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Development of Seasonal Influenza Vaccination Recommendations: Relevance and Influence of the Evidence on the Decision-Making Process in France and the Netherlands

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ABSTRACT

Background: Target groups for seasonal influenza vaccination are defined at the country level and are based on several factors. However, little is known about the national decision-making procedures.

Objective: The purpose of this study was to compare the evidence used for the development of recommendations and its impact on the choice of target groups in France and the Netherlands.

Methods: A preliminary documentary analysis identified institutions to include in the assessment: governmental authorities, research institutions, associations, and manufacturers. At least one expert from each group was invited to our study. Thirty-three semi-structured interviews were conducted in 2013 (16 France, 17 the Netherlands). We used NVivo10® to perform a thematic content analysis.

Results: Clinical/epidemiological studies were the evidence most used in both countries. Economic models were increasingly being used; these had greater influence on the decision making in the Netherlands than in France, probably because of the presence of a modeler. Generally, the quality of the evidence

used was poor, although no systematic use of standard protocol for its assessment was observed. A general protocol was sometimes used in France; however, the personal judgment of the experts was crucial for the assessment in both countries.

Conclusions: There were differences in the target groups, for example, pregnant women, recommended only in France. France and the Netherlands use similar evidence for developing vaccination recommendations, although different decisions are sometimes made regarding target groups. This could be associated with the lack of systematic standard appraisals, increasing the influence of the experts' judgment on decision making. The development of standards for the appraisal of evidence is recommended.

INTRODUCTION

More than one-third of countries in the world include seasonal influenza vaccination in their national immunization schedules [1]. However, in Europe, vaccination coverage rates (VCRs) have either stagnated or decreased since the 2008-2009 season [2], despite annual investments from the member states in vaccination campaigns. For example, the Netherlands maintained VCRs above 75% for the elderly until the 2011-2012 season; they have since decreased. In contrast, France has never achieved these VCRs [2].

The national recommendations for seasonal vaccination are constantly changing as they follow ever-changing international recommendations and advice (e.g., from the World Health Organization [WHO] and the European Centre for Disease Prevention and Control [ECDC]), as well as new findings from studies on target groups for influenza vaccination and new vaccine technologies [3] and [4]. In several countries, the development (modification or update) of seasonal recommendations is performed by National Immunization Technical Advisory Groups (NITAGs) [5], [6] and [7]; for instance, the Technical Committee on Vaccination (Comité technique des vaccinations) in France and the Committee on the National Immunization Program (within the Health Council) in the Netherlands. However, international literature explaining the decision-making process of the development of the recommendations is scarce. There are only a few studies outside of the United States that have investigated this subject during the influenza pandemic of 2009 [8], [9], [10] and [11]. Reviews have highlighted that the pandemic policies from 2009 have been an important determinant for subsequent seasonal influenza recommendations [3]. Interestingly, the failure of these pandemic policies was noted as one of the reasons for the decreasing acceptance of further seasonal recommendations [12]. The NITAG Resource Center is a platform recently made available by the WHO with the main objective of "supporting evidence-informed decision making for immunization programs and policies" [13]. To increase the acceptance and broaden the implementation of seasonal recommendations, the NITAGs often use a systematic and transparent approach to improve the quality and credibility of their advice [13] and [14]. This type of approach often requires robust evidence and standard procedures for decision making [13]. To our knowledge, an in-depth investigation of the evidence used in the decision-making procedures undertaken for the development of recommendations for seasonal influenza vaccination has not been

carried out in Europe. For this type of analysis, qualitative methods should be used to enable clarification of the beliefs of the NITAG experts and all stakeholders involved directly and indirectly (e.g., stakeholders who provide information to the process) in the decision-making process, and explore their thoughts on this subject [8] and [15]. We conducted a qualitative study in France and the Netherlands that compared the evidence used in the development of seasonal influenza vaccination recommendations and its impact on the choice of target groups. We were particularly interested in France and the Netherlands because they are geographically close yet culturally different. Therefore, we were interested in knowing whether such differences could play a role in their differential use of evidence and, consequently, choice of target groups [16] and [17]. For example, although both France and the Netherlands target the elderly for vaccination, the cutoff age is higher in France (France ≥ 65 years, the Netherlands ≥ 60 years), and pregnant women are targeted only in France [2]. In addition, we have collaborations with French and Dutch research teams (see coauthor affiliations), which facilitated the work in this study.

METHODS

A documentary analysis and semi-structured interviews were used for data collection. Each technique is described in detail below.

Documentary Analysis

A documentary analysis was used to identify the stakeholders engaged in forming the influenza policies in France and the Netherlands and the experts directly and indirectly involved in the development of vaccination recommendations. We used a wide electronic search engine (Google®) and entered keywords in English, French, and Dutch to search for hits regarding health care systems, influenza vaccination policies, and stakeholders. The search was limited to the last 10 years because policy procedures are constantly evolving, and older documents are probably obsolete. All stakeholder Web sites that were involved in policy processes were retained. The identified Web sites were carefully searched using the search strategy presented in Table 1 (see additional material in Supplemental Materials found at doi:10.1016/j.jval.2016.02.006). Two independent researchers screened the texts on the basis of their titles and abstracts. Documents were included in the study if they provided a description of the development of vaccination recommendations, the type of evidence used, and the stakeholders involved. Additional searches were performed in the libraries of our collaborating research teams, but no further suitable documents were identified.

[TABLE 1]

Interviews

We grouped the stakeholders identified in the documentary analysis into four categories: governmental authorities, research institutions, associations, and manufacturers. For each stakeholder (institution/organization), we identified the experts who were directly or indirectly (e.g., information providers) involved in the development of vaccination recommendations (Table 2). An invitation letter to join the study was sent by e-mail or post; after 2 weeks, we phoned those who did not respond to the first invitation. The invitation specified that the information provided and the participant's identity would remain anonymous.

[TABLE 2]

A guide for the semi-structured interviews was developed (see Annex 1 in Supplemental Materials found at doi:10.1016/j.jval.2016.02.006). It was prepared in French and then translated into English. It is well known that most Dutch experts are comfortable with an interview conducted in English; in our study, all Dutch experts spoke English to a high level. The guide focused on the objectives of our study. The French and English guides were validated using pilot interviews with influenza experts in both countries. All three pilot interviews (two France, one the Netherlands) were included in the analysis. One interviewer (M.L.S.) conducted the 33 interviews (28 face-to-face and 5 telephonic) in 2013: 16 in France during the summer and 17 in the Netherlands during the autumn (Table 2). In general, decisions regarding vaccination recommendations are made before the summer in both countries; hence, the timing of interviews was very close (France) or quite close (the Netherlands) to these decisions. Telephone interviews were solely conducted if a face-to-face interview was not possible. No major differences were observed between both types of interviews. Each interview was audio recorded, under oral consent of the interviewee, and then transcribed.

The transcripts were analyzed using thematic content analysis, in which common themes are identified and grouped into codes. The codes constitute the unit of analysis and are derived from recurring patterns of speech and vocabulary [18]. One investigator developed the first coding scheme by identifying answers from the verbatim transcripts that were relevant to the study questions (in vivo coding). After discussion with other investigators, the in vivo codes were completed with supplementary codes on the basis of literature. Transcripts were then recoded using NVivo10. Points of difference between investigators were solved by comparing the first coding and the second coding, and a final set of themes was developed. Finally, verbatim coding within all relevant themes was compared and analyzed to identify the overall findings, as well as any differences in the interview responses across countries.

Combining the Data from the Documents and Interviews

Combining the documents retrieved and interview results, we described and compared the type of evidence used for the development of recommendations in France and the Netherlands. Two important steps in the decision-making process were analyzed, namely, the selection and evaluation of the evidence in each country. Factors identified as influential are presented and compared between the countries. Finally, we provide a comparative table that describes the impact that the evidence had on the selection of target groups in France and the Netherlands.

RESULTS

Only 3 of the 24 invited stakeholders did not participate in our survey; they were members of the health care insurance boards in both countries and the French Medicines Evaluation Board (Table 2). In the following sections, we present the main results from the study, combined from the documentary analysis and interviews.

Evidence Used for the Development of Seasonal Vaccination Recommendations

Type of evidence

Most of the interviewees ranked clinical and epidemiological studies as the most important evidence used for developing recommendations. The clinical studies mainly described the characteristics of the disease and the vaccine (e.g., efficacy/effectiveness and safety), and the epidemiological studies generally explored the burden of influenza to society (e.g., severity, morbidity, and mortality). National bulletins about influenza surveillance and national recommendations produced in other countries, such as the United States and the United Kingdom, were also considered as highly relevant. As determined in our documentary analysis, this “gray literature” served as a basis and source of comparison for the development of recommendations in both France and the Netherlands.

The gray literature produced by international organizations (e.g., the WHO and the ECDC) was also taken into account. However, the perceptions of the interviewees differed. Dutch experts were skeptical about the applicability of WHO recommendations and ECDC advice to their national priorities. In contrast, most French experts emphasized the importance of the organizations’ review and evaluation of the existing literature, and considered it could be helpful for their national experts. The reports of the European Medicines Agency were often mentioned as useful by experts in both countries.

Both sets of interviewees stressed the importance of information produced locally by national research institutes, which was sometimes requested by the NITAGs. In the Netherlands, participants highlighted the RIVM (*Rijksinstituut voor Volksgezondheid en Milieu*/National Institute for Public Health and the Environment) as the major information provider, which frequently developed studies for the Dutch NITAG. Likewise, the Institut de Veille Sanitaire (Institute for Public Health Surveillance) in France was referred to as an important provider of epidemiological information. Analyses of the costs and benefits of influenza vaccination programs, cost-effectiveness analyses, and mathematical and epidemiological models were considered as minor sources of information by the NITAGs, although these studies were increasingly being discussed between experts. In the Netherlands, the models and economic studies seemed to be taken more into account, probably because modelers attending the Dutch NITAG helped other experts with the interpretation of these studies. The French interviewees discussed the importance of economic evaluations, but they complained about the lack of local studies relevant to the development of recommendations.

The selection and ranking of evidence

The selection of the appropriate evidence for the development of recommendations was highlighted in both countries. Dutch participants mentioned the important role of the secretariat of the Health Council in reviewing the literature and making it available to the NITAG. Differently, French participants stated that the collection and selection of the evidence is not executed outside the NITAG (e.g., by a secretariat, as in the Netherlands) but by a working group composed of Comité technique des vaccinations (French NITAG) members established before the plenary discussion.

As observed in our documentary analysis, the ranking of the selected evidence is an important subsequent step. Standardized procedures for this evaluation could provide an impartial assessment of the quality (internal validity) and relevance (external validity) of the studies selected for the decision-making process [19], [20] and [21].

However, the French and Dutch participants rarely mentioned the existence and/or the systematic use of standard procedures, such as a checklist or protocol to aid in the ranking of the evidence. Some Dutch interviewees mentioned a set of seven criteria used for the inclusion of vaccines into the national public program (e.g., seriousness and extent of the disease burden; effectiveness, safety, and acceptability of vaccination) [22]. As revealed in our documentary analysis, the purpose of these criteria is to aid in the selection of studies for the decision-making procedure. However, this set of criteria does not assess the internal validity and external validity of the selected studies. Similarly, some French participants mentioned a general guideline [23] for the appraisal of the internal and external validity of the evidence used for recommendations. This guideline was originally developed by the Haute Autorité de Santé (HAS [French National Authority for Health]) and was sometimes adapted for the evaluation of influenza studies. In contrast to the Dutch criteria, the HAS guidelines, explored in our documentary analysis, suggest measures to grade the quality of evidence (*niveau de preuve*), that is, the ability of the study to support the decision-making process.

Most of the interviewees were aware of the low quality of the evidence used to make recommendations. However, they believed that the inherent issues associated with this complex disease (e.g., influenza case definition, mortality ascertainment, and unexpected and fast virological mutations) hindered high-quality studies. Only one interviewee (the Netherlands) suggested that influenza studies of better quality could improve the decision-making process by decreasing the uncertainty in the experts' decisions. This participant also suggested that the quality of influenza studies could be improved with, for example, the standardization of methodology, which could provide more reliable data and enhance comparisons between studies. "Even if international organizations provide meta-analyses of the existing influenza literature, we should determine whether they were properly designed."

Other Factors Influencing the Development of Recommendations

In addition to scientific evidence, other factors were mentioned as influencing the development of vaccination recommendations. The opinion of the public was a predominant factor, although it was perceived differently in the two countries. In the Netherlands, the interviewees frequently mentioned the decreasing public trust regarding recommendations that, unconsciously or not, influenced the NITAG's discussions. Dutch participants associated this decreasing trust with characteristics related to the vaccine (e.g., lack of effectiveness, adverse events, vaccine injection pain, and annual frequency) and the decision-making process (e.g., lack of reliable evidence, transparency of advice, and experts' conflicts of interest). In France, only a few interviewees discussed the influence of public trust on the recommendations. However, in both countries, participants called for better communication between the governmental authorities and the public to reduce the current lack of response to rumors raised by antivaccination associations (especially in France) and to improve compliance with the recommendations, notably by the vaccinators and target groups. In France, numerous participants stressed the important influence of vaccinators, especially general practitioners (GPs), on vaccine uptake.

Many participants from both countries noted the influence of mass media (e.g., Internet, radio, and TV) and social media (e.g., blogs and online channels) that had a "selective interest in influenza." Following the launch of the seasonal influenza vaccination campaign by the respective Ministry of Health, the media gave wider

emphasis to the subject, although usually accenting the negative aspects, such as the lack of vaccine effectiveness and over-reacting to any unusual adverse effects. Interviewees believed that the negative information published by the media could decrease VCRs and indirectly affect NITAG discussions.

The role of the media was often observed as a challenge to the NITAGs, for example, when the media required clarity on expert advice (e.g., quality and relevance of evidence chosen) and transparency of the declaration of interests. Interviewees also mentioned that mass media is profit-orientated; its main goal is the generation of revenue through advertising. Some interviewees mentioned that the media often publish negative stories about influenza vaccination, which are sometimes sensationalist and not always evidence based. Despite these issues, the role of the media was considered important for the communication of scientific information to the general public.

Impact of the Evidence on the Choice of Target Groups

In general, the scientific evidence was often from international sources and interpreted by the NITAGs. These interpretations can often lead to different conclusions (see examples in Table 3). As determined in our documentary analysis and interviews results, despite the similarity in the evidence used for the development of seasonal vaccination recommendations, there are differences in the target groups in France and the Netherlands. In Table 3, we have compared the differences and similarities in both countries using five target groups: the elderly, people with chronic diseases, pregnant women, healthy children, and health care workers.

[TABLE 3]

We also observed that national and international recommendations for vaccination against the influenza pandemic of 2009-2010 were an important driver for modifications to subsequent seasonal recommendations. In this section, we discuss in detail the decisions about target groups presented in Table 3.

Healthy children

As found in our documentary analysis, healthy children are not a recommended target group for vaccination in France or the Netherlands, and according to the interviews (in 2013), it is unlikely that this recommendation will change. However, both countries declared that international pressure to include this group was growing, that is, the recent marketing authorization by the European Medicines Agency of a live attenuated nasal vaccine for children from 2 years to younger than 18 years, the consequent recommendation by the WHO [24], and the specific policy for vaccinating healthy children in the United States [25], parts of Europe [2], and other countries (e.g., Canada and Australia) [26].

One French interviewee mentioned that vaccinating children could reduce the costs of influenza treatment in the general population (notably in the elderly), but it was not the objective of the current French influenza vaccination strategy: “immunizing all children of school age would considerably reduce the costs of influenza (...), but reducing the number of cases is not a priority in France” (translated from French).

Likewise in the Netherlands, because children were not part of the influenza vaccination strategy, there were no discussions about changing the current recommendations, neither adopting the live attenuated vaccine.

No further details explaining the reasons that children were not target for vaccination were retrieved for either country.

Elderly: Cutoff age

In both France and the Netherlands, the elderly are one of the target groups for vaccination, even though the influenza vaccine is thought to have limited effectiveness. The recommendations differ between the two countries regarding the minimal age to start vaccination: France 65 years and the Netherlands 60 years, as observed in our documentary analysis. Although the main evidence used by both countries was similar, the Dutch also based their decision on a broader policy for the elderly, where vaccination is part of “healthy-aging” [27]: “whether or not to vaccinate healthy elderly is not only a matter of evidence but also how do you see elderly people.” In addition, Dutch interviewees believed that there was an economic benefit to vaccinating people who were 60 years and older [28], [29] and [30].

In contrast, French interviewees specified that lowering the cutoff age for vaccinating the elderly was not under discussion, notably because to date, the budgetary impact for vaccination of people aged 60 to 65 years is considered too high (e.g., number of vaccines for production, distribution, and administration, in addition to communication campaigns).

Pregnant women

The interviewees had divergent ideas about recommending influenza vaccination for pregnant women, and this was reflected in the different recommendations in each country. As determined in our documentary analysis, in France, women are part of the target groups for seasonal vaccination during the whole pregnancy period (first, second, and third trimesters). Following international recommendations, pregnant women were permanently included in the seasonal French recommendations after the 2009 influenza pandemic when, according to several interviewees, more conclusive clinical data became available [31].

Our documentary analysis revealed that in the Netherlands, seasonal influenza vaccination is not currently recommended for pregnant women. However, as in France, pregnant women were one of the target groups for the pandemic vaccination of 2009. In the following year, pregnant women were also a target group for seasonal vaccination in the Netherlands. However, in subsequent years (2011–2012 season onward), they were no more included in the seasonal recommendations.

All the Dutch respondents endorsed the inclusion of pregnant women during the influenza pandemic of 2009 because there was strong evidence to support the recommendation (e.g., high risk of complications). However, one of the interviewees criticized this decision because it was made “under the pressure of the pandemic, as some sort of precautionary measure.” Several Dutch participants confirmed that the studies that investigated seasonal influenza vaccine were not convincing, and the evidence was not robust enough to recommend seasonal vaccination of pregnant women. Some of the interviewees mentioned that there is international pressure (e.g., by the WHO and the ECDC) to reinclude them as a target group in the seasonal recommendations.

Chronic diseases

Only a few interviewees discussed the inclusion of persons of any age presenting with an underlying disease on the list of target groups for influenza vaccination. The Dutch and the French lists of underlying diseases are similarly based on clinical studies and vaccine effectiveness. As observed in our documentary analysis, the target population is defined as people who are more susceptible to influenza complications, such as individuals with cardiovascular diseases, diabetes mellitus, lung diseases, and serious kidney conditions. The list of chronic conditions for which influenza vaccination (in 2013) is indicated in each country is detailed in Table 3 (footnote), where we can observe that the diseases are similar, although the French list is more detailed.

In France, several participants mentioned the influence of patients' associations on the inclusion of underlying diseases in the list of target groups, for instance, people presenting with chronic hepatitis. According to participants, this recent inclusion was triggered by the pressure on health authorities made by patients' associations with chronic hepatitis: "that was the result of a referral from the General Health Directorate, requested by patient associations, as part of the Hepatitis Plan" (translated from French). In addition, clinical studies of influenza complications on patients with chronic hepatitis published after the 2009 influenza pandemic were important to support their inclusion on the list of target groups.

Dutch participants emphasized the lack of studies and had different ideas about the robustness and quality of the evidence on vaccine effectiveness. Nevertheless, all the interviewees mentioned the remarkable VCRs in chronic hepatitis, particularly driven by the direct incentives from GPs to the target groups. In contrast, some French interviewees highlighted that the lack of actions, from GPs and health authorities, to encourage vaccination of the chronic diseases group is responsible for the low VCR.

Health care workers

Several interviewees declared the importance of vaccinating health care workers, including physicians, nurses, and other professionals who provide close health care to patients. Interviewees in both countries mentioned the ideology of "not only protecting yourself, but others" as the main argument for vaccinating this target group: "they should be proud to have a protection not for themselves but for their clients." They also said that the evidence on vaccine effectiveness (as in other target groups) is not convincing, but strong enough for continuing the recommendation. As observed in our documentary analysis, the VCRs of health care workers are not sufficient in both countries, and are much lower in France than in the Netherlands. The major reason, as previously explained for other target groups, is the lack of evidence. A few interviewees in France mentioned that health care professionals' distrust of vaccination would have a negative influence on the vaccine intake of their patients.

Another reason for the low VCRs, as pointed out by participants in both countries, was the lack of knowledge on vaccinology among health care workers. In France, even though several incentives for the vaccination of health care workers are provided by health authorities, the VCRs vary between them, and are remarkably low among nurses who do not seem to perceive the benefits and are supported by the nonobligation of vaccination [32]. In the Netherlands, no traditional reasons were

declared; instead, one interviewee mentioned that studies investigating the reasons of the low VCRs were under development [33].

DISCUSSION

We found that the evidence used by the French and Dutch NITAGs for the development of seasonal influenza recommendations was quite similar, although the decisions regarding specific target groups were sometimes different. Both NITAGs used similar sources of scientific information, often published in international peer-reviewed journals. International guidelines provided by the WHO and the ECDC were also considered in both countries. However, in both countries, national experts were sceptical about the quality of the influenza studies and the applicability of the recommendations developed by international organizations.

The uncertainty about the quality and relevance of the evidence for the vaccination recommendations meant that the personal judgments of the experts were often used in the decision-making process. Nevertheless, as emphasized by a previous work, voting was used as a democratic method to enhance a fair decision [34]. The example of pregnant women illustrates this situation: they were a target group only in France, where the scientific evidence was considered robust enough. In the Netherlands, the same evidence was judged too weak, and the experts postponed the decision until better studies become available. The French decision is supported by international organizations (e.g., the WHO) that recommend the vaccination of pregnant women. Surprisingly, neither country uses a standard protocol or checklist on a regular basis to evaluate the evidence selected for the decision-making process. Only a few participants cited the existence of some type of tool for the assessment of the evidence. The seven criteria for the inclusion of vaccines in the Dutch public programs [22] do not assess the quality of the studies selected for vaccination recommendations. In contrast, the French criteria, developed by the HAS [23], enable an evaluation of the suitability of a scientific study for the decision-making process. In both countries, the evidence used was considered to be of low quality. It seems that the lack of standards for the appraisal of evidence contributed to the larger influence of expert opinion on the decisions made by the NITAGs.

The low quality of influenza vaccine studies has been widely demonstrated, for example, by reviews published on behalf of the Cochrane [26] and [35], and vehemently mentioned by our interviewees. However, because no formal grading of evidence is used in France or the Netherlands, the quality of the studies might be considered to be a perception of the interviewees.

Standard protocols should be used to justify the selection of evidence and should include the assessment of the quality and the relevance of the scientific studies to improve the transparency of the decision-making process [36] and [37]. This would demonstrate, for example, the reasons behind the rejection of information from consideration, explaining why a study was not strong enough, was low quality, or was simply not suitable for certain discussions by the NITAGs [38] and [39]. Indeed, together with the description of the evidence used to justify decisions (that are currently part of the recommendations), the main reasons that evidence was rejected should also be published in the recommendations. Some studies using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach as protocol for the evidence appraisal have been published and might be used as an example [20], [21] and [40]. This could reduce the influence of personal judgment

and decrease uncertainty in the decision-making process, which would increase the transparency of the process [41], [42] and [43].

We believe that harmonizing some methodologies for the development of influenza vaccination recommendations through international collaboration would be beneficial to improving the credibility of recommendations among vaccinators and target groups [44]. For instance, the ECDC has developed the VENICE (Vaccine European New Integrated Collaboration Effort) project, in which it collects, shares, and disseminates information on national vaccination programs in collaborating European countries. The VENICE project intends to harmonize data to improve the comparison of the VCR data of European countries and to provide a strategy for improving data, methodology, and resource sharing between different NITAGs [2]. However, we should note that differences in health care systems in various countries are still a limit for these comparisons.

Our results confirm findings from the recent literature [45], [46] and [47] regarding the tendency of the media to focus more on the potential risks of vaccination than on its benefits. This focus on vaccination risks increases the distrust of the general public toward vaccination recommendations and may influence the decision-making process. To reverse this trend, it is important that authorities provide strong scientific information, for example, by tailoring communications and patient education with styles adapted to different targets, presenting in a transparent manner the benefits of vaccination. This could lead to improved VCRs [46]. It is important to mention that in January 2016, the French Health Minister announced an action plan on vaccination policy as an effort to enhance public confidence in vaccines, that is, by providing better information to the public and health professionals and ensuring better governance of the vaccination policy [48] and [49].

Our findings also endorse the literature showing the impact of cultural differences on distinct decisions [50] and [51]. We observed these differences between French and Dutch actors participating in the decision-making process for the development of influenza vaccination recommendations. For example, despite the use of similar evidence, pregnant women are recommended the vaccine only in France. We also observed, through the perceptions of interviewees, that health care workers' personal decisions regarding vaccine intake may be related to traditional issues such as the low perception of influenza risk and the distrust of health authorities' policies, which were stronger in France [52] and [53]. Further investigation should be done to verify the extent of these impacts.

Limitations

The views of individuals outside the health care system were not represented in this study, notably people who are against vaccination, because all the participants were attached to public or private health systems. Although this suits our objectives, the findings represent only one perspective.

The French and Dutch health care insurance boards (CNAMTS and CVZ, respectively) indicated that they were not interested in our interview because they do not directly participate in the development of recommendations and only execute decisions from the Ministry of Health. In addition, the French Medicines Evaluation Board (Agence Nationale de Sécurité du Médicament et des produits de santé), which is responsible for influenza vaccine authorization, did not contribute to our study. These absences may have biased our French results; however, information provided by participants from other institutions reduced these missing data.

We have used only two methodological techniques to conduct this project: documentary analysis and interviews. These two methods investigate what experts write and tell, but not what they do in real-life. A triangulation with our methods and observational studies would have enabled a real-world analysis [15]. However, the on-site observation of the decision-making process would have been difficult due to time constraints and the possible denial of our participation in decision-making meetings [15].

The database selected for the documentary analysis may have resulted in some biases. For example, the replicability of Google search results is hindered by factors such as the geographical localization of the users and their previous search behavior [54]. However, Google was selected to retrieve the largest number of documents in the two countries studied and to avoid missing any relevant data.

The most important biases of interviews are declaration bias, affiliation bias, and recall bias. Declaration bias is related to the expression of a given theme. On the one hand, the exploration of a theme could have remained superficial (underdeclaration); for example, in both countries, the interviewees provided little information about why children are not recommended for vaccination, despite the international recommendations. On the other hand, the exploration of another theme could have been excessively intense (overdeclaration); for example, Dutch interviewees overemphasized the public's lack of confidence about vaccination recommendations (because of remaining negative perceptions about the pandemic vaccine overpurchase, low vaccine effectiveness, side effects, etc.) as a factor influencing their decisions. The bias from our affiliation with a research group in economics was sometimes perceived during the interviews, when participants overexpressed their concern about models and economic evaluations. Recall bias does not seem relevant to our study because participants were interviewed during the discussions or a few weeks after the update of vaccination recommendations.

Because of time constraints of interviewees, five interviews could only be done by telephone and not face-to-face. This might be a limit because interaction between investigator and interviewee is less direct/intense and the exchange of information is different from face-to-face. Nevertheless, we obtained answers for each of the themes of the interview guide for all five telephone interviews as for the face-to-face interviews. In addition, no major differences were observed between both types of interviews.

Language barriers are another limitation of our study because the investigator who conducted the interviews does not speak Dutch. We used online translations of Dutch documents, which may lack accuracy. To address this issue, a Dutch influenza expert validated the data in the translated documents. Language barriers were mitigated during the interviews because all Dutch experts spoke English.

The coding process may have some limits. The *in vivo* coding could have led to an underestimation or overestimation of the importance of the citations perceived by the first investigator. To minimize the impact of this limitation on our data analysis, other investigators completed the *in vivo* codes with supplementary codes before the recoding of the transcripts using NVivo10 [55]. A comparison between the first coding and the second coding aimed to reduce classification mistakes and neglected citations [15,56]. Both codings were similar and very few differences were observed.

CONCLUSIONS

Although the evidence used for the development of influenza vaccination recommendations in France and the Netherlands is comparable, the choice of target groups can differ in each country. The quality of the evidence is often considered as poor and, furthermore, there is no systematic use of standards for the assessment of the quality and/or relevance of influenza studies. This provides an opportunity for different interpretations, thus increasing the influence of the experts' judgment on decision making. The development of standards for the critical appraisal of the evidence would improve the quality and transparency of the decision-making process.

The different decisions on target groups for influenza vaccination may be linked to two factors: cultural differences and the influence of the experts. However, further investigation is necessary to evaluate the impact of these factors on the decision-making process. Supranational projects with the collaboration of European countries might be emphasized to improve comparability of data, reduce differences, and improve the decision-making process in these countries.

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TABLES

Table 1. Strategy for online database searches, keywords (English, French, and Dutch), and main sources of material obtained for France and the Netherlands

1. Demographics and socioeconomic context		
Keywords (similar for both countries): health, Gross Domestic Product (GDP), indicators, economy		
Web sites (similar for both countries): OECD (http://data.oecd.org.proxy.library.uu.nl/gdp/gross-domestic-product-gdp.htm) WHO (http://data.euro.who.int/healthatlas/CoreIndicatorAP/corenotes.htm)		
2. Health systems		
Keywords:	Système de santé, réforme, France	Gezondheidszorg, hervorming, Nederland
Web sites (similar for both countries): European Observatory on Health Systems and Policies (http://www.euro.who.int/en/about-us/partners/observatory)		
	http://www.cairn.info.proxy.library.uu.nl/revue-les-tribunes-de-la-sante.htm	
3. Influenza vaccination policies and 4. Stakeholders involved in policies*		
Keywords:	Grippe, vaccination, vaccin, remboursement, stratégie vaccinale, recommandation, avis, rapport, conseil	Griep, influenza, vaccinatie, vaccin, vergoeden, vaccinatiestrategie, rapport, advise, recommandatie
Web sites:		
Ministries of health	http://www.sante.gouv.fr	http://www.rijksoverheid.nl/ministeries/vws
Governmental authorities	http://www.hcsp.fr/explore.cgi	http://www.gezondheidsraad.nl.proxy.library.uu.nl
	http://www.has-sante.fr	http://www.cbg-meb.nl/cbg/nl
	http://ansm.sante.fr	http://www.zorginstituutnederland.nl
	http://www.ameli.fr.proxy.library.uu.nl	http://www.rivm.nl
Laboratories, surveillance networks	http://grog.org	http://www.nivel.nl
	http://www.invs.sante.fr	http://www.snpg.nl
Associations	http://www.infectiologie.com	https://www.nhg.org
	http://www.grippe-geig.com	

Dutch Web sites were automatically translated to English using the Chrome® browser.

Table 2. Institutions directly or indirectly involved in the decision-making process of influenza vaccination recommendations in France and the Netherlands.

Groups of stakeholders	Stakeholder	France			The Netherlands		
		Stakeholder acronym	Experts interviewed		Stakeholder acronym	Experts interviewed	
			ID	Involvement in the process		ID	Involvement in the process
Governmental authorities	Ministry of Health	MS	Int33*	Direct	VWS	Int19	Direct
	Health Directorate	DGS	Int09*	Direct			
			Int15†	Direct			
	Health Council	HCSP/	Int10	Direct	GR	Int18	Direct
		CTV	Int08	Direct		Int21	Direct
			Int12	Direct		Int23	Direct
		HAS/CT	Int06	Indirect			
	Medicines Evaluation Board	ANSM	–	Indirect	CBG	Int27	Indirect
	Health Care Insurance Board	CNAMTS	–	Indirect	CVZ	–	Indirect
	Medicines Regulatory/ Financial Board	CEPS	Int13	Indirect	RIVM/	Int28†	Indirect
DVP							
Research institutions	Influenza surveillance	GROG	Int02	Indirect	NIVEL	Int16	Indirect
	networks		Int03	Indirect		Int26	Indirect
	National Influenza Centre	CNR Paris	Int05*	Indirect	NIC	Int32	Indirect
		CNR Lyon	Int01	Indirect	Rotterdam		
	Institute of Public Health Research & Monitoring	InVS	Int11	Direct	RIVM	Int20	Direct
						Int22	Direct
						Int24*	Direct
						Int29*	Direct
					Int30	Direct	
					Int31	Direct	

Groups of stakeholders	Stakeholder	France			The Netherlands		
		Stakeholder acronym	Experts interviewed		Stakeholder acronym	Experts interviewed	
			ID	Involvement in the process		ID	Involvement in the process
Associations	Society of experts/College of GPs	SPILF	Int07	Indirect	NHG	Int25	Indirect
Vaccine manufacturers		GSK	Int04†	Indirect	Abbott	Int17	Indirect
		SPMSD	Int14	Indirect			
Total number of interviews conducted			16			17	

ANSM, Agence National de Sécurité du Médicament et des produits de santé; CBG, Medicines Evaluation Board; CEPS, Comité Économique des Produits de Santé; CNAMTS, Caisse nationale de l'assurance maladie des travailleurs salariés; CNR, Centre National de Référence; CT, Commission de la Transparence; CTV, Comité technique des vaccinations; CVZ, National Health Care Institute; DGS, Direction Générale de la Santé; DVP, National service for vaccine provision of prevention programs; HAS, Haute Autorité de Santé; GR, Health Council; GROG, Groupes Régionaux d'Observation de la Grippe; GSK, GlaxoSmithKline; HCSP, Haut Conseil de Santé Publique; ID, interview identification; InVS, Institut de Veille Sanitaire; MS, Ministère des Affaires sociales et de la Santé; NHG, Dutch College of General Practitioners; NIC, National Influenza Centre; NIVEL, Netherlands institute for health services research; RIVM, National Institute of Public Health and Environment; SPILF, Société de Pathologie Infectieuse de Langue Française; SPMSD, Sanofi Pasteur Vaccines; VWS, Ministry of Health, Welfare and Sport.

□ No longer at the position during the interview

† Face-to-face interview conducted with more than one person, as suggested by the invited expert

Table 3. Information and factors that influence decisions on influenza vaccination target groups: Similarities and differences between France and the Netherlands (combined from the document analysis and interviews)

Target group	Main information and factors that influence decisions	
	France	The Netherlands
Healthy children	Not recommended	Not recommended
Similarities	The recommendation provided by the WHO and other countries, together with the market authorization of a new vaccine more appropriate for children, may change the discussions on targeting children for influenza vaccination	
Differences	Vaccinating children could reduce influenza costs because children are an important vector for virus transmission	Current vaccine available in the program (inactivated subunit) is not adapted for children
Elderly	≥65 y	≥60 y
Similarities	Although vaccine effectiveness is not high, there is evidence for reduction in influenza complications and hospitalizations	
Differences	Budgetary impact was the main factor impeding lowering the age limit to 60 y	Cost avoidance was the main factor encouraging the lower age limit of 60 y
VCR	Mean 55.7% (51.9–64.8%)	Mean 78.9% (72.2–82.5%)
Pregnant women	Recommended	Not recommended
Similarities	Following the WHO, the ECDC, and other countries' recommendations, together with clinical evidence of influenza complications, pregnant women were targeted for vaccination during the 2009 pandemic	
Differences	On the basis of clinical evidence generated during the 2009 pandemic, pregnant women were included as a target group for further seasonal influenza vaccinations	On the basis of clinical evidence generated during the 2009 pandemic, pregnant women were included as a target group only for the influenza vaccination seasons 2009–2010 and 2010–2011
Chronic diseases	Various*	Various†
Similarities	The list of people presenting with underlying diseases who are more susceptible to influenza complications was mainly based on clinical studies and vaccination effectiveness	
Differences	The low VCR is a result of the lack of information for this population. In addition, they are skeptical about the need and effectiveness of the vaccination. The associations of patients may influence the inclusion of new underlying diseases in the list of target groups	On average, three-fourths of the target population is vaccinated; however, since the 2009 pandemic, the VCR has been decreasing. The important role played by GPs in informing patients about the benefits of vaccination still ensures a remarkable VCR

Target group	Main information and factors that influence decisions	
	France	The Netherlands
VCR	Mean 39.2% (37.2–47.2%)	Mean 76.4% (70.5–80.6%)
Health care workers	Recommended	Recommended
Similarities	Although highly recommended, the VCRs are low because of personal beliefs and the lack of evidence on vaccination effectiveness	
Differences	French health care workers are known to be skeptical about vaccines. Recent studies from universities [56, 57] show that vaccination refusal is fundamentally considered a protest based on personal beliefs and professional traditions	Studies investigating the reasons for vaccination refusal are in progress among Dutch health care workers. Advised by the Health Council, the Ministry of Health ordered these studies, which aim to implement actions that increase the VCR
VCR (2010–2011)	28%	65%

GPs, general practitioners; VCR, vaccination coverage rates, mean (min/max) rates from 2010 to 2014.

□ Chronic obstructive bronchopulmonary diseases (some cases), chronic respiratory failure (some cases), dysplasia bronchopulmonary (some cases), cystic fibrosis, congenital heart disease (some cases), severe heart failure, severe valve disease, serious rhythm disorders (some cases), coronary diseases, history of stroke, severe neurological and muscular disorders (some cases), paraplegia and tetraplegia (some cases), severe chronic nephropathy, nephrotic syndrome, sickle cell/homozygous and heterozygous double, thalassemia, diabetes type 1 and type 2, immunodeficiency (some cases), and chronic liver disease.

† Cardiovascular diseases, diabetes mellitus, lung diseases, serious kidney conditions, and poor resistance due to other illnesses or medical treatment such as chemotherapy.

SUPPLEMENTARY MATERIALS

ANNEX 1: ENGLISH VERSION OF THE INDIVIDUAL SEMI-STRUCTURED INTERVIEW GUIDE

Before starting the interviews, the interviewer will briefly develop the following points:

- Self presentation and provide some details about the research objectives
- Ensure the anonymity of the interview and ask permission to audio record

Opening point

- 1) What do you think about the seasonal influenza vaccination strategy in the Netherlands/France?

Types of scientific information

- 1) Which scientific studies were considered during the decision-making process?
 - a. RCT, vaccine safety, and vaccine effectiveness studies?
 - b. Epidemiological studies (incidence, morbidity and mortality, epidemic impact of influenza)?
- 2) How were economic evaluations considered during the process (cost-effectiveness, cost-benefit, cost-effectiveness analysis, mathematical models)?

Relevance of each type of scientific information

- 1) What was the degree of influence of these studies on the decision made?
 - a. Could you rank their influence (e.g. RCT, epidemiological, economic evaluations)?
 - b. What do you think about the information used (quality, relevance, interpretation, assessment, generalizability)?
- 2) How was the quality and relevance of the results verified?
 - a. Who was responsible for this verification?
 - b. What were the barriers for the interpretation of the studies' results?
- 3) How do you feel about using a protocol (or a checklist) to assist in the evaluation of the scientific studies?
- 4) Were they Dutch/French studies? If not, how did you verify the applicability of the results to the local situation?
- 5) In general, did the information provided by these studies cover the needs of the meeting group?
 - a. What information was missing?

Other types of information considered

- 1) Apart from scientific studies, what other information was considered during the decision-making process?
 - a. Bulletins, reports from surveillance networks, and virology laboratories (ECDC)?
 - b. International recommendations (WHO)?
- 2) What was the degree of influence of this information on the decision made?

Sources of information

- 1) In what form was the information available (experts, request of the institutions involved, manufacturers, literature review, etc.)?
 - a. Who was responsible for providing the information?
 - b. How do you feel about having a group responsible for providing literature reviews and assessing the quality of studies?
- 2) Do you think that its source could influence the consideration of the information?

Factors of influence

- 1) What other arguments (logistic, political, economic, social) could be part of the discussion during the policy-making meetings?
 - a. What would be the most important argument?
- 2) Do you think the media could play a role on the policy-making process?
- 3) According to your opinion, what could be the role of influenza vaccine manufacturers in the policy-making process? What kind of influence could they have on it?

Reflections on target groups for influenza vaccination

- 1) What is the reason for the increasing number of target groups for vaccine recommendations over the years?
- 2) Who could be responsible for requesting the revision of target groups?
- 3) Do you think it would be useful to have:
 - a. State mandatory influenza vaccination for health professionals, for example?
 - b. Widespread influenza vaccination for the entire population (universal vaccination)?

Closing points

- 1) Is there any additional information or comments you would like to share?
- 2) Can you recommend another person with whom I should speak to get a perspective that complements or is completely different to yours?