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Research paper

Poor adherence to population-based vaccination in two counties after meningococcal B:14:P1.7,16 outbreak: an illustration of the growing vaccine hesitancy in France

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ABSTRACT

Background: *Neisseria meningitidis* is a virulent bacteria provoking outbreaks of invasive meningococcal disease (IMD) that authorities may try to control with population-based vaccinations. Such campaigns are most often thoroughly followed. We assess the response of poor adherence during a population-based vaccination after a meningococcal B:14:P1.7,16 outbreak.

Methods: Between July, 2012, and April, 2013, six cases including one fatality of invasive meningococcal disease related to *N. meningitidis* B:14:P1.7,16/ST32 were reported in two neighboring counties. A vaccination campaign with MenBVac[®] targeting 6911 inhabitants was implemented. People entering the vaccination schedule from January 2014 received 4CMenB.

Results: The number of immunized patients proved to be low, with 1721 (24.1%) receiving at least one dose out of 5069 doses administered. However, the incidence of IMD in the zone dramatically fell, with only one purpura fulminans case in June 2014 with a good outcome. The campaign was stopped after 1 year and a 2-year monitoring period was implemented until June, 2016, with no new cases.

Conclusions: This outbreak probably self-terminated in a context of a low incidence of serogroup B IMD during 2014 in France. Poor adherence illustrates the growing vaccine hesitancy in France. Similar campaigns will have to be thoroughly planned and implemented in terms of timing, modalities of injections, and mass communication.

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1. Abbreviations

AMM *Autorisation de mise sur le marché* (Marketing Authorization)

ARS *Agence régionale de santé* (Regional Health Agency)

CNR *Centre national de référence* (National Reference Centre)

HCSP *Haut conseil de santé publique* (French High Council of Public Health)

GP general practitioner

IMD invasive meningococcal disease

OMV outer membrane vesicle

PMI *Protection maternelle et infantile* (Child and Maternal Protection Centers)

PCR polymerase chain reaction

2. Introduction

Neisseria meningitidis may cause meningitis, arthritis, sepsis (invasive meningococcal disease, IMD) and, in its most severe form, purpura fulminans, a life-threatening condition for which early recognition and aggressive treatment are necessary to prevent fatality [1]. In France, IMDs must be reported as part of the National

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Table 1
Description of the six cases of infections related to *N. meningitidis* B:14:P1.7,16.

Patient	1	2	3	4	5	6
Date	2012, July	2012, Sept.	2012, Sept.	2012, Sept.	2013, April	2013, April
Age (months)	212	72	21	92	16	43
Sex	F	M	M	M	M	M
Clinical signs	Purpura, meningitis	Purpura, meningitis	<i>Purpura fulminans</i>	Arthritis	<i>Purpura fulminans</i>	Meningitis
Outcome	Favorable	Favorable	Deceased	Favorable	Favorable	Favorable

Notifiable Disease Surveillance System to Santé Publique France, the National Public Health Agency, and to the Neisseria Unit of the French National Reference Centre for Meningococci (CNR, *Centre National de Référence du Méningocoque*, Institut Pasteur, Paris, France). Among the 12 different serogroups of *N. meningitidis*, serogroup B is involved in more than 60% of epidemic clusters in Europe [2]. Six cases of B14 IMD, including one fatality, were reported in two neighboring counties of the Pyrénées-Atlantiques department (southwestern France, Nouvelle-Aquitaine region) during an 8-month period. The strain identified was *N. meningitidis* serogroup B, serotype 14, serosubtype P1.7,16 and sequence type 32 (B:14:P1.7,16/ST 32), known for its particular virulence and its implication in many outbreaks worldwide [3]. This prompted the implementation of a local vaccination campaign between June 2013 and January 2014, with the 4CMenB vaccine (Bexsero[®], Novartis, Basel, Switzerland and now licensed by GSK, London, UK).

This study aimed at describing the modalities and outcomes of this program.

3. Material and methods

The two neighboring counties of Lagor and Navarrenx are located in the Pyrénées-Atlantiques department (southwestern France). They cover approximately 170 km², with 17 towns and 14,000 inhabitants in Lagor County, and almost 6000 inhabitants and 23 towns in Navarrenx.

Between September 2012 and April 2013, six cases of invasive meningococcal B:14:P1.7,16 were notified (Table 1). The first four

cases in the area (see Fig. 1, Zone 1) were reported between July and September 2012, including a toddler who died following purpura fulminans. The estimated attack rate of invasive meningococcal B:14:P1.7,16 diseases within the area increased to 18.7 per 100,000 inhabitants, whereas it was 0.6 per 100,000 in France in 2012 [4]. A vaccination campaign with MenBvac[®] for relatives and contacts of the cases was started based on a two-dose regimen (week 0 and week 6). A Ministry of Health circular (HCSP, *Haut Conseil de Santé Publique*, French High Council of Public Health) dated February 22, 2013, stated that if further invasive diseases related to that particular strain were to occur in the area by September 2013, targeted vaccinations of people aged 2 months to 24 years would be implemented with MenBvac[®] [5]. Two more cases in siblings were reported in April 2013, belonging to Zone 3. They were linked to the area because their day care center was located within the area. This prompted the implementation of the campaign.

N. meningitidis was identified in cerebrospinal fluid, blood cultures, synovial liquid, and biopsy of a purpura lesion, either directly, after culture, or via a PCR (polymerase chain reaction). The local laboratory reports each suspected case to the CNR, which carries out further investigations on biological samples to determine the precise serotype of the strain. The community survey is initiated by the *Santé Publique France* (National Public Health Agency), which alerts the Ministry of Health (*Ministère de la Santé*, Paris, France) in case of a circumscribed outbreak.

MenBvac[®] is a vaccine that has been produced in Norway since 1983 (National Institute of Public Health, Norway) [6]. Its mechanism is based on the recognition of particles constituting

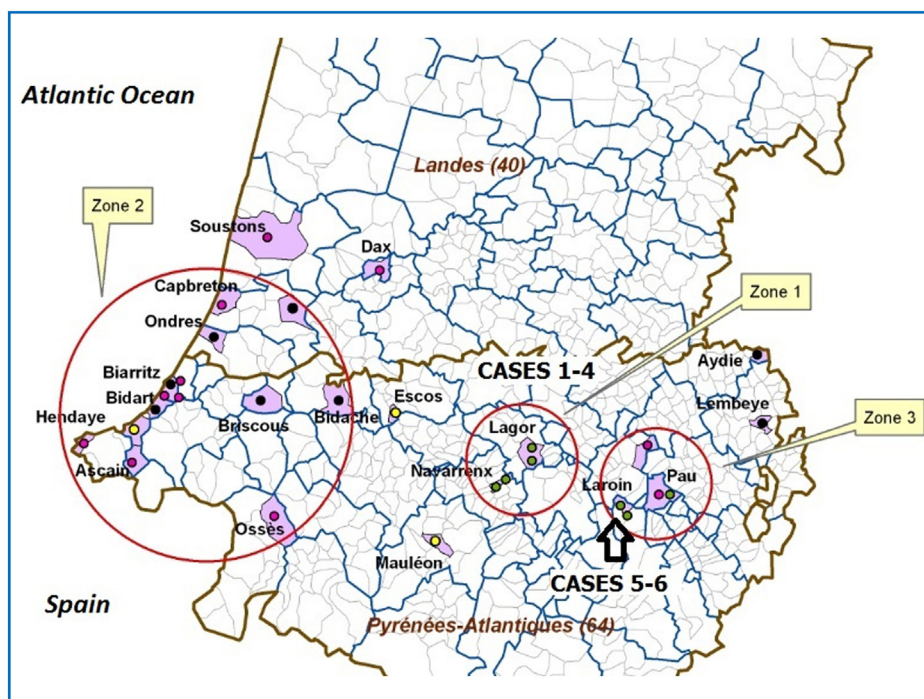


Fig. 1. Locations of the different cases of invasive meningococcal diseases in southwestern France, 2012–2013. Cases related to B:14:P1.7,16 are represented by a green dot.

the outer membrane vesicle (OMV). MenBvac[®] is specifically designed to target B15 subtypes but has been proven efficient in controlling previous B14 outbreaks in France [7]. Its main advantage was its immediate availability, as producing a “tailor-made” vaccine is too time-consuming in the context of an outbreak. Immunization schedules were based on previous campaigns, with injections at week 0, week 6, week 12, and a booster 1 year later for children under 2.

The vaccination campaign was modified after 6 months, when Bexsero[®] became available in France in January 2014. New patients entering the immunization program at this point received Bexsero[®], while patients who had received at least one injection of MenBvac[®] were supposed to continue with the same product. The vaccination schedule for Bexsero[®] was based on its Summary of Product Characteristics (three doses and a booster after 1 year for infants aged 2–5 months, two doses for children aged more than 6 months with a booster after 1 year for patients aged 6 months to 2 years).

The immunization program primarily targeted people from the ages of 2 months to 24 years, either living or working in the two counties. Children living outside these two areas were included whenever their schools, child minders or day care centers were inside the area. Data were collected from health insurance files, lists of the Ministry of Education, and data from occupational medicine services (Table 2). A final total of 6911 people were targeted. The aim was to immunize 70% of the population in order to induce herd protection.

Injections were performed in three municipal halls or in Child and Maternal Protection Centers (PMI, Protection Maternelle et Infantile) opened from Monday to Friday. Patients could also be vaccinated by their general practitioners (GP) if they had been included in the plan. GPs were asked to complete a form that was returned to the ARS (Agence Régionale de Santé, Regional Health Agency) after the injection. Due to the poor adherence to the campaign (see the Results section below), schools were added to municipal halls beginning in January 2014.

Targeted individuals were entered in a computerized database using the Gestimes[®] software, which was also used as a phone call center to schedule appointments in a vaccination center or in the office of a GP inside the zone.

Doses of MenBvac[®] and Bexsero[®] were centralized in the pharmacy of one of the nearest hospitals (Pau Hospital) and progressively sent to vaccination centers and GPs' offices. The campaign started on June 24, 2013, and ended on July 10, 2014. A note published by the French High Council for Public Health (Haut Conseil de Santé Publique, Paris, France) confirmed the end of the campaign [8].

Data were extracted from the Gestimes[®] software into an Excel[®] database (Microsoft Excel[®], Microsoft Inc., Redmond, WA, USA). Statistical analyses were conducted using SAS[®] version 9.4 (SAS Institute, Cary, NC, USA) by Dr. Stéphane Debeugny.

4. Results

In July 2014, among the 6911 people targeted, 1853 (26.8%) had phoned the call center to make an appointment and 1721 (24.1%)

were immunized with at least one dose. Therefore, 132 people did not receive immunization despite having an appointment. Eight people had scheduled appointments since June 23, 2014, which means that a few children were likely to receive their first doses during the last days of the program.

Overall, 5069 doses were administered (Table 3). With 6911 people targeted, the expected number of injections was 14,513 (based on a 70% coverage rate and three injections).

Differences were noted between age classes (Table 4), and immunization rates decreased with age. Nearly half of the infants aged less than 1 year received at least one dose of vaccine, versus 4% in the 20- to 24-year-old age class. This diminishing trend was confirmed by the unilateral Cochran-Armitage trend test ($P < 0.0001$).

The implementation of immunizations in schools beginning in January 2014 increased the number of children vaccinated in the 10- to 19-year-old age class, which accounted for 66% of first doses administered in 2014 vs. 37% in 2013 (Table 5). However, 78% of the cohort received their first doses of MenBvac[®] in 2013 ($P < 0.001$).

Adherence to the complete schedule after the first doses was good, with 80 and 67% of patients receiving two and three doses, respectively.

The number of vaccinated people was lower in Lagor county, confirmed by the chi-squared test ($P < 0.0001$, Table 6).

In June 2014, a 9-year-old girl living in Lagor county demonstrated purpura fulminans related to *N. meningitidis* B:14:P1.7,16. She had previously received three doses of MenBvac[®], the last of them 5 months earlier. The outcome proved excellent, but she required mechanical ventilation, fluid resuscitation, and norepinephrine infusion. An immune deficiency was suspected, but immunological tests were all normal.

At the same time, the incidence of IMD in the zone dropped dramatically, and during the 2-year survey period (from June 2014 to June 2016), no further cases were reported within the area.

5. Discussion

The number of patients immunized proved to be low. There are several possible reasons for this. The campaign began in June, just before the summer holidays. Additionally, enhancing the campaign with school-based injections was decided a few days before Christmas break during winter 2013–2014.

It is noteworthy that children were likely to receive their first doses almost 1 year after the start of the campaign. Even if a shorter campaign duration with a better adapted period and strong communication seems more efficient, communication should be maintained throughout the duration of vaccination. The number of new patients vaccinated in 2014 could have been higher, as 78% of the cohort had started the program with MenBvac[®] in 2013.

In France, vaccination schedules are mainly carried out by GPs, not by public institutions. The targeted population was not linked to a unique place of life or work (e.g., a university), and despite a

Table 2
Age distribution of patients in the area.

Age (years)	Lagor County	Navarrenx County	Other counties	Total
< 1	115	44	7	166
01–04	660	238	96	994
05–09	979	343	119	1441
10–14	1018	438	82	1538
15–19	1018	362	77	1457
20–24	879	258	151	1315
Total	4669	1710	532	6911

Table 3
Number of doses administered.

	MenBvac [®]	Bexsero [®]
Dose 1	1313	360
Dose 2	1193	298
Dose 3	1143	3
Dose 4	759	–
Total	4408	661
	5069	

Table 4
Number of patients receiving at least one dose in each age class.

Age (years)	Number of patients for each age class	Patients receiving at least one dose (%)
< 1	166	78 (47)
01–04	994	368 (37)
05–09	1441	473 (32)
10–14	1538	449 (29)
15–19	1457	300 (20)
20–24	1315	52 (4)
Total	6911	1720 ^a

^a Age not specified in one case.

Table 5
Age at first injection, stratified per year.

Age (years)	First dose in 2013 (%)	First dose in 2014 (%)	Total
< 1	62 (79)	16 (21)	78
01–04	334 (91)	34 (9)	368
05–09	403 (85)	70 (15)	473
10–14	318 (71)	131 (29)	449
15–19	185 (62)	115 (38)	300
20–24	44 (58)	8 (15)	52
	1346 (78)	374 (22)	1720 ^a

^a Age not specified in one case.

Table 6
Number of people vaccinated with at least one dose in each county.

County	MenBvac [®]	Bexsero [®]	Total	CR (%)
Lagor	758	206	964	20.6
Navarrenx	508	52	560	32.7
Others ^a	93	104	197	37
Total	1359	362	1721	24.9

CR: coverage rate.

^a People living outside the two zones.

Table 7
Comparison between the two French campaigns targeting the meningococcal strain.

	Population	First dose	Second dose	Third dose
Seine-Maritime 2003–2005 (MenBvac [®] only, Rouaud 2006 [11])	4189	2859 (68%)	2835 (67%)	2747 (65%)
Pyrénées-Atlantiques 2013–2014 (MenBvac [®] and Bexsero [®])	6911	1721 (24%)	1371 (20%)	1146 (16%)
		$P < 0.0001$	$P < 0.0001$	$P < 0.0001$

rather small surface encompassing only two counties, vaccination centers were scattered and not numerous enough.

The regimen with 3 + 1 or 2 + 1 injections may have frightened people. However, the coverage rate was higher in toddlers during the period in which the number of routinely recommended vaccines was the highest.

Switching the product from MenBvac[®] to Bexsero[®] during the program might also have confused the population.

The percentage of patients receiving second and third doses was 80 and 67%, respectively. This means that the largest possible number of individuals must have been reached during the very first days of the campaign, given that thereafter the schedule was followed well.

The difference of adherence between the two counties could be related to disparate socioeconomic levels. Navarrenx was primarily agricultural, with some older and wealthy families, whereas Lagor County has a low-income population in a more urban setting. Disparities within a territory are challenging, but sociological aspects in the two counties should have been addressed to increase motivation through a more aggressive communication in pre-selected areas [9].

In France, physicians and institutions face a climate of growing distrust toward vaccination. The comparison of this campaign to previous community immunizations against IMD showed a lower acceptance of the vaccine with a low final coverage rate. In 2002, an outbreak of meningococcal C infection led to vaccination in three departments in southwestern France, including Pyrénées-Atlantiques [10]. The targeted population was very similar to the 2013–2014 campaign, with children aged 2 months to 20 years and adults aged 21–24 living in collective settings. The schedule was simpler, with only one required dose of meningococcal serogroup C conjugate vaccine (Meninvact[®], Aventis Pasteur MSD, France), except for infants under 1 year of age, for whom two more doses were necessary. GPs played a major role in the campaign, because doses of vaccines were available in their offices. Nine weeks later, vaccine coverage was estimated after inquiries in selected schools and the rate of immunized people was close to 80% in the Pyrénées-Atlantiques department.

We also compared our data with another immunization program that took place in Northern France from 2003 to 2005, also targeting *N. meningitidis* B:14 P:1.7,16, with MenBvac[®] [11]. The number of vaccinated patients after 1 year was summarized and compared to the Lagor-Navarrenx county program (Table 7). The rates of vaccinated individuals after first, second, and third doses were reduced approximately threefold. Compared to the Seine-Maritime campaign, no collective fear emerged, and local media did not thoroughly spread the information, but prompted publications of new disputes concerning vaccination (see below).

These two previous campaigns may have indicated that the Lagor-Navarrenx campaign would be accepted and thoroughly followed by the population. However, the goal of a 70% coverage rate was not reached, and even if these three programs are not strictly comparable, the differences in coverage rates raise questions.

A recent worldwide inquiry, including 67 countries and 65,819 people, showed that France had the highest rate of suspicion against vaccination (41%) [12]. In France, the widespread vaccination of French inhabitants against influenza H1N1 in 2009 seriously disoriented the population because the mass vaccination proved expensive, and the flu was less severe than predicted [13]. Hepatitis B and human papillomavirus vaccines remain controversial because of a suspected link to demyelinating diseases that has not been proven to date [14,15]. The media places the focus on isolated cases, and social networks play the role of amplifiers. In November 2013, shortly after injection of a quadrivalent HPV vaccination, a young patient experienced symptoms evocative of multiple sclerosis. Interestingly, the patient lived in Bordeaux, where the nearest university hospital from the two counties is located.

(http://www.lemonde.fr/sante/article/2013/11/24/premiere-plainte-contre-le-vaccin-anticancer-gardasil_3519409_1651302.html). The information made the front cover of local newspapers, a position never reached by the vaccination campaign. Such news places the focus on the so-called danger of vaccines and adds to the suspicion concerning immunization. However, there are now strategies to fight against vaccination hesitancy [16]. The only patient who exhibited an IMD in the zone had received three doses of MenBvac[®]. The level of antibodies

have been proven to diminish even with a three-dose-schedule, which may explain this vaccination failure [17]. Lastly, in 2014 in France, the number of meningococcal infections proved low, with 426 infections and 230 (55.8%) concerning *N. meningitidis* serogroup B [18]. The latter figure was a 20-year low in France. We could therefore hypothesize that the outbreak self-terminated in a context of diminished circulation of the bacteria. It is also possible that people outside the targeted areas were vaccinated with Bexsero[®] after its marketing authorization in January 2014, further diminishing the spread of the strain.

6. Conclusion

Given the low rate of immunized individuals, it would be questionable to consider that the campaign succeeded in controlling the outbreak. It is more likely that the outbreak self-terminated.

Many lessons can be drawn from this program. The death of a toddler is unfortunately not sufficient to raise public awareness about the benefits of vaccination. Stakeholders cannot rely on previous successful campaigns. To be successful future campaigns would require improved organization, including appropriate timing and strong communication strategies. Strategies for addressing vaccine hesitancy must be applied, and such programs in restricted areas could be opportunities to test them. Professional communication agencies could be involved in informing targeted populations, with a special focus on low-income areas. A short and intense campaign is probably more efficient than a long program, given that the majority of first doses were injected in the first 6 months. We believe that GPs should be very involved, as they are on the front lines of vaccination schedules in France. French authorities must fight against vaccine hesitancy via survey programs, including social networks, to identify and close websites that promote fears and lies about immunizations. Fear of vaccines continues to grow and could surpass fear of meningitis.

Disclosure of interest

The authors declare that they have no competing interest.

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References

- [1] Rosenstein NE, Perkins BA, Stephens DS, et al. Meningococcal disease. *N Engl J Med* 2001;344:1378–88.
- [2] Annual Epidemiological Report 2016–Invasive meningococcal disease. Stockholm: European Centre for Disease Prevention and Control; 2016, <http://ecdc.europa.eu/en/healthtopics/meningococcal-disease/Pages/Annual-epidemiological-report-2016.aspx> [cited 2017 Jun 28].
- [3] Raeloz VN, Luiz SJ. The elusive meningococcal meningitis serogroup: a systematic review of serogroup B epidemiology. *BMC Infect Dis* 2010;10:175.
- [4] Barret AS, Deghmane AE, Lepoutre A, et al. Les infections invasives à méningocoques en France en 2012 : principales caractéristiques épidémiologiques. *Bull Epidemiol Hebd (Paris)* 2014;1–2:25–31.
- [5] Haut Conseil de la Santé Publique. Avis relatif à la vaccination ciblée contre les infections invasives à méningocoque liées au clone B14:P1.7,16 du complexe clonal ST-32 avec les vaccins MenBvac[®] et Bexsero[®] dans le département des Pyrénées Atlantiques; 2013, <http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=324> [cited 2017 Jun 28].
- [6] Bjune G, Høiby EA, Grønnesby JK, et al. Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. *Lancet* 1991;338:1093–1096.
- [7] Caron F, Parent du Chatelet I, Leroy JP, et al. From tailor-made to ready-to-wear meningococcal B vaccines: longitudinal study of a clonal meningococcal B outbreak. *Lancet Infect Dis* 2011;11:455–63.
- [8] Haut Conseil de la Santé Publique. Avis relatif à la nécessité de poursuivre les campagnes de vaccination contre le clone B:14:P1.7,16 en Seine-Maritime, dans la Somme et les Pyrénées-Atlantiques; 2014, <http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=452> [cited 2017 Jun 28].
- [9] Hill HA, Elam-Evans LD, Yankey D, et al. Vaccination coverage among children aged 19–35 months – United States, 2015. *MMWR Morb Mortal Wkly Rep* 2016;65:1065–71.
- [10] Charron M, Hemery C. Étude de la couverture vaccinale suite à la campagne de vaccination contre le méningocoque C dans les Landes les Pyrénées Atlantiques et les Hautes Pyrénées en 2002. Saint-Maurice: Institut de Veille Sanitaire; 2004, [http://invs.santepubliquefrance.fr/pmb/invs/\(id\)/PMB_5959](http://invs.santepubliquefrance.fr/pmb/invs/(id)/PMB_5959) [cited 2017 Jun 28].
- [11] Rouaud P, Perrocheau A, Taha MK, et al. Prolonged outbreak of B meningococcal disease in the Seine-Maritime department, France, January 2003 to June 2005. *Euro Surveill* 2006;11:178–81.
- [12] Larson HJ, de Figueiredo A, Xiahong Z, et al. The state of vaccine confidence 2016: global insights through a 67-country survey. *EBioMedicine* 2016;12:295–301.
- [13] Boiron K, Sarazin M, Debin M, et al. Opinion about seasonal influenza vaccination among the general population 3 years after the A(H1N1)pdm2009 influenza pandemic. *Vaccine* 2015;33:6849–54.
- [14] Collange F, Fressard L, Pulcini C, et al. General practitioners' attitudes and behaviors toward HPV vaccination: a French national survey. *Vaccine* 2016;34:762–8.
- [15] Monteyne P, André FE. Is there a causal link between hepatitis B vaccination and multiple sclerosis? *Vaccine* 2000;18:1994–2001.
- [16] Jarrett C, Wilson R, O'Leary M, et al. SAGE Working Group on Vaccine Hesitancy. Strategies for addressing vaccine hesitancy – A systematic review. *Vaccine* 2015;33:4180–90.
- [17] Caron F, Delbos V, Houivet E, et al. Evolution of immune response against *Neisseria meningitidis* B:14:P1.7,16 before and after the outer membrane vesicle vaccine MenBvac. *Vaccine* 2012;30:5059–62.
- [18] Santé Publique France. Les infections invasives à méningocoque en France en 2014 [Internet]. <http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-infectieuses/Maladies-a-prevention-vaccinale/Infections-invasives-a-meningocoques/Donnees-epidemiologiques/Les-infections-invasives-a-meningocoque-en-France-en-2014> [cited 2017 Jun 28].