Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Biologicals 76 (2022) 15–23

Contents lists available at ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

A gaps-and-needs analysis of vaccine R&D in Europe: Recommendations to improve the research infrastructure

Stefan Jungbluth [a,*], Hilde Depraetere [a], Monika Slezak [a], Dennis Christensen [b], Norbert Stockhofe [c], Laurent Beloeil [d]

[a] European Vaccine Initiative (EVI), Heidelberg, Germany
[b] Statens Serum Institut, Dept. Infectious Disease Immunology, Copenhagen, Denmark
[c] Wageningen University/Wageningen Bioveterinary Research, Lelystad, The Netherlands
[d] BIOASTER Technology Research Institute, Lyon, France

ARTICLE INFO

Keywords:
Vaccines
Research and development
Research infrastructure
Science policy
Platform technologies
Manufacturing

ABSTRACT

The COVID-19 pandemic has brought into sharp focus the importance of strategies supporting vaccine development. During the pandemic, TRANSVAC, the European vaccine–research-infrastructure initiative, undertook an in-depth consultation of stakeholders to identify how best to position and sustain a European vaccine R&D infrastructure. The consultation included an online survey incorporating a gaps-and-needs analysis, follow-up interviews and focus-group meetings.

Between October 2020 and June 2021, 53 organisations completed the online survey, including 24 research institutes and universities, and 9 pharmaceutical companies; 24 organisations participated in interviews, and 14 in focus-group meetings. The arising recommendations covered all aspects of the vaccine-development value chain: from preclinical development to financing and business development; and covered prophylactic and therapeutic vaccines, for both human and veterinary indications.

Overall, the recommendations supported the expansion and elaboration of services including training programmes, and improved or more extensive access to expertise, technologies, partnerships, curated databases, and-data analysis tools. Funding and financing featured as critical elements requiring support throughout the vaccine-development programmes, notably for academics and small companies, and for vaccine programmes that address medical and veterinary needs without a great potential for commercial gain. Centralizing the access to these research infrastructures via a single on-line portal was considered advantageous.

1. Introduction

1.1. Context & background

Vaccination is one of the most effective public health tools available to humanity [1,2]. Outstanding achievements of vaccines include the control or eradication of several previously devastating human diseases such as smallpox (eradicated) and the near eradication of polio. The COVID-19 pandemic has also brought into sharp focus the importance of vaccination and the strategies behind vaccine development [3–6]. Moreover, the new vaccines targeting the COVID-19–causing virus, SARS-CoV-2, arise from new platform technologies, including mRNA-based vaccines and adenovirus-based vaccines.

Veterinary vaccines play a major role in protecting animal health by preventing and controlling animal diseases, improving animal welfare, reducing economic loss for farmers, and lowering the consumption of antimicrobials and consequently antimicrobial resistance and environmental impact [7–9]. Moreover, veterinary vaccines also have a direct impact on human health by ensuring safe food supplies and preventing animal-to-human transmission of zoonotic pathogens that represent two-thirds of the infectious agents affecting humans.

In addition to prophylactic vaccines being used to prevent infection, therapeutic vaccines are increasingly gaining importance as an alternative to treating chronic diseases in humans and are currently being

Abbreviations: CMC, Chemistry, Manufacturing, and Control; GLP, Good laboratory practice; GMP, Good manufacturing practice; IP, Intellectual property; QA, Quality assurance; QC, Quality control; R&D, Research and development; SME, Small and medium-sized enterprise.

* Corresponding author.
E-mail address: stefan.jungbluth@euvaccine.eu (S. Jungbluth).

https://doi.org/10.1016/j.biologicals.2022.02.003
Received 2 November 2021; Accepted 21 February 2022
Available online 26 February 2022

developed for some chronic viral infections, bacterial infections and the treatment of cancer [10–15], amongst others.

For all vaccines, a successful research and development (R&D) programm begins with the identification of a public-health need or animal-health need and ends with an effective and affordable product licensed and being available in the market. In between these milestones lies an ever-changing landscape with a complex set of highly skilled, scientific-technical, and administrative steps, governed by an evolving regulatory framework. All these steps require significant financial resources and technical capabilities. TRANSVAC – a research infrastructure initiative funded by the EU since 2009 (https://www.transvac.org) can partially address some of the problems of vaccine developers. It has been established to support vaccine R&D by offering scientific-technical services to the vaccine-development community and by providing cutting-edge training in vaccinology, in which theoretical and practical training go hand-in-hand [16]. TRANSVAC is a distributed, network-based research infrastructure that currently integrates the expertise and facilities of 25 leading European research organisations from ten European countries. More recently, TRANSVAC has been awarded complementary funding by the EU (via the TRANSVAC-DS project) with the aim to consolidate the conceptual and technical design and ultimate implementation of a European vaccine R&D infrastructure. This overall aim included identifying the needs and gaps in current vaccine development programmes, and to make recommendations to further improve the design and positioning of a sustainable European vaccine R&D infrastructure. This was achieved through conducting an in-depth consultation of European stakeholders in vaccine development. The consultation took the form of an online survey incorporating a gaps-and-needs analysis, follow-up interviews and focus-group meetings.

2. Material and methods

2.1. Survey design and scope

The content of the survey questionnaire was prepared based on a review of literature about gaps and needs in the vaccine field. The survey included a generic list of questions identical for each topic and was presented as an online form. The scope of the survey included:

- General research infrastructure landscape
- Preclinical development
- Clinical development
- Manufacturing and platform technologies
- Biobanking facilities
- Adjuvants and vaccine formulation
- Delivery systems
- Regulatory aspects and licensing
- Data management, data analysis and e-infrastructure
- Support spanning vaccine development (Transversal support).
- Prophylactic and therapeutic vaccines, for both human and veterinary indications.

Participants were selected from a stakeholder registry that was developed within the TRANSVAC-DS consortium, and they were individually invited by email to take the online survey. Participants had the opportunity to contribute to the survey in anonymity.

Identical statements or closely related answers for a given topic were merged in the processing phase.

2.2. Interviews with vaccine experts

Vaccine experts participating in the survey were given the opportunity to identify themselves after taking the survey and indicate their willingness to participate in an individual follow-up interview with TRANSVAC members. The selection of vaccine experts for interviewing was based on the contribution of their respective organisations to the survey (interest in the survey's objective, willingness to participate and the content in the replies to the survey). The interviews lasted approximately 30 minutes and addressed a set of questions focussing on sub-optimal or missing strategies, services, capabilities, processes, practices, technologies, or skills, and invited recommendations. Views were also solicited on the lessons learnt from vaccine development in response to the COVID-19 pandemic.

2.3. Focus group meetings

Three focus group meetings were convened with additional vaccine experts selected from the stakeholder registry with the aim of elaborating on the gaps, needs, and recommendations for development programmes in veterinary vaccine, human prophylactic vaccines and human therapeutic vaccines, respectively. The participants were provided with a report of the results of the survey and interviews.

2.4. Reporting

The information gathered during the consultation process was integrated in a single report, the anonymised findings of which are presented in the present article. All personal data (such as contact data etc) were handled in compliance with the European Union (EU) General Data Protection Regulation (GDPR; 2016/679).

3. Results and discussion

3.1. Participants

Around 400 organisations were invited to participate in the online survey. Representatives of 53 organisations based mainly in Europe completed the survey (Fig. 1A). Twenty organisations were research institutes or universities (including spin-offs), and nine organisations were pharmaceutical companies. Twenty-two organisations were based in France, Germany, or The Netherlands. The survey was conducted between October to December 2020.

Based on the comprehensive nature of the replies to the survey, representatives of 24 organisations were selected to participate in 30-minute structured interviews (tele- or videoconference) to elaborate on, or clarify, the responses to the survey (Fig. 1B). Twelve of the organisations were public institutions or pharmaceutical companies; and 12 of the organisations were based in France or Germany. These interviews were conducted from October 2020 to January 2021.

Three focus group meetings of selected representatives from 14 organisations were convened in June 2021 to review and complement the findings of the survey and interviews with respect to the areas of human prophylactic vaccines, therapeutic vaccines, and veterinary vaccines, respectively.

3.2. Overview of research infrastructure needs

In the consultation, it was widely accepted that the vaccine research infrastructure should provide: (i) a platform to bring together stakeholders and facilitate the formation of networks and partnerships; (ii) access to research facilities and services, and technical expertise; (iii) access to funding (and risk sharing); (iv) access to training; (v) access to regulatory advice; and (vi) access to sustainable and curated databases (Fig. 2). Preferably, the vaccine research infrastructure should be accessible via on on-line portal as a one-stop shop for requesting all the activities from discovery to approval.

The major obstacles to vaccine development related to identifying the appropriate platform technology to produce the vaccine and to its funding (Fig. 3). Although expertise, adjuvants and access to models and assays were less of an impediment, these categories featured as part of identifying the appropriate platform technology.

Access to expertise for delivery systems, quality assurance, and

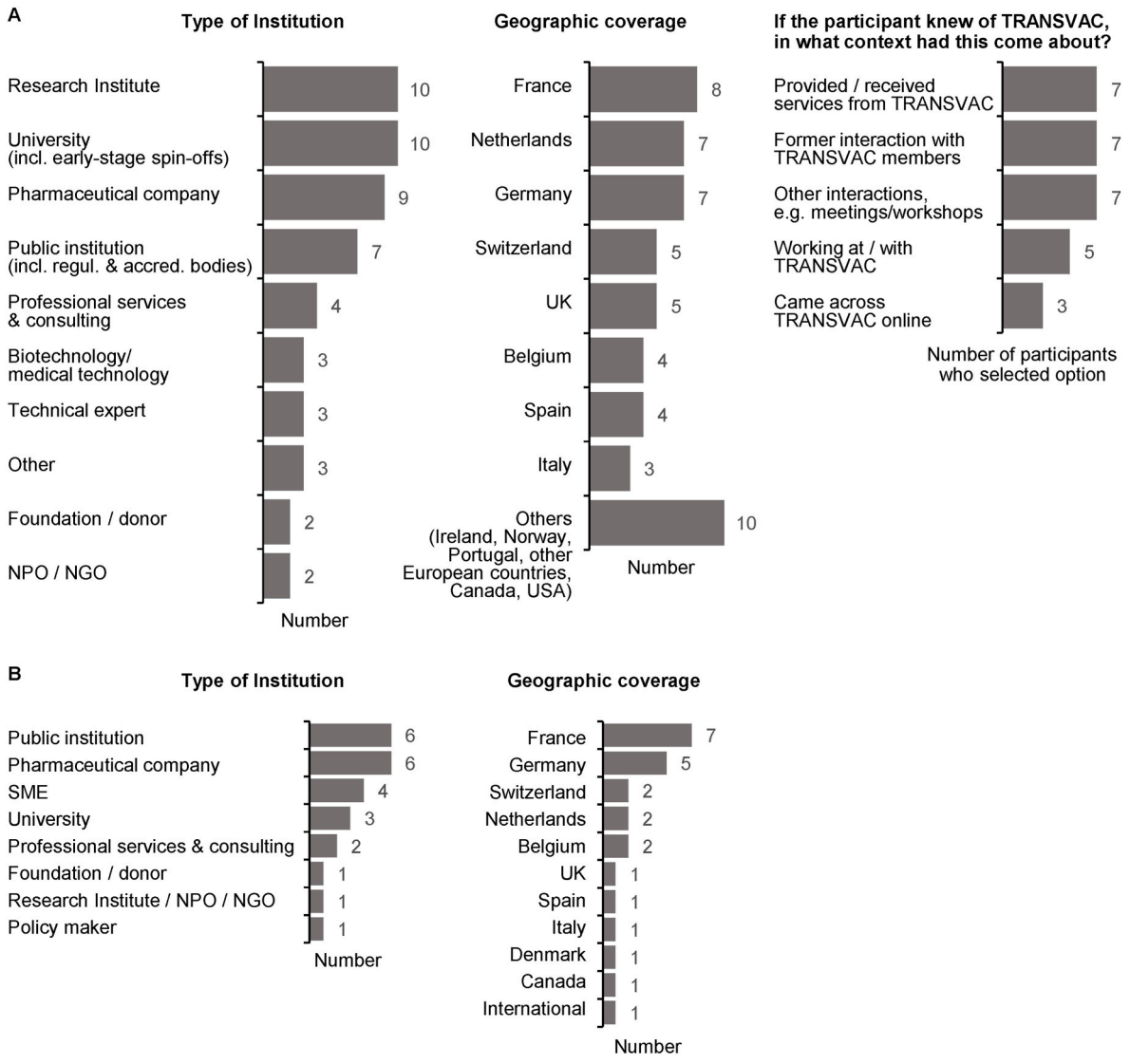

Fig. 1. Participants in the gaps-and-needs analysis.
(A) Survey participants by institution affiliation, relationship to TRANSVAC, and geographical location. (B) Interview participants by institution affiliation, and geographical location.

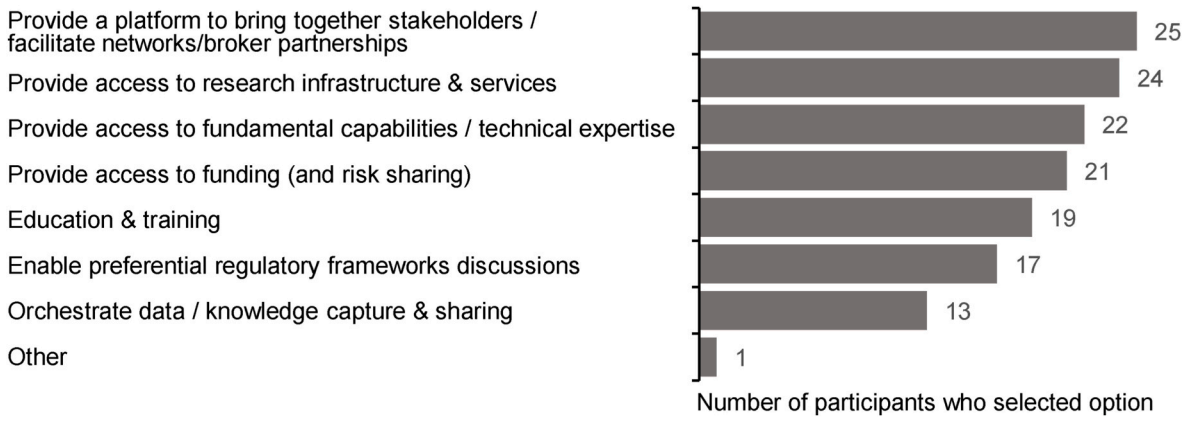

Fig. 2. Potential roles for a European vaccine infrastructure.

vaccine production for preclinical safety-tox studies represent needs that can be addressed by including additional capacities to the vaccine research infrastructure. Funding was identified as an issue in all aspects of vaccine development and is discussed in detail later in this section. For veterinary vaccines, funding from an early stage in vaccine development was viewed as a critical factor.

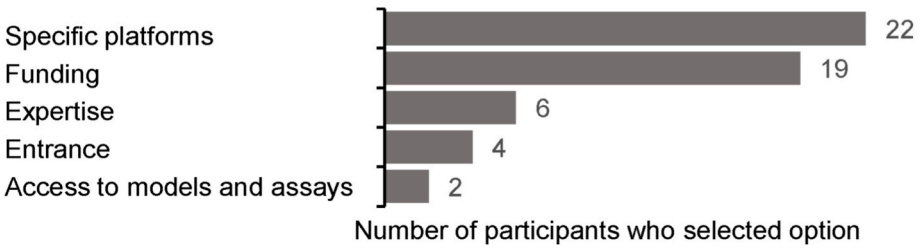

Fig. 3. Key obstacles that impede current vaccine development in Europe.

Some of the gaps and needs can be addressed by extending the existing preclinical services and resources offered by TRANSVAC, to include access to different expression systems, formulation expertise (including different types of adjuvants), access to facilities and expertise on large variety of animal models, and access to analytical tools (for assay development and standardisation).

3.3. Platform technologies: antigen expression and vaccine formulation

The recommendation for access and expertise in the selection of the appropriate platform technology encompassed two aspects: (i) antigen expression and (ii) vaccine formulation (Table 1).

Antigen production lies at the core of the platform technology. The expression system also defines the secondary, tertiary and quaternary structures of protein antigens. The expression system could be for vaccines which include the synthesised antigen, or for vaccines which contain RNA or DNA templates which code for the antigen. Ideally, the expression system should be selected based on being the best fit for the intended application, rather than on the availability of the technology. This would therefore require the provision of comparing different expression systems at an early stage in vaccine development, and the provision of expert support for using those different systems, and for assessing the structural integrity and purity of the expressed antigens. This could be supported by offering access to a range of complementary platform technologies, which to some extent was what was provided by TRANSVAC at the time of the consultation.

The key recommendations for vaccine formulation included identifying whether or what type of an adjuvant was required and identifying the appropriate delivery system (Table 1). It was recognised that formulation (i) can affect the cellular targeting, presentation and duration of exposure of vaccine antigens and adjuvant, and (ii) that there was not a one-size-fits-all solution. Moreover, the formulation should not disrupt antigen conformation, and a suboptimal formulation could lead to the rejection of an otherwise good vaccine.

In the area of therapeutic vaccines, antigen discovery was also critical, especially as the immunotherapy may be targeted at particular tumour types or even individual patients. Hence, there were recommendations; (i) for greater access to neoantigen discovery technologies, potentially in the form of an online platform that also offers in silico modelling, structural characterisation, and access to sequencing data, and genome mining; and (ii) for greater access to fresh patient-derived tissues including tumour biopsies, and immune cells from those biopsies, that can then be used in ex vivo or in vitro models. For biobanked tissues, better freezing protocols are needed to improve the recovery of live cells. For organ-on-chip models, the incorporation of immune cells into would provide a useful advance.

3.4. Preclinical development

3.4.1. Animal models and in vitro models

It was recognised that advances have been made on validating the replacement of animal models by in vitro models in support of the 3Rs approach (replace, reduce, refine), but the replacement models generally have not reached the level of being acceptable by the regulatory agencies. Therefore, the animal models need to be used preferably under conditions of good laboratory practice (GLP), and sparingly, to avoid the unnecessary duplication of studies or repeating studies for regulatory purposes. Among several recommendations from the survey for improving the use of preclinical animal models (Table 1), included better access to partners with expertise in design and execution of studies in each model. Nevertheless, there remains a need for more animal models, including challenge models, that closely simulate the disease condition under investigation, for both human and veterinary vaccines. Although murine models have improved and reduced the need for large animal models, the canine spontaneous-tumour model, remains useful for evaluating therapeutic cancer vaccines, and many reagents are available. To maximise the output from animal experiments, a greater access to expertise in their design and execution was recommended, including the incorporation of non-invasive analyses (e.g., immune imaging). These animal models could be provided by academic groups or CROs. For veterinary applications, these models could also be accessed through the One-Health initiative (https://www.cdc.gov/onehealth/index.html). Another recommendation was to have access to small-scale GLP-toxicology studies offered as a service (with expertise for the selection of the appropriate model) for refining the selection of the formulation to be used for GMP-production, but before launching a full clinical programm.

It was recognised that the appearance of new technologies such as microfluidics and organ-on-chip represented new avenues for the replacement of animal models. In particular, these technologies featured in the recommendation for the development of GLP-compliant in vitro assays and models for vaccine/product characterisation, including validated in vitro models for formulation screening including those based on clinically relevant biomarkers of inflammation.

3.4.2. Veterinary vaccine development

For the development of veterinary vaccines, the recommendations encompassed approaches to streamline development and reducing related costs by having greater access to facilities and expertise for early- and late-stage vaccine evaluations, and for reagents and diagnostics (Table 1).

As with vaccine development in general, one recommendation was for greater access to expertise on the selection of the antigen and on the production platform, early in the vaccine development programm. The selection of the antigen could also be coupled to advice on appropriate assays for evaluating efficacy. The selection of the production platform could be supported by the development of a database of available technologies coupled with information for a given platform on the anticipated immune response to a vaccine, and the anticipated costs of vaccine production. Having a clearer view of production feasibility and budget was viewed as important for securing financing, potentially in the form of in-licensing deals.

A second recommendation was for greater access to companies/institutions that provide adjuvants and expertise. The use of adjuvants is more likely to be permitted in companion animals (pets) than in livestock animals for human consumption. However, time, budget and regulatory constraints drive veterinary-vaccine developers to use adjuvants that are already approved and available on the market, even

Table 1
Summary of recommendations from the survey and follow-up interviews.

Platform technologies: antigen expression and vaccine formulation	
	Recommendations for access to:
Platforms for vaccine manufacture	• New protein-expression, and RNA and DNA platforms and technologies •Expertise in optimising expression, e.g., codon optimisation for different expression systems
Formulation	•Vaccine formulation and characterisation •Analytical validation development for QC purposes •Stability testing
Adjuvants	•Commercialised adjuvants for both SMEs and research institutes • Relevant GMP-quality adjuvants for early clinical PoC trials •Adjuvants in vaccines approved for human use (in terms of fair price and conditions of use) •Non–GMP-grade adjuvants in research and early development (free access, where licence restriction occurs at a later [e.g. clinical stage in vaccine]. •A data repository for available adjuvants •Expertise for selection of an appropriate adjuvant for preclinical studies •Appropriate preclinical models to evaluate adjuvants (not only in vitro or small rodents) •Data or reports from in-depth mode of action studies on adjuvants relevant to the human immune system
Delivery systems	•Expertise in vaccine formulation and characterization •New delivery systems for their validation in research and early development (free access) •Relevant animal models for testing different routes of administration •Expertise on the selection of different routes of administration among needle-free technologies (e.g., intranasal, oral, subdermal) •Expertise for routes of administration targeting the mucosa.
Preclinical development	
	Recommendations for access to:
Use of animals	•Novel and relevant animal models for evaluating vaccine efficacy and safety. This access should extend to those animal models that are new or refined versions of the ones currently available. The access could be administered by infrastructures or organisations dedicated for that purpose. •Dedicated partnering organisations with expertise on designing and conducting animal studies, which would enable using animal material for other relevant analyses (systems biology, serological assays etc.) •Expertise for regulatory support starting from early preclinical phase of vaccine development •Coordinated network of services for preclinical testing (coordination of work between different groups to gather all necessary data for the regulatory dossier) •Relevant animal target species for veterinary vaccines •Reagents for studying the immune response to the vaccine in a given animal model (especially for veterinary vaccines) •Knowledge on relevant (immune) differences between species e.g., mice, guinea pigs, ferrets, rabbits, NHPs, pigs and humans.
GLP-compliant assay development	•Novel, relevant in vitro assays for better prediction of vaccine efficacy, including the identification of biomarkers for potency. •Pathogen-specific assays for product characterisation. •Systems serology and standardised serology assays. •Expertise on predictive vaccinology and the de-risking the development of in vitro models that evaluate molecular reactogenicity and immunogenicity, notably those models that are based on microfluidics and organ-on-chips.
Veterinary vaccine development	•Regulatory-affairs support •Field-like facilities for vaccine evaluation •Experimental facilities with scientific expertise •Analytical tools and know-how for defining correlates of protection (to avoid costly challenge studies) •Reagents (e.g., specific-species antibodies for immunology studies) •Expertise on, and relevant animal models for, testing and selecting different routes of administration •Diagnostics for use in field studies
Clinical development	
	Recommendations for access to:
Partners for	•Clinical trial sites •Project management (CROs) •Biobank creation and maintenance •Immunomonitoring facilities •Industrial development •Manufacturing of clinical trial material (CMO)
Expertise in	•Preparing of the clinical development plan •Defining Target Product Profile •Defining the testing strategy •Supporting grant writing and grant scouting •Implementing strategies to move rapidly from PoC testing to clinical testing and testing in specific target groups •Improving clinical-study subject enrolment •The selection and use of controlled human infection models (CHIMs)
Data/data-management tools to interrogate	•Clinical-trial cohort registries •Specific populations •Epidemiological data •Data-management systems
Technology/expertise	•Clinical-study assays for assessment of vaccine-adjuvant activity
Manufacturing	
	Recommendations for access to:
Technology and infrastructure	•GMP production at affordable cost •New production technologies •Small-scale/pilot-scale production •Flexible manufacturing capacity/multipurpose manufacturing units •Critical analytical equipment
Partners for	•Contract manufacturing (CMOs) with implemented quality systems
Expertise in	•Quality assurance, regulatory affairs •Optimising upstream and downstream steps in the manufacturing process •Stabilisers and product stability •GMP regulations, including those related to. •manufacturing standards required for the different stages of clinical development •scale-up and technology transfer. •in vitro potency assays.
Regulatory Affairs	
	Recommendations for access to:
Expertise in	

(*continued on next page*)

Table 1 (*continued*)

Platform technologies: antigen expression and vaccine formulation	
	•The development of regulatory pathway to licensure •The guidelines to be followed at different steps of vaccine development •GMP guidelines/requirements at different stages of vaccine development •Early interactions with the regulators •GMO regulations •Training related to regulatory expectations/ guidelines.
Support spanning vaccine development (transversal support)	
	Recommendations for access to:
Communication and collaboration	•A comprehensive map of capabilities and facilities in Europe to support vaccines R&D, incorporated into an online database. e.g. clinical trial sites, sites to conduct CHIMs, partners for scaling up to Phase 2 and beyond, innovators in manufacturing etc. •Networks or partners to promote knowledge sharing and collaboration across the vaccines ecosystem, initially via a database of regulatory authorities, SMEs, researchers, research institutes etc. •A mechanism to increase the visibility of small companies so as to establish partnerships with larger industrial companies for sharing risk in developing innovative technologies. •Database of experts (for example freelance consultants) via TRANSVAC partner network in a variety of vaccine development areas to help in the design of strategies for the vaccine-development plan, regulatory affairs, clinical development; manufacturing (QA), epidemiology, or public health (to find alignment between research goals and public-health needs), etc. •Project management support (methodology and expertise for vaccine development) – a project team helping inventors with the transition from research into development (pre-clinical testing, QC developments, formulation, upscaling etc.) to increase the quality of projects and the chances of being taken-up by industry through licensing deals.
Data management, data analysis and e-infrastructure	•A long-term sustainable data warehouse dedicated to gathering, curating, and organising data for further analysis (in formats accessible to different users). The data warehouse would need to accommodate various types of data from different platforms (and extend access to data from biobanks offering animal materials, and repositories of reagents). •Support for data gathering or sharing from NHPs and other animal models and human subjects (to understand the link between vaccine efficacy and genetic [species] background) •Support for the analyses of the large volumes of multidimensional data generated in translational clinical studies, notably those analyses that aim to identify potential correlates of protection. •Support for improving the quality and value of preclinical data: mechanisms to support the consistency, standardization, distribution/ collection of big data, data integration, storage, accessibility; integration of multi-omics data. •Support for the implementation of FAIR principles for data management (findability, accessibility, interoperability, and reusability)
Training	•Centralised inventory of TRANSVAC training programme •Communication networks highlighting available trainings and targeting potential participants •Centralised resource highlighting training courses in vaccinology offered by various providers including the Global Vaccinology Training Network, ADVAC (https://www.advac.org), Oxford Vaccinology courses (https://www.conted.ox.ac.uk/about/vaccinology), and LIVE programme. •Coaching programmes for researchers, for developing business skills among researchers that would help them to build a business case for their ideas. •High-quality certified training courses, either on-site or online (for global outreach), and regularly available. •Regulatory affairs (priority area for research community) •Business skills (e.g., pitching ideas to raise finance) •Statistics •Study design •Data quality •Hands-on practical training, e.g., for cytometry, animal models, analytical methods, systems biology, and other state-of-the-art technologies. •GMP production (requirements), QC release, method validation •In the veterinary field, early development, practical training on manufacturing
Funding	
	Recommendations
Funding levels	•Both at EU and national level, public funding should be increased for vaccine R&D (without cannibalising on funding for other areas) •Funding for vaccine R&D should maintained at appropriate levels once the pandemic emergency has passed. •More funding and incentives for researchers developing vaccines with high potential for public health but limited commercial return •More funding for GMP manufacturing and toxicology studies, which are expensive steps in (human) vaccine development •More funding for early to mid-stage technology readiness levels (TRLs) for both human and veterinary vaccines •More funding for training and continuous learning in vaccinology, to sustain and improve the critical mass of people with level of knowledge and expertise required in vaccine development.
Funding mechanisms rules and scope	•New funding agency and/or funding mechanisms that anticipate needs and provide quick access to appropriate funding •Funding and/or funding mechanisms for cross-sectorial consortia would allow to explore novel opportunities in vaccine development. This includes funding for One Health and veterinary vaccine consortia •More funding mechanisms that provide funding/ financing for SMEs and that support collaborative projects between public and private R&D organisations
Funding and financing measures	•More funding mechanisms that offer longer and broader funding perspectives staged by predefined (go/no-go) milestones (e.g., CEPI-type funding; https://cepi.net). (Project funding with narrow limits with respect to time and scope, substantially slows down vaccine development)

(*continued on next page*)

Table 1 (*continued*)

Platform technologies: antigen expression and vaccine formulation	
	•Relaxation of co-funding requirements (where relevant): perceived bias towards organisations that can easily engage partners for co-funding. •Greater distribution of funding to groups outside the institutions or researchers that typically receive most funding, to encourage a wider and hence more successful participation in innovation •Mechanisms to increase access to financing from private investors in Europe •Mechanisms to increase financing for innovations in vaccine development
Access to expertise for	•Investor scouting, including communications and relationship management •Assessing commercial viability (market, pricing and profitability), and analytics on success of development •Creating the business case (for researchers/SMEs to attract investment) •Identifying funding opportunities and preparing grant applications (e.g., via consulting services) •Portfolio management (prioritisation and optimisation)

Abbreviations: CHIM, controlled human infection/challenge model; CMO, contract manufacturing organisation; CRO, contract research organisation; GLP, good laboratory practice; GMP, good manufacturing practice; GMO, genetically modified organisms; IP, intellectual property; NHP, non-human primate; PoC, proof-of-concept; QA, quality assurance; QC, quality control; R&D, research and development; and SME, small and medium-sized enterprise; TRL, technology readiness level.

though the adjuvant may be suboptimal.

A third recommendation was to have more access to data for interspecies comparisons with different vaccine technologies, including from vaccines that failed to proceed further in development. A main obstacle of a given animal model is the extrapolation of the results to the target species, and whether the administration route/adjuvant or delivery system would be appropriate in the target species. Funding for basic research in this area has also been difficult to obtain.

A fourth recommendation was to push for greater standardisation of animal models and the development of new (challenge) models. Standardisation of models combined with the use of comparators comprising approved vaccines would also help in interspecies extrapolation of results. Standardised challenge studies could be offered as GLP-compliant or reflecting in-field conditions.

3.5. Clinical development

The recommendations to support clinical development primarily fell into three categories: (i) access to partners, (ii) access to expertise, and (iii) access to data and data-management tools (Table 1). One further recommendation was for greater access to assays that assess vaccine-adjuvant activity in clinical studies. In general, the recommendations reflected the requirement for (i) partnering in clinical trial operations, in manufacturing, and in GLP-analytics, and (ii) for expertise in designing the clinical strategy, and for managing clinical trial applications and interactions with national and European regulatory authorities. The latter aspect could be supported by developing a strong collaboration with the existing infrastructure ECRIN (https://ecrin.org).

In the area of human therapeutic vaccines, one recommendation was for more biomarkers that capture the response to a therapeutic vaccine, including adverse events; and tools to better assess immune tolerance, and tumour-associated macrophages. Therapeutic cancer vaccine development would be further supported by the development of more immune-checkpoint inhibitors and inhibitors of tumour associated macrophages.

In the area of veterinary vaccines, the recommendation for mid-to late-stage vaccine development was having better access to partners, expertise on development strategies, IP rights and funding. This could be administered through an on-line portal/platform. Multidisciplinary teams and public-private partnerships were viewed as important factors for success.

3.6. Manufacturing

The recommendations to support manufacturing fell into three categories: (i) access to technology and infrastructure, (ii) access to partners and (iii) access to expertise (Table 1).

The recommendation for technology and infrastructure was for access to good manufacturing practise (GMP) production at affordable cost; new production technologies; small-scale production facilities; manufacturing units with flexible capacity and multipurpose; and critical analytical equipment. Partners were needed for contract manufacturing that included the necessary quality systems in place. Expertise was needed in optimising the manufacturing process, scale-up feasibility, product stability, quality assurance (QA) and regulatory affairs including GMP regulations.

One recommendation was to promote the importance of early regulatory planning in vaccine development. Manufacturing scalability is an important criterion for turning a good vaccine candidate into a good product. Therefore, a manufacturing partner should use vaccine production methods that can be scaled up to be GMP-compliant.

Access to industrialisation expertise to develop scale up, and access to expertise in Chemistry, Manufacturing, and Control (CMC) is a critical part of the overall manufacturing and quality aspects when moving from small scale preclinical to larger scale GMP production. For in-licensing projects, well-executed technology transfer and scale-up strategies should help accelerate development to phase 1 in humans.

These recommendations complement and add to the services already offered by TRANSVAC, which currently include pre-clinical GLP production for several platform technologies. A new service offering small scale GMP manufacturing, perhaps via a European or state-funded multifunctional pilot/scale GMP manufacturing facility, should accelerate the progression of candidate vaccines into first-in-human clinical trials.

3.7. Regulatory

The recommendations to support regulatory aspects of all stages of vaccine development were all concerned with access to expertise (Table 1). It was recognised that interactions between regulatory experts and scientists were needed early in the vaccine development process. Indeed, the preclinical stage of vaccine development features as part of the regulatory dossier for human vaccines and contributes to the entire regulatory dossier for veterinary vaccines. Therefore, the recommendations included better access to expertise on interactions with regulatory authorities, GMP regulations, the use of genetically modified organisms, and QA and data-management processes, all of which could be supported by access to training courses.

In the area of therapeutic vaccines, it was considered that the absence of a distinct regulatory pathway related to an insufficient number of therapeutic-vaccine development projects to justify a distinct set of guidance, and a lack of recognition of the mode-of-action of a therapeutic vaccine, and how its mode-of-action may differ from a prophylactic vaccine, a monoclonal antibody therapy, and biological gene therapy. Nevertheless, a therapeutic vaccine may be complicated from a regulatory standpoint for several reasons: (i) by its use in combination with an immune-checkpoint inhibitor (the combination therapy then becomes the product), or in patients undergoing chemotherapy; (ii) it may require an adjuvant to compensate for immune-hyporesponsiveness in the recipient cancer patient; (iii) it may be in the form of a personalized vaccine (using neoantigen from patient); and (iv) it may be in the form of a cell-based vaccine (e.g., a dendritic-

cell vaccine) where the switch from autologous to allogeneic applications would need to be considered. One proposal for promoting a distinct regulatory guidance was to identify a therapeutic vaccine as a branch of immunotherapy and emphasise more that the target populations are patients (e.g., cancer patients). It was also recommended that the streamlining of regulatory guidance for therapeutic vaccines should be harmonised between EU nations and the European Medicines Agency (EMA).

In the area of veterinary vaccines, the recommendation was to have access to training in regulatory requirements at an early stage in veterinary vaccine development, notably in terms of considerations up to the proof-of-concept, and in terms of the differences in regulatory requirements for livestock and companion animals.

3.8. Recommendations for transversal support spanning vaccine development

The recommendations for support spanning vaccine development (transversal support) primarily fell in to three categories: (i) communication and collaboration, (ii) data management, data analysis and e-infrastructure, and (iii) training (Table 1).

Some of these recommendations would augment or add to web-based services, resources, and networks of potential partners/collaborators that are offered by TRANSVAC. Other recommendations focussed on support for smaller companies and researchers, notably in providing advice and training for business development.

3.8.1. Communication and collaboration

The main recommendation was to have access to a centralised web-based vaccinology resource that would systematically integrate already existing databases, networks (Table 1). Hence this resource would constitute a comprehensive map of capabilities and facilities in Europe to support vaccines R&D; a portal to networks and partners to promote knowledge sharing and collaboration, for clinical development and public health, and for project-management support. This will require collaboration between SMEs, research institutes and regulatory authorities, but also more communication between infrastructures already operating in Europe.

3.8.2. Data management, data analysis and e-infrastructure

The main recommendation was to have access to a sustainable data warehouse dedicated to gathering, curating, and organising data for further analysis (in formats accessible to different users; Table 1). The data warehouse would need to accommodate various types of data from different platforms (and extend access to data from biobanks offering animal materials, and repositories of reagents). The resource would help identify extrapolation of results (e.g., for reactogenicity and efficacy) between species, correlates of protection and the design of clinical endpoints. The generation of this resource could dovetail with existing initiatives such as EOSC-Life (https://www.eosc-life.eu).

3.8.3. Training

The recommendations for the form of training included one-to-one coaching, theoretical and practical courses, and workshops (Table 1). The topics should be relevant for vaccinology but tailored to the participants needs and background (e.g., young investigators, regulators, small and medium enterprises (SMEs), or [GMP] production engineers). Providing the training with some form of certification or accreditation, should ensure quality and sustainability: an accredited training course could feature as part of the required continuing-education strategy for industry. Similarly online content including recorded training sessions and E-learning could also support a sustainable training platform with global reach.

Some of the recommended topics could be offered as a module, such as for vaccine regulatory strategy (an area which was viewed as a priority), which would cover clinical trial design, vaccine development plan, GLP-like experiments, regulatory and safety, gold standard assays, GMP production (requirements), Quality-control (QC) release, method validation.

Similarly, a business coaching module was viewed as a priority for SMEs and public-sector research groups, which would cover business skills, pitching to investors, regulatory pathways, legal advice and IP protection, business plans, communications with industrial partners, and technology transfer.

3.9. Funding

The recommendations for support of funding and financing featured as critical elements throughout the vaccine-development programm (Table 1), where funding was considered as sponsored awards and grants, and financing was considered as investments from private sources. It was recognised that the funding for vaccine development should remain higher than it was before the COVID-19 pandemic, even though funding levels during the height of the pandemic are likely to subside. Also, the funding of therapeutic vaccine projects in Europe appeared more difficult than in the USA or China, to the extent that many European companies enlist on NASDAQ to get access to US funding, and SMEs tend not to commercialise their own products.

Several recommendations related to identifying novel solutions to broaden the access to funding and financing for academics and SMEs, and for funding to support vaccine programmes that address medical and veterinary needs without a great potential for commercial gain. In addition to recommendations for funding, the scope, mechanisms and measures for funding and financing, access to expertise was also recommended for investor scouting, assessing commercial viability, and creating the business case; and for identifying funding opportunities and preparing grant applications. It was also recognised that being able to secure funding and financing was dependent on good management practice in intellectual property (IP) and technology transfer. Therefore, one recommendation was to identify a support process that facilitate the management of patents and freedom-to-operate in the development of a vaccine product. Potentially, this process could take the form of an on-line service (e.g., resource for searching relevant patents etc.).

3.10. Recommendations with respect to COVID-19 vaccine strategies

During the consultation, recommendations were sought with respect to the COVID-19 vaccination campaign. This aspect of the consultation was completed by January 2021, at a point where the COVID-19 vaccination campaign in Europe was into its first month with two vaccines approved by the EMA [5]. Many of the recommendations overlapped with those identified in other aspects of the consultation, as follows:

- More flexibility in the regulatory-approval process without lowering standards, facilitated by more interactions between the vaccine developer and the authorities: full validations could be completed at a later stage of clinical development.
- Availability of a wider range of vaccine technology platforms. Several approved COVID-19 vaccines use new platforms (i.e., mRNA-based and adenovirus vectors), and various other vaccines in late-stage clinical development are using other new platforms (novel adjuvants, DNA, other viral vectors, modified antigen-presenting cells) [6].
- Flexible approaches to funding and investment that accelerated clinical development and GMP manufacturing.
- Adoption of strategies to circumvent or alleviate cold-chain restrictions for vaccines.
- Adoption of strategies in which vaccine evaluations were performed in parallel.
- More on-line scrutiny of adverse events during and after clinical trials.

- Clinical evaluations also performed in vulnerable populations (e.g., pregnant women, children, the elderly).

4. Conclusions

Fifty-three organisations based mainly in Europe, representing various vaccine-development stakeholders, participated in one or more phases of the consultation between October 2020 and June 2021. Several of the gaps and needs identified in the consultation were brought into sharp focus by the contemporaneous and rapid development of vaccines in response the COVID-19 pandemic. The conclusions of the consultation mainly focused on European vaccine R&D, with a specific emphasis on how the gaps and needs identified could be potentially addressed by a European vaccine research infrastructure. Therefore, our analysis may not provide the complete solution at a worldwide level.

Clearly, not all gaps and needs identified can best be addressed by a vaccine infrastructure, such as TRANSVAC. For example, the need for additional capacity for vaccine GMP manufacturing cannot easily be satisfied by any existing research infrastructures, and the generation of additional manufacturing facilities would require very substantial financial and other investments that are currently out of reach and beyond the possibilities of existing infrastructure initiatives. Nevertheless, many of the needs and gaps identified in the present analysis can and could be addressed by dedicated European vaccine research infrastructure offering a corresponding catalogue of scientific-technical and other types of services.

Although some of the services required to address the identified gaps and needs in vaccine R&D, such as access to animal models, are already offered by some of the biomedical research infrastructures existing in Europe, at the time of the consultation, there was no existing research infrastructure, or combination thereof, that could address the majority of the key gaps and needs. It is our view that many of these key gaps and needs would be best served by a dedicated, sustainable European vaccine infrastructure offering a portfolio of targeted services. In addition to providing these services, a dedicated vaccine research infrastructure could also undertake joint research activities among the partner institutions underpinning the infrastructure, with the aim of improving existing services and developing new services. Such joint research activities should address human and veterinary vaccines, according to One Health concept. The infrastructure should endeavour to harmonise and standardise assays to allow data comparisons between different groups of vaccine developers.

Overall, the recommendations supported the expansion and elaboration of services including training programmes, and improved or more extensive access to expertise, technologies, partnerships, curated databases, and-data analysis tools. Funding and financing featured as critical elements requiring support throughout the vaccine-development programm, notably for academics and SMEs, and for vaccine programmes that address medical and veterinary needs without a great potential for commercial gain. Centralizing the accessing to these research infrastructures via a single on-line portal was considered advantageous. Capitalising on its more than ten years' experience as a vaccine-development infrastructure, an expanded and broadened TRANSVAC could act as a portal for many of these services and resources. Findings from the present gaps and needs analysis will be extremely useful for consolidating and finalising the conceptual and technical design and ultimate implementation of a stable European vaccine R&D infrastructure and for proposing a business model that will allow such an infrastructure to be sustainable in time.

Acknowledgements

This work has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 951668 (TRANSVAC-DS). We gratefully acknowledge the support from the entire TRANSVAC-DS consortium to this analysis.

References

[1] Doherty M, Buchy P, Standaert B, Giaquinto C, Prado-Cohrs D. Vaccine impact: benefits for human health. Vaccine 2016;34:6707–14. https://doi.org/10.1016/j.vaccine.2016.10.025.
[2] Greenwood B. The contribution of vaccination to global health: past, present and future. Philos Trans R Soc Lond B Biol Sci 2014;369:20130433. https://doi.org/10.1098/rstb.2013.0433.
[3] Black S, Bloom DE, Kaslow DC, Pecetta S, Rappuoli R. Transforming vaccine development. Semin Immunol 2020;50:101413. https://doi.org/10.1016/j.smim.2020.101413.
[4] Ura T, Yamashita A, Mizuki N, Okuda K, Shimada M. New vaccine production platforms used in developing SARS-CoV-2 vaccine candidates. Vaccine 2021;39:197–201. https://doi.org/10.1016/j.vaccine.2020.11.054.
[5] EMA. COVID-19 vaccines: authorised. 2021. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised. [Accessed 19 July 2021].
[6] WHO. COVID-19 vaccine tracker and landscape. 2021. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. [Accessed 19 July 2021].
[7] Charleston B, Graham SP. Recent advances in veterinary applications of structural vaccinology. Curr Opin Virol 2018;29:33–8. https://doi.org/10.1016/j.coviro.2018.02.006.
[8] Cunningham AA, Daszak P, Wood JLN. One Health, emerging infectious diseases and wildlife: two decades of progress? Philos Trans R Soc Lond B Biol Sci 2017;372. https://doi.org/10.1098/rstb.2016.0167.
[9] Pastoret PP, Jones P. Veterinary vaccines for animal and public health. Dev Biol 2004;119:15–29.
[10] Blass E, Ott PA. Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nat Rev Clin Oncol 2021;18:215–29. https://doi.org/10.1038/s41571-020-00460-2.
[11] Hollingsworth RE, Jansen K. Turning the corner on therapeutic cancer vaccines. NPJ Vaccines 2019;4:7. https://doi.org/10.1038/s41541-019-0103-y.
[12] Jansen KU, Anderson AS. The role of vaccines in fighting antimicrobial resistance (AMR). Hum Vaccines Immunother 2018;14:2142–9. https://doi.org/10.1080/21645515.2018.1476814.
[13] Song Q, Zhang CD, Wu XH. Therapeutic cancer vaccines: from initial findings to prospects. Immunol Lett 2018;196:11–21. https://doi.org/10.1016/j.imlet.2018.01.011.
[14] Tait DR, Hatherill M, Van Der Meeren O, Ginsberg AM, Van Brakel E, Salaun B, et al. Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. N Engl J Med 2019;381:2429–39. https://doi.org/10.1056/NEJMoa1909953.
[15] Al Mahtab M, Akbar SMF, Aguilar JC, Guillen G, Penton E, Tuero A, et al. Treatment of chronic hepatitis B naive patients with a therapeutic vaccine containing HBs and HBc antigens (a randomized, open and treatment controlled phase III clinical trial). PLoS One 2018;13:e0201236. https://doi.org/10.1371/journal.pone.0201236.
[16] Leroy O, Geels M, Korejwo J, Dodet B, Imbault N, Jungbluth S. Roadmap for the establishment of a European vaccine R&D infrastructure. Vaccine 2014;32:7021–4. https://doi.org/10.1016/j.vaccine.2014.08.014.