A literature review to identify factors that determine policies for influenza vaccination

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ABSTRACT

Objectives: To conduct a literature review of influenza vaccination policy, describing roles and interactions between stakeholders and the factors influencing policy-making.

Methods: Major databases were searched using keywords related to influenza vaccination, decision-making and healthpolicy. Titles and abstracts were screened according to defined criteria using independent reviewers. Selected articles were analysed and compared against a checklist.

Results: 342 papers were identified, but only 111 included. A wide range of countries was represented in articles published in 1994–2012. We identified numerous stakeholders at the national and international level and found a variety of interactions between them. Using these data, we suggest a scheme for the most important stakeholders and their interactions. Determinants of policy-making were mainly related to the vaccine/disease, political-economic context, and stakeholders communication. The most relevant evidence was clinical/epidemiological studies. After the 2009 pandemic: the importance of mathematical modelling and ethical issues was greater; and the need for better communication between stakeholders was emphasised.

Conclusions: The relevance of evidence and factors influencing policy-making varied between countries, according to complex interactions between the stakeholders involved at different levels of decision-making process. These interactions remain unclear, especially at national level, where the most important influenza policy decisions are made. To better define and understand

the exact interactions and use of evidence, we recommend undertaking future qualitative studies at national level using small number of countries.

HIGHLIGHTS
• We analyse 111 articles related to decision-making on influenza vaccination policy.
• We assess stakeholders' interactions, information used and factors of influence.
• The complex interaction between stakeholders is presented in a holistic scheme.
• The most relevant evidence for policy-making is clinical and epidemiological studies.
• Models, economic studies and ethics have greater importance since the 2009 pandemic.

1. BACKGROUND

The important medical and economic burdens of influenza to society, including the decline of major physical functions resulting in direct costs (i.e.: hospitalizations) and indirect costs (i.e.: loss of productivity) [1] and [2], require that policy-makers provide strategies for prevention and control, such as vaccines. The scarcity of health resources calls for policy-makers to set priorities for influenza vaccination [3] and [4]. There are only a few studies that have investigated influenza vaccination policy-making in seasonal and pandemic contexts. For example, the pandemic context is handled with preparedness plans, previously devised to minimise uncertainty [5]. However, many factors can influence the development of these policies, such as time constraints for the decision-making, lack of real-time information and communication between multiple levels of public health. Moreover, political factors and logistics can impact the policy-making [5] and [6]. Policies developed for seasonal influenza are regularly used as the basis for pandemic plans [7]. They are often established in accordance between the government, policy-makers, and programme managers with the help of National Immunization Technical Advisory Groups [8] and [9].

Seasonal influenza affects the worldwide population every year, while pandemic influenza is an unpredictable threat. According to the World Health Organization (WHO), annual epidemics result in 3–5 million cases of severe illness and 250–500 thousand deaths worldwide [10]. Following the WHO recommendations for the prevention and control of influenza, more than 40% of global nations currently include vaccinations in their public health policies [11] and [12]. However, a large debate has developed about the evidence used, transparency of the decision-making process, and role of the institutions involved [13], [14] and [15]. Even though influenza studies have increased after the last pandemic (influenza A(H1N1)pdm09 virus), investigations concerning influenza vaccination policy-making are still scarce.

The chain of influenza vaccination policy-making has four main segments: vaccination recommendations, vaccine composition (strain selection), vaccine license (market authorisation) and vaccine funding (purchase and reimbursement). Previous

literature reviews have usually focused on vaccination recommendations: the revision of target groups (i.e. inclusion of pregnant women, certain chronic diseases, healthy working adults, children at scholar age, and healthcare workers) [16], [17], [18], [19], [20] and [21] and the outcomes of the vaccination campaign (i.e. vaccine coverage and the effectiveness of influenza vaccine campaigns) [22], [23] and [24]. Few reviews have investigated other segments of the chain. Additionally, most of the studies available have investigated pandemic contexts only, though it is widely known that the seasonal influenza policy is crucial for pandemic preparedness. Therefore, policy-makers and stakeholders might have difficulties in developing a holistic overview of the decision-making process because the literature available is frequently fragmented and focused only on pandemics.

To bridge this gap, we conducted a literature review aimed at providing a general overview of influenza vaccination policy-making at the global and national levels, describing: (1) roles, relationships, and interactions of the stakeholders involved in the policy chain and (2) the information used to develop these policies and possible factors that influence these decisions.

This literature review provides a general picture, as well as global overview of policies in several countries. It is also an important prologue for further work in this field. The results of this review are intended for policy-makers at the national level, to improve the decision-making process and its transparency.

2. METHODS

The main electronic databases were used for this study: Web of Science, Google Scholar, PubMed, EconLit, HEED, and The Cochrane Library. No restrictions on the date or location were applied. A combination of the following search terms was used (the detailed search strategies used for each database can be found in Annex 1):

•Influenza vaccines;
•Vaccinations AND influenza;
•Decision support techniques OR decision making;
•Policy OR public health OR public health administration OR health policy OR public policy OR management.

Papers without abstracts and where the full text was written in a language other than English, French, Spanish, German, Italian, or Portuguese were excluded. Using a checklist, the studies were screened, selected, and the data were extracted. The data recorded comprised: the first author, year of the study, influenza context (pandemic or seasonal), segment of the influenza policy chain investigated, actors, institutions, stakeholders involved and the interactions between them, information used to develop the policies, and factors that influenced this process. Papers were only included if they met the following criteria:

(i)Presence of macro level decision-making (at the community, regional, national, supranational or international levels) regarding the influenza vaccination policy chain;

(ii)Description of the stakeholders (actors and shareholders) involved in this decision;

(iii)Description of the information used during the decision making process was assessed.

We also searched for documents published on the websites of widely recognized organizations that play a major role in influenza vaccination policy, such as the US Centers for Disease Control and Prevention (CDC) reports, European ECDC advice, and WHO bulletins. These documents were only used for discussion.

The information (i.e.: scientific studies, grey literature, ethics, logistics) that influenced the decision process was identified in each article. The data were grouped by theme (i.e.: morbidity/severity, cost-analysis/economic models). We then created information and factor categories using terms frequently employed in the literature (i.e.: epidemiology, economic studies). The degree of importance assigned to the categories developed was established by the number of papers that mentioned each category (Annex 2). Therefore, our findings are presented based on these categories and their importance, illustrated with examples of specific papers.

The papers obtained from the electronic database searches (n = 4743) were screened based on their title and abstract (Fig. 1 [25]). Based on this screening, 4401 papers were excluded and 342 were retained for full text reading. On reviewing the papers, 231 (68%) were excluded. Most of the excluded articles concerned local decision-making processes (meso/micro level) (n = 134), primarily related to the personal choice of being vaccinated (especially by people who are targeted for vaccination). Other excluded articles (n = 83) did not concern policy-making but related to the influenza vaccines specifically, i.e. composition, virus strain selection (virology and immunology assays), vaccine efficacy/effectiveness (randomized clinical trials, economic evaluations and modelling), adverse events of vaccines and vaccination rates. Decisions solely regarding antiviral policy were also excluded (n = 14).

[FIG. 1.]

A total of 111 papers from primary and secondary sources met our inclusion criteria (Annex 3). We believe that both primary and secondary documents are important and complementary sources, although the latter are easier accessible as they are often published in scientific journals.

3. RESULTS

Two thirds of the papers included in our analysis (n = 76) were secondary documents that were written by research institutes or universities often indirectly involved in policy-making, and explained or discussed policy. One third of papers (n = 35) were primary documents, mainly from the health departments of national governments (esp. US, Canada and Australia) and international organizations (i.e.: WHO, ECDC) directly involved in policy-making.

3.1. Description of the study populations

Most of the studies (n = 44, 40%) evaluated the United States' (US) policies at the local, state, or federal levels. The US federal policy was compared to the Canadian, European, and Latin American policies in seven other studies. Eight of the studies were conducted in Canada and mainly evaluated their influenza pandemic preparedness plans and compared their national influenza vaccine strategies to other countries. Countries from the WHO European Region (France, Germany, Italy, Israel, and the Netherlands) published twelve studies; one of the studies was a comparison with the Canadian and US strategies.

Representing the eastern side of the globe, Australia (n = 7), India (n = 2) and Hong Kong (n = 1) evaluated their seasonal influenza vaccination strategy and pandemic preparedness plan. Twenty-nine of the studies (26%) did not focus on a particular location for the analysis, instead making a global comparison about vaccination policies and influenza pandemic preparedness plans.

The following sections offer an overview of the segments of the influenza vaccination policy chain from various perspectives: during seasonal and pandemic contexts, among different levels of decision in various countries, describing the stakeholders involved, and comparing the information and factors influencing policy-making in these locations. In Table 1 we present our findings illustrating the main information and factors mentioned in the papers that have an impact on the decision-making process for influenza vaccination policy.

[TABLE 1]

3.2. INFORMATION INFLUENCING DECISIONS AND OTHER FACTORS

Fourteen categories of information and factors influencing the vaccination policy-making were developed and ranked according to the number of papers reporting them (Annex 2). We found that the variety of information and factors used in policy-making has increased over time. Scientific information related to the vaccine and disease, such as safety, efficacy/effectiveness, clinical trials, and epidemiological studies, have always been reported [26] and [27], but immunological, virological, and antigenic studies are a more recent phenomenon [28], [29] and [30]. Regarding economic studies, for example, cost-effectiveness analyses of influenza vaccination were first reported in the US in 1997 [27], and later in 2003 in the Netherlands, together with mathematical modelling [31]. Following the 2009 pandemic, the use of these studies, jointly risk and uncertainty assessments, were frequently reported in European countries, the US, and Canada [32], [33] and [34]. Table 1 summarizes the information and factors by segment of the policy chain and gives examples of countries that emphasised them as having a strong impact in the decision-making process of influenza vaccination policy.

The evidence used by policy-makers was often associated with adjectives like 'best', 'solid', or 'empirical' in both primary [35] and [36] and secondary documents [37], [38], [39] and [40]. Frequently, the type of evidence used was not explicitly stated;

instead, the term 'scientific evidence' was employed [41], [42] and [43]. The guidelines provided by international organisations, national governments, or advisory boards were often the source of references for scientific studies and used for comparison with the realities in other countries [44] and [45].

The advice from the advisory boards was based on a combination of scientific data and the opinions of those involved [33]. The acceptability of the advice provided by policy-makers was usually influenced by the national political-economic context, public opinion, and logistics of vaccine distribution and availability [46] and [47]. Especially after the last pandemic (2009), ethics and international pressure were prominent factors in deciding the resources allocated for vaccine adoption and target groups for vaccination [48], [49] and [50].

The use of information and the factors influencing policy-making are specific to each country and are a function of the interactions of the stakeholders involved. In the next section, we reveal our findings for each segment of the influenza vaccination policy chain.

3.3. THE ROLE AND RELATIONSHIP OF THE STAKEHOLDERS

In principle, the interactions among the stakeholders involved in the policy chain, located at the macro (international, supranational, and national organisations), meso (healthcare providers), and micro (consumers) levels, could be generalised for all countries included in the review. In Fig. 2, we propose a schematic illustration of these interactions across the levels for the actors, stakeholders, and consumers. This illustration is based on the data extracted from the papers and is a suggestion for a global overview of the information and factors that impact the decision-making process of the influenza vaccination policy chain (Table 1).

[FIG. 2.]

3.3.1. Vaccination recommendations

The selection of risk groups to target for influenza vaccinations was often done at the international and national levels. In between there was a supranational level, where institutions, such as the ECDC in Europe and the PAHO (Pan American Health Organization) in the Americas, gathered national data to produce general guidance for concerned countries (linked to the supranational institution). The WHO (international level) has also gathered intrinsic data from countries to produce global recommendations. At the national level, recommendations from both international and supranational levels were frequently used during decision-making. For example, since the WHO established the current goals for vaccination coverage (2003), nations have been encouraged to improve their vaccination rates, beginning with the increased purchasing and reimbursement of vaccines for target groups [51].

By contrast, pandemic actions often reflected seasonal recommendations. For instance, pregnant women, obese people, and healthcare workers were subsequently targeted more for vaccination after the 2009 pandemic [52]. In this case, international

policy-making also affected national choices: following the United States, some European countries (UK and Finland) targeted healthy children for vaccinations [53] and [54].

The selection of vaccines for the influenza vaccination program was also considered as part of the vaccination recommendations, which was mostly done at the national level. This selection directly involved the other segments of the policy chain: to be adopted, the vaccine depended on market authorisation ('vaccine license'), and once adopted, it had to be purchased and reimbursed ('vaccine funding').

The interactions between the stakeholders involved in the determination of vaccination recommendations within countries appeared to be similar; however, differences were observed according to the geographic size and influenza vaccination expertise of the locale. In larger countries, such as the US, Canada, and Australia, the communication between the federal government, states/provinces, and communities was crucial for the execution of recommendations, especially during pandemics [35], [38] and [46]. In Europe, the strength of the expert opinion, represented by national advisory committees, universities, and national research institutes, was important [28], [32], [36], [47], [55] and [56]. The influence of the WHO was remarkable in India [49] and [57] and Israel [39], where they seemed to seek expertise. A similar relationship was observed with the PAHO in Latin America [51].

3.3.2. Vaccine composition

Each year the WHO recommends the virus strains that should compose the future seasonal vaccine for the Northern and Southern Hemispheres. For almost 60 years, this decision was made in cooperation with the WHO Collaborating Centres, National Influenza Centres, and animal influenza networks, which provide antigenic and genetic information [58]. Surveillance networks around the globe and grouped by region (i.e. European Influenza Surveillance Network and CDCs) were also important stakeholders and information providers [58], [59], [60], [61] and [62]. While mathematical modelling and analyses of risk benefit and transmissibility were reported, they were considered less important [58], [59], [60], [61] and [62]. The WHO recommended the vaccine composition to manufacturers, who usually adopted the recommendations. However, other types of influenza vaccines could be produced depending on the manufacturers' interests. This process required a close relationship between the vaccine manufacturers and the WHO [30], [58], [61], [63], [64], [65] and [66].

3.3.3. Vaccine license

The process of vaccine authorisation generally began with submission of the manufacturers' requirements to regulatory agencies. These agencies could be at the national level (e.g. US Food and Drug Administration [FDA] or Japanese Pharmaceuticals and Medical Devices Agency) or at a more global level (European Medicines Agency [EMA]) [67] and [68]. Each of these agencies has specific licensing requirements and regulations. The FDA clinical trials are an interesting example, as they are transferable to most European countries, providing an incentive

to license US vaccines for the European market; however, transfer from European countries to the US is impossible [67].

Surprisingly, we found that the procedures for licensing pandemic vaccines were similar to seasonal vaccines. Indeed, having a licensed seasonal vaccine influenced the licensing of a pandemic vaccine from the same manufacturer. For example, until recently, the FDA declared that a license for an adjuvanted pandemic vaccine could only be obtained if the manufacturer presented evidence of the clinical efficacy of a similarly adjuvanted seasonal influenza vaccine [68].

3.3.4. Vaccine funding

Actors in vaccination funding may be public or private and may belong to international or national organisations. At the international level (e.g. during last 2009 pandemic), the WHO has established a 'virtual international vaccine stockpile and advanced purchase mechanism' to secure resources to buy vaccines for developing countries [69]. At the national level, governments and healthcare providers represented the main purchasers for the public and private sector, respectively [70]. In the US, for example, the largest consumer of influenza vaccines was the federal government, with contracts established between the CDC and manufacturers for millions of doses each year [71]. However, the state and local health departments, pharmacies, and private healthcare providers (i.e. private general practitioners, nursing homes, and hospitals) were also purchasers of vaccines [71]. Likewise, in Australia, vaccine purchase was the responsibility of the Commonwealth government, who considered recommendations from experts, and was mostly financed by the state governments [72]. Similarly, in Latin America and Europe, vaccines offered through the public sector were purchased through governmental funds and available to the public free of charge [32], [51] and [52].

The reimbursement of vaccination costs to the patient or healthcare facilities, including hospitals, nursing homes, and medical offices, could be performed by public health departments at the national or local levels or by insurance companies, depending on the particular healthcare system of the country. In accordance with a paper by Ng et al. [52], we classified vaccine subsidies into three groups by country and found that: (1) 85% of countries provided vaccines without any charge to the recipient ('free'); (2) 6% of countries subsidised part of the vaccine and administration fee ('partial reimbursed'); and (3) 9% of countries covered vaccines subsidies with national health insurance programs for specific risk groups ('insured').

During the last pandemic (2009), decisions regarding which vaccine to buy varied between countries. For instance, in Canada, as in Europe, the government and its advisors chose to purchase an adjuvanted vaccine, in contrast to the US and Australia [33] and [72]. Contracts were negotiated either by the national authorities with immediate effect or by certain prompts, such as the declaration of a phase 6 pandemic by the WHO [53].

Purchasing decisions regarding vaccine supply during seasonal influenza were commonly based on epidemiological data (trend predictions for the number of

contaminated people the following year) and demographic data (a possible increase in the elderly population) [53] and [66]. This information was generally provided by surveillance networks, virology laboratories, and national health institutes. By contrast, for pandemics, modelling had a greater impact [73], [74] and [75]. Furthermore, new factors influenced the decision because of the limited data regarding the clinical and epidemiological aspects of pandemics and the ethical and logistical challenges, including public acceptability [33]. The media attention was also considerably higher during the 2009 pandemic, which was likely triggered by official declarations regarding the morbidity and mortality, for example [53]. There was a high level of uncertainty regarding the severity and potential time course of a pandemic when decisions on vaccine purchases had to be made [53].

4. DISCUSSION

4.1. Limitations

Our study design and review strategy allowed investigation of a variety of segments of the influenza vaccination policy chain over a long period (1994–2012). This enabled exploration of the different interactions among policy-makers in several countries. Indeed, this review provides a broad outline of the literature in this field. However, there are some limitations to this study.

Our analysis was mainly based on secondary documents, which are often published by researchers who are indirectly involved in the policy-making process. These documents may not necessarily represent the reality of the process, but the opinions of researchers. However, these researchers may also have a holistic perspective that the experts directly involved in the policy-making may not have. Therefore, we believe that, based on the objectives of our review, these researchers' opinions are relevant and complementary to the primary documents. The primary documents, which are considered the most reliable source of information, comprised only one third of papers analysed. This is most likely due to the fact that they were not published in the databases we searched, or simply not published anywhere, hindering public access. Hence, we believe that analysing both primary and secondary documents provides insight into the development of specific statements and a general perspective of the policy-making process, respectively.

The databases we searched were selected in order to retrieve the largest number of documents pertinent to our objectives. Google Scholar together with other conventional literature retrieval tools were selected instead of extremely broad search engines (i.e.: Google) to improve the relevance of documents and to reduce the time needed to sort through the results [76]. However, this choice may have resulted in missing some relevant data. For example, documents published by the National Influenza Vaccine Summit on the CDC website were not found, although two of the articles that we analysed referred to its key role in influenza policy in the USA [44] and [77]. The choice of database could have generated bias in the inclusion of important documents, but also the application of the inclusion criteria and further checklist for full-text reading, may have contributed to that bias.

We observed an over-representation of studies conducted in the US. This might be related to the fact that the US government is responsible for buying and distributing influenza vaccines in the US, work that is largely carried out by the CDC. As a result, there are many US publications in the public domain regarding this issue, which appear every year. For example, the CDC gives a regular update on vaccine supplies each winter. This situation is not comparable to other countries, where other procedures are used and supply is often derived from the private market.

Studies we did examine were unclear on their geographical position, and varied in their grade of suitable descriptions of the policy-making process, role and relationship between the stakeholders involved, information used, and various other factors that influenced the policy-making process. We found that the relationship between the actors and institutions within countries and among different levels of decision-making were under-reported (i.e.: public institutes and vaccine manufacturers), especially during seasonal influenza outbreaks. Furthermore, because there was a peak in publications after the last pandemic human influenza (A(H1N1)pdm09), our findings could have been influenced by an over-representation of pandemic policy-making, consequently under-reporting seasonal influenza policy-making.

In addition to the global over/under-declaration of certain policy-making determinants, we also observed that each of the documents analysed emphasised different information and factors influencing vaccination policy. For example, authors investigating policy-making during annual epidemics rarely mentioned the possible influence of the media and anti-vaccination actions [53]. In contrast, we observed over-declarations of how evidence was used, emphasised by adjectives such as "best" or "solid" [35], [36], [37], [38], [39] and [40]. Moreover, primary documents were more likely to highlight the uncertainty of the process [46], [59] and [78], whereas secondary documents were more likely to mention the influence of experts opinions and ethical issues [33] and [42].

For all these reasons, care should be taken when comparing these studies because of the differences in the methodologies and context in which they were studied. Most of the studies evaluated policy-making during pandemics, providing detailed, real-time information about the measures applied; however, these suffered from a limited perspective. Other pandemic studies used retrospective document analysis, providing larger overview of the whole process but with less detailed information. Pandemic studies generally investigated the implementation of policies, often neglecting the role of the stakeholders, relationships, and information used. The few studies that provided surveys, interviews, and workshops with the stakeholders aided in the understanding of their interactions and attitudes towards the information used and influencing factors. These techniques have not been used during seasonal influenza outside of the US and Australia.

Despite the large number of studies included in this review, most reports were only concerned with one segment of the policy chain: vaccination recommendations. The number of studies providing a holistic picture of the entire policy chain was a minimum. For future studies, we believe that a general overview of the policy chain

would help policy-makers and stakeholders to improve their performance in this process (Fig. 2).

4.2. Information influencing decisions and other impacting factors

Clinical and epidemiological studies were the most relevant data used by several actors in each segment of the policy chain. In general, the type of information used in both influenza contexts was similar, but a wider variety was reported in studies exploring the pandemic context. We hypothesise that the concepts of uncertainty, risk management, and emergency actions were usually adopted because of the risk faced by the policy-makers. For instance, during pandemics, budget and logistical factors (vaccine availability and distribution) were of main importance when deciding which vaccines to purchase. In the same context, experts' opinions, outside of the circuit of actors and stakeholders, had a higher impact in pandemics than in annual epidemics, where target groups were selected for vaccination recommendations. We found that the routine annual influenza policy became an uncertainty in the context of risk management when a pandemic was declared.

In the European Union, the response strategy for the last pandemic influenza was coordinated by the Health Security Committee (HSC), with the collaboration of the ECDC and the EMA. Member states considered the HSC a 'useful platform for public health risk management and risk communication as well as for coordinating at EU level the response' [79]. In addition, those European organisations had agreed that it was important that 'those being offered the vaccines had [been] given clear guidance and information on the likelihood of them being affected by the virus and of experiencing severe outcomes to enable them to make informed choices' [59]. However, the interactions between these organisations and the national governments were weak, resulting in a communication failure with the physicians and general public. A communication failure was also observed among the regulatory authorities and vaccine manufacturers. In the US, Macher and Springs remarked there was 'insufficient written guidance and consultation with manufacturers available on the licensure requirements for new influenza vaccines using alternative technologies' [80]. This lack of communication, allied with the possible limited expertise of the regulatory authorities on testing new products, could hinder manufacturers' incentives and R&D efforts related to alternative influenza virus vaccine technologies. Additionally, the entire research, development, and approval process can require 10 years or more, costing approximately US \$110–802 million [81]. For pandemic vaccines, at least 20 weeks are required from the time the pandemic virus is identified until the first vaccine doses become available [82].

Interestingly, some information, such as mathematical modelling and ethical issues, were often reported but appeared to be underused [58], [59], [60], [61] and [62]. As previously mentioned, this could be because the information used and factors that influenced policies were underreported. However, during 2009 pandemic we observed a clear impact of mathematical modelling and other new factors of influence, such as the limited data regarding clinical and epidemiological aspects, and ethical and logistical challenges including public acceptability (which was also an important factor influencing purchase during seasonal influenza) [33]. A lack of

data was reported as a crucial limiting factor for a robust policy-making process, especially during pandemics when decisions must be made faster than during seasonal influenza. From an economic perspective, we observed that cost-effectiveness evidence was often required but not significantly taken into account. As presented by Drummond et al., we believe that the political visibility and budgetary impact of introducing a new vaccination programme is higher than simply reimbursement approval of a new, standard, pharmaceutical product. Furthermore, in most countries, there was a lack of communication between the authorities responsible for vaccine licensing and those for other health technologies, and different criteria may apply [83].

A scarcity of resources and other issues incited providers (national influenza programs and healthcare insurance) to prioritise some groups for receiving influenza vaccine for free or with reimbursement. The 'best' or 'optimal' strategy for including or excluding certain groups for vaccine prioritisation has not yet been fully clarified [52]. We observed that after the last pandemic, policy-makers and their advisors were worried about presenting the clinical and epidemiological evidence used and how the advice was established. Establishing the advice is a key step in the decision process, as this advice is commonly used to justify the actions taken by policy-makers. It is therefore important to understand how this advice is created. However, public access to meetings is still difficult, especially in Europe. The US has largely improved the transparency of their decision-making process by making meeting transcripts publicly available through official websites.

We suggest that efforts should be made to facilitate better communication between the stakeholders involved in the policy chain. This collaboration will produce more robust information and provide transparency in the evidence used in the decision-making process [84]. Additionally, communication with people concerned about vaccination should be enhanced with the goal of improving funding and reimbursement for both providers and patients [11] and [81]. Indeed, vaccination recommendations alone were insufficient in improving vaccination rates in various countries, regardless of their development status [11] and [81]. However, recommendations are still a crucial tool for boosting vaccine use [11]. In France, for example, vaccine reimbursement was placed under the following restriction: a vaccine not recommended by health authorities was never reimbursed, whereas a recommended vaccine was theoretically reimbursed [85].

4.3. Role and relationship of the stakeholders as determinants of policy-making

The actors, institutes, and stakeholders, who are involved in the influenza policy-making chain at different levels, have complex interactions. Although it was difficult to categorise all of the stakeholders involved in the policy-making process, their relationships, and their respective segments in the policy chain into one scheme, we have amalgamated these data and provided a holistic overview, shown in Fig. 2. To the best of our knowledge, there is no similar scheme found in the literature.

Studies that reported on seasonal influenza, which differ from pandemic studies, provided worse explanations of the interactions between the stakeholders; possibly

because routine procedures hide the importance of a clear definition of the stakeholders' role in the process and the impact of their relationship on the use of information. We found that the internal relationships among the institutes at the national level were not well described in the literature. However, their interactions with organisations at the international level and the latter with vaccine manufacturers were better reported.

As the international authority for health within the United Nations, the WHO successfully adopted responsibility for providing global guidance on influenza vaccine recommendations. The composition of vaccines is assessed yearly through an exchange of information, technology and communication among experts. However, their relationship with vaccine manufacturers may be strained during a pandemic. For example, during pre-pandemic preparation in 2007, the Indonesian government and the WHO failed to resolve the virus-sharing issue with manufacturers who 'developed, and patented, influenza vaccines that the Indonesian authorities could not purchase' [86]. This was considered a "breakdown of trust" in the global influenza surveillance network [87].

Another example of the relationship between the WHO and vaccine manufacturers acting as main stakeholders is the effort to develop a 'universal vaccine'. This promising vaccine, if it addresses the issue of seasonal variations in the influenza virus, could dramatically influence immunisation policies in the future [88]. Indeed, new formulations for the vaccine have been proposed. Responding to vaccines recently licensed in the US (2012) and Europe (2013) that contain four strains of the virus, the WHO has started to recommend strain compositions for quadrivalent vaccines, along with the previous trivalent vaccines, since the 2013–14 influenza season. At present, no evidence of any incremental clinical benefit for quadrivalent over trivalent vaccines has been shown [89], though we think that quadrivalent vaccines represent a step in the progression of vaccine development.

There are currently only a few influenza vaccine manufacturers, and only three of these have recently proposed new technologies, such as quadrivalent vaccine composition and nasal administration [80]. Interestingly, 70% of vaccine production occurs in North America, Europe (France and the UK), Australia, and Japan [86] and [90]. This could cause a problem for the vaccine supply. However, there is an active interaction between the WHO and industrialised countries, manufacturers, and the entire international community to promote global solidarity and collaboration. The low number of manufacturers, which could subsequently lead to a disruption in the vaccine supply, might be a result of the high cost of vaccine production technology and numerous regulatory requirements, mentioned earlier.

We observed that vaccine manufacturers and the WHO have a close relationship, which is necessary for efficient responses to influenza outbreaks. However, occasionally, especially during times of uncertainty (pandemic), this relationship transparency became weak and raised suspicions that there were conflicts of interest in the decisions made. We propose strengthening the transparency of these interactions, for example by making the minutes or transcriptions of policy meetings available to the public domain.

5. CONCLUSIONS

This review has highlighted two important findings. First, the most relevant evidence for influenza policy-making remains clinical and epidemiological studies, although mathematical modelling and ethical issues have acquired greater importance since the last pandemic. Indeed, recommendations in response to the 2009 pandemic triggered changes in seasonal influenza policies in later years. Though political issues, together with international pressure, were rarely mentioned as a justification, they nevertheless seemed to be influential in seasonal and pandemic influenza national policies.

Second, the interactions between the stakeholders in the influenza vaccination policy chain may change according to whether one is dealing with seasonal or pandemic influenza. These complex interactions should be considered one of the determinants of the policy-making process. A notable example is the unsuccessful pandemic policy of 2009, which can be attributed to communication failures, especially with the physicians and general public. The role and relationship of the stakeholders, including the actors at different levels and vaccine manufacturers, remains unclear, especially during seasonal influenza. Nevertheless, as a result of improved transparency, national governments and the WHO increasingly provide declarations of interest of the actors involved and also emphasise the use of evidence in policy-making (this development is particularly clear after the last pandemic).

Generally, our global literature review could not define precise interactions or detailed use of evidence because of the complexity and numerous factors that influenced the decision-making process. Therefore, we recommend that further work should be carried out at a national level for only a few countries, using qualitative exploratory methods that would enable a holistic perspective and a better assessment of the stakeholder viewpoints and interactions. In addition, this approach will reduce the declaration bias regarding the analysis of policy-making processes and especially policy-making determinants.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HMS designed the systematic search strategy. MLS and HMS extracted data from the papers. MLS, HMS, LP, JP, and AM participated in the data analysis. MLS, LP, JMC, JP, AM, and HMS prepared the manuscript. All authors read and approved the final manuscript.

Acknowledgments

[APPENDIX A]

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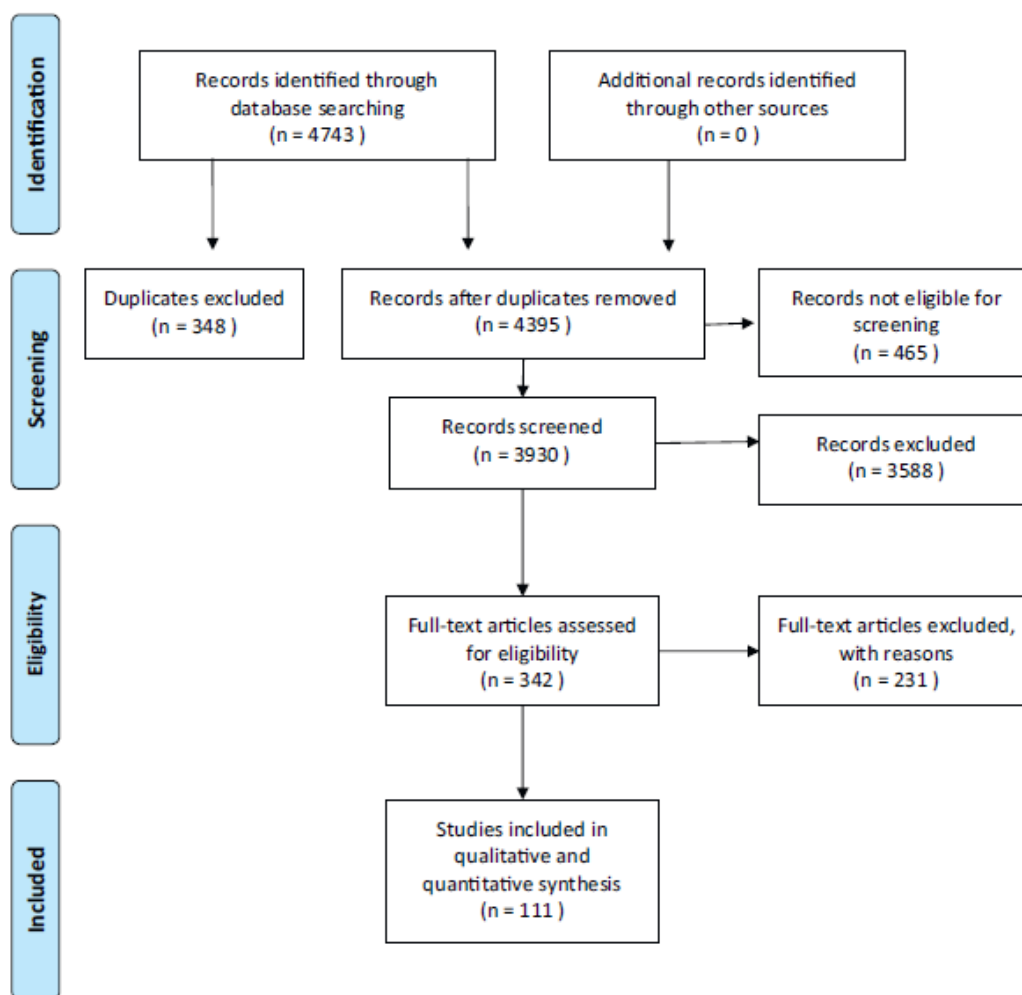
TABLES AND FIGURES

Fig. 1. Flowchart for article selection, based on Ref. [25].

Table 1
Segments of the influenza vaccination policy chain, stakeholders involved, main information and factors influencing policy-making.

Policy segment	Stakeholders involved	Main information used	Factors of influence	#
Vaccination recommendations n – 78, 70%	(I) WHO, ECDC (N) Ministry of Health, Department of Health, Governmental authority (St) Advisory boards, universities, Research institutes	Epidemiological and virological studies, Economic evaluations, Models i.e.: Australia, Canada, France, Germany, India, Italy, Netherlands, UK, US	Ethics, Vaccine availability, Expert opinion, Media, Political willingness i.e.: Australia, Canada, China, Israel, US	(S) 1, 28, 34, 36, 43, 44, 65, 86, 93, 103, 109, 107, 110 (B) 37, 52, 83, 87 (P) 02, 03, 05, 07, 08, 10, 12, 13, 14, 15, 19, 20-22, 24, 25, 27, 31, 32, 35, 38, 39, 40, 41, 45, 46, 47, 48, 49, 50, 54, 55, 57, 58, 60, 62, 63, 66, 67, 69, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 88, 91, 95, 96, 97, 100, 101, 102, 105, 106
Vaccine composition n – 11, 10%	(I) WHO (St) NIC, WHOcc, Surveillance networks, Manufacturers	Virological and epidemiological studies, Zoonotic studies i.e.: EU, US	Expert opinion i.e.: US	(S) 6, 29, 42, 90, 108 (B) 64 (P) 4, 53, 56, 59, 98
Vaccine license n – 2, 2%	(I) EMA (N) Regulatory agency (St) Advisory boards, Manufacturers	Vaccine safety, Efficacy/effectiveness. Cost-effectiveness, Immunological studies	International pressure	(S) 89 (P) 85
Vaccine funding n – 20, 18%	(I) WHO (N) Ministry of Health, Governmental authority, Healthcare providers (St) Advisory boards, Research institutes, Manufacturers	Epidemiological studies, Economic evaluations, Models i.e.: Canada, EU, US	Demographics, Public opinion, Budget, Logistics i.e.: Canada, UK, US,	(S) 33, 51, 70, 77, 92 (B) 9 (P) 11, 16, 17, 18, 23, 26, 30, 61, 68, 84, 94, 99, 104, 111

Key: # number attributed to the article during full text reading (Annex 3); (I) actors at the international level; (N) actors at the national level; (St) stakeholders all levels; (S) seasonal influenza; (B) both seasonal and pandemic; (P) pandemic influenza; WHO, World Health Organization; ECDC, European Centre for Disease Control and Prevention; NIC, National Influenza Centre; EMA, European Medicines Agency; EU, European Union; UK, United Kingdom; US, United States.
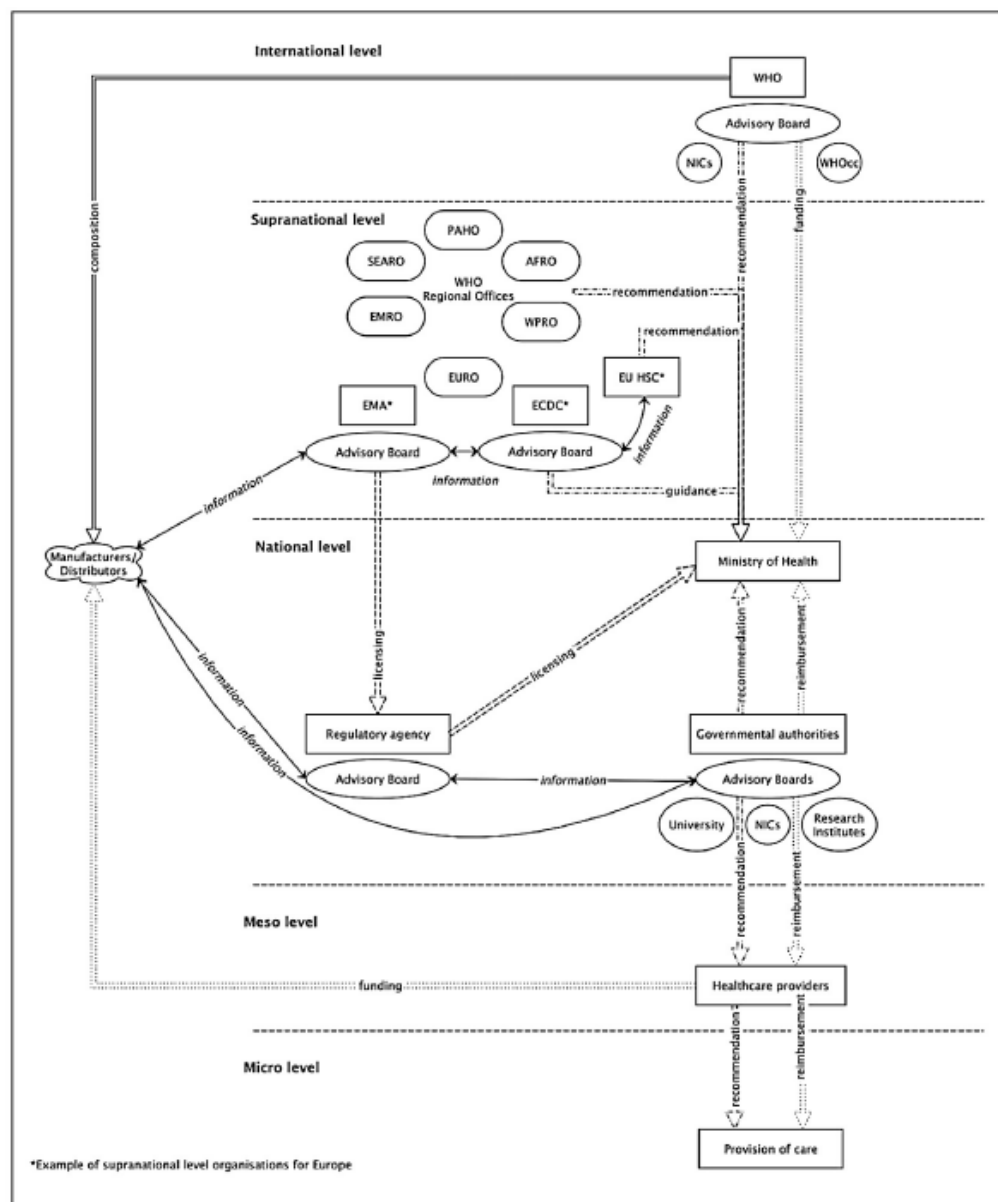
Key: WHOcc, World Health Organization collaboration centers; PAHO, Pan American Health Organization; AFRO, WHO Regional Office for Africa; SEARO, WHO Regional Office for South-East Asia; EMRO, WHO Regional Office for the Eastern Mediterranean; WPRO, WHO Regional Office for the Western Pacific; EURO, WHO Regional Office for Europe; NICs, National Influenza Centres; EU HSC*, European Union Health Security Committee; EMA*, European Medicines Agency; ECDC*, European Centre for Disease Prevention and Control; information, information exchange between the actors and stakeholders.

Fig. 2. General overview of the interactions between the stakeholders involved in the influenza vaccination policy chain. Key: WHOcc, World Health Organization collaboration centers; PAHO, Pan American Health Organization; AFRO, WHO Regional Office for Africa; SEARO, WHO Regional Office for South-East Asia; EMRO, WHO Regional Office for the Eastern Mediterranean; WPRO, WHO Regional Office for the Western Pacific; EURO, WHO Regional Office for Europe; NICs, National Influenza Centres; EU HSC*, European Union Health Security Committee; EMA*, European Medicines Agency; ECDC*, European Centre for Disease Prevention and Control; information, information exchange between the actors and stakeholders.