Optimising vaccine immunogenicity in ageing populations: key strategies

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Vaccination has been shown to be the most effective means of preventing infectious diseases, although older people commonly have a suboptimal immune response to vaccines and thus impaired protection against subsequent adverse outcomes. This Review provides an overview of the existing mechanistic insights into compromised vaccine response for respiratory infectious diseases in older people, defined as aged 65 years and older, including immunosenescence, epigenetic regulation, trained immunity, and gut microbiota. We further summarise the latest proven or potential strategies to strengthen weakened immunogenicity. Insights from these analyses will be conducive to the development of the next generation of vaccines.

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Introduction

Since 1990, the ageing population has contributed substantially to the increase in global disability-adjusted life-years[1] and heightened vulnerability to respiratory infections such as influenza, respiratory syncytial viruses, and coronaviruses.[2] Older adults face increased risks of severe illness and mortality from these infections, with data from the US Centers for Disease Control and Prevention indicating a ten-fold increase in the risk of dying from COVID-19 for every 20 years of age.[3] Vaccination, although the optimal strategy to combat respiratory viruses, offers poor protection to older people because of factors such as immunosenescence. These age-related changes, along with shifts in gut microbiota, suppress immune responses and diminish vaccine efficacy.

To improve vaccine responses in older people, several strategies are under exploration. Adjuvants, which enhance immune responses, are being incorporated into vaccines to boost their efficacy. For instance, the use of MF59 in influenza vaccines has shown promise in eliciting stronger immune responses in older adults than for vaccines without an adjuvant. High-dose vaccines, such as the high-dose influenza vaccine, are designed to overcome immunosenescence by providing a high antigen concentration. Another approach involves designing vaccines that target conserved viral components less likely to mutate, thus ensuring broader and more durable protection. Research is also focused on the modulation of epigenetic factors to rejuvenate immune function[4] and improve vaccine responses. Additionally, interventions to restore gut microbiota balance, such as probiotics and dietary modifications, are being considered to enhance systemic immunity. These strategies, alongside ongoing research into the molecular mechanisms of immune system ageing, aim to guide the development of next-generation vaccines that are more effective in protecting older people against respiratory viruses. Investigations have identified multiple factors responsible for the diminished vaccine immunogenicity in older adults, and this Review integrates insights from cellular, molecular, and genetic perspectives (figure 1).

Current interpretations on reduced vaccine immunogenicity in older people

Immunosenescence and inflammageing

Vaccination typically engages both innate and adaptive immune responses, crucially involving interactions between antigen-presenting cells and lymphocytes. However, ageing is commonly accompanied by immune system dysfunction (ie, immunosenescence) and chronic inflammation (ie, inflammageing), which heighten disease susceptibility and severity while compromising vaccine efficacy in older people (table).[30]

Innate immunity, primarily mediated by antigen-presenting cells such as dendritic cells, monocytes, and macrophages, provides initial rapid protection upon vaccine administration.[31] Dendritic cells from older adults display impaired toll-like receptor function, dysregulated cytokine production, and reduced co-stimulatory capacity, compromising the effectiveness of vaccines.[21] Similarly,

Key messages

- The global trend of population ageing further increases the disease burden of respiratory viral infections. Clinical means of prevention and treatment are scarce; thus, vaccination for active defence remains the optimal option.
- The ageing process is generally accompanied by chronic inflammation, immune system dysfunction, and organ dysfunction. The ageing of immune cells leads to weakened immune function, increased susceptibility to infectious diseases, and poor responses to vaccines.
- Epigenetic changes are a major feature and important cause of ageing, and age-related changes of the gut microbiota weakens the vaccine response.
- The main strategies to address poor vaccine efficacy in older people include increasing the dose, adding adjuvants, and altering the route of vaccination based on the characteristics of the pathogen.
- Innovative strategies to mitigate the ageing process are expected to improve the immunogenicity of vaccines for older people, and more research is needed to support their effectiveness.

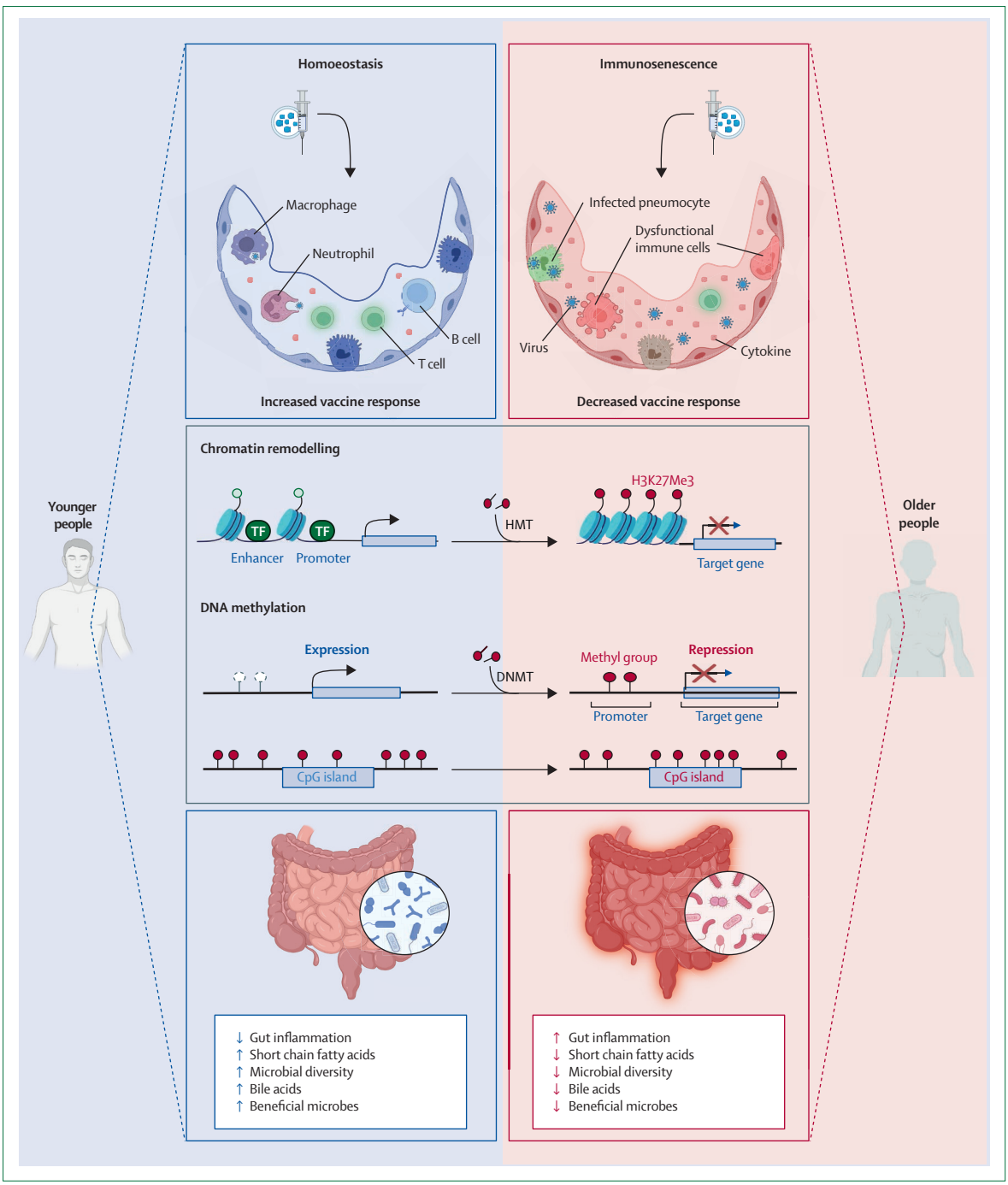

Figure 1: **Decreased vaccine protection in older people results from a combination of factors**
The diminished vaccine effectiveness in older people arises from immunosenescence, which disrupts innate and acquired immune responses, and is compounded by hormonal and cytokine shifts. Additionally, epigenetic changes, such as DNA methylation and histone modifications, contribute to altered immune-cell functionality, affecting vaccine responsiveness. The ageing microbiota in the gut further complicates vaccine efficacy by directly influencing immune response and interacting with the immune system. DNMT=DNA methyltransferase. HMT=histone methyltransferase. TF=transcription factor.

the cytotoxicity, intracellular killing, and antigen-presentation functions of monocytes and macrophages decrease with age.[22] Natural-killer cells also show diminished cytotoxicity and cytokine secretion, impairing the body's ability to respond to new infections.[23] Neutrophils, the early response effector cells, show declined chemotactic functions with age, contributing to increased systemic inflammation.[20] These age-related alterations in innate

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	Ageing-related changes
Immunosenescence	
Haematopoietic stem cells	Regenerative capacity declining with age[5]
B cells	Proportion of B-1 cells ↓; isotype conversion of B-2 cells ↓;[6] total number of B cells ↓; diversity of B-cell subpopulations ↓; plasma cells ↓;[7] B-cell antigen receptor repertoire diversity ↓;[8] age-associated B cells ↑;[9,10] geometric mean frequency of memory B cells ↓;[11] B-cell intrinsic defects in class-switch recombination and somatic hypermutation[12]
T cells	Thymic involution;[13] insufficient epitope-specific T-cell clones;[14] diversity of the T-cell repertoire ↓;[14,15] co-stimulatory molecules (eg, CD27 and CD28) ↓;[14,15] fewer cytokine-positive CD4 T cells;[16] spatial dysregulation of T-follicular helper cells;[17] IL-10-producing T-follicular helper cells ↑;[17] $CD4^+$ T-cell response ↓[18,19]
Innate immunity	Neutrophil chemotaxis ↓;[20] dysregulated cytokine production and impaired toll-like receptor function in dendritic cells;[21] cytotoxicity, intracellular killing, and antigen presentation in monocytes and macrophages ↓;[22] natural killer cytotoxicity and cytokine secretion ↓[23]
Germinal centres	Impaired germinal centre responses;[12] poor functional follicular dendritic-cell network[12]
Ageing	
Signalling pathways	Immune function ↓[24]
Inflammation	Inflammatory cytokine ↑[25,26]
Gut microbiota	
Gut dysbiosis	Gut microbial translocation;[27] impairment of host immune function;[28] diversity and stability of the microbiota ↓[29]

Table: **Factors affecting vaccine immunogenicity in older people**

immune functions compromise the overall effectiveness of the immune response, highlighting the need for tailored vaccination strategies for older people.

The efficacy of most vaccines relies on the generation of protective antibodies, facilitated by interactions between B cells and T-follicular helper cells. Both B and T lymphocytes are derived from haematopoietic stem cells in the bone marrow, whose regenerative capacity declines with age.[5] The ageing of haematopoietic stem cells has a central role in immune system ageing and is regulated by epigenetic reprogramming.[32] The thymus, essential for T-cell development, gradually shrinks and degenerates with age, reducing the production of new T cells.[15] T-cell ageing is characterised by a decline in the diversity of the T-cell repertoire, downregulation of co-stimulatory molecules such as CD27 and CD28, and age-related changes in T-cell population dynamics. Insufficient epitope-specific T-cell clones likely contribute to impaired cellular immunity to inactivated SARS-CoV-2 vaccines in older adults.[14] Additionally, older individuals have fewer cytokine-positive CD4 T cells after vaccination.[16] Augmenting CD4 T-cell responses and ensuring the correct spatial localisation of T-follicular helper cells are crucial for enhancing vaccine efficacy in this population.[17,18]

Ageing also affects B-cell function, as shown by a decline in the proportion of B-1 cells and impaired isotype switching of B-2 cells.[6] Overall, ageing leads to a decrease in the total number of B cells and the diversity of B-cell subpopulations, resulting in fewer plasma cells and a weakened antibody response to vaccination.[7] Decreased diversity in the B-cell receptor and T-cell receptor pools further diminishes vaccine responses.[8,14] Age-associated B cells have been found to reduce vaccine response by weakening the affinity maturation process of germinal centre responses,[9] making them a promising marker for vaccination response.[10]

Inflammageing, characterised by elevated serum concentrations of inflammatory cytokines and mediators, can suppress antigen-specific immunity and reduce vaccine effectiveness.[25] Studies on severe acute respiratory syndrome and SARS-CoV-2 in mice have shown that decreasing prostaglandin D2 concentrations in the lung microenvironment enhances respiratory dendritic cell function, attenuates inflammation, and improves survival in older mice.[33,34] These findings provide a theoretical basis for the treatment of respiratory coronavirus infections and are particularly relevant for vaccine development for the older population.

Epigenetic regulation

Epigenetics involve changes in genome function without altering the nucleotide sequence, such as DNA methylation, histone modifications, or non-coding RNA.[35]

DNA methylation and hypomethylation are important epigenetic modifications associated with ageing and immune responses.[36] DNA methylation regulates B-cell development and maturation,[37] influences germinal centre B-cell differentiation,[38] and modulates the proportion of memory B cells.[11] T-helper cell differentiation[39] and regulatory T-cell function are also epigenetically regulated. FoxP3 expression is crucial for regulatory T-cell development,[40] with differential methylation patterns in regulatory T cells and other CD4 T-cell subsets.[41] T-cell factor 1, a transcription factor, modulates the longevity and recall responses of CD8 memory T cells, which are crucial for vaccine development.[42] Furthermore, some CpG sites are associated with age-related changes,[43] with older adults exhibiting more methylated CpG sites, affecting vaccine responses.[44]

Histone modifications influence gene transcription and regulate immune function by altering chromatin accessibility. The CTCF protein modulates $CD8^+$ T-cell heterogeneity by altering transcription factor interactions.[45] Increased phosphorylation of STAT5 affects chromatin accessibility and age-related T-cell responses.[46] DOT1L-dependent His3Lys79me2 regulates CD4

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T-helper cell differentiation by suppressing T-helper 1 lineage-specific gene expression.[47] Age-related declines in histone modifications influence immune responses to vaccines. Vaccines can induce persistent epigenomic changes in innate immune cells,[48] with decreased His3Lys27ac concentrations associated with immunotherapy resistance in vaccine-induced immune cells.[49]

Non-coding RNA expression in long-lived populations suggests some differentially expressed long non-coding RNAs might contribute to resistance against ageing.[50] MicroRNA (miR-29c-3p) has a key role in systemic senescence by targeting gene repression, and shows promise as a target for reversing senescence.[51] Changes in the three-dimensional chromatin structure of ageing mouse progenitor B cells, accompanied by epigenetic modification, lead to defects in B-cell development and function, contributing to ageing-related immune function decline.[52]

Overall, age-related epigenetic alterations substantially impact immune-cell homoeostasis and responsiveness, linking closely to ageing and age-related diseases. Future work is needed to elucidate the implications of these epigenetic modifications in immune function and their potential for enhancing immunotherapies and vaccines.

Trained immunity

Trained immunity is the immunological process in which innate immune cells acquire immunological memory.[53] Three specific histone modification sites (His3Lys4me3, His3Lys4me1, and His3Lys27ac) have been implicated in trained immunity. In monocytes and macrophages, the non-specific protection given by the BCG vaccine and β-glucan against secondary infections relies on methylation modifications of lysine (His3Lys4me1 or His3Lys4me3).[53] Mice deficient in SETD7, the enzyme responsible for inducing H3K4me1, did not develop β-glucan-induced trained immunity.[54] Notably, genes downregulated in ageing naive T cells frequently show H3K4me1 modifications.[19] Additionally, the expression of proteins associated with H3K4me3 modification diminishes during ageing, accompanied by reduced H3K4me3 concentrations.[55] These findings suggest that age-related epigenetic changes might hinder the formation of trained immunity in older people.

BCG was found to induce an increase in H3K27ac in several trained immune-related signalling pathways.[56] Immune-related genes upregulated with ageing show extensive H3K27ac modifications, progressively declining with age,[57] whereas H3K27ac enrichment occurs in regions of low accessibility,[58] hinting at compromised trained immunity in older people. Moreover, regions with enhanced chromatin accessibility induced by BCG are linked with immune function.[59] This alteration originates in haematopoietic stem cells in bone marrow and persists in differentiated cells.[60] This persistence explains why immunisation-induced immune memory can last for months and potentially affect subsequent generations.[61]

In summary, trained immunity enhances the host's defence against secondary stimulation, potentially assisting older people in combating viral infections and bolstering anti-tumour immunity.[62] However, in-depth work is needed to understand the interplay between epigenetic changes in the older population and the epigenetic mechanisms of trained immunity.

Gut microbiota

Gut microbes drastically influence systemic immunity through microbiota–immunity interactions, and age-related changes of the gut micobiota impairs host immune function and vaccine response.[28] Regional differences in vaccine efficacy align with geographical disparities in gut microbiota composition,[63] with populations in low-income and middle-income countries showing lower immune responses to vaccines, especially oral vaccines, than in high-income countries.[64]

Disrupting intestinal ecology with broad-spectrum antibiotics reduces BCG vaccine efficacy,[65] impairs the proliferation and differentiation of adaptive immune cells,[66] and decreases hepatitis B vaccine-specific antibody production,[67] ultimately impairing immune persistence. Microbial translocation can lead to an increase in dendritic cells presenting microbiota-derived antigens, suppressing immunogenicity of vaccine antigens.[27] Conversely, restoring gut microecology through microbiota transplantation can alleviate antibiotic-induced reductions in vaccine efficacy.

Gut microbiota contribute to the long-term maintenance of vaccine-induced immune responses by acting as natural immune adjuvants, promoting antibody production, recruiting persistent memory immune cells,[29] and influencing vaccine efficacy through cross-immunisation. Cross-reactive T cells at baseline are positively correlated with immune responses to influenza vaccines.[68] Microbial-derived short chain fatty acids influence vaccine response by inhibiting histone deacetylase activity, increasing histone acetylation (H3K9Ac), and supporting intestinal B-cell differentiation and antibody production.[69] Improving microbiota composition in middle-aged mice delayed age-related changes in naive T lymphocyte and regulatory T-cell populations, enhancing humoral responses to the influenza vaccine.[70] Similarly, reconstitution of the gut microbiota with NOD2 agonists can improve vaccination responses.[71]

The gut–lung axis highlights the regulation of pulmonary immune responses by gut microbiota.[72] Respiratory viruses can alter the abundance and diversity of the lung's microbiota, affecting immune function.[73] Conversely, gut microbiota can stimulate alveolar macrophages by modulating ERK signalling via GM-CSF, improving pathogen clearance and respiratory defence.[74] These factors suggest that gut microbiota have an important role in respiratory mucosal immunity.

Gut microbiota also regulate the immune system at the epigenetic level. They direct tuft-cell differentiation via

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the histone deacetylase 3-Spry2 pathway,[75] essential for initiating and maintaining type 2 immunity.[76] Butyric acid from *Clostridium perfringens* inhibits histone deacetylase, promoting regulator T-cell differentiation, increasing IL-10 secretion,[77] and enhancing macrophage antimicrobial activity.[78] These findings highlight the potential of epigenetic interventions in the immune system, affecting vaccine responses.

Overall, the gut microbiota influences immune responses to vaccines and modulates immune function at the epigenetic level. Targeted modulation of microbiota composition can enhance immune system function in older adults, improving vaccine efficacy.

Current strategies to enhance vaccine immunogenicity in older people

The compromised immunogenicity in older people poses a great threat to this ever-growing population, and several approaches have been proposed to address this issue (figure 2).

Increase of the dose or dosage

Standard-dose influenza vaccines frequently have poor protective efficacy in older people,[79] whereas high-dose influenza vaccines have been shown to enhance humoral and cell-mediated immune responses in the older population.[80] The recombinant haemagglutinin vaccine, which contains three times more haemagglutinin than standard vaccines, is effective in preventing influenza in older people.[81] The recombinant haemagglutinin vaccine enhances T-follicular helper-cell recruitment and improves the production of antibodies that activate natural-killer cells.[82] Moreover, the number of naive T cells and the diversity of T-cell receptors decline with age.[83] High-dose vaccination can compensate for this decline by increasing the density of dendritic cells that show antigens to T cells in secondary lymphoid organs, thereby enhancing the likelihood of productive interactions between T cells and dendritic cells, and promoting effective cellular immune responses.[84]

Single-dose COVID-19 vaccines often do not elicit a high concentration of neutralising antibodies in older adults, necessitating booster vaccinations.[85] Boosters can be administered homologously or heterologously. Studies have shown major decreases in neutralising antibody titres 4–5 months after completing the routine COVID-19 vaccine programme.[86] Contrastingly, 5 months after two doses of the BNT162b2 mRNA vaccine (Pfizer–BioNTech, Mainz, Germany), a homologous booster with a third dose led to a 57·9-fold increase in serum-neutralising antibody concentrations in individuals aged 60 years and older.[87] Similarly, homologous booster immunisation with the inactivated CoronaVac vaccine (Sinovac, Beijing, China) resulted in a three-fold to five-fold increase in serum neutralising antibodies, prolonged antibody duration, and enhanced concentrations against mutant strains.[88] These findings indicate that homologous booster immunisation substantially increases neutralising antibody concentrations and reduces symptomatic SARS-CoV-2 infection rates. Heterologous boosters might benefit further: large cohort studies found that heterologous booster immunisation induces stronger anti-omicron neutralising antibodies in older adults than to homologous boosters, potentially offering improved immune protection similar to that in younger adults.[89]

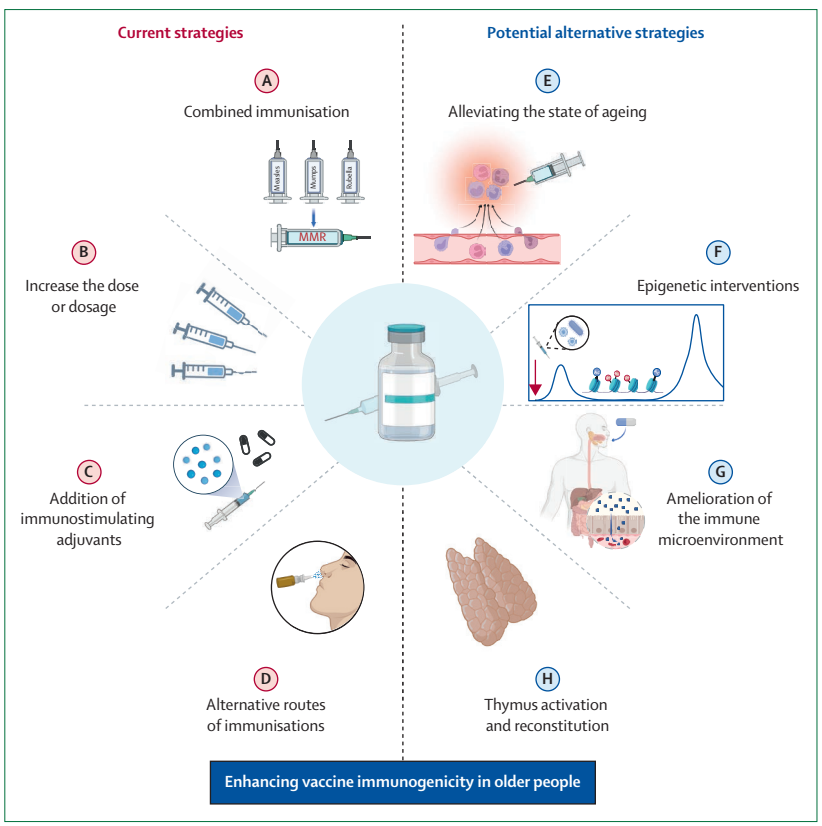

Figure 2: **Strategies to enhance vaccine immunogenicity in older people**
Traditional strategies primarily focus on enhancing vaccine effectiveness from the perspective of quantitative increase, achieved by either augmenting the vaccine dose or incorporating immunostimulatory components. However, this approach overlooks interventions in the unique physiological state of older people. By contrast, emerging methods revolve around making use of the underlying mechanisms of ageing, such as epigenetic reprogramming, to induce a qualitative change. These innovative approaches aim to ameliorate the ageing process through diverse pathways, thereby renewing the immune system of older individuals and augmenting vaccine immunogenicity. Ac=acetylation. Me=methylation. MMR=measles, mumps, and rubella.

Combined immunisation

Co-immunisation, the administration of combined vaccines and multiple vaccines for combined vaccination, holds promise in effectively combating multiple pathogens.[90] This approach reduces the number of vaccinations required, enhances immunisation coverage, and improves population adherence to vaccination protocols.[91] Clinical trials have shown that combining pneumococcal and influenza vaccination considerably reduces the incidence of pneumonia compared with administering the influenza vaccine or pneumococcal vaccine alone.[92] Representative combined vaccines, such

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as the measles, mumps, and rubella vaccine, show excellent protective efficacy in infants and young children, highlighting the broad potential of combined immunisation strategies. Moreover, receiving simultaneous vaccination of COVID-19 and influenza vaccines offers effective protection.[93] Wang and colleagues[94] developed a novel dual-acting vaccine against influenza virus and SARS-CoV-2 by combining the receptor-binding domain of the SARS-CoV-2 spike protein with inactivated influenza A virus H1N1, providing a solution to the challenge of dual infection with SARS-CoV-2 and influenza. Therefore, the development of new dual-acting vaccines might be an appealing option for the older population.

Addition of immunostimulating adjuvants

Adjuvants represent an excellent strategy for enhancing vaccine protection without increasing the dose, particularly in older people, in whom vaccine reactogenicity is diminished. The addition of MF59, an oil-in-water emulsion, to vaccines in older populations has been highly effective. Studies show that MF59 increases anti-haemagglutinin IgG titres considerably,[95] seroconversion rates,[96] and amplifies the humoral immune response. MF59 also enhances the recruitment of inflammatory cells to the injection site, activates T cells, and fosters the germinal centre response responsible for antibody production, broadening the spectrum and efficacy of antibody responses.[97] Notably, 336 days after immunisation, the MF59-adjuvanted subunit vaccine showed greatly heightened immunogenicity against the influenza virus subtype H3N2, compared with controls,[98] which is particularly important as this subtype predominantly affects older people.[99]

Clinical trials also showed that another adjuvant, AS03, elicits robust antibody response and enhances immunogenicity in older people, reducing influenza-related morbidity.[100] The use of a novel saponin-based adjuvant, Matrix-M, shows great promise in influenza vaccines.[101] With advancements in modern immunology, there is anticipation that novel adjuvant vaccines will continue to emerge, offering enhanced safety profiles for older populations. Furthermore, other adjuvants and strategies, such as CpG oligodeoxynucleotides (ie, AS01 and AS04), toll-like receptor agonists, combination adjuvants, nanoparticle-based adjuvants, cytokine adjuvants, glycoconjugates, and immunostimulatory complexes,[102] are being explored and might elicit even more pronounced immune responses.

Alternative routes of immunisations

Most approved vaccines are administered via direct intramuscular injection. Parenteral immunisation predominantly induces systemic IgG antibody responses and rarely induces strong mucosal IgA and T-cell immunity, resulting in minimal protection against respiratory pathogens.[103] In pursuit of enhanced vaccine immunogenicity, alternative routes of vaccine administration, such as oral, intranasal, and intradermal, have been explored.

Studies have shown that intradermal vaccination results in increased antigen-presenting cell functionality and subsequent mucosal immunity.[104,105] Investigations into influenza vaccines among older people have found that intradermal injection increases neutralising antibody titres and seroconversion rates compared with traditional intramuscular injection.[106] Notably, in older adults, 60% of the intradermal influenza vaccine dose has shown efficacy similar to that of a full dose of intramuscular influenza vaccine, albeit with a substantial increase in adverse reactions to intradermal injection.[107] Moreover, studies indicate that the efficacy of an unadjuvanted intradermal influenza vaccine has similar effects to that of the MF59-adjuvanted influenza vaccine in older adults, suggesting heightened immunogenicity of the intradermal vaccine in this demographic. Nasal vaccines also hold promise for the older population. Individuals aged 60 years and older can mount an immune response similar to that of individuals aged 18–59 years.[108] Furthermore, intranasal vaccination is less likely to be affected by pre-existing immunity.[109]

Potential alternative strategies

Rejuvenation of the ageing state

Immunosenescence, the accumulation of inflammatory and senescent cells, is the primary cause for reduced vaccine efficacy in older people. Mitigating inflammation, inhibiting immunosenescence, and eliminating senescent cells could be promising strategies for enhancing vaccine responses in older people.

The thymus is essential for producing naive T cells, which are crucial for responding to new antigens. Thymus involution, the gradual decline in the function and size of the thymus with age, greatly affects the immune system and vaccine response.[13] Although the exact molecular mechanisms of age-related thymic involution remain unknown, several therapies have shown effectiveness in preventing thymic involution. Fibroblast growth factor-21 has been found to prevent thymic involution and extend the lifespan of older mice,[110] and keratinocyte growth factor enhances thymopoiesis and improves T-cell-dependent antibody production.[111] Lowering sex-hormone concentrations and particular receptor antagonists has been suggested as a potential means to promote thymic regeneration.[112] Cellular therapies, such as delivering more progenitor cells to the thymus and activating the Notch1 signalling pathway, have shown promise in increasing thymic and peripheral T-cell populations.[113,114] Additionally, constructing functional thymic tissues with human stem cells[115] and identifying thymic stem cells for immune function improvement are under intensive study.[116] These interventions suggest that thymic ageing can be addressed, but their effect on enhancing vaccine immunogenicity in older people warrants further study.

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The mTOR signalling pathway greatly influences immune functionality in ageing individuals. Sirolimus, an mTOR inhibitor, has been shown to enhance antibody titres by more than 20% when administered before influenza vaccination.[24] Clinical trials with another mTOR inhibitor, RTB101, have shown enhanced interferon-induced antiviral responses and reduced viral respiratory tract infections.[117] Although evidence is promising, further studies are needed to fully understand the long-term safety and efficacy of mTOR inhibitors in enhancing vaccine responses in older adults.

Chronic inflammation negatively effects vaccine efficacy. Inhibiting inflammatory cytokine production by blocking p38 mitogen-activated protein kinase has been shown to improve the efficacy of the herpes zoster vaccine in older adults.[26] Diabetes medications, such as metformin, show anti-inflammatory effects and might enhance the immune response to vaccines by reducing systemic inflammation.[118] Caloric restriction and fasting have also been shown to reduce inflammation and enhance immune function in older people.[119]

Senolytics, which selectively eliminate senescent cells, offer another option for slowing down ageing and improving vaccine efficacy. Studies have shown that senolytics can attenuate senescence-induced changes in CD4 T-helper cell subpopulation differentiation during influenza infection and reduce mortality in coronavirus infections in older mice.[120,121] Prevaccination therapy with senolytic agents is expected to improve vaccine efficacy in older people without requiring new vaccine development. Future studies should elucidate the detailed mechanisms of the response of senolytics to vaccines to support their use.

Modification of epigenetic status

Modulation of trained immunity

Changes at the epigenetic level might produce a broader spectrum of long-lasting effects, which are particularly important for vaccines in older people. Trained immunity, mediated by bone marrow progenitor cells and peripheral cells (such as monocyte macrophages, natural-killer cells, and epithelial cells), can maintain immunoprotective effects for months, or even years.[122] Some studies show that BCG vaccination contributes to the down-regulation of pathogenic inflammatory responses in older people and can reduce respiratory infections by 75% compared with placebo.[123,124] Moreover, BCG vaccination contributed to enhanced cytokine responses to influenza and SARS-CoV-2, leading to higher antibody titres after SARS-CoV-2 infection.[125]

One dose of BCG vaccine administered monthly for three consecutive months to an older population substantially prevented acute respiratory infections.[126] Similarly, trained immunity from BCG vaccination of newborns and young children helped to protect against SARS-CoV-2.[127] Research published in 2022 explored the development of a recombinant BCG vaccine by incorporating two Epstein–Barr virus genes, which exhibited a notable immunosuppressive effect on Epstein–Barr-positive tumours.[128] Additionally, reports have emerged of nano-immunotherapies that target haematopoietic stem cells and stimulate the formation of immune memory, achieving more effective eradication of cancer cells in the body.[129] These studies underscore the potential use of trained immunity to devise more efficacious antiviral vaccines.

Intervention of epigenetic status

Emerging research underscores the potential for modulating the immune system through epigenetic mechanisms.[130] Studies show that vaccine efficacy correlates more strongly with epigenetic age than chronological age,[131] suggesting that epigenetic factors have a crucial role in identifying vaccine responses.

Epigenetic drugs, widely used in cancer therapy, show the feasibility of pharmacological interventions to improve immune function.[132] DNA methyltransferase inhibitors and histone deacetylase inhibitors have been proven effective in reactivating genes suppressed during senescence, thereby enhancing immune-cell function.[133,134] For instance, HDAC3 modulates His3Lys27Ac rates, crucial for dendritic-cell development and cell-fate determination.[135] Additionally, memory B-cell differentiation is affected by IRF4-mediated epigenetic imprinting. This imprinting promotes the re-engagement of vaccine-induced memory B cells in the germinal centre response, potentially increasing the production of broad-spectrum neutralising antibodies.[136]

Amelioration of the immune microenvironment

Intestinal microbiota and vaccines have intricate interactions.[137] Antibiotics, probiotics, and engineered bacteria have been observed to modulate the microbiota, thereby enhancing vaccine effectiveness.[138]

Antibiotics are capable of modulating the gut microecology. Clinical trials have shown that vancomycin potentiates oral rotavirus vaccination and augments the diversity of the gut microbiota.[139] Although influenza vaccination concomitant with antibiotic use can weaken the IgG1 and IgA response,[140] enriching the gut micrrobiota can mitigate this effect. Additionally, short chain fatty acids (metabolites of the microbiota) can enhance immune responses,[141] affirming the potential of modulating gut microbes to improve vaccine efficacy.

Probiotic supplementation optimises vaccine immune responses while promoting a healthier microbiota composition.[142] For instance, *Bifidobacterium* enhances the specific mucosal IgA response to polio vaccine,[143] with the proportion of *Bifidobacterium* positively correlating with IgA titres.[144] Moreover, *Bifidobacterium* has been shown to have positive effects on various vaccines, including BCG and SARS-CoV-2,[145] contributing to their efficacy.

Engineered bacteria hold immense potential for enhancing vaccine efficacy. Recent studies from 2000 to

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Search strategy and selection criteria

A search was conducted of PubMed, Web of Science, and Google Scholar for articles published in English between July 1, 2004, and July 1, 2024. The search strategies submitted combined the terms of "aging", "vaccine", "respiratory viruses in older adults", "interpretations", and "strategies". Substantive reviews identified on the subject were also cited to provide readers with more details and references than this Review can accommodate.

2020 show that oral vaccines with recombinant *Lactobacilli* elicit stronger systemic and mucosal-specific immune responses.[146] Furthermore, engineered bacteria not only improve vaccine efficacy but also serve as mucosal vaccine carriers,[147] enhancing the immune efficacy of delivered vaccines.

Local immune responses involve components of innate immunity, such as mucosal-associated invariant T cells and natural-killer cells,[148] providing an important first line of defence. Mucosal immunity generates local memory responses, with tissue-resident memory T cells offering long-term protection and a rapid response to reinfection.[149] Mucosal vaccines (eg, nasal sprays) can stimulate these local immune responses directly at the site of infection, potentially providing increased protection for older adults whose systemic immune responses are typically weaker than younger individuals.[150]

Conclusion and perspectives

Despite advances in the fields of infectious diseases and ageing research, the effectiveness of vaccines in protecting older people against complex infectious diseases, such as influenza and COVID-19, remains unsatisfactory for several reasons. First, the development of vaccines for older people has not received sufficient attention, and vaccines for this demographic are scarce. Second, there is a short supply of suitable ageing animal models for the development of specific vaccines, and the reliability of study results still requires verification. Finally, in part due to the vaccine hesitancy of older people, clinical trials rarely enrol individuals older than 80 years, posing challenges in obtaining pertinent clinical data for vaccine research and development, and hindering the timely assessment of vaccine efficacy.

In this Review, we outlined proven strategies (such as optimising vaccination administration) and proposed innovative approaches that might lead to a solution, including epigenetic modulation and microenvironment amelioration. However, the interactions between senescence, immune responses, and vaccine mechanisms of action require further elucidation. Although most studies have reported that the reduction in vaccine efficacy is linked to immunosenescence, effective countermeasures are still scarce. Perhaps multiple approaches are required for restoring immunogenicity in older people.

Overall, scientists should pay attention to the characteristics of respiratory viral infections and the unique physiological characteristics of older people, deeply understand the intrinsic connection between immunogenicity and ageing, elucidate the epigenetic ageing process and viral pathogenesis, and rationally design vaccines for older people to generate effective, long-lasting, and broad-spectrum protective immune responses. Performing these actions will ultimately promote healthy ageing and safeguard the welfare of global public health.

Contributors

JY and DZ supervised and revised the manuscript. GJ and YZ wrote and edited the manuscript. All authors contributed to the Review and approved the submitted version.

Declaration of interests

We declare no competing interests.

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