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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
No data was used for the research described in the article

Dr Gregory A Poland
Editor-in-Chief, Vaccine

Soest, 12 October 2018

Dear Dr Poland

We are pleased to submit our paper 'Why we need more collaboration in Europe to enhance post-marketing surveillance of vaccines' to your Journal, Vaccine for the ADVANCE supplement. This paper describes the background of the ADVANCE project and the different stakeholders' needs. It is the first of the series of 10 papers that will be included in the supplement.

On behalf of all co-authors

Prof. dr. Miriam CJM Sturkenboom

***Author Agreement**

I, the undersigned, Prof. dr. Miriam CJM Sturkenboom declare that all authors have seen and approved the final version of the manuscript being submitted. We warrant that the article is our original work that has not been previously published and is not under consideration for publication elsewhere

Prof. dr. Miriam CJM Sturkenboom

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Key messages

- Europe needs a system for timely, high-quality information on vaccine benefits and risks
- European vaccine stakeholders have different perspectives but similar information needs
- The ADVANCE project has developed and tested a system to generate the necessary information

Abstract

The influenza A/H1N1 pandemic in 2009 taught us that the monitoring of vaccine benefits and risks in Europe had potential for improvement if different public and private stakeholders would collaborate better (public health institutes (PHIs), regulatory authorities, research institutes, vaccine manufacturers). The Innovative Medicines Initiative (IMI) subsequently issued a competitive call to establish a public-private partnership to build and test a novel system for monitoring vaccine benefits and risks in Europe. The ADVANCE project (Accelerated Development of Vaccine benefit-risk Collaboration in Europe) was created as a result. The objective of this paper is to describe the perspectives of key stakeholder groups of the ADVANCE consortium for vaccine benefit-risk monitoring and their views on how to build a European system addressing the needs and challenges of such monitoring. These perspectives and needs were assessed at the start of the ADVANCE project by the European Medicines Agency together with representatives of the main stakeholders in the field of vaccines within and outside the ADVANCE consortium (i.e. research institutes, public health institutes, medicines regulatory authorities, vaccine manufacturers, patient associations). Although all stakeholder representatives stated they conduct vaccine benefit-risk monitoring according to their own remit, needs and obligations, they are faced with similar challenges and needs for improved collaboration. A robust, rapid system yielding high-quality information on the benefits and risks of vaccines would therefore support their decision making. ADVANCE has developed such a system and has tested its performance in a series of proof of concept (POC) studies. The system, how it was used and the results in from the POC studies are described in the papers in this supplementary issue.

Why we need more collaboration in Europe to enhance post-marketing surveillance of vaccines

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Abbreviations used

ADVANCE: Accelerated Development of Vaccine benefit-risk Collaboration in Europe

CIRN: Canadian Immunisation Research Network

EC: European Commission

ECDC: European Centre for Disease Prevention and Control

EFPIA: European Federation of Pharmaceutical Industries and Associations

EMA: European Medicines Agency

EU: European Union

IMI: Innovative Medicines Initiative

PHI: public health institute

MAH: marketing authorisation holder

POC: proof of concept

VAERS: Vaccine Adverse Event Reporting System

VSD: Vaccine Safety Datalink

Abstract

The influenza A/H1N1 pandemic in 2009 taught us that the monitoring of vaccine benefits and risks in Europe had potential for improvement if different public and private stakeholders would collaborate better (public health institutes (PHIs), regulatory authorities, research institutes, vaccine manufacturers). The Innovative Medicines Initiative (IMI) subsequently issued a competitive call to establish a public-private partnership to build and test a novel system for monitoring vaccine benefits and risks in Europe. The ADVANCE project (Accelerated Development of Vaccine benefit-risk Collaboration in Europe) was created as a result. The objective of this paper is to describe the perspectives of key stakeholder groups of the ADVANCE consortium for vaccine benefit-risk monitoring and their views on how to build a European system addressing the needs and challenges of such monitoring. These perspectives and needs were assessed at the start of the ADVANCE project by the European Medicines Agency together with representatives of the main stakeholders in the field of vaccines within and outside the ADVANCE consortium (i.e. research institutes, public health institutes, medicines regulatory authorities, vaccine manufacturers, patient associations). Although all stakeholder representatives stated they conduct vaccine benefit-risk monitoring according to their own remit, needs and obligations, they are faced with similar challenges and needs for improved collaboration. A robust, rapid system yielding high-quality information on the benefits and risks of vaccines would therefore support their decision making. ADVANCE has developed such a system and has tested its performance in a series of proof of concept (POC) studies. The system, how it was used and the results in from the POC studies are described in the papers in this supplementary issue.

Keywords: Vaccine benefit-risk; Europe; Post-marketing monitoring; Collaboration; Electronic healthcare databases

1. Introduction

1.1 Vaccines are needed

Immunisation has a major impact on global health [1]. Today, vaccines are licensed for protection against more than 20 diseases (Fig 1) and are now one of the most successful and cost-effective medical interventions to protect billions of people [2, 3]. Immunisation is estimated to prevent 2 to 3 million deaths annually across all age groups [4]. High vaccination coverage in a population and subsequent herd immunity can protect those who cannot be vaccinated. Additionally, advancements in maternal immunisation have led to protection of new-borns against vaccine-preventable diseases, such as tetanus, pertussis and influenza. Over the next decade, the world's population can also expect to benefit from vaccines for diseases and pathogens such as HIV/AIDS and Group B Streptococcus [5]. In the future, vaccines may play a more prominent role in the fight against antimicrobial resistance, one of the largest public health threats. In the European Union (EU), vaccine products are licensed through the European Medicines Agency (EMA) or a national regulatory authority, and are subsequently monitored by the regulatory authorities; vaccination programmes are monitored by public health institutes (PHIs) [6]. Vaccine manufacturers have their own legal responsibility for monitoring product-specific benefit-risk.

1.2 Vaccination hesitancy is concerning

Despite the well-documented benefits of vaccination, some population groups in a number of European countries are hesitant about vaccination, reporting mistrust in vaccine safety and questioning the trustworthiness of government, regulatory and public health authorities and pharmaceutical companies [7]. Hesitancy has been partly fuelled by the Wakefield publication that claimed autism was caused by MMR vaccine, which was later identified as fraudulent research and retracted 12 years after its publication [8]. Vaccination programmes are also victims of their own success, as some vaccine-preventable diseases are now so rare that the

benefits of vaccination are less obvious to the public, who are more concerned about vaccine risks than disease risks, as well as by the increasing number of injections administered. Some studies show trends of healthcare professionals themselves starting to hesitate about vaccination [9]. This is a problem given their position as a trusted source of vaccine information for parents and other individuals and their influence on the level of confidence in vaccination as a health option [10].

In 2016, a global survey in 67 countries on vaccine hesitancy indicated that Europe was the region in the world with the least confidence in vaccine importance, safety and effectiveness [11]. The results showed that 45% of the French population disagreed with the statement 'vaccines are safe' compared with an average of 17% in Europe, and a global average of 13%. Similarly, a systematic literature review found that the most common vaccine concern among European populations is the fear of adverse events, with the perceived risk varying between vaccines [7]. A recent WHO/UNICEF assessment of vaccine hesitancy showed that hesitancy was common (>90% of countries), and that lack of scientific evidence on benefit-risk was the most frequently cited reason. The authors concluded that these measurements provided some of the evidence for the 2017 Assessment Report of the Global Vaccine Action Plan recommendation that each country should develop a strategy to increase acceptance and demand for vaccination, which should include ongoing community engagement and trust-building, active hesitancy prevention, regular national assessment of vaccine concerns, and crisis response planning [12]. The monitoring of on-line news media during a risk assessment for HPV vaccines by the EU regulatory network in 2015, revealed that those critical about the safety of these vaccines had a wide range of questions on safety issues, the underlying data, the methods to analyse these data and the safety surveillance system overall [13]. The decline in HPV vaccine uptake following safety scares in Denmark, the decline in influenza vaccine uptake in Germany following the 2009 pandemic, and the decline in MMR uptake in the UK

following the Wakefield publication, and currently numerous measles outbreaks across Europe are some examples of the consequences of how confidence and acceptance of vaccination can be undermined [14-18].

1.3 Why we need post-marketing evidence

Like with other pharmaceutical products, adverse reactions can occur after vaccination. However, unlike the majority of pharmaceutical products, vaccines are generally administered to healthy individuals and, particularly, to healthy young children thereby resulting in a very low level of risk acceptance. Hence, the standard of safety for vaccines is expected to be even higher than that for medications administered to people with diseases (e.g. antibiotics, insulin). This translates into a greater need for high quality and timely evidence on any adverse events following immunisation and clear communication about post-marketing benefit-risk assessments.

The background incidence rates of some serious adverse events suspected to be associated with vaccines are very low, e.g. Guillain-Barré Syndrome (2/100,000 person-years) and narcolepsy (1/100,000 person-years). Pre-licensure efficacy and safety clinical trials, that can detect more frequent events such as fever, are not sized to detect events with a frequency of <1/10,000 person-years [19, 20]. As a result, continuous post-marketing monitoring of vaccine safety is needed to identify and evaluate potentially rare adverse events and to enable re-assessment of vaccine benefit-risk. Passive spontaneous reporting of adverse events is still the cornerstone of most post-marketing safety monitoring systems, but with the increasing availability of electronic healthcare data, new options for safety surveillance have become available [21-23]. The potential of these large, linked data sources for vaccine safety monitoring was first recognised in the USA in 1990, with the establishment of a collaboration between the US Centres for Disease Control and Prevention and eight health maintenance organisations to create the Vaccine Safety Datalink (VSD) [24, 25].

2. Why we need to collaborate

The added-value of vaccine benefit-risk monitoring across individual healthcare plans or provinces was recognised and publicly-funded in North America (US: VSD in 1990 and Sentinel in 2010, Canada: Canadian Immunisation Research Network (CIRN) in 2009) [26-28]. In contrast, in Europe, most of the monitoring of vaccine coverage, benefit and risk is done nationally, and long-term public funding for a system to collaborate to monitor vaccine benefits and risks on a European level is not available [29].

During the 2009 influenza pandemic, several new vaccines were licensed and used in large populations. This demonstrated the need for collaboration at many levels and highlighted how post-marketing monitoring systems in the EU could be improved by developing [30]:

- Increased and transparent interactions between public and private stakeholders, in particular between vaccine manufacturers and public health organisations
- Clear communication on the respective roles and responsibilities of the various European bodies and agencies (i.e., European Commission (EC), EMA and European Centre for Disease Prevention and Control (ECDC)), the responsibilities of national bodies and vaccine manufacturers and the vaccine licensure process
- Common approaches to definitions, study designs, data collection and protocols for readiness to respond to public and expert concerns
- Strengthened collaborative pan-European vaccine benefit-risk monitoring
- Communication strategies to share new data on vaccine risks, safety and benefits, with their associated uncertainties, promptly and transparently.

Collaboration and sharing of data should increase the capacity to quantify risks and benefits, allow comparisons between product brands and vaccination schedules, and promote knowledge sharing.

Ultimately, continuous and rapid benefit-risk monitoring throughout the life-cycle of vaccines

will be necessary to meet the needs of different target groups and stakeholders for making informed decisions (e.g. health ministries, regulatory authorities, public health agencies, vaccine manufacturers, healthcare providers, parents, insurance companies). The need for collaboration to generate evidence for benefits-risk monitoring was recognised and presented to the Innovative Medicines Initiative (IMI) by the vaccine manufacturers. IMI is an initiative jointly-funded by the EC and the European Federation of Pharmaceutical Industries and Associations (EFPIA). IMI issued a call for proposals for a public-private partnership to build and test methods for and components of a collaborative, distributed system for benefit-risk monitoring of vaccines and, as a result, they funded the ADVANCE (Accelerated development of vaccine benefit-risk collaboration in Europe) project.

The ADVANCE project was built on the premise that an integrated, sustainable, continuous vaccine monitoring system is of paramount importance for obtaining up-to-date, accessible information on the coverage, benefits, risks and impact of vaccines. Readily accessible information might help to build and maintain public trust in vaccines and facilitate informed decision-making for the regulation of vaccines, immunisation policies and vaccination of individuals. ADVANCE focuses on the secondary use of available, existing EU healthcare data, which could provide real-world evidence on vaccine benefit-risk to inform on the best use of vaccines. The ADVANCE consortium comprises key public and private vaccine stakeholders in Europe including the ECDC and EMA, with 47 full and associate partners in multiple domains (16 academic/public research institutions, 3 small medium enterprises (SMEs), 2 charities, 10 public health organisations, 9 medicines regulatory authorities, 7 vaccine manufacturers) (see appendix).

3. The needs of different European vaccine stakeholders

A needs assessment was conducted within the ADVANCE project as well as during a face-to-face broader stakeholder forum that was organised by the EMA at the beginning of the

project. The various stakeholders have some common, shared, multiple needs. The identified common needs include

- Up-to-date, valid and easily accessible information for decision-making by regulatory authorities, PHIs, vaccine manufacturers (marketing authorisation holders: MAHs), healthcare professionals and consumers
- Detailed insight into available electronic healthcare data sources throughout Europe, their content, accessibility and whether they are suitable for vaccination coverage, benefit and risk studies
- Established and validated methods to assess vaccination coverage, benefits and risks in available electronic healthcare databases
- Transparency about the roles, responsibilities and contributions of all stakeholders
- Effective scientific and communication methods to address public concerns about vaccination benefits and risks to maintain public trust in vaccination programmes.

The challenges for generating such information across EU member states are numerous, including governance models for public-private collaborations, code of conduct for collaborative studies, the various coding systems and language used in the different data sources and the diverse implementation of European directives and regulations regarding re-use of health data. Stakeholders with specific EU-wide responsibilities for vaccine coverage, benefit and risk monitoring face also many challenges when using real-world data from electronic healthcare databases. These challenges include trust in the quality of the data and the interpretation, the speed at which evidence can be made available and the methods for pooling evidence, which all require close attention, particularly when evidence is combined from several sources [31].

To provide insight into the background of specific needs we describe the perspectives of the regulatory authorities, public health institutes and vaccine manufacturers, each of which may

need to consider an EU perspective when making decisions on licensing, vaccine programmes and risk management.

3.1 Regulatory agency perspective

The EU medicines regulatory network is responsible for the protection of the public by authorising safe and effective vaccines and by continuously monitoring their post-marketing benefits and risks [32]. Spontaneous reporting of suspected adverse reactions by healthcare professionals and the public is at the core of this post-marketing monitoring. From 2012 to 2017, 175,184 reports (5.5% of all reports) to EudraVigilance reviewed by a national regulatory agency in an EU member state or the EMA were vaccine-related individual case reports. Confirmed signals of potential safety issues detected through this system undergo rigorous scientific evaluation of all available evidence [33]. Real-world evidence on the use, benefits and risks of vaccines during the entire life-cycle of the vaccine is needed to assess these signals. To assess safety signals quickly, regulatory authorities and vaccine manufacturers compare observed versus expected numbers of cases of adverse events [34]. This analysis requires near-real-time exposure data, appropriately stratified background incidence rates of specific adverse events (to calculate the expected number of cases) and sensitivity analyses around these measures. However these observed/expected analyses are frequently affected by uncertainties regarding the numbers of vaccinated individuals and age-specific background incidence rates [35]. The availability of such population data and quick access to it are often issues, particularly in situations where regulatory authorities need evidence quickly, as in the case of rapid employment of mass vaccination [36].

Regulator authorities can require vaccine manufacturers to conduct a post-authorisation safety study (PASS) to investigate a safety concern, or to agree with the company that a PASS will be included in the product's risk management plan. Secondary use of routinely-collected data in electronic healthcare databases is frequent in such studies because these data are already

available for transformation into evidence, thus making evidence available faster than collecting primary data, especially if a large study population is needed. The framework developed by ADVANCE may, therefore, become an essential component of vaccine benefit-risk monitoring for regulators by enabling access to and supporting the analysis of an extensive range of multi-national real-world data from various data sources to create and monitor evidence on vaccine coverage, benefits and risks, which may facilitate regulatory decision-making during the entire product life-cycle. Access to and use of relevant sources of information for the EU regulatory network could be supported by ADVANCE through:

- Identification and characterisation of relevant electronic healthcare data sources, and harmonisation of their output formats, when possible
- Use of validated and transparent methods to interpret, analyse and, where appropriate, integrate evidence from heterogeneous sets of underlying data
- Clear communication about vaccine risks, safety and uncertainties
- Use of best epidemiological and data management practices (e.g. double programming, blinding of case evaluation as appropriate, quality control, auditable system)
- Robust governance, including mechanisms for collaboration between stakeholders and across borders
- Sustainable funding mechanisms.

3.2 Public health institution perspective

As stated above, vaccination is the most effective and cost-effective public health intervention for the prevention of infectious disease [2]. PHIs are key organisations responsible for epidemiological surveillance and control of vaccine-preventable diseases, and for providing advice and guidance about the use of vaccines in national immunisation programmes. Comprehensive, real-world evidence of vaccine effectiveness and impact (post-marketing) at

the EU level could result in more effective control of vaccine-preventable diseases. Access to larger sample sizes than in national or sub-national studies and the ability to compare the impact of different vaccination schedules and recommendations are some examples of the added-value of using the available healthcare data sources in Europe for evidence generation. During the early phases of the ADVANCE project, participating PHIs defined the following success measures, reflecting their needs and perspectives:

- Faster and trustworthy analyses on coverage, benefits, risks and benefit-risk in Europe
- Analyses performed in an integrated and harmonised framework rather than separately by different research groups
- 'Validation' of the system through publications in peer-reviewed journals
- A common validated approach to analyse vaccine benefits and risks that is widely accepted as reliable
- Stimulation of European countries that have a lower capacity to perform vaccine benefit-risk evaluations to improve their capacity
- A description of such a sustainable system.

3.3 Vaccine manufacturer (marketing authorisation holders) perspective

Vaccine marketing authorisation holders (MAHs) have legal obligations to monitor the benefits, safety and benefit-risk profiles of their licensed vaccines, throughout their life cycle. As the vaccine moves from the pre-marketing to post-marketing period and as years of experience with its use accrue, the types of activities required evolve. During early vaccine development, MAHs can conduct studies to understand the background epidemiology of the disease in the targeted population. They can also estimate the expected background incidence rates of some anticipated adverse events to be able to evaluate if the rates of these events observed during the clinical programme and, ultimately in the post-marketing period, exceed the expected rates. MAHs are obliged to monitor the safety of their products during the post-

marketing period and submit reports of suspected adverse reactions concerning their products licensed in Europe to EudraVigilance. Additional studies, beyond regular resources (e.g., the placebo group from a trial, surveillance of benefits, spontaneous reporting of suspected adverse reactions) may be necessary in case of concerns at or after licensing. These may be voluntary or required and may be conducted to study potential risks and effectiveness of the products as part of the pharmacovigilance risk management plan that is approved by the EMA at licensure and is periodically updated during the product life cycle. The feasibility of these studies is directly dependent on the availability of data and access to persons who can transform these data into the required evidence in a timely manner. The expectations of MAHs are that, with the quality-assured and tested ADVANCE system, companies will more easily be able to use data and experts to provide evidence, which would otherwise not be accessible. The ultimate goal is to ensure timely provision of evidence on brand-specific vaccine coverage and utilisation data, background incidence rates of events of interest to support evaluations of safety issues, and if needed national or multi-country vaccine effectiveness and safety studies.

4. Conclusions

Based on the lessons learned from the 2009 influenza pandemic, the needs expressed by stakeholders and their common goal to improve the continuous and rapid monitoring of the benefits and risks of vaccines, the ADVANCE project has brought together European vaccine stakeholders to design, implement and evaluate the environment, workflows and systems to generate actionable evidence on vaccine coverage, benefits and risks within our public-private collaborative framework. All stakeholders share needs for valid evidence and they can provide unique expertise and play an important role in the process of evidence generation. Although evidence on benefits and risks is not, by itself, enough to build trust when safety concerns arise, the absence of evidence and answers may generate mistrust, and lack of

328 scientific evidence on benefits and risks was listed most frequently as a reasons for hesitancy
329 in the WHO/UNICEF investigation [12]. The rapid availability of such evidence will
330 therefore ultimately serve society as a whole.
331 To date, the ADVANCE consortium has addressed a number of the stakeholders' expressed
332 needs and delivered tools, methods and best practice guidance [37, 38] (www.advance-
333 vaccines.eu). The papers in this supplement describe the ADVANCE system components for
334 evidence generation from real world health data, their evaluation in proof of concept studies
335 and the lessons learned from these different studies [references to other papers in supplement
336 to be added].
337

Disclaimer statement

The views expressed in this article are the personal views of the authors and should not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organisations with which the authors are affiliated.

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Declaration of potential conflicts of interest

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Miriam Sturkenboom declared that she has received grants from Novartis, CDC and Bill & Melinda Gates Foundation for work unrelated to the work presented here.

Antonella Chiucchiuini declared that she received personal fees from Takeda Pharmaceuticals International AG during the study.

Alena Khromava and Laurence Torcel-Pagnon declared that they are employed by Sanofi Pasteur and hold company shares/stock options.

Heidi J Larson declared that her research group has received funding from Merck to convene a research symposium, and research funding from GSK for a global study on maternal vaccine acceptance.

Simon de Lusignan declared he has university-based research (enhanced surveillance of influneza vaccines) funded by GSK, he is also a member of Seqirus and Sanofi Pasteur Advisory Boards for influenza.

Lina Titievsky declared that she is employed by Pfizer and holds company stocks/shares.

Vincent Bauchau declared that he is employed by GSK Vaccines and holds restricted company shares.

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Figure captions

Figure 1: Summary of vaccine introduction against more than 20 infectious diseases since 1798 up to 2016 (from WHO [3])

Appendix 1: Organisations and persons actively involved in the ADVANCE consortium

ADVANCE Full partners

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios (www.aemps.es)

ARS-Toscana: Agenzia regionale di sanità della Toscana (https://www.ars.toscana.it/it/)

ASLCR: Azienda Sanitaria Locale della Provincia di Cremona (www.aslcremona.it)

AUH: Aarhus Universitetshospital (kea.au.dk/en/home)

ECDC: European Centre of Disease Prevention and Control (www.ecdc.europa.eu)

EMA: European Medicines Agency (www.ema.europa.eu)

EMC: Erasmus Universitair Medisch Centrum Rotterdam (www.erasmusmc.nl)

GSK: GlaxoSmithKline Biologicals (www.gsk.com)

IDIAP: Jordi Gol Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (http://www.idiapjordigol.com)

JANSSEN: Janssen Vaccines - Prevention B.V. (http://www.janssen.com/infectious-diseases-and-vaccines/crucell)

KI: Karolinska Institutet (ki.se/meb)

LSHTM: London School of Hygiene & Tropical Medicine (www.lshtm.ac.uk)

MHRA: Medicines and Healthcare products Regulatory Agency (www.mhra.gov.uk/)

MSD: Merck Sharp & Dohme Corp. (www.merck.com)

NOVARTIS: Novartis Pharma AG (www.novartisvaccines.com)

OU: The Open University (www.open.ac.uk)

P95: P95 (www.p-95.com)

PEDIANET: Società Servizi Telematici SRL (www.pedianet.it)

PFIZER: Pfizer Limited (www.pfizer.co.uk)

RCGP: Royal College of General Practitioners (www.rcgp.org.uk)

RIVM: Rijksinstituut voor Volksgezondheid en Milieu (www.rivm.nl)

SCIENSANO: Sciensano (https://www.sciensano.be)

SP: Sanofi Pasteur (www.sanofipasteur.com)

SSI: Statens Serum Institut (www.ssi.dk)

SURREY: The University of Surrey (www.surrey.ac.uk)

SYNAPSE: Synapse Research Management Partners, S.L. (www.synapse-managers.com)

TAKEDA: Takeda Pharmaceuticals International GmbH (www.tpi.takeda.com)

UNIBAS-UKBB: Universitaet Basel – Children's Hospital Basel (www.unibas.ch)

UTA: Tampereen Yliopisto (www.uta.fi)

ADVANCE Associate partners

AIFA: Italian Medicines Agency (www.agenziafarmaco.it)

ANSM: French National Agency for Medicines and Health Products Safety (ansm.sante.fr)

BCF: Brighton Collaboration Foundation (brightoncollaboration.org)

EOF: Helenic Medicines Agency, National Organisation for Medicines (www.eof.gr)

FISABIO: Foundation for the Promotion of Health and Biomedical Research

(www.fisabio.es)

HCDCP: Hellenic Centre for Disease Control and Prevention (www.keelpno.gr)

ICL: Imperial College London (www.imperial.ac.uk)

IMB/HPRA: Irish Medicines Board (www.hpra.ie)

IRD: Institut de Recherche et Développement (www.ird.fr)

NCE: National Center for Epidemiology (www.oek.hu)

NSPH: Hellenic National School of Public Health (www.nsph.gr)

PHE: Public Health England (www.gov.uk/government/organisations/public-health-england)

THL: National Institute for Health and Welfare (www.thl.fi)

UMCU: Universitair Medisch Centrum Utrecht (www.umcu.nl)

UOA: University of Athens (www.uoa.gr)

UNIME: University of Messina (www.unime.it)

Vaccine.Grid: Vaccine.Grid (http://www.vaccinegrid.org/)

VVKT: State Medicines Control Agency (www.vvkt.lt)

WUM: Polish Medicines Agency - Warszawski Uniwersytet Medyczny (https://wld.wum.edu.pl/)

Figure 1

< 1899	1900-1950	1950-1979	1980-1999	2000 ->
		1955 Polio (IPV)		
		1962 Polio (OPV)		
		1963 Measles		
		1967 Mumps		
	1923 Diphteria	1969 Meningitis		
	1923 Tuberculosis	1970 Rubella	1981 Hepatitis B	
1798 Small pox	1924 Tetanus	1969 Meningitis	1986 Meningitis B	
1885 Cholera	1926 Pertussis	1970 Rubella	1988 Jap. Encephalitis	
1885 Rabies	1927 Tetanus	1972 H. Influenzae	1989 Hepatitis A	2000 Pneumococcal conjugate
1891 Anthrax	1935 Yellow fever	1976 Viral Influenzae	1995 Varicella Zoster	2006 Human Papillomavirus
1896 Typhoid	1937 Tick borne encephalitis	1976 Pneumococcal polysaccharide	1998 Rotavirus	2011 Hepatitis E
1897 Plague	1943 Typhus	1977 Meningitis C polysaccharide	1999 Meningitis C (conjugate)	2016 Dengue