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European strategy for vaccine development against infectious diseases

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ABSTRACT

Immunisation efforts save millions of lives every year, but vaccines hold the potential to deliver even greater health benefits for mankind. Vaccine research and development is highly complex, and it requires concerted public funding efforts to support. In this paper we discuss EU funding priorities and the resulting recent advancements in European vaccine research, and we lay out the EU strategy for aiding promising vaccine candidates to successfully reach the market.

1. Introduction

Each year immunisations prevent 2–3 million deaths from diphtheria, tetanus, pertussis and measles [1]. Mortality rates from diseases such as measles have crashed globally, smallpox has been eliminated entirely, and polio is on the precipice of eradication. The advancements in health that have been delivered by vaccines cannot be underestimated. Despite this progress it is crucial that we focus, in Europe and globally, on ways to better select and support new vaccine candidates to develop, on ensuring that vaccines are easy to use in countries with weak health systems, and on meeting the vaccination requirements of specific groups such as infants and the elderly.

A key priority for the EU is to expand the list of preventable diseases in the future. Europe has traditionally been the major player in vaccine discovery, development and manufacturing. More than 80% of vaccines for worldwide use are produced in and exported from Europe. The economic potential for Europe is thus a second driving factor for the EU to prioritise vaccine research and innovation. In addition, our global responsibility, commitments and international leadership on the UN Sustainable Development Goals represent a third important factor.

A concerted effort at EU level, in coordination with Member States, is needed, considering the substantial scientific challenges ahead. The steps required to develop new safe and effective vaccines are highly complex, involving significant scientific, regulatory, clinical, and often public acceptability hurdles along the way. To assist in this complex process, the EU has designed different mechanisms to support vaccine candidates at various stages. With more diseases being covered by vaccine research programmes, and with the candidates being better supported throughout the full pathway of vaccine development, we should see significant progress on crucial gaps in the coming years.

2. Achievements so far

Between 2007 and 2014, more than €400 million was invested by the EU in vaccine and vaccine-related research and development (R&D) in infectious diseases, including €38 million under the Innovative Medicines Initiative [2] (IMI), a partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations. A further €67.7 million of the total was committed under the European and Developing Countries Clinical Trials Partnership [3] (EDCTP), which now involves 14 European and 14 Sub-Saharan African countries. These investments are delivering results. For instance, ADITEC [4], with an EU contribution of €30 million, has developed and tested a new generation of adjuvants, novel viral and bacterial vectors, as well as new immunisation strategies. To date ADITEC has performed no less than 12 clinical trials. As part of these trials, the group demonstrated, for instance, that infant immune responses are enhanced when using a trivalent inactivated adjuvanted influ-

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enza vaccine [5]. The excellence of the science underpinning ADITEC's approach has been recognised through the more than 148 publications in peer reviewed journals thus far.

NEWTBVAC [6] is another project dedicated to the discovery and preclinical development of new generation vaccines, this time specifically for tuberculosis. Through their work they have accelerated the development of 6 novel vaccine candidates to preclinical stage and 4 candidates to early clinical development. In total this project has contributed to approximately 50% of the TB vaccine candidates in the global clinical pipeline. In addition, novel antigens, viral carriers, adjuvants and promising biomarkers were discovered in the course of their work.

HOOKVAC [7] developed the first and only vaccine for human hookworm infection. It is a bivalent, low-cost vaccine candidate which is now being clinically tested for the first time in an African, disease-endemic, population. The importance of vaccine development for diseases where there is no preventative intervention is especially important.

One of the challenges in resource-poor settings where the burden of vaccine-preventable diseases is particularly high, is the limited capacity to conduct high quality research. EDCTP has played a major role in establishing the infrastructures and expertise to conduct clinical trials to regulatory standards in Sub-Saharan Africa. To date, more than 500 scientists and clinicians have been trained, and ethics committees have been established in countries that had no, or limited, capacities (Benin, Democratic Republic of Congo, Gabon, Liberia, Mozambique and Rwanda). Since 2003, EDCTP has supported six projects that include clinical trials of vaccines and projects that have a focus on immunological responses and capacity building for vaccine trials. Notable among the vaccine trials funded by EDCTP is the Malaria Vectored Vaccine Consortium (MVVC). This group aims to develop a liver stage malaria vaccine based on the thrombospondine-related adhesion protein (TRAP) that is fused to a string of multiple T cell epitopes (ME), administered in two different viral vectors. The two viral vectors ChAd63 (a simian adenovirus vector) and MVA (Modified Vaccinia Ankara) both express ME-TRAP and are administered in a prime-boost regimen, which aims to provoke a strong cellular immune response directed against TRAP. The MVVC phase Ib study conducted in The Gambia and in Kenya showed good safety and immunogenicity in adults, as well as in Gambian children and infants [8]. Furthermore, data obtained from a follow-up phase II clinical trial study in Kenya demonstrated that 67% protective efficacy against infection with *Plasmodium falciparum* can be achieved with a promising T cell-inducing vaccination strategy, among adults living in a malaria-endemic area in the country [9]. In a follow-up project (MVVC2), also supported by EDCTP, the consortium carried out a phase I trial (VAC058) to assess for the first time the safety and immunogenicity of ChAd63 ME-TRAP–MVA ME-TRAP heterologous prime-boost vaccination, co-administered with Expanded Programme for Immunisation (EPI) vaccines in Gambian infants. Final results for this trial are expected within the coming months, and are highly anticipated. Another example of the vaccine trials funded by EDCTP is the multicentre phase II trial of an MVA vector expressing the conserved mycobacterial antigen 85A (MVA85A) candidate against tuberculosis, which is being tested in HIV-positive adults in South Africa and Senegal. The results showed that vaccinating adults infected with HIV-1 with MVA85A is safe and well tolerated, but the cellular immunogenicity is low and does not confer protection against infection with *M. tuberculosis* or TB disease [10]. Results like this may not entail all the success that we hope, however this is still a significant scientific advance. While challenges remain, trials such as this bring us a great step closer to the goal of effective prevention of this disease in HIV-positive individuals.

Another challenge is ensuring the uptake of effective vaccines. To address this, IMI just launched the project ADVANCE [11] which brings together the European Centre for Disease Prevention and Control and the European Medicines Agency, as well as national public health and regulatory bodies, vaccine manufacturers and academic experts. The aim of this is to develop and test methods and guidelines that would enable the rapid delivery of reliable data on the benefits and risks of vaccines on the market. This framework should help both regulators and public health authorities make decisions on vaccination strategies, and help maintain public confidence in immunisation as an effective public health tool to control infectious disease.

To incentivise innovation in the vaccine development sector, the European Commission launched its first inducement Prize [12]. In 2014 CureVac [13] was awarded the prize of €2 million for having developed a novel technology which offers excellent conditions for transport and storage of vaccines. Their technology is based on messenger RNA and displays improved stability at a range of temperatures and other environmental conditions. Subsequently, CureVac's innovation was recognised by the Bill and Melinda Gates Foundation with an investment of €46 million and the separate funding of vaccine development programmes in 2015. This funding is now supporting further development of CureVac's technology platform, and the construction of an industrial scale Good Manufacturing Practice (GMP) production facility. This demonstrates the potential power of innovation-supporting tools such as prizes capable of recognising an accomplishment and giving not only a monetary reward, but importantly, a far wider recognition.

3. Future perspectives – Horizon 2020

Europe's new research funding programme, Horizon 2020, addresses the entire innovation cycle, from basic research to implementation in order to support crucial discoveries, as well as drive economic growth and job creation. Over €200 million has already been invested in vaccine research against infectious diseases, reflecting the programme's greater emphasis on supporting innovation and addressing prevention in health. The first funding calls targeted the development of vaccines against tuberculosis and HIV. These two diseases remain amongst the leading causes of infectious disease death globally [14]. While a vaccine for tuberculosis exists, a more efficient vaccine would make a dramatic difference in terms of reduced global mortality and morbidity. It has been estimated that between 2024 and 2050 a tuberculosis vaccine targeting adolescents/adults in low-income countries with a 10 year duration and 60% efficacy could prevent 17 million tuberculosis cases by 2050, and would be highly cost-effective at $149 per DALY averted [15]. However, experience during the last 95 years since the introduction of the BCG vaccine, which gives only limited protection against adult pulmonary tuberculosis, has shown that developing a better tuberculosis vaccine is a formidable scientific problem. The lack of biomarkers that correlate with protective immunity against tuberculosis disease of *M. tuberculosis* infection is still a central challenge of tuberculosis vaccine R&D. As a response to these challenges two large collaborative projects on preclinical TB vaccine research were selected for funding totalling €26 million: TBVAC2020 [16] and EMI-TB [17]. Two other complementary projects: EAVI2020 [18] and EHVA [19], with an EU contribution of €45.1 million, address vaccine development for HIV/AIDS. This is another disease which has posed enormous challenges to the research community which has made endless efforts to develop an effective vaccine. In these new partnerships, European scientists will work together in collaboration with researchers from outside Europe to successfully develop predictive tools and

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