Vaccine development has played a hugely important role in combating infectious disease. Despite this success, there is still a great need for new vaccines and these are emerging far more slowly than we would wish. Despite the massive expansion in understanding of immune responses to infection, research is often hindered by a lack of understanding of the immune responses required specifically for protection, or by a lack of approved adjuvants and delivery systems to induce the required responses. In addition, the financial commitment required to license new vaccines is significant, and the more lucrative markets are often not those with the greatest need. In this review, we discuss many of the hurdles that new vaccines must overcome in order to reduce morbidity and mortality, and some of the initiatives that are being attempted to supply new vaccines to those that need them most.

**The immunological challenges**

Vaccine development has played a hugely important role in combating infectious disease. The successful eradication of smallpox (worldwide cases reduced from 2 million per year in 1959 to zero in 1978) (Enserink, 2010), and estimated avoidance of 2.5 million deaths per year from diphtheria, tetanus, whooping cough and measles through immunization (WHO/UNICEF, 2010), exemplify their power and significance for global health. Despite this success, there is still a great need for new vaccines and these are emerging far more slowly than we would wish. Most of our current vaccines were developed by determining the components that consistently stimulated antibody responses in infected patients, and often without having a very detailed knowledge of the immune mechanisms required for protection. A large number of vaccines were simply formulated with aluminium hydroxide as the adjuvant and are administered by injection. Clearly such approaches have been effective in many cases, but unfortunately proved to be completely inadequate for several important pathogens. The problems are gradually being overcome, as new vaccines continue to appear on the market; however, the scientific and financial challenges are considerable. This article will discuss some of the outstanding issues and barriers for successful vaccine development; priorities for overcoming these barriers are listed in Table 1.

There is broad agreement that development of new and effective vaccine products cannot proceed without a detailed understanding of the immune correlates of protection. This provides essential information for rational vaccine design, and also guides the parameters to be measured when evaluating vaccine efficacy. Gathering such data is usually dependent upon having material from patients, for example those who have recovered from a natural infection, and the availability of an animal model which responds to the infection and the vaccine formulation in a very similar manner to humans. Where these are lacking, vaccine development is considerably more problematic, and this has too often led to disappointing clinical trials results or even serious safety concerns. For example, a trial of an intranasally administered influenza vaccine, containing the heat-labile enterotoxin from enterotoxigenic *Escherichia coli* as a mucosal adjuvant, resulted in some participants developing Bell’s palsy despite a strong track record of safety in animal models (Mutsch *et al.*, 2004).

The immunodominant antigens recognized, and the mechanisms of protective immunity exhibited in animal models such as mice, guinea pigs and rabbits, may differ considerably from humans (Dannenberg, 2010). A very common model employed in vaccine development is the mouse, yet its immune system is known to differ quite radically from that of humans (Mestas & Hughes, 2004). For example, the innate immune sensing of infectious organisms via Toll-like receptors (TLRs) differs. The expression of TLRs on immune cells such as dendritic cells, which strongly dictate the type of immune response induced, and downstream signalling following TLR activation vary considerably between mice and humans (Mestas & Hughes, 2004; Peng, 2005; von Bernuth *et al.*, 2008). In terms of adaptive immunity, their antibody classes and subclasses do not accurately correspond in terms of function and abundance; for example, high concentrations of IgA1 and IgA2 are present in human serum whilst murine IgA is of a single class and present at very low levels in the serum (Gibbons & Spencer, 2011). There is also evidence to suggest that the polarization of T-helper (Th) cell subsets is...
Table 1. Priorities for overcoming the outstanding issues and barriers in successful vaccine development

<table>
<thead>
<tr>
<th>Problem</th>
<th>Actions required</th>
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</thead>
<tbody>
<tr>
<td>Inadequate preclinical data and lack of detailed information on protective correlates of immunity contribute to product failure in clinical trials</td>
<td>Development of more relevant animal models; more human samples to be collected and analysed; increased use of experimental human challenge infections</td>
</tr>
<tr>
<td>Lack of information on the infectious exposures of intended vaccine recipients</td>
<td>More human samples to be collected and analysed</td>
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<tr>
<td>Vaccines are to be used in populations with less-responsive immune systems</td>
<td>Gain a greater understanding of the mechanisms of action of currently used adjuvants; development of vaccine delivery systems specifically for use in immunocompromised populations</td>
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<tr>
<td>Antigenic variation requires constant updating of vaccine formulations</td>
<td>Seek conserved antigens; monitor genetic variation of infectious organisms in the community</td>
</tr>
<tr>
<td>High costs of vaccine development result in premature abandonment of potentially useful products</td>
<td>More investment in vaccine research</td>
</tr>
<tr>
<td>Inadequate access to vaccines in poorer countries, especially those for use against tropical diseases</td>
<td>More tiered pricing strategies; facilitate the development of vaccines in developing countries</td>
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not as clear cut in humans as it is in mice, and that regulation of Th differentiation may also be different (Gibbons & Spencer, 2011; Mestas & Hughes, 2004).

In addition to the physiological differences between animals and humans, the well-controlled laboratory conditions under which animal studies are conducted represent a potential cause of disparity when advancing the work to human trials. Several Phase II clinical trials have reported disappointing results, possibly because the vaccine recipients or target population have a natural tendency for impaired immune responsiveness (Dannenberg, 2010; Sauerwein et al., 2011). For example, this could be caused by a high prevalence of chronic and/or immunosuppressive infections (e.g. intestinal helminths and HIV), they may be very young or affected by old age, have poor nutrition, suffer from obesity, have pre-existing immunity to vaccine vectors (such as recombinant adenovirus) or are naturally exposed to antigenically similar organisms to the target pathogen (Elias et al., 2001; Karlsson et al., 2010; Kaufman et al., 2011; Moretto et al., 2008; Rutstein et al., 1994; Sasaki et al., 2011; Sekaly, 2008). Vaccine formulations must be found that can succeed, despite these difficult circumstances. In the light of this, there is a call for the increased development and use of experimental human challenge infections (Ferreira et al., 2011; Graham et al., 2004; Minassian et al., 2011; Sauerwein et al., 2011).

Antigen selection methods have changed dramatically in the post-genomic era, with the development of bioinformatic, systems biology and high-throughput screening approaches (He et al., 2010; Pulendran, 2009; Sette & Rappuoli, 2010). Over the last decade, these major scientific advancements have permitted researchers to identify vaccine antigens for new and emerging pathogens, and also for those organisms that are particularly dangerous to work with or difficult to culture. Their usefulness is illustrated by the identification of the meningococcal antigen GNA1870. This binds to human complement factor H (fH), allowing the organism to survive in the human body (Madico et al., 2006). The protein was found to be unable to bind fH from mice or rats however, leading to a critical understanding of why meningococcal infection models had failed in these animals, and led to the development of human fH transgenic mouse strains to further vaccine research (Beernink et al., 2011). Despite this particular success, the general impact of genomic approaches on the number of new vaccines appearing on the market has not been so great as first anticipated. Reasons for this include problems with selective pressures and antigenic variability of pathogens, improving the antigenicity of non-protein antigens, and a lag in the availability of adjuvants and delivery systems to induce the required protective immune responses, often with fairly weak immunogens.

In many cases, antibody responses against surface molecules play a major role in eradicating an infection. In bacterial infections, for example, the binding of antibodies to surface-exposed antigens results in complement-mediated lysis and opsonization for phagocytosis. There is therefore likely to be a strong selective pressure to vary such surface-exposed antigens, and this means that vaccines may be strain-specific, requiring a multivalent formulation which is changed frequently. Progress is being made in this area to avoid having to constantly update vaccines. Recently, researchers have identified broadly neutralizing human antibodies against influenza haemagglutinin, which could be exploited to develop a universal flu vaccine (Corti et al., 2011; Ekiert et al., 2009, 2011). However, for organisms that exhibit very substantial genetic diversity and variation, particularly in...
target antigens (for example HIV, group B meningococci and malaria), this is a real barrier to the development of effective formulations. Strategies to better understand pathogenic mechanisms, population dynamics and epidemiology are urgently required if this is to be overcome (Moxon & Siegrist, 2011).

The realization that immunodominant antigens may not necessarily be protective but could be expressed by pathogens as immunological ‘smokescreens’ has led to a more intensive and refined search for vaccine candidates. Such antigens may be quite weak immunogens, and thus more powerful adjuvants are required to activate innate immune cells such as macrophages and dendritic cells, to stimulate B and T lymphocytes, and induce protective levels of immunity safely without needing multiple dose regimens. This being said, we still do not completely understand the mechanism of action for many of the adjuvants that have been licensed and used for years (Pulendran & Ahmed, 2011; Seubert et al., 2011). Alum has been in use since the 1930s, yet surprisingly its mode of adjuvanticity is only just coming to light (Kool et al., 2012).

A new generation of adjuvants is being developed that activate innate immunity directly via interactions of pathogen-associated molecular patterns (PAMPs), such as bacterial cell wall material and DNA, with microbial pattern recognition receptors (PRRs), such as the TLRs, NOD-like receptors and C-type lectin receptors (Higgins & Mills, 2010). This approach is thought to be safe since many current whole-cell and inactivated vaccines naturally contain PAMPs and these are thought to contribute greatly to their immunogenicity (Higgins et al., 2006; Pulendran, 2009; Schreibelt et al., 2010). One example of a PRR-stimulating adjuvant in development is β-glucan particles (Huang et al., 2010). These are prepared from Saccharomyces cerevisiae cell walls, so are rich in fungal PAMPs and strongly stimulate the C-type lectin Dectin-1, which is highly expressed by dendritic cells, macrophages and neutrophils. ISCOMATRIX is another very promising innate immune cell-stimulating adjuvant. It has been tested in a range of animal models and human studies and been shown to induce potent, long-lived and protective humoral and cellular immune responses (Baz Morelli et al., 2012; Duewell et al., 2011). In addition to being able to stimulate higher levels of antibodies, new adjuvants are being created with the aim of tailoring the mode of immune stimulation so that a particular type of cellular immune response is generated. This could involve stimulating particular CD4+ Th cell subsets such as Th1, Th2 or Th17, or perhaps the generation of a potent CD8+ cytotoxic T-cell response, in order to provide a more exact match with the desired immune correlates of protection (Ebensen & Guzmán, 2009).

Costs, profits and markets

Despite much underpinning vaccine research being performed in academia or not-for-profit organizations, it must be recognized that vaccines are developed and brought to market by pharmaceutical companies. Thus when considering vaccine development, one cannot ignore market. One dilemma for pharmaceutical companies is that demand tends not to coincide with an ability to pay. For example, when assessing the market and the potential profits to be made from a vaccine against HIV-1, it is unsurprising that the majority of the market value was predicted to lie in high-income countries and the majority of the demand in low-income countries (Marzetta et al., 2010). Thus, for vaccines already developed for high-income countries, tiered pricing has been suggested as a way of benefiting all parties: developing countries get access to a product that would have been unattainable if the vaccines were offered at a uniform price, producers benefit from increased revenues and profits, and the developed countries benefit from slightly lower prices than would be the case in the absence of the low-price market (Plahte, 2005). However, this approach causes understandable angst in developed nations, particularly the USA, who see themselves paying significantly more for the same product (reviewed by Plahte, 2005). In the era of ‘health tourism’, pharmaceutical companies may also feel concerned that cheap vaccines available in developing nations may actually represent a threat to their lucrative rich nation markets by access to cheaper vaccines by the back door. This becomes particularly acute when considering the limited time that patent protection applies to a new product, versus the lengthy timescales required to take a product through development and regulatory approval, and thus the narrow window during which a company can maximize its cost recovery.

Often a new vaccine is only produced by a single manufacturer, and thus price competition is not a driver to reduce costs. This can restrict access to effective vaccines, even in developing nations where the cost–benefit analysis may be the primary influence, as compared to poorer countries where affordability would be the deciding factor. An interesting example of the cost–benefit analysis is the impact of chickenpox vaccination. This vaccine is routinely included in the panel of childhood vaccines in many developed countries, but not the UK. This reflects the health-care systems in place in different countries. In countries such as the USA, the individual is at the centre of insurance-funded health care, and thus the child is vaccinated to prevent chickenpox. However, in the UK, the National Health Service (NHS) has to consider the impact on the community, and thus children are not currently vaccinated, as circulating virus in the community boosts the immunity in adults and reduces the number of cases of shingles in older people (NHS, 2010). As the cost of treating an increased number of adults with shingles is greater than that of treating what is usually a mild illness in children (Rozenbaum et al., 2008), children are left unvaccinated by the NHS (Salisbury et al., 2006), although it is available privately. Also, whereas there have been significant publicity campaigns to promote uptake of this vaccine in countries such as Australia where it is seen as beneficial, the vaccine is almost unheard of by the general population in the UK.
True costs for development of new vaccines are not disclosed by pharmaceutical companies. Common estimates for R&D for a single vaccine are often based on development costs for new drugs and fall into the $1–2 billion range (reviewed by Light et al., 2009). A reason for these high costs that is often given is high failure rates (it is often cited that only 1 in every 5000–10 000 compounds screened is approved by the FDA). Costs associated with research, development and clinical studies in particular are high, and the company has to recoup its investment which could have tied up capital for a decade or more (Light et al., 2009). Interestingly, the risk of failure lies predominantly in the early stages of development, and by the time leads enter the very expensive stages of late licensing, the failure rate is actually only 1 in 2 or 3 (Goozner, 2004). Using similar arguments, critics have held that it is in the interests of companies to claim high development costs, and as these are confidential data they cannot be interrogated to see whether such claims are justified (reviewed by Light et al., 2009). As these claims cannot be independently verified, Light et al. (2009) attempted to calculate actual R&D costs of rotavirus vaccines, in order to provide a model to influence policy, and found them to be significantly lower than those indicated by industrial sources. The lack of transparency regarding true costs subsequently impacts on purchasers’ abilities to make informed decisions regarding reasonable, fair, affordable prices.

Many ‘push’ and ‘pull’ options have been identified to increase access to vaccines by poorer nations, including voluntary licensing, compulsory licensing, advance market commitments and tiered pricing. Some have proposed that making relevant patents accessible to low-income countries in return for a minimal payment intended to cover a percentage of R&D costs would be one way to increase access for developing nations, the so-called Generic Open license (Outterson & Kesselheim, 2008). However, no single approach is likely to be a panacea to global pharmaceutical access. For example, the Generic Open license proposal hypothesizes that an increase in generic products will lower prices through greater competition and increase vaccine availability in low-income markets. However, the proposal is unlikely to function as envisioned in the vaccine market (reviewed by McCelligott, 2009). Vaccine developers will be unlikely to participate in the programme because the payments are not considered to adequately compensate for lost profits. Additionally, the price reductions from competitive entry are unlikely because the vaccine market is already characterized by low, and in some cases unsustainable, prices.

A global health partnership, the GAVI Alliance (GAVI Alliance, 2011), established with the primary aim of supplying vaccines to low-income countries, has negotiated significant discounts from pharmaceutical companies such as GlaxoSmithKline, Merck, Johnson and Johnson, and Sanofi (Butler, 2011). Despite these savings, the planned programme would still require billions of dollars of funding to become a reality, which requires a philanthropic approach by developed nations to support it. Private philanthropy has played a significant role in obtaining access to vaccines for developing nations since the inception of the Bill and Melinda Gates Foundation and its Global Health Program. However, supporting such programmes is not always altruistic. Eradication campaigns in developing countries can benefit richer nations by reduced morbidity and reducing the need to vaccinate their own populations in addition to benefitting developing nations. For example, vaccination against poliomyelitis, although costing $8 bn in the period 1988–2010 (The Global Polio Eradication Initiative, 2010), is ultimately anticipated to result in economic benefits of up to $50 bn. The Global Polio Eradication Initiative to date has reduced the annual burden of disease to fewer than 2000 cases of paralysis annually. In the developed nations, vaccine-associated polio is a more significant risk than natural imported infection, which in turn affects the cost–benefit considerations of vaccinating the population and the type of vaccine chosen (Thompson et al., 2008).

Whereas vaccines available in developing nations can be made available through various initiatives such as the GAVI Alliance, there is little commercial interest in developing vaccines for neglected tropical diseases which are the most common infections of the world’s poor. These neglected diseases include hookworm infection, sleeping sickness or Chagas’ disease and are themselves a cause of poverty because of their adverse effects on child development and worker productivity, thus vaccines against such diseases have been called ‘antipoverty vaccines’ (Hotez, 2011). Some vaccines for these neglected diseases are now entering the clinical pipeline, but require novel approaches to further development such as through pooled funding for innovation, developing-country manufacturers and public–private partnerships for product development (Hotez, 2011). The World Health Organization Initiative for Vaccine Research (WHO IVR) is a scheme designed to meet some of the challenges of developing and licensing affordable vaccines for the needs of developing countries. In addition, some of these vaccines will only ever be needed in developing countries, and thus should be evaluated in line with Good Clinical Practice, and applicable ethical and regulatory requirements in developing countries, requires significant investment, and thus the IVR is also investing in the capabilities to facilitate vaccine development for these vaccines.

**Future prospects**

A larger number of vaccine products than ever are currently on the market, and these are being taken up by more recipients (WHO, 2009). Despite this, in low-income countries, over a third of deaths occur in children, and the predominant cause is infectious disease (WHO, 2008). This
highlight the importance of overcoming the complex issues raised in this article. Encouragingly, a recent report from the Pharmaceutical Research and Manufacturers of America listed 145 new vaccines undergoing clinical trials testing, with many targeting infections for which there is no current vaccine (PhRMA, 2010). The scientific, financial and ethical challenges are considerable; however, important breakthroughs continue to be made.

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