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Baseline immune states (BIS) associated with vaccine responsiveness and factors that shape the BIS

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A B S T R A C T

Vaccines are among the greatest inventions in medicine, leading to the elimination or control of numerous diseases, including smallpox, polio, measles, rubella, and, most recently, COVID-19. Yet, the effectiveness of vaccines varies among individuals. In fact, while some recipients mount a robust response to vaccination that protects them from the disease, others fail to respond. Multiple clinical and epidemiological factors contribute to this heterogeneity in responsiveness. Systems immunology studies fueled by advances in single-cell biology have been instrumental in uncovering pre-vaccination immune cell types and genomic features (i.e., the baseline immune state, BIS) that have been associated with vaccine responsiveness. Here, we review clinical factors that shape the BIS, and the characteristics of the BIS associated with responsiveness to frequently studied vaccines (i.e., influenza, COVID-19, bacterial pneumonia, malaria). Finally, we discuss potential strategies to enhance vaccine responsiveness in high-risk groups, focusing specifically on older adults.

1. Introduction

Vaccines induce an immune response that develops into immunological memory against a specific antigen which are currently mostly derived from infectious pathogens [1,2]. B and T cells together with antigen-presenting cells (APC) such as Dendritic Cells (DCs) play critical roles in the formation of this immunological memory. In fact, building a sufficient antibody titer to neutralize the pathogen or rapidly generating effector cells that can eliminate the infected cells represent major mechanisms of protection from infectious agents. Upon infection or vaccination, APCs, including DCs migrate from infected sites to the draining secondary lymphoid organs such as lymph nodes (LNs), where they present peptides via MHC-II molecules. Recognition of the peptide–MHC-II complex through T-cell receptors (TCR), along with co-stimulation and cytokine signals, results in the activation, differentiation, and proliferation of naïve $CD4^+$ T cells, which then migrate to the infected tissue through the blood to help clear pathogens. Most of the effector $CD4^+$ T cells do not persist beyond pathogen clearance, yet a minor fraction generates long-lived memory T cells that are able to mount quicker and stronger responses to future reinfections. Therefore, developing an effective immune response to vaccination involves a cascade of immunological events starting with the activation of APCs in the tissue (e.g., in the muscle for intramuscular vaccine administration) and ending with the generation of B- and T-cell memory.

Upon antigenic exposure, B cells undergo affinity maturation via somatic hypermutation (SHM) and isotype switching, mostly within germinal centers (GCs) [3,4], thereby resulting in the selection of B cells producing high-affinity antibodies [5]. B and T cell interactions in the LNs are critical for the generation of protective antibodies. Specifically, follicular helper T cells (T_{FH}) prime B cells for the selection and maturation of the antibody responses (e.g., to increase antibody affinity and to generate different antibody isotypes [6,7]). Hence, circulating T_{FH} cells can be monitored to track immune responses to vaccination. Several studies, including ours, showed that the induction of circulating T_{FH} cells that peaked seven days after influenza vaccination correlated significantly with antibody responses at day 28 [8,9]. Short-lived plasma cells rapidly secrete antigen-specific antibodies over the following two weeks, whereas memory B cells mediate long-term immune memory. Immune memory is boosted by long-lived plasma cells, which can reside in bone marrow niches and produce antibodies for decades [10]. In humans, post-vaccination increases in plasmablast (PB) signatures are predictive of antibody responses to different vaccines, including influenza and pneumococcal vaccines [11–13].

$CD4^+$ T cells promote class switching, SHM, and memory

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differentiation among B cells. They also assist $CD8^+$ T cells by helping their proliferation and differentiation into memory T cells. T cell memory is also critical for combatting future pathogenic challenges, allowing memory $CD8^+$ T cells to rapidly proliferate when they encounter the same pathogen and give rise to effector T cells that kill the infected cells. $CD4^+$ T cells can induce cytotoxicity through the secretion of cytokines such as IFN-G and TNF [14]. For instance, upon influenza virus infection, cytotoxic $CD4^+$ T cells expressing granzyme B can compensate for the diminished $CD8^+$ T cell responses characteristic of older adults [15]. Longitudinal responses to vaccination have been discussed in excellent reviews [16–18]. Here, we will review 1) major clinical/biological factors that remodel the baseline (i.e., pre-vaccination) immune states (BIS) and responses and 2) the BIS that have been associated with vaccine responsiveness in systems immunology studies. Finally, we will discuss strategies to improve vaccine responsiveness through the modulation and/or monitoring of the BIS (Fig. 1).

2. Biological factors affecting the baseline immune state (BIS)

The efficacy of a vaccine depends on the vaccine's ability to elicit immune responses (i.e., its immunogenicity) and the recipient's ability to mount an immune response (i.e., immune competence). The immunogenicity of a vaccine depends on its formulation (e.g., antigen, adjuvants, vehicle) as well as its regimen (e.g., dose, route, and frequency of vaccination [19]), whereas the immune competence varies among individuals and depends on multiple clinical and biological factors that affect their BIS. This section will review how aging (chronological and biological), biological sex, genetics, past infections – via trained immunity – and latent infections (e.g., CMV) change the BIS, particularly focusing on the changes that might affect vaccine responses. For a more exhaustive list of both intrinsic and extrinsic factors that affect the immune response to vaccination, we refer you to an excellent review here [20].

2.1. Aging

Immunosenescence – the aging of the immune system – is one of the most important factors that contribute to declining immune competence and reduced vaccine responsiveness [21–24]. Aging significantly affects innate and adaptive immunity both at the tissue level and in the periphery (reviewed in depth in [25–29]). In the B cell compartment, aging affects cell compositions and cell-intrinsic functions [30,31]. For example, aging has been linked to decreases in naïve B cells, increases in switched-memory and double negative (DN) memory (IgD^- $CD27^-$) B cells (also referred to as age-associated B cells (ABCs)), and reduced differentiation into plasma cells [32–35]. The evolution of antibodies by SHM is critical for effective antibody responses. In mice, aging has been associated with a reduction of SHM [36] and a contraction of GC size [37]. Also in humans, aging has been shown to impair the GC reaction and the memory B cell response [38]. A recent study reported age-dependent defects in T_{FH} cells localization within GCs, resulting in a poor antibody production upon immunization in mice. Interestingly, some of these changes were reversed by transferring TFH cells from young mice into aged mice that can localize in the light zone [39]. In the context of influenza vaccination, older adults had diminished naïve B cell repertoire and reduced intra-lineage mutational diversification, resulting in reduced naïve B cell precursors for initiating novel responses and impaired SHM processes [40]. Furthermore, there is age-associated declines in TCR and B-cell receptor (BCR) repertoire diversity, possibly following repeated exposure to pathogens, which contributes to impaired immune responses in older adults [41–43].

In the T cell compartment, major age-related changes include the decline in naïve $CD4^+$ and naïve $CD8^+$ T cells due to thymic involution and an increased proportion of activated cells – including terminally differentiated T cells – due to continuous antigenic challenges with age [44,45]. Aging is-associated to an expansion of Granzyme K (GZMK)-expressing $CD8^+$ T cells in mice tissues (e.g., spleen, lungs, kidney, and liver) and in human peripheral blood mononuclear cells (PBMCs) [46]. GZMK released by these cells promotes Senescence Associated Secretory Phenotypes (SASP) in mice fibroblasts, likely contributing to cellular senescence and inflammation. Another hallmark of $CD8^+$ T-cell aging is the expansion of senescent $CD8^+$ TEMRA cells, which acquire NK like features, including cytotoxic functions while losing their costimulatory T cell receptors CD28 and CD27. These 'aged' $CD8^+$ T cells can induce TCR-independent killing of NK cell receptor

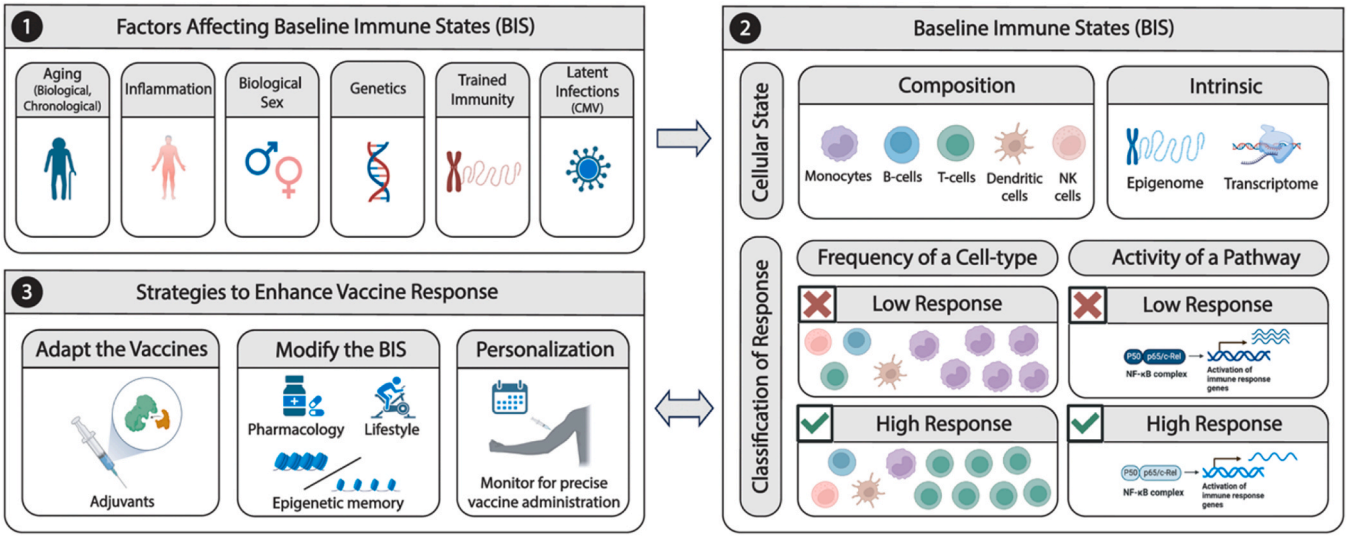

Fig. 1. Factors contributing to the baseline immune state (BIS), relevance to vaccine responsiveness, and strategies for remodeling. 1) The BIS of an individual can be affected by various factors including aging, inflammatory status, biological sex, genetics, trained immunity, and latent infections such as CMV. **2)** These factors can impact the cell-compositional (i.e., immune cell frequencies) and cell-intrinsic states (e.g., transcriptomic and epigenetic profiles). Distinct baseline cell-compositional and/or cell intrinsic-states have been associated with responsiveness to different vaccines using systems immunology approaches. **3)** Three potential strategies that can be explored to optimize the immune responses of older adults including i) adapting the vaccines, ii) modifying the BIS prior to vaccination to compensate for immuno-deficiencies; and iii) personalization: stratifying and closely monitoring the population to find the right time and the right vaccine for each donor. CMV: cytomegalovirus. Image created with BioRender.com.

(NKR)-ligand expressing cells, which increase with inflammation [47,48]. Profound genomic changes associated with aging in immune cells include: (i) gene expression changes in PBMCs and sorted immune subsets [49–51], as well as in tissues in human and mice [46,52]; (ii) DNA methylation changes at CpG sites [45,53–57] that give rise to epigenetic clocks, and (iii) chromatin accessibility changes in PBMCs and sorted $CD8^+$ T cell subsets that impair cellular responses [45,58]. These age-related alterations in the T cell compartment and the accumulation of senescent immune cells predispose older adults to infectious diseases and diminish their ability to benefit from vaccines [59].

One of the hallmarks of immunosenescence is the chronic activation of inflammatory responses, termed 'inflammaging' – a concept introduced by Franceschi in 2000 [60–62]. IL6, TNF and IL1B are markers used to assess chronic inflammation, which are mainly produced by myeloid cells in the periphery (e.g., monocytes, DCs). Aging affects monocyte phenotype and function, resulting in decreased proportions of $CD14^+$ $CD16^-$ classical monocytes and an increase in $CD14^+$ $CD16^+$ intermediate and $CD14^-$ $CD16^+$ non-classical monocytes [63,64]. Moreover, aged monocytes release more proinflammatory cytokines such as TNF and IL-8, likely contributing to 'inflammaging' [65–68]. Independent of external stimuli, aging leads to NLRP3 inflammasome activation in multiple tissues, which increases local inflammation and the incidence of chronic diseases [69,70]. However, which molecular and cellular components of inflammaging stem from chronic disorders, lifestyle, diet changes, or frailty (a clinical marker of unhealthy aging), and which ones are associated with chronological aging itself, remains to be understood.

2.2. Biological age

Chronological age is a major risk factor for reduced immune responses to infections and vaccination. However, it is not sufficient to explain donor-level heterogeneity in health and lifespan outcomes [71]. This led to the concept of 'biological age' that quantifies age at the cellular level using specific biomarkers and uses it to explain deviations from the chronological age [72]. Several factors, including body mass index (BMI), comorbidities, and lifestyle, contribute to the biological age. For example, obesity is associated with decreases in vaccine responses and increases in late/exhausted memory B cells among both young and older adults [73]. Different assays are used to investigate biological aging biomarkers, which led to the discovery of epigenetic, metabolic, transcriptional, and proteomic 'clocks' (reviewed in [74,75]). Some of these 'clocks' specifically focus on estimating immune age and health and are utilized to predict certain clinical outcomes (e.g., all-cause mortality) [76]. However, the utility of these clocks to link immune dysfunction to specific immune cell functions and types has been limited, and further research is needed in this area. Furthermore, the effects of biological age on BIS and immune responses to vaccination are unclear. The Human Immunomics Initiative (HII) will explore the impact of biological age, including humoral age (humoral biomarkers of immune age), on the efficacy of COVID-19 vaccines in the presence and absence of other vaccines routinely offered to older adults [77]. The impact of co-morbidities (and associated medication) on vaccine responsiveness and BIS is largely explored. For instance, a recent study showed that reduced immune responses to COVID-19 vaccine are associated with comorbidities (diabetes, renal disease) in indigenous people. Non-indigenous people with comorbidities also have similar immune perturbations, suggesting that reduced vaccine responses are driven by comorbidities rather than ethnicity [78]. However, there is little known on this topic especially for older adults [21]. Future studies are warranted to investigate this question by establishing larger cohorts to properly address inter-individual variation and tease out the effects of co-morbidities and medication use.

2.3. Biological sex

There is increasing evidence and appreciation that men's and women's immune systems age, function, and manifest diseases differently [79–82]. For example, 80% of autoimmune diseases occur in women [79], whereas men typically experience infectious diseases more severely, including COVID-19 [83,84]. Overall, women mount stronger responses to vaccination (e.g., for influenza, dengue, hepatitis, smallpox). However, this sex bias is both vaccine- and age-group specific [79,85]. 'Accelerated aging' of men's immune system has been observed in several studies [86–88]. We previously showed that differences between male and female PBMCs increase with age. Furthermore, men display more pronounced age-related changes in T cells (e.g., downregulation of T-cell signaling pathways) and in innate cells (e.g., upregulation of pro-inflammatory molecules) compared to clinically matched women [80]. The age-related decline in B-cell numbers and percentages was also more significant in men [80,87]. Genotype-Tissue Expression (GTEx) is a large consortia effort to study cell-type specific gene expression programs in human cells and tissues. Analyses of transcriptomic data from the GTEx project revealed that sex biased gene expression is widespread and tissue specific; where 37% of genes are exhibit sex differences in at least one of the 44 tissues studied [89]. These sex biased genes were enriched in immune response related pathways and included important immune response molecules (e.g., *IRF1*, *STAT5B*, and *NFKB1*).

Genetics and sex hormones both contribute significantly to the observed sex differences. Women have two copies of the X chromosome that harbor many genes critical for immune cell functions, including Toll-like receptors (*TLR7, TLR8*), cytokine receptors (*IL2RG, IL13RA2*), and transcription factor genes (*FOXP3*) [90]. Although during development, one of the copies of the X chromosome is inactivated in females (i.e., X chromosome inactivation (XCI)), some genes escape XCI and contribute to the female bias of autoimmune diseases (reviewed in [91]). Furthermore, genetic variants in the sex chromosomes also contribute to sex differences in immune responses and health. For example, a *TLR7* gain-of-function variant has been linked to the etiology of Systemic Lupus Erythematosus (SLE), an auto-immune disease where 90% of the patients are women [92,93]. Immune cell responses also differ between men and women. Large consortium projects uncovered age- and sex-dependent differences in immune responses to in vitro stimuli [81,94], suggesting that the genomic differences observed in previous studies have functional and clinical consequences. In alignment, men who recovered from mild COVID-19 responded differently to influenza vaccination and had higher innate, PB, and antibody responses compared to women [95]. Sex differences were also observed in bone marrow neutrophils that are critical for innate and inflammatory responses. Upon lipopolysaccharide (LPS) stimulation, neutrophils from male mice produced higher levels of elastase, a critical molecule for their ability to extrude chromatin to kill pathogens. A similar sex bias was also observed in human proteomics data from blood neutrophils [96].

2.4. Genetics

Genetic variation also contributes to the heterogeneity in BIS and vaccine responsiveness (reviewed in [97]). Single nucleotide polymorphisms (SNPs) are associated with differences in infectious disease severity [98], treatment response [99,100], and antibody response to vaccination (influenza and measles) [101,102]. Some of these associations are observed in multiple cohorts and involve important immune response genes, including interferon-stimulated genes (e.g., *OAS1*), cytokines (*IL6*, *IFNL3*), cytokine receptors (*IL2RA*, *IL10RA*), and HLA class I and II genes, [97,101,103–105]. While most vaccine studies have been conducted in Caucasians, a few studies showed that race and ethnicity might also play an important role in modulating immune cells and responses. For instance, donors with African ancestry mount higher IgG antibody responses to the H1N1 virus compared to donors with European ancestry [106]. African ancestry donors also have a higher baseline

of circulating B cells (for most B cell subsets) compared to European ancestry, which might also contribute to their high risk for certain immune diseases, including SLE [107]. Genes expression profiles from blood samples of donors with an African or European ancestry highlighted an age-independent enrichment for myeloid genes, pointing to potential differences in innate immune responses [106]. Confirming the importance of ethnic variation in vaccine responses, a genome-wide association study of smallpox vaccine in a healthy multi-ethnic cohort (n = 1071) revealed that different SNPs and target genes were associated with vaccine responsiveness in different ancestry donors (European, Hispanic, and African ancestry) [108].

Expression Quantitative Trait Locus (eQTL) analyses are also effective strategies to uncover the role of genetics in modulating immune responses by linking genetic variation to gene expression levels (steady-state expression and expression upon activation) (reviewed in [109]). QTL studies revealed genetic variants associated with changes in in vitro responses to infectious agents and in vivo responses to trivalent influenza vaccination [104,110–112]. In one of these QTL studies, 146 SNPs were linked to transcriptional responses to influenza vaccination; these genes were involved in antigen processing and presentation, cytotoxic killing of target cells, and DC maturation and function [104]; a subset of these QTL genes (n = 20) also correlated with antibody responses confirming their importance for immune responses to vaccination (Table 1 [104]). In human DCs, QTL studies uncovered 121 common genetic variants associated with transcriptional responses to diverse stimuli (i.e., E. coli, influenza, or interferon-β) [113] (e.g., IFN-regulatory factor IRF7). These genetic variants also affected the binding sites of key transcription factors (TFs) for immune responses such as IRFs and Signal transducer and activator of transcription (STATs). A recent study from 80 male donors with varying degrees of European versus African ancestry confirmed the significant role of genetics in interferon responses and showed that European ancestry is associated with stronger type I and II interferon responses upon influenza viral infection [114]. Moreover, genes differentially expressed between African and European ancestry donors also included genes linked to COVID-19 disease severity.

2.5. Trained immunity

The field of trained immunity, termed by Netea et al. [115,116] in 2011, challenged the concept that immune memory is exclusive to adaptive immune cells. Internal or external immune insults (e.g., infection, vaccination) can functionally reprogram innate immune cells via epigenetic remodeling, altering their responses to future immune challenges [117]. One of the first documented examples of trained immunity was the observation that Bacillus Calmette-Guérin (BCG) vaccination confers heterologous protection from secondary infections (e.g., *Candida albicans*, *Mycobacterium tuberculosis*) [118–120]. Interestingly, this protection was T cell independent but dependent on macrophages and pro-inflammatory cytokines secreted from these cells [121]. Paradoxically, these innate immune cells live only a few days; hence it was unclear how short-lived innate immune cells can maintain such long-lasting changes in their responses. Mice studies uncovered a mechanistic explanation to this paradox by showing that the access of BCG vaccine to the bone marrow changed the transcriptional programs of hematopoietic stem and progenitor cells (HSPC) inducing them to generate epigenetically modified macrophages that provided better protection against viral insults [118]. However, molecular features of trained immunity have been more difficult to establish in humans since it is difficult to obtain bone marrow samples. Recently, our team overcame this challenge by developing a novel workflow to effectively study human HSPCs from blood, termed Peripheral Blood Mononuclear Cell analysis with Progenitor Input Enrichment (PBMC-PIE). Using PBMC-PIE, we showed that past COVID-19 infections induce long-lasting epigenetic changes in blood-derived monocytes and HSPCs, which alter cellular responses of monocytes from convalescent COVID-19 patients to in vitro activation compared to healthy controls [122]. Further research is needed to uncover (i) how trained immunity

Table 1

Baseline gene-expression signature(s) associated with vaccine responsiveness. From top left: **Vaccine Type:** influenza, pneumococcal (light purple), malaria (light gray) or different vaccines in the same study (light blue); **Immunization Season:** represents the calendar year for vaccination(s); **Age:** age (years) of the donors enrolled in the study; **Signature:** transcriptional signatures associated with vaccine responses; **Direction:** represents whether the transcriptional signature is positively or negatively associated with vaccine responsiveness; **Method(s):** assays used to identify the transcriptional signature; **Antibody Response:** assays used to quantify antibody responses. High hemagglutination inhibition, HAI; VNA, virus neutralization assay; Microneutralization, MN; Enzyme-linked immunosorbent assay, ELISA; influenza antibody surface plasmon resonance (SPR); quantitative polymerase chain reaction, qPCR; Plaque Reduction Neutralization Test, PRNT; Serum Bactericidal Assays, SBAs; Opsonophagocytic Assay, OPA, is the type of assay used for antibody quantification.

		Vaccine Type	Immunization Season(s)	Age	Signature	Direction	Method(s)	Antibody Response	Source
Gene Expression Signature	Influenza	TIV	2008-2013	20-90	9 genes; BCR signaling (M54) & inflammatory response (M33)	↑	RNA-seq	HAI & VNA assays	HIPC-CHI Signatures Project Team et al. [164]
					6 genes; ETF1 targets (M10.0) & enriched in T cells (M223)	↓			
		Fluzone	2019-2020	18-85	36 genes; immunoglobulin functionality (M11)	↑	RNA-seq	HAI assay	Forst et al. [158]
					9 genes; inflammatory response (M37)	↓			
		TIV	2008-2012	18-40	20 genes; antigen transport and processing	↑	Microarray	MN & HAI assays	Franco et al. [104]
		Fluvirin/H1N1 pandemic	2009	21-62	Innate pathways: (PRR signaling, TREM1 signaling & interferon-related genes); B cell development and activation	↑	Microarray	MN assay	Tsang et al. [153]
					Innate pathways: (PRR signaling, TREM1 signaling & interferon-related genes)	↓			
		Flucelvax/HD Fluzone	2020-2021	18-65<	13 genes; T cell activation (M7.3)	↑	CITE-seq & whole blood RNA-seq	MN assay & influenza antibody SPR	Sparks et al [95]
		TIV	2010-2011	50-74	10 genes; B cell response	↑	mRNA-seq & B Cell ELISPOT	HAI assay	Zimmermann et al [157]
	Pneum - ococcal	Prevnar (PCV13)	2017-2018	60-88	260 genes; NK cell mediated cell cytotoxicity	↓	Bulk RNA-seq & scRNA-seq	OPA assay	Ravichandran et al [13]
		Pneumovax (PPSV23)			134 genes; Cell cycle and transcriptional regulation processes	↓	Bulk RNA-seq		
	Malaria	CPS, MAL68, BSPZV1 & IMRAS	2011-2012 & 2014-2016	18-50	Inflammatory pathways & TLR signaling	↑	RNA-seq	IFA, ELISA	Neal et al [217]
		RTS,S/AS01E	2011-2012	<1.7	TLR, NF-KB, interferon and monocyte-related	↑	Microarrays	ELISA	Moncunill et al [216]
		CPS		18-35	Intrinsic capacity to respond to immunization	↑		qPCR	
	Different Vaccines	Fluvirin/H1N1 pandemic/ Fluzone/YF-17D	2008-2012	20-60	TGSig (10 genes; Type I IFN response & DC activation (EPHB1 shared between SLE and vaccine signature)	↑	Microarray	HAI assay	Kotliarov et al [154]
		Pan-vaccine meta-analysis	2007-2014	18-55	14 genes; Proinflammatory cytokines and chemokines and NFKB signaling	↑	Microarray & Bulk RNA-seq	HAI, MN, ELISA, PRNT and SBAs	Fourati et al [165]
					NFKB regulated proinflammatory genes; Nuclear acid sensing innate immune processes	↑			
					Cytotoxic genes in NK; Interleukin signaling in T cells; Transcriptional markers of B cells	↓			

shapes the BIS including a better understanding of which features/components of trained immunity is predictive of vaccine responsiveness; (ii) how long are the effects of this epigenetic remodeling last, and (iii) to what extent the epigenetic remodeling of immune cells helps to boost immune responses to future challenges. Towards addressing the last question, a recent study showed that influenza vaccination can remodel the epigenetic landscape of innate immune cells and boost responses to orthologous viruses [123–125], indicating for the first time that epigenetic remodeling of immune cells can have an adjuvant effect (termed epigenetic adjuvants).

2.6. Latent infections

Latent infections, hidden or dormant infections, can remodel the BIS by continuously triggering immune responses. In the context of aging, latent cytomegalovirus (CMV) infections are among the most studied since they are a common virus and contributes to aging-related immune deficiencies [126,127]. In the US, more than 50% of the adults are infected with CV by age 40. CMV virus stays in the body for life and can reactivate, most people with CMV infections have no symptoms; hence they do not know that they are infected. At the cellular level, CMV infections particularly affect the $CD8^+$ T-cell compartment, where CMV-specific T cells acquire an advanced, terminally differentiated phenotype [44,128–130]. These cells are characterized by the lack of CD45RO expression and the re-expression of the naïve T-cell marker CD45RA (known as TEMRA cells). Expansion of TEMRAs is more predominant in CMV infections compared to other latent infections (e.g., EBV, HIV) [131,132], which might be due to different differentiation states of HIV- and CMV-specific memory $CD8^+$ T cells [133,134]. The effects of latent infections on future immune responses are largely unknown. Earlier work suggested a beneficial effect of CMV infection on the immune response to influenza vaccine in young individuals [135]. However, it is unclear whether this relationship between CMV positivity and vaccine responsiveness is generalizable, especially to older adult cohorts. Indeed, a meta-analysis of vaccine-response data from 17 studies showed that there is no significant association between CMV positivity and influenza vaccine responsiveness [136]. In alignment, we did not detect an association between CMV positivity and responsiveness to bacterial pneumonia vaccines in older adults [13]. For a more detailed discussion on the effects of CMV infections on antibody responses to influenza vaccination we refer you to this excellent review [136].

3. Baseline immune states (BIS) associated with vaccine responsiveness

BIS, defined as the baseline immune status of an individual (i.e., prior to vaccination), is shaped by various factors. Systems immunology approaches, which involve the comprehensive analysis of the immune system, represent an ideal framework to characterize the BIS and its association with responsiveness to diverse vaccines [12,137]. Initial work in this area was done on Yellow Fever (YF) vaccines and showed that BIS signatures could predict the immunogenicity of the attenuated viral vaccine (YF-17D) [138]. Most of the systems immunology studies on vaccine responses focuses on influenza due to prevalence of the influenza infections and vaccination as well as the urgency to understand mechanisms behind the reduced influenza vaccine responsiveness among the most vulnerable populations (e.g., older adults, infants, and immunocompromised individuals). Therefore, most of our knowledge on BIS associated with vaccine responses stems from influenza studies, which we will review here. We will also discuss the BIS associated with COVID-19, bacterial pneumonia, and parasitic malaria vaccines, other frequently administered and studied vaccines in humans.

3.1. BIS associated with influenza vaccine responses

Seasonal influenza is a major public health burden. Worldwide, Influenza epidemics result in 3–5 million cases of severe illness and about 290,000–650,000 deaths each year [139]. Despite the widespread use of vaccines, 90% of influenza-related deaths occur among older adults [140]. There are different types of influenza vaccines. In the US for people 65 and younger, inactivated influenza vaccine (IIV), the recombinant influenza vaccine (RIV), and the live attenuated influenza vaccine (LIAV) are available for use [141]. Three influenza vaccines are preferentially recommended over standard-dose unadjuvanted vaccines: (i) high-dose FluZone® (a subunit vaccine with four times the Hemagglutinin (HA) content as standard-dose flu vaccines) [142], (ii) FluBlok® (a recombinant HA protein with three times the HA content as standard-dose flu vaccines) [143,144], and (iii) FluAd® (an MF59 adjuvanted vaccine) [145,146]. Fluzone® and FluAd® provide broader protection against influenza infections with age, both in humans and mice [145]. Influenza vaccine's efficacy varies by season, influenza virus subtype, and age groups. For instance, data from two concurrent CDC studies in Wisconsin found that effectiveness of the 2022–23 influenza vaccine was 54% for preventing medically attended influenza A infection among persons aged under 65 years and 71% effective for preventing symptomatic influenza A illness among individual under 18 years [147]. Improving the immune response to the influenza vaccine through a better understanding of the factors limiting its effectiveness is therefore essential [148,149].

3.2. Transcriptional and cell compositional BIS signatures

Longitudinal transcriptional profiling of PBMCs upon vaccination showed that innate cell responses peak one day after vaccination, whereas adaptive cell responses, including PB and T_{fFH} responses, peak around day seven [11,150,151]. However, fewer studies have examined how inter-individual variation in BIS affects vaccine responsiveness. Different approaches were applied to answer this question, including the analysis of immune cell compositional changes (e.g., flow cytometry), transcriptomic profiling (e.g., microarray, bulk RNAseq), epigenetics, and more recently, multi-omics (e.g., CITE-seq [152]). The Human Immunology Project Consortium (HIPC) and the Center for Human Immunology (CHI) conducted one of the first studies in this area. They collected multidimensional PBMC microarray, serum antibody titers, and flow-cytometry data from 126 cell subsets to investigate the associations between the BIS of 63 healthy adults (21–62 years old) and the responses to the pandemic H1N1 (pH1N1) influenza vaccine (2009 season) [153]. Vaccine responsiveness is typically measured by comparing the baseline (pre-vaccination) antibody titer to the post-vaccination titer (day 70 used in [153]), referred to as maximum fold change (MFC). Since baseline titers were associated with vaccine responsiveness, an adjusted MFC (adjMFC) metric was developed and utilized to mitigate the effects of baseline titer variations. This study linked the baseline frequencies of 12 cell populations to influenza vaccine responsiveness, including B-cell subsets (memory, naïve, and transitional $CD20^+$ $CD38^+$), IFNα+ DCs, and several activated $CD4^+$ T-cell populations. Interestingly, the B-cell signature ($CD20^+$ $CD38^+$) was independent of PBs ($CD20^-$ $CD38^+$), which alone could not predict the responses [153]. A recent study used the baseline expression of 10 genes to define a transcriptional signature (TGSig) that robustly correlated with the frequency of $CD20^+$ $CD38^+$ B cells and with influenza vaccine responses in healthy adults (Table 1 [154]). "High" responders had higher TGSig scores compared to "low" responders, as confirmed across three independent influenza vaccine studies. A follow-up study showed that the activity of TGSig genes also correlated with SLE disease activity in a subset of patients with PB-associated flares [155], suggesting that BIS signatures related to vaccine responsiveness might also be informative in immune diseases. Single-cell PBMC RNA-seq data from top and bottom responders confirmed the TGSig and $CD20^+$ $CD38^+$

B-cell associations to vaccine responses and showed that the TGSig transcriptional signature likely stems from plasmacytoid DCs (pDCs) through the expression of Type I interferon, rather than from B cells (Table 1). Interestingly, the TGSig signature was not associated with age. Although women had higher TGSig scores than men, the TGSig was associated with responsiveness in both sexes. Additionally, the baseline TGSig expression was associated with responses to YF-17D vaccine in three independent cohorts [138,154,156].

Machine learning (ML) models are frequently used to uncover and quantify BIS features that could predict vaccine responsiveness. One ML-based study uncovered a 10-gene signature predictive of vaccine responses from 159 adults vaccinated with TIV, these genes were associated with DCs, T cells, and classical monocytes (Table 1 & Table 3 [157]). Another such study conducted in a larger cohort (275 donors, 18–85 years old) uncovered gene modules predictive of responses to FluZone®; these genes were associated with antigen binding and activation of adaptive immune responses and genes encoding immunoglobulins (Table 1 [158]). Accuracy of predictive ML models improved when other types of data are integrated along with the gene expression profiles including baseline Hemagglutination inhibition (HAI) titers, BMI, and vaccine history of donors, reinforcing the importance of considering biological factors while studying vaccine responses. Studies describing the BIS associated with the lack of responses among older adults are still limited. A recent study from 27 older individuals (>65 years old) vaccinated with adjuvanted FluAd® vaccine showed that non-responders exhibited high frequencies of regulatory T cells (measured by flow cytometry), suggesting that low vaccine responsiveness was driven by inhibitory mechanisms. Single-cell (sc)RNA-seq data from this study also showed an association between increased NK and T_h17 cells, decreased naïve $CD4^+$ T cell frequency, and reduced vaccine responses (Table 2 [159]). NK cells from non-responders had limited IFNγ+ secretion upon vaccination, suggesting functional defects in the NK cells of non-responders. In contrast, responders had strong vaccine-induced cytokine release from both $CD8^+$ and $CD4^+$ T cells. Vaccine responsiveness upon FluAd® administration was higher in women, further highlighting that biological sex is a key factor in this process.

3.3. Other omics BIS signatures

Baseline microbiome and epigenome states have also been linked to influenza vaccine responses. Antibiotic treatment is used to understand how perturbations of the gut microbiota homeostasis modulate the responsiveness to the FluZone® influenza vaccine (n = 22, 18–40 years old). Independent of the antibody titer levels, antibiotic treatment was associated with a high inflammatory state, perhaps driven by increased inflammasome signaling due to impairments in bile acid metabolism by the gut flora. Further investigations into how the gut microbiota modulates the BIS and the immune response to vaccines in older adults would be valuable (Table 2 [160–162]).

Earlier studies revealed baseline differences in DNA methylation between responders and non-responders to influenza vaccines. Specifically, 142 differentially methylated CpG sites in young adults (n = 21, <50 years old) and 305 in older adults (n = 23, >50 years old) were associated with TIV and FluBlok® responsiveness, respectively (Table 3 [163]). These differentially methylated regions were associated with immunosenescence and innate immune response–related molecules (*CD40, CXCL16, ULK1, BCL11B, BTC*). ML models applied to these data revealed predictive CpG sites that harbor binding sites of CTCF – a TF critical for 3D chromatin structure – and *MYC*, an oncogene involved in multiple cellular functions (Table 3). Interestingly, among different predictive models, the one using the methylation data alone was the most effective in discriminating top and bottom responders [157], highlighting the significance of epigenetic BIS states. Upon administration of the AS03-adjuvanted TIV vaccine, a novel epigenetic state was uncovered in human monocytes using single-nucleus (sn) ATAC-seq technology[125]. This state involves chromatin closing at the AP-1 binding sites (i.e., innate refractoriness state) and chromatin opening

Table 2

Baseline cell-compositional signatures associated with vaccine responses. From top left: **Vaccine Type:** influenza, pneumococcal (light purple), COVID-19 (light green), malaria (light gray) or different vaccines in the same study (light blue); **Immunization Season:** represents the calendar year for vaccination(s); **Age:** age (years) of the donors enrolled in the study; **Signature:** cell-compositional signatures associated with vaccine response; **Direction:** represents whether the cell-compositional signature is positively or negatively associated with vaccine responsiveness; **Method(s):** assays used to identify the cell-compositional signature; Treg cell-specific demethylated region, TSDR; **Antibody Response:** assays used to quantify antibody responses. High hemagglutination inhibition, HAI; Enzyme-linked immunosorbent assay, ELISA; Plaque Reduction Neutralization Test, PRNT; Microneutralization, MN; influenza antibody surface plasmon resonance (SPR); Serum Bactericidal Assays, SBAs; Opsonophagocytic Assay, OPA, is the type of assay used for antibody quantification.

		Vaccine Type	Immunization Season(s)	Age	Signature	Direction	Method(s)	Antibody Response	Source
Cell Compositional Signature	Influenza	Fluad	2014-2016	65-80	TH17 (CD4+ CXCR3- CCR6+) cells	↓	Flow cytometry, TSDR	MN & HAI assays	Riese et al [159]
					Treg (CD4+ CD127low CD25+ FOXP3+) cells	↓			
					IFNγ+ NK cells	↓			
		Fluvirin/H1N1 pandemic	2009	21-62	IL22+ of CD161-CD4+ T cells, IL2+ of CD4+ T cells, CD38+ of IgD+CD27+ memory B cells, CD38+ of Naive B cells,	↑	Flow cytometry & microarray	MN assay	Tsang et al [153]
					CD27+CCR7− of memory CD4+ T cells (ID36), Perforin+ of CD8+ T cells (ID50)	↓			
		Fluzone	2014-2016	18-40	CD123++ pDCs (antibiotic treatment)	↑	Flow cytometry	MN & HAI assays	Hagan et al [162]
		Flucelvax/HD Fluzone	2020-2021	18-65<	GPR56+ frequency of CD8+ EM cells in Covid19-infected men	↑	Flow cytometry; CITE-seq	MN assay & influenza antibody SPR	Sparks et al. [95]
	Pneumococcal	Prevnar (PCV13)	2017-2018	60-88	Th1 cells	↑	Flow cytometry	OPA assay	Ravichandran et al [13]
					Th17 cells	↓			
					CD56dim CD16+ NK cells	↓	scRNA-Seq		
		PCV7 + PPSV23	2002-2004	35-55	CD4+CXCR5+ TFH cells	↑	Flow cytometry	ELISA assay	Rabian et al [197]
	COVID-19	CoronaVac	2021	21-60	CD8+ T cells & CD4+ memory activated T cells	↑	CIBER-sort & LC-MS/MS	Neutralizing antibody titer	Wang et al [176]
		BNT162b2	2021-2022	18-60<	CD69+ MAIT & CD38+ MAIT cells	↓	Flow cytometry	Imunoassay	Boulouis et al [180]
	Mala-ria	RTS,S/AS01E	2007-2008	<1.7	Monocytes to lymphocyte ratio	↓	Coulter counter	ELISA assay	Warimwe et al [215]
	Different Vaccines	Fluvirin/H1N1 pandemic/ Fluzone/YF-17D	2008-2012	20-60	CD19+CD20+CD38++ B cells	↑	Flow cytometry	HAI assay	Kotilarov et al [154]
		Pan-vaccine meta-analysis	2007-2014	18-55	Naive B cells (CD19+CD27−IgG−IgA−)	↓	Flow cytometry & immune deconvolution (from microarray & bulk RNA-seq)	HAI, MN, ELISA, PRNT and SBAs	Fourati et al [165]
					CD8+ T cells (CD3+CD8+CD45RA+)	↓			
					Monocytes, Nonclassical monocytes & mDCs	↑			

Table 3

Baseline epigenetic/protein signatures associated with vaccine responses. From top left: **Vaccine Type:** influenza, COVID-19 (light green); **Immunization Season:** represents the calendar year for vaccination(s). NA, not applicable; **Age:** age (years) of the donors enrolled in the study; **Signature:** epigenetic or proteomic signatures associated with vaccine responses; **Direction:** represents whether the epigenetic or proteomic signature is positively or negatively associated with vaccine responsiveness. NC, no change between responders and non-responder groups; **Method(s):** assays used to identify the epigenetic or proteomic signature. LC-MS/MS, liquid chromatography tandem mass spectrometry. **Antibody Response:** high hemagglutination inhibition (HAI) and neutralization titer assays are used for antibody quantification.

		Vaccine Type	Immunization Season(s)	Age	Signature	Direction	Method(s)	Antibody Response	Source
Epigenetic Signature	Influenza	TIV/Flublok	2009-2011	19-90	120 CpG sites between the older subject R & NR; 64 CpG sites between the younger subject R & NR; 43 CpG sites between all subject R & NR	↑	Genome-wide DNA methylation	HAI assay	Gensous et al [163]
					185 CpG sites between the older subject R & NR; 78 CpG sites between the younger subject R & NR; 40 CpG sites between all subject R & NR	↓			
		TIV	2010-2011	50-74	28 CpG sites; Metabolic activity- lipid and glucose metabolism	↑	DNA methylation & B Cell ELISPOT	HAI assay	Zimmermann et al [157]
		TIV/H5N1/H5N1 + AS03	2014-2015	18-40	Decreased Innate Refractoriness (AP1); Increased antiviral vigilance (IRFs)	↑	Bulk ATAC-seq & scATAC-seq	Not tested	Wimmers et al [125]
	Pneumococcal	Prevnar (PCV13)	NA	<2	Hypomethylation of HLA-DPB1 & hypermethylation of IL16	↑	Illumina Infinium Methylation 450K BeadChip assay	OPA	Pischedda et al [198]
Proteomic Signature	COVID-19	CoronaVac	2021	21-60	5 proteins; Innate and adaptive immunity protein biomarkers	↑	LC-MS/MS	Neutralization titer	Wang et al [176]
					2 proteins; Innate and adaptive immunity protein biomarkers	NC			
					5 proteins; Innate and adaptive immunity protein biomarkers	↓			

at the interferon response (IRF) and STAT family TF binding sites (i.e., antiviral vigilance state) (Table 1 [125]). Interestingly, while immune cells still retained this epigenetic state (42 days post-vaccination), they mounted stronger in vitro responses to heterologous dengue and zika viruses. This study underscores the use of epigenetic remodeling of immune cells as a strategy to boost immune responses (i.e., epigenetic adjuvants). Further studies are needed to uncover the mechanisms behind this epigenetic boosting, including the role of HSPCs, given the short half-life of circulating DCs and monocytes and long-lasting effects of these epigenetic states.

Because chronic inflammation is one of the hallmarks of immunosenescence, the role of baseline inflammation levels on vaccine responses has been investigated in multiple studies. Meta-analyses of blood-transcriptome data from multiple influenza vaccine studies (from the HIPC and the CHI cohorts) discovered an inflammatory response module associated with stronger responses to influenza virus vaccination in young adults and weaker responses in older adults (Table 1 [164]). A recent pan-vaccine study from a larger cohort ($n = 820$, 18–55 years old) confirmed the age-dependent effects of inflammation on vaccine responses, showing that young adults with higher baseline expression of 'proinflammatory' genes mounted stronger antibody responses. However, this association did not hold in the case of antibody responses to influenza, hepatitis B, and varicella-zoster vaccines (VZV) in older adults [165]. In other studies, higher expression of proinflammatory genes at baseline was negatively associated with vaccine responses in older adults [166–169]. These studies uncovered that the effects of inflammation on immune responses are complex and age-dependent, but the mechanism behind this dimorphic effect remains to be understood. Future studies are needed to dissect the inflammatory molecules and pathways and their distinct effects on vaccine responses in young and older adults.

3.4. BIS associated with COVID-19 vaccine responses

With the record-time development of COVID-19 vaccines, we witnessed a revolutionary advance in vaccine technology and deployment. Numerous studies analyzed the immune response to COVID-19 vaccines pre- and post-vaccination in different cohorts, including healthy adults, young children, and pregnant women [170–174]. However, only a few studies explored the BIS associated with the responsiveness to different COVID-19 vaccines, including inactivated viral and mRNA vaccines. By coupling proteomics and ML in a cohort of 163 donors (21–60 years old) who received two doses of the inactivated viral vaccine, Sinovac-CoronaVac (39.4% effective in preventing symptomatic COVID-19 cases [175]), a set of 12 proteins was found to predict responsiveness (Table 3 [176]). Furthermore, non-responders had fewer $CD8^+$ T cells and fewer activated memory $CD4^+$ T cells compared to responders based on CIBER-sort inferred cell-compositional data (Table 2 [176]). In contrast to inactivated viral vaccines, mRNA vaccines are very effective in preventing COVID-19, where a two-dose regimen of BNT162b2 vaccine was 95% effective in protecting against COVID-19 in healthy donors [177] with waning effectiveness in individuals over 65 years of age [178] and immuno-compromised adults [179]. The analysis of BIS in donors vaccinated with the BNT162b2 vaccine ($n = 108$, 18–60 < years old), showed that the upregulation of immune cell activation markers – including CD69 and CD38 in a subset of unconventional T cells (MAIT cells) – correlated negatively with antibody responses at day 35 in healthy donors, primary immunodeficiency (PID) donors and in people living with HIV (PLWH) donors (Table 2 [180]).

3.5. BIS associated with bacterial pneumonia vaccine responses

Pneumococcal infections caused by *Streptococcus pneumoniae* result in thousands of hospitalizations and deaths each year, especially affecting infants and older adults [181–183]. In the U.S., two types of vaccines are approved for children under two years of age, adults aged 65 and above, and younger adults with underlying medical conditions: Pneumovax® (PPSV23), a capsular polysaccharide vaccine targeting 23 serotypes of *Streptococcus pneumoniae*, and protein-polysaccharide conjugated alternatives (e.g., PCV7, PCV13, PCV15, PCV20) [184]. PPSV23 antigens elicit type 2, T-cell-independent antibody responses, which boost phagocytic-cell activity leading to the killing of pneumococcus [185,186]. On the other hand, conjugated alternatives include a non-toxic variant of diphtheria toxin (CRM197) with aluminum phosphate as an adjuvant, which facilitates T-cell assistance in antibody production, to increase immunogenicity and sero-protection in high-risk groups [187–190]. Similar to influenza vaccines, the effectiveness of pneumococcal vaccines declines with age. PCV13 is 90% effective (confidence interval [63.9 – 97.2%]) in infants and young children with two or more doses [191], whereas its efficacy declines to 72.8% (confidence interval [12.8–91.5%]) among older adults (>65 years old) [192]. Likewise, the efficacy of PPSV23 against invasive pneumococcal disease (IPD) is reported to be around 54% (confidence interval [32 – 69%]) among adults older than 50 years of age [193]. Notably, there is a considerable variation in antibody responses to these vaccines in both pediatric and geriatric populations [13,194]. Earlier studies used pneumococcal IgG antibodies in serum to quantify (e.g., with ELISA) the responses to these vaccines. Opsonophagocytosis assays (OPA) measure

the capacity of the antibodies to opsonize pneumococcal serotypes, providing an alternative functional assessment for vaccine responsiveness [195,196]. Studies by us and others have identified baseline cellular and molecular signatures of pneumococcal vaccine responsiveness in healthy and immunocompromised individuals across different age groups [13,165,197]. One of the early studies investigating bacterial pneumonia vaccine responses was conducted on HIV-positive adults. This study found that those with a higher baseline frequency of $CD4^+$ $CXCR5^+$ T_{FH} cells responded better to a two-vaccine regimen (PCV7 followed by PPSV23 four weeks later). This response was associated with increased and sustained levels of Streptococcus pneumoniae polysaccharide-specific IgG antibodies (Table 2 [197]). In addition, there is evidence from epigenetic studies that changes in DNA methylation levels can predict vaccine responses. Specifically, hypomethylation around *HLA-DPB1* gene and hypermethylation around *IL16* gene were linked to stronger PCV13 responses in healthy children under the age of two (Table 3 [198]).

Recently, we performed a longitudinal analysis of the antibody responses of older adults (n = 39, 60–88 years old) to conjugated PCV13 and unconjugated PPSV23. We showed that although the antibody responses of the two cohorts were comparable, the BIS associated with these two types of vaccines are distinct and mutually exclusive [13]. Analyses of baseline RNA-seq data revealed two independent gene sets that are negatively associated with responsiveness to PCV13 and PPSV23. The gene set associated with PCV13 responsiveness was enriched in genes coding for cytotoxicity- and NK cell-associated molecules (e.g., *NCAM1*, *PRF1*, and *GNLY*), and it was hence referred to as the CYTOX signature. The scRNA-seq data showed that the CYTOX signature stems from $CD16^+$ NK cells. Non-responders have more $CD16^+$ NK cells, and their cells express cytotoxic genes at higher levels compared to responders. Furthermore, baseline flow-cytometry data revealed that having lower T_h1 and higher T_h17 frequency is linked to reduced PCV13 responses. The baseline frequency of $CD16^+$ NK cells negatively correlated with T_h1 and positively correlated with T_h17 frequencies, though, as we discuss in the following paragraph, it remains to be established whether NK cells directly regulate T cell populations and responses (Table 1 & Table 2). Age and biological sex were also associated with CYTOX. Older and male donors were more likely to have the CYTOX signature. A distinct transcriptome module associated with cell cycle and transcription regulation was linked to reduced PPSV23 responsiveness (Table 1 [13]).

$CD16^+$ NK cells associated with low PCV13 responses have antibody-dependent cell-mediated cytotoxicity (ADCC) functions. Although the production of ADCC-proficient antibodies is a key factor linked to vaccine responsiveness, including for bacterial pneumonia vaccines [199–203], several studies showed that activation of NK cells can negatively impact vaccine responses [204,205]. For example, the frequency of activated NK cells at day seven was linked to reduced yellow fever vaccine (YF-17D) responses [205]. Similarly, transcriptional activation of NK cells post-vaccination was linked to reduced malaria vaccine responses [204]. Our study showed that a baseline NK signature is linked to reduced vaccine responses, specifically to the T-dependent PCV13. NK cells exert immunosuppressive effects on adaptive immune responses through their cytolytic activity or by specifically recognizing and eradicating activated $CD4^+$ and $CD8^+$ T cells [206]. Moreover, in the context of viral infections, NK cells have the capacity to eliminate both T_H and T_{FH} cells, which leads to impaired cytotoxic T lymphocyte responses, diminished formation of GCs, compromised maturation of B-cell affinity, and reduced production of neutralizing antibodies in mice [207–211]. In addition, NK cells also modulate the quality and magnitude of vaccine responses in mice [206,209]. Further studies are needed to uncover the role of human NK cells in vaccine responses.

3.6. BIS associated with malaria vaccine responses

Malaria infections caused by *Plasmodium falciparum* resulted in 247 million cases of malaria worldwide and 619,000 deaths in the year 2021 alone [212], especially affecting infants and children. The RTS,S/AS01, malaria vaccine, was approved by the WHO for use in children in 2021, and phase IV trials are underway [213]. The RTS,S/AS01 vaccine is only partially protective, with an efficacy of 25.9% for newborns (6–12 weeks old) and 36.6% for children aged 5–17 months [214]. Cell-composition analysis of PBMCs led to the use of baseline monocyte-to-lymphocyte ratio (ML ratio) to predict responsiveness to RTS,S/AS01 malaria vaccine (n = 610, <1.7 years old). A high ML ratio was associated with reduced responsiveness, while a low ML ratio was associated with higher responsiveness to the vaccine (Table 2 [215]). The ML ratio can potentially be employed as a valuable clinical marker for predicting vaccine responsiveness by helping identify individuals who would benefit the most from this vaccine. The comparison of transcriptomic profiles of 279 PBMC samples from: (i) malaria-naïve healthy adults after antimalarial chemoprophylaxis (CPS) immunization and (ii) infected African children and infants yielded BIS signatures of protective immunity against malaria, including gene signatures associated with interferon, NF-kB, and TLR pathways that were increased in responders (Table 1 [216]). A meta-analysis study from four malaria vaccine trials (n = 84, 18–50 years old, efficacy: 36–54%) uncovered that increased baseline expression of inflammatory genes was associated with stronger responses to malaria vaccines (Table 1 [217]), confirming previous reports that increased inflammation could have a positive effect on vaccine responses among young individuals [164,165]. These studies provide key insights into how the BIS of a donor can influence the different outcomes of malarial vaccination among the most vulnerable individuals, including infants and young children.

4. Potential strategies to address reduced vaccine responsiveness

The systems immunology studies discussed here uncovered distinct BIS signatures linked to vaccine responsiveness in different populations (Tables 1–3). These studies were also instrumental in deciphering immune responses to vaccination at the cellular and molecular level; some of which might explain the decreased responses in the rapidly growing older adult population. In the U.S., the population of adults 65 years and older is projected to double from 52 million to 95 million and constitute ~23% of the total population by 2060. Given this demographic shift and the significant effects of aging on the immune system and responses, rejuvenating vaccine responses among older adults is fundamental to extending the health and lifespan of individuals. Here, we will discuss three strategies toward this goal: 1) adapting vaccines and administration strategies; 2) modifying the BIS prior to vaccination; 3) personalizing vaccination strategies and timing.

4.1. Adapting vaccines and vaccination strategies

Adapting and improving vaccines to confer enhanced protection is an active area of research. In the past, simple strategies like increasing the dosage of antigens or the frequency of vaccination proved fruitful. For example, the high-dose trivalent inactivated influenza vaccine (IIV3-HD, FluZone®-HD) which contains four times as much antigen as the standard dose, is more effective in inducing antibody responses and protecting older adults against influenza illness [218]. Consequently, high-dose influenza vaccines have become the standard of care for older adults (65 years and older) in many countries. Vaccine adjuvants have emerged as another promising strategy to boost immune responses. Adjuvants have been in use since 1932 [219,220]. They are included in the vaccine formulation to enhance antigens' immunogenicity. Initially, adjuvants such as aluminum were used empirically, but contemporary research is moving toward tailored adjuvant design that can address reduced vaccine responses in older adults (e.g., Toll-like receptor (TLR) agonists [221]). Notably, adjuvants act, in part, through the activation of DCs, which play a fundamental role in initiating and shaping the

immune response. By activating these cells, adjuvants enhance the overall immune response to the vaccine, including the recruitment of components of the IFN pathway, which crucially link innate and adaptive immunity. For instance, TLRs are pathogen recognition receptors (PRRs) that recognize pathogens and initiate an innate response to infection. Activation of TLRs via adjuvants can help rejuvenate immune responses that are reduced with age. Diverse adjuvant systems (e.g., AS01, AS02, AS03, and AS04) have been developed, which differ in their ability to potentiate vaccine responses. For example, the AS01B adjuvant, which contains the TLR4 agonist MLP was used in herpes zoster subunit vaccine with high efficacy (i.e., >%95 responsiveness even among older adults) [222]. Similarly, the AS03-adjuvanted influenza vaccine – an oil-in-water emulsion containing α-tocopherol (a form of vitamin E) and squalene (a naturally occurring oil) – induced stronger and more persistent immune responses in older adults [223]. Another frequently used adjuvant is the MF59-squalene-based oil-in-water emulsion, which enhances the uptake of antigens by the DCs [224]. MF59-adjuvanted trivalent influenza vaccine (FluAd®) also induced stronger immune responses among older adults [225]. Emerging evidence suggests that, beyond DCs, other cells may also be activated or targeted by adjuvants, including innate immune leukocytes, such as monocytes and granulocytes, and adaptive immune cells, such as B cells (reviewed in [219]). Given their efficacy and safety, adjuvanted influenza vaccines are adopted in several countries for the immunization of older adults [226,227]. For an in-depth review on adjuvants we refer the readers to [219].

Novel vaccine platforms with strong intrinsic adjuvant properties may also help address age-related vaccine hypo-responsiveness, as in the case of mRNA vaccines. Indeed, the remarkable efficacy of Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines in older adults during the COVID-19 pandemic is well documented [228]. Their mechanism allows direct antigen production by host cells, potentially overcoming age-related limitations in antigen uptake and presentation [229]. In addition, mRNA vaccines exert potent adjuvant effects through the stimulation of PRRs, leading to rapid production of inflammatory cytokines, which might help overcome age-related immune deficiencies. An mRNA-based vaccine candidate to prevent cytomegalovirus (CMV) demonstrated immunogenicity and was generally well-tolerated during a phase 2 trial [230]. Virus-like particle vaccines, composed of viral proteins that mimic the structure of viruses, can also stimulate strong immune responses, making them an attractive option for addressing age-related immunosenescence [231,232]. Finally, vectored vaccines, which use harmless viruses or bacteria to deliver specific genes from a pathogen into host cells, have the potential to generate robust immune responses in older adults, as demonstrated by the adenovirus-vectored COVID-19 vaccine (AstraZeneca/Oxford) [233].

4.2. Modulating the BIS to combat age-related immune deficiencies

4.2.1. Epigenetic remodeling to modulate BIS

An alternative strategy to adjuvant usage, is to remodel the BIS to overcome the age-related decline in vaccine responsiveness [156]. Targeted strategies can be designed to modulate specific components of the BIS highlighted by previous studies. For example, baseline NK-driven cytotoxic signatures were linked to reduced responsiveness to PCV13, Yellow fever (YF-17D), and malaria (RTS,S) vaccines [13,204,205]. However, how NK cells play a role in these vaccines are not known. Thus, further research is needed to elucidate whether modulating NK cell activity and cytotoxicity can impact responses to these vaccines (reviewed in depth in [207]). A promising strategy to remodel the BIS is via epigenetic remodeling[234]. It has been shown that a certain epigenetic state of the immune cells upon AS03-adjuvanted H5N1 influenza vaccination improved responses to other viral infections [123–125]. Along these lines, men who had mild COVID-19 responded stronger to influenza vaccine compared to healthy controls, possibly due to epigenetic remodeling of immune cells upon infection [235]. Enhanced interferon and inflammatory responses are induced upon the administration of the second dose of COVID-19 mRNA vaccines [236,237], a finding consistent with the transient epigenetic reprogramming observed following SARS-CoV-2 infection and COVID-19 mRNA vaccination [238]. The gut microbiome also plays a significant role in shaping the host immune response, including innate immunity and vaccine responsiveness [239,240], and has the potential to enhance vaccine efficacy [160].

4.2.2. Anti-aging strategies to modulate BIS

Anti-aging strategies, including those modulating the chronic inflammation associated with age, might also constitute ways to remodel the BIS and therefore enhance immune responses to vaccines. Lifestyle interventions such as a healthy diet, regular exercise, adequate sleep, and stress management, dietary restriction (DR) are strategies that are frequently studied to slow down or reverse aging [241]. Pharmacological interventions, including biologics targeting IL-1B [242] or non-steroidal anti-inflammatory drugs such as aspirin or ibuprofen, are also under consideration [243,244]. Regular moderate exercise appears to boost immune function, although the mechanisms behind this effect are not yet fully understood [245,246]. Moderate cardiovascular exercise improved the responses to the influenza vaccine in older adults [247,248]. The mTOR (mammalian target of rapamycin) signaling pathway, which governs cell growth and metabolism, is among the most frequently studied longevity pathways [249]. While DR without starvation can inhibit mTOR signaling and delay aging in model organisms [250], the effects of DR and DR-mimicking fasting strategies on human health and lifespan are unknown. Ongoing trials, such as the Comprehensive Assessment of Long-term effects of reducing intake of energy (CALERIE), might answer some of these open questions [251,252]. The mTOR pathway can also be targeted pharmacologically using rapamycin [253]. Rapamycin is an immune inhibitor [254], despite this, treatment of older adults with the well-tolerated mTOR inhibitor RAD001 for six weeks improved their responses to influenza vaccination by 20% [255] and reduced the percentage of $PD1^+$ $CD4^+$ and $CD8^+$ T cells. This promising study suggests that inhibiting mTOR signaling can remodel the immune baseline of older adults and rejuvenate immune responses to vaccination [256,257]. The ongoing TAME (targeting aging by metformin) trial will uncover the effects of metformin, another mTOR inhibitor, on human aging and aging diseases [258]. Other strategies to reverse immunosenescence to rejuvenate vaccine responses include using senolytics that are designed to selectively kill senescent cells [259,260], and thymic regeneration [261]. Future studies will reveal which of these anti-aging strategies is more effective in boosting immune responses among older adults.

4.3. Stratify populations based on the BIS to optimize vaccine responses

With the exception of age, current vaccination strategies overlook any of the factors that impact vaccine responses (e.g., BIS, biological sex). Studies discussed here provide an opportunity to improve this strategy and stratify the population to optimize vaccine responsiveness (i.e., precision vaccinology). Precision vaccinology aims to tailor the vaccine type and administration to the characteristics of individuals or sub-populations of individuals [262]. Evaluating the BIS of donors prior to vaccination using targeted assays, guided by systems immunology–-driven approaches, is a promising strategy. These immune assessment modalities could be integrated into the clinical decision-making process for implementing vaccine regimens. For example, our recent study provided the first framework to optimize the administration of two different pneumococcal vaccines to a stratified population of older adults based on distinct and novel baseline predictors. Quantifying the CYTOX signature - by measuring *NCAM1* expression or the $CD16^+$ NK frequency in the blood prior to vaccination - could be utilized for point-of-care clinical stratification in older adults. Donors with low CYTOX should receive PCV13, whereas donors with high CYTOX should

receive PPSV23. Our study also calls for a much-needed consideration of biological sex while administering these vaccines. In fact, women mounted stronger responses to T-dependent PCV13 compared to men, whereas responses to PPSV23 was similar for men and women.

5. Conclusion

Although more work is needed to uncover and validate the BIS associated with response to diverse vaccines, several critical key immune states (i.e., inflammation, cytotoxicity) have already been linked to vaccine responsiveness. How these states are established and maintained at the cellular level, how they contribute mechanistically to vaccine responses, and whether we can remodel these baseline states remain to be characterized. Furthermore, how distinct BIS components (e.g., inflammation, cytotoxicity) relate to each other and which biological factors contribute to these baseline states need further investigation. Studies so far showed that BIS depends on the vaccine formulation (e.g., adjuvanted or not) as well as the demographics of the vaccinee population (e.g., young vs. old). Comparative–systems vaccinology studies have already yielded key insights about immune aging and age-related changes in vaccine responsiveness. This knowledge holds great promise for the implementation of personalized vaccination strategies, thereby potentially improving vaccine effectiveness, especially among older adults. As we continue to develop and apply and further multi-omics approaches to unveil novel BIS signatures, these could further enhance precision vaccinology and guide the strategies to rejuvenate immune responses. Thus, the coming years could usher in a new era of improved understanding of immune responses to vaccines, paving the way for healthier, more resilient aging populations.

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