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Review

Innovation Partnership for a Roadmap on Vaccines in Europe (IPROVE): A vision for the vaccines of tomorrow

Donata Medaglini [a,b,*], Magdalena R. De Azero [c], Odile Leroy [d], Florence Bietrix [e], Philippe Denoel [f]

[a] University of Siena, Department of Medical Biotechnologies, Viale Bracci, 53100 Siena, Italy
[b] Sclavo Vaccines Association, Via Fiorentina 1, 53100 Siena, Italy
[c] Vaccines Europe, Rue du Trone 108/1, 1050 Brussels, Belgium
[d] European Vaccine Initiative, UniversitätsKlinikum Heidelberg, Voßstraße 2, Geb. 4040, 69115 Heidelberg, Germany
[e] EATRIS ERIC, De Boelelaan 1118, 1081 HZ Amsterdam, The Netherlands
[f] GSK Vaccines, Rue de l'Institut 89, 1330 Rixensart, Belgium[1]

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ABSTRACT

A clear vision for vaccines research and development (R&D) is needed if Europe is to continue to lead the discovery of next generation vaccines. Innovation Partnership for a Roadmap on Vaccines in Europe (IPROVE) is a collaboration between leading vaccine experts to develop a roadmap setting out how Europe can best invest in the science and technology essential for vaccines innovation. This FP7 project, started in December 2013, brought together more than 130 key public and private stakeholders from academia, public health institutes, regulators, industry and small and medium-sized enterprises to determine and prioritise the gaps and challenges to be addressed to bolster innovation in vaccines and vaccination in Europe. The IPROVE consultation process was structured around seven themes: vaccine R&D, manufacturing and quality control, infrastructure, therapeutic vaccines, needs of small and medium-sized enterprises, vaccines acceptance and training needs.

More than 80 recommendations were made by the consultation groups, mainly focused on the need for a multidisciplinary research approach to stimulate innovation, accelerated translation of scientific knowledge into technological innovation, and fostering of real collaboration within the European vaccine ecosystem. 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 of both the general public and healthcare professionals.

Bringing together a wide range of stakeholders to work on the IPROVE roadmap has increased mutual understanding of their different perspectives, needs and priorities. IPROVE is a first attempt to develop such a comprehensive view of the vaccine sector. This prioritisation effort, aims to help policy-makers and funders identify those vaccine-related areas and technologies where key investment is needed for short and medium-long term success.

Contents

Abbreviations: DG, Directorate General; EC, European Commission; EU, European Union; FP7, Seventh Framework Programme for Research and Innovation; GMP, Good Manufacturing Practices; IT, Information Technology; R&D, Research and Development; R&I, Research and Innovation; SME, Small and Medium size Enterprise; IPROVE, Innovation Partnership for a Roadmap on Vaccines in Europe; WHO, World Health Organisation.

* Corresponding author at: University of Siena and Sclavo Vaccines Association, 53100 Siena, Italy.
E-mail address: donata.medaglini@unisi.it (D. Medaglini).

[1] Chair of the Vaccines Europe R&D group.

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1. Vaccine R&D in Europe: need for a joint roadmap

Vaccination, together with hygiene and antibiotics has brought a reduction in child mortality over the past few decades and contributed to increased disability-free life expectancy in Western societies. However, for some important diseases there are still no vaccines, and for others, currently available vaccines could be improved. Therefore priority should be given to research and development of vaccines. Today, vaccine discovery is highly sophisticated, requiring a multi-disciplinary and public-private approach to both science and funding [1,2].

Europe has a long history of vaccine research, development and manufacturing, and a strong industrial infrastructure. More than 80% of vaccine doses from the major research manufacturers are produced in Europe and exported for worldwide use [3]. Europe's numerous centres of excellence in vaccinology and related disciplines give it the ability to lead discovery of the next generation of vaccines. A clear roadmap of vaccine R&D, political, legal, economic and structural measures was needed to incentivise, reward and accelerate research and maintain Europe's lead in this key sector.

Vaccine development can take 15–20 years with a further 6.4 years to achieve effective access for the population to be vaccinated. Several years of laboratory research are followed by clinical trials of the candidate vaccine that may involve thousands of volunteers. Vaccine manufacture is a complex process and, mainly due to extensive quality control measures, 6–24 months may elapse between availability of vaccine in bulk form and its distribution. Opening a new production facility may take more than 5 years and cost US $100mio–600mio [4].

Given the complexity of vaccine research and development, a supportive and innovative R&D environment is critical for the development of new vaccine technologies, and to attract skilled scientists and sustainable investment. Strong partnerships and cooperation across academic, industrial, political, social and economic fields are also essential [5]. To ensure continued vaccine innovation and efficient manufacture and supply – a European strategy covering all these aspects was needed.

2. The IPROVE approach

The IPROVE (Innovation Partnership for a Roadmap on Vaccines in Europe) FP7 project was conceived to propose a roadmap for European investment in innovative science and technology for vaccines [6]. It covers vaccine discovery, development, production and access and reflects on political, legal, economic and structural measures to incentivise, reward and accelerate the development of vaccines. IPROVE is the first EU-funded attempt to develop a holistic view of the vaccine sector. Its goal is to maintain Europe's competitive advantage in the development and delivery of innovative prophylactic and therapeutic vaccines. The IPROVE consortium consists of four leading European vaccines-related organisations: Vaccines Europe [3], European Vaccine Initiative [7], Sclavo Vaccines Association [8], and European Infrastructure for Translational Medicine [9]. Focused on key areas of unmet medical needs, rather than on disease-based approaches, the roadmap concentrates on technologies and transversal research, taking a helicopter view across innovative projects and collaborators.

IPROVE brought together over 130 key public and private stakeholders from academia, public health institutes, regulators, industry, small and medium-sized enterprises to determine the gaps and challenges to be addressed to boost innovation in vaccines and vaccination in Europe [10]. This consultation was structured into seven themes (i) Vaccine R&D; (ii) Therapeutic Vaccines; (iii) Production and Manufacturing; (iv) Infrastructures; (v) Vaccine SMEs needs; (vi) Training; (vii) Communications and Acceptance of Vaccination (see Fig. 1). Each theme was addressed through dedicated multi-stakeholder workshops (Supplement S1). The resulting draft roadmap was submitted to the IPROVE

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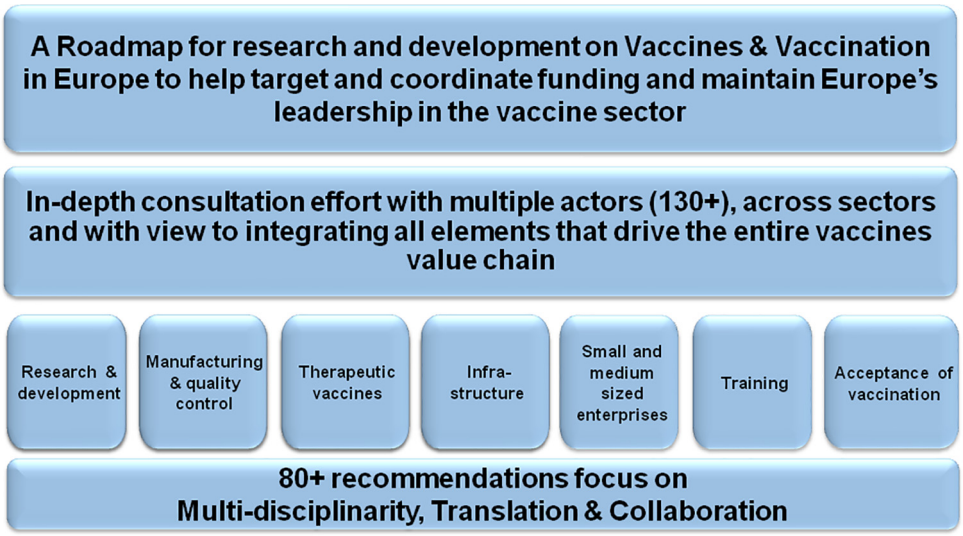

Fig. 1. The IPROVE approach.

consortium partners, IPROVE Advisory Board (Supplement S2) and IPROVE Affiliate Members Group (Supplement S3) who refined the priorities and recommendations. Further stakeholders were consulted via a publicly accessible web-based platform. The final IPROVE Roadmap [11] was launched in occasion of a dedicated European Parliament event. Vaccines community members were present, from academia, industry, civil society and regulatory bodies, including key opinion leaders in vaccine R&D and representatives from the European Commission, European Parliament, and European Union Member States.

3. The IPROVE roadmap

The IPROVE roadmap [11] is expected to guide future European research commitments and investment to create an environment that stimulates vaccine research, know-how, and innovation. For each roadmap theme, gaps and challenges in investment, science and structure are presented which, if met, would reinvigorate new vaccine development.

The roadmap shows the need to continue investing in basic science but in a multidisciplinary and connected way across different disciplines including microbiology, immunology, structural biology, systems biology and bioinformatics. Priority should be given to rational approaches to antigen selection and vaccine design and to research into novel adjuvants, vaccine vectors, prime-boost strategies, and novel routes of immunisation.

Simpler, more evidence-based design of clinical studies and better tools for the collection, extraction, analysis, and interpretation of data should be sought to support the translation of scientific knowledge into technological innovation. The roadmap draws attention to the potential benefits of innovation in manufacturing, regulatory and quality control, leading to affordable, faster, more flexible and less wasteful production.

The consultation showed that vaccine implementation programme efficacy affects the extent and quality of the preventive cover that vaccines provide to populations. More must be done to understand and address the reasons for vaccination hesitancy of the general public and healthcare professionals.

The key elements of the 80 recommendations made by IPROVE are summarised in Table 1.

4. Gaps, challenges and recommendations for future investment

4.1. Vaccine R&D

The consultation covered key vaccine R&D needs for prophylactic and therapeutic vaccines:

- Antigen Selection and Vaccine Design
- Novel Technologies & Routes of Immunisation
- Clinical Studies and Data Interpretation

4.1.1. Antigen selection and vaccine design

Understanding pathogens and host-pathogen interactions is a key challenge for vaccine developers. Pathogens for which no vaccine exists often have complex life cycles. Several antigens could potentially be targets for protective responses during different phases in these life-cycles, but because the antigens are often polymorphic in nature, traditional development approaches are not viable. A rational approach is preferred, based on understanding of the immunogenicity of key antigens and host-pathogen interaction. Insight into the protective human immune response to infection is thus key to the selection and design of effective vaccine antigens. This calls for investment in research to identify a new generation of assays able to measure not only the frequency but also the biological function of human B and T cell populations. Novel human B cell technologies have enabled human monoclonal antibodies to be identified that inhibit pathogen infection or promote pathogen killing [12]. These antibodies can be used to discover protective antigens for novel vaccines, for example, antibodies have been isolated that neutralise viral infections by targeting conserved sites present in viral protein antigens, such as influenza [13] or HIV gp120 [14]. Studying these antibodies can instruct the design of novel antigens focused on protective epitopes [15]. More research is needed on structural vaccinology and evolution of the antibody response to enable innovative antigens capable of eliciting cross-reactive antibodies to be designed.

4.1.2. Novel technologies and routes of immunisation

Novel adjuvants are needed to develop preventive and therapeutic vaccines targeting infectious diseases against which con-

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Table 1
The IPROVE Roadmap.

Main priorities	Specific recommendations
Challenge 1: Research and Development (R&D)	
Support an integrated, multidisciplinary approach to antigen selection	• 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
Strengthen the science of vaccine adjuvants	• 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 • Cross-species studies of vaccine adjuvants to pinpoint predictability of animal models
Sustain research on vectors and alternative routes of immunisation	• 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 • 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
Innovative design and harmonisation of clinical trials data and development of analyses frameworks	• 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
Continue to invest in biomarkers of safety in vaccines, and correlates of protection and of efficacy	• 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
Challenge 2: Therapeutic vaccines	
Establish collaborative cross-expertise network at EU level	• Exchange best-practice, including successful and unsuccessful approaches, share know-how and technology • Design and perform multi-centre clinical studies
Foster early dialogue with regulatory bodies	• 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
Develop targeted funding opportunities	• 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
Challenge 3: Innovative processes for vaccine manufacturing and quality control	
Translate innovations into technologies	• 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
Develop flexible manufacturing systems	• 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
Bridge technology and science: collaboration between engineers and biologists	• 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
Improve manufacturing operations and identify new purification techniques	• Improved chromatographic techniques adapted to adenoviruses or particle-based vaccines
Challenge 4: Research Infrastructures	
Reinforce vaccine Research Infrastructures	• 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
Provide support to clinical research infrastructure	• Map centres with methodological competences and map volunteers/specific populations • Identify or develop cohorts (registries) • Enable human challenge models

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Table 1 (*continued*)

Main priorities	Specific recommendations
	• Further develop and structure clinical trial centres coupled with immune-monitoring, imaging, laboratory testing and functional monitoring of physiological parameters
Improve GMP manufacturing capabilities	• 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
Challenge 5: Vaccine small and medium enterprises (SMEs)	
Establish a network of vaccine SMEs involved in human vaccine R&D at EU-level	• 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
Ease SMEs access to scientific and technical resources and skills at the most critical phases	• Facilitate SMEs' access to new technologies to reduce R&I costs and timing • Effective matchmaking and interaction between SMEs and large companies
Support better SMEs early access to regulatory expertise	• 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
Foster competitive collaborative projects between SMEs and larger companies	• 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
Sharpen financial instruments and attracting risk capital towards SMEs	• Invest in improving the public perception of vaccines as a strategic public health tool • Better adapt current instruments to vaccines SMEs needs
Challenge 6: Training	
Identify and profile target groups for training	• Adapt the training offering in terms 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	• 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
Invest in training the trainers	• 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
Challenge 7: Communication on immunisation and the hesitancy challenge	
Implement stratified monitoring of acceptance attitudes and sentiments towards vaccination	• 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
Establish multi-disciplinary networks of expertise and an EU level centre of excellence	• 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
Make healthcare professionals and public health stakeholders effective advocates of vaccination	• 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
Engage with civil society organisations	• Provide appropriate funding and build partnerships to collaborate with such organisations to help building awareness, disseminating and creating knowledge on vaccination needs

EU = European Union, GMP = Good Manufacturing Practice, R&I = Research and Innovation, R&D = Research and Development, SME = small and medium enterprise.

ventional formulations have failed. They could also improve vaccines for certain population groups whose immune response is suboptimal e.g. elderly, infants and chronically infected subjects.

Several adjuvants have been tested, but more effort is needed as few have been approved by regulatory authorities [16,17]. Further study of the mechanisms of action by which adjuvants increase the antigen specific immune response could inform rational vaccine design and use. A new generation of adjuvants would use compounds with well-characterised molecular and cellular targets that enhance the nature, quality and breadth of the immune response. Their pharmacokinetic and pharmacodynamic properties would optimise vaccine efficacy and safety with the potential to improve tolerability. The immune response to adjuvanted vaccines have been recently studied using a systems biology approach [18–20]. The ADITEC FP7 high impact project on advanced immunisation technologies made also a first attempt to profile different adjuvants in head-to-head testing by a applying systems biology approach [21–25].

Traditional adjuvants may not enhance vaccine immunogenicity enough to make therapeutic vaccines effective. Successes of cancer immunotherapy using monoclonal antibodies that target checkpoint inhibitors such as CTLA4 and PD1 suggest that combining adjuvants and checkpoint inhibitors could work for therapeutic vaccines.

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Adjuvant combinations that join their molecular and immunological mechanisms of action may be one solution to increase vaccine efficacy and safety [4,17,26]. Alternative routes of immunisation should be investigated including novel strategies for mucosal vaccination using purified subunit antigens and needle-free vaccine delivery [16].

Vaccine vector technologies need to be developed in a way that secures safe and appropriate use. Many centres of excellence are specialised in only one vector/vector family, so collaboration between them would facilitate innovation and the development of heterologous prime-boost strategies.

4.1.3. Clinical studies and data interpretation

The size, length and cost of clinical trials should be reduced and methods of data collection and analysis standardised. Biomarkers of safety and correlates of protection and efficacy need to be identified and systems biology, mathematical models and bioinformatics applied to advance our knowledge in this field [18–21,23,27]. More collaboration would enable techniques and sampling methods to be aligned and encourage earlier involvement of regulators in defining safety and efficacy.

Lack of harmonisation of data analysis frameworks prevents the integration of data from different sources in pooled analyses. Standards and norms for data collection, storage and analysis are needed as are ontologies, harmonisation of semantics, and adverse event coding in terms that facilitate data comparison and pooling.

4.1.4. Recommendations for EU level action

IPROVE stakeholders made 22 recommendations to drive innovation and improve efficiencies in vaccines R&D (Table 1). They called on EU and national authorities to support an integrated, multidisciplinary approach. In particular, an EU-supported large project, on advanced immunization technologies including antigen design, novel adjuvants, vectors and delivery systems, would be of critical importance for the development of next generation vaccines specifically designed for the different age groups. Such a project would be able to capitalize on the great achievements in the vaccine field obtained by the EU-supported research in the last decade. In addition to the topics mentioned above, attention should be devoted to cover preclinical validation using new *in vitro* and *in silico* techniques and *in vivo* (animal) models highly predictive of vaccine efficacy and safety in humans. It is also proposed that research continues to simplify clinical data collection and analysis and facilitate data comparison and integration using a sytems biology approach. A sustainable framework should be created to enable data (including data descriptors) to be aggregated at different levels. European clinical trial expertise and supporting infrastructures should be further developed. EU and international funding of shared programmes would avoid duplication of investment and facilitate access to advanced technologies, large populations cohorts, and rare outcomes.

4.2. Therapeutic vaccines

4.2.1. Gaps, challenges and needs

Therapeutic vaccines are intensively researched by academia and industry. The pipeline for therapeutic vaccines contains an estimated 470 products targeting more than 70 diseases or conditions. Currently, >70% of therapeutic vaccine candidates are being developed by biotech companies or SMEs which often lack the broad capabilities and long-term technological and therapeutic expertise to drive development through to licensing. Therapeutic vaccines could potentially reduce the burden of chronic diseases or conditions affecting Europe' ageing population, making healthcare less costly than anticipated.

Therapeutic and prophylactic vaccines mostly share the same R&D challenges and gaps along the value chain. Main European-level challenges include the lack of a therapeutic vaccines network, an unclear regulatory framework for their development, and the absence of reliable funding. Europe needs a more connected ecosystem for therapeutic and prophylactic vaccines. A transversal project would improve market momentum by stimulating cooperation across the major European vaccines manufacturers.

4.2.2. Recommendations for EU level action

Research and funding of therapeutic vaccines should have a higher priority. A collaborative network of European therapeutic vaccines stakeholders should be set up to exchange approaches, scientific know-how and technology aimed at shortening development times. Regulatory challenges should be addressed through EC-facilitated collaborations between therapeutic vaccines developers and regulatory agencies.

4.3. Vaccine manufacturing and quality control

4.3.1. Gaps, challenges and needs

Vaccines contain large, complex and often hybrid biologically active molecules. They are produced in a multiple-step process lasting 6–36 months. This is tightly controlled to ensure vaccine reproducibility and consistency [4,28]. Quality control tests are required by regulators and product release authorities and account for 70% of vaccine production time (Fig. 2). The complexity, cost and length of production mean that only a small number of companies can supply vaccines. Shorter cycle times and faster, more predictable production of vaccines is urgently needed because global vaccine demand outstrips supply.

The consultation focused on ways to address global vaccine shortages through innovation in vaccine production and release; ways to increase production capacity and shorten cycle times; and how to minimise the costs and unpredictability of development and production processes. A quality-by-design approach and improvements in process analytical technology leading to new in-process assays could improve these factors [29]. The industry's ability to respond to future epidemics/pandemics depends on it being able to rapidly produce large quantities of vaccine. This could be achieved by process innovation, disposable technologies, shorter approval and release pathways, modular facilities for flexible platform technologies manufacturing different vaccine candidates, and processes/facilities that can be easily switched and scaled up. Scaffold-based technologies able to express a large range of antigens in a highly stable form, close to their native conformation, would simplify combination vaccine production by reducing the risk of conflicting formulations.

4.3.2. Recommendations for EU level action

Research priorities and associated funding should be focused on improving vaccine production and formulation through closer collaboration among scientists, engineers and regulators. Priority investment should be made in the flexibility of manufacturing systems, decentralisation of manufacturing capacity (to avoid supply interruption), and thermostability (to reduce reliance on the cold-chain). Potency assay platforms enabling rapid characterisation of antigens in different manufacturing systems, robust in-process control assays and new purification techniques should be developed and validated.

4.4. Vaccine infrastructures

4.4.1. Gaps, challenges and needs

Vaccines are usually co-developed and licensed through public-private partnerships. Efforts have been made to harmonise

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Unlike other pharmaceuticals, vaccine development can take up to 15-20 years without counting the time it takes to achieve effective population access (on average, a median time-lag of an extra 6.4 years after marketing authorisation). A vaccine may require clinical testing in 15-20 times as many subjects as for pharmaceutical drugs [28], and may cost up to US $900 million per vaccine production unit [4].

The manufacturing itself is a complex and lengthy process. Six 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 a colossal investment. 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 dollars or more [4].

Fig. 2. Time and cost of vaccine development and production.

access to biomedical research infrastructures for vaccines R&D in Europe: European Infrastructure for Translational Medicine (EATRIS [9]), European Clinical Research Infrastructure Network (ECRIN [30]), Biobanking and Biomolecular Resources Research Infrastructure (BBMR [31]), Europe's research hub for structural biology (INSTRUCT [32], and European life-sciences Infrastructure for biological Information (ELIXIR [33]). Moreover, the European Network of Vaccine Research and Development collaborative infrastructure projects (TRANSVAC and TRANSVAC 2 [34]), infrastructure funded by the EC (FP7 and H2020), were set up to enhance research and training and create a permanent research infrastructure for early vaccine development in Europe [35]. Furthermore, the ADITEC High Impact project [21,22] has significantly contributed to the development of a platform of advanced immunisation technologies that were made available through open calls to SMEs and Public Health Organisations. This favourable, translational European ecosystem of vaccine R&D expertise, facilities and successful public-private collaborations could be built on. If supported by better access to innovative technology platforms and R&D, it could further advance vaccine innovation and development. Now, a joint effort is needed to capitalise and create a centralised European Vaccine Infrastructure.

4.4.2. Recommendations for EU-level action

It is proposed that the EU promotes the creation of an European Vaccine Research Infrastructure trough the network of European R&D facilities and expertise whilst maintaining, upgrading or developing new vaccine-related infrastructures to fill gaps or boost capacity, for example in antigen selection, vaccine design, advanced immunisation technologies and preclinical validation, clinical development, manufacturing and quality control.

4.5. Vaccine SMEs

4.5.1. Gaps, challenges and needs

Although vaccine SMEs often bridge discoveries made in academic research and clinical development of candidate vaccines, their role is poorly understood. As a result, they receive limited support from European financial markets and they lack the international visibility, resources and capacity needed to fully implement their projects.

The IPROVE consultations identified two main gaps in vaccine development, from preclinical to Phase III, that are bottlenecks or challenges for SMEs: acquiring multiple skills and obtaining funding. Vaccine development, particularly mid to late-stage, requires access to advanced technologies, expertise in testing, production and clinical trials, and the ability to meet regulatory requirements. These capabilities are concentrated within a handful of large pharma companies, national institutes and academic platforms. SMEs are currently unable to access public/private translational platforms with industrial expertise in vaccines. They need better collaboration from other stakeholders in order to gain key expertise for certain stages of their vaccine development. In return, this would improve industry's perception of the contribution that innovation by SMEs makes to early-stage development.

Promising, early-stage vaccine candidates need funding to move into clinical development, particularly for feasibility studies to assess GMP manufacturing potential and to design clinical development plans. SMEs mainly bridge R&D gaps between basic discovery and early clinical development. The vaccines they work on will take a several years to be marketed. SME access to technologies, facilities and know how should be made easier, for example, ADITEC made six open calls offering access, at no cost, to immunisation technologies developed by the consortium; thus supporting over 20 European SMEs.

4.5.2. Recommendations for EU-level action

The 12 recommendations of the IPROVE roadmap include more opportunities for vaccine-related networking and collaboration, access to resources and skills including regulatory expertise, and use of financial tools to attract more capital to SMEs. EC support is needed to stimulate innovation by building a network for interactions, transfer of experience, and early matchmaking between companies with needs and stakeholders who can meet those needs. The resulting community would give European SMEs a forum to promote better understanding of their needs in order to deliver innovative vaccine candidates or technologies. It would also rationalise big pharma and academia's approach to SME vaccine development strategies, facilitating matchmaking and advisory activities. The funding ecosystem should support SME innovation by reducing bureaucracy and becoming less risk averse.

4.6. Training

4.6.1. Gaps, challenges and needs

Vaccinology covers a wide range of disciplines including basic sciences, biotechnology, infectious diseases, epidemiology, public health, health economics. It spans preclinical and clinical development, production processes, quality control, cold chain/supply management, ethics, regulatory aspects, public health and communication.

There are currently vaccine-related courses and people with relevant expertise at EU level. Course uptake could be improved by raising awareness that some institutions propose industrial placement as part of their course.

Moreover, as recommended in the TRANSVAC roadmap [36], advanced courses to be run by a European Vaccine Research & Development Infrastructure, or the current Master in Vaccinology and Pharmaceutical Clinical Development [37], would strengthen links between European institutions providing vaccine-related scholarships [35]. Other important educational channels include: Advanced Course of Vaccinology (ADVAC) [38], European Programme for Intervention Epidemiology Training [39]; European Malaria Graduate School [40], and European Medicines Research Training Network [41]. The exchange of expertise between countries could be enhanced through Massive Open Online Courses, Erasmus Mundi programmes, and Marie Skłodowska-Curie actions fellowships.

4.6.2. Recommendations for EU-level action

Europe requires specialised, in-depth and accredited training for vaccine processes from R&D to licensure. Training should be

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Table 2
Framework conditions for vaccine R&D.

Framework conditions	Existing structures/setting	Identified gaps and challenges
EU funding mechanisms	• Sixth and Seventh Framework Programmes • Horizon 2020 • European Investment Bank financing facilities • Partnerships (eg., IMI, European and Developing Countries Clinical Trials Partnership)	• Misalignment between the maximum project duration under EC funding (5 years or less) and the lengthy development time for vaccines (10–20 years). • Fragmentation of research funding combined with duplication in some Members States • Challenges in accessing private sources of funding in Europe.
Capacity to respond to public health threats	• Demonstrated extraordinary capacity to mobilise within exceptionally short timelines (eg Ebola vaccine)	• Reactive rather proactive system • There is need to build all of the necessary components of a rational framework to protect national and global public health.
Regulatory challenges	• EU-specific challenges around regulatory decision making and decision-making on reimbursement and pricing	• Disconnect between regulatory data in different member states
	• Regulatory requirements are generally increasing • Requirement to demonstrate efficacy through classical randomised clinical trials	• Increasingly complex and risky vaccine developments • Improved collaborations are needed to generate robust data-packages in the post-approval phase

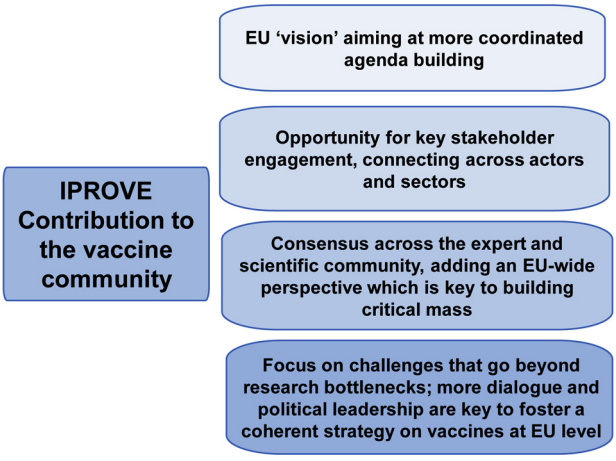

Fig. 3. IPROVE contribution to the vaccine community.

embedded in career paths and enhance individual career prospects. Methods should be compared to determine whether national or pan-European approaches are more successful. Teams of teachers who have acquired vaccines-related competencies should be established. The impact of such training on ease of recruitment of talent by the vaccines industry should be assessed.

4.7. Communication about immunisation and the challenge of vaccine hesitancy

4.7.1. Gaps, challenges and needs

The drive to develop new vaccines using innovation and science should be accompanied by improvements in access to vaccines so as to achieve their intended public health, economic, and societal objectives. Vaccine hesitancy is a complex challenge rooted in an ever-changing demographic and socio-psychological context [42–44]. A multi-disciplinary approach involving social, cognitive, communication and public engagement sciences is needed to address it [45].

The IPROVE consultations found that communication to the public about vaccines is often insufficiently evidence-based, misses its intended target and is not integrated into vaccination programmes. Communications effectiveness has not been evaluated during and after vaccination campaigns, neither has the associated return on investment. Communications training is lacking within the healthcare sector. Few new digital communication tools are used, although online media are a primary source of information about vaccination for the general public. A communication strategy is required that would engage the public, health community and media in vaccination programmes.

4.7.2. Recommendations for EU-level action

A tool is needed to monitor public attitudes to vaccination, establish baseline levels of risk awareness and feelings at the EU level, such as the Vaccine Sentimeter [46]. Metrics of vaccination acceptance would be developed to monitor the impact of targeted communication. Leadership from the European Centre for Disease Prevention and Control and WHO Europe Regional Office are essential for success.

The consultation recommends creating multi-disciplinary networks of experts in social and behavioural sciences, social marketing, social media, neuroscience, communication sciences, health education and communications to research and develop evidence-based communications strategies. Topics such as infectious diseases, immunology, vaccination and public health should be taught in schools so that future generations appreciate the risk posed by diseases that they may not experience first-hand. This will help to 'institutionalise' vaccination as a cornerstone of public health.

5. IPROVE expected strategic impact and perspectives

Europe has numerous centres of excellence in vaccinology and related disciplines and, with these, the ability to lead discovery of the next generation vaccines. The IPROVE roadmap sets out gaps and needs in Europe's research activities to guide those working in vaccine policy, research, programming, and finance. IPROVE proposes ways to optimise allocation of existing resources within EU and national vaccines-related funding programmes. By setting medium-to-long-term priorities for funding, IPROVE facilitates follow-up of progress and future evaluation of the impact of funding on specific parts of the vaccines value chain. Although IPROVE did not look deeply into the regulatory and financial conditions that favour innovation, some factors were identified that could limit it (Table 2).

We expect the roadmap to be considered in the context of the European Commission's strategic priorities: Directorate General (DG) for RESEARCH through the Horizon 2020 programme and beyond, DG SANTE's [47] public health approach to prevention, DG CONNECT's investment in health IT and technology infrastructure, and DG GROWTH's support for the industrial competitiveness to address public health needs. At national and regional level, the IPROVE roadmap will help policy makers and funders to define research priorities.

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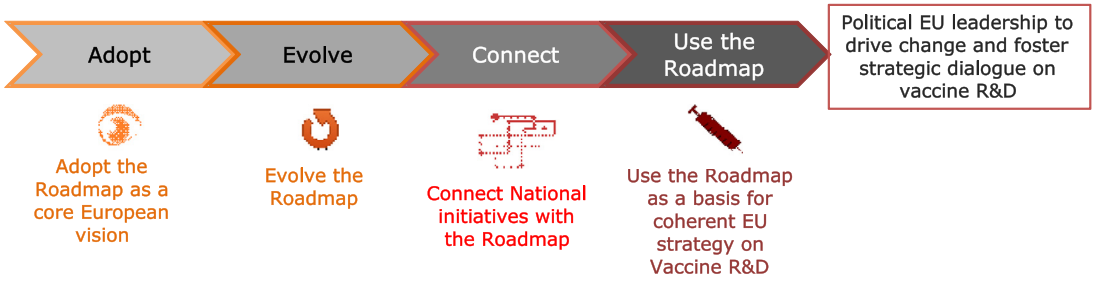

Fig. 4. Next steps for the IPROVE Roadmap.

The outcome of the IPROVE consultation confirms and builds on existing research initiatives in various European countries. In addition to the proposed priorities for EU intervention to support vaccines research and development, IPROVE's collaborative approach and general recommendations are applicable worldwide. During the consultation different stakeholders shared and aligned their ideas for actions to maintain a competitive vaccines industry in Europe.

The IPROVE roadmap represents the voice of the vaccines community on filling gaps in infrastructure, funding and technology and removing bottlenecks on the path from breakthrough research to innovative vaccines (Fig. 3). It will help decision makers build a coherent investment strategy to maximise the impact of vaccines funding across Europe, thus contributing to the advancement of public health in Europe and the world.

6. Conclusions

IPROVE should be regarded as the first step in an EU-level vaccine strategy. To be successful, its recommendations need to be implemented, particularly at the political level (Fig. 4). IPROVE can help create a vibrant, multi-disciplinary vaccine research community, avoid duplication of effort through enhanced collaboration between different European Member States, and identify the most appropriate organisations/consortia to implement specific recommendations. The result would be a more vaccine-friendly economic environment in the EU. The roadmap is expected to encourage the development of formal and informal networks of collaboration in the EU and worldwide, fostering a truly cooperative, cross-functional and effective translational approach to vaccines R&D in Europe. Carried forward by the right processes, political will, and social and economic environment, Europe can continue to lead in vaccines – a strategic and vital health sector.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2017.11.069.

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