The contribution of vaccination to global health: past, present and future

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Vaccination has made an enormous contribution to global health. Two major infections, smallpox and rinderpest, have been eradicated. Global coverage of vaccination against many important infectious diseases of childhood has been enhanced dramatically since the creation of WHO’s Expanded Programme of Immunization in 1974 and of the Global Alliance for Vaccination and Immunization in 2000. Polio has almost been eradicated and success in controlling measles makes this infection another potential target for eradication. Despite these successes, approximately 6.6 million children still die each year and about a half of these deaths are caused by infections, including pneumonia and diarrhoea, which could be prevented by vaccination. Enhanced deployment of recently developed pneumococcal conjugate and rotavirus vaccines should, therefore, result in a further decline in childhood mortality. Development of vaccines against more complex infections, such as malaria, tuberculosis and HIV, has been challenging and achievements so far have been modest. Final success against these infections may require combination vaccinations, each component stimulating a different arm of the immune system. In the longer term, vaccines are likely to be used to prevent or modulate the course of some non-infectious diseases. Progress has already been made with therapeutic cancer vaccines and future potential targets include addiction, diabetes, hypertension and Alzheimer’s disease.

1. Introduction

It is often stated that vaccination has made the greatest contribution to global health of any human intervention apart from the introduction of clean water and sanitation, but this is a claim that needs some qualification. Study of the pattern of infectious diseases in industrialized countries from the end of the nineteenth century onwards shows that there was a large and progressive decline in child mortality, owing largely to a reduction in mortality from infectious diseases, prior to the development and deployment of vaccines. This was associated with improvements in housing, nutrition and sanitation. Nevertheless, it is indisputable that vaccination has made an enormous contribution to human and animal health, especially in the developing world. Mortality from smallpox and measles was massive in the pre-vaccination period with up to a half of the population dying from the former during epidemics and measles was only a little less lethal in susceptible populations.

This review describes briefly some of the major past achievements of vaccination, the present situation in relation to the global use of vaccines and some of the ways in which vaccination could contribute to global health in the future.

2. Past contribution of vaccination to global health

(a) Jenner and the eradication of smallpox

The development of vaccination as a public health tool is attributed to Edward Jenner and his experiments with cowpox in 1796 (figure 1), although the practice of variolation using ‘wild’ smallpox virus had been practiced in some countries for much longer [1]. Variolation worked but carried a significant risk of severe disease or even death in the recipient. This risk was reduced dramatically by...
Smallpox is the only human infection to have been eradicated, although eradication of guineaworm infection is close. Eradication of the rinderpest virus, formally recognized by the World Health Organization in 2011, is less widely recognized than eradication of smallpox, but this represents another major milestone in the control of infectious diseases and has been a major contribution to global health [5,6]. Rinderpest, closely related to measles and distemper viruses, can cause high mortality in cattle, impoverishing families in developing countries dependent upon their cattle and making them susceptible to malnutrition and many infectious diseases. Recently, there has been closer interaction between research groups developing human and veterinary vaccines through organizations such as the Jenner Vaccine Institute (www.jenner.ac.uk (accessed 8 November 2013)), a development to be encouraged as common technologies can be applied in each area and some vaccines, for example a tuberculous vaccine, could be used in man and his domestic animals.

(b) The next generation of vaccines

The next human vaccine to be developed using the principle of attenuation was rabies vaccine, developed by Pasteur and first tested in man in 1885, nearly a century after Jenner’s experiments [7]. This vaccine was based on material obtained from infected rabbit brain attenuated by drying, an uncertain process, and vaccines prepared in this way frequently caused serious side effects. Most human rabies vaccines are now based on inactivated virus grown in tissue culture [8]. Acquisition of the ability to grow viruses in tissue culture for an extended period led to the development of attenuated vaccines against measles and poliomyelitis in the 1950s and the 1960s [9]. Subsequently, many other vaccines have been developed using the principle of attenuation, including rubella, influenza, rotavirus, tuberculosis and typhoid vaccines. Vaccines based on attenuated organisms generally induce a strong and sustained immune response, induce more effective immunity at mucosal surfaces than killed vaccines and are usually relatively easy and cheap to make. Because the vaccine components are alive, they can spread to non-vaccinated subjects, extending the impact of vaccination to the community at large (table 1). However, because these vaccines are alive, mutations may occur in the attenuated vaccine strain with a reversion to virulent strains, as seen rarely with oral polio vaccine which causes paralysis in about one in two million recipients, and they may cause significant illness in subjects with impaired immunity, as has been seen with the anti-tuberculosis vaccine bacille Calmette Guérin (BCG) when given to immunodeficient patients, including those with human immunodeficiency virus (HIV) infection [10].

An alternative way of making microorganisms safe for use in a vaccine is to kill them, and at the beginning of the twentieth century a number of vaccines based on killed whole organisms, including the pneumococcus, meningococcus and typhoid bacillus, were developed and used. These vaccines were usually poorly immunogenic and often caused significant side effects (table 1), so that whole-cell vaccines have largely given way to subunit vaccines. However, there has recently been a renewed interest in use of whole-cell vaccines, which have the advantage of presenting multiple antigens, and whole-cell, attenuated pneumococcal [11] and malaria [12,13] vaccines have recently been developed and are being evaluated in clinical trials. The
symptoms and signs of tetanus and diphtheria are caused by soluble toxins produced by the causative bacteria, and at the beginning of the twentieth century anti-toxins were developed to treat and prevent these infections with some success. However, the prevention provided by anti-toxins was only short lived, and in the 1920s it was shown that sustained protection against these infections could be achieved by immunization with a modified toxin (toxoid); these straightforward and safe vaccines are still being used widely today. Tetanus toxoid, diphtheria toxoid and a killed pertussis (whooping cough) vaccine (DPT) was developed in 1931 and remains a key component of infant immunization programmes across the world. In many countries, the original whole-cell pertussis component of DPT has been replaced with a less reactogenic, acellular pertussis component, and DPT is now used widely in combination with hepatitis B and *Haemophilus influenzae* type b (Hib) vaccines, a combination widely known as pentavalent vaccine or ‘penta’.

By the late 1950s, the majority of children in developed countries were receiving routine vaccination with DPT and polio vaccines and, in some countries, vaccination against tuberculosis. Consequently, the incidence of these infections as important public health problems declined substantially, although in the case of pertussis and measles, success has not been complete as outbreaks of these infections still occur in industrialized countries, including the UK, owing to periodic declines in vaccine coverage. These declines in coverage are often a consequence of the activities of an active anti-vaccination lobby, as was the case in the UK following the spurious reports of a link between autism and a combined measles, mumps and rubella vaccine [14]. The measles virus has a high reproductive potential, and a high, sustained level of vaccine coverage is required to interrupt transmission.

By the 1960s, the vast majority of deaths and severe illnesses attributable to the common infectious diseases of childhood preventable by vaccination were occurring in children in the developing world, where coverage with vaccines such as measles was frequently less than 5% and restricted largely to children of the small, wealthy section of the community, the group at least risk of a serious outcome from an infection such as measles. At this time, the early 1960s, about one-third of African children did not reach the age of 5 years and infectious diseases, particularly measles, accounted for a substantial proportion of these deaths. In the face of this challenge, the World Health Organisation (WHO) established the Expanded Programme on Vaccination (EPI) in 1974 to increase the uptake of routine childhood vaccines across the world. This programme has been very successful, with coverage rates of EPI vaccines climbing rapidly from less than 5% to over 80% in many low and low middle-income countries [15]. By the 1980s, coverage with EPI vaccines in many low-income countries was similar to, or even better than, that achieved in many parts of the industrialized world where the infectious diseases of childhood were no longer seen as a significant threat.

The success of the EPI programme was achieved in part because of sound leadership in WHO and in many developing countries, and in part through financial support from the international community. Because EPI vaccines are relatively cheap when mass produced, full immunization of a child cost around $15 in the 1990s. Introduction of effective national EPI programmes in most developing countries has led to major reductions in deaths and hospital admissions from measles and neonatal tetanus. It has been estimated that in 2012 there were about 157 000 deaths from measles (www.who.int/topics/measles (accessed 8 November 2013)), a dramatic decrease from the situation 20 years ago (figure 2) but still an unacceptable burden from a preventable infection. There has also been a dramatic reduction in the number of deaths from neonatal tetanus (over 90% since the 1980s), achieved through routine immunization of mothers attending antenatal clinics with tetanus toxoid, but it is estimated that there were still about 60 000 preventable deaths from this infection in 2012 (www.who.int/topics/tetanus (accessed 8 November 2013)). The impact of vaccination has not been limited to the developing world, and a recent review from the USA [16] estimated that 103 million cases of selected infectious diseases had been prevented by vaccination since 1924.

Work conducted largely in Guinea Bissau, but supported by some studies conducted elsewhere, has shown sex differences in the response to routine EPI vaccines and also suggested that in developing country situations, EPI vaccines have non-specific effects on child mortality independent of their impact on the disease at which they are directed [17]. Much of the information supporting these ideas has come from observational studies because of the difficulty in conducting placebo controlled trials with established vaccines, but a recent randomized trial of BCG given to low birth weight babies showed a significant reduction in neonatal but not in infant mortality [18]. Acceptance of the results of these studies has, until recently, been met with some scepticism because of the lack of an apparent mechanism through
which these effects could be achieved. However, recent animal studies which have shown a sustained epigenetic effect of BCG immunization on monocyte function provide a potential mechanism by which BCG could have an indirect effect against infections other than tuberculosis [19]. Further carefully controlled trials are needed to establish the clinical importance of non-specific vaccine effects, but there are constraints on how these can be conducted ethically. A WHO committee is currently reviewing the topic of non-specific vaccine effects and it is expected that this committee will make some recommendations on how to carry this controversial issue forward.

3. Current challenges for global immunization

Current challenges in ensuring that currently available vaccines achieve their maximum impact on global health include enhancing the uptake of the old ‘EPI’ vaccines even further than achieved so far, eradication of polio and introduction of recently developed vaccines into the routine immunization of low- and middle-income countries, where they are likely to achieve their maximum impact.

(a) Enhancing uptake of current vaccines

Although coverage with the initial package of routine infant vaccines (BCG, DPT, measles and polio) is now as high in many low- and middle-income countries as it is in the industrialized world (table 2), pockets remain where this is not the case, often among the poorest and most vulnerable sections of the community. Many further lives could be saved by reaching these populations with routine EPI vaccines such as measles. Finding better ways of reaching these groups, who account for an increasing proportion of child morbidity and mortality in many developing countries, with appropriate health interventions is likely to be a key target of the post-2015 development goals. Methods being explored include gaining a better understanding of why these communities or individuals are resistant to vaccination, making vaccination more accessible through home visits and using mobile phone technologies for reminders and data collection.

However, more operational research is needed on how to help these vulnerable groups [20].

Handling sensitively the issue of vaccine safety is a key factor in ensuring high vaccine uptake. All vaccines have side effects in a small proportion of vaccine recipients and that needs to be acknowledged while at the same time stressing the benefits that accrue from vaccination. Recently developed rotavirus vaccines provide a good example of this principle. Both widely used rotavirus vaccines cause the serious condition of intussusception in a small proportion of vaccine recipients, perhaps one to five additional episodes per 100 000 vaccines, an acceptable risk considering the major reduction in hospital admissions and deaths achieved with these vaccines [21].

The issue of true vaccine side effects needs to be separated from incorrect claims such as the reported association between MMR vaccine and autism [14], and such false claims vigorously rebutted.

(b) Eradication of poliomyelitis

In 1988, the World Health Assembly made a decision to support the eradication of poliomyelitis with an initial target date of 2000. However, eradication of polio has proved to be a more challenging task than had been envisaged originally; the target date for eradication has had to be extended on several occasions and this is now 2014/2015 (www.polioeradication.org (accessed 15 February 2014)). One of the three serotypes of polio virus (type 2) has been eradicated, and this is probably also the case for serotype 3, but serotype 1 has proved more stubborn and this virus continues to circulate in three countries (Nigeria, Pakistan and Afghanistan) with periodic spread to other countries including Chad, Somalia and recently Syria (figure 3) [22]. Nevertheless, there has been a 99.9% drop in the number of polio cases since the start of the eradication programme and in 2013 only 400 cases were reported. Reaching the final goal of eradication of the last polio virus faces a number of challenges—technical, financial and social. Routinely used oral polio vaccines contain viruses belonging to each of the three serotypes and this can lead to an unbalanced immune response directed predominantly at one or two of the serotypes. This problem has been overcome by the development and deployment.
of bivalent and monovalent serotype 1 vaccines. The polio eradication programme has been expensive, both financially and in the use of scarce human resources. Currently, the campaign costs about $1 billion a year, provided largely by international donors and foundations, including the Bill & Melinda Gates Foundation and the Rotary Club which have both made major contributions to the campaign. Currently, there are no signs of a lack of intent among the international donors to pursue the campaign through to a successful conclusion but expenditure on a single infection at this level could not be sustained indefinitely. Finally, there is the challenge of resistance to vaccination in some countries, especially Nigeria and Pakistan, where this has been sufficiently extreme to lead to the murder of health workers. It would be a tragedy if the polio eradication campaign failed at this point, not only because of the resurgence in cases that would inevitably follow, but also because of the negative effect that this might have on international support for global health issues overall. Recent success in eliminating all wild polio viruses from India provides grounds for optimism. If the wild virus is eradicated successfully in 2014 or 2015, then a decision will be needed on when to stop immunization with oral polio vaccine virus which can, very rarely, mutate to a more virulent virus causing paralysis. Some countries may decide to use the more expensive killed polio vaccine for a few years until all vaccine type polio viruses have disappeared [23].

(c) Introduction of newer vaccines
Since the establishment of the global EPI programme in 1974, a number of new vaccines has been introduced into routine use

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### Table 2. Vaccine coverage (percentage) by WHO region, 2012 (data from [15]). BCG, bacille Calmette Guérin vaccine; DTP3, three doses of diphtheria, tetanus, pertussis vaccine; MCV1, at least one dose of measles vaccine; HepB3, three doses of hepatitis B vaccine; Hib3, three doses of Haemophilus influenzae type b vaccine; rotavirus, received the last dose of the recommended rotavirus series of immunizations; PCV3, three doses of a pneumococcal conjugate vaccine.

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Figure 3. Cases of paralytic poliomyelitis in 2013 (www.polioeradication.org (accessed 15 February 2014)). (Online version in colour.)
in industrialized countries including hepatitis B, *Haemophilus influenzae* serotype b (Hib), pneumococcal and meningococcal polysaccharide/protein conjugate, rotavirus and human papilloma virus (HPV) vaccines. Uptake of these vaccines in the developing world has generally been slow despite their proven efficacy and a high burden from many of the diseases that they could prevent. Uptake of hepatitis B vaccine into the routine EPI of developing countries in Africa and Asia took over 20 years, despite the fact that the hepatitis B virus is a major cause of liver cancer in many parts of sub-Saharan Africa and parts of Southeast Asia. This delay was due in part to the initial high cost of the vaccine but also to difficulty in persuading health officials and communities to accept vaccination of a child for a potential benefit that would not become apparent for 30 or 40 years. Coverage with hepatitis B vaccine now approaches 80% at the global level and its uptake has been facilitated by a fall in cost and its incorporation into the pentavalent vaccine described above.

Pneumonia and diarrhoea still account for a high proportion of deaths and severe disease in children in the developing world (figure 4) [24]. The most frequent cause of severe pneumonia in children is *Streptococcus pneumoniae* (the pneumococcus), followed by Hib, while rotavirus is the most frequent cause of severe diarrhoea. Thus, the development of effective vaccines against the pneumococcus and rotavirus [25,26] and their incorporation into the EPI programmes of countries with a high child mortality should result in a further major reduction in childhood deaths. Whether pneumococcal conjugate and rotavirus vaccines in developing countries will have the dramatic effect on non-vaccinated subjects observed in industrialized countries, through the induction of herd immunity, remains to be seen. Incorporation of these vaccines in the routine immunization programmes of the developing world countries, where they could have their greatest impact, has faced a number of challenges. Firstly, these vaccines are more difficult to produce than the first generation of paediatric vaccine (pneumococcal conjugate vaccines contain 10 or 13 different components) and they are consequently more expensive to produce. Secondly, much less was known by the target populations about the infections that these vaccines prevent than had been the case for measles or poliomyelitis. To address the first issue, the Global Alliance for Vaccines and Immunization (GAVI) (www.gavialliance.org (accessed 8 November 2013)), established in 2000, has obtained substantial support from international donors, currently over $1 billion per year, enabling the organization to subsidize the costs of these new vaccines for countries with a GDP of less than $1550 and to provide support for improvements in vaccine delivery programmes. Introduction of pneumococcal conjugate vaccines has also benefited from another novel funding process, the Advanced Market Commitment, which has attracted substantial funds from a number of major donors.

To assist potential recipient countries in an appreciation of the value to their communities of introducing these new vaccines, GAVI established three special interest groups, the pneumococcal and rotavirus Accelerated Development and Introduction Plans (ADIPs) and the Hib Initiative. These groups, based in academic institutions but working closely with Ministries of Health and Finance, non-governmental agencies and the pharmaceutical industry, helped to generate local information on the burden of disease by providing education to all sectors of the community on the importance of the infection in question and, in some cases, undertaking detailed epidemiological studies and even vaccine trials [27]. They also assisted in negotiations with the pharmaceutical industry over pricing arrangements. As a result of the activities of these groups and others, Hib and pneumococcal conjugate vaccines have been introduced more rapidly into countries with a high child mortality than was the case for hepatitis B vaccine (figure 5). Currently, 30 and 15 of the 56 GAVI eligible countries have introduced pneumococcal conjugate and rotavirus vaccines, respectively (www.gavialliance.org (accessed 8 November 2013)). A number of GAVI eligible countries are making good economic progress and will soon move above the GDP level that makes them eligible for GAVI support. Finding ways of supporting routine immunization in these countries as they become lower middle-income countries will be a challenge—use of a tiered pricing system and mass purchasing are two of the options that are being explored.

The vaccination schedule currently used in the majority of developing countries was developed, largely empirically, when there was only a limited number of vaccines in the routine immunization schedule and when it was considered that vaccines should all be given in the first year of life when clinic attendance is highest. However, as more and more vaccines are added to the immunization schedule, this approach has had to be reviewed because of the potential for immunological interference between vaccines when given together and because the immunization schedule developed for the original EPI vaccine may not be the one that will give the best immune response for a number of the recently developed vaccines. Thus, it is likely that more frequent attendances at a vaccination clinic will be needed and that vaccination of children will need to extend into the second year of life, as is already the case in many industrialized countries. Because vaccination responses, as well as the epidemiology of many infectious diseases, can vary significantly between populations, immunization schedules need to be designed to meet local needs and a ‘one-size fits all’ approach is no longer appropriate.

Vaccination programmes in the developing world focused initially on prevention of potentially lethal infections in young children because of the high burden of mortality in this age group. However, there is increasing recognition that the public health benefits provided by vaccination are
not restricted to the first year of life but are much broader, for example the prevention of cancer in adults through the immunization of older children with HPV vaccine [28] and immunization of older children and young adults against meningococcal disease in the African meningitis belt through mass campaigns [29].

4. The next generation of vaccines

(a) Developing the new vaccines

Developing the next generation of vaccines will be increasingly challenging as many of the organisms at which they are targeted have complex structures and life cycles, for example the malaria parasite, or are very effective at outwitting the human immune response through antigenic diversity, such as HIV and influenza viruses. Development of new vaccines against other important infectious disease targets such as dengue or novel corona viruses should be easier using established technologies but the modest efficacy of a recently tested dengue vaccine [30] emphasizes that challenges remain even in the development of more conventional vaccines. The limited success obtained with the most promising malaria vaccine RTS,S/AS01 [31,32] and with a prime boost HIV vaccine regimen [33] and the failure of a new tuberculosis vaccine [34] illustrate how challenging developing effective vaccines against these important infections will be. However, many novel approaches to the development of new vaccines are being explored [35–37], for example use of attenuated whole organisms (as described earlier), reverse vaccinology, which identifies potential candidate antigens through interrogation of the genome, and detailed structural studies, which are helping to define the antigenic determinants that might be able to induce an immune response that would be effective across strains of highly variable organisms such as influenza and HIV viruses. Additional approaches that are being explored are production of novel particles, and the use of RNA instead of DNA to induce an immune response. Nevertheless, it seems likely that for complex infectious agents, such as malaria, a combination of different antigens and/or vaccine formulations will be needed to provide a high level of protection, for example combination of a component that induces a strong antibody response with one that induces a strong CD4 or CD8 T cell response. New adjuvants directed at improving the immune response are being tried and the success of the RTS,S vaccine [31,32] is due in large part to the use of the powerful adjuvant AS01. Better methods of preserving vaccines at ambient temperature are being developed [38] and alternative delivery systems including needle-less devices are being explored [39], both of which could facilitate uptake of vaccines in hard to reach areas.

(b) Financing the development of new vaccines

Table 3 indicates some of the organisms that are currently the target of vaccine research; recent and continuing technical advances should make it technically possible to develop effective vaccines against most of these pathogens. However, whether all these vaccines will prove cost effective or be used widely enough to provide a sufficient financial return to the manufacturer is uncertain, as illustrated by the recent case of a serogroup B meningococcal vaccine developed using an innovative technical approach but whose deployment in the UK is being queried on the grounds of cost effectiveness [40].

It has, until recently, been the usual practice to have a standard national vaccination policy implemented country-wide. However, as vaccination programmes include an increasing number of vaccines and more complex schedules, targeted vaccination programmes based on a sound local knowledge may become an important way of improving efficiency and reducing costs. For example, in Nigeria, with its large population, the new serogroup A meningococcal conjugate is being deployed only in the states that are known to be at risk of epidemics.

Developing a new vaccine to the high standards required is expensive and new vaccines are bound to be costly until these recovery costs have been paid off. However, once
research and development costs have been recouped through the sale of the vaccine at an appropriate price in industrialized countries and sale volume has been increased through adoption of the vaccine in developing countries with their large populations, experience has shown that the costs of a vaccine fall, a fall sometimes aided by vaccine manufacture in a developing country.

5. The long-term future of vaccination

It is probable that effective vaccines will be developed against the major infections such as HIV, TB and malaria, although it is difficult to predict how long this will take, and that eventually these infections will cease to be a major public health priority even if they cannot be eradicated completely. Ensuring the maximum benefit that vaccination can provide against infectious diseases will be achieved only if there is global, high-level surveillance to detect the emergence of new potentially dangerous infections and also to detect the emergence of strains resistant to the vaccines in routine use as quickly as possible so that countermeasures can be put into place.

As the incidence of infectious diseases declines and living standards improve across the developing world, many developing countries are entering a transition phase in which they have a residual challenge from infectious diseases, such as HIV and tuberculosis, while at the same time experiencing major challenges from emerging non-infectious diseases such as diabetes, cardiovascular disease and cancer. Could vaccination have a role to play in ameliorating this increasing global burden of non-infectious diseases? Prevention of a substantial proportion of liver and cervical cancers should be achievable by ensuring universal hepatitis B and HPV vaccination, and prevention of some stomach and nasopharyngeal cancers might be possible in communities where there is a high risk of these cancers by vaccination against _Helicobacter pylori_ and Epstein Barr virus infections, respectively. Vaccination to prolong survival from other cancers, as recently demonstrated for prostate cancer, may become practicable, but highly personalized cancer immunotherapy is likely to be too expensive for universal use in even middle-income countries [41].

Management of chronic conditions such as diabetes and hypertension is difficult in communities with limited access to healthcare and it is possible that vaccination against these conditions could help by reducing the need for frequent contacts with the health system, although there is much work to be done before this approach could become a practical reality. Some progress is being made in developing vaccines which modulate the course of diabetes and hypertension [42]. Vaccination against addiction, including smoking, is also feasible, although very high antibody concentrations are required to achieve an effect [43], and there are early results suggesting that vaccination against Alzheimer’s disease might slow the progress of this condition [44]. In the coming decades, vaccination is likely to expand its scope beyond prevention of the common infections of childhood which has been its main success so far.

6. Conclusion

Vaccination has achieved much since the original work of Jenner 200 years ago, and many new vaccines are likely to be developed within the next decade, including some directed at non-infectious diseases. Which of these new vaccines are cost effective and affordable is likely to generate much debate. New vaccines will be more expensive than the vaccines whose developmental costs have been met, and this is likely to pose a major challenge to developing countries where many of these vaccines could be of most use. Currently, it is envisaged that the enhanced costs of an expanded national programme of immunization will be met through international aid, primarily through GAVI, but a number of developing countries, including some in sub-Saharan Africa, are making substantial economic progress so that they are, or shortly will be, no longer eligible for GAVI support. Although methods are being developed to facilitate this transition, existing and new lower middle-income countries are likely to be required to make a greater contribution to the costs of their national vaccination programme than is currently the case. There is no better way in which national revenue could be spent.
References