12 EU funding mechanisms and capacity to respond to public health threats

The European Union has demonstrated commitment to funding vaccine research. This is illustrated by the range of existing funding instruments and collaborative research promoted through the Sixth and Seventh Framework Programme's, (FP6 and FP7), Horizon 2020, the European Investment Bank (EIB) financing facilities, as well as partnerships such as the Innovative Medicines Initiative (IMI) and the European and Developing Countries Clinical Trials Partnership (EDCTP).

During the **last programming period** (**FP7 2007 – 2013**) more than €465 million were invested in projects[73] of which, on average €50 million per year was invested in vaccine research and development against **infectious diseases**. The majority of the funds (€234 million) were allocated to collaborative projects (a third of which was for clinical trials), €41.5 million for emerging epidemics), €82.7 million for poverty-related diseases (malaria, tuberculosis and HIV/AIDS),), €42.4 million for neglected infectious diseases) and €42.2 million for cross-infectious diseases combining more than one of the former categories.).

More recently, the EIB also launched a new instrument specifically dedicated to supporting R&D in the field of infectious diseases: the **InnovFin Infectious Diseases**[74], which aims to stimulate investments in the development of innovative vaccines or infrastructures. The EIB will provide loans between €7.5m and €75m to fund developers that have successfully completed the pre-clinical stage and would require clinical validation or be ready for later stage clinical trials.

Also at national level, the EU Member States are investing specifically in research contributing to vaccines development. Figures published in 2012 showed the overall "Contribution to Global Vaccination Efforts" from G20 countries[75] for the period 2007 - 2012[76] ; the United States invested $1,3 billion, Japan $6,5 million, India $22 million and Canada $17 million. The four top European countries invested altogether a total of $315,4 million[77].

These investments demonstrate a commitment to support research projects and support Europe's leadership in vaccines development. Despite this funding environment, a number of **limitations and gaps were highlighted** during the IPROVE stakeholder consultation process, although IPROVE did not conduct a systematic analysis of the funding instruments available at EU level as part of its consultation exercise. Nevertheless, given how fundamental the financing framework is to encouraging innovation the identified limitations and gaps are reported along with specific suggestions on how governments, EU institutions or private investors could improve on the current European vaccines R&D funding environment.

Sustainability of public funding. One major gap lies in the misalignment between the maximum project duration under EC funding (5 years or less) and the **lengthy development time** for vaccines (10 to 20 years). All along the R&D cycle, there is a need to better match duration of funding with the durations of the activity to be funded to ensure optimal efficiency. In some cases, the uncertainty created by a grant limited to five years constitutes an obstacle to application and vaccine research. Stakeholders expressed the view that existing schemes could be adapted to last for more than five years and possibly be granted continuation of funding after the successful completion of contractual milestones corresponding to the vaccine development timeline, e.g. proof of principle, first time in human, phase II, phase III.

Pooling funds at EU and Member State level. The **fragmentation of research** funding combined with **duplication** in some Members States also needs to be addressed. The funding of specific research or innovation projects may sometimes have limited impact and the European Commission and Members States may consider developing larger-scale programmes that provide the financial critical mass to support more impactful projects or even portfolio management[78]. Larger funding quanta will in turn produce a critical mass of European scientific and industry leaders who in turn can lead and complete more ambitious large-scale and multi-partners projects that could fully develop in-vitro, in-silica or in-vivo models, conduct head-to-head comparisons of candidate vaccines technologies or tests. Such large-scale projects could be financed through a combination of the various existing instruments at national and EU level.

[73] D. Gancberg, et al. (2015) Opportunities for vaccine research in Europe, Human Vaccines & Immunotherapeutics, 11:8, 1917-1920, DOI: 10.1080/21645515.2015.1016680

[74] http://www.eib.org/attachments/documents/innovfin_infectious_diseases_flysheet_en.pdf

[75] https://g20.org/about-g20/g20-members/

[76] A. Glassman, et al. (2012). "Measuring Government Commitment to Vaccination." CGD Policy Paper 008. Washington DC: Center for Global Development, http://www.cgdev.org/content/publications/detail/1426396

[77] UK: $196 million, France: $ 66,5 million, The Netherlands: $ 28,7 million, Germany: $24,2 million, Norway: $ 15,4 million, Spain: $ 19,6 million, Denmark: $ 12,7 million, http://www.cgdev.org/content/publications/detail/1426396

[78] E.g. TBVAC2020, HIV consortium or ADITEC

Attracting private capital. Stakeholders also highlighted challenges in accessing private sources of funding in Europe. The majority of **venture capitalist investments are led by US funds**, and increasingly by emerging markets and sovereign funds. There is a need to create in Europe an economic and institutional environment that is more favourable to innovation: grants and risk capitals should not only be available to innovative researchers at early stages (pre-clinical), but also at later development stages. Challenges also persist as to the possibility of adequately matching private investor funding with public grants, given the above-described time limitations and inflexibility of the latter. To facilitate the flow of long-term capital, particularly to smaller operators such as SMEs, experts recommended to analyse the feasibility of establishing programmes akin to the US' Small Business Investment Company (SBIC)[80], established since 1958. There may also be tax and other fiscal incentives that would increase the level of venture capital investment in European projects. For example the Advanced Market Commitment for Pneumococcal vaccines has functioned extremely well by providing a clear market incentive for investing in vaccine production capabilities and capacity. The same mechanism could be used to incentivise investment in vaccines R&D by committing to stage-gated European funding for vaccines R&D and commitments to purchase pre-agreed volumes of vaccines at pre-agreed prices over pre-agreed periods of time. Reviews of projects selected for their high innovation profile by the EC could be organised exclusively for overseas investors to promote investments in European SME.

Addressing health emergencies and biodefense. Finally, important gaps were pointed out with regards to emergency preparedness and capacity to respond timely and rationally to the need to develop vaccines and medical countermeasures in health threats situations. The vaccine sector should be regarded as a critical strategic capability in enabling a country to protect its populations and ensure availability as well as access to the relevant vaccines. This applies to responses to any biothreat, whether it be from bioterrorism or emerging public health emergences such as pandemic influenza, Ebola, HIV, or MersCoV.

Specifically, in the case of Ebola, the European Union and the Commission demonstrated an extraordinary capacity to mobilise within exceptionally short timelines the necessary funds to support research for the development of an Ebola vaccine. In September 2014 the Commission mobilised €24.4 million plus an additional €215 million through an emergency fast track IMI Ebola+ call launched in November 2014. No doubt this experience showed flexibility and political leadership to support and encourage efforts undertaken by several different groups. Nevertheless, it is evident that more is needed to build a proactive rather than reactive system that responds and adapts to crises ad hoc rather than build all of the necessary components of a rational framework to protect national and global public health. More than just funding is needed to put such a system in place in Europe.

The current gold standard for the development and purchase of the vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies is the **Biomedical Advanced Research and Development Authority** (BARDA), within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services.

BARDA embraces the reality of emerging and re-emerging diseases and the ever present risk of bioterrorist threats. Given the threat of emerging and re-emerging epidemics the need for a European equivalent appears unavoidable. The publication of IPROVE, Horizon 2020 and the momentum created by Ebola offer a unique opportunity to put such a capability in place in the EU.

Such a capability should have the following elements:

- A prioritised list of biothreats and preferred medical, vaccine, diagnostic and other countermeasures
- Funding to create a matching pipeline of medical and vaccine countermeasures with multiple candidates in each development channel to account for expected attrition and to ensure the R&D capability and capacity is spread out across multiple geographies, researchers and producers
- As products come off the biodefence pipeline a facility will be needed to fund purchase, stock and stockpile biothreat countermeasures in secure facilities. This may in turn provide a stockpiling capability and capacity that could be used for other routine vaccines in case of supply shortages
- It is recognised that such an initiative will require cross-national prioritisation, funding and co-operation that is historically more associated with military defence rather than biodefense but such a pan-European biodefence would provide a catalyst for better cross-border cooperation for all vaccines R&D

[80] https://www.sba.gov/category/lender-navigation/sba-loan-programs/sbic-program-0

The 2015 budget projection for BARDA in the USA totals $996 million. This includes $415 million for Advanced Research and Development (ARD) including $79 million of ARD funding of new classes of antimicrobial drugs. $20 million is to establish an independent, non-profit "Strategic Investor" to support emerging and promising biodefense businesses. $16 million is to support the first-year operating costs for three 'Centers for Innovation' in Advanced Development and Manufacturing (CIADM), expected to become operational during 2014. The remaining budget is to support operations and development projects in: anthrax; smallpox; Acute Radiation Syndrome illnesses, including thermal burns; and new antidotes for treating exposure to chemical agents. $166 million is targeted for U.S. and global efforts against pandemic influenza and emerging infectious diseases. Funds are also directed towards research and development of universal flu vaccines, and towards developing and stockpiling pre-pandemic vaccines.

13 Regulatory Challenges

It is generally accepted that vaccines designed to prevent infectious diseases are one of the most cost-effective interventions in public health and have prevented illness and death from a variety of diseases. Yet, there remain many infectious diseases that have an important medical impact for which safe and effective vaccines remain elusive. At the same time, there are infectious diseases for which vaccines are already available, but for which it is known that the efficacy should be further improved. The development of innovative vaccines will require innovative technologies that are inherently complex and whose development is both expensive and risky. For several of these innovative vaccines it is expected that demonstration of efficacy through classical randomised clinical trials will be very difficult if not unfeasible. Regional aspects that have to be taken into account during vaccines development add further complexity and challenges. The EU environment brings a series of specific challenges (e.g. regulatory decision making, decision making on reimbursement and pricing) that are not conducive for vaccine development. Therefore, there is a risk that new and innovative vaccines for which there is a real medical need will not be developed and available to the EU citizens. In general regulatory requirements are further increasing, which drives up both the cost and time required to authorise new vaccines. In addition, since the full benefit/risk profile of a vaccine can be assessed only once it gets used, large amounts of real time safety and effectiveness data are key, resulting in a substantial increase in costs associated to the development. Generating such data greatly depends on external networks and organisations. At present there is only limited support from EU and country governmental institutions to help the generation of such real time data. Since for some innovative vaccines it will not be feasible to generate the type of evidence that regulators currently are expecting to have available even prior to authorisation, it will be critical to improve the collaborations that are needed to generate robust data-packages in the post-approval phase.

Another challenge is that the data generated to support the marketing authorisation of the vaccines is not necessarily in line with the data that recommending bodies/payers in the different EU member states want to have available prior to decision making. However, in order to commit to the effort to develop a new vaccine, there need to be clear pathways to ensure that once successfully developed and authorised by regulators innovative vaccines will be recommended and used. A mechanism is needed by which exchange and interaction across stakeholders early in development is possible, to ensure that precious resources are not expended on development activities for vaccines for which the likelihood of approval, recommendation and implementation would be low.

In the EU, an active debate is on-going on adaptive pathways for medicinal products, aiming to bring important medicinal products earlier to the patients. The time could be ripe to discuss whether adaptive pathways also need to be developed for vaccines in order to ensure that new innovative vaccines will become available for the public. Key stakeholders involved in vaccine development, registration, recommendation and implementation should get together to design and put in place new mechanisms that build on the latest progress of science and technology to support sustainable vaccine innovation in EU while keeping vaccine safety, efficacy and quality at the core of all activities.

Importantly, the non-conducive environment in the EU is also hampering the development of vaccines in the rest of the world, as the EU today still takes a leading position and is seen for many countries as a reference worldwide.