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Vaccine market access pathways in the EU27 and the United Kingdom – analysis and recommendations for improvements

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ABSTRACT

Background: Vaccine market access (VMA) pathways across the European Union (EU) and the United Kingdom (UK) are complex, lengthy, and heterogeneous, particularly when compared with pharmaceuticals. The knowledge base to inform recommendations for optimization of VMA is lacking. We therefore conducted a comprehensive evaluation of EU VMA pathways.
Methods: Research in two phases included: (1) mapping VMA pathways in each EU member state (including the UK) based on a literature review, expert interviews, and mathematical archetyping; and (2) interviews with vaccine experts to identify barriers, drivers, and recommendations for regional VMA alignments.
Results: Key steps in VMA across the EU include horizon scanning, early advice, National Immunization Technical Advisory Group (NITAG) recommendation for inclusion in national immunization programs, health technology assessment (HTA), final decision and procurement. We found significant complexity and heterogeneity, particularly for early advice, and in the roles, decision-making criteria, and transparency of NITAGs and HTA bodies. The most important drivers for rapid VMA included demonstration of disease burden and vaccine benefit (e.g., efficacy, safety, economic). Key barriers were budget limitations and complexity/clarity of VMA processes (e.g., need for national-regional consensus, clarity on process initiation, and clarity on the role of HTA). Recommendations for alignment at EU and member-state levels include information sharing, joint clinical assessment, initiatives to address funding and political barriers, and improved transparency by decision-making bodies. Early engagement with vaccine stakeholders was a key recommendation for manufacturers.
Conclusions: There is significant potential for alignment, collaboration, and improvement of VMA across the EU. Roles, responsibilities, and transparency of key bodies can be clarified. The COVID-19 pandemic response should stimulate policies to improve access to all vaccines, including routine ones, and form the foundation upon which a consistent vaccine ecosystem can be created for the EU, one that is resilient, consistent between member states, and fit for purpose.

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1. Introduction

Vaccines have the potential to significantly reduce disease, disability and mortality [1–4]. In addition to the rigorous licensing steps that also apply to pharmaceuticals, vaccines follow complicated market access pathway processes and are subjected to mandatory local standards, [5,6] which add complexity and time to the recommendation and reimbursement of national immunization programs. The COVID-19 pandemic has underscored both the need and possibility for agile vaccine mobilization, even within existing vaccine market access frameworks [7–9]. However, the pandemic has also highlighted the need to improve vaccine procurement strategies and cooperation across Europe [10,11]. Aside from the present pandemic, under-recognition of the long-term societal benefits of vaccines, including their value from economic perspectives, which may be locally driven, represent barriers to vaccine market access [12].

Within the European Union (EU), vaccine market access (VMA) is nationally led. Following marketing authorization, member states individually decide on inclusion of a vaccine within their national immunization program (NIP). A common step of VMA across the region involves a recommendation by the National Immunization Technical Advisory Group (NITAG) in each country [13,14]. However, there are significant differences and specificities in VMA pathways within and beyond the NITAG recommendation. As such, VMA across the EU has historically appeared complex and opaque [15,16]. Thus, while it is timely to align on approaches to enhance the rapidity of VMA, the knowledge base to inform such recommendations is lacking. For this purpose, we conducted a comprehensive evaluation of VMA pathways across the EU region, from marketing authorization to population access.

This research was conducted on behalf of Vaccines Europe, part of the European Federation of Pharmaceutical Industries and Associations (EFPIA), [17,18] to establish VMA pathways across the 28 EU member states including United Kingdom (UK), which was an EU member at the time of the research. The objective was to provide an evidence base on which to inform policy recommendations at national and EU levels, with the goal of optimizing VMA across the region. To facilitate this goal, we systematically mapped and evaluated VMA pathways in each member state.

2. Materials and methods

Secondary and primary research was conducted in 2018–2019 in two phases: (1) mapping VMA pathways in each EU28 member state based on a literature review and local data collection by industry vaccine experts, culminating in mathematical archetyping and defining exemplar countries; and (2) primary research with non-industry vaccine experts in exemplar countries to validate phase 1 findings. This exercise also enabled the identification and analyses of barriers and drivers of VMA across the EU28, and recommendations for alignment.

2.1. Phase 1

2.1.1. Literature search

A literature search (covering January 1, 2015 to September 25, 2018) was conducted to establish an understanding of VMA pathways and develop data collection instruments (country cards). Peer-reviewed publications covering the key aspects of the VMA pathways in the EU28, including relevant stakeholders, processes, and time to population access (TTPA), were identified. Searches of full publications were conducted in Embase® and Medline® databases. Scientific presentations were searched in the International Society for Pharmacoeconomics and Outcomes Research database, Health Technology Assessment International (HTAi) Vortal® and a Creativ-Ceutical Proprietary Database. The full search strategy and inclusion/exclusion criteria are provided in Supplemental File 1; Table 1. Titles and abstracts were screened by a single experienced reviewer to select relevant records subject to predefined inclusion and exclusion criteria; full-text publications were obtained for the selected literature.

2.1.2. Country card completion

To obtain detailed descriptions of VMA pathways in each of the EU28 countries, we conducted primary research (in Q4 2018) with national industry experts identified and recruited by Vaccines Europe from each member state. Narrative descriptions of the country-specific VMA pathways were collected on data collection instruments (country cards). Country card sections included: key steps of the VMA process, key stakeholders such as NITAG and health technology assessment bodies (HTABs) and their roles, and the number of vaccinations included in the NIP. On NITAGs and HTABs specifically, each expert assessed key decision-drivers and details of early advice, if given, and perceived transparency level. Transparency was defined as the presence of a formal decision-analysis/health technology assessment (HTA) framework, a systematic approach for evidence appraisal, and publication of the decision and rationale. The level of transparency was considered low if 0 or 1 criterion was met; medium if 2 criteria were met; and high if all 3 criteria were met. The experts also provided supportive references for all local VMA information, where available.

Quantitative data were also obtained from the industry experts on TTPA, defined as the time between marketing authorization and the date when funding was effectively implemented, either via public procurement or reimbursement [19]. TTPA data were obtained for the overall process and specifically for three vaccines: a pneumococcal vaccine (PCV13), a human papilloma virus (HPV) vaccine (Gardasil 4), and a quadrivalent influenza vaccine (Fluarix Quadrivalent; Fluarix Tetra for France and the UK; Influsplit Tetra for Germany). Our selection rationale was to include vaccines targeting widespread and/or common diseases adopted for routine use in multiple member states, across a spectrum of populations (namely pediatric, adolescent, and adult).

Range and 95% confidence intervals (CI) were calculated. The TTPA data for these vaccines were analyzed to examine the trends in VMA compared with the data presented in the literature.

All questionnaires were checked for completeness and consistency and clarifications and adjustments were made if needed. Responses were further reviewed by 11 non-industry vaccine experts and amended if needed (in 2019). Finally, information was cross-checked by a separate group of industry experts in 2020 to ensure robustness of data and to reflect recent changes not previously captured. Therefore, the information in this report relates to the status of VMA as of Q1 2020.

2.1.3. Archetype and exemplar development

Based on findings from the primary research with industry experts, we conducted a hierarchical clustering exercise to classify the member states according to selected VMA attributes. Manual clustering was used to assess the face validity of results obtained by mathematical algorithms. Three attributes were selected, informed by industry vaccine experts, to perform the manual clustering: (1) involvement of HTAB (yes/no); (2) procurement type (formal tender-driven process and/or non-tender/individual product-driven process); and (3) level of decision-making (national and/or regional).

A mathematical agglomerative approach to clustering was used, including a standard method for categorical attributes (Jaccard metrics) to measure the "distance" between country data. A

Table 1
Attributes used for preliminary mathematical clustering of EU28 VMA pathways.

Clustering attribute
1. Applicability of horizon scanning (yes/no)
2. Availability of formal early advice (yes/no)
3. NITAG formal terms of reference (yes/no)
4. NITAG formal decision-analysis framework (yes/no)
5. Level of decision making* (national/regional/both)
6. Mandatory (binding) funding of at least one vaccine following inclusion of vaccination in immunization program (yes/no)
7. Procurement type (tender-driven/individually-driven†/both)
8. Level of tenders (national/regional/both)
9. Published award criteria and clear selection process for tenders (yes/no)
10. Number of vaccinations in immunization program (<10/10–15/>15)
11. Involvement of HTAB (yes/no)
12. NITAG preferential recommendation towards vaccine type (yes-always or usually/yes-sometimes/no)
13. NITAG main decision drivers (clinical/economic/population-based/clinical and economic/clinical and population-based/clinical and economic and population-based/other)
14. HTA main decision drivers (clinical/economic/population-based/clinical and economic/clinical and population-based/clinical and economic and population-based/other)
15. Transparency of NITAG/HTAB (low/medium/high)
16. HTA binding for the respective authority (low/medium/high)
17. Can marketing authorization holder initiate the assessment (yes/no)
18. Time to population access (<2 years/2–6 years/>6 years)

HTA, health technology assessment; HTAB, health technology assessment body; NITAG, National Immunization Technical Advisory Group.
* Issuing recommendation for inclusion into vaccination program and funding.
† Reimbursement list for vaccines.

Complete-Linkage method was performed thereafter to evaluate the distance between the farthest two points from different clusters. The Average-Linkage method was used for sensitivity analysis, which evaluated the average distance from any country of one cluster to any country of another cluster. The optimal number of clusters was selected based on silhouette average width, which describes the distance of each country in one cluster to countries in the neighboring cluster. To compare the clusters created based on different sets of attributes, the Adjusted Rand Index (ARI) was used as a measure of cluster similarity. Finally, the appropriateness of clusters was checked by Dunn's index (DI; i.e., a ratio between the minimum inter-cluster distances to the maximum intra-cluster diameter) with DI > 1 being a necessary and sufficient condition and higher value indicating a better fit [20,21]. Each country was treated separately, and clusters were merged until stopping criteria were met. Attributes for which answers were "not applicable" were excluded from the clustering to avoid false homogeneity for this response. The remaining attributes were used for the preliminary mathematical clustering. These analyses were conducted using the 'hclust' function in R (© The R Foundation Software, version 3.5.0).

Exemplar countries were then selected (and cross-validated by the vaccine industry experts) for each cluster: first, those representing the main European (EU5) markets (France, Germany, Italy, Spain and the UK) [22,23]. In the absence of at least one EU5 member state within a given cluster, the state with the highest population size/growth rate was selected. The results of mathematical clustering and manual clustering were compared, to ensure face validity and consistency. Created clusters were further validated by the industry experts, with final validation by non-industry experts from exemplar countries.

2.2. Phase 2

2.2.1. Expert stakeholder interviews

Up to two non-industry experts were recruited from each exemplar country to validate the pathway descriptions and VMA archetypes. Experts were recruited based on their individual experience in vaccine decision making, participation in decision-making working groups, and relevant publications. This validation exercise was also conducted with a non-industry expert providing EU-level input.

Before the one-hour telephone interviews, respondents received pre-reading material and a semi-structured questionnaire grouped in three main sections: overview of VMA and EU-level collaboration, vaccine assessment frameworks, and archetypes of VMA across the EU28. Findings from the expert interviews were collated to describe drivers, barriers, and other critical steps of the VMA pathway. The non-industry experts also provided recommendations to improve VMA at the national and EU levels.

3. Results

3.1. Phase 1

3.1.1. Literature review

The literature search (Supplemental File 1; Fig. 1.1) identified 17 references representing 16 original studies (14 peer-reviewed journal articles, two congress poster presentations, and one book chapter), which were classified as country-specific or cross-country comparisons, [15,16,24–32] topics on clinical and economic assessments of vaccines, [12,14] or vaccination program implementation studies [33–36].

The literature confirmed the varying timeframes, complexity, and heterogeneity of VMA across the EU28, with numerous stakeholders involved [6,16,25]. For example, one study reported substantial variability in TTPA across countries, ranging from 11 months in Belgium to 135 months in Italy [16] and others estimated up to 77 months (6.4 years) [19].

Some countries evaluated vaccination programs at the population or societal levels, rather than on individual or healthcare levels. Broader measures of vaccination value were also identified e.g., community externalities such as disease control, herd immunity, elimination, or eradication [12,14].

3.1.2. Information from country cards

Country card data from the industry experts further clarified the key features of VMA pathways and marketing authorization in each of the member states (Supplemental File 2). An example country card for Germany describes a process with both NITAG and HTAB involvement (Fig. 1).

Country card: Germany	
National Immunization Technical Advisory Group (NITAG)	
Name of the relevant body	NITAG: STIKO
Are there any specific eligibility criteria for vaccination programs to be assessed by NITAG?	Yes (burden of disease, medical need, availability of a licensed vaccine, vaccine profile)*
Who initiates the process?	NITAG
Does NITAG have formal terms of reference (i.e., defined purpose and structures of the organization)?	Yes
Does NITAG have a formal decision analysis framework (i.e., structured approach for decision making)?	Yes
Main decision drivers: 1 – highest relative importance 3 – lowest relative importance.	1. Burden of disease 2. Safety and tolerability 3. Public health impact
Other attributes considered by NITAG in their decision-making process	• Unmet needs • Efficacy • Effectiveness • Cost-effectiveness • Societal impact (friction cost approach for base case and human capital approach for sensitivity analysis) • Public perception of disease and/or vaccine • Transmission models • Ethical issues • Public acceptance • Organizational/implementational and equity attributes
Does NITAG make any preferential recommendations towards the vaccine type?**	Yes – sometimes
Is GRADE or any similar tool used for grading the quality of evidence and risk of bias assessment?	Yes
Are there specific timelines in place for the assessment?	No
Are NITAG recommendations and rationale publicly available?	Yes
Level of transparency†	High
WHO criteria of functionality‡	All six criteria met: • Legislative/administrative basis • Formal terms of reference • Conflict of interest policy implemented • At least five expertise areas • Meets at least once a year • Circulation of the agenda and background paper a week before meeting
Health Technology Assessment Body (HTAB)	
Name of the relevant body	G-BA (however, no HTA assessment conducted by G-BA)
Are there any specific eligibility criteria for vaccines to be assessed by the HTAB?	NA
Who initiates the process?	NA
Is the process conducted before/after/at the same time as the process conducted by NITAG?	NA
Does the HTAB have a vaccine-specific decision analysis framework in place?	NA
Main decision drivers: 1 – highest relative importance 3 – lowest relative importance	NA
Other attributes considered by the HTAB in their decision-making process	NA
Is GRADE or any similar tool used for grading the quality of evidence and risk of bias assessment?	NA
Are there specific timelines in place for the assessment?	NA
Are HTAB recommendations and rationale publicly available?	NA
Level of transparency†	NA
Is HTAB recommendation binding for respective health authorities?	NA

Fig. 1. Country card example: Germany. *See chapter 4 of STIKO Standard Operating Process [44]. **Issuing the recommendation toward the particular brand by NITAG. †High–3/3 criteria (formal decision-analysis framework in place; publication of decision with rationale; systematic approach for evidence appraisal) met; medium–2/3 criteria met; low–1/none criteria met. ‡NITAG Resource Center [45]. G-BA, Federal Joint Committee (Gemeinsamer Bundesausschuss) GRADE, Grading of Recommendations Assessment, Development and Evaluation; HTA, health technology assessment; HTAB, health technology assessment body; NA, not applicable; NITAG, National Immunization Technical Advisory Group; STIKO, Standing Committee on Vaccination (*Ständige Impfkommission*); WHO, World Health Organization.

3.1.3. Vaccine market access pathways

Based on responses gathered per key topic, descriptive statistical analysis was conducted and a market access pathway, from marketing authorization to population access, was summarized for each country. In addition, an overview of all EU28 VMA pathways was developed.

3.1.4. Country-specific VMA pathway examples: Germany and France

Fig. 2 shows the VMA pathways for Germany (Fig. 2a) and France (Fig. 2b) [37–40].

3.1.5. Overall EU vaccine market access pathway

Key steps of the VMA pathway across the region include horizon scanning, early advice, initiation of assessment, NITAG recommendations for consideration of vaccine into NIP and funding, HTAB recommendation, final decision, NIP inclusion, and procurement (Fig. 3).

The presence or absence of steps followed by each EU28 country are represented in Fig. 4. ***Horizon Scanning,*** conducted once or twice a year, is performed in 15 countries, usually by the NITAG, Ministry of Health (MoH) or other institutions. Experts highlighted that early advice from the relevant body is crucial for acceleration of the access pathway process. ***Formal Early Advice,*** featured in five countries, usually involves a NITAG or HTAB and is defined as a separate, established process with criteria that may include whether a vaccine is eligible for the process, documentation, timelines and, in some cases, fees. ***Informal Early Advice,*** featured in eight countries, is usually provided verbally, in face-to-face meetings, without a fee. The German VMA pathway did not feature early advice, but manufacturers may present their data in meetings with the Robert Koch Institute (RKI).

Assessment of a new vaccine is initiated by the marketing authorization holder in 14 countries. In Finland, assessment is initiated by the HTAB, whereas in Croatia and Spain it is initiated by

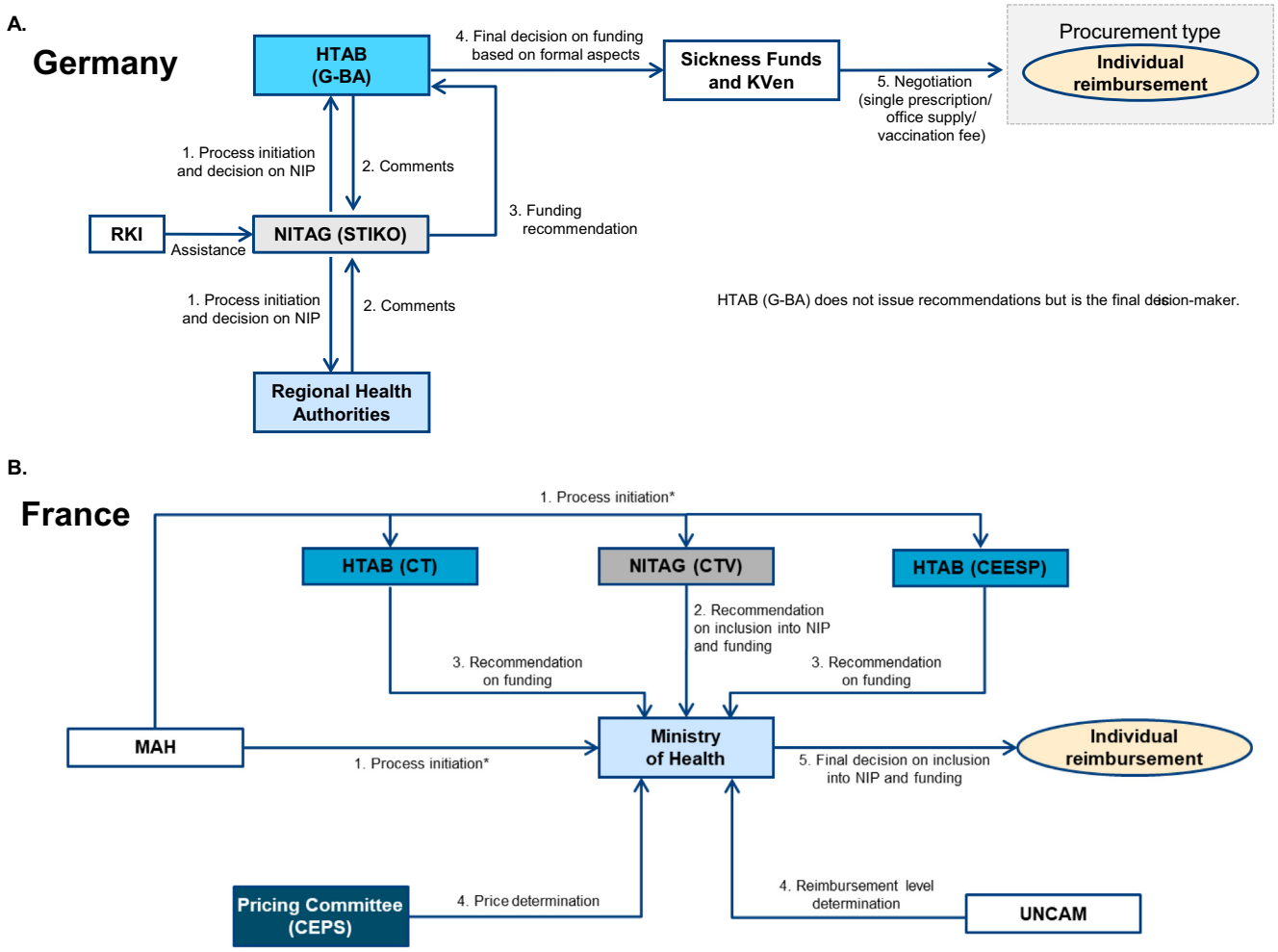


Fig. 2. **(a)** Key steps and stakeholders in the VMA decision-making and procurement process for Germany. In Germany, [37–40] horizon scanning is conducted annually by the RKI in discussion with the vaccine marketing authorization holder concerning new evidence. Assessment is initiated by the German NITAG (STIKO). The initiation of the assessment depends on the availability of a licensed vaccine, the vaccine profile, burden of disease, and medical need. The STIKO decides on inclusion into the NIP, following a formal decision-analysis framework process and assisted by the Immunization Unit 33 at the RKI. While safety, tolerability, population-based aspects, and cost-effectiveness of the vaccination constitute the main decision drivers, burden of disease has a greater impact on the timing of the decision than on the decision itself. Afterwards, the evidence is summarized and sent to the G-BA and the Regional Health Authorities. Based on their comments, which STIKO is not obliged to consider, the STIKO issues a recommendation on funding, which is published in the national epidemiological bulletin by the RKI. The final G-BA decision is aligned with the STIKO recommendation; however, G-BA maintains the right to disagree for procedural (not scientific or cost-related) reasons. In case of a positive decision, sickness funds (insurers) have to reimburse the vaccination. Therefore, sickness funds and the KVen negotiate whether there will be a single prescription (pick up in pharmacies) or office supply and what vaccination fee will apply. In general, sickness funds may voluntarily reimburse a vaccination before STIKO and G-BA as long as a vaccine with market authorization is available. No formal scientific advice is possible with STIKO as this is provided by the regulatory authority (Paul-Ehrlich institute). **(b)** Key steps and stakeholders in the VMA decision-making and procurement process for France. In France, the marketing authorization holder initiates the assessment. CEESP, National Authority for Health-Economic and Public Health Assessment (Commission Evaluation Economique et de Santé Publique); CEPS, Pricing Committee (Comité Economique des Produits de Santé); CT, National Authority for HTA (Comité Economique des Produits de Santé); CTV, Technical Vaccination Committee (Comité Technique des Vaccinations); G-BA, Federal Joint Committee (Gemeinsamer Bundesausschuss); HTAB, health technology assessment body; KVen, Regional Association of Statutory Health Insurance Physicians (Kassenärztliche Vereinigung); MoH, Ministry of Health; NIP, national immunization program; NITAG, National Immunization Technical Advisory Group; RKI, Robert Koch Institute; STIKO, Standing Committee on Vaccination at the Robert Koch Institute (Ständige Impfkommission am Robert-Koch-Institut); UNCAM, National Union of Health Insurance Funds (Union Nationale des Caisses d'Assurance Maladie). *MoH as well as approved patient associations, national colleges of professionals or learned societies may request a recommendation.

the Public Health Institute and the Public Health Commission, respectively. In some states, other stakeholders, such as scientific or patient associations, may also initiate assessment. HTA, in the 12 member states where it applies to vaccines, usually follows a marketing authorization holder submission, but can also be initiated by other stakeholders, such as the MoH in the Netherlands and NITAGs in Estonia and Ireland.

In all member states (except Romania) the NITAG recommends inclusion of a vaccine in the NIP and makes recommendations on funding. Drivers of NITAG recommendations are clinical, economic, or public health factors in most member states. Only clinical factors are considered key recommendation drivers in Greece, whereas in four member states, additional economic factors drive the NITAG recommendation. In the remaining nine member states, the NITAG recommendation is driven by clinical and public health factors. In eight of 16 member states with economically driven recommendations, budget impact is considered most relevant by NITAGs, whereas in approximately one-third of member states cost-effectiveness analysis is a key driver. In the remaining two member states, both cost-effectiveness analysis and budget impact are the main decision drivers.

The ***HTAB Recommendation*** follows or is made in parallel (as in France) to the *NITAG Recommendation*, in 12 of the EU28 countries. No eligibility criteria apply for vaccination programs to undergo an

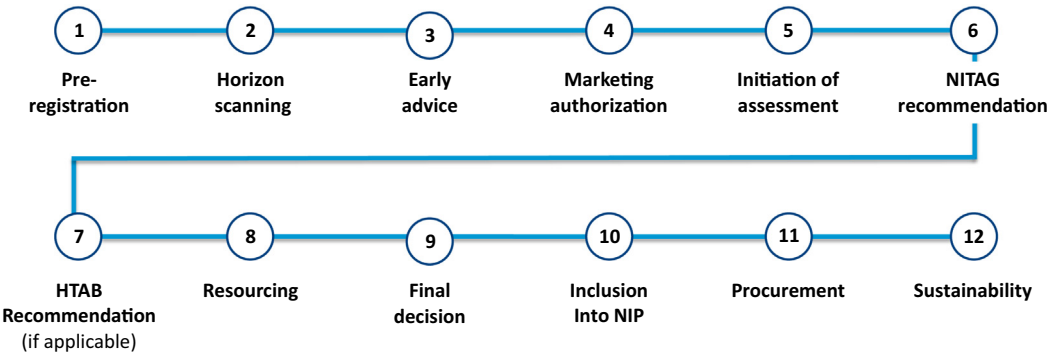


Fig. 3. Key features of VMA pathways in the EU28 member states. *HTA may be conducted before or in parallel with the assessment by NITAG. HTA, Health Technology Assessment; HTAB, Health Technology Assessment Body; NIP, National Immunization Program; NITAG, National Immunization Technical Advisory Group.

	Horizon scanning	Early advice	Initiation of assessment	NITAG Recommendation	HTAB Recommendation	Binding funding following final decision	Final decision/ NIP inclusion	Procurement
Austria		Informal	MoH*	E(BI), Clin			N Lev	N Lev, R Lev
Belgium	1 or 2/yr	Informal	MoH*	Clin, PH	E(BI), E(CE)		N Lev	R Lev
Bulgaria				E(BI), Clin	E(BI)		N Lev	N Lev
Croatia	1 or 2/yr		PH Inst	Clin, PH			N Lev	N Lev
Cyprus	Ad hoc		MoH*	E(BI), Clin			N Lev	N Lev
Czech Republic				E(BI), Clin			N Lev	N Lev
Denmark	Ad hoc	Formal	NITAG	Clin, PH			N Lev	N Lev
Estonia			NITAG	E(CE), Clin	E(CE)		N Lev	N Lev
Finland	1 or 2/yr		HTAB	E(CE), Clin	E(BI), E(CE)		N Lev	N Lev
France	1 or 2/yr	Formal		E(CE), Clin	Clin		N Lev	N Lev
Germany	1 or 2/yr		NITAG	E(CE), Clin			N Lev	N Lev
Greece			NITAG	Clin	E(BI)		N Lev	N Lev
Hungary			NITAG	E(BI),E(CE),Clin			N Lev	N Lev
Ireland	Ad hoc	Informal	NITAG	Clin, PH	E(BI), E(CE)		N Lev	N Lev
Italy		Informal	MoH*	Clin, PH	E(BI), E(CE)		N Lev, R Lev	R Lev
Latvia			NITAG	Not indicated			N Lev	N Lev
Lithuania			NITAG	E(BI), Clin			N Lev	N Lev
Luxembourg	1 or 2/yr		MoH*	Clin, PH			N Lev	N Lev
Malta	1 or 2/yr		MoH*	E(BI), Clin	E(BI)		N Lev	N Lev
The Netherlands	1 or 2/yr	Formal	MoH*	E(BI), Clin	E(BI)		N Lev	N Lev
Poland		Formal	MoH*	Local epi			N Lev	N Lev
Portugal	Ad hoc	Formal	MoH*	Clin, PH			N Lev	N Lev
Romania			MoH*	Not Applicable				-
Slovakia		Informal		Clin, PH	E(BI)		N Lev	N Lev
Slovenia			MoH*	Clin, PH			N Lev	N Lev
Spain	Ad hoc	Informal	PH Inst	E(BI),E(CE),Clin			N Lev, R Lev	N Lev, R Lev
Sweden	1 or 2/yr	Informal	NITAG	E(CE), Clin	E(CE)		N Lev, R Lev	N Lev, R Lev
United Kingdom	1 or 2/yr	Informal	MoH*	E(CE), Clin				N Lev

Fig. 4. Presence/absence of key steps in the vaccine access pathways of EU28 member states. *Can also be initiated by marketing authorization holder; Green/darker-shaded boxes represent presence of step in the member-state pathway. E(BI), Driver: Economic, budget impact; E(CE), Driver: Economic, cost-effectiveness; Clin, Driver: Clinical; PH, Driver: Public health; Local epi, Local epidemiology; N Lev, National level; R Lev, Regional level; HTAB, health technology assessment body; NITAG, National Immunization Technical Advisory Group; yr, year; MoH, Ministry of Health; PH Inst, Public Health Institution or Commission.

assessment by HTAB in any of the 12 member states where HTA is conducted. In nine member states that conduct HTA for vaccines, no vaccine-specific decision-analysis framework is in place; therefore, vaccines are assessed similarly to therapeutic drugs. Of the 12 member states that conduct HTA, seven base recommendations for funding on clinical and economic aspects. Public health impact is considered as a key decision-making factor in Finland, Netherlands, and Slovakia and is considered a significant factor by >3/4 member-state NITAGs, in contrast to HTABs, which generally do not consider public health impact as a significant factor for decision making.

In 24 member states, decision making is mainly conducted at the national level. National *and* regional decision making is conducted in four member states. ***Final Decision*** and ***NIP Inclusion*** is usually made by the MoH. Experts from Poland, Sweden, and Italy indicated this to be the critical step for VMA in their respective countries. Experts in Poland and Sweden expressed a lack of transparency in decision making prior to the final decision being

made. In Italy, there is requirement for unanimous regional consensus prior to granting a final positive national-level decision.

Mandatory (i.e., legally binding) funding, based on a positive final decision, is made in all member states except Romania. Because the costs of a vaccination program go beyond the cost of the vaccine and include other costs associated with implementation and organization of the immunization, the decision on funding of vaccination programs may or may not include funding/reimbursement of a vaccine, depending on the country. In 25 EU states, binding funding following inclusion of the vaccine in the immunization program applies. However, Cyprus and France approach funding differently, and no details were provided for Malta.

Procurement of vaccines is tender driven in 22 member states, with tenders usually conducted at the national level (Fig. 4). Tenders are conducted at the regional level in two countries, whereas in Austria, Spain, and Sweden, both national and regional tenders occur. In five member states, an "individual-driven" market dominates with a reimbursement list for individual vaccines. Price negotiations in member states dominated by the individual-driven market, are typically conducted at the national level. However, in Germany, vaccine price is determined by the mandatory rebate and price moratorium, or an EU rebate. In Belgium, there is no dominating procurement type with both regional tenders for universal mass vaccination (UMV) and a reimbursement list for vaccines not included in UMV representing similar shares of the market.

3.1.6. Transparency ratings

The level of NITAG transparency was rated low in 19 of 27 (70%) member states; and high in four of 27 (15%) member states (Fig. 5). For HTABs, transparency was rated low for six of the 12 (50%) member states that conducted HTAs for vaccination programs, and high for four of 12 (33%) member states.

3.1.7. Estimation of time to population access

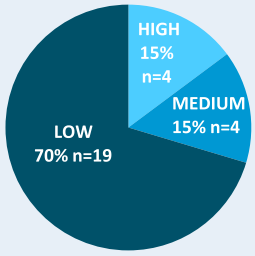
The descriptive data on TTPA indicated that the median time from marketing authorization to funding was 7 months (95% CI, 5–67 months) for PCV13 based on data from 15 member states, 39 months (95% CI, 23–84 months) for Gardasil 4 based on data from 27 states, and 53 months (9–64 months) for the quadrivalent influenza vaccines in the three member states where they were approved at the time of study, including one without an available funding date (hence, the 95% CI could not be calculated). The number and proportions of member states with TTPA of < 2 years, 2–6 years and > 6 years, respectively, between key VMA milestones, are shown in Fig. 6.

3.1.8. Vaccine access archetyping

The first 10 of the 18 attributes used for preliminary mathematical clustering (Table 1) were included in the final mathematical clustering, which led to the identification of four overall clusters.

Because the results of the primary clustering (Supplemental File 1; Table 1.3) varied significantly from the results of manual clustering, it was hypothesized that certain attributes provided little information to identify patterns inherent in the dataset. Therefore, based on initial clustering, a set of the most relevant 10 attributes was agreed upon with industry vaccine experts and subsequently selected to facilitate visualization of the pattern in the dataset. Five attributes were identified as the most important for market access; three concerned transparency (formal NITAG terms of reference, formal NITAG decision-analysis framework, and published award criteria and clear tenders selection process), one potentially affected time to access (national tenders, sub-national tenders, or both) and one constituted a proxy for the efficiency of the market access process (number of vaccines in the national immunization program). Statistical parameters were checked versus preliminary clustering to confirm appropriateness of attributes selection. All

NITAG (n=27) transparency criterion	n	Transparency level
Formal decision-analysis framework	7	
GRADE or a similar tool used for the quality of evidence and risk of bias assessment	2	
Recommendations publicly available	16	
Rationale for the decision publicly available	14	



HTAB (n=12) transparency criterion	n	Transparency level
Vaccine-specific decision-analysis framework	3	
GRADE or a similar tool used for the quality of evidence and risk of bias assessment	6	
Recommendations publicly available	8	
Rationale for the decision publicly available	7	

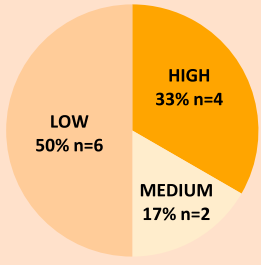


Fig. 5. NITAG and HTAB transparency ratings in the EU28 member states (excluding Romania). Transparency was rated based on the following three criteria: (1) a formal decision-analysis framework is in place; (2) presence of a systematic approach for evidence appraisal; and (3) publication of the decision with rationale. The level of transparency was considered low if 0 or 1 criterion was met; medium if 2 criteria were met; and high if all 3 criteria were met. GRADE, Grading of Recommendations Assessment, Development and Evaluation; HTA, health technology assessment; HTAB, health technology assessment body; NITAG, National Immunization Technical Advisory Group.

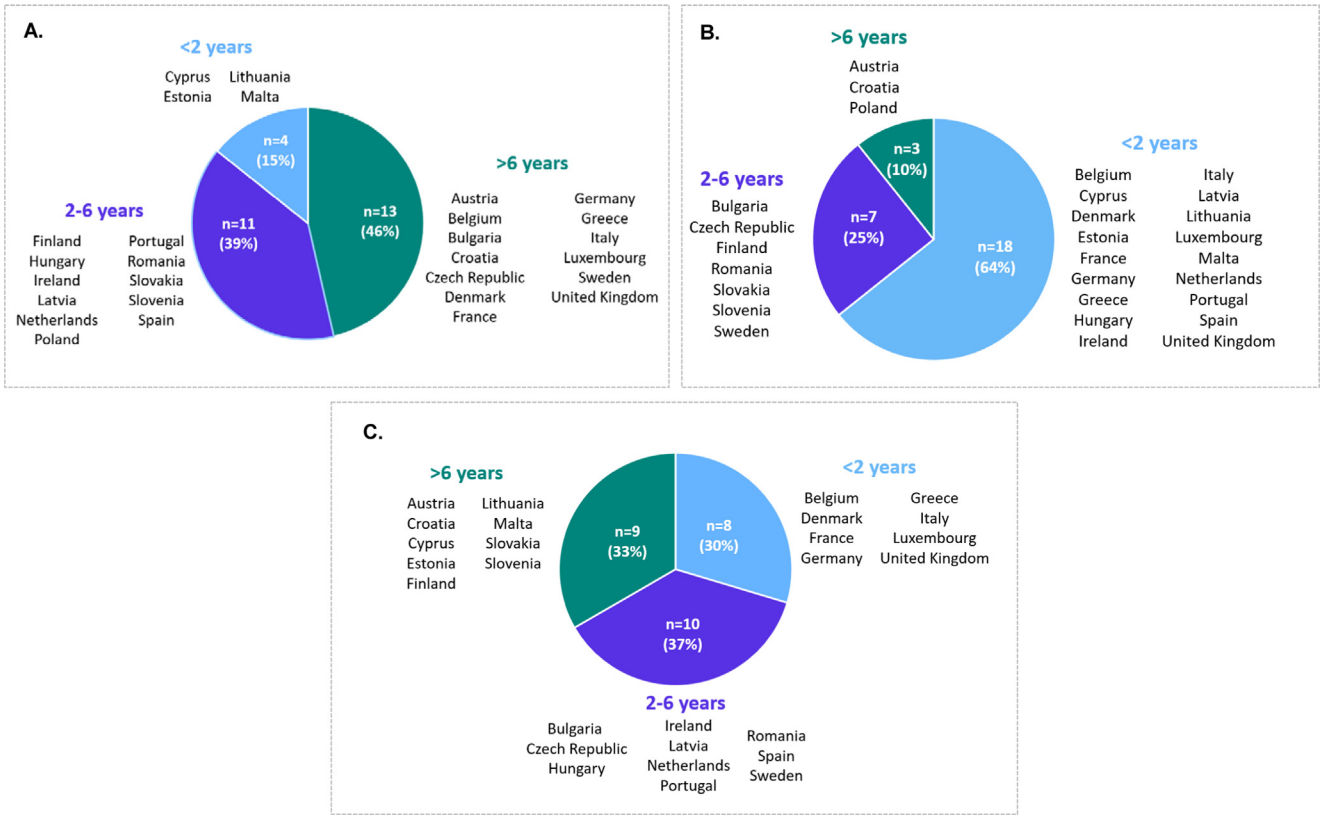


Fig. 6. Estimates of time to population access between the key VMA milestones of: **(a)** marketing authorization to NITAG recommendation; **(b)** NITAG recommendation to funding; **(c)** marketing authorization to population access. TTPA could not be estimated for Poland, as none of the selected vaccines were funded at the time of the research. NITAG, National Immunization Technical Advisory Group; TTPA, time to population access; VMA, vaccine market access.

statistical parameters indicated the advantage of the following approach: silhouette average width (0.38 vs 0.14 for the preliminary clustering); ARI (0.91 vs 0.74 for the preliminary clustering); and DI (1.10 vs 1.05 for the preliminary clustering). Therefore, the approach with the reduced number of attributes was used as the final clustering method.

The most populous cluster was separated to differentiate countries according to median gross domestic product (GDP); the need for this step was identified during face validity and discussion with industry experts to provide more granularity within the clustering while balancing size. This resulted in a total of five clusters or "archetypes" of VMA pathways (Table 2).

In Cluster 1 with ***national and regional decision-making and mandatory (binding) funding***, population-based impact is considered for recommendation of immunization program in addition to individual-based benefits. Tenders are conducted at the regional level (in Belgium, both regional and national levels apply) with published award criteria and clear selection process. Formal early advice for vaccines is not available. Within Cluster 2 countries with ***national decision-making with national tendering***, the UK is the only country with a truly influential NITAG in the cluster. Horizon scanning for vaccines is performed in all three of these countries, but formal early advice is not available. In Cluster 3 countries with ***individual reimbursement*** (defined as procurement based on a reimbursement list for individual vaccines, versus tenders), a national level of decision-making applies and NITAGs have formal terms of reference; HTA, if in place, is not binding for respective authorities. Having ***national decision-making and binding funding***, all member states in Clusters 4 and 5 are also characterized by national tenders (in Austria, regional tenders also apply) with published award criteria and clear selection processes. Clusters 4 and 5 featured countries with **higher** or **lower GDPs**, respectively.

The results of sensitivity analysis (Supplemental File 1; Table 1.4) indicated that clusters remained stable across analyses. Similar patterns in manual and mathematical clustering (both by the complete-linkage and single-linkage method) indicated a good fit for these clusters.

Typology of archetypes includes attributes that discriminated among countries and are common for all countries included in a single cluster. Analysis of archetypes identified formal early advice and NITAG formal decision-analysis framework as areas requiring improvement, irrespective of the archetypes, as these two attributes are lacking in most countries and thus they did not discriminate between the clusters.

By archetype, the median time from marketing authorization to funding for the three selected vaccines was the shortest in Cluster 3 (individual reimbursement, 12 months [95% CI, 5–64 months]) and the longest in Cluster 5 (national decision-making with binding funding and lower GDP, 65 months [95% CI, 23–119 months]). The estimated median time from marketing authorization to NITAG recommendation was also the shortest in Cluster 3 (5 months [95% CI, 0–12 months]) and was the longest in Cluster 4 (national decision-making with funding and higher GDP, 39 months [95% CI, 7–100 months]), whereas the median time from NITAG recommendation to funding was the shortest in Cluster 2 (national decision-making and national tendering, 2 months [95% CI not calculable]) and the longest in Cluster 5 (16 months [95% CI, 2–96 months]).

For further analysis and primary research, a total of seven exemplar member states were selected representing each archetype of VMA and included: Italy from Cluster 1; UK from Cluster 2; France and Germany from Cluster 3; the Netherlands from Cluster 4; Poland from Cluster 5; additionally, Sweden (Cluster 1) was selected to represent northern Europe.

Table 2
EU28 country clusters based on vaccine market access pathway characteristics.

Cluster 1 **National and regional decision-making + mandatory funding**	**Cluster 2** **National decision-making+ national tendering**	**Cluster 3** **Individual reimbursement**	**Cluster 4** **National decision-making+ mandatory funding (GDP Higher)**	**Cluster 5** **National decision-making + mandatory funding (GDP Lower)**
Countries				
• Belgium[a] • **Italy** • Spain[b] • **Sweden**[b]	• Cyprus • Malta • **UK**[c]	• Czech Republic • **France** • **Germany** • Greece • Slovakia	• Austria[b] • Denmark • Estonia • Finland • Ireland • Luxembourg • **The Netherlands** • Slovenia	• Bulgaria • Croatia • Hungary • Latvia • Lithuania • **Poland**[d] • Portugal • Romania
Shared attributes				
• No formal early advice • Population factor–driven NITAG recommendation • Regional tendering • Published award criteria and clear selection process for tendering	• Horizon scanning in place • No formal early advice	• National level of decision making • NITAG formal terms of reference in place • HTA not binding for respective authorities (if HTA in place; but final decision usually in line with HTA recommendation)	• Public health-driven NITAG recommendation (except Estonia) • NITAG terms of reference (except Ireland) • HTA not binding for respective authorities (if HTA in place; but final decision usually in line with HTA recommendation) • National tendering • Published award criteria and clear selection process for tendering	• No HTA for vaccines (except Bulgaria) • No formal decision analysis framework used by NITAG (except Croatia and Portugal) • Low/medium transparency of decision-making • National tendering • Published award criteria and clear selection process for tendering • Time to access >2 years

Exemplar member states in each cluster are in bold font.
GDP, gross domestic product; HTA, health technology assessment; NITAG, National Immunization Technical Advisory Group.
[a] Recommendation for immunization program issued at national level and recommendation for funding issued at both national and regional levels.
[b] National and subnational tendering.
[c] The UK is the one country in this cluster having truly influential NITAG with formal terms of reference and mandatory (binding) funding at the cost-effective price following inclusion of a vaccine in the immunization program.
[d] Regional level of issuing recommendation on funding also applies but national level of decision-making dominates; mandatory (binding) funding applies only to obligatory vaccination.

Table 3
Drivers and barriers for vaccine access as reported by non-industry vaccine experts in seven exemplar EU member states.

Vaccine access driver or barrier	Exemplar country						
	FR	DE	IT	NK	PL	SW	UK
Drivers							
Burden of disease/actual benefit	■	■	■	■	■	■	■
Vaccine efficacy/effectiveness/safety	■	■	NR	■	■	■	■
Vaccine cost-effectiveness	NR	NR	■	■	■	■	■
Political support	■	NR	■	NR	■	NR	NR
Budget availability/favorable budget impact or price	NR	NR	■	NR	■	■	NR
Availability of registries/experience from other countries	■	■	NR	NR	NR	NR	NR
Barriers							
Budget unavailability	■	■	■	■	■	■	■
Vaccine safety issues or lack of effectiveness	■	NR	NR	■	NR	NR	■
Unclear market access process (e.g., complexity due to the need for a national-regional consensus, or a lack of clarity on process initiation and the role of HTA)	NR	NR	■	NR	■	NR	NR
Organization of vaccination at regional level	NR	NR	■	NR	NR	■	NR
Lack of communication with providers and end-users following vaccination introduction	NR	NR	■	NR	NR	NR	■

Green or red box represents presence of vaccine access driver or barrier, respectively.
FR, France; DE, Germany; HTA, health technology assessment; IT, Italy; NK, the Netherlands; NR, not reported; PL, Poland; SW, Sweden; UK, the United Kingdom.

Table 4
Initiatives or actions to improve VMA*

EU Level
- Improved collaboration to avoid duplication of effort and reduce time to vaccine access for local populations
- Enhanced scientific activities and information sharing (e.g., literature reviews)
- Joint HTA/clinical assessment and development of framework guidelines
- Initiatives to address barriers such as limited research funding and lack of political or health authority support

Targeting NITAGs
- Provision of formal early advice
- Input of appropriate vaccine expertise, recognizing that many vaccine experts may be currently excluded from NITAGs due to potential conflicts of interest
- Formalization of horizon scanning, definition of recommendation timelines, and prioritization criteria to select in dossier

Targeting NITAGs and HTABs
- Definition and standardization of NITAG and HTAB roles and decision-making processes
- Greater transparency in assessment and decision-making processes
- Consideration of vaccination demographic effects, equity, country macroeconomic development, and increases in the cost-effectiveness thresholds for vaccines
- Establishment of national public HTABs in charge of independent vaccine evaluations

Targeting vaccine industry/manufacturers
- Early company engagement with vaccine assessment authorities
- Early generation of evidence of vaccine effectiveness
- Securing supply and stocks to avoid delay in the implementation of vaccination programs following the final/local coverage decisions

HTAB, health technology assessment body; NITAG, National Immunization Technical Advisory Group.
* List includes ongoing, partially completed, planned (such as a joint HTA-clinical assessment framework) and new/additional recommendations.

3.2. Phase 2

3.2.1. Expert stakeholder interviews

Interviews were conducted with 11 non-industry experts from the seven archetype exemplar countries i.e., two each from France, Italy, Poland, and the UK and one each from Germany, the Netherlands, and Sweden. One of the French experts provided an EU-level perspective. At least two interviews per member state representing each archetype were planned, 55 recognized vaccine experts were initially identified and 11 participated. The most frequent reason for non-participation was insufficient knowledge of the entire VMA process. All experts perceived VMA as more complex and

complicated than for therapeutic drugs in all countries except the UK.

The most important drivers for VMA included disease burden or actual benefit (all seven exemplar states); followed by vaccine effectiveness, efficacy, and/or safety (six exemplar states); and vaccine cost-effectiveness (five exemplar states; Table 3). In France, given that horizon scanning and early advice processes are conducted, there is formal opportunity for interaction between industry and authorities during the early stages of VMA. In Italy, other attributes perceived as important for VMA included unmet need, prior access at the regional level and recommendation by scientific societies (which were historically involved for vaccine recommendations before implementation of a national advisory body for vaccines in 2018/2019).

The most important barriers reported for all member states analyzed were budget limitations, high vaccine price and not being cost-effective (Table 3). Vaccine safety issues or the lack of effectiveness were indicated as barriers for France, the Netherlands, and the UK. Unclear VMA processes (e.g., complexity due to the need for a national-regional consensus or a lack of clarity on process initiation and the role of HTA) were reported for Italy and Poland. Italian and Swedish experts mentioned issues with organization at the regional level (e.g., pertaining to distribution or administration of vaccines), and experts from Italy and the UK listed the limited awareness of new vaccines in the NIP and their value among vaccination providers and public as a barrier. Further barriers included the lack of data on vaccine experience from other member states, and requirements for additional medical consultations resulting from changes in vaccination schedules (the UK). The expert from France reported a lack of timelines/prioritization criteria for issuing a recommendation as barriers.

Overall, NITAG recommendation was identified as the most critical step in the VMA process. However, experts also noted challenges associated with NITAGs such as exclusion of vaccine experts with industry ties due to potential conflicts of interest, lack of standard timelines for issuing a recommendation (in France), and low tolerance of uncertainty during vaccine assessment (in Germany and the UK). NITAG recommendations had the greatest influence in VMA in Germany, the Netherlands, and the UK; whereas both NITAG recommendations and HTA assessments had the greatest influence in France and Italy; and country MoH/government final decisions had the greatest influence in Italy, Poland, and Sweden.

While not an intrinsic barrier to VMA, the expert in Poland cited vaccine shortages as a barrier to broader population access, as most vaccines are imported and reimbursed at a lower price relative to other EU countries, meaning Poland is not prioritized for vaccine supply. Vaccine hesitancy and anti-vaccine movements were also mentioned by experts as barriers to population access across Europe.

3.2.2. Expert recommendations for alignment at EU and member-state levels

Non-industry experts who identified the VMA drivers and barriers also provided several recommendations to enhance VMA (Table 4). At the EU level, recommendations included information sharing, joint clinical assessments, and initiatives to address funding and political barriers. At the member-state level, recommendations targeted the specific or collaborative remits of NITAGs and HTABs, including improved transparency in their roles. Early company engagement with vaccine stakeholders was a key recommendation for manufacturers.

4. Discussion

The objective of this quantitative and qualitative research was to understand VMA at the member-state level and establish a basis for updating policies to improve transparency, coordination, and potential collaboration between decision-makers across the EU27 and the UK to ensure timely and evidence-based VMA and vaccination programs. Toward this aim, these findings confirm the heterogeneity and reveal further complexities and lack of transparency in the key steps of the VMA pathways across the region.

Key areas requiring improvement include the introduction of formal early advice, which was available in only five member states, and regular horizon scanning, which was absent in 18 member states.

In all but one member state, NITAGs play a critical role in VMA; although HTABs are also involved in almost half of the member states, the evidence and decision-making requirements of HTABs were often unclear, and NITAG–HTAB interactions within countries appeared to be limited.

Complexity, heterogeneity, segmentation, and limited transparency of processes may explain the discrepancies in the time from marketing authorization to NIP implementation between member states and between different vaccines within a given country. In our study, industry experts estimated TTPA for adolescent HPV vaccine to be between 5 and 147 months and TTPA for adult influenza vaccine to be 9–64 months, with NITAG assessment accounting for most of the time. Although limited data were available to inform a full TTPA analysis, insights drawn for the sample vaccines considered here are consistent with estimates reported by others in the literature [16,19]. The average TTPA for non-vaccine pharmaceutical drugs reported by Blank *et al.* (0.0–1.3 years) [19] and for oncology treatments by Prada *et al.* (266–770 days) [41], in addition to the rapid processes recently followed for COVID vaccine evaluations, argues strongly for the potential to shorten vaccine evaluation and decision-making. To facilitate benchmarking and comparative analysis, we recommend national bodies make public their TTPA timelines.

Barriers such as these have likely placed VMA in the situation that had been faced by therapeutic drugs, when the role of HTA was not well defined [42,43]. Ultimately the VMA pathways may be improved with gaining greater consensus on vaccine assessment across the EU, leading to more predictable, rapid, and transparent evaluations. The development of a joint clinical "fit for purpose" vaccine HTA may help reduce workload. In addition, formal early dialogue with relevant authorities at national and EU level should be more widespread.

Finally, the non-industry vaccine experts, who validated the initial findings, also provided recommendations for timely VMA at the EU and member-state levels, and proposed recommendations directed toward NITAGs, HTABs, and vaccine manufacturers. While NITAG recommendations were most frequently viewed as a critical step in VMA, the final decision by the MoH (or other relevant body) and HTA (where applicable) were also deemed critically important. The experts recommended enhanced collaboration at the EU level, specifically in scientific activities (e.g. literature reviews), information sharing, and vaccine assessment guidelines (Table 4). The anticipated HTA regulation to facilitate joint clinical assessments may be a future driver of VMA.

A key feature of this study was the objective analysis of country archetypes that allowed for selection of representative non-industry experts with whom data gathered in the first phase of the project were explored and validated. The country archetypes themselves were reviewed by non-industry experts from member states representing each archetype. Despite being a simplification of reality, the archetyping allows for practical analysis and identification of key areas for improvement beyond the individual country level and thus provides insights for generating policy. We acknowledge that criteria for exemplar-country selection favored the EU5 and more populous countries, which is a limitation, and

more research is needed into smaller countries and countries with lower per-capita GDP.

Although our analysis did not aim to compare income, size, or at-risk groups, the findings suggest that citizens in smaller, lower-GDP per-capita countries, as well as the adult population, may face longer times to vaccine population-level access compared with larger, higher-GDP per-capita countries, and pediatric and adolescent populations. In this context, greater EU-level collaboration, including joint clinical assessments and HTAs, may have the potential to reduce inequity in time to access, by providing the same robust assessment of clinical evidence to inform the decision-making process across all EU countries, regardless of size, income, or at-risk populations.

To ensure reliability, data provided by industry experts were from referenced sources. In addition, the VMA pathways for seven exemplar member states were validated by stakeholders who perceived the archetypes as being generally robust, although some indicated that due to inevitable differences between countries, each cluster represents a simplification.

Our findings must be considered in light of the limitations of our research. We utilized a range of methods and relied on qualitative, descriptive, and potentially subjective expert opinion. Non-industry expert knowledge of overall VMA pathways was often fragmented and incomplete. However, results from different groups of experts were cross-validated and confirmed to reduce potential confounding effects and bias. The TTPA analysis, while limited by the data available, generated findings consistent with other reports [16,19].

5. Conclusions

VMA pathways have the potential to be optimized across Europe. Our findings provide a comprehensive description of VMA processes across the EU region and point to the need for policy changes at the member-state level, leveraging EU-level interactions and facilitation. It is evident that in the existing paradigm, VMA is too heterogeneous to allow shared responsibilities or learning and delays population access [24]. The roles and responsibilities of all stakeholders involved in the processes can be further clarified, [16] and guidelines and transparency can be significantly improved. The sense of momentum in response to the COVID-19 pandemic should stimulate consideration of policies to improve access to all vaccinations and inform the foundation on which a consistent vaccine ecosystem can be created, one that is resilient and fit for purpose now, and in the face of future challenges. The societal benefits inherent in more transparent and inclusive VMA processes may also enhance the trust of end-users, reducing vaccine hesitancy and increasing uptake and confidence in vaccination programs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Valérie Laigle is an employee of Merck Sharpe & Dohme (MSD) a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may own stocks and/or stock options.

Maarten J Postma received grants and honoraria from various pharmaceutical companies, including those developing, producing and marketing vaccines. Also, he holds stocks of Pharmacoeconomics Advice Groningen (Groningen, The Netherlands) and Health-Ecore (Zeist, The Netherlands) and is advisor to Asc Academics (Groningen, The Netherlands), all consultancies in health economics' advice. He is a member of the Joint Committee of Vaccination & Immunization (London, UK).

Mira Pavlovic reports no conflicts of interest.

Ekkehard Beck is an employee of and holds shares in the GlaxoSmithKline group of companies.

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Chiara Cadeddu reports no conflicts of interest.

All authors attest they meet the ICMJE criteria for authorship.

Appendix A. Supplementary material

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References

[1] Andre FE, Booy R, Bock HL, Clemens J, Datta SK, John TJ, et al. Vaccination greatly reduces disease, disability, death and inequity worldwide. Bull World Health Organ. 2008;86(2):140–6.
[2] Ozawa S, Clark S, Portnoy A, Grewal S, Stack ML, Sinha A, et al. Estimated economic impact of vaccinations in 73 low- and middle-income countries, 2001–2020. Bull World Health Organ. 2017;95(9):629–38.
[3] Roush SW, Murphy TV. Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA 2007;298:2155–63.
[4] Access to Medicines Foundation. Now online: 2021 Access to Medicine Index, https://accesstomedicinefoundation.org/news/now-online-2021-access-to-medicine-index, date accessed 29 January 2021.
[5] European Network for Health Technology Assessment (EUnetHTA). HTA Core Model, https://eunethta.eu/hta-core-model/, date accessed 6 April 2021.
[6] Toumi M. Introduction to market access for pharmaceuticals. Boca Raton, FL: Crc Press; 2017.
[7] World Health Organization. Coronavirus disease (COVID-19): Vaccine research and development. https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccine-research-and-development, date accessed 10 March 2021. 2020.
[8] European Commission. EU Strategy for COVID-19 vaccines. https://ec.europa.eu/info/sites/info/files/communication-eu-strategy-vaccines-covid19_en.pdf, date accessed 29 January 2020. 2020.
[9] European Medicines Agency. COVID-19 vaccines: development, evaluation, approval and monitoring. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring, date accessed 29 January 2021. 2020.
[10] World Health Organization. Immunization, Vaccines and Biologicals; Procurement mechanisms and systems. https://www.who.int/immunization/programmes_systems/procurement/mechanisms_systems/en/, accessed 10 March 2021. 2018.
[11] World Bank Group. Saving Lives, Scaling-up Impact and Getting Back on Track - World Bank Group COVID-19 Crisis Response Approach Paper. http://documents1.worldbank.org/curated/en/136631594937150795/pdf/World-Bank-Group-COVID-19-Crisis-Response-Approach-Paper-Saving-Lives-Scaling-up-Impact-and-Getting-Back-on-Track.pdf, 10 March 2021. 2020.
[12] Standaert B, Rappuoli R. How is the economic assessment of vaccines performed today? J Mark Access Health Policy. 2017;5:1335163.

[13] World Health Organization. National advisory committees on immunization. https://www.who.int/immunization/sage/national_advisory_committees/en/, accessed 29 January 2021. 2019.
[14] Standaert B, Rappuoli R. Towards a more comprehensive approach for a total economic assessment of vaccines? The building blocks for a health economic assessment of vaccination. J Mark Access Health Policy. 2017;5(1):1335162. https://doi.org/10.1080/20016689.2017.1335162.
[15] Ricciardi W, Toumi M. National Immunization Therapeutic Advisory Group: it is time for experience sharing and best practice learning. J Mark Access Health Policy. 2015;3:29276. https://doi.org/10.3402/jmahp.v3.29276.
[16] Sheikh S, Biundo E, Courcier S, Damm O, Launay O, Maes E, et al. A report on the status of vaccination in Europe. Vaccine. 2018;36:4979–92.
[17] Vaccines Europe. About Us. https://www.vaccineseurope.eu/about-us, 28 January 2021. 2021.
[18] European Federation of Pharmaceutical Industries and Associations (EFPIA). About us. https://efpia.eu/about-us/, date accessed 28 January 2021. 2021.
[19] Blank PR, Schwenkglenks M, Sardos CS, Patris J, Szucs TD. Population access to new vaccines in European countries. Vaccine. 2013;31:2862–7.
[20] Dunn JC. A fuzzy relative of the ISODATA process and its use in detecting compact well-separated clusters. J Cybern 1973;3:32–57.
[21] Rivera-Borroto OM, Rabassa-Gutiérrez M, Grau-Ábalo RDC, Marrero-Ponce Y, García-de la Vega JM. Garcia-de la Vega JM. Dunn's index for cluster tendency assessment of pharmacological data sets. Can J Physiol Pharmacol 2012;90:425–33.
[22] Eurostat. Annual national accounts (t_nama10 GDP). https://ec.europa.eu/eurostat/web/national-accounts/data/main-tables, 10 March 2021. 2016.
[23] Worldometer. Countries in the EU by population. https://www.worldometers.info/population/countries-in-the-eu-by-population/, date accessed 10 March 2021. 2021.
[24] Toumi M. Market Access of Vaccines in Developed Countries. Boca Raton, FL: CRC Press; 2017.
[25] Ricciardi GW, Toumi M, Weil-Olivier C, Ruitenberg EJ, Dankó D, Duru G, et al. Comparison of NITAG policies and working processes in selected developed countries. Vaccine. 2015;33:3–11.
[26] Takla A, Wichmann O, Carrillo-Santisteve P, Cotter S, Lévy-Bruhl D, Paradowska-Stankiewicz I, Valentiner-Branth P, D'Ancona F, the VENICE III NITAG Survey Group Collective. Characteristics and practices of National Immunisation Technical Advisory Groups in Europe and potential for collaboration, April 2014. Euro Surveill. 2015;20(9):21049. https://doi.org/10.2807/1560-7917.ES2015.20.9.21049.
[27] Takla A, Wichmann O. Current practices in immunisation policymaking in European countries. ECDC technical report. https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/Currentpractices-on-immunisation-policymaking-processes-Mar-2015, date accessed 30 October 2018. 2015.
[28] Nijsten D, Houweling H, Durupt A, Adjagba A. Overlapping topics in advisory reports issued by five well-established European National Immunization technical advisory groups from 2011 to 2014. Vaccine 2016;34(50):6200–8.
[29] Hill CA, Mockler C, Balman E. Steering vaccines through the UK system-what factors influence the likelihood of positive and negative recommendations? Value Health. 2015;18(7):A593. https://doi.org/10.1016/j.jval.2015.09.1534.
[30] Loulergue P, Floret D, Launay O. Strategies for decision-making on vaccine use: the French experience. Expert Rev Vaccines 2015;14:917–22.
[31] Seib K, Pollard AJ, de Wals P, Andrews RM, Zhou F, Hatchett RJ, et al. Policy making for vaccine use as a driver of vaccine innovation and development in the developed world. Vaccine. 2017;35:1380–9.
[32] Droeschel D, Vollmer L, Krone FA, Walzer S. Are vaccinations really different to pharmaceuticals with respect to market access in Germany? Value in Health. 2015;18:A548–9.
[33] Silva ML, Perrier L, Paget JW, Mosnier A, Buthion V, Cohen JM, et al. Influenza vaccination policy-making processes in France and The Netherlands: Framework and determinants. Health Policy 2016;120:293–305.
[34] Caro Martínez A, Espín Balbino J, Lemgruber A, Martín Ruiz E, Olry de Labry Lima A, García-Mochón L, et al. Adoption of the HPV vaccine: a case study of three emerging countries. J Comp Eff Res. 2017;6:195–204.
[35] van der Putten IM, Paulus ATG, Hiligsmann M, Hutubessy RCW, Evers SMAA. Evidence-informed vaccine decision making: The introduction of Human Papilloma Virus (HPV) vaccination in the Netherlands. Health Policy 2019;123:260–6.
[36] Silva ML, Paget WJ, Mosnier A, Buthion V, Cohen JM, Perrier L, et al. Development of seasonal influenza vaccination recommendations: relevance and influence of the evidence on the decision-making process in France and the Netherlands. Value Health. 2016;19:670–9.
[37] Robert Koch Institut. Standing Committee on Vaccination webpage. https://www.rki.de/EN/Content/infections/Vaccination/Vaccination_node.html, date accessed December 2018. 2016.
[38] Robert Koch Institut. Unit 33: Immunization. https://www.rki.de/EN/Content/Institute/DepartmentsUnits/InfDiseaseEpidem/Div33/div33_node.html, date accessed 19 April 2021. 2021.
[39] Gemeinsamer Bundesausschus. Federal Joint Committee, https://www.g-ba.de/english/, date accessed 19 April 2021.
[40] Vaccines Europe. Data on file 2019. Last updated Q1 2020.
[41] Prada M, Ruggeri M, Sansone C, De Fazio D, Tettamanti A, Mantovani M. Timeline of authorization and reimbursement for oncology drugs in Italy in the last 3 years. Medicine Access @ Point of Care. 2017. https://doi.org/10.5301/maapoc.0000007.
[42] Vaccines Europe. Developing a specific and coordinated framework for Health Technology Assessment of Vaccines in Europe. http://www.vaccineseurope.eu/wpcontent/uploads/2013/01/Vaccines-HTA-High-Level-PaperVE_FIN.pdf, date accessed 1 June 2020. 2014.
[43] HTAi. Panel Session Report. Assessing the value of vaccines - what is needed to make evidence-based health policy decisions? https://htai.org/wp-content/uploads/2018/02/HTAi_Panel_Session_Report_final.pdf, date accessed 19 April 2021. 2015.
[44] STIKO. Vaccination recommendations by STIKO. https://www.rki.de/EN/Content/infections/Vaccination/recommandations/recommendations_content.html, date accessed 20 April 2021. 2021.
[45] NRC. Media Centre. https://www.nitag-resource.org/media-center, date accessed 23 May 2019. 2019.