

Perspectives

RECENT TRENDS IN ANTIMICROBIAL RESISTANCE AMONG *STREPTOCOCCUS PNEUMONIAE* AND *STAPHYLOCOCCUS AUREUS* ISOLATES: THE FRENCH EXPERIENCE

Anonymous (b.coignard@invs.sante.fr)¹

1. Contributors are listed at the end of the paper. The indicated corresponding author summarised the data and coordinated the editorial process.

In France, the overall proportion of penicillin-non-susceptible *Streptococcus pneumoniae* has decreased from 53% in 2002 to 38% in 2006, and the proportion of methicillin-resistant *Staphylococcus aureus* from 33% in 2001 to 26% in 2007. Although the rates remain very high compared to northern European countries, these trends suggest that the prevention efforts implemented since 2000 through two national programmes (the national plan for preserving the efficacy of antibiotics and the national infection control programme) and updated recommendations for pneumococcal vaccination are successful.

Introduction

Antimicrobial resistance is a multifaceted threat of global concern in the European Union. In this article, we illustrate results and efforts to counteract its spread in France through two microorganisms, *Streptococcus pneumoniae* and *Staphylococcus aureus*, that are frequently isolated from community-acquired or hospital-acquired infections, respectively*. The proportion of resistance in these species is a good indicator of the evolution of antimicrobial resistance in France and these bacteria are key targets of two national programmes: the national plan for preserving the efficacy of antibiotics [1] and the national programme for infection control [2]. Quantitative targets were included in these programmes in 2004 [3], aiming to reduce, by 2008, the proportion of penicillin-non-susceptible strains among *S. pneumoniae* isolates to under 30% and the proportion of methicillin-resistant (MRSA) strains among *S. aureus* isolates to under 25%.

Streptococcus pneumoniae resistance trends

Data sources

Antimicrobial susceptibility in *S. pneumoniae* is studied by a group of 22 regional laboratory networks (*Observatoires Régionaux du Pneumocoque*), covering the 22 French metropolitan regions (excluding overseas regions) and coordinated by the French national reference centre for *S. pneumoniae* (CNRP). The CNRP collects all blood or cerebrospinal fluid (CSF) isolates from children under the age of 15 years, all CSF isolates from adults, and a selection of strains isolated from adults with respiratory tract infections (respiratory or blood isolates) or from children with acute otitis media [4].

Since 2001, susceptibility testing results for invasive isolates (blood or CSF) have been submitted to the European Antimicrobial

Resistance Surveillance System (EARSS; <http://www.rivm.nl/earss/>). All laboratories use agar dilution and recommendations from the Antibigram Committee of the French Society for Microbiology (CA-SFM, <http://www.sfm.asso.fr/>) for antimicrobial susceptibility testing and breakpoints. However, yearly data submitted by France to EARSS only included the first six months of a given year due to time constraints in the European data collection process; the data presented in the following include all strains received annually by the CNRP.

Results

Participation of laboratories has been stable since 2001. In 2006, for instance, the CNRP collected 1,411 strains from 406 private or public microbiological laboratories that provide support for 444 healthcare facilities covering 61.4% of admissions to French medical wards. Among those strains, 857 (61%) were isolated from invasive infections (blood or CSF) and 554 (39%) were isolated from respiratory tract infections.

Overall, the proportion of penicillin-non-susceptible *S. pneumoniae* (PNSP) was negligible before 1987 and then increased regularly every year, up to 53% in 2002 (48% and 46% of blood and CSF isolates, respectively). Between 2003 and 2005, the proportion of PNSP decreased, and remained stable (38%) in 2006 (34% for blood and CSF isolates) (Figure 1) [4].

Among invasive *S. pneumoniae* isolates, the overall proportion of PNSP decreased from 47% in 2001 to 34% in 2006. This corresponded to a decrease from 51% to less than 32% in children under the age of 15 years, and from 45% to 35% in adults (Table 1). A sharp reduction was noted in the proportion of PNSP (from 67% to 27%) among CSF isolates from children under the age of two years. The change in blood isolates in the same age group was less pronounced, with the proportion of PNSP remaining at or above 40% throughout this period and even increasing in 2006.

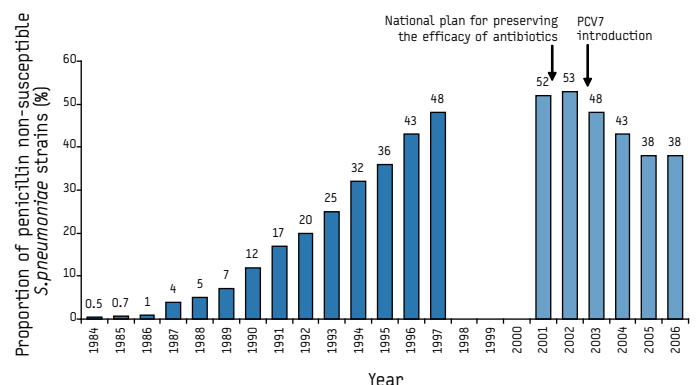
Discussion: prevention and control activities

The observed decrease in PNSP started after the implementation in November 2001 by French public health authorities of the first national plan for preserving the efficacy of antibiotics (Figure 1). Two studies helped to define actions of this plan targeting the community: In 2000, a controlled, population-based trial was conducted in three French regions and demonstrated that intensive

educational strategies aimed at optimising antibiotic use could significantly reduce the rate of PNSP colonisation [5]. In 2002, a study conducted by the French National Insurance Fund for Salaried Workers (CNAMTS) showed that both physicians and patients had little knowledge on antibiotics, resulting in poor antibiotic practices.

A multifaceted programme was then initiated by CNAMTS to avoid inappropriate antibiotic use in outpatients. The “Antibiotics aren’t automatic!” campaign (<http://www.antibiotiquespasautomatiques.com/>) aimed at increasing awareness of physicians as well as the public on good antibiotic practices. Using humoristic television commercials, it targeted specific populations likely to ask for antibiotics (young mothers, young workers, the elderly) and

FIGURE 1
Proportion of penicillin non-susceptible *S. pneumoniae* among all strains studied by CNRP, France, 1984 to 2006 (n=50,300)



Note. no national figures from 1998 to 2000, as CNRP activities were interrupted. CNRP: national reference centre for *S. pneumoniae*; PCV7: 7-valent pneumococcal protein conjugate vaccine.

TABLE 1
Proportion of penicillin non-susceptible *S. pneumoniae* among invasive isolates, by age and type of isolate, France, 2001 to 2006

	2001		2002		2003		2004		2005		2006	
	N	%	N	%	N	%	N	%	N	%	N	%
Children												
<2 years												
Blood isolates	143	62.2	104	59.6	170	58.8	83	39.8	145	41.4	99	46.5
CSF isolates	87	66.7	69	62.3	99	44.4	72	50.0	76	39.5	67	26.9
2-15 years												
Blood isolates	150	30.7	87	37.9	183	33.9	123	31.7	206	23.8	133	23.3
CSF isolates	39	51.3	37	37.8	37	35.1	41	29.3	55	30.9	33	30.3
All isolates from children	419	50.8	297	51.2	489	44.8	319	37.6	482	32.4	332	31.6
Adults (>15 years)												
Blood isolates	828	46.0	678	46.0	635	41.6	232	44.8	461	36.2	308	34.1
CSF isolates	213	42.3	214	42.3	255	42.4	209	38.3	294	36.1	215	36.3
All isolates from adults	1,041	45.2	892	45.2	890	41.8	441	41.7	755	36.2	523	35.0
Total	1,460	46.8	1,189	47.5	1,379	42.9	760	40.0	1,237	34.7	855 ¹	33.7

¹ age missing for two of the 857 strains reported in 2006.
N: strains tested for susceptibility; %: proportion of PNSP among tested strains.

promoted prudent use of antibiotics. The campaign has been repeated every winter since 2002 and become widely known and popular, parents becoming more and more aware of the benefits and limits of antibiotics [6].

Other interventions since 2002 have been aimed at general practitioners, including academic detailing, peer-to-peer visits by health insurance delegates and the promotion of the streptococcal group A rapid diagnostic test for sore throat, that CNAMTS distributed to physicians free of charge. Data sent to the European surveillance of antimicrobial consumption (ESAC) network by the French Health Product Safety Agency (Afssaps) show that the overall antimicrobial consumption in ambulatory care in France has decreased from 33.0 defined daily doses per 1,000 inhabitants per day in 2001 to 27.9 in 2006, a reduction of 15%; the consumption of broad-spectrum penicillins (ATC4 code J01CA) has decreased by 20% and the consumption of macrolides (ATC4 code J01FA) by 39% (<http://www.esac.ua.ac.be/>). CNAMTS later demonstrated that its campaign was cost-effective [7].

In addition to reduced consumption of antibiotics, the introduction in March 2002 of the 7-valent protein conjugate vaccine (PCV7) for children under the age of two years [8] is likely to have contributed to the larger and faster decrease of PNSP rates among this age group than among adults. In 2002, serotypes covered by PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F) accounted for 71% of invasive pneumococcal disease in France; most of them (68%) were PNSP, as compared to 44% for non-vaccine serotypes [4]. From 2004 to 2007, PCV7 vaccine coverage increased from 27% in six-month-old children to 56% in six- to 12-month-old children [9,10]. In children under the age of two years, the incidence between 2001/02 and 2006 of pneumococcal meningitis and bacteraemia decreased from 8.0 to 6.0 and from 21.8 to 17.5 cases per 100,000, respectively [11].

A partial replacement of vaccine serotypes by non-vaccine serotypes such as 19A, a serotype with a proportion of 85% PNSP in 2006, may explain why the decrease in the proportion of PNSP was not sustained in 2006 [12].

Staphylococcus aureus resistance trends

Data sources

Data on methicillin resistance among *S. aureus* strains are issued from four different sources; all involved laboratories follow the recommendations from the Antibigram Committee of the French Society for Microbiology (CA-SFM, <http://www.sfm.asso.fr/>) for antimicrobial susceptibility testing and breakpoints.

The first source is the data submitted each year since 2001 by France to EARSS (<http://www.rivm.nl/earss/>), collected by three microbiological networks that contribute to the "Observatoire national de l'épidémiologie de la résistance bactérienne aux antibiotiques" (Onerba). They include 19 teaching hospitals of the Azay-Resistance network, nine general hospitals of the Ile-de-France network, and, since 2004, 26 hospitals, mostly general hospitals, of the Reussir network (<http://www.onerba.org/>). These data allow calculating the proportion of methicillin-resistant *S. aureus* (MRSA) isolates among all *S. aureus* invasive isolates.

The second source is the national multidrug-resistant bacteria surveillance network (BMR-Raisin, <http://www.invs.sante.fr/raisin/>), which includes the five interregional infection control coordinating centres (CClin) and has been collecting data on MRSA isolates from all diagnostic specimens (excluding screening isolates) since 2002. More than 450 microbiological laboratories participate on a voluntary basis each year (between 478 in 2002 and 675 in 2006, when it accounted for 47% of all French hospital beds), making it possible to calculate the incidence density of MRSA infections in healthcare facilities per 1,000 patient days (pd) [13].

The third source is national prevalence surveys on nosocomial infections, which have been conducted every five years in French healthcare facilities since 1996. Antibiotic susceptibility profiles are recorded for selected pathogens (including *S. aureus*) that are recovered from any nosocomial infection, thus providing a measure of the prevalence of patients infected with MRSA [14].

The fourth and last source is a network of 39 teaching hospitals in the Paris area belonging to a single organisation, the "Assistance publique - Hôpitaux de Paris" (AP-HP); MRSA surveillance started

there in 1993 and provides the longest continuous time series available on this topic in France.

Results

According to the latest EARSS report [15], France remained in 2006 one of the European countries with the highest proportion of MRSA among *S. aureus* isolates. However, while MRSA rates in most countries were increasing in 2006 (including those with the lowest rates), the report highlighted decreasing rates in two countries: France and Slovenia. In France, the MRSA proportion has decreased from 33% in 2001 to 26% in 2007. The additional 26 French laboratories enrolled in the EARSS data collection since 2004 actually slowed this downward trend, as they accounted for 38% of all *S. aureus* strains in 2006 and their MRSA proportions were higher than in other participating laboratories (Table 2).

The decreasing proportion of MRSA among *S. aureus*, as reported by EARSS, is confirmed by national incidence data collected through the BMR-Raisin network. Data from 227 laboratories that have participated in this network since 2003 (totalling more than 4,000,000 pd each year) point to a decreasing incidence density of MRSA infections in acute care wards, which fell from 0.89 MRSA infections per 1,000 pd in 2003 to 0.64 MRSA infections per 1,000 pd in 2007. This trend was even more pronounced in intensive care units, where the incidence density fell from 2.37 MRSA infections per 1,000 pd in 2003 to 1.59 MRSA infections per 1,000 pd in 2007 (Figure 2) [Raisin, unpublished data].

A decrease in MRSA rates was also noted in national prevalence surveys, through comparison of data from the 1,351 healthcare facilities having contributed to the surveys in 2001 and 2006 which included 550,637 patients (279,490 patients in 2001 and 271,147 in 2006). In these 1,351 healthcare facilities, the proportion of nosocomial infections with a microbiological diagnosis increased from 72% in 2001 to 78% in 2006, as did the proportion of *S. aureus* strains tested for antimicrobial susceptibility (93% in 2001 and 96% in 2006). The proportion of MRSA among *S. aureus* isolates decreased from 62% in 2001 to 50% in 2006. The prevalence of MRSA-infected patients decreased from 0.49% in 2001 to 0.29% in 2006, a reduction of 41%. This trend was

TABLE 2

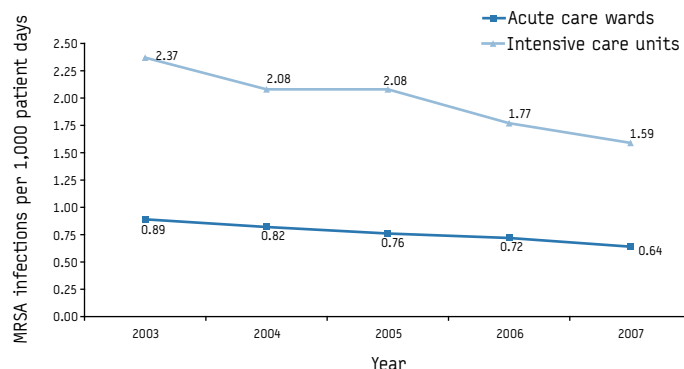
Proportion of methicillin-resistant *S. aureus* among strains isolated from invasive isolates, by network contributing to EARSS, France, 2001 to 2007

Year	Azay-Resistance		Ile-de-France		Reussir		Total	
	N	%	N	%	N	%	N	%
2001	1,459	32.8	248	35.5	-	-	1,707	33.2
2002	1,425	32.9	238	33.2	-	-	1,663	32.9
2003	1,419	28.3	285	31.9	-	-	1,704	28.9
2004	1,596	26.4	319	28.2	1,409	31.6	3,324	28.8
2005	1,905	24.9	204	30.9	1,343	29.9	3,452	27.2
2006	2,078	25.7	276	25.0	1,444	28.4	3,798	26.7
2007*	2,429	25.3	287	20.2	1,535	27.7	4,251	25.7

*preliminary data as of July 2008;
N: strains tested for susceptibility; %: proportion of MRSA among tested strains; EARSS: European Antimicrobial Resistance Surveillance System; MRSA: methicillin-resistant *S. aureus*;

FIGURE 2

Methicillin-resistant *S. aureus* incidence density in healthcare facilities that have participated since 2003 in the BMR-Raisin Network, by type of unit, France, 2003 to 2007 (n=227)

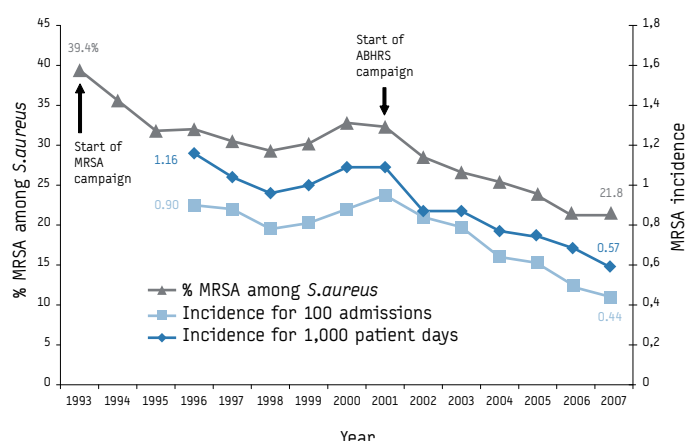


MRSA: methicillin-resistant *S. aureus*.

observed across all types of healthcare facility, from university hospitals to long-term care facilities, and across all subspecialties but obstetrics (Table 3); it remained significant after adjusting for the patients' case-mix in a multivariate analysis [14].

Finally, in the AP-HP group, the proportion of MRSA among *S. aureus* isolated from clinical specimens in acute care decreased from 39% in 1993 to 22% in 2007. At the same time, the incidence density of MRSA decreased from 1.16 MRSA infections per 1,000 pd in 1996 to 0.57 MRSA infections per 1,000 pd in 2007 (Figure 3) [AP-HP, unpublished data].

FIGURE 3
MRSA proportion among *S. aureus*, and MRSA incidence, 39 teaching hospitals of the Paris area, 1993 to 2007



Source: Assistance publique - Hôpitaux de Paris
MRSA: methicillin-resistant *S. aureus*. ABHRS: alcohol-based hand rub solutions

Discussion: prevention and control activities

Interventions that may account for the decrease in MRSA rates in France started in 1992, when the first European study on MRSA reported that the proportion of MRSA among *S. aureus* was 33.8% in France, the second highest proportion after Italy [16]. In 1995, a first multicenter survey in 43 hospitals showed that the median MRSA incidence in French intensive care units was 2.82 MRSA infections per 1,000 pd [17]. At that time, infection control teams were progressively implemented in French healthcare facilities, CClin had just been created, and antimicrobial resistance surveillance networks were being developed. A group of French intensive care specialists and microbiologists decided to start acting first in their own hospitals within the AP-HP group, and produced in 1993 (Figure 3) the first recommendations for prevention and control of multidrug-resistant bacteria [18].

The AP-HP recommendations provided the basis for the first national guidelines issued in 1999 by the French Ministry of Health and its Hospital Infection Control Advisory Committee [19]. They were disseminated to healthcare facilities and services through the CClin who coordinate regional networks of infection control teams and targeted diagnosis of multidrug-resistant bacteria, contact precautions, reinforcement of hand hygiene, isolation and cohorting, screening of patients, prudent antimicrobial use and evaluation through audits of practices and surveillance.

Interestingly, the fact that it is still necessary nowadays to include these key targets into national plans, shows that the fight against antimicrobial resistance is a long road. Interestingly, most of these key targets are still included in national plans nowadays, suggesting that patience is required in the fight against antimicrobial resistance. In addition, it takes time to provide the resources for adequate infection control nationwide – in 2006, 92% of French healthcare facilities had an infection control team, according to a yearly survey performed by the Ministry of Health [20] – and to integrate recommendations in the daily clinical practice – in 2001, a study assessing the implementation of recommendations in 395 French intensive care units found that 70% performed active surveillance cultures for MRSA and that 88% flagged and isolated carriers [21]. Even if there is still room for improvement,

TABLE 3
Prevalence of methicillin-resistant *S. aureus* infected patients, by type of ward and year of survey; French national prevalence surveys, 2001 and 2006

Specialty	2001			2006			Δ (%)
	Patients	Infected		Patients	Infected		
	N	N	%	N	N	%	
Acute care	146,445	708	0.48	147,908	437	0.30	-39
- medicine	72,933	325	0.45	76,418	212	0.28	-38
- surgery	49,086	253	0.52	47,776	148	0.31	-40
- obstetrics	18,313	6	0.03	18,356	10	0.05	
- intensive care	6,113	124	2.03	5,358	67	1.25	-38
Rehabilitation	42,737	331	0.77	43,203	173	0.40	-48
Long term care	55,370	295	0.53	44,720	161	0.36	-32
Psychiatry	34,867	24	0.07	33,791	8	0.02	-66
Other	71	2	2.82	1,525	2	0.13	
Total	279,490	1 360	0.49	271,147	781	0.29	-41

Note: This analysis was restricted to nosocomial infections acquired in the 1,351 healthcare facilities that participated in both surveys.
 Δ (%) = relative difference in prevalence between 2006 and 2001

the situation appeared to be considerably better than the one in the United States, a country with very high MRSA rates, where only 18% of hospitals performed MRSA surveillance cultures in high risk units in 2003 [22].

More recently, MRSA control in France has been reinforced through the extensive promotion and use of alcohol-based hand rub solutions for hand hygiene. An intensive campaign to promote their use was launched within the AP-HP group (Figure 3), and the overall usage increased from 1 to 21 litres per 1,000 pd from 2000 to 2007 [AP-HP, unpublished data]. Similar campaigns were conducted in other hospitals and regions, e.g. in Western France where a survey recently reported that the usage of alcohol-based hand rub solutions has doubled in the period from 2002 to 2005 [23].

Other factors that possibly contributed to the decrease of MRSA in France may have been the strong and coordinated national infection control programme that allocates infection control resources and sets quantitative objectives through indicators, as well as patients' associations asking for more results and transparency. The benefits and pitfalls of public reporting of infection control indicators remain a matter of debate. Such indicators have been progressively implemented in France since 2006 by the Ministry of Health (<http://www.icalin.sante.gouv.fr/>). They include scores that rate nosocomial infection control organisation and activities in each hospital (ICALIN) and the overall consumption of alcohol-based hand rub products (ICSHA) [24]. Our experience suggests that they provide a strong incentive for healthcare facilities to develop infection control activities and may be a key element for a sustainable decrease in MRSA rates.

Conclusion

PNSP and MRSA rates remain very high in France compared to Northern Europe countries [15]. Although the recent trends are encouraging, it is difficult to relate them to specific actions, as the interventions were multifaceted and implemented simultaneously. However, they suggest that the prevention efforts implemented since 2000 were successful and the national targets set in 2004 for 2008 will hopefully be reached.

According to a modelling study published in 2006, it may take more than 10 years to lower MRSA rates in countries with high prevalence [25]. The trends observed in France confirm that the fight against antimicrobial resistance is a long and demanding challenge and suggest that the dissemination of recommendations for a rational use of antibiotics, infection control and vaccination should be actively pursued.

* Data on other multidrug-resistant bacteria in France are available through the InVS website at <http://www.invs.sante.fr/ratb/> (French and English versions).

Acknowledgments

For their contribution to these results, we thank the French microbiological laboratories, infection control teams, healthcare facilities, healthcare professionals and institutions involved in antimicrobial resistance surveillance, infection control and antibiotic stewardship.

Contributors in alphabetical order:

JM Azanowsky¹, C Brun-Buisson², A Carbone³, P Cavalie⁴, B Coignard^{3,5}, T Demerens⁶, JC Desenclos⁷, D Guillemot⁸, L Gutmann⁹, V Jarlier^{3,9}, A Lepoutre³, D Levy-Bruhl³, S Maugat^{3,5}, L May-Michelangel², P Parneix³, B Schlemmer¹, JM Thiolet^{3,5}, E Varon⁸

1. Plan national pour préserver l'efficacité des antibiotiques (French national plan for preserving the efficacy of antibiotics), Health Ministry, Paris, France
2. Programme national de lutte contre les infections nosocomiales (French national infection control programme), Health Ministry, Paris, France
3. Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales (Raisin, National nosocomial infection alert, investigation and surveillance network), Saint-Maurice, France
4. Agence française de sécurité sanitaire des produits de santé (Afssaps, French health products safety agency), Saint-Denis, France
5. Institut de veille Sanitaire (InVS, French institute for public health surveillance), Saint-Maurice, France
6. Caisse nationale d'assurance maladie des travailleurs salariés (CNAMTS, French National Insurance Fund for Salaried Workers), Paris, France
7. Institut Pasteur, Paris, France
8. Centre national de référence des pneumocoques (CNRP, French national reference centre for pneumococci), Paris, France
9. Observatoire national de l'épidémiologie de la résistance bactérienne aux antibiotiques (Onerba, French national observatory for epidemiology of the bacterial resistance to antimicrobials), Paris, France

References

1. French Ministry of Health. [2007-2010 national plan to preserve the efficacy of antibiotics]. [In French]. Paris: Ministère de la Santé; 2007. Available from: http://www.sante.gouv.fr/htm/dossiers/plan_antibio_2001/sommaire.htm
2. French Ministry of Health. [2005-2008 national infection control programme]. [In French]. Paris: Ministère de la santé; 2004. Available from: http://www.sante.gouv.fr/htm/actu/infect_nosoco181104/prog.pdf
3. French Ministry of Health. [Circular n°DGS/SD1C/2005/123 regarding the introduction of dispositions 88 to 96 of the law regarding public health policy]. [In French]. Paris: Ministère de la santé; 2005. Available from: http://www.sante.gouv.fr/htm/dossiers/biomedicale_circulaire/05_123t0.pdf
4. Varon E, Gutmann L. [National reference centre for pneumococci; 2007 activities report]. [In French]. Paris: Centre National de Référence des Pneumocoques; 2007. Available from: http://www.invs.sante.fr/surveillance/cnr/rapport_cnr_pneumo_2007.pdf
5. Guillemot D, Varon E, Bernede C, Weber P, Henriot L, Simon S, et al. Reduction of antibiotic use in the community reduces the rate of colonization with penicillin G-nonsusceptible *Streptococcus pneumoniae*. *Clin Infect Dis*. 2005;41(7):930-8.
6. Goossens H, Guillemot D, Ferech M, Schlemmer B, Costers M, van Breda M, et al. National campaigns to improve antibiotic use. *Eur J Clin Pharmacol*. 2006;62(5):373-9.
7. Inspection générale des affaires sociales (IGAS). [Knowledge of general practitioners on medication]. [In French]. Report n°RM 2007-136P. Paris: IGAS; 2007. p. 226. Available from: <http://lesrapports.ladocumentationfrancaise.fr/BRP/074000703/0000.pdf>
8. Pebody RG, Leino T, Nohynek H, Hellenbrand W, Salmaso S, Ruutu P. Pneumococcal vaccination policy in Europe. *Euro Surveill*. 2005;10(9):pii=564. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=564>
9. Cohen R, Gaudelus J, Pexito O. [Anti-pneumococcal conjugate vaccine: estimation of the target population. Survey with 1739 mothers]. [In French]. *Médecine et Enfance*. 2005;25(4):237-42.
10. Gaudelus J, Cohen R, Hovart J. [Vaccine coverage with the heptavalent pneumococcal conjugate vaccine in 2007. Comparison with previous years and other paediatric vaccines: analysis of vaccination booklets]. [In French]. *Médecine et Enfance*. 2007;27(5):1-4.
11. Lepoutre A, Varon E, Georges S, Gutmann L, Levy-Bruhl D. Impact of infant pneumococcal vaccination on invasive pneumococcal diseases in France, 2001-2006. *Euro Surveill*. 2008;13. *Euro Surveill*. 2008;13(35):pii=18962. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18962>
12. Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med*. 354(14):1455-63.
13. Carbone A, Arnaud I, Coignard B, Trystram D, Marty N, Maugat S, et al. Multidrug-resistant bacteria surveillance, France, 2002-2005. 17th European Congress of Clinical Microbiology and Infectious Diseases; 2007 March 31-April 3; Munich, Germany. 2007. [Abstract #0364].