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Vaccine-preventable Pediatric Acute Bacterial Meningitis in France

A Time Series Analysis of a 19-Year Prospective National Surveillance Network

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Accepted for publication September 8, 2023

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This work was supported by an unrestricted grant from Pfizer and from ACTIV.

A.R. reports personal fees from MSD outside the submitted work and nonfinancial support from Pfizer and AstraZeneca. N.O. reported receiving grants from Pfizer to his institution during the conduct of the study and travel grants from Pfizer, Sanofi, and GlaxoSmithKline outside the submitted work. E.V. reports grants from a French public health agency, during the conduct of the study, grants from Pfizer and from MSD, outside the submitted work. M.K.T. performs contract work for the Institut Pasteur funded by GSK, Pfizer and Sanofi Pasteur. M.K.T. has a patent NZ630133A Patent with GSK "Vaccines for serogroup X meningococcus" issued. F.A. reports receiving personal fees from MSD, Sanofi, and AstraZeneca outside the submitted work. R.C. reported receiving personal fees from Sanofi, Pfizer, MSD, and GSK; travel grants from Pfizer and MSD, and grants from Sanofi, Pfizer, MSD, and GSK outside the submitted work. C.L. reported receiving grants from Pfizer during the conduct of the study, personal fees from Pfizer and MSD, and nonfinancial support from Pfizer outside the submitted work. The other authors have no conflicts of interest to disclose.

Original idea, concept and design: A.R., R.C. and C.L. Data acquisition and curation: N.O., E.V., M.K.T., S.Bo. and S.Bé. Statistical analysis: A.R., N.O. and S.Bé. First draft of the article: A.R. Critical revision of the article for important intellectual content: N.O., E.V., M.K.T., S.Bo., S.Bé., F.A., R.C. and C.L. Supervision: R.C. and C.L.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

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ISSN: 0891-3668/24/431-7483
DOI: 10.1097/INF.0000000000004134

Background: In France, vaccination has been implemented against Hi serotype b (Hib), *pneumococcus* with pneumococcal conjugate vaccines (PCV), and *Neisseria meningitidis* serogroup C (MenC). These interventions with different coverage and uptake have disrupted the epidemiology of vaccine-preventable acute bacterial meningitis (ABM).

Methods: We analyzed data from a French prospective surveillance network of ABM in children ≤15 years old enrolled by 259 pediatric wards (estimated national coverage: 61%). From 2001 to 2020, the effect of vaccine implementation was estimated with segmented linear regression.

Results: We analyzed 7,186 cases, mainly due to meningococcus (35.0%), pneumococcus (29.8%), and Hi (3.7%). MenC ABM incidence decreased (−0.12%/month, 95% CI: −0.17 to −0.07, $P < 0.001$) with no change for the overall meningococcal ABM when comparing the pre-MenC vaccination and the post-MenC vaccination trends. Despite a decreasing MenB ABM incidence without a vaccination program (−0.43%/month, 95% CI: −0.53 to −0.34, $P < 0.001$), 68.3% of meningococcal ABM involved MenB. No change in pneumococcal ABM incidence was observed after the PCV7 recommendation. By contrast, this incidence significantly decreased after the switch to PCV13 (−0.9%/month, 95% CI: −1.6 to −0.2%, $P = 0.01$). After May 2014, a rebound occurred (0.5%/month, 95% CI: 0.3–0.8%, $P < 0.001$), with 89.5% of non-PCV13 vaccine serotypes. Hib ABM incidence increased after June 2017.

Conclusions: PCV7 and MenC vaccine introduction in France, with slow vaccine uptake and low coverage, had no to little impact as compared to the switch from PCV7 to PCV13, which occurred when coverage was optimal. Our data suggest that MenB and next-generation PCVs could prevent a large part of the ABM incidence in France.

Key Words: acute bacterial meningitis, vaccine implementation, time series analysis, nonpharmaceutical interventions, epidemiology

(*Pediatr Infect Dis J* 2024;43:74–83)

Acute bacterial meningitis (ABM) is a major cause of mortality worldwide, with an estimated 134,000 deaths in children ≤15 years in 2019.[1] Despite advances in medical and critical care, a high proportion of survivors present long-term sequelae.[2]

During the last 3 decades, several vaccines have been implemented to prevent the burden of ABM. In France, vaccination has been implemented against Hi serotype b (Hib), *Streptococcus pneumoniae* with pneumococcal conjugate vaccines (PCV) and *Neisseria meningitidis* serogroup C (MenC).[3–5] Despite undeniable progress, *N. meningitidis* and *S. pneumoniae* remained the most common pathogens involved in pediatric ABM.[6]

Recently, several nonpharmaceutical interventions (NPIs) were implemented against COVID-19.[7] These interventions, although not intended to decrease non-COVID-19 infections, led to a major decrease in several bacterial infections.[8–10]

Despite these interventions, pediatric ABM remains a major global health issue.[1] Using a unique long-standing population-based prospective surveillance (19 years) of clinical and microbiological ABM in French children, we aimed to describe the epidemiology of vaccine-preventable ABM and the effect of vaccinations and NPIs on their incidence.

MATERIAL AND METHODS

Study Design

We performed a quasi-experimental interrupted time series analysis using a long-standing population-based prospective surveillance of pediatric ABM. This surveillance network was approved by the Créteil Hospital Ethics Committee and the French National Data Protection Commission (no. 913006). The study was registered at ClinicalTrials.gov (NCT04664569).

Study Data and Settings

From January 2001 to December 2020, 259 pediatric wards and 168 microbiology laboratories (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/F272) prospectively enrolled all reported cases of ABM in children ≤15 years throughout France. The methodology was previously described.[11] Briefly, a standardized form was completed for each case and transmitted to the investigating center after patient discharge. The form covered data on date of birth, sex, underlying conditions (meningeal breach, recurrent meningitis, cochlear implant, asplenia, immunodeficiency or cardiopathy), vaccination status and short-term outcome. In a capture–recapture study, the coverage of this surveillance network was estimated at 61% [95% confidence interval (CI): 58–65] of the French hospitals.[12]

Outcomes

The main outcome was the estimated monthly ABM incidence due to meningococcus, pneumococcus, and Hi per 100,000 children ≤15 years over time. The incidence per 100,000 children was estimated by using the estimated study coverage and the annual age-specific population (https://www.insee.fr/). Secondary outcomes were (1) the serotype distribution among pneumococcal ABM, (2) the serogroup distribution among meningococcal and Hi ABM and (3) the monthly pathogen-specific case fatality rate (CFR). We used ABM incidence due to group B *Streptococcus* (GBS) as a control outcome, as neither vaccination nor NPI are expected to influence this pathogen.

Definitions

ABM was defined by at least one criterion among (1) positive culture of cerebrospinal fluid (CSF), (2) presence of soluble antigens in CSF, (3) positive polymerase chain reaction (PCR) results for CSF, (4) pleocytosis in CSF (≥10 cells/μL) associated with either a positive blood culture and/or PCR of a biopsy of a skin lesion consistent with meningitis. Bacterial isolate identification was performed in local microbiology centers. Pneumococcal serotyping was performed by the National Reference Center for Pneumococci by latex agglutination as previously described.[10] Similarly, meningococcal grouping and Hi serotyping (since 2017) were performed by the National Reference Center for Meningococci and Hi by PCR and/or latex agglutination.[13,14]

National Interventions in France

Neisseria meningitidis

Since June 2009, 1 dose of MenC vaccine has been recommended for children 12 months old, with a catch-up program for people ≤24 years.[3] Since April 2017, a dose of MenC vaccine has been recommended for children 5 months of age. At the end of 2016, vaccine coverage was 70.0% for children 24 months but only 34.8% for those 10–14 years and 25.1% for adolescents 15–19 years of age.[15] During the study period, meningococcal B conjugated vaccine (MenB) was recommended only for at-risk groups and for outbreak control. Moreover, regional or local vaccination campaigns (against MenC and MenB) took place during this period. To our knowledge, there is no available data on MenB vaccine coverage between its approval (January 2013) and the end of the study (December 2020), particularly it was not monitored by the French public health agency before 2022.[16] A survey in November 2019 suggested that MenB vaccine coverage was extremely low, particularly in older children: vaccine was proposed by only 30% of general practitioners, and among them, only 38% for teenagers, compared with 56% for children 6 months to 1-year old.[17]

Streptococcus Pneumoniae

In January 2003, PCV7 was recommended as a targeted vaccination for children younger than 2 years who were at risk in France, with a complex definition, which led to slow vaccine uptake.[4,18] Indeed, 1 year later, only 56% of children younger than 1 year had received at least 1 PCV7 dose.[4] In June 2006, PCV7 was recommended for all children, which led to higher vaccine coverage.[4] In 2009, PCV7 was recommended with a 2+1 doses schedule instead of a 3+1 doses schedule before. In June 2010, PCV7 was replaced with PCV13.[4,18] The change occurred without a catch-up program[18] and vaccine coverage was about 90%.[19] Catch-up is not recommended for non-high-risk children >24 months old. Therefore, vaccine coverage in children 4–5 years old is similar to that of children 24 months of age 2–3 years before.

Hi serotype b

Vaccine against Hib has been recommended since 1992 in France, initially with a 3+1 schedule (2, 4, 5 and 16–18 months), then a 2+1 schedule since 2013 (2, 4 and 11 months).[5] Vaccine coverage with a booster at age 24 months, which was about 88% before 2013, increased to 95% between 2016 and 2019, after the simplification of the vaccination schedule.[20]

Group B Streptococcus

Chemoprophylaxis to prevent early-onset sepsis due to GBS has been recommended in France since 2001 and guidelines have not been modified since.[21]

Mandatory Vaccination

Since January 2018, recommended vaccines for children younger than 2 years, including PCV13, MenC, and Hib, are mandatory for all children born after this date.[22] This law led to vaccination coverage greater than 90% for children born after 2018.[22]

Interventions Against the Spread of COVID-19

In March 2020, a strict lockdown was implemented to reduce the spread of COVID-19.[23] The lockdown was gradually followed by various mitigation strategies, including social distancing, wearing of face masks by adults and children older than 6 years and a night-time curfew. The NPIs implemented in France are detailed by the European Centre for Disease Prevention and Control.[7]

Statistics

We analyzed the outcomes by using segmented linear regression with autoregressive error.[18] The model accounted for autocorrelation, trends before and after interventions, and seasonality using an additive model.[24] We hypothesized that changes in

TABLE 1. Characteristics of Children 15 Years of Age and Younger with Meningococcal Acute Bacterial Meningitis Between January 2001 and December 2020

	Prevaccination (January 2001–July 2009) N = 1,540	MenC Vaccine With 1 Dose (August 2009–March 2017) N = 739	MenC Vaccine With 1+1 Doses (April 2017–March 2020) N = 223	NPI (April 2020–December 2020) N = 16	Overall Study (January 2001–December 2020) N = 2,518
Estimated annual incidence per 100,000 children (95% CI)*	2.44 (2.24–2.62)	1.40 (1.21–1.59)	0.95 (0.66–1.24)	0.36 (0–0.89)	1.74 (1.53–1.96)
Monthly changes in incidence of MenC meningococcal ABM (95% CI)*	−1.20% (−1.48 to −0.92) $P < 0.001$	−0.12% (−0.17 to −0.07) $P < 0.001$	−6.7% (−14.6 to +1.1) $P = 0.08$	NA	NA
Monthly changes in incidence of overall meningococcal ABM (95% CI)*	−0.46% (−0.64 to −0.28) $P < 0.001$	−0.70% (−4.5 to +3.1) $P = 0.71$	−0.04% (−0.11 to +0.04) $P = 0.34$	NA	NA
Age (years), median (IQR)	2.2 (0.7–5.5)	1.8 (0.6–5.4)	1.3 (0.5–3.6)	1.4 (0.4–3.6)	2.0 (0.7–5.3)
Sex (male), n (%)	822/1,495 (55.0)	410/714 (57.4)	115/214 (53.7)	9/16 (56.2)	1,356/2,439 (55.6)
Serogroups available, n (%)	1,423/1,540 (92.4)	704/739 (95.3)	208/223 (93.3)	15/16 (93.8)	2,350/2,518 (93.3)
Serogroups, n (%)					
B	933 (65.6)	521 (74.0)	142 (68.3)	14 (93.3)	1,610 (68.5)
C	397 (27.9)	128 (18.2)	24 (11.5)	1 (6.7)	550 (23.4)
W	31 (2.1)	19 (2.7)	29 (13.9)	0 (0)	79 (3.4)
Other	62 (4.4)	36 (5.1)	13 (6.2)	0 (0)	111 (4.7)
Diagnosis by only PCR, n (%)	225/1,540 (14.6)	175/738 (23.7)	55/217 (25.3)	2/16 (12.5)	457/2,511 (18.2)
Preterm, n (%)	102/897 (11.4)	45/450 (10.0)	15/128 (11.7)	4/12 (33.3)	166/1,487 (11.2)
Underlying conditions, n (%)	25/1,540 (1.6)	12/739 (1.6)	5/223 (2.2)	1/16 (6.2)	43/2,518 (1.7)
Case fatality rate, n (%)	104/1,526 (6.8)	21/736 (2.8)	6/222 (2.7)	2/16 (12.5)	133/2,500 (5.3)
Monthly change in case fatality rate (95% CI)*	−0.50% (−1.06 to +0.06) $P = 0.07$	−1.21% (−17.2 to +14.7%) $P = 0.88$	+3.09% (−0.66 to +6.8) $P = 0.10$	NA	NA

*Estimated with segmented regression.
ABM indicates acute bacterial meningitis; CI, confidence interval; IQR, interquartile range; MenC, meningococcal C; NPI, nonpharmaceutical intervention.
Data are n (%) unless specified otherwise.

vaccination would have a progressive impact,[18] whereas NPI implementation would have an immediate impact.[10] The identification of a decrease or rebound in incidence without vaccination or NPI was identified with models providing the best fit.

Periods

For overall meningococcal and MenC ABM: the "pre-vaccination period" was from January 2001 to July 2009, "MenC vaccine with 1 dose period" from August 2009 to March 2017 and "MenC vaccine with 1+1 doses period" from April 2017 to March 2020. For pneumococcus: the "pre-PCV7 period" was from January 2001 to December 2002, the "targeted PCV7 period" from January 2003 to May 2006, the "PCV7 period" from June 2006 to May 2010, the "early PCV13 period" from June 2010 to April 2014 and the "late PCV13 period" from May 2014 to March 2020. For Hi: the "Hib vaccine with 3+1 doses" was from January 2001 to April 2013, the "early Hib vaccine with 2+1 doses" from May 2013 to May 2017 and the "late Hib vaccine with 2+1 doses" from June 2017 (corresponding to a rebound) to March 2020. For GBS and MenB, no specific intervention was implemented, and no "knot" (ie, a time when the trend changed significantly) was identified. Therefore, we defined a "pre-NPI" period from January 2001 to March 2020. Finally, we defined the "NPI period" from April 2020 to December 2020.

Quantitative data were compared by the Student *t* test and categorical data by χ^2. All statistical tests were two-sided, and the results were considered significant at $P < 0.05$. Data were entered with 4D software (versions 6.4–15.2) and analyzed with Stata/SE (StataCorp. 2013, Stata Statistical Software: Release 15.0 College Station, TX) and R (R Core Team, Version 3.6.3. https://www.R-project.org/).

RESULTS

Between January 2001 and December 2020, 7,186 ABM cases were reported in children ≤15 years. *N. meningitidis* was isolated in 35.0% of cases (2,518), *S. pneumoniae* in 29.8% (2,145) and Hi in 3.7% (264). ABM diagnosis was mainly made because of positive CSF culture (79.7%), positive CSF PCR (10.2%), positive blood culture and CSF pleocytosis (4.3%) and the presence of soluble antigens in CSF (3.2%), while other case definitions were used for <3% of the cases.

Neisseria Meningitidis

The main serogroup was B (68.5%). The proportion of diagnoses performed solely by PCR increased during the study (Table 1). When considering all meningococcal ABM cases, the incidence decreased significantly before MenC vaccination implementation (Fig. 1), with no significant change observed after MenC vaccine recommendation. The incidence of MenB ABM significantly decreased during the pre-NPI period [−0.43%/month, 95% confidence interval (CI) −0.53 to −0.34, $P < 0.001$]. We observed no significant change in CFR between periods (Figure, Supplemental Digital Content 2, http://links.lww.com/INF/F273).

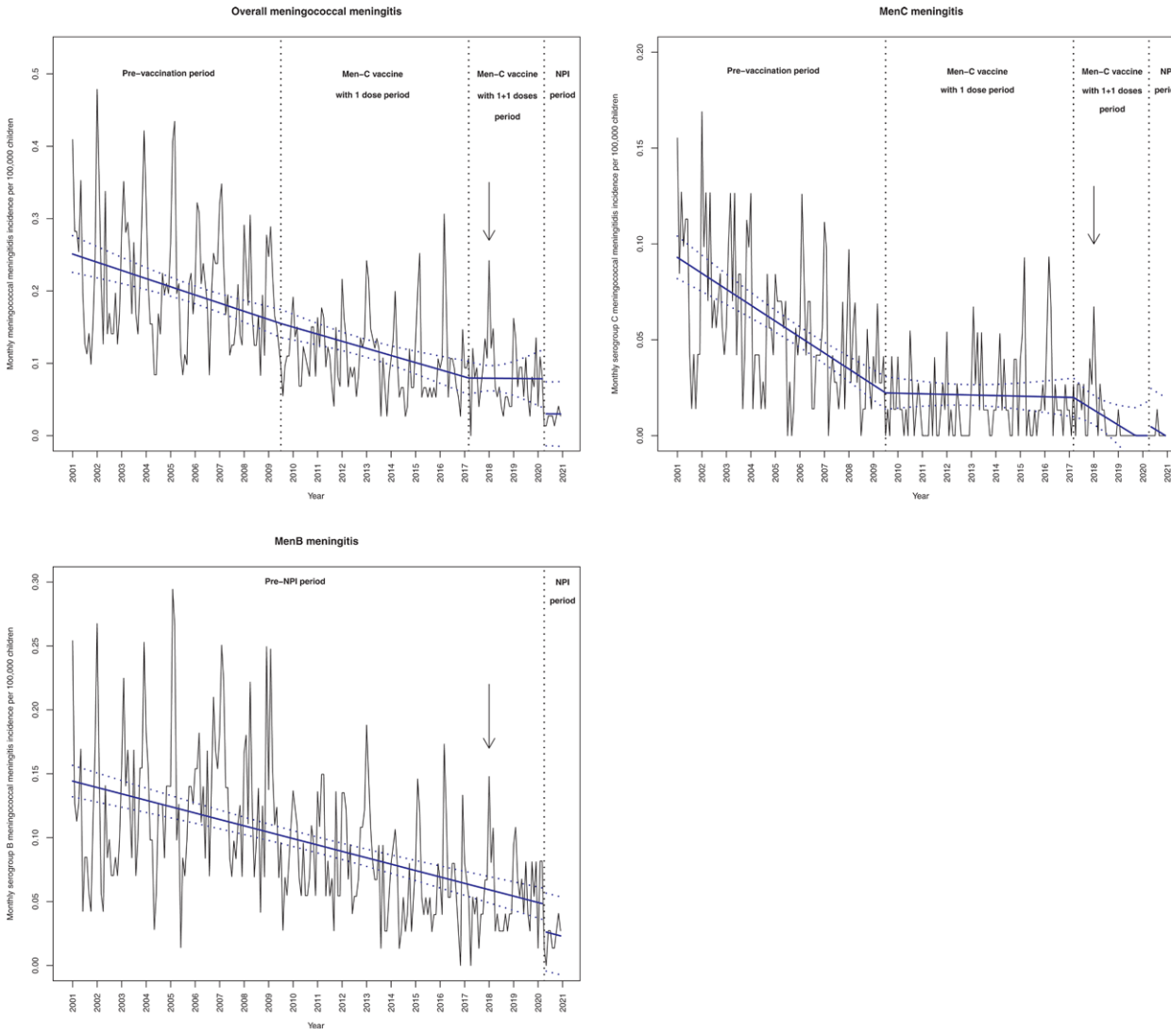

FIGURE 1. Monthly incidence per 100,000 children 15 years of age and younger for overall, serogroup C, and serogroup B meningococcal acute bacterial meningitis over time. MenC vaccine coverage remained <80% for children 24 months old until 2018 and <25% for children 20–24 years old during the study. Since January 2018 (black arrow), MenC vaccine has become mandatory for children <2 years, leading to an increase in vaccine coverage. The "prevaccination period" was from January 2001 to July 2009, the "MenC vaccine with 1 dose period" from August 2009 to March 2017, and the "MenC vaccine with 1 + 1 doses period" from April 2017 to March 2020. For serogroup B, the "pre-NPI period" was from January 2001 to March 2020. The "NPI period" was from April 2020 to December 2020. The black line shows the observed data. The blue slope lines were estimated with a segmented regression model. The blue dotted lines show the 95% confidence interval estimated with the segmented regression model. A total of 2,518 children was included in the analysis for all meningococcal strains, 550 children for serogroup C, and 1,610 children for serogroup B. MenB indicates meningococcal B; MenC, meningococcal C; NPI, nonpharmaceutical intervention. full color online

Streptococcus Pneumoniae

Overall pneumococcal ABM incidence was stable during the pre-, targeted- and the generalized PCV7 periods (Fig. 2). After PCV13 implementation, the incidence decreased by 0.9%/month (95% CI: −1.6 to −0.2, $P = 0.01$). After May 2014, a rebound was observed (+0.5%/month, 95% CI: 0.3–0.8, $P < 0.001$). Between the pre-PCV7 and late PCV13 periods, the proportion of PCV13-vaccine serotypes decreased from 84.0% to 10.6% while the proportion of children with an underlying condition regularly increased from 11.8% to 21.5% (Table 2). Figure, Supplemental Digital Content 3, http://links.lww.com/INF/F274 shows the incidence of ABM due to PCV7 serotypes and to PCV13 serotypes. Of note, during the late PCV13 period, ABM due to PCV13 serotypes increased (+0.7/month, 95% CI: 0.4–1.1, $P < 0.001$), mostly due to the persistence of 2 vaccine serotypes: 19 F (21/483, 4.3%) and 3 (14/483, 2.9%). During this period, 30 cases were due to PCV13 serotypes (6.2%), while non-PCV13/PCV15 serotypes accounted for 67 cases (13.9%) and non-PCV15/PCV20 for 125 cases (25.9%) as detailed in Table, Supplemental Digital Content 4 http://links.lww.com/INF/F275. We observed no significant change in CFR after the introduction of national guidelines for PCVs.

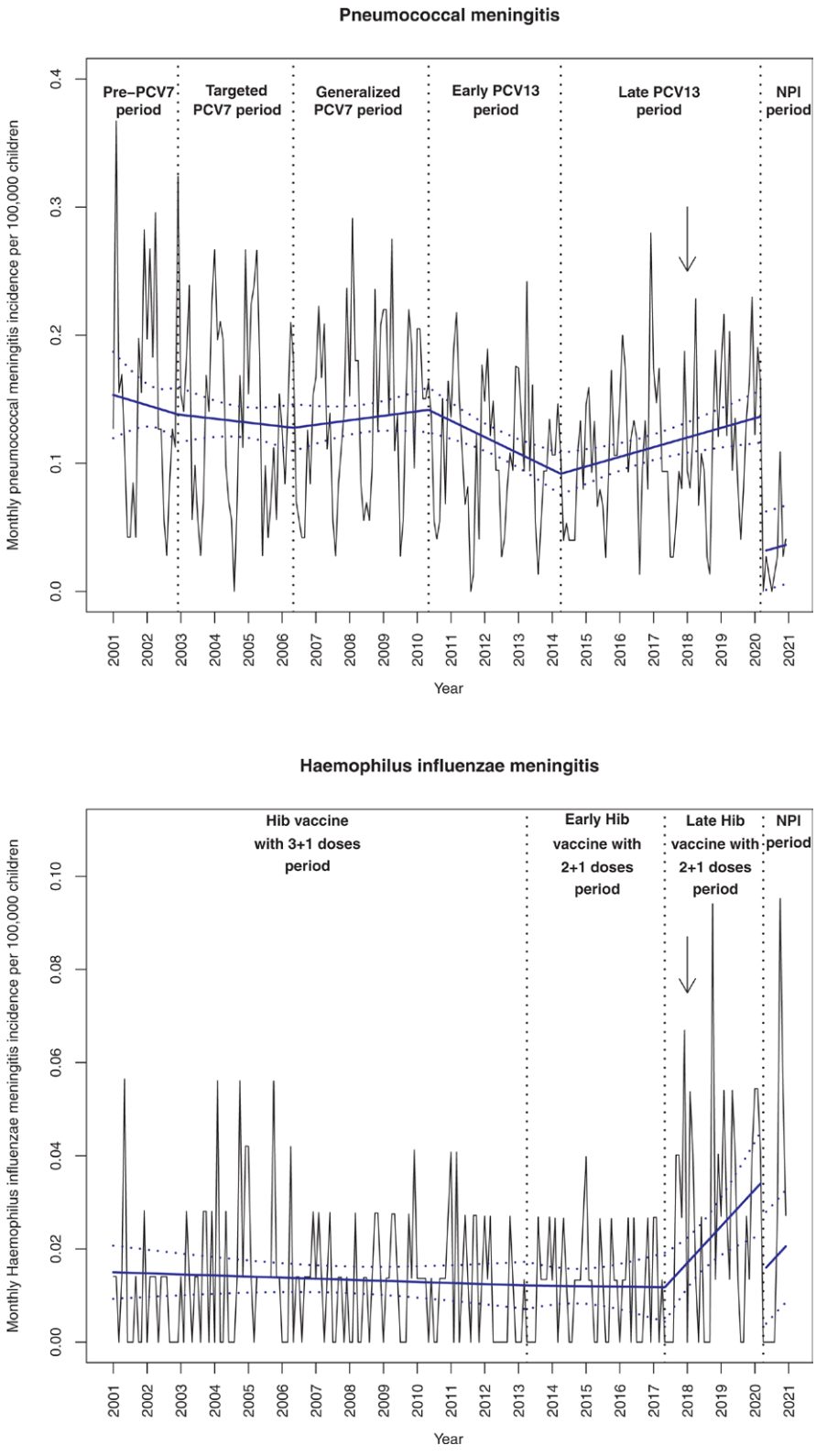

FIGURE 2. Monthly incidence per 100,000 children 15 years of age and younger for pneumococcal, and Haemophilus influenzae acute bacterial meningitis over time. Complete PCV vaccination at 24 months remained <80% until 2007. Complete Hib vaccination at 24 months was about 88% until 2013 and about 92% after. Since January 2018 (black arrows), 13-valent pneumococcal conjugate vaccine and *H. influenzae* serogroup b have become mandatory for children <2 years, leading to an increase in vaccine coverage. The "pre-PCV7 period" was from January 2001 to December 2002, the "targeted PCV7 period" from January 2003 to May 2006, the "PCV7 period" from June 2006 to May 2010, the "early PCV13" period from June 2010 to April 2014, and the "late PCV13" period from May 2014 to March 2020. The "Hib vaccine with 3+1 doses period" was from January 2001 to April 2013, the "early Hib vaccine with 2+1 doses period" from May 2013 to May 2017, and the "late Hib vaccine with 2+1 doses period" from June 2017 to March 2020. The "NPI period" was from April 2020 to December 2020. The black lines show the observed data. The blue slope lines were estimated with a segmented regression model. The blue dotted lines show the 95% confidence interval estimated with the segmented regression model. Hib indicates *Haemophilus influenzae* type b, NPI, non-pharmaceutical intervention; PCV, pneumococcal conjugate vaccine. full color online

Hi serotype b

We observed no significant change until June 2017, when a significant increase of Hi ABM incidence by 2.8%/month (95% CI: 0.3–5.3%, $P = 0.02$) was noted (Supplemental Digital Content 5, http://links.lww.com/INF/F276). Moreover, we found no difference in age, vaccination status, underlying condition and CFR before

TABLE 2. Characteristics of Children with Pneumococcal Acute Bacterial Meningitis Between January 2001 and December 2020

	Pre-PCV7 (January 2001–December 2002) N = 263	Targeted PCV7 (January 2003–May 2006) N = 402	PCV7 (June 2006–May 2010) N = 484	Early PCV13 (June 2010–April 2014) N = 378	Late PCV13 (May 2014–March 2020) N = 599	NPI (April 2020–December 2020) N = 19	Overall study (January 2001–December 2020) ~~N = 2,145~~
Age (years), median (IQR)	0.8 (0.5–2.9)	0.9 (0.5–3.2)	1.0 (0.5–4.2)	1.0 (0.5–4.8)	1.3 (0.5–5.6)	0.9 (0.5–1.7)	1.0 (0.5–4.3)
Sex (male)	145/262 (55.3)	231/395 (58.5)	282/474 (59.5)	214/371 (57.7)	353/593 (59.5)	11/17 (64.7)	1,235/2,111 (58.5)
Diagnosis by only PCR	2/263 (0.8)	6/402 (1.5)	17/484 (3.5)	12/378 (3.2)	20/599 (3.3)	0/18 (0)	57/2,144 (2.7)
Preterm	18/171 (10.5)	35/383 (12.4)	44/334 (13.2)	49/269 (18.2)	63/425 (14.8)	1/16 (6.2)	210/1,498 (14.0)
Underlying condition	31/263 (11.8)	53/403 (13.1)	76/484 (15.7)	84/378 (22.2)	129/599 (21.5)	3/19 (15.8)	376/2,145 (17.5)
Case fatality rate	32/263 (12.2)	40/397 (10.1)	48/481 (10.0)	41/378 (10.8)	51/598 (8.2)	2/19 (10.5)	211/2,135 (9.9)
Overall annual incidence/100,000 children (95% CI)*	1.75 (1.49–2.00)	1.59 (1.41–1.77)	1.62 (1.46–1.78)	1.39 (1.24–1.55)	1.37 (1.21–1.53)	0.41 (0.04–0.78)	1.47 (1.29–1.65)
Monthly changes in overall incidence (95% CI)*	−0.4% (−1.8 to +0.9) $P = 0.5$	−0.2% (−1.4 to +1.0) $P = 0.7$	0.2% (−0.3 to +0.7) $P = 0.4$	0.9% (−1.6 to −0.2) $P = 0.01$	0.5% (+0.3 to +0.8) $P < 0.001$	NA	NA
Annual incidence due to PCV7 serotypes/100,000 children (95% CI)*	1.01 (0.82 to 1.21)	0.60 (0.46 to 0.74)	0.22 (0.09 to 0.34)	0.06 (0 to 0.17)	0.06 (0 to 0.18)	0.0003 (0 to 0.29)	0.28 (0.14 to 0.41)
Monthly changes in incidence of PCV7 serotypes (95% CI)*	−1.8% (−3.6 to −0.1) $P = 0.04$	−1.6% (−6.2 to +2.9) $P = 0.48$	−3.5 (−23.2 to +16.2) $P = 0.72$	+1.4 (−0.2 to +3.0) $P = 0.09$	−0.8 (−6.6 to +4.9) $P = 0.77$	NA	NA
Annual incidence due to PCV13 serotypes/100,000 children (95% CI)*	1.01 (0.86–1.16)	0.83 (0.73–0.94)	0.72 (0.63–0.82)	0.38 (0.29–0.47)	0.12 (0.03–0.21)	0.0009 (0–0.22)	0.50 (0.39–0.60)
Monthly changes in incidence of PCV13 serotypes (95% CI)*	−0.9 (−2.3 to +0.5) $P = 0.19$	−0.4 (−1.7 to +0.9) $P = 0.52$	−0.2 (−1.6 to +1.1) $P = 0.71$	−3.3 (−5.6 to −1.0) $P = 0.004$	+0.7 (+0.4 to +1.1) $P < 0.001$	NA	NA
Monthly change in case fatality rate, mean (95% CI)*	−1.7% (−5.4 to +1.9) $P = 0.3$	+0.4% (−0.5 to +1.4) $P = 0.4$	−0.3% (−1.4 to +0.8) $P = 0.6$	+0.1% (−0.6 to +0.8) $P = 0.7$	−0.9% (−3.1 to +1.2) $P = 0.4$	NA	NA

*Estimated with segmented regression.
CI indicates confidence interval; IQR, interquartile range; NPI, non-pharmaceutical intervention; PCV, pneumococcal conjugate vaccine
Data are n (%) unless specified otherwise.

and after the rebound in June 2017 (Table, Supplemental Digital Content 6, http://links.lww.com/INF/F277). After the increase, the main serogroup involved was serogroup b (45.4%, Figure, Supplemental Digital Content 7, http://links.lww.com/INF/F278). The CFR did not significantly change.

Control Outcome: GBS

During the study, 1,180 cases of ABM due to GBS were reported. The GBS ABM incidence was stable during the study (−0.05%/month, 95% CI: −0.14 to 0.04, $P = 0.3$).

Effect of NPI Implementation in March 2020

We observed a significant decrease of pneumococcal (−77.6%, 95% CI: −100 to −50.3, $P < 0.001$) and Hi (−56.9%, 95% CI: −100 to −5.9, $P = 0.03$) ABM incidence after NPI implementation. By contrast, no significant change was observed for Men and GBS (Table, Supplemental Digital Content 8, http://links.lww.com/INF/F279).

DISCUSSION

When analyzing data from a long-standing population-based prospective national surveillance network with 7,186 ABM cases in children from 2001 to 2020, we observed major changes in the incidence and characteristics of ABM and a striking reduction in the incidence of the most frequent pathogens transmitted via the respiratory route after NPI. Furthermore, we observed no significant change in pathogen-specific CFR after national interventions.

We observed that low vaccine coverage and slow implementation could diminish their effectiveness. Indeed, we found only a modest impact of MenC vaccine implementation in France, with no significant change after the recommendation to add an additional MenC vaccine dose. Several hypotheses could explain these observations. The catch-up recommendation has been poorly followed,[15] particularly for teenagers, who are meningococcus carriers and play an important role in its transmission. Furthermore, before any vaccine implementation, the overall meningococcal ABM incidence decreased, as did MenC incidence, making it difficult to demonstrate a benefit with time series analysis.

Similarly, to the meningococcal ABM incidence following vaccine rollout, there was little evidence of a decrease in the incidence of pneumococcal ABM following the introduction of PCV7 in France, unlike other countries where vaccine coverage increased rapidly. Indeed, by comparing before and after PCV7 implementation, a decrease of 42% in the overall invasive pneumococcal disease (IPD) incidence in children <5 years of age was reported in Israel, while the decrease was 62% in children 2–23 months of age in the United States.[25,26] In France, the low vaccine coverage has decreased

the benefit of the vaccine implementation on IPD. In addition, it has been hypothesized that the slow vaccine uptake may have favored pneumococcal carriage serotype replacement.[4] Multiple factors may explain these suboptimal implementations. Larson et al.[27] reported that France had the lowest confidence in vaccine safety globally. Since the publication of that study in 2016, mandatory vaccination has been voted on and has increased both vaccine coverage and confidence in vaccination.[22] Furthermore, the lack of a specific strategy focusing on older children and especially teenagers, such as a school vaccination program, may explain the poor efficacy of a catch-up strategy.

Moreover, epidemiologic changes can occur without any intervention or decrease in vaccine coverage. For pneumococcus, the major benefit of PCV13 was eroded by a rebound 5 years after its introduction. During the late PCV13 period, the main serotype was 24F, and only 10.5% of pneumococcal cases were due to PCV13 serotypes. By comparison, 20.1%–84.9% of these serotypes were included in third-generation PCVs highlighting the potential benefit of next-generation PCVs. Among serotype 24F strains, a predominant lineage, GPSC10, has been identified in France.[28] This lineage has been transmitted in Europe and other continents. Concerningly, this serotype is frequently multidrug-resistant and is not included in most of the upcoming PCVs.

For Hi, incidence increased 4 years after the immunization changed from a 4-dose to a 3-dose schedule. Despite a relatively low incidence as compared with other pathogens and the prevaccination incidence, this observation is both worrying and unexpected. The lower level of antibodies protecting against Hib (anti-PRP IgG) observed in French children with a "lightened" vaccination schedule may explain this rebound in part.[29] In the Netherlands, a similar pattern driven by serogroup b was observed in 2020 and 2021. Invasive diseases caused by non-b Hi serogroups were substantially lower as compared with previous years.[30] Unlike France, in the Netherlands, the increase was observed in children and in adults.[14] Of note, a similar change in the national Dutch vaccine schedule occurred in 2020.[30] Several hypotheses for this increase, such as diminished long-term protection because of vaccine schedule modification or an increase in Hib carriage in children, have been raised.[30] Further studies are required to explore this phenomenon.

Finally, we reported secular changes, as illustrated by MenB, which decreased during the study without any specific vaccination. Similar patterns, which remain largely unclear, have been observed in Europe, with a 56% decrease in MenB invasive infections between 2008 and 2017, although the MenB vaccine was rarely used during this period.[31] However, MenB remained the main meningococcal serogroup. MenB vaccine, which has been recommended and reimbursed since 2022 in France, could prevent a large proportion of the cases.

After NPI implementation, both pneumococcal and Hi ABM incidence greatly decreased. Pneumococcal carriage, a prerequisite for infection, was stable during this period, while an association with a change in viral dynamics suggested that this decrease was mainly driven by the reduction of respiratory viral infections.[10,32] For meningococcus, we observed a similar but not significant trend, probably because of the very low number of cases. Similarly, changes in viral dynamics may have affected its transmission.[33] Concerns about possible future outbreaks exceeding the prepandemic period after NPI relaxation have been raised.[34] For example, an unusual outbreak of invasive MenB disease was described in the United Kingdom in autumn 2021.[35] Similarly, an increased incidence of pediatric IPD was reported in England during July–December 2021.[36]

We observed no significant change in the pathogen-specific CFR after specific national interventions, highlighting the importance of prevention. Furthermore, we observed a high proportion of preterm patients (18.8% compared with the national rate of 5–6%),[37] and a high proportion of children with an underlying condition (8.5%) among ABM cases. Especially, 17.5% of children had an underlying condition when pneumococcus was implicated. Prevention strategies should focus on these populations with "tailor-made" vaccination schedules.

We cannot exclude that a fraction of the decrease in ABM incidence may be related to underreporting, especially after the COVID-19 pandemic which has altered the healthcare system. The stability of GBS ABM, which was used as a control outcome because no specific vaccination occurred during the study and because NPI were not expected to have an impact on the transmission of this pathogen, with a steady number of centers participating in the study, are against this hypothesis. Considering the extreme severity of ABM, it is unlikely that parents did not seek medical attention, as has been described for other diseases since the COVID-19 pandemic.[38] Furthermore, we observed an increasing proportion of ABM for which the diagnosis involved solely PCR, especially for meningococcal ABM. This increase may have improved the diagnosis and therefore does not explain the decreasing meningococcal ABM incidence. For other pathogens than *N. meningitidis*, cultures are sufficient in more than 97% of cases. For this study, the case definition was wider compared with other studies based solely on positive CSF culture.[6] However, the case definition has not changed over the study period. Futhermore, children with pleiocytosis associated with either a positive blood culture and/or PCR of a biopsy of a skin lesion, which may lack of sensitivity, involved only a few patients (<3%) who mostly had a significant pleocytosis (median 365 cells/µL with 83% of neutrophils). Times-series analysis relies on a temporal association, and we cannot prove a causal relation. However, it is important to note that interrupted time series analysis is the optimal design when randomization is not feasible, particularly for the evaluation of public health measures.[39] As an illustration, Pirçon et al. analyzed the effect of PCV implementation in children on the incidence of IPD in adults >65 years old.[40] They found opposite results for the Finish dataset, with no heard effect comparing before-after, whereas a clear heard effect was identified with interrupted time-series analysis. Despite this design, secular changes, as observed for Men ABM incidence, remain challenging for the evaluation of public interventions, especially when studying over a long period. For this study, we used only data on ABM, one of the most severe bacterial infections, while other invasive bacterial infections are not accounted for. The epidemiology in non-meningitis invasive bacterial infections may differ from our results. Finally, we have used data published from other sources for vaccine uptake. Indeed, vaccination status was often missing, particularly for vaccines against other pathogens than the one responsible for the ABM while vaccine coverage in children with ABM may differ from healthy children.

In conclusion, our study highlights that poor vaccine coverage and slow vaccine uptake have decreased the benefit of vaccine introductions such as the PCV7 and MenC vaccines. Furthermore, the recent epidemiology of pediatric ABM underlines the large part of the burden that could be reduced through vaccination (especially with the MenB vaccine and third-generation PCVs). The observation of major epidemiological changes, sometimes unrelated to vaccine implementation, highlights the need for continuous surveillance. Finally, ABM caused by pathogens transmitted via the respiratory route should be monitored closely because their reduction during the NPI period could be followed by a rebound with a higher incidence than during the pre-NPI period.

ACKNOWLEDGMENTS

We are grateful to the ACTIV team: Isabelle RAMAY, Aurore PRIEUR, Mathilde SERVERA, and Pauline DAUMERIE.

We thank Laura Smales for language editing (https://www.biomedediting.com/).

We thank the former and present investigators of the French pediatric meningitis network: Abadie Véronique, Abdanne Mohamed, Abdelhadi Mohamed, Aberrane Said, Ackermann Steffen, Adam Marie-Noëlle, Adamon Latif, Adi Ghassan, Akitani Sylvia, AL Jazayri Ziad, AL Junaidi Ashraf, AL Mazini Céline, Alba-sauviat Catherine, Albertini Marie-Thérèse, Allia Abdelatif, Allouche Chantal, Amama Habib, Amara Marlene, Amirault Patrick, Amsallem Daniel, Andre Maud, Andriantahina Isabelle, Anxionnat Raphaël, Arlet Guillaume, Armouche Samar, Astruc Dominique, Auburtin Brigitte, Audry Degardin Elena, Autret Fanny, Ayadi Nabil, Ayaz-bensultana Naima, Bachelier Marie-Nadège, Baleine Julien, Balitalike Jadot, Bandin Olivia, Banegas Danielle, Banerjee Anandadev, Baret Marie, Barnaud Guilène, Baron-joly Sandrine, Barrans Alain, Barrey Catherine, Barsotti Katia, Barthez Marie-Anne, Baruteau Remi, Basmaci Romain, Bassil Joachim, Battaglini Paula, Beaumier Soizic, Bednarek Nathalie, Belgaid Abdelmalek, Belivier Elisabeth, Bellulo Sophia, Ben Said Mohamed, Benabdelmalek Faouzi, Benbih Mohamed, Benchekroun Khalil, Benezech Catherine, Bengrina Mabrouk, Benmahammed Abdelkader, Benmonsour Lahbib, Benmoulai Ismail, Benoist Gregoire, Benoit Catherine, Bensaid Philippe, Benseddik Zehaira, Berche Patrick, Beretta-Salaun Guenaëlle, Bergounioux Jean, Berneau Pauline, Berterottiere Dominique, Bertrou Anne, Biessy Hélène, Bilger Marie, Billaud Nicolas, Billion Patrick, Bina André, Bineau Philippe, Biran Valérie, Blacnkaert Camille, Blanc Philippe, Blanc Stéphane, Blasquez Amandine, Blondel Elodie, Blondin Gilles, Boileau Pascal, Boize Philippe, Bolot Pascal, Bonacorsi Stéphane, Bongo Boina Ruffin, Bonnin Martine, Boquet Patrice, Bosdure Emmanuelle, Bosi Claude, Bost-Bru Cécile, Boukezia Nourredine, Boukhris Samira, Boulard Stephane, Boulfoul Djamila, Boumecid Hocine, Bour Jacqueline, Bourennane Malek, Bourgeois-Nicolaos Nadège, Boussadia Hafidha, Boussard Noel, Boussicault Gerald, Boutry Morgane, Boyer Sophie, Branger Catherine, Brechet Caroline, Bresson Violaine, Breuil Jacques, Briennon Claire, Brieu Natalie, Brisset Sarah, Brocard Anne, Broenen Emmi, Brouard Jacques, Bruna Anne-Laure, Bucher Julie, Bueno Benjamin, Buisson-Touati Caroline, Butin Marine, Cabaret Blandine, Cadot Lucile, Caillon Jocelyne, Callamand Pierre, Cambon Dominique, Cambonie Gilles, Canis Frédérique, Canzi Anne-Marie, Carbajal Ricardo, Carbonnelle Bernard, Carre-Cavellier Joelle, Carrer Amélie, Carriere Christian, Carroger Guy, Cartier-Riviere Bernadette, Cascarigny Françoise, Casha Paul, Castelnau Pierre, Cattoen Christian, Cattoir Vincent, Caurier Bernard, Cavalier Ariane, Cazau Clémence, Cecille Agnès, Celton Gaelle, Chaabane Aouatef, Chabrol Brigitte, Chacé Anne, Chahine Jamilé, Chaix Yves, Chalumeau Martin, Chalvon Demersay Arnaud, Chamouilli Jean-Marc, Champion Valérie, Chantelat Pascal, Chantreuil Julie, Chaplain Chantal, Charachon Sylvie, Charbonneau Anne, Chardon Hubert, Charpentier Sabine, Charreton Claire, Chellun Pamela, Chenel Claude, Cheron Mireille, Cheuret Emmanuel, Chevallier Bertrand, Chevrel Jean, Chevret Laurent, Chognot Didier, Chomienne Francis, Chosidow Anais, Chrisment Delphine, Ciupek Catherine, Clair Perrine, Claris Olivier, Clavel Catherine, Cochat Pierre, Coche Delphine, Coinde Edeline, Colombani Jean-Claude, Combe Jean Charles, Cordier Anne-Marie, Cormier Philippe, Corniau Francoise, Costa Guillaume, Costa Yannick, Cottin Jane, Coumenges Pascal, Courcol René, Courdavault Laurence, Courouble Gery, Courtade Henri, Craiu Irina, Crepet Françoise, DA Edwige, Daire-Chabanon Isabelle, Dalmon Fabienne, Danan Claude, Danekova Nevena, Danjean-Deguin Marie-Pierre, Danquigny Anne Laure, Dao-Dubremetz Anne, Daoud Patrick, Daoudi Florence, Darai Emile, Darnaud Cécile, Darras Jean Philippe, Dassieu Gilles, Dauger Stéphane, DE Barbentane Marie-Christine, DE Champs Christophe, DE Decker Laurent, DE Montclos Henri, DE Pontual Loïc, Debriel Dominique, Decoster Anne, Degas Vanessa, Delacour Thierry, Delamare Catherine, Delaporte Gilles, Delarbre Jean-Marie, Delavelle Chantal, Delbeke Emmanuel, Delesalle Sophie, Deligne Delphine, Delimele Marylin, Delorme Delphine, Deluca Daniele, Delvart Céline, Demachy Marie-Claude, Demarcq Marie-Joelle, Demarque Nathalie, Demayer Nadia, Demay-Legros Gaelle, Demonchy Diane, Desbois Delphine, Deschamps Nina, Desfrere Luc, Deshayes DE Cambronne Romain, Desse Blandine, Dessein Rodrigue, Dessioux Emmanuelle, Desson Julienne, Desvigne Ghislaine, Deville E., Dewitte Aude, Dhaoui Tahar, Didier-Wright Catherine, Dieckmann Katherine, Doit Catherine, Dolfi Fiette Helene, Dolhem Philippe, Dommergues Marie-Aliette, Dorangeon Elodie, Doucet-Populaire Florence, Dubois Franck, Dubourdieu Béatrice, Ducrocq Sarah, Dudin Anwar, Dufour Marie-José, Dumoulard Bruno, Dupre Jean-Michel, Durand Marie-France, Duthilly Arnaud, Dutron Sarah, Duval Véronique, Eicher Emmanuel, Eitenschenck Laurence, EL Hamri Mohamed, Elena-Daumas Martine, Elharrif Zoubida, Elias Ossam, Emond Jean-Philippe, Enchery Sophie, Epaud Ralph, Escoba Simon, Estapa Laurence, Esteve Vincent, Estevez Cyrielle, Etienne Jerôme, Evers Annie, Evrard Dominique, Evreux Françoise, Eyer Didier, Eyssette-Guerreau Stéphanie, Fabbro Christelle, Faibis Frédéric, Fargeot Espaliat Anne, Farges Anne, Farhat Skander, Faul Valérie, Favaretto Giovanni, Favier Marion, Faye Albert, Feldmann Marc, Ferey Janine, Ferroni Agnès, Fiette Hélène, Filippi Jean-François, Filleron Anne, Flipo Jean-Louis, Flurin Vincent, Foca Michaela, Foix Laurence, Fos Marie Pierre, Francois-Chervet Catherine, Frey Ulrike, Gaillard Jean-Louis, Gaillot Théophile, Gajdos Vincent, Gallet Serge, Gallou Gildas, Ganivala Idris, Garandeau Caroline, Garbarg-Chenon Antoine, Garcera Yves, Garcia Sanchez Claudio, Garnier Fabien, Garrabe Eulalie, Gaschet Anne, Gaschignard Jean, Gascoin Géraldine, Gaudelus Joël, Gauduchon Valérie, Gavignet Martine, Geffroy Françoise, Geniez Laurent, Georget Emilie, Ghosn Ezat, Giacobbi Milet Vannina, Gilles Isabelle, Gillet Yves, Giorgi Catherine, Girard Florent, Girard Juliette, Giraudon Adeline, Giroux Nathan, Glatz Isabelle, Gleize Elodie, Gobet Sophie, Goguelin Annie, Goissen Celine, Goudeau Alain, Gougeon Anne, Goumy Pierre, Gouraud François, Gouriet Frédérique, Goux Alain, Grailles Aurélie, Graine Houria, Grancher Céline, Grando Anna, Gras-Le-Guen Christelle, Greco Magali, Gressier Bernard, Grimal Isabelle, Grimprel Emmanuel, Grise Geneviève, Gruss Richard, Guerin François, Guibert Sophie, Guichard Henriette, Guiddir Tamazoust, Guiet Pascal, Guigonis Vincent, Guilbert Julia, Guillermet Fromentin Christine, Guilluy Olivier, Guitton Corinne, Haas Andreas, Haas Hervé, Habib Alexandre, Hachani Abdelatif, Hachem Guilda, Hadjadj Sarah, Haegy-Doehring Isabelle, Hage Chehade Mohamed, Hallage Houria, Hallalel Fazia, Halna Muriel, Hamdad Farida, Haouisee Severine, Harchaoui Samir, Hatahet Rihad, Hay Fréderique, Hedjem Noureddine, Hees Laure, Heidt Annie, Hentgen Véronique, Heraud Marie-Christine, Herve Christian, Heurte Joelle, Heusse Emmanuelle, Heyman Rachel, Hivert Céline, Hochart Anne-Cécile, Hombrouck-Alet Cécile, Honoré Stéphanie, Horea Cosmina, Hubert Nathalie, Hubert Philippe, Huet Frédéric, Huin Nicole, Huvenne Hélène, Idres Nourredine, Ikounga Patrick, Ingrao Tara, Izopet Jacques, Jacob Jean Louis, Jacquet Coralie, Jalloul Mohamad, Jan Didier, Jaouen Anne-Christinne, Jarlier Vincent, Jarreau Pierre-Henri, Jaulhac Benoit, Javouhey Etienne, Jehan Josette, Jensen Cecile, Jeziorski Eric, Jokic Mikael, Joly-Guillou Marie-Laure, Joly-Sanchez Lydie, Joram Nicolas, Jorion Claude, Jullian Eric, Juvin Marie-Emmanuelle, Kalach Nicolas, Kayal Samer, Khaled Mohamed, Khalfi Ali, Khorsi Slimane, Kieffer Francois, Kitzis Marie-Dominique, Kom Rémi, Kone-Paut Isabelle, Kovacs Tamas, Kozisek Stanislas, Kucerova Johana, Kuntzel Bernard, Labarthe

Francois, Labenne Marc, Laborie Marie-Jose, Labrune Philippe, Lacroix Delphine, Lafendi Abdelhamid, Lagier Evelyne, Lagier Jeremy, Lahrach Hakim, Laidj, Laisney Norbert, Lakhdari Mustapha, Lamant Marie, Lamarcq Mélanie, Lambert Christine, Lamoureux Sylvie, Landragin Danielle, Lanotte Philippe, Laoudi Yacine, Lapeyre Delphine, Lapeyre Fabrice, Lapostolle Claire, Laugel Vincent, Laulan Afaf, Launay Elise, Lavigne Jean-Philippe, Le Bideau Marc, Le Coustumier Alain, Leboucher Bertrand, Lecine Thierry, Ledru Sylvie, Lefevre Fabrice, Legagneur Michel, Legalle Marie-Ange, Leger Pierre-Louis, Legros Antoine, Lehours Philippe, Lelievre Nathalie, Lelioux Jean, Leluan Philippe, Lemaitre Nadine, Lemarié Carole, Lemble Chantal, Lemenand Olivier, Leneveu Michel, Leotard Sophie, Lepage Jm, Leret Nathalie, Lerouge-Bailhache Marion, Leroux Pascal, Lesage Fabrice, Lescanne Emmanuel, Letellier Claire, Leteurtre Stéphane, Letreust Muriel, Leuvrey Maeva, Levast Marion, Levy Marc, Levy Michael, Levy Pierre-Yves, Lienhardt Anne, Ligios Agnès, Long Laurence, Lorrot Mathie, Louf Sylvie, Loznewski Alain, Lureau Pierre, Maakaroun-Vermesse Zoha, Macchi Pascal, Madhi Fouad, Mager Guy, Magny Jean-François, Malige Laurence, Mammes Olivier, Mandelcwajg Alexis, Mandjee Aziza, Mangeol Alain, Manin Cécile, Mansir Thierry, Manteau Céline, Marcou Valérie, Marguet Christophe, Mariette Sylvie, Marin Mariana, Marmonier Alain, Marret Stéphane, Martha Sandrine Anne, Martin Claude, Martinat Laurence, Martinez Ozenda Muriel, Marty Sophie, Masserot Caroline, Mathieu Laurent, Mathieu Pierre, Matoussi Zied, Maugard Thierry, Maurin Damien, Mazataud Richard, Mazeghrane Mustapha, M'bamba Célestin, Mellier Joelle, Melon Monique, Menager Cedric, Menguy Anne-Claude, Menouar Mohamed, Menouni-Foray Odile, Merlin Etienne, Merlot Elodie, Mermet Jeanvoine Fabienne, Mermond Sylvain, Meslin Pauline, Meunier Patricia, Mezgueldi Ellia, Micaelo Maite, Michel Fabrice, Mignard Sophie, Mignot Loïc, Mikail Izzat, Milcent Karen, Milh Mathieu, Milleret-Proyart Marie-José, Millou Catherine, Minodier Philippe, Moquet Olivier, Moreigne Michel, Morisot Cyril, Morle Sophie, Mornand Pierre, Moulene Eric, Moulin Pierre, Mouly Laurence, Mowendabeka Audrey, Muller Stéphanie, Murbach Valérie, Nakhleh Jean, Nathanson Sylvie, Naudot Xavier, Navarro Caroline, Nemes Raluca, Neri Schiavini Dominique, Nerome Simone, Neuwirth Catherine, Ngalula Guy, Nguyen Dzu Joel, Nicola Nawal, Ninot Alain, Nobili-Dubarry Céline, Noulard Marie-Noëlle, Osman Hatem, Osman Zafer, Ould Hocine Houria, Ouldali Naim, Oulebsir Abdelaziz, Oules Olivier, Ouziel Antoine, Pages Anne-Sophie, Pages Marie-Christine, Paget Corinne, Palette Xavier, Pancher Marie, Pantalone Letitia, Paon Jean-Christophe, Pateyron Fabienne, Patoz Pierre, Paul Gérard, Paul Jean-Gabriel, Pauquet Emilie, Peigne Chantal, Pejoan Hélène, Pellegrino Béatrice, Pelloux Isabelle, Penaud Antoni, Penel Delphine, Pere Bastien, Perez Noémie, Perrier Coline, Pesenti Delphine, Petitboulanger Nelly, Phan Florence, Pharaon Isabelle, Pierre Marie-Hélène, Pierrejean Denys, Pietrement Christine, Pina Patrick, Pindi Béatrice, Pinlou Elisabeth, Pinquier Didier, Pinturier Marie-Frédérique, Plaisant Franck, Planchenault Deborah, Plassart Claire, Ploton Marie-Caroline, Plouvier Emmanuel, Poggioli Isabelle, Poilane Isabelle, Pons Charlotte, Porcheret Huong Thi Ngoc, Pouessel Guillaume, Poyard Claire, Pradeaux Laurent, Prere Francoise, Priqueler Laurence, Prudent Muriel, Queinnec Christèle, Raber Cécile, Ragot Jeanne, Raignoux Julie, Raobison Aina, Raoult Didier, Rault Jean-Pierre, Ravanel Nadia, Raymond Josette, Raynaud Marie-Françoise, Rebaud Philippe, Renaud Vialet, Rennes, Retornaz Karine, Rey Agnes, Richardin Florence, Richelme Christian, Rimet Yves, Rimpici Didier, Riviere Brigitte, Robert Blandine, Roche Christine, Rolland Christophe, Romain Olivier, Romeo Bernard, Ros Barbara, Roubin Denis, Roudaut Veronica, Roudiere Laurent, Rouget Sébastien, Rougier Catherine, Roullaud Sylvie, Roullet Renoleau Nicolas, Rousseau Florence, Roussellier Patricia, Roux Anne Laure, Roybet Danielle, Roze Jean Christophe, Rozental Jonathan, Sadik Ahmed, Saf Marc, Said-Menthon Marie-Hélène, Sakr Samir, Salomon Charles, Sanchez Richard, Sarlangue Jean, Sarthou Laurent, Sartre Jacques, Saumureau Simone, Savoy Isabelle, Scat Yves, Schaefer Jean-Louis, Schneider Fanny, Schneider Jean-Marc, Schweitzer Cyril, Sebag Olivier, See Helene, Sevin Odile, Seys Elsa, Sfez Annie, Shawali Cédric, Simon Ludovic, Simonin Catherine, Siouala Boualem, Sivadon-Tardy Valérie, Smati Salim, Smets Aurelie, Sommabere André, Soto Bertrand, Soustelle Nicolas, Stefaniuk Jean, Stephan Robin, Surdu Alina, Sweertvaegher Anne, Szulc Marie, Tahiri Cedric, Tahraoui Soad Linda, Tauzin Manon, Tchanga Jean-Pierre, Terki Mustapha, Tete Carmell, Texier Anthony, Therond Patrice, Thibault Michel, Thiriez Gérard, Thore Jean, Thouvenin Maxime, Tiry Catherine, Tisserand Elodie, Tissieres Pierre, Tixier Anne, Toubiana Julie, Touroult-Jupin Pauline, Toyer Anne-Lise, Tran Tu Anh, Trentesaux Anne Sophie, Tronc Frédéric, Truong Jeanne, Ursulescu Nicoletta, Vachee Anne, Vaillant Christine, Valade Aurélie, Valayer Patrick, Valensi Mickaël, Vallee Eric, Vallet Christelle, Van De Perre Philippe, Vandenesch François, Vanel Noémie, Vaucel Jacques, Veauvy-Juven Agnès, Venot Christine, Verdan Matthieu, Verdet Charlotte, Vergnaud Michel, Vergne Christiane, Vernet-Garnier Véronique, Vervel Christine, Viala Céline, Vialette Véronique, Vic Philippe, Vignaud Olivier, Violette Jérémie, Vittecoq Catherine, Vu Thien Hoang, Wasels Richard, Wiedemann-Fode Arnaud, Worcel Isabelle, Yangui Mohamed Amine, Youssef William Azzam, Ythier Hubert, Zarzour Ali, Zelinsky-Gurung Arianne, Zemouri Neila, Zenkhri Ferielle, Zimmermann Brigitte, And Zini Justine.

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