Vaccination of cancer patients treated with chemotherapy: a survey among general practitioners.

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ABSTRACT

Objectives. Despite specific recommendations issued by the French Public Health Council (Haut Conseil de Santé Publique), the vaccination coverage of patients with cancer or malignant blood disease remains insufficient. The aim of this study was to assess the vaccination of chemotherapy patients by their general practitioner (GP).

Methods. A survey was conducted between March and July 2017 in 4 French departments to describe the immunization practices of GPs for their chemotherapy patients and provide solutions to help to increase the vaccination rate.

Results. Of the 1,610 GPs who received the questionnaire, 287 (17.8%) returned a usable form. 92.6% were globally pro-vaccine. One third of GPs (37.3%) declared that they vaccinated all their chemotherapy patients. The GPs (n = 180) who never or only sometimes vaccinated their chemotherapy patients mainly voiced concerns about not being properly trained (45.6%) and the lack of easily available information on vaccination (35.0%). Three-quarters (n = 212; 74%) of the GPs wanted to improve their level of medical knowledge via continuing education (52.4%) or by reading guidelines available on-line (39.6%). GPs suggested that a specific vaccination schedule be included in the letter they receive from the cancer specialist (72.8%) and that patient awareness be increased (50.5%)

Conclusions. GPs are in favor of the vaccination of cancer patients. The main obstacles stated are the lack of education and the lack of easily available information. Vaccination coverage could be increased by improving the doctor-to-doctor relation between GPs and cancer specialists.

Key words: Cancer, chemotherapy, malignant blood disease, vaccination

INTRODUCTION

The World Health Organization (WHO) estimates that vaccination avoids 2 to 3 million deaths annually. In 2016, 130 countries had reached infant vaccination rates of at least 90% for diphtheria, tetanus and whooping cough [1]. In France, for three decades now, there is a feeling of relative mistrust in vaccination in the general population. While the vaccination rate is appropriate in children, it is much less so in adults. The last nationwide vaccination coverage data were published in 2002 and showed that only 58.4% of adults were up to date with their diphtheria vaccine, 66.1% with tetanus and 63.4% with polio, which means that 40% of the adult population is not correctly protected [2].

The results are of even more concern in immunocompromised patients. Patients treated with chemotherapy for a solid tumor or malignant blood disease should be immunized against invasive pneumococcal disease and seasonal influenza. A booster vaccine against diphtheria, tetanus and polio is also required six months after the end of treatment. In 2013, the AVNIR study, an anonymous on-line survey of 3,653 immunocompromised patients, 294 of whom had been treated with chemotherapy, revealed that only 72% of patients were immunized against influenza and 39% against pneumococcal disease [3].

Despite specific national recommendations [4], the vaccination rate of immunocompromised oncology-hematology patients is still far from satisfactory. Immunization is generally performed by local general practitioners (GPs) who are globally pro-vaccination [5]. This study assumed that cancer patients treated with chemotherapy were rarely immunized by their GP and investigated the reasons that prevented such vaccination. Once the obstacles hindering immunization were

identified, we suggested ways of improving the vaccination coverage rate.

MATERIAL AND METHODS

Study design. This study is based on a survey, sent to general practitioners, to describe vaccination practices for patients with cancer or malignant blood disease treated with chemotherapy.

Study population. Doctors registered in 2016 with the French Medical Association (*Conseil National de l'Ordre des Médecins*) as working actively as a general practitioner, either partially or totally self-employed (self-owned private practice), in four departments in the west of France (Vienne, Deux-Sèvres, Charente, Charente Maritime). Based on the data collected by the French National Institute of Statistics and Economic Studies (*Institut National de la Statistiques et des Etudes Economiques*, INSEE), 1,683 GPs were registered in these 4 departments on January 1, 2016, that is a density of 1 GP for 1,075 inhabitants. Among the 88,886 GPs registered in France in 2016, 63.4% were either totally or partially self-employed (i.e. 56,353).

The following exclusion criteria were applied: retired GPs, new GPs registered in 2017, full-time hospital doctors, doctors who are neither primary care physicians nor self-employed, doctors who practice only as mesotherapists, acupuncture physicians, homeopathic physicians or chiropractors.

Data collection. GP practices were contacted one by one between March 15 and July 15, 2017, using the telephone directories available on Internet and asked by which means they preferred to receive the study questionnaire: fax, postal mail or

email. The questionnaire consisted of 10 questions (see Supplementary figure). The demographic data collected for the GPs were: sex, start of practice (year), kind of practice, estimated total number of patients. Their general acceptance of vaccination was evaluated. GPs were asked to estimate the number of adult patients who received chemotherapy in 2016, the number who were given a prescription for immunization, and the number of chemotherapy patients who were actually immunized. They were also asked to assess the obstacles that hinder vaccination, their need for education on the vaccination of chemotherapy patients, and to propose potential solutions for improving the vaccination coverage of this at-risk patient population. A 5-point Likert scale including the category “Don't know” was used [6].

Statistical analysis. Quantitative variables are reported as mean $\pm$ standard deviation (SD). Qualitative variables are reported as percentages with the 95% confidence interval (CI95). The qualitative data for the GPs included in the study were compared with the data for all GPs registered in the 4 departments by means of a Chi2 test. The significance threshold applied was $p < 0.05$. The primary endpoint was the proportion of general practitioners that immunized their cancer or malignant blood disease patients who were currently treated, or had been treated during the previous year with chemotherapy. Secondary endpoints were analyzed by logistic regression and were the proportion of vaccine recommendations fulfilled in immunocompromised patients treated with chemotherapy. Variable collinearity was tested. Variables with a p-value < 0.25 as determined by univariate analysis were then included in multivariate analysis, following log-linear assessment of quantitative variables. Bivariate interactions with a p-value < 0.25 were included. Finally, multivariate logistic regression analysis was performed using a descending stepwise selection procedure that first removed interactions, then variables with a p-value

> 0.05. The goodness of fit of the model was determined using the Hosmer-Lemeshow test. Analyses were carried out using SAS9.4 (NYC, USA).

RESULTS

Study population. In all, 1,610 GPs working in 806 private primary care practices were contacted. Among the 708 practices (87.8%) that agreed to receive the questionnaire: 105 received it by fax, 317 by postal mail, and 286 by email. In all, 298 self-employed GPs (17.7%) completed the survey, and 287 questionnaires could be processed (**Figure 1**). GP demographic data is provided in **Table 1**. The population of GP responders was representative of the overall GP population in the 4 departments ($p = 0.775$). GPs who had been practicing medicine for over 30 years represented 29.6% of the sample ($n = 85$), those practicing for less than 10 years represented 26.8% ($n = 77$). On average, GPs cared for a pool of $1,203 \pm 523$ patients, among which 13 were treated with chemotherapy (that is 1.0% of the practice population). Most GPs (92.8%) were pro-vaccine or strongly pro-vaccine in general (**Figure 2**).

Vaccination of chemotherapy patients by their GPs Only 37.3% ($n = 107$; CI95 [33-41%]) of GPs in the sample stated that they vaccinated all of their chemotherapy patients as per recommendations, 58.2% ($n = 167$; CI95 [54-62%]) vaccinated only certain patients, and 4.5% ($n = 13$; CI95 [3-7%]) vaccinated none of their patients. In the study sample, 32.4% ($n = 93$) of GPs said they had prescribed vaccination for at least half of their chemotherapy patients, and 67.6% ($n = 194$) for less than half of their patients. For example, in the Vienne department and according to health insurance services, 27.7% patients treated for cancer or blood disease were

vaccinated against influenza between September 1, 2016 and March 31, 2017. 19.2% (n = 55) of GPs stated that they thought that their patients received a prescription for vaccination from the oncologist or hematologist. Multivariate analysis that took into account confusion factors (**Table 2**) showed that the 107 GPs who implemented the guidelines for vaccination were three times more likely to be willing to receive education on the vaccination of chemotherapy patients (OR = 3.23 [1.85-5.66]; $p < 0.001$).

Obstacles hindering the vaccination of chemotherapy patients. In the questionnaire, GPs who only vaccinated certain patients or vaccinated no patients were asked what they believed the reasons that prevented vaccination were. There were no significant differences in the number of years of medical practice or the location of the practice (rural or urban area) between the GPs who stated that they vaccinated all their chemotherapy patients and those who did not. Among the 180 GPs (62.7%) who did not vaccinate all their chemotherapy patients, 45.6% (n = 82) mentioned inappropriate training and 35.0% (n = 63) stated they found no readily available information to overcome this drawback. At the same time, 39.4% (n = 71) stated they experienced difficulties trying to convince their patients, and for 23.9% (n = 43) of GPs the lack of vaccination was due to patient refusal. The brevity of primary care consultations were also a limiting factor for 14.4% (n = 26) of GPs. Finally, 6.7% (n = 12) of GPs mentioned the lack of efficacy of vaccines during the period a patient is treated with chemotherapy. An insignificant proportion (3.3%, n = 6) forgot to talk about vaccination during the consultation.

Need for education. Nearly three-quarters of GPs (73.9%, n = 212) expressed the need for training about the vaccination of chemotherapy patients. They suggested that such information be dispensed through continuing medical education (52.4%,

n = 111), specific guidelines available on-line (39.6%, n = 84) and medical journals (24.5%, n = 52). A website dedicated to vaccination was suggested by 35.8% (n = 76) of the responders. They also suggested that it be included in their self-education program (24.1%, n = 51) and peer meetings (21.7%, n = 46).

Solutions for improving the vaccination coverage rate. Potential solutions for improving the vaccination coverage rate in chemotherapy patients are summarized in **Figure 3**. The GPs who suggested including a vaccination schedule in the letter from the oncologist/hematologist did not differ significantly from the other GPs in the study, both in terms of years or kind of practice.

DISCUSSION

The global opinion of general practitioners about vaccination has been repeatedly addressed in the literature [7]. However, their position about the vaccination of immunocompromised patients is much less documented (30).

This survey that included 287 French GPs is to our best knowledge the first study to investigate vaccination by GPs in patients treated with chemotherapy for a solid tumor or malignant blood disease. Only one third of the GPs stated that they vaccinated all their chemotherapy patients (or patients having received chemotherapy) as per the guidelines. This subgroup of GPs showed raised awareness compared with other GPs about their need for education. The results of our survey are in line with a study conducted by the cancer center for the same French region that receives the patients of the four departments. The authors of that study demonstrated poor influenza vaccine coverage (33.5%) and very low anti-pneumococcal vaccine coverage (7.9%) [8]. Despite these findings, 92.6% of the

GPs who responded to the survey stated that they were globally pro-vaccine. This is similar to national figures [7] with over 95% of GPs claiming to be pro-vaccine. These figures are nevertheless tempered when GPs are questioned about a particular vaccine. For example, similarly to British GPs, French GPs are less favorable to the hepatitis B vaccine with only 69% of favorable British GPs and [9] 74% of favorable French GPs [7].

There are probably several explanations behind this poor vaccination coverage rate. In the subgroup of GPs who provided reasons to justify why they did not vaccinate all their chemotherapy patients, 45.6% complained of a lack of appropriate training. In a nationwide study on how 6th-year medical school students felt about their initial education on vaccination, 33% stated that globally they did not feel adequately prepared for future practice [10]. GPs often recommend the vaccines for which they feel comfortable about explaining to the patients the benefits and risks and when they trust the official sources of information. On the other hand, they are less likely to recommend a vaccine that they feel is associated with frequent adverse effects or if they doubt its clinical relevance [11,12]. In a survey conducted in 2014 by the French Directorate for Research, Evaluation studies and Statistics (DREES) and including over 1,500 GPs, 32% of the participants stated that the vaccine against seasonal flu contains an adjuvant (which is not the case) and 43% did not express an opinion [5]. Only 6.7% of the GPs taking part in our study and questioned about the obstacles for vaccination claimed to be convinced of the safety of vaccines for chemotherapy patients. As a general rule, many GPs seem to doubt the usefulness of vaccines. A study conducted by Verger *et al.* that included 1,712 French GPs demonstrated that 16% of GPs never recommended any particular vaccine and 43% provided different levels of recommendation depending on the vaccine [12]. This is

not observed in France alone. In 2017, a meta-analysis conducted by Paterson *et al.* showed that articles addressing vaccination hesitancy among health professionals originated from 33 different countries. Among these countries, the most represented were the United States (16%), the United Kingdom (14%) and China (7%) [13].

The lack of easily available information was also an obstacle for 35.0% of the GPs. They often see the complexity of the immunization schedule and its constant changes to include new vaccines and new guidelines as a constraint [14]. To this should be added a new tendency to critic official recommendations and guidelines, that they consider to be ill-suited to primary care practices and to the patients themselves [15]. It is therefore obvious that if a physician expresses reservations over the usefulness of a vaccine, he/she will be less likely to recommend it to his/her patients and less likely to answer the patient's questions about the safety of vaccination in a satisfactory manner [16]. In our study, 39.4% of GPs claimed to experience difficulties when trying to convince their chemotherapy patients about vaccination when the patients were not aware of the risks.

Many infectious diseases have disappeared from western countries but are still not fully eradicated. When the patient perceives that he/she is not at risk, then GPs are confronted with their refusal to be vaccinated, as for 23.9% of the cases in our study. Confusion between adverse events and adverse effects has given rise to much controversy since the end of the 90s, for example neurodegenerative diseases imputed to hepatitis B vaccination [17] and criminal complaints filed for adverse effects attributed to the vaccine against papillomavirus. A link between autism and the MMR vaccine was suggested in a study on 12 cases published in 1998 in the *Lancet* [18]. There was no serious scientific basis behind this affirmation and it has since been dismantled by numerous studies using sound methodologies [19–21].

However, the rumor caused by this assertion led to a decrease in the vaccination coverage rate in English-speaking countries and an increase of the incidence of measles and the related morbidities. The presence of aluminum in some vaccines is also controversial. The debate about macrophagic myofasciitis that arose exclusively in France, originated from the results reported by a single team, now largely proven wrong [22]. The inappropriate management of the vaccination campaign during the 2009 H1N1 flu pandemic also contributed to the global feeling of discontent, both in patients and health professionals, even those in favor of vaccination [23].

Despite the doubts voiced by patients, and sometimes by doctors, the benefits of vaccination have been ascertained and due to the efficacy of vaccines, the individual and collective memories of the diseases they prevent are being forgotten. Discussing the respective risks and benefits of vaccination assumes that doctors are better informed than their patients. However, it should be noted that 73.9% of them requested education on vaccines via various complementary means and materials. Continuing medical education, easier access to guidelines and articles in medical journals are the main means of providing information to GPs found in the literature [24]. According to a study on GPs working in rural areas in three different countries, distance learning is also a relevant tool, as shown in our study [25]. Distance learning is more readily accessible, would therefore help train a greater number of GPs, and would be just as efficient as face-to-face education.

In our study, 72.8% of the GPs stated that a vaccination schedule should be included in the letter they receive from the oncologist. Many GPs criticize a lack of communication and coordination between hospital doctors and primary care practices [26,27], and take for example hospital reports that are of little use to GPs [28]. According to a study performed in 2004 by DREES and the French National Institute

of Health & Medical Research (INSERM), patients being treated by chemotherapy globally declared to be satisfied by the information provided by their oncologist or organ specialist, but considered in 33% of cases that “too much information” was provided and in 48% of cases that it “was too complicated” [29]. Providing different kinds of crucial information when announcing to a patient that he/she has a solid tumor or malignant blood disease explains why vaccination might seem to be of lesser importance during this period. However the risk of contracting pneumococcal disease is 12 to 14 times higher for patients with acute leukemia or lung cancer than in the general population [30], and flu-related mortality ranges from 11-33% in cancer patients, depending on studies [31].

The challenge of including vaccination in chemotherapy patient follow-up when only a very few such patients are followed by each GP (approx. 1%) and because they consult their GP less during chemotherapy because of their frequent visits to the onco-hematology department, are some of the reasons that explain the suboptimal vaccination rate. Although the vast majority of GPs are in favor of the outpatient management of cancer and blood disease patients [32], some insist that in fact they receive very few visits from chemotherapy patients during this period [33]. At the same time, oncologists report that they receive an increasing number of requests from their patients during their treatment about primary care conditions.

The French healthcare authorities, in collaboration with public consultation and several patient associations have proposed to create an individual electronic vaccination record, as suggested in our study [34]. Other measures have also been considered such as simplifying the vaccination schedule, regaining patient trust by a greater transparency of the proceedings of health authorities and more involvement of public health services via the vaccination of immunocompromised patients in

hospitals. The latter was approved by one third of the GPs who took part in our study.

This study has a few limitations. Due to controversy that exists only in France regarding the potential harmfulness of some vaccines that significantly increases vaccination hesitancy, some of our results apply only to France. On the other hand, the solutions we suggest could be applied in other countries [11,35]. Furthermore, even though the size of our sample of GPs is limited compared with the 88,886 GPs practicing in France in 2016, it is representative of the GPs in 4 French departments and the participation rate obtained is higher than for other similar studies [36].

It should also be noted that the study is based on declarative data. It is therefore subject to the same biases as other surveys on declarative data. There is potentially a selection bias caused by the fact that doctors in favor of vaccination are more likely to respond to this kind of survey. Declarative bias is also possible, that is a difference between the doctors' opinions, their declared vaccination practices and their real practices. Finally, memory bias should also be taken into consideration, mainly because of the low number of chemotherapy patients followed by each GP and their less frequent visits during chemotherapy [33].

CONCLUSION

Despite being regarded as central for prevention practices, GPs do not always follow current recommendations and routinely vaccinate their chemotherapy patients. According to primary physicians, the lack of easily available up-to-date information and education are a serious obstacle when trying to convince vaccine hesitant patients. The solutions put forward are based on continuing medical education, articles in medical journals and specific recommendations. Increasing the vaccination coverage rate in chemotherapy patients will also be achieved by improving the

coordination between hospital services and outpatient care. Information and instructions on both preventive measures via vaccination and treatment when necessary should be included in the letter the GP receives from the oncologist or hematologist. This study also reveals that GPs call for stronger involvement of public authorities by providing better information on vaccination for patients.

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Figure legend

Supplemental figure. Survey sent to 1,413 general practitioners

Figure 1. Flowchart showing the organization of the survey on cancer patient vaccination sent to general practitioners

Figure 2. Opinion on vaccination among the 287 French general practitioners who responded to the survey on cancer patient vaccination.

Figure 3. Solutions proposed by general practitioners to improve the vaccination coverage of chemotherapy patients

Other: provide a specific vaccination form in the chemotherapy follow-up file given to the patients by their oncologist, create an app for smartphones, make compulsory vaccination against flu and invasive pneumococcal diseases, and send automatic reminders for specific vaccines via the health insurance system to all declared cancer patients

CONFLICTS OF INTEREST

MG and MP have no conflicts of interest.

FR is president of the French Language Pathology Society.

BR was invited to a conference as a speaker by MSD and Gilead.

BR is principal investigator of a clinical trial for Janssen.

BR was invited to conferences as an auditor by Pfizer.

BR has performed ad hoc consulting activities for Astellas.

ETHICS APPROVAL

This study was approved by the French Data Protection Authority (CNIL).

AUTHOR CONTRIBUTIONS

MG, BR, and FR designed the study protocol. MP performed statistical analyses. MG collected the data. MG, BR, and MP analyzed the data. MG and BR wrote the manuscript. All authors read and approved the complete manuscript.

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None

Figure legend

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Translation of pie chart legends:

Très favorable = Strongly favorable

Favorable = Favorable

Moyennement favorable = Somewhat favorable

Peu favorable = Somewhat unfavorable

Ne sait pas = Don't know

Figure 3. Solutions proposed by general practitioners to improve the vaccination coverage of chemotherapy patients

Table 1.

Demographic characteristics of the 287 French general practitioners questioned about the vaccination of their chemotherapy patients

		Study population.	All GPs in the 4 departments*
		n (%)	n (%)
Population		287	1683
Women		104 (36.2)	588 (34.9)
Type of practice	Urban	74 (25.8)	461 (27.4)
	Semi-rural	107 (37.3)	576 (34.2)
	Rural	106 (36.9)	646 (38.4)

*Partially or totally self-employed

No significant differences between the study population and the overall population of GPs in the 4 departments; $p = 0.775$

Table 2.

Univariate and multivariate analysis regarding compliance with recommendations in the population of 287 French general practitioners

Variable	Univariate analysis	Multivariate analysis	
		OR (CI95)	p value
Sex	0.95		
1st year of practice	0.18		
Total number of patients	0.62		
Kind of practice	0.22		
Number of chemotherapy patients	0.52		
Opinion on vaccination	0.05		0.50
Need for information	< 0.001	3.23 (1.85-5.66)	< 0.001

OR: Odds Ratio; CI95: 95% confidence interval