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Emergency Task Force (ETF)

# Report of the EMA workshop on the future of vaccine effectiveness studies in Europe

## Building a European framework to generate real-world evidence

**Background**

In 2016, during the revision of the influenza vaccines guidelines for developers by the Vaccine Working Party (VWP) and the Committee for Human Medicinal Products (CHMP), European experts agreed that the optimal way to monitor the performance of flu vaccines over time was to generate high quality vaccine effectiveness data. Influenza vaccines have the peculiarity that their composition must be adapted almost every year to match the highly variable circulating virus strains in order to remain protective. With the understanding that small clinical trials on immunogenicity and safety are not always able to provide useful information, observational (non-interventional) studies are likely to be better placed to give insights into how vaccines work in real-world settings. Moreover, results of observational effectiveness studies may indicate a specific concern (e.g. due to a quality issue with a specific vaccine), which may require further investigation and might trigger regulatory actions. The availability of effectiveness data is considered essential for all vaccines, not only for vaccines that are authorised principally on the basis of immunogenicity data. Moreover, data per brand is necessary for decision making by regulatory authorities.

Several groups have explored the possibility to generate robust brand-specific effectiveness data for influenza vaccines, including I-MOVE (a public consortium) and DRIVE (a public private partnership - PPP). However, providing yearly effectiveness data specific for each influenza vaccine has proven challenging due to several factors, notably the unpredictable use of each brand across EU Member States (MSs), sample size and logistical issues, and the challenges for industry to

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partner with public health agencies (PHAs). Many PHAs are not in the position to collaborate directly with the pharmaceutical industry due to their national legislation in matters of conflicts of interest, restricting the possibilities of effective PPPs.

In 2022, the new legislation on the EMA extended mandate1 established the requirement for EMA to support the work of the Emergency Task Force (ETF) in preparation for and during public health emergencies by "coordinating independent monitoring studies on the use, effectiveness and safety of medicinal products intended to treat, prevent or diagnose diseases related to the public health emergency, using relevant data, including, where relevant, data held by public authorities", where "coordination as regards vaccines shall be conducted in conjunction with the ECDC, in particular, through a new vaccine monitoring platform". Similar provisions were introduced for the ECDC in the revised version of their founding regulation2.

As a consequence of the extended mandate of both Agencies, the Vaccine Monitoring Platform was established in May 2022 in collaboration with ECDC. The VMP provides the legal basis and environment to explore the pathways that can lead to sustainable and sufficiently sized studies for monitoring in real-world settings the effectiveness of influenza vaccines and other vaccines recommended in the EU, including at brand level .

**Scope**

The workshop was organised by EMA to bring together relevant stakeholders to discuss needs and challenges and identify possible solutions to be included into a roadmap. The long-term vision is to create a pan-European framework that brings together appropriate stakeholders, resources and infrastructures to facilitate the conduct of large, reliable vaccine effectiveness studies, including during public health emergencies.

**The objectives of the workshop were:**

Mapping current needs and challenges

Identifying potential next steps/roadmap for funding and sustainability of vaccine effectiveness studies and a regulatory framework

**Representatives of the following entities attended the workshop:**

European Medicines Agency (EMA)

EU consortia (DRIVE)

Study investigators (Charité – Universitätsmedizin Berlin)

European Centre for Disease Prevention and Control (ECDC)

US Centers for Disease Control and Prevention (CDC)

EU/EEA National Immunisation Technical Advisory Groups (NITAGs)

Public Health Authorities (PHAs)

EMA Emergency Task Force (ETF)

EU National Competent Authorities

[1] Publications Office (europa.eu)

[2] EU strengthens its disease prevention and control capacity | News | European Parliament (europa.eu)

Immunisation and Vaccine Monitoring Advisory Board (IVMAB) of the Vaccine Monitoring Platform (VMP)
EMA Patients Working Party and Health Care Professionals Working Party
European Commission (DG SANTE / HERA /RTD)
Industry: Vaccines Europe

**The views of stakeholders**

The workshop agenda is attached as an appendix to this report.

Representatives from EMA, ECDC and EU NITAGs presented their views on the importance of VE study results from a regulatory and public health perspective to inform their respective decision-making processes.

Regulatory requirements for brand-specific effectiveness data for influenza vaccines were introduced in 2017 with the revised influenza vaccines guideline, and the progress and challenges encountered since in the generation of evidence were highlighted. Fragmentation of research networks and difficulties to reach sufficiently large sample size by individual networks necessary for reliable brand-specific results are key challenges that need to be faced. A further layer of complexity is related to the need for logistical and financial cooperation between private and public institutions, which was often not feasible due to national legal provisions prohibiting collaboration with industry. Lack of immunisation registries and records of infectious diseases in several MSs hampers the possibility of secondary use of data for effectiveness studies.

ECDC presented evidence generation activities in the area of vaccine effectiveness, focusing on the VEBIS2 project and outlining public health priorities in this area, i.e. the need for overall in-season influenza vaccine effectiveness to inform public health practice. ECDC also showed substantial increases in sample size of vaccine effectiveness studies needed for brand-specific estimates and presented programmatic challenges of brand-specific vaccine effectiveness studies.

The Vaccine Monitoring Platform recently established by EMA and ECDC, as required by the respective new EU regulations of 2022, was also presented. Although still in its early stages and with relatively limited capacity, the EU legislator envisaged the platform as an opportunity to foster public research in the EU, especially to support timely regulatory and public health decision-making in the preparation for and response to emergencies. However, resources and public funds are currently limited. It was concluded that different vaccine effectiveness research questions might require primary data collection or be addressed though secondary analysis of healthcare data. The latter holds promises as it can deliver results at lower cost albeit not devoid of challenges from the perspective of methods and data sources. It was recommended to further explore the secondary use of healthcare data and one avenue to pursue is the use of DARWIN EU as well as procuring such studies from other independent research networks. The existing regulatory framework for effectiveness studies in the post-authorisation phase, particularly with regard to the obligations to be placed on Marketing Authorisation Holders (MAHs) requires clarification to better define responsibilities (and is currently under discussion by EMA and the EC).

Representatives from EU consortia and from vaccine manufacturers presented what has been achieved in terms of PPPs to comply with the request for vaccine brand-specific data for influenza

vaccines and related pitfalls, including the reluctance of PHAs to be involved with private partners for reasons related to conflict of interest. DRIVE and COVIDRIVE are now expanding their scope from influenza and COVID-19 to all vaccine-preventable infectious diseases under the new consortium name "id.DRIVE".

The US CDC described the system in place to generate influenza VE data by means of a centralised CDC-led platform coordinating various networks established across public, academic, and healthcare institutions, publicly funded by or through the CDC.

The EC recognised the importance for generating reliable, quality VE results in the EU population through independent studies, looking also at vaccine hesitancy and the need to counteract the spread of misinformation on vaccines. EC is currently funding EMA and ECDC VE studies as those are part of their extended mandates, but this is not secured into the future. The options for public funds in the EU currently have limitations imposed by the EU budget system, which is agreed for 7 years at a time. The next EU budget cycle will start in 2027 and may provide opportunities for the future. Further discussion will be required with the EC to secure longer term public support towards EU-conducted effectiveness studies.

The public health emergencies of COVID-19 and mpox have tested the EU capability for generating timely VE data and provided insights for lessons learned and improvement. The lack of adequate resources and coordination hampered the ability to deliver fast results in face of a public health emergency, and left authorities with the need to supplement decision-making with data generated in other regions. It is however increasingly clear that VE data must be obtained from different regions in the world as several factors, including background immunity of the population and vaccination strategies, can affect how well vaccines perform in real-world settings.

Outcome of the discussion

The EMA proposed a vision for the future of vaccine effectiveness studies in the EU that builds on the various existing initiatives and is sustained by the contributions of both private and public stakeholders within the limits imposed by legislative provisions and funding options.

The existing legal framework allows the Vaccine Monitoring Platform to be used to provide central coordination to VE study networks. Coordination would include creating a robust governance model between EMA, ECDC and the EC and the support of the stakeholders to ensure transparency and independence. The reinforced VMP would adopt an annual research agenda including priorities for vaccine effectiveness studies with advice from the existing IVMAB and ETF. This concept was generally agreed by all stakeholders but requires careful design as e.g. ECDC, along its mandate, cannot collaborate with commercial entities nor engage in public-private partnerships. A robust and sustainable EU platform of networks would facilitate the generation of VE results including results at brand level, where required.

Concerning the existing networks, it would be useful to explore consolidation into fewer entities of large size that are assigned specific research areas to avoid duplication and improve efficiency. Network capacity should be expanded. The scientific expertise and methodological skills of individual experts should be leveraged. Capacity and methods for secondary use of data should be further developed together with ECDC to support evidence generation in a complementary fashion to studies which use primary data collection. Availability of (near) real-time data in electronic

health care data sources should be explored to generate timely evidence. Interactions with consortia dedicated to vaccine research should be further explored to leverage expertise and limit existing or perceived conflicts of interest. For example, PPPs could handle aspects not directly related to study set-up and conduct but aiming to expand scientific knowledge impacting on study design (e.g. endpoints, methodology, required precision for meaningful data, network building). Patient-reported outcomes and their collection should be explored in the future.

In the longer term, surveillance systems and secondary use of healthcare data should be strengthened. Stakeholders expressed the need to improve protocol guidance (which design to apply in which circumstances, use of target trial emulation, pragmatic trials, etc.). The European Health Data Space (EHDS) provides an opportunity to leverage the wealth of data in the EU to address scientific questions for vaccines. EU data sources are clearly an advantage where available, and the idea to establish an "EU vaccination registry" was proposed for future discussion.

Funding remains a limitation for the time being, therefore it is critical to maximise on what is currently available and to explore mechanisms for contributions by all stakeholders without triggering conflicts of interest. The VMP as a centralised coordinating platform could, in the long term, support allocation of funds, perhaps similarly to the US mechanism handled by the CDC. The ongoing efforts by ACT-EU and HERA on funding mechanisms for Clinical Trials in emergencies could provide useful lessons in this respect and provide a complementary funding tool specifically for vaccine clinical trials. The discussion with the EC will need to continue with a view to secure adequate long-term funding for observational studies in future budget allocations.

Having heard the needs and recommendations of the stakeholders who attended the workshop, the EMA will prepare a roadmap of actions to turn the proposed vision for the future of vaccine effectiveness studies (including brand-specific studies where needed) in the EU into reality, for the benefit of citizens and patients also beyond the Union. This roadmap will represent a starting point for further discussion and agreement at various levels with relevant stakeholders.

**Appendix: Agenda of the workshop**

| AGENDA | |
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| **Welcome by the chair**<br>*Chair: Marco Cavaleri (Head of Public Health Threats Department at EMA and ETF cochair)*<br><br>**Opening by Emer Cooke, Executive Director EMA** | **10:00 CET** |
| **Session 1**<br>**Stakeholders' perspectives and alignment on problem statement**<br>(brand data and sample size, funding, identification of concerns and needs from PHAs) | **10:10 CET** |
| ***Moderators**: Peter Arlett (Head of Data Analytics and Methods Task Force, EMA) and Eleonora Wijnans (IVMAB, VWP and ETF member)* | |
| a. Regulatory requirements for brand-specific VE data and evidence generation via the VMP<br>*Speaker: Manuela Mura (EMA-ETF) and Catherine Cohet (EMA)* | 20’ |
| b. Public Health Agencies: evidence needs, limitations and constraints of public and private fundings<br>*Speaker: Hanna Nohynek (Finnish Institute for Health and Welfare)* | 20’ |
| c. ECDC activities on evidence generation<br>*Speaker: Piotr Kramarz (ECDC)* | 20’ |
| d. DRIVE / COVIDRIVE / id.DRIVE: achievements, challenges, and future plans<br>*Speakers: Cédric Mahe (Sanofi), Javier Díez Domingo (Fisabio), and Kaatje Bollaerts (P95)* | 30’ |
| e. Vaccines Europe: RWE generation in the EU by Marketing Authorisation Holders (MAHs)<br>*Speakers: Charlotte Vernhes (Vaccines Europe secretariat) and Elizabeth Begier (Pfizer)* | 30’ |
| f. US CDC: public funding model for vaccine effectiveness studies in the US *Speaker: Brendan Flannery (US Centers for Disease Control and Prevention, Influenza Division)* | 20’ |
| **Moderated discussion** | 30’ |
| **LUNCH BREAK** | **13:00 – 14:00 CET** |

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| **Session 2**<br>**The framework for VE studies in the EU - Regulatory and funding aspects** | **14:00 CET** |
| ***Moderators**: Marco Cavaleri (EMA and ETF cochair) and Jean-Michel Dogné (IVMAB, ETF and PRAC member)* | |
| a) DG SANTE perspective on VE studies<br>*Speaker: Rainer Becker (DG SANTE director of Medical Products and Innovation)* | 10’ |
| b) EMA perspective on the regulatory framework for VE studies<br>*Speaker: Thomas Girard (EMA)* | 10’ |
| c) VMP case study: mpox vaccine monitoring, the experience of the investigators<br>*Speaker: Leif Sander (Prof. Infectious Diseases at Charité)* | 10’ |
| d) Industry perspective<br>*Speakers: Vaccines Europe representatives* | 20’ |
| **Moderated discussion** | **30’** |
| **BREAK –** *Industry leaves the room* | **15:20 – 15:35 CET** |
| **Session 3**<br>**Overall discussion and conclusion** (closed to industry) | **65’** |
| ***Moderator**: Emer Cooke (Executive Director EMA)* | |
| **Discussion** | **45’** |
| Considerations for discussions for future vaccine effectiveness studies on funding, sustainability of vaccine effectiveness studies, and regulatory framework | |
| **Wrap up and conclusion by the chair**<br>*Marco Cavaleri (EMA and ETF cochair)* | **20’** |
| **Close of day** | **16:40 CET** |