NIAID workshop on secondary vaccine effects

On 27–29 July 2021, the National Institute of Allergy and Infectious Diseases (NIAID) hosted a virtual workshop on the topic of secondary vaccine effects to discuss existing evidence, potential immunological mechanisms and associated public health implications.

Vaccines are powerful tools for preventing infection or disease from the infectious pathogens they target, but they may induce additional effects unrelated to the intended targets. Similar to other pharmaceutical products, vaccines may cause side effects, but tolerance to these is extremely low due to the use of vaccines in healthy people, particularly children. Although very rare, vaccine side effects may lead to contraindications and restrictions in use[1]. Distinct from side effects, numerous epidemiological studies and limited randomized clinical trials (RCTs) suggest that vaccines may lead to unintended consequences or collateral benefits beyond what would be expected due to primary antigen-specific protective effects. The causes of these 'secondary vaccine effects' (SVEs), also referred to in the literature as 'non-specific effects', 'heterologous effects', and 'non-targeted effects', remain largely unknown. Recognizing the need for further mechanistic understanding of the immunology underlying SVEs, the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health (NIH), convened a workshop on 27–29 July 2021, with the goal of identifying knowledge gaps and potential immunologic mechanisms responsible for SVEs.

SVE studies have mostly examined the measles vaccine (MV), Bacillus Calmette–Guérin (BCG), oral poliovirus vaccine (OPV), whole-cell diphtheria-tetanus-pertussis vaccine (wDTP) and measles–mumps–rubella vaccine (MMR)[2]. Peter Aaby and Christine Benn introduced epidemiologic evidence for SVEs, including an early observation that the introduction of MV in low-income countries (1970–1980s) resulted in mortality reductions that were too large to be solely explained by prevention of measles deaths alone[3]. Subsequent studies did not find the same association for high-titer MV (HTMV), for which RCTs in children from West Africa reported full protection against measles but also a two-fold higher female mortality rate than the standard MV[4]. A later reanalysis of the data, however, suggested that the mortality changes previously attributed to HTMV may have been confounded by off-setting effects of wDTP given after HTMV. These associations motivated suggestions to explore a change in vaccination schedule[4]. These results, and others, also suggest that live-attenuated vaccines lead to different SVEs than inactivated vaccines. Aaby and Benn also presented a variety of beneficial SVEs associated with BCG from RCTs and observational studies, including: decreased susceptibility to non-tuberculosis (TB) respiratory infections[5,6]; reductions in fatal neonatal sepsis[7]; and reductions in respiratory infections in elderly populations revaccinated with BCG[8]. Evidence for SVEs associated with OPV included a double-blind RCT comparing OPV and inactivated poliovirus in infants in Bangladesh that found an association between OPV and a nonspecific reduction in days of bacterial-induced diarrhea for males[9].

Stanley Plotkin presented an overview of how SVEs fit into the larger field of vaccinology — pointing out that SVEs are real effects of certain vaccines, yet the conditions under which they occur and their potential impact on public health remains uncertain. Past attempts to analyze the potential impacts of SVEs include a 2013–2014 review commissioned by the World Health Organization (WHO) to evaluate whether updates to the Expanded Program on Immunization were necessary. The report highlighted evidence suggesting beneficial effects of immunization with BCG and MV on mortality in high-risk populations[10], but ultimately recommended that further

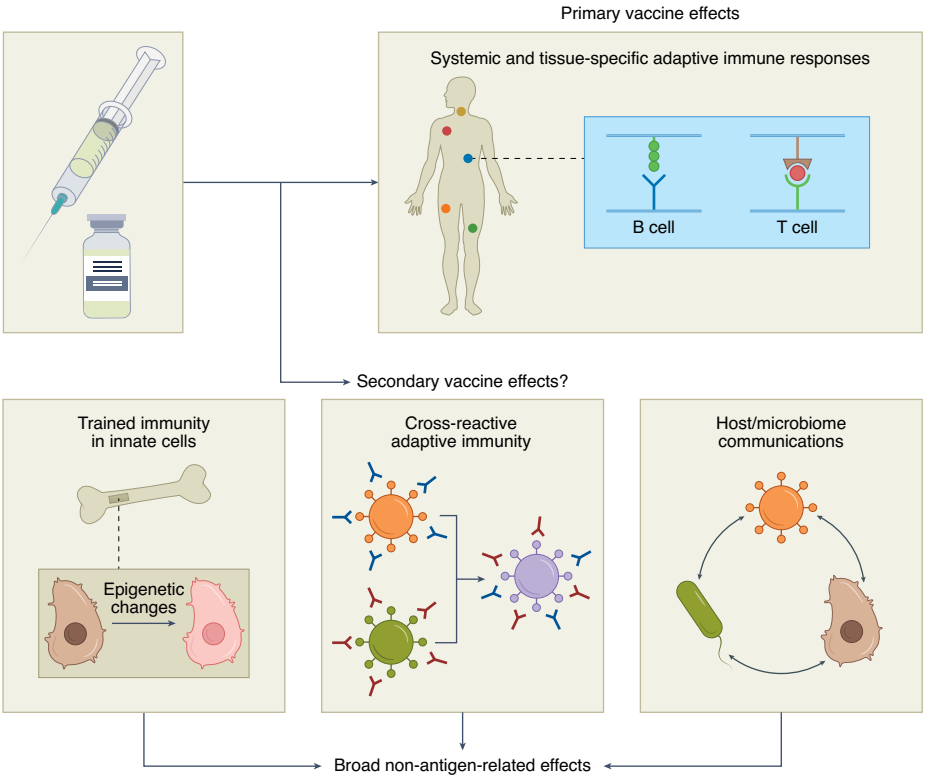

Fig. 1 | Overview of vaccine effects. Vaccines can induce a variety of immunological effects. Primary vaccine effects include antigen-specific protection and memory in adaptive immune cells throughout the body. SVEs are less understood, but could potentially be explained by mechanisms involving innate immunity, adaptive immunity and host–microbiome interactions.

evidence be gathered from RCTs prior to updating immunization practices based on SVEs.

SVE research raises many questions, such as: why do SVEs appear to differ for live-attenuated and non-live vaccines; how long-lived are SVEs; why do some SVEs appear to differ by sex; how does the order of vaccine administration affect SVEs (including revaccination and maternal vaccination); what environmental factors affect SVEs; and do SVEs differ across age groups? While the epidemiological evidence for SVEs is compelling[2,10], the fundamental immunological explanations for SVEs need further elucidation prior to the translation of research findings into clinical practice and vaccine products and schedules. Improved mechanistic understanding, including the immunological pathways at play and the conditions required for SVEs to occur, would enable progress in vaccinology, infectious disease control, and global public health. An overview of potential mechanisms underlying SVEs is depicted in Fig. 1.

Indications for SVEs within innate immunity

Recent studies have suggested that immunologic memory characteristics can be induced in innate immune cells such as myeloid cells or natural killer (NK) cells, which in turn boosts their host defense properties. Such de-facto innate immune memory has been termed 'trained immunity', and has been proposed as an explanation for some SVEs[11]. Numerous examples of trained immunity induced by BCG were shown by Mihai Netea. Aside from the known B and T cell responses induced by BCG, studies show that BCG protects mice with severe combined immunodeficiency (SCID) against heterologous infections, arguing for additional vaccine induced effects independent of lymphocytes[12]. Trained immunity induced by BCG results in improved cytokine (tumor necrosis factor, interleukin (IL)-1β, IL-6) responses by monocytes[10], and more effective release of reactive oxygen species, antimicrobial proteases and enhanced pathogen killing by neutrophils[13].

The mechanisms involved in trained immunity are thought to depend on chromatin structure rearrangement. The molecular processes responsible for these effects are represented by changes in chromatin accessibility due to chemical processes at DNA (methylation) and histone (methylation, acetylation) levels, leading to a more effective transcription of genes important for host defense[14]. The duration and maintenance of the innate memory response, however, remain subjects of intense investigation. In the context of infectious disease and vaccination, there are three known factors that can impact the epigenetic programming of an immune cell — direct interaction with a pathogen, pathogen-associated molecular patterns (PAMPs) from microorganisms, and endogenous cytokines released during the induction of the host response. Maziar Divangahi described key factors affecting the duration of trained immunity that occur centrally, at the level of hematopoietic stem cells (HSCs) in the bone marrow, and peripherally, at the tissue-specific level. A recent study demonstrated that both BCG and β-glucan reprogram bone marrow HSCs towards myelopoiesis and generate trained immunity, while the duration of memory characteristics in innate immune cells have been shown to last for months or even years[15,16]. These studies provide a logical explanation of how short-lived innate immune cells acquire memory.

Bali Pulendran presented data demonstrating SVEs and evidence of trained immunity associated with influenza vaccines. In a study using cutting-edge immunologic and epigenomic techniques, Pulendran's group showed that vaccination against influenza (both seasonal influenza and adjuvanted H5N1) led to distinct epigenetic changes in monocytes and myeloid dendritic cells that were indicative of broad antiviral protection, yet increased susceptibility to bacterial pathogens. Peripheral blood mononuclear cells collected from individuals after adjuvanted H5N1 vaccination showed improved resistance to both Zika and dengue virus, confirming the broad antiviral protections induced by influenza vaccines[17].

NK cells have also been shown to display memory characteristics mediated through changes in NK receptor expression and epigenetic rewiring. Studies in mice presented by Dr Joseph Sun showed that the activating receptor Ly49H is expressed on NK cells and binds with high specificity to the mouse cytomegalovirus (MCMV)-encoded glycoprotein m157, which is expressed on infected cells to drive the expansion of virus-specific NK cells during the acute phase of MCMV infection. This proliferation of NK cells depended on the presence of $CD8^+$ T cells[18]. The dependence of NK cell expansion and memory on adaptive immune cells points to another potential pathway for exploring SVEs — namely the potential effect of live vaccines, which are known to initiate adaptive immune responses, on NK cell memory and function.

Indications for SVEs within adaptive immunity

The adaptive immune system has evolved to develop highly specific immune responses against specific pathogens that included the induction and maintenance of antigen-specific immune memory. However, recent data have indicated that exposure to one pathogen (or perhaps a particular vaccine) may influence the immune response against other unrelated pathogens. While many of the current explanations for SVEs rely on trained immunity of innate cells, there is mounting evidence of heterologous pathogen control directed by B and T cells.

Mark Davis recounted the discovery of HIV-specific $CD4^+$ T cells in blood bank samples from HIV-negative donors[19]. Similar memory phenotypes for CMV and HSV antigens were found in other pathogen-naive subjects. He also discussed evidence of B cell cross-reactivity in CMV-positive young adults that transiently produce influenza-specific antibodies. Wider analysis of cross-reactive T and B cell responses has highlighted the critical role of particular pathogens in reshaping repertoires, which may lead to the generation of broader and more flexible T and/or B cell responses. Galit Alter pointed out that although T cell receptor (TCR) and B cell receptor (BCR) repertoires are formed by random recombination of genomic elements with high combinatorial diversity, different subjects exposed to the same pathogens often share immune repertoires (known as public repertoires). Generation of public repertoires has been associated with enhanced T cell control of HIV, cross-reactive humoral immunity across flaviviruses[20], and enhanced protection against COVID-19 in individuals previously exposed to common coronaviruses[21]. Evidence for the presence of polyreactive antibodies within public repertoires and their importance for protection against various pathogens was reviwed[22,23]. Notably, existing public repertoires are not always beneficial, as has been observed for dengue virus infection, where reinfection with a different dengue subtype may lead to enhanced disease (known as antibody-dependent enhancement). The public B and T cell repertoires induced by vaccines may be a key consideration when searching for immunological explanations for SVEs.

Another way in which adaptive immune cells can be non-specifically altered by vaccines is in shaping tissue resident cellular phenotypes via T-helper (T_H) biases. Notably, the measles and smallpox vaccines are known to drive robust T_H1

responses in infants and thought to lead to increased cytotoxic T and B cell responses to subsequent pathogen encounters. Furthermore, different vaccines may shape tissue-specific immunity differently. Along these lines, BCG vaccination has broadly improved respiratory health outcomes in infants, which could be explained by enhanced immune-vigilance in the lung compartment. It has been shown, however, that the lung-specific immune response is variable depending on the mode of administration (for example, subcutaneous, intramuscular or intravenous), with intravenous BCG administration in non-human primates leading to enhanced T cell responses in blood, spleen, bronchoalveolar lavage and lung lymph nodes[24]. Shabaana Khader described how lymphoid innate immune responses could be targeted in both the lung and bone marrow of mice by vaccination with intravenous BCG and through use of combination adjuvants. These insights provide compelling evidence that different vaccines, adjuvants and administration routes will demonstrate distinct tissue/cell tropisms and inflammatory effects — an important consideration for trying to understand SVEs.

Indications for SVEs in the microbiome

Yasmine Belkaid presented research showing that microbiota sensing in the skin leads to transcription of endogenous retrovirus (ERV) genes and a subsequent anti-viral response[25]. This finding points to another new potential mechanism for SVEs — namely that some vaccines and/or adjuvants could influence immune response broadly via ERV expression. Following the theme of microbiome-mediated immunity, Stacey Burgess described results from her lab indicating that a gut-colonizing commensal bacterium, *Clostridium scindens*, can provide general protection against amebiasis in mice by promoting granulocyte–monocyte progenitors in the BM[26]. Together, these microbiome-related discoveries highlight new avenues for exploration when considering non-traditional immune responses to pathogen and vaccine exposure.

Public health considerations and implications of SVEs

Research that improves our immunological understanding of SVEs may create opportunities to optimize vaccines to increase their overall benefits. Ofer Levy described BCG-induced SVEs in human neonates — including epigenetic changes, induction of granulopoiesis, metabolic programming and reshaping of the plasma membrane lipidome. Vaccine trials conducted by Levy in newborns from low-income countries found that timing of BCG vaccination affects rates of sepsis, with vaccination on the day of birth being more beneficial than vaccination delayed up to 7 days[27]. Furthermore, the benefits of BCG were not observed when it was given in combination with hepatitis B vaccine, suggesting that both the timing and order of vaccines is important for SVE-mediated health outcomes. Carlos Martin discussed the development of a novel TB vaccine that aims to obtain increased protection from TB compared to BCG and suggested study designs that could support the consideration of SVEs[28], while Willem Mulder raised the opportunity to understand trained immunity using licensed vaccines and the development of nanobiologic-based immunotherapies. These presentations highlighted the benefits and considerations that need to be addressed for SVEs early in the vaccine development process.

Before any beneficial SVEs can be utilized in the real world, vaccines will require licensure based on the SVE. National regulatory authorities such as the US Food and Drug Administration (FDA) consider multiple factors as they evaluate the full body of evidence submitted by manufacturers for license applications. In this regard, Philip Krause of the FDA described the strong evidence base required to demonstrate safety and effectiveness, noting that specific evidence from highly powered RCTs is prioritized over real-world evidence. On the topic of RCTs, Nigel Curtis stressed that large RCTs will likely be required to provide sufficient statistical power for studying SVEs. While immune response data could ultimately demonstrate SVEs for a particular vaccine, weak SVEs would probably require a number of very large studies to be conducted to provide persuasive evidence of efficacy.

Following vaccine licensure, clinicians and health systems may evaluate a vaccine for use and potential inclusion in national immunization schedules, with recommendations made by national immunization technical advisory groups. Amanda Cohn of the Centers for Disease Control and Prevention (CDC) and the US Advisory Committee on Immunization Practices (ACIP) gave an overview of current vaccine schedules and reflected on the evidence required to support any changes. Cohn noted that changes to the current US schedule based on SVEs would be unlikely due to limited available evidence at this time. At the global level, Folake Olayinka presented the factors considered by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) — the principal vaccine advisory group for WHO. Recommendations from SAGE are used by many different countries and policymakers to formulate, adapt and update their vaccination policies. It was pointed out that the prior systematic review of SVEs commissioned by SAGE did not find the available evidence actionable and further studies have been requested[10,29].

Economic incentives play an essential role in vaccine commercialization and use. Dean Jamison described different types of metrics that could be used to quantify health and economic outcomes of SVEs and highlighted the value of information analyses in helping to motivate further research in the context of substantial uncertainty. In addition, Kimberly Thompson highlighted the need for clear framing of economic analyses to focus on a specific intervention in a specific population with defined, measurable outcomes that are attributed distinctly to the primary vaccine effects, SVEs, and any non-vaccine or baseline effects, and she highlighted the expected net risks, costs and health losses of repurposing and reintroducing OPV for SVEs in the United States in 2020 (ref. [30]).

Conclusion and recommendations

Epidemiological evidence for SVEs points to the ability of vaccines to impact future immune responses in ways that can be either beneficial or detrimental. To properly understand and harness SVEs, we must elucidate the immune mechanisms driving these observations. We recommend three main tasks to accomplish this: identification of immune signature changes and biomarkers corresponding to SVEs; explanation of the cellular and molecular immune mechanisms behind these signature changes; and clarification of factors impacting SVEs (for example, age, sex, environmental factors, prior vaccine/pathogen exposure, maternal vaccine exposure and so on). These individual points will probably need to be studied in parallel to properly fill current gaps in SVE understanding. We expect the path forward will require diverse research strategies, including in-depth immunologic analyses of longitudinal cohorts, development and use of animal models that recapitulate human responses, and the conduct of well-controlled and sufficiently powered RCTs.

With only a few exceptions, such as the WHO decision to withdraw HTMV in 1992 (ref. [4]), SVEs have not widely factored into public health decision-making or in risk–benefit strategies, but this situation could shift as evidence of SVEs increases. Current pharmacovigilance

mechanisms may not detect or monitor SVEs for vaccines, but opportunities exist to modernize pharmacovigilance building on recent developments in systems biology[31]. Hypotheses generated from new pharmacovigilance activities could then help to design RCTs, if the specified endpoints can be accomplished with manageable trial sizes. As more is learned about SVEs, it will be important to consider public communication strategies, particularly to ensure that SVEs are not viewed as vaccine adverse events but, rather, as natural immune responses that can be harnessed to improve future vaccines and vaccination programs. Furthermore, it will be necessary to emphasize that currently approved vaccines have undergone extensive and rigorous review to ensure safety and efficacy for protection against targeted pathogens.[32]

The concept of SVEs has reached the point at which decades of epidemiological evidence is converging with advanced immunological techniques. The burgeoning field of trained immunity, increased understanding of microbiota –immune-system interactions and recent observations of heterologous adaptive immunity provide good starting points for more intensive exploration into the fundamental immunology underlying SVEs. With improved understanding, the broad term of 'secondary vaccine effects' can be replaced with detailed mechanistic descriptions. Furthermore, vaccine formulations and administration strategies can be optimized based on this understanding. The NIAID workshop on SVEs represents the beginning of interdisciplinary discussions around a novel field in vaccinology with great potential impact for public health. ❐

Secondary Vaccine Effects Workshop Planning Committee

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Competing interests

The authors declare no competing interests.