Despite the controversies that sometimes surround immunisation, vaccines have transformed several diseases that caused distress, disability and death just a generation ago into, potentially, clinical curiosities. According to the WHO, vaccines prevent two to three million deaths annually. That figure could rise by at least six million if every child received the recommended vaccines. Vaccination is also responsible for the only two infections wiped out by human innovation – smallpox in 1979 and the livestock disease rinderpest in 2011 – and has brought measles and polio to the verge of extinction. Nevertheless, there is a pressing need for innovative immunisations, although finding new vaccines is increasingly difficult. “We’ve picked the low-hanging fruit,” says Georgina Drury, programme manager for immunology at the UK MRC’s Infections and Immunity Board. About 20 major global infections do not have vaccines, including hepatitis C virus, Streptococcus groups A and B, leishmaniasis, HIV and, Bacillus Calmette-Guérin (BCG) notwithstanding, tuberculosis. Ideally, we also require vaccines for emerging infections (such as Zika, Ebola and Marburg virus disease) and widespread pathogens – including Clostridium difficile, MRSA and rhinovirus. So, what are the prospects for these much-needed vaccines?

Towards a universal vaccine

For a while, headlines seemed to suggest every poorly pig, diseased duck or sickly swan potentially heralded the long-feared apocalyptic influenza pandemic. The hype might have faded, but the problem remains. After all, influenza A has a notoriously high mutation rate and the potential to leap species barriers. The binding sites of haemagglutinin and neuraminidase, both proteins found on the surface of influenza virus (see Figure 1), mutate readily (antigenic drift), which keeps the strain circulating. Pandemic strains arise through antigenic shifts, where a new subtype emerges when distinct influenza viruses co-infecting a bird, pig or another host swap genes. So, the vaccine changes each year to keep pace with influenza’s rapid evolution.

This genetic instability prompted the search for a ‘universal influenza vaccine’, which targets multiple strains and, as a result, may be more effective against novel, including potentially pandemic, strains. Most vaccines directly gener-
ate humoral responses, characterised by a rise in antibody levels (titres). One approach to developing a universal flu vaccine induces T cell responses, which evoke cellular and, indirectly, humoral responses (see Box 1).

Another approach induces antibodies against antigens that do not change rapidly (highly conserved) across strains. A highly conserved ion channel called matrix protein 2 (MP2), expressed in large numbers by cells infected by influenza, offers one target. Recent studies, however, suggest that there are several MP2 variants, which may compromise development of a universal vaccine using this epitope. Another approach targets haemagglutinin, which resembles three lollipops stuck together, their sticks embedded in the membrane. The binding site changes readily. However, the ‘stalk’ supporting the binding site is relatively well conserved.3,4 “Recent advances in understanding how to preserve the structure of the stem antigen in the vaccine suggests that a universal vaccine for flu is a realistic prospect,” says Dr Drury. “All being well, a candidate vaccine could be available in 10 to 15 years.”

Developing a ‘universal vaccine’ for some pathogens means devising a formulation that protects life against strains that might mutate. “The complexities of pathogen biology, immune response and the vaccine type can make this challenging,” Dr Drury explains. When using a single antigen in a universal vaccine is not possible, researchers will often develop ‘multivalent’ formulations. These contain multiple antigens and so target several strains of the pathogen. “A multivalent vaccine could achieve much the same effect as a universal vaccine,” Dr Drury adds. “For example, a multivalent Ebola vaccine, which covers two out of four strains and Marburg, is currently being developed. A multivalent meningitis vaccine to cover different strains, and a malaria vaccine that tackles all the stages in the parasite’s life cycle would also be desirable.”

Similarly, a multivalent approach might lead to the long-sought-after common cold vaccine. Prokarium, a biotech company in Keele, to take one example, genetically engineer Salmonella enterica

The immune system has two main branches: the innate and the adaptive. Innate immunity is relatively nonspecific and offers an initial line of defence as the specific adaptive response takes time to develop. For example, innate immune cells engulf pathogens, secrete cytokines that promote inflammation and release chemicals that attract and activate other immune cells.1

The adaptive immune system responds to specific areas in the infected cell or pathogen called ‘epitopes’. The adaptive immune system has two elements: humoral and cellular. For example, when a receptor expressed by a B lymphocyte binds to a matching epitope, it matures into a plasma cell that secretes antibodies – the humoral response.1 Cellular immunity largely depends on antigen-specific T lymphocytes. Almost all cells express major histocompatibility complex class 1 (MHC-1) molecules on their surface. Infected cells present epitopes from the pathogen complexed with MHC-1. Cytotoxic T lymphocytes with a matching cell receptor bind to the MHC-1, which kills infected cells. Some T cells augment antibody production by B cells. The proliferation of B and T cells allows the body to deal with the infection. Usually, some cells remain to allow the immune system to respond more rapidly to future infections.1

**Box 1. The many faces of the immune system**

to produce oral vaccines (see below). One of their projects aims to engineer a bacterium that produces vaccines against up to 75 of the most prevalent strains of rhinovirus responsible for common colds. “This vaccine is aimed at cutting exacerbations of asthma and COPD, but could also reduce absenteeism due to the common cold in the general population, especially if it can match the price of the annual flu jab,” says Ted Fjällman, chief executive officer of Prokarium. Developing a conventional vaccine against 75 rhinovirus strains would not be cost effective. There are no guarantees, but Dr Fjällman predicts that their rhinovirus vaccine could reach the market by 2026.

**Reverse vaccinology**

Until 20 or so years ago, vaccine development involved isolating, inactivating and injecting the pathogen or part of the micro-organism (see Table 1).5 This approach led to today’s suite of licensed vaccines. However, the traditional approach had limited scope for identifying potential novel antigens (neo-antigens). This hindered development of vaccines against pathogens such as hepatitis C, which do not grow in vitro, or where the cellular components that dominate the immune response closely resemble elements of human tissues (eg serogroup B meningococcus).2

Then in 1995, researchers sequenced the first genome of a free-living organism, the bacterium *Haemophilus influenzae*.6 Sequencing allows researchers to search for neo-antigens based on predicted proteins encoded in the pathogen’s genome. “Termed ‘reverse vaccinology’ – because the starting point is the ‘reverse’ of the conventional route – this approach offers huge opportunities to isolate and synthesise novel vaccine antigens,” Dr Drury says. “Indeed, reverse vaccinology was used to develop a vaccine for meningococcus B, which is the first landmark product to be licensed using this approach.”

In addition, reverse vaccinology can cut the time to develop a vaccine by generating more candidate antigens to test for immune responses. “In principle, reverse vaccinology can express all potential antigens, including highly conserved regions in the genome,” Dr Drury comments. “This provides scope to target several strains of a given pathogen at once, making the prospect of a universal vaccine more likely.”

**Innovations in vaccine delivery**

Many current vaccines require booster shots to ensure that the person remains immunised. “Booster shots are often needed because the vaccine does not quite mimic the exposure to the pathogen, and doesn’t therefore induce the same kind of life-long immune responses,” Dr Drury explains. “By better understanding the interaction with the pathogen and the immune system, we can design more
effective vaccines, which may involve innovations in delivery.”

“The body’s immune system functions via different mechanisms depending on the route of infection,” Dr Fjällman says. “An injectable vaccine nicely mimics an insect bite, for example, while an oral vaccine might be more appropriate for a mucosal pathogen.” For example, the gastrointestinal mucosa ‘cross talks’ with other mucosal tissues, such as the genitalia and lungs. This potentially makes an oral vaccine a more suitable candidate for respiratory infections and sexually transmitted diseases, such as chlamydia, than an injectable. “In animal models, an oral vaccine for tuberculosis resulted in decolonisation of Mycobacterium tuberculosis in the lung,” Dr Fjällman adds.

In other words, innovative routes of delivery seem to allow some novel vaccines to recruit the same cellular repertoire and trigger the same immunological pathways as the pathogen. “The recent recognition that Zika can be sexually transmitted inspired our organisation to develop an oral vaccine for this emerging public health threat,” Dr Fjällman says. Again, there are no guarantees. However, he suggests that the Zika vaccine might be available in 2026.

### Enhancing the immune response

Adjuvants enhance immune responses to a vaccine. Using adjuvants is particularly important for vaccines made from recombinant antigens or DNA, which do not generally produce a protective response. Adjuvants also bolster immunogenicity in certain patient groups – such as the elderly, young children and the immunocompromised – who often respond suboptimally to vaccination. Adjuvants may also be dose sparing and, as a result, extend the supply of a vaccine.⁷

Vaccines that are closer to the original pathogen are inherently more immunogenic and, therefore, might not need an adjuvant. But researchers need to tread a fine line: in general, the more immunogenic a vaccine is, the more likely side-effects become. “Nonspecialists often don’t fully appreciate the importance of adjuvants,” says Dr Drury. “In addition, our current understanding of how adjuvants work is relatively poor

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**Table 1. Examples of classes of vaccine**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Example</th>
<th>Year first used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterologous</td>
<td>Closely related micro-organism</td>
<td>Cowpox for smallpox</td>
<td>1796</td>
</tr>
<tr>
<td>Attenuated</td>
<td>Weakened, but viable, micro-organism</td>
<td>Rabies, polio, typhoid fever, measles-mumps-rubella</td>
<td>1885 (rabies)</td>
</tr>
<tr>
<td>Inactivated</td>
<td>‘Killed’ micro-organism</td>
<td>Cholera, Salk polio vaccine</td>
<td>1896 (cholera)</td>
</tr>
<tr>
<td>Toxoid</td>
<td>Inactivated toxin</td>
<td>Diphtheria</td>
<td>1923</td>
</tr>
<tr>
<td>Subunit</td>
<td>One or more antigens from the pathogen</td>
<td>Hepatitis B virus</td>
<td>1986</td>
</tr>
<tr>
<td>Conjugate</td>
<td>Weakly immunogenic antigen attached to a more immunogenic protein</td>
<td><em>Haemophilus influenzae</em> type b</td>
<td>1987</td>
</tr>
<tr>
<td>Reverse vaccinology</td>
<td>Produced from the pathogen’s genetic sequence</td>
<td>Meningococcal group B</td>
<td>2015*</td>
</tr>
</tbody>
</table>

* UK introduction
and there are a limited number of useful adjuvants. This is an area of research the MRC aims to encourage.”

Currently, aluminium-based adjuvants are the most widely used and enhance humoral responses to vaccines, without influencing cellular responses. Their mechanism of action – which is, according to a recent review, “not completely understood and still widely debated” – probably depends on the vaccine, route of administration and organism. 

Broadly, aluminium seems to stimulate innate immune cells at the site of vaccination. In particular, aluminium seems to attract immature dendritic cells, which then mature and present the vaccine to T-helper cells in lymph nodes. In turn, these T-helper cells stimulate B cells that encounter the vaccine to generate high titres of antibodies. Nevertheless, safety concerns surround some adjuvants. Aluminium-based adjuvants have been associated with macrophagic myofascitis, for example.

Against this background, invading micro-organisms may express ‘pathogen-associated molecular patterns’. One of the best studied is lipopolysaccharide (also called endotoxin) found in the outer cell wall of gram-negative bacteria, which elicits a strong immune response. A modified part of lipopolysaccharide called monophosphoryl lipid A increases the immune response but does not, unlike the natural version, stimulate cytokine release. Monophosphoryl lipid A adjuvants have reached the market, such as in some vaccines for human papilloma virus (HPV).

“The widely used aluminium-based adjuvants produce a broad-spectrum immune response,” notes Dr Drury. “In the future, as we better understand the ways in which adjuvants elicit immune responses, and we deepen our understanding of immunological correlates of protection, we should be able to develop adjuvants that stimulate a specific, protective immune response. This is some way off, but I am very positive that it will happen.”

Some vaccines in development aim to avoid adjuvants, by being more ‘innately immunogenic without crossing the line into the reactivity that may lead to adverse events. For example, studies from the USA and UK performed during the 1940s and 1950s that followed people up to 21 years of age found that the BCG vaccine reduced mortality from conditions other than tuberculosis by 25% overall and by up to 41% in some studies. Indeed, the WHO concluded that BCG and measles vaccines almost halved overall mortality. Prevention of tuberculosis or measles respectively could not fully account for the benefit. One theory holds that attenuated vaccines prime white blood cells to respond to a second nonrelated stimulus – so-called trained innate immunity.

On the other hand, some inactivated vaccines – including diphtheria-tetanus-pertussis, hepatitis B and inactivated polio – protect against their target diseases, but seem to increase susceptibility to other pathogens. Optimising available vaccines and improving those in development means understanding the mechanisms underlying these nonspecific effects.

Figure 2. Prokarium’s oral vaccine delivery platform (the Vaxonella platform). The vaccine is expressed in attenuated strains of Salmonella enterica, which are ingested, pass through the stomach and transverse the lining of the small intestine via M cells into lymphatic nodules called Peyer’s patches. There they are phagocytosed by antigen-presenting cells (APCs) such as macrophages, and express the antigen genes. The antigens are processed and presented by the APCs to stimulate humoral and cellular immune responses (From: http://prokarium.com/vaxonella-platform, with permission)
when patients take an oral vaccine based on attenuated strains of *S. enterica*, the bacterium moves across the lining of the small intestine into lymphatic nodules called Peyer’s patches (see Figure 2). Microfold cells (M cells) transport antigens from the gut lumen to Peyer’s patches. Once in the patch, macrophages and other antigen-presenting cells engulf and express the antigen genes. This stimulates humoral and cellular immune responses. “*S. enterica* is a potent immunostimulator, so no additional adjuvant is needed,” Dr Fjällman says. “*S. enterica* acts as a biological factory, producing the vaccine from inside the body’s own immune cells.”

In addition, *S. enterica* is stable for 14 weeks at 40°C and an oral vaccine does not depend on highly trained staff for administration. Technologies that reduce the need for a cold chain and highly trained staff offer obvious benefits in resource-poor countries. But they are also valuable in, for example, nursing homes where a vaccine could be added to a standard medication round and for travel vaccines, especially for trips at short notice. “Often travel vaccines need a booster dose,” Dr Fjällman notes. “You could take the primer dose at home and then carry the booster oral dose in your luggage. It’s not ideal. But even partial protection is a big advantage.”

**Unanswered questions and bottlenecks**

It is now 220 years since Jenner’s pioneering experiments with cowpox, yet numerous unanswered questions and unresolved issues remain. Intriguingly, for example, some vaccines seem to have benefits beyond their target pathogen (see Box 2). Dr Drury points out that future research needs to determine the differences between general immune responses to a pathogen or vaccine, and the responses that confer protective long-term immunity. One approach studies individuals who show naturally acquired immunity, eg sex workers in Kenya with immunity to HIV. This could provide insights into true correlates of protection and identify potential candidate antigens. But translating such insights into marketable vaccines means widening several bottlenecks.

“At the moment, there is a bottleneck at each step in vaccine development,” Dr Drury observes. “To overcome these, we need integrated political policy and co-operation among stakeholders. The recently published EU roadmap on vaccines research [iprove-roadmap.eu] goes some way to laying out the gaps, opportunities and priorities – and collectively addressing these will enable us to find more effective ways of identifying promising candidates and translating results in animals into successful human trials.” She notes, for example, the UK is a world leader in basic vaccinology, but lacks a manufacturing base.

“There are major bottlenecks in basic research into the pathogens, how these interact with the immune system and how vaccines may elicit the same immunological correlates of protection as the pathogen,” Dr Drury adds. Advancing basic and applied vaccinology, will involve, for example, using the latest technological and computational advances – vaccine research generates huge amounts of data – to bridge the gaps between the effect *in vitro* and that in individual patients, and between each vaccine recipient and the effect on the population as a whole. Dr Drury notes that new computational methods and programmes along with better immune-informatic tools can find patterns in, and predict, immune responses. But integration of vaccine-related data into common and accessible platforms is another bottleneck, as is the available server capacity to boost storage and integration.

Against this background, the MRC is working alongside other funders (including the Biotechnology and Biological Sciences Research Council and the Wellcome Trust) and the Department of Health to advance vaccine research. The UK Vaccine Network is a group of experts from a number of related vaccine research and development fields, including basic research, clinical trials, regulation and public policy. Set up in the wake of the 2014 Ebola outbreak, their mandate is to develop vaccines for the most threatening outbreak diseases through to phase 1 trials. Dr Drury notes that vaccines tested at phase 1 that have the right safety and immunogenicity profiles could then be rapidly deployed to relevant populations if there is an outbreak of the infection. “In addition to funding specific projects to tackle the threat of the world’s deadliest diseases, the network is building the partnerships needed to address many of the broader issues and challenges in vaccine research and development,” she says.

“This is an exciting time in the UK,” Dr Drury concludes. “We are joining up research and development priorities to make transformational steps to produce the next generation of vaccines. Multidisciplinary partnerships between funders, academia, clinicians and industry are essential to accelerate vaccine research, and ensure that the UK remains in the forefront of vaccine development.”

**References**


**Declaration of interests**

Mark Greener is a full-time medical writer and, as such, regularly provides editorial and consultancy services to numerous pharmaceutical, biotechnology and device companies and their agencies. He has no shares or other financial interests.

*Mark Greener is a freelance medical writer*