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► To cite this version:

J. Truong, C. Levy, S. Prot-Labarthe, H. P. K. Nguyen, E. Grimprel, et al.. Vaccine-preventable meningitis in French children with incorrect vaccination status from 2011 to 2013. Archives de Pédiatrie, 2020, 27 (1), pp.1-5. 10.1016/j.arcped.2019.10.008 . hal-03489876

HAL Id: hal-03489876

<https://hal.science/hal-03489876>

Submitted on 7 Mar 2022

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Vaccine-preventable meningitis in French children with incorrect vaccination status from 2011 to 2013

Short title: Vaccine-preventable meningitis in children with incorrect vaccination status

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This work was presented at the European Society for Paediatric Infectious Diseases in Madrid on the 25th of May 2017 and at the Congrès des Sociétés de Pédiatrie in Lyon on the 25th of May 2018.

Funding: Financial support was provided in part by Pfizer and the Pediatric Infectious Diseases Group (GPIP) of the French Pediatric Society (SFP) and the Association Clinique et Thérapeutique Infantile du Val de Marne (ACTIV).

Ethics: The data collection was approved by the French Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) and by the French National Data Protection Commission (CNIL, no. 913006).

Acknowledgments:

We thank all pediatricians and microbiologists of the “Observatoire National des Méningites” who participated in this study.

We thank Dr. O. Gaillot (Centre National de Référence *Haemophilus* until 2018, Centre Hospitalier Régional Universitaire de Lille, Lille, France), Dr. MK. Taha (Centre National de Référence des méningocoques, Institut Pasteur, 75724 Paris cedex 15, France), and Dr. E. Varon (Laboratoire de microbiologie, Hôpital Européen Georges-Pompidou, 75908 Paris Cedex 15, France).

Abstract

The objective of this study was to determine the number of cases of pediatric meningitis or purpura fulminans associated with an incorrect vaccination status from 2011 to 2013 in France. A total of 48 children with vaccine-preventable meningitis or purpura fulminans, including three deaths, had an incorrect vaccination status: 26 cases were due to *Neisseria meningitidis* group C (54.2%), 19 to *Streptococcus pneumoniae* (39.6%), and three to *Haemophilus influenzae* type b (6.3%). The majority of patients ($n=35$, 72.9%) had received no injection of the vaccine concerned. Over a 3-year period, 48 cases of bacterial meningitis or purpura fulminans in children could have been avoided if the French immunization schedule had been followed.

Keywords: bacterial meningitis; children; vaccine

1. Introduction

Bacterial meningitis is responsible for about 135,000 deaths every year worldwide [1]. *Streptococcus pneumoniae* (*S. pneumoniae*) and *Neisseria meningitidis* (*N. meningitidis*) are the most common agents implicated in childhood bacterial meningitis, followed by *Haemophilus influenzae* type b (Hib) [2]. Major sequelae occur in 24.7%, 7.2%, and 9.5% of survivors, respectively, for these three bacterial species [3,4].

The implementation of the Hib vaccine, the 7-valent pneumococcal conjugate vaccine (PCV-7), followed by the 13-valent pneumococcal conjugate vaccine (PCV-13) and the serogroup C meningococcal conjugate vaccine (MenCC) contributed to a decline in the incidence of bacterial meningitis. The guideline data for immunization against Hib, *N. meningitidis* group C, and *Streptococcus pneumoniae* are summarized in Table 1 [5].

Owing to the public perception that severe infectious diseases have been eliminated and to concerns about the side effects of vaccines, vaccine hesitancy has increased in high-income countries and particularly in France [6,7].

The main objective of this study was to determine the number of children with vaccine-preventable meningitis or purpura fulminans associated with an incorrect vaccination status for the bacterial species responsible for the infection from 2011 to 2013 in France.

2. Material and Methods

2.1 Population

Since 2001, the Pediatric Infectious Diseases Group of the French Pediatric Society (GPIP of the SFP), along with the Association Clinique et Thérapeutique Infantile du Val de Marne (ACTIV), has established a national surveillance network of bacterial meningitis and purpura

fulminans in children in France [8]. A total of 233 pediatric wards prospectively enrolled all reported cases of community-acquired meningitis or purpura fulminans in children aged 1 day to 18 years old (yo). A capture–recapture analysis showed that this network covers approximately 61% (95% CI 60%; 66%) of childhood meningitis occurring in France.

In this prospective observational study, we analyzed all cases of vaccine-preventable meningitis and purpura fulminans reported in this network from January 2011 to December 2013. The following inclusion criteria were used:

- Clinical signs of meningitis associated with cerebrospinal fluid (CSF) pleocytosis (>10 cells/ μ L) with positive CSF culture, or positive CSF antigen testing, or positive CSF polymerase chain reaction (PCR) findings, or positive culture or PCR in blood;
OR
- Purpura fulminans and positive culture or PCR in CSF, blood, or cutaneous biopsy.

We included only cases with bacterial species for which there is a recommended vaccination in the general population: Hib, *N. meningitidis* group C, or *S. pneumoniae*.

For this hospital-based active surveillance, a clinical investigator in each participating ward was contacted three times a year for information on new cases. After patient discharge, a standardized form was completed on site by a designated clinical investigator and was sent to the investigating center (ACTIV). The standardized form covered the following data: date and term of birth, gender, age during hospitalization, bacterial etiology of meningitis or purpura fulminans, vaccination status, short-term outcome, and mortality.

2.2 Bacteriology and serotyping

Bacterial species were identified by standard methods and/or PCR in the microbiology laboratory of each hospital. Each strain was serotyped in the French National Reference Center corresponding to the bacterial species.

2.3 Definition of incorrect vaccination status

Vaccination status was documented in the immunization chart of each child. The age and birthdate of the child was analyzed according to the French immunization schedule of each year [5]. The definitions used were the following:

- No vaccine administered: children who should have received a vaccination according to their age and the bacterial species and who had not received any dose.
- Vaccination delay: the vaccination delay for each dose of different vaccine, according to the French immunization schedule 2013 for children younger than 2 years, was defined by Gras et al. using the Delphi process [9]. The consensus was: 15 days after the recommended date for the first two doses of the diphtheria–tetanus–acellular pertussis–inactivated poliovirus–Hib vaccine and for the first two doses of PCV-13, 2 months after the recommended date for the booster of diphtheria–tetanus–acellular pertussis–inactivated poliovirus–Hib vaccine and for the booster of PCV-13 and 1 month after the recommended date for the MenCC.
- Missing dose(s): children who did receive at least one injection of the specific vaccine but who also missed at least one dose. The exact dates of injection were unknown for those children and thus we could not classify them as “vaccination delay.”

2.4 Statistical analysis

Statistical analyses were conducted using Excel[®] software (Microsoft[®] 2011). Results are expressed as numbers and percentages for categorical variables and as medians, minimum and maximum values for continuous variables, according to their distribution.

2.5 Ethics

The data collection was approved by the French Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) and by the French National Data Protection Commission (CNIL, no. 913006).

3. Results

From 2011 to 2013, among 1110 cases of meningitis or purpura fulminans, 125 (11.3%) were due to bacterial species preventable by vaccination in the general population and 78.4% of these cases ($n=98$) had available vaccination data. A total of 48 children (49%) had an incorrect vaccination status (no or incorrect specific vaccination). We focused only on these 48 cases. The remaining 50 cases are detailed in Figure 1; 42 of them were too young/ too old to be vaccinated according to the French vaccination schedule (including 16 patients with *N. meningitidis* group C meningitis aged 2–12.1 months old [mo] at diagnosis).

Among the 48 children with an incorrect vaccination status, there were 41 cases of bacterial meningitis and seven cases of purpura fulminans. The bacteria involved were *N. meningitidis* group C ($n=26$, 54.2%), following by *S. pneumoniae* ($n=19$, 39.6%), and Hib ($n=3$, 6.3%) (Figure 1).

The majority of these patients ($n=35$, 72.9%) had received no vaccine injection. Three patients (6.3%) had a delay in the vaccination (primovaccination, booster, or catch-up) (median: 34 days; minimum 30 days, maximum 35 days) and 10 (20.8%) had missed at least one injection (primovaccination, booster, or catch-up) (Figure 1).

The sex ratio was 0.5. The median age was 3 yo (minimum 2.6 mo, maximum 16.9 yo). Three deaths (6.3%) in patients with incorrect vaccination status were reported: one due to *N. meningitidis group C* (age: 16.1 yo) and two due to *S. pneumoniae* (ages: 6.1 mo and 3.6 yo). The other complications reported were: one opisthotonos, one 1 immunological reaction, one osteomyelitis, one reactive arthritis, one upper limb motor deficit, one limb amputation, one intracranial hypertension, one hydrocephalus, three seizures, and one mydriasis.

Regarding the children with *N. meningitidis group C* meningitis and incorrect vaccination status ($n=26$), primovaccination was missing for five of them and catch-up for 21 of them.

Regarding children with *S. pneumoniae* meningitis and incorrect vaccination status, the pneumococcal serotypes were distributed as followed: 19A: $n=8$ (42.1%); 19F: $n=4$ (21.1%); 14: $n=3$ (15.8%); 7F: $n=2$ (10.5%); 23F: $n=1$ (5.3%); 1: $n=1$ (5.3%). All the serotypes were included in the vaccine the child should have received.

4. Discussion

In France, there were 48 vaccine-preventable cases of meningitis or purpura fulminans and three deaths in children with incorrect vaccination status over a 3-year period. Most of them (72.9%) had received no injection at all for the vaccine concerned. To our knowledge, our study is the first to provide data on these three vaccine-preventable meningitis cases and the vaccination status of the patients in a meningitis nationwide surveillance network.

Most of these cases could have been avoided if the vaccination schedule had been followed: vaccination at the appropriate age, without forgetting vaccine boosters and catch-up. Indeed, the risk of bacterial meningitis in infants can be decreased through worldwide vaccination.

Davis et al. indicate that approximately three quarters of meningitis deaths are preventable with existing Hib and pneumococcal conjugate vaccines [10]. As for the MenCC, several countries observed a significant decline in serogroup C disease after vaccination campaigns reaching more than 98% in the United Kingdom and in The Netherlands [4]. The majority (54.2%) of incorrectly vaccinated patients in our study had *N. meningitidis group C* meningitis, supporting the need for particular effort for vaccination with MenCC.

Vaccine efficacy is related not only to individual protection but also to herd immunity (conjugate vaccines). For example, in the United Kingdom after implementation of the MenCC, the significant decrease in this type of meningitis (98%) was attributed to both direct protection and herd immunity thanks to the high vaccination coverage [11]. On the other hand, in France, the vaccination coverage remained low (50% of 1–4 yo, 13% of 15–19 yo children in 2013) [12]. During the study period, MenCC was recommended from the age of 1 yo to 24 yo in France because it was hypothesized that herd immunity could protect unimmunized infants younger than 12 mo [13]. However, because of low vaccination coverage, herd immunity is insufficient in France [12]. For example, in our cohort, 16 patients with *N. meningitidis group C* meningitis were 2–12.1 mo at diagnosis. Most of these cases could have also been avoided if vaccination coverage had been higher in France [14]. Thus, because of insufficient herd immunity, French recommendations were reviewed in 2017 allowing infants to receive MenCC from 5 mo [5].

Indeed, vaccine hesitancy has increased in high-income countries [15]. Vaccination-related global reduction in the incidence of infectious diseases gives the impression that the severity of and susceptibility to these diseases has decreased and that vaccination has become unnecessary. Moreover, concerns about vaccine safety have increased [16]. Controversies on

vaccination led to a crisis of public confidence in vaccinations despite campaigns aimed at restoring public trust in immunization. In this context, it seemed important to provide an overview of vaccine-preventable meningitis cases and incorrect vaccination status.

Our study has several limitations. First, although the bacterial meningitis network GPIP-ACTIV has existed for 17 years, the number of meningitis cases might be underestimated. Secondly, data about vaccination status were lacking for some cases. Thirdly, we chose not to analyze cases of patients who were too young to be vaccinated according to the French recommendations. Indeed, these cases should have benefited from herd immunity, but with a low vaccination coverage in France, this herd immunity effect is complicated to evaluate.

5. Conclusion

There are still far too many children with vaccine-preventable disease and incorrect vaccination status. Increasing information on vaccines and improving vaccination compliance must become a priority. For this purpose, mandatory vaccination of children younger than 2 yo against 11 pathogens (including Hib, *N. meningitidis* group C, and *S. pneumoniae*) in France was established in January 2018 [17]. Nevertheless, in our study, 21 cases of vaccine-preventable meningitis were associated with a lack of catch-up for MenCC. These children aged over 2 yo would not have been included in the mandatory vaccination program. Thus, further follow-up is needed to determine whether this new measure of mandatory vaccination is helpful enough to improve vaccination protection in France.

Conflict of interest:

J. Truong: none

C. Levy: received personal fees and non-financial support from Pfizer.

S. Prot-Labarthe: none

HPK. Nguyen: none

E. Grimpel: none

A. Faye: none

R. Cohen: received personal fees and non-financial support from Pfizer, personal fees from MSD, GSK, Sanofi and AstraZeneca.

M. Lorrot: received non-financial support from Pfizer and Sanofi

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Table 1: French vaccine recommendations since 2002 for children in the general population (unless otherwise specified)

Vaccines	French immunization schedule
Hib (Hib conjugate vaccine)	<ul style="list-style-type: none"> - Until 2013: 2,3 and 4 mo and booster at 16–18 mo - Since 2013: 2 and 4 mo and booster at 11 mo
<i>N. meningitidis group C</i> (meningococcal C conjugate vaccine)	<ul style="list-style-type: none"> - Until 2010: only for high-risk children*¹ - From 2010 to 2013: 1 injection between 12 and 24 mo and extended vaccine catch-up to 24 yo during the implementation period - From 2013 to 2017: 1 injection at 12 mo and vaccine catch-up to 24 yo - Since 2017: 2 injections at 5 and 12 mo and 1 injection for vaccine catch-up between 1 and 24 yo
<p><i>S. pneumoniae</i> (PCV-7/PCV-13)</p> <p>Serotypes PCV-7: 4; 6B; 9V; 14; 18C; 19F; 23F</p> <p>Serotypes PCV-13: 4; 6B; 9V; 14; 18C; 19F; 23F; 1; 3; 5; 6A; 7F; 19A</p>	<ul style="list-style-type: none"> - From 2002 to 2006: PCV-7 for children <2 yo considered at high risk*² of invasive pneumococcal infections - From 2006 to 2008: PCV-7 at 2,3 and 4 mo with a booster at 12 mo for children < 2 yo - From 2008 until the 22nd of April 2010: PCV-7 at 2 and 4 mo with a booster at 12 mo - From 2010 to 2013: PCV-13 at 2 and 4 mo and booster at 12 mo - For 2010 (year of transition PCV-7 to PCV-13): PCV-13 catch-up until 2 yo even if already vaccinated with PCV-7 - Since 2013: PCV-13 at 2 and 4 mo and booster at 11 mo

Hib: *Haemophilus influenzae type b*

PCV-7: 7-valent pneumococcal conjugate vaccine; **PCV-13:** 13-valent pneumococcal conjugate vaccine

mo: month(s) old ; **yo:** year(s) old

*¹ close contact with a *N. meningitidis group C* case or underlying health disorders

*² underlying health disorders or living conditions

Figure 1: Vaccine-preventable meningitis or purpura fulminans in children from 2011 to 2013 in France

The vaccination status is presented for the bacterial species concerned and according to the French immunization schedule of the birth year and age

* according to the vaccination schedule in general population

Hib: *Haemophilus influenzae type b*

N. meningitidis: *Neisseria meningitidis*

S. pneumoniae: *Streptococcus pneumoniae*

