ECDC Management Board

Thirty-second Meeting

Stockholm, 18-19 November 2014

Continuation of the Working Group on New Business Models and Financing of Large-scale EU Level Activities

Document: MB32/12	Date: 30 October 2014
Summary:	In June 2012 a discussion was initiated in the MB about the ECDC Vision on EU level monitoring and evaluation of immunisation programmes and related vaccines (doc MB25/11) in relation to ECDC's capacity to continue funding of all related projects (sustainability). Further to this first discussion the MB agreed to establish a small working group consisting of the European Commission, ECDC, EMA and Member States to discuss the funding options for an improved post authorization monitoring of vaccines and their use in the EU. The final composition of the WG was France (chair), Finland, Germany, the Netherlands, and Spain. EMA and ECDC participated in the meetings as appropriate, and the EC provided requested information during a separate meeting. The WG report provides an overview of issues that should be considered to *facilitate a common understanding at the MB* level (and beyond) : - The respective role of different stakeholders in the evaluation of vaccines and immunization programme effects in the post authorization phase; - The need for data on vaccine effects by different stakeholders as well as benefits and barriers to their collaboration; - Potential funding mechanisms for large-scale studies in the post authorization phase in the EU, including public, private and public-private funding sources (with the respective partnerships). ***Based on this report, The WG would welcome a discussion on the different issues identified, and the opinion of the MB on the level of involvement of ECDC related to the coordination and funding of studies on immunisation as this what triggered the establishment of the WG.***

	The WG would welcome comments from the MB prior to finalising the report. A decision on the future of the WG, and way forward has to be made.
Action:	For decision.
Background:	Document MB25/11 - ECDC Vision on EU level monitoring and evaluation of immunisation programmes and related vaccines Document MB26/12 Rev.2 - ECDC vision on EU-level monitoring and evaluation of immunisation programmes and related vaccines Document MB27/15 - ECDC and WP7 in a full project proposal to develop a Blueprint for EU level monitoring of vaccine benefit/risk (ADVANCE/IMI 7th call) Document MB27/14 - Proposal: ECDC Management Board Working Group on new business models and financing on large-scale EU level actions for which ECDC budget is insufficient Document MB WGNBM1/2 Redrafted proposal: ECDC Management Board Working Group on New Business Models and Financing on Large-scale EU Level Activities (Terms of Reference) Meetings of the Working Group

Report of the MB WG on « New Business Models and Financing on Large-scale EU Level Activities »

Draft report (28 October 2014)

1. Background and rationale for the setting-up of the WG

In June 2012, a discussion was initiated in the MB about the ECDC Vision on EU level monitoring and evaluation of immunization programmes and related vaccines (doc MB25/11). The topic was brought up as related to the capacity of ECDC to continue funding of projects related to vaccine effectiveness as there were other competing priorities and needs within ECDC's mandate (doc MB25/11). In this first discussion several issues were raised:

- respective roles of EMA and ECDC with regards to vaccines and immunization, including the funding of projects related to effects of vaccines in the post authorization phase, particularly vaccine effectiveness.
- new pharmacovigilance legislation (effective in July 2012), a legal analysis of the new pharmacovigilance legislation was requested by the MB. Indeed a clear analysis with regards:
    - to the possibility to collect fees
    - to the requests by EMA to include more post marketing safety and effectiveness studies in the risk management plans (RMP)
    - conflict of interest (actual, perceived, direct or indirect) with vaccine Industry leading to co-production of the study design, co-production of results and therefore to a lack or a perceived lack of independence
- funding sources with a focus on IMI[1]-funded projects.

Further to this first discussion the MB agreed to establish a small working group consisting of the European Commission, ECDC, EMA and Member States to discuss the funding options for an improved post authorization monitoring of vaccines and there use in the EU.

In fall 2012 a debate emerged in some MS about the possibility for ECDC and some NPHIs to be involved in IMI-funded projects. This debate occurred at a time where some National Public Health Institutes (NPHIs) and ECDC were considering joining a consortium under the 3rd Call of IMI related to vaccination. Questions arose among the participants about the role of public health in such projects, intellectual property rights, partnership agreement leading some NPHIs to withdraw their participation.

After a lengthy debate in the MB related to the understanding of the IMI governance, funding principles and selection process, the MB requested a clear and concise document, a written analysis on the possible risks and conflict of interests. The Board requested a WG to be established to support ECDC in identifying alternative sources of funding.

In March 2013 (MB27), the issue of ECDC participation in the ADVANCE full proposal was discussed in the MB (ADVANCE was the proposal selected under the IMI call after the 1rst step of selection. ADVANCE aims at developing a blueprint for EU level monitoring of vaccine benefit/risks. Based on the previous discussion related to independence and transparency, ECDC was willing to lead one WP (*WP7"implementability analysis"*[2]) knowing that ECDC would be the exclusive leader of this WP, industry will not be involved in this

[1] Innovative Medecines Initiative (http://www.imi.europa.eu/)

[2] WP 7-'Implementability analysis' – two objectives:

WP[3], ECDC would review the outputs of the other WPs, would be quite independent from the rest of the project given the foreseen modalities of governance. Based on the explanation given by ECDC, the MB approved the participation of ECDC in the ADVANCE project under the conditions presented to the MB.

With regards to the WG, the Commission expressed its concerns about a WG whose mandate is to seeking additional sources of funding for such projects. The Commission would rather explore this issue on a case by case basis even though it is opened to explore different options. At that meeting it was agreed to update the mandate of the WG and discuss it in June 2013.

In June 2013, the membership of the WG was approved (Finland, France, Spain, Germany and the Netherlands). The Commission agreed to support the WG if need be while not participating to the WG.

2. Mandate and scope of the WG

2.1 Agreed scope and aim of the WG

Given the changing environment in which the WG was set up, there were in the first and second meeting discussions about workable terms of references for the group. Finally it was agreed that:

- Even though the WG is entitled "New Business Model and Financing on large-scale EU-level activities", its scope will be limited to vaccines and immunization programmes, and will focus on post-marketing monitoring of vaccine safety and vaccine effectiveness (as suggested in the redrafted proposal MB WGNBM1/2 as of 24 May 2013). Questions were raised in the MB about including other health products such as antibiotics. It was clear for the WG that what makes the difference between vaccines and other health products is that vaccines can be included in national immunization programmes which are funded by public money. It was felt also that a wider scope would not be workable by the WG.
- With regards to identifying sources of funding, the WG decided to consider all options foreseeable (i.e. public, private and public-private partnerships) and will consider by which means sustainability can be achieved.
- The WG worked in parallel and independently from other initiatives such as ADVANCE project. Indeed, ADVANCE will last for 5 years and the relevant output of ADVANCE deliverables (e.g. code of conduct of collaboration and data sharing between public and private entities) is expected to be delivered not before 2018 (see annex 4).
- There was a need for clarifying regulatory needs and public health needs (or non-regulatory needs). With regards to the public health needs, it was felt that they should be addressed in a more systematic way at an EU level and there should be an increased awareness of those needs by ECDC well beyond the MB.

a. To assess the 'implementability' of solutions proposed by other Work Packages. "Implementability" is defined in the context of this project as real life *feasibility* of solutions proposed as part of the Blueprint and the framework for EU-level vaccine benefit /risk assessment and their *usefulness* in terms of meeting the requirements of various stakeholders / potential users included in Implementability Advisory Board (IAB);

b. To develop a blueprint of a framework for an integrated benefit-risk assessment system in the EU.

[3] Nevertheless Industry is involved in the review panels set up by ECDC

- From inception, the WG highlighted that transparency and independence from (commercial and other) interests are key issues and should be considered in prioritization of studies to be carried out at the EU level and in any of the proposed funding options.
- It was agreed that the WG will aim at bringing all MB members at the same level of understanding of the issue to avoid ambiguity and misunderstanding in view of further discussion within the MB, in particular when it comes to discuss the involvement of ECDC in immunization studies and use of its annual budget and if the MB is consulted on the ECDC/EMA joint EU vision on immunization which is under preparation.
- To summarize the mandate of the WG is to work towards a common understanding within the MB (and beyond) on items listed below and to provide an overview of :
    - The respective role of different stakeholders ECDC, EMA, NPHIs, National Regulatory Agencies (NRAs), and Vaccine Manufacturers in respect to the evaluation of vaccines and immunization programme effects in the post authorization phase.
    - The need for data on vaccine effects by different stakeholders (ECDC, EMA, vaccines manufactures, National Regulatory Agencies and NPHIs) as well as the benefits and barriers to their collaboration.
    - Potential funding mechanisms for large-scale studies on vaccine effects in the post authorization phase in the EU, including public, private and public-private funding sources (with the respective partnerships).

2.2 Changing environment between 2012 and 2014

The WG believes that it is important to put here into perspectives some of the events or decisions taken by ECDC over the past 2 years relevant to this topic, to illustrate the constantly changing environment. The WG members are fully aware that ECDC cannot postpone such important decisions until the WG submits its final report to the MB, but a lack in transparency resulted in some difficulties of the WG to react on the changing environment and created the risk of duplicating efforts. The WG worked independently of any other initiatives taken by ECDC on this topic.

At ECDC level

- Decision by ECDC to stop the funding of I-Move because of other priorities (2013 budget), several MS requested the continuation of these activities (seeMB25/11).
- Approval of the MB with regards to the participation of ECDC as a partner in the ADVANCE consortium (an–IMI-funded project (in2013) provided some guarantee that ECDC will not let its independence jeopardized and find an appropriate role and position within the consortium.
- Preparation of a joint EMA/ECDC paper on an EU vision on vaccines and immunization programmes, the draft was meant to be shared with the WG when agreed by the two agencies (see WG minutes of the first meeting, audioconference held 12 Oct 2013). However, a short version of this vision paper was briefly introduced to the WG by ECDC not before the end of the last WG meeting (12 June 2014).
- In spite of the approval of the MB to stop the funding of I-Move, a call for tender was launched by ECDC in March 2014 (deadline April 2004) for 2-4 years for the monitoring of vaccine effectiveness during seasonal and pandemic influenza in EU/EEA.
  http://ecdc.europa.eu/en/aboutus/calls/_layouts/forms/Call_DispForm.aspx?List=02511b7b-3a16-4c4b-9304-54cfc08a1647&ID=688.
  This tender was not awarded in the first instances and was re-launched in July 2014 (deadline 2 Sept 2014):

http://www.ecdc.europa.eu/en/aboutus/calls/_layouts/forms/Call_DispForm.aspx?List=02511b7b-3a16-4c4b-9304-54cfc08a1647&ID=707

- A new call for tender for a framework service contract was launched in June 2014 with deadline on 6 October 2014 for setting up a sentinel system to assess the burden of whooping cough in EU/EEA. This tender includes the effectiveness of the pertussis vaccine in infants younger than 1 year of age (two reports on vaccine effectiveness among the deliverables).

At the Health Council level (Summer 2014)

During the summer 2014, the Health Working Party started drafting the Council conclusions on immunization which are to be approved formally in December 2014.

At the Commission level (September 2014)

In the Juncker Commission, responsibility over Pharmaceuticals and EMA is expected to be transferred from DG SANCO to DG ENTERPRISE: http://ec.europa.eu/about/juncker-commission/docs/annex-portfolios_en.pdf

3. Scientific background and immunization-related definitions

Vaccines can have different effects, both at individual and at population level.

At individual level the direct protective effect of a vaccine can be measured in randomized controlled trials (RCTs), which is the protective effect under idealized conditions (so-called "**vaccine efficacy**"). Data from such trials are required for the market authorization of a vaccine product by a Regulatory Agency. The protective effect of a vaccine measured in the post-authorization phase under ordinary conditions of a public health programme is called **vaccine effectiveness (VE),** which is usually assessed in observational studies but may also be measured e.g. through cluster community randomized trials that estimate also in a randomized-controlled fashion indirect effects (also called herd protection). If more than one vaccine product targeting the same disease is available on the market, it is often a challenge to obtain exact and sufficient product-specific data to calculate product-specific VE in observational studies. Therefore, often only the combined VE of all vaccines on the market targeting a specific disease is assessed in observational studies (so-call antigen-specific VE, e.g. VE of influenza vaccination in a population). Alternatively and if data allow, VE can be also calculated for a specific vaccine type (e.g. adjuvanted or non-adjuvanted influenza vaccines), or for a specific vaccine product, especially in countries or regions where only one product at that moment is exclusively used in a national immunization programme. Most often, both in pre-authorization RCTs and post-authorization effectiveness studies VE is assessed against either a placebo or no vaccination. However, in RCTs also a different vaccine product targeting the same disease can be used (so-called "head-to-head" studies) to calculate **comparative (or relative) vaccine efficacy**. If more than one vaccine product targeting the same disease is on the market, also in observational studies the comparative vaccine effectiveness can be calculated.

At population level, **impact studies** can estimate the **effect or the overall effectiveness[4] of a vaccination programme**, which depends on the epidemiology of the disease (burden of the disease), the nature of the

[4] Overall effectiveness of vaccination programme can also be called impact or effect of the vaccination programme.

vaccine, the vaccination strategy chosen, the achieved vaccination coverage and the direct and indirect VE (so called herd protection). A typical study design that assesses the impact of vaccination is the so-called before-and-after study, where the disease incidence is compared before and after introduction of a vaccine. Such a measure is a good indicator for the overall impact and success of a vaccination programme on public health.

Undesired outcomes at individual level (i.e. **vaccine safety**) are assessed in RCTs before market authorization. Very rare adverse events such as narcolepsy following the large-scale use of A/H1N1 pandemic vaccine, however, can often be assessed only in observational studies in the post authorization phase when the vaccine has been widely used. Undesired effects can potentially occur also at population-level, such as serotype replacement or -if a programme targets young children- shift of age at infection towards older age-groups. Such population level effects can usually not be assessed in pre authorization RCTs since they require a considerable vaccine uptake in a large population and a longer time horizon, but will influence the impact of a vaccination programme.

4. Important issues to consider when discussing the involvement of ECDC in post authorization studies at the EU level, vaccine effectiveness studies and impact of immunization programmes

4.1 Why are large-scale EU-level studies needed? What is the added value of EU-level collaboration and data synthesis?

As indicated in the column "EU level public health need" of Table 1, the collection of post-authorization data is often not only of high interest to the respective country that broadly uses the vaccine, but generation of such data have an added value also at EU-level in Public Health. Context-specific aspects such as vaccine uptake *per se* are usually of limited interest for other countries. However, data on the impact of vaccination on the disease epidemiology, particularly when they can be generated early, are of more interest to other countries. For instance, there is a clear added value of comparing, for a given vaccine, the impact of various modalities of implementation in terms of target population chosen and level of coverage reached. This allows documenting the relationship between the proportion of the population immunized and the level of induction of herd protection. Context-free aspects such as vaccine effectiveness and safety are even more relevant as expected to be largely similar in EU countries.

The added value of jointly conducting research on these context-free aspects of vaccine effects and to some extent on population vaccine impact is to strengthen policy/initiatives with regards to immunization at EU and national level by providing stronger scientific evidence on vaccines and immunization programmes once used at the population level.

In particular, EU level studies allow:

- to increase public trust in immunization programmes by providing high quality data free of conflict of interest issues
- to avoid duplication of efforts and thereby unwise spending of (public) money and maintaining current public structures and expertise working on these reporting systems;
- to collect post-authorization data in early adopter countries (i.e. countries that decided to introduce a vaccine soon after it became available on the market) / countries with sufficient vaccine uptake to inform decision-making in other countries that have not yet introduced the respective vaccine;

- to increase sample size (e.g. for rare adverse events or product-specific VE) that allows obtaining robust data;
- to explore potential variability of effects on a wider geographic scale ;
- to improve efficiency: a well-designed, EU-wide coordinated and funded study is more effective than several studies with heterogeneous methods and limited sample size and therefore more efficient .

A side effect of the EU level studies is to strengthen expertise and and/or infrastructure when it is suboptimal at country level.

4.2 To which extent post authorization studies at the EU level i.e. vaccine effectiveness studies and impact of immunization programmes fall within the mandate of ECDC?

The ECDC Founding regulation set the boundaries of action for ECDC and limits its action to foster the exchange of best practices and experience with regard to vaccination programmes (see *Annex 2*) and to the coordination of data collection, validation, data collection, validation, analysis and dissemination of data at Community level, including on vaccination strategies (article 11).

In the MB 25/11 document, the role of the Centre was defined by ECDC and projects funded were justified as follows:

- Regarding immunization programmes in the EU is, for the interest of public health, to pay attention to the credibility of the national vaccination programmes and their possible impact on the confidence of the general public in immunization.
- Based on its mandate ECDC collects and disseminate data on infectious diseases under EU surveillance including on vaccination strategies, provide scientific guidance to member states and if knowledge gaps are identified perform epidemiological studies to bring those gaps. ECDC's role therefore encompasses enhancement of surveillance activities in the field of VPD and Influenza and coordination of relevant activities that cannot be performed by individual MS. This provides data for informing vaccination strategy development and implementation at MS level.
- According to its role and mandate ECDC has started specific projects further developing immunization registers in the MS, monitoring of vaccine coverage and effectiveness of influenza and of vaccine impact of pneumococcus, epidemiological investigation of possible vaccine safety signals and enhanced surveillance (see annex 3)

By funding the vaccine effectiveness projects, ECDC filled a gap, which was proven to be very useful in particular with regards to a better knowledge on the variability of the influenza vaccine effectiveness (I-MOVE) from one year to another. .

4.3 To which extent the pharmaceutical legislation addresses the issue of vaccine effectiveness and impact of immunization programme – see annex 5 (contribution from EMA)

Vaccine effectiveness studies are discussed more frequently nowadays since the new pharmacovigilance legislation strengthens the role of EU regulators on post-authorization measures

Beforehand vaccine effectiveness was not that much in the scope of NRAs which are mainly involved in pharmacovigilance and granting market authorization.

Regarding new vaccines, EMA/NRAs request in principle vaccine efficacy studies for market authorization. If a similar vaccine is already authorized or the target disease is very rare (which would

require e.g. for meningococcal vaccines several 100,000 participants in one RCT), immunogenicity studies may be sufficient, especially if a valid correlate of protection has been defined for the disease in question.

With regards to immunogenicity studies, a major change was recently introduced by EMA with the influenza vaccines due to the seasonality and to the low predictive value of the immunogenicity data with regards to changes in effectiveness. Annual immunogenicity data are no longer required from the market authorization holder but effectiveness data will have to be provided.

The market authorization holder is responsible for the implementation and the funding of such effectiveness studies (which are now part of the risk management plan). To conduct these studies, EMA encourages industry to work with public health experts and to develop joint projects. However, due to conflict of interest problems, not all public health experts or agencies can collaborate with industry. Unfortunately it does not seem to the WG that potential barriers to public-private collaborations and acceptable funding mechanisms were identified as an issue and discussed with the public health authorities prior to endorsing this new legislation.

4.4 What make vaccines different from other health products (e.g antibiotics, new cancer treatment)?

What makes vaccines different from other medicinal products and deserve special attention and funding for EU surveys – why effectiveness of vaccines should have more importance than the effectiveness of a very expensive cancer drug treatment for example?

Several reasons worth being highlighted:

- Vaccines are used in healthy people to prevent a disease that may occur in the future. To motivate people and improve vaccine uptake in a population, immunization is often implemented in publically funded programmes where the government or National Public Health institute are also responsible to conduct communication activities and justify the public investments.
- Vaccines are applied at a population level and many –if there is sufficient uptake- can also induce herd protection by which vulnerable (unvaccinated) population sub-groups can be indirectly protected (e.g. children too young to be vaccinated or immunocompromised patients). Therefore, the total effect of the immunization programme should also be assessed at the population level within the routine implementation of the immunization programme to assess its full range of public health benefit.
- In addition, recent experience with new vaccines has shown that vaccine effectiveness may be lower than estimated in RCTs or decrease over-time e.g. because of pathogen escape mechanism or waning immunity. In addition to the influenza vaccine, this has been particularly true for the pneumococcal vaccines and may be the case for the acellular whooping cough vaccine. Similar concern has been raised for the HPV vaccine.
- Immunization programmes are highly vulnerable to mistrust in the population and rumours. The 2009 pandemic has shown in multiple countries that suboptimal or lack of communication activities and lack of transparency in decision-making can lead to mistrust about public recommendations and low acceptance of a vaccines. Therefore, immunization policy decision-making should be communicated in a transparent way and should be based on solid evidence to maintain high acceptance toward immunization. Evidence about the risk and benefits, which is the basis of such decisions, should be generated by high quality studies in a transparent way and –if possible- independent from commercial and other interests

4.5 How vaccine effectiveness and comparative VE studies are considered in Health Technology Assessment?

HTA is an expert process which covers medical, social, economic, and ethical issues. It provides policy-makers with objective information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective.

Depending on countries and health systems, HTA scope covers the life phases of public health interventions (such as vaccination strategies): analysis of opportunity of implementation (mainly based on efficacy/effectiveness results and sometimes modelling tools), reviews of opportunity, once the vaccine is used in the population, in order to maintain or modify strategies that are more and more based on effectiveness or cost effectiveness

Some of HTA bodies have the ability to recommend post-marketing studies to anticipate further reviews. Vaccine effectiveness data use for HTA are (for example) necessary when;

- vaccine is widely used to reduce major public health threats with a cost benefit ratio that is under discussion,
- the vaccine is known as having a potential for changes in epidemiology or microbial ecology,
- there may be vaccine escape mechanism of the agent targeted by the vaccine,
- the vaccine strategy may interfere with other PH strategy such as screening.

HTA bodies are not working in all EU countries on immunization-related topics. In many countries such work is performed by National Immunization Technical Advisory Boards (NITAGs) or equivalent expert groups that advise Ministries of Health or National Public Health Institutes.

4.6. Do we need studies for all vaccines? Do we need to have them every year? for all MS? What could be the basic considerations for priority setting?

There is neither the need of studies for all vaccines nor to conduct such studies in all MS. Surveillance of the disease incidence before and after vaccine introduction, well-designed pharmacovigilance surveillance, and monitoring of the characteristics of the agent (done by the national reference centres) is the basic tool for Public Health Authorities to monitor the effects of immunization programmes in general. However, for specific agents/vaccines there is a need for specific research or may be a need to consider vaccine effectiveness study based on the results of surveillance observation or on biological/immunological grounds. This need is clear for influenza and for any new vaccine on the market for which such data are lacking (e.g. when a vaccine is licensed purely on immunogenicity data).

5. Analysis of data needs and responsibilities by the WG

5. 1 Role and responsibilities of different stakeholders at national and EU level

At national level, the role and responsibilities of stakeholders involved in the immunization programme, vaccine research and in registration approval can vary from country to country and depend to a great extent on the national public health system and the specific missions given to public health and/or regulatory bodies.

Different public health capacities (laboratories, surveillance) exist in MS to conduct or contribute to these EU Level studies. Public health capacities are of key importance to allow the MS to contribute to the EU level studies.

In almost all EU countries, National Immunization Technical Advisory Groups (NITAGs) provide advice to the Ministry of Health or the National Public Health Institute (NPHI) in respect to vaccine introduction decisions or immunization strategies. The NPHI or the national (sometimes regional) Health Authority is responsible for the implementation of vaccination strategies and the management of the immunization programmes. NPHIs are often involved in the following activities: communication with health professionals and the target public, monitoring of vaccine uptake, and for post-marketing research on vaccine effectiveness through observational studies and impact of the implemented strategy / programme to be able to adjust –if necessary– strategies and to justify the public health investment. Pharmacovigilance is conducted by the pharmaceutical industry that regularly provides the information to the national regulatory authorities according to the EU legislation, and may also by address by the NPHI according to the immunization programmes.

At national level other stakeholders might be involved in immunization policy-making or programme implementation, depending on the public health system in place: For example health insurance companies (if they pay for the vaccination) or professional societies. In respect to research activities related to vaccine effects, universities and other research institutions may play an important role. However, often they are either contracted by pharmaceutical industry or receive research grants from other entities, which make many of their activities not sustainable. Regulatory authorities (either National Regulatory Authorities (NRA) or EMA) have the main responsibility to grant market authorization to a vaccine product based on three main pillars: product safety, potency (incl. efficacy/immunogenicity) and quality (incl. approved manufacturing and quality control processes). Based on pharmacovigilance legislation, EMA/NRAs can request from the marketing authorization holders to provide respective data also after licensure of their product. These data requests form an important part of the risk management plans requested by the regulatory legislation. Thus regulatory authorities are focused on the vaccine effects in relation to a specific product. Safety and potency are relative, and usually there is no clear cut-off for authorization: The benefit must outweigh the risk. Therefore, several vaccine products with different profiles (e.g. effectiveness vs safety) can be approved/marketed targeting the same disease; so it remains in the responsibility of NITAGs/NPHIs to select the most efficient product for their national immunization programme and identify the population that benefits most and should be targeted by the programme.

The aim of the manufacturer is that regulatory authorities would grant the marketing authorization of their product, NITAGs recommend their product, their product to be included in a national programme/covered by health insurances, and that the vaccine uptake in the population to be high given the decision taken by the national health authorities.

5.2 Data needs by different stakeholders

Data on vaccine effects are generated before and after the marketing authorization of the product. Depending on their role and responsibility, stakeholders at national or at EU-level have different data needs in respect to post-approval vaccine effects. An overview of these different needs is given **in Table 1**. The level of interest in the data represents the view of this working group but not necessarily the view of the

respective stakeholder. A few examples of the different data needs and the reasons behind are provided here:

The main interest of NITAGs/NPHIs in post-authorization data relates to two aspects: (i) for vaccine introduction decision-making and the identification of the best vaccination strategy, and (ii) for monitoring the performance of the recommended strategy or programme. For vaccine introduction decisions data e.g. on vaccine efficacy/effectiveness and safety, cost-effectiveness, acceptance of the programme, as well as experiences from other countries on vaccine impact and undesired effects at population level are relevant. For monitoring, generation of data on the vaccine uptake in target-groups, vaccination impact in the own country and undesired effects at population level are crucial.

Since NPHIs are often responsible for or involved in the implementation of an immunization programme and also involved in communication activities, data on the vaccine uptake in vaccination target groups are crucial to inform and tailor their communication activities and to interpret the epidemiological impact of the programme. For industry such data are of interest to better promote their product and to regularly report to the national regulatory authorities in the periodic safety updated reports. Since vaccine uptake data are country/context specific, they are of some interest but in general of lower value at European level / for other countries.
Industry has no easy access to vaccine coverage date and in many cases when no specific study is performed, sales data are used to estimate vaccine coverage

Impact studies are of main interest to NPHIs to monitor the success of their implemented immunization programme or strategy at population level. Here the antigen-specific VE (direct and indirect) plays a key role, but if both impact and antigen-specific VE is acceptable, data on product-specific VE are less important for NPHIs. Even though the impact of a vaccination programme is dependent on several country-specific particularities (e.g. vaccine uptake, disease epidemiology) these data are of interest to other countries or at EU level (e.g. ECDC), specially for countries considering the introduction of the vaccine in their National Immunization Programmes, but not as important as to the NPHI that is responsible for the implemented programme.

Since regulatory authorities have the role to grant market authorization to a vaccine product, they are more interested in product-specific safety and VE but less interested in antigen-specific VE. The manufacturer is more interested in the safety and VE of its own product. If there are indications from antigen-specific VE studies that VE is impaired, this is of concern for regulatory authorities and industry, but based on antigen-specific VE data no regulatory decisions can be made. If different products with different product profiles are approved by NRA/EMA and available on the market, the NPHI and NITAG would be interested in direct comparisons of these products to be enabled to endorse a preferential recommendation or to consider these differences in cost-effectiveness analyses or for tender decisions to purchase vaccines. For a manufacturer, however, direct comparisons with other products (in so-called head-to-head studies) is more expensive and often not in its interest unless the manufacturer is very confident that this study demonstrates a superior effect of its product that would lead to their preferential use. For EMA such product comparative studies are not required by the regulatory legislation and so they are of low interest as long as both products have a positive benefit-risk-profile.

5.3 Differences in access to data needed by different stakeholders

Depending on the health system, political decisions and available financial resources, stakeholders have different access to various data sources to assess post-approval effects of vaccines after their broad use in a population. However, not always a stakeholder has access to all data that are useful for him in his role. Collaboration and data-sharing between stakeholders is sometimes complicated due to potential conflicts of interest and in the absence of a clear code of conduct that fits all stakeholders and complies with national practices and regulation. With the recent movement of regulatory authorities (EMA/NRAs) to request from industry more post-marketing VE data, this leads to a dilemma because of the different access to data and difficulties in collaboration between industry and public health.

The collection of case-based disease data is in the responsibility of NPHIs (usually through communicable disease reporting systems) and form the basis for Public Health decisions among others disease incidence calculations needed for vaccine impact studies or decisions to implement or adjust immunization strategies. However, these data can be also used for the ascertainment of cases for case-control-studies or the estimation of VE by applying the screening method or case-cohort method. Furthermore, NPHI are involved in outbreak investigations, which allows –depending on the setting– the conduct of retrospective cohort studies or case-control studies to assess VE. This is in of interest if the disease is otherwise rare (e.g. if the programme is in place for already quite some time). NRAs nor industry nor academia have usually immediate access to such investigations or use of the communicable disease reporting system. Finally, NPHI commonly also collect data on vaccine uptake in the total population or specific vaccination target groups.

Databases or national registries on medical causes of health care utilization, vaccination status of cases of diseases and laboratory investigations data can be linked in some countries and provide a unique opportunity to address questions related to **the impact or effect of vaccination programmes** but also to the effectiveness and safety of vaccines. Regarding the effectiveness of vaccines, usually new data have to be generated through vaccine effectiveness studies; this explains why vaccine effectiveness data are not routinely conducted.

NPHIs very often either own or have access to these databases (or other national authorities). However, not all questions can be addressed by these databases due to issues related to quality, completeness and timeliness of data as well as to safeguard and comply with data protection legislation.
Industry has the legal requirement to report post-approval data on the protective effect and safety of their product to the regulatory authorities (risk management plans), but very often they do not have access to these data sources and so have either to generate them themselves or request them from the NPHIs.
In order to fulfil the requirements of the risk management plans, industry may approach NPHIs or academic research teams to collect specific data which may require a specific project-base funding, NPHIs might then find themselves in a difficult situation to provide those data for the following reasons:

- in many European countries NPHIs cannot accept private funding or perform research for industry (to avoid real or perceived conflict of interests with industry),
- NPHIs do not have all the resources that are required to conduct all these relevant studies (in particular Vaccine effectiveness studies) and research,
- the data needs of the NPHIs and how timely the data are reported may differ from the needs of industry and regulatory authorities. Indeed, VPD surveillance data can be transmitted to industry only once there are made available by the NPHIs and in some cases once there are reported to the health authorities.

6. Possible funding sources for EU level activities for post-marketing studies of vaccination programmes.(see Table 2)

7. Key messages from the WG to the MB

In order to make progress in the area of post-authorization studies within the MB of ECDC and beyond, the WG has identified key issues

- Share the same language and definitions between all stakeholders involved in the regulatory and non-regulatory aspects of vaccines and immunization programmes, have a common understanding of the issues.

- Awareness about the public health needs (i.e. non-regulatory needs) in relation to post authorization data on vaccine effects should be raised among all stakeholders, including industry, EMA, ECDC, Commission, NRAs, NPHIs.

- Post-authorization studies include not only product-specific vaccine safety studies but also product-specific, antigen-specific and comparative vaccine effectiveness studies as well as impact studies of immunization programmes in connection with vaccine uptake data (including undesired population-level effects of vaccination)

- Important safety data on vaccines are only available after a wide use in the population (i.e. rare and very rare adverse event). Other important data that can be generated usually only in the post-authorization phase include effectiveness of vaccines targeting rare diseases (e.g. meningococcal vaccines, which are licensed only based on immunogenicity data), duration of vaccine protection, level of herd protection or effects on pathogen carriage (e.g. for meningococcal or pneumococcal vaccines), or undesired population-level effects such as serotype-replacement. Registration data include investigation of the safety and efficacy profile of the vaccine.

- It should be acknowledged that those who have the expertise on effectiveness measurement are usually not those involved in pharmacovigilance. In addition, data needs are very different for the measurement of effectiveness compared to pharmacoepidemiology.

- Independence from vaccine manufacturers and transparency are key to build public trust and for the credibility of the conclusions of the relevant studies. Guidelines to guarantee independence should be clearly established and transparent (priority setting for allocation of resources, study design and interpretation of results).

- EMA requests industry to conduct product-specific studies while many of the data requested are collected by National Public Health Institutes. A common guidance or code of conduct should be considered in respect to how these two players (industry and NPHIs) should exchange views and data.

- The respective roles of ECDC and EMA should be further clarified with regard to immunization.
  The role of ECDC should be acknowledged in particular for:
  - impact studies of immunization programmes through epidemiological surveillance and monitoring of vaccine coverage
  - studies to assess antigen- or vaccine-type specific effectiveness
  - the epidemiological investigation of signals identified by pharmacovigilance systems[5]

[5] This might need explanation between the WG and EMA

- Vaccine effectiveness studies and Impact studies of immunization programmes should be funded either through a public funding or through a publicly-controlled funding scheme to be independent of industry.

- It would be more appropriate if resources for post-marketing studies would come from a structural (not project-based) mechanism that would allow sufficient and continued funding, with an agreement between stakeholders on who sets the priorities.

  In view of this WG, public health entities should set the priorities to decide upon the use of the available funding to study vaccine effects included in publically-funded immunization programmes, no matter what type of financial contributions (public private) are agreed on. National governments and/or National Public Health Institutes are responsible for the decision-making if a vaccine is included in a national programme, for the communication on risk/benefits of vaccination to motivate the population to get vaccinated, and for justifying the investment of public money which also requires an evaluation of the decision/investment. Generally speaking, the new mechanism should be discussed between all relevant stakeholders including NRAs and NPHIs (which requires therefore a member state involvement).

8. Way forward

The WG considers that it is not in its role to go further than bringing all the members of the Management Board at the same level of understanding of the issues which triggered the establishment of the working group.

To allow a strategic discussion at the MB level on the role of ECDC and the use of its resources (FTE and €) in the immunization area a comprehensive information package should be made available containing:

- An in-depth analysis of relevant pieces of the pharmaceutical legislation as already requested by the MB
- A compilation of information on national priorities and above all on capacities in the MS to carry out the vaccine effectiveness and impact of immunization programmes. The WG is not in a capacity to gather this information (resources available in the MS use of these resources (incl. data bases and human resources, practices for data sharing and data access) but the network of the VPD National Focal Points and the AF should be able to provide this information to ECDC, .
- A set of priority criteria and a proposed mechanism to define studies/vaccines to be implemented each year (and funded) at the EU level
- An estimation of the level of funding needed yearly should be made available.

With regards to vaccine effectiveness studies, responsibilities between EMA and ECDC should be taking into account the different ways of looking at such studies (responsibilities cover assessment of data, coordination, funding…):

- On one side, vaccine effectiveness is a measurement of the frequency of vaccine failures, which can be considered as an AEFI and therefore falls under the mandate of NRAs/EMA. However, disease reporting data are often reported to National Public Health Institutes only and an additional reporting of breakthrough-cases to NRA would create duplication of reporting and extra workload for physicians and local public health offices (depending on the reporting structure in the country);

- On the other side, vaccine effectiveness is a strong determinant of the vaccination epidemiological impact which measurement, at EU level, falls under the umbrella of ECDC. In addition, data on the vaccination status of a diseased patient (defining a case as a vaccine failure if sufficiently vaccinated) are usually reported within national disease reporting systems to National Public Health Institutes and are also transmitted by many member states to Tessy.

This would be a matter of debate between the two agencies with their scientific advisers (VPD NFPs and AF for ECDC)

Relevant entities (Commission Services?) should carefully review the funding options and provide in due course a solid and transparent analysis leading to an outline of possible new funding mechanisms that could be set up at the EU level as this is beyond the capacities (resources and skills of this WG). The options should be discussed with all relevant stakeholders including member states.

ECDC should have a more clearly recognised role in the immunisation area in Europe, this could be achieved through an active participation in creating a coordinating mechanism and in the priority setting of public health data needs.

Given the information provided by the WG, the WG would welcome the opinion of the MB on the level of involvement of ECDC related to the coordination and funding of studies on immunisation.

The WG would welcome comments from the MB prior to finalising the report.

Table 1. Overview of data needs by different stakeholders in the EU

Vaccine effects	Public Health needs		Regulatory needs	Industry needs	Responsible for data collection**
	National level (NITAGs, NPHI)	**EU level**	**EMA / NRA**		
Vaccine effectiveness, VE*					**Manufacturer:**
a) Antigen-specific	**+++**	++	+	+	(tool: *specific studies*, often with academia)
b) Vaccine-type specific	**+++**	**+++**	++	++	**NPHI:**
c) Product-specific	++	++	**+++**	**+++**	(tool: e.g. reporting of breakthrough disease,
d) Comparative VE (head-to-head studies)	**+++**	**+++**	+	+	database analyses, *specific studies*)
Leadership : ECDC and EMA?					
Vaccination impact at population level					**NPHI:** (tool: population-based disease reporting, database analyses or sentinel surveillance)
a) overall VE of the immunization programme	**+++**	+++	+	+	
b) undesired effects (e.g. shift in age distribution, serotype replacement)	**+++**	+++	++	++	**NPHI:** (tool: population-based disease reporting, database analyses, molecular surveillance)
Leadership : ECDC?					
Product-specific vaccine safety	**+++**	**+++**	**+++**	**+++**	**NRA**, in some countries NPHI: (tool: national pharmacovigilance system, *specific studies*) **Manufacturer** (tool: *specific studies, database*)
Leadership : EMA?					
Vaccination coverage in the general population or specific target groups	**+++**	++	+	++	**NPHI:** (tool: national immunization register, other national monitoring systems or surveys)
Leadership : ECDC?					

- (+) of interest; (++) of high interest; (+++) of very high interest, crucial for decision-making
- NITAG=National Immunization Technical Advisory Group
- NRA=National Regulatory Authority
- NPHI=National Public Health Institute
- *VE=Vaccine effectiveness

- Antigen specific VE = effectiveness of vaccination against a specific pathogen (e.g. influenza)
- Vaccine-type specific VE = effectiveness of a specific vaccine type (e.g. adjuvanted influenza vaccine or live-attenuated influenza vaccine);
- Product specific VE = effectiveness of a specific vaccine product (e.g. trivalent inactivated influenza vaccine ABC® of company X).
- **Responsibility from the view of the WG to conduct these assessments; other players (e.g. academia) can also conduct these studie

Table 2: Possible funding sources for EU level activities for post-marketing studies of vaccination programmes.

Considering the possible options for funding, several aspects are important. In the table below, we try to value each funding option on the same aspects, resulting in a score of - -, -, +, or ++.

1. **Source of the funding**. Is the funding raised amongst public partners, i.e. the Member states or the European Commission, or are private partners involved? In the table below, the options are divided between public funded, private funded or a combination of the both.

2. **Amount of money** that can be raised by the chosen funding option. In the US, for similar activities, 30 M dollars are spent yearly, which indicate the magnitude of the funding which is required [6].
   Is the funding **option sustainable**? Funding options can vary between structural and project based. With structural funding, we mean a yearly continuous fund, even though the studies performed can be project-based. Structural funding might mean to clarify the roles of EU agencies (ECDC and EMA) and the Commission, their assignments, and funding responsibilities. Project-based funding can be realized within the existing or new funding mechanisms at the EU level for health research or public health. Clearly, funding is ideally structural, since it enables multiannual programming, and repetition of studies if needed. Project-based funding will lead to repeated discussion on the need for funding and will not ensure the sustainability

3. **Who determines** the agenda (studies and priority). EU and member states will want to determine the subject of the studies and the priority. In the priority setting for EU level studies, the added value above existing national studies, the need for new or repeated studies for the different vaccines, the fulfilment of both regulatory and public health needs should be considered.

4. If manufacturers are co-funders, they will want to influence on the topics and priority settings. Manufacturers that are already ensured of a large sales market, might not be willing to pay for comparative studies. This might restrict the freedom of the public health partners to choose the topics and priority.
   It is likely that manufacturers are only willing to pay for studies related to their own products. Within the WHO PIP framework, this was used for overall benefit of the manufacturers and the countries. Manufacturers of influenza vaccine are aware of the fact that many countries have insufficient capacities to counter a pandemic in an adequate way. Helping these countries to build their capacities, will lead to more countries with an adequate immunization programme, and hence enlargement of sales market. PIP stands for Pandemic Influenza Preparedness. During H1N1

[6] Could ECDC tell how much is spent by MS on this type of research?

pandemic there was a shortage on vaccine. Besides, many countries could not afford vaccine and antivirals. WHO coordinated a discussion in order to stimulate countries to prepare for a pandemic (capacity building) and stimulate industrial partners to contribute to the global immunization surveillance and response system.

5. Besides the actual influence that manufacturers will want on the topics and priority setting, co funding by private partners might lead to the **perception** that the performed studies are not independent and the results might by criticized. This can affect public trust on immunization programmes.

6. Finally the options are scored for their feasibility. Especially options that require new legislation of market authorization will not be very feasible, although they might score very positive on all other aspects.

Table 2. Possible funding sources for EU level activities for post-marketing studies of vaccination programmes.

		Funding Option	Size of funding available	Sustainability	Level of influence on priority setting	Independency/ perception of independence	feasibility	What should be clarified
Public	1 a	Initiative by the Commission Commission decides to install a fund with Member State + EU contributions Ear-marking some of the funding to the monitoring of vaccination	unknown	-- Supplies susceptible for cut down	++ Priority setting only by public partners (EC, member states or expert centres)	++ No influence for manufacturers	+ Depending on commitment of MS and or new commission	Who is coordinating body : ECDC Can amount of money raised fulfil our needs?
	1.b	Joint actions, agreement between the MS to set up a joint action within EU framework (health programme, horizon 2020) with EC contribution.	+-	-- not a sustainable funding as it is a project.	++ Purely public	++	++	

	2	Initiative by a MS or group of MS: Joint programme between MS (all or some), possibility for being out of the EU framework?	-- Various choices in member states Limited supplies available, competing interests between national and EU level	+- Uncertainty in funding.	+- Difficult to set agenda	++ Depending on national choices	++ Depending on commitment of MS, but no additional assignments needed	Who takes the initiative to establish a joint activity: MS or group of MS? Who should be in charge of the implementation of the studies? Which member states want to join? Request wider commitment at the Member States
Public Private								
	3a	Innovative Medicine Initiative/ EC (DG RTD) – Industry contribution compulsory	+- Reasonable	-- Temporarily	+-- No real priority setting by the health authorities (focus on innovation and research) dependent on	-- A project can exist only if there is an interest from industry. (independence) Codes of	++ Seems to correspond to recent programmes	

					the interest of industry - if no request from industry there is no project	conduct (independence, data ownership and access to data)		
	3b	Research project funded by Horizon 2020(DG RESEARCH) : no need to have industry on board, innovation and research very important so might not be relevant for the purpose.	Reasonable		No real priority setting by the health authorities	Codes of conduct (independence, data ownership and access to data)		
Private	4	Creating a fund						
	4a	Any kind of voluntary contributions from vaccine producers, commit a certain percentage of income/profit from per sold vaccine dose to an EU funds (see PIP)	++	+-	++ Lead through EC or ECDC possible	-- Manufacturer might demand influence on priorities and choices	-- It will be hard to convince manufacturers to contribute, no benefits for them	Is there support from private partners to contribute and will they accept a model with steering by public health partners
	4b	4a + Add a fee for public health needs to registration demands or	++	++	++	++	--	Is there support to add demands to legislation?

		a certain percentage of income/profit from per sold vaccine dose (see estimation of doses of vaccines sold) or other model. 10c/sold vaccines = enough for sustainability of studies. Compulsory.			Not all public needs can be added to registration demands?	Can be a public control fund.	It will be hard if not impossible to add new demands on the registration legislation. Support to new legislation difficult, might require public health to support manufacturers 'post marketing studies by sharing / providing data	How long will procedure to add demands take How many products are registered yearly and does this fill the fund up to the amount needed? Should we demand a fee for the yearly re-registration?
	4c	Yearly voluntary replenishment event to which governments and other potential stakeholders such as foundations are invited	+-	+- Uncertainties on amount of money raised	++	-- Vaccine Effectiveness does not appeal for sense of	?	

		with the aim of further mobilizing financial resources. (The replenishment mechanism of the Global Fund has proven to be successful and should be studied for potential replication				responsibility as it is for Global Health.		
Combi-nation of two or more of funding options 1-4		EU funding + compulsory contribution or fee or euros per sold doses. 50% 50%		++	++	+- (feasibility)		

ANNEXES

Annex 1: Members of the WG, meetings

Members: Finland (Taneli Puulainen), France (Anne-Catherine Viso), Germany (Ole Wichman); Spain (Karoline Fernandez de la Hoz and Inmaculada Navarro-Perez), The Netherlands (Marieke Mossink)

Chair of the WG: Anne-Catherine Viso.

The group felt that technical inputs were needed from EMA (written contribution) and from members of their respective organizations involved in VPD and immunization. The Group thanks them for their time and valuable inputs

WG Meetings

- 15 October 2013 (audio conference)
- 12 Nov 2013 (Stockholm) – Participation Marco Cavaleri (EMA)
- 26 March 2014 (Stockholm)
- 4 June 2014 (Brussels) – Participation of Marco Cavaleri (EMA)
- 12 September 2014 (Stockholm)
- Bilateral meeting with DG SANCO, 23 July 2014
- Bilateral meeting with DG RTD, 23 July 2014

Annex 2: ECDC Founding regulation

In the Founding regulation

In Whereas 8)

In this way, **the Centre** will enhance the capacity of the scientific expertise in the European Community and support Community preparedness planning. It should support existing activities, such as relevant Community action programmes in the public health sector, with regard to the prevention and control of communicable diseases, epidemiological surveillance, training programmes and early warning and response mechanisms, and **should foster the exchange of best practices and experience with regard to vaccination programmes.**

In Article 11

Collection and analysis of data

1. **The Centre shall coordinate data collection, validation, analysis and dissemination of data at Community level, including on vaccination strategies**. The statistical element of this data collection will be developed in collaboration with Member States using, as necessary, the Community statistical programme, to promote synergy and avoid duplication.

Annex 3: projects funded by ECDC related to vaccine effectiveness and vaccine safety

Contract no: **FWC 07/015**
Title: **Monitoring vaccine effectiveness during seasonal and pandemic influenza in EU/EEA**
Duration: 4 years
Dates: Dec 2007 – Dec 2011
Total sum: €3,000 000
Website: I-MOVE project; https://sites.google.com/site/epiflu/Home
Objective: Measure influenza vaccine effectiveness in Europe

Contract no: **FWC 14/026**
Title: **Monitoring vaccine effectiveness during seasonal and pandemic influenza in EU/EEA**
Duration: 4 years
Dates: October 2014 – on-going
Total sum: Maximum € 4,000 000 million (1st request for service to be initiated now)
Website: I-MOVE project; https://sites.google.com/site/epiflu/Home
Objective: Measure influenza vaccine effectiveness in Europe using GP and hospital networks

Contract no: **GRANT 2009/003**
Title: **Vaccine adverse event surveillance and communication**
Duration: 4 years
Dates: February 2009 – February 2013
Total sum: €1,845 000
Website: http://vaesco.net/vaesco.html
Objective: To develop guidelines and a sustainable infrastructure for post licensure vaccine safety assessment in the European Region.

Contract no: **FWC 09/041**
Title: **Impact of rotavirus vaccination**
Duration: 2 years
Dates: Dec 2009 - Dec 2011
Total sum: €200,000
Website: None active any more
Objective: Measure impact of rotavirus vaccination following introduction of rotavirus vaccines in immunization programmes

Title: Set-up of a sentinel system for assessing impact of different immunisation strategies for pertussis

- Expense title: Scientific study: Setting up a sentinel system for assessing impact of different immunisation strategies for pertussis
- Project initiated in 2014
- Procurement aimed to start in 2015 (call for tender launched 2014 aim to start outsourced activities in Jan 2015)
- Amount allocated 2015: 199 000 €
- Linked to SMAP deliverable: *10.6.1 Monitored vaccination programmes, with particular reference to vaccine coverage, effectiveness and impact at the EU level*
- Linked to SMAP Milestone: *10.6.1.1 Framework for programme monitoring set up for priority diseases*
- Link to call for tender: http://www.ecdc.europa.eu/en/aboutus/calls/_layouts/forms/Call_DispForm.aspx?List=02511b7b-3a16-4c4b-9304-54cfc08a1647&ID=704
-

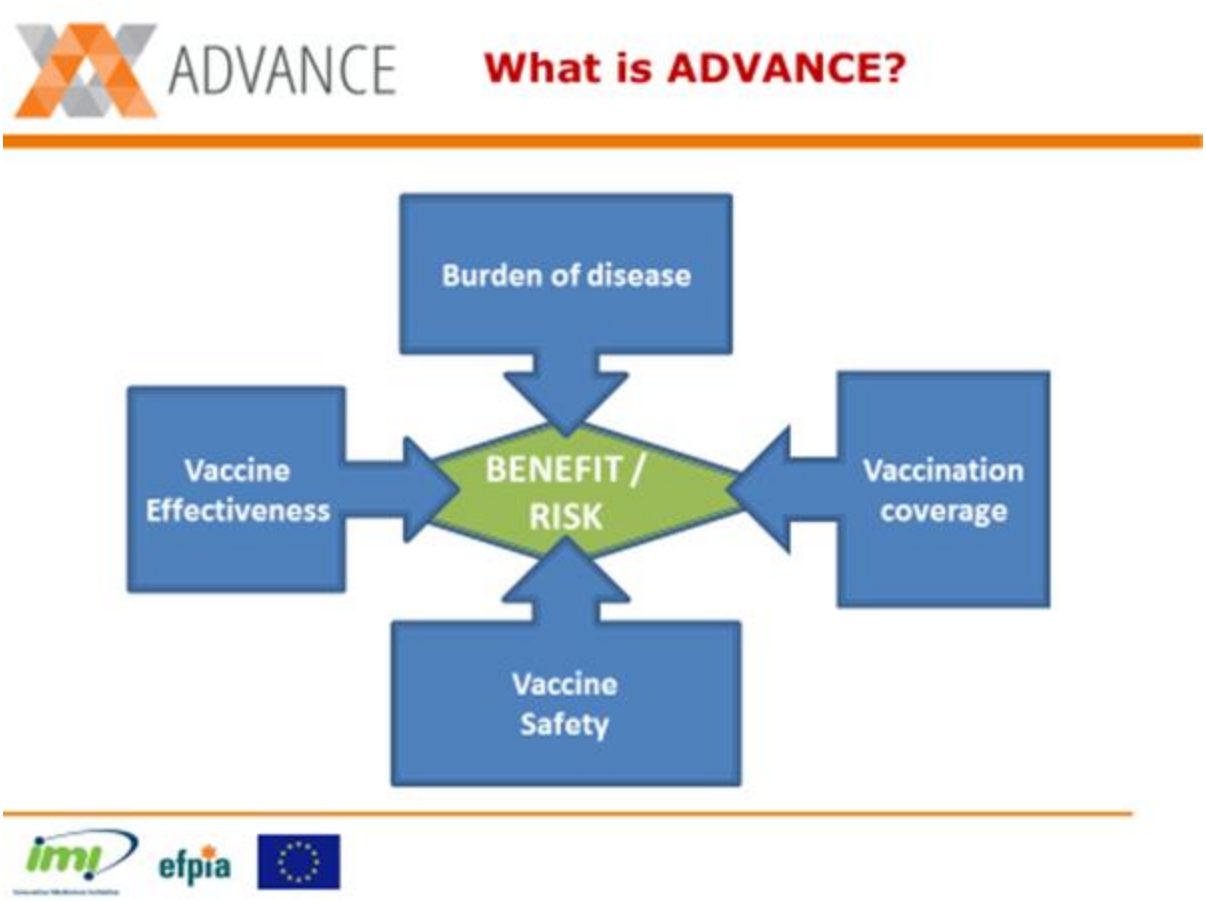
Title: SpIDNET framework implementation

- Expense title: Scientific study: SpIDNet framework implementation for assessing vaccination impact on the epidemiology of the invasive pneumococcal disease in Europe
- Project initiated in April 2012 (under a Framework Contract)
- Procurement aimed in 2015 (new Framework contract to be launched for outsourced activities in 2015)
- Amount allocated 2015: 450 000 €
- Linked to SMAP deliverable: *10.6.1 Monitored vaccination programmes, with particular reference to vaccine coverage, effectiveness and impact at the EU level*
- Linked to SMAP Milestone: *10.6.1.1 Framework for programme monitoring set up for priority diseases*

Annex 4: ADVANCE

ADVANCE : Accelerated Development of VAccine beNefit-risk Collaboration in Europe, IMI-funded project

- Started October 2013- 5 years
- Goal is to develop a blueprint for a framework capable of rapidly delivering reliable data on the benefits and risks of vaccines. The framework would help both health professionals and the public make informed decisions on immunisation.
- €10.8 million project represents unique collaboration between key players in sector, including European Centre for Disease Prevention and Control (ECDC), European Medicines Agency (EMA), plus national public health and regulatory bodies, vaccine manufacturers, SMEs, and academic experts. Following companies: GSK, Sanofi Pasteur, Sanofi {asteru MSD, Novartis, Crucell, Pfizer, Takeda.



Annex 5: Answers of EMA to questions from the WG (23 September 2014)

Questions to EMA from WG Business Model of ECDC Management Board

- What changes have been done in the pharmaceutical legislation / guidelines affecting the marketing authorization holders of seasonal influenza vaccines in relation to the obligation to submit immunogenicity studies and effectiveness studies in the registration dossiers and annual variations?
  Two scientific guidelines have introduced some changes concerning the requirement to submit immunogenicity studies for initial marketing authorisation applications and for subsequent annual strain update variations: 1) the *Explanatory note on the withdrawal of the Note for guidance on harmonisation of requirements for influenza Vaccines and of the core SmPC/PL for inactivated seasonal influenza vaccines*, which was adopted in February 2014 and can be found here, and 2) the *Clinical and non-clinical Module* of the new Influenza guideline, which has been published in July 2014 for 6 months public consultation and can be found here.
  As indicated in the first guideline mentioned above, the clinical trials so far requested in support of applications for annual strain updates in the context of seasonal vaccine use should no longer be routinely submitted (applicable from the 2015-2016 influenza season) because based on the current knowledge they are not considered sufficiently informative of the expected efficacy and safety of the vaccine prior to approval of the annual strain change. In addition the guideline indicates that companies should put in place a strengthened and sustainable monitoring of vaccine performance over the years, which should be achieved by means of product-specific effectiveness studies and adequate plans to ensure enhanced surveillance of vaccine safety. These specific measures must be included in the EU-RMP, which should be in place for all influenza vaccines (i.e. both centrally and nationally authorised products, CAPs and NAPs). The submission of effectiveness study results or safety surveillance data does not need to coincide with the annual update submission as it is not a prerequisite for strains update. Further details can be found in the above mentioned guidelines.
  Concerning the use of immunogenicity studies for the registration of new vaccines in the EU, the new requirements have been designed having in mind the gaps in knowledge for the efficacy of currently approved vaccines. In essence, comparative immunogenicity studies are still considered sufficient in some populations for demonstrating efficacy of new vaccines that have an established vaccine counterpart already authorised (i.e. demonstration of non-inferiority in adults and elderly for inactivated non-adjuvanted vaccines and demonstration of superiority for adjuvanted vaccines). On the contrary, immunogenicity studies may no longer be sufficient for naïve children, i.e. demonstration of efficacy is requested if efficacy data is not already available for a similar type of vaccine construct.
  For further details please consider chapter 4 of the Clinical and Non-Clinical Module of the new Influenza Guideline linked above.
- Which is the aim of replacing the classical assays for immunogenicity studies for effectiveness studies? EMA has initiated a number of activities to improve appraisal of influenza vaccines following the lessons learned from the 2009-2010 influenza A(H1N1) pandemic. In this context options to improve the appraisal of annual changes in the antigen composition of seasonal vaccines have been taken into account. This has led to the dismissal of the small annual clinical trials so far requested for each influenza season, as discussed in the point above. The Note for Guidance CPMP/BWP/214/96 and its Annex (CPMP/BWP/2490/00) will be withdrawn by the end of 2014 as overall their content is considered outdated with respect to current understanding of critical elements of the annual strain update. The re-appraisal exercise has been an opportunity to recognise the value of introducing further activities aimed at eliciting strengthened post-marketing monitoring of the benefit/risk profile of seasonal influenza vaccines, including enhanced safety surveillance and effectiveness studies.

- Do these changes correspond to the legislation on quality or to the legislation on pharmacovigilance? These changes have not been introduced as a result of provisions included in the Pharmacovigilance or other legislation.
- When these changes came into force? These changes have been published in February 2014 with a staggered approach for implementation: the dismissal of immunogenicity studies in support of the annual strain update variations is applicable as of the 2015-2016 season; the implementation of the enhanced safety surveillance entered into force with the publication of the Explanatory Note mentioned above, i.e. companies have been already discussing with the PRAC details of the monitoring system and safety results should become available in the coming weeks/months.
  Concerning the submission of product-specific effectiveness studies, a specific date has not been envisaged due the difficulties related to the implementation and conduct of such studies. The methodological details of such studies are included in the Clinical and Non-Clinical Module of the new Influenza Guideline, which is currently under consultation, and companies are encouraged to discuss issues and proposals with the competent authorities as soon as possible.
- Has been analysed the feasibility of marketing authorization holders / pharmaceutical companies for conducting these effectiveness studies? This is part of the discussion between companies and regulatory authorities which is expected to take place in the coming months. A pragmatic approach is foreseen for the implementation of this requirement, as the difficulties inherent to this approach are acknowledged.
- Is it expected that pharmaceutical companies would perform these effectiveness studies by themselves, both in terms of funding and resources - public structure needed, clinical, laboratory, etc..? Cooperation between industry and public health authorities would be expected but funding and resources are beyond the remit of the EMA scientific guidelines for industry; nevertheless options could be discussed with the Agency, if needed. Legally, the MAH is responsible for conducting the studies and for providing timely results for regulatory review, as agreed in the EU-RMP.
- How is it expected that these studies would be conducted - multicenter, in several countries, size of the sample, type of variables to be observed, etc..? For details of the proposed study design please consult the Clinical Module as indicated above.
- Are these effectiveness studies expected to be realized by trademark, type/subtype of antigen or what type of variable? Effectiveness studies are expected to generate vaccine brand-specific data.
- Is there a plan foreseen to ensure the sustainability of these vaccine effectiveness studies on EMA side? As the requirements for the effectiveness study relate to any seasonal strain change, the Agency expects that effectiveness results are available each year following any strain change variations. This should ensure that brand-specific effectiveness studies are conducted throughout the lifecycle of a seasonal influenza vaccine.
- How the different activities and responsibilities in this field are going to be coordinated (expertise from Public Health Institutes and the private finance)? The MAH is responsible for conducting the studies and for coordinating the research centres and the data collection. EMA encourages the dialogue between the MAH and national public health experts, but such coordination is outside of the Agency remit. EMA can also recommend pooling of resources from different MAHs to conduct joint studies, but this cannot be formulated as a formal request.
- Are there examples of some kind of partnership/consortium between the pharmaceutical industry and the European / European Commission or its agencies of joint agreements in terms of financing studies / providing data? At the international level an example could be the WHO framework for exchange of pandemic influenza viruses. http://apps.who.int/gb/pip/pdf_files/pandemic-influenza-preparedness-en.pdf
  I-MOVE, ADVANCE and ENCePP could be considered as examples of such partnership/consortium.