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Understanding immunosenescence and its impact on vaccination of older adults

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Abstract

Older adults are more susceptible to viral and bacterial infection, and experience higher incidence and severity of infectious diseases. Although vaccination is the most logical solution in preventing infectious diseases, primary vaccine responses in individuals aged ≥65 years-old fail to generate complete protection. This is presumably attributed to immunosenescence, a term that describes functional differences associated with the immune system and natural age advancement. Both the innate and adaptive immune systems experience age-related impairments that contribute to insufficient protection following vaccination. This review addresses current knowledge of age-related changes that affect vaccine responsiveness; including the deficits in innate cell functions, dampened humoral and cell-mediated immune responses, current vaccination schedules for older adults, and concludes with potential strategies for improving vaccine efficacy specifically for this age group. Due to an age-related decline in immunity and poor vaccine responses, infectious diseases remain a burden among the aged population.

Keywords

immune; senescence; vaccine; older adults

1. Introduction

Currently, the United Nations reports that there are 700 million individuals over the age of 65 years old globally, and population projections indicate that the population size will double by year 2050 [1]. While growing at an unprecedented rate, the population size of older adults (≥65 years) will exceed the global population of young individuals (≤15 years) as a result. In the United States, older adults constitute 16% of the total population, but

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Declaration of competing interest

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account for 27% of medical practitioner visits and 38% of all hospital discharges [2]. The over-representation of older adults at medical facilities reflects an age-associated increase in prevalence and severity of some infectious diseases, specifically dominated by respiratory, gastrointestinal and urinary tract infections [3]. Compared to younger individuals, older adults often experience long-term sequelae and increased morbidity as a result of infection as well [4]. For example, influenza, respiratory syncytial virus (RSV), herpes zoster (HZ) or shingles, pneumococcal disease, and foodborne illnesses disproportionately affect the elderly [5–8]. Due to continuous improvements in life expectancy, age-related diseases are of critical concern and warrant scientific interest to improve the quality of life of the elderly population.

A series of age-associated changes to the immune system, termed immunosenescence, greatly contribute to the increased vulnerability to infections among older adults. In tandem with biological aging, there is a progressive decline in immune function that results in impaired humoral and cellular responses to pathogens [9]. Importantly, primary vaccine responses in older individuals fail to generate complete protection and exhibit reduced efficacy. For example, inactivated influenza vaccines effectively prevent disease in 70-90% of children and younger adults, but efficacy decreases dramatically to 30-50% in older adults [10, 11]. The duration of long term protection is compromised in older individuals as well, as the rate of antibody decline increases with advancing age [12, 13]. Therefore, due to the age-related decline in immunity and vaccine responses, infectious diseases remain a burden among the older adult population. This review will discuss our current knowledge of key features of immunosenescence (summarized in Figure 1), its implications for vaccinating older adults, and vaccination strategies designed to specifically target the aged immune system for improved protection.

2. Deficits in innate immunity in older adults

The innate immune system functions as the first line of defense, in which physical barriers and immune cells nonspecifically respond to pathogens to protect the host. Studies on aged mice and samples from individuals ≥ 65 years old provide evidence of a dysregulated innate immune system as we age. Older adults obtain chronically elevated levels of pro-inflammatory cytokines, termed “inflamm-ageing”, that is specifically characterized by increased basal unstimulated levels of IL-6, TNF-α, and acute phase reactants [14, 15]. This low-grade inflammation is thought to contribute to other age-associated diseases and is a common feature of innate immunosenescence.

Innate cell types, such as dendritic cells (DCs), monocytes, neutrophils and natural killer (NK) cells as discussed herein, appear affected by age and contribute to age-associated immune dysfunction. Functioning as the bridge between innate and adaptive immunity, DCs patrol the body, recognize and phagocytose antigens, then migrate to the draining lymph nodes where they secrete cytokines and present antigen to T cells to launch an immune response. Although the quantity and morphology of circulating DCs appear unaffected by age, DCs from aged hosts exhibit defects at each one of these steps [16]. First, prominent pattern recognition receptors, such as toll-like receptors (TLRs) on DCs demonstrate an age-associated decline. Studies examining the function of TLRs on DCs revealed that DCs from

older subjects displayed decreased production of pro-inflammatory cytokines, such as IL-6, IL-12, and TNF-α, when stimulated with TLR specific ligands [17]. This decrease in stimulated cytokine secretion can be attributed to both the reduced surface expression of TLR1, TLR3, and TLR8 and defects in intracellular signaling in older subjects, when compared to young adults [18]. Further, it has been hypothesized that deficient TLR function negatively affects DC activation and could further diminish activation of adaptive immune responses.

Regarding vaccination, one study presents a relationship between reduced TLR-induced cytokine production and influenza antibody response in older adults receiving Fluzone®. Intracellular cytokine staining of DCs from vaccinated young and older adults revealed that older individuals demonstrated deficits in IL-6, IL-12, and TNF-α levels, and are shown to be associated with lower hemagglutination antibody inhibition (HAI) titers and seroprotection rates to Fluzone®. [17]. This highlights the functional significance of age-associated TLR defects in immunized humans.

Secondly, several studies suggest that aged DCs have an impaired capacity to achieve complete T cell priming and activation [18]. For example, CD8+ T cells from HLA-$A2^{+}$ older volunteers primed with HLA-matched DCs *in vitro* have been shown to expand and express effector memory (CD45RA− CCR7−) cell markers at lower levels, suggesting less efficient activation, in comparison to samples from middle-aged adults; the same trend holds true for murine CD4+ T cells [19, 20]. This is partially attributed to the age-associated decline in antigen uptake, subsequent presentation and expression of co-stimulatory molecules [16]. DCs from older adults demonstrated decreased uptake of FITC dextran compared to that of younger subjects, representing impaired phagocytic abilities with age. To investigate the impacts of ageing on antigen presentation, an *in vivo* study of aged mice showed a decrease in peptide-MHC surface expression on DCs from lymph nodes of immunized mice, compared to adults [19]. Further, the expression of the co-stimulatory molecule, CD86, remained comparable among both aged and adult mice, however, upregulation of CD40 was impaired in the old DCs [19]. Since CD4+ T cells rely on continuous antigen presentation and strong expression of co-stimulatory molecules for their proliferation and differentiation, these DC-intrinsic deficits likely augment the age-associated decrease in CD4+ T cell function (discussed further in subsequent sections). Collectively, these defects negatively impact generation of an immune response to novel antigens and contribute to vaccine hyporesponsiveness in older adults.

While other innate cell types in older adults have yet to be extensively studied, it is apparent that the function of monocytes, neutrophils, and NK cells declines with age. Aged human monocytes display impaired phagocytosis, and macrophages from aged mice produce lower levels of nitric oxide, suggesting there may be defects in bacterial killing by older macrophages [21, 22]. Additionally, neutrophils from aged humans demonstrate impaired phagocytosis of opsonized *Streptococcus pneumoniae* and reduced ability to kill these organisms [23]. Lastly, aged human NK cells exhibit decreased cytokine and chemokine production, as well as diminished cytotoxicity [24]. These age-associated defects in innate cells collectively hinder protective immunity induced by vaccines.

3. Deficits in adaptive immunity in older adults

Age-associated changes to the adaptive immune system are equally relevant to vaccine efficacy, as older adults experience only incomplete protection upon vaccination [25]. While the mechanisms underlying the decline in both cellular and humoral immunity remain unclear, clinical and animal studies provide critical information about age-associated defects. These studies demonstrate that T and B cells share certain altered attributes that are accompanied with advancing age; such as a reduction in naïve cell output, shift in T and B cell phenotype, changes in clonal composition and breadth of diversity, and impaired differentiation potential.

Both B and T lymphocytes progenerate from hematopoietic stem cells (HSC) residing in the bone marrow. However, the regenerative capacity of HSCs decline as we age and [26] recent studies revealed a bias towards myeloid cell lineages with a decrease in lymphoid cells that occurs with aging [27]. These factors compromise production of mature B cells and result in fewer B cells exiting the bone marrow in older adults [28]. Although the number and function of bone marrow-derived T cell precursors remain unaffected with age, the thymus, site of T lymphocyte maturation, shrinks in size and is replaced by adipose tissue by the age of 40-50 [29–31]. The progressive thymic atrophy, termed thymic involution, leads to a decrease in naïve T cell emigration from the thymus, which results in a continuous decline in peripheral naïve T cells throughout life. Specifically, homeostatic proliferation of CD4+ T cells is sufficient to maintain adequate numbers, but a severe age-related decrease in CD8+ T cells has been reported in humans [32]. However, this decrease in naïve T lymphocytes is compensated by an increase in terminally differentiated memory T cells as pathogens are encountered with age [33, 34]. Additionally, peripheral maintenance factors, such as B cell activating factor (BAFF) and IL-7 that promote survival of naïve B and T cells, continuously decrease with age [35, 36]. The progressive decline in naïve cells limits the ability to generate robust *de novo* immune responses, as in the case of a novel vaccine antigen.

The absolute number of T cells, but not B cells, in circulation remain constant throughout life, but older individuals obtain strikingly different phenotypic changes to their lymphatic pool [37, 38]. As mentioned, due to the accumulation of antigen-experienced lymphocytes and changes to the bone marrow and thymus, memory B and T cells comprise the main populations identified in the periphery; while naïve cells exist at lower frequencies. Of the differentiated B and T cells, a newly discovered B cell subset, termed age-associated B cells, is present in aged mice and will be discussed further in later sections. Additionally, a T cell subset, known as terminally differentiated memory T cells accumulate within the human T cell compartment with age, and share phenotypic features with effector T cells but are described as hypofunctional [39].

Another hallmark of the aging immune system is the reduced proliferation potential of B and T cells. Similarly to other cell types, B and T cells have a finite number of cell divisions, that is associated with telomere length [40]. Since B and T cells undergo extensive clonal expansion throughout the duration of an immune response, several studies illustrate an age-associated progressive shortening of telomeres that occurs as a consequence of activation and differentiation of lymphocytes [41, 42]. Likewise, blunting of telomeres in human HSCs

with each cell division is correlated with age [42], potentially presenting a mechanism that limits lymphocyte activation and subsequent expansion.

3.1 T cells

The cellular immune response comprises T helper lymphocytes (Th) and cytolytic T lymphocytes (CTLs), also known as CD4+ and CD8+ T cells, respectively. Upon infection or vaccination, activated CD4+ T cells secrete cytokines to orchestrate and assist surrounding immune cells also involved in the protective response. CTLs traffic to sites of infection to lyse infected cells and secrete pro-inflammatory cytokines. Therefore, many vaccines aim to target CD4+ and CD8+ T cells to provide a protective immune response. However, increasing evidence displays age-associated cell-mediated immunity (CMI) defects that presumably limit vaccine efficacy and increase vulnerability to infections [43]. There are phenotypic alterations of the T cell population with aging, as the aged T cell pool comprises a higher ratio of CD4+ to CD8+ lymphocytes and fewer naïve T cells, that is accompanied by an increase in differentiated memory T cells. Phenotypically, the loss of surface CD28 expression among CD8+ T cells, a principal co-stimulatory molecule, occurs in elderly individuals and appears to be a consistent biomarker of the aging human immune system [44]. Since CD28+ T cells downregulate co-stimulatory molecules after stimulation, CD8+ $CD28^{null}$ T cells represent a population that has previously experienced repeated exposure to antigen. Therefore, $CD28^{null}$ T cells accumulate with age and importantly, are associated with replicative senescence and chronological aging [45, 46]. While the pre-existing T cell pool that previously encountered pathogens earlier in life remain uncompromised, aged naïve T cells demonstrate reduced proliferative capacity after antigen recognition, decreased cytokine secretion, higher activation thresholds, limited receptor repertoire, and insufficient effector functions upon vaccination [47].

Early investigations in aged mice demonstrated defective T cell proliferation and IL-2 production upon mitogenic anti-T cell receptor (TCR) stimulation [48]. Further, Haynes et al. [49] previously reported that in contrast to memory CD4+ T cells generated in young mice, those generated in aged mice produce less IL-2, exhibited decreased expansion, and showed altered differentiation patterns upon antigen stimulation. Indeed, recent studies report that naïve CD4+ T cells from older adults display an age-dependent reduction in TCR signaling that results in decreased clonal expansion and may provide a mechanistic explanation for the dampened levels of T cell activation seen in older individuals [36, 45, 50].

Due to the age-associated alterations in frequencies of naïve and effector T cells, immunosenescence is associated with a decline in TCR repertoire. Healthy adults possess 2-5- fold times greater diversity in TCRs compared to aged individuals [51]. Specifically, human studies reveal that older adults contain a more restricted oligoclonal CD4+ TCR repertoire [52]. In addition, studies using murine models demonstrate that in contrast to young mice primed with influenza A live vaccine, primed aged mice exhibit reduced CD8+ TCR diversity and lack of clonotypes that respond to immunodominant epitopes [53]. However, the functional significance of the reduction in receptor repertoire remains unclear, since the early primed mice were not better protected than aged mice when both groups were

challenged with influenza virus. Regardless, due to the age-dependent decline in breadth of TCRs, it would be beneficial to consider the decrease in clonotypic diversity when designing vaccines.

Taken together, both the quantitative and qualitative properties of aged naïve T cells impede the generation of primary immune responses to new antigens. Despite the defects in priming aged T cells, antigen-specific memory T cells that were generated during younger ages are maintained for 40-60 years even in the absence of antigen [54]. Thus, in the context of vaccination, older individuals will have difficulty mounting a robust cellular immune response when encountering unique vaccine antigens for the first time. This concept is supported by the success story of the Shingles vaccine; since both shingles and chickenpox are caused by varicella zoster virus (VZV), VZV-specific immunity targets both diseases. The shingles vaccine relies on a pre-existing T cell population to undergo a recall response, rather than attempting to generate *de novo* antigen-specific cellular immunity [55]. Since administration of this vaccine is analogous to a booster response, it appears that immunosenescence plays a lesser role in impairing vaccine efficacy in older adults [56]. Collectively, this observation highlights the age-associated decline in naïve T cells and presents advantages to vaccines that prime the immune system earlier in life.

Clinical evidence suggests that increased risk of infection in the elderly is due to a decline in pathogen-specific antibody activity post-vaccination and serves as an indicator of poor vaccine efficacy. However, other studies and investigators argue that the abundance of $CD28^{null}$ T cells serves as a predictor of immune incompetence and may forecast vaccine responsiveness in the elderly [44]. Most studies demonstrate that $CD28^{null}$ T cells are terminally differentiated effectors and have lower proliferation potential, which is supported by their shortened telomeres [57]. CD28 loss in CD8+ T cells is associated with reduced perforin and granzyme activity and thus inadequate killing of infected cells [58]. Likewise, in tandem with lower CD28 expression, CD4+ $CD28^{null}$ T cells fail to display CD40L and unsuccessfully provide B cell help that normally promotes B-cell proliferation and antibody production [59]. The age-related accumulation of $CD28^{null}$ T cells leads to a reduction in high-affinity B cell responses and may be indicative of immune unresponsiveness. Indeed, aged non-responders to the influenza vaccine possess clonally expanded T cells that are dominated by the CD8+ $CD28^{null}$ phenotype, and is associated with a reduction in HAI neutralizing titers [47]. An additional study showed that in ≥65 year-olds, the likelihood of unsuccessful influenza vaccination correlated with higher frequencies of $CD28^{null}$ CD8+ T cells and inability to produce CTL-specific cytokines, while antibody metrics were not indicative of developing subsequent influenza illness [46, 60]. Therefore, these findings present the potential for an additional metric when assessing vaccine responsiveness in the older population.

3.2 B cells

It is well established that humoral immunity plays an indispensable role in providing vaccine-mediated protection, and importantly, this arm of the immune response also experiences an age-associated decline in immune competence. In comparison to younger adult counterparts, vaccines in older adults fail to elicit protective antibody titers and induce

lower levels of antibodies with functional activity [61–64]. For example, aged individuals vaccinated with tetanus, diphtheria and two pertussis antigens elicited lower antibody levels than younger adults [61, 65]. Additionally, a booster dose at age 60 still failed to elicit protective levels of antigen-specific antibody levels, further highlighting the decline in humoral immunity with age [61]. Due to great societal importance, many studies focus on influenza vaccines; in which older adults overwhelmingly exhibit lower seroconversion rates and protective HAI titers [66].

Specific mechanisms responsible for B cell intrinsic defects remain to be completely understood. Along with declining B cell numbers, several phenotypic differences among B cell subsets in aged individuals have been reported; an accumulation of $CD27^+$ B cells (marker of B cell memory) have been discussed throughout the literature, as well as a decrease in plasma cell differentiation [12]. Further, there is an increase in frequency of class-switched memory B cells with age in comparison to B cells that have yet to encounter antigen [67, 68]. Surprisingly, in comparison to younger adults immunized with consecutive influenza vaccines, older individuals obtained similar frequencies of memory B cells and plasmablasts. However, vaccine-specific serum titers and Blimp-1 expression levels (plasma cell master regulator) appeared drastically lower in the aged group, indicative of a defect in the ability of memory B cells to differentiate into plasma cells, which actively produce antibodies [12]. In addition, spectratype analysis revealed that individuals aged 86+ years obtained much lower B cell receptor (BCR) diversity, in comparison to younger adults [69]. Therefore, similarly to the T cell compartment, the contraction of receptor repertoire accompanied by an increase in class-switched B cell frequency most likely reflects the cumulative exposure to antigens throughout life. Furthermore, the reduced pool of naïve B cells available in older individuals restricts the number of possible clones able to respond to novel antigens. Indeed, aged individuals vaccinated against influenza obtain hypermutated IgG but produce fewer B cell lineages in comparison to adults, indicating that a germinal center reaction occurred but resulted in fewer responding clones [70]. Importantly, vaccine-induced antibodies failed to elicit optimal effector functions that are normally induced in younger adults. Specifically, reduced protective HAI titers following trivalent influenza vaccination and lower opsonization activity in the case of the 23-valent pneumococcal polysaccharide vaccine (PPV23) are observed in older individuals [66, 71]. Therefore, even when sufficient antibody titers are generated, the protective capacity of the vaccine-induced antibodies may be significantly reduced in the aged population.

There are age-associated cellular mechanisms that compromise the generation of isotype-switched high-affinity antibodies in B cells. Human studies reveal that activation-induced cytidine deaminase (AID), an enzyme responsible for facilitating class switch recombination (CSR) and somatic hypermutation (SHM) during germinal center reactions, is expressed at lower levels in adults of advanced age [68]. Indeed, aged mice demonstrate AID-associated impaired CSR and decreased effector antibody isotypes [72], and it has been shown that a decline in AID mRNA in human B cells correlates with decreased antibody affinity maturation following influenza vaccination [73].

Interestingly, a subset of mature B cells was identified in aged mice, termed age-associated B cells (ABCs), and are described as responsive to innate stimuli but resistant to BCR and

CD40 stimulation [74, 75]. The presence of this senescent subset remains to be confirmed in humans, however, B cells with a similar profile have been identified during autoimmune diseases and viral infections in people [74, 76]. The functional consequences of ABCs in humans and the distinction from exhausted B cells requires further investigation, but these cells likely contribute to humoral immunosenescence and warrant attention during vaccine development.

3.3 Lymphoid tissue and germinal center reactions

In addition to intrinsic B cell defects, insufficient germinal center reactions may be attributed to diminished CD4+ T cell cognate functions and reduced antigen presentation capacity of follicular dendritic cells, as both have been shown to contribute to weakened humoral responses [77, 78]. T follicular helper cells (T_{FH}, CXCR5+ CD4+) are a critical subset of T cells residing in B cell follicles of lymphoid tissue that provide antigen-experienced B cell signals during germinal center reactions to facilitate their proliferation, SHM, isotype switching, and subsequent generation of memory B cells and plasma cells. As with other cell types, T_{FH}'s perturbations correlate with age and likely negatively affect humoral responses [79, 80]. Indeed, studies show that older adults fail to produce increased numbers of activated circulating T_{FH} cells, characterized by lack of ICOS expression, following influenza vaccination, while younger individuals elicit significantly heightened levels of this subset. Since $ICOS^{+}$-T_{FH} correlates with HAI titers in the young, the defects in vaccine-induced T_{FH} activation may underly reduced influenza-specific antibody responses and presumably functions as an immune biomarker in the aged population [80]. Further, using a murine adoptive transfer model, it has been reported that transfer of aged CD4+ T cells to nucleoprotein (NP)-immunized 2-4 month old mice led to a decrease in NP-specific IgG titers, that can be attributed to reduced expansion and differentiation of B cells within observed germinal centers. Within this model, it appears the migration of CD4+ T cells are unaffected, but expression of CD40L is reduced and presumably impairs the cognate helper functions of CD4+ T cells as well [77].

Likewise, recent studies reveal age-associated alterations to lymphoid structures that negatively impact both B and T cells and results in decreased vaccine efficacy [81]. Specifically, reduced lymph node size and fibrosis of lymphoid tissue has been reported and thought to compromise adaptive immunity [82–84]. Furthermore, factors promoting B cell survival, such as BAFF and APRIL, are detected at lower levels in serum and correlate with decreased B cell survival in older adults [85]. Since these stromal microenvironments maintain lymphocytes throughout life, it has been proposed that restoring the lymphoid structure may provide a therapeutic strategy for rejuvenating the aging immune system to improve vaccine responses [81].

4. Current vaccine status for older adults

Given these age-associated immune shortcomings, vaccine-induced protection remains challenging in the elderly. Older adults are disproportionately affected by several viral and bacterial infections and experience higher case fatality rates to these infectious diseases. Prominent infectious agents of clinical concern include influenza virus, RSV, herpes zoster

virus, *Streptococcus pneumoniae, Klebsiella pneumoniae, Pseudomonas aeruginosa, Clostridium difficile* and *Staphylococcus aureus.* Since vaccination serves as a viable and efficient strategy to establish protective immunity for some of these diseases, the Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC), recommends that adults aged 65+ years obtain immunization against HZ virus, *Streptococcus pneumoniae*, and influenza virus (Table 1). The subsequent portion describes the vaccines that are currently licensed for older adults.

4.1 Influenza

A placebo-controlled trial conducted by Govaert et al. in 1994 demonstrated that administration of influenza vaccine to older individuals reduced the risk of obtaining clinically and serologically confirmed influenza by about 50% [86]. In addition, of the currently licensed vaccines for older adults, the protective efficacy of both live attenuated influenza vaccine (LAIV) and trivalent inactivated influenza virus vaccine has shown to be reduced in older adults [87], and is potentially attributed to a reduction in antibody titers and dampened effector function upon vaccination [62, 71]. Taken together, the disparity in humoral responses with age is consistent with defective B cell function among older individuals.

However, recently licensed adjustments to the influenza vaccine, such as increased dosage and addition of an adjuvant, have improved immunogenicity in older adults. First, Fluzone® High-Dose (containing 4X the antigen dose) has demonstrated significant improvements in influenza-specific humoral responses in comparison to the standard dose; generating higher anti-HA titers and seroconversion rates [88]. Secondly, Fluad®-MF59®-Adjuvanted quadrivalent Influenza, containing four-component inactivated influenza vaccine plus adjuvant, is a recently approved vaccine formulation used specifically in older adults that has demonstrated improved HAI titers, greater protection against influenza and reduced the need for hospitalization [89].

4.2 Shingles

Another prominent disease affecting aged individuals, HZ or shingles, manifests as a result of reactivation of latent varicella zoster virus (VZV). In the 1970s, Takahashi and colleagues developed an attenuated varicella virus, termed the Oka strain, to protect against pediatric chickenpox caused by VZV [90]. However, despite previous vaccination, an age-associated decline in VZV-specific CMI responses allow for reactivation of virus and results in HZ disease [91]. More recently, the Oka strain was granted licensure in the US for individuals aged >50 to prevent shingles. This vaccine, known as Zostavax®, comprises 14 times more virus than the vaccine strain used to target chickenpox in children and provides older adults protection against HZ [92]. However, Zostavax® vaccine efficacy for HZ declines by 7 years following vaccination (61.1% versus 37.7%), and efficacy has been shown to decrease with age of the vaccinee; vaccine efficacy for adults aged 50-59 years-old is 70% and drops to 37% in adults aged ≥70 years [88, 93]. Due to these shortcomings, a recently approved $ASO1_B$-adjuvanted subunit HZ vaccine, Shingrix® (RZV), is preferred for vaccinating older adults against HZ complications. RZV comprises a mixture of HZ glycoprotein E (gE) antigen and $AS01_B$ adjuvant, and demonstrates high efficacy among all age groups ranging

from 50 to ≥70 years old, with protection maintained at least 9 years following vaccination [89]. Therefore, Shingrix®, or the combination of subunit antigen and adjuvant, potentially exemplifies a general strategy for vaccines in circumventing immunosenescence in older adults.

5. Strategies to overcome age-related limitations

Development of successful vaccines will provide tremendous improvements to the health and quality of life of older adults. To design the best possible preventative strategies, we must specifically target well understood pathways that deleteriously affect immune aging, with the goal of ameliorating their effects. Previously reported approaches include the use of adjuvants, increased antigen dose, and additional vaccine booster doses.

5.1 Adjuvants

By definition, adjuvants enhance immunogenicity of vaccine antigens and importantly, can reduce non-responsiveness in target populations. Therefore, research efforts aim to develop vaccine formulations that contain a protective antigen and an adjuvant with immune stimulatory properties that circumvent the limitations of immunosenescence. Approved adjuvants currently in use for the older population include Novartis' MF59® and GSK's Adjuvant System (AS), approved for influenza vaccine and recombinant HZ gE antigen respectively [94–96]. A large-scale study spanning three influenza seasons provides estimates that Fluad®-MF59®-Adjuvanted influenza vaccine further prevents influenza- and pneumonia-related hospitalizations by 25%, compared to nonadjuvanted vaccine [89]. These adjuvants encompass similar compositions, as they all comprise squalene in an oil-water emulsion. While the exact mechanisms of action remain unknown, it has been hypothesized that these adjuvants induce a local pro-inflammatory environment that results in increased innate immune cell recruitment and antigen-presenting cell (APC) activation that subsequently amplifies T and B cell expansion to increase immune competence.

5.2 Increased dosage

As mentioned, high-dose vaccines have proven to be effective clinically in the case of influenza and HZ. Immunization with increased dosage is believed to generate greater numbers of antigen-presenting follicular DCs that ultimately results in increased B cell stimulation. The 7- and 9-valent pneumococcal conjugate vaccines (PCV7 and PCV9) were assessed for dose-dependent immune responses in subjects aged 70 years or older [97]. Despite demonstrating improved immunogenicity in individuals that received the high-dose vaccine, PCV7 and PCV9 as well as other vaccines containing an increased dosage specifically for the older population have yet to reach the market. However, these findings provide insight into the biology of immune aging, in which older adults may require more antigen to reach activation thresholds of immune cells and ultimately mount an immune response.

5.3 Multiple doses

Another approach to improving vaccine responsiveness in aged individuals involves regular booster vaccinations every 10-20 years. Healthy subjects of the ages 59-91 that received a

booster of multivalent vaccine containing antigens from tetanus, diphtheria, pertussis, and polio produced better humoral responses than the younger individuals receiving a single dose [61]. Likewise, administration of an additional booster dose of Zostavax® spaced 10 years apart given to individuals over 70 years of age showed great success in improving antibody titers and representative CMI cytokines [98]. Therefore, routine vaccine booster programs may be sufficient in inducing humoral immunity to provide protection.

5.4 Other approaches

Other novel vaccination approaches in early developmental stages include the use of viral vectors, exploring intradermal routes, signaling pathway inhibitors, and genetically engineering live vaccines with targeted alterations to enhance immunogenicity. Since CD8+ T cell responses to some viruses appear unperturbed in aged individuals, vector-based vaccines are currently being explored as a solution to generating protective adaptive immunity. For example, recent studies investigating the use of Vaccinia virus Ankara (MVA) expressing influenza antigens demonstrated that older adults obtain detectable levels of influenza-specific CD8+ polyfunctional T cells [99]. In addition, administration of Fluzone® via the intradermal route confers a superior immune response in comparison to the currently licensed intramuscular vaccination [100]. It has been postulated that intradermal administration results in accelerated immune cell recruitment that subsequently leads to generation of a more potent immune response. Since increasing evidence indicates that the cellular aging process can be manipulated with signal transduction modifiers, recent studies investigated the use of a rapamycin analog (mTOR inhibitor to block cell cycle) treatment 6 weeks prior to influenza vaccination. Rapamycin-treated older individuals produced higher antibody titers and exhibited a lower percentage of T cells expressing inhibitory molecules. Due to the enhanced vaccine response and sufficient safety profile, mTOR inhibitors demonstrate substantial promise to be used in conjunction with vaccines to ameliorate age-related immunosenescence [101]. Finally, a novel approach involves creating genetically engineered live attenuated vaccines in which genes that contribute to immune suppression are removed, with the ultimate goal of eliminating immune barricades to enhance immunogenicity [102].

6. Conclusion

It is evident that there are distinct differences between the immune systems of older and younger adults, and the implications on vaccine responses have yet to be completely understood. However, it has been established that some of these age-associated immune changes result in reduced vaccine efficacy and an increased susceptibility to infections. Recent interventions to vaccines for older adults, such as increased dosage and addition of adjuvants, have demonstrated great promise for protecting this population. However, a complete mechanistic understanding of immunosenescence will further our knowledge of immune aging and instruct rational vaccine design for the aged population, with the overall goal of improving the quality of life of older adults.

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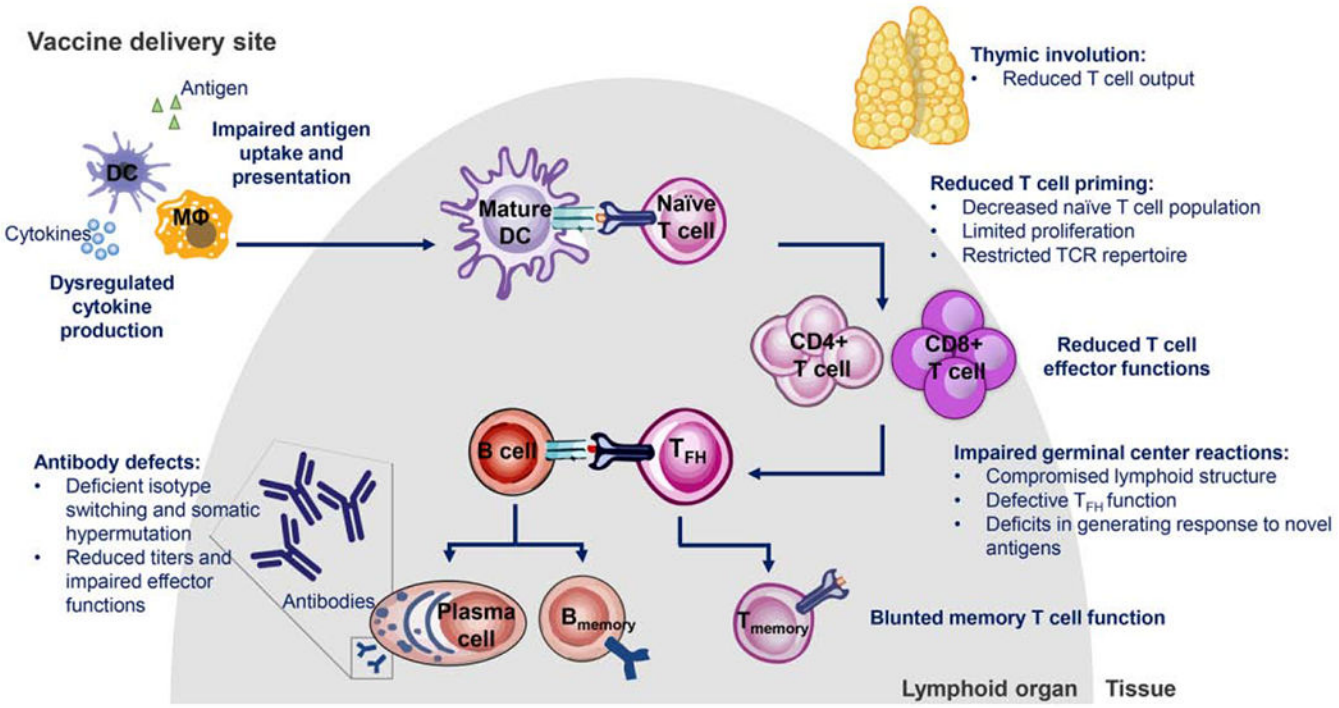

Figure 1.

Schematic diagram of immune deficits in older adults. Abbreviations: DC, dendritic cell; MΦ, macrophage; TFH, T follicular helper; TCR, T cell receptor.

Table 1.

Vaccines licensed for use in older adults

Infectious agent	Vaccine	Vaccine formulation
Influenza virus	Fluzone® High-Dose Quadrivalent Inactivated influenza vaccine (IV)	60 μg HA[a] antigen of each recommended influenza strain
	FLUAD® IV with adjuvant	15 μg HA antigen of each recommended influenza strain + MF59® adjuvant
Streptococcus pneumoniae	Pneumovax® 23-valent polysaccharide vaccine (PPV23)	25 μg polysaccharide of each serotype
	Prevnar® 13-valent conjugated vaccine PCV13	2.2 μg polysaccharide of each serotype conjugated to CRM_{197} + 0.125 mg aluminum phosphate
Varicella zoster virus	Zostavax® Zoster live vaccine	20,000 Plaque forming Units (PFU) Oka strain
	Shingrix® Recombinant zoster vaccine	50 μg VZV[b] glycoprotein E (gE) + $AS01_B$ adjuvant

[a] HA, hemagglutinin

[b] VZV, Varicella Zoster Virus