 Doses (Proportion)
Statewide PCV13 Uptake 4 Doses (Proportion)

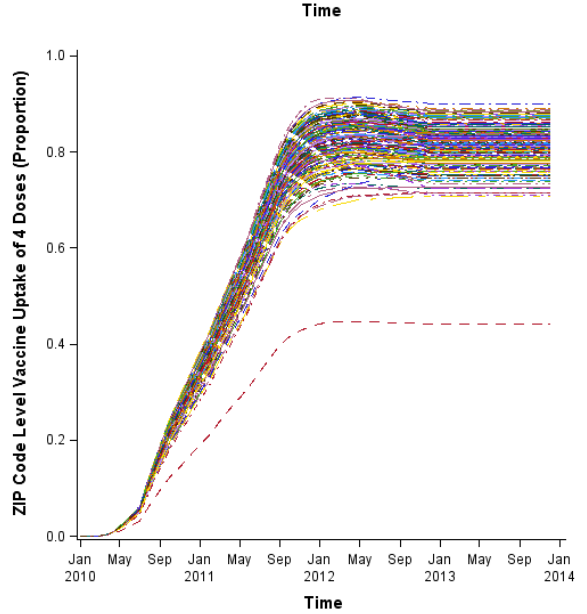

D
ZIP Code Level Vaccine Uptake of 4 Doses (Proportion)
1.0
0.8
0.6
0.4
0.2
0.0
Jan
May
Sep
Jan
May
Sep
Jan
May
Sep
Jan
May
Sep
Jan
2010
2011
2012
2013
2014
Time

Figure 3

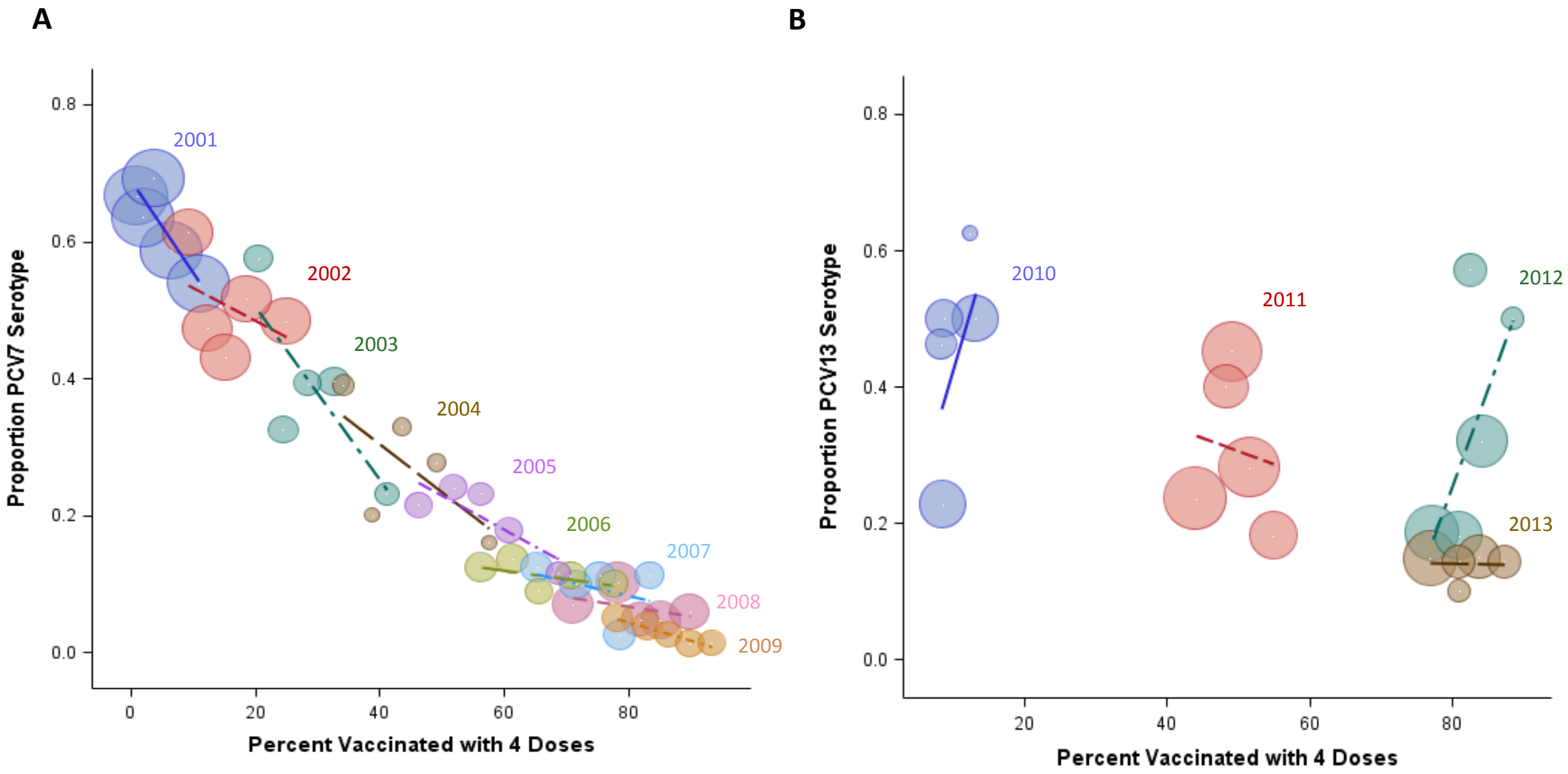

A
Proportion PCV7 Serotype
0.0
0.2
0.4
0.6
0.8
0
20
40
60
80
Percent Vaccinated with 4 Doses
2001
2002
2003
2004
2005
2006
2007
2008
2009
B
Proportion PCV13 Serotype
0.0
0.2
0.4
0.6
0.8
20
40
60
80
Percent Vaccinated with 4 Doses
2010
2011
2012
2013

Figure 4

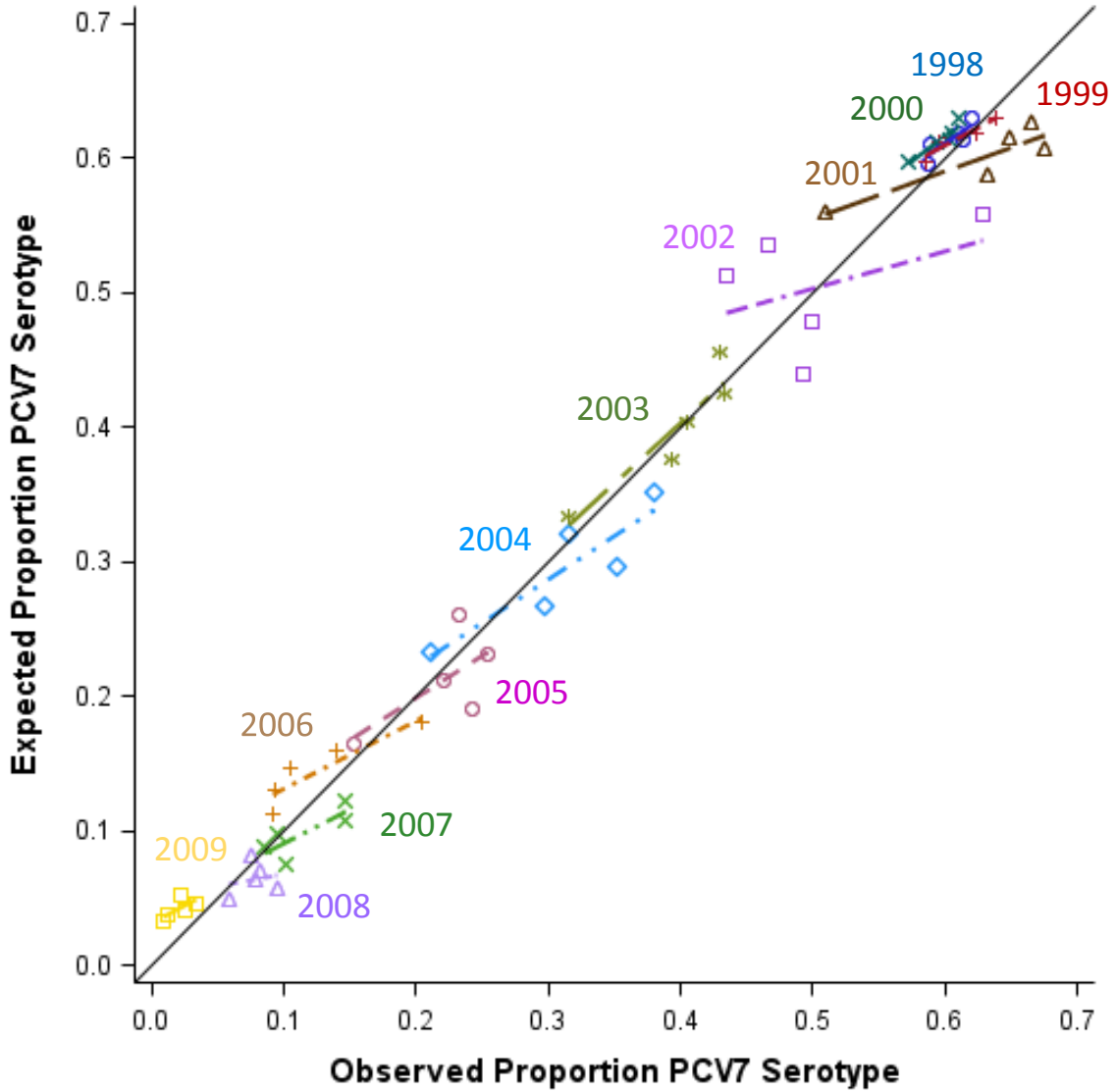

Expected Proportion PCV7 Serotype
Observed Proportion PCV7 Serotype
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009

Figure 5

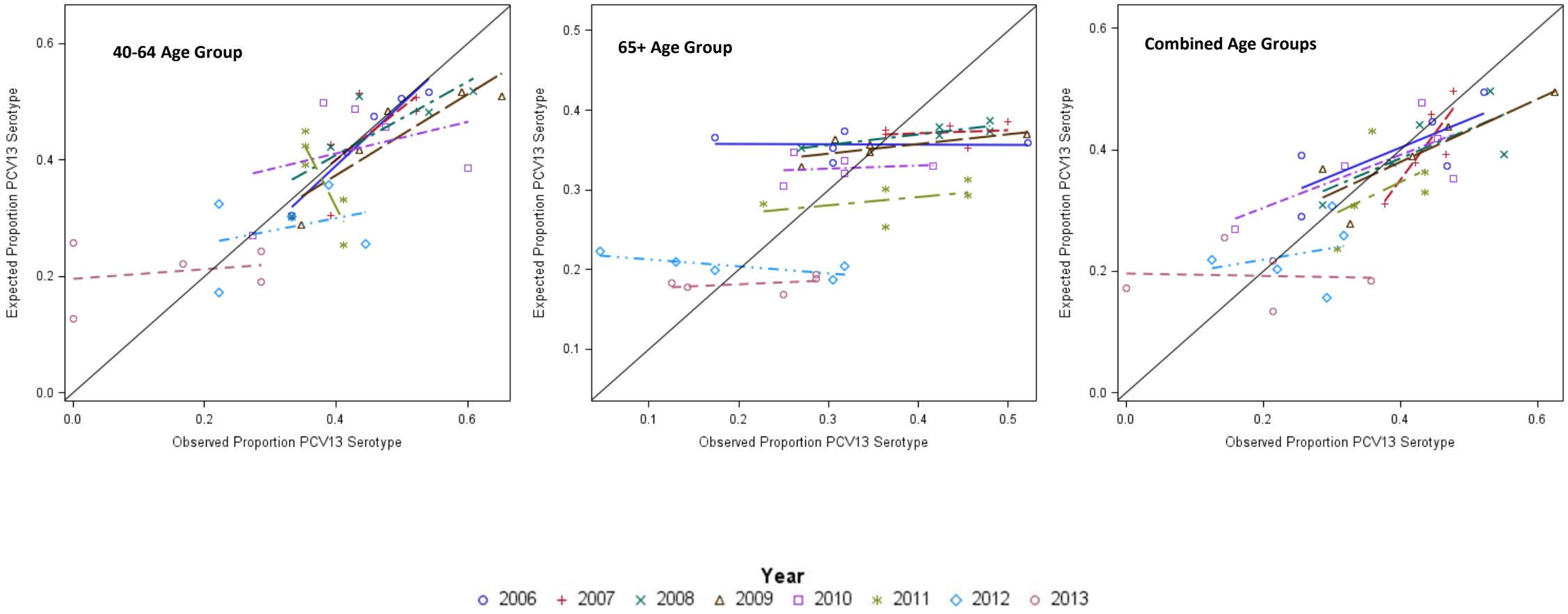

40-64 Age Group
65+ Age Group
Combined Age Groups
Expected Proportion PCV13 Serotype
Observed Proportion PCV13 Serotype
Year
2006
2007
2008
2009
2010
2011
2012
2013

Figure S1

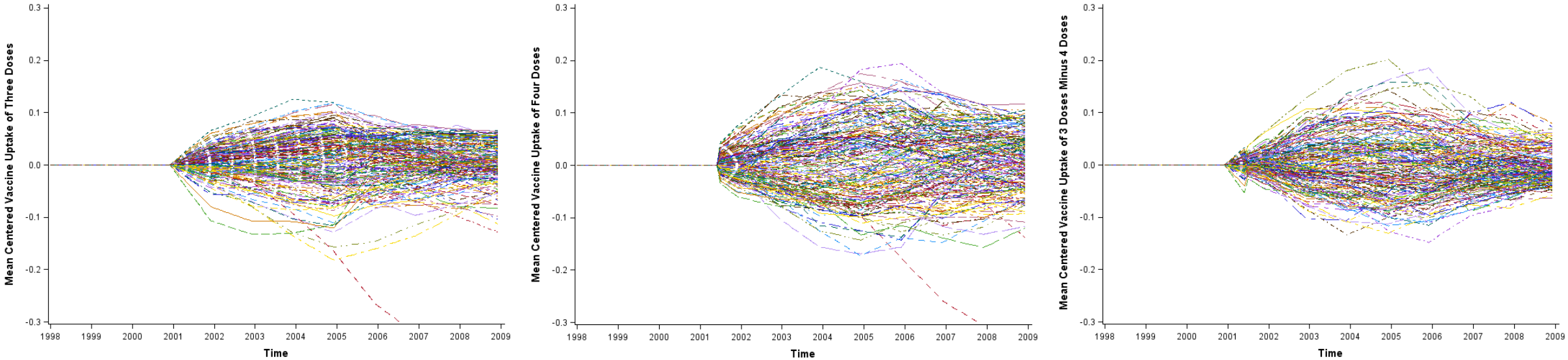
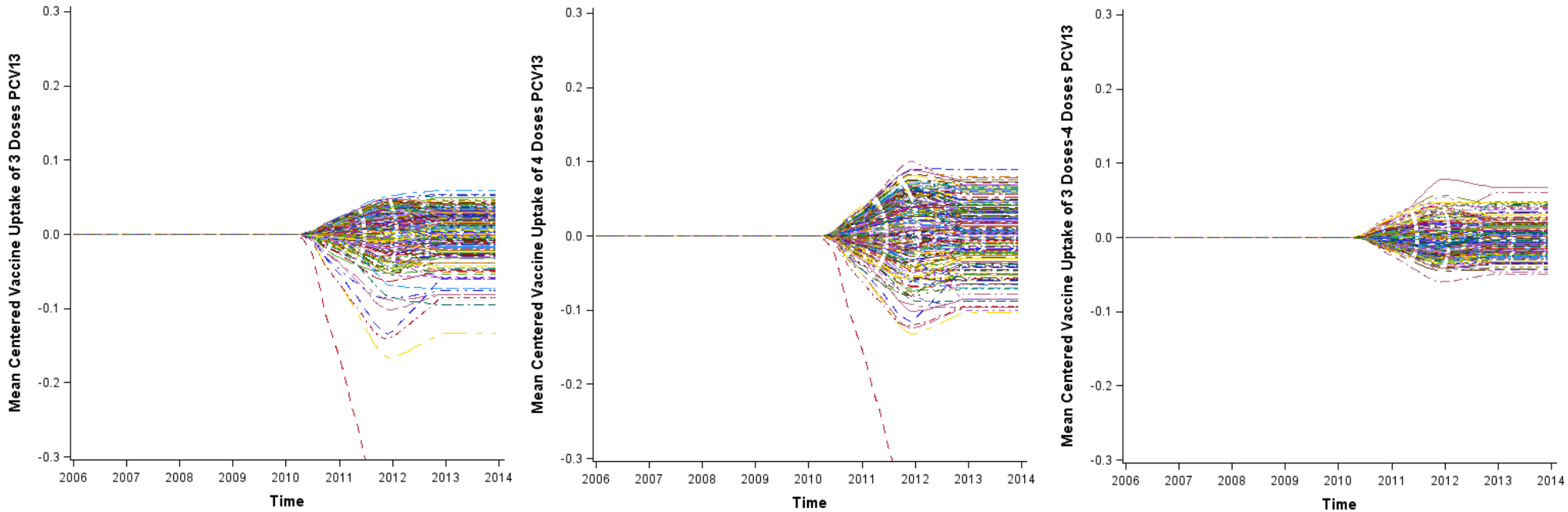

Mean Centered Vaccine Uptake of Three Doses
Mean Centered Vaccine Uptake of Four Doses
Mean Centered Vaccine Uptake of 3 Doses Minus 4 Doses
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
Time

Figure S2


Mean Centered Vaccine Uptake of 3 Doses PCV13
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
2006
2007
2008
2009
2010
2011
2012
2013
2014
Time
Mean Centered Vaccine Uptake of 4 Doses PCV13
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
2006
2007
2008
2009
2010
2011
2012
2013
2014
Time
Mean Centered Vaccine Uptake of 3 Doses-4 Doses PCV13
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
2006
2007
2008
2009
2010
2011
2012
2013
2014
Time