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Original Contribution

Association of Pneumococcal Conjugate Vaccine Coverage With Pneumococcal Meningitis: An Analysis of French Administrative Areas, 2001–2016

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Geographic variations of invasive pneumococcal disease incidence and serotype distributions were observed after pneumococcal conjugate vaccine introduction at regional levels and among French administrative areas. The variations could be related to regional vaccine coverage (VC) variations that might have direct consequences for vaccination-policy impact on invasive pneumococcal disease, particularly pneumococcal meningitis (PM) incidence. We assessed vaccine impact from 2001 to 2016 in France by estimating the contribution of regional VC differences to variations of annual local PM incidence. Using a mixed-effect Poisson model, we showed that, despite some variations of VC among administrative areas, vaccine impact on vaccine-serotype PM was homogeneously confirmed among administrative areas. Compared with the prevaccine era, the cumulative VC impact on vaccine serotypes led, in 2016, to PM reductions ranging among regions from 87% (25th percentile) to 91% (75th percentile) for 7-valent pneumococcal conjugate vaccine serotypes and from 58% to 63% for the 6 additional 13-valent pneumococcal conjugate vaccine serotypes. Nonvaccine-serotype PM increases from the prevaccine era ranged among areas from 98% to 127%. By taking into account the cumulative impact of growing VC and VC differences, our analyses confirmed high vaccine impact on vaccine-serotype PM case rates and suggest that VC variations cannot explain PM administrative area differences.

administrative area variations; Bayesian inference; mixed-effect Poisson model; National Health Insurance data; pneumococcal conjugate vaccine; pneumococcal meningitis; vaccine coverage

Abbreviations: CrI, credible interval; FNHI, French National Health Insurance; IPD, invasive pneumococcal disease; NRCP, National Reference Center for Pneumococci; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PM, pneumococcal meningitis; VC, vaccine coverage

Geographic variations in invasive pneumococcal disease (IPD) incidence and serotype distributions between Europe and the United States were observed before pneumococcal conjugate vaccine (PCV) introduction (1), with reported US IPD incidences being up to 8-fold higher than those in Europe (1, 2). Regional differences were also observed among and within European countries, with reported incidence per 100,000 children aged <2 years ranging from 11.3 cases in Italy to 93.5 cases in Spain (3–5). The introduction of the 7-valent (PCV7) and 13-valent (PCV13) vaccines, which protect against carriage and infection by 7 and 13 (7 + 6 additional) serotypes, respectively, showed consistent impact on vaccine-serotype diseases, which declined homogeneously in the target group (children aged <2 years). However, their impact was more heterogeneous on the rest of the population and nonvaccine-serotype IPDs, and serotype-replacement phenomena were more country-specific (6–11).

There are several reasons for these incidence and distribution diversities before PCV introduction and the persistence of some thereafter. The most cited explanation reflects health-care services and systems, particularly the selection of patients to undergo blood or cerebrospinal fluid cultures (2, 5, 12, 13). Notable differences in disease-surveillance systems among European countries were also observed (14). Other clinical

practices that might influence local IPD incidence are antibiotic prescriptions and hospital-admission criteria (2, 12). Geographic variations can also be attributed to a number of IPD risk factors, such as medical conditions, demographic factors and socioeconomic status, or meteorological, environmental, and terrain conditions, which contribute to the IPD burden in different ways, as well as according to age group (15–20).

Because of its severity, pneumococcal meningitis (PM) seems to be subject to less variability than are other IPDs, because cerebrospinal fluid and blood cultures are good medical practices when it is suspected (1, 2, 4, 5). Nevertheless, population coverage (i.e., % of vaccinated people) differences for vaccines, designed to target PM as a priority among all IPDs, could have a major impact on local PM incidence. Different prevalences of risk factors, such as environmental conditions, respiratory virus incidences, or antibiotic exposures, could also play roles (21–25).

We used mixed-effect Poisson models, quantifying the contribution of local vaccine coverage (VC), to examine the variability of annual PM incidences in regional administrative areas of metropolitan France from 2001 to 2016. We also assessed vaccine impact over the whole population and the 2 most exposed age groups, children aged <5 years and adults aged >64 years.

METHODS

Data sources

PM data. Annual PM data (2001–2016) were obtained from the French National Reference Center for Pneumococci (NRCP). Since 2001, the NRCP has received all *Streptococcus pneumoniae* strains isolated from cerebrospinal fluid (PM) collected through the Observatoires Régionaux du Pneumocoque, a network of about 400 laboratories present in all French regions (67% of public and private French laboratories, covering approximately 60% of the French population over the period considered). For each isolate, the date of infection, patient's age, administrative area location, and serotype were recorded. Although the NRCP database does not cover the entire French population, its surveillance system stably recorded PM cases (26, 27).

PCV data. In France, 2 PCVs were introduced through national vaccination campaigns during the study period; PCV7 was recommended in June 2003 and replaced in June 2010 by PCV13. Annual PCV data were obtained from the French National Health Insurance (FNHI). FNHI covers all medical care provided by outpatient and private-practice physicians and pharmacies (28). Reimbursement data on PCV doses provided by the 2 main FNHI agencies, which cover >90% of the French population, were used (28). Since 2006, an individual anonymized code for each recipient was added to reimbursement information allowing monitoring of individual drug and health-services consumption.

Population data and administrative area details. To take into account French population growth during the study period and the population-specific demographics of each regional administrative area, we extracted demographic data from the French National Institute of Statistics and Economic Studies (http://www.insee.fr, accessed July 4, 2017). Geographic levels considered herein refer to the 95 administrative areas in force, all in metropolitan France. PM data from the Alpes de Haute-Provence territory were not available in the NRCP database, and Corsica was withdrawn from the analyses because of the island's peculiarities in terms of epidemiology and surveillance-system reporting. Thus, 93 administrative areas were included in the analysis (Web Figure 1, available at https://academic.oup.com/aje). Each area was classified according to 4 population-density classes defined by distribution quartiles of all values: low, medium, high, or very high density.

VC estimation

Because individual anonymized codes were available only from 2006 onwards, the total number of PCV7 doses reimbursed per administrative area was computed from the vaccine's introduction and until 2005. The individual anonymized codes enabled the numbers of PCV7 and PCV13 doses for each individual and each administrative area from 2006 until 2016 to be computed. To estimate VC for children who were 12 months old during the year, we referred to the primary vaccination schedule used by the French public health agency and recommended by the French Ministry of Health (29, 30). For children born before 2008, 3 doses before 12 months were needed to be considered adequately immunized. For children born after 2008, the vaccine schedule required only 2 doses before 12 months. The VC estimate was then defined as the numbers of vaccinated children per area divided by the local, 12-month-old, juvenile population. Because no reimbursement-recipient code information was available for each reimbursement for the period 2003–2005, VC was estimated by dividing the aggregated local number of vaccine doses reimbursed by 3, and then dividing by the local number of juveniles 1–2 years old. Because this approach could slightly overestimate VC percentages, the ratio of the difference between the 2 methods for the year 2007 was applied to 2003 through 2005.

Statistical analyses

Descriptive statistics. Descriptive statistics for PM and VC were used first. Three different PM-serotype groups, according to vaccine composition, were defined: PCV7 (4, 6B, 9V, 14, 18C, 19F, 23F), the delta-6 of PCV13 (the serotypes in PCV13 other than those in PCV7: 1, 3, 5, 6A, 7F, 19A), and other non-vaccine serotypes. To take into account population-size differences and enable comparisons between administrative areas, PM numbers were divided by the local population and calculated per 100,000 inhabitants to obtain the incidence rate for each area. Even though the calculated incidence rates are not the real PM-incidence rates in France, because of the nonexhaustiveness of the NRCP database, the stability of this surveillance system's recording allows comparison of the calculated incidence rates among areas and years. The most exposed age groups were also considered: children aged <5 years and adults aged >64 years old. Summary statistics were computed for annual PM cases and VC for the studied populations.

Mixed-effect Poisson models. We investigated PM-incidence variability and the incremental vaccine impact derived by VC on the 3 different PM-serotype groups. Random effects were considered to take into account the geographical variability not explained by the chosen model variables. Three mixed-effect Poisson models were devised: model 1, including an intercept,

geographic and temporal random effects, and an offset term; model 2, adding the VC variables; and model 3, adding to model 2 a population-density variable with low-density class as the reference group. Finally, as sensitivity analysis, a zero-inflated Poisson model was fitted (model 4). For more details, please see Web Appendix 1 and Web Figure 2.

To improve interpretation, the exponentials of the regression-coefficient estimates were computed. The exponentials of the intercepts give, for model 1, the mean number of PM cases per 100,000 inhabitants (referred to as incidence rates hereafter) of each serotype group's PM cases throughout the study period and among all administrative areas; for model 2, because VC was null for the first 3 years of the study period, the mean incidence rate during the prevaccine era (2001–2003); and for model 3, the mean incidence rate during the prevaccine era in low-density areas. Exponentials of the other regression-coefficient estimates can be interpreted as the relative changes of the mean numbers of PM cases expected to occur for a 1-unit increase of the corresponding covariable (31); they are defined hereafter as relative risks. Thus, variables associated with PM reductions have relative risks <1, while those associated with PM increases have relative risks >1. Because a 1-unit (i.e., 1 percentage point) increase in VC impact on PM incidence is not very meaningful, VC results are discussed for a 10-unit (i.e., 10 percentage points) increase. Exponentials of the predictions for each random effect define the residuals or unexplained relative risks for each administrative area and each year compared with the estimated mean incidence rate.

A Bayesian approach was used to estimate model parameters (Web Appendix 1). Exponentials of the intercepts, relative risks, and their corresponding 95% credible intervals are reported. The final model was reproduced with data for the 2 most exposed age groups (aged <5 years and aged >64 years old).

RESULTS

Descriptive statistics

PM cases. Between January 2001 and December 2016, 5,859 PM cases were recorded in the NRCP database. Over the entire study period, the mean incidence rates for PCV7, delta-6, and nonvaccine serotypes, respectively, were 0.13 (standard deviation, 0.29), 0.13 (standard deviation, 0.23), and 0.28 (standard deviation, 0.36) (Table 1). Numerous administrative areas (32%) had 0 annual PM cases. PM cases among individuals aged <5 years and those aged >64 years represented almost half of the national PM cases observed during the study period (Web Table 1). Indeed, mean incidence rates were higher for these 2 most exposed groups—especially children (Web Tables 2 and 3). Maximum rates were 3-fold higher for the elderly and 8-fold higher for young children than for the total population. Administrative area distributions of children and elderly were mainly stable throughout the study period (Web Table 4).

Vaccine coverage. Since PCV introduction, mean coverage for 12-month-old children increased annually until reaching a plateau of approximately 80% in 2009 and a maximum of 85% in 2016 (Table 2). The standard deviation remained stable around 6% throughout the study. In 2016, VC exceeding the 75th percentile was strongly concentrated in northern and northeastern

Table 1. Annual Numbers of Pneumococcal Meningitis Cases per 100,000 Inhabitants in 93 French Administrative Areas, 2001–2016

Year	PCV7-Serotype PM Cases		Delta-6-Serotype PM Cases		Nonvaccine-Serotype PM Cases		Areas With 0 Cases	PM Cases Observed
	Mean (SD)	Maximum	Mean (SD)	Maximum	Mean (SD)	Maximum		
Full study period	0.13 (0.29)	2.69	0.13 (0.23)	2.60	0.28 (0.36)	3.96	483[a]	1,488
2001	0.23 (0.46)	2.23	0.07 (0.16)	0.89	0.13 (0.30)	1.82	62	93
2002	0.22 (0.36)	1.52	0.08 (0.19)	1.06	0.09 (0.22)	1.20	52	93
2003	0.27 (0.50)	2.53	0.12 (0.22)	1.06	0.12 (0.25)	1.41	51	93
2004	0.19 (0.32)	1.41	0.07 (0.17)	0.87	0.14 (0.24)	1.14	46	93
2005	0.21 (0.43)	2.69	0.13 (0.24)	1.20	0.19 (0.34)	1.44	54	93
2006	0.18 (0.39)	2.63	0.11 (0.24)	1.30	0.15 (0.29)	1.56	47	93
2007	0.21 (0.25)	1.63	0.29 (0.42)	2.60	0.27 (0.30)	1.51	10	93
2008	0.10 (0.16)	0.72	0.17 (0.22)	1.18	0.26 (0.26)	1.33	22	93
2009	0.08 (0.12)	0.55	0.26 (0.26)	1.46	0.35 (0.30)	1.40	12	93
2010	0.06 (0.14)	0.81	0.19 (0.23)	1.30	0.33 (0.31)	1.30	16	93
2011	0.06 (0.12)	0.68	0.17 (0.19)	0.70	0.46 (0.37)	1.68	8	93
2012	0.05 (0.11)	0.69	0.13 (0.21)	1.30	0.33 (0.36)	1.97	18	93
2013	0.06 (0.14)	0.83	0.08 (0.13)	0.69	0.42 (0.34)	1.44	16	93
2014	0.03 (0.10)	0.83	0.06 (0.12)	0.62	0.32 (0.46)	3.57	25	93
2015	0.04 (0.13)	0.83	0.05 (0.10)	0.44	0.32 (0.33)	1.57	25	93
2016	0.04 (0.10)	0.69	0.07 (0.14)	0.74	0.50 (0.56)	3.96	19	93

Abbreviations: delta-6, the 6 serotypes added to PCV7 to obtain PCV13; PCV7, 7-valent pneumococcal conjugant vaccine; PM, pneumococcal meningitis; SD, standard deviation.

[a] Value for summed annual number of administrative areas with zero cases over the study period.

Table 2. Mean Coverage Rates for Pneumococcal Conjugate Vaccine Among 12-Month-Old Children, Estimated From the Number of Doses Reimbursed by French National Health Insurance in 93 French Administrative Areas, 2001–2016

Year	Vaccine Coverage, %		
	Mean (SD)	Minimum	Maximum
2004	13 (5)	3	23
2005	24 (6)	9	37
2006	29 (6)	16	42
2007	39 (6)	21	50
2008	48 (6)	27	60
2009	79 (8)	54	99
2010	74 (6)	54	87
2011	72 (6)	53	83
2012	72 (6)	54	82
2013	74 (6)	54	84
2014	79 (6)	62	89
2015	80 (6)	64	90
2016	85 (6)	66	97

Abbreviation: SD, standard deviation.

France, while coverage below the 25th percentile was mostly in the south, with some exceptions for Parisian and northwestern regional areas (Figure 1).

Mixed-effect model

Entire population. For the whole study period, model 1's mean incidence-rate estimate was higher for nonvaccine serotypes than for the PCV7- and delta-6-serotype groups (Table 3). Incidence rates varied more as a function of geography than they did by year. After adding VC variables (model 2), incidence rates for the prevaccine era were highest for PCV7-serotype PM (Table 3). An association of PCV7 coverage with all 3 serotype groups was confirmed. A mean 10-unit (10-percentage-point) PCV7-coverage increase was associated with a 6.1% (95% credible interval (CrI): 5.11, 7.20) decrease of PCV7-serotype PM incidence, compared with the previous year, and with 3.4% (95% CrI: 2.23, 4.55) and 3.1% (95% CrI: 1.94, 4.01) increases in delta-6-serotype PM and nonvaccine-serotype PM, respectively. In contrast, PCV13 coverage was associated only with delta-6- and PCV7-serotype PM. A mean 10-unit PCV13-coverage increase was associated with a decrease, compared with the previous year, in PCV7- and delta-6-serotype PM by 1.4% (95% CrI: 0.69, 2.14) and 3.2% (95% CrI: 2.44, 3.90), respectively (computed from values in Table 3).

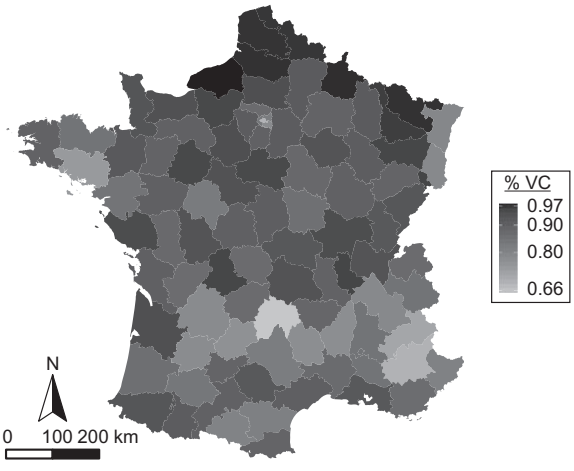

Figure 1. Pneumococcal vaccine coverage (VC) in all administrative areas in metropolitan France in 2016. Calculated as the ratio of the estimated number of 12-month-old children vaccinated divided by the number of 12-month-old children alive at the beginning of the year.

Figure 2 shows local percentage variations of PM case numbers, compared with the prevaccine era, associated with the cumulative VCs for the years 2009 and 2016. The extent among administrative areas of median (25th, 75th percentile) local PM reduction were of 76% (72%, 79%) in 2009 and 89% (87%, 91%) in 2016 for PCV7 serotypes; delta-6-serotype PM cases increased 123% (107%, 140%) in 2009 but declined by 61% (58%, 63%) in 2016, while nonvaccine-serotype PM cases increased 104% (92%, 119%) in 2009 and 112% (98%, 127%) in 2016.

Including VC in model 2 did not affect geographic random-variance estimates, unlike temporal variance, which declined drastically (Web Figure 3 vs. Figure 3 and Table 3). All 3 serotype groups shared a striking cluster of 3 administrative areas in western France (Maine-et-Loire, Vienne, and Indre-et-Loire), which stand out from the other areas because of their elevated relative risks.

The inclusion of a population-density variable in model 3 led to similar estimates of PCV7 and PCV13 coefficients, as well as geographic and temporal random-effect variances (Table 3 and Web Figure 4). Low-density (reference value) areas had lower PM incidence rates compared with the others.

Children aged <5 years and adults aged <64 years. As expected, mean model 3 incidence-rate estimates were higher for both young children and the elderly, as well as for all 3 PM-serotype groups (Web Table 5). VC-impact results were confirmed for the most exposed age groups. For children, VC-associated relative risks were higher than those estimated for the entire population. For the elderly, VC-associated relative risks were similar to those obtained for the whole population. The estimated relative risks for the geographic random effects changed for some administrative areas in these population subgroups; several areas' relative risks fell to approximately 1 and a few changed direction to slightly over or under the threshold of 1 (Web Figures 5 and 6). Geographic random-effect variances of both exposed subgroups were slightly higher for PCV7-serotype PM cases and remained about the same for the 2 other serotype groups. Temporal random-effect variances remained small for both populations.

Sensitivity analysis

As shown in Table 3, model 4 results were quite similar to the others, but the deviance information criterion was higher than for model 3 (12,177.8 for model 4; 11,052.0 for model 3),

Table 3. Exponentials of Estimated Parameters From the Different Models, 93 French Administrative Areas, 2001–2016

	Model[a]											
	1			2			3			4 (Poisson Only)		
	Value	95% CrI	Variance	Value	95% CrI	Variance	Value	95% CrI	Variance	Value	95% CrI	Variance
Fixed Effect												
Intercept												
PCV7	0.058	0.034, 0.097		0.167	0.127, 0.219		0.118	0.088, 0.158		0.178	0.129, 0.238	
Delta-6	0.100	0.074, 0.133		0.093	0.075, 0.115		0.064	0.049, 0.084		0.101	0.077, 0.132	
Nonvaccine	0.230	0.181, 0.294		0.148	0.123, 0.180		0.104	0.080, 0.135		0.157	0.124, 0.202	
VC for PCV7 serotypes												
PCV7				0.994	0.992, 0.995		0.994	0.993, 0.995		0.993	0.992, 0.994	
Delta-6				1.003	1.002, 1.004		1.003	1.002, 1.004		1.002	1.001, 1.003	
Nonvaccine				1.003	1.001, 1.004		1.003	1.002, 1.004		1.001	1.000, 1.002	
VC for PCV13 serotypes												
PCV7				0.999	0.998, 0.999		0.999	0.998, 0.999		0.998	0.998, 0.999	
Delta-6				0.997	0.996, 0.998		0.997	0.996, 0.997		0.997	0.996, 0.997	
Nonvaccine				1.000	0.999, 1.001		1.000	0.999, 1.001		1.000	0.999, 1.001	
Population density												
Low							1			1		
Medium							1.462	1.159, 1.864		1.465	1.160, 1.844	
High							1.723	1.349, 2.226		1.686	1.317, 2.154	
Very high							1.725	1.349, 2.226		1.671	1.319, 2.115	
Random Effect												
Geographic (μ)												
PCV7			1.053			1.064			0.963			0.682
Delta-6			0.377			0.362			0.339			0.270
Nonvaccine			0.283			0.278			0.290			0.241
Temporal (δ)												
PCV7			0.844			0.012			0.011			0.015
Delta6			0.238			0.025			0.025			0.017
Nonvaccine			0.173			0.021			0.022			0.019
Goodness of fit (DIC)		11,058.2			11,065.3			11,052.0			12,177.8	

Abbreviations: CrI, credible interval; delta-6, the 6 serotypes added to PCV7 to obtain PCV13; DIC, deviance information criterion; PCV7, 7-valent pneumococcal conjugant vaccine; PCV13, 13-valent pneumococcal conjugant vaccine; VC, vaccine coverage.

[a] Model 1, empty model; model 2, vaccine-coverage model; model 3, covariate model; model 4, zero-inflated Poisson model.

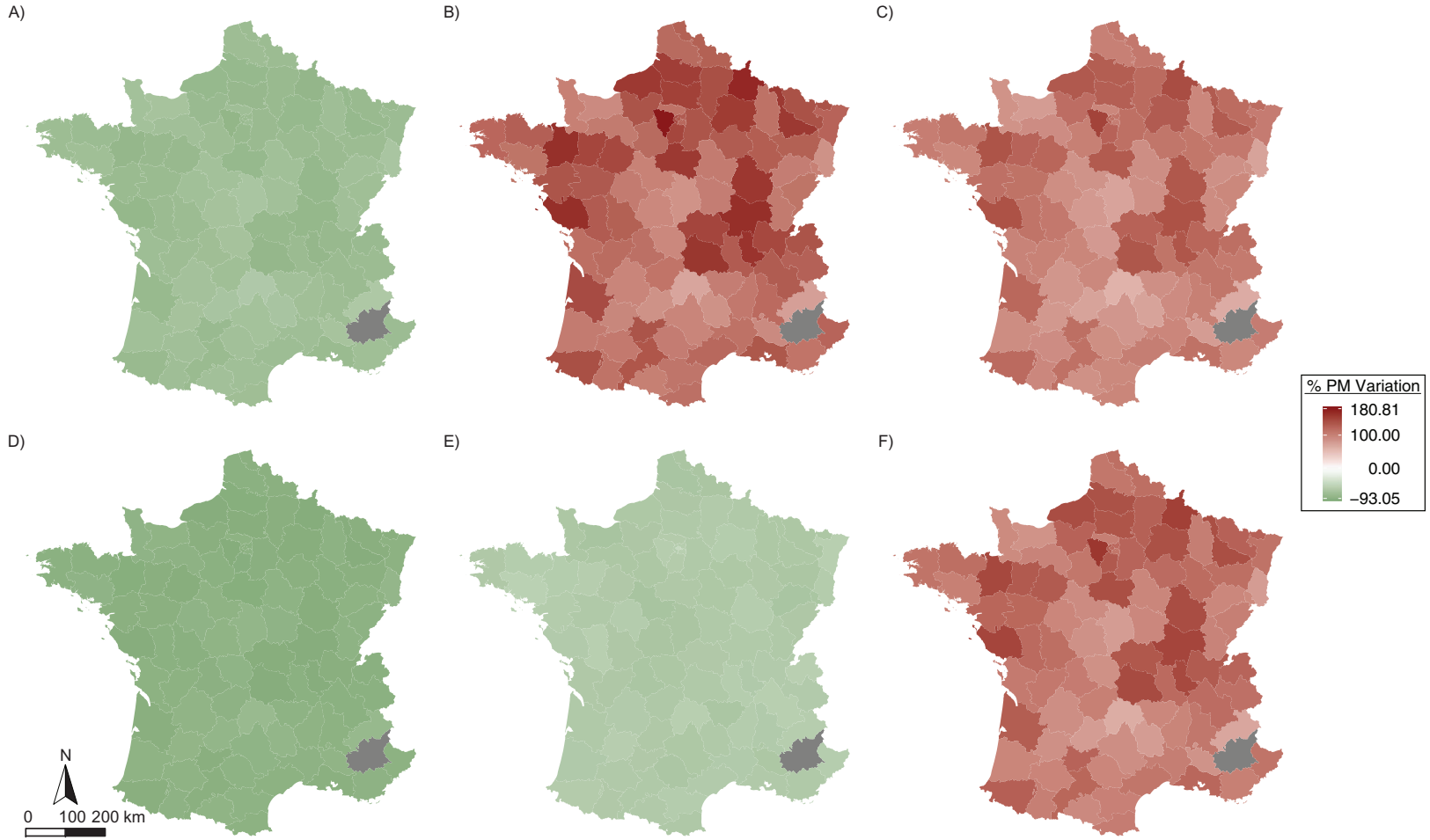

Figure 2. Cumulative impact of vaccine coverage on pneumococcal meningitis cases (PMs) for each French administrative area, 2009 and 2016. A) 7-valent pneumococcal vaccine serotypes in 2009; B) delta-6 serotypes in 2009; C) nonvaccine serotypes in 2009; D) 7-valent pneumococcal vaccine serotypes in 2016; E) delta-6 serotypes in 2016; F) nonvaccine serotypes in 2016. The cumulative impact of 7-valent pneumococcal vaccine and 13-valent pneumococcal vaccine coverages on PM incidence rates was obtained for the exponentials of model 2–estimated values of the term $z_{i,16,d}$. The only missing administrative area is shown in gray. Delta-6 refers to the 6 serotypes added to 7-valent pneumococcal vaccine to obtain 13-valent pneumococcal vaccine.

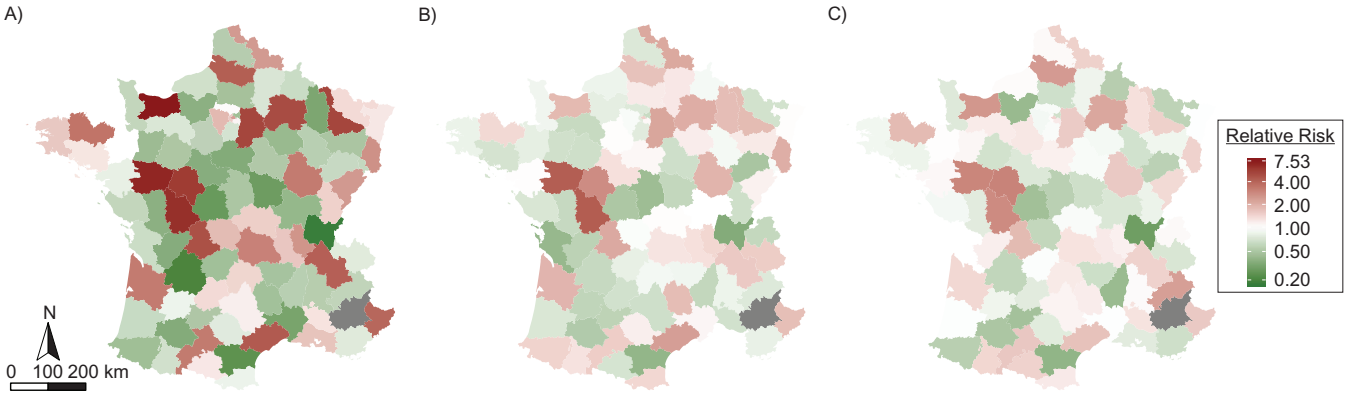

Figure 3. Relative risks obtained from model 2–predicted random effects for 93 French administrative areas, 2001–2016. A) 7-valent pneumococcal vaccine serotypes; B) delta-6 serotypes; C) nonvaccine serotypes. Values are the exponentials of the means of the marginal posterior distribution of the geographic random effects $\mu_{i,d}$. The only missing administrative area is shown in gray. Delta-6 refers to the 6 serotypes added to 7-valent pneumococcal vaccine to obtain 13-valent pneumococcal vaccine.

suggesting lower model parsimony. Web Figures 7 and 8 also show similar estimates compared with the Poisson models. These results confirmed our first findings and led to the conclusion that Poisson models are well-adapted to our data set.

DISCUSSION

Our study was undertaken to investigate variability of the numbers of PM cases among French administrative areas by exploring and quantifying the association with VC variation as the main potential factor. We provide modeling results supporting direct VC impact on vaccine-serotype PM and indirect impact on nonvaccine-serotype PM as well as estimates of its impact extent. In previous studies, PM case variation observed across France coincided with PCV7 and PCV13 introductions (26, 27, 32, 33), showing fewer vaccine-serotype PM cases after vaccine implementation, countered by increased nonvaccine-serotype PM cases, a phenomenon known as "serotype replacement." However, a statistical association between PCV coverage and PM incidence-rate evolution has, to our knowledge, not yet been observed.

FNHI reimbursement data enabled VC estimation for each French administrative area throughout the study period. Hence, we could evaluate the statistical relationship between VC and PM cases, and thus estimate the PM variation magnitude corresponding in our data to VC extent. Our findings confirmed vaccine impact on vaccine-serotype PM.

Partial serotype-replacement phenomena, described in other studies as following PCV7 introduction (27, 32), was also found. Nevertheless, nonvaccine-serotype PM increases associated with PCV13 coverage were not found. Vaccine impact on PCV7- and delta-6-serotype PM resulting from VC was more variable among areas at the end of the PCV7-vaccination period (2009) than in 2016, when variations were smoothed by herd immunity benefits accumulated during all of the vaccination periods. Estimation of the extent of VC-attributed serotype-replacement phenomena showed a broader range of values among administrative areas, suggesting more variability than direct vaccine impacts; therefore, nonvaccine-serotype PM increases in some areas could not be linked automatically to the magnitude of the gap created by fewer vaccine-serotype PM cases, but rather to other possible factors.

Population density was found to be associated with local PM cases, with the low-density area class being protective compared with higher population-density classes.

Including geographic and temporal random effects in the models enabled exploration of the respective contribution of each dimension to local PM variability. Administrative-area clustering variation was higher than that of temporal clustering in our data. While variances of yearly random effects declined with the introduction of VC in model 2, variances of geographic random-effect and local relative risks remained about the same, suggesting that VC contributed to the differences in the numbers of PM cases from one year to another but PM-case number variations among administrative areas were not driven by VC differences. That result highlights that other factors might be at work in PM-case number variations among French administrative areas. A cluster of 3 western areas stood out because of their elevated adjusted relative risks, and this result makes us wonder about possible higher exposure due to presence of some other unexplored factors shared by those 3 areas.

Results concerning vaccine impact were also confirmed for children aged <5 years and adults aged >64 years, the 2 most exposed age groups. PM incidence rates for those 2 subgroups were higher than for the entire population, so differences in regional age structure might contribute to geographic variation. However, these 2 age classes are homogeneously represented in all administrative areas, and the ranges of their adjusted relative risks estimated from the geographic random effects did not change.

Although the high number of areas with no PM cases in our data set could justify the use of a zero-inflated Poisson model, our sensitivity analysis results supported our findings and the choice of Poisson models. Due to the annual temporal scale chosen for our analysis, our model does not allow the impact of covariables following a seasonal pattern to be studied. As a consequence, we did not investigate other potentially relevant factors that could contribute to PM incidence rates, as indicated in

the literature, such as "flu-like" syndrome incidence (34, 35), antibiotic consumption (36), and meteorological factors (19, 20, 37–39).

A possible limitation of our study is that our VC estimates based on reimbursement data were not exhaustive, because those data do not include vaccinations performed in local maternal and childhood health protection (PMI) services, which dispense free vaccinations (not recorded in FNHI reimbursements, thereby explaining their exclusion). Vaccine sales in the public sector, estimated to account for only approximately 4.5% of total sales in 2009 (40), could explain minor VC differences among areas, more specifically those in the Parisian area, where recourse to PMI care is particularly high (41). Furthermore, this is an ecological study that, due to the absence of an individual-level analysis of the link between vaccination status and disease occurrence, could only suggest an association and not causation between VC and PM evolutions.

The present study is, to our knowledge, the first to relate data for vaccine-dose reimbursements and data for PM incidences in France. Our analysis supports PCV impact on PM and gives an estimation of the extent of the vaccine-serotype PM-case increases and serotype replacements for nonvaccine-serotype PM cases associated with local VC extent. Our model, which can easily be transposed to a multilevel-model framework or used with a finer temporal scale, adequately described a cumulative impact of increasing VC and enabled examination of the roles of other factors potentially impacting the disease of interest. Our study focused only on PM because the vaccine effect is higher for this disease and because of the availability of good-quality data with serotype information. Indeed, wherever disease-surveillance systems provide data allowing it, the same analysis could be reproduced for IPD, and a more extensive list of risk factors could be studied.

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REFERENCES

1. Hausdorff WP. Invasive pneumococcal disease in children: geographic and temporal variations in incidence and serotype distribution. *Eur J Pediatr*. 2002;161(suppl 2):S135–S139.
2. Hausdorff W, Siber G, Paradiso PR. Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children. *Lancet*. 2001;357(9260):950–952.
3. Cartwright K. Pneumococcal disease in Western Europe: burden of disease, antibiotic resistance and management. *Eur J Pediatr*. 2002;161(4):188–195.
4. Jefferson T, Ferroni E, Curtale F, et al. *Streptococcus pneumoniae* in Western Europe: serotype distribution and incidence in children less than 2 years old. *Lancet Infect Dis*. 2006;6(7):405–410.
5. Klemets P, Lyytikäinen O, Ruutu P, et al. Trends and geographical variation in invasive pneumococcal infections in Finland. *Scand J Infect Dis*. 2008;40(8):621–628.
6. Feikin DR, Kagucia EW, Loo JD, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. *PLoS Med*. 2013;10(9):e1001517.
7. Rosen JB, Thomas AR, Lexau CA, et al. Geographic variation in invasive pneumococcal disease following pneumococcal conjugate vaccine introduction in the United States. *Clin Infect Dis*. 2011;53(2):137–143.
8. Hausdorff WP, Black S. What is the heterogeneity in the impact seen with pneumococcal conjugate vaccines telling us? *Vaccine*. 2017;35(31):3797–3800.
9. Shiri T, Datta S, Madan J, et al. Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5(1):e51–e59.
10. Davis SM, Deloria-Knoll M, Kassa HT, et al. Impact of pneumococcal conjugate vaccines on nasopharyngeal carriage and invasive disease among unvaccinated people: review of evidence on indirect effects. *Vaccine*. 2013;32(1):133–145.
11. Hanquet G, Kissling E, Fenoll A, et al. Pneumococcal serotypes in children in 4 European countries. *Emerg Infect Dis*. 2010;16(9):1428–1439.
12. Ihekweazu CA, Dance DAB, Pebody R, et al. Trends in incidence of pneumococcal disease before introduction of conjugate vaccine: South West England, 1996–2005. *Epidemiol Infect*. 2008;136(8):1096–1102.
13. Schønheyder H, Sørensen H, Kristensen B, et al. Reasons for increase in pneumococcal bacteraemia. *Lancet*. 1997; 349(9064):1554.

14. Pebody RG, Hellenbrand W, D'Ancona F, et al. Pneumococcal disease surveillance in Europe. *Euro Surveill* 2006;11(9): 171–178.
15. Takala AK, Jero J, Kela E, et al. Risk factors for primary invasive pneumococcal disease among children in Finland. *JAMA*. 1995;273(11):859–864.
16. Levine OS, Farley M, Harrison LH, et al. Risk factors for invasive pneumococcal disease in children: a population-based case-control study in North America. *Pediatrics*. 1999;103(3): E28.
17. Watson M, Gilmour R, Menzies R, et al. The association of respiratory viruses, temperature, and other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia. *Clin Infect Dis*. 2006;42(2):211–215.
18. Lynch J, Zhanel G. *Streptococcus pneumoniae*: epidemiology, risk factors, and strategies for prevention. *Semin Respir Crit Care Med*. 2009;30(2):189–209.
19. Murdoch DR, Jennings LC. Association of respiratory virus activity and environmental factors with the incidence of invasive pneumococcal disease. *J Infect*. 2009;58(1):37–46.
20. White AN, Ng V, Spain CV, et al. Let the sun shine in: effects of ultraviolet radiation on invasive pneumococcal disease risk in Philadelphia, Pennsylvania. *BMC Infect Dis*. 2009;9(1):196.
21. Cohen R, Varon E, Béchet S, et al. Comparative impact of pneumococcal conjugate vaccines on pneumococcal meningitis according to underlying conditions. *Vaccine*. 2016; 34(41):4850–4856.
22. Weisfelt M, de Gans J, van der Ende A, et al. Community-acquired bacterial meningitis in alcoholic patients. *PLoS One*. 2010;5(2):e9102.
23. Lundbo LF, Benfield T. Risk factors for community-acquired bacterial meningitis. *Infect Dis (Lond)*. 2017;49(6):433–444.
24. Adriani KS, Brouwer MC, van de Beek D. Risk factors for community-acquired bacterial meningitis in adults. *Neth J Med*. 2015;73(2):53–60.
25. Hénaff F, Levy C, Cohen R, et al. Risk factors in children older than 5 years with pneumococcal meningitis: data from a national network. *Pediatr Infect Dis J*. 2017;36(5):457–461.
26. Lepoutre A, Varon E, Georges S, et al. Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001–2012. *Vaccine*. 2015;33(2):359–366.
27. Alari A, Chaussade H, Domenech de Cellès M, et al. Impact of pneumococcal conjugate vaccines on pneumococcal meningitis cases in France between 2001 and 2014: a time series analysis. *BMC Med*. 2016;14(1):211.
28. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: from the Système National d'Information Interrégimes de l'Assurance Maladie (SNIIRAM) to the Système National des Données de Santé (SNDS) in France. *Rev Epidemiol Sante Publique*. 2017; 65:S149–S167.
29. Institut de Veille Sanitaire. Estimation of vaccination coverage in the private sector through the "échantillon généraliste des bénéficiaires" in France, 2004–2009 [In French]. http://invs.santepubliquefrance.fr/publications/2010/couverture_vaccinale_egb/rapport_couverture_vaccinale_EGB.pdf. Published August 17, 2010. Accessed March 1, 2019.
30. Institut de Veille Sanitaire. Déterminants socio-économiques des vaccinations BCG et pneumocoque chez les enfants de la région parisienne [In French]. http://invs.santepubliquefrance.fr/Publications-et-outils/Rapports-et-syntheses/Maladies-infectieuses/2013/Determinants-socio-economiques-des-vaccinations-BCG-et-pneumocoque-chez-les-enfants-de-la-region-parisienne. Published May 3, 2013. Accessed March 1, 2019.
31. Austin PC, Stryhn H, Leckie G, et al. Measures of clustering and heterogeneity in multilevel Poisson regression analyses of rates/count data. *Stat Med*. 2018;37(4):572–589.
32. Lepoutre A, Varon E, Georges S, et al. Impact of infant pneumococcal vaccination on invasive pneumococcal diseases in France, 2001–2006. *Euro Surveill*. 2008;13(35). pii: 18962.
33. Levy C, Varon E, Picard C, et al. Trends of pneumococcal meningitis in children after introduction of the 13-valent pneumococcal conjugate vaccine in France. *Pediatr Infect Dis J*. 2014;33(12):1216–1221.
34. Opatowski L, Varon E, Dupont C, et al. Assessing pneumococcal meningitis association with viral respiratory infections and antibiotics: insights from statistical and mathematical models. *Proc Biol Sci*. 2013;280(1764):20130519.
35. McCullers JA, McAuley JL, Browall S, et al. Influenza enhances susceptibility to natural acquisition of and disease due to *Streptococcus pneumoniae* in ferrets. *J Infect Dis*. 2010; 202(8):1287–1295.
36. Domenech de Cellès M, Pons-Salort M, Varon E, et al. Interaction of vaccination and reduction of antibiotic use drives unexpected increase of pneumococcal meningitis. *Sci Rep*. 2015;5:11293.
37. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. *Clin Infect Dis*. 1996;22(1):100–106.
38. Jusot JF, Neill DR, Waters EM, et al. Airborne dust and high temperatures are risk factors for invasive bacterial disease. *J Allergy Clin Immunol*. 2017;139(3):977–986.e2.
39. Ciruela P, Broner S, Izquierdo C, et al. Invasive pneumococcal disease rates linked to meteorological factors and respiratory virus circulation (Catalonia, 2006–2012). *BMC Public Health*. 2016;16(1):400.
40. Institut de Veille Sanitaire. Mesure de la couverture vaccinale en France: sources et données actuelles [In French]. http://invs.santepubliquefrance.fr/Publications-et-outils/Rapports-et-syntheses/Maladies-infectieuses/2012/Mesure-de-la-couverture-vaccinale-en-France. Published November 20, 2012. Accessed March 1, 2019.
41. Direction de la Recherche, des Études, de l'Évaluation et des Statistiques 2015. Les services de PMI: plus de 5000 sites de consultations en 2012 [In French]. https://drees.solidarites-sante.gouv.fr/IMG/pdf/er913.pdf. Published April, 2015. Accessed March 1, 2019.