A guide to vaccinology: from basic principles to new developments

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Abstract | Immunization is a cornerstone of public health policy and is demonstrably highly cost-effective when used to protect child health. Although it could be argued that immunology has not thus far contributed much to vaccine development, in that most of the vaccines we use today were developed and tested empirically, it is clear that there are major challenges ahead to develop new vaccines for difficult-to-target pathogens, for which we urgently need a better understanding of protective immunity. Moreover, recognition of the huge potential and challenges for vaccines to control disease outbreaks and protect the older population, together with the availability of an array of new technologies, make it the perfect time for immunologists to be involved in designing the next generation of powerful immunogens. This Review provides an introductory overview of vaccines, immunization and related issues and thereby aims to inform a broad scientific audience about the underlying immunological concepts.

Antigens
Parts of the pathogen (such as proteins or polysaccharides) that are recognized by the immune system and can be used to induce an immune response by vaccination.

Protection
The state in which an individual does not develop disease after being exposed to a pathogen.

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Vaccines have transformed public health, particularly since national programmes for immunization first became properly established and coordinated in the 1960s. In countries with high vaccine programme coverage, many of the diseases that were previously responsible for the majority of childhood deaths have essentially disappeared[1] (FIG. 1). The World Health Organization (WHO) estimates that 2–3 million lives are saved each year by current immunization programmes, contributing to the marked reduction in mortality of children less than 5 years of age globally from 93 deaths per 1,000 live births in 1990 to 39 deaths per 1,000 live births in 2018 (REF.[2]).

Vaccines exploit the extraordinary ability of the highly evolved human immune system to respond to, and remember, encounters with pathogen antigens. However, for much of history, vaccines have been developed through empirical research without the involvement of immunologists. There is a great need today for improved understanding of the immunological basis for vaccination to develop vaccines for hard-to-target pathogens (such as *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis (TB))[3] and antigenically variable pathogens (such as HIV)[4], to control outbreaks that threaten global health security (such as COVID-19 or Ebola)[5,6] and to work out how to revive immune responses in the ageing immune system[7] to protect the growing population of older adults from infectious diseases.

In this Review, which is primarily aimed at a broad scientific audience, we provide a guide to the history (BOX 1), development, immunological basis and remarkable impact of vaccines and immunization programmes on infectious diseases to provide insight into the key issues facing immunologists today. We also provide some perspectives on current and future challenges in continuing to protect the world's population from common pathogens and emerging infectious threats. Communicating effectively about the science of vaccination to a sceptical public is a challenge for all those engaged in vaccine immunobiology but is urgently needed to realign the dialogue and ensure public health[8]. This can only be achieved by being transparent about what we know and do not know, and by considering the strategies to overcome our existing knowledge gaps.

What is in a vaccine?

A vaccine is a biological product that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen. To achieve this, the vaccine must contain antigens that are either derived from the pathogen or produced synthetically to represent components of the pathogen. The essential component of most vaccines is one or more protein antigens that induce immune responses that provide protection. However, polysaccharide antigens can also induce protective immune responses and are the basis of vaccines that have been developed to prevent several bacterial infections, such as pneumonia and meningitis caused by *Streptococcus pneumoniae*, since the late 1980s[9]. Protection conferred by a vaccine is measured in clinical trials that relate immune responses to the vaccine antigen to clinical end points (such as prevention of infection, a reduction in disease severity or a decreased rate of hospitalization).

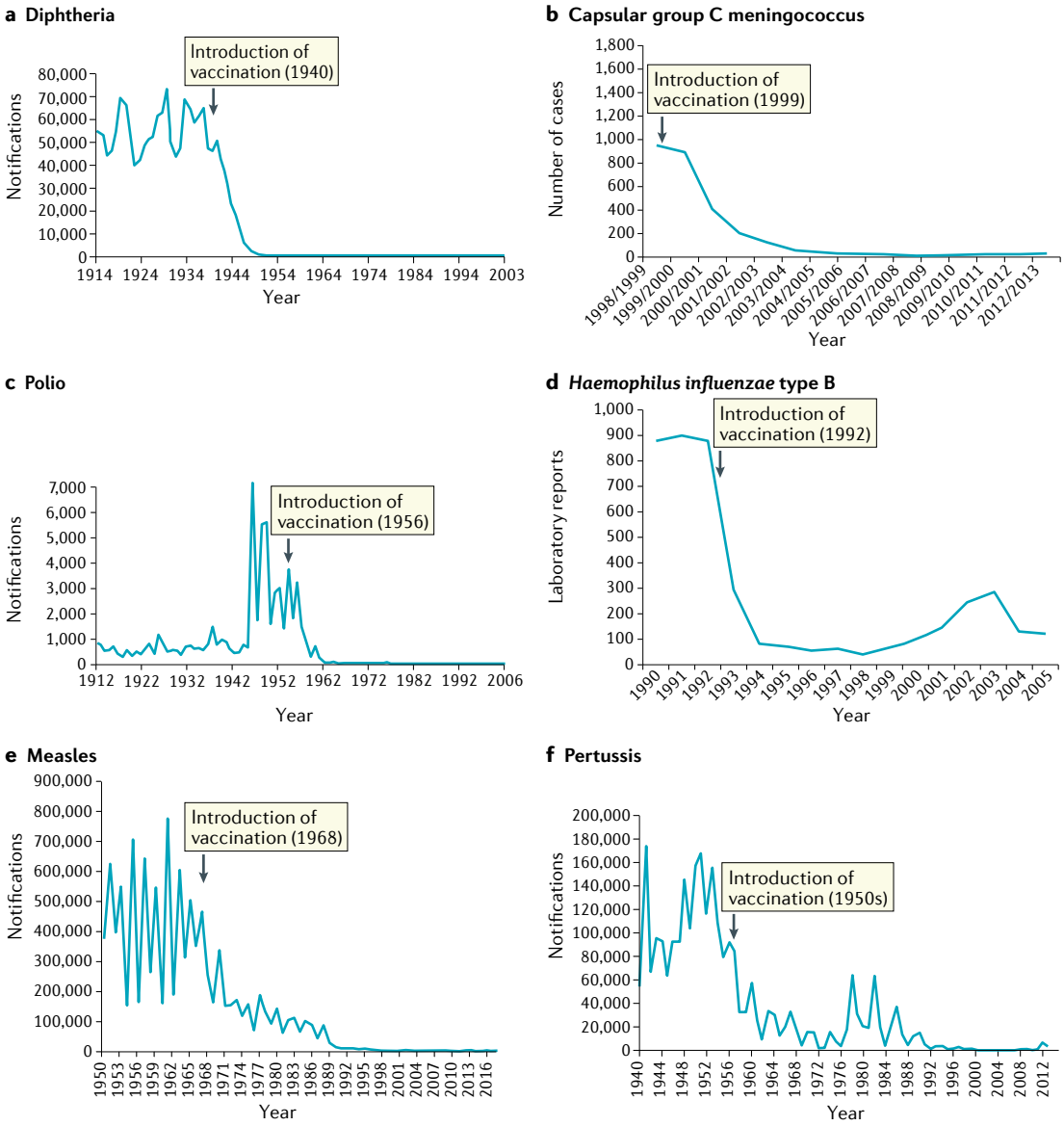


Fig. 1 | **The impact of vaccination on selected diseases in the UK.** The introduction of vaccination against infectious diseases such as diphtheria (part **a**), capsular group C meningococcus (part **b**), polio (part **c**), *Haemophilus influenzae* type B (part **d**), measles (part **e**) and pertussis (part **f**) led to a marked decrease in their incidence. Of note, the increase in reports of *H. influenzae* type B in 2001 led to a catch-up vaccination campaign, after which the incidence reduced. For pertussis, a decline in vaccine coverage led to an increase in cases in the late 1970s and 1980s, but disease incidence reduced again after vaccine coverage increased. Adapted with permission from the Green Book, information for public health professionals on immunisation, Public Health England, contains public sector information licensed under the Open Government Licence v3.0.

Finding an immune response that correlates with protection can accelerate the development of and access to new vaccines[10] (BOX 2).

Vaccines are generally classified as live or non-live (sometimes loosely referred to as 'inactivated') to distinguish those vaccines that contain attenuated replicating strains of the relevant pathogenic organism from those that contain only components of a pathogen or killed whole organisms (FIG. 2). In addition to the 'traditional' live and non-live vaccines, several other platforms have been developed over the past few decades, including viral vectors, nucleic acid-based RNA and DNA vaccines, and virus-like particles (discussed in more detail later).

The distinction between live and non-live vaccines is important. The former may have the potential to replicate in an uncontrolled manner in immunocompromised individuals (for example, children with some primary immunodeficiencies, or individuals with HIV infection or those receiving immunosuppressive drugs), leading to some restrictions to their use[11]. By contrast, non-live vaccines pose no risk to immunocompromised individuals (although they may not confer protection in those with B cell or combined immunodeficiency, as explained in more detail later).

Live vaccines are developed so that, in an immunocompetent host, they replicate sufficiently to produce a

Attenuated
A reduction in the virulence of a pathogen (through either deliberate or natural changes in virulence genes).

Virus-like particles
Particles constructed of viral proteins that structurally mimic the native virus but lack the viral genome.

Adjuvant
An agent used in a vaccine to enhance the immune response against the antigen.

Danger signals
Molecules that stimulate a more robust immune response together with an antigen. Endogenous mediators that are released in response to infection or injury and that interact with pattern recognition receptors such as Toll-like receptors to activate innate immune cells such as dendritic cells.

Innate immune system
The evolutionarily primitive part of the immune system that detects foreign antigens in a non-specific manner.

AS01
A liposome-based adjuvant containing 3-*O*-desacyl-4′-monophosphoryl lipid A and the saponin QS-21. AS01 triggers the innate immune system immediately after vaccination, resulting in an enhanced adaptive immune response.

strong immune response, but not so much as to cause significant disease manifestations (for example, the vaccines for measles, mumps, rubella and rotavirus, oral polio vaccine, the *Mycobacterium bovis* bacillus Calmette–Guérin (BCG) vaccine for TB and live attenuated influenza vaccine). There is a trade-off between enough replication of the vaccine pathogen to induce a strong immune response and sufficient attenuation of the pathogen to avoid symptomatic disease. For this reason, some safe, live attenuated vaccines require multiple doses and induce relatively short-lived immunity (for example, the live attenuated typhoid vaccine, Ty21a)[12], and other live attenuated vaccines may induce some mild disease (for example, about 5% of children will develop a rash and up to 15% fever after measles vaccination)[13].

The antigenic component of non-live vaccines can be killed whole organisms (for example, whole-cell pertussis vaccine and inactivated polio vaccine), purified proteins from the organism (for example, acellular pertussis vaccine), recombinant proteins (for example, hepatitis B virus (HBV) vaccine) or polysaccharides (for example, the pneumococcal vaccine against *S. pneumoniae*) (FIG. 2). Toxoid vaccines (for example, for tetanus and diphtheria) are formaldehyde-inactivated protein toxins that have been purified from the pathogen.

Non-live vaccines are often combined with an adjuvant to improve their ability to induce an immune response (immunogenicity). There are only a few adjuvants that are used routinely in licensed vaccines. However, the portfolio of adjuvants is steadily expanding, with liposome-based adjuvants and oil-in-water emulsions being licensed in the past few decades[14]. The mechanism of action of aluminium salts (alum), although extensively used as an adjuvant for more than 80 years, remains incompletely understood[15], but there is increasing evidence that immune responses and protection can be enhanced by the addition of newer adjuvants that provide danger signals to the innate immune system. Examples of these novel adjuvants are the oil-in-water emulsion MF59, which is used in some influenza vaccines[16]; AS01, which is used in one of the shingles vaccines and the licensed malaria vaccine[17]; and AS04, which is used in a vaccine against human papillomavirus (HPV)[18].

Vaccines contain other components that function as preservatives, emulsifiers (such as polysorbate 80) or stabilizers (for example, gelatine or sorbitol). Various products used in the manufacture of vaccines could theoretically also be carried over to the final product and are included as potential trace components of a vaccine, including antibiotics, egg or yeast proteins, latex, formaldehyde and/or gluteraldehyde and acidity regulators (such as potassium or sodium salts). Except in the case of allergy to any of these components, there is no evidence of risk to human health from these trace components of some vaccines[19,20].

Box 1 | **A brief history of vaccination**

Epidemics of smallpox swept across Europe in the seventeenth and eighteenth centuries, accounting for as much as 29% of the death rate of children in London[137]. Initial efforts to control the disease led to the practice of variolation, which was introduced to England by Lady Mary Wortley Montagu in 1722, having been used in the Far East since the mid-1500s (see Nature Milestones in Vaccines). In variolation, material from the scabs of smallpox lesions was scratched into the skin in an attempt to provide protection against the disease. Variolation did seem to induce protection, reducing the attack rate during epidemics, but sadly some of those who were variolated developed the disease and sometimes even died. It was in this context that Edward Jenner wrote 'An Inquiry into the Causes and Effects of the Variole Vaccinae…' in 1798. His demonstration, undertaken by scratching material from cowpox lesions taken from the hands of a milkmaid, Sarah Nelms, into the skin of an 8-year-old boy, James Phipps, who he subsequently challenged with smallpox, provided early evidence that vaccination could work. Jenner's contribution to medicine was thus not the technique of inoculation but his startling observation that milkmaids who had had mild cowpox infections did not contract smallpox, and the serendipitous assumption that material from cowpox lesions might immunize against smallpox. Furthermore, Jenner brilliantly predicted that vaccination could lead to the eradication of smallpox; in 1980, the World Health Assembly declared the world free of naturally occurring smallpox.

Almost 100 years after Jenner, the work of Louis Pasteur on rabies vaccine in the 1880s heralded the beginning of a frenetic period of development of new vaccines, so that by the middle of the twentieth century, vaccines for many different diseases (such as diphtheria, pertussis and typhoid) had been developed as inactivated pathogen products or toxoid vaccines. However, it was the coordination of immunization as a major public health tool from the 1950s onwards that led to the introduction of comprehensive vaccine programmes and their remarkable impact on child health that we enjoy today. In 1974, the World Health Organization launched the Expanded Programme on Immunization and a goal was set in 1977 to reach every child in the world with vaccines for diphtheria, pertussis, tetanus, poliomyelitis, measles and tuberculosis by 1990. Unfortunately, that goal has still not been reached; although global coverage of 3 doses of the diphtheria–tetanus–pertussis vaccine has risen to more than 85%, there are still more than 19 million children who did not receive basic vaccinations in 2019 (REF.[105]).

Vaccines induce antibodies

The adaptive immune response is mediated by B cells that produce antibodies (humoral immunity) and by T cells (cellular immunity). All vaccines in routine use, except BCG (which is believed to induce T cell responses that prevent severe disease and innate immune responses that may inhibit infection; see later), are thought to mainly confer protection through the induction of antibodies (FIG. 3). There is considerable supportive evidence that various types of functional antibody are important in vaccine-induced protection, and this evidence comes from three main sources: immunodeficiency states, studies of passive protection and immunological data.

Immunodeficiency states. Individuals with some known immunological defects in antibodies or associated immune components are particularly susceptible to infection with certain pathogens, which can provide insight into the characteristics of the antibodies that are required for protection from that particular pathogen. For example, individuals with deficiencies in the complement system are particularly susceptible to meningococcal disease caused by infection with *Neisseria meningitidis*[21] because control of this infection depends on complement-mediated killing of bacteria, whereby complement is directed to the bacterial surface by IgG antibodies. Pneumococcal disease is particularly common in individuals with reduced splenic function[22] (which may be congenital, resulting from trauma or associated with conditions such as sickle cell disease); *S. pneumoniae* bacteria that have been opsonized with antibody and complement are normally removed from the blood by phagocytes in the spleen, which are no longer present in individuals with hyposplenism. Antibody-deficient

Box 2 | **Correlates of protection**

The identification of correlates of protection is helpful in vaccine development as they can be used to compare products and to predict whether the use of an efficacious vaccine in a new population (for example, a different age group, medical background or geographical location) is likely to provide the same protection as that observed in the original setting. There is considerable confusion in the literature about the definition of a correlate of protection. For the purposes of this discussion, it is useful to separate out two distinct meanings. A mechanistic correlate of protection is the specific functional immune mechanism that is believed to confer protection. For example, antitoxin antibodies, which are induced by the tetanus toxoid vaccine, confer protection directly by neutralizing the activity of the toxin. A non-mechanistic correlate of protection does not in itself provide the protective function but has a statistical relationship with the mechanism of protection. An example of a non-mechanistic correlate of protection is total IgG antibody levels against pneumococci. These IgG antibodies contain the mechanistic correlate (thought to be a subset of opsonophagocytic antibodies) but the mechanism of protection is not being directly measured. Correlates of protection can be measured in clinical trials if there are post-vaccination sera available from individuals who do or do not develop disease, although large-scale serum collection from participants is rarely undertaken in phase III clinical efficacy trials. An alternative approach is to estimate the correlates of protection by extrapolating from sero-epidemiological studies in a vaccinated population and relating the data to disease incidence in the population. Human challenge studies have also been used to determine correlates of protection, although the dose of challenge bacterium or virus and the experimental conditions may not relate closely to natural infection, which can limit the utility of these observations.

individuals are susceptible to varicella zoster virus (which causes chickenpox) and other viral infections, but, once infected, they can control the disease in the same way as an immunocompetent individual, so long as they have a normal T cell response[23].

Passive protection. It has been clearly established that intramuscular or intravenous infusion of exogenous antibodies can provide protection against some infections. The most obvious example is that of passive transfer of maternal antibodies across the placenta, which provides newborn infants with protection against a wide variety of pathogens, at least for a few months after birth. Maternal vaccination with pertussis[24], tetanus[25] and influenza[26] vaccines harnesses this important protective adaptation to reduce the risk of disease soon after birth and clearly demonstrates the role of antibodies in protection against these diseases. Vaccination of pregnant women against group B streptococci[27] and respiratory syncytial virus (RSV)[28] has not yet been shown to be effective at preventing neonatal or infant infection, but it has the potential to reduce the burden of disease in the youngest infants. Other examples include the use of specific neutralizing antibodies purified from immune donors to prevent the transmission of various viruses, including varicella zoster virus, HBV and measles virus[29]. Individuals with inherited antibody deficiency are without defence against serious viral and bacterial infections, but regular administration of serum antibodies from an immunocompetent donor can provide almost entirely normal immune protection for the antibody-deficient individual.

Immunological data. Increasing knowledge of immunology provides insights into the mechanisms of protection mediated by vaccines. For example, polysaccharide vaccines, which are made from the surface polysaccharides of invasive bacteria such as meningococci (*N. meningitidis*)[30] and pneumococci (*S. pneumoniae*)[31], provide considerable protection against these diseases. It is now known that these vaccines do not induce T cell responses, as polysaccharides are T cell-independent antigens, and thus they must mediate their protection through antibody-dependent mechanisms. Protein–polysaccharide conjugate vaccines contain the same polysaccharides from the bacterial surface, but in this case they are chemically conjugated to a protein carrier (mostly tetanus toxoid, or diphtheria toxoid or a mutant protein derived from it, known as CRM_{197})[32–34]. The T cells induced by the vaccine recognize the protein carrier (a T cell-dependent antigen) and these T cells provide help to the B cells that recognize the polysaccharide, but no T cells are induced that recognize the polysaccharide and, thus, only antibody is involved in the excellent protection induced by these vaccines[35]. Furthermore, human challenge studies offer the opportunity to efficiently assess correlates of protection (BOX 2) under controlled circumstances[36], and they have been used to demonstrate the role of antibodies in protection against malaria[37] and typhoid[38].

Vaccines need T cell help

Although most of the evidence points to antibodies being the key mediators of sterilizing immunity induced by vaccination, most vaccines also induce T cell responses. The role of T cells in protection is poorly characterized, except for their role in providing help for B cell development and antibody production in lymph nodes. From studies of individuals with inherited or acquired immunodeficiency, it is clear that whereas antibody deficiency increases susceptibility to acquisition of infection, T cell deficiency results in failure to control a pathogen after infection. For example, T cell deficiency results in uncontrolled and fatal varicella zoster virus infection, whereas individuals with antibody deficiency readily develop infection but recover in the same way as immunocompetent individuals. The relative suppression of T cell responses that occurs at the end of pregnancy increases the severity of infection with influenza and varicella zoster viruses[39].

Although evidence for the involvement of T cells in vaccine-induced protection is limited, this is likely owing, in part, to difficulties in accessing T cells to study as only the blood is easily accessible, whereas many T cells are resident in tissues such as lymph nodes. Furthermore, we do not yet fully understand which types of T cell should be measured. Traditionally, T cells have been categorized as either cytotoxic (killer) T cells or helper T cells. Subtypes of T helper cells (T_H cells) can be distinguished by their profiles of cytokine production. T helper 1 (T_H1) cells and T_H2 cells are mainly important for establishing cellular immunity and humoral immunity, respectively, although T_H1 cells are also associated with generation of the IgG antibody subclasses IgG1 and IgG3. Other T_H cell subtypes include T_H17 cells (which are important for immunity at mucosal surfaces such as the gut and lung) and T follicular helper cells (located in secondary lymphoid organs, which are important for the generation of high-affinity antibodies (FIG. 3)).

AS04
An adjuvant consisting of aluminium salt and the Toll-like receptor agonist monophosphoryl lipid A.

Complement system
A network of proteins that form an important part of the immune response by enhancing the opsonization of pathogens, cell lysis and inflammation.

Opsonized
A state of a pathogen in which antibodies or complement factors are bound to its surface.

Opsonophagocytic antibodies
Antibodies that bind to a pathogen, which subsequently can be eliminated by phagocytosis.

T cell-independent antigens
Antigens against which B cells can mount an antibody response without T cell help.

T cell-dependent antigen
An antigen for which T cell help is required in order for B cells to mount an antibody response.

Human challenge studies
Studies in which volunteers are deliberately infected with a pathogen, in a carefully conducted study, to evaluate the biology of infection and the efficacy of drugs and vaccines.

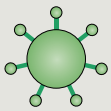
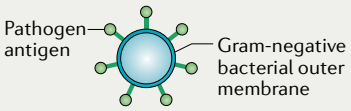
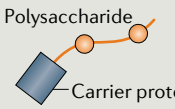
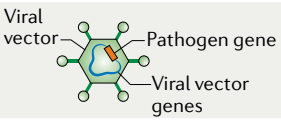
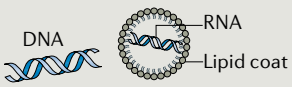
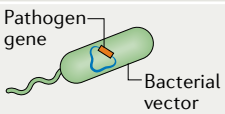
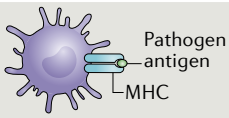
Type of vaccine		Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid		Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle		Human papillomavirus	1986 (hepatitis B)
Outer membrane vesicle		Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored		Experimental	–
Antigen-presenting cell		Experimental	–

Fig. 2 | **Different types of vaccine.** Schematic representation of different types of vaccine against pathogens; the text indicates against which pathogens certain vaccines are licensed and when each type of vaccine was first introduced. BCG, *Mycobacterium bovis* bacillus Calmette–Guérin.

Studies show that sterilizing immunity against carriage of *S. pneumoniae* in mice can be achieved by the transfer of T cells from donor mice exposed to *S. pneumoniae*[40], which indicates that further investigation of T cell-mediated immunity is warranted to better understand the nature of T cell responses that could be harnessed to improve protective immunity.

Although somewhat simplistic, the evidence therefore indicates that antibodies have the major role in prevention of infection (supported by T_H cells), whereas cytotoxic T cells are required to control and clear established infection.

Features of vaccine-induced protection

Vaccines have been developed over the past two centuries to provide direct protection of the immunized individual through the B cell-dependent and T cell-dependent mechanisms described above. As our immunological understanding of vaccines has developed, it has become apparent that this protection is largely manifested

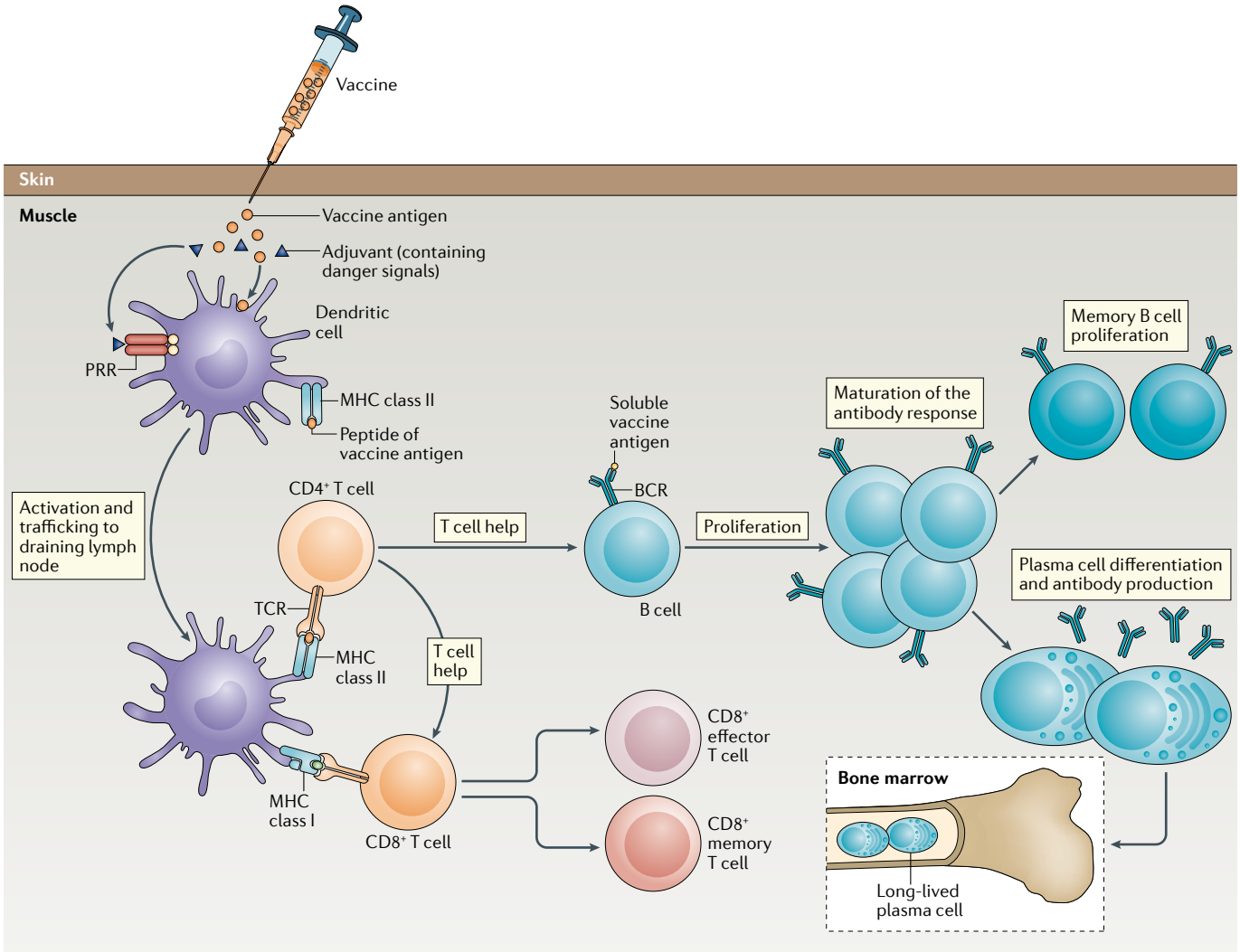


Fig. 3 | **The generation of an immune response to a vaccine.** The immune response following immunization with a conventional protein antigen. The vaccine is injected into muscle and the protein antigen is taken up by dendritic cells, which are activated through pattern recognition receptors (PRRs) by danger signals in the adjuvant, and then trafficked to the draining lymph node. Here, the presentation of peptides of the vaccine protein antigen by MHC molecules on the dendritic cell activates T cells through their T cell receptor (TCR). In combination with signalling (by soluble antigen) through the B cell receptor (BCR), the T cells drive B cell development in the lymph node. Here, the T cell-dependent B cell development results in maturation of the antibody response to increase antibody affinity and induce different antibody isotypes. The production of short-lived plasma cells, which actively secrete antibodies specific for the vaccine protein, produces a rapid rise in serum antibody levels over the next 2 weeks. Memory B cells are also produced, which mediate immune memory. Long-lived plasma cells that can continue to produce antibodies for decades travel to reside in bone marrow niches. $CD8^+$ memory T cells can proliferate rapidly when they encounter a pathogen, and $CD8^+$ effector T cells are important for the elimination of infected cells.

through the production of antibody. Another important feature of vaccine-induced protection is the induction of immune memory. Vaccines are usually developed to prevent clinical manifestations of infection. However, some vaccines, in addition to preventing the disease, may also protect against asymptomatic infection or colonization, thereby reducing the acquisition of a pathogen and thus its onward transmission, establishing herd immunity. Indeed, the induction of herd immunity is perhaps the most important characteristic of immunization programmes, with each dose of vaccine protecting many more individuals than the vaccine recipient. Some vaccines may also drive changes in responsiveness to future infections with different pathogens, so called non-specific effects, perhaps by stimulating prolonged changes in the activation state of the innate immune system.

Immune memory. In encountering a pathogen, the immune system of an individual who has been vaccinated against that specific pathogen is able to more rapidly and more robustly mount a protective immune response. Immune memory has been shown to be sufficient for protection against pathogens when the incubation period is long enough for a new immune response to develop (FIG. 4a). For example, in the case of HBV, which has an

Immune memory
The capacity of the immune system to respond quicker and more effectively when a pathogen is encountered again after an initial exposure that induced antigen-specific B cells and T cells.

Incubation period
The period from acquisition of a pathogen to the development of symptomatic disease.

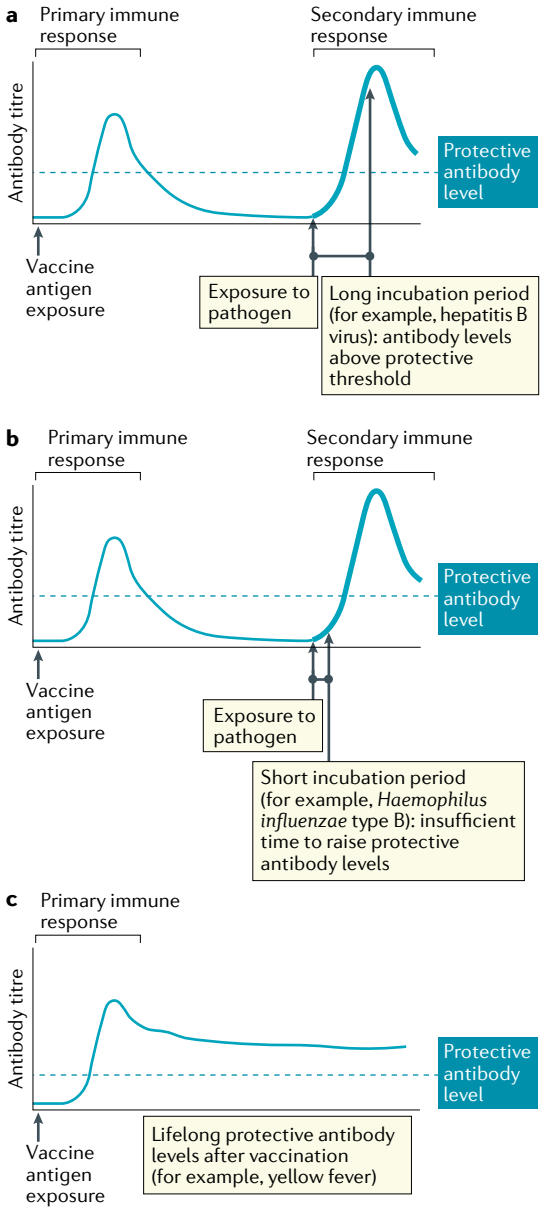


Fig. 4 | **Immune memory is an important feature of vaccine-induced protection.** Antibody levels in the circulation wane after primary vaccination, often to a level below that required for protection. Whether immune memory can protect against a future pathogen encounter depends on the incubation time of the infection, the quality of the memory response and the level of antibodies induced by memory B cells. **a** | The memory response may be sufficient to protect against disease if there is a long incubation period between pathogen exposure and the onset of symptoms to allow for the 3–4 days required for memory B cells to generate antibody titres above the protective threshold. **b** | The memory response may not be sufficient to protect against disease if the pathogen has a short incubation period and there is rapid onset of symptoms before antibody levels have reached the protective threshold. **c** | In some cases, antibody levels after primary vaccination remain above the protective threshold and can provide lifelong immunity.

incubation period of 6 weeks to 6 months, a vaccinated individual is usually protected following vaccination even if exposure to the virus occurs some time after vaccination and the levels of vaccine-induced antibody have already waned[41]. Conversely, it is thought that immune memory may not be sufficient for protection against rapidly invasive bacterial infections that can cause severe disease within hours or days following acquisition of the pathogen[42] (FIG. 4b). For example, there is evidence in the case of both *Haemophilus influenzae* type B (Hib) and capsular group C meningococcal infection that individuals with vaccine-induced immune memory can still develop disease once their antibody levels have waned, despite mounting robust, although not rapid enough, memory responses[43,44]. The waning of antibody levels varies depending on the age of the vaccine recipient (being very rapid in infants as a result of the lack of bone marrow niches for B cell survival), the nature of the antigen and the number of booster doses administered. For example, the virus-like particles used in the HPV vaccine induce antibody responses that can persist for decades, whereas relatively short-term antibody responses are induced by pertussis vaccines; and the inactivated measles vaccine induces shorter-lived antibody responses than the live attenuated measles vaccine.

So, for infections that are manifest soon after acquisition of the pathogen, the memory response may be insufficient to control these infections and sustained immunity for individual protection through vaccination can be difficult to achieve. One solution to this is the provision of booster doses of vaccine through childhood (as is the case, for example, for diphtheria, tetanus, pertussis and polio vaccines), in an attempt to sustain antibody levels above the protective threshold. It is known that provision of five or six doses of tetanus[45] or diphtheria[46] vaccine in childhood provides lifelong protection, and so booster doses of these vaccines throughout adult life are not routine in most countries that can achieve high coverage with multiple childhood doses. Given that, for some infections, the main burden is in young children, continued boosting after the second year of life is not undertaken (for example, the invasive bacterial infections including Hib and capsular group B meningococci).

The exception is the pertussis vaccine, where the focus of vaccine programmes is the prevention of disease in infancy; this is achieved both by direct vaccination of infants as well as by the vaccination of other age groups, including adolescents and pregnant women in some programmes, to reduce transmission to infants and provide protection by antibody transfer across the placenta. Notably, in high-income settings, many countries (starting in the 1990s) have switched to using the acellular pertussis vaccine, which is less reactogenic than (and therefore was thought to be preferable to) the older whole-cell pertussis vaccine that is still used in most low-income countries. It is now apparent that acellular pertussis vaccine induces a shorter duration of protection against clinical pertussis and may be less effective against bacterial transmission than is the whole-cell pertussis vaccine[47]. Many high-income countries have

Booster doses
Repeat administration of a vaccine after an initial priming dose, given in order to enhance the immune response.

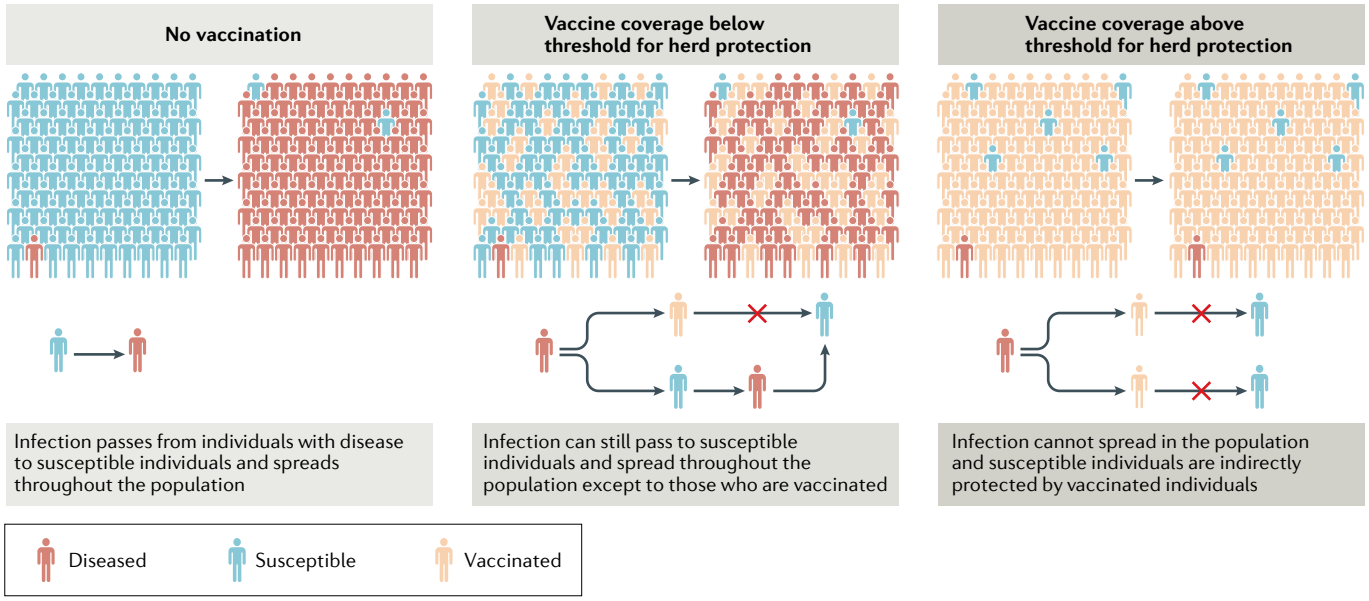


Fig. 5 | **Herd immunity is an important feature of vaccine-induced protection.** The concept of herd immunity for a highly contagious disease such as measles. Susceptible individuals include those who have not yet been immunized (for example, being too young), those who cannot be immunized (for example, as a result of immunodeficiency), those for whom the vaccine did not induce immunity, those for whom initial vaccine-induced immunity has waned and those who refused immunization.

observed a rise in pertussis cases since the introduction of the acellular vaccine, a phenomenon that is not observed in low-income nations using the whole-cell vaccine[48].

By contrast, lifelong protection seems to be the rule following a single dose with some of the live attenuated viral vaccines, such as yellow fever vaccine[49] (FIG. 4c), although it is apparent that protection is incomplete with others. In the case of varicella zoster and measles–mumps vaccines, some breakthrough cases are described during disease outbreaks among those individuals who have previously been vaccinated, although it is unclear whether this represents a group in whom immunity has waned (and who therefore needed booster vaccination) or a group for whom the initial vaccine did not induce a successful immune response. Breakthrough cases are less likely in those individuals who have had two doses of measles–mumps–rubella vaccine[50] or varicella zoster vaccine[51], and cases that do occur are usually mild, which indicates that there is some lasting immunity to the pathogen.

An illustration of the complexity of immune memory and the importance of understanding its underlying immunological mechanisms in order to improve vaccination strategies is provided by the concept of 'original antigenic sin'. This phenomenon describes how the immune system fails to generate an immune response against a strain of a pathogen if the host was previously exposed to a closely related strain, and this has been demonstrated in several infections, including dengue[52] and influenza[53]. This might have important implications for vaccine development if only a single pathogen strain or pathogen antigen is included in a vaccine, as vaccine recipients might then have impaired immune responses if later exposed to different strains of the same pathogen, potentially putting them at increased risk of infection or more severe disease. Strategies to overcome this include the use of adjuvants that stimulate innate immune responses, which can induce sufficiently cross-reactive B cells and T cells that recognize different strains of the same pathogen, or the inclusion of as many strains in a vaccine as possible, the latter approach obviously being limited by the potential of new strains to emerge in the future[54].

Herd immunity. Although direct protection of individuals through vaccination has been the focus of most vaccine development and is crucial to demonstrate for the licensure of new vaccines, it has become apparent that a key additional component of vaccine-induced protection is herd immunity, or more correctly 'herd protection' (FIG. 5). Vaccines cannot protect every individual in a population directly, as some individuals are not vaccinated for various reasons and others do not mount an immune response despite vaccination. Fortunately, however, if enough individuals in a population are vaccinated, and if vaccination prevents not only the development of disease but also infection itself (discussed in more detail below), transmission of the pathogen can be interrupted and the incidence of disease can fall further than would be expected, as a result of the indirect protection of individuals who would otherwise be susceptible.

For highly transmissible pathogens, such as those causing measles or pertussis, around 95% of the population must be vaccinated to prevent disease outbreaks, but for less transmissible organisms a lower percentage of vaccine coverage may be sufficient to have a substantial impact on disease (for example, for polio, rubella, mumps or diphtheria, vaccine coverage can be ≤86%). For influenza, the threshold for herd immunity is highly

variable from season to season and is also confounded by the variability in vaccine effectiveness each year[55]. Modest vaccine coverage, of 30–40%, is likely to have an impact on seasonal influenza epidemics, but ≥80% coverage is likely to be optimal[56]. Interestingly, there might be a downside to very high rates of vaccination, as the absence of pathogen transmission in that case will prevent natural boosting of vaccinated individuals and could lead to waning immunity if booster doses of vaccine are not used.

Apart from tetanus vaccine, all other vaccines in the routine immunization schedule induce some degree of herd immunity (FIG. 5), which substantially enhances population protection beyond that which could be achieved by vaccination of the individual only. Tetanus is a toxin-mediated disease acquired through infection of breaks in the skin contaminated with the toxin-producing bacteria *Clostridium tetani* from the environment — so, vaccination of the community with the tetanus toxoid will not prevent an unvaccinated individual acquiring the infection if they are exposed. As an example of the success of herd immunity, vaccination of children and young adults (up to 19 years of age) with capsular group C meningococcal vaccine in a mass campaign in 1999 resulted in almost complete elimination of disease from the UK in adults as well as children[57]. Currently, the strategy for control of capsular groups A, C, W and Y meningococci in the UK is vaccination of adolescents, as they are mainly responsible for transmission and vaccine-mediated protection of this age group leads to community protection through herd immunity[58]. The HPV vaccine was originally introduced to control HPV-induced cervical cancer, with vaccination programmes directed exclusively at girls, but it was subsequently found to also provide protection against HPV infection in heterosexual boys through herd immunity, which led to a marked reduction in the total HPV burden in the population[59,60].

Prevention of infection versus disease. Whether vaccines prevent infection or, rather, the development of disease after infection with a pathogen is often difficult to establish, but improved understanding of this distinction could have important implications for vaccine design. BCG vaccination can be used as an example to illustrate this point, as there is some evidence for the prevention of both disease and infection. BCG vaccination prevents severe disease manifestations such as tuberculous meningitis and miliary TB in children[61] and animal studies have shown that BCG vaccination reduces the spread of *M. tuberculosis* bacteria in the blood, mediated by T cell immunity[62], thereby clearly showing that vaccination has protective effects against the development of disease after infection. However, there is also good evidence that BCG vaccination reduces the risk of infection. In a TB outbreak at a school in the UK, 29% of previously BCG-vaccinated children had a memory T cell response to infection, as indicated by a positive interferon-γ release assay, as compared with 47% of the unvaccinated children[63]. A similar effect was seen when studying Indonesian household members of patients with TB, who had a 45% reduced chance of developing a positive interferon-γ release assay response to *M. tuberculosis* if they had previously been BCG vaccinated[64]. The lack of a T cell response in previously vaccinated individuals indicates that the BCG vaccine induces an innate immune response that results in 'early clearance' of the bacteria and prevents infection that induces an adaptive immune response. It will be hugely valuable for future vaccine development to better understand the induction of such protective innate immune responses so that they might be reproduced for other pathogens.

In the case of the current pandemic of the virus SARS-CoV-2, a vaccine that prevents severe disease and disease-driven hospitalization could have a substantial public health impact. However, a vaccine that could also block acquisition of the virus, and thus prevent both asymptomatic and mild infection, would have much larger impact by reducing transmission in the community and potentially establishing herd immunity.

Non-specific effects. Several lines of evidence indicate that immunization with some vaccines perturbs the immune system in such a way that there are general changes in immune responsiveness that can increase protection against unrelated pathogens[65]. This phenomenon has been best described in humans in relation to BCG and measles vaccines, with several studies showing marked reductions in all-cause mortality when these vaccines are administered to young children that are far beyond the expected impact from the reduction in deaths attributed to TB or measles, respectively[66]. These non-specific effects may be particularly important in high-mortality settings, but not all studies have identified the phenomenon. Although several immunological mechanisms have been proposed, the most plausible of which is that epigenetic changes can occur in innate immune cells as a result of vaccination, there are no definitive studies in humans that link immunological changes after immunization with important clinical end points, and it remains unclear how current immunization schedules might be adapted to improve population protection through non-specific effects. Of great interest in the debate, recent studies have indicated that measles disease casts a prolonged 'shadow' over the immune system, with depletion of existing immune memory, such that children who have had the disease have an increased risk of death from other causes over the next few years[67,68]. In this situation, measles vaccination reduces mortality from measles as well as the unconnected diseases that would have occurred during the 'shadow', resulting in a benefit that seems to be non-specific but actually relates directly to the prevention of measles disease and its consequences. This illustrates a limitation of vaccine study protocols: as these are usually designed to find pathogen-specific effects, the possibility of important non-specific effects cannot be assessed.

Factors affecting vaccine protection

The level of protection afforded by vaccination is affected by many genetic and environmental factors, including age, maternal antibody levels, prior antigen exposure, vaccine schedule and vaccine dose. Although most of these factors cannot be readily modified, age of

Interferon-γ release assay
An assay in which blood is stimulated with *Mycobacterium tuberculosis* antigens, after which levels of interferon-γ (produced by specific memory T cells if these are present) are measured.

Epigenetic changes
Changes in the expression of genes that do not result from changes in DNA sequence.

vaccination and schedule of vaccination are important and key factors in planning immunization programmes. The vaccine dose is established during early clinical development, based on optimal safety and immunogenicity. However, for some populations, such as older adults, a higher dose might be beneficial, as has been shown for the influenza vaccine[69,70]. Moreover, intradermal vaccination has been shown to be immunogenic at much lower (fractional) doses than intramuscular vaccination for influenza, rabies and HBV vaccines[71].

Age of vaccination. The highest burden of and mortality from infectious disease occur in the first 5 years of life, with the youngest infants being most affected. For this reason, immunization programmes have largely focused on this age group where there is the greatest benefit from vaccine-induced protection. Although this makes sense from an epidemiological perspective, it is somewhat inconvenient from an immunological perspective as the induction of strong immune responses in the first year of life is challenging. Indeed, vaccination of older children and adults would induce stronger immune responses, but would be of little value if those who would have benefited from vaccination have already succumbed to the disease.

It is not fully understood why immune responses to vaccines are not as robust in early infancy as they are in older children. One factor, which is increasingly well documented, is interference from maternal antibody[72] — acquired in utero through the placenta — which might reduce antigen availability, reduce viral replication (in the case of live viral vaccines such as measles[73]) or perhaps regulate B cell responses. However, there is also evidence that there is a physiological age-dependent increase in antibody responses in infancy[72]. Furthermore, bone marrow niches to support B cells are limited in infancy, which might explain the very short-lived immune responses that are documented in the first year of life[74]. For example, after immunization with 2 doses of the capsular group C meningococcal vaccine in infancy, only 41% of infants still had protective levels of antibody by the time of the booster dose, administered 7 months later[75].

In the case of T cell-independent antigens — in other words, plain polysaccharides from Hib, typhoid-causing bacteria, meningococci and pneumococci — animal data indicate that antibody responses depend on development of the marginal zone of the spleen, which is required for the maturation of marginal zone B cells, and this does not occur until around 18 months of age in human infants[76]. These plain polysaccharide vaccines do not induce memory B cells (FIG. 6) and, even in adults, provide protection for just 2–3 years, with protection resulting from antibody produced by plasma cells derived from marginal zone B cells[77]. However, converting plain polysaccharide vaccines into T cell-dependent protein–polysaccharide conjugate vaccines, which are immunogenic from 2 months of age and induce immune memory, has transformed prevention of disease caused by the encapsulated bacteria (pneumococci, Hib and meningococci) over the past three decades[78]. These are the most important invasive bacterial pathogens of childhood, causing most cases of childhood meningitis and bacterial pneumonia, and the development of the conjugate vaccine technology in the 1980s has transformed global child health[9].

Immune responses are also poor in the older population and most of the vaccines used in older adults offer limited protection or a limited duration of protection, particularly among those older than 75 years of age. The decline in immune function with age (known as immunosenescence) has been well documented[79] but, despite the burden of infection in this age group and the increasing size of the population, has not received sufficient attention so far amongst immunologists and vaccinologists. Interestingly, some have raised the hypothesis that chronic infection with cytomegalovirus (CMV) might have a role in immunosenescence through unfavourable effects on the immune system, including clonal expansion of CMV-specific T cell populations, known as 'memory inflation', and reduced diversity of naive T cells[80,81].

In high-income countries, many older adults receive influenza, pneumococcal and varicella zoster vaccines, although data showing substantial benefits of these vaccines in past few decades in the oldest adults (more than 75 years of age) are lacking. However, emerging data following the recent development and deployment of new-generation, high-dose or adjuvanted influenza vaccines[82] and an adjuvanted glycoprotein varicella zoster vaccine[83] suggest that the provision of additional signals to the immune system by certain adjuvants (such as AS01 and MF59) can overcome immunosenescence. It is now necessary to understand how and why, and to use this knowledge to expand options for vaccine-induced protection at the extremes of life.

Schedule of vaccination. For most vaccines that are used in the first year of life, 3–4 doses are administered by 12 months of age. Conventionally, in human vaccinology, 'priming' doses are all those administered at less than 6 months of age and the 'booster' dose is given at 9–12 months of age. So, for example, the standard WHO schedule for diphtheria–tetanus–pertussis-containing vaccines (which was introduced in 1974 as part of the Expanded Programme on Immunization[84]) consists of 3 priming doses at 6, 10 and 14 weeks of age with no booster. This schedule was selected to provide early protection before levels of maternal antibody had waned (maternal antibody has a half-life of around 30–40 days[85], so very little protection is afforded to infants from the mother beyond 8–12 weeks of age) and because it was known that vaccine compliance is better when doses are given close together. However, infant immunization schedules around the world are highly variable — few high-income or middle-income countries use the Expanded Programme on Immunization schedule — and were largely introduced with little consideration of how best to optimize immune responses. Indeed, schedules that start later at 8–12 weeks of age (when there is less interference from maternal antibody) and have longer gaps between doses (8 weeks rather than 4 weeks) are more immunogenic. A large number of new vaccines have been introduced since 1974 as a result of remarkable developments in technology, but

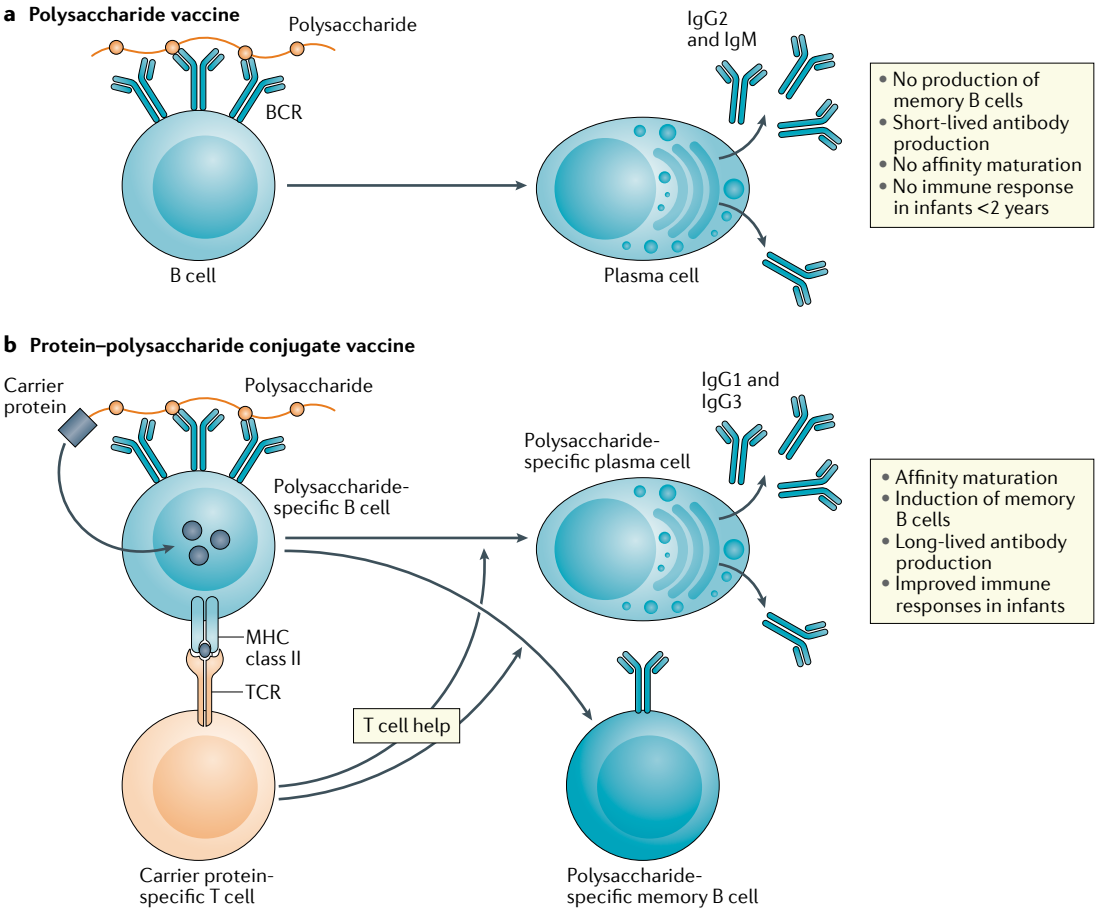


Fig. 6 | **Immune responses to polysaccharide and protein–polysaccharide conjugate vaccines. a** | Polysaccharide vaccines induce antibody-producing plasma cells by cross-linking the B cell receptor (BCR). However, affinity maturation of the antibody response and the induction of memory B cells do not occur. **b** | Protein–polysaccharide conjugate vaccines can engage T cells that recognize the carrier protein, as well as B cells that recognize the polysaccharide. T cells provide help to B cells, leading to affinity maturation and the production of both plasma cells and memory B cells. TCR, T cell receptor. Adapted from REF.[35], Springer Nature Limited.

these have generally been fitted into existing schedules without taking into account the optimal scheduling for these new products. The main schedules used globally for diphtheria–tetanus–pertussis vaccine are presented in Supplementary Table 1, and the changes to the UK immunization schedule since 1963 are presented in Supplementary Table 2. It should also be noted that surveys show vaccines are rarely delivered on schedule in many countries and, thus, the published schedule may not be how vaccines are actually delivered on the ground. This is particularly the case in remote areas (for example, where health professionals only visit occasionally) and regions with limited or chaotic health systems, leaving children vulnerable to infection.

Safety and side effects of vaccines

Despite the public impression that vaccines are associated with specific safety concerns, the existing data indicate that vaccines are remarkably safe as interventions to defend human health. Common side effects, particularly those associated with the early innate immune response to vaccines, are carefully documented in clinical trials. Although rare side effects might not be identified in clinical trials, vaccine development is tightly controlled and robust post-marketing surveillance systems are in place in many countries, which aim to pick these up if they do occur. This can make the process of vaccine development rather laborious but is appropriate because, unlike most drugs, vaccines are used for prophylaxis in a healthy population and not to treat disease. Perhaps because vaccines work so well and the diseases that they prevent are no longer common, there have been several spurious associations made between vaccines and various unrelated health conditions that occur naturally in the population. Disentangling incorrect claims of vaccine harm from true vaccine-related adverse events requires very careful epidemiological studies.

Common side effects. Licensure of a new vaccine normally requires safety studies involving from 3,000 to tens of thousands of individuals. Thus, common side effects are very well known and are published by the regulator at the time of licensure. Common side effects of many vaccines include injection site pain, redness and swelling and some systemic symptoms such as fever, malaise and headache. All of these side effects, which occur in the

first 1–2 days following vaccination, reflect the inflammatory and immune responses that lead to the successful development of vaccine-induced protection. About 6 days after measles–mumps–rubella vaccination, about 10% of 12-month-old infants develop a mild viraemia, which can result in fever and rash, and occasionally febrile convulsions (1 in 3,000)[86]. Although these side effects are self-limiting and relatively mild — and are trivial in comparison with the high morbidity and mortality of the diseases from which the vaccines protect — they can be very worrying for parents and their importance is often underestimated by clinicians who are counselling families about immunization.

Immunodeficiency and vaccination. Most vaccines in current use are inactivated, purified or killed organisms or protein and/or polysaccharide components of a pathogen; as they cannot replicate in the vaccine recipient, they are thus not capable of causing any significant side effects, resulting in very few contraindications for their use. Even in immunocompromised individuals, there is no risk from use of these vaccines, although the induction of immunity may not be possible, depending on the nature of the immune system defect. More caution is required for the use of live attenuated, replicating vaccines (such as yellow fever, varicella zoster, BCG and measles vaccines) in the context of individuals with T cell immunodeficiency as there is a theoretical risk of uncontrolled replication, and live vaccines are generally avoided in this situation[87]. A particular risk of note is from the yellow fever vaccine, which is contraindicated in individuals with T cell immunodeficiency and occasionally causes a severe viscerotropic or neurotropic disease in individuals with thymus disease or after thymectomy, in young infants and adults more than 60 years of age[88]. In individuals with antibody deficiency, there may be some merit in the use of routine live vaccines, as T cell memory may be induced that, although unlikely to prevent future infection, could improve control of the disease if infection occurs.

The myth of antigenic overload. An important parental concern is that vaccines might overwhelm their children's immune systems. In a telephone survey in the USA, 23% of parents agreed with the statement 'Children get more immunizations than are good for them', and 25% indicated that they were concerned that their child's immune system could be weakened by too many immunizations[89]. However, there is ample evidence to disprove these beliefs. Although the number of vaccines in immunization programmes has increased, the total number of antigens has actually decreased from more than 3,200 to approximately 320 as a result of discontinuing the smallpox vaccine and replacing the whole-cell pertussis vaccine with the acellular vaccine[90,91]. Vaccines comprise only a small fraction of the antigens that children are exposed to throughout normal life, with rapid bacterial colonization of the gastrointestinal tract after birth, multiple viral infections and environmental antigens. Moreover, multiple studies have shown that children who received vaccinations had a similar, or even reduced, risk of unconnected infections in the following period[92–95]. Looking at children who presented to the emergency department with infections not included in the vaccine programme, there was no difference in terms of their previous antigen exposure by vaccination[96].

Significant rare side effects. Serious side effects from vaccines are very rare, with anaphylaxis being the most common of these rare side effects for parenteral vaccines, occurring after fewer than one in a million doses[97]. Individuals with known allergies (such as egg or latex) should avoid vaccines that may have traces of these products left over from the production process with the specific allergen, although most cases of anaphylaxis are not predictable in advance but are readily managed if vaccines are administered by trained health-care staff.

Very rare side effects of vaccines are not usually observed during clinical development, with very few documented, and they are only recognized through careful surveillance in vaccinated populations. For example, there is a very low risk of idiopathic thrombocytopenic purpura (1 in 24,000 vaccine recipients) after measles vaccination[86]. From 1 in 55,000 to 1 in 16,000 recipients of an AS03-adjuvanted 2009 pandemic H1N1 influenza vaccine[98,99], who had a particular genetic susceptibility (HLA DQB1*0602)[100], developed narcolepsy, although the debate continues about whether the trigger was the vaccine, the adjuvant or some combination, perhaps with the circulating virus also having a role.

Despite widespread misleading reporting about links between the measles–mumps–rubella vaccine and autism from the end of the 1990s, there is no evidence that any vaccines or their components cause autism[101,102]. Indeed, the evidence now overwhelmingly shows that there is no increased risk of autism in vaccinated populations. Thiomersal (also known as thimerosal) is an ethyl mercury-containing preservative that has been used widely in vaccines since the 1930s without any evidence of adverse events associated with it, and there is also no scientific evidence of any link between thiomersal and autism despite spurious claims about this[102]. Thiomersal has been voluntarily withdrawn from most vaccines by manufacturers as a precautionary measure rather than because of any scientific evidence of lack of safety and is currently used mainly in the production of whole-cell pertussis vaccines.

The risk of hospitalization, death or long-term morbidity from the diseases for which vaccines have been developed is so high that the risks of common local and systemic side effects (such as sore arm and fever) and the rare more serious side effects are far outweighed by the massive reductions in disease achieved through vaccination. Continuing assessment of vaccine safety post licensure is important for the detection of rare and longer-term side effects, and efficient reporting systems need to be in place to facilitate this[103]. This is particularly important in a pandemic situation, such as the COVID-19 pandemic, as rapid clinical development of several vaccines is likely to take place and large numbers of people are likely to be vaccinated within a short time.

Anaphylaxis
A severe and potentially life-threatening reaction to an allergen.

Parenteral vaccines
Vaccines that are administered by means avoiding the gastrointestinal tract (for example, by intramuscular, subcutaneous or intradermal routes).

Idiopathic thrombocytopenic purpura
An acquired autoimmune condition characterized by low levels of platelets in the blood caused by antibodies to platelet antigens.

Narcolepsy
A rare chronic sleep disorder characterized by extreme sleepiness during the day and sudden sleep attacks.

Challenges to vaccination success

Vaccines only work if they are used. Perhaps the biggest challenge to immunization programmes is ensuring that the strong headwinds against deployment, ranging from poor infrastructure and lack of funding to vaccine hesitancy and commercial priorities, do not prevent successful protection of the most vulnerable in society. It is noteworthy that these are not classical scientific challenges, although limited knowledge about which antigens are protective, which immune responses are needed for protection and how to enhance the right immune responses, particularly in the older population, are also important considerations.

Access to vaccines. The greatest challenge for protection of the human population against serious infectious disease through vaccination remains access to vaccines and the huge associated inequity in access. Access to vaccines is currently limited, to varying degrees in different regions, by the absence of a health infrastructure to deliver vaccines, the lack of convenient vaccine provision for families, the lack of financial resources to purchase available vaccines (at a national, local or individual level) and the marginalization of communities in need. This is perhaps the most pressing issue for public health, with global vaccine coverage having stalled; for example, coverage for diphtheria–tetanus–pertussis-containing vaccines has only risen from 84% to 86% since 2010 (REF.[104]). However, this figure hides huge regional variation, with near 100% coverage in some areas and almost no vaccinated children in others. For the poorest countries in the world, Gavi, the Vaccine Alliance provides funding to assist with new vaccine introductions and has greatly accelerated the broadening of access to new vaccines that were previously only accessible to high-income countries. However, this still leaves major financial challenges for countries that do not meet the criteria to be eligible for Gavi funding but still cannot afford new vaccines. Inequity remains, with approximately 14 million children not receiving any vaccinations and another 5.7 million children being only partially vaccinated in 2019 (REF.[105]).

Other important issues can compromise vaccine availability and access. For example, most vaccines must be refrigerated at 2–8 °C, requiring the infrastructure and capacity for cold storage and a cold chain to the clinic where the vaccine is delivered, which is limited in many low-income countries. The route of administration can also limit access; oral vaccines (such as rotavirus, polio or cholera vaccines) and nasal vaccines (such as live attenuated influenza vaccine) can be delivered rapidly on a huge scale by less-skilled workers, whereas most vaccines are injected, which requires more training to administer and takes longer. Nevertheless, these hurdles can be overcome: in Sindh Province, Pakistan, 10 million doses of injected typhoid conjugate vaccine were administered to children to control an outbreak of extensively drug-resistant typhoid in just a few weeks at the end of 2019 (REF.[106]).

The anti-vaccination movement. Despite access being the main issue affecting global vaccine coverage, a considerable focus is currently on the challenges posed by the anti-vaccination movement, largely as a result of worrying trends of decreasing vaccine coverage in high-income settings, leading to outbreaks of life-threatening infectious diseases, such as measles. In 2018, there were 140,000 deaths from measles worldwide, and the number of cases in 2019 was the highest in any year since 2006 (REF.[107]). Much has been written about the dangerous role of social media and online search engines in the spread of misinformation about vaccines and the rise of the anti-vaccination movement, but scientists are also at fault for failing to effectively communicate the benefits of vaccination to a lay public. If this is to change, scientists do not need to counter or engage with the anti-vaccination movement but to use their expertise and understanding to ensure effective communication about the science that underpins our remarkable ability to harness the power of the immune system through vaccination to defend the health of our children.

Commercial viability. A third important issue is the lack of vaccines for some diseases for which there is no commercial incentive for development. Typically, these are diseases that have a restricted geographical spread (such as Rift Valley fever, Ebola, Marburg disease or plague) or occur in sporadic outbreaks and only affect poor or displaced communities (such as Ebola and cholera). Lists of outbreak pathogens have been published by various agencies including the WHO[108], and recent funding initiatives, including those from US and European governments, have increased investment in the development of orphan vaccines. The Coalition for Epidemic Preparedness Innovations (CEPI) is set to have a major role in funding and driving the development of vaccines against these pathogens.

Immunological challenges. For other pathogens, there is likely to be a commercial market but there are immunological challenges for the development of new vaccines. For example, highly variable pathogens, including some with a large global distribution such as HIV and hepatitis C virus, pose a particular challenge. The genetic diversity of these pathogens, which occurs both between and within hosts, makes it difficult to identify an antigen that can be used to immunize against infection. In the case of HIV, antibodies can be generated that neutralize the virus, but the rapid mutation of the viral genome means that the virus can evade these responses within the same host. Some individuals do produce broadly neutralizing antibodies naturally, which target more conserved regions of the virus, leading to viral control, but it is not clear how to robustly induce these antibodies with a vaccine. Indeed, several HIV vaccines have been tested in clinical trials that were able to induce antibody responses (for example, RV144 vaccine showed 31% protection[109]) and/or T cell responses, but these vaccines have not shown consistent evidence of protection in follow-up studies, and several studies found an increased risk of infection among vaccine recipients[110].

For other pathogens, such as *Neisseria gonorrhoeae* (which causes gonorrhoea) and *Treponema pallidum* (which causes syphilis), antigenic targets for protective immune

Orphan vaccines
Vaccines that are intended for a limited scope or targeting infections that are rare, as a result of which development costs exceed their market potential.

responses have not yet been determined, partly owing to limited investment and a poor understanding of the mechanisms of immunity at mucosal surfaces, or have thus far only resulted in limited protection. For example, the licensed malaria vaccine, RTSS, provides only 30–40% protection and further work is needed to develop suitable products[111]. New malaria vaccines in development target more conserved antigens on the parasite surface or target different stages of the parasite life cycle. Combinations of these approaches in a vaccine (perhaps targeting multiple stages of the life cycle), together with anti-vector strategies such as the use of genetically modified mosquitoes or Wolbachia bacteria to infect mosquitoes and reduce their ability to carry mosquito parasites[112], as well as mosquito-bite avoidance, have the potential to markedly reduce malaria parasite transmission.

Seasonal influenza vaccines have, in recent decades, been used to protect vulnerable individuals in high-income countries, including older adults, children and individuals with co-morbidities that increase risk of severe influenza. These vaccines are made from virus that is grown in eggs; purified antigen, split virions or whole virions can be included in the final vaccine product. The vaccines take around 6 months to manufacture and have highly variable efficacy from one season to another, partly owing to the difficulty in predicting which virus strain will be circulating in the next influenza season, so that the vaccine strain may not match the strain causing disease[113]. Another issue that is increasingly recognized is egg adaptation, whereby the vaccine strain of virus becomes adapted to the egg used for production, leading to key mutations that mean it is not well matched to, and does not protect against, the circulating viral strain[114]. Vaccine-induced protection might be improved by the development of mammalian or insect cell-culture systems for growing influenza virus to avoid egg adaptation, and the use of MF59-adjuvanted vaccines and high-dose influenza vaccines to improve immune responses. Because of the cost of purchasing seasonal influenza vaccines annually, and the problem of antigenic variability, the search for a universal influenza vaccine receives considerable attention, with a particular focus on vaccines that induce T_H cells or antibodies to conserved epitopes[115], but there are currently no products in late-stage development.

Although BCG is the most widely used vaccine globally, with 89% of the world population receiving it in 2018 (REF.[105]), there is still a huge global burden of TB and it is clear that more effective TB vaccines are needed. However, the optimal characteristics of a prophylactic TB vaccine, which antigens should be included and the nature of protective immunity remain unknown, despite more than 100 years of TB vaccine research. A viral vector expressing a TB protein, 85A, has been tested in a large TB-prevention trial in South Africa but this vaccine did not show protection, which was attributed by the authors to poor immunogenicity in the vaccinated children[116]. However, the publication of a study in 2019 showing that a novel TB vaccine, M72/AS01E (an AS01-adjuvanted vaccine containing the *M. tuberculosis* antigens MTB32A and MTB39A), could limit progression to active TB disease in latently infected individuals with efficacy of 50% over 3 years gives a glimmer of hope that TB control may be realized in the future by novel vaccine approaches[117]. Questions remain about the duration of the effect, but the demonstrated efficacy can now be interrogated thoroughly to determine the nature of protective immunity against TB.

Future vaccine development

There are several important diseases for which new vaccines are needed to reduce morbidity and mortality globally, which are likely to have a market in both high-income and low-income countries, including vaccines for group B *Streptococcus* (a major cause of neonatal meningitis), RSV and CMV. Group B *Streptococcus* vaccines are currently in trials of maternal vaccination, with the aim of inducing maternal antibodies that cross the placenta and protect the newborn passively[118]. RSV causes a lower respiratory tract infection, bronchiolitis, in infancy and is the commonest cause of infant hospitalization in developed countries and globally one of the leading causes of death in those less than 12 months of age. As many as 60 new RSV vaccine candidates are in development as either maternal vaccines or infant vaccines, or involving immunization with RSV-specific monoclonal antibodies that have an extended half-life. A licensed RSV vaccine would have a huge impact on infant health and paediatric hospital admissions. CMV is a ubiquitous herpesvirus that is responsible for a significant burden of disease in infants; 15–20% of congenitally infected children develop long-term sequelae, most importantly sensorineural hearing loss, and CMV thus causes more congenital disease than any other single infectious agent. A vaccine that effectively prevents congenital infection would provide significant individual and public health benefits. A lack of understanding of the nature of protective immunity against CMV has hampered vaccine development in the past, but the pipeline is now more promising[119,120].

Another major line of development of new vaccines is to combat hospital-acquired infections, particularly with antibiotic-resistant Gram-positive bacteria (such as *Staphylococcus aureus*) that are associated with wound infections and intravenous catheters and various Gram-negative organisms (such as *Klebsiella* spp. and *Pseudomonas aeruginosa*). Progress has been slow in this field and an important consideration will be targeting products to the at-risk patient groups before hospital admission or surgery.

Perhaps the largest area of growth for vaccine development is for older adults, with few products aimed specifically at this population currently. With the population of older adults set to increase substantially (the proportion of the population who are more than 60 years of age is expected to increase from 12% to 22% by 2050 (REF.[121])), prevention of infection in this population should be a public health priority. Efforts to better understand immunosenescence and how to improve vaccine responses in the oldest adults are a major challenge for immunologists today.

Novel technologies. Important challenges to overcome in the following years are genetic diversity (for example, of viruses such as HIV, hepatitis C virus and influenza), the

requirement for a broader immune response including T cells for protection against diseases such as TB and malaria, and the need to swiftly respond to emerging pathogens and outbreak situations. Traditionally, vaccine development takes more than 10 years[122], but the COVID-19 pandemic has demonstrated the urgency for vaccine technologies that are flexible and facilitate rapid development, production and upscaling[123].

Novel technologies to combat these hurdles will include platforms that allow for improved antigen delivery and ease and speed of production, application of structural biology and immunological knowledge to aid enhanced antigen design and discovery of better adjuvants to improve immunogenicity. Fortunately, recent advances in immunology, systems biology, genomics and bio-informatics offer great opportunities to improve our understanding of the induction of immune responses by vaccines and to transform vaccine development through increasingly rational design[124].

New platforms include viral vectored vaccines and nucleic acid-based vaccines. Antigen-presenting cells such as dendritic cells, T cell-based vaccines and bacterial vectors are being explored as well, but are still at early stages of development for use against infectious pathogens. Whereas classic whole-organism vaccine platforms require the cultivation of the pathogen, next-generation viral vectored or nucleic acid-based vaccines can be constructed using the pathogen genetic sequence only, thereby significantly increasing the speed of development and manufacturing processes[125].

Viral vectored vaccines are based on a recombinant virus (either replicating or not), in which the genome is altered to express the target pathogen antigen. The presentation of pathogen antigens in combination with stimuli from the viral vector that mimic natural infection leads to the induction of strong humoral and cellular immune responses without the need for an adjuvant. A potential disadvantage of viral vectored vaccines is the presence of pre-existing immunity when a vector such as human adenovirus is used that commonly causes infection in humans. This can be overcome by using vectors such as a simian adenovirus, against which almost no pre-existing immunity exists in humans[126]. Whether immune responses against the vector will limit its use for repeated vaccinations with different antigens will need to be investigated.

Nucleic acid-based vaccines consist of either DNA or RNA encoding the target antigen, which potentially allows for the induction of both humoral and cellular immune responses once the encoded antigens are expressed by the vaccine recipient after uptake of the nucleic acid by their cells. A huge advantage of these vaccines is that they are highly versatile and quick and easy to adapt and produce in the case of an emerging pathogen. Indeed, the SARS-CoV-2 mRNA-based vaccine mRNA-1273 entered clinical testing just 2 months after the genetic sequence of SARS-CoV-2 was identified[127] and the BNT162b2 lipid nanoparticle-formulated, nucleoside-modified RNA vaccine was the first SARS-CoV-2 vaccine to be licensed[128]. One of the disadvantages of these vaccines is that they need to be delivered directly into cells, which requires specific injection devices, electroporation or a carrier molecule and brings with it a risk of low transfection rate and limited immunogenicity[129]. Furthermore, the application of RNA vaccines has been limited by their lack of stability and requirement for a cold chain, but constant efforts to improve formulations hold promise to overcome these limitations[130,131].

A beautiful example of how immunological insight can revolutionize vaccine development is the novel RSV vaccine DS-Cav1. The RSV surface fusion (F) protein can exist in either a pre-fusion (pre-F) conformation, which facilitates viral entry, or a post-fusion (post-F) form. Whereas previous vaccines mainly contained the post-F form, insight into the atomic-level structure of the protein has allowed for stable expression of the pre-F protein, leading to strongly enhanced immune responses and providing a proof of concept for structure-based vaccine design[132,133].

In addition to the novel vaccine platforms mentioned above, there are ongoing efforts to develop improved methods of antigen delivery, such as liposomes (spherical lipid bilayers), polymeric particles, inorganic particles, outer membrane vesicles and immunostimulating complexes. These, and other methods such as self-assembling protein nanoparticles, have the potential to optimally enhance and skew the immune response to pathogens against which traditional vaccine approaches have proven to be unsuccessful[129,134]. Furthermore, innovative delivery methods, such as microneedle patches, are being developed, with the potential advantages of improved thermostability, ease of delivery with minimal pain and safer administration and disposal[135]. An inactivated influenza vaccine delivered by microneedle patch was shown to be well tolerated and immunogenic in a phase I trial[136]. This might allow for self-administration, although it would be important for professional medical care to be available if there is a risk of severe side effects such as anaphylaxis.

Conclusions and future directions

Immunization protects populations from diseases that previously claimed the lives of millions of individuals each year, mostly children. Under the United Nations Convention on the Rights of the Child, every child has the right to the best possible health, and by extrapolation a right to be vaccinated.

Despite the outstanding success of vaccination in protecting the health of our children, there are important knowledge gaps and challenges to be addressed. An incomplete understanding of immune mechanisms of protection and the lack of solutions to overcome antigenic variability have hampered the design of effective vaccines against major diseases such as HIV/AIDS and TB. Huge efforts have resulted in the licensure of a partially effective vaccine against malaria, but more effective vaccines will be needed to defeat this disease. Moreover, it is becoming clear that variation in host response is an important factor to take into account. New technologies and analytical methods will aid the delineation of the complex immune mechanisms involved, and this knowledge will be important to design effective vaccines for the future.

Apart from the scientific challenges, sociopolitical barriers stand in the way of safe and effective

Outer membrane vesicles
Blebs made from the outer membrane of Gram-negative bacteria, containing the surface proteins and lipids of the organism in the membrane.

vaccination for all. Access to vaccines is one of the greatest obstacles, and improving infrastructure, continuing education and enhancing community engagement will be essential to improve this, and novel delivery platforms that eliminate the need for a cold chain could have great implications. There is a growing subset of the population who are sceptical about vaccination and this requires a response from the scientific community to provide transparency about the existing knowledge gaps and strategies to overcome these. Constructive collaboration between scientists and between scientific institutions, governments and industry will be imperative to move forwards. The COVID-19 pandemic has indeed shown that, in the case of an emergency, many parties with different incentives can come together to ensure that vaccines are being developed at unprecedented speed but has also highlighted some of the challenges of national and commercial interests. As immunologists, we have a responsibility to create an environment where immunization is normal, the science is accessible and robust, and access to vaccination is a right and expectation.

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The authors contributed equally to all aspects of the article.

Competing interests
A.J.P. is Chair of the UK Department of Health and Social Care's (DHSC) Joint Committee on Vaccination and Immunisation (JCVI), a member of the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) and a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in this article do not necessarily represent the views of the DHSC, JCVI, NIHR or WHO. E.M.B. declares no competing interests. Oxford University has entered into a partnership with AstraZeneca for the development of a viral vectored coronavirus vaccine.

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