Advancing health through vaccine innovation

Report prepared by Vaccines Europe

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Table of Contents

Foreword

Vaccination is the single most effective public health intervention to prevent infectious diseases, saving millions of lives every year. However, new vaccines have the potential to prevent infections caused by pathogens for which conventional technologies have failed. Progress in genomics, immunology, microbiology, formulation and antigen optimisation will allow the development of innovative vaccines to address unmet medical needs.

The combination of new technologies, such as adjuvants, viral and nucleic acid vectors and antigen delivery systems may enable the development of therapeutic vaccines to cure cancer and immunological disorders. In addition, innovative approaches may improve the efficacy and safety of vaccines administered to challenging target populations such as the elderly, infants and immune-compromised patients. Science-based innovation is the key factor to address unmet medical needs and to compete in the vaccine market of the future. Europe is a leader in vaccine research and manufacturing, with a long history of innovations. However, emerging markets are now increasing their vaccine development and production, and competition is becoming greater every year. Protecting Europe's lead in vaccines will require a comprehensive vision on innovation, and improved coordination between academic and industrial sectors. This document contains the European research-based **vaccine industry vision on vaccine innovation**, with a special focus on research and development. The goal is to provide input for the definition of a strategic European vaccine roadmap to be developed and implemented with all relevant stakeholders across private and public sectors to increase innovation, efficiency and competitiveness of vaccine research. In turn, this is expected to contribute to the EU's economic growth and to improving public health worldwide.

Background

Several initiatives have been launched globally to better capture the full potential of vaccination. These include Decade of Vaccines[1], an initiative launched by the Bill and Melinda Gates Foundation[2] at the World Economic Forum in Davos in January 2010[3], committed $10 Billion to vaccine research, and to the development and delivery of safe and effective vaccines for the poorest countries, with the aim of saving 8-10 million lives by 2020. The Institute of Medicine[4] launched an initiative with the aim to develop an evidence-based approach and methodology to identify and prioritize the needs for new preventive vaccines of domestic and global importance.

This global interest in vaccines can be easily explained by looking at the impact that vaccination has had on global health in the last century. Vaccination has been shown to be one of the most effective means to reduce disease and death from infectious diseases. It is believed that vaccines save at least 2 to 3 million lives per year globally [2].

With the exception of water sanitation, no other public health intervention, even antibiotics, has had such a major effect on the reduction of mortality, improved health and population growth [3]. Smallpox has been eradicated and other diseases have almost disappeared, such as polio, which remains endemic only in Pakistan, Nigeria and Afghanistan[5],. In the US, Europe and other developed countries most of the viral and bacterial diseases that traditionally affected children have virtually disappeared thanks to immunisation.

These vaccine prevented diseases include diseases like diphtheria, tetanus, *Haemophilus influenzae*, mumps, measles and rubella – albeit there have been recent measles and rubella outbreaks in the EU during the period 2011-2012 due to suboptimal vaccination coverage and decrease in public confidence towards vaccination. Other childhood diseases like pertussis, rotavirus, varicella, hepatitis A and B and pneumococcal pneumoniae have been drastically reduced (Table 1 describes the reduction of morbidity in the United States compared to 20th century and Table 2 summarises the impact of vaccination in Europe since 1980).

[1] http://www.dovcollaboration.org/
[2] http://www.gatesfoundation.org/
[3] http://www.weforum.org/events/world-economic-forum-annual-meeting-2010
[4] http://www.iom.edu/
[5] http://www.who.int/mediacentre/factsheets/fs114/en/

Table 1. Vaccine-preventable diseases in the US

Impact of Vaccines in the 20th & 21st Centuries

Comparison of 20th Century Annual Morbidity & Current Morbidity

Disease	20th Century Annual Morbidity*	2010 Reported Cases†	% Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Pertussis	200,752	21,291	89%
Tetanus	580	8	99%
Polio (paralytic)	16,316	0	100%
Measles	530,217	61	>99%
Mumps	162,344	2,528	98%
Rubella	47,745	6	>99%
CRS	152	0	100%
Haemophilus influenzae (<5 years of age)	20,000 (est.)	270 (16 serotype b and 254 unknown serotype)	99%

Sources:

* *JAMA*. 2007;298(18):2155-2163

† CDC. *MMWR* January 7, 2011;59(52);1704-1716. (Provisional *MMWR* week 52 data)

Comparison of Pre-Vaccine Era Estimated Annual Morbidity with Current Estimate

Disease	Pre-Vaccine Era Annual Estimate	2008 Estimate	% Decrease
Hepatitis A	117,333*	11,049	91%
Hepatitis B (acute)	66,232*	11,269	83%
Pneumococcus (invasive)			
All ages	63,067*	44,000†	30%
<5 years of age	16,069*	4,167¶	74%
Rotavirus (hospitalizations <5 years of age)	62,500§	7,500‡	88%
Varicella	4,085,120*	449,363	89%

Sources:

* *JAMA*. 2007;298(18):2155-2163

† CDC. Active Bacterial Core surveillance Report; *S. pneumoniae* 2008. (www.cdc.gov/abcs/survreports/spnew08.pdf)

¶ 2008 Active Bacterial Core surveillance

§ CDC. *MMWR*. February 6, 2009 / 58(RR02); 1-25

‡ New Vaccine Surveillance Network

Table 2: Impact of Vaccines on communicable diseases in Europe 1980-2009

WHO Global and regional immunization profile 2010
***rubella cases from 2000**

Disease	Cases 1980	Cases 2009	Change
Diphteria	618	41	**-93%**
Measles	851.849	7.499	**-99%**
Pertussis	90.546	29.226	**-68%**
Polio	549	0	**-100%**
Tetanus	1.715	181	**-89%**
Rubella*	621.039	11.623	**-98%**

Table 3. Vaccines against infectious diseases licensed for human use

Table 3 summarises available vaccines directed against infectious diseases worldwide. The vaccines have been grouped into six classes based on the method of production: live attenuated, killed whole organisms, toxoids/proteins, polysaccharides, glycoconjugates and recombinant. With the exception of rabies, which can be used for both pre and post-exposure prophylaxis, all the vaccines listed in table 3 are used to prevent infections. Other therapeutic vaccines capable of targeting chronic infections such as HIV, tuberculosis or hepatitis C are still being developed**.**

Vaccine class	Licensed vaccines
Live attenuated	Smallpox, Rabies, Tuberculosis (BCG), Yellow Fever, Polio (OPV), Measles; Mumps, Rubella, Typhoid, Varicella, Rotavirus, Influenza (cold adapted), Zoster
Killed whole organism	Typhoid, Cholera, Plague, Pertussis, Influenza, Typhus, Polio (IPV), Rabies, Japanese Encephalitis, Tick-born Encephalitis, Hepatitis A
Toxoid/Protein	Diphteria, Tetanus, Acellular pertussis, Anthrax, Influenza subunit
Polysaccharide	Pneumococcus, Meningococcus, Haemophylus Influenzae B, Typhoid (Vi)
Glycoconjugate	Haemophylus influenzae B ; Pneumococcus (7, 10 and 13 valent), Meningococcus C, Meningococcus ACWY
Recombinant	Hepatitis B, Cholera Toxin B, Human Papillomavirus; Meningococcus B

Vaccine research and development also make a **key contribution to Europe's economy, competitiveness and research base**. While the major vaccine manufacturers are global in nature, the majority of their production and research and development activities are based in Europe.

In 2010, 79% of the Vaccines Europe members[6,] production took place in Europe, and at least 90% of this was exported globally. Nearly 45% of the exports were directed to humanitarian groups in support of public health worldwide.

Between 2002 and 2010, a 47% growth in global R&D investment was reported, with about half of R&D projects based in Europe. 70% of innovative R&D projects reported in 2010 focused on new antigens or new combinations of antigens. Vaccine manufacturers are committed to investing in innovation and in the development of new vaccines targeting unmet medical needs, as well as new combinations or improvements in the process technology.

Such sustained investment in vaccine innovation generates an important spin-off for the EU's knowledge-based economy, playing an important role in creating high skill employment with an estimated 65% of vaccines R&D employees based in Europe.

Although this demonstrates industry's commitment over time to investing in innovation in Europe – as well as the current capability and capacity of European R&D to support it – the number of R&D projects in Europe has remained steady over the past eight years (2002 to 2010). During this time there has been an increase in the number of R&D projects in other regions, such as China and India and other emerging markets, which have also captured about 8% of the global vaccine production between 2008 and 2010.

Vaccine research should be sustained and enhanced by continuing to shape an innovation friendly and enabling environment where the appropriate push and pull mechanisms are in place to favour the delivery of breakthrough vaccines.

Key facts

- **Europe is at the heart of the global vaccine industry**
- **Majority of the global vaccine manufacturers' production takes place in Europe**
- **Vaccines produced in Europe are exported to diverse geographical regions contributing to global public health worldwide**
- **Vaccines Europe members continuously invest in innovative vaccine R&D**
- **Majority of R&D employees of global vaccine manufacturers are based in Europe**
- **Strong vaccine industry and research base competitiveness contributes to Europe's economic growth and the EU2020 strategy**

[6] Vaccines Europe conducts a biennial survey providing insight into the innovation, research and development, employment and manufacturing undertaken by its members. The Vaccines Europe surveyed members in 2010 are: Abbott Biologicals, MedImmune, Baxter, Crucell, GSK Vaccines, MSD, Novartis Vaccines, Pfizer, Sanofi Pasteur and Sanofi Pasteur MSD.

Vaccines in the 21st century

1.1 Scientific innovation and technology are the major driving forces in the success of vaccines

Progress in science and innovation has always been the major drive for vaccine development and Europe has always played a major role. European scientists such as Pasteur, Koch, Ramon and Mérieux established the germ theory and developed vaccines based on inactivated pathogens or toxins, which protected against rabies, diphtheria, tetanus, pertussis, and TB. This first golden age of vaccines was accompanied by the establishment of national vaccine institutes in Europe such as the Pasteur Institute, Wellcome Trust, the Robert Koch Institute, the Sclavo Institute and many others. Over the last few decades progress in science and innovation has created a second golden age of vaccine discovery. Improved cell culture technologies allow for effective inactivated vaccines such as inactivated polio (IPV), hepatitis A and live-attenuated vaccines such as Mumps, Rubella, Measles (MMR), Rotavirus and varicella vaccines. New molecular biology techniques enable the development of recombinant vaccines to prevent Hepatitis B and HPV infections. Both vaccines are made of a purified recombinant protein antigen that self assemble in a non-infectious viral-like particle (VLP). The ability to isolate capsule components from pathogenic bacteria led to the development of polysaccharide vaccines against some strains of pneumococcus and meningococcus.

Nevertheless not all of these vaccines were effective in the youngest children. Progress in immunology, chemistry and microbiology led to the development of glycoconjugate vaccines against *Haemophilus influenzae*, and *Streptococcus pneumoniae*. These vaccines are more efficient compared to non-conjugated polysaccheride-based vaccines, because they generate good protective immune responses in all age groups including children. Glycoconjugate vaccines have also been successfully developed for the strains A, C, W and Y of *Neisseria meningitidis* (meningococcal meningitis). More recently the application of genomics in a process called “reverse vaccinology” allowed for the development of the first vaccine against *Neisseria meningitidis* B strain based on a combination of recombinant proteins.

The history of vaccination teaches us that unmet medical needs were addressed through the application of innovative solutions that had never been used before. Therefore, investing in science and innovation now is the best approach to being successful in the vaccine field in the future. One of the aims of this document is to identify which novel technologies can be developed today that can enable the development of better and novel vaccines in the future capable of meeting the public health needs of future populations.

1.2 Need for innovative vaccines

1.2.1 Prophylactic vaccines

There are still many infectious diseases that cause death, disease and disability worldwide for which vaccines are not yet available, which could be preventable by vaccination. Table 4 lists those human pathogens for which there are still no vaccines. These include viruses (e.g. hepatitis C virus (HCV), human immunodeficiency virus (HIV), Dengue, respiratory syncytial virus (RSV), and cytomegalovirus (CMV)); parasites (e.g. *Plasmodium, Leishmania, Schistosoma, Trypanosoma*) and bacteria (e.g.

Mycobacterium tuberculosis (TB), *Group A streptococcus* (GAS), *Group B Streptococcus* (GBS), *Staphylococcus aureus*, *Shigella*, pathogenic *E. coli and Pseudomonas aeruginosa*).

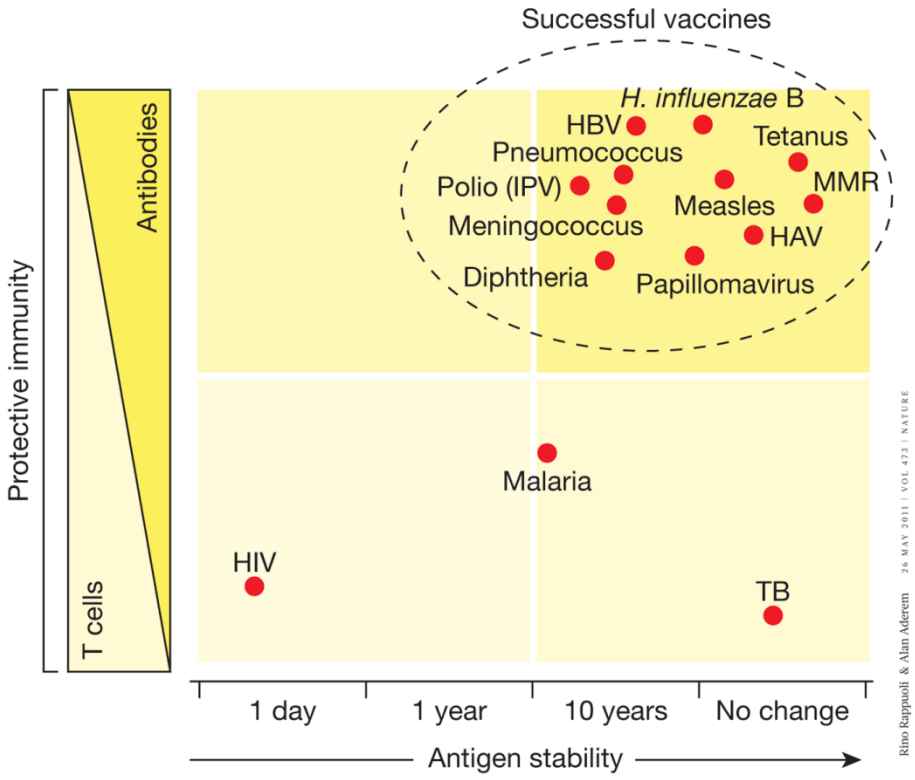
Table 4. Infectious diseases for which there are currently no vaccines

Bacteria	Viruses	Parasites
Tuberculosis	HIV	Malaria
Group A streptococcus	HCV	*Leishmania*
Group B streptococcus	RSV	*Schistosoma*
Staphylococcus aureus	EBV	*Trypanosoma*
Shigella	HSV	*Toxoplasma*
Salmonella	CMV	*Brucella*
Clamydia	Dengue	*Cryptosporidium*
Pathogenic *E.coli*	Enteroviruses	*Entoamoeba*
Pseudomonas aeruginosa	Ebola	
Clostridium difficile	Marburg hemorragic fever	
Non-typeable Haemophilus	Parvovirus	
Klebsiella pneumoniae	Norovirus	

Existing vaccines based on inactivated or attenuated pathogens, or on purified pathogen subunits such as toxins, proteins and polysaccharides, have been efficient in preventing infections of pathogens with low degree of antigen variability. These vaccines work mainly by eliciting antibodies that neutralise pathogens and toxins or kill the microorganism through complement or cell-mediated mechanisms. However, today we still face the challenge of developing vaccines against pathogens whose surface antigens undergo a high mutation rate and evade the antibody response during the course of the same infection. Another challenge is the prevention of infections that are not controlled by antibodies but by cellular immunity. In this case, better understanding molecular immunologic mechanism will drive innovative discoveries, and if we consider that infections caused by some of the most variable pathogens such as HIV and HCV, are probably not preventable only by antibodies, but require a combination of humoral and cellular immune responses (McElrath and Haynes, 2010), the questions become more complex.

As technology progresses in the fields of genomics, immunology, microbiology, formulation and antigen optimisation we are able to design a new generation of vaccines that are safer and more effective than traditional vaccines developed in the last several decades. One of the future goals for vaccine manufacturers is to design and create innovative vaccines that prevent diseases for which conventional technologies have failed. Novel technologies, such as adjuvants and new antigen delivery vectors, can also contribute to the development of more effective vaccines for pathogens characterised by complex antigen variability, which will require a contribution of both humoral and cellular responses for protection.

Figure 1. Successful vaccines have been developed against pathogens with stable surface antigens



1.2.2 Therapeutic vaccines

Vaccines are usually considered as prophylactic since they are typically administered to healthy individuals in order to prevent disease. Nevertheless, there is a growing effort to develop therapeutic vaccines to alleviate the suffering of those with disease. The past few years have seen a renewed focus on therapeutic vaccines. A key milestone was reached in 2010, when the FDA approved the first therapeutic vaccine for prostate cancer: The vaccine has been shown to extend life by about four months in men with a certain type of metastatic prostate cancer. Many companies have announced important steps forward in the development of an array of new therapeutic vaccines for other cancers, infectious diseases, Alzheimer's disease, and other conditions. It is likely that multiple first-of-their-kind therapeutic vaccines will become available in the next decade, possibly including the first vaccines for breast and lung cancer. The first licensed therapeutic vaccine provides evidence that therapeutic vaccines can work; future efforts need to be coordinated to ensure that other therapeutic vaccines will become available in a timely fashion.

By the end of 2011, the pipeline for therapeutic vaccines had grown to an estimated 399 products and was larger than the pipeline for prophylactic vaccines [13]. This demonstrates some of the potential for this therapeutic approach. The vaccines in development cover more than 70 different conditions. There is a strong focus on areas of high unmet need, for example, vaccines for cancer and infectious diseases (including HIV and hepatitis B and C) account for 55% and 24% of the vaccines in the pipeline respectively. Particular attention is being paid to late-phase products. Products in phase III include potential treatments for multiple cancers, allergies, diabetes, and addictions. Therapeutic vaccine companies must choose among a variety of replicating and non replicating vectors, delivery systems, immunepotentiators / adjuvants, product technologies, and production platforms — with

many of these factors being unique to therapeutic vaccines. These companies are also developing new immunological assays for the identification and validation of novel vaccine candidates.

Major hurdles limiting efficacy of cancer vaccines

In recent years, many studies have also identified the main hurdles in cancer vaccine development. The first resides in the weak immunogenicity of tumour antigen-based vaccines, as they are self-antigens.6 A second relates to the difficulty in achieving the right balance of CD4 and CD8 T cells induced by antigen mimics: while short peptides mainly induce CD8 T cells, recombinant proteins mainly induce CD4 T cells. With regard to genetic viral-based vaccines, the intrinsic immunogenicity of the vector sequences has to be considered, as they can compete with the cloned antigen sequence. A third hurdle is the limited longevity of the elicited responses, and there is a strong need for vaccines that address a robust memory response. Finally, the major obstacle is likely the instability of the functional competence of T-cells at the tumour site. Very recent reports have uncovered multiple immune regulatory checkpoints operating intrinsically in antigen activated T cells and extrinsically within the tumour microenvironment7,8.

Combined strategies of cancer immunotherapy

Immune checkpoint blockade has come to the forefront of both tumour immunology research and clinical cancer immunotherapy. A major breakthrough was the approval of monotherapy with anti-CTLA-4 for second line treatment of metastatic melanoma.9 Moreover, promising results were reported with anti-PD-110 and anti-PD-L111 blocking antibodies in patients with various types of cancer. Thus the stage is set to combine vaccination and immune checkpoint blockade, with the possibility to target more than one immune checkpoint for blockade.12

Anticancer drugs and radiotherapy as adjuvant immunotherapies

Chemotherapy, radiation therapy and antiangiogenic therapy are well established in oncological practice. Until recently they were perceived as approaches targeting respectively the tumour cells or the tumour feeding vessels. Recent studies, however, have initiated a paradigm shift, whereby an important part of their therapeutic effect in fact requires an intact immune system, in particular the presence of adaptive CD8 T-cell responses. The mechanisms underlying the cross talk with the immune system are being outlined in experimental models.13 On the other hand, tumour neovessels are generally not permissive for T-cell migration from the circulation into the tumour parenchyma. Anti-angiogenic drugs have been shown in pre-clinical models to promote intra-tumour trafficking of

[7] , Baitsch, L. et al. Exhaustion of tumor-specific CD8 T cells in metastases from melanoma patients. J Clin Invest 121, 2350-2360.
[8] Calcinotto, A.,et al. (2012). Modulation of microenvironment acidity reverses anergy in human and murine tumor-infiltrating T lymphocytes. Cancer Res 72, 2746-2756.
[9] Hodi, F.S.,et al. (2010). Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363, 711-723.
[10] Topalian, S.L. et al. (2012). Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366, 2443-2454.
[11] Brahmer, J.R., , et al. (2012). Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 366, 2455-2465.
[12] Sakuishi, K. et al. (2010). Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. J Exp Med 207, 2187-2194.
[13] Galluzzi, L., Senovilla, L., Zitvogel, L., and Kroemer, G. (2012). The secret ally: immunostimulation by anticancer drugs. Nature reviews. Drug discovery 11, 215-233.

immune effector cells, enhance endogenous antitumor responses and synergize with immunotherapy protocols.14 Thus, the current focus of research in addition to careful mechanistic studies is the characterization of synergies between chemo and anti-angiogenic therapies with vaccination.

1.3 New vaccines for different age groups and specific populations

Vaccination served the needs of a 20th century society that had a life expectancy of about 55-65 years Today, life expectancy is over 80 years in many higher-income countries and there is a shift in the age distribution towards a lower proportion of children and young adults, and a higher proportion of elderly people. This situation raises questions associated with addressing new unmet medical needs and new societal challenges. Vaccination represents a key primary prevention measure not only for paediatric populations, but also for adolescents, adults and the elderly. To enable different age groups to fully benefit from vaccination across different stages of life, a comprehensive R&D agenda must be developed to favour the development of innovative solutions capable of targeting unmet medical needs across all societal segments.

Elderly

The elderly are an important target group for the development of new vaccines. The first specific medical need of this population is that their aging immune system makes them more vulnerable to many infections against which they were previously immune. Susceptibility to infections is more frequent due to the ageing immune system and, in addition, booster vaccinations may be needed. Yet even as they become more vulnerable their waning immune system will require innovative solutions in order to generate a protective or therapeutic response.

A key medical need for the elderly is immunity to antibiotic-resistant bacteria that are acquired during hospitalisation since these types of infections are most frequent in this age group. In the future it is expected that vaccines capable of targeting AMR bacteria such as *Staphylococcus aureus*, *Clostridium difficile*, *Candida spp*., *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae* will be available for use.

Pregnancy

In the past, pregnant women would have had high levels of antibodies since they were often exposed to a variety of pathogens and they transferred protective immunity to their unborn foetuses and then to their newborn babies via trans-placental transfer of antibodies and breast feeding. Today young women are less exposed to infectious agents. Also fewer mothers breast feed and when they do so it is generally for a shorter period. This means that newborns are not protected against a variety of pathogens, including cytomegalovirus, influenza virus, serogroup B streptococcus, hepatitis B virus, meningococcus groups A,B,C,Y and W135 (mainly B and C in Europe), *Bordetella pertussis*, respiratory syncytial virus, rotavirus and tetanus.

Current immunisation schedules usually start at two months of age, and therefore do not induce protective immunity against the majority of these diseases until the fifth month of life, or later. This leaves a period of vulnerability during the first 4-6 months of life that is associated with significant

[14] Hamzah, J., et al. (2008). Vascular normalization in Rgs5-deficient tumours promotes immune destruction. Nature 453, 410-414.

mortality and morbidity. A recent increase in the frequency of pertussis cases and mortality in infants younger than 5 months is an example of this trend.

The success of the vaccination of pregnant women against neonatal tetanus and influenza virus to promote protective immunity in neonates shows that vaccination before birth is safe and very effective in providing newborns and their mothers with protection from these pathogens. These studies show that vaccination can promote the natural immune protection in newborns.

Infants and children

This age group is the only one that at present benefits from a clear vaccination schedule. However newborn children are generally unprotected in the first four to six months of life, the period between the waning of maternal antibodies and the full activation of their own immune systems. Even with the availability of effective vaccines and comprehensive vaccination schedules, issues of awareness and acceptance of key childhood vaccines can lead to sub-optimal uptake and protection. One example of this is the MMR vaccine that is recommended as a two-dose schedule in all EU countries. In Finland where high uptake (>95%) has been achieved since the introduction of MMR in 1982, indigenous MMR disease was eliminated by the mid-1990s [8]. In the UK, with a low vaccine uptake rate of 85%, the number of confirmed measles cases rose from 56 in 1998 to 971 in 2007 [9]. In Romania an outbreak of rubella was reported amongst adolescents in 2011; 98% of those infected had not received MMR vaccination [10]. In the period July 2011 to June 2012, ECDC reported that vaccination status was known for 88% (9 130) of the 10 427 reported measles cases in Europe. Of the cases with known vaccination status, 83% (7 583 cases) were unvaccinated and 12% (1 141) had received one dose of measles vaccine. The proportion of unvaccinated cases was high across all age groups, including those targeted by vaccination programmes [11]. Strong and long-term public health and political commitment is vital for achieving and maintaining high uptake [12] as well as developing strategies to inform parents about the population and individual benefits of vaccination [9].

Vaccines for other groups

In addition to the vaccines required for different age groups, there are a number of other groups with specific needs that should also be addressed:

Travellers: Travellers at all ages should be vaccinated against the diseases that are present in their destination. Increased mobility across borders makes the case for strengthened immunisation policies for individuals travelling not only to avoid contracting diseases widespread in specific geographic locations, but also in order to avoid the phenomenon of disease exporting and importing. The importance of the latter clearly emerged during the recent measles outbreak, where Europe became a net exporter of the disease. Although some vaccines exist for several of these diseases, there is a significant need for effective vaccines against dengue, cholera, ETEC, malaria, shigella, and paratyphoid fever.

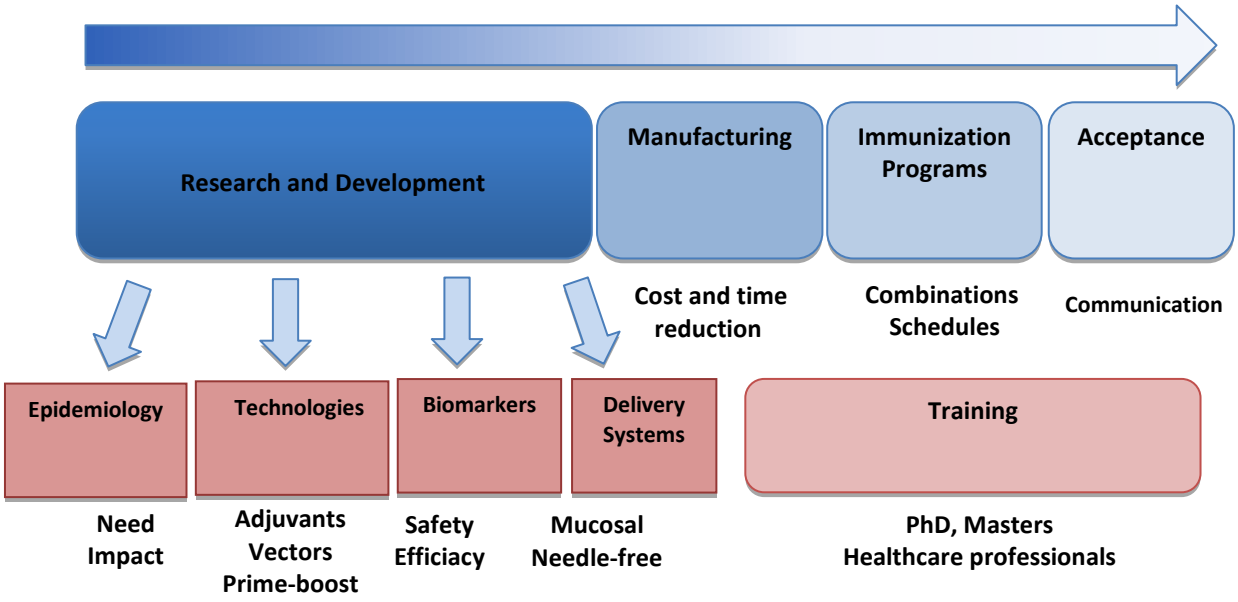
Chronic diseases: People with chronic diseases, such as autoimmune diseases, immunosuppressive disorders and individuals with chronic respiratory or cardiac disease have special vaccination needs specific to their condition.

HIV: Effective vaccines for patients affected by HIV are also needed. Given that live-attenuated vaccines may be not well tolerated and could even be dangerous since these subjects are immune-compromised, inactivated vaccines, possibly with potent adjuvants may be required to elicit protective responses.

2. The Vision

Vaccines Europe has identified some areas, listed below, as most critical for the success of innovative vaccines in the future. We have identified gaps along the entire vaccine innovation chain starting from the prioritisation of vaccine targets through to development, production, delivery, and including the acceptance of the vaccine after it has been licensed and distributed **(Fig.2)**.

Fig.2 Activities required to support vaccine innovation and competitiveness in Europe



2.1 Improved surveillance to define unmet medical needs

Summary

European, national and sub-national epidemiology, burden of disease and vaccine safety data, as well as the percentages of target population vaccinated, should be coordinated at EU level and processes for optimising/harmonising their collection at national level should be put in place. In addition, this data should be stored in a single integrated database to ease access to different relevant stakeholders.

Need for reliable country specific surveillance data on vaccine preventable diseases

In order to define unmet medical needs in a population, valid data on disease frequency and other disease-specific data (such as serotype distribution) are essential. Epidemiologic data should be available for the incidence of the disease in different target populations (frequency measurements), for the disease-type, as well as cost benefit and overall cost of medical care for an individual patient, as well the societal costs involved. These data are the pre-requisite for prioritising new vaccine development. These same data allow for a more targeted 'vaccine product profile' and they allow the future impact of a vaccine to be tracked.

Currently, vaccine manufacturers only have access to published data on unmet medical needs or to summary data from research collaborations. Clearly, there is a need for a stronger public/private partnership for the collection, analysis and distribution of data on unmet medical needs. The development of new vaccines requires not only valid disease specific incidence data, which defines the need and assesses the feasibility of conducting suitably-sized trials with clinical efficacy and clinical safety endpoints, but also detailed microbiologic data, e.g. serotype distribution, genotypes, and even levels of antigen expression that will provide guide choices in vaccine composition. Additionally, it will be useful to have early-detection/diagnostic processes for new micro-organisms, and new types or resistant strains of existing ones. In the absence of accurate and comprehensive data on the medical need vaccine development is less likely to be effectively prioritised and less likely to be developed to respond optimally to the need.

Vision for the future

Ideally, publicly commissioned data would allow each country to develop a 'National Vaccination Plan' to prioritise their specific needs, and perhaps a European-wide plan to prioritise common needs. This would allow objectives to be prioritised enabling the vaccine research, development and manufacturing community to coordinate, align and focus resources to develop new solutions based on the identified needs.

There is a clear need for European, national and sub-national integrated database that gathers epidemiology and burden of disease data, as well as vaccine safety data, and numbers of target population vaccinated. Public health systems in EU Member States continue to provide information of their various vaccination programmes and operation of their surveillance systems, however a union of these efforts among countries would:

1) Allow nationally representative data to be retrieved for all diseases, communicable and non-communicable, reportable and non-reportable (evaluation of burden of diseases; disease background rates for the evaluation of causality of adverse events). Data can be retrieved from both inpatient and outpatient settings; on a population basis, to allow incidences to be estimated for specific populations; in order to provide support for evidence based decision making and rapid and accurate tracking of impact once a vaccine is introduced..

2) An integrated database would allow linkage of disease specific surveillance data with: patient specific data (past and current medical history including vaccination status; current and past use of medical resources); administrative data (cost of care, duration) and public / government databases e.g. for notifiable diseases.

3) Additional goals that may be achieved through an integrated European database are: i) epidemic intelligence and rapid responses to concerns over emerging or re-emerging diseases, and to concern over vaccine safety and efficacy or adverse events; ii) comparison of data between countries in the European Union; iii) and the development of enhanced integrated systems that will improve the health of all EU citizens.

Possible actions

The following steps will help to achieve this vision:

- Assess current European databases/surveillance systems that gather data on infectious and non-infectious disease burden in different populations, including 'at-risk-subjects' like pregnant women, the elderly, infants etc.

- Optimise and align methodologies to detect and diagnose vaccine-preventable diseases.

- Optimise and align methods to detect new and emerging pathogens, as well as define all relevant clinical presentations/diagnoses.

- Develop technologies to ensure secure connections between national laboratory and medical information for appropriate data protection at all levels.

- Improve data sharing across governments and government agencies to guide informed decision-making about the implementation of vaccines.

- Identify important gaps in all of the above and address those that are critical.

Outcomes/deliverables

- Development, through a public-private partnership, of a transparent and comprehensive EU database on unmet medical needs

2.2 Advancing immunisation technologies for development of new preventive and therapeutic vaccines

Summary

Novel immunisation technologies are needed to improve vaccine efficacy and safety. Coordinated exploratory activities involving private and public European sectors aimed at developing novel viral vectors, nucleic acid vaccines and adjuvants are required. The application of these technologies in isolation or in prime-boost regiments may allow the development of preventive vaccines against difficult pathogens and of therapeutic vaccines against cancer, chronic infections and inflammatory disorders.

Need for novel immunisation technologies

Thanks to the revolutionary technologies of the last 20 years existing vaccines have been improved and vaccines that were not previously possible have become possible. For instance, recombinant DNA technology made possible the development and large scale manufacture of the hepatitis B vaccine; the conjugation technology made possible the development of vaccines against *H. influenzae serotype b*, pneumococcus and meningococcus. Novel technologies such as adjuvants, viral vectors and nucleic acid vaccines are promising to continue this revolution in vaccinology.

Adjuvants

Adjuvants are included in vaccine formulations to increase their efficacy. Adjuvants can increase the magnitude and the duration of the immune response induced by vaccination and allow for antigen sparing. In addition, adjuvants can modulate the quality of the adaptive immunity favouring protective cellular and humoral responses such as viral neutralization, bacterial opsonization and killing of infected cells. Finally, adjuvants can increase the breadth of protection of vaccines directed against pathogens such as influenza, that are characterized by antigen variability or that circulate in different strains or clades. In the last decades oil-in-water emulsions and liposome- based adjuvants have been licensed in Europe. In addition, several novel adjuvants targeting other TLRs are in advanced developmental stage either alone or in combination with different classes of adjuvants such as alum, emulsions, saponins and liposomes.

There is an increasing need for novel adjuvants for preventive vaccines targeting infectious diseases for which conventional formulations have failed. New adjuvants are also needed to improve existing vaccines in elderly, infants and chronically infected subjects that mount a suboptimal immune response. In addition, adjuvants could be very useful for the development of effective therapeutic vaccines against chronic infections and cancer.

New adjuvants will be available for use in human vaccines in the future. The availability of these adjuvants in various combinations will greatly help to rationally design vaccine formulations with distinct properties resulting in increased vaccine efficacy.

Viral vectors

Attenuated or non-pathogenic virus can be genetically manipulating to express an exogenous antigen and generate strong antigen specific humoral and cellular responses including T cell killer cells that are very difficult to induce by subunit vaccines even in the presence of strong adjuvants. One example of attenuated strains of virus are the modified *Vaccinia* Ankara (MVA) evaluated in both non-human primates and humans as vector vaccines for HIV, malaria, influenza, TB and other infectious diseases. Other poxviruses tested as vector vaccines include fowlpox and canarypox. Replication-incompetent

recombinant adenoviral vectors (rAd) have been successfully tested in many human clinical trials, particularly for HIV and cancer. Pre-existing immunity, in particular neutralising antibodies, may be present in subject who receive the viral vectors, limiting the efficacy of these vaccines. New vectors based on viruses that do not infect humans are required for preventive and therapeutic vaccines.

Nucleic acid-based vaccines

DNA based vaccines are composed of plasmid DNA containing an antigen gene sequence. A significant amount of experimental work has been performed in the last two decades to apply DNA vaccination to many disease targets with both prophylactic and therapeutic approaches. Similarly to viral vector vaccines the antigen expressed through DNA injection is synthesised within host cells facilitating correct folding of conformational neutralizing epitopes and MHC class I antigen presentation, allowing generation of CTL responses. An additional advantage of DNA vaccines compared to viral vectors is that there is not preexisting vector immunity. Clinical studies have demonstrated that DNA vaccination is safe and able to stimulate an immune response, however immunogenicity is usually lower than expected based on the results of animal studies. More exploratory work needs to be performed to improve the immunogenicity of DNA vaccines. In addition to DNA, several studies have demonstrated the potential to use RNA for vaccination either as mRNA or as a replicon able to self- amplification after cellular internalization. However RNA immunization has never been tested in human yet.

Prime-boost strategies

Heterologous prime-boost regimens mainly use a viral vector or a DNA vaccine at priming followed by a boost with a protein based vaccine, although other options have also been used. This immunization schedule results in the induction of a strong cellular immune response, with generation of both CD4+ and CD8+ antigen-specific T cells, associated with a higher and more specific antibody response against the vaccine target compared to homologous immunization. More experimental work is needed to define the optimal prime-boost strategy for preventive and therapeutic vaccines.

Possible actions

- Continue to better understand the host immune system in health, disease and throughout life and translate this understanding into better vaccine design, development and delivery.
- Continue to better understand pathogens interaction with the human body and translate this into better vaccine design, development and delivery.
- Better understanding of the immunological mechanism of action of adjuvants, viral vectors and nucleic acid vaccines
- Improve coordination between public and private sectors on discovery of new adjuvants, viral vectors and nucleic acid vaccines.
- Implement a more rational coordinated approach to compare and combine different immunisation technologies

Outcomes/deliverables

- Better antigen design and delivery
- Novel adjuvants and adjuvant/delivery systems combinations

- More efficient vectors without pre-existing immunity
- Novel nucleic acid vaccines with improved immunogenicity
- Prime boost strategies targeted to the disease

2.3 Approaches to early clinical and non-clinical prediction of vaccine efficacy and safety

Summary

Vaccine development time is often very long and requires very expensive efficacy trials. Novel biomarkers able to predict vaccine efficacy and safety in early clinical trials are required to shorten the vaccine development cycle. A better understanding of the immunological mechanism of vaccination will enable the discovery of disease correlates of protection and the identification novel biomarkers that can predict vaccine safety and efficacy.

Assessment of efficacy and safety

A major problem in vaccine development is the lack of biomarkers to predict vaccine efficacy and safety, which limits our ability to screen the best candidate vaccines in early clinical trials. Another major problem, for many diseases targeted by vaccines, is the lack of a clear immunological correlates of protection. As a consequence of these limitations the final answers on the safety and efficacy of experimental vaccines are generally obtained only very late in development, through very large phase III efficacy trials. The ability to screen multiple candidate vaccines in early clinical trials using adequate biomarkers for safety and efficacy would considerably reduce the time required for vaccine development and the associated costs.

It is important to understand the immune response in order to design innovative vaccines that are safe and efficacious. A better understanding of the immune response to natural infections and vaccination could help to identify immunological correlates of protection.

New large-scale whole human genome sequencing programmes now allow the identification of genetic variations that could influence the response to vaccination. The identification of these gene targets could help developing novel tools to increase vaccine efficacy in non-responders.

Vision: approaches to efficacy and safety assessment

New technologies in human immunology allow a more detailed analysis of the immune response to vaccination in different age groups. These technologies are often the result of advancements in the field of genomics; they can generate complex data sets that need to be analysed with adequate bioinformatics tools. The use of systems biology approaches could help identify novel biomarkers for vaccine efficacy and safety. The same technologies can be applied to improve our understanding of the immune response to infection and to identify novel immunological correlates of protection. Moreover, new human genome programs should help understand the influence of human genetic variations on vaccine response and non-response. Some examples of novel technologies that could be used to study human immunology to improve early efficacy and safety assessment of vaccines are:

Quantitative gene expression platforms (DNA microarray, Nanostring and RNA sequencing); Multi-parameter analyses of blood cell subsets (single cell RT-PCR, CyTOF); Deep sequencing of human genome/ genome wide association scans; Antibody binding/neutralization assays; High throughput B cell repertoire analysis; High throughput HLA & TCR sequencing.

Possible actions

- Analysis of the immune response to vaccination in different age groups (infants, adolescents, adults and elderly)

- Analysis of the immune response to vaccination in pregnant women and immuno-compromised subjects.
- Analysis of the immune response to infection and identification of novel correlates of protection
- Impact of adjuvants or vaccine vectors on the immune response to vaccination
- Genome-wide association scans of response to vaccination

Outcomes/deliverables

- Better understanding of the immunological mechanisms of vaccination;
- Novel biomarkers to predict vaccine efficacy and duration of protective responses;
- Novel biomarkers to predict vaccine safety;
- Identification of novel targets to overcome immune-senescence;
- Identification of novel human sequence variants that contribute to the response to vaccination

2.4 Novel technologies in vaccine administration

Summary

Most of licensed vaccines are administered by injection. Innovative research to develop improved means for the safe and efficient administration of vaccines could help to improve uptake, delivery, and the perception of vaccines and the vaccination process

New delivery systems

Current vaccines are generally injected by subcutaneous or intramuscular routes. This mode of administration of vaccines can induce pain and local reactions that contribute to the poor perception of vaccines, at least in some populations. There is a need for new delivery systems that allow for more 'natural' vaccine administration that minimises discomfort. Some of the approaches that have been tested include:

- Soft contact of the vaccines with the skin (e.g. patch, cream, powders) with immunity induced via the skin immune system
- Ingestion of the vaccine orally as a pill, as for drugs (this will required a better understanding of the mucosal immunity)
- Any other device that will enable self-vaccination the under safe conditions (e.g. inhalator).

Mucosal vaccines

Mucosal vaccination is a needle- and medical-waste-free vaccine strategy that provides protective immunity against pathogenic bacteria and viruses in both the mucosal and systemic compartments. However, mucosal vaccines must overcome two major hurdles, i.e. effectiveness and safety, which are both relatively difficult tasks compared with systemic vaccine development because of the uniqueness of the mucosal environment. Mucosal delivery, particularly through oral, intranasal and pulmonary routes, aim to improve both vaccination convenience and immune response compared with injection routes. Several oral vaccines to prevent rotavirus, polio, cholera and one intranasal vaccine against seasonal flu are already marketed; these vaccines are made of live-attenuated pathogens. Oral administration represents the most convenient route, however, the antigen stability necessary to avoid degradation in the stomach and intestine is a major challenge, particularly for development of mucosal subunit vaccines. Intranasal delivery is associated with high immunogenicity, but there are concerns about dose reproducibility and safety. More work is needed to develop new generation mucosal vaccines based on purified or recombinant antigens formulated with appropriate adjuvants.

Needle free delivery into the skin

Needle-free vaccine delivery into and through the skin is another important focus of vaccine research, with key technologies including intradermal patches, micro-needles and needle-free liquid, solid and powder injectors. Since the skin is recognised as an important immunologic organ, it is thought that an improved immune response could be obtained using this route. Both transdermal patch and micro-needle technologies, targeting the epidermal layer of the skin, have shown promising profiles. Challenges for the various approaches include the delivery of high doses and large molecules, as well as the need to reformulate existing vaccines. New generation needle-free injection devices allow the delivery of vaccines quickly, without the risk of needle-stick injuries. However, some technologies in this field are still associated with injection site pain, or require external power sources, making them unsuitable for widespread use.

Micro-needles have been used to deliver a broad range of different low molecular weight drugs, bio-therapeutics and vaccines in more than 350 published studies, including a number of studies with small-molecule, protein drugs and vaccines in humans. Influenza vaccination using a hollow micro-needle is in widespread clinical use. The successful application of micro-needles depends on a device that facilitates micro-needle insertion and possible infusion into skin, skin recovery after micro-needle removal, and drug stability during manufacturing, storage and delivery, and on patient outcomes, including lack of pain, skin irritation and skin infection, in addition to drug efficacy and safety.

Possible actions

- Coordinated research on mucosal and skin immune systems
- Development of delivery systems based on the characteristics of the mucosal and skin immune systems
- Clinical trials to demonstrate the efficacy of the novel delivery systems
- Development of easy-to use, zero-error and safe delivery system
- Evaluation of the acceptability (population perception, legal and regulatory hurdles, safety and impact on coverage and costs) of vaccine delivery outside of the HCPs and of self-delivery

Outcomes/deliverables

- Better understanding of the skin immune system
- Better understanding of the mucosal immune system
- More favourable perception of vaccines and the vaccination process
- Improved vaccine uptake and lower vaccination costs

2.5 Research and innovation in vaccine production processes

Summary

Exciting technical developments, particularly from the biotechnology field, in areas such as microbiology, immunology, protein chemistry and many other disciplines that make up the multidisciplinary science of vaccinology will improve research and innovation in vaccine production processes

Vaccine manufacturing issues

The scalable production of vaccines relies on manufacturing methods that have been proven to be effective and consistent over time or through rigorous and extensive development and validation. These methods are approved by the regulatory authorities and must meet specific standards directed both at product safety and efficacy and at assuring product quality through every step of the manufacturing process. The vaccine itself, as released, must meet standards for identity, purity, potency, safety, efficacy, stability, and consistency.

There are many issues related to existing production facilities that may be improved by innovation. The first is cost; it may cost almost €400 million for the production of a single vaccine product. The second is facility design; most facilities are unable to produce multiple vaccines or change rapidly for the production of another vaccine, due to the plant design. A third is capacity; most vaccine plants are usually already at or near full-capacity and are unable to increase production during periods of vaccine shortage. A fourth is that there is a significant concern with the potential cross-contamination of a product when multiple agents are used in a facility. The remaining difficulty is how the vaccine manufacturing industry can rapidly and effectively respond to a public health requirement for protection against a biological threat, starting from the identification of the index case to the release of a safe and effective vaccine product in the face of an emerging pandemic.

Vision for research and innovation in vaccine production processes

Scientific innovation can improve all steps of vaccine manufacturing from the very first step of production to vaccine release. Novel technologies in the manufacturing process can enhance flexibility, increase yields, reduce cost, increase stability and reduce production time. For example, improvements in bioreactor technologies, including more rapid culture expansion methods that provide consistent growth environments, may lead to improved yields and reduced cost. Use of synthetic seeds in vaccines such as influenza can speed up the production by bypassing the requirements for a natural seed. This would be particularly important for the rapid response to pandemic influenza outbreak. Innovation in research could also help to develop new in vitro vaccine release assays that do not require animal testing. New technologies in formulation platforms could improve the stability of the vaccines and may reduce the requirement for cold chain. .

Possible actions

- Miniaturisation, automation, and process integration
- Implementation of new culture media, free of human- or animal-derived components
- Utilisation of new permissive cell lines
- Implementation of more rapid culture expansion methods
- Development of synthetic seeds

- Development of novel formulation

Outcomes/deliverables

- Improvements in product packaging and shipping
- Manufacturing cost reduction
- Batch to batch reproducibility
- Reduce manufacturing time to allow rapid response to pathogens

2.6 Innovation in operational research

Summary

As EU Member State face increasing healthcare services budgetary restraints, novel approaches to vaccination and to the implementation of immunisation programmes should be devised. This would allow maximising efficiencies and reduce the burden of disease across populations.

Beyond the discovery of new vaccines to fight new diseases and the better understanding of pathogens and immunology to develop improved vaccines, the implementation of vaccination policies faces programmatic and operational challenges. Specific questions have to be addressed to enable the EU to continue to play a prominent role in global health and to contribute to enhance the health of EU citizens.

The future of vaccine programmes

Depending on the vaccine and age-range, vaccine coverage has either reached a plateau or remains low in the EU. Multiple inter linked factors such as policies, funding, convenience, education, communication, perception, etc. have a role in this.

The financial sustainability of European health systems is being challenged by both the severely restricted public health budgets at a time of economic crisis and the ageing population, leading to new medical needs. One way to address these needs is to invest in cost effective preventive measures.

Several actions aimed at improving vaccine impact and coverage are possible, including the simplification of vaccination schedules through novel combinations and co-administrations; and innovative ways to reach the vaccine target populations.

Possible actions

- Combination of vaccination with other prevention measures (horizontal integration):
- vaccine co-administration and combinations
- improving access to the healthcare professionals and to vaccination
- incentivise uptake and use of e-prescription
- over-the-counter vaccines
- home-delivery of vaccines
- temperature-stable vaccines
- auto-injection with convenient and safe devices

2.7 Develop training programmes in vaccinology and on the benefits of vaccination

Summary

Education and training in vaccinology, which is a multidisciplinary topic, needs to be developed for the many actors (healthcare professionals, public health officers and decision-makers, research scientists and the general public) involved in vaccines research, development, production and delivery.

Need for more training dedicated to vaccinology

Vaccinology covers a wide range of disciplines including immunology, microbiology, epidemiology, infectious diseases, paediatrics, clinical development, biotechnology, production processes, quality control, quality assurance, preservation, shipping, cold chain/supply chain management, public health, health economics, sociology, ethics, communication, to mention a few. Despite an increase in the number of vaccinology courses and training modules availability in the EU (primarily at undergraduate level), there are still major gaps in knowledge and competences for healthcare professionals administering the vaccines and advising members of the public on vaccination.

The VACSATC (Vaccine Safety-Attitudes, Training and Communication) [16] study showed that among medical students less than 60% reported to have received training in safety issues and vaccination controversies; Only 44% received training on how to communicate with patients and parents about vaccination; and only 50% stated to have received practical training on how to administer vaccines. Further gaps were identified in postgraduate education and the introduction of PhDs and Masters combining a broad base in vaccinology with various combinations of specialised modules, including modules of applied vaccinology.

Needs are also envisaged at the level of trainers (for example school teachers in health education) and top scientists operating in the public domain as well as science journalists and media to favour understanding of the complexities around vaccinology and vaccination.

Possible actions

- Identify in cooperation with public and private stakeholders areas of intervention where strengthening skills in vaccinology is necessary

- Implement healthcare professionals-targeted training courses on the benefits of vaccination and vaccination needs at different stages of life, including use of e-learning tools

2.8 Improving awareness and acceptance of vaccines

Summary

Improved understanding of how to effectively communicate on vaccines and vaccinology (including the identification of the most effective engagement strategies for different target groups) will improve awareness and acceptance of the importance of vaccines

Issues around perception of vaccines/vaccination

Vaccine research and development and vaccination programmes have directly supported the elimination or even eradication of some infectious diseases, however vaccination coverage both in the European Union and globally is not yet at 100%. For some adult vaccines, such as pertussis and influenza, it is far lower than this and far below the level acceptable for infant and childhood vaccination. We need to improve our understanding of the issues that drive these decisions both from the perspective of the patients as well as that of those that recommend and administer the vaccines. The phenomenon of 'vaccine hesitancy' is recognised as a result of a complex interplay of socio-cognitive factors as well as awareness and education [17].

This need to be better researched and understood in order to develop better adapted approaches to improving vaccination coverage and therefore the public health benefit of vaccines. The limited research that has been done to look at the reasons for vaccine hesitancy has been mostly focused on parents, particularly mothers. Given the number of vaccines for other target populations, such as adolescents, adults and the elderly, research on vaccine hesitancy will also need to cover these groups as well as healthcare professionals, in terms of their personal vaccination records and the recommendations they make to their patients. Most results show that the majority of the general public perceive vaccination as important and necessary; generally in most surveys about 15% feel that vaccination is not necessary or unsafe [18-22]. One study by ASTHO (Association of State and Territorial Health Officials) found that parents who refused to vaccinate their children with some vaccines felt that diseases such as flu and chickenpox 'are not that serious' [23]. Some believe that vaccines do not work or that they cause the disease they are intended to prevent. Even some of those with a positive perception of vaccination have concerns about safety of the vaccines or 'over-loading' the immune system with too many antigens.

The increasing role played by social media in access to information should also be taken into account

Most studies report that paediatricians are the most influential source of information for parents; public health authorities are generally ranked lower [18,19,21,23]. However, vaccination coverage is too low in healthcare professionals, who are supposed to know about diseases and the benefits of vaccination, and they are an important source of information and advice for their patients.

Vision: communication on vaccines and vaccinology

True understanding of the drivers for and barriers to acceptance of immunisation will require in-depth studies. In a recent report published by Save the Children (Reference: Finding the Final Fifth – Inequalities in immunisations 2012), the factors that hinder immunisation rates in lower income countries are: 1) supply of, and access to quality services, 2) parental attitudes and knowledge, 3) household characteristics (rural vs. urban, and 4) communication and information. This proves that there is a need for culturally sensitive communication that targets the public's fears and their questions about vaccines.

The outputs of these attitudinal studies will allow the construction of vaccination acceptance tracking tools. These tools will in turn need to be validated and shared widely and then used on an on-going

basis to enable longitudinal tracking or perception and the impact of engagement strategies. All of the above will require the input of broad range of social scientists who will in turn gain and experience and expertise that they will be able to apply to a broad range of healthcare and lifestyle issues therefore providing broad benefit for healthcare and healthcare costs.

Possible actions

- Create broad interdisciplinary networks of anthropologists, psychologist, key-opinion leaders, and communication and engagement scientists to design and implement a needed innovative approach in understanding the reasons for vaccination hesitancy
- Use this understanding to design more effective and measurable engagement strategies to address the identified barriers and support the identified drivers of vaccination acceptance
- Implement this knowledge to broader areas of social marketing and public health promotion.

Outcomes/deliverables

- Move away from the empty vessel model of vaccine acceptance to a more sophisticated socio-cognitive model of vaccine acceptance
- Better tools for measuring and tracking vaccination acceptance
- Improved vaccination coverage for all target populations

References

1. Alexander P. (2006) Creating a technology road map. http://www.entrepreneur.com/article/83000 Accessed on: 26 August 2012.

2. UNICEF/WHO. (2012) Expanding immunization coverage. http://www.unicef.org/immunization/index_coverage.html Accessed on: 26 August 2012.

3. CDC. (2011) Global vaccines and immunization. http://www.cdc.gov/vaccines/programs/global/default.htm Accessed on: 26 August 2012.

4. Vaccines Europe (2012) Vaccines' contribution to Europe's economy, global health and European innovation - 2010 data. http://www.vaccineseurope.eu/about-vaccines-europe/vaccines-europe-in-figures/ Accessed on: 27 March 2013.

5. European Commission. (2012) Research & Innovation - Horizon 2020. http://ec.europa.eu/research/horizon2020/index_en.cfm Accessed on: 26 August 2012.

6. European Commission. (2011) Commission staff working paper - Impact assessment. http://www.eurosfaire.prd.fr/7pc/doc/1323446223_horizon_2020_impact_assessment_report.pdf Accessed on: 27 August 2012.

7. European Commission. (2012) Frequently asked questions on the European Research Area. http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/12/564& Accessed on: 27 August 2012.

8. Davidkin I, Kontio M, Paunio M, Peltola H (2010) MMR vaccination and disease elimination: the Finnish experience. Expert Rev Vaccines 9: 1045-1053.

9. McIntyre P, Leask J (2008) Improving uptake of MMR vaccine. BMJ 336: 729-730.

10. Janta D, Stanescu A, Lupulescu E, Molnar G, Pistol A (2012) Ongoing rubella outbreak among adolescents in Salaj, Romania, September 2011-January 2012. Euro Surveill 17.

11. ECDC (2012) Surveillance Report - Measles and Rubella Monitoring - August 2012. http://www.ecdc.europa.eu/en/publications/Publications/SUR-Monthly-measles-and-rubella-Aug-2012.pdf Accessed on: 27 March 2013

12. Derrough T, Bacci S, Lopalco PL (2012) Letter to the editor: commitment needed for the prevention of congenital rubella syndrome in Europe. Euro Surveill 17.

13. WHO. (2011) Global alert and reponse: measles outbreaks in Europe. http://www.who.int/csr/don/2011_04_21/en/index.html# Accessed on: 5 November 2012.

14. MedTrack. (2011) http://oneview.medtrack.com/UI/Shared/Admin/Login.aspx Accessed on: 15 September 2012.

15. TRANSVAC. (2011) EU Project: TRANSVAC. 'http://www.transvac.org/ Accessed on: 26 August 2012.

16. TRANSVAC. (2011) Networking: European vaccine stakeholder working groups. http://www.transvac.org/Stakeholder%20Working%20Groups Accessed on: 26 August 2012.

17. VACSATC. (2010) EU project: Vaccine Safety-Attitudes, Training and Communication. http://www.vacsatc.eu Accessed on: 26 August 2012.

18. Thomson A, Watson M (2012) Listen, understand, engage. Sci Transl Med 4: 138ed136.

19. Freed GL, Clark SJ, Butchart AT, Singer DC, Davis MM (2010) Parental vaccine safety concerns in 2009. Pediatrics 125: 654-659.

20. Kennedy A, Basket M, Sheedy K (2011) Vaccine attitudes, concerns, and information sources reported by parents of young children: results from the 2009 HealthStyles survey. Pediatrics 127 Suppl 1: S92-99.

21. Jenkins-Smith H, Silva CL, Song G (2010) Health policy survey 2010: a national survey on public perceptions of vaccination risks and policy preferences. Norman, Oklahoma, USA: University of Oklahoma. 8 p.

22. EVM (2004) Better health through vaccination: European perspectives (unpublished).

23. Yarwood Y. (2010) Public perception of the benefits of vaccines - MMR in the UK. https://docs.google.com/viewer?a=v&q=cache:bLAM66TIg1wJ:ec.europa.eu/eahc/documents/news/technical_meetings/Public_Perception_of_vaccines_UK.pdf+&hl=fr&gl=fr&pid=bl&srcid=ADGEESjp_g1zyB1jXngDeLQydeCmq1LEGAVSZeY8ZMERu8TXEznW-5BimKHSyK6ZkQHBdZD3Qf4IQgXEh0SFDvVxSkOzJumrLFfNdDaLQtNXwhtemZILIf4Hcf6hm_F73v5e3OOjkhoY&sig=AHIEtbTgq1FkG5tIf7fQGEhW25USYbFacQ Accessed on: 26 August 2012.

24. ASTHO. (2009) ASTHO: Communicating effectively about vaccines. http://www.vdh.state.va.us/VDHMaster/MasterApp/SearchResults.aspx?cx=010288947432536274840%3Aebew06qv2hy&cof=FORID%3A11&sa=Search&q=astho%20vaccines; Accessed on: 26 August 2012.