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Review article

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Immunological factors linked to geographical variation in vaccine responses

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Abstract

Vaccination is one of medicine's greatest achievements; however, its full potential is hampered by considerable variation in efficacy across populations and geographical regions. For example, attenuated malaria vaccines in high-income countries confer almost 100% protection, whereas in low-income regions these same vaccines achieve only 20–50% protection. This trend is also observed for other vaccines, such as bacillus Calmette–Guérin (BCG), rotavirus and yellow fever vaccines, in terms of either immunogenicity or efficacy. Multiple environmental factors affect vaccine responses, including pathogen exposure, microbiota composition and dietary nutrients. However, there has been variable success with interventions that target these individual factors, highlighting the need for a better understanding of their downstream immunological mechanisms to develop new ways of modulating vaccine responses. Here, we review the immunological factors that underlie geographical variation in vaccine responses. Through the identification of causal pathways that link environmental influences to vaccine responsiveness, it might become possible to devise modulatory compounds that can complement vaccines for better outcomes in regions where they are needed most.

Sections

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Introduction

It is estimated that vaccines have prevented 37 million deaths in the past 20 years[1], thereby having a substantial impact on global health. However, the full potential of some vaccines is hampered by their low and variable efficacy across populations and geographical areas (Box 1). This was first noted for bacillus Calmette–Guérin (BCG) vaccine efficacy, which was reported to vary with geographical latitude[2]. It is now increasingly recognized that several other vaccines induce variable responses in populations living in different geographical areas or of different socioeconomic status (Fig. 1). These include more recently developed vaccines such as rotavirus vaccines[3–6] and those under development, such as the whole-organism malaria radiation-attenuated *Plasmodium falciparum* sporozoite (PfSPZ) vaccine[7–12] and the PfSPZ–chemoprophylaxis attenuated vaccine (PfSPZ–CVac)[12–14], which show remarkable variation in efficacy. Variable vaccine immunogenicity has been observed when comparing low-income and/or middle-income regions with high-income regions of the world not only for the aforementioned vaccines but also for vaccines that target yellow fever virus[15] and Ebola virus[16]. Lower performance of such vaccines, which we refer to as vaccine hyporesponsiveness, is seen not only in low- and middle-income countries, but also in poor rural areas compared with affluent urban regions within the same country[17,18]. It is estimated that worldwide 77 million children receiving BCG and 5 million receiving rotavirus vaccine are insufficiently protected against the diseases targeted by these vaccines[19].

Although genetic factors hard wire immune and vaccine responsiveness[20], twin studies have indicated that non-heritable factors contribute by more than 70% to shaping the immune response to vaccines[21,22]. Numerous environmental and non-heritable factors have been implicated in vaccine hyporesponsiveness, including nutritional status, the microbiome and exposure to microorganisms and parasites[23–28] (Box 2). However, interventions to target some of these factors, such as micronutrient supplementation and/or probiotics[29] and anthelmintic treatment[30,31], have had variable success. This highlights that vaccine responses are modulated by multiple factors, which poses a challenge in applying public health measures to overcome vaccine hyporesponsiveness. Therefore, it is important to understand the mechanisms through which environmental factors drive vaccine hyporesponsiveness. Advances in technologies such as transcriptomics, metabolomics and epigenetic analyses at the single-cell level as well as high-dimensional cytometry allow us to study vaccine-specific immune responses in greater breadth and depth (Box 3), helping to identify new pathways and networks of immunological events that can be targeted for more effective vaccines[32,33].

In this Review, we discuss the immunological factors and proposed mechanisms that underlie variation in efficacy or immunogenicity of vaccines across populations from different geographical areas. We largely focus on vaccines against tuberculosis, rotavirus gastroenteritis, yellow fever and malaria, which are worldwide, highly prevalent and life-threatening infectious diseases (Box 1).

Immunological factors linked to vaccine hyporesponsiveness

Several immunological contexts may underlie vaccine hyporesponsiveness, including pre-existing immunity, exuberant immune activation, skewed immune responses and restructured lymphoid tissue (Fig. 2), and may explain the varied efficacy of vaccines between different geographical areas and populations.

Pre-existing immunity to similar or cross-reactive antigens

One of the most intensively discussed effects of pre-exposure to a pathogen on performance of a vaccine that targets the pathogen has been the impact of environmental mycobacteria on BCG vaccine efficacy. The BCG vaccine consists of live attenuated *Mycobacterium bovis*, which mainly infects cattle but is closely related to the human pathogen *Mycobacterium tuberculosis*, and its protective effect can be affected by interference of cellular immune responses to non-tuberculous mycobacteria in the environment[2]. The mechanism that underlies this interference has been hypothesized to be via either a 'blocking' or 'masking' mechanism. According to the blocking hypothesis, pre-existing immune responses accelerate the clearance of BCG by preventing the multiplication of live attenuated bacteria required for the induction of an effective vaccine response. Essential to this hypothesis is that exposure to non-tuberculous mycobacteria induces no or little protection against tuberculosis. The masking hypothesis postulates that exposure to non-tuberculous mycobacteria provides significant protection against tuberculosis and thereby masks the effect of BCG, as vaccine efficacy is calculated by comparing disease incidence between vaccinated and unvaccinated individuals[34]. Although these two hypotheses are not mutually exclusive, a study by Barreto et al.[35] supports the notion that blocking rather than masking is the predominant mechanism behind the geographical variation in BCG vaccine efficacy.

Interestingly, the blocking hypothesis might apply to the rotavirus vaccine, as children with higher titres of maternal anti-rotavirus IgG have a lower seroconversion rate after vaccination[36–38]. Similarly, the blocking effect of pre-exposure on vaccine responses seems to have a role in the reduced immunogenicity of the RTS,S malaria subunit vaccine. Analysis of data from a phase III trial of the RTS,S/AS01E vaccine showed that high levels of pre-vaccination antibodies to circumsporozoite epitopes were associated with low levels of vaccine-induced antibodies, particularly in infants[39]. The same principle might apply to the superior immunogenicity of a malaria vaccine candidate, the RH5.1 antigen, when boosting is delayed. The delayed boosting schedule corresponded to a time point when antibody levels from previous doses were declining[40]. Mechanistically, the binding of pre-existing antibodies to vaccine antigens in the lymph nodes (LNs) could interfere with boosting of vaccine-induced antibody responses[41]. With respect to the efficacy of live attenuated malaria vaccines, which are associated with cellular immune responses that target liver-stage parasites, pre-exposure to malaria parasites might also have a role[28], but in a different way. Through repeated exposure to malaria parasites, both enhanced innate immunity through a type I interferon response and memory liver-resident $CD8^+$ T cells can impede the entry of vaccine-delivered sporozoites to the liver, thereby reducing the induction of protective immune responses[42,43]. However, pre-vaccination antibody titres against yellow fever virus do not seem to have a role in reduced responses to the yellow fever vaccine, as yellow fever vaccination resulted in higher seroconversion in Mali (91.0%) than in Ghana (63.5%) even though the pre-vaccination antibody titres were higher in Mali and, indeed, were not associated with post-vaccination antibody titres[44]. As the yellow fever vaccine induces an extremely robust protective response, and a fractional dose of this vaccine induces strong immunity[45], it is possible that the ability of the vaccine to self-replicate is not sufficiently hampered by the pre-existing neutralizing antibodies. A full understanding of pre-existing immunity could enable a better design in terms of selecting adjuvants, targeting of multiple epitopes or timing of boosting to help overcome any blocking effects on vaccine performance (Fig. 2).

Box 1

Vaccine hyporesponsiveness: efficacy and immunogenicity

Vaccine performance can be studied through the assessment of immunogenicity, efficacy or effectiveness. Immunogenicity reveals the extent of an immune response evoked by a vaccine, whereas efficacy and effectiveness assess the beneficial effects of the vaccine in a trial setting or under real-life conditions, respectively. Immunogenicity, in contrast to efficacy and effectiveness, can be studied all over the world irrespective of whether the target disease is prevalent in a particular area and requires only a limited number of vaccinated individuals. However, with the increasing use of safe controlled human infection models in testing vaccines, it is now also possible to assess vaccine efficacy in different populations and geographical areas[11,150–152]. In such studies, healthy volunteers are given a vaccine or a placebo and thereafter are challenged with an infectious dose of the target pathogen that is known to establish infection with well-defined time to patency, burden and/or symptoms. Through this approach any protective effect of the administered vaccine against the given challenge can be assessed. Such models are increasingly complementing the traditional phase I or II studies in the field[150], although these cannot fully replace placebo-controlled trials. Differences in immunogenicity and efficacy of both licensed and newly developed vaccines have become apparent between populations living in geographical areas that differ in environmental and socioeconomic conditions.

Tuberculosis

The bacillus Calmette–Guérin (BCG) vaccine is currently the only tuberculosis vaccine approved and licensed for use, and it consists of live attenuated *Mycobacterium bovis*[153]. This vaccine is recommended to be given at birth in 157 countries[154], and its protective efficacy has largely been attributed to $CD4^+$ T cell-mediated immunity that can stimulate monocytes and/or macrophages to destroy intracellular mycobacteria; however, $CD8^+$ T cell-mediated cytotoxicity towards mycobacteria-infected cells has also been shown[155]. The efficacy of the BCG vaccine progressively increases further from the equator; with 23% efficacy at less than 20 degrees latitude, 32% at 20–40 degrees latitude and 69% at more than 40 degrees latitude[156] (Supplementary Table 1).

Rotavirus gastroenteritis

The rotavirus vaccine developed to protect against severe diarrhoea is a live attenuated vaccine that is administered orally[157]. The first vaccine dose is given before 15 weeks of age, followed by one or two additional doses before 8 months of age[158]. It mediates protection mainly through the generation of antibodies to rotavirus[159]. The highest efficacy of Rotarix, one of the currently licensed rotavirus vaccines, over the first year of life, was seen in high-income countries (>95%), whereas this was lower in middle-income countries (>80%) and low-income countries (<75%), with the lowest reported performance in Malawi (49.2%)[26,160]. This trend was confirmed in a meta-analysis[161] (Supplementary Table 2). The recently developed rotavirus RV3-BB vaccine showed a high cumulative serum immune response (76%) in neonates in Java, the most well-developed island of Indonesia[162]; however, in Malawi, the cumulative serum IgA seroconversion rate was 57% for neonates and 59% for infants 4 weeks after vaccination[163], which resembles the seroconversion rate of Rotarix in Malawian infants (57%)[164].

Yellow fever

The yellow fever vaccine is a live attenuated vaccine (17D strain) that can be given from the age of 9 months[165], and it protects by generating neutralizing antibodies[166]. Such live attenuated vaccines replicate and thus mimic a natural infection, which leads to a prolonged activation of multiple innate immune pathways and can induce appropriate humoral and cellular responses[167]. Although there were no vaccine efficacy studies performed, the vaccine is considered highly effective, and immunogenicity determined by seroconversion rates after vaccination was statistically significantly higher in Europe and the USA (99%) than in Latin American countries, including Brazil and Colombia (94%)[168]. Furthermore, a study that compared 9-month-old children reported that the seroconversion rate was lower in rural Ghana (63.8%) than in urban Mali (91.0%)[44] (Supplementary Table 3). A comparison of immunological responses to yellow fever vaccines in Switzerland and Uganda noted that, although antibody titres reached protective levels in both cohorts, individuals from Switzerland had significantly higher titres of neutralizing antibodies than individuals from Uganda[15].

Malaria

RTS,S is a subunit malaria vaccine adjuvanted with AS01, which is the only licensed malaria vaccine and is given in four doses to children from 5 months of age in areas of moderate and high malaria transmission[169]. It leads to antibody responses to circumsporozoite protein on sporozoites[170]. RTS,S/AS01 showed promising efficacy in malaria-naive adults[171]; however, variable efficacy was reported in a large phase III clinical trial in seven African countries, with an average 36% efficacy after three doses and booster regime in children aged 5–17 months[172] (Supplementary Table 4). Whole-sporozoite vaccines such as the live *Plasmodium falciparum* sporozoite (PfSPZ) vaccine are currently under development. This vaccine is ultimately to be given to children from 6 months of age[173], and it works through the induction of $CD8^+$ T cell responses that target *P. falciparum*-infected hepatocytes[146]. In controlled human infection, in American malaria-naive subjects of various ethnic backgrounds, PfSPZ vaccine protected 12 of the 13 recipients (92.3%), whereas in a malaria-endemic area in Tanzania it protected only 4 of the 20 recipients (20%)[8,11]. Moreover, efficacy was shown to be much lower in a setting of natural infection in Mali[9,10]. Recent studies of PfSPZ–chemoprophylaxis attenuated vaccine (PfSPZ–CVac), which is a live chemo-attenuated *P. falciparum* vaccine, protected 100% of Dutch[174] and German[13] volunteers, whereas double the dose protected only 8 of the 13 recipients (55%) in Equatorial Guinea[12] (Supplementary Table 5).

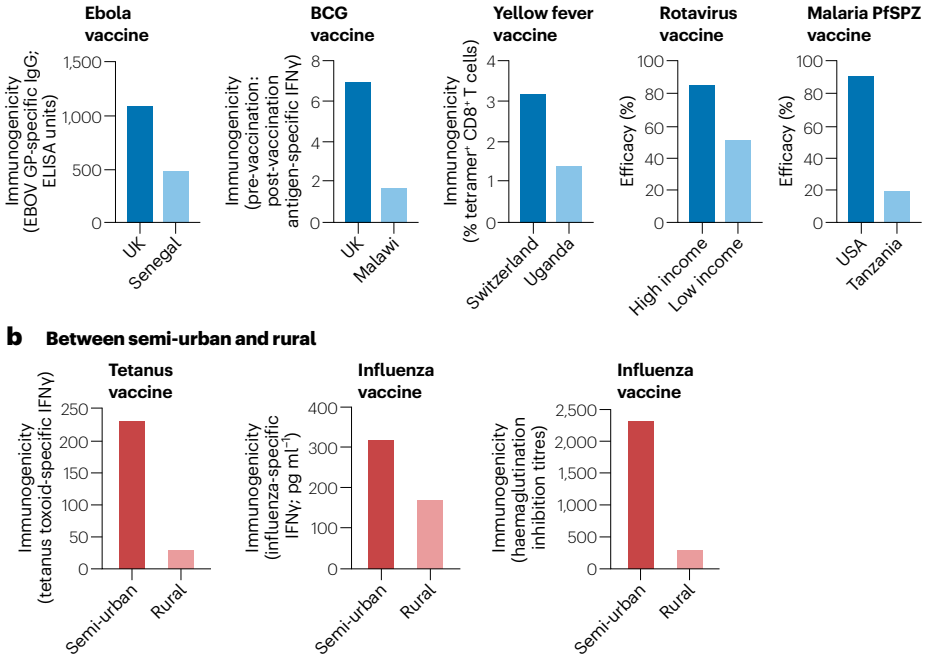

Fig. 1 | Variations in vaccine immunogenicity or efficacy across populations. a, Vaccine immunogenicity varies between countries. The immunogenicity of: Ebola vaccine in the UK and Senegal was assessed by specific IgG antibodies[89]; bacillus Calmette–Guérin (BCG) vaccine in the UK and Malawi was assessed by the increase in interferon-γ (IFNγ) production in response to tuberculin purified protein derivative from pre-vaccination to post-vaccination[148]; yellow fever vaccine in Switzerland and Uganda was determined by the percentage of yellow fever antigen-specific tetramer-positive $CD8^+$ T cells[15]; rotavirus vaccine in high- and low-income countries was assessed by vaccine efficacy[6]; and irradiated malaria *Plasmodium falciparum* sporozoite (PfSPZ) vaccine in the USA[8] and Tanzania[11] was assessed by vaccine efficacy. **b**, The immunogenicity of vaccines varies between semi-urban and rural settings. In semi-urban and rural Gabon, tetanus vaccine was assessed by tetanus toxoid-stimulated IFNγ production by peripheral blood mononuclear cells (PBMCs)[149]; influenza vaccine was assessed by either influenza virus-stimulated IFNγ production by PBMCs or antibody titres through the haemagglutination inhibition assay[18]. EBOV, Ebola virus; ELISA, enzyme-linked immunosorbent assay; GP, envelope glycoprotein.

Heightened inflammation and immune activation

The activation status of the immune system before vaccination is of great importance to the quality of the induced immune response. In high-income countries, poor responses to some vaccines in elderly subjects have long been recognized and attributed to dysregulated immune interactions[46,47], raising the question of whether there are immunological commonalities with younger populations of low- and middle-income countries where vaccine hyporesponsiveness is seen. In elderly individuals, age-related alterations, such as lifelong exposure to immunological triggers and reduced ability of immune cell self-renewal, result in smaller naive T and B cell pools, which along with low-grade sterile inflammation, can underlie poor responses to vaccines[48,49]. In many areas of low- and middle-income countries, the continued challenge of the immune system, largely through exposure to microorganisms and parasites starting early in life, can lead to inflammation and a state of heightened activation of both innate and adaptive immune cells[50,51], clonal expansion and depletion of the naive lymphocyte pool[52], impairing the immune response to vaccination. Therefore, persistent inflammation and continuous reactivation of immune cells can result in immune exhaustion and immunosenescence. These terms, which are often used indiscriminately, represent still not fully understood[53], distinct, yet overlapping, processes that mark an immune state that is detrimental to the outcome of vaccination. Detailed understanding of the characteristics of different states of the immune system associated with vaccine hyporesponsiveness might be helpful for designing interventions to improve vaccine performance.

Gradual loss of naive T and B cells occurs naturally with ageing, but variation in their numbers has also been observed between various aged-matched populations from various geographical locations with different levels of exposure to infections[54–56]. For example, a study of age-matched children from Bangladesh and the USA found considerable similarity in immune profiles in the first year of life but at the age of 2–3 years, children from Bangladesh had higher numbers of differentiated $CD4^+$ T cells and fewer monocytes and naive T cells compared with their counterparts from the USA. Importantly, T cell maturity in children from Bangladesh resembled that of adults in the USA[54]. These results are in line with studies showing that Malawian adolescents (aged 12–15 years) had a lower percentage of naive $CD4^+$ and $CD8^+$ T cells ($CD45RO^-CD62L^{hi}CD11a^{low}$) than their UK counterparts. The percentage of naive T cells was negatively associated with cytomegalovirus seropositivity, which was more common in Malawian populations (100%) than in UK populations (36%)[55]. Also comparing immune profiles of individuals living in rural and urban areas of Senegal with those in the Netherlands showed a gradient in the proportion of naive T and B cells in young adults, with the lowest in rural Senegal, then urban Senegal followed by the Netherlands. This correlates with the highest exposure to microorganisms and parasites in rural Senegal and the lowest in the Netherlands[52]. Lower naive T cell numbers before vaccination have been associated with reduced responses to attenuated vaccinia virus in non-human primates[57], and with lower PfSPZ malaria vaccine-induced antibody responses in a study that compared adult vaccinees from Tanzania and the USA[11].

More recently, acute immune activation has been studied by examining responses following controlled malaria infection in healthy volunteers. It was shown that both *Plasmodium vivax* and *P. falciparum* infection can induce widespread immune activation, affecting myeloid cells and strongly activating 25% of T cells, which were marked by high CD38 expression and low BCL-2 expression[58]. The high level of immune activation has been observed in individuals with lifelong exposure to malaria[50] alongside lower malaria vaccine responses[11]. The impact of immune activation on vaccine responses has also been reported by Muyanja et al.[15], who studied the baseline immune profiles

and vaccine responses to yellow fever vaccine in Uganda and Switzerland. The innate immune compartment was more activated in individuals from Uganda compared with individuals from Switzerland, as evidenced by an increased frequency of activated natural killer (NK) cells ($CD16^+HLA\text{-}DR^+$), recently activated $CD16^-$ NK cells (secreting interferon-γ (IFNγ) after restimulation ex vivo) and pro-inflammatory intermediate monocytes ($CD14^+CD16^+$), with higher expression of PDL1 and HLA-DR. In addition, in the adaptive arm, both the $CD4^+$ and $CD8^+$ T cell and B cell compartments exhibited more differentiated and memory profiles in individuals in Uganda compared with those in Switzerland. Upon yellow fever vaccination, the frequency of pro-inflammatory monocytes and activated $PD1^+CD8^+$ T cells at baseline was negatively associated with the induction of neutralizing antibodies, linking the increased immune activation status to impaired vaccination outcome[15].

Needless to say, in children, the length of exposure to environmental factors is shorter and, therefore, the level of immune activation might be less, with little impact on vaccines that are given early in life. However, both rotavirus and cholera vaccines were less effective in children from Bangladesh[59,60]. In a separate study of children from Bangladesh, heightened immune activation was seen at 2 years of age but less so in the first year of life[54], when rotavirus vaccination is given. It would be helpful to assess immunological profiles of children and vaccination outcomes in the same cohorts to conclude with certainty whether immune activation has a role in rotavirus vaccine hyporesponsiveness.

Data generated from immunophenotyping of blood samples from infants and children during the RTS,S malaria vaccine phase III trial was consistent with the idea that the immune system ages at different rates in different geographical areas; however, a more aged or mature immune system in children was associated with a stronger antibody response to RTS,S vaccine[61]. Such discrepancies in how the immune activation status in young children is associated with responses to distinct vaccines highlights the need for more studies: first, to disentangle immune maturation from heightened immune activation; second, to examine local rather than peripheral blood immune profiles, which might be more relevant, for example, for rotavirus vaccine efficacy; and third, to unravel whether different mechanisms underlie hyporesponsiveness to different vaccines. Therefore, a more in-depth understanding of the mechanisms that underlie, rather than correlates of, vaccine hyporesponsiveness are needed. Given the data generated so far, it would be worth testing strategies to reduce inflammation or heightened immune activation in both elderly individuals and in those living in areas where exposure to microorganisms and parasites is high.

Box 2

Linking environmental factors to varied vaccine responses is complex

Variations in vaccine response have been linked to exposure to and/or infections with viruses (for example, cytomegalovirus)[16], environmental mycobacteria[156] and parasites (such as helminths)[31,175]. However, confirming the impact of a single pathogen on vaccine responses is complicated; indeed, treatments that target a single type of pathogen, for example, anthelmintics, have had variable success[30,31]. This might be due to co-infections that are not removed by the given treatment or by incomplete reversal of the effect of past exposure by the treatment[114,115,176].

High exposure to pathogens is often coincident with other key factors that influence vaccine responsiveness, such as malnutrition or altered gut microbiome composition. For example, helminth infections are often associated with poor nutritional status[177,178], as well as altered microbiome composition[179,180]. Poor nutritional status negatively impacts the immune system[181–183], and new insight into the links between the diet, the microbiome and the immune system indicate that even well-nourished individuals may have altered vaccine responses via mechanisms that involve food-derived metabolites that originate from dietary intake, such as flavonoids[133].

The association between microbiome composition and vaccine responses has been studied for several vaccines, including the rotavirus vaccine[24,36,184]. A recent study showed that several bacterial taxa (such as *Streptococcus* and Enterobacteriaceae) positively correlate with rotavirus seroconversion, whereas phage diversity, enterovirus B and multiple cosaviruses were negatively associated[184]. However, in a multicentre cohort study, microbiota diversity was negatively associated with neonatal rotavirus vaccine seroconversion in infants from India but not in infants from the UK, but no specific bacterial taxa could be linked to vaccine outcome in this case[36]. In addition to these associations, in one intervention study, antibiotics were administered before influenza vaccination, which reduced antibody induction in subjects with low pre-existing immunity to influenza virus and who had not been exposed to the influenza vaccine in the preceding 3 years. Antibiotic treatment had little effect if vaccinees had higher pre-vaccination antibodies and therefore showed lower seroconversion rates. This suggests that the microbiome has an adjuvant effect on the antibody response to vaccination in individuals with relatively little prior exposure to the antigen, but that immune memory caused by prior exposure to the antigen can withstand even the most severe perturbation of the microbiome[185]. Larger studies are needed to confirm these findings, and it remains to be determined whether such perturbation would affect other vaccine responses. Moreover, a causal link showing an effect on vaccine responses by faecal microbiome transplantation[186] or introduction of a combination of microbiota species is lacking.

Taken together, these studies highlight the fact that multiple factors have a role in modulating responses to vaccines and indicate how complex it might be to intervene at the level of environmental factors. Therefore, it is crucial to fully understand the downstream impact of environmental exposures on the immune system to identify immunological traits that are linked to, and could be targeted to improve, vaccine hyporesponsiveness.

Box 3

High-dimensional methods to predict vaccine responses

Differences in response to vaccination may in part be due to variations in baseline or early post-vaccination immune signatures. By combining high-dimensional immunological data with mathematical and computational analyses, it has been possible to define early signatures that predict vaccine immunogenicity, analysis that has mostly been done in cohorts in the USA. Studies of immune responses after vaccination showed that the generalizability of immune signatures was limited; predictive signatures for one particular vaccine could not predict outcomes for other vaccines[187,188]. A meta-analysis study sought to identify universal predictors of vaccine-induced responses with data from 820 adults in 28 studies against 13 different vaccines. They found a consistent association between peak plasmablast levels and antibody induction after vaccination, but there was no other common signature that predicted a response to all vaccines; the responses depended on vaccine type and adjuvant type administered[189].

Similar analyses of baseline samples (before vaccination) have also been carried out to predict the outcome of vaccination[190] (see the table). The first study integrated microRNA and transcriptomic profiling to predict responses to a seasonal influenza vaccine in young adults, older individuals and individuals with diabetes across seasons and showed that immune signatures at baseline could distinguish between high and low vaccine responders[191]. Plasmablast and innate immunity modules at baseline predicted influenza-specific antibody levels at 1 month after vaccination, but not the longevity of the response. Baseline signatures of T and B cell gene modules correlated positively, whereas a monocyte inflammatory signature correlated negatively with antibody responses at 1 month, but showed little correlation with longevity of the response. This landmark study was followed by a combined effort examining six influenza vaccine cohorts that spanned distinct locations, ages and seasons[192]. Nine genes and three gene modules were found to be associated with the magnitude of the antibody response in all study cohorts. Analysis in independent cohorts validated the baseline signatures predicting responses in young adults, but surprisingly, they had an inverse correlation in older adults[192].

Using a similar systems biology approach, Kotliarov and coworkers[193] identified a signature that predicts both influenza and yellow fever vaccine outcome. Ten genes involved in type I interferon responses were identified in immune cells at baseline that predicted antibody levels in three out of four influenza vaccine trials, as well as the antibody response to the yellow fever vaccine[193]. Another recent study analysed pre-vaccination transcriptome data of 820 adults from different vaccination studies[194]. Taking an unbiased approach, a common pre-vaccination transcriptional signature with an overall predictive value of 62.3% for 13 different vaccines was identified, although the performance varied with different vaccines. The predictor consisted of an inflammatory gene signature downstream of nuclear factor-κB (NF-κB) and interferon regulatory factor 7 in the innate immune cell compartment. Of interest, the inflammatory signature did not predict vaccine responses in elderly individuals, suggesting that the type of inflammation reflected by the signature in this age group has a different origin[194] (see the table). Given that the signalling networks regulated by NF-κB are enhanced in inflammageing[195], these results also suggest that the extent of the activation of these networks might be crucial: their activation favours vaccine responses, yet their overactivation hampers vaccine responses.

Recent pioneering studies of large numbers of children and infants who were protected from clinical malaria following vaccination with RTS,S/AS01E (phase III trial) have shown that signatures that include NF-κB, Toll-like receptors and monocyte-related blood transcriptional modules, in baseline peripheral blood mononuclear cell cultures, depending on type of stimulation, can associate either positively[196] or negatively[197] with vaccination outcomes. Altogether, although systems biology approaches have proved valuable for identifying signatures that predict vaccine outcome, it is not clear how well these signatures hold up across populations from diverse geographical regions with different baseline inflammatory profiles and vaccine responses. Future studies should include a diversity of geographical locations and populations experiencing distinct environmental exposures to determine whether there are shared molecular pathways that underlie vaccine hyporesponsiveness.

Signature at baseline	Predictive for	Study populations (number)	Refs.
Positive correlation: B cell-enriched modules, T cell-enriched modules and T cell surface markers Negative correlation: monocyte-enriched module; cell cycle and its transcriptional regulation	Influenza vaccine Signatures similar across young (<65 years) and older (>65 years) subjects and patients with type 2 diabetes	Discovery cohorts: influenza vaccination from 2007, 2008, 2009, 2010 and 2011 (n=212), including older subjects (n=54) and patients with type 2 diabetes (n=17) Validation cohorts: influenza vaccination from 2008 and 2009 (n=218)	191
Positive correlation (in subjects <35 years; negatively correlated in subjects >65 years): B cell receptor signalling, cell structure and motility, inflammatory responses and platelet activation	Influenza vaccine	Discovery cohorts: influenza vaccination from 2008, 2010, 2011 and 2012 (n=293), including young (<35 years) and older (>65 years) adults Validation cohorts: influenza vaccination from 2009 and 2010 (n=223)	192
Positive correlation: activated B cells ($CD20^+CD38^{++}$), cell cycle activation, type I interferon response Negative correlation: effector memory $CD4^+$ T cells	Influenza vaccine, yellow fever vaccine (YF-17D), systemic lupus erythematosus Independent of age	Discovery cohort: influenza vaccination (n=63) Validation cohorts: influenza vaccination from 2008, 2011 and 2012 (n=42); yellow fever vaccination from two trials (n=22) Systemic lupus erythematosus cohort (n=34)	193, 198

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Signature at baseline	Predictive for	Study populations (number)	Refs.
Positive correlation: interferon-stimulated genes and pro-inflammatory genes, such as innate immune sensors in monocytes and dendritic cells Negative correlation: transcriptomic markers of natural killer cells, T cells and B cells; target genes of pathways involved in cell proliferation and metabolism (*E2F* and *MYC*)	13 vaccines against influenza virus, yellow fever, HIV, Ebola virus, malaria, hepatitis A virus, hepatitis B virus, tuberculosis, smallpox, meningococcus, pneumococcus	Training on the entire cohort (*n*=820), transcriptional profiles revealed three endotypes: high, middle and low inflammatory; immune subsets and antibody responses were compared between these endotypes	194
Positive correlation: B cell activation Negative correlation: inflammation, effector memory CD4$^+$ T cells (CD28)	Hepatitis B virus vaccine Signature correlated with age	First approach: entire cohort of adults aged 25–83 years (*n*=174) Second approach: training cohort (*n*=116) and test cohort (*n*=58)	48

This could, for a short period of time, before vaccination, either involve more general drugs, such as metformin, which not only reduces inflammation but also can boost memory formation[62], or more selective compounds that target specific immune pathways such as IL-1β or IL-6 (ref. 63), which have shown some beneficial effects in decreasing inflammation, to potentially reverse vaccine hyporesponsiveness[64] (Fig. 2). However, the benefits and risks associated with such trials will need to be carefully considered given the high infection burden in the environments in which vaccine hyporesponsiveness is often seen to avoid limiting immune control of infections.

Immune exhaustion

Repeated antigenic stimulation of lymphocytes and chronic activation can eventually lead to a state of dysfunction that is broadly termed exhaustion. Exhaustion in various lymphocyte populations, including NK cells, B cells and conventional CD4$^+$ and CD8$^+$ T cells, is generally associated with a progressive hierarchical loss of effector function and proliferative capacity, and the increased expression of inhibitory receptors, such as PD1, CTLA4, LAG3 and TIM3 (refs. 53,65). However, these inhibitory receptors are also transiently upregulated on functional effector T cells after T cell receptor stimulation. Therefore, recent studies of CD8$^+$ T cells at various differentiation stages that identified TOX and eomesodermin[66,67] as specific transcription factors that regulate exhaustion might help to better define exhausted T cells[53]. Immune exhaustion can be caused by several persistent infections, including malaria and those caused by helminth parasites, *M. tuberculosis*, HIV and hepatitis B and C viruses, as well as by cancer[68–72].

Immune cell exhaustion occurring in the context of chronic hepatitis C virus infection was associated with lower antigen-specific T cell responses and seroconversion following hepatitis B vaccination compared with responses in healthy individuals or in individuals who spontaneously cleared hepatitis C virus infection[73]. Although many studies report the upregulation of inhibitory receptors during hepatitis C virus infection, not many studies have linked this upregulation to poor vaccine responses. Comparing hepatitis C virus-infected subjects after hepatitis B vaccination, TIM3 expression on monocytes[74] and PD1-expressing CD4$^+$ T cells[73] were increased in subjects that did not respond to the vaccine. Chronic exposure to malaria parasites is also associated with alterations in monocytes that might arise from epigenetic changes in precursor cells that reprogramme them towards a less inflammatory phenotype[75], as well as increased expression of PD1 by T cells, suggesting T cell exhaustion[76]. Antibody-mediated blockade of PD1 in in vitro assays improved hepatitis B virus antigen-specific responses[73,77] and malaria antigen-specific responses[78]. Amplification of antigen-specific T cell responses has been shown in vivo when PD1 antagonists were combined with adenovirus-based or irradiated sporozoite-based malaria vaccines in mouse models[79,80].

The combination of immune checkpoint blockade, such as monoclonal antibodies to PD1, PDL1 or CTLA4, and therapeutic cancer vaccines is being studied extensively, but there are very few studies that combine immune checkpoint blockade with vaccines for infectious diseases[81]. However, vaccination against infectious diseases in patients with cancer treated with immune checkpoint blockade is generating some interesting insights. Recent work has shown that a subset of patients with cancer who are undergoing anti-PD1 antibody therapy and are vaccinated for influenza virus show higher increases in circulating CD4$^+$ T follicular helper cells than patients not receiving anti-PD1 treatment[82]. Increases in plasmablasts and antibody titres indicated the potential of anti-PD1 antibody to enhance vaccine responses in humans in the context of immune exhaustion (Fig. 2). Although these findings highlight the potential of using anti-PD1 and other antibodies to immune checkpoints to overcome reduced vaccine efficacy, much more needs to be done to assess the risk of developing strong collateral autoimmune or autoinflammatory responses. Indeed, patients with cancer on anti-PD1 treatment who showed heightened responses to vaccines also had a higher risk of developing immune-related adverse events[82]. Alternative approaches to overcome immune exhaustion, such as the use of Toll-like receptor (TLR) agonists, have been tested in patients on renal replacement therapy who show hyporesponsiveness to vaccines[83]. Indeed, the use of a hepatitis B vaccine with the TLR9 agonist CpG resulted in higher seroprotective antibody titres in patients with chronic kidney disease[84], indicating the ability to improve responses also in the context of immune exhaustion.

Thus, more work is needed to better understand the exhaustion phenotype of T cells as well as of other cell types such as myeloid cells and the mechanisms that underlie its association with vaccine hyporesponsiveness. Studies of exhaustion in the context of cancer show that there are subtypes of exhausted T cells — TCF1- exhausted T cells and self-renewing TCF1$^+$ stem-like exhausted T cells[85] — with distinct responses to checkpoint inhibitors, yet very little is known about these subtypes during chronic exposure to microorganisms and parasites in humans. The same applies to the paucity of information on how repeated exposure to pathogen-associated molecular patterns can alter antigen presentation and the control of responses to vaccination.

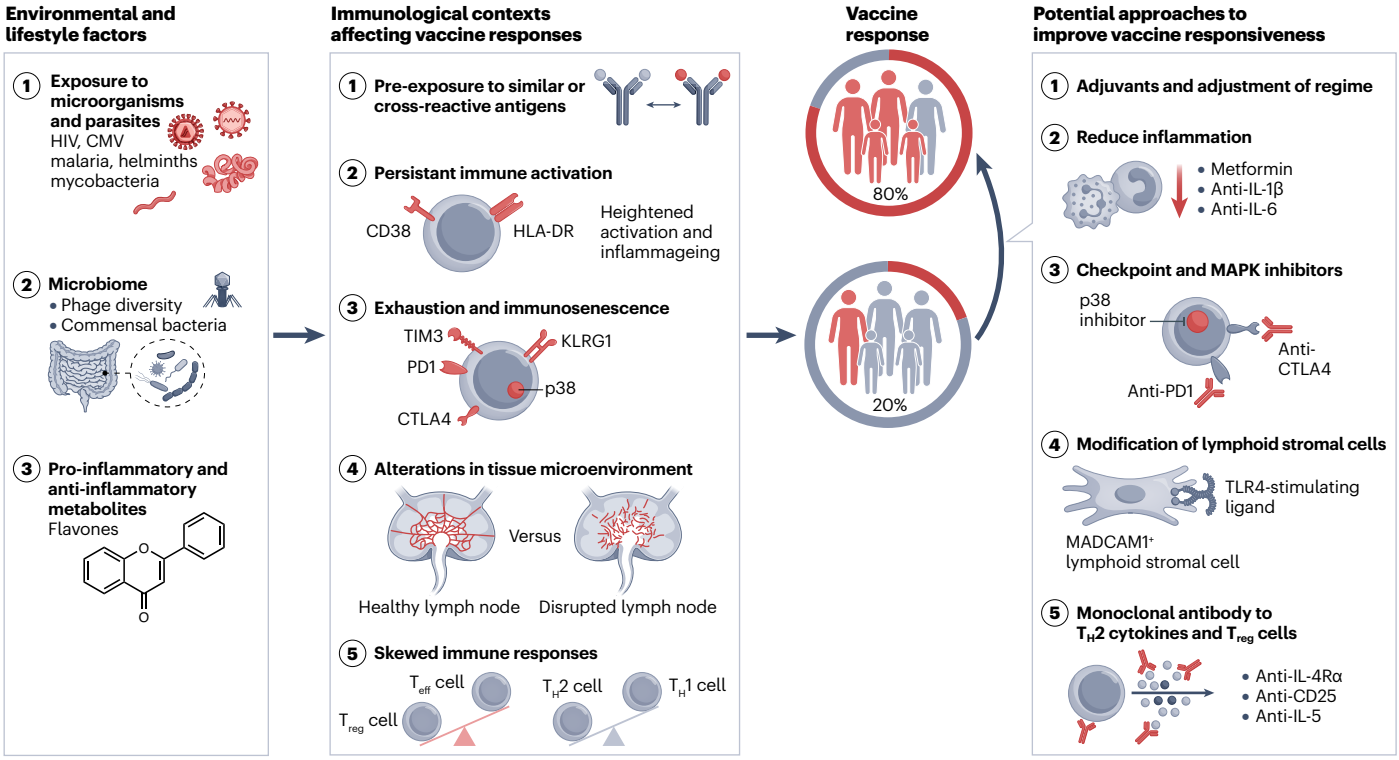

Fig. 2 | Factors and immunological mechanisms driving vaccine efficacy variation between populations. Immune reactivity to vaccines is shaped by previous exposure to several environmental and lifestyle factors. Immunological contexts that negatively affect vaccine responses include pre-existing immunity that results from exposure to similar or cross-reactive antigens, persistent challenges of the immune system that lead to naive T cell depletion, heightened immune activation, immune exhaustion and immunosenescence that impair the response to vaccines, restructuring of the lymphoid tissue and skewing of the immune system. This may be reflected in the different vaccine efficacies observed between different populations. Approaches to overcome vaccine hyporesponsiveness could be envisaged through various immunological interventions. CMV, cytomegalovirus; KLRG1, killer cell lectin-like receptor subfamily G member 1; MADCAM1, mucosal addressin cell adhesion molecule 1; T_{eff} cell, effector T cell; T_H1, T helper 1 cell; T_H2, T helper 2 cell; TLR4, Toll-like receptor 4; T_{reg} cell, regulatory T cell.

Blocking the receptors and signalling pathways involved in exhaustion of different immune cells might lead to a degree of reversal and enhanced vaccine efficacy, although further studies are needed to assess the safety and benefits of such interventions.

Immunosenescence

Immunosenescence refers to the gradual dysregulation of the immune system as a consequence of ageing, potentially attributed to chronic low-grade antigenic stimulation. It encompasses reduced production of T cells in the thymus, as well as increased sterile, low-grade, chronic inflammation that can contribute to age-associated decline in vaccine efficacy[86]. Although immunosenescence and exhaustion both lead to reduced proliferative capacity and immune function, the pathways involved can be distinct, as reviewed elsewhere[87]. Senescence is characterized by shortening of telomeres, loss of telomerase activity and expression of CD57 and killer cell lectin-like receptor subfamily G member 1 (KLRG1)[87], although CD57 and KLRG1 can also be co-expressed with exhaustion markers such as PD1 (ref. 88).

In addition to biological ageing, immunosenescence has been associated with latent viruses that might reactivate, such as cytomegalovirus. An immunization study of individuals in the UK and Senegal, involving priming with the chimpanzee adenovirus type 3-vectored Ebola Zaire vaccine (ChAd3-EBO-Z) and boosting with the modified vaccinia Ankara Ebola Zaire-vectored (MVA-EBO-Z) vaccine, found a comparable induction of cytokine-producing T cells but a significantly decreased antibody response in individuals in Senegal compared with the UK[89]. Cytomegalovirus carriage, which was higher in Senegalese, was correlated with increased numbers of phenotypically senescent $CD4^+$ and $CD8^+$ T cells ($CD57^+KLRG1^+$), and the frequency of these cells was negatively associated with the vaccine-specific antibody responses[16]. It is important to note that other infections such as malaria can also contribute to the immunosenescent phenotype seen in Senegalese individuals[90]. The disconnection between comparable T cell cytokine responses yet poorer antibody responses in Senegalese compared with UK vaccinees might be related to the ability of senescent cells to produce cytokines, but this remains to be fully understood.

There is great interest in finding ways to reverse immunosenescence[91], with some progress in animal models using senolytics, such as dasatinib and quercetin, which promote the clearance of senescent cells[92]. Moreover, the control of telomere length in immunosenescent cells is an area that is intensely studied at the molecular level, but currently far from clinical application[93]. However, studies using a p38 mitogen-activated protein kinase inhibitor, losmapimod, in elderly subjects has shown promise in enhancing skin immune reactions to

varicella zoster virus antigen[94]. In addition, targeting metabolic pathways, for example, using pan mTOR inhibition by AZD8055, has been shown to reverse senescence in skin fibroblasts[95] and, when the same pathway was targeted in elderly subjects before influenza vaccination, it improved vaccine-induced responses[96]. Yet, to what extent such molecular pathways are specific for senescent cells is largely unknown, as they also affect inflammation (Fig. 2).

Therefore, a more precise characterization of overlapping and distinct pathways underlying exhaustion, senescence and heightened activation of the immune system in different human populations is needed to help understand the variation in vaccine responsiveness across geographical areas and design immunological interventions. Are we dealing with a vicious circle of inflammation and regulation that we should disrupt using anti-inflammatory interventions simultaneously with checkpoint blockade for better vaccine outcomes?

Skewed immune responses

The proper functioning of the immune system involves a tight balance between pro-inflammatory and anti-inflammatory responses to allow the development of sufficiently strong immune responses to pathogens yet prevent overzealous inflammation and tissue damage[97,98]. In a simplified view, the immune system deals with a range of pathogens through the induction of various T helper cell subsets, such as T_H1, T_H2 and T_H17 cells, alongside matched innate effector cells, that are suited for optimal control of a particular type of pathogen. These responses are kept in check by regulatory populations, such as regulatory T (T_{reg}) cells, regulatory B cells[99] and anti-inflammatory monocytes or macrophages[100]. T cell responses can also be regulated cell-intrinsically through the upregulation of inhibitory receptors or other molecules that limit their inflammatory activity after activation. For example, in the setting of chronic helminth infection, the protective T_H2 cell responses are compromised by a regulatory environment, generating a so-called 'modified T_H2 cell response' associated with high IL-10 and IgG4 levels and low IgE levels, rather than the typical T_H2 cell response characterized by high IL-4, IL-5 and IgE[101]. T_{reg} cells can be induced in response to inflammatory signals such as tumour necrosis factor (TNF)[102] but also by certain pathogens that express immunomodulatory molecules to allow their long-term survival within the host[98].

Parasitic helminth infections are highly prevalent in rural areas of low- and middle-income countries and have been shown to be associated with increased numbers of T_H2 cells, group 2 innate lymphoid cells (ILC2s), T_{reg} cells and regulatory B cells[51], which can modulate responses to *P. falciparum* and *M. tuberculosis*[103,104]. A study of T_{reg} cells in an area endemic for helminth infections showed that the suppressive activity of $CD25^{hi}FOXP3^{+}$ T_{reg} cells was higher in helminth-infected children than uninfected children. In vitro T cell proliferative and IFNγ responses to BCG and malaria antigens increased following depletion of T_{reg} cells only in samples from individuals infected with helminths and not in those from uninfected subjects[105]. A role for helminth-induced immune regulation was further substantiated by an anthelmintic trial showing that T cells expressing the inhibitory molecule CTLA4 decreased significantly following the reduction in helminth load, allowing the induction of stronger inflammatory TNF responses to malaria antigens[68]. Similarly, during blood-stage malaria infection, strong regulatory responses have been observed[106–108]; the number of T_{reg} cells in the blood positively correlated with blood-stage parasite burden and hampered the development of natural or vaccine-induced protection, as shown in a study that assessed the efficacy of the malaria vaccine candidate GMZ2 using controlled human malaria infection. Moreover, they showed that in addition to increased numbers of T_{reg} cells, levels of HLA-G, which interacts with inhibitory receptors on T cells, B cells, NK cells and neutrophils, were negatively correlated with vaccine-specific antibody concentrations[108].

Given that a T_H1-type and inflammatory status supports vaccine-induced IgG antibody responses, vaccination in the context of a T_H2-type and regulatory environment would be expected to limit vaccine efficacy. A meta-analysis by Wait et al.[109] revealed poorer vaccination outcomes in populations infected by helminths at the time of vaccination. Moreover, the study found that chronic parasite infections, but not acute parasite infections, were associated with worse immunization outcomes[109]. Indeed, a study that examined the immune response to RTS,S vaccination showed that individuals with a T_H1-type and pro-inflammatory response to vaccination (such as production of IFNγ, IL-15 and GM-CSF) were protected from subsequent malaria infection, whereas those that produced the T_H2 cytokine IL-5 were not[110]. Similarly, a negative association has been found between helminth infections and protection induced by another malaria vaccine candidate, GMZ2 (ref. 111). However, anthelmintic treatment has had variable effects on vaccine responses[18,30,31,112,113]. One potential explanation is that the anti-inflammatory immune status is not directly reverted upon helminth removal but can persist[114–116].

Altogether, larger studies are needed to delineate the relative contribution of T_H2 and regulatory cells to vaccine hyporesponsiveness and to devise appropriate interventions. The blocking of T_H2 cytokines and their downstream effects has shown promise in the field of asthma, where clinical trials using anti-IL-5 or anti-IL-4Rα show fewer acute exacerbations and reduced eosinophilia[117]. In the field of cancer, there has been significant interest in evaluating the clinical benefits of targeting T_{reg} cells to improve T_H1-type antitumour immune responses. Although success from early clinical trials using the human CD25-specific antibody daclizumab to deplete T_{reg} cells has been modest, more recent approaches using modified antibodies with superior capacity to induce antibody-dependent cell cytotoxicity are more promising[118] (Fig. 2).

Alterations in the lymphoid tissue microenvironment

The lymphoid tissues are essential for correct functioning of the immune system by providing organized structures that support interaction between cells and immune mediators. Structural changes in the

Glossary

Plasmodium falciparum sporozoite (PfSPZ) vaccine
An experimental vaccine against malaria based on radiation-attenuated whole sporozoites of *P. falciparum* malaria parasite.

PfSPZ–chemoprophylaxis attenuated vaccine
(PfSPZ–CVac). An experimental vaccine against malaria *Plasmodium falciparum* sporozoites (PfSPZ) based on chemically attenuated whole sporozoites, by co-administering the whole sporozoites of *P. falciparum* together with an anti-malaria drug, often chloroquine.

RTS,S malaria subunit vaccine
A subunit vaccine against malaria adjuvanted with AS01, which is currently the only licensed malaria vaccine.

Seroconversion
Achievement of a quantifiable antibody level after vaccination, which is expected to correlate with protection.

LNs have been observed in older individuals, patients with HIV infection (including those on antiretroviral therapy) and healthy individuals from low-income countries (such as Uganda)[119–121]. With normal ageing, the number of LNs decreases, and there may be reductions in the area and volume of LN paracortical, cortex and medullary regions[122,123]. Furthermore, naive $CD8^+$ T cell and $CD20^+$ B cell numbers in LNs are reduced and there is a decrease in the relative and absolute dimensions of germinal centres, indicating a more static microarchitecture in older compared with younger individuals[124]. In the context of active HIV-1 replication, inflammation and tissue remodelling cause damage to the LN architecture, limiting its ability to support normal T cell numbers and thereby contributing to the reduced $CD4^+$ T cell numbers observed in these patients[121]. Of interest, examination of LN sections of HIV-negative individuals from Uganda also showed LN architecture disruption, characterized by collagen formation in the parafollicular T cell zone, similar to that observed in HIV-positive individuals from the USA, suggesting that LN remodelling is not limited to HIV infection and may occur with other chronic endemic infections. In addition, the fibroblastic reticular cell network, an essential network for T cell–antigen interaction, was diminished in HIV-negative Ugandans compared with HIV-negative North Americans, as measured by desmin positivity. Moreover, the depleted fibroblastic reticular cell network was associated with a smaller $CD4^+$ T cell population in the LNs. Vaccination of these HIV-negative Ugandans with the yellow fever vaccine YF-17D resulted in a blunted and short duration antibody response, and the more damage to the fibroblastic reticular cell network the smaller the peak antibody titre. Finally, confocal imaging revealed a lack of T follicular helper cells and diminished B cell follicle formation in HIV-negative Ugandans that was not rescued by vaccination[120].

The importance of an altered lymphoid tissue microenvironment to the development of immune and vaccine responses is also supported by a study that shows that changes to the LN microenvironment during ageing, rather than to the immune cells themselves, contribute to age-related immune dysfunction[124]. In aged mice, lymphoid tissue stromal cells expressing mucosal addressin cell adhesion molecule 1 (MADCAM1) failed to respond to immunization and support germinal centre responses. Targeting TLR4 by adjuvants improved the response to vaccination by $MADCAM1^+$ stromal cells, which correlated with improved germinal centre responses[125] (Fig. 2). Although alterations in the local microenvironment are receiving more attention lately, more in-depth studies are needed, also in humans, to reverse detrimental alterations in the microenvironment, which appears to be crucial for the vaccine response.

Emerging areas for future of vaccinology

A detailed understanding of the immune system is essential for the development of effective vaccines. However, much of our knowledge of immunology is based on studies carried out in laboratory animals and in humans living in affluent countries, such as the USA or Europe. As the environment has a tremendous impact on the immune system, the future of vaccinology will foremost need to include populations that are exposed to different environments.

Parallels between the immunological changes during cancer and (chronic) infectious diseases might open new possibilities to overcome vaccine hyporesponsiveness. Both advanced cancers and chronic infections can induce persistent activation and inflammation, which can lead to T cell exhaustion, increased numbers of immunosuppressive and regulatory cell populations, as well as a shift from protective T_H1-type immunity to T_H2-type immunity or from pro-inflammatory to anti-inflammatory innate effectors[72,126–128]. These changes can compromise the T cell functions necessary for adequate responses to pathogens and tumour cells as well as to vaccines. Biologics that have been developed for cancer treatment are increasingly being studied in the context of chronic infectious diseases and may be worth exploring to increase vaccine efficacy in those with persistent pathogen exposure[79,80,129,130].

The potential role of the microbiome in enhancing vaccine responses is an emerging area of research, which has been the subject of a recent review[24]. Indeed, a growing number of metabolites derived from the microbiota[131] and foods[132] have been shown to modulate the immune system. A recent study that compared immune responses of residents of urban and rural Tanzania found more anti-inflammatory immune profiles in rural participants, which were associated with increased plasma levels of food-derived flavones[133]. Specifically, the plant-derived flavonoid apigenin showed anti-inflammatory effects reflected in cytokine profiles assessed after cell stimulation[133]. Another study linked iron bioavailability to a reduced response to malaria vaccine (RTS,S) in African children. African children with anaemia had fewer isotype-switched memory B cells and plasmablasts than healthy children, and increasing iron bioavailability in vitro was able to restore the defective B cell proliferation and plasmablast differentiation[61]. With the development of highly sensitive metabolomic and proteomic platforms that better enable specific molecules in biofluids to be linked to immune responsiveness and investigation of the mechanisms that underlie their immunomodulatory effects, it is likely that additional pathways will be discovered as targets for improving vaccine responses.

Previous exposures to microorganisms and parasites are also known to have lasting effects on the innate immune compartment — through processes termed trained immunity and tolerance[134]. Trained immunity refers to a baseline quiescent innate immune cell status that is modulated, at the epigenetic level, by previous exposures, to induce a faster and stronger response to a secondary exposure. Tolerance is the opposite phenomenon by which the response to a secondary exposure is lower than the first. Such a framework (elegantly reviewed recently[134]) needs to be dissected precisely to examine whether and/or how it underpins heightened immune activation, exhaustion and senescence and their relation to vaccine hyporesponsiveness.

Another important area of research that can shed light on the mechanisms that govern vaccine hyporesponsiveness and thereby help to identify actionable targets to overcome hyporesponsiveness is the field of immunometabolism. During the past decade it has become increasingly clear that a wide range of immune cell properties, including those leading to trained immunity and tolerance[135], exhaustion[136], senescence[137] and hyperactivation[138], are associated with and dependent on engagement of particular metabolic programmes. Recent systems vaccinology work linked changes in metabolic pathways to shingles vaccine-induced T and B cell responses[139], and follow-up work in mice pinpointed the importance of sterol metabolism in B cells for antibody production following immunization[140]. These insights have sparked interest in exploring whether immune cell metabolism could be harnessed to direct immune responses for therapeutic gain. These developments are most advanced in the field of cancer, in which targeted modulation of metabolism of tumour-associated myeloid cells and adaptive immune cells has shown promise as a viable means to negate immune dysfunction commonly observed in tumour microenvironments[141,142]. Some of the metabolic principles that underpin immune dysfunction in a tumour context are likely to overlap with

those that lead to vaccine hyporesponsiveness, and as such can inform the rational design of approaches that target immune cell metabolism to restore vaccine responsiveness. Efforts in this direction are still in their infancy. However, the clinical trial in which the mTOR inhibitor RAD001 was shown to ameliorate immunosenescence in elderly individuals and improve their response to influenza vaccination[143] provides the first evidence of therapeutic potential of modulation of immune cell metabolism in the context of vaccines. To further this field, a key first step will be to map in detail the metabolic characteristics of immune cell subsets in populations that are affected by poor vaccine responses, to identify therapeutic targets.

Finally, studying compartments other than the peripheral blood seems to be the next frontier in vaccinology. A recent study by Wagar et al.[144] showed how cultures of tonsil tissue can provide a secondary lymphoid organ model to study adaptive immune responses to vaccines. In addition, by taking serial fine needle aspirates of a single LN germinal centre in response to a vaccine over time has provided unique insight into responses to mRNA-based vaccines[145]. Moreover, tissue-resident immune cells studied in malaria vaccine responses of non-human primates highlight that vaccine-induced $CD8^+$ T cells or γδ T cells are present in much higher numbers in the liver, where infected hepatocytes are targeted, than can be appreciated from examining the peripheral blood[146,147]. Studies beyond the peripheral blood also provide the opportunity to examine the stromal cell compartment, which provides essential signals for immune function locally and might also be influenced by, for example, inflammation.

Conclusion

Large-scale omics approaches that combine the study of transcriptomes and proteomes, such as through CITE-seq, show promise for determining baseline vaccine response predictors (Box 3), with further insight now being gained from also assessing epigenomes[33] and metabolomes[139]. Such approaches should also now be applied to cohorts from populations that reside in different environmental settings where exposure to microorganisms and parasites, nutrient and food intake, as well as lifestyle, differ greatly as do vaccine responses. We are hopeful that the dissection of immunological mechanisms that link environment to vaccine responsiveness will unravel pathways that are amenable to modification and identify immunomodulatory compounds that complement vaccines to provide effective vaccination programmes for those who need it most.

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Competing interests
The authors declare no competing interests.

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