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Vaccines: innovation and human health

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Foreword

The introduction of vaccines to prevent many infectious diseases has contributed to major advances in public health in both industrialised and developing countries. But there are still unmet public health needs, and there is also the prospect of newly-emerging infections that warrant renewed effort to support vaccine innovation in the European Union.

This report is the second in a series published by EASAC (the European Academies Science Advisory Council) on strategic issues in combating infectious disease. Our first report, *Infectious diseases - importance of co-ordinated activity in Europe* (May 2005), outlined some of the general priorities for Europe-wide action with regard to disease surveillance and control, public health infrastructure, public sector research, the provision of skilled scientists and the development of novel products. This, second, report focuses on the innovation and public health policy issues surrounding established vaccine use and new vaccine research and development.

At the present time, there is continuing concern about the potential for a new influenza pandemic – and a recurrence on the scale of 1918 is not impossible. In addition to the very considerable public health impact, such a pandemic would have great economic impact (the World Bank has estimated $800 billion in global losses). The acute demands involved in preparing for, and responding to, pandemic influenza illustrate some of the critical issues for vaccine innovation. In addition, many other infectious diseases pose a major threat in the EU, and globally.

We present here an analysis of the current position with respect to societal needs, scientific opportunity and the impediments to innovation as the basis for identifying what now can be achieved by both the public and private sectors and what is needed by way of support from policy-makers. Our recommendations range from increasing collaboration and coherence at the European level to supporting industrial innovation and competitiveness, promoting university research capability, and encouraging vaccine uptake. There is an overwhelming case for major investment in vaccine research, clinical development and strategies to promote vaccine acceptance. Some of our recommendations may seem controversial but it is imperative to capitalise on the historical success of vaccine research, development and production in Europe by renewing commitment to building public-private partnerships, by supporting company investment, by clarifying and sharing risk and by streamlining science-based regulation.

The report is addressed to policy-makers in the EU Institutions and at Member State level, to research funders, professional and regulatory bodies, and to all other interested parties. Our objective is to provide the scientific evidence to inform and stimulate further debate on the challenges and to indicate some specific options for change while recognising, of course, that much is already being achieved in Europe. I believe that this report provides further testimony to the growing experience and capability of EASAC to serve as a means for the science Academies of the EU to work together to provide expert, independent advice at the European level about the scientific aspects of public policy issues.

This report, undertaken at EASAC's own initiative and expense, was prepared by a Working Group chaired by Professor Volker ter Meulen and was reviewed following procedures established by the Council of EASAC and approved for publication by the Council of EASAC. On behalf of EASAC, I should like again to express my thanks to Professor ter Meulen and his colleagues for giving their time so generously – it is their expertise that has created a comprehensive and compelling report.

EASAC will continue to build the links necessary to take forward the present recommendations as well as continue to follow up other issues within the broad domain of infectious diseases policy outlined in the first report. I should greatly welcome feedback on any of the points raised.

Professor David Spearman
Chairman, EASAC

Summary

Infectious diseases pose a major threat in the European Union and globally. The threat comes from existing and re-emerging infections as well as from new microbes. The use of vaccines has had, and will continue to have, very considerable impact on public health. It is therefore of the greatest importance to maintain a co-ordinated strategy for surveillance and preparedness in infectious disease. This necessitates both increasing funding and reducing impediments to vaccine R&D, and improving vaccine uptake.

In a previous report, EASAC stressed the importance of a co-ordinated, EU-wide response to the threat of infectious disease. That report highlighted in particular the need for action on: surveillance and control systems; public health infrastructure; the development of vaccines, diagnostics and therapeutics; and training greater numbers of skilled basic and clinical scientists. In this report we take up one of these issues – the role of vaccines. We identify a series of matters that have to be tackled at European level to exploit the potential of vaccines in the fight against infectious disease, reviewing the latest scientific developments and their implications for public health strategies.

Our major policy recommendations arising from this analysis are in the following areas:

- Increasing the role and responsibility of the European Commission in public health
- Equipping the European Centre for Disease Control
- Incentives to manufacture vaccines
- Improving the research capacity of regulatory authorities
- Strengthening public sector support for vaccine R&D with particular regard to (i) Framework Programme 7 priorities; (ii) Collaboration with developing countries; (iii) Research infrastructure; (iv) Clinical research capacity; (v) Training and skills
- Promoting vaccine uptake

Our overriding messages are that vaccines are a crucial part of the armoury for dealing with infectious diseases; that the European Commission, European Parliament and European Centre for Disease Control need to give more coherent and co-ordinated leadership in developing and implementing strategies for deploying vaccines; and that the Commission should find ways of reducing obstacles to the commercial manufacture of vaccines. As the threat of infectious disease grows, these matters become more and more urgent.

1 Introduction

1.1 An era of increasing concern

Infectious diseases are of global concern and represent a major health problem in both industrialized and developing countries. It has been estimated (Heymann, 2005) that infectious diseases caused one quarter of total deaths in 2003.

Fifty years ago, the prevalence of infectious diseases in Europe was in decline, in response to improved public health, improved surveillance, and the introduction of antibiotics, vaccines and insecticides. These successes in the prevention and treatment of infection encouraged the assumption that the major problems had been solved.

This confidence was premature. By the end of the last century, infectious diseases were presenting significantly greater societal challenge (Morens et al., 2004), partly as a result of changing ecology and the increasing risk factors associated with urbanization and mobility, social disruption, misuse of medical technology and environmental change (Weiss and McMichael, 2004).

At the same time, there has been increasing momentum for development of international health regulation to address the problems of infectious disease at a global level[1]. In some respects the EU is particularly vulnerable to infectious disease (Nicoll et al., 2005): its legislative base for public health (Article 152 of the Consolidated Treaty) is weak, judged considerably weaker than the legal basis for the protection of animal health, and the increasing free internal movement of goods and people encourages the spread of infection.

1.2 EASAC priorities

In a previous report (EASAC, 2005) we argued that a co-ordinated Europe-wide programme of research, training and preparation was needed to track and counter biological threats, not only to humans but also to animals. In that report, we highlighted the priorities for EU action in terms of: (i) disease surveillance and control systems; (ii) public health infrastructure; (iii) development of applications (therapeutics, diagnostics, vaccines); and (iv) research and training.

Innovation requires a large investment in basic microbiology, immunology and molecular biology to understand pathogens and their host interaction, and to develop improved antimicrobial drugs, diagnostics and vaccines. Key R&D opportunities and challenges have been summarised in the EASAC report and in a recent report by the European Science Foundation (ESF, 2005).

Policy-makers in the EU and at Member State level have to pay considerable attention to vaccine innovation if they are to build better strategic capacity to face infectious diseases – particularly with regard to supporting a world-class industry sector and making the most of the R&D opportunities for collaboration between industry and academia. In this report, we provide further detail on some of the vaccine issues that face EU policy-makers.

1.3 The societal value of vaccines

The outcome of immunization can be viewed as the greatest medical achievement of the twentieth century. Notwithstanding the rise of new problems and new pathogens, vaccines have provided a means to prevent many infectious diseases that had been principal causes of mortality and morbidity, and their use has had a major impact on public health. Smallpox has been eradicated and diphtheria has been controlled where the vaccine has been used. Vaccination programmes in children have had a dramatic effect on other previously common diseases – the number of US cases of pertussis has been reduced by 98.4% from the peak incidence, measles by 99.9%, mumps by 99.4%, congenital rubella syndrome by 99.9%, polio by 99.9% (CDC data, 1992). There have been similar trends in Europe – equivalent detailed data are not yet available but their collection for the EU as a whole is seen as an important priority for the European Centre for Disease Control (ECDC).

The societal impact can be measured not just in terms of improved public (and individual) health but also in economic terms – for example with regard to reducing the cost of health care and decreasing lost labour force productivity. The pneumococcus conjugate vaccine provides a good example of impact. It is less used in Europe, but in the USA vaccine use has resulted not only in markedly reducing the incidence of disease in children but also has had major impact on adult disease, with significant economic impact. The use of cost-effectiveness studies to demonstrate that vaccination campaigns lead to substantial savings in medical costs was reviewed recently by Bloom and co-workers (2005) who noted, however, that such studies do not take full account of the broader economic impacts of immunization.

There is significant further opportunity to use economic evaluation studies to help substantiate the public health goals. Globally in 2002, 1.4 million children under five years old died of diseases for which vaccines are already widely available[2] – and action to address the global

1 WHO World Health Assembly adopted revised International Health Regulations in May 2005 for control of transboundary infectious disease (www.who.int/gb/ebwha/pdf_files/WHA58_3-en.pdf), reviewed recently by Merianos and Peiris (2005).

2 For instance, measles, neonatal tetanus, Hepatitis B, Hib, Pneumococcus, Meningococcus vaccines. The extent to which vaccines can prevent mortality is the extent to which they reach the vulnerable children; a strategy for delivery to all children must be implemented together with other improvements in public health infrastructure (for example, clean water).

challenges is now being undertaken by the Global Alliance for Vaccines and Immunization (GAVI). GAVI is an alliance between the private and public sector – UNICEF, WHO, World Bank, NGOs, industrialized and developing country Governments and vaccine industry, Research and Public Health Institutes and The Bill and Melinda Gates Foundation[3]. Using the broader approach to assess the impact of vaccination (Bloom et al., 2005; covering effects on cognitive development, educational attainment, labour productivity, income, savings, investment, and fertility) the immediate rate of return to the GAVI programme has been conservatively estimated at 12% in 2005, rising to 18% by 2020.

1.4 How vaccines work

The first vaccines were living micro-organisms that had been naturally or artificially attenuated so as to render them less virulent but still capable of inducing immunity. These attenuated organisms recruit both major components of the immune response, humoral (antibodies) and cellular (T cells) and work, like natural immunity, by promoting recovery and preventing re-infection. More recently, vaccines have been devised that protect the host from initial infection with a micro-organism. These vaccines produce 'sterilising immunity' and, in the case of viruses, this depends entirely on the formation of antibodies, since T cells can recognise viruses only when they are seen in the context of a cell's histocompatibility antigens. Similarly, immunity from disease caused by exotoxins (for example, diphtheria and tetanus) also depends entirely on antibodies. However, there are many pathogenic organisms (TB and HIV are examples) for which it has not proved possible to obtain sterilising immunity and in these cases vaccination still aims at promoting recovery and preventing re-infection. For promoting recovery, T cells are essential and much effort in vaccinology has been devoted to stimulating powerful and appropriate T cell responses.

Successful vaccines are highly effective, protecting from disease for lengthy periods. To be successful, a vaccine must find widespread use. Public-private partnerships can often be the best route to funding and delivering a reliable global supply of vaccine.

Successful vaccines were developed mainly for those diseases where natural infection leads to (life long) persistence of immunity. The major challenge now is to develop vaccines for those 'difficult' diseases where this is not the case, such as HIV, malaria and TB. Furthermore, it can be anticipated that some (re-)emerging and zoonotic infections will also have a tendency to be 'difficult' by virtue of the fact that they have a tendency to mutate and, thereby, newly emerge or develop trans-species migratory capacity. This is a major reason for the need for further investment in understanding the mechanisms of protective immunity and the ways that micro-organisms evade or subvert them.

European vaccine research is strong in many areas but there are impediments to its successful translation into the health services. Concerns have been expressed in Europe and elsewhere about inadequate development capacity, fear of litigation as a disincentive to R&D, regulatory requirements that cannot be justified by risk-benefit analysis, weak health system infrastructure, inadequate funding and lack of commitment by governments to vaccine research and manufacture. These concerns – and the implications for policy-makers – are discussed in further detail in the following chapters.

3 New funding for GAVI has been provided by the launch (in September 2005) of the International Finance Facility for Immunization by several Member States.

2 Defining the global challenges for infectious disease and vaccine development

The spectrum of current infectious disease problems and threats has been extensively reviewed by the Institute of Medicine (Stratton et al., 2000), WHO (2004) and the American Academy for Microbiology (2005). The AAM defined 'problems' in terms of diseases that have relatively high incidence, high morbidity or mortality or high economic impact, and 'threats' to include those diseases that are currently comparatively rare but have the potential to escalate (Box 1). Highly effective vaccines are not yet available to combat the greatest problems such as HIV and malaria, or many of the other pathogens listed.

Box 1 Principal infectious disease problems and threats

Problems
- Sexually-transmitted agents, eg Human immunodeficiency virus (HIV), Human papilloma virus (HPV), Chlamydia, Herpes simplex virus Type 2
- Respiratory agents, eg Influenza virus, Respiratory syncytial virus, Streptococcus pneumoniae
- Enteric agents, eg Salmonella species, Rotavirus, Shigella species
- Nosocomial agents, eg Staphylococcus aureus, Pseudomonas species, E.coli
- Vector-borne agents, eg Plasmodium falciparum, Dengue fever virus, Tick borne encephalitis virus, Japanese encephalitis virus
- Others, eg Group A and B Streptococcus, Hepatitis C virus

Threats
- Zoonotic agents, eg Influenza virus H5N1
- Emerging agents, eg Multi-antibiotic resistant pathogens, West Nile virus
- Agents susceptible to accidental release, eg SARS, Influenza virus H2N2
- New enteroviruses and retroviruses
- Intentional release and bioterrorism, eg Variola virus, Bacillus anthracis

Adapted from American Academy for Microbiology (2005), to cover diseases of most relevance to European public health and European research efforts

The American Academy for Microbiology also reviewed the barriers to developing and using vaccines. Some of these will be considered further below in the context of EU action. Among the main obstacles identified are:

- *Technical* – issues for Good Manufacturing Practice (such as those relating to product contamination or compliance difficulties), issues of antigen incompatibility in combination products, narrow range of adjuvants and challenges to replace excipients banned in some countries (such as Thimersal). Technical barriers may also impede deployment of vaccines in developing countries – problems of transport and storage and inadequate health services infrastructure.

- *Economic* – problems of pricing structures that fail to provide sufficient return on investment to manufacturers, when development costs for a single vaccine may total $300-$800 million (Plotkin, 2005). It is also difficult to justify new R&D for vaccines that have uncertain socio-economic value.

- *Opposition to vaccination* – problems of rejection of vaccination by individuals because of mistaken perception of risk or on grounds of conviction.

- *Legal* – intellectual property protection issues in the global use of vaccines, litigation issues for manufacturers and complications in clinical trial design involving more than one experimental product.

- *Scientific* – microbes evolve to subvert immune mechanisms and there are particular problems for vaccine development associated with antigenic variation (HIV), large genome (malaria) and ineffectiveness of antibodies against intracellular pathogens.

Despite the obstacles, R&D is progressing to improve the present generation of vaccines and to develop vaccines for the hitherto unmet medical problems. The American Academy for Microbiology report provides a comprehensive summary of the current status of R&D advances.

Our report is designed to focus on the major challenges, to identify scientific opportunities and to emphasise the importance of market pull in defining priorities, clarifying where the responsibility is at EU or Member State level. We take a broad view of the needs of European vaccine strategy with regard to the research and health policy issues relating to:

- Standard preparations, currently used in national vaccine programmes – both childhood vaccines (eg measles, mumps, rubella, polio, pertussis, meningitis) and others (eg tick-borne encephalitis)

- New vaccines for the EU – pandemic influenza; new combinations (eg against enteric, respiratory, sexually transmitted diseases); established disease (eg TB, HIV, HPV, RSV); co-infections (eg HIV and TB); emerging/re-emerging diseases (eg SARS, West Nile virus)

- New vaccines predominantly for countries where the infection is endemic and for travellers to those countries (eg malaria, dengue)

- Vaccine responsiveness for potential biodefence needs (eg smallpox, anthrax, plague)

- Development of veterinary vaccines for diseases likely to affect humans, because some zoonotic diseases come from farm and companion animals

In addition to tackling the current disease burden, it is highly desirable to build in the flexibility to prepare for unknown future challenges. The global vaccine market is expected to expand in consequence of higher vaccination rates in developing countries as a result of the GAVI initiative, an emerging middle class in countries such as China and Brazil and new vaccine antigens, delivery systems and combinations for both industrialized and developing country needs.

3 What policy problems need to be addressed?

There is a wide range of policy issues relating to research, innovation and health care strategies throughout the extended lifecycle of established vaccines and vaccination programmes, development of novel vaccines and basic research related to vaccines. This chapter reviews some of the principal issues in the context of current strengths and weaknesses in Europe and identifies where there are possibilities for progress.

3.1 Established vaccines – production and marketplace issues

The public sector must provide inducement for companies to remain in this area. The drivers of growth for vaccine markets are countered by fear of litigation against vaccine manufacturers and by cost-containment pressures. These factors are manifested in the unwillingness of some governments to support vaccination, compounded by anti-vaccination lobbying and inadequate education of the public on the benefits of vaccines.

3.1.1 Valuing vaccines

Too few companies in the EU are involved in development and production of the current generation of vaccines. There have therefore been deficiencies in the supply of vaccines in major markets. For some vaccines, there is only one supplier and if a technical problem arises during manufacturing there is significant difficulty in satisfying the market. Some Member States have no endogenous vaccine manufacturing capacity.

Vaccines have high social value but the manufacturer's return on investment is less than for other pharmaceutical products and there may be a particular problem of exposure to legal liability[4]. It is important to remove obstacles to new product development – where it is appropriate to do so – and one hurdle is the manufacturer's fear of expensive litigation. This fear is a particular disincentive for smaller companies to engage in vaccine R&D. The European Commission should give high priority to finding ways of reducing manufacturers' exposure to the threat of litigation (drawing on the experience gained in the USA for childhood vaccines). This and other incentives to private sector R&D would help to support EU aspirations to build leadership in biotechnology[5].

Companies and public policy makers face difficult choices in balancing benefit, risk and cost[6]. As noted in the EASAC (2005) report, current methods for estimating the economic value of vaccines incorporate health care costs and some societal costs (such as benefit of working days saved) but exclude what has been described as the intangible value. The concept of the intangible value of vaccines has been proposed, to capture some of the broader economic costs of infectious disease that are not otherwise covered in the conventional cost-effectiveness assessment to define industry R&D investment priorities. For example, the global cost of SARS, including the impact on travel, tourism, economic growth and financial markets, was estimated at about $80 billion. Similarly, the economic cost of avian influenza is already high in terms of the impact on agriculture systems and farmers' income. Understanding better this intangible societal value of vaccines would provide political justification for more public investment and new incentives to company R&D investment (see next section).

These broader aspects of evaluating socio-economic value should receive more attention in Framework Programme initiatives to strengthen vaccine research in Europe. For example, the final Call for Framework Programme 6 Priority 1 (Life Sciences, Genomics and Biotechnology for Health) requested impact assessment of past and current EU actions for vaccine research in the private and public sectors. In order to identify this impact of EU support, it is also necessary to do better in identifying the impact of vaccines.

3.1.2 Creating incentives

In order to stimulate industry to increase its efforts in vaccine R&D, there is broad need for international harmonization and streamlining of technical and regulatory requirements (see section 3.2.1) and, conceivably, a new EU approach to pricing and product liability. While some prospective novel vaccines may have high economic value, for example HPV for preventing cervical cancer, vaccine development in general is a challenge for sector economics. The business model needs to be reconsidered (Plotkin, 2005). This will necessitate a co-ordinated strategy across the EU, governments, industry and academe.

The report 'Fighting Infection' by the UK House of Lords Committee on Science and Technology (2003) suggests some options for Member States. Extrapolating to the European level, the European Commission should consider co-ordinating efforts by Member States to develop and maintain evidence-based guidelines about vaccine requirements, and should create appropriate financial incentives to enable research, development and

4 For example, the price of some whooping cough vaccine preparations increased markedly in consequence of failure to obtain liability insurance.

5 Report from the Commission 'Life Sciences and Biotechnology – A Strategy for Europe, Third Progress Report and Future Orientations' (COM (2005) 286 final): the Commission has commenced a process of reflection on the role of biotechnology in the renewed Lisbon Agenda.

6 Public policy makers often see risk mainly in terms of safety issues but for companies, risk also covers risks to innovation from inadequate patent protection, lack of funding, increasing regulation, and market vagaries. A recent survey of vaccine companies by Eden Biodesign identified the major determinants of the increasing cost of development as: more onerous clinical trials; overcoming technical challenges in product development, scale-up and manufacture; increasing regulatory requirements.

commercialisation of vaccines. Furthermore, given that there is little vaccine production capability in many Member States, the Commission, working with Member States, should establish a strategy to identify priorities and ensure that there is secure access to vaccine supplies in advance of outbreaks of disease.

3.1.3 Safety concerns

Some Member States struggle to implement their voluntary vaccination programmes (for example, measles in the UK, hepatitis B in France). One impediment is public perception of vaccine safety. Vaccine safety issues are critically important: adverse events, real or perceived, destroy public confidence. Nowadays, there are higher public expectations of safety for vaccines than for other pharmaceutical products. Older vaccine preparations (for example, for smallpox and pertussis) were associated with side effects but new vaccines are usually much safer.

As with any other medicinal intervention that has a biological effect, vaccination is not completely free from risk, but adverse effects are usually minor (POST, 2004 for UK experience and implications for policy-makers). Nonetheless, there have recently been some vaccine scares, for example the alleged association of hepatitis B vaccine with Multiple Sclerosis (mainly in France) and the alleged association of MMR (Measles, Mumps and Rubella) vaccine with autism and inflammatory bowel disease (mainly in UK). There is no sound epidemiological or other scientific evidence for these associations, although it is formally impossible to prove in these or other scares that a causal association never occurs (Lachmann, 2004). Other anecdotal links have also been discredited but both proven and discredited safety issues are important to public health services because misperceptions about vaccines undermine vaccine acceptance. Where an association has been substantiated, for example the risk of anaphylaxis after the first MMR dose, the overall risk of the vaccine must then be balanced against the risk of the disease. For the MMR vaccine, for example, it is relevant that one in a thousand people with measles will experience encephalitis, but encephalitis occurs in fewer than one in a million MMR vaccinations[7] (Duclos and Ward, 1998) and subacute sclerosing panencephalitis (SSPE), a devastating complication of measles, is prevented. Satisfying the objective of public expectations on safety requires better communication on what constitutes a reasonable risk-benefit balance and, broadly, engagement between researchers and the community-at-large to build trust (Academy of Medical Sciences, 2003).

The safety of vaccines has improved considerably over the last couple of decades. Efficacious vaccines with some side effects (for example, rabies vaccine derived from neural tissue) have been removed from the market and replaced by safer versions. Other safer versions are in prospect, for example for Japanese encephalitis vaccine, to replace the current preparation grown on mouse brain. All new vaccines are now based on technologies that deliver a very high standard of safety (Rappuoli, 2004).

The vaccine safety scares and media attention highlight bioethical issues (Lachmann, 2004; Ritvo et al., 2005). Vaccination to confer herd immunity (normally effective at an immunization rate of about 95% for measles and at lower levels for some other infections) presents an ethical challenge because non-vaccinated individuals can nevertheless benefit from the vaccination that others undergo and refusal by the individual can compromise herd immunity. Although compulsory vaccination is effective to control certain diseases it is mostly unenforceable (Lachmann, 2004). Nonetheless, vaccination is strongly encouraged in some countries (eg USA) by schools requiring pupils to provide vaccination certificates before enrolment.

Both the scientific and regulatory communities must communicate better on the public health benefits and good safety record of vaccines, and work with patient groups and community groups to draw on their perspectives, expertise and motivation, for example, as demonstrated by the important role that Rotary International played in supporting the poliovirus vaccine programme. There is an issue of trust. In the USA, perhaps because there are several independent bodies providing recommendations (the Food and Drugs Administration, Center for Disease Control, ACMP), the public may be more disposed to believe their recommendations than in those EU Member States where there is only one national-level expert body, with a remit that also includes licensing.

3.2 New vaccine development – responding to scientific opportunities

3.2.1 Linking science and policy

There is a major opportunity now for the European Centre for Disease Control to improve public health by helping to support a coherent science base for vaccine development and use, and by harmonising surveillance and reporting systems. The European CDC should consider developing long-term goals for EU priorities:

- Providing standardised and unified surveillance statistics so that vaccines can be designed for all of the EU.

7 In UK, 2004-5, the percentage of children being immunized with MMR vaccine has increased for the first time since 1995-6, but is only 81% of the cohort of children reaching their second birthday.

- Setting priorities for development and use of vaccines according to disease burden.
- Providing a single EU-level recommendation for the use of each vaccine (analogous to single US market), so that manufacturers do not need to negotiate separately with multiple Member States and can capitalise on the centralised procedure for product approval.
- Promoting a single EU-level evidence-based schedule for vaccination dosage requirements, to accelerate clinical development and reduce development costs.
- Partnering with WHO, US CDC, industry and other stakeholders, to promote the value of vaccines to society.
- Ensuring co-ordination with the agenda for infectious disease control in zoonoses in domestic and other animals.

3.2.2 Vaccinology

As noted previously, novel vaccination strategies for the control of major diseases such as AIDS depend on efficacious stimulation of T cell responses. Recent insights into immunology have defined the ways to (i) stimulate different T cell populations; (ii) induce memory; and (iii) avoid stimulation of suppressive regulatory T cells. This knowledge can now be translated into modern vaccination strategies against diseases controlled by T cells.

There has also been very rapid progress in the sequencing of bacterial and viral genomes (Rappuoli, 2004) that has created the new discipline of pathogenomics . In addition to providing information about individual genes, this sequencing has facilitated research (reverse vaccinology; reverse genetics to facilitate identification of relevant epitopes for vaccines) on those pathogens that cannot be cultivated in vitro, such as hepatitis C virus, or where vaccine development was beyond the reach of conventional approaches, such as meningococcus B. Basic research is essential to underpin vaccine discovery and the basic groundwork is needed now – for example, generic study of flaviviruses, filoviruses, parvoviruses, bunyaviruses – rather than waiting for the next 'mystery' disease.

With the recent achievements in cell biology, molecular biology, immunology and genomics as well as other 'omics', rational strategies for developing vaccines have become feasible. Recent achievements include: (i) design of novel adjuvants to be used for oral and parenteral application (see section 3.2.8); vaccination schedules comprising heterologous prime/boost regimens; (iii) recombinant vaccine carriers, which induce powerful immune responses; (iv) in silico identification of candidate vaccine antigens.

Many novel types of vaccines are predicted to be available within the next two decades as a result of the current advances in reverse vaccinology, DNA vaccines, non-replicating vectors and the understanding of the innate immune system (Rappuoli, 2004). If DNA vaccines can be made to work adequately in humans , then it may be possible to create a universal vector backbone into which any gene from a new disease pathogen could be inserted. This flexibility would accelerate new vaccine development but requires much basic research to prove its validity (American Academy for Microbiology, 2005).

While there are many innovative approaches in prospect, manufacturers usually do not make direct comparisons of, for example, vectors or delivery systems. There is a role for the EU in funding R&D to encourage standardisation of tools and assays and to support direct comparisons to identify optimal approaches.

The importance of rational vaccination strategies has been recognized increasingly (although still insufficiently) by decision-makers in governmental and non-governmental organizations. On the international level, efforts by the NIH in the USA, the Bill & Melinda Gates Foundation Grand Challenges, the WHO and the EU (for example, the poverty-related diseases research funded by Framework Programme 6 and the EDCTP) are notable. Success depends critically on bringing academic research institutions, best equipped to design novel experimental vaccination systems and protocols, together iteratively with private companies, best suited for further product development and conduct of clinical trials. Such public-private partnership provides fertile ground for new vaccination strategies from the bench to the field.

The opportunities provided by molecular biology and structural proteomics for identifying novel antigens to initiate original approaches to producing efficient vaccines reinforce the need for appropriate protection of intellectual property. Indeed, this is a prerequisite to commercialisation. So it is important for all vaccine researchers to have access to advice on the criteria for patentability and the practical details of how and when to patent. It is also important to continue to monitor the operation of the European Patent Convention (EPC), to which a large number of Member States are signatories, to ensure that it does provide the required protection for those who are signatories. National patent law should similarly be reviewed in those Member States that are not signatories to the EPC.

3.2.3 European vaccine industry and global collaboration

The vaccine manufacturing sector has a strong presence in Europe and there are significant opportunities for EU companies to capitalise on research advances (Box 2).

8 The Commission funds a Network of Excellence, Europathogenomics in Framework Programme 6.
9 DNA is excellent for priming the response but may require augmenting in prime/boost strategies (for example, in malaria using a viral vector).

Box 2 Current status of European vaccine sector

- A survey by European Vaccine Manufacturers (EVM) Association of manufacturers accounting for 85% of worldwide vaccine sales (www.evm-vaccines.org) found that 90% of that production (in 2002) originated with European companies, though Europe represents only 30% of the global market[10]. Half of exports were destined for humanitarian aid agencies.
- Average R&D investment is 24% of sales.
- EVM survey in 2004 disclosed high European support for vaccination as important health procedure: 82% of general public (similar support in all Member States surveyed) and 98% of health care professionals.
- European vaccine industry has initiated partnerships with public sector R&D to address neglected diseases, eg Global Alliance for Vaccines and Immunization, International AIDS Vaccine Initiative, Malaria Vaccine Initiative.

The magnitude of the global challenge in addressing relatively neglected diseases is becoming increasingly well defined (for example, Diamond, 2005). There is growing momentum on Public Private Partnerships, and research on HIV, TB and malaria will again be a priority for the health theme in Framework Programme 7. In September 2005 the European Parliament emphasised the need for the EU to assign higher research priority also to other neglected diseases (for example, sleeping sickness, dengue fever, leprosy, leishmaniasis, trachoma) and to identify support mechanisms for industry development.

Global integration is not just a matter of addressing developing country needs – although that is a priority – but also of European countries capitalising on human and other resources for innovation outside of the EU and USA, to build the world economy. New expertise in bioscience innovation – in Asia and Latin America, for example – represents an opportunity for collaboration as well as competition. There are also opportunities for Member State companies to draw on particular expertise and capability in the production of biologicals in other countries, for example the Finlay Institute in Havana, Cuba.

There are weaknesses in R&D in Europe, however, particularly in terms of lack of adequate capacity for clinical trials financed by the public sector (where many consider that the EU suffers from the absence of a body analogous to the NIH in USA), lack of EU priority-setting in public health and lack of an EU-level instrument to facilitate industry-academia R&D partnerships. In supporting innovation, EU policy-makers should encourage and fund multidisciplinary centres to catalyse and co-ordinate effective collaboration between academia and industry research and also ensure that views of patient groups are taken into account in devising R&D objectives and trial design[11]. More harmonization is also needed between EU, USA and other international research objectives and strategies.

3.2.4 Correlates of protection

Clinical trials, which depend on measuring the prevention of disease, can be lengthy (Kaufmann and McMichael, 2005). It is important, therefore, to identify biomarkers (proxy indicators), which serve as correlates of infection, protection and susceptibility/resistance and which will help to shorten the duration of vaccination trials significantly[12]. This is particularly necessary where animal models cannot provide information on protection. An iterative approach, involving both basic and clinical research, is required to screen and validate markers – it is often the clinical outcomes that inform pre-clinical understanding, leading to development of both better animal models and biomarkers.

3.2.5 Safety evaluation of novel vaccines

The Academy of Medical Sciences in the UK recently published the report (2005b) from its project 'Safer Medicines', covering a range of issues for creating a coherent, evidence-based approach to the safety evaluation of vaccines (Box 3), concentrating on what is judged to be relevant in exploring the immune response and reversing the current trend to apply a non-selective approach to characterisation of immune response. Many of the points for safety evaluation (Box 3), requiring the introduction of new models, application of new technologies and building clinical trial research capacity, reinforce points already made about new approaches to evaluation of efficacy.

10 Data from the US Tufts Centre for Drug Development (http://csdd.tufts.edu) shows, however, that about two-thirds of candidate vaccines currently in R&D pipeline are sponsored by US companies (many with only one or two candidates). Many of the pathogens addressed in current R&D are those defined by NIH as posing a risk to US national security.

11 For example, there is a role for asthma awareness groups in supporting research on vaccines for Respiratory Syncytial Virus (American Academy for Microbiology, 2005).

12 Clinical hurdles have generally become a major impediment to fast development, particularly in terms of the size of phase III trials now required. The safety database covered about 1,000 patients for Recombivax HB in the 1980s but will be around 75,000 for Rotateq in 2005.

Box 3 Critical areas for safety assessment of vaccines

- *Infectious pathogenesis* – research on pathogen entry, local replication, dissemination to other sites and hosts, mechanism of host damage and determinants of vaccine-adverse events.
- *Designing novel animal models* – developing validated alternatives to current safety evaluation models of doubtful or illusory scientific value, eg neurovirulence testing and exploring opportunity for transgenic rodent models to replace primate models. There may be increasing role for animal testing of those new vaccines that cannot easily be evaluated in humans, eg anthrax.
- *Process controls* – systematic use of modern methods, eg protein sequencing and molecular markers, for control of starting materials in vaccine production, for consistency in manufacturing and for detection of potential contaminants.
- *Product testing* – opportunities to replace in vivo testing of vaccine batches by in vitro testing or physico-chemical characterization, but new approaches must be validated as fit for purpose.
- *Clinical trials* – introduction of genomic and other 'omic' technologies to obtain more information on safety as well as efficacy.
- *Post-marketing surveillance* – long-term follow up of vaccine recipients with active surveillance of adverse events will benefit from new approaches to record linkage and commitment to more robust, hypothesis-based, exploration of anecdotal observations.

Adapted from Report from Vaccines Working Group, 'Safer Medicines', Academy of Medical Sciences, 2005b

There is a pervasive challenge for companies to anticipate rare adverse events when developing vaccines – the solution lies both in improving the predictive value of animal tests and in improving post-marketing surveillance. In addition to the general issues for improving clinical research capacity, there is currently lack of resource in the epidemiology of rare diseases. For example, knowledge of the background incidence of intussusception has been critical in interpreting the response for rotavirus vaccine and Guillain-Barre syndrome for influenza vaccine.

The challenge for post-marketing surveillance to clarify safety issues provides a significant new research opportunity for the EU. Collection of relevant information on vaccine safety, in common with other drug safety, is often incomplete and access to such data may be barred by data confidentiality and legal considerations. Member States have an opportunity and a responsibility to develop networks to share data in order to support future research as well as to monitor product performance. The US CDC and several private managed care organisations developed the US Vaccine Safety Databank, a large database of patient information including data on vaccination history, health outcome and patient phenotype that is accessible by external researchers. While concerns have been expressed about the fairness and transparency of the policy and procedures governing the data sharing and the need to involve other stakeholders in setting research priorities (IOM, 2005), this database does represent a major research resource and offers a model for what might be achievable across the EU.

3.2.6 Underpinning regulation with science and expediting approval

The EU should consider building a research support role for the vaccine regulatory functions, analogous to the FDA's Center for Biologics Evaluation and Research, so as to facilitate development of needed biological products – for example, by ensuring the availability of virus isolates for vaccine stock and co-ordinating technical approaches to vaccine testing. Thus, a new responsibility for the European Medicines Agency (EM(E)A) in providing scientific feedback to manufacturers would be facilitated by incorporating a laboratory function together with a mechanism to consult with external scientific and medical experts. One important goal is to ensure standardised and unified registration of side effects of vaccines.

The European authorities should emulate FDA good practice in designating certain vaccine candidates as fast-track (for example, variola and anthrax in US) or orphan (CMV in US) status. The EMEA Committee on Orphan Medical Products recently recommended for orphan designation in EU the candidate MVA TB vaccine (recombinant modified vaccinia virus Ankara expressing TB antigen 85A) and an octavalent conjugate vaccine for the prevention of Pseudomonas aeruginosa infection in patients with cystic fibrosis, because the market would be unlikely to justify the R&D investment. These are the first products for which orphan status has been recommended on this basis – with incentives of market exclusivity within the EU for up to 10 years plus access to regulatory and vaccine development advice. This may be an important EU precedent for other vaccines.

The EU and other regulatory authorities and vaccine manufacturers can also draw on more support and advice from WHO expertise in vaccines and biologicals. To this end, the WHO *Guidelines on clinical evaluation of vaccines: regulatory expectations* provides a flexible framework.

While it is important to build the specific regulatory science function in the EU, it is also important to ensure that other EU policy initiatives do not have unintended negative consequences for vaccine R&D. For example, there was dismay expressed within the clinical research community that the European Clinical Trials Directive will have a negative impact on the ability of academic groups to initiate and conduct clinical trials. However, while this Directive has introduced major additional regulatory and cost hurdles, for example with regard to Good Manufacturing Practice, the introduction of uniformity across the EU pharmaceutical industry can be welcomed. In general, the lesson learnt from this episode is that the clinical academic community needs to be more pro-active in communicating its advice to EU policy-makers early in the legislative lifecycle and that policy-makers should consult more widely to avert unintended consequences of legislation.

3.2.7 Microbial challenge studies

One area where it has been suggested that there should be more oversight of research, relates to microbial challenge studies. Historically, such studies – the deliberate infection of human volunteers with micro-organisms – have greatly contributed to understanding of pathogenesis and the immune response, and may furnish proof-of-concept for a therapeutic intervention, significantly reducing the time required to realise key milestones in vaccine development (Academy of Medical Sciences, 2005a). However, such research is not covered by the European Clinical Trials Directive, and the Academy of Medical Sciences in the UK recently recommended the formation of a UK National Expert Advisory Committee to identify mechanisms to protect the safety and welfare of human subjects involved in microbial challenge studies. It is desirable to consider introducing equivalent functions across the EU – perhaps at European Commission level – to provide expert advice on the relevant scientific, ethical, safety, legal and societal issues relating to this research.

3.2.8 Vaccine delivery

Careful consideration is needed on how vaccines are formulated and delivered. Formulation includes addition of adjuvants, where appropriate. Delivery specification needs to take into account optimal dose, optimal time and route of administration.

Adjuvants are used in vaccine formulation to enhance, modify, prolong or accelerate the immune response to vaccines. Just one adjuvant, alum (aluminium hydroxide), accounts for most of the current market (with the oil-in-water emulsion MF 59 also registered for influenza) but various others are in the pipeline. There is a need for comparative studies. Improved adjuvants will find a particular place in formulations for the elderly, where there is additional need to enhance the immune response, and in those circumstances where vaccine protein supply is limited and it is desirable to reduce the antigen dose.

Recent research has identified an evolutionarily conserved innate immune defence against pathogens, mediated primarily by Toll-like receptors, which sense pathogen-associated microbial signals (Rappuoli, 2004). This molecular understanding provides a new opportunity for promoting the immune response by developing novel adjuvants.

There are also regulatory implications – there is no precedent for approving an adjuvant on its own – and the newer products present greater demands for manufacture and analytical control. Researchers need to consider if it is feasible to advance the case that once an adjuvant is proven safe with one protein, the development phase for other protein-adjuvant combinations can be accelerated rather than having to repeat the whole of the safety evaluation. However, as the effect of an adjuvant is influenced by its formulation, and as the safety of the preparation may depend on interaction of antigen and adjuvant, there is also need to perform more research on adjuvant formulations.

3.2.9 Vaccines produced by recombinant DNA technology

Recombinant DNA is being used for vaccine development in several broad ways.

First, the gene(s) from a pathogenic micro-organism that encodes important antigens against which immune responses are needed may be expressed at high levels in microbes, purified and administered as a non-infectious antigen preparation. The best example here is the vaccine used worldwide against hepatitis B virus. This vaccine is produced in yeast by expression of the hepatitis B virus surface antigen and has been marketed since 1986. It has had an enormous impact in reducing hepatitis B infection globally and thereby the subsequent development of hepatocellular carcinoma. There is great potential to produce other vaccines in this way.

Second, micro-organisms can be engineered to express foreign antigens and the live recombinant micro-organism used as the vaccine. This was pioneered with vaccinia virus (the smallpox vaccine) in 1983. An advantage of this approach is that no purification of the antigen is needed because it is simultaneously synthesised and delivered to the immune system during infection in vivo. The concept established with vaccinia virus has been applied to many other viruses and micro-organisms. A useful feature of this approach is that multiple foreign genes may be expressed simultaneously from one organism to create polyvalent vaccines.

A third approach is to produce oral vaccines. Many probiotic bacteria (for example, lactic acid bacteria, LAB) have been used for years by the food industry, have a history of safe use and can be given orally in relatively large doses without risk of potential side effects (Hanniffy et al., 2004). The development of efficient expression systems enables successful expression of vaccine antigens in recombinant LAB. These bacteria would be ideally given orally and used for large-scale vaccination in populations at risk. Moreover LAB-based vaccines could also elicit protective mucosal immune responses as some of these strains possess immunostimulatory properties. There is also some prospect for producing 'edible' vaccines in plants: the protein antigen is expressed in recombinant plants where it may be coupled to a bacterial protein that allows its transport across the gut wall. This approach is not yet so far advanced and faces some basic immunological difficulties with regard to oral tolerance, but it does offer the potential to produce vaccines cheaply and may have particular relevance for developing countries. There is much to be done to clarify issues for efficacy and safety. A Framework Programme 6 project (Pharma-Planta) is exploring proof-of-concept and evaluating the utility of a range of plants (tobacco, maize, potatoes, tomatoes) through to clinical trials.

3.2.10 Supporting the co-ordinated R&D strategy

(i) *Human-veterinary research synergy*. In order to capitalise on new scientific advances, there must be better co-ordination of human and veterinary vaccine research and development agendas. Veterinary vaccines are important in the context of animal reservoirs of human pathogens, as well as representing an important set of policy issues for veterinary care. Veterinary vaccines can be tested in experimental challenge models and can also often provide proof-of-principle to aid the development of human vaccines. They may do this for DNA vaccines (taking into account the complexity of interspecies differences in response); the first DNA vaccines to have been registered are veterinary vaccines.

(ii) *Biosafety in vaccine research*. There is insufficient provision of biosafety containment facilities (at levels 3 and 4) in the Member States, especially with regard to appropriate containment of early animal research studies (when virus pathogenicity and transmissibility may be unclear). This is an urgent problem in the Member States – and the EU has responsibility to ensure effective provision of shared facilities. The prospect of further failure of laboratory containment also has implications for Member State strategies for prevention and control of disease outbreaks, building on the lessons learned from the episodes of accidental release of smallpox and SARS.

Optimal containment facilities are important to progress research proposals to create new virus hybrids (eg avian flu H5N1-human flu crossover) in re-assortment studies. This issue has become very visible since the recent reconstruction of the 1918 influenza virus. That work has been criticised because of the threat of escape from the laboratory, particularly since the work was done at biosafety level 3 (rather than 4) and because publication of the full genome sequence provides information that could be used by bioterrorists. However, the research is of great scientific value and many researchers assert that its value greatly outweighs its risks. The EU must take a lead in clarifying strategy and laboratory safeguards for priority research directed to the development of broader, cross-protective influenza vaccines and the full synthesis of pathogen genomes (see section 3.3.2 – the synthesis of poliovirus has attracted particular recent attention).

(iii) *Newer Member States*. The EASAC (2005) report noted the problems for research funding and prioritisation in some of the newer Member States. Enlargement of the EU has also provided an opportunity to facilitate research on infectious diseases that may be of particular importance to some of the newer Member States and Accession States, such as the hantaviruses that are endemic in regions of Eastern Europe and can be the cause of haemorrhagic fevers. For example, a recent Framework Programme 6 project involves the Vilnius Institute of Biotechnology in a consortium to develop a bivalent hantavirus vaccine.

3.2.11 Skills and training needs

All of the activities described in the preceding paragraphs require trained scientists. It is important to reiterate the point made in the EASAC (2005) report – there is a lack of trained researchers both in conventional clinical microbiology and for more speculative research, and the erosion of the knowledge base in veterinary research is even worse.

Skill shortages affect vaccine innovation and the problem is compounded by shortage of trained staff to work in vaccine development (for example, in process and analytical steps, quality assurance and control, regulatory science, clinical development and

pharmacovigilance). The training deficit is exacerbated by the general underfunding of the translational research necessary to bridge the gaps between early stages of antigen discovery, establishing proof-of-principle, drug development and health services delivery. The response in the UK, providing one model for resolving the shortage of vaccine development skills, has included creation of the UK National Biomanufacturing Centre (www.biomanufacturing.co.uk), supported by EU Regional Development funding. This Centre provides a training function and Good Manufacturing Practice facility available to smaller companies for vaccine production. One other model to help produce skilled researchers is exemplified by the Framework Programme 6 Network of Excellence 'Europathogenomics' as an European Graduate Academy to train PhD students.

3.3 Vaccination strategies – new science-based approaches to European public health

Much has already been achieved in developing strategy both for established vaccines and to prepare for emerging diseases. But the strategy should include generic preparedness for the unknown. It can reasonably be assumed that future diseases, as yet unknown, will be mainly viral, respiratory, highly transmissible and originating from animals. Therefore, modelling and simulation can identify public health implications, for example in terms of providing the infrastructure for quarantine and other population protection and control measures.

Additional research priorities are to clarify the immune status and needs of special groups, for example in maternal and neonatal immunization, and the effect of ageing and comorbidity on the immune system. The projected growth in the elderly population in the EU is one of the biggest demographic challenges in European history. It is also important to take account of the growing evidence base from epidemiological research to inform selective vaccination strategies, eg clarification of significance of individual 'super-spreaders' in infection (epidemiological evidence from HIV, SARS).

3.3.1 H5N1 influenza

Box 4 outlines the current status of H5N1 influenza. The prospect of an influenza pandemic provides a critical test for vaccine preparedness strategies. As the new coordinator of the UN systems to combat the threat said, 'We expect the next great influenza pandemic to come at any time now' (Ress, 2005).

Box 4 EU preparedness for H5N1 influenza?

- There were four global influenza A pandemics in the twentieth century.
- The H5N1 virus appeared in Hong Kong in 1997, with a major outbreak in poultry occurring in several Asian countries in 2004. This sub-type had not previously infected man.
- There have been 169 laboratory-confirmed human cases of H5N1 reported to WHO, of which there were 91 deaths, by mid-February 2006.
- H5N1 is endemic in poultry and wild birds in Asia and has now spread to Europe. Economic loss so far is estimated as up to 12 billion Euros.
- H5N1 avian virus currently lacks characteristics of efficient transmission between humans but this could occur in consequence of re-assortment or of mutation.
- If H5N1 becomes transmissible between humans, a pandemic on the scale of 1918 is not impossible. WHO issued guidance for planning in 2005.
- The US Pandemic Influenza Response and Preparedness Plan (www.hhs.gov/nvpo/pandemic/index.html) covers increased surveillance, expansion of vaccine manufacturing and co-ordinated response. American Academy for Microbiology (2005) reviews practical issues for designing and producing H5N1 vaccine.
- The EU is becoming better prepared. The Commission has published Community Influenza Pandemic Preparedness and Response Planning strategy (COM (2004) 201 final). The ECDC has a central role in working with Member States to develop early warning and response systems, though detailed plans need strengthening and vaccine production must be improved (Coulombier and Ekdahl, 2005). The European Commission is now co-funding Member State surveillance plans and also urges them to develop more vaccines.
- Planning now for a pandemic vaccine requires: (a) current influenza vaccination programmes to provide increased coverage of groups at risk; (b) accelerated development of prototype pandemic vaccine (necessitating EU financial support for companies and fast-track regulatory approval); (c) anticipating production requirements for pandemic vaccine (European vaccine Manufacturers, 2005).
- Recent publications on global issues for surveillance and responsiveness, including vaccine discovery and development, are collected on the Nature website www.nature.com/nature/focus/avianflu/index.html. An ongoing Royal Institution-World Science Assembly 'Pandemic Preparedness Project' is reviewing opportunities for development of global public health communications systems, regionalised global strategies to develop response capacity and cost-benefit analysis for public health intervention (www.rigb.org)[13].

13 The EASAC (2005) Report also noted issues for intensive animal husbandry practices in promoting infection. Concern on transmission of avian influenza and other zoonoses is one factor in development of the DG Research 'Knowledge-Based Bio-Economy' theme for Framework Programme 7 to explore the potential for novel farming systems.

Serious consideration should be given to a potentially novel approach to attenuating influenza by using antibody. There is a long history of using immunoglobulins from convalescent subjects to prevent or attenuate viral infection, for example hepatitis A, measles and chicken pox, and there is recent research in mice demonstrating the relative role of immunoglobulin classes in protecting from influenza (Renegar et al., 2004). Thus, immunoglobulins obtained from patients who have recovered from infection with influenza could be used prophylactically in those at risk, to attenuate the infection while allowing active immunity to develop. Additionally, or alternatively, it could be possible to manufacture monoclonal antibodies to the haemagglutinin of the pandemic strain and use these in a similar way.

The current heightened state of awareness about the pandemic potential of H5N1 should not detract from the fact that other human influenza viruses continue to cause substantial burden of disease – more than 500,000 deaths a year (Guan and Chan, 2005). The shortcomings of current efforts to control influenza indicate that existing vaccination resources need to be managed better and new agents need to be developed. For example, there is evidence that concentrating on vaccinating school-age children to confer herd protection translates into lower incidence of influenza in adults. This may be more effective at preventing influenza deaths in the elderly than vaccinating the elderly themselves (when vaccination often does not induce a robust immune response) and selection strategies may be increasingly relevant if there is insufficient vaccine available for all at-risk groups (Cohen, 2004).

3.3.2 Eradication of disease

The global eradication of smallpox, announced 25 years ago, was one of the most significant achievements in public health. Money spent on the eradication project (estimated at $313 million, Editorial in Lancet, 2005) was also clearly a worthwhile investment in economic terms, savings on immunisation and treatment in the US alone surpassed the total cost of eradication after just two months.

The potential for eradication only applies to human-specific, acute disease. It does not apply when there is a reservoir of infection outside man or where the infection is persistent – so most infections need to be considered in terms of control rather than eradication. Paradoxically, the success of smallpox eradication and the termination of vaccination against smallpox in the 1970s have led to a large proportion of the world's population being immunologically naïve for orthopoxviruses, or not to have had vaccination for approximately 30 years. Recent studies have shown that the immune responses to smallpox vaccination are long lasting and both antibody and T cell responses are evident 50 years post vaccination. However, because there are no clear correlates of protection, it is uncertain if these declining immune responses would provide protection. Consequently, recent fears about deliberate release of variola virus, the cause of smallpox, has caused some nations to re-introduce limited vaccination against smallpox and to purchase new stocks of vaccine. As noted by the EASAC (2005) report, there are policy issues for emergency planning for manufacturing and stockpiling for a newly susceptible population. Further evidence is needed to inform the Community decision on whether to accumulate an EU level smallpox stockpile (with equivalent access for all) in addition to the stockpiles in individual Member States. There is also an urgent need to develop second and third generation smallpox vaccines that are less reactogenic than the first generation vaccines. A difficulty with development of such vaccines is the inability to prove efficacy in the absence of human smallpox.

While the prospect for eradicating other diseases in the near future is rather disappointing (Kurth and Rasch, 2005), the WHO target for eradicating polio is within sight and the global incidence was reduced by 99% over the period 1988-2004[14]. Eradicating polio will introduce additional practical issues, such as how to maintain expertise in the technically demanding polio vaccine safety assays – with policy implications for sharing technical expertise internationally and for funding continuing training facilities. Continuing preparedness also includes the means for therapy and production and application of a vaccine. As with smallpox, following the interruption to human transmission of wild poliovirus, the risk of re-introduction from a laboratory or manufacturing facility for inactivated polio vaccine will grow as populations lose their immunity. It will be necessary to develop an international stockpile of monovalent oral polio vaccine plus new forms of inactivated polio vaccine (manufactured from weakened live virus) and agree a response mechanism in the eventuality that poliovirus re-emerges (Heymann et al., 2005).

Conceptually, a virus cannot now ever be presumed extinct because – in the era of genomics and synthetic biology – it is possible that certain viruses can be re-synthesised (Mueller et al., 2005). As noted by the EASAC (2005) report, this has policy implications for bioterrorism and national security, with regard for example to open publication of scientific literature and mobility and vetting of researchers.

3.3.3 Threat of bioterrorism

The threat of bioterrorism has raised new issues and also imparted new urgency to efforts to combat infectious disease (Box 5).

14 WHO also aims to eliminate measles and to reduce hepatitis B seroprevalence to less than 2% by 2012.

Box 5 Policy developments to combat bioterrorism

- In 2002, Member States adopted a joint programme on chemical, biological, radiological and nuclear risks. The political strategy covered risk assessment, protective measures, detection and response. In 2003, the European Commission published its Communication On Co-operation in the European Union on Preparedness and Response to Biological and Chemical Agent Attacks. DG Health and Consumer Protection has now also published European Clinical Guidelines for bioterror agents.
- The EU-NATO Forum[15] 'New Defence Agenda' notes that the Biological and Toxin Weapons Convention does not have a full verification regimen, unlike the Chemical Weapons Convention and the Nuclear Non-Proliferation Treaty, even though biological agents are the most vulnerable to misuse and impervious to detection.
- The role of R&D in EU common security strategy is receiving attention in the planned Framework Programme 7, but there is little specific attention to bioterror pathogens.
- There has been a dramatic increase in demand for some established vaccines (smallpox, anthrax). There are policy issues associated with the continuing manufacturing of preparations based on old technology (for example, assurance of efficacy and safety, quality control).
- At the second annual 'Worldwide Security Conference' organised by the NGO EastWest Institute (February 2005), concern was expressed at the lack of preparedness for new outbreaks of disease. Existing vaccines are available in only limited quantities and there are no stockpiles at EU level. Potentially many new toxins could be developed from natural or genetically-modified sources but there is little R&D in EU to combat their potential threats.
- The US BioShield initiative provides 10 year funding for government purchase and stockpiling of vaccines and antidotes, with expedited peer review for those research projects deemed important for biodefence. The US NIH Vaccine Research Centre is focused entirely on agents that might be used by terrorists.

The responsibility to devote significant resources to preparing for the eventuality of a bioterrorist-induced epidemic is troubling if it results in diversion of resources that could be effectively deployed in reducing the burden of diseases that are already preventable. This dilemma is well described in a special issue of EMBO Reports 'Science and Society' (2003). There is, however, a significant opportunity to ensure that R&D advances made in response to the threat of bioweapons are also used to develop products and tools for the detection, diagnosis, treatment and prevention of other infections – that is maximising the applicability of 'dual-use' technologies.

3.4 Stakeholders in science and policy of infectious diseases

In addition to the roles and responsibilities of the Member States, European Commission and European Parliament in addressing the policy strands, other stakeholders are very active at the European and global level. Among the leaders are:

- International bodies – in particular, WHO, G8 Ministers
- Philanthropic bodies – the foundations, NGOs and community groups such as Rotary International
- European agencies – in particular, EM(E)A and the Committee for Proprietary Medical Products
- European companies and their trade bodies – in particular European Vaccine Manufacturers , as part of the European Federation of Pharmaceutical Industry Associations, and EuropaBio (European Association of Bioindustries)
- Member State research funding agencies
- Individual national Academies of science and medicine and their Federations
- Professional societies – in particular, the international Union of Microbiological Societies, Federation of European Microbiological Societies and European Molecular Biology Organization.

Some of these stakeholders have already been mentioned in specific contexts and have done much to shape the environment in which future science and policy decisions must be made.

In 2004 the Commission's public health DG launched a reflection process on the future of EU health policy (http://europa.eu.int/comm/health/ph_overview/strategy/health_strategy_en.htm). This signalled a shift in emphasis from the former, essentially defensive, approach of addressing ill health to the more forward-looking approach to promote health and reduce health inequalities. This change in emphasis can be expected to underpin the importance of vaccination strategies.

Public health is a relatively recent policy area for the EU – introduced in Article 152 of the Maastricht Treaty in 1992 and exemplified in further detail in the Amsterdam Treaty in 1997. The initiatives to develop the European CDC and to adopt an integrated Public Health Programme (2003-2008) and the new Health and Consumer Protection Programme (2007-2013) are valuable. But there is a good case to be made for an enhanced EU-level role and responsibility in public health to cover issues for disease surveillance and vaccination. This may require further modification to the Treaty to

15 www.forum-europe.com/NDA

allow DG Health and Consumer Protection more executive powers and the effective instruments to act in support of public health preparedness, responsiveness and, when necessary, crisis management.

There should also be greater recognition of the importance of vaccine research in Framework Programme 7 with regard to the priorities for disease and the underpinning technologies for efficacy and safety. And, in support of the increasing EU public health focus, there must be improved co-ordination between the relevant Directorates-General (with responsibilities for health, research, innovation and competitiveness) to facilitate vaccine development, in particular to support the early stages of development.

4 Recommendations

Infectious diseases continue to pose a major threat in the EU and globally. The continuing threat comes from existing and re-emergent infections as well as new microbes. Vaccines are the best course of action: 'Prevention is better than cure'. Therefore, there is an overwhelming case for major investment in vaccine research, clinical development, and strategies to increase vaccine uptake.

While a wide range of individual policy themes has been described in the previous chapter, some common cross-cutting needs can be identified: providing incentives for industry R&D; building public-private partnership for capitalising on scientific advance and addressing the disease priorities; applying new models, tools and technologies to facilitate vaccine R&D; incorporating streamlined, evidence-based regulatory and decision-making processes; clarifying and articulating vaccine risk-benefit and cost-effectiveness issues.

Our specific recommendations are the following.

1 Increasing the role and responsibility of the European Commission in public health

It is important that DG Health and Consumer Protection be given more executive powers to address public health priorities, with instruments to act in support of preparedness, responsiveness and crisis management in infectious disease. The Commission should now consider how best to develop this greater role, and whether this will require further revision of the Treaty.

There must be improved strategic co-ordination across DGs to facilitate vaccine development, in particular to develop mechanisms and ensure public funding to support early-stage development. Increasing Commission leadership in this area also requires the Commission to work with Member States to establish a strategy to identify and agree infectious disease priorities and enable access to vaccine supplies in advance of disease outbreaks.

A more coherent strategy for public-private partnership is needed to promote the translation of research advances made in academia into products, and to compare alternative approaches to vaccine innovation. It is also important for DG Research to support additional research to assess the socio-economic value of vaccines and, thereby, make the evidence-based case for a central role for vaccines in public health strategy.

2 Equipping the European Centre for Disease Control

In preparedness for new threats, the ECDC must become active in the EU-wide surveillance of current and emerging infection, and in co-ordinating and sharing best practice to ensure that Member State authorities provide standardised and detailed surveillance statistics. The ECDC should also develop long-term goals (i) for European epidemiology; (ii) for consolidating recommendations for the development and use of vaccines; and (iii) for underpinning a co-ordinated approach to zoonoses. It should work to remove unnecessary barriers in surveillance mechanisms for human and animal infections.

3 Incentives to manufacture vaccines

Vaccines have high social value, but manufacturers' returns on investment may be less than for other pharmaceutical products and there are other disincentives to commercial activity in this field. The European Commission should give high priority to finding ways of reducing or eliminating these disincentives – for example, reducing manufacturers' exposure to threat of litigation and promoting effective protection of intellectual property.

In addition to the removal of specific disincentives to company innovation, there is continuing need for the European Commission with Member States, companies and other stakeholders to consider the criteria for the optimum business model in support of the sector, building for example, on the initiative of the G10 Medicines Group. In this context, it is important to ensure that the recently expressed commitment by the Commission to renewed examination of pharmaceutical sector strengths and weaknesses – and mechanisms for EU support – covers vaccines.

4 Regulatory authority research capacity

The EU must build a research support role for the regulatory functions of the European Medicines Agency, analogous to the Biologics Evaluation capacity of the Food and Drugs Administration in the USA, helping to co-ordinate technical approaches to testing. Increasing scientific support for evaluation of vaccines should be accompanied by increasing use of other initiatives to streamline regulatory processes, for example fast-tracking of applications or designation of orphan status. The EU research community should also consider how best to review research on human subjects involved in microbial challenge studies.

Following concern expressed at the unintended negative impact of the European Clinical Trials Directive on public sector/small company clinical research capacity, it is important that, in the future, the Commission increases its efforts to consult widely with researcher and other stakeholders, early on in the policy development-legislative lifecycle.

5 Strengthening public sector support for vaccine R&D

(i) *Framework Programme 7*. There should be greater recognition of the importance of vaccine research in Framework Programme 7 with regard to the disease priorities and the underpinning technologies for evaluating efficacy and safety. Key areas for support in Framework Programme 7 include: better understanding of innate immunity and how T cell responses are induced and regulated; mechanisms of the genetic variability of pathogens; immunology in special populations (eg maternal, neonates, elderly); correlates of protection; molecular epidemiology; modelling and simulation studies (eg for spread of infection and for the economic value of vaccines).

(ii) *Collaboration with developing countries*. It is also important for the Commission to consider extending research collaboration with developing countries (going beyond the current limited remit of the European and Developing Countries Clinical Trials Partnership in Africa (www.edctp.org));

(iii) *Research infrastructure*. There must be increasing support for multidisciplinary research centres and strategic co-ordination of clinical-veterinary research agendas. The Commission can also do more in co-ordinating existing P4 facilities in Member States as a research network and enabling access by other researchers, as part of the broader strategic consideration of the need for facilitating research within appropriate laboratory safeguards.

(iv) *Clinical research capacity*. It is particularly necessary for the Commission to address current strategic weaknesses in public sector-funded clinical trial capacity, lack of priority setting in clinical research and lack of EU-level instruments to facilitate public-private sector partnerships for vaccine R&D. There is also now a major opportunity to use patient information databases for research.

(v) *Training and skills*. Research initiatives at the EU level must also provide better support for training and skill development – coupled with EU proactive encouragement of career development by longer term-planning for responsiveness in infectious disease.

6 Promoting vaccine uptake

The European Commission and European Parliament must do more, in association with bodies such as the ECDC, to support the research community in articulating the value of vaccines. This is necessary to combat anti-vaccination lobbies and to improve communication with the public-at-large on the balance of benefit and risk. The EU should also explore the options for increasing vaccine uptake by promoting implementation of best practice in the requirements for children to be vaccinated before entry into the school system.

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Appendix B Expert consultation

This report was prepared by consultation with a group of experts acting in an individual capacity and was reviewed and approved by the EASAC Council. We are grateful to all who contributed.

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