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Immune Aging, Immunosenescence, and Inflammaging: Implications for Vaccine Response in Older Adults

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ABSTRACT

Background and Aims: Population aging is a significant demographic change while vaccines are mostly made for children and young adults and their effectiveness might be low in the older population. Age-associated decline in the immune function (immunosenescence) is a process that may lead to poor vaccine response in the older population. This comprehensive review aims to discuss changes in the immune system with age and their impact on vaccine response to develop strategies to enhance vaccine efficacy in the elderly.

Methods: This literature review on how the immune system changes with age and affects vaccine responses in older adults was carried out by examining English-language publications. The search involved relevant keywords such as “Antibody response,” “Vaccine Efficacy,” “Vaccine Response,” “Immune Aging,” “Immunosenescence,” “Inflammaging,” and “Older Adults” across multiple databases, including Google Scholar, PubMed, Scopus, and Web of Science.

Results: Age-related changes in the immune system, such as structural changes in lymphatic tissues, a decrease in the number of naive cells, an increase in the number of dysfunctional memory cells, along with a change in the microbiota profile and its contribution to inflammaging and an increase in the number of senescent cells are factors that lead to vaccine effectiveness decreases with age.

Conclusion: A deeper understanding of age-related alterations and their effect on vaccine efficacy can provide new insights into the enhancement of vaccine-induced immunity in the older population.

1 | Introduction

In old age (aged 65 and older), the function of body tissues and systems decreases [1]. Age-associated alteration in the immune system leads to a decrease in the function of the immune system [2]. Immune system dysfunction is associated with suboptimal vaccine-induced immunity in the older population [2, 3]. Age-related decline in immune function in its various parts such as primary lymphoid tissues (bone marrow structural changes,

thymic involution), secondary lymphoid tissues (fibrosis in lymph nodes and reducing the number and size of the germinal center), number and function of immune cells (reduction of naive T cells or decreased phagocytic activity of macrophages), level of antibodies (antibody titer is low), antigen recognition receptors (such as an age-related decrease in toll-like receptors), and so forth, have been reported [2, 4]. With age, the thymus's involution causes the proportion of naive T cells to decline and the memory population to rise. This could potentially result in a

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reduction in the immune system's capacity to react to novel antigens, including vaccine antigens [5]. Exposure to common cold coronaviruses has been linked to the presence of cross-reactive memory responses to SARS-CoV-2 in serum samples before the pandemic (due to the epitope similarity between the proteins of common cold and SARS-CoV-2 coronaviruses), these memory responses may have beneficial or detrimental effects on the outcome of COVID-19 infection and the immunogenicity of COVID-19 vaccines, although their effects on COVID-19 vaccines are still unclear [6], one research has demonstrated that the BNT162b2 vaccine response was positively impacted by the presence of cross-reactive T cells before vaccination administration (associated with prior exposure to coronaviruses) [7]. Although regarding the presence of cross-reactive B cells at the time of vaccine administration, no beneficial effects were observed on antibody responses after the COVID-19 vaccination [8].

Age-related alterations induce a decrease in the function of the innate, humoral, and cellular immune systems in the older population. Age-associated deterioration in the immune function is called immunosenescence [3]. Inflammaging is common in older adults and is defined as persistent low-grade inflammation in older persons, indicating dysregulation of the immune system with age.

Vaccines are one of the most successful interventions to control infectious diseases. Vaccination prevents infection and/or limits transmission, and/or reduces disease severity. Vaccine-induced immunity includes both cellular immunity and antibody production, although antibody production has been recognized as the main correlate of vaccine response in many cases. The purpose of vaccination is to create "immunological memory" or long-lived immunological response [3], through which the first exposure to an infectious agent is remembered and in case of re-exposure/re-infection, leads to an increase in memory responses that either inhibit re-infection or alleviate infection severity [9].

Long-lasting protective immunity is generated by inducing antigen-specific memory T and B-cells and long-lived plasma cells (which constitutively generate high-affinity antibodies), which create immunological memory against invading microorganisms and prevent reinfections [4].

Memory T cells include CD4+ and CD8+ T cells, which rapidly differentiate into effector cells and can kill infected cells or produce pro-inflammatory cytokines that prevent pathogen replication. CD4+ effector T cells help CD8+ T and B cells [9].

A successful vaccine can activate naive cells and create memory B and T lymphocytes. Vaccine antigens, like natural infections, must be recognized by naive cells, then lead to the activation of naive cells, their expansion, and their differentiation into effector and memory cells. Memory B and T cells have a long lifespan, if later a pathogen enters the body, they multiply rapidly differentiate into effector cells, and eliminate the pathogen [4].

Here, we discuss how T- and B-cell responses to vaccination are formed and how these responses change with age. We also review the sources of inflammaging and highlight possible strategies to increase vaccine efficacy in aged individuals.

2 | Immunosenescence and Inflammaging

Immunosenescence involves a decline in innate and adaptive immune function. For example, the phagocytic activity of dendritic cells decreases, and in this way, the uptake and presentation of antigens to the adaptive immune cells and their activation are impaired. During aging, thymus atrophy leads to a decline in new T cells and antigen-experienced T cells accumulate [10].

Inflammaging is one of the hallmarks of aging and is caused by the chronic activation of the immune system. Inflammaging is a low-grade, systemic, and sterile chronic inflammation in which macrophages play a central role [11]. This condition is associated with high levels of pro-inflammatory cytokines such as interleukin 6, TNF, and high levels of CRP. The mechanisms that lead to inflammaging in older persons are diverse and include cellular senescence, defective autophagy, the decreased phagocytic function of macrophages, changes in the composition and diversity of intestinal microbiota, and latent and chronic infections. Possible mechanisms that contribute to the development of inflammaging include the following:

(i) Increased DAMP production and impaired elimination/disposal pathways in the older population: The main source of inflammation appears to be molecules and endogenous products of damaged/dead cells, old organelles, misfolded proteins, and products resulting from cell metabolism, which act as damage-associated molecular patterns (DAMP) and are identified by innate immune system receptors [11]. The production of these substances is physiological, although their production increases with age, and at the same time their elimination systems such as autophagy weaken, increasing their accumulation [12].

(ii) Increase in senescent cells with age: Cellular senescence is a condition in which the cell cannot proliferate due to telomere erosion and shortening [13]. With age, the number of senescent cells increases [13]. Senescent cells can produce various factors and have a secretory phenotype called senescent secretory phenotype (SASP). SASP includes growth factors, metalloproteinase enzymes, inflammatory cytokines, and chemokines [13] and contributes to inflammaging by intensifying inflammation [12].

The main purpose of SASP production by senescent cells is to activate the innate immune system (macrophages) to phagocytose SASP-producing senescent cells and prevent the accumulation of senescent cells in the body [14]. With aging, the phagocytic activity of macrophages decreases [13], thus in older adults, senescent cells are not effectively eliminated by the innate immune system, so the number of senescent cells and the amount of SASP increase and contribute to inflammaging [15].

Immunosenescence and cellular senescence have a complex relationship [16]. Immunosenescence is a condition in which the immune system is unable to get rid of senescent cells [17]. As a result, senescent cells accumulate in different organs, including lymphoid organs like the thymus, bone marrow, and lymph nodes, which are essential for immune responses. Immunosenescence is facilitated by the accumulation of senescent

cells in these organs through a variety of mechanisms [16]. The accumulation of senescent cells in the bone marrow leads to Hematopoietic stem cell exhaustion and myeloid skewing, which leads to a decrease in the production of lymphocytes, one of the characteristics of immunosenescence. In addition, SASP, like a chemoattractant, leads to the recruitment of immune cells to lymphoid tissues and causes continuous chronic inflammation in these tissues, which prevents the normal function of lymphoid tissues [16].

(iii) Changes in intestinal microbiota profile with age: The gut microbiota and the immune system have a close bidirectional relationship [1]. The microbiota has an important role in the formation of the immune system [1, 18]. Changes in the composition and diversity of microbiota affect immune responses [1]. Dysbiosis or negative change in the composition of microbiota is common in older adults people [1]. As the age increases, the abundance of beneficial bacteria decreases, and instead, pathobiont bacteria and bacteria with inflammatory characteristics increase [19]. Dysbiosis is associated with inflammation, and inflammation can lead to damage to the intestinal mucosal barrier, bacteria and their metabolites leave the intestine, and inflammatory responses are formed [19]. In young and healthy people, the microbiota is limited in the intestinal lumen, but when the intestinal barrier is damaged, it passes from the intestine and leads to inflammation. Leaky gut is common in the older adults, in this situation, microbiota and their metabolites leave the intestinal lumen and enter the bloodstream, leading to the induction of inflammatory responses and thereby contributing to inflammaging [1]. In this situation, the microbiota as a rich source of antigens leads to continuous and chronic stimulation of the immune system, which leads to immune exhaustion [20].

In addition, with age tryptophan-consuming bacteria, Enterobacteriaceae, increase in the older adults and lead to a decrease in tryptophan in the plasma of the older adults [21, 22]. The reduction of tryptophan leads to the activation of the immune system and contributes to the formation of inflammaging [23]. The abundance of anti-inflammatory gut microbiota is reduced in aged adults [24]. For example, Clostridium cluster XIVa and Bifidobacterium decrease, but Streptococcus spp., Staphylococcus spp., Enterococcus spp. increase [24].

In addition, an age-related decrease in the production of SCFAs (n-propionate, acetate, and n-butyrate) has been observed [11]. Short-chain fatty acids are produced by commensal intestinal bacteria, and in addition to being a source of energy, they are powerful anti-inflammatory mediators that reduce intestinal inflammation [25]. For example, butyrate facilitates the differentiation of CD4⁺ T cells into Treg cells and induces the production of interleukin 10 and the secretion of TGF- β [25]. These fatty acids prevent the leakage of bacteria and bacterial metabolites into circulation by reducing intestinal inflammation. Decreased SCFA production in older people can contribute to inflammation and inflammaging [11].

(iv) Chronic/latent viral infections and inflammaging: In addition to chronological aging, which leads to an increase in the number of senescent cells with SASP in older adults, exposure

to pathogens, especially chronic infections, accelerates the aging of immune cells [26–28]. In this context, cellular senescence of immune cells means reduced proliferation, while the formation of immune responses against infection or vaccine antigens depends on the extensive proliferation of T and B lymphocytes [4].

During chronic or latent viral infections, antigens are continuously or intermittently presented to immune system cells. This continuous presentation of antigens leads to increased production of inflammatory cytokines by the innate and adaptive immune systems. In addition, the continuous presentation of antigens leads to T-cell exhaustion [29, 30] and cellular senescence [31]. For example, CMV infection is known as one of the drivers of immunosenescence. CMV infection in older adults has been reported to be associated with a less effective influenza vaccine [31, 32].

(v) An increase in adipose tissue is one of the elements that cause inflammation and contribute to inflammaging [33]. Adipose tissue grows and changes with aging, leading to dysfunction of the adipose tissue. These alterations include modifications to the secretory profile, senescent cell accumulation, and cell composition. Adipose tissue contains cells including adipocytes, mesenchymal stem cells, T-lymphocytes, and macrophages. The changes of macrophages in adipose tissue with age and the predominance of M1 macrophages compared to M2 macrophages are among the factors that contribute to inflammation by adipose tissue with age. M1 macrophages produce more inflammatory cytokines and exhibit an inflammatory phenotype [33]. Furthermore, during aging, senescent cells with the SASP phenotype accumulate in adipose tissue [34].

In recent years, a more complete understanding of inflammaging has emerged and its sources have been identified. In addition, findings support the role of inflammaging in vaccine response. The presence of baseline inflammation and prevaccine inflammatory profile are predictors of impaired vaccine response [35]. In one study, a transcription-based prevaccination predictor of HBV vaccine response was developed and evaluated in older adults. Findings showed that poor responses to the vaccine were associated with higher frequencies of pro-inflammatory innate cells and higher levels of transcripts of inflammation-related genes [36]. Even though the aforementioned findings show that inflammaging affects vaccine-induced immune responses, more mechanistic research is required to fully comprehend how inflammation affects the immune system and vaccine response. This will help develop new strategies for improving vaccines in older adults.

3 | Changes in Innate Immunity With Age

Innate immunity plays an important role against invading infectious agents in the early stages and provides a rapid and nonspecific response [37]. The innate immune system occasionally plays a role in the development of immunopathogenesis in addition to its defense against infections. The overabundance of inflammatory cytokines during the recent COVID-19 pandemic, also known as the “cytokine storm,” has

been documented as a hallmark of the immunopathology of the innate immune system [38]. This phenomenon is linked to a higher severity and mortality rate from COVID-19 infection. Cytokine storm is more common in older adults [38]. Cytokine storm formation is influenced by immune dysregulation and inflammaging, both of which are associated with aging [39]. It is crucial to take into account the potential for cytokine storm development following a COVID-19 vaccination. A cytokine storm has been documented after COVID-19 vaccination [40]. As a result, the formulation of COVID-19 vaccines should be designed in such a way that there is no risk of a cytokine storm following vaccination [39].

Dendritic cells, macrophages, and neutrophils are the main cells of the innate immune system [37]. The phagocytic activity of neutrophils and macrophages decreases with age [13]. Also, the migration of dendritic cells is reduced, and dendritic cells, which are the bridge between innate and acquired immunity, migrate to the lymph nodes after antigen recognition, where these cells present the processed antigens to lymphocytes to generate immune responses. Studies have shown that with age, the migration of these cells is impaired [26].

TLRs are part of pattern recognition receptors (PRRs) that recognize PAMPs and are involved in antimicrobial response [41]. Although the expression level of TLRs does not appear to change with age, impairment of function and downstream signaling of TLRs has been described in older adults [42]. Age-related decline in TLR function and its impact on influenza vaccine efficacy have been investigated. Disruption of TLR function has been shown to impair vaccine-induced antibodies [41]. Also, TLR polymorphisms are different in older adults people, which can affect TLR function [43]. The existence of specific SNPs in TLR genes was related to the efficacy of the measles vaccine [44]. In a study, the genotypes of less functional TLRs 1 and 6 have been described in older adults people [43]. Although their relationship to vaccine response is unclear, they may have negative effects on vaccine immune responses.

The production of interferons declines with age, and part of this decline may be explained by the reduction in plasmacytoid dendritic cells, which are a source of interferon production, in older adults [26]. Even so, interferon production rises in the presence of senescent cells. Senescent cells accumulate with age and as a result of the immune system's declining ability to eliminate them. These cells contain damaged DNA, which can be identified by DNA sensors like cGAS-STING. Signaling through these pathways triggers the activation of transcription factors and the synthesis of interferons [45].

4 | Changes in Humoral Immunity With Age

Although changes in T cells and dendritic cells likely affect the development of the humoral immune response, there are direct age-related defects in the B cell repertoire. As the number of naïve T cells decreases with age due to thymus destruction, the number of naïve B cells in aged mice also decreases due to bone marrow changes. These changes appear to also occur in older adults. As the number of naïve B cells decreases, the ability of B cells to respond to new antigens from infection or vaccination is

reduced. As mentioned earlier, tissue changes occur in lymphoid organs and bone marrow with age. Senescent cells accumulate in the bone marrow and in this condition, the bone marrow cannot function normally. SASP and ROS produced by senescent cells mediate dysfunction and DNA damage in hematopoietic stem cells (HSCs), respectively, and lead to changes in the HSC pool and exhaustion of HSCs. Increased inflammation caused by ROS and SASP causes damage to surrounding cells through the bystander effect. In the absence of rapid clearance of SnCs, this becomes a cycle of dysfunction and injury, causing severe immunosenescence and reduced lymphopoiesis [16].

In addition, with age, hematopoietic stem cells in the bone marrow tend to be myeloid rather than lymphoid, which can lead to a decrease in B-cell precursors and their numbers [15].

Tissue alterations in the bone marrow and lymphoid organs result in a drop in the quantity of naïve B and T cells as well as a decrease in the output of these organs. Strong homeostatic forces that maintain the number of lymphocytes through the proliferation of existing clones serve as a compensatory mechanism to maintain the number of cells. This results in a greater number of cells that have reached their proliferation limit and, as a result, have less proliferative power at the time of infection or vaccination, which lowers immune responses, including antibody responses [46].

Aging-related changes in BCR repertoire diversity have a deleterious impact on B cell response and the germinal center reaction. Research has demonstrated that older humans have a significantly lower diversity of BCR repertoires among naïve B cells and antigen-experienced B cells [47]. The decline in BCR diversity may be caused by several factors, including an increase in clonality among antigen-experienced cells and a decrease in the production of new B cells from the bone marrow [47]. In addition, V(D)J recombination is a type of somatic recombination mechanism that occurs in the first stages of maturation of B and T lymphocytes and leads to the creation of a very diverse repertoire of TCR and BCR in T and B cells, respectively [48]. This process is carried out during the development of lymphocytes and through RAG 1 and RAG 2 enzymes. The aged B lymphocyte pool has less BCR diversity, which is partly explained by age-dependent decreased expression of RA-1 in B lymphocyte progenitor cells in the bone marrow [48].

Additionally, somatic hypermutation (SHM) should be discussed because it diversifies BCRs and influences how the body reacts to vaccination. That being said, SHM is also impacted by the age-related decline in AID expression [47]. Overall, decreased antibody response to novel antigens is linked to a reduction in the diversity of the BCR complex [47].

Additionally, B cell function is impaired with age, which is related to structural changes in the bone marrow and lymph nodes as well as intrinsic B cell defects [46]. With age, intrinsic defects in B lymphocytes develop. Aged memory B lymphocytes show less ability to differentiate into plasma cells at the time of challenge, and antigen-specific antibody titer decreases with age [3].

Protective humoral immune responses depend on the production of high-affinity, isotype-switched antibodies in germinal centers. However, age-related intrinsic defects in SHM and class switch recombination (CSR) pathways negatively affect the quality of antibody production. The frequency of class switch recombination and the production of effective antibodies are significantly reduced in aged mice, which is related to a lower expression of activation-induced cytidine deaminase (AID) enzyme. AID is essential for these two processes and its expression decreases with age [3]. However, in general, the occurrence of CRS after vaccination is a very rare event [49].

Aging is accompanied by a decline in the number, size, and volume of germinal centers [47]. Germinal centers are specialized structures in secondary lymphoid organs where antibody-producing plasma cells and memory B cells (memory cells can become long-lived antibody-producing plasma cells upon subsequent exposure to antigen) are formed [47]. Humoral immune responses and antibody production are developed in the germinal centers. Somatic hypermutation (to generate high-affinity antibodies) and isotype switching are performed in the germinal centers [47]. The generation of humoral immune responses in GC depends on the interaction of different cell types, including B cells, follicular dendritic cells (FDCs), T follicular regulatory cells (Tfr), and T follicular helper cells (Tfh) [47]. The weakened function of germinal centers in older adults is a contributing factor in reducing humoral immune responses and levels of antibodies (also antibodies with reduced affinity) after encountering an infection or vaccine in the older adults.

In fact, not only does antibody titer decrease with age, but the duration of antibody-mediated protection also decreases. Decreased antibody half-life is also related to disruption of germinal centers. Vaccine-induced antibodies are produced in two ways: first: extrafollicular, and second: in the germinal centers. First, extrafollicular response: B cells in extrafollicular areas undergo expansion and differentiation after antigen recognition (vaccine or infection) and activation, and differentiate into short-lived plasma cells. These plasma cells secrete antibodies and play a role in fighting infection in the early stages (or in the early stages after immunization), but do not provide long-term immunity [47, 50]. Second, in the germinal centers: Long-lived plasma cells that secrete antibodies are formed in the germinal centers. B cells in the dark zone of the germinal center undergo SHM of immunoglobulin genes, and in the light zone, B cells with self-reactive B-cell receptors (BCRs) are removed while B cells with functional high-affinity BCRs are selected [51].

At this stage, antigens are presented to B cells by follicular dendritic cells (FDCs) and autoreactive B cells are eliminated. Then, during the selection process, B cells present antigens to Tfh cells receive survival signals from these cells (Tfh cells), and return to the dark zone for further rounds of proliferation and SHM. The selected B cells eventually leave the germinal centers as long-term antibody-secreting plasma cells or memory cells [47]. Long-term antibody-secreting plasma cells migrate to the bone marrow and they continue to generate high antibody titers [47, 52]. Memory B cells differentiate into plasma cells more efficiently and produce antibodies upon secondary exposure to

antigens. As such, GC is important for the induction of long-term antibody production and is required for vaccine efficacy [47].

In older adults, a low antibody titer has been observed after vaccination as well as a rapid fall in antibody levels [47]. As the function of germinal centers decreases with age, the generation of functional memory B cells is also impaired in older adults [47].

The generation of humoral immune responses in GC depends on the interaction of different cell types, including B cells, T follicular helper cells (Tfh), follicular dendritic cells (FDCs), and T follicular regulatory cells (Tfr). A defect in the number or function of each of these cells leads to damage in the function and output of the germinal centers. For example, age-related defects in naïve T cells or CD4 + T cell subsets can affect antibody responses produced by germinal centers. Because naïve T cells are the source of TFH cell production, a reduction in the number of naïve T cells causes a decrease in TFH cell and germinal center activity [47].

The decrease in the function of FDCs with increasing age can also have a negative effect on antibody responses in the germinal center [46]. These cells play an important role in the activation of B lymphocytes and the formation of antibody responses in the germinal center. The expression of FC receptors on the FDCs of old mice has decreased compared to young mice, which leads to a decrease in antigen capture and delivery to B cells and a decrease in the retention of immune complexes in the germinal center [53], and may be related to the shortened duration of antibody responses in the older adults [46].

5 | Changes in Cellular Immunity With Age

The thymus is one of the lymphoid tissues, where thymocytes become mature naïve T cells [3]. Thymic involution during aging reduces the frequency of naïve T cells and reduces TCR diversity, as a result, the immune system of aged people does not recognize new antigens well. Naïve T lymphocytes have the main role in creating immune responses against infectious agents and vaccine antigens. A key characteristic of immune aging is the reduction of naïve T cells. Alterations in the quantity and quality of T cells with age are associated with poor vaccine responses in older individuals [4].

The reduction in the number of naïve T cells and the reduction in the diversity of the TCR repertoire with increasing age have a negative impact on the initial phase of recognition of vaccine antigens. This is followed by fewer vaccine-specific T cells.

There is also impaired TCR signaling in aged naïve T cells. In CD4 naïve T cells from older individuals, reduced expression of miR-181a leads to impaired TCR signaling [54]. Decreased miR-181a with age could lead to reduced effector responses and reduced generation of memory cells [4].

Cellular senescence is one of the factors that negatively affect the activation and expansion phase (T cells proliferate less and have less expansion due to cellular senescence) [4]. Reduced

expression of the CD28 receptor on T cells in the elderly has been associated with reduced cell proliferation and defective T cell activation [3].

An efficient T cell response to vaccination depends on the appropriate balance between the production of effector T cells and T follicular helper (TFH) cells, which are involved in the production of high-affinity antibodies, and the induction of long-term memory cells. But during aging, T lymphocytes become short-lived effectors rather than memory cells or TFH cells [4]. Several factors and mechanisms are likely to contribute to this bias: The metabolic program of T cells changes with age: The mammalian target of rapamycin (mTOR) is a metabolic regulator that plays a role in the differentiation and fate of T cells, favoring the formation of effector T cells over memory T cells [54].

Increased expression of microRNA 21 with age in aged naive CD4 T cells favors the differentiation of these cells into short-lived effector cells, microRNA 21 maintains mTORC1 activation and thus inhibits the development of memory T cells [54]. Another factor is the increased expression of CD39 on aged T cells, which affects the fate of T cells. Individuals carrying the low-expressing CD39 variant responded better to vaccination with increased vaccine-specific memory T cells. Increased CD39 on T cells in the elderly leads to impaired development of memory T cells and follicular helper T cells [54, 55].

Changes in CD25 expression in aged naive CD4 T cells also occur with age [54, 56]. Increased CD25 expression is associated with reduced development of CD4 memory T cells after antigen challenge in mice. Cells with low CD25 are more efficiently converted to CD4 memory T cells and TFH [54].

In brief, thymus degeneration and bone marrow structural changes, structural changes in secondary lymphoid organs, genetic and epigenetic changes, shifted metabolic programs and changes in microRNA profiles that occur in T cells with aging are all factors that influence T cell responses in the elderly [54].

Generally, the effective response of T cells after vaccination is formed as follows: After exposure of naive T cells to vaccine antigens, upon recognition of vaccine antigen by TCR, these cells are activated and undergo massive clonal expansion. Then, these cells are differentiated into short-lived effector cells or memory precursor cells (MPECs). T follicular helper cells are also produced, which are necessary for the germinal centers for the production of high-affinity antibodies. After the vaccine antigen is cleared, about 90%–95% of the effector cells die. Memory progenitor cells (MPECs) survive and differentiate long-lived memory T cells. Long-lived memory T cells protect against the next infection or vaccination booster doses. In case of infection, these memory cells are activated and provide protection. Memory cells have a long lifespan and can last for years or decades [4].

Defects in any of the above cells or steps can lead to a poor T-cell response to the vaccine. With age, T cells tend to become short-lived effectors rather than memory cells or TFH cells. This trend in aging causes the immunological memory not to form well and with the reduction of TFH cell production, antibodies with high affinity are produced less [4].

6 | Strategies to Enhance Vaccine Response in Older Adults

To improve the effectiveness of the vaccine in older adults, various strategies such as using adjuvants and novel adjuvants, using higher doses of antigen in the vaccine, changing the route of vaccine injection, etc. have been used, which have been reviewed elsewhere [42, 57], so several approaches (adjuvants and immunomodulatory, senolytics drugs and probiotic supplement) are discussed here.

7 | Adjuvants

Adjuvants are substances used in the formulation of vaccines to strengthen the immune system and stability of the vaccine. Aluminum salts (alum) are one of the oldest adjuvants [58]. Currently, other adjuvants have been introduced to increase the immunogenicity of vaccines [58]. An increase in antibody responses, for instance, has been linked to the use of adjuvant (emulsion-based adjuvant) MF59 in seasonal influenza vaccinations. The antibodies generated were also found to be cross-protective against multiple influenza strains [59]. While the exact mechanism of action of MF59 remains unclear, research has demonstrated that this adjuvant enhances B cell differentiation in the germinal centers and increases the production of inflammatory cytokines [60].

It has been noted that alum does not improve the immunogenicity of some vaccines in older adults, indicating that stronger adjuvants might boost immune responses. It has been shown that using a TLR ligand can boost adjuvant potency and boost the immune response to vaccinations [61].

TLR agonists, which increase TLR signaling, are another class of adjuvants. As a TLR agonist, monophosphoryl lipid A has been added to the Cervarix vaccine [62]. As a TLR4 agonist, glucopyranosyl lipid A has been incorporated into influenza vaccine formulations, and while its impact on antibody responses is unknown, it has been shown to boost T-cell responses and cytokine production in older adults [63]. The new adjuvant 1018, a TLR9 agonist, was used in the formulation of the new hepatitis B vaccine (HEPLISAV-B) and resulted in a significant increase in vaccine immunogenicity compared to the alum-adjuvant vaccine [64].

Another group of adjuvants are lipid nanoparticles that have been used in COVID-19 vaccines (mRNA vaccines). In these vaccines, mRNA is encapsulated by lipid particles [58, 65]. Matrix adjuvant is a nanoparticle used as an adjuvant in the COVID-19 protein vaccine developed by Novavax. Matrix M adjuvant consists of two parts: saponins (stimulation of the immune system) and lipids (formation of nanoparticle structure and facilitating absorption by immune cells) [58, 66].

AS0 adjuvant systems are a newer group of adjuvants that combine a classical adjuvant molecule (such as alum) and an immunostimulatory molecule (such as a TLR agonist). AS0 adjuvant systems are formulated in different vaccines. The Shingrix vaccine, which is designed to prevent shingles and post-herpetic neuralgia in the elderly, uses the AS01 adjuvant

system (3-O-desacyl-4'-monophosphoryl lipid A (MPL), which is a TLR4 ligand, combined with *Quillaja saponaria* Molina fraction 21 (QS21)) [67].

In the lymph nodes at the injection site, resident cells like CD8+ T cells and NK cells release IFN γ in the early hours following injection of the AS01-adjuvanted vaccine. As a result of this early IFN γ production, the AS01-formulated vaccine activates dendritic cells and induces Th1 immunity [67]. The immune response to the AS01 adjuvant is marked by a rise in polyfunctional CD4+ T cells, which include T cells that produce IL-2, IFN γ , and TNF, specific to the antigen administered, as well as an increase in functional antibodies. AS01 appears to have a significant ability to overcome "immune aging" among licensed adjuvants [68].

Although the above evidence shows the beneficial effects of adjuvants on the immunogenicity of vaccines, more comprehensive studies need to be conducted, and the effect of different adjuvants on a similar vaccine should be investigated and compared to choose the best adjuvant formulation to enhance immunity. Also, with a better understanding of immunosenescence and its underlying mechanisms, new insights will be provided regarding the development of novel adjuvants that target immunosenescence in older adults.

8 | Immunomodulatory, Senolytics Drugs, and Probiotic Supplement

Immunomodulatory medications may influence the immune system's reaction to a vaccination. Through an increase in T and B cell responses, the administration of mTOR inhibitors in conjunction with the BNT162B2 vaccine in kidney transplant recipients has resulted in a rise in vaccine immunogenicity [69]. Given that older adult individuals and transplant recipients share a weakened immune system, using these medications may be a novel way to boost the older adult population's response to vaccinations.

Also, in the investigation of the effect of RAD001 (mTOR inhibitor) on the effectiveness of the influenza vaccine in older adults, an increase in the effectiveness of the vaccine was reported, and the results also showed that RAD001 led to a decrease in the number of TCD4 and CD8 cells expressing the programmed death-1 (PD-1) [70]. This evidence suggests that using these medications improves the response to vaccinations; however, more research is needed to determine which medication is more effective and associated with fewer side effects in older adults.

Aging is linked to increased basal inflammation and inflammaging, as previously mentioned. Pre-existing inflammation may be a factor influencing vaccine efficacy, and thus modulating baseline inflammation before vaccination may be a promising approach to enhance vaccine response [42]. Previous research on HBV vaccination in older adults indicated that an elevated inflammatory gene expression profile at baseline was predictive of poorer response to vaccination [36]. In line with the idea that anti-inflammatory interventions could be effective ways to improve vaccine response with age, one study showed

that compared to younger subjects, older subjects had a lower immune response at the skin's site of the VZV antigen challenge. This has been linked to older people's skin having more sterile inflammation. After pretreatment with an oral p38 mitogen-activated protein kinase inhibitor, systemic inflammation was inhibited in the older adults, strengthening their skin responses to the VZV antigen challenge [71].

The accumulation of senescent cells with increasing age was mentioned as one of the drivers of inflammaging [24]. Senolytic drugs with the selective removal of senescent cells can be investigated as novel pharmacological interventions to enhance the immunogenicity of vaccines in future vaccinology studies [57].

The negative change in microbiota population and dysbiosis were also mentioned as another source of inflammaging in aging [24]. Several factors affect the microbiota profile [72], among which diet is one of the modifiable factors that affect the immune system by affecting the microbiota community and needs to be given more attention in older people [73]. Probiotics' positive effects have been demonstrated more in parenteral influenza vaccinations and oral vaccinations [74]. Further research is necessary to determine the best strains, optimal dose, and best time of administration to vaccination. Probiotic administration is practical and affordable intervention to restore the disturbed microbiome population in older adults, who frequently suffer from dysbiosis. This may have a positive impact on immune responses and vaccines.

9 | Conclusion

Immunosenescence is the term for a compromised immune system in older adults. A decrease in naive cells, an increase in memory cells, a decrease in cell function, dysregulation of immune and inflammatory responses, and structural alterations in lymphoid tissue are all components of immunosenescence. Apart from these modifications, chronological aging is linked to shifts in the diversity and composition of microbiota as well as an increase in senescent cells. All of these elements immunosenescence, altered microbiota, and senescent cell accumulation may be detrimental to the immune system and the body's reaction to the vaccination. In this regard, strategies based on microbiota and probiotic supplements and possibly senolytics drugs may be effective, because microbial components can act as natural adjuvants [37] during vaccination, and senolytics drugs by removing senescent cells may have the potential to enhance immune responses to the vaccine.

Author Contributions

Shahab Falahi: conceptualization, methodology. **Amir Abdoli:** conceptualization, methodology. **Azra Kenarkoohi:** conceptualization, methodology, writing – review and editing.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data is included in the article.

Transparency Statement

The lead author Azra Kenarkoohi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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