Introduction

Vaccines and global health

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Vaccines have made a major contribution to global health in recent decades but they could do much more. In November 2011, a Royal Society discussion meeting, ‘New vaccines for global health’, was held in London to discuss the past contribution of vaccines to global health and to consider what more could be expected in the future. Papers presented at the meeting reviewed recent successes in the deployment of vaccines against major infections of childhood and the challenges faced in developing vaccines against some of the world’s remaining major infectious diseases such as human immunodeficiency virus (HIV), malaria and tuberculosis. The important contribution that development of more effective veterinary vaccines could make to global health was also addressed. Some of the social and financial challenges to the development and deployment of new vaccines were reviewed. The latter issues were also discussed at a subsequent satellite meeting, ‘Accelerating vaccine development’, held at the Kavli Royal Society International Centre. Delegates at this meeting considered challenges to the more rapid development and deployment of both human and veterinary vaccines and how these might be addressed. Papers based on presentations at the discussion meeting and a summary of the main conclusions of the satellite meeting are included in this issue of Philosophical Transactions of the Royal Society B.

Keywords: global health; vaccine introduction; new vaccines

1. INTRODUCTION

In the 200 years since Edward Jenner’s dramatic demonstration that smallpox could be prevented by deliberate infection with the relatively innocuous cowpox virus, vaccination has probably saved as many lives as any other public health innovation with the possible exception of improvements in sanitation and water safety. Since the start of the Expanded Programme on Immunization (EPI) in 1974, the proportion of the world’s children who receive their basic vaccines has increased from 15 per cent to nearly 90 per cent, although considerable regional, national and local differences remain. Vaccination has led to eradication of smallpox and the elimination of poliomyelitis and measles from large parts of the world, saving millions of lives. However, despite these successes, vaccination still has the potential to make an even greater contribution to global health. Three million children still die each year from vaccine preventable diseases [1]. Pneumonia, meningitis and diarrhoea account for a quarter of childhood deaths, many of which could be prevented with currently available vaccines. Malaria and improved tuberculosis vaccines are on the horizon and vaccination against human immunodeficiency virus (HIV) may ultimately become possible. The scope of diseases that can be prevented by vaccination is expanding. Hepatitis B virus (HBV) and human papilloma virus (HPV) vaccines are already being used successfully to prevent liver and cervical cancers, and progress is being made on the therapeutic use of vaccines in the treatment of cancer and in the management of non-communicable disease such as hypertension, diabetes and addiction.

There is increasing recognition by organizations such as the One Health Initiative (www.onehealthinitiative.com) of the need to integrate management of human and veterinary diseases more effectively than has been the case in the past. Loss of a cow may be as devastating a blow to a poor farmer in the developing world as a serious illness in his child. Improving the health of domestic animals can improve nutrition of the family and generate wealth, making access to effective treatment more attainable for family members when this is needed, improving child survival. In industrialized countries, outbreaks of infections in domestic animals which are potentially preventable by vaccination, such as foot and mouth disease (FMD), can cause massive economic loss [2]. Thus, development of new, improved and affordable veterinary vaccines has an important contribution to make to health in both the industrialized and developing world.

If the full, global potential of vaccination is to be achieved, advances must be made in three main areas. Firstly, the fundamental science that leads both to new ways of designing vaccines and of delivering them...
more effectively needs increased support. Secondly, transition of new discoveries in the laboratory into practical vaccines needs to be accelerated. Thirdly, mechanisms need to be developed which make existing vaccines, and the increasing number of new vaccines on the horizon, available to those who need them most, ensuring that every child is reached and that vaccination provides protection for life and not just during childhood. Each of these topics was considered at a Royal Society discussion meeting, ‘New vaccines for global health’, held in London on 15 and 16 November 2010 and at a subsequent satellite meeting, ‘Accelerating vaccine development’, held at the Kavli Royal Society International Centre on 17 and 18 November 2010. Papers based on presentations at the discussion meeting and a summary of the main conclusions of the satellite meeting are presented in this issue of Philosophical Transactions of the Royal Society B, beginning with this paper which introduces some of the topics covered in more detail later in the issue.

2. DESIGN AND DEVELOPMENT OF NEW VACCINES
(a) Introduction
Development of the earliest generation of vaccines, following on the example of Jenner, was to some extent empirical and involved the use of whole killed organisms, attenuated organisms or inactivated toxins, and took place in the absence of any detailed understanding of how the vaccines worked. Development of new vaccines can now take advantage of a much greater knowledge of the complexities of the immune system and of the development of powerful molecular techniques that allow targeted changes to be made in pathogenic organisms and in experimental hosts. Vaccine development has become much more sophisticated with immunologists working closely with molecular biologists and chemical engineers to design and produce highly purified vaccines that are safe, consistently manufactured and effective. However, it is thought provoking that some of the older approaches to vaccine development, such as use of whole, attenuated organisms, are being explored once again despite major advances in immunology and molecular biology, for example, in the development of new vaccines against Streptococcus pneumoniae [3] and Plasmodium falciparum [4].

Several of the newer approaches to vaccine development were reviewed during the course of the discussion meeting, including DNA vaccines [5], vaccines based on antigens expressed in viral vectors [6] and those developed through a process known as reverse vaccinology [7]. It is remarkable that injection of DNA from a pathogen into a mammalian host can lead to incorporation of foreign DNA into the genome of host cells, with subsequent expression by host cells of the foreign antigen which then acts as a vaccine. Initial experiments with this approach in experimental animals gave encouraging results. Results in man have not been so encouraging, in part because of problems in finding a suitable delivery system to generate strong immune responses and in part because of long-term safety concerns. Although the DNA approach is still being considered as a potential way of developing vaccines against cancer and some non-communicable diseases [5], it has largely fallen out of favour as a way of developing vaccines against infectious agents in man.

The use of viral vectors to express a vaccine antigen has generally been a more successful approach in the development of human vaccines than the use of DNA. A number of viral vectors have been used including modified vaccinia virus, fowlpox and human and chimpanzee adenoviruses. Use of chimpanzee rather than human adenoviruses has the advantage that fewer vaccine recipients have neutralizing antibodies against the viral vector than when human adenoviruses are used. Viral vectored vaccines appear to work best when two different viral vectors are used in sequence or when a protein antigen is given after the vectored vaccine, an approach known as prime boost immunization. Prime boost immunization has been used successfully to develop candidate malaria vaccines [6] and is being used increasingly to develop vaccines against other pathogens.

Reverse vaccinology is the term used to describe the process by which selection of potential candidates for vaccine development is made at the genetic rather than at the protein level [7]. Genes are selected on the basis that they are likely to lead to the expression of a protein that has characteristics desirable in a vaccine candidate antigen, for example, expression on the surface of a pathogen. Once selection of candidate genes has been made, these are introduced into a suitable expression system and the immunogenicity of the expressed proteins is studied in experimental animals. Screening of a large number of proteins is facilitated when there is an immunological assay that is known to reflect protective immunity in the host, such as a bactericidal assay. This approach to vaccine development has been used to develop a serogroup B Neisseria meningitidis vaccine now being evaluated in a large-scale clinical trials [8], and is being explored as a potential way of developing vaccines against a number of other organisms including S. pneumoniae.

Incorporation of an adjuvant which boosts the immune response has been the key to the development of several successful vaccines. Use of an adjuvant may convert a vaccine candidate antigen from one that gives too weak an immune response to be useful to one that induces a strong enough response to provide clinical protection. The malaria vaccine candidate RTS,S provides a good example of this phenomenon [9]. This vaccine, based on the P. falciparum sporozoite antigen circumsporozoite protein (CSP), was successful in providing protection against clinical malaria only when it was combined with a powerful adjuvant (AS02 or AS01). Powerful adjuvants have also been essential to the success of other vaccines, including therapeutic cancer vaccines. Use of an adjuvant may allow the dose of antigen in the vaccine to be reduced [10], an important consideration in times of potential vaccine shortage as during the 2009/2010 influenza pandemic.

Despite their importance to vaccine development, only a few adjuvants are licensed for clinical use and development of new, safe and effective adjuvants is an important part of vaccine research [11]. How even widely used adjuvants achieve their effect is still
only partially understood although, in most cases, an important mode of action is likely to involve facilitation of effective presentation of antigen by antigen presenting cells to T cells through the activation of co-stimulatory molecules that form part of the innate immune system. Toll-like receptors (TLRs) are the most extensively studied family of innate receptors that sense microbial products and amplify immune responses. The TLR family is complex, comprising at least 10 different receptors which each responds to a distinct range of activators as described in the paper by Akira [12]. Other important receptor systems present on antigen presenting cells include RNA helicases, activated by viral RNA, and NOD-like receptors (NLRs) activated by bacterial products. A wide range of receptors are now recognized, activation of which can lead to an enhanced helpful, or harmful, immune responses. Knowledge of the characteristics of each receptor and its activation pathway, and of the consequences of its activation provides opportunities for modulating the immune response in a way that ensures that an antigen induces a protective and not a harmful immune response.

Research is needed not only on the development of new vaccines but also on ways of delivering them. Development of non-reusable syringes for vaccination has cut down the risk of vaccination-related transmission of infection, once a major concern in developing countries and one that is still a challenge. However, it would be more convenient if vaccines that currently need to be given by an injection with a needle and syringe could be given in an alternative way, and methods of doing this are being explored using skin patches and micro-needles and administration via inhalation [13]. Research is also taking place into ways of making vaccines more thermostable, reducing the need for a cold chain for their storage and delivery [14].

(b) Vaccines and infectious diseases

Three major infectious diseases have attracted special attention from the international public health community during the past decade—HIV, malaria and tuberculosis—and major efforts have been made to develop effective vaccines against each of these infections.

(i) HIV

Initial optimism that advances in molecular biology would lead to the rapid development of safe and effective HIV vaccines has been dashed. Although success has been achieved in animal models, only one of many trials conducted in man has given any suggestion of protection [15]. This has been the case despite a massive investment in HIV vaccine research which has resulted in the development of candidate vaccines inducing humoral or cellular immune responses to several viral antigens. A major reason for the failure of these first generation vaccines is the extraordinary ability of the HIV to mutate its key surface proteins involved in binding to host cell receptors. Thus, any highly effective HIV vaccine must be able to induce an immune response that provides protection against each of these mutant strains.

The disappointing efficacy of HIV vaccines evaluated so far has led to a return to the laboratory and renewed attempts to define in more detail the antigenic structure and potential variability of key HIV proteins and the immune responses that they induce, research described in the paper by Nabel and colleagues [16]. It has been shown that a minority of individuals infected with HIV develop antibodies that neutralize HIV across strains and it has been possible to produce a few monoclonal antibodies which possess this property and to study their specificity. This work, combined with improved knowledge of the structure at the atomic level of key HIV proteins, should help in the rational design of HIV vaccines that provide cross-strain protection.

(ii) Malaria

Residents of endemic areas who are exposed repeatedly to malaria infection develop some protective immunity but this is never complete. The mechanisms that underlie naturally acquired immunity to malaria are still not fully understood but it is probable that both humoral and cellular immune mechanisms are involved and this knowledge has influenced approaches to malaria vaccine design as described in the paper by Hill [17]. Vaccines are being developed that induce immune responses against sporozoites injected by an infected mosquito before or during their development in the liver (pre-erythrocytic vaccines), against parasites while they are within or transiting between host red blood cells (erythrocytic vaccines) or against the sexual stages of the parasite present either in the blood of the host or in the gut of a mosquito (transmission blocking vaccines). Vaccines that block transmission are receiving increasing attention as they are likely to play an important role in malaria elimination, which is becoming more feasible in some areas [18].

RTS,S is currently the most advanced malaria vaccine candidate [9]. RTS,S has given a 30–50% protection against clinical attacks of malaria in initial clinical trials and it is now being tested in a large phase 3 trial involving more than 15 000 children in Africa. RTS,S induces a very strong antibody response to the CSP antigen of P. falciparum when given with a powerful adjuvant and this antibody is thought to play an important role in protection as some correlation has been found between antibody titre following vaccination and the degree of protection against clinical malaria in individual vaccine recipients.

A different approach to the development of a pre-erythrocytic malaria vaccine is being followed by other groups including the Jenner Institute, Oxford, with a focus on the development of vaccines which induce primarily cellular immune responses [17]. This has been achieved using viral vectors to deliver the antigen thrombospondin-related adhesion protein (TRAP) which, like CSP, is found on the surface of sporozoites. Several viral vectors have been tried including fowlpox, modified vaccinia virus Ankara (MVA) and a chimpanzee adenovirus. Viral vectored malaria vaccines have given substantial protection in volunteers challenged experimentally with malaria but they have not yet achieved success in the field. The viral vector approach is also being used to develop vaccines against blood and sexual stages of
the parasite with successful induction of both humoral and cellular immune responses [17].

Several other approaches to malaria vaccine development are being tried including DNA vaccines, peptides and parasites attenuated by radiation or mutation. It is probable that to achieve very high levels of protection, malaria vaccines will need to contain a combination of antigens and perhaps a mixture of antigens that induce immune responses against more than one stage of the parasite’s life cycle.

(iii) Tuberculosis
A vaccine against tuberculosis, an attenuated strain of Mycobacterium bovis—bacillus Calmette–Guérin (BCG), has been available for 90 years, but BCG induces only limited protection which varies in degree from country to country. BCG protects best against tuberculosis that has spread from the lungs to other organs but provides little protection against more prevalent pulmonary tuberculosis. Thus, although millions of doses of BCG are given to newborn babies across the developing world each year, it is an inadequate tool to control tuberculosis. This is now experiencing a resurgence as a consequence of the HIV epidemic, causing nearly two million deaths each year, predominantly in the developing world [19]. New and more effective anti-tuberculosis vaccines are needed urgently.

Two main approaches to the development of new tuberculosis vaccines are being explored, development of an improved BCG vaccine and development of a vaccine that boosts the immune response induced by BCG, as described in the paper by McShane [20]. Two ways of developing a more effective BCG vaccine are being investigated. One involves genetic manipulation of the bacterium to increase its expression of a 30 kDa secretory antigen which is thought to play a key role in the induction of the protective immune response induced by BCG. The second approach involves incorporation of a bacteriolysin gene from Listeria monocytogenes into BCG. This may result in the self destruction of BCG when ingested by host macrophages, releasing BCG antigens into the cell cytoplasm and enhancing the immune response [21].

Several approaches are being explored to develop a vaccine to boost the immune response induced by BCG. A vaccine called MTB 72F, developed by GlaxoSmithKline, comprises two protein antigens given with a powerful adjuvant; this vaccine is in early phase 2 clinical trials, as is an adenovirus-based vaccine developed by Crucell. Another vaccine, developed at the Jenner Institute, Oxford, is based on the 85A antigen of Mycobacterium tuberculosis expressed in the viral vector MVA. Initial trials showed that this vaccine is safe and immunogenic in young children and HIV positive subjects, key target groups, and the vaccine is now being evaluated in a large efficacy trial in South African infants [22]. This vaccine is also being tested in cattle as tuberculosis in cattle remains an important veterinary problem in many countries, including the UK.

(iv) Pneumococcal disease
Pneumonia is the most important cause of death in childhood, killing around two million children each year, mostly in the developing world [1]. S. pneumoniae, the pneumococcus, is the most important cause of pneumonia in children [23]. Thus, the development of pneumococcal polysaccharide/protein conjugate vaccines that are effective in young children has been a major step forward in reducing global child mortality. Virulent pneumococci possess a capsule which is composed of one of more than 90 different polysaccharides, each of which induces a specific immune response. Thus, pneumococcal conjugate vaccines must contain a sufficient number of individual components to provide protection against the majority of disease-causing pneumococcal strains circulating in the target population. The first pneumococcal conjugate vaccine to be licensed (Prevenar) contains seven polysaccharides conjugated to the protein CRM197. Second generation vaccines contain 10 or 13 conjugates.

Incorporation of pneumococcal conjugate vaccines into routine infant immunization programmes in the USA and elsewhere has provided a great deal of new information about the biology and epidemiology of pneumococcal infection, information which is reviewed in the paper by Klugman [24]. In the United States, Prevenar has protected not only the infants who received the vaccine but also their adults, and especially their elderly contacts by preventing nasopharyngeal carriage and thus stopping transmission, a dramatic example of the induction of herd immunity by vaccination. However, in some communities, including the UK, deployment of Prevenar has led to an increase in the incidence of invasive pneumococcal disease caused by pneumococci of non-vaccine serotypes, a phenomenon known as serotype replacement, and this has eroded some of the gains made by the prevention of disease caused by vaccine serotypes. The recent development of vaccines containing 10 and 13 conjugates is a step towards overcoming this problem but one that may be only a temporary solution. Alternative approaches are, therefore, being explored, including the development of vaccines based on proteins found in all pneumococcal serogroups.

Study of the impact of pneumococcal conjugate vaccines on respiratory disease has provided new evidence to support the old idea that emerged from experience during previous influenza pandemics that many deaths from influenza are due to co-infection with the pneumococcus [25].

(v) Influenza
Influenza viruses possess two dominant proteins, a neuraminidase and haemagglutinin which facilitate invasion of cells of the respiratory tract. These proteins are polymorphic and viruses possess one of a number of different variants of each. Major new strains of virus may emerge as a result of recombination (antigenic shift) with smaller changes occurring from year to year (antigenic drift). Variant strains differ in their ability to infect man and in the pattern of disease that they cause. The current strain of avian flu (H5N1) is not highly transmissible in humans but has the potential to cause a very serious illness with a high mortality rate when it does. The recent variant of swine flu (H1N1) is not especially virulent but causes serious illness in younger subjects more frequently than do the

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influenza strains that have circulated in industrialized countries in recent years. In temperate climates, influenza occurs as regular seasonal outbreaks interspersed with periodic large epidemics associated with the emergence of a new strain.

Although variations in the incidence of seasonal influenza occur from year to year, planning for vaccination against this form of influenza is relatively straightforward with vaccination being offered each year to at risk groups, including the elderly, as described in the paper by Osterhaus [26]. Either inactivated vaccine given by injection or attenuated vaccine given intranasally can be used. On the basis of results obtained through an extensive surveillance network, an informed guess is made as to which influenza strains are likely to be circulating in the following influenza season and vaccines are made accordingly so that they are available for implementation prior to the seasonal outbreak. Vaccination against pandemic influenza is much more challenging as it is not known when new strains will emerge and production capacity and funding may not be sufficient to provide an appropriate vaccine for all those at risk.

In an attempt to overcome the problem of antigenic shift and drift, research is being undertaken on the development of flu vaccines containing conserved internal antigens such as the nucleoprotein or matrix protein antigens [27]. Using a viral vectored system, strong T cells’ responses have been obtained with a nucleoprotein plus matrix protein vaccine expressed in an MVA vector which may provide some cross-strain protection.

Influenza vaccines are used widely in the poultry industry and so development of influenza vaccines is an important area where work on veterinary and human vaccines can interact productively.

(vi) Vaccines against enteric infections

Acute gastrointestinal infections vie with pneumonia as the most important cause of death in children in the developing world [1]. Cholera is endemic in South East Asia and in parts of Africa and regularly causes major epidemics. Salmonella typhi and related bacteria are major causes of severe illness, especially in Asia, and non-typhoidal salmonella infection is an important cause of severe illness in children and HIV-infected adults in Africa.

Vaccines against enteric bacterial infections, including typhoid and cholera, have been available for many years but their use has been restricted largely to tourists and travellers and they have been little used in developing countries where they would be of most value. The paper by Clemens [28] reviews some of the reasons why this has been the case. However, as a result of recent epidemiological studies, there is increasing recognition of the high burden of disease attributable to bacterial enteric infections and of the role that more widespread deployment of these vaccines could play in improving health, especially in Asia.

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vaccines that have been developed against these viruses can play an important role in reducing the increasing burden of cancer in the developing world. There are many strains of HPV but, fortunately, only a few appear to play an important role in the causation of cervical cancer so that the currently available HPV vaccines are likely to be highly effective in preventing this cancer [34].

The aim of therapeutic anti-cancer vaccines is to enhance the naturally occurring host immune responses that are able to contain many cancers, the importance of which is illustrated by the increased risk of cancer in individuals who are immunosuppressed as the result of an infection such as HIV or administration of immunosuppressive drugs [33]. Cancer vaccines must be targeted at an antigen expressed by a particular cancer and thus may need to be somewhat patient specific. They also need to induce an immune response that overcomes self-tolerance mechanisms and the immunomodulating effect induced by cancer in an attempt to enhance its survival. Achieving the latter has usually required the use of powerful adjuvants. Although there are many examples of transitory success in a few patients as a result of anti-cancer vaccination, only one anti-cancer vaccine has so far been licensed in the USA (Provenge), a vaccine against prostate cancer which targets the enzyme prostatic acid phosphatase [35]. Therapeutic anti-cancer vaccines, especially if they have to be individualized, are likely to remain very expensive and thus have to have a limited impact on the overall global impact of cancer. In contrast, vaccines directed at the causes of these cancers have the potential to make a major contribution to improvements in global health.

(ii) Chronic non-infectious diseases
Vaccination has, so far, been targeted primarily at children but there is increasing interest in the possibility of using vaccination to help in the control of chronic, non-infectious diseases in adults, as discussed in the paper by Bachmann [36]. The rationale underlying this approach is to target one or more of the key biological mediators of these diseases. In the case of hypertension, some preliminary success has been achieved in lowering blood pressure by vaccination with the angiotensin II peptide presented in a virus-like particle vaccine construct [37] and similar approaches are being explored in diabetes.

Smoking is an important risk factor for cardiovascular disease as well as cancer, and vaccination could play a role in the control of these chronic diseases by helping smokers to overcome their addiction to nicotine. High titres of anti-nicotine antibodies can be induced by vaccination with a nicotine peptide expressed in a virus-like particle vaccine. These antibodies prevent nicotine from activating reward centres in the brain and can help smokers to overcome their addiction [38]. The same approach is being explored in the management of other drug addictions.

Although there are many challenges in identifying the right targets and in being able to produce an immune response against them which does not have collateral harmful effects, the use of vaccination to help in the control of various kinds of chronic, non-infectious diseases is likely to gain increasing attention in the coming years and could be especially valuable, if it could be made affordable, in developing countries where the population with diabetes and cardiovascular diseases is exploding and where provision of the detailed care needed to manage these conditions successfully is lacking.

3. IMPLEMENTING NEW VACCINES
Before any new vaccine is introduced into a national immunization programme an important series of discussions is needed as to whether this is a ‘good buy’ and how the investment in a new vaccine will match up with other priorities. Once a decision has been made to introduce a new vaccine, a number of major challenges need to be overcome which are summarized in Box 1.

Box 1. Challenges to the introduction of a new vaccine.

— collection of sufficient information to allow national decision makers to make a rational decision on whether or not to support introduction of the new vaccine
— generation of acceptance by the population at whom the vaccine is targeted that the vaccine is safe and effective
— practical issues related to introduction of the new vaccine into the routine immunization programme
— financing introduction of the new vaccine

(a) Making a choice
Over the past decade, national immunization programmes have been offered several new vaccines or vaccines in new combinations. These new products have generally been introduced first into industrialized countries, next into countries eligible for support from the Global Alliance for Vaccines and Immunization (GAVI), and finally into lower middle income countries. The main driver for introduction has been the availability of resources and there has not been an appropriate, rational process for global priority setting. If countries have to make choices between introducing pneumococcal conjugate or rotavirus vaccine how should they choose one over the other? Should the arbiter be the number of deaths, the numbers of cases, sequelae or economic considerations? If a composite indicator such as a quality adjusted life year (QALY) is used, how sensitive is such an indicator in the poorest countries? In some countries, such as the UK and the USA, cost-effectiveness analysis is used routinely to inform policymaking on vaccine choice. In the UK, if the cost of introducing a new vaccine is less than £30 000 per QALY (£33 000; $45 000), then, under the National Health Service (NHS) Constitution for England (http://www.dh.gov.uk/prod_consum_dh/groups/dh.digitalassets/@dh/@en/@ps/documents/digitalasset/dh_113645.pdf) the government is obliged to fund the new programme. Resources are unlikely to be agreed if the cost per QALY exceeds
this figure. In the USA, cost-effectiveness is consider-
red by the Advisory Committee on Immunization
Practices but there are no fixed criteria that define
acceptability. A second dose of conjugate meningococcal
vaccine was recommended recently in the USA despite
the cost per QALY being around $150,000 (http://
www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-
oct10/02-3-mening-CostEffect.pdf). In this case,
preadiness to pay was more persuasive than the
cost-effective use of resources. If this experience indi-
cates that the public decides on what vaccines should
be provided and how government funds should be
used, how will choices be made and justified when
external resources drive the availability of new vaccines?
The balance between national autonomy and external
benevolence is currently far from clear. Unless some
broadly acceptable rubric for comparing choices is
found, the process of new vaccine introduction is likely
to become even more complex.

(b) Gaining acceptance by ministries of health
The time lag between demonstration of the effectiveness
of hepatitis B and Haemophilus influenzae type b (Hib)
vaccines in industrialized countries and their intro-
duction into the routine immunization programmes of
developing countries, a period of 10–20 years, was unac-
ceptable. To prevent this happening again with other new
vaccines, GAVI was established by WHO, the United
Nations Children’s Fund (UNICEF), the World Bank
and the Bill and Melinda Gates Foundation in 2000 to
make existing and new vaccines more widely available
in the developing world, as described in the papers by
Lob-Levyt [39] and Nossal [40]. GAVI established
two Accelerated Development and Introduction Plans
(ADIPs) to support the introduction of pneumococcal
conjugate and rotavirus vaccines into the national immu-
nization programmes of the developing countries where
these vaccines would be an appropriate intervention.
Subsequently, a similar programme, the Hib Initiative,
was established to support the introduction of Hib con-
jugate vaccine when it was realized that introduction of
this vaccine in developing countries was progressing
too slowly. The primary tasks of these groups were to esti-
mate the burden of these diseases in GAVI eligible
countries, determine whether introduction of these new
vaccines would be cost effective and, if so, demonstrate
how this could best be achieved. The lessons learnt by
the ADIPs and the Hib Initiative on how introduction
of new vaccines can be accelerated are described in the
paper by Hajijeh [41].

Early lessons learnt by the ADIPs and Hib initiative
were that ministers of health (and finance) were more
likely to support introduction of a new vaccine when
there were local data that demonstrated clearly
that the disease in question was an important cause of
serious illness and death in their country. Additional
points on which they needed reassurance were cost,
even though the vaccine might be available to them
through GAVI at a highly subsidized price, and the sus-
tainability of vaccine supply and funding. Other lessons
learnt were the importance of communication between
the wide range of partners involved in the introduction
of a new vaccine and the need for coordination between
these various groups. The Hib Initiative was successful
in its primary objective and 66 of 72 countries eligible for
GAVI support have now adopted Hib vaccination [42].

(c) Gaining acceptance by the public
Introduction of a new vaccine will proceed smoothly
only if it has public acceptance. Resistance to vacci-
nation is a universal phenomenon seen in both
industrialized and developing societies with fears over
mumps, measles, rubella (MMR) safety in the UK
being a prominent example of the former and resist-
ance to polio vaccination in Nigeria an example of
the latter. Anti-vaccine lobbyists are influential
through the involvement of celebrity figures and the
use of an increasing number of professional-appearing
websites in both wealthy and developing countries.
Ways of countering this challenge to the intro-
duction of new vaccines of proven benefit and excellent safety
profile were considered at both the discussion and sat-
ellite meetings and some examples of how this has
been achieved successfully were described. In the
UK, community surveys of children and their parents
helped to identify the age at which HPV vaccination
would be acceptable to both groups and involvement
of girls in the target age group in the design of pro-
motional material contributed to a very successful
national HPV immunization programme [43]. It was
agreed that the scientific community needs to take a
more active role in promoting the value of vaccination
and in countering the often misleading information
provided on anti-vaccine websites. Advocacy for vac-
ination needs to be entirely objective, giving clear
recognition of the considerable benefits of vaccination
and putting into appropriate context the extremely
small risks of any serious outcomes. Advice must be
seen to be free from any influence from vaccine man-
ufacturers and so independent groups such as the
Sabin Vaccine Institute and the Jenner Vaccine Foun-
dation have an important role to play in this arena.

(d) Logistic challenges to introduction of
a new vaccine
Introduction of a new vaccine may bring added stresses
to an already overstretched national immunization pro-
gramme. For example, additional refrigeration capacity
may be needed to store the new vaccine, vaccination
schedules and vaccine records may need to be amended
and staff retrained. The logistic implications of introdu-
cing a new vaccine need to be thought through well
before the planned date of introduction. Introduction of
the pneumococcal conjugate vaccine Prevenar into the
first adopter countries in Africa was delayed because this
vaccine was provided initially in glass syringes which
require high temperature incineration for their safe
destruction, a facility sparsely available in Africa.

(e) Funding of new vaccines
New vaccines are generally more complex than the
ones used in previous immunization programmes,
more difficult to manufacture and hence more expen-
sive. Vaccines costing $40–$50 a dose will not be used
in developing countries. To facilitate the introduction
of new vaccines in poor countries, GAVI subsidizes
their cost in countries with an average national income of less than $1000, covering the difference between the contribution from the national vaccination programme and the costs charged by the manufacturer [39]. GAVI has developed a number of innovative approaches to the funding of vaccines for developing countries including establishing the Innovative Financing Facility for Immunization (IFFMIIm) which raises bonds on the private financial markets which are guaranteed by donors. Another approach towards making new vaccines more affordable has been the establishment of the advanced market commitment which has initially focused on pneumococcal conjugate vaccines [39]. This project has raised over $2 billion for the purchase of pneumococcal conjugate vaccines that meet specified criteria at a lower than market price but one that is still acceptable to the manufacturer and guaranteed over a set period of years. Whether this experiment will work and a similar approach will be used for other new vaccines remains to be seen. The use of innovative funding mechanisms to support the introduction of new vaccines in developing countries has been very successful and the GAVI initiative is credited with saving the lives of at least five million children since it was established 10 years ago.

4. ACCELERATING VACCINE DEVELOPMENT AND DEPLOYMENT

The satellite meeting discussed how development and deployment of new vaccines could be accelerated and a summary of these discussions is provided in the paper by Bregu et al. [44]. A key outcome of the meeting was the recognition that there is no single step that can be taken to radically reduce the time needed to take a new candidate antigen through the complicated process from first identification to licensure (figure 1), but that progress can be made in shortening the overall process by introducing small changes at several individual steps in the pathway. Some of the areas where such changes might be made are summarized in Box 2. The consultative group recognized that no one group has the responsibility for all the steps needed for the development and introduction of a new vaccine and that some forum in which discussions of this kind could take place is needed.

Box 2. Steps that could be taken to accelerate vaccine development.

— increasing the facilities available to academic investigators that would allow production of small batches of vaccine produced to the standards of good manufacturing practice that could be used in clinical trials
— establishing the capacity to move rapidly from the production of one vaccine to another
— improving manufacturing processes
— adopting accelerated approaches to clinical development while not compromising safety, for example, by moving rapidly to target groups
— accelerating regulatory processes
— ensuring that the public is well informed about a new vaccine well before introduction is planned

5. CONCLUSIONS

Considerable progress has been made in the past decade in strengthening immunization programmes across the world and in the development and deployment of new vaccines, many of which will become
available within the next decade as pointed out in the paper by Rappuoli [45]. Acquisition of the ability to produce new vaccines with increasing rapidity will raise new challenges. One of these will be finding the scientists to undertake this work. Currently, many of the scientists who work on vaccine development in academia do so as a sideline to their work as an immunologist, molecular biologist, social scientist or economist. A career as a full time vaccinologist needs to become an attractive option for bright young scientists who are provided with appropriate post graduate training and an opportunity to move to and from between academia and the pharmaceutical industry. A second major challenge to an expanded programme of vaccine development is a financial one. Development of a new vaccine from first concept to a licensed product is an expensive process, perhaps costing as much $500–1000 million. It is estimated that by 2030 there may be as many as 20 vaccines in routine use [40] whose application across the world might cost as much as $20 billion a year, a sum far in excess of the $1–2 billion a year currently available to GAVI [39]. It cannot be expected that donors will contribute all the additional funds required and increasing contributions from recipient countries will be needed.

For many infectious diseases, the ultimate goal of vaccination is eradication, achieved so far for smallpox and rinderpest and potentially in sight for poliomyelitis [40]. Although the last stages of the poliomyelitis eradication campaign have proved technically and logistically more challenging than had been expected initially and although the campaign has already cost about $8 billion, its eventual success will provide encouragement to take on the eradication of other major vaccine preventable infectious diseases with measles probably being the next target.

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REFERENCES


