

A STRATEGIC EUROPEAN ROADMAP FOR THE VACCINES OF TOMORROW:

A JOINT
STAKEHOLDER
REFLECTION



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Glossary

ADCC	Antibody-dependent cell-mediated cytotoxicity
ADITEC	Advanced Immunization Technologies
ARD	Advanced Research and Development
BARDA	Biomedical Advanced Research and Development Authority
BBMRI	Biobanking and Biomolecular Resources Research Infrastructure
BSL_{2,3,4}	Biosafety level 2, 3, 4
CD8	Cluster of differentiation 8 (glycoprotein on the surface of killer cells)
CIADM	Centre for innovation in Advanced Development and Manufacturing
CRO	Contract Research Organisation
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
DNA	Deoxyribonucleic acid
EATRIS	European Advanced Translational Research Infrastructure in Medicine
ECDC	European centre for Disease prevention
ECRIN	European Clinical Research Infrastructures Network
EDCTP	European and Developing Countries Clinical Trials Partnership
EIB	European Investment Bank
ELIXIR	Distributed infrastructure for life-science information
EMA	European Medicine Agency
EMTRAIN	European medicines research training network
EPIET	European program for intervention epidemiology
ERA	European Research Area
ERC	European Research Council
ERIC	European Research Infrastructure Consortium
EU	European Union
FDA	Food and Drug Administration
FP6, FP7	Sixth, Seventh Framework Programme
GMP	Good Manufacturing Practices
H₁N₁	or swine flu, subtype of influenza A virus
H₂020	Horizon 2020
HEA	Health Economics Analysis
HIV/AIDS	Human immunodeficiency virus
HPV	Human papillomavirus
HTA	Health technology assessment
IMI	Innovative Medicines Initiative
INSTRUCT	Europe's integrated research infrastructure for structural biology.
IP	Intellectual Property
IPROVE	Innovation Partnership for a Roadmap on Vaccines in Europe
ISCOM	Immunostimulating complex
mAb	Monoclonal antibody
MMR	Measles, mumps, and rubella
MOOC	Massive open online course
mRNA	Messenger RNA (ribonucleic acid)
MS	Multiple Sclerosis

NGO	Non-Governmental Organisation
NITAG	National Immunization Technical Advisory Groups
PAT	Process analytical technology
PD1	Programmed cell death protein 1
PoC	Proof of Concept
PPP	Public-Private Partnership
QbD	Quality by Design
R&D	Research and Development
R&I/RI	Research and innovation
SAGE	Strategic advisory group of experts
SBIR	Small Business Innovation Research
SME	Small and Medium-sized Enterprise
TBVAC2020	Tuberculosis vaccine research project
TF	Task force
TRL	Technology readiness level
VACSATC	Vaccine Safety-Attitudes, Training and Communication
VC	Venture capital
VLP	Virus-like Particle
WHO	World Health Organization



Europe has traditionally been the major player in vaccine research, achieving a tremendous health impact by drastically reducing cases of devastating diseases, such as diphtheria, polio, smallpox, and providing new research strategies for combatting emerging diseases like EBOLA and now the ZIKA virus.

Many more infectious and non-infectious diseases could possibly be eradicated by preventive and therapeutic vaccines. However, for some of these diseases, such as AIDS/HIV, the development of effective vaccines poses particularly complex scientific challenges, which should best be addressed by global multidisciplinary collaborative research. The European Union successive Framework Programmes for Research and Innovation have been drivers in helping meeting these challenges by supporting partnerships dedicated to all phases of vaccine development to eradicate or cure diseases. Over the past 12 years, the Union has spent over €50 million per year on vaccine R&D under Framework Programmes 6 and 7 (FP6 and FP7), including activities under the public-private partnership Innovative Medicines Initiative (IMI), and the public-public partnership European & Developing Countries Clinical Trials Partnership (EDCTP). Looking ahead, the Union continues to support vaccines under Horizon 2020, including within successor programmes IMI2 and EDCTP2, or the InnovFin Infectious Diseases. In this context, the FP7-funded IPROVE project is an important contributor to build a strategic vision for the future European activities in the entire innovation chain for vaccines, and to maintain Europe's leading position in this important area of research, which is at the heart of European citizens.

Ruxandra Draghia-Akli

Director Health Directorate DG Research & Innovation,
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Vaccination is, without doubt, one of the greatest contributors to medical, social and economic development of all time. In concert with good sanitation, education, clean water and good nutrition, it makes us healthier people better able to build a healthier, wealthier and happier

world. Vaccination has eradicated smallpox and it will soon eradicate polio. In 80% of the world, diphtheria, tetanus, measles, mumps and rubella are now extremely rare events rather than the predominant killers of our children.

Europe's vaccine pioneers such as Jenner, Pasteur, Ramon, Ehrlich, Von Behring, Merieux, Sclavo and Koch, its researchers, its producers and its policymakers and vaccinators have distinguished Europe as a leader in vaccines and vaccination.

Yet, recent epidemics, the absence of vaccines for HIV, TB, Malaria, HSV, RSV, HCV, MRSA, etc. and the promise of therapeutic vaccines, tell us that we can do far better. We can do better if we continue to invest in understanding immunology and immunity, host-pathogen interaction and why people choose to be vaccinated or not. We can do far better if we bring antigen discovery, development, formulation and production into the 21st century.

We can better align the control and release tests with today and tomorrow's technology and we can do far better if we learn how best to sustainably deliver vaccination to

all segments of the population and all populations. We can do far better if we have a shared vision of our priorities and we better nurture transfer of technology from academia to start-ups and start-ups to international players. We can also push back the boundaries with therapeutic vaccines for cancer and autoimmune diseases.

Achieving all of this requires a vision. The vision must guide Europe on what research and development is most needed, where funding and investment is most lacking and how we can better link our undoubted centers' of excellence. A vision will allow us to minimise duplication, maximise synergies and more rapidly and effectively translate from basic research to public health impact. Our intention is that IPROVE provides such a vision. As the first vaccine R&D roadmap for Europe we would never claim that it will be the last word on the topic, but we urge all those who share our passion for vaccination to embrace IPROVE as a shared starting point that will drive and pull Europe and the world to new heights in vaccination.

Michael Watson

Chair IPROVE
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MAIN PRIORITIES	SPECIFIC RECOMMENDATIONS
<p>CHALLENGE 1 – R&D</p> <p>Support an integrated, multidisciplinary approach to antigen selection</p> <p>Strengthen the science of vaccine adjuvants</p> <p>Sustain research on vectors and alternative routes of immunisation</p> <p>Innovative design and harmonisation of clinical trials data and development of analyses frameworks</p> <p>Continue to invest in biomarkers of safety in vaccines, and correlates of protection and of efficacy</p>	<ul style="list-style-type: none"> ➤ Research on host-pathogen interactions in vivo ➤ Research for the refining of animal models ➤ Development and exploration of new assays to rapidly screen antibody and T cell functions ➤ Explore emergent in-vitro bioassay technologies and improve in-vitro assay for antibody functional screening ➤ Research for selection and analysis of epitopes ➤ Develop new bioinformatics tools applied to genomics, antigen diversity and antigen expression ➤ Support research on structural vaccinology ➤ Create toolbox of adjuvants with well-defined profile to shape the immune response ➤ Employ systems/comics analysis to improve the discovery of biomarkers predictive of adjuvants' effect ➤ Develop toxicology research on adjuvant-induced inflammation ➤ Combine different adjuvants in prime-boost studies ➤ Cross-species studies of vaccine adjuvants to pinpoint predictability of animal models ➤ Better approach to a combined use of vectors, adjuvants, routes of immunisation ➤ Evidence-based development of heterologous prime-boost strategies to induce long-lasting immunity of alternative routes of immunisation and their testing in pre-clinical and clinical studies ➤ Development of more potent synthetic nucleic acid-based vectors for rapid outbreaks response ➤ Research for the development of novel strategies for mucosal vaccination using purified subunit antigens ➤ Enable access to "big data" at the micro and macro level ➤ Build capacities to enable data aggregation across functions, inclusive of data descriptors ➤ Rapidly develop multi-parametric technologies in cell biology ➤ Identify innovative design of clinical trials and methodologies to profile volunteers earlier on in the process ➤ Develop expertise and support infrastructures to perform controlled challenges in humans ➤ Set up collaborative cost-sharing programmes in the EU and at international levels (Transatlantic, Asia) to facilitate access to advanced technologies, large populations, rare outcomes, and avoid duplication in investments
<p>CHALLENGE 2: THERAPEUTIC VACCINES</p> <p>Establish collaborative cross-expertise network at EU level</p> <p>Foster early dialogue with regulatory bodies</p> <p>Develop targeted funding opportunities</p>	<ul style="list-style-type: none"> ➤ Exchange best-practice, including successful and unsuccessful approaches, share know-how and technology ➤ Design and perform multi-centre clinical studies ➤ Facilitate early interactions and regular dialogue with regulators, e.g. through EC led workshops ➤ Regulators to assess the feasibility of developing EU-level guidance for therapeutic vaccines, including in specific disease areas ➤ Bridge the gap between research and market and create efficient financial markets ➤ Government policies to improve equity financing ➤ Lower financial risk perception through appropriate mechanisms, including interactions with payers
<p>CHALLENGE 3: INNOVATIVE PROCESSES FOR VACCINE MANUFACTURING AND QUALITY CONTROL</p> <p>Translate innovations into technologies</p> <p>Develop flexible manufacturing systems</p> <p>Bridge technology and science: collaboration between engineers and biologists</p> <p>Improve manufacturing operations and identify new purification techniques</p>	<ul style="list-style-type: none"> ➤ Promote closer collaboration among scientists, engineers and regulators ➤ Offer continuity of funding beyond concept demonstration ➤ Set up a task force of regulators and policy-makers to support plans based on scenario planning ➤ Investigate how to decentralise manufacturing capacity through a more localised supply base ➤ Support the adoption of single use systems and technologies to minimise variations between sites ➤ Investing in thermostability enabling technologies ➤ Test alternative delivery devices: increasing vaccine stability and new fill-in ➤ Investment in formulation expertise in the research process ➤ Develop and validate improved potency assays to increase relevance while simplifying testing ➤ Develop assay platforms allowing for rapid characterization for different manufacturing systems ➤ Develop robust assays for in-process control for both up-stream and down-stream processing ➤ Improved chromatographic techniques adapted to adenoviruses or particle-based vaccines
<p>CHALLENGE 4: RESEARCH INFRASTRUCTURES</p> <p>Reinforce vaccine Research Infrastructures</p> <p>Provide support to clinical research infrastructure</p> <p>Improve GMP manufacturing capabilities</p>	<ul style="list-style-type: none"> ➤ Develop the network of existing EU facilities and cross border connection to rapidly set-up trials and recruit subjects ➤ Upgrade or create new infrastructures in the areas where gaps exist or capacity is insufficient ➤ Promote harmonisation/standardisation among facilities in five key areas: genomics and bioinformatics facilities; repository and collections ; high throughput protein production and crystallography facilities; animal facilities; immunisation technologies ➤ Develop and promote access to innovative technology platforms: live vectors, adjuvant, formulation ➤ Consolidate and provide access to repository and collections: biobanks and well-characterised pathogen strains ➤ Map centres with methodological competences and map volunteers/specific populations ➤ Identify or develop cohorts (registries) ➤ Enable human challenge models ➤ Further develop and structure clinical trial centers coupled with immunomonitoring, imaging, laboratory testing and functional monitoring of physiological parameters ➤ Secure clear guidance on GMP level for manufacturing and quality control ➤ Establish funding schemes to fund the GMP manufacturing of vaccines for testing up to phase 2 ➤ Facilitate the access to infrastructure required for GMP manufacturing ➤ Establish a central European platform to measure the purity of GMP vaccine batch
<p>CHALLENGE 5: VACCINE SMEs</p> <p>Establish a network of vaccine SMEs involved in human vaccine R&D at EU-level</p> <p>Ease SMEs access to scientific and technical resources and skills at the most critical phases</p> <p>Support better SMEs early access to regulatory expertise</p> <p>Foster competitive collaborative projects between SMEs and larger companies</p> <p>Sharpen financial instruments and attracting risk capital towards SMEs</p>	<ul style="list-style-type: none"> ➤ Create forums and a European network to push innovation, share knowledge and experience, as well as to conduct a comprehensive needs assessment ➤ Create a vaccine innovation community portal to improve the exchange information, opportunities, services and infrastructures at EU level ➤ Facilitate SMEs' access to new technologies to reduce R&I costs and timing ➤ Effective matchmaking and interaction between SMEs and large companies ➤ Facilitate the establishment of early stage contacts with regulatory bodies ➤ Enhance the visibility of services that regulatory bodies can provide at national and EU level ➤ Develop an advising mechanism to provide SMEs with easier access to existing facilities and platforms ➤ Organise commercial contact-making workshops ➤ Set-up new instruments allowing SMEs to share R&D projects on the 'Bio-Europe' partnering model ➤ Establish an EC "window" awards to successful large pharma-SMEs R&I collaborations ➤ Invest in improving the public perception of vaccines as a strategic public health tool ➤ Better adapt current instruments to vaccines SMEs needs
<p>CHALLENGE 6: TRAINING</p> <p>Identify and profile target groups for training</p> <p>Review and adapt training formats, accessibility and recognition</p> <p>Invest in training the trainers</p>	<ul style="list-style-type: none"> ➤ Adapt the training offering in terms of content and format to specific groups ➤ Map out and describe competency profiles for different vaccinology related functions ➤ Collaborate with higher education organisations and companies to incentivise training in vaccinology and increase accreditation ➤ Set-up specialised initial and life-long training including courses covering the entire process from vaccine R&D to licensure ➤ Establish vaccine training platforms to allow the sharing and shipment of equipment required for training ➤ Fund the establishment of facilities devoted to training for GMP manufacturing and train the trainers
<p>CHALLENGE 7: COMMUNICATION ON IMMUNISATION AND THE HESITANCY CHALLENGE</p> <p>Implement stratified monitoring of acceptance attitudes and sentiments towards vaccination</p> <p>Establish multi-disciplinary networks of expertise and an EU level center of excellence</p> <p>Make healthcare professionals and public health stakeholders effective advocates of vaccination</p> <p>Engage with civil society organisations</p>	<ul style="list-style-type: none"> ➤ Establish a tool capable of monitoring acceptance attitudes, risk awareness, sentiments towards vaccines and vaccination programmes at EU level ➤ Develop metrics of vaccination acceptance ➤ Design and pilot interventions ➤ Support regional and national immunisation advisory groups with regards to vaccine hesitancy ➤ EU institutions to facilitate the formation of a European community of practice on vaccination uptake ➤ Bring together experts from social and behavioural science, neuroscience, social marketing, communication and health education ➤ Implement innovative shifts in the curricula offerings for healthcare workers to equip them with the right skills and confidence to appropriately assess vaccination needs and effectively communicate on vaccination ➤ Fund vocational and on-the-job communication training programmes for public health staff and immunisation programme managers ➤ Educate future generation about infectious disease, immunology and public health, e.g. through school-based educational programmes, with a view to institutionalising the role of vaccination as a cornerstone of public health ➤ Provide appropriate funding and build partnerships to collaborate with such organisations to help building awareness, disseminating and creating knowledge on vaccination needs

Innovation Partnership for a Roadmap on Vaccines in Europe (IPROVE) represents a collaborative effort of the leading vaccine experts in Europe to develop a roadmap on how the future of vaccine- and vaccinology-related research in the EU should look over the coming decade. The project, funded under the EU FP7 programme, brought together key public and private stakeholders from academia, public health institutes, regulators, industry, and SMEs to build critical stakeholder consensus on the priority gaps and challenges that must be addressed to bolster innovation in vaccines and vaccination in Europe.

Europe has a long history of vaccine discovery, development and manufacturing, and benefits from a strong industrial infrastructure. More than 80% of the vaccines for worldwide use are produced in and exported from Europe. With its numerous centers of excellence in vaccinology and related disciplines, Europe has the capacity and capability of continuing to lead the discovery of next generation vaccines capable of addressing unmet medical needs and emergency situations. However, without **a clear roadmap** for Europe's **vaccines R&D** and the **political, legal, economic and structural measures** that will best incentivise, reward and accelerate this research, today's **leadership is at risk**.

Despite the strong heritage in **vaccines R&D**, **Europe does not have an integrated vaccines R&D agenda. Nor does it have the sort of vaccine** and biotechnology R&D clusters that are proving so productive in other parts of the world. **IPROVE is the first EU funded** attempt to develop such a **holistic view on this important sector**. IPROVE has concentrated efforts on **integrating all elements that drive** the entire vaccines value chain from basic research through to development and implementation of vaccination programmes. The ultimate goal of IPROVE is to help steer European competitiveness in this field for the delivery and benefit of innovative prophylactic and therapeutic vaccines.

The roadmap was developed through a joined up and **participatory stakeholder consultation process** organised around seven main thematic topics of consultation; i) Vaccine R&D; ii) Therapeutic Vaccines; iii) Production and Manufacturing; iv) Infrastructures; v) Vaccine SME needs; vi) Training; vii) Communications and Acceptance of Vaccination. Each of these thematic areas was addressed through separate multi-stakeholder consultation workshops. The intention was to cover as much as possible of the critical areas of intervention relevant to the entire innovation value chain.

The roadmap has highlighted that it remains a clear necessity to continue investing in the basic and fundamental science underpinning vaccine research. This research needs to be **multidisciplinary and connected** across microbiology, immunology, structural biology systems and bioinformatics. A more rational approach for **antigen selection and vaccine design** should be prioritised and recommendations are made on the need

to support and accelerate research into **novel adjuvants**, the development of vaccine vectors, and **prime-boost strategies**, as well as, the investigation of novel **routes of immunisation**. From a development perspective, goals include the simplification and **a more evidence-based and less empirical approach to the design of clinical studies**, better tools and approaches for data collection, extraction, analysis, and interpretation in order to support more efficient translation of innovation into practice. Furthermore, the roadmap calls for more attention to innovation of the **manufacturing, regulatory and quality control cycle**, to enable more affordable, faster, more flexible and less wasteful production. We critically point out the need for more funding and partnership across sectors to support the networks and multidisciplinary **infrastructures that are essential to vaccines' R&D innovation**.

The consultation also reinforced the fact that vaccines are only as good as their **vaccine implementation programmes**, and that more must be done to understand and address vaccination hesitancy on the part of both the general public and healthcare professionals.

Perhaps reassuringly, the IPROVE findings and recommendations are broadly consistent with those of similar initiatives in EU Member States or further afield. IPROVE highlights the potential added value of a more pan-European approach that has the political will, policy and financial environment which reinforces co-operation but also facilitates the development of physical European Research Clusters for vaccines that bring the science, entrepreneurs, investors and the most innovative vaccine producers together. Such a pan-European approach will require a political, policy and fiscal framework across public health, regulatory, and funding domains that recognises, incentivises and rewards the immense value of vaccination. In this regard, developing a long-term vision and commitment is paramount in respect to facilitating the establishment of effective partnerships across stakeholders at all levels.

It is beyond the scope of IPROVE to define the specific mechanisms and financial instruments that can build this pan-European vaccine ERA, however reflection is invited, and it is recommended that the EU fosters such thinking as a critical next step in order to sustain its leadership in this strategic sector.

IPROVE Scope & Ambition



1 Why is a Vaccine R&D roadmap essential for Europe today?

There is no doubt that vaccination is one of **public health's most valuable pillars**. Immunisation through vaccines has prevented more premature deaths, permanent disability, and suffering in all regions in the world, than any other medical intervention¹. Without vaccination many of the health, and therefore economic and social gains of the past 200 years would simply not have been possible.

*Vaccination has eradicated smallpox in man and rinderpest in cattle and it has dramatically reduced the burden of numerous infectious diseases, especially in infants and children². It has **freed societies and economies from a huge burden of childhood morbidity and mortality and underpinned individual and social growth, prosperity and wellbeing**. In the coming decade, vaccines are projected to save 25 million more people³, and there is no doubt that both prophylactic and therapeutic vaccines with the potential to prevent, or even cure, communicable and non-communicable diseases will continue to be **fundamental to public health in the future**⁴.*

Nevertheless, the demand for new and improved vaccines to address unmet and emerging medical needs requires the right technical and scientific skill set, sustained and sufficient investment, as well as, a structural framework that incentivises and rewards research and innovation. **Strengthening partnership and coordination across relevant actors and sectors is as essential to vaccine innovation and supply as the underlying scientific and technical capabilities and capacity.**

A strategic and forward-looking approach is key. All of the challenges affecting the current vaccine and vaccination landscape in Europe require joint stakeholder reflection to ensure a coherent EU strategy for vaccination. The **IPROVE (Innovation Partnership for a Roadmap on Vaccines in Europe)** FP7-funded Coordination and Support Action⁵ was

conceived to propose a roadmap for how Europe can best invest in the science and technology essential for vaccines innovation. The task was to cover all areas from discovery and development to production and uptake, as well as to initiate reflection on the political, legal, economic and structural measures that will best incentivise, reward and accelerate the development of vaccines.

This roadmap is expected to **guide and inform the future European research commitments and investment priorities** in order to create an appropriate enabling environment to spur vaccine research, know-how, and innovation. The ultimate goal is to **safeguard and advance public health in Europe and the world** and ensure the **competitiveness of Europe** in the area of vaccines, where the region has **traditionally held a leadership position**.

Since vaccines are widely recognised as essential tools in maintaining public health, an adequately **supportive and innovation-friendly R&D environment is absolutely critical to drive the development of novel vaccine technologies**. This requires **putting in place the appropriate "push"** (e.g. capacity, capability, funding, tax incentives and infrastructure) and **"pull"** (such as priorities, attractive markets, stable demand, and favourable procurement policies) **mechanisms**. These need to be shepherded by the right processes, political will, and social and economic environment, **allowing Europe to stay at the leading edge of competitiveness for this strategic and vital health sector**.

MEETING TODAY'S AND TOMORROW'S PUBLIC HEALTH CHALLENGES

With changes to the social and demographic structure of the population in the EU, there is a need to re-think the way we deliver healthcare. Increasingly we must focus on preventative approaches that will help individuals continue leading healthy lives. Currently, spending on health prevention represents less than 3% of the overall healthcare spending in the EU (OECD, 2013), and there is room for identifying more efficiencies to optimise health promotion and disease prevention programmes.

Access to essential vaccinations must go beyond childhood. Indeed adults are no less valuable than children and a **life-course approach to immunisation is required if we are to ensure equal access across all ages, geographies and societies**.

¹ Armstrong G, et al. (1999) Trends in Infectious Disease Mortality in the US During the 20th Century Journal of American Medical Association 281: 61–66

² Plotkin S (2008), Vaccines, Elsevier Health Sciences

³ Rappuoli R. (2014) Presentation at the New Horizon for Vaccine R&D&I in Europe Conference, March 2014

⁴ Pronker E et al (2013), Risk in Vaccine Research and Development Quantified

⁵ European Framework Programme 7 funding scheme, dedicated to actions that cover not the research itself, but the coordination and networking of projects, programmes and policies

Source: EC research and innovation, FP7 in brief. https://ec.europa.eu/research/fp7/understanding/fp7inbrief/funding-schemes_en.html

This calls for better implementation of currently available vaccines, but also for the innovative R&D of 'personalised' vaccines designed to meet specific target group needs in specific healthcare settings. Such an agenda requires putting in place the appropriate infrastructure that can help identifying population needs, but also understand the performance of current vaccination schemes, thus appropriately monitoring epidemiology, coverage, and effectiveness of the programmes in place.

Vaccination also has an important role to play in the global fight **against the rising threat of antibiotic resistance**. While the effective use of existing vaccines can help reduce the need for antibiotics or promote a more rational use, renewed research efforts targeting new generations of **vaccines aimed to tackle antibiotic resistant bacteria and healthcare associated infections** should be of primary importance⁶.

In order to deliver such innovation, there is a need for tools that enable us to prioritise targets for vaccine innovation. Once this prioritisation is clear, the process of developing innovative vaccines requires considerable investments, and efforts to adapt existing or establish new breakthrough technologies. The process can take up to 20 years from R&D to availability on the market.

EUROPE'S TRADITIONAL LEAD NEEDS TO BE SUSTAINED

Did you know?

Europe is a long-standing leader in both vaccines and public health. The first golden age of vaccination was led by the European pioneers of germ theory, pathogen culture and vaccines such as Pasteur, Koch, Ramon, Mérieux, Sclavo, Von Behring and others and the development of vaccines, which protected against rabies, diphtheria, tetanus, pertussis, and TB. This was accompanied by the establishment of national vaccine institutes in Europe and around the world, e.g. the Pasteur Institute, Wellcome, the Robert Koch Institute, and the Sclavo Institute.



80% OF VACCINES

from the major research manufacturers are produced in Europe and exported for worldwide use⁷.



R&D INVESTMENT 47%

growth in global R&D investment by the major Europe-based vaccine manufacturers⁷.

Expertise exists in Europe in most of the critical disciplines required for vaccines innovation. Europe is prominent in the field of adjuvants, and has also an excellent track record of inventing and exploiting novel routes of delivery. Beyond knowledge, cutting-edge critical mass exists in key areas such as infrastructures (e.g. animal facilities, BSL-3/4 containment facilities), and supporting technologies (bio-imaging, histo-pathology, tracing, immuno-monitoring). The know-how, regulatory framework and capacity to conduct clinical trials also constitute strong assets for Europe. Furthermore, most of the technology suppliers for vaccines manufacturing are based in Europe, ensuring access to state-of-the-art innovation.

Even though existing figures demonstrate the capacity of European R&D to support vaccine innovation, the number of R&D projects in Europe has plateaued in the period 2002 to 2010 in favour of **increased investments in emerging economies**. Increasingly me-too and state-supported innovative vaccine development and production are taking place elsewhere in the world.

Figure 1: Number of Vaccine Clinical Trials 2000 – 2009

Source: clinicaltrials.gov

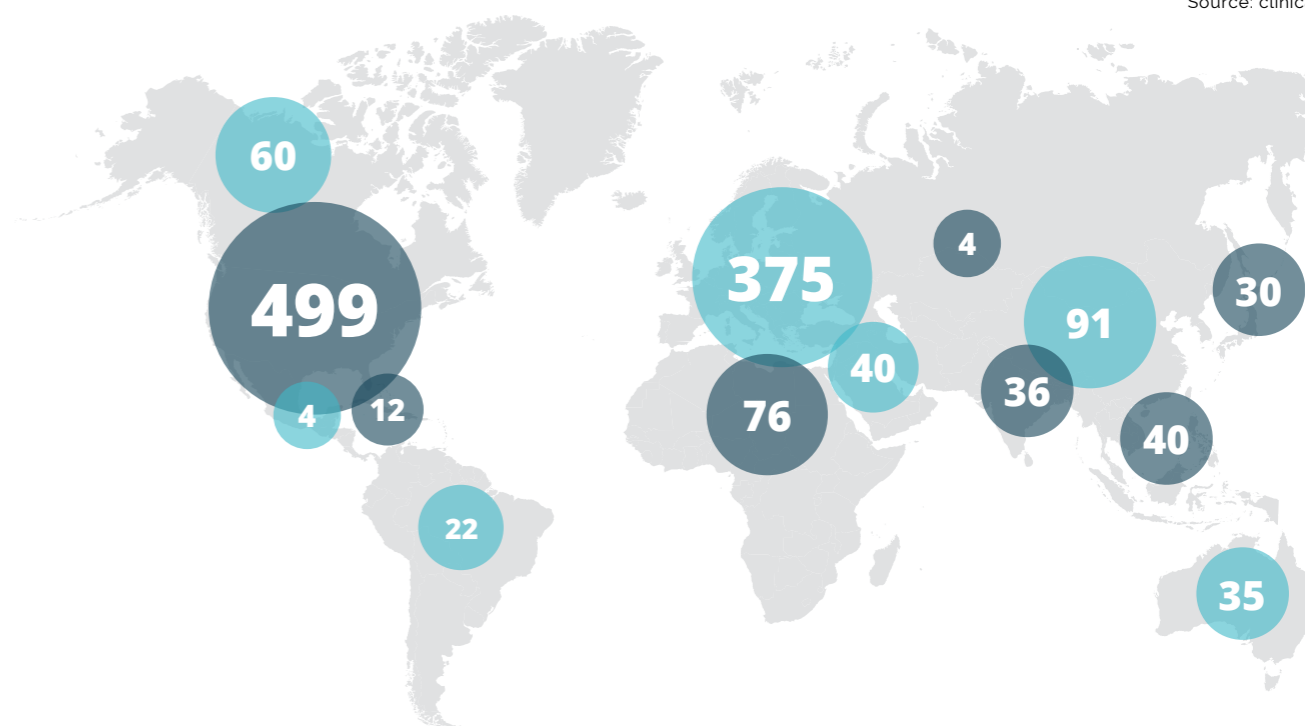
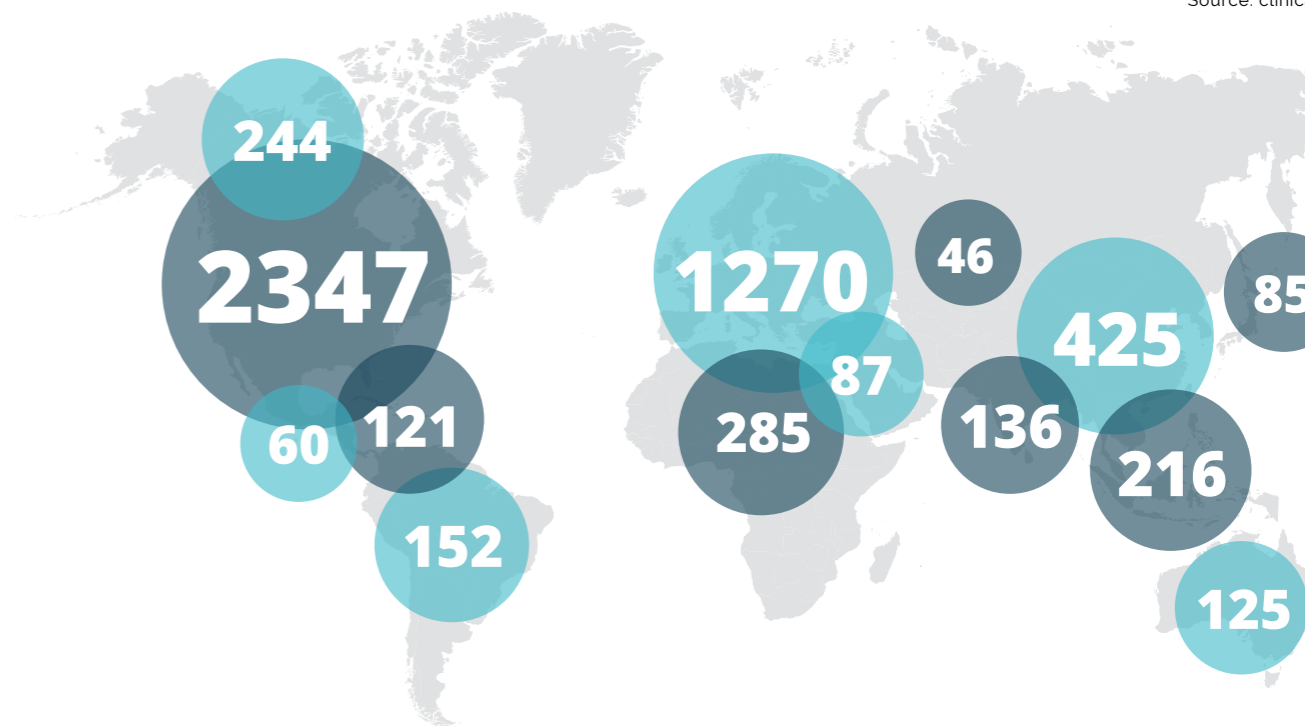


Figure 2: Number of Vaccines Clinical Trials 2010 – 2015

Source: clinicaltrials.gov



⁶ O'Neill AMR Review (2016), Vaccines and Alternative Approaches: Reducing our dependence on Antimicrobials, available at www.amr-review.org

⁷ Vaccines Europe members' figures for the year 2014. Accessible at www.vaccineseurope.eu



CLINICAL TRIALS IN THE EU

75%

as many trials as the US between 2000-2009 (EU: 375 vs US: 499).



NUMBERS OF CLINICAL TRIALS IN

2010 - 2015

has decreased to about half compared to the US (1270 vs 2374).

CLINICAL TRIALS IN ASIA



from 42% to 51%

From 2010 to 2015, the number of clinical trials in Asia (China, India, Japan) have increased compared to Europe.

This shifting balance is a consequence of the broader recognition of the **strategic social as well as economic value of vaccine production**. Consequently many **governments in emerging countries are investing heavily in developing domestic vaccine** research, development and production in order to achieve the necessary critical mass and, more importantly, to **secure access to vaccines**. We currently witness the establishment or re-establishment of vaccine capability and capacity in countries such as China, India, Vietnam, Indonesia, Thailand, South Africa, Brazil, Mexico, Argentina, and elsewhere⁸.

Keeping Europe's lead in such a key sector requires a concerted and coordinated effort to better **pool and leverage the capacity and capability distributed across Europe in its centres of excellence**.

Vaccinology is intrinsically multi-disciplinary, and therefore functions most effectively if the necessary critical mass of capacity, capability, financing, translation and cooperation is reached and combined, particularly through co-localisation. This explains the concentration of vaccine-related critical mass in geographical clustering of vaccine research, development, venture capital, SMEs and large vaccine producers in the last decades. This has been most notable on the East and West coasts of the USA and is starting to develop in India (e.g. Hyderabad) and China (e.g. Shenzhen). By bringing together a broad range of critical stakeholders, IPROVE aims to build a comprehensive and clear **overview of the gaps in investment, science and structure that, if filled, would reinvigorate EU vaccination leadership**.

THE VIABILITY OF THE CURRENT VACCINE R&D MODEL IS AT RISK

Whilst recent innovation in vaccine research and development is widely acknowledged, the **unique characteristics and challenges of vaccine R&D are less well recognised**. Vaccines are distinctive from other medicinal products for at least two reasons; first, they are preventative in nature and, as such, intended for a larger number of healthy subjects and so must have an appropriate risk-benefit profile. Secondly, they are highly technical process-dependent biological products that are hard to characterise as finished products, so require strict process control to minimise their innate variability and unpredictability.

These special features make the development and production of vaccines particularly time-consuming, demanding, complex and costly and expose it to numerous risks. Even the development in very early stages, such as exploratory and pre-clinical research and development, to simply **identify a candidate vaccine can cost up to US \$20 million**.

Did you know?

Unlike other pharmaceuticals, vaccine development can take **up to 15 - 20 years** without counting time to **effective population access** (on average a median time-lag of an extra 6.4 years⁹ after marketing authorisation). A vaccine may require **clinical testing in 15-20 times as many subjects as for pharmaceutical drugs¹⁰** and **costing up to US \$ 900 million per vaccine production unit¹¹**.

The **manufacturing** itself is a complex and lengthy process. **6 to 24 months** may elapse between the vaccine being available in bulk form and it being distributed, with **70% of the production times consumed by quality control**. Opening and qualifying a new production facility may take more than 5 years and represents colossal investments. While the average cost of a **single biological manufacturing site** depends on its location and product, the cost can range from US\$ 100 million to **600 million dollars¹² or more**.

In addition, increasing **hurdles on the demand side** are undermining the competitiveness of the vaccine sector as a whole and its ability to continue investing in innovative R&D. Growing trends of low price **driven procurement policies** fail to recognise the cost of quality, supply reliability and innovation of vaccines. Health Economic Analyses (HEA) fail to factor in broader and indirect economic and societal benefits of vaccines.

There is certainly a need to foster the development of appropriate and comprehensive evaluation of frameworks that are adapted to the specificities of vaccines and immunisation in general. In particular, it is thought that the EU could benefit from further

developing the network of existing National Immunisation Technical Advisory Groups (NITAGs), and improving coordination and expertise with Health Technology Assessment (HTA) bodies. This is in the interest of citizens' public health. It is also in their interest to incentivise R&D efforts in vaccines, fully capitalising on the complexity of their research and manufacturing.

VACCINE RESEARCH IN EUROPE NEEDS CONNECTING

The panel participants in the IPROVE consultation voiced the opinion that the European **vaccine field could be better interconnected**. They felt that the sub-optimal fragmentation may be driven by the fact that European countries have their own national vaccination decision-making processes. As a result, whilst Europe is a single economic community it is not a single or even interconnected public health or vaccination community. Indeed in some EU countries there are as many vaccination programmes as there are autonomous states/regions (e.g. Spain). This separation of economic and public health unity is driven by the European principle of subsidiarity in healthcare in Europe. The result is an inevitable heterogeneity of **vaccination programmes and associated diversity of vaccine priorities and vaccine R&D focus and funding**. This means that while there are many centres of vaccine excellence around Europe, their sharing of agendas, expertise, experience and personnel is limited.

Sub optimally connected European vaccine R&D programmes reduce the capacity to compete or collaborate with the huge critical mass of vaccines and vaccination R&D found in clusters such as Cambridge MA, USA. The panel therefore proposed that this apparent fragmentation should be addressed through an appropriate mix of push and pull mechanisms as well as being shepherded by the right processes, political will, and social and economic environment.

Some reviewers have nevertheless observed that the postulated sub-optimal integration of Europe's vaccines R&D capability and capacity is not evidence-based. It may, therefore, be appropriate for the EU to conduct a baseline study to check this assumption and if confirmed to track the progress of future initiatives to improve it.

⁸ http://www.dcvmn.org/sites/default/files/files/DCVMN_jan_2013.pdf Overview of DCVMN capabilities; Dr. Suresh Jadhav Dr. Suresh Jadh "Opportunities for emerging vaccine markets" http://ec.europa.eu/research/health/pdf/event17/s3-10-suresh-jadhav_en.pdf

⁹ Blank PR et al. (2013). Population access to new vaccines in European countries. Vaccine; 31(27): 2862-7

¹⁰ BIOTECCanada (2010). Research and Development: Fostering vaccine innovation in Canada

¹¹ IFPMA (2013). Vaccine Research & Development. <http://farm9.staticflickr.com>

¹² IFPMA (2014). Maintaining the vaccines innovation edge: <http://www.ifpma.org/resources/infographics.html>

2 IPROVE approach

IPROVE is a first attempt to develop a holistic view on this important sector as no similar project with a European scope has ever been funded by the EU's programme. Three main features contribute to the uniqueness of the IPROVE initiative.

TAKING A CROSS-CUTTING CAPABILITIES, CAPACITIES RATHER THAN A DISEASE-BASED APPROACH

IPROVE focused on **building critical stakeholder consensus on the priority gaps and challenges as well as recommendations for EU-level action** on common topics of interest to bolster vaccine innovation across the entire innovation chain. The consortium considered that certain disease-based approaches have already been funded and explored to some extents with the support of existing and previously funded initiatives at national, EU, and international levels, including based on the publication of the recently updated WHO Report on Priority Medicines for Europe¹³. Therefore, the project **concentrated efforts on technologies and cross cutting horizontal bottlenecks** that must be overcome to allow the delivery of new generation vaccines in each of the key areas of unmet medical needs.

It is thought that this could help to support a more targeted approach in the allocation of funding, by strategically investing in the most promising and forward-looking partnership models. Efforts should be directed towards projects and players with higher potential for delivering true innovation in order **to clearly meet the health, demographic change, well-being and security challenges of today, in line with the goals of the EU multi-annual financial framework**.

ALIGNING AND PRIORITISING ON FUTURE EU EFFORTS

Much of what emerged from the IPROVE consultation process confirms and builds on research initiatives already happening across different countries in Europe. These however lack the intent for pan-European coordination and alignment across the different sets of stakeholders at EU level that should help their implementation.

Therefore, the added value of IPROVE is that it allowed different sets of stakeholders to share their ideas on what should be on top of the vaccine R&D agenda, align their thoughts, and finally prioritise on the main focus areas for EU intervention, with potential for cross-fertilisation. Through this prioritisation, the aim is to help policy-makers and funders identify the most relevant technologies where investment is key in the short and medium term.

FOSTERING BETTER INTERACTION BETWEEN EU STAKEHOLDERS

Europe currently benefits from the presence of a core set of more or less formalised national and regional vaccine 'clusters' in some EU Members States, such as France (Lyon Biopôle), UK (UK Vaccines R&D Network), Belgium, Italy, and the Netherlands. Building on this environment, IPROVE created the momentum and gave impetus to encourage increased interaction not only within but also across such clusters. This should help laying the foundation for favouring the establishment of an actual European working network across disciplines and experts between public and private, but also public-to-public and private-to-private players.

IPROVE should be regarded as a first milestone in the above directions, and the success of its ambition will depend on stakeholder ownership and responsibility to implement its recommendations, particularly at the EU political level. Furthermore, though agreement on the content of such recommendations exists, more coordination and investment will be needed as to better understand what the best models of collaboration and financing mechanisms are.

3 IPROVE methodology

The IPROVE methodology allowed a broad and comprehensive stakeholder consultation, with a view to increasing chances that the resulting roadmap is holistic, and realistic, and able to meaningfully inform structures, processes, projects and funding that truly address the shared needs across public and private vaccine research at both national and EU level.

This bottom-up stakeholder consultation process was structured around six pillars/thematic areas. Each pillar was the subject of a specific stakeholder consultation workshop. The pillars or thematic areas identified were: 1) Vaccine R&D, 2) manufacturing and quality control, 3) infrastructure, 4) therapeutic vaccines, 5) SMEs, 6) vaccines acceptance and training needs.

Each workshop aimed to engage a range of high-level experts whose roles and expertise matched the scope and breadth of the topic and roadmap. Participants represented stakeholders from across the entire vaccine and vaccination innovation spectrum, from industry, academia, and public health to national vaccine research institutes, international organisations, and funding agencies. Furthermore, experts of the European Commission and regulatory agencies were invited and participated in the workshops to complement the external stakeholder engagement.

All of the stakeholder consultation workshops were aimed to achieve the following objectives:

- ▶ Identify common critical gaps, fragmentation and silo challenges affecting each of the specific areas tackled during the consultation
- ▶ Provide specific theme-based recommendations where consensus could be found on priority areas for investment through EU and national funding programmes
- ▶ Describe changes in framework conditions that would help drive, incentivise and facilitate prioritised vaccines R&D in Europe in the defined topic areas dealt with.

A first draft roadmap resulting from this broad consultation was submitted to three main groups of stakeholders for iterative consultation, in order to refine the priorities and recommendations:

- ▶ The IPROVE consortium partners, inclusive of their respective networks of experts
- ▶ The IPROVE Advisory Board of four independent scientific experts¹⁴ and

- ▶ The IPROVE Affiliate Members Group, comprising of leading vaccine experts and representatives of public authorities in charge of vaccine programmes and funding at national level¹⁵

The draft roadmap was finally put to further stakeholder consultation through a publicly accessible web-based platform targeting the leading exponents of the vaccine community in Europe that participated in the workshops¹⁶.

This roadmap is intended and expected to be of use to the European Commission and relevant national and regional institutes and institutions operating at the Member State level, in view of informing their funding programmes.

4 Limitations

The IPROVE Consortium believes that the following main limitations should be duly considered.

Though striving to address the entire value chain, the consortium had to operate a selection of priority topics and sub-topics to be tackled throughout the consultation. Hence there is scope for further exploring certain areas in greater detail. Furthermore, workshops are limited to a certain number of participants, and not every invitee was available on the dates set for each workshop. Finally the identification of relevant participants proved to be challenging in fields where networks have not yet been established (this was particularly the case for therapeutic vaccines). As a mitigation strategy, an open public consultation and web-based platform was created to garner further feedback and validate the findings in the roadmap.

Other limitations, due to resource limitations, relate to the fact that IPROVE could not extensively cover in-depth consultations on key areas representing framework conditions that are enablers of innovation, such as in the regulatory and financing domains. These require further reflection and research to understand how to better link the regulatory and science agenda as well as the industrial dimension, as the three are strictly intertwined.

Lastly, due to the same challenges described above, IPROVE could not get into the details of a technical implementation plan of the vision set out in this roadmap document. The European Commission and other national stakeholders responsible for incentivising the R&I of vaccines are invited to continue supporting the IPROVE network in coordinating such implementation through their programmes and policies.

¹³ WHO (2013). Priority Medicines for Europe and the World (Update), accessible at: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf

¹⁴ The list of IPROVE Advisory Board members is provided at the end of this report

¹⁵ More information on the IPROVE Governance structure can be found at www.iprove-eu.eu

¹⁶ A full list of all of the stakeholders consulted is provided at the end of this report

Gaps and Recommendations for Future Investment



5 Vaccine R&D

The consultation exercise on the key R&D needs covered both needs for prophylactic and therapeutic vaccines. The consultation was organised around three main areas of focus, for which short and medium term investment is considered key:

- **Antigen Selection and Vaccine Design**, encompassing more specifically host-pathogen interaction, B-cell & T-cell immunology, structural vaccine approach
- **Novel Technologies & Routes of Immunisation** to enable innovation in the field mainly through adjuvants, vectors, alternative route of immunisation and prime-boost strategies
- **Clinical Studies and Data Interpretation** with key topics being biomarkers of vaccine safety and efficacy and tools to facilitate data management and use

One overarching gap identified as relevant across R&D has been the need for a **multidisciplinary approach including microbiology, immunology, structural biology and bioinformatics**. Scientific advances have enabled a paradigm shift from an empirical approach of 'isolate, inactivate and inject' to the more rational approach of 'sequence, select and synthesise'. Participants highlighted the fact that such a rational approach inherently depends on a deep mechanistic understanding, which will rely on a continuous improvement in the underlying sciences, including highest quality novel immunology and pathogen biology, as well as, an optimised systems approach to data sharing and analysis.

Here below are reported the main outcomes of the IPROVE consultation process for each of the sub-themes identified above and around which the stakeholder consultation was organised.

ANTIGEN SELECTION AND VACCINE DESIGN

Gaps and Challenges

The lack of full understanding of the pathogen and the host-pathogen interactions certainly represents a key challenge for vaccine developers.

Infectious pathogens for which a vaccine still does not exist often present complex life cycles, and even though several antigens could be feasible targets of protective responses at distinct phases during the cycle, such antigens are often polymorphic. Traditional development approaches are thus not viable. A rational approach inherently depends on a better understanding of pathogens and the immunology of key antigens, as well as, host-pathogen interaction^{17 18 19}.

A clear understanding of the protective human immune response to infection is thus key to selecting and designing the right vaccine antigens. This calls for research investment and support to identify new generation assays for human B and T cell responses.

By using novel human B cell technologies, it is now possible to identify human monoclonal antibodies that inhibit pathogen infection or promote pathogen killing. These antibodies can be used to discover protective antigens for use in novel vaccines. In some cases, it has been possible to identify and isolate antibodies that broadly neutralise viral infections by targeting conserved sites present in viral protein antigens, such as influenza hemagglutinin or HIV gp120. The information derived from these antibodies can instruct the design of novel antigens focused on protective epitopes. However, little has been achieved in designing immunogens able to elicit antibodies with the same properties.

More research on structural vaccinology and on the evolution of the antibody response starting from germline precursors is needed to design innovative antigens eliciting cross-reactive antibodies.

Recommendations for EU level action

- It is agreed among the expert community that the EU should support an integrated and multidisciplinary approach to antigen selection, adapted to the characteristics of the pathogen and target disease. This should include multi-disciplinary research programs, as well as training across expertise, notably training scientists in both biology and information technology in order to harness the potential of IT advances in the field

¹⁷ Nora et al. (2013), Malaria vaccines: high-throughput tools for antigen discovery with development potential

¹⁸ Zielinski et al. (2011), Dissecting the human immunologic memory for pathogens

¹⁹ Aebischer (2014), Leishmania spp. Proteome data sets: a comprehensive resource for vaccine development to target visceral leishmaniasis

► In order to support a better understanding of pathogens and host-pathogen interaction, the stakeholder consultation pointed to the following priority areas for investment:

- + Incentives and funding should specifically cover research into the knowledge base on host-pathogen interactions in vivo (e.g. representative strain collections, molecular epidemiology to define antigen variability and strain coverage, molecular modelling, high-throughput crystallography, high-throughput epitope mapping, particularly for therapeutic vaccines)
- + Specific investment to refine animal models in order to maximise relevance to infections in humans

► As for the better understanding of human immune response, the consultation highlighted the need to further support research related to the following topics:

- + New generation assays able to screen as rapidly as possible for antibody and T cell functions relevant to human infection
- + Exploration of emergent in-vitro bioassay technologies (e.g. organ-on-a-chip and human tissue engineering and in-silico approaches)
- + Improved in vitro assay for antibody functional screening (e.g. neutralisation, ADCC, complement dependent killing)
- + Epitope selection and analyses are of particular relevance for all novel vaccine research, including therapeutic vaccines
- + Support development of new bioinformatics tools applied to genomics, antigen diversity and antigen expression

► Finally, specific support for structural vaccinology is key, as to fully enable exploiting the knowledge derived from human immunology and molecular microbiology and translating it into more effective antigens.

NOVEL TECHNOLOGIES AND ROUTES OF IMMUNISATION

Gaps and Challenges

1. The need for novel adjuvants

Adjuvant expertise is high in Europe, yet there is an increasing need for novel adjuvants for preventive and therapeutic vaccines targeting infectious diseases for which conventional formulations have failed.

New adjuvants are also needed to improve existing vaccines in different population groups for which the activity of current adjuvants may differ, e.g. the elderly, infants and chronically infected subjects that mount a suboptimal immune response to vaccination. For example, the expression of pattern recognition receptors is different in cells from new-borns and young adults, requiring **adjuvants targeted for specific age groups**. The development of more effective vaccines adapted to the pathogens and to the target population will require novel adjuvants, rationally designed and formulated based on the knowledge of their molecular mechanism of action.

Although several types of adjuvants have been identified and tested in different laboratory settings – be it in academia or industry – only very few have been approved by regulatory authorities. The mechanisms by which some traditional adjuvants approved for human use such as alum or emulsions, can induce an immunogenic response are still unclear and need to be further investigated to direct their rational use.

A new generation of adjuvants would use compounds with well-known and characterised molecular and cellular targets that are optimised to enhance the nature, quality and breadth of the immune response, using pharmacokinetic and pharmacodynamic properties that optimise impact whilst minimising reacto-genicity and safety concerns. More robust and reliable assays have emerged that can be successfully applied to the study of the immune response to adjuvanted vaccines using a systems biology approach.

Traditional adjuvants enhancing vaccine's immunogenicity may not be sufficient for effective therapeutic vaccines. The success of immunotherapy of cancer using monoclonal antibodies targeting checkpoint inhibitors such as CTLA4 and PD1 suggests that a combination of adjuvants and checkpoint inhibitors may represent an attractive strategy for therapeutic vaccines.

In addition, **combinations of adjuvants** which may increase vaccine efficacy and safety should be systemically investigated and the molecular and immunological mechanisms of action of these combinations should be characterised in detail. Their rational combination in **heterologous prime-boost schedules** should also be pursued.

Finally, a particular need within adjuvants is the **development of mucosal adjuvants enabling effective needle-free subunit vaccines**. Several adjuvants have been efficiently tested in preclinical models, however none of them is currently available for humans, which makes the development of mucosal vaccines based on purified antigens very difficult.

2. The development of vaccine vectors needs to be accelerated

Viral vectors are attenuated or non-pathogenic viruses, genetically modified to express an inserted gene and generate strong antigen specific humoral and cellular responses. In particular, they can generate CD8 responses that are hard to induce with inactive or subunit vaccines, even in the presence of strong adjuvants. A broad spectrum of replicating and non-replicating vectors is available but their functioning mechanisms and risks require further investigation.

The area of vaccine vectors requires significant work to better understand the impact of pre-existing anti-vector immunity on efficacy (for instance Ad5 vector in the HIV trials²⁰) and to address questions about

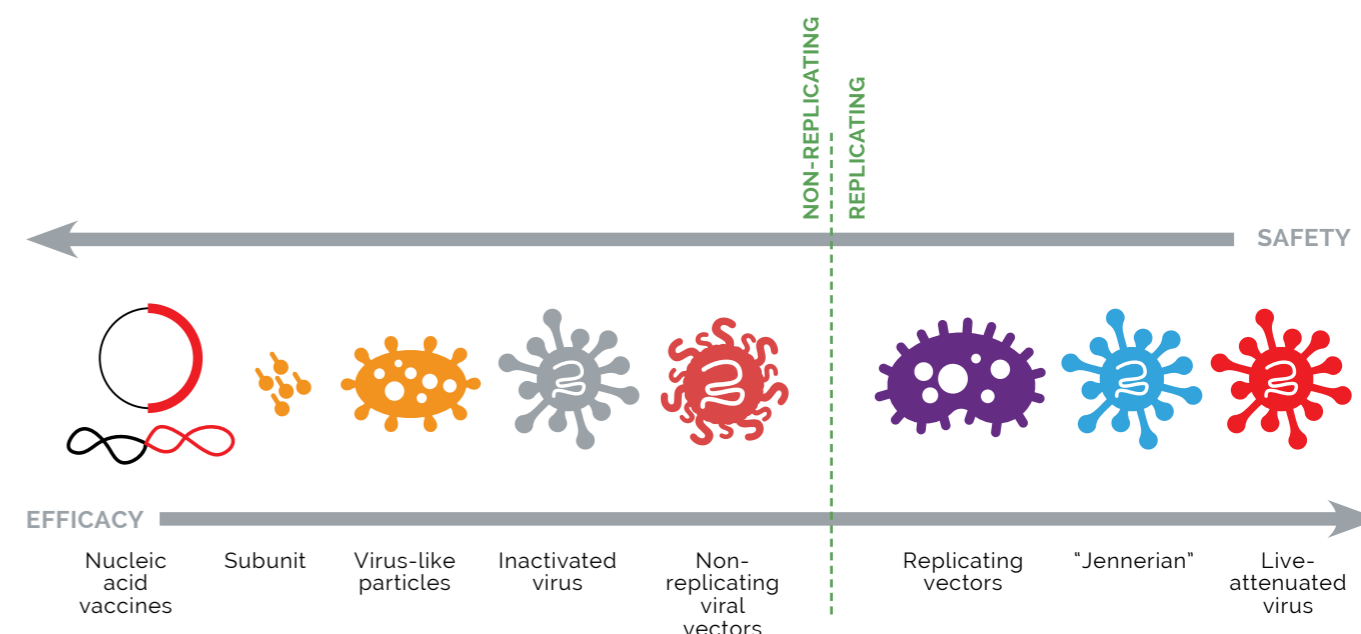
safety raised by experiences. Another obstacle to be overcome is that many of the centres of excellence are specialised in only one vector or vector family. Innovation and development of heterologous prime-boost strategies would benefit from more collaboration between these groups, as shown in the context of the Ebola vaccine development to respond to the most recent outbreak.

The IPROVE consultation stressed the need for further research to better master the technology and secure its safe and appropriate use. It also identified **a need to improve and develop new vectors as well as better defining their usage**.

One of the limitations of viral vectors is the interference of anti-vector immunity, which often decreases their potency and the ability to boost after a first dose. A potential solution is the use of fully synthetic nucleic acid vectors (e.g. nanocarriers, virosomes, ISCOMs, liposomes) based on DNA, messenger RNA or RNA replicons delivered to the cells by non-antigenic delivery systems or by electroporation.

Figure 3: Safety and efficacy of replicating and non-replicating vaccine approaches

Source: <http://www.iavireport.org>



²⁰ Delany et al. (2014) Vaccines for 21st century, EMBO Mol Med June 6(6): 708-720

So far these vectors have been less potent in humans than viral vectors, however work aimed at improving their potency could have a strong impact in future development of effective CD8 vaccines. Another promising approach is the **prime-boost strategy**, based on priming the immune system to a target antigen delivered by a vector and then selectively boosting the secondary response by using a different vaccine formulation (e.g. a different vector or a recombinant protein). This approach is specifically aimed at the generation and enrichment of high avidity T cells and antibodies specific for the target antigen.

3. Alternative routes of immunisation are still needed

One of the major needs highlighted by the participants is the **development of novel strategies for mucosal vaccination using purified subunit antigens**. The low immunogenicity and weak stability of free protein antigens in the mucosal settings, requires an optimised vaccine formulation and delivery, suitable for the immunisation route selected. Adjuvants and/or delivery systems to be used for intranasal vaccination should induce the required immune responses, be safe and avoid reactogenicity. Other routes for inducing mucosal immunity include the sublingual, vaginal, rectal and transcutaneous routes. Sublingual administration is a promising approach that results in induction of mucosal and systemic T cell and antibody responses with a broad dissemination to different mucosae, including the gastrointestinal and respiratory tracts, and the genital mucosa. Many of these data, obtained in animal models, need to be confirmed in human studies.

The development of topically administered vaccines, whether for mucosal or transcutaneous administration, requires efficient delivery devices, able to deliver the vaccine directly to the key immune cells. Needle-free technologies, like inhalers, nasal sprays, forced air injectors and patches, by virtue of their potential for improved efficacy and better patient compliance, are promising and effective vaccine delivery strategies need to be further researched and developed.

Recommendations for EU level action

The EU should support research and innovation activities for the rational development of novel immunisation technologies with a particular focus on vaccine adjuvants, novel delivery and prime-boost strategies. The

Commission should support multidisciplinary R&D with the aim of addressing the above described unmet needs. The following set of specific recommendations for future research was formulated through the IPROVE consultation:

► Need for multidisciplinary research and innovation on vaccine adjuvants:

- + Create a toolbox of adjuvants, with a well-defined profile to shape the immune response, which can be applied to vaccines against diverse pathogens
- + Employ systems/omics analysis of the effect of vaccine adjuvants on the immune response to vaccines, to help define biomarkers of adjuvants' activity both in animals and humans
- + Head-to-head comparison of vaccine adjuvants
- + Focussed research on vaccine adjuvants formulation
- + Conduct cross species (rodents, NHP and humans) studies of vaccine adjuvants to pinpoint predictability of animal models for adjuvant research
- + Develop toxicology research on adjuvant-induced inflammation: better animal models or human immunological investigations to evaluate local, regional and systemic effects, as well as, to understand mechanisms of adjuvant-induced inflammation
- + Combine different adjuvants in prime-boost studies (i.e. using a different adjuvant for primary immunisation and boosters) to optimally direct the immune response
- + Develop new adjuvants, new adjuvant formulations and adjuvant combinations to be used to improve vaccines adapted for the needs of specific target populations (i.e. elderly, infants, immune-compromised...)
- + Develop vaccine adjuvants for mucosal administration

► Needs for research and innovation on vectors and novel routes of immunisation:

- + Move towards a more evidence-based combination of vectors and other type of "carriers" (nanoparticles, nucleic acids), adjuvants, routes and schedule of immunisation
- + Evidence-based development of heterologous prime-boost strategies for the induction of broad and long-lasting immunity
- + Development of more potent synthetic vectors based on both conventional antigens and nucleic acids for rapid response to pathogens outbreaks

CLINICAL STUDIES AND DATA INTERPRETATION

Gaps and Challenges

The innovative design of clinical trials aims to allow for clinical studies' acceleration and optimal use of the outcomes to demonstrate vaccines efficacy and safety. The gaps identified through the consultation mainly revolve around two aspects: finding the way forward to harmonise and standardise clinical data collection and analysis as well as finding better focused designs to reduce the size, lengths and costs of clinical trials.

There are few predictive biomarkers for vaccine safety beyond the common biologically predictable events. This makes large phase 2 & 3 clinical studies necessary. Equally, immunological biomarkers/predictors of vaccine efficacy are lacking for many disease targets. Identifying these biomarkers is challenging because they may be complex combinations of several biological responses. Further advances in this field require overcoming several challenges:

- Design clinical investigations around better and more clearly defined questions versus an 'opportunistic' approach
- Profile in-depth genetic background and baselines before vaccination of volunteers using systems biology approaches and conduct the investigation over a long run; and focus on outliers (non-responders, high reactogenic, high immune response, etc.)
- Develop new mathematical models and bioinformatics tools to extract biological knowledge from data sets: invest in new tools to compare biomarker data from recent clinical trials with data collected in the past on both licensed and failed vaccine candidates
- Allow for more collaborative work, which requires from the research community to better align the techniques and samples to be favoured for each purpose (e.g. muscle biopsy for reactogenicity analysis vs. blood samples for vaccines efficacy...)
- Anticipate and involve regulators early enough in such definitions, in order to accelerate clinical developments

Harmonisation and, to a certain degree, standardisation of data analysis frameworks is lacking, posing a big challenge to pooled data analysis. Different research groups use different analytical softwares, and data sets can be difficult to compare without pooling.

The integration of different data sources has not sufficiently been addressed. In addition, there is a need for setting standards and norms for data collection, storage and analysis as well as ontologies and harmonisation of semantics, and a new language for adverse event coding. These will all facilitate data comparison and pooled analyses.

Recommendations for EU level action

- Enable access to "big data" at the micro and macro level through the following actions:
 - + European research should continue supporting projects to identify ways to simplify data collection and analysis. It should also enable comparability and developing capacity to extract biologically relevant knowledge from the data to generate innovation
 - + More efficient quality control on data collection, analysis, reporting and standardisation is key and the link between bioinformatics competencies and clinical and experimental data should be strengthened
 - + Clinical trials must be smartly designed around clear and specific questions to avoid informational pitfalls
- Create a framework to sustainably fund the structures/institutions that will enable data to be aggregated at different levels and inclusive of data descriptors, pushing towards investment in the following areas:
 - + Semantics harmonisation, making available data on candidate vaccines, including abandoned projects to help learning and better understanding safety issues
 - + Explore different computational analyses and ways of visualising the data
 - + Establish a working group for concluding on biomarkers and harmonised processes
- Rapidly develop multi-parametric technologies in cell biology as to provide deep insight in basic mechanisms, potentially identifying predictive markers and algorithms
- Develop more research concentrated on identifying innovative design of clinical trials and methodologies to profile volunteers in advance. To do so, it will be essential to focus on outliers and have already from the onset the possibility of doing further in-depth studies and increase predictability of vaccination outcomes

- Develop expertise and support infrastructures for performing controlled challenges in humans
- Secure a European environment for clinical trials e.g. by having public operational Groups who can manage the tasks between idea and first human data

- Set up collaborative cost-sharing programmes in the EU and at international levels (transatlantic, Asia) to facilitate access to advanced technologies, large populations, rare outcomes, and avoid duplication in investments



R&D		
R&D - Antigen selection	GAPS & CHALLENGES	Recommendations
	Lack of understanding of pathogen and host-pathogen interactions	<ul style="list-style-type: none"> ➤ EC to support an integrated, multidisciplinary programmes approach to antigen selection, adapted to the characteristics of the pathogen and of target disease ➤ Research into the knowledge base on host-pathogen interactions in vivo. ➤ Research for the refining of animal models
	Lack of understanding of the protective human immune response to infection	<ul style="list-style-type: none"> ➤ Development and exploration of new assays to rapidly screen antibody and T cell functions ➤ Explore emergent in-vitro bioassay technologies and improve in-vitro assay for antibody functional screening ➤ Research for epitope selection and analysis using novel technology platforms ➤ Develop new bio-informatics tools applied to genomics, antigen diversity and antigen expression
	Successful application of structural vaccinology and design effective vaccine antigens	<ul style="list-style-type: none"> ➤ Support continued research on structural vaccinology
R&D - Novel technologies & routes of immunisation	GAPS & CHALLENGES	Recommendations
	Need for novel adjuvants: <ul style="list-style-type: none"> + Minimise reacto-genicity + Improving immune stimulation + Targeted for specific populations + Mucosal adjuvants + Adjuvants and check-point inhibitors for therapeutic vaccines. 	Vaccine Adjuvants: <ul style="list-style-type: none"> ➤ Create toolbox of adjuvants with well-defined profile to shape the immune response ➤ Employ systems/omics analysis to improve the discovery of biomarkers predictive of adjuvants' effect ➤ Develop toxicology research on adjuvant-induced inflammation. ➤ Combine different adjuvants in prime-boost studies ➤ Develop new adjuvants to address specific target populations, emerging/zoonosis infectious diseases or to target mucosal administration ➤ Cross-species studies of vaccine adjuvants to pinpoint predictability of animal models
	Needs for acceleration of vectors development <ul style="list-style-type: none"> + Minimise reacto-genicity & anti-vector immunity + Develop new vectors + Better define vectors' usage 	Vectors & Routes of Immunisation: <ul style="list-style-type: none"> ➤ Better approach to a combined use of vectors, adjuvants, routes and routes of immunisation ➤ Evidence-based development of heterologous prime-boost strategies to induce long-lasting immunity of alternative routes of immunisation and their testing in pre-clinical and clinical studies ➤ Development of more potent synthetic nucleic acid-based vectors for rapid outbreaks response
	Needs for alternative routes of administration <ul style="list-style-type: none"> + Novel strategies for mucosal vaccination + Efficient delivery devices to the key immune cells 	<ul style="list-style-type: none"> ➤ Research on the development of novel strategies for mucosal vaccination using purified subunit antigens
R&D - clinical studies & data interpretation	GAPS & CHALLENGES	Recommendations
	Innovative design and harmonisation of clinical trials data and development of analyses frameworks	<ul style="list-style-type: none"> ➤ Enable access to "big data" at the micro and macro level ➤ Build capacities to enable data aggregation across functions, inclusive of data descriptors ➤ Rapidly develop multi-parametric technologies in cell biology ➤ Identify innovative design of clinical trials and methodologies to profile volunteers earlier in the process ➤ Develop expertise and support infrastructures to perform controlled challenges in humans
	Lack of clear biomarkers of safety in vaccines, and correlates of protection and of efficacy	<ul style="list-style-type: none"> ➤ Set up collaborative cost-sharing programmes in the EU and at international levels (transatlantic, Asia) to facilitate access to advanced technologies, large populations, rare outcomes, and avoid duplication in investments



6 Therapeutic Vaccines

For many years, vaccines have been used to successfully prevent devastating infectious diseases such as smallpox, measles and polio and more recently human papillomavirus (HPV) and pneumococcal infections. These public health triumphs illustrate the major contributions that vaccines have made in saving countless lives around the world.

Nevertheless vaccines are not only for preventing infectious diseases, some help the body fight a range of illnesses by activating the immune system to recognise and attack disease. Therapeutic vaccines have been the subject of massive R&D efforts, both from academics and industry, most notably biotech companies. Since 2010, more than 800 publications have addressed the topic²¹. In 2013, Science Magazine designated cancer immunotherapy as "Breakthrough of the Year"²².

In 2010, a new cancer vaccine, Provenge (Dendreon), for the treatment of prostate cancer was approved in the United States, and many more immunotherapeutic vaccines are in development. In 2014, the EMA accepted Dasiprotimut-T BiovaxID marketing authorisation application for the treatment of non-Hodgkin's follicular lymphoma in patients who have achieved a first complete remission.

Today, the pipeline for therapeutic vaccines has grown to an estimated 470 products. The vaccines in development cover more than 70 different conditions. There is a strong focus on areas of high unmet need, such as vaccines against cancer and infectious diseases, accounting for 55% and 24% of the pipelines respectively. Products in late stage development include potential treatments for multiple cancers, infectious diseases (HIV, Hepatitis...), allergies, diabetes, and addictions. Therapeutic vaccine companies must choose among a variety of delivery systems, immunopotentiators/adjuvants, product technologies, and production platforms — with many of these factors being unique to therapeutic vaccines. Companies are also developing new immunological assays for the identification and validation of novel vaccine candidates (MedTrack, 2015).

Today there is no clear single definition of a therapeutic vaccine, however in general today's therapeutic vaccines mediate their effect through in vivo induction or amplification of the antigen-specific host immune response.

Immunotherapeutic products thus comprise a broad range of approaches: antibodies, peptides, proteins, nucleic acids, immune cells (i.e. dendritic cells, T-cells...) or stem cells, tumour antigen specific proteins and gene therapy products. Often, the therapeutic regime includes different combinations of these tools (e.g. antivirals to reduce viral loads, followed by therapeutic antibodies to maximise immune responses and minimise immune exhaustion, and a prime boost vaccine for chronic infection).

Therapeutic vaccines are intensely explored in the area of oncology (54% of therapeutic vaccines clinical developments in 2012), as can be seen in the recent major deals between BMS and Bavarian Nordic²³ and Roche and Immatics biotechnologies (November 2013), and Boehringer Ingelheim and CureVac (2014), for such innovations. This perspective calls for the need for a European agenda on this type of vaccines' R&D. T-cell-based of therapeutic cancer vaccines, combined to standard care therapies and/or immune checkpoint blockades, are considered to be the most relevant therapy to tackle cancers. Such combinations are overcoming both efficacy issues by targeting specific cancer biomarkers and safety issues by limiting toxicity induced by standard of care therapies and immune-related adverse events induced by immune checkpoint blockades.

Therapeutic vaccines are also being studied in a number of therapeutic areas outside of oncology. Research spans from Parkinson's and Alzheimer's disease to multiple sclerosis, rheumatoid arthritis, diabetes and Crohn's and celiac disease. Many of these activities are rather driven by market size or business potential than scientific advancements, e.g. developing a therapeutic vaccine against coeliac diseases is preferred to an orphan disease such as myasthenia gravis, since the former is more attractive to venture capitalists than the latter. Considering the progressive ageing of the European population and increasing burden of chronic diseases, the application of therapeutic vaccines to these diseases could clearly be an area of great potential in support of future health policies of the European Union.

Despite these promising approaches, many hurdles still exist, and if the number of clinical trials is used as the metric, Europe is lagging behind the US, (see Figure 4 on the next page).

²¹ Scopus.com

²² Cancer immunotherapy, (Dec. 2013), Science (vol.342)

²³ Exclusive Agreement with Bavarian Nordic for PROSTVAC

As highlighted by the IPROVE consulting panel, on top of high occurrence of undesired outcomes or unsatisfying efficacy, the transition of clinical trials in therapeutic vaccines to the next stage or to submission is challenging in respect to time, for the following reasons:

- **Organisational capacity and capability for development:** therapeutic vaccines research is often conducted in a university spin-off or is dependent on one inventor, either of which has limited organisational capabilities.
- **Financing issues:** acquiring funding in the early stages and retain sustained financial support over the development phases is a particular hurdle. Proof-of-concept takes at least 5-8 years. Furthermore, efficacy studies in therapeutic vaccines take a long time, e.g. it takes 7-8 years to demonstrate the efficacy of a cancer vaccine to reduce cancer recurrence.
- **Re-orientation of programmes:** founders and board members of companies investing in the field might have different ideas on the direction of further development; consolidating a real strategy can take years.

As a result, **an R&D agenda is needed for the R&I of therapeutic vaccines. From a purely R&D perspective, therapeutic vaccines share most of the challenges and gaps along the value chain that occur in prophylactic vaccines**, described in the roadmap. However, on top of these, the workshop dedicated to therapeutic vaccines highlighted three key additional types of challenges specific to therapeutic vaccines that are discussed separately in the sections below.

GAPS AND CHALLENGES

A first gap is the lack of a therapeutic vaccines network at European level.

During the consultation, the **lack of a therapeutic vaccines network has been stressed** as a critical gap that would need to be addressed in order to drive innovation in this field. Currently, over 70% of clinical therapeutic vaccine candidates are being developed by biotech or small to mid-size pharma companies, which often lack the broad capabilities and long-term expertise in both technology and therapeutic areas to

fully drive the development. Overcoming this national fragmentation is essential to providing therapeutic vaccines with the necessary market perspective needed to develop products for global medical needs.

A lot of research is conducted on adjuvants or delivery mechanisms but the community is often not aware of the ongoing research of all the various groups. There is a tradition of **collaborating** projects in prophylactic vaccines; e.g. ADITEC²⁴ where adjuvants from different companies are shared and a head to head comparison of different antigens with the same adjuvants is performed, or TBVAC2020²⁵ where candidate vaccines are compared head-to-head before going into further clinical development. Similar partnerships and large projects in the field of therapeutic vaccines are also needed.

The second main challenge appears to be that the applicable regulatory framework to the development of therapeutic vaccines is considered to be unclear in Europe today.

Currently, at EU level, the Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 regulates the area of therapeutic vaccines and is split into gene therapy, somatic cell therapy and tissue-engineered products. The Guideline on the evaluation of anti-cancer medicinal products in man provides some guidance on therapeutic vaccines for oncology, but guidance is missing for other indications.

While the European Medicines Agency considered that it would be difficult and not warranted to have a regulatory guideline that could cover all possible clinical developments for therapeutic vaccines, some of the stakeholders consulted suggested to work on a **better legal definition** of "therapeutic vaccines" around one comprehensive concept to simplify the regulatory environment for the field. The US' Clinical Considerations for Therapeutic Cancer Vaccines', (October 2012) is taken as an example of good practice specifically in the field of cancer vaccines. Stakeholders consider that having clarity on the regulatory side would allow competing on the same basis and in a

Figure 4: Therapeutic Vaccines Trials conducted between 2010 and 2015

Source: clinicaltrials.gov

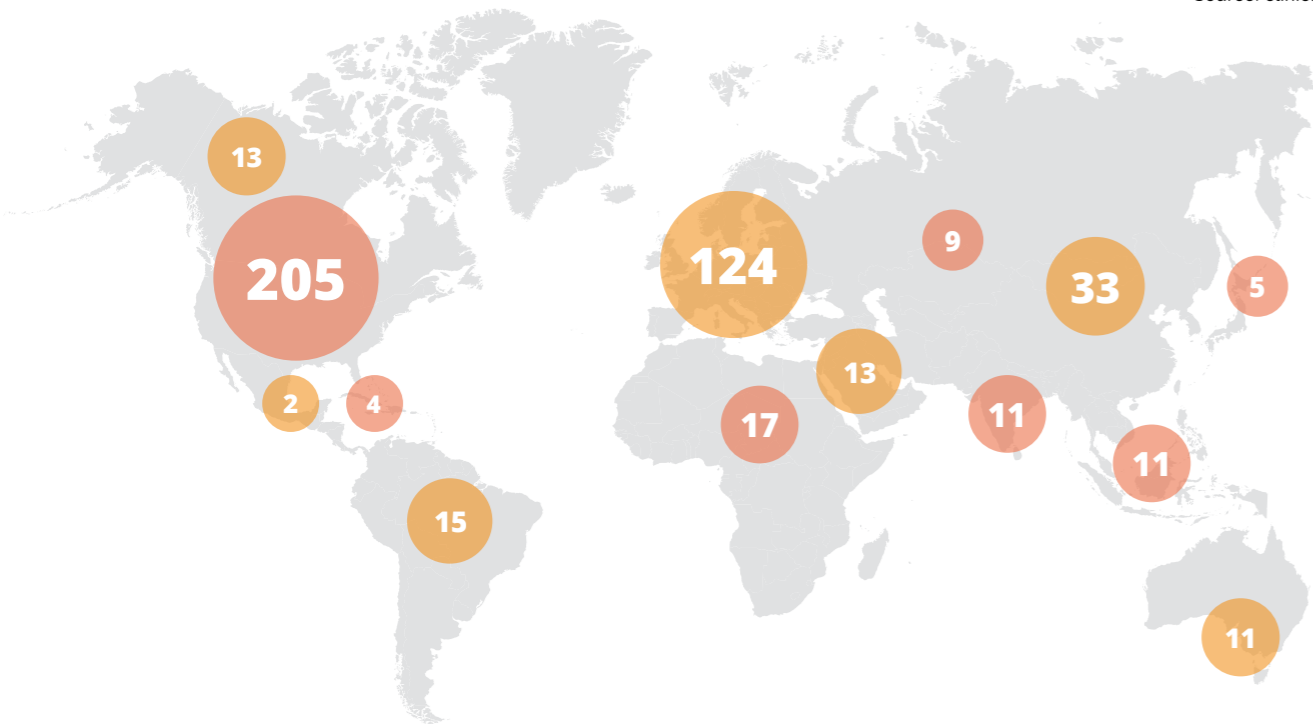
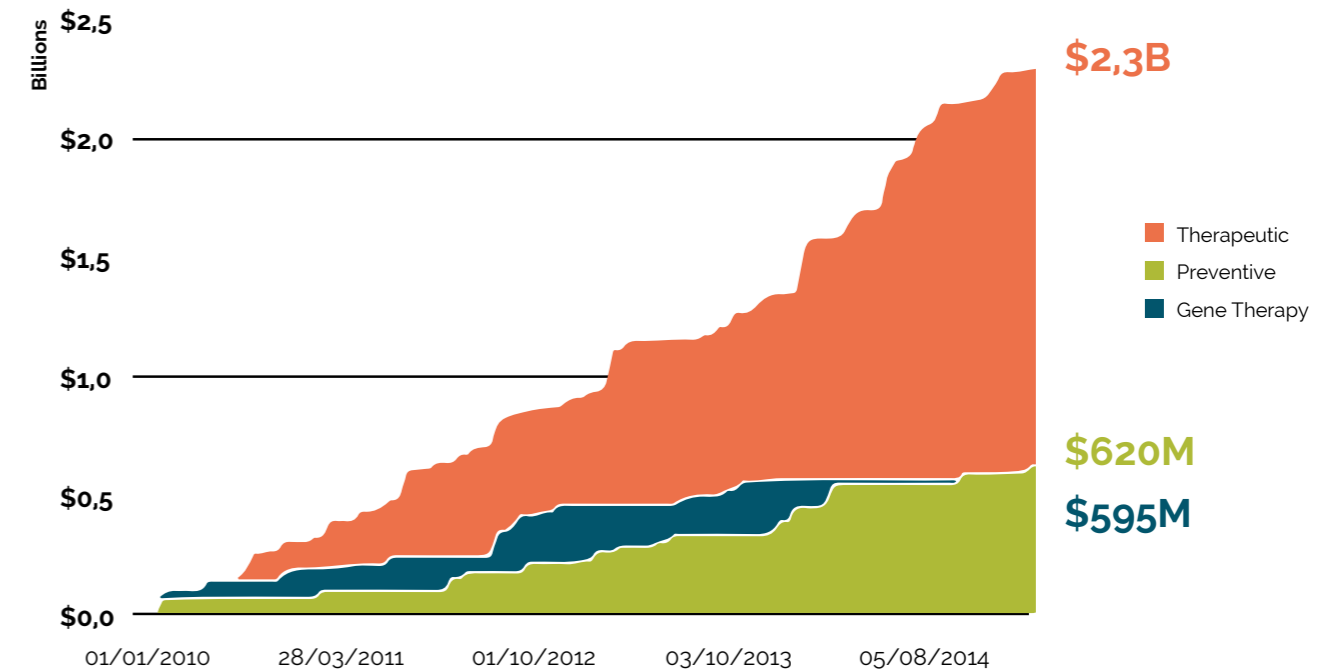


Figure 5: Venture Capital targeting vaccines

Source: Courtesy of Dr. Michael Watson, Sanofi Pasteur



²⁴ <http://www.aditecproject.eu>
²⁵ <http://www.tbvi.eu/projects/tbvac2020.html>

levelled regulatory environment across regions. The EMA recommended interacting early on with regulators on the basis of specific plans, when starting vaccine development in new areas, especially since some consultations are free for certain stakeholder categories.

Finally, there is a gap in creating a reliable funding environment appropriate for companies developing therapeutic vaccines.

This is a long, complex and expensive process. It often starts with the translation of fundamental research to biotechnology start-up companies, often funded by venture capital. There is some indication that the interest of venture capitalists is increasingly in therapeutic rather than prophylactic vaccines. The EC's Horizon 2020 programme, Juncker's investment plan and the programmes of the European Investment Bank – in particular the "Infectious Disease Finance Facility"²⁶ – are all expected to contribute positively to the situation in Europe. However, the consensus from the workshop participants was that Europe lags behind the USA in its ability to structure and fund biotech and university spin-offs in the area of oncology. For example 70% of all VC investments are led by US funds and there is no EU equivalent of the US's National Cancer Institute (NCI), which plays the role of a catalyst for therapeutic cancer vaccines.

As for prophylactic vaccines, there was a consensus that, beyond funding considerations, Europe could benefit from a more connected ecosystem for therapeutic vaccines. Examples in the US include networks of academics, innovative SMEs and VCs often geographically co-located. In Europe networks are only starting to emerge in a more or less formalised way in certain countries or regions (e.g. in Belgium and Netherlands). In this regard a transversal project could help to increase the momentum of this market, stimulating cross-fertilisation across the major European players in this area.

RECOMMENDATIONS FOR EU LEVEL ACTION

In the end, the consultation resulted in four main recommendations:

Firstly, the workshop concluded that **the field of therapeutic vaccines as a whole should be moved up** within research programming and funding priorities. The consultation also concluded **not to prioritise within the field** (rare diseases vs. severe, more frequent diseases, as well as private vs. public prioritisation).

In the short term, a task force should be set up involving all stakeholders active in the field of therapeutic vaccines at EU level, in order to develop a collaborative network. Such a collaborative network would benefit advances in therapeutic vaccines in 4 ways:

- Exchange findings and potentially bundle efforts, exchange best practice, successful and unsuccessful approaches, and sharing know-how and technology
- Make it easier for big pharmaceutical companies to identify interesting new research developments and allow them to support initiatives financially or capacity-wise
- Help with the understanding of underlying disease mechanisms and the interaction of disease-causing agents with the human immune system
- Design and perform multi-centre clinical studies

This in turn is likely to lead to shorter development times and lower attrition of viable projects.

Thirdly, the EC could facilitate close collaboration between therapeutic vaccines developers and regulatory agencies in order to address the regulatory challenges.

- In the short term, EC could support the organisation of regular workshops between therapeutic vaccine developers and regulatory agencies, such as the Committee for Advanced Therapies' workshop on gene-therapy or the Paul-Ehrlich Institute's workshop on viral vectors, in order to promote the exchange of information and discussion with the therapeutic vaccine community.
- In the longer run, such discussions could aim at clarifying the regulatory environment. Such evolution would require regulators to assess, where relevant, the feasibility of developing EU wide guidance for the development of therapeutic vaccines; for instance this could be in the area of cancer therapeutic vaccines akin to the US FDA model, in view of fostering an equally competitive environment from a regulatory perspective for new thriving research.

Finally, the EC could support the field through actions promoting targeted funding opportunities.

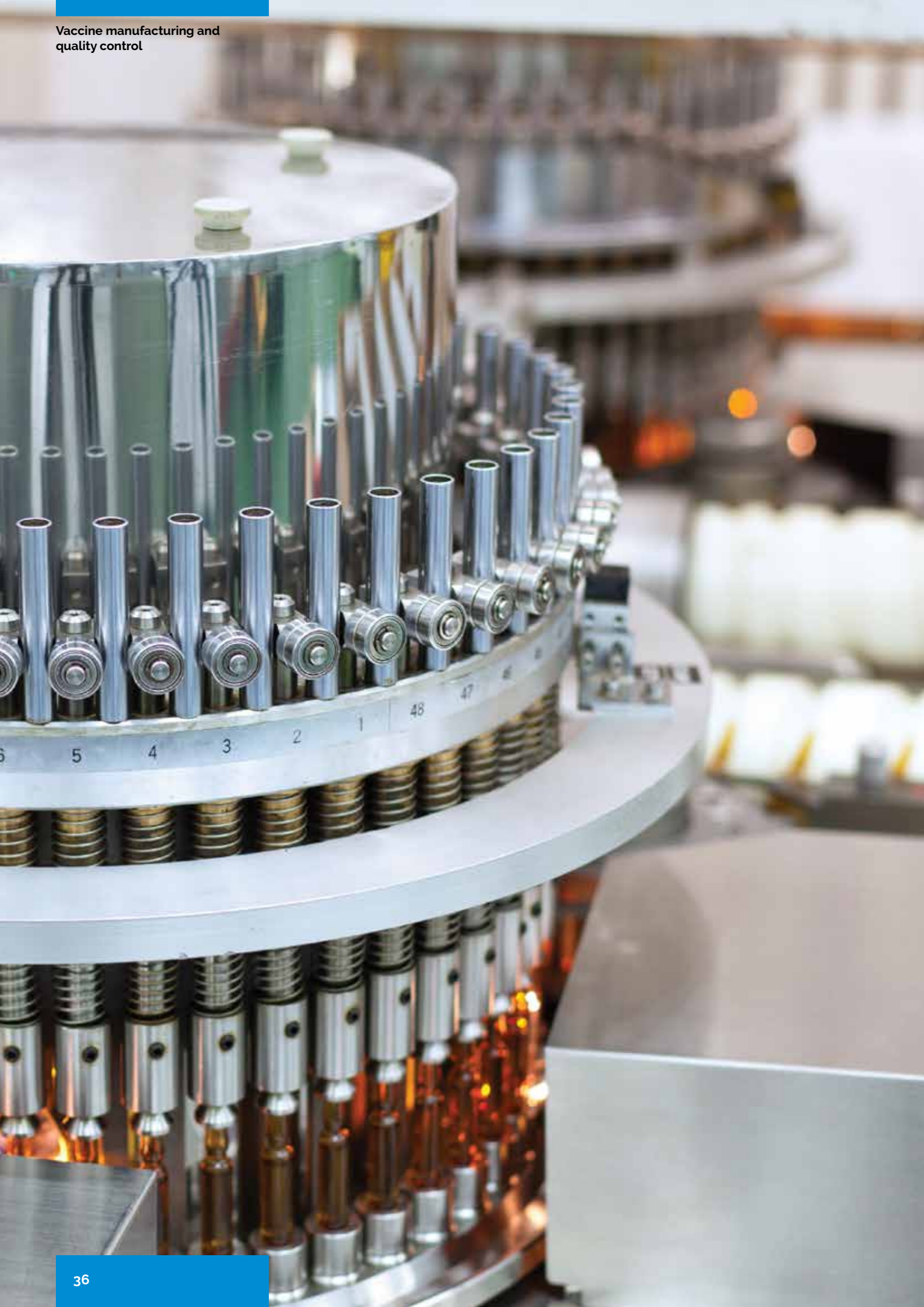
Although funding programs exist at EU level and the efforts to facilitate SMEs' inclusion have been acknowledged, four levers have been identified to create a supportive financial environment:

1. Bridging the gap between research and market: it is key to concentrate EC policies for promoting availability of grants and risk capital on innovative researchers mainly for early stages (pre-clinical), but also during development stages.
2. Creating Efficient Financial Markets: Taking the different financial markets of EU Member States into consideration, governments need to assure that their financial markets operate efficiently so that most deserving firms would have access to financing and successful ones would adequately be rewarded.

3. Government policies to Improve Equity Financing: Access to funding via similar or new vehicles has to be improved in Europe. The Juncker Investment Plan & the European Investment Bank should play a pivotal role in implementing an innovative financing strategy.
4. Lower risk perception: Funding opportunities could be increased by lowering the risk perception of investors. A big incentive for investors would be a possibility to have an agreement with payers.

Therapeutic Vaccines	
GAPS & CHALLENGES	Recommendations
<p>Organisational challenges: no therapeutic vaccines' network at EU level</p>	<p>Provide greater visibility and investment in the field of therapeutic vaccines as a whole within EU research programming.</p> <p>Establish collaborative cross-expertise EU level network</p> <ul style="list-style-type: none"> ➤ Exchange best-practice, including successful and unsuccessful approaches, share know-how and technology ➤ Design and perform multi-centre clinical studies ➤ Facilitate the identification of new research developments
<p>Regulatory challenges: EU regulatory framework is unclear</p>	<p>Foster early dialogue with regulatory bodies</p> <ul style="list-style-type: none"> ➤ Facilitate early interactions and regular dialogue with regulators, e.g. through EC-led workshops ➤ Regulators to assess the feasibility of developing EU-level guidance for therapeutic vaccines, including in specific disease areas
<p>Financial challenges: gap in creating a reliable funding environment appropriate for companies developing therapeutic vaccines</p>	<p>Develop targeted funding opportunities</p> <ul style="list-style-type: none"> ➤ Bridge the gap between research and market and create efficient financial markets ➤ Government policies to improve equity financing ➤ Lower risk risk perception through appropriate mechanisms, including interactions with payers

²⁶ InnovFin infectious diseases. (2015). A new Finance Facility to stimulate investment in Infectious Disease R&D



7 Vaccine manufacturing and quality control

GAPS AND CHALLENGES

Vaccines are large, complex often hybrid biological molecules. They are produced through multiple steps of production and formulation for which the end product (vaccine or combination vaccine) is often a combination of many component products (antigens or vaccines). As a result the final product cannot be characterised in the same way as a small molecule medicine. The structure, consistency and integrity of the final product is assured by ensuring that the production process itself is as reproducible and consistent as possible, thereby ensuring a reproducible and consistent end product. This requires a production system that can be very tightly controlled and a team able to consistently implement such processes. The manufacturing also encompasses a set of well characterised quality control tests that document the process parameters and agreement with regulators and product release authorities on the best tests to use and parameters of acceptability. The end result is a product that is defined more by its production process than by the final output.

The resulting production process takes between 6-36 months of which 70% of the time is consumed by control testing. As a result anything that can be done to standardise the production process, modernise and standardise release tests and ensure a streamlined process and standardised regulatory and release requirements, will allow shorter cycle times and faster and more predictable production of vaccines. This is urgently needed as today, global demand outstrips supply for all but a very few vaccines. This gap between supply and demand is a result of the complexity, cost and duration of production and the paucity of producers able to meet the demanding standards and costs.

The main areas of focus of the consultation were:

- How to innovate vaccine production and release, to address the global shortage of almost all vaccines
- How to increase production capacity and shorten cycle times
- How to minimise costs and minimise unpredictability of development and production

Achieving better global vaccine supply

One of the key needs identified during the consultation on manufacturing and quality control was the need to support **technologies** that will address the current **global vaccine supply shortage**. **Overarching principles that could increase production speed, production yields and production predictability** were Quality by Design (QbD) approach and improvements in process analytical technology (PAT) mechanisms. After a decade of development, PAT has become a reality for small molecule production, and has proven its ability to increase process robustness and reduce costs. However, this concept is still emerging for bio manufacturing, and technologies and know-how need further development to be applied in vaccines. Currently the specificity and reliability of these tools are lower for vaccines and cannot be used for quantitative purposes. Therefore, very basic in-process assays are not yet established. Further work is also required to better monitor impurities as well as measuring the 3D structure of the vaccines. This would allow better characterisation of the folding of the antigen being presented and thereby allow better predictability of its potency.

The panel of experts consulted emphasised that innovative technological approaches are also desirable to make **vaccines easier to deliver and administer**. This should include work to develop **thermostable vaccines** to overcome the need to keep vaccines in a cold chain^{27, 28}. Participants also agreed that new delivery systems could enhance the ability to deliver vaccines and thereby increase vaccination coverage.

Increasing production capacity and improving timelines especially in epidemic or pandemic settings

The need to be able to rapidly produce large quantities of vaccine in a very short time is essential to the ability to respond to future epidemics and pandemics. This is already a priority in a number of countries (e.g. BARDA²⁹ in the US), but should become a priority throughout Europe.

²⁷ IFPMA. The complex journey of a vaccine. 2014

²⁸ Karp CL et al. (2015) Evaluating the value proposition for improving vaccine thermostability to increase vaccine impact in low and middle income countries

²⁹ Biomedical Advanced Research and Development Authority. <https://www.medicalcountermeasures.gov/barda.aspx>

This will require innovation in the process, in disposable technologies and in the approval and release process. Progress made for epidemic and pandemic preparedness is likely to be rapidly transferable to the production of routine vaccines.

The main need identified by the participants was for modular facilities, combining **platform technologies flexible** enough to manufacture a multitude of candidates and **processes/facilities that are easy to switch and scale up**. Modular facilities would allow the facilities to be used for routine vaccines and then switch rapidly to production of epidemic and pandemic vaccines as was done for the flu vaccine during the H1N1 pandemic. Alternative models include disposable technologies or the combination of warm-based production and stockpiling as is done for the smallpox vaccine.

Today, most current facilities are at or close to full capacity. There is, therefore, the need for a global increase in vaccines production capacity³⁰. Approaches such as insect cell culture-based vaccine production may offer greater flexibility with lighter **infrastructure, which could in turn reduce costs by 80-90%** compared to traditional approaches³¹.

Disposable bioreactors and downstream equipment also offer the ability for flexible production in BSL2 environments. However, these approaches are not currently possible for all vaccines and work is required to extend their use and develop other novel approaches.

Other production goals include the need to develop scaffold-based technologies able to express a large range of antigens in a highly stable form, and as close as possible to native conformation, that could be combined with other antigens in combination vaccines with minimal risk of conflicting formulations.

Improving affordability and reducing development risks

There are also human and organisational facilitators to vaccine production process optimisation. For example, early and continuous collaboration between the manufacturing teams, process development teams and early research teams is essential. There is also a need to develop tools that allow researchers and companies to better predict from a mL scale production to how a candidate vaccine will behave at commercial scale. Improved understanding in this area will help to de-risk the scale-up phases, identify early potential production bottlenecks or constraints and thus accelerate the time to market of vaccines as well as optimise vaccines affordability.

Lastly, novel **expression systems** such as algae or plants offer the potential for high capacity production in cell lines that are easier to work with and represent a far wider species gap. This would provide a further strategy for addressing the global supply shortage. However, these approaches have yet to prove themselves fully and further development is required.

There are other technologies, such as fully synthetic biology, whereby proteins, DNA or mRNA molecules could theoretically be synthesised chemically rather than biologically. Such an approach would bring huge benefits but would require significant advances in chemistry and associated adaptation of production facilities and regulatory and release requirements³².

RECOMMENDATIONS FOR EU LEVEL ACTION

The recommendations of the manufacturing subgroup were predominantly on the need for more focused research priorities and associated funding that would drive forward a vaccine production and formulation R&D agenda that would allow:

- Better translation of innovative research into applied production innovation as a result of **better connection of research, process technology and regulators**. This would be in order to promote closer collaboration among scientists, engineers and regulators.
- **Supporting the continuity of funding beyond concept demonstration**; this is especially crucial in the context of emergencies:
 - + e.g. by setting up a task force (TF) of regulators and policy-makers to support procedures based on scenario planning. This will allow a better assessment of cost-effective ways of handling emergency situations through establishing appropriate infrastructures in a pragmatic way.
 - + Funding innovation for easier administration and delivery to increase vaccine coverage.

With regards to **funding priorities**, the following research areas were mentioned:

- Funding directed at flexible manufacturing systems
 - + Investigate/research how to decentralise manufacturing capacity through a more localised supply base to avoid supply interruption in case of issues and shorten transport/delivery timelines.

- + To support the adoption of single use systems and technologies should help minimising variations between sites.
- Bridging technology and science: collaboration between engineers and biologists

Move away from the constraints of the cold-chain through investing in thermostability. This will enable technologies that ease the vaccine supply process, preventing the problem of deviation from the required temperatures, particularly in the context of low and middle income countries.

- Test alternative delivery devices: increasing vaccine stability and new fill-in allowing to avoid volume loss
- More investment in formulation expertise in the research process

- Develop and validate improved potency assays that better link potency and safety attributes of the product, in order to increase relevance while simplifying the testing
- Develop assay platforms allowing for rapid characterisation in different manufacturing systems
- Develop robust assays for in-process control for both up-stream and down-stream processing
- Improve manufacturing operations and identify new purification techniques to achieve better resolution between impurities and product, e.g. through improved chromatographic techniques adapted to adenoviruses or particle-based vaccines, since current techniques remain limiting being primarily based on mono-clonal antibodies.

Innovative processes for vaccine manufacturing and quality control	
GAPS & CHALLENGES	Recommendations
Achieving better global vaccine supply	<ul style="list-style-type: none"> ➤ Translate innovative research into applied production innovation: <ul style="list-style-type: none"> + Promote closer collaboration among scientists, engineers and regulators + Offer continuity of funding beyond concept demonstration (especially in the context of emergencies) + Set up a task force of regulators and policy-makers to support plans based on scenario planning
Increasing production capacity and improving timelines especially in epidemic or pandemic settings	<ul style="list-style-type: none"> ➤ Develop flexible manufacturing systems <ul style="list-style-type: none"> + Investigate how to decentralise manufacturing capacity through a more localised supply base to avoid supply interruption in case of issues and shorten transport as well as delivery timelines + Support the adoption of single use systems and technologies to minimise variations between sites
Improving affordability and reducing development risks, by assessing early enough vaccines candidates in terms manufacturing efficiency potential at commercial scale with large titers in a cost-effective way	<ul style="list-style-type: none"> ➤ Bridge technology and science: collaboration between engineers and biologists <ul style="list-style-type: none"> + Investing in thermostability enabling technologies + Test alternative delivery devices: increasing vaccine stability and new fill-in to reduce volume loss + Investment in formulation expertise in the research process + Develop and validate improved potency assays to increase relevance while simplifying testing + Develop assay platforms allowing for rapid characterisation for different manufacturing systems + Develop robust assays for in-process control for both up-stream and down-stream processing ➤ Improve of manufacturing operations and identification of new purification techniques <ul style="list-style-type: none"> + Improved chromatographic techniques adapted to adenoviruses or particle-based vaccines

³⁰ Vaccines Europe. (2013) Advancing health through vaccines innovation, accessible at www.vaccineseurope.eu

³¹ Presentation: Rahul Singhvi. (2010) Manufacturing Enabled Global Influenza Vaccine Solution; cited in T. Mukhopadhyay presentation 2015)- IPROVE R&I workshop

³² T. Mukhopadhyay presentation (2015), IPROVE R&I workshop



8 Vaccine Infrastructures

Current vaccine development is a highly collaborative effort, in which public-private partnerships for co-development or licensing have become the standard business model^{33 34 35} and special effort within the European community has been made to harmonise access to the Biomedical Research Infrastructures (RIs) relevant to vaccines R&D (i.e. EATRIS, ECRIN, BBMRI, INSTRUCT & ELIXIR). Consequently, the vaccine R&D expertise and facilities available in Europe provide an outstanding opportunity for further advancing the development of a favourable eco-system for vaccine innovation in Europe.

GAPS AND CHALLENGES

A recent analysis of R&D patent and publication networks over 10 years shows that Europe remains a collection of national innovation systems and that cross-border collaboration is below expectation for an integrated European research area. The relatively recent introduction of biomedical RIs such as ECRIN, EATRIS and BBMRI (all of which formally received ERIC status in late 2013 or 2014), has allowed the establishment of permanent legal entities with pan-European scope of activity. These RIs already deliver high quality services and access to vaccine infrastructure, but their relatively recent establishment gives rise to the need to further embed their activities in the vaccines research arena and promote innovation in Europe and beyond.

Consequently, the vaccine R&D expertise available in Europe, combined with facilities and infrastructures existing at the level of EU Member States, provides Europe with the chance to further drive the development of an environment which nurtures vaccine innovation.

This should include the establishment of a seamless European infrastructure pipeline dedicated to vaccine R&D.

Several successful initiatives already exist to stimulate and facilitate effective public-private collaboration

such as largest existing Innovative Medicines Initiative in the non-competitive research sphere and research infrastructures such as the EATRIS ERIC. These should be built upon to work on bottlenecks, including lack of legal and business development expertise within academia, industry investments shifting away from early research towards later development and the limited infrastructure available for post-licensure studies on effectiveness and safety of vaccines.

As raised during the IPROVE SMEs and R&D workshops, there is a need for promoting access to cutting edge technology platforms and innovative services serving the R&D need for translational and clinical development;

- Antigen selection and vaccine design
- Immunisation technologies
- Clinical development of vaccines
- Manufacturing & quality control

RECOMMENDATIONS FOR EU LEVEL ACTION

- Develop the network of existing facilities and expertise across Europe
- Maintain, upgrade or develop new infrastructures in areas where gaps exist or capacity is insufficient, as following:

+ Antigen selection and vaccine design and immunisation technologies

- Genomics and bioinformatics facilities
- Repository and collections (biobanks, well-characterised pathogen strains)
- High throughput protein production and crystallography facilities
- Animal facilities including bio-containment facilities (BSL-3 and 4), and state-of-the art platforms including histopathology, immune monitoring and imaging for small animal models (e.g. conventional, modified and humanised mice), and large animals, e.g. pigs and non-human primates. Develop and allow access to libraries (monoclonal antibodies)
- Immunisation technologies
- Live vectors platform
- Adjuvant platform
- Delivery systems/nanotechnologies
- Formulation platform
- Infrastructure for human challenge models

³³ Business Insights. (2009) - The Vaccines Market Outlook To 2014. Competitive landscape, pipeline analysis, growth, opportunities and market forecasts

³⁴ PricewaterhouseCoopers Pharmaceutical and Life Sciences. (2009) - Pharma 2020: Challenging business models - Which path will you take?

³⁵ PricewaterhouseCoopers Pharmaceutical and Life Sciences. (2010) - Biotech reinvented - Where do you go from here?

+ Clinical development of vaccines

- Provide ethical and regulatory knowledge
- Map centers with methodological competences
- Map volunteers/specific populations
- Identify or develop cohorts (registries)
- Develop cross border connection able to rapidly set-up a trial and recruit patient volunteers
- Clinical imaging
- Biomarkers for stratification and follow-up of vaccinees
- Facilities for performing controlled challenge studies in humans, including BSL2 containment
- Clinical trial centers that can perform clinical studies in a hospital setting, and have access to facilities for standardised immune-monitoring, imaging, laboratory testing, and functional monitoring of physiological parameters

+ Manufacturing and quality control

- Secure clear guidance for GMP level for manufacturing and quality control of IP's for phase I-II
- Establish funding schemes that fund the GMP manufacturing of vaccines for their testing in clinical trials up to phase 2
- Allow or facilitate the access to infrastructure required for GMP manufacturing, on the basis of current capacities and bottlenecks
- Organise and provide funding for training programmes in GMP manufacturing, including the establishment of or access to GMP training facilities

- Establish a central platform for measuring the purity of GMP vaccine batches e. g. measurement of host cell proteins
- Establish link between biomarker working groups with potency assay development
- Promote harmonisation/standardisation among facilities
- Foster cross talk with the veterinary field to make use of the experience previously acquired by both specialties

- Foster cross talk with leading experts and nutrition companies in Europe that can support drive research and development in some of the microbiota applications
- Data integration and analysis:
 - + Alignment of methods, analysis and tools
 - + Storage and integration of data from preclinical and clinical sources



Research infrastructures

GAPS & CHALLENGES	Recommendations
Enabling an optimal academia – industry collaboration process is a key challenge	<ul style="list-style-type: none"> ➤ Develop the network of existing EU facilities and cross border connection to rapidly set-up trials and recruit subjects ➤ Upgrade or create new infrastructures in the areas where gaps exist or capacity is insufficient
Reinforce vaccines research infrastructures	<ul style="list-style-type: none"> ➤ Promote harmonisation/standardisation among facilities in five key areas: Genomics and bioinformatics facilities; Repository and collections; High throughput protein production and crystallography facilities; Animal facilities; Immunisation technologies ➤ Develop and promote access to innovative technology platforms: live vectors, adjuvant, formulation ➤ Consolidate and provide access to repository and collections: biobanks and well-characterised pathogen strains
Clinical development of vaccines: lack of support to clinical research infrastructure	<ul style="list-style-type: none"> ➤ Map centres with methodological competences and map volunteers/specific populations ➤ Identify or develop cohorts (registries) ➤ Enable human challenge models ➤ Further develop and structure clinical trial centres coupled with immunomonitoring, imaging, laboratory testing and functional monitoring of physiological parameters
Manufacturing & quality control: need to improve GMP manufacturing capabilities	<ul style="list-style-type: none"> ➤ Secure clear guidance on GMP level for manufacturing and quality control ➤ Establish funding schemes to fund the GMP manufacturing of vaccines for testing up to phase 2 ➤ Facilitate the access to infrastructure required for GMP manufacturing ➤ Establish a central European platform to measure the purity of GMP vaccine batch



9 Vaccine SMEs' Needs

- Viral vectors with ArenaVax, XBrane bioscience
- Adjuvants with DUOTOL, Crossbeta Biosciences, Microbiotec
- Delivery with Sigmoid, DUOTOL, Bioneedle technologies
- CROs (Conforma, Central, WIL research, etc.) and bioprocess equipment developers (Sartorius, etc.)

As in most innovative sectors, SMEs play a critical role in bridging basic discoveries from academic research to clinical development³⁶. This could be seen over the last decade with the increasing amount of both business and licensing deals being signed between small players and larger manufacturers.

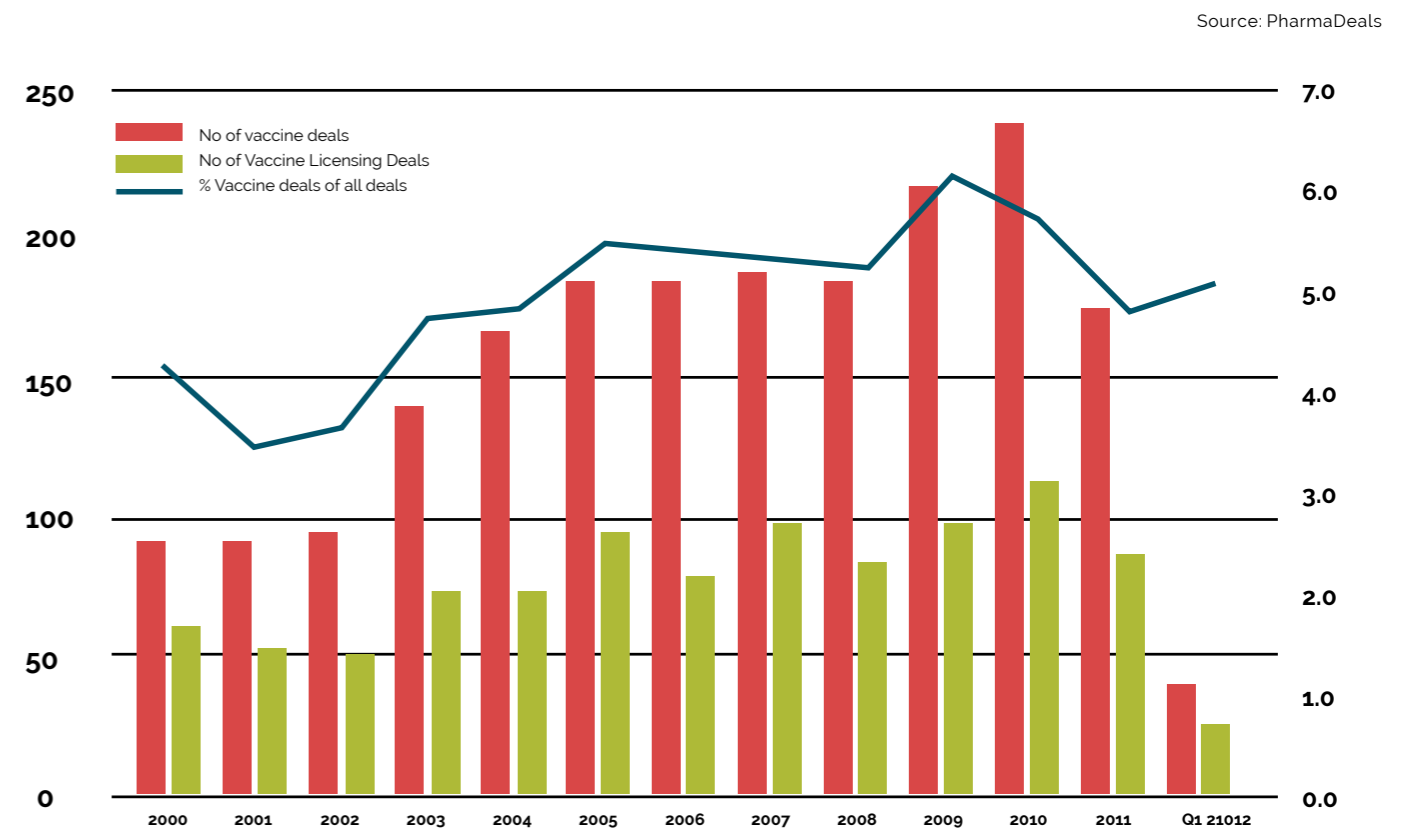
These innovative SMEs range from SMEs developing vaccines, SMEs specialised in standard or innovative platforms for vaccines development (3D molecular modelling services, cell lines, formulation, biologics delivery systems, etc.) and SMEs active in connected disciplines, such as biology, nutrition, immunology, mathematics, modelling, etc.) Even if limited in number, part of European SMEs are leading in some specific fields throughout the value chain, as for example (non-exhaustive list):

GAPS AND CHALLENGES

The number of vaccine SME players in the EU is low mainly due to the limited, fragmented nature of the European financial market to support these ventures. It was estimated by workshop participants that around 80 companies operate in the field of vaccines in the EU. Furthermore, these SMEs are mostly active at a regional level and lack visibility at EU level. The main European hubs where SMEs working on vaccine development can be found in France, Switzerland, Austria and the United Kingdom and growth trends can be seen in Hungary³⁷ as well.

Several gaps have been pointed out by the participants in the development phases from preclinical to proof-of-concept (PoC) through to Phase III.

Figure 6: PharmaDeals - Vaccine deal trends 2000 – 2015³⁸



³⁶ European Commission (2013)- DG Research vaccine SMEs workshop, March 20th 2013

³⁷ IPROVE vaccine SMEs' needs workshop (2014): 15 May 2014

³⁸ Courtesy of GSK - Philippe Denoel (2014) IPROVE workshop on vaccine SMEs' needs; 15 May 2014

These gaps can be clustered around two main challenges identified as the main bottlenecks for SMEs investing in vaccines development to grow further:

- The multiple skills challenge
- The funding challenge

The "multiple-skills" challenge

Although placed right in the 'middle' of the pipeline, i.e. in between academia and industry, SMEs lack resources and capacity to implement their projects. Vaccine development requires from the beginning **specific and broad know-how** for tests, production, and clinical trial settings but also to deal with regulatory constraints and requirements. These skills are concentrated within a handful of large pharma companies, few national institutes and academic platforms. This often leaves SMEs 'out of the game'. There is currently a gap in **securing SMEs access to translational platforms** (public and/or private) that have specific expertise for vaccines. This is indeed one of the key levers to overcome the access to the "skills bottleneck".

Similarly, the consultation of European SME representatives revealed that clinical trials remain extremely challenging for SMEs in Europe, because timelines for regulatory and ethical committees' clearance are long, and perceived deficiencies in the regulatory framework are moving leading-edge technologies elsewhere.

Hence, SMEs **need enhanced collaboration across stakeholders** in order to bridge the expertise/skills gaps they face at specific development stages and to validate the industry's perceived value of SMEs innovation early on. Currently this step is left to individual initiative and could be made more effective through cooperation at EU level.

The funding challenge

The consultation pointed out two recurrent causes of difficult access to private investors for vaccines SMEs: the lack of strong support for vaccines acceptance and the perception of a static environment slow in accepting and embracing innovation. As for **EU funding**, there is a need to better tune existing EU instruments to the specificities of SMEs and vaccines.

Overall, despite the large amount of public funds, several participants stressed that some characteristics of existing funding schemes **do not favour SME research** in vaccine development.

- Funding for promising, early-stage vaccine candidates ready to make the step towards clinical development is very scarce. Financing (possibly through use of a voucher system) directed at feasibility studies to assess GMP manufacturing potential and design coherent clinical development plans would be of great value. However, current SME instruments do not fund products that envisage more than 2-3 years to commercialisation, thereby excluding such projects.
- Follow-up funding of such projects of ca. 3 year duration, allowing scale-up to GMP early clinical trials would fill a current gap
- Also, funding for Phase 2 clinical trials is critical but not part of current SMEs instruments
- Repayment of loans is not fit for actual vaccine research, as the payback timings are lengthy. The loan scheme may only be valid for technology platforms

The assessment criteria to access the existing funding instruments are perceived as inappropriate for vaccine SMEs:

- Up to now, the viability check for SMEs is counter-productive, since many biotechnology companies are only investing in research and the absence of revenue is perceived as a risk requiring additional guarantees or imposing restrictions in accessing funding.
- The same applies to Technology Readiness Levels (TRLs) mechanism, which is inadequate for vaccines developed by SMEs. Vaccine SMEs are rarely or not at all able to deliver a product on the market within 2-3 years and are therefore excluded from most funding instruments.

More broadly, SMEs remain convinced that **more private investors** could be involved to improve the overall financing situation.

RECOMMENDATIONS FOR EU LEVEL ACTION

Five main recommendations arose from the consultation.

1. Map out and create spaces for structured and unstructured networks: EC support is needed to build a network and structure the community:

- Create opportunities/forums to push innovation, increasing interaction and discussing success stories as well as examples of failures to learn from a scientific, regulatory, and market point of view and to facilitate early matchmaking

- Such a network would serve innovation in two complementary aspects:
 - + First, it would allow SMEs to engage and share knowledge and expertise to drive innovation, and would constitute a forum for gathering EU SMEs voice and allow the EC to better understanding of their specific needs
 - + Second, it would ease dialogue with big players and academics, enabling match-making mechanisms and advisory activities tuned to SMEs specific strategies

2. Ease SMEs access to scientific/technical resources and skills, at the most critical phases:

- Pushing and driving support for innovation by identifying innovative ways to facilitate SMEs access to new technologies to reduce R&I costs and timing through collaborative projects and open calls for commissioned research: secured budgets, 'fast track' like processes for innovative SMEs
- Facilitating collaborations between SMEs, large pharma and universities:
 - + EC should support effective matchmaking facilitation mechanisms enabling large companies to provide adequate feedback on initial discussions and extend bilateral collaboration to academia where appropriate
 - As an example: A process set-up at EU level to support SMEs in improving their value proposition/enabling early assessment of SMEs technology/research innovation with large pharma. Create a pull mechanism by providing better support to the interaction between the two, creating meetings with more time available to discuss and explore partnerships
- In the mid-term, create a vaccines innovation community portal in order to:
 - + Improve the exchange of information and facilitate the development of a platform/hub
 - + Strengthen the visibility of available opportunities/services/infrastructures at EU level

3. Supporting SMEs early access to regulatory expertise

- Help with establishing early stage contacts with regulatory bodies, large companies, organisations providing services. Furthermore training initiatives on when to interact with regulatory bodies can be developed teaching how to use existing opportunities. This would serve to give more rapid and formal scientific feedback and aid openness towards the evaluation of new technologies

- Enhance visibility of services that regulatory agencies can provide. Although these services exist, their visibility and accessibility to SMEs could be strengthened

4. Foster competitive collaborative projects between SMEs and larger vaccine companies

- In order to foster collaborative models with large pharma, participants considered that the Commission could be supporting the following activities, within the existing funding mechanisms:
 - Develop an **advising mechanism** that could provide SMEs with easier access to existing facilities and platforms across EU, enabling SMEs to benefit from new technologies. Furthermore it could reduce R&I costs, risks and timings, and help large companies in devising risk management plans to favour a greater extent of collaboration with SMEs³⁹
 - **Commercial contact-making workshops**, which should be a good source of leads
 - A platform or a forum at EU level to facilitate **early contact** making with new models of co-development
 - New instruments allowing SMEs to share R&D projects on the 'Bio-Europe' partnering model
 - Initiatives to support large pharma to provide scientific advice and evaluate projects presented by SMEs
 - An EC "window" awards to successful large pharma-SMEs R&I collaborations, contributing a share of pre-agreed milestones payments upon their achievement: funds should be targeted to successful projects only.

5. Sharpen financial instruments and attracting risk capital towards SMEs:

- The overarching recommendation in this area is to **make the ecosystem more receptive** to innovation for SMEs, reducing the level of bureaucracy and risk:
 - + Invest in improving the public perception of vaccines as a strategic public health tool, fighting back anti-vaccination activists. Uncertain market demand automatically creates uncertainties for researchers and investors and there is a need to ensure that there is a healthy market for vaccines
 - + Supporting **early contact with big pharmaceutical companies** (at least in a consultative role), e.g. by developing EU tailored programmes or call concepts focused on end of pre-clinical and phase I stages

³⁹ Further elaborated in the infrastructure section of the roadmap

+ Better **adjusting public investment to development timelines**, and allowing for funding extension upon development success (US-SBIR-alike system) instead of the current project grant system. Such system is expected to positively bolster innovative SMEs in two ways: reducing risks of gaps in funding, by financing the full development process and helping to drive private investment as a risk sharing approach

> In addition, the consultation proposed to **better adapt current** instruments to vaccines SMEs needs.
 + Foster a dedicated instrument to draft 'calls for proposals' that are relevant for both SMEs and large companies (H2020, IMI). As for IMI specifically, define IMI topics enabling large companies to work with SMEs in the competitive sphere, including in phases 1-2.



Vaccine SMEs	
GAPS & CHALLENGES	Recommendations
<p>The multiple skills challenge: vaccine development requires specific and broad know-how for tests, production and clinical trial settings.</p>	<p>> Establish a network of vaccines SMEs involved in human vaccine R&D at EU-level</p> <ul style="list-style-type: none"> + Create forums and a European network to push innovation, share knowledge and experience, as well as to conduct a comprehensive needs assessment + Create a vaccine innovation community portal to improve the exchange of information, opportunities, services and infrastructures at EU level <p>> Ease SMEs access to scientific and technical resources and skills at the most critical phases</p> <ul style="list-style-type: none"> + Facilitate SMEs access to new technologies to reduce R&I costs and timing + Effective matchmaking and interaction between SMEs and large companies <p>> Support better SMEs early access to regulatory expertise</p> <ul style="list-style-type: none"> + Facilitate the establishment of early stage contacts with regulatory bodies + Enhance the visibility of services that regulatory bodies can provide at national and EU level <p>> Foster competitive collaborative projects between SMEs and larger companies</p> <ul style="list-style-type: none"> + Develop an advising mechanism to provide SMEs with easier access to existing facilities and platforms + Organise commercial contact-making workshops + Set-up new instruments allowing SMEs to share R&D projects on the 'Bio-Europe' partnering model + Establish an EC "window" awards to successful large pharma-SMEs R&I collaborations
<p>The funding challenge: throughout the development phases from preclinical to proof-of-concept (PoC) and then in Phase III</p>	<p>> Sharpen financial instruments and attracting risk capital towards SMEs</p> <ul style="list-style-type: none"> + Invest in improving the public perception of vaccines as a strategic public health tool + Better adapt current instruments to vaccines SME needs: project duration adapted to development timelines, more flexibility in funding extension, publish specific topics enabling large companies to work with SMEs in the competitive sphere, including in phases 1-2

10 Training Needs

Vaccinology covers a wide range of disciplines including immunology, microbiology, epidemiology, infectious diseases, pediatrics, clinical development, biotechnology, production processes, quality control, quality assurance, preservation, shipping, cold chain/supply chain management, public health, health economics, sociology, ethics and communication, to only mention a few.⁴⁰

Furthermore, the diversity of profiles involved in vaccine innovation success throughout the value chain raises the challenge of adapting educational programmes to specific needs. This applies to many stakeholders, from scientists developing innovative vaccines, to engineers in manufacturing as well as healthcare workers that must convince the population about the value of vaccination.

The VACSATC⁴⁰ (Vaccine Safety-Attitudes, Training and Communication) study showed that among medical students less than 60% reported to have received training in safety issues and vaccination controversies; only 44% received training on how to communicate with patients and parents about vaccination; and only 50% stated to have received practical training on how to administer vaccines. Further gaps were identified in postgraduate education and the introduction of PhDs and Masters combining a broad base in vaccinology with various combinations of specialised modules, including modules of applied vaccinology.

Certainly, several key courses⁴¹ and relevant expertise exist at EU level, ranging from courses providing a comprehensive overview of vaccinology, from immunological concepts to vaccine development and implementation of immunisation programs, to post-graduate courses in vaccine related fields such as epidemiology, vaccine safety and efficacy, policies for vaccine implementation, and GMP for vaccine manufacturers. Many others exist, but all are not readily identifiable.

Moreover, as an outcome of the TRANSVAC roadmap⁴², EVRI advanced courses, with a strong hands-on component,

are expected to link the best institutions in Europe. EVRI-recognised Centres of Excellence in Vaccinology throughout Europe should be able to deliver a strong educational mandate.

In broader terms, in Europe, several other education channels exist that can be leveraged such as the European Programme for Intervention Epidemiology Training (EPIET); the European Malaria Graduate School; the European Medicines Research Training Network (EMTRAIN); and finally other tools that can enable a more flexible approach to education and vocational training, including through favoured exchange of expertise across countries, i. e. MOOCs, Erasmus Mundi programmes, and Marie-Curie actions.

GAPS AND CHALLENGES

The IPROVE stakeholder consultation workshop enabled the identification of key needs that were organised per type of stakeholder, according to what is reported in the table here below:

SKATEHOLDERS	TRAINING GAPS AND NEEDS
Public Health staff	<ul style="list-style-type: none"> ➤ Basic knowledge for medical students, nurses, pharmacists, doctors etc., is spread across different courses. Knowledge and information needs to be more comprehensive and visible ➤ Accurate information for the personnel who is in charge of vaccinating is not always available ➤ Sociological and anthropological studies on hesitancy should form part of the Training
Researchers (from both industry and academic/public centres)	<ul style="list-style-type: none"> ➤ Manufacturing (considered to be a largely neglected area) ➤ Process development <ul style="list-style-type: none"> + Upstream + Downstream ➤ Quality Assurance <ul style="list-style-type: none"> + New assays to include novel technologies + Faster assessment + Reduced in vivo-testing + Train more 'academic' Qualified Persons

⁴⁰ VACSTAC is a European collaboration project with 14 partner countries ran in 2006-2009, aiming to improve immunisation programs related to knowledge about attitudes to immunisation, training of medical and paramedical personnel, and number of websites that fulfill criteria set up by GACVS (the WHO Global Advisory Committee on Vaccine Safety)

⁴¹ Non exhaustive list can be found at <http://www.euvaccine.eu/node/307>

⁴² www.transvac.org

SKATEHOLDERS	TRAINING GAPS AND NEEDS
<p>Researchers (from both industry and academic/public centres)</p>	<ul style="list-style-type: none"> ➤ Formulation <ul style="list-style-type: none"> + Thermostability + Adjuvants + Novel delivery devices ➤ Animal models to assess efficacy <ul style="list-style-type: none"> + Opportunities to develop a wider range of animal models + Increase expertise and resources having in-vivo skills with existing models, at all containment levels, starting at the PhD level⁴³ ➤ Immunology <ul style="list-style-type: none"> + Biomarkers and correlates of protection + Immunomonitoring
<p>Staff working in the regulatory field</p>	<ul style="list-style-type: none"> ➤ Training in regulatory science and training for "inspectors"/reviewers
<p>School teachers</p>	<ul style="list-style-type: none"> ➤ Vaccine education at school should be provided for both pupils and parents. School education related to vaccines can come at different stages, general knowledge earlier, followed by specific knowledge surrounding certain vaccines. Education can be plugged into relevant subjects such as biology, etc.
<p>Media</p>	<ul style="list-style-type: none"> ➤ Mass media journalists need access to scientifically robust and accessible information, that can be readily disseminated to a broad public ➤ Training needs for journalists might vary from country to country

RECOMMENDATIONS FOR EU LEVEL ACTION

Audience and training offer in Europe:

- Target groups for training should be better identified as needs between groups are quite different. Each group should be offered the most appropriate training (both in content and format) addressing their specific needs. This could be the topic of a specific study funded at EU level

Training format, accessibility and recognition

- Short-term training only is not enough: Europe requires specialised and in depth long-term training as well as continuous training (life-long learning)
- Training courses should cover the entire process from vaccine R&D to licensure
- Training should be embedded in and compatible with the careers people are working in
- Training in vaccinology needs to be incentivised in order to make it attractive for participants from EU countries
- Training offered needs to be accredited by relevant higher education organisations

Training providers

- Establishment of vaccine training platforms would allow the sharing and shipment of equipment required for

training to the sites/organisations most suited for the organisation of training courses

- Funding for the establishment of infrastructure facilities devoted to training for GMP manufacturing is required as training in existing industrial facilities is not possible

Recommendations as for implementation – moving forward:

- Wherever possible use up-to-date vaccinology training courses, such as various IMI-funded projects (e.g. EMTRAIN, LifeTrain) and providers of online education such as massive open online Course - MOOC (e.g. Iversity, edX)
- Both traditional, face-to-face and online education should be offered, as they can be complementary
- Both country-specific and pan-European training should be provided, evaluating which activities are better implemented at national or at EU level
- Short- and long-term training is required to address specific training needs for different career paths and stages
- Mapping of competency profiles for different jobs related to vaccinology might be useful for developing a comprehensive training offer addressing training needs for different career paths and stages
- Establishment of teams of teachers bringing together different competencies should be fostered,

- as knowledge today is too broad for a single person to be an expert in everything
- Liaison between public sector and vaccine industry is important and should be fostered based on clear codes of conduct for guiding decisions and procedures
- Measuring the impact of training provided is important to demonstrate the added value of training programmes

- Achieve a critical mass by federating and networking of existing platforms and competencies
- Sustainability is key for maintaining competencies and the infrastructures developed.

Training	
GAPS & CHALLENGES	Recommendations
<p>Gaps are based on the need for appropriate training according to specific target groups needs, i.e.:</p> <ul style="list-style-type: none"> ➤ Public health staff ➤ Researchers ➤ Regulators ➤ School teachers ➤ Media 	<ul style="list-style-type: none"> ➤ Identify and profile target groups for training responding to their needs <ul style="list-style-type: none"> + Adapt the training offering in term of content and format to specific groups + Map out and describe competency profiles for different vaccinology related functions ➤ Review and adapt training formats, accessibility and recognition: <ul style="list-style-type: none"> + Collaborate with higher-education organisations and companies to incentivise training in vaccinology and increase accreditation + Set-up specialised initial and life-long training covering the entire process from vaccine R&D to licensure, compatible with career paths ➤ Invest in training the trainers <ul style="list-style-type: none"> + Establish vaccine training platforms to allow the sharing and shipment of equipment required for training + Fund the establishment of facilities devoted to training for GMP manufacturing and train the trainers ➤ Further actions to support implementation <ul style="list-style-type: none"> + Leverage existing platforms, e.g. IMI-funded projects (e.g. EMTRAIN, LifeTrain) and MOOCs (e.g. Iversity, edX) + Achieve a critical mass by federating and networking of existing platforms and competencies + Establish teams of teachers bringing together different and complementary skills + Appropriate measurement of training provider's impact with clear and established metrics

⁴³ <https://www.mrc.ac.uk/documents/pdf/review-of-vulnerable-skills-and-capabilities/>



11 Communication on Immunisation and the Hesitancy Challenge

A vaccine is 0% effective if it remains in the vial. In recent years, there has been increasing recognition⁴⁴ of the importance of vaccine hesitancy as a cause of suboptimal immunisation rates⁴⁵. 'Immunisation hesitancy' is considered to be a new concept and a growing area of study by teams of experts across disciplines. Interest in this area is developing as countries and communities are faced with reluctance (or delay) in accepting the recommended national vaccination offering⁴⁶.

Vaccine hesitancy potentially leads to disease outbreaks. A survey conducted in 2008 – 09 found that up to 20% of parents from five EU countries reported doubts about having their child vaccinated⁴⁷. Since 2010, the EU has seen a series of measles and rubella outbreaks, notably in the UK, France, Italy, Spain, Belgium, Romania, Bulgaria, and, more recently, Germany. The ECDC reported more than 4,000 cases of measles between July 2014 and July 2015⁴⁸. The European Commission reported that only half of all EU countries have achieved the 95% coverage target for two doses of the measles vaccine⁴⁹. Since the 2009 H1N1 pandemic experience, a decline in vaccination against seasonal flu has been reported for key target groups⁵⁰. All but two EU countries are falling short of the 75% coverage target set by the Council⁵¹, leaving 60 million vulnerable adults unvaccinated every year⁵².

Vaccine hesitancy, the human side of vaccination, is a complex and fluid challenge with myriad possible demographic or socio-psychological root causes, which change with context and over time^{53 54}.

Studies of national promotional campaigns and other interventions have shown that almost nothing currently being done to address this problem is actually working^{55 56 57}. Understanding and addressing this challenge requires a multidisciplinary approach that should implicate the social, cognitive, communications and public engagement sciences⁵⁸.

This challenge is indeed a question of vaccine hesitancy, not vaccine refusal. It is the "fence-sitters", where hesitancy can have its root in specific questions with regards to certain vaccines that present the most important challenge. Hesitancy may arise from cognitive influences such as beliefs or heuristics or due to broader societal circumstances. These include factors such as "increasingly 'crowded' vaccination schedules, lower prevalence of vaccine-preventable diseases and thus complacency towards disease risks, greater access to and more rapid dissemination of, vaccine-critical messages via digital networks, hyper-vigilance of parents in relation to children and risk, and an increasingly consumerist orientation to healthcare"⁵⁹.

In alignment with other EU and international initiatives (e.g. the work conducted by the WHO SAGE Working Group dealing with vaccine hesitancy), the IPROVE consultation focused on the latter above-described category of individuals, who are looking for answers to their questions, and who therefore need support to make the right public and individual health decisions. Targeted communication tailored to the needs of this group is considered to be a priority and needs to be informed by stronger evidence on the drivers and determinants of such hesitancy⁶⁰.

Echoing the words of former EU Commissioner for Research Geoghegan-Quinn, "the best vaccine in the world is worth nothing if people don't use it - be it because the vaccines don't reach them, because they are too expensive, because the health system doesn't reach out to the most vulnerable populations, or because people believe rumours about potential side effects"⁶¹.

⁴⁴ Hickler B et al. (2015) Vaccine Special Issue on Vaccine Hesitancy. *Vaccine*, 33(34):4155-6

⁴⁵ ECDC (2012). Systematic literature review of the evidence for effective national immunisation schedule promotional communications. Technical Report

⁴⁶ Dubé E et al. (2015). Vaccine hesitancy, vaccine refusal and the anti-vaccine movement: influence, impact and implications. *Expert Rev Vaccines*, 14(1): 99-117

⁴⁷ Stefanoff, P. et al. (2010). Tracking parental attitudes on vaccination across European countries: The Vaccine Safety, Attitudes, Training and Communication Project (VACSATC). *Vaccine* 28, 5731-5737

⁴⁸ ECDC (2015). Measles and Rubella Monitoring, July 2015. Available online at http://ecdc.europa.eu/en/publications/_publications/measles-rubella-quarterly-surveillance-july-2015.pdf

⁴⁹ DG SANCO (2012). Europe's got measles. Presentation to the EU Health Policy Forum. Available at: http://ec.europa.eu/health/interest_groups/docs/ev_20120510_co04_en.pdf

⁵⁰ European Commission (2014). SWD (2014) 8 final. State of Play on the Implementation of the 2009 Council Recommendation on seasonal influenza vaccination.

http://ec.europa.eu/health/vaccination/docs/seasonflu_staffwd2014_en.pdf

⁵¹ Council Recommendation (2009/1019/EU).

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ.L:2009:348:0071:0072:EN:PDF>

⁵² Preaud E et al. (2014) Vaccines Europe influenza working group. Annual public health and economic benefits of seasonal influenza vaccination: a European estimate. *BMC Public Health*, 14:813

⁵³ Eskola J et al. (2015) SAGE Working Group on Vaccine Hesitancy. How to deal with vaccine hesitancy? *Vaccine* 33(34):4215-7

⁵⁴ Wheelock A et al. (2013) Social and psychological factors underlying adult vaccination behaviour: lessons from seasonal influenza vaccination in the US and the UK. *Expert Rev Vaccines* 12:893-901

⁵⁵ Cairns G et al. (2012) Systematic literature review of the evidence for effective national immunisation schedule promotional communications. Stockholm: ECDC

⁵⁶ Dubé E et al. (2015) SAGE Working Group on Vaccine Hesitancy. Strategies intended to address vaccine hesitancy: Review of published reviews. *Vaccine*, 33(34):4191-203

⁵⁷ Sadaf A et al. (2013) A systematic review of interventions for reducing parental vaccine refusal and vaccine hesitancy. *Vaccine*, 31(40):4293-304

⁵⁸ Larson H et al. (2013) A Multidisciplinary Research Agenda for Understanding Vaccine-Related Decisions. *Vaccines*, 1(3):293-304

⁵⁹ Leask J et al. (2014). The big picture in addressing vaccine hesitancy. *Human Vaccines & Immunotherapeutics* 10:9, 2600-2602

⁶⁰ Leask J (2011). Target the fence sitters. *Nature* Vol. 473, 443-445

⁶¹ Commissioner Geoghegan-Quinn (2014). Presented on the 2nd day of the Conference on New Horizons for Vaccine Research and Innovation, Brussels 13 March 2014

Driving innovation and science into new vaccines does not happen in isolation from other factors, such as creating the appropriate conditions to ensure that the vaccines are used and achieve their intended public health, economic, and societal objectives. Re-thinking the way communication on vaccines has been approached so far is instrumental in this regard and justifies the need to build a real EU research agenda on this fundamental discipline, with a view to establishing the necessary tools and metrics to build effective communications.

GAPS AND CHALLENGES

The 'stakeholder consultation exercise' first endeavoured to list and prioritise the main challenges and gaps that exist in Europe to implement effective communication programmes that can help tackle the issue of vaccine hesitancy. Such gaps have already been largely recognised by the expert community and the scientific literature published on the subject, and the IPROVE stakeholder consultation helped to confirm those findings.

A first fundamental challenge is the heterogeneous nature of the target population. Immunisation programmes target a very broad scope in terms of populations, sub-populations but also vaccinations and immunisation settings. Since a 'one-size fits all' approach does not lend itself to immunisation⁶², there is a need to better capture and study the true nature of individuals' particular vaccine and/or vaccination concerns⁶³. This should start by building a tool for the effective monitoring of attitudes and sentiment behind vaccination, as well as the psychological and social dimensions impacting it, thereby truly enabling researchers to breakdown and analyse the scope of hesitancy.

The segmentation of such populations drawing from social marketing frameworks⁶⁴ is considered to be a first critical step to understand the type and nature of concerns that exist, and direct communication resources more efficiently and in a more targeted manner⁶⁵ than is the case today.

Although the existing literature published on the subject has shown that a set of different and combined channels and methods of communications are deployed to promote vaccination, the consultation highlighted three main issues:

- ▶ Communications are often not sufficiently evidence-based, i.e. with limited information on how these should be designed and implemented to maximise impact and success of interventions. The generation of communications thus tends to be more 'assumption-based' rather than 'evidence-based', often with the risk of rolling out counter-productive approaches
- ▶ Mid-term and ex-post evaluations of communications efforts remain weak, with limited understanding of the return on investment, as well as limited opportunity to re-direct resources or target interventions in a different manner
- ▶ Traditional tools remain the standard way of communicating on vaccines. These methods tend to rely on a one-dimensional or mechanistic approach to disseminating messages⁶⁶. Uptake or adaptation to new and digital tools is low despite the fact that online media are a primary source of information for a large share of the public looking for answers on the topic of vaccination

This latter point is crucial as promotional campaigns are not the only source of information. A wealth of information and misinformation is increasingly available through online and broadcast media from different sources, be it through personal stories or through organised networks. In particular, the viral and wide-reaching effect of social media is to be noted. When online misinformation becomes the primary source of information, hesitant behaviour can quickly be exacerbated⁶⁷.

The approach to risk communication also needs to be better tailored. Risk communication messages often fail to reach the intended targets, particularly those at most risk, due to inconsistency and incoherence of messaging. In addition, the public's diverse levels of knowledge, understanding and perception of risk, is based on cultural and/or environmental sensitivities⁶⁸.

Advance planning efforts through needs assessment and public engagement plans still need further development through cooperation at EU level. Instead of emergency ad-hoc responses to crises, contingency plans and effective risk communication should be conducted well before a crisis occurs⁶⁹.

A broader challenge highlighted by the expert community during the consultation is that communication in public health tends to be regarded as the 'elephant in the room'⁷⁰.

The approach to communications across the public health discipline is insufficiently integrated and often does not constitute a systematic part of the implementation of vaccination programmes.

For instance, some of the experts consulted pointed to the low level of communications training across the public health function and immunisation managers, beyond the low general spending on vaccination campaigns or external communications activities directly targeting the 'vaccinees'.

This represents a missed opportunity. Spending on the purchase of the vaccines and the infrastructures necessary to deliver them is often unable to reach the target populations in an optimal way, due, inter alia, to gaps in communications. As much as a rigorous science is applied and underpins the development of novel vaccines, there is a need for a similar level of commitment to invest in identifying the right strategy that can address hesitancy and bridge the communications gap.

Relevant engagement with civil society, the health community and media were also considered a key current gap. Besides the generally low number of global advocates for vaccination, representatives from the NGO community expressed the fact that they lack sufficient funding and support to partner in promoting immunisation and raising awareness on preventable diseases and their risks. It was also considered that public authorities and health facilities should better engage at the grassroots level long before a new vaccine is introduced. This would help to build awareness and appropriate partnerships to mobilise the necessary critical mass that can contribute to a successful implementation campaign, once the vaccine becomes available and the vaccination programme is rolled out.

The well-known challenges of healthcare workers' own vaccination rates, as well as the recognised gaps in training on how to engage with vaccine-hesitant individuals, were also raised during the consultation. Previous reviews found that while interventions aiming to improve knowledge levels among the general public did not necessarily result in increased vaccine uptake or intention to be vaccinated, interventions aimed to improve knowledge levels among healthcare workers did report, to some extent, evidence of success in this regard. The IPROVE consulted experts thus considered that investments and a real drive for change should take account of these findings.

Last but not least, the consulted panel pointed to the general gap in actual implementation and testing of innovative approaches to understand and implement tools to address the phenomenon of 'immunisation hesitancy'. Recognising the need for further research on how to tackle existing gaps, specifically in the EU context, it has been raised that a wealth of evidence on innovative approaches is already available and should be tapped. This body of knowledge must be put into practice through programmes and pilots that can foster a progressive shift in the overall approach to communications on public health, and specifically, vaccination.

RECOMMENDATIONS FOR EU LEVEL ACTION

As many of the challenges identified are to be addressed at the national level, through the appropriate leadership and ownership by the stakeholders concerned, the IPROVE consultation focused on the development of recommendations that are relevant for EU level action, which demand a certain degree of European cooperation. These are the following:

- ▶ Devise and establish a tool that is capable of enabling a detailed and stratified monitoring of acceptance attitudes, baseline levels of risk awareness, as well as sentiments towards specific vaccines and vaccination programmes at EU level. This should help to support the appropriate measurement of the scope and extent of 'vaccine hesitancy'. Such tool should act as a sentinel or mechanism enabling an active and on-going monitoring of acceptance over time and across tools, using reliable measures capable of capturing sufficiently large datasets to enable the formulation of target group or vaccine-specific conclusions:

⁶² Weinrich (1999). Targeting the general public is like using scattershot ammunition to try to hit a bull's eye. It is possible, but not very efficient

⁶⁴ WHO SAGE working group dealing with vaccine hesitancy (2014). Strategies for addressing vaccine hesitancy – A systematic review

⁶⁵ Nowak G et al (2015). Addressing vaccine hesitancy: The potential value of commercial and social marketing principles and practices, *Vaccine* 2015, <http://dx.doi.org/10.1016/j.vaccine.2015.04.039>

⁶⁶ WHO Europe (2013). The Guide to Tailoring Immunisation Programmes

⁶⁷ European Commission (2014). SWD (2014) 8 final. State of Play on the Implementation of the 2009 Council Recommendation on seasonal influenza vaccination, http://ec.europa.eu/health/vaccination/docs/seasonflu_staffwd2014_en.pdf

⁶⁸ ECDC (2012). Systematic literature review of the evidence for effective national immunisation schedule promotional communications, Technical Report

⁶⁹ Larson H. (2014). Measuring the Vaccine Confidence Gap. Presentation to the ECDC available at <http://ecdc.europa.eu/en/press/events/Documents/Vaccine-confidence-Heidi-Larson.pdf>

⁷⁰ ECDC (2013). A literature review on effective risk communication for the prevention and control of communicable diseases in Europe, Technical Report

⁷⁰ Odugleh-Kolev A. (2014). Building national communication capacity for public health. IPROVE workshop on communications and acceptance, 28 October 2014

- + A monitoring tool of this kind should enable the capturing and extraction of online conversations across countries and languages, and should be used to inform the development of national communications strategies on immunisation to be implemented at country level
- + It is thought that such an undertaking would best be coordinated and funded at EU level, pooling expertise across leading centres of excellence and building upon previous research. The involvement and leadership of bodies such as the European Centre for Disease Prevention and Control (ECDC) and the WHO Europe Regional Office are considered essential to help Member States in their efforts, while respecting individual data privacy
- Invest in the creation and support of multi-disciplinary networks of expertise, including social and behavioural sciences, social marketing, neuroscience, communication sciences, health education and communications, and social media analysts, that can both research and develop evidence-based communications strategies at both an EU and national level. This should include:
 - + Research to develop instruments⁷¹ that can determine and weigh the relative importance of social and behavioural determinants of vaccination acceptance in different contexts, and develop metrics to allow tracking of vaccination acceptance over time and monitoring and evaluation of interventions⁷²
 - + Implementational research to design and pilot interventions aimed at increasing vaccination acceptance and uptake
 - + On-going monitoring of vaccination acceptance at national and EU levels. This would include routine monitoring of the public conversation in mainstream and social media, and of vaccination acceptance at population level
 - + Regional and national immunisation advisory groups should add vaccine hesitancy to their remit and incorporate these tools to better understand and monitor vaccine hesitancy
- EU institutions to support a European initiative to mobilise and federate researchers and practitioners through meetings and other platforms, to facilitate collaborative projects, knowledge sharing, and the formation of a European Community of Practice on vaccination uptake
- Encourage and implement innovative shifts in the training and curricula offerings of the key stakeholders at the core

of the implementation of immunisation programmes. In particular, target the following:

- + R&D to develop evidence-based approaches and tools to enable healthcare workers to understand the importance of vaccinating, and to effectively discuss vaccination with the public. This should focus on healthcare workers who vaccinate or have discussions on vaccination with parents, adolescents and adults. Efforts should not be limited to general practitioners, but also nurses, carers, mid-wives, specialists dealing with older people or patients with chronic conditions, as well as pharmacists in countries where they play an active role in vaccination
- + Fund vocational and on-the-job training programmes aimed at public health staff and immunisation programme managers on the discipline of communications, and the extent to which this supports the achievement of operational public health goals, as well as how to specifically approach the discipline in the context of immunisation
- + Introduce basic infectious diseases, immunology, vaccination and public health training in young children's school curricula to educate future generations against complacency towards the risks of diseases they no longer see and 'institutionalise' the role of vaccination as a cornerstone of public health
- Build partnerships and allocate appropriate funding to collaborate with key civil society organisations, recognising their fundamental role in building awareness, disseminating and creating knowledge on vaccination needs. In addition, educate both the general public and policy makers on the value of vaccination, and how this contributes to multiple 'wins' in public health, economic, and societal terms in the short and longer terms.

Communication on Immunisation and the Hesitancy Challenge	
GAPS & CHALLENGES	Recommendations
<p>Heterogeneous nature of the target population: lack of segmentation along vaccination concerns</p>	<p>➤ Implement stratified monitoring of acceptance attitudes and sentiments towards vaccination</p> <ul style="list-style-type: none"> + Establish a tool capable of detailed and stratified monitoring of acceptance attitudes, risk awareness, sentiments towards vaccines and vaccination programmes at EU level + Develop metrics of vaccination acceptance + Design and pilot interventions
<p>Gaps in the combined communication channels & methods used:</p> <ul style="list-style-type: none"> ➤ Not enough evidence-based ➤ Mid-term & ex-post evaluation <p>Risk communication not tailored enough</p> <p>Communication insufficiently integrated to vaccination programmes implementation</p> <p>Lack of engagement with civil society, health community & media</p>	<p>➤ Invest in the creation and support of multi-disciplinary networks of expertise that can both research and develop evidence-based communications strategies at both an EU and national level:</p> <ul style="list-style-type: none"> + Support regional and national immunisation advisory groups with regards to vaccine hesitancy + EU institutions to facilitate the formation of a European community of practice on vaccination uptake + Bring together experts from social and behavioural science, neuroscience, social marketing, communication and health education
<p>Gaps in training healthcare workers to engage vaccine hesitant individuals</p>	<p>➤ Make healthcare professionals and public health stakeholders effective advocates of vaccination</p> <ul style="list-style-type: none"> + Implement innovative shifts in the curricula offerings for healthcare workers to equip them with the right skills and confidence to appropriately assess vaccination needs and effectively communicate on vaccination + Fund vocational and on-the-job communication training programmes for public health staff and immunisation programme managers + Educate future generations about basic infectious diseases, immunology and public health, e.g. through school-based educational programmes, with a view to institutionalising the role of vaccination as a cornerstone of public health
<p>Lack of implementation & testing of innovative approaches</p>	<p>➤ Engage with civil society organisations</p> <ul style="list-style-type: none"> + Provide appropriate funding and build partnerships to collaborate with such organisations to help building awareness, disseminating and creating knowledge on vaccination needs

⁷¹ Wheelock A et al. (2014) Socio-Psychological Factors Driving Adult Vaccination: A Qualitative Study. PLoS ONE 9(12); Brown KF et al. (2011) Attitudinal and demographic predictors of measles, mumps and rubella (MMR) vaccine acceptance: development and validation of an evidence-based measurement instrument. Vaccine. 29(8):1700-9

⁷² Leask J et al. (2014) The big picture in addressing vaccine hesitancy. Hum Vaccin Immunother; 10:2600-2602

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 projects⁷³ 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 countries⁷⁵ for the period 2007 - 2012⁷⁶; 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 million⁷⁷.

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 management⁷⁸. 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.

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

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

⁷⁵<https://g20.org/about-g20/g20-members/>

⁷⁶A. 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>

⁷⁷UK: \$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>

⁷⁸E.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 emergencies 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

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.

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.

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

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

14 Expected Strategic Impact

The first fundamental direct impact contributed by IPROVE is the opportunity it provided for very different sets of stakeholders to sit together and improve the mutual understanding of their different perspectives, needs and priorities, thus breaking down silos. The expectation is that this in turn will encourage the development of formal and informal networks of collaboration, fostering a truly cooperative, cross-functional and more effective translational approach to vaccines R&D.

The roadmap provides stakeholders operating across the policy, research, programming, and financing domains with evidence of Europe's research gaps and needs with the aim of informing how best to allocate existing resources within both EU and national funding programmes. This will help improve the efficacy and efficiency of research funding and likewise increase the drive to develop innovative vaccines through novel cooperative approaches, risk sharing and venture capital attraction. This is in line with the driving rationale underpinning the Horizon 2020 strategy on the need to create a science environment encompassing a 'research to market product' approach.

The development of a global and more coordinated vision should also help aligning the activities of the major stakeholders from public and private sectors, including industry, national bodies and academia, with the aim of promoting synergies between centres of excellence in different disciplines making up the meta-discipline of vaccines and minimise competition and unnecessary duplication. Additionally, by providing a set of medium to long term priorities and recommendations for funding, IPROVE indirectly also provides a set of indications that could be used in the future to inform evaluations and follow-up on progress in terms of topics and funding allocated to specific priorities along the value chain.

As noted in the earlier chapters, however, research funding is not the only solution to boost innovation. There is a need for more engagement and inclusive dialogue

to understand how to facilitate the translation of the priorities agreed upon by the relevant stakeholders into programmes, through the appropriate partnership models but also through establishing a supportive environment with appropriate instruments, framework conditions, management and technical capabilities.

Clearly, achieving all of the intended objectives and the short and long term expected impact, will largely depend on the political leadership and willingness to take up the recommendations provided, along with the invitation for further long term reflection on what will truly drive innovation. At both EU and national level, this should translate into good dissemination and cross-sector dialogue across the Health, Research, and Industry and Enterprise portfolios, as this would be the first step towards a more coherent vaccine life science strategy and towards building understanding of how the policies of each impact the other, as well as the entire vaccine landscape.

At EU level it is expected that the findings of the roadmap inform strategic priority setting for the Directorate-General (DG) for RESEARCH through the Horizon 2020 programme and beyond, but also the DG SANTE's public health approach to the area of prevention and the support it provides to help Member States implement effective vaccination programmes as well as its Health Programme. The investment in health IT and the appropriate technology infrastructure to support meeting R&D and public health goals will also continue to stay key, under the responsibility of DG CONNECT and its investments in the eHealth sphere. Finally, and more broadly the industrial sector's competitiveness and the understanding of how market dynamics in the vaccine sector impact its role and capacity to address public health needs are of fundamental importance to create an enabling environment, and the engagement with and of DG GROW is essential.

Ultimately, IPROVE aims to:

- (i) Contribute to healthcare systems sustainability
- (ii) Improve EU citizens' quality of life and
- (iii) Boost the sector's competitiveness in the EU
 - all of which will be based on understanding, vision, feasibility and overcoming resistance to change, which will all be essential for fostering a climate of trans-border, truly European-wide collaboration.

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I PROVE List of Stakeholder Consultation Workshops

Topic	Date	Place
Vaccine SME needs	15 May 2014	Brussels
Vaccine communication and hesitancy	28 October 2014	Brussels
Training needs	28 October 2014	Brussels
Vaccine R&D	12-13 March 2015	Brussels
Manufacturing and quality control	12 March 2015	Brussels
Infrastructures	13 March 2015	Brussels
Therapeutic vaccines	26 May 2015	Brussels

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Table of figures

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Figure 2: Number of Vaccines Clinical Trials 2010 – 2015; Source: clinicaltrials.gov

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Figure 4: Therapeutic Vaccines Trials conducted between 2010 and 2015; Source: clinicaltrials.gov

Figure 5: VC targeting vaccines; Source: courtesy of Dr. Michael Watson, Sanofi Pasteur

Figure 6: PharmaDeals - Vaccine deal trends 2000 – 2015

