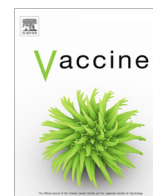




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Review

Guidance for the governance of public-private collaborations in vaccine post-marketing settings in Europe



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ABSTRACT

Introduction: The 2009 influenza pandemic highlighted challenges for vaccine post-marketing monitoring in Europe, particularly the need to have appropriate infrastructures to strengthen public-private collaborations (PPCs) with suitable processes to improve stakeholder interactions and collection and analysis of safety and effectiveness data. The ADVANCE consortium comprises public and private stakeholders who have worked together to build and test new system components for vaccine post-marketing projects, one component being a governance framework for efficient, transparent and trustworthy PPCs. **Methods:** Based on the results of a landscape analysis and screening of formalised existing governance structures, we identified the elements of a governance framework and developed recommendations to support stakeholders willing and able to implement collaborative projects. These proposals and their implementation were discussed by 70 experts during a workshop to gain from their experience. **Results:** We identified core governance principles and defined five fundamental functions (decision-making, scientific advice, quality control and audit, implementation and management, and financial administration) that can be attributed to individual partner organisations or to a committee with representatives from more than one partner organisation. We propose a generic governance model with options for its adaptation to specific contexts and projects. The advantages and disadvantages of PPCs were also examined. Stakeholders' concerns (e.g. scientific integrity and public trust) were addressed through recommendations about transparent decision-making rules and conflict of interest management. **Conclusions:** No one-size-fits-all solution for PPC governance exists but our recommendations could be used to set-up a tailored-made and fully transparent governance structure supporting collaborative projects in the European vaccine post-marketing environment. To allow the rapid establishment of robust projects, the next steps will involve this guidance being used by real-world collaborations to assess what works and what does not work and what added-value can be obtained from these collaborations.

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Abbreviations: CRO, contract research organisation; IMI, Innovative Medicines Initiative; MAH, marketing authorisation holder; PHI, public health institute; PPC, public-private collaboration; RA, regulatory authority.

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[☆] See Appendix A for list of ADVANCE consortium and steering committee members.

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Contents

1.	Introduction	3279
1.1.	The challenging environment of post-marketing monitoring of vaccines in Europe	3279
1.2.	ADVANCE project and best practice guidance	3279
2.	Methods	3279
2.1.	Landscape analysis via stakeholder survey and literature review	3280
2.2.	Development of the governance framework	3280
2.3.	Internal and external consultations	3280
3.	ADVANCE proposals and recommendations	3281
3.1.	Potential advantages and disadvantages of PPCs	3281
3.2.	Core governance principles and functions	3281
3.2.1.	Core governance principles	3281
3.2.2.	Core governance functions	3281
3.3.	Generic model and recommendations for governance	3283
3.3.1.	Governance bodies	3283
3.3.2.	Decision-making rules	3283
3.3.3.	Patient associations and civil society organisations	3284
3.3.4.	Management plan for conflicts of interest	3285
3.4.	Contractual considerations for PPCs	3285
4.	Discussion and conclusions	3285
5.	Prior presentations	3286
	Funding	3286
	Declarations of interest	3286
	Disclaimer	3286
	Acknowledgements	3286
	Appendix A.A.1. ADVANCE consortium partner organisations	3286
	Appendix B.B.1. Definitions	3287
	Appendix C. ADVANCE survey questionnaire used to identify existing public–private collaborations	3287
	Appendix D. Key stakeholders in vaccine benefit/risk monitoring in Europe	3288
	Appendix E. Summary of the roles and responsibilities of the core governance functions	3289
	Appendix F. Supplementary material	3289
	References	3289

1. Introduction

1.1. The challenging environment of post-marketing monitoring of vaccines in Europe

The influenza pandemic in 2009 highlighted the limited capacity to rapidly collect post-marketing data on the pandemic vaccine exposure, safety and effectiveness in Europe, which was needed to provide a robust and timely benefit/risk assessment [1,2]. The absence of a formally-established European infrastructure providing access to large data sources, and the lack of collaboration between stakeholders and common methods for data collection were recognised as major limiting factors for the timely collection, analysis and reporting of available data, for benefit and risk assessments [1,2]. Additional limiting factors such as lack of funding mechanisms and communication channels, compliance with regulatory requirements resting on vaccine marketing authorisation holders (MAHs), while most of the data resided with public health institutes (PHIs), and lack of public trust were identified [3].

1.2. ADVANCE project and best practice guidance

In 2013 the Innovative Medicines Initiative (IMI), funded a consortium of more than 47 public and private partners, the Accelerated Development of VAccine benefit-risk Collaboration in Europe, (ADVANCE) for a five-year period [4–6] (See Appendix A for list of ADVANCE partners). The aim of this consortium is to implement an efficient, trustworthy framework with transparent governance rules for collecting valid and timely post-marketing data supporting vaccine benefit-risk monitoring, while respecting stakeholders' mandates and enabling each of them to make informed decisions [7]. The ADVANCE consortium, composed of

European public and private stakeholders, including national PHIs, the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), national RAs, research institutes, universities, contract research organisations (CROs), and vaccine MAHs, was a unique forum for stakeholders to establish common rules for future public-private collaborations (PPCs).

ADVANCE has developed two components of best practice guidance: a code of conduct for collaborative vaccine benefit-risk studies and governance guidance for transparent, ethical and trustworthy PPCs. Please refer to Appendix B for definitions of the terms PPC, governance, study and project, as used in this paper. The published ADVANCE code of conduct is a set of good practice principles for individuals working in organisations collaborating to perform vaccine studies [8]. The ADVANCE governance guidance summarised in this paper is complementary to the ADVANCE code of conduct and the ENCePP guidelines for pharmacoepidemiological and pharmacovigilance studies as it intends to provide a set of governance proposals for stakeholders wanting to establish transparent, ethical and trustworthy PPCs to perform vaccine benefit-risk studies [8,9]. As studies carried out within PPCs may be partially supported by diverse stakeholders (through funding or in-kind contributions), good governance principles should ensure that the research is not influenced by commercial, financial, personal or institutional interests of study funders where there is a potential to threaten scientific independence.

2. Methods

The overall methods used for the development of the governance guidance proposal are summarised in Fig. 1. The process was initiated in March 2014 and the proposal for guidance was finalised in September 2017.

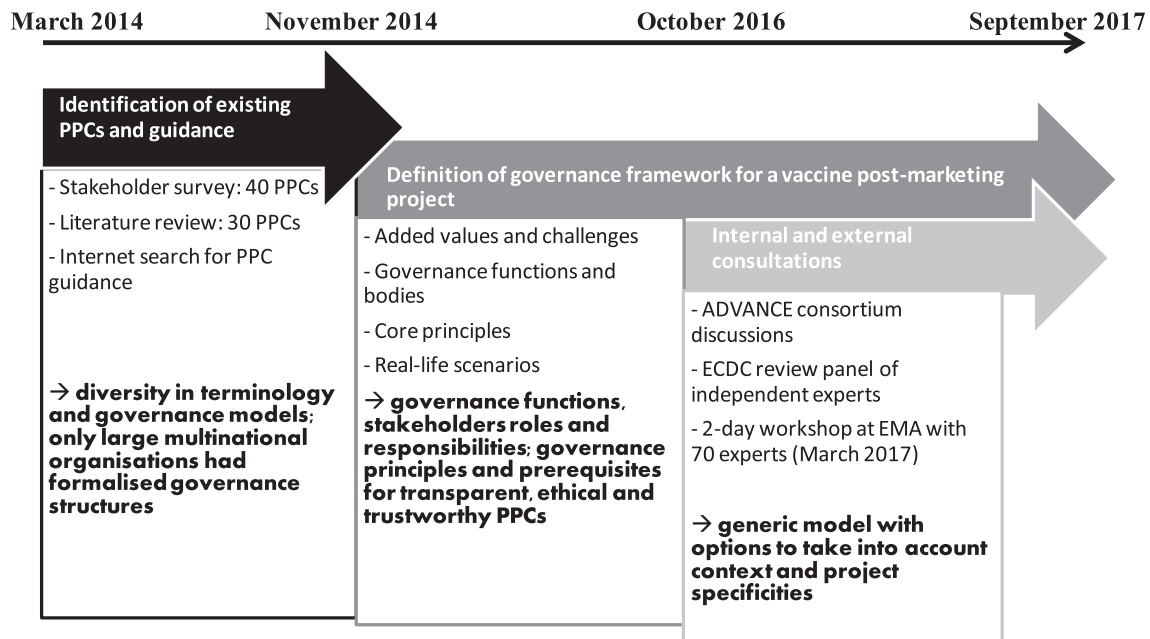


Fig. 1. Timeline and summary of activities for developing governance guidance for public-private collaborations (PPCs).

2.1. Landscape analysis via stakeholder survey and literature review

The first step was a landscape analysis through a survey of European stakeholders and a literature review to identify existing PPCs in the field of public health, and more specifically in the vaccine area. It is important to understand that the aim of the landscape analyses was not to perform an exhaustive search, as is required for systematic reviews of evidence for treatment or pharmacoepidemiology, but to identify what type of governance structures other public-private collaborative partnerships use. A more detailed description of the landscape analyses and results can be found in Supplement Online Information.

Briefly, a questionnaire, with 19 open-ended questions, was sent by email to the members of the ADVANCE consortium and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) to collect information about the PPCs they were involved in, including types of interaction, governance, structural funding and lessons learnt (Appendix C). A total of 48 organisations were contacted; 27 responded. Information on 40 collaborations was collected. The responses to the survey provided useful information on the potential added-value of PPCs as well as the challenges and lessons learnt for possible improvements. They highlighted the need for governance guidelines that are adaptable to project specificities.

A PubMed search for vaccine post-marketing collaborative studies published between 1 January 2013 and 19 May 2014, using the keywords [partner* OR collaborat* OR working* OR network*] AND [vaccine*] identified 30 additional collaborations (i.e., described a collaboration in the acknowledgement or disclaimer section) among the 1155 publications that were initially screened. Among the 70 collaborations identified, 38 (54%) were between public and private stakeholders and 32 (46%) between public stakeholders only. We observed high diversity in terminology, in the governance models applied and in the distribution of roles and responsibilities, interactions and funding mechanism between the different stakeholders. In parallel, a non-systematic Google Internet search for available governance guidelines on PPCs revealed that explicitly formalised governance structures are used mainly by large multinational organisations such as the Global Fund, the IMI or GAVI [10–12]. No clear guidelines were identified

at a project level, a project being defined as a set of activities put in place to organise one or several studies (see Appendix B).

2.2. Development of the governance framework

In the second step, a working group comprising the authors of this paper, developed the following aspects of a governance framework, using information from the PPCs identified in the landscape analyses: identification of potential advantages and disadvantages of PPCs in the vaccine area; clarification of governance functions; establishment of core principles at the project level to guide the implementation of efficient, transparent and trustworthy PPCs in the European vaccine post-marketing setting. Scenarios frequently encountered by the co-authors (taking into account their different real-life research questions and contexts) were used to explore the potential added-value and challenges of PPCs and to describe the possible functions, roles and responsibilities of the different stakeholders in a PPC and the prerequisites for governance bodies.

2.3. Internal and external consultations

In the third step, the working group sought internal input from other members of the ADVANCE consortium and external input from a review panel of independent experts appointed by the ECDC. This panel pointed out that an important challenge for setting up PPCs in the vaccine post-marketing setting was the divergent attitudes to PPCs (expected added-value and governance model), even within the same group of stakeholders in Europe, particularly between PHIs. Therefore, a 2-day workshop was organised in March 2017 at the EMA to seek input about our governance analysis and proposals from a broader group of stakeholders. The participants invited to the workshop were experts involved in or interested in vaccine benefit/risk monitoring in Europe or in the development of public-private interactions proposed by members of the ADVANCE consortium. The aim was to have representatives of different stakeholders, such as public health institutes (scientists with infectious disease expertise from at least 10 European countries), regulatory authorities (from at least 5 different countries), academics, contract research organisations (CROs) (from at least 10 different organisation), at least 5 representatives from patient

associations and healthcare organisations and at least 5 lawyers from different participating organisations. The workshop was attended by almost 70 experts representing various stakeholders. There were 14 participants from national public health institutes and the ECDC, 8 from national regulatory authorities and the EMA, 20 from academic institutions and CROs, 16 from vaccine marketing authorisation holders (MAHs), and 8 from patients' associations and health organisations. The countries represented were Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Norway, Poland, Spain, Sweden, Switzerland and UK.

The initial workshop assumption was that, in some circumstances, there is a need for PPCs which have an added-value for vaccine post-marketing projects with shared interests, and the workshop discussed the question of how this need can be addressed. The workshop participants confirmed the need to establish a clear, transparent governance framework that is understandable and accepted by the vaccine scientific community, as well as applicable to the European context for PPCs responsible for vaccine post-marketing projects. Importantly, the attendees emphasised that the level of acceptability of such sensitive interaction and the acceptance of the governance proposals might not be the same for all stakeholders or for all countries. The legal experts present agreed that there are no legal restrictions for developing PPCs for vaccine post-marketing projects at the European level, although there may be legal or institutional constraints that could restrict implementation of PPCs in some European countries. The positive effect of having trust between participating stakeholders within a PPC and between participating and non-participating stakeholders on innovative outcomes and the overall performance of such projects was discussed. A fully transparent process, based on open communication, information-sharing and shared decision-making can increase support for PPCs. Consistent, timely and proactive communication is primordial to help build public trust. The full workshop report is available on the ADVANCE website [13]. Based on the discussions held during the workshop, we adapted our governance framework to a generic model with options to enable adjustments to take into consideration the context and project specificities.

3. ADVANCE proposals and recommendations

Based on input from reviewers and workshop participants a set of governance proposals and recommendations were made.

3.1. Potential advantages and disadvantages of PPCs

In this section, we summarise the discussions held within ADVANCE about the potential advantages and disadvantages of PPCs perceived by the participants, which help to shape the governance proposals. Bringing together the expertise and knowledge of the various stakeholders and the complementarity and resource sharing could be major benefits gained through a PPC (Fig. 2; Appendix D). Multi-stakeholder collaborations that can create scientific, resource and communication synergies may have a greater impact for benefit-risk monitoring than a single stakeholder and could provide more robust results covering diverse populations and larger specific population groups than a single stakeholder. Established PPCs would be more rapidly able to respond to an emergency as the creation of such collaborations can take a considerable time.

One of the major disadvantages of PPCs was found to be the potentially increased complexity and administrative burden due to the need to satisfy the various mandates and obligations of the different stakeholders. MAHs may have to observe stricter obli-

gations than others, for example in terms of time-consuming and resource-intensive traceability and documentation processes. Concerns about scientific integrity and independence due to potential or real conflicts of interest when public authorities and vaccine MAHs collaborate could also have a negative impact on public trust. Undue influence from any of the PPC partners could affect the validity of the results since vaccine post-marketing projects frequently use observational study designs with data that have been collected for other purposes which are more susceptible to bias compared with randomised clinical trial designs, which may result in lower internal validity and raise doubts about the findings. This emphasises the need to acknowledge and carefully consider the risks associated with real or perceived potential conflicts of interest.

Potential partners should discuss the advantages and disadvantages of a PPC for a given project in a transparent manner in order to decide if a PPC is the desirable form of collaboration. We propose that stakeholders should consider PPCs as a mean of facilitating scientific exchange and discussions with the aim of performing high quality studies and obtaining robust scientific evidence, due to the complementarity of the partners and the federation of resources. We recommend, therefore, that PPCs should only be envisaged if the anticipated advantages of the collaboration outweigh the expected disadvantages for all the stakeholders involved. A plan to mitigate any disadvantages arising from the PPC could be developed when the collaboration is initiated.

3.2. Core governance principles and functions

We recommend that the following guiding principles are implemented for project governance.

3.2.1. Core governance principles

The governance model should be as simple as possible, transparent, acceptable to all partners, and appropriately-sized to ensure efficiency. The roles and responsibilities and decision-making rules should be agreed between the partner organisations and included in the project contract. The structure and processes of the governance model should reflect mutual respect and shared benefits. The governance structure should ensure that the perspectives of all partners will be taken into consideration during the collaboration.

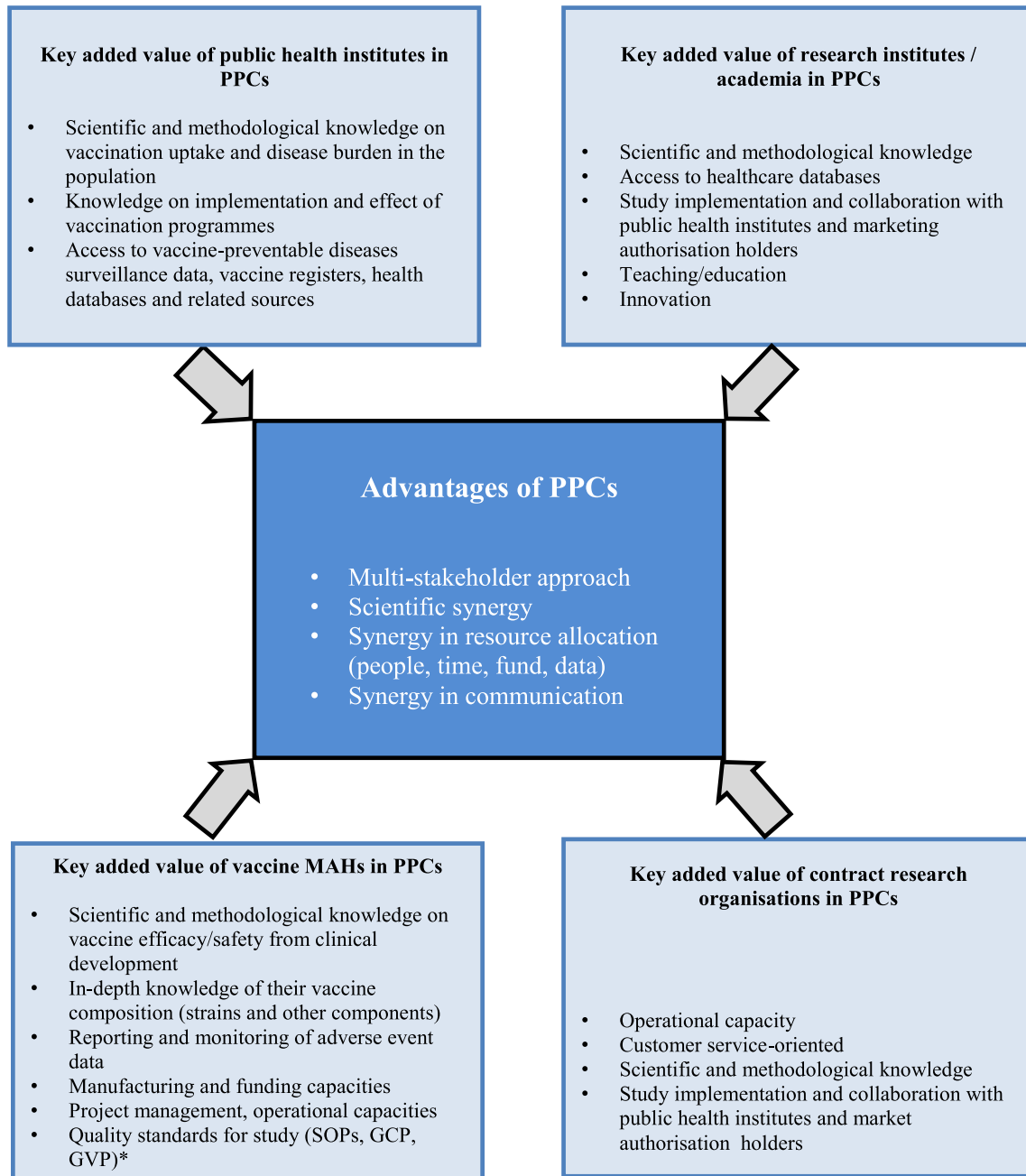
The decision-making process should reflect a fair balance of these perspectives. All decisions, key communication and minutes from governance committee meetings should be recorded to facilitate compliance monitoring. Relevant documents should be made publically available on the project website. A communication plan should be developed and agreed between partners at project initiation.

Participating organisations should develop and promote the scientific autonomy of their employees and reflect this in their internal governance policies and processes. Procedures related to compliance with good practices should be shared between partners and specific training to promote compliance with these should be provided. The same principles defined in the ADVANCE should be applied to the study CoC [8].

3.2.2. Core governance functions

We identified five fundamental functions that can be attributed to individual partner organisations or to a governance body or committee with representatives from more than one partner organisation (Fig. 3; Table 1; Appendix E). The roles and responsibilities of each organisation will be defined by the functions they assume in the structure.

The decision-making function will require leadership for the strategic direction, allocation of funds and resources and all



*SOPs: standard operating procedures; GCP: good clinical practice; GVP: good pharmacovigilance practice

Fig. 2. Key added-value from main stakeholders and advantages of public-private collaborations (PPCs) for vaccine post-marketing setting.

decision-making related to the project. The scientific advice function will involve making recommendations on the scientific, methodological and ethical aspects of the project and studies. All documents related to the studies performed within the PPC should be submitted for ethics committee approval in compliance with local regulations. The quality control & audit function will involve responsibility for quality control and audit of the studies and will provide advice on the governance. The implementation and management function will involve the implementation and execution of the project and studies, and the financial management function will manage the project funds. Both of these functions will receive guidance from the decision-making function.

The scientific advice functions and the quality control & audit functions are pivotal for guaranteeing scientific relevance, acceptability, ethics and transparency and therefore they must be independent from the decision-making and implementation and management functions. The decision-making function should record how advice and recommendations received from these two advisory functions have been taken into consideration.

It is important to consider that some functions could be merged and be under the responsibility of one or more partner organisations depending on the rationale, scope and objective of the project. For example, if there is a single study planned in a given project, the implementation and management function could be merged with the decision making function.

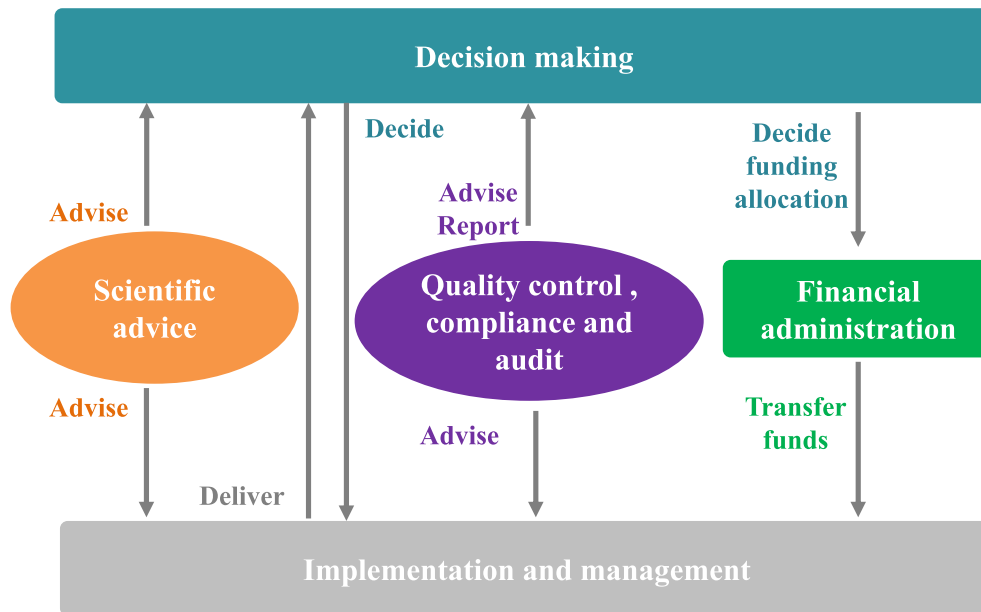


Fig. 3. Schematic representation of fundamental governance functions and their interactions.

3.3. Generic model and recommendations for governance

Our internal discussions and external consultations have led us to propose a generic governance model, with options, as an optimal and flexible solution that could take into consideration the wide range of project specificities that may be present in the vaccine post-marketing setting in Europe. Here, we summarise the recommendations for the roles the various partners can play in PPCs (Fig. 4, Table 1).

3.3.1. Governance bodies

3.3.1.1. Decision maker or steering committee. The decision-making function can be attributed to a single partner (the decision maker) or to two or more partners as a shared decision-making body (the steering committee) (Table 1). Diverse models for decision-making could be possible, including delegation of defined responsibilities. Rules should be established and agreed by the participating partners when the PPC is being set-up. The decision maker or steering committee should be responsible for selecting members of the scientific and the quality control & audit committees, using a transparent and documented process allowing the selection process to be verified.

3.3.1.2. Scientific committee. This committee will provide scientific, methodological and ethical advice and written recommendations for the project to the decision-making body and for the studies to the implementer or study teams. They will not be responsible for the ethical review of study protocols; these will be reviewed by regular ethics committees in compliance with local regulations. How their recommendations are taken into consideration and, if applicable, the reason(s) why they have not been implemented should be documented.

3.3.1.3. Quality control & audit committee. This committee should be set up at an early stage to enable it to assess, manage and mitigate potential conflicts of interest and provide advice for the selection of the members of the scientific committee. This committee should provide quality control and audit reports, compliance advice and written recommendations for the project to the decision-making body and for the studies to the implementer or

study teams. How their recommendations are taken into consideration and, if applicable, the reason(s) why they have not been implemented should be documented.

3.3.1.4. Implementer. The implementation and management function could be attributed to one partner (the implementer) with in-house expertise and resources to assume this function, with the study team members selected in-house. Alternatively, one partner could coordinate the various activities or studies to be conducted by several partners and the study team members could be selected from more than one partner.

3.3.1.5. Financial administrator. When PHIs and vaccine MAHs are involved in the PPC or when more than one funder or countries are involved, a financial administrator should be appointed to manage the funds. The decision maker will be responsible for appointing the financial administrator, after consulting all partners. In all cases, allocation of funds should be transparent and funding sources always clearly identified.

3.3.2. Decision-making rules

At the start of the PPC, the partners should agree what decision-making process will be used to ensure achievement of the objectives. Consensus for decision-making is strongly recommended since this will encourage partners to seek an agreement that incorporates all points of view. However, we recommend that there is a back-up option with a majority-voting process when consensual decisions cannot be reached to ensure that the project goes ahead. If this option is selected, before PPC initiation, the partners should decide on the quorum of members to be present or represented (e.g. two-thirds), and what would constitute a majority vote (e.g. >50%, >75%). Discordant viewpoints should be recorded with the final decision or deliverable. When decisions cannot be reached or when major issues, concerns or objections are raised, advice should be sought internally from the project advisory bodies (scientific committee and quality control and audit committee) or externally from other experts and non-partner organisations.

Table 1
Summary of ADVANCE's governance recommendations for PPCs in vaccine post-marketing setting in Europe.

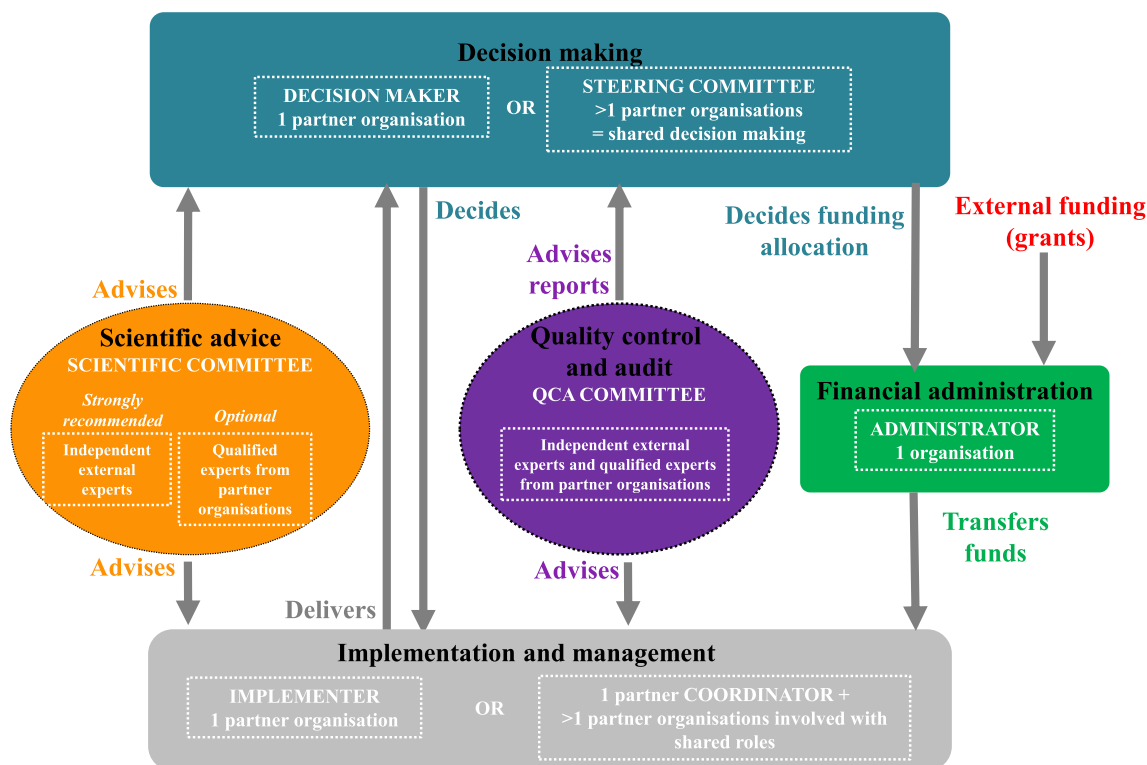
	Governance bodies				
	Decision-maker or steering committee	Scientific committee	Quality control and audit committee	Implementer	Financial administrator
Role	Full leadership for the project, including strategic direction, allocation of funds and resources, and all decision-making related to the project Selection of the scientific and audit committees using a transparent and documented process and justified by individual expertise relevant for the project	Written recommendations for the technical, scientific and related ethical aspects of the project, including reviewing and providing documented advice on study scientific deliverables	Written recommendations on governance and quality of the project and on quality control and audit of the studies. Management of conflict of interests documentation for the project	Implementation and execution of the project and studies	Management of the project funds
Composition & stakeholders	representation	<p>Option 1: one single partner (decision maker); the decision maker should be a public partner (a national PHI, a national RA, a research institute, or the ECDC)^a.</p> <p>Option 2: >1 partner (Steering Committee with shared decision making between partners); the composition of the Steering Committee should reflect a balanced representation according to the contributions from the different partners; it could be decided upfront as equal between public and private sectors or not, depending on the project specificities. Representatives with appropriate expertise from learned societies, patient associations and civil society organisations are recommended, at least as observers but preferably as regular partners with voting rights.</p>	<p>Option 1: Independent external experts from non-partner organisations (such as other PHIs, research institutions, RAs, ECDC, EMA, WHO, research institutes, civil society organisations)^a.</p> <p>Option 2: In some circumstances, duly justified by the need for specific expertise for the project or the studies, the decision maker may select in addition qualified scientists from partners' organisations (such as PHIs, vaccine MAHs, research institutes or CROs); but they should not be the majority and should not be involved in decision-making or implementation & management functions. Experts from partner organisations (MAH or any other organisations) shall have demonstrated expertise and scientific knowledge in the area and/or methods of the research and be affiliated to a Medical/Scientific function. Representatives with appropriate expertise from learned societies, patient associations and civil society organisations are recommended.</p>	Independent external experts from non-partners organisations and qualified persons from partners' organisations (PHIs, vaccine MAHs, research institutes, or CROs) not involved in the decision-making & managements functions. Qualified persons from vaccine MAHs are relevant if the project or the studies are performed to satisfy a regulatory commitment for which vaccine MAHs are accountable. Representatives with appropriate expertise from learned societies, patient associations and civil society organisations are recommended	<p>Option 1: one partner with a study team composed of their staff; the implementer should be a PHI, research institute, or a CRO with sufficient in-house expertise and resources^a.</p> <p>Option 2: one coordinator with roles in the study teams shared between partners; could be any of the partners in the PPC with experience and capacity in running the specific type of study</p>
	<p>Option 1: could be the partner in charge of the implementation and management function;</p> <p>Option 2: an independent organisation; strongly recommended when PHIs and MAHs are involved in a PPC or when there are more than one funder or country</p>				

^a If a single partner option is selected for one function, the other partners should be represented in the other governance functions based on their expertise for the particular function

3.3.3. Patient associations and civil society organisations

The active participation of patient associations and civil society organisations is strongly recommended because of their added-value for a productive vaccine post-marketing benefit-risk evalua-

tion, as well as for their support for enhancing transparency and public trust. They could be involved as members of the steering committee (with voting rights or as observers), or as members of the scientific committee or quality control & audit committee for



*As a prerequisite for a PPC, the funder(s) should be considered as partner organisation(s), which means that their involvement should go beyond providing funding. However, additional project funding could be received from non-partner organisations; e.g. external funding through grants from research foundations or the European Commission.

Fig. 4. ADVANCE proposal as a generic governance model for public-private collaborations (PPCs).

those with the relevant expertise. They could also be involved as independent external experts, e.g., for reviewing project information in external communication material for the lay public.

3.3.4. Management plan for conflicts of interest

All actors involved in PPCs can have potential conflicts of interests (CoIs) which can be financial or non-financial (e.g. professional interests, personal or family relationships, commercial or academic competition, beliefs). Since vaccine MAHs have specific, large commercial interests, their roles in PPCs should be clearly defined and completely transparent as indicated in Table 1. The impact of the CoIs on the governance functions should be evaluated at both individual and organisational levels, using a transparent CoI management plan implemented at project initiation, under the responsibility of the quality control and audit committee. As recommended in several guidelines, e.g. WHO, EMA, OECD, the constructive management of CoIs should focus on identifying and mitigating the related risk on the project rather than systematically excluding stakeholders with potential CoIs [14–16]. Despite this, in some instances, CoIs may lead to exclusion of individual experts or organisations for some decision-making or governance functions that may be unduly affected by the consequence of these CoIs. However, they do not have to be excluded from the whole project since they may assume other functions within the PPC that are not impacted by their CoIs. Alternatively, a shared decision-making body composed of stakeholders with different interests (e.g. academic, commercial, public health, regulatory) could be envisaged. This could avoid undue influence by a specific stakeholder and dilute any potential negative impact from CoIs. The same approach could be used for the study team (in compliance with the ADVANCE CoC) [8].

3.4. Contractual considerations for PPCs

A single contract should be signed by all partners to avoid multiple bi-partner or heterogeneous contracts and to improve transparency. The contract should clearly define the project objectives, the rational of the collaboration, the role, obligations, rights and responsibilities of each partner, the financial terms, the confidentiality rules, the data protection rules, CoI management rules, ethical considerations and other general information, such as the dates of the project start and end, termination terms etc. Dissemination and publication plans for the results should be described in the contract. The ownership and rights for usage of results from the PPC should be discussed on a case-by-case basis and the decision rules clearly defined in the contract. In all cases, publications should comply with international guidance, such as the recommendations from the International Committee of Medical Journal Editors (ICMJE) [17].

The objective of this guidance is to make the process for starting a project more efficient by providing governance structure and guidelines. Since the complexity of the research question, the number of partners and the project duration and settings will vary, it is very difficult to provide a range of timelines. Real-life collaborations in the future should help by providing some estimates of the project duration.

4. Discussion and conclusions

In this article we have described a set of governance proposals (functions, core principles and generic model) and recommendations aiming to support stakeholders willing and able to develop European PPCs in a post-marketing setting for vaccines. Together

with the ADVANCE code of conduct, these governance proposals are expected to generate a favourable environment for the conduct of trustworthy, valid studies, which will also satisfy the ENCePP guidelines and criteria on quality, transparency and scientific integrity. At the European level, collaborative vaccine post-marketing projects taking into consideration unmet medical needs for vaccines, regulatory requirements and PHIs' priorities are hampered by the current context of vaccine hesitancy and public distrust in institutions. In this light, ADVANCE has developed guidance for appropriate communication strategies for vaccine benefit/risk results produced by PPCs. The discussion about methods initiated in ADVANCE needs to be continued to address the specificities of vaccine-preventable diseases and to involve all stakeholders with the participation of the main European institutions, i.e., the ECDC and the EMA.

The IMI is a PPC between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA) which was launched in 2008 [5,18,19]. In the 10 years of their existence, they have financed almost 100 collaborative projects, mainly focused on early phases of drug and vaccine development. These successful projects have highlighted how collaborations can accelerate important innovations in medical research and drug development in Europe [20].

While our ADVANCE European governance model is based on existing high-level principles which can be found, for example, in the GAVI and Global Fund models, to our knowledge, there are no other governance frameworks or recommendations to date that are directly applicable to the setting of vaccine post-marketing benefit/risk assessment. Nevertheless, the proposed framework can be readily adapted to other scientific settings or regions in the world.

We conclude that in vaccine post-marketing settings there is no one-size-fits-all solution for governance of PPCs. The governance structure should be transparent and flexible, avoiding unnecessary complexity, to ensure that the project objectives are achieved, i.e., delivery of evidence on vaccines and vaccination programs to enable informed decision-making which will contribute to improved public health. We acknowledge that a PPC will not be suitable for all projects and that collaboration between public and private partners may be viewed with scepticism by some, particularly if COLs are not managed properly. These proposals for governance guidance now need to be applied in real-life collaborations (e.g. one potential collaboration is the DRIVE project, also funded by the IMI) to assess what works and what does not work and what added-value can be obtained from these collaborations.

5. Prior presentations

Oral presentation at the International Society of Vaccines congress in Paris 5–7 October 2017 entitled: *ADVANCE governance framework for public-private collaborations: Towards strengthening vaccine benefit-risk monitoring in Europe*.

Oral presentation at the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) in Malta 21–23 November 2018 entitled: *Guidance for the governance of public-private collaborations in vaccine post-marketing settings in Europe*.

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Declarations of interest

Laurence Torcel-Pagnon, Cédric Mahé, Anne Charrat are employed by Sanofi Pasteur; Vincent Bauchau is employed by GlaxoSmithKline; Myint Tin Tin Htar, is employed by Pfizer Inc.; Patrick Mahy, Marianne van der Sande, Tyra Grove Krause, François Simondon, Xavier Kurz declare no conflicts of interest.

Disclaimer

The views expressed in this article represent those of the authors and not necessarily those of their respective institution or company.

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Appendix A

A.1. ADVANCE consortium partner organisations

- **P95.** P95 (Belgium), Coordinator
- **UNIBAS.** Universitaet Basel (Switzerland) - Managing entity of the IMI JU funding
- **EMA.** European Medicines Agency (United Kingdom)
- **ECDC.** European Centre for Disease Prevention and Control (Sweden)
- **SURREY.** The University of Surrey (United Kingdom)
- **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands)
- **SYNAPSE.** Synapse Research Management Partners, S.L. (Spain)
- **OU.** The Open University (United Kingdom)
- **LSHTM.** London School of Hygiene and Tropical Medicine (United Kingdom)
- **PEDIANET.** Società Servizi Telematici SRL (Italy)
- **KI.** Karolinska Institutet (Sweden)
- **ASLCR.** Azienda Sanitaria Locale della Provincia di Cremona (Italy)
- **AEMPS.** Agencia Española de Medicamentos y Productos Sanitarios (Spain)
- **AUH.** Aarhus Universitetshospital (Denmark)
- **UTA.** Tampereen Yliopisto (Finland)
- **SCIENSANO.** Institut Scientifique de Santé Publique (Belgium)
- **MHRA.** Medicines and Healthcare products Regulatory Agency (United Kingdom)
- **SSI.** Statens Serum Institut (Denmark)
- **RCGP.** Royal College of General Practitioners (United Kingdom)
- **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu * National Institute for Public Health and the Environment (Netherlands)
- **GSK.** GlaxoSmithKline Biologicals, S.A. (Belgium) – EFPIA Coordinator
- **SP.** Sanofi Pasteur (France)
- **NOVARTIS.** Novartis Pharma AG (Switzerland)*
- **MSD.** Merck Sharp & Dohme (France)
- **JANSSEN.** Janssen Vaccines & Prevention B.V. (Netherlands)

- **PFIZER.** Pfizer Limited (United Kingdom)
- **TAKEDA.** Takeda Pharmaceuticals International GmbH (Switzerland)
- **ARS Toscana** - Agenzia Regionale di Sanità, Toscana (Italy)
- **IDIAP JORDI GOL.** Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (Spain)

*Effective 9 November 2015, bioCSL, the vaccine and pharmaceutical business of CSL, acquired the influenza vaccines business of Novartis, to create Seqirus, a CSL company. Seqirus and Novartis operate at interim under the Sale and Purchase Agreement governing the sale to CSL as well as the relevant TSAs and TDSA.

- ADVANCE Associate Partners
- ESDY. National School of Public Health, Department of Public Health (Greece)
- HCDCP. Hellenic Center for Disease Control and Prevention (Greece)
- IMB. Irish Medicines Board (Ireland)
- AIFA. Italian Medicines Agency (Italy)
- ANSM. French Medicines Agency (France)
- VVKT. State Medicines Control Agency (Lithuania)
- WUM. Polish Medicines Agency (Poland)
- PHE. Public Health England (United Kingdom)
- BCF. Brighton Collaboration Foundation (Switzerland)
- ICL. Imperial College London (United Kingdom)
- UOA. University of Athens (Greece)
- NCE. National Centre for Epidemiology (Hungary)
- FISABIO. FISABIO-Public Health, Foundation for the promotion of Health and Biomedical Research in the Valencian Region (Spain)
- EOF. Hellenic Medicines Agency, National Organisation for Medicines (Greece)
- THL. National Institute for Health and Welfare (Finland)
- UNIME. University of Messina (Italy)
- IRD. Institut de recherche pour le développement (France)
- VGRID. VACCINE.GRID Foundation (Switzerland)
- UMCU. Utrecht Medical Center (Netherlands)

*Steering committee members: Xavier Kurz (EMA), Vincent Bauchau (GSK), Jorgen Bauwens (UNIBAS/UKBB), Mendel Haag (NOVARTIS/Seqirus), Simon de Lusignan (University of Surrey), Alena Khromava (Sanofi Pasteur), Kaat Bollaerts (P95), John Weil (Takeda), Miriam Sturkenboom (P95), Lina Titievsky (Pfizer), Natasha Yefimenko and Eva Molero (Synapse), Antonella Chiucchiuini (Takeda), Piotr Kramarz and Maarit Kokki (ECDC), Tin Tin Htar Myint (Pfizer), Laurence Torcel-Pagnon (Sanofi Pasteur), Patricia Saddier (MSD), Patrick Mahy (Sciensano), Tyra Grove Krause (SSI), Hester de Melker and Susan Hahne (RIVM).

Appendix B

B.1. Definitions

Private-public collaboration (PPC): an engagement of public and private organisations, who share common interests in vaccine benefit-risk monitoring, to work together in a project. The roles and responsibilities of each partner organisation are agreed and formalised through a contract agreement. This could be a short-term (study-specific) or a long-term broader project.

Governance: processes of interaction and decision-making among the stakeholders involved in a PPC.

Study: investigation carried-out to answer a well-defined research question on vaccine benefit-risk monitoring in post-marketing settings.

Project: set of activities to organise one or several studies or other long-term activities (such as database network or multi-year vaccine monitoring) designed to address vaccine benefit-risk monitoring in post-marketing settings.

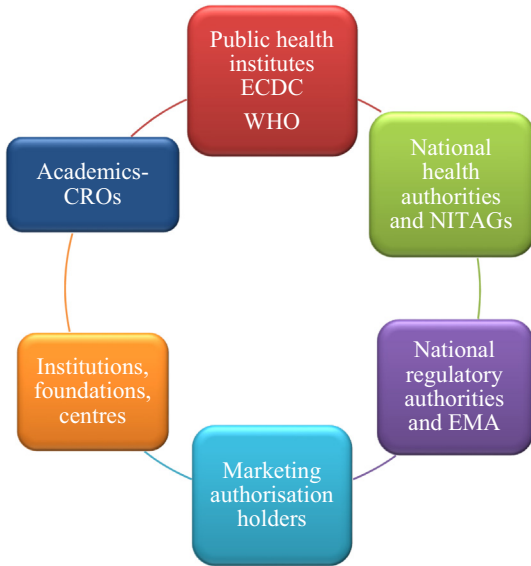
Appendix C

ADVANCE survey questionnaire used to identify existing public-private collaborations

Item	Description
Who fill in:	Name, company/organisation and involvement in the model
Model:	Model type: private/public, number of stakeholders, Europe and vaccines or not
Title:	Name or short title of the model
Topic/aim:	Why the model was build
Initiative/Rational:	Who has initiated the model and how multi-stakeholders have been chosen/involved
Governance:	Multi-stakeholders with their responsibilities, rights and obligations (sponsor, funder, data provider, services provider ...)
Flexibility of the leadership:	Who is leading and how multi-stakeholders communicate
Contracts/Agreements:	How contracts have been engaged (several bipartite contracts, one multi-partite contract, repeated contracts or amendments for case studies)
Confidentiality:	How confidentiality was respected
Transparency:	How transparency was respected (registration on public website/publication etc.)
Funding:	Name of the funders and how the budget has been shared (equal parts, proportional to data etc.)
Scientific independence:	How independence from funding sources was respected (ownership of results, data property and sharing, publication rules, etc.)
Countries:	Countries which were data sources
Duration/time period:	When the model was created, is it planned to be repeated/extended
Case study details:	Was the model was focussed on one case study ; could it be extended to several case studies
Regulatory/ethical reviews:	Which regulatory process, applicable law, compliance rules and ethical reviews were applied to the model and/or the case study (commitment, scientific committee, referential like ENCePP ..)
What went well:	Perceived successes
Which difficulty was encountered:	Perceived issues (solved or not)
What should be improved:	Areas for improvements
Comments:	Add any additional information which may be relevant for the model description

Appendix D

Key stakeholders in vaccine benefit/risk monitoring in Europe



<p>Public health institutes (National)</p> <ul style="list-style-type: none"> ✓ Continual benefit-risk evaluation of vaccination programmes to give timely evidence-based guidance to their NHA; ✓ Design and conduct studies or develop surveillance networks to collect relevant routine national data. 	<p>National health authorities</p> <ul style="list-style-type: none"> ✓ Decide on vaccination-related policies and programmes. 	<p>National regulatory authorities</p> <ul style="list-style-type: none"> ✓ Assess the quality, efficacy and safety of vaccines submitted to the national authorisation procedure ✓ Monitor the marketed vaccines on their territory, which includes communicating important pharmacovigilance information to the public and healthcare professionals. 	<p>Marketing authorisation holders</p> <ul style="list-style-type: none"> ✓ Responsible, by law, for assessing and monitoring the benefit-risk profile of their vaccines ✓ Conduct post-authorisation studies to monitor the benefit-risk profile of their vaccines, as required by competent authorities or on a voluntary basis ✓ Communicate safety information, in compliance with pharmacovigilance obligations, to competent authorities (through reporting of individual safety case reports) and ongoing monitor of the benefit-risk profile of their vaccines (through a risk management plan) ✓ Communicate validated safety signals that may have implications for public health and the benefit-risk profile of their vaccines to the competent authorities, and when appropriate, include proposals for action ✓ Manufacturer and marketing of their vaccines. 	<p>Institutions, foundations, centres</p> <p>A variety of entities such as health insurance funds or pension funds, managers of patient registries, occupational medicine study centres or epidemiological institutions may play a role as data controllers with the following responsibilities:</p> <ul style="list-style-type: none"> ✓ Determine the purposes and means of processing of personal data ✓ Provide ethical approval for use of the data ✓ Assure the quality of data and be responsible for data protection ✓ Receive requests from data subjects to exercise their rights. 	<p>Academics</p> <ul style="list-style-type: none"> ✓ Develop and test methodologies, conduct research and disseminate results through teaching, publication and technology transfer ✓ Develop and use information, methods and technologies relevant for vaccine benefit-risk monitoring <p>Includes entities such as a universities or research institutes, irrespective of their legal status (public or private) or funding modalities.</p>
<p>ECDC</p> <ul style="list-style-type: none"> ✓ Coordinate PHI activities to strengthen Europe's defences against infectious diseases; ✓ Provide expertise in risk assessment, diseases surveillance, technical guidance and funding to support vaccine benefit-risk monitoring. 	<p>National immunisation technical advisory groups (NITAGs)</p> <ul style="list-style-type: none"> ✓ Provide scientific recommendations to health ministries for evidence-based decisions 	<p>EMA</p> <ul style="list-style-type: none"> ✓ Coordinate scientific resources of Member States for the evaluation, supervision and pharmacovigilance of vaccines ✓ Coordinate the work of committees and working parties providing independent, science-based recommendations on the quality, safety and efficacy of vaccines Implement measures for continual evaluation of the quality, safety and efficacy of authorised vaccines to ensure that their benefits outweigh their risks. 			
<p>WHO Regional Office for Europe</p> <ul style="list-style-type: none"> ✓ Advocate for the establishment or strengthening of national advisory bodies; ✓ Build capacity of national experts; <p>Introduce best practices identified in countries that have long-established NITAGs</p>					

Appendix E

Summary of the roles and responsibilities of the core governance functions

Governance function	Roles and responsibilities
Decision making	<ul style="list-style-type: none"> responsibility for scientific, ethical, legal and compliance aspects of the project; overall project governance: endorsement of work plan, high-level follow-up of progress in project critical areas and implement appropriate corrective actions, when necessary, and implement project contingency and risk management plans; allocation and reallocation of funding and resources to ensure project remains aligned with its objectives; seek advice from other parties or committees for technical, scientific, quality and compliance considerations; approval of project deliverables; management of external communication and advocacy related to the project and ensure that project results are published and disseminated
Scientific advice	<ul style="list-style-type: none"> provide advice and recommendations on technical, scientific and ethical topics for the project contribute to, review and providing advice on the study scientific deliverables, e.g., research plan, protocol(s), analyses, interpretation of results, report(s), scientific communication and publications
Quality control and audit	<ul style="list-style-type: none"> audit to ensure that the principles and rules of governance are respected for the project: <ul style="list-style-type: none"> verify transparency of funding sources and funding allocation; verify transparency of the decision-making process and appropriate documentation; verify adequate declaration of potential conflicts of interest; evaluate potential conflicts of interest; report any specific issues to the decision maker; ensure adequate quality control and corresponding auditing for the studies: <ul style="list-style-type: none"> verify compliance with relevant guidelines, and national and international standards and requirements; oversee project compliance report findings, provide advice, recommendations and proposed action plan, when needed.
Implementation and management	<ul style="list-style-type: none"> manage daily operational aspects of the project and study(ies), i.e., perform technical, legal (e.g., contracts) and administrative (e.g., ethics and data-protection-related submissions) tasks under the decision maker's authority and liaison with the project partner organisations, as required; ensure oversight of studies (either directly or through sub-contracting); produce study scientific deliverables, e.g., research plan, protocol(s), statistical analysis plan(s), report(s), publications and other scientific communication
Financial administration	<ul style="list-style-type: none"> manage the budget with appropriate accounting and invoicing to ensure financial transparency and independency; distribute funds independently of funders, under the supervision of the decision maker; report to the decision maker on traceability of the funding sources and beneficiaries.

Appendix F. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.04.073>.

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