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Biological challenges to effective vaccines in the developing world

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The reason for holding a meeting to discuss biological challenges to vaccines is simple: not all vaccines work equally well in all settings. This special issue reviews the performance of vaccines in challenging environments, summarizes current thinking on the reasons why vaccines underperform and considers what approaches are necessary to understand the heterogeneity in responses and to improve vaccine immunogenicity and efficacy.

Introduction

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1. Introduction

Vaccinating against infectious diseases saves over 2.5 million lives each year [1]. However, we can do better, much better. We do not yet have vaccines for major causes of morbidity and mortality, such as HIV and malaria. Furthermore, existing vaccines against many infections do not offer complete protection, leaving even vaccinated children at risk of disease. At current levels of vaccination coverage, an estimated 4–19 million children born each year (3–13% of the birth cohort) receive routine vaccines against childhood infections such as diphtheria, pertussis, tetanus and measles, but remain unprotected as a result of limited vaccine effectiveness (figure 1). This figure stands at 77 million for vaccination with bacille Calmette–Guérin (BCG) against tuberculosis (TB), and currently 10 and 5 million for invasive pneumococcal disease and rotavirus gastroenteritis, respectively, although these figures will rise as vaccine coverage increases. As a consequence of limited effectiveness, a significant fraction of infections occurs in vaccinated individuals, particularly during disease outbreaks in well-vaccinated communities [17].

One of the main factors underlying the limitations in the performance of existing vaccines is variation in the immune response among individuals. Antibody levels and cellular immune markers show considerable variation after vaccination and in some individuals this translates into reduced efficacy. However, the causes of this variation and the significance of different immune markers for vaccine efficacy have not been established for many vaccines [18]. Twin studies demonstrating significant heritability in the immune response indicate a significant role for human genetic factors [19,20]. However, early life exposure to infection and other vaccines, maternal factors, breastfeeding, age, nutritional status and other environmental factors can also be significant determinants of vaccine immunogenicity [21–24]. In some cases, such as for oral vaccines against poliomyelitis and rotavirus gastroenteritis or for BCG, these differences are observed at the population level [4,25–27]. In particular, lower efficacy of these vaccines in low-income countries has limited their health impact and in the case of poliomyelitis has acted as a significant barrier to eradication [28].

Individual variation in immune parameters measured after vaccination can be informative about the biological mechanisms important for an effective immune response to the vaccine. Where these data are collected as part of a clinical trial of vaccine efficacy, or where immune correlates of protection have previously been identified, the mechanisms underlying protective immunity can in principle be discovered. For example, variation in the cytotoxic T-cell

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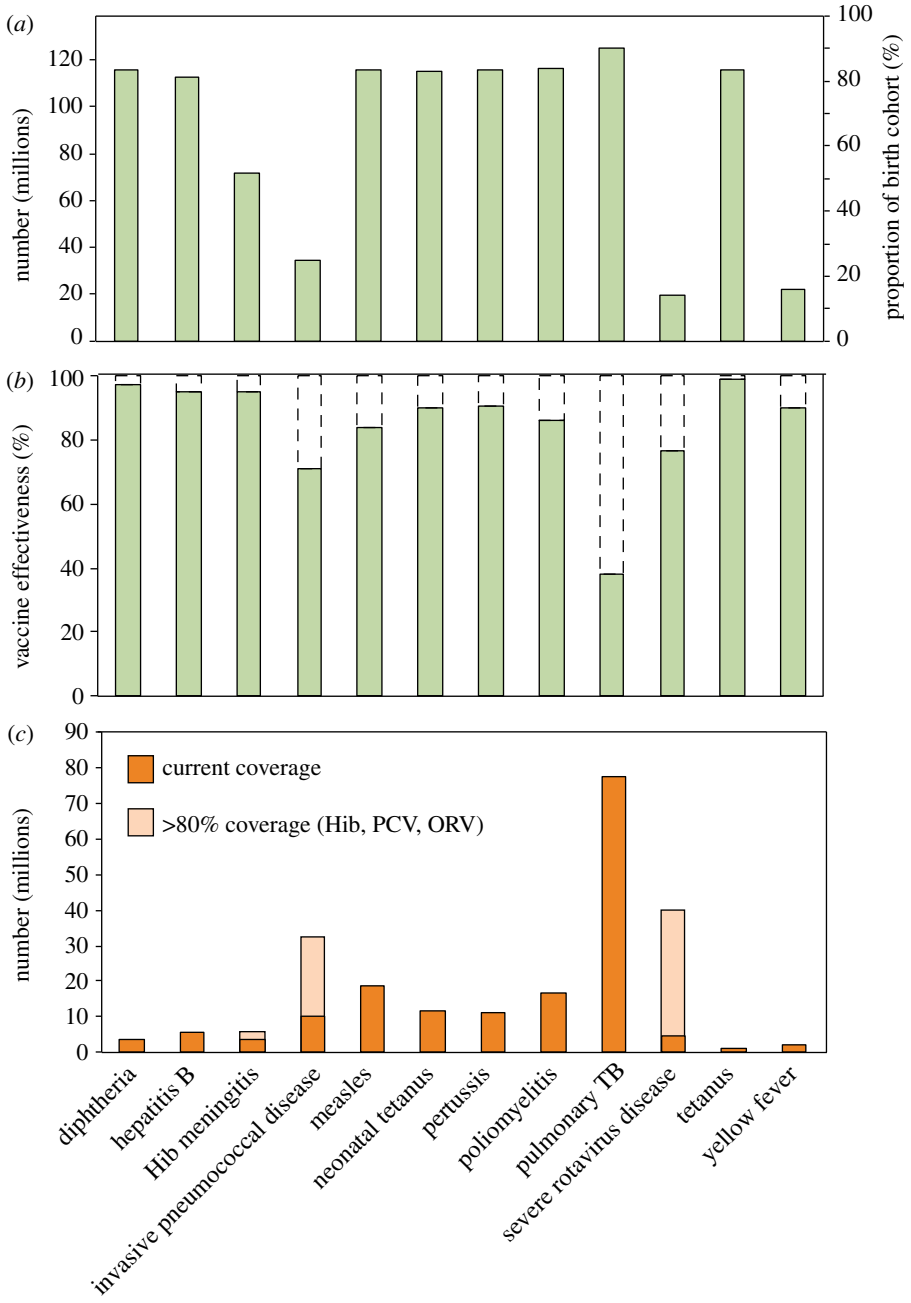

Figure 1. Limited or variable effectiveness of existing vaccines leaves children at risk of infection. (*a*) The number of children born each year who are vaccinated with commonly used vaccines based on country-specific estimates of immunization coverage and numbers of births for 2013 [2,3]. Coverage of the birth cohort is shown on the right-hand axis. (*b*) Estimated individual effectiveness of each vaccine presented as a global average based on country-specific estimates weighted by the number of children immunized in each country. (*c*) The number of children born each year who are vaccinated but remain unprotected based on the estimates in A and B at current levels of coverage or if coverage with *Haemophilus influenzae* type B (Hib), pneumococcal vaccine (PCV) and oral rotavirus vaccine (ORV) reached at least 80% in each country. Children who are incompletely vaccinated are not included in these estimates. Country-specific vaccine effectiveness estimates are based on published data for BCG vaccination against pulmonary tuberculosis (assuming 70% for more than 40° latitude and 30% for 0–40° [4]), diphtheria toxoid [5], tetanus toxoid [6,7], acellular or whole-cell pertussis vaccines using predominant usage patterns by WHO region [8], hepatitis B vaccine (ignoring the effect of limited coverage birth dose administration [9]), Hib vaccine against meningitis [10], single dose measles vaccine [11], pneumococcal vaccine against invasive pneumococcal disease caused by vaccine serotypes (mainly based on PCV9 or PCV7 [12]), trivalent oral poliovirus vaccine [13,14], oral rotavirus vaccine [15] and yellow fever vaccine [16]. (Online version in colour.)

response to influenza vaccination in the elderly correlates with protection against laboratory-confirmed influenza illness and implicates the cellular immune response as a determinant of protection in addition to antibody [29]. The emergence of new technologies to measure vaccine response and its determinants in humans offers exciting opportunities to probe deeper into the variation observed in the immune response to vaccines and their biological significance for protection against disease. These include high-throughput approaches to characterizing immune cell dynamics, gene expression, innate signalling, antibody repertoire, the human genome and microbiome, among others. For example, transcriptional profiling of peripheral blood mononuclear cells (PBMCs) following yellow fever vaccination has been used to identify gene expression profiles that are associated with the magnitude of the humoral and cellular immune response [30]. Similar approaches have been used with some success to identify molecular pathways associated with protection following vaccination with adjuvanted RTS,S against falciparum malaria challenge [31].

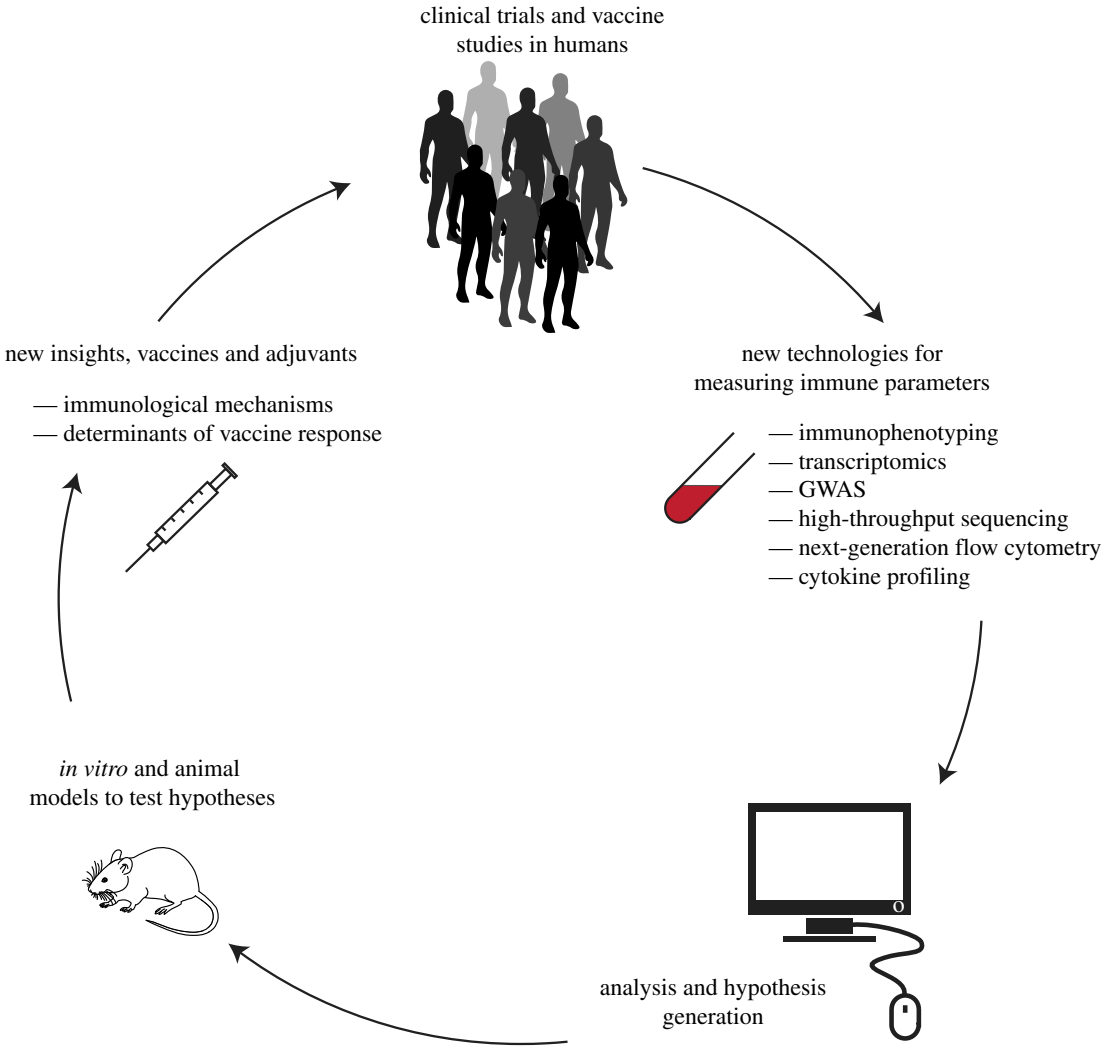

Figure 2. A new paradigm for vaccine research that starts with analysis of variation in the human immune response to vaccination. Adapted from [34]. (Online version in colour.)

The focus of this issue of the *Philosophical Transactions of the Royal Society*, based on a Discussion Meeting held at the Royal Society in November 2014, is on the lessons learned from individual variation in vaccine response with regard to protective immunological mechanisms and the implications for vaccine design. At the meeting and reiterated in this special issue was the articulation of this approach as a new paradigm for vaccine research [32,33]. Rather than beginning with extended preclinical studies in mice and other animals, it was proposed that variation in the immune response to vaccines or infection in humans measured in clinical trials or observational studies would identify potential biological mechanisms underlying protective immunity. These mechanisms could then be probed and tested in the laboratory and in relevant animal models, before designing new vaccines, adjuvants or investigative approaches in humans from which more would be learnt and the cycle repeated (figure 2). Where high-throughput technologies are used this approach has been called *systems vaccinology*, recognizing the important role for the computational tools and analytical methods of systems biology [34,35]. Indeed, a major challenge with this approach is the complexity of the system in addition to limitations in our understanding of the underlying immunological mechanisms.

This journal issue is organized into four sections corresponding to the main topics presented and discussed at the Royal Society.

2. Human genetic and environmental determinants of vaccine response

The immune response to vaccination in children may be determined by their individual characteristics such as age, nutritional status and genome, as well as environmental factors such as infection history or exposure to maternal antibodies and antigens in breast milk. The importance of these variables is explored for a number of important vaccines in five articles published in this issue. Mentzer *et al.* [36] review the evidence for human genetic polymorphisms associated with the immunogenicity of hepatitis B, measles and rubella vaccines, with a focus on their association with vaccine failure. The review offers a critical appraisal of past studies and describes exciting new initiatives for large-scale genome-wide association studies (GWAS) for vaccine immunogenicity. This includes the VaccGene consortium that will provide a meta-analysis of GWAS for vaccine response in over 10 000 infants from the developing world. The potential for these studies to identify molecular mechanisms of vaccine response and implications for a personalized approach to vaccination are explored. This theme is taken up in the article from Majumder [37], which presents the findings from a study of single nucleotide polymorphisms (SNPs) in regions encoding close to 300 candidate genes and their association with antibody response following administration of injected polysaccharide typhoid vaccine or oral inactivated, whole-cell cholera vaccine. A small number of distinct SNPs are shown to be separately

associated with the antibody response to these two vaccines, implicating specific innate and adaptive immune pathways, and in the case of oral cholera vaccine an interesting association with a gene involved in intestinal homeostasis.

Three papers consider environmental determinants of vaccine response. Mawa *et al.* [38] examine maternal latent tuberculosis infection in Uganda, which the authors estimate to be present in up to 60% of mothers, as a potential determinant of poor BCG immunogenicity. They report a reduced T-cell response to *Mycobacterium tuberculosis* purified protein derivative in infants born to mothers with latent infection compared with uninfected mothers, and now plan a larger study to investigate this in more detail. Prendergast [39] reviews the evidence for an effect of malnutrition on the immunogenicity of injected vaccines. In general, seroconversion appears to be unaffected by even severe malnutrition, although antibody titres were found to be lower for some vaccines in some studies. T-cell response to BCG appeared to be impaired by malnutrition, but very few studies have examined the T-cell response to vaccines in the context of malnutrition. Dr Prendergast concludes that studies on the immunology of malnutrition using modern laboratory methods are largely absent and represent an important research need. Finally, Verhasselt [40] reviews recent findings on the immune response in neonatal mice to antigen found in breast milk and the modulatory effect of maternal antibodies and vitamin A. Antigens that contain natural adjuvants such as dust mite antigen are shown to induce a Th2 response and allergic sensitization, while inert antigens result in immune ignorance or tolerance depending on the presence of maternal antibodies. These findings from basic science have implications for maternal immunization and its impact on the immune response to the same antigen in the infant.

3. Oral vaccines as a special case

Given that the bulk of infections enter through mucosal surfaces, using mucosal vaccinations to establish protective immunity could be expected to overcome some of the limitations of current parenteral vaccines. Successful oral or mucosal vaccination has many advantages of ease of delivery, safety and cost, in addition to induction of immune responses both systemically and at mucosal surfaces, with the latter poorly induced by parenteral vaccination. However, efficient delivery of vaccine antigens to innate, local and systemic immune systems and the breaking of the tolerogenic environment appear to be extremely challenging in poorer environments. Over the past five decades, since oral vaccines were first introduced, experience in developing countries has shown that immune responses may be lower and less consistent than in more industrialized countries.

Only a few commercial oral vaccines are currently available, against poliovirus, rotavirus, cholera and typhoid, and only oral poliovirus and rotavirus vaccines are widely used in national immunization programmes. Gilmartin & Petri [41] review the body of work on the performance of oral poliovirus vaccine and report partial results of the Performance of Rotavirus and Oral Polio Vaccines in Developing Countries (PROVIDE) study being conducted in Bangladesh and India (clinicaltrials.gov ref NCT01375647). In children belonging to a low socio-economic class who were infected by a mean of two pathogens at 6 weeks and three pathogens by 10 weeks, levels of intestinal inflammation were high by 12 weeks of age, and stunting increased from 10% at birth to 28% at 1 year of age. Among these children, failure to respond to trivalent oral poliovirus vaccine (tOPV) was associated with the presence of non-polio enteroviruses at 6 weeks, intestinal epithelial damage and inflammation, as measured by a panel of biomarkers and malnutrition. In an attempt to circumvent the poor response induced by environmental enteropathy, a booster dose of inactivated poliovirus vaccine was compared with tOPV at 40 weeks and induced much stronger immune responses to polioviruses 1 and 3, which are the less immunogenic viruses in the trivalent vaccine.

In other studies to enhance the performance of oral vaccines, Lisulo & Kelly [42] build on evidence from work in animal models which suggests that all-*trans* retinoic acid (ATRA), a form of vitamin A, can alter the homing receptor expression of T lymphocytes. Exposure to the highly transcriptionally active ATRA increased expression of $\alpha 4\beta 7$ integrin and the chemokine receptor CCR9, which can redirect T cells to the gut. They describe early work in human male volunteers in Zambia that suggests that oral ATRA administration 1 h prior to dosing with oral typhoid vaccine increases secretion of specific IgA against vaccine-derived lipopolysaccharide into the gut. ATRA for 8 days increases IgA specific to oral typhoid vaccine in gut secretions but does not affect a killed cholera vaccine. A combination of ATRA and oral typhoid vaccine appeared to increase T-cell expression of gut homing markers in a subset of volunteers, and this work is being further investigated by transcriptome analysis, with a view to determining whether ATRA may be a suitable adjuvant to enhance the performance of one or more orally delivered vaccines in the developing world.

In a review of the performance of other potential adjuvants, Praharaj *et al.* [43] compared the results of supplementation with specific strains of probiotics on the performance of a range of oral or mucosal vaccines in high- and low-income settings. Probiotics have been shown to have modulatory effects on intestinal and systemic immune responses in animal models. However, most published studies in children and adults have been small and results have varied by age, antigen, type of antibody response and probiotic strain. Use of anthelminthic drugs in children has been shown to possibly increase immunogenicity following oral cholera vaccination, lending further support to the rationale for modulation of the immune response to oral vaccination through the intestinal microbiome. The availability of newly developed technology and analytic methods supports the investigation of the intestinal microbiota and its ability to activate a multitude of pathways that control innate and adaptive immunity in the gut, which could explain the marked differences in the structure and the luminal environment of the gut in developing countries.

4. What should we measure in vaccine studies?

Despite their widespread use, few vaccines have very clearly defined correlates of protection. For most, these are empirically derived from titres of antibody induced by a given vaccine, above which disease is unlikely to occur.

However, such correlates only exist for very few vaccines—like *Haemophilus influenza*e type B (Hib) vaccine—and others are primarily inferred. For example, the vaccine against meningococcus serotype C was licensed on immunogenicity data

only. To comprehend why certain vaccines fail to protect certain individuals remains a challenge, which is amplified in the context of vaccines required to induce cell-mediated immunity in order to achieve protective efficacy, as for TB, HIV or malaria. The absence of clear correlates of protection continues to hamper the successful development of such vaccines.

Nakaya & Pulendran [32] introduced the concept of systems vaccinology—the study of molecular networks activated by immunization, which has begun to provide unprecedented insight into mechanisms leading to vaccine-induced protection from infection or disease. Primarily based on analyses of the transcriptome, these powerful tools are now enabling us to dissect the more complex interactions of cellular and humoral elements of the responses to infection or vaccination. The understanding of pathways induced by vaccines known to induce excellent protection (like the yellow fever vaccine) is useful to guide the development of other vaccine candidates. To bring this field to maximum fruition, however, it is crucial that statisticians, systems biologists and computational scientists work closely with immunologists. The right statistical approaches need to be developed to complement the biology-driven quests and abstractions of immunologists in proposing mechanistic studies, and planning adequately powered and well-designed experiments necessary for testing the hypotheses.

The paper by Amenyogbe *et al.* [44] argues that all published reports of systems vaccinology have focused on either adults or at most children and older infants. Unfortunately, few data exist from those most in need of progress, i.e. newborns and very young infants, who after all are the most vulnerable to infections and in receipt of the majority of vaccines currently in use. Although systems vaccinology has provided important new insights relevant to two major goals in vaccinology—the elucidation of a vaccine's mechanism of action, and the identification of a molecular signature able to predict a subject's response to vaccination (i.e. biomarkers that indicate whether or not the vaccine will confer protection)—the main challenge is to now go 'beyond the transcriptome', include other large-scale profiling technologies, and achieve integration of data from samples collected during vaccine studies conducted under comparable protocols.

The main reasons for heterogeneity in immune responses are illustrated and summarized in the paper by Kampmann & Jones [45], which focuses on innate and vaccine responses in early infancy. Even if similar tools are applied, intra- and interhost variability in immune responses still need to be understood and captured in vaccine studies, including those using systems biological approaches. Some of the variability can be explained by age, as substantial changes in innate immunity occur early in life. Quite apart from the genetic and ontogenic factors already mentioned, the type and timing of vaccines used and the location of the host also play an important role. Co-infections such as HIV or malaria, malnutrition or the presence of maternal antibody further influence vaccine immunity, and such confounders also need to be taken into account in vaccine studies.

5. Prospects for new and better vaccines in low-income countries

The final papers in this issue look forward to the prospect of new and better vaccines against infectious diseases based on advances in immunology and laboratory technologies that are permitting a new paradigm in vaccine research. In this new paradigm, variation in the immune response among humans is a key part of the vaccine development cycle (figure 2). Wilson & Karp [33] discuss the progress being made towards vaccines for HIV and malaria. In particular, they show how detailed investigation of the immune response to natural infection or vaccination in humans is being used to guide antigen selection and vaccine regimens that are 'better than nature' in inducing durable, broadly protective antibody responses. They describe the example of broadly neutralizing antibodies against HIV, where detailed antibody gene sequencing and binding assays in HIV infected individuals are now guiding vaccine design.

Czerkinsky & Holmgren [46] describe the specific challenges facing the development of mucosal vaccines against enteric infections that are major causes of morbidity and mortality, particularly in the developing world. The authors review the immunological mechanisms of intestinal mucosal immunity with a special focus on findings from human clinical studies with currently licensed vaccines. They note the limitations in our understanding of both innate and adaptive mechanisms of protection at mucosal sites and the technical challenges facing the measurement of cellular immunity in these studies. However, they also point to a healthy vaccine pipeline and new opportunities informed by a better understanding of the mucosal immune response. For example, advances in our understanding of cell trafficking to mucosal sites and the role of innate immunity in programming the adaptive mucosal immune response underlie the development of alternative routes of vaccine administration (e.g. sublingual) and new mucosal adjuvants that hold promise for new and better vaccines against enteric infections.

The evolution of vaccinology from the empirical approaches of the 1930s towards a new paradigm based on high-throughput technologies is characterized in the final article from Barocchi & Rappuoli [47]. This article goes beyond a discussion of recent scientific challenges and successes in vaccine development to consider important economic issues, in particular the failure of the market to drive vaccine development for infectious diseases in the developing world. This failure was felt particularly acutely during the recent Ebola epidemic, but is a persistent problem. Barocchi & Rappuoli note the importance of economic incentives for industry that can be achieved through funding agencies such as the Vaccine Alliance (GAVI) and also highlight the contribution being made by a number of not-for-profit research and vaccine development institutes.

To conclude, this journal issue describes an emerging paradigm in vaccine research where discovery begins with detailed, typically high-throughput, immunological investigation in humans following vaccination or infection. We hope that it provides a broad overview and some tantalizing details that will motivate the reader and inspire new research ideas.

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