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Age-related changes in immunity: implications for vaccination in the elderly

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Average life expectancy is continuously rising in all developed countries, leading to an ever-increasing elderly population. Of the many functions of the body affected by the complex process of ageing, the immune system in particular undergoes various changes, collectively termed immunosenescence. As a result, elderly people are more susceptible to infections and are frequently less protected by vaccines. This review summarises the effect of ageing on immunity, emphasising the age-associated changes within T and B cells at a molecular and cellular level. Furthermore, it discusses strategies, such as the addition of immunostimulatory adjuvants and the use of potent antigen-delivery systems, that may counteract age-related defects in immune responses to vaccination. A proper understanding of how immunological memory is affected by ageing, and the introduction of strategies to ameliorate vaccine efficacy in the elderly, might reduce the incidence and the severity of infectious disease within this fragile age group and have a strong impact on the quality of life of elderly individuals.

Thanks to improved public health measures and standards of living, and the advent of antibacterial drugs, large-scale vaccinations and other advances of medical treatment, human longevity has been considerably prolonged, causing a dramatic change in the age structure of developed countries. It has been predicted that ~40% of the population in Europe and the USA will be more than 60 years of age in 2050 (Ref. 1). Unfortunately, the overall increase in average lifespan has not come without a price. Over the past 20 years, the UK has gained about four years in both female and male life expectancy, but only two years in healthy female life expectancy (Ref. 2). Data from the Netherlands corroborate the UK findings: during the 1990s, average life expectancy increased by two years accompanied by an increase in the number of years with disease (Ref. 3). Thus, the increase in average lifespan is accompanied by an incremental burden of age-associated diseases (Ref. 4), with a significant

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percentage of the newly gained years spent in poor health.

In addition to age-associated diseases such as Alzheimer's disease, atherosclerosis, diabetes mellitus, sarcopenia and osteoporosis – which have been associated with an unregulated systemic inflammation that typically appears in old age as a result of the broad range of changes that the immune system undergoes during ageing (Refs 4, 5, 6, 7) – the elderly population is very susceptible to infectious diseases. The increased prevalence and severity of infectious diseases among this age group reflects dysfunction of the aged immune system. Pneumonia and infections of the urinary tract, skin and soft tissue (Ref. 8), and reactivation of latent pathogens such as varicella zoster virus (VZV) (Ref. 9), mycobacteria (Ref. 10) and cytomegalovirus (CMV) (Ref. 11), occur very commonly in the elderly. Influenza and its secondary complications represent the fourth leading cause of death in persons over the age of 65 in the USA (Ref. 12). In Austria, it is estimated that between 1000 and 6000 people die during an epidemic influenza outbreak (Ref. 13), with the elderly and immunocompromised persons being at enhanced risk. A newly recognised health issue in the geriatric population is acquired immune deficiency syndrome (AIDS): 11% of patients with AIDS are over 50 years of age in the USA, and ageing itself represents an independent risk factor for rapid progression of the disease (Refs 14, 15).

Vaccines constitute cost-effective measures for preventing disease. The ultimate goal of a vaccine is to develop long-lived immunological protection, whereby the first encounter with a pathogen is 'remembered', leading to an improved memory response that prevents or at least reduces the severity of the disease upon re-infection (Ref. 16). This goal is achieved by generating antigen-specific memory T and B cells together with serum antibodies (Ref. 17) (Fig. 1). The memory T-cell compartment consists of both $CD4^+$ and $CD8^+$ T cells that can rapidly acquire effector functions to kill infected cells and/or secrete pro-inflammatory cytokines that inhibit replication of the pathogen. Effector $CD4^+$ T cells also help B-cell responses and enhance $CD8^+$ T-cell development, through the activation of antigen-presenting cells (APCs) or secretion of cytokines such as interleukin (IL)-2, IL-4 and IL-5. The memory B-cell compartment consists of long-lived effector B cells (plasma cells), which secrete high-affinity 'neutralising' antibodies (Ref. 16) (Fig. 1). A periodic re-exposure to the pathogen is of fundamental value for effectively maintaining high levels of immunity.

Vaccines are routinely administered worldwide, based on the common-sense principle that it is better to keep people from falling ill than to treat them once they are ill. Mass immunisation programs have led to the virtual eradication of several diseases that used to be associated with significant morbidity and mortality. It is estimated that more than 2 million deaths were averted worldwide in the year 2003 by immunisation (Ref. 18). Vaccine efficacy depends on the ability of the individuals to exhibit an adequate immune response. Thus, the immunisation of very young infants, the elderly and immunocompromised persons poses a great challenge. In industrialised countries, where an increasing proportion of the population is over 65 years of age, public health immunisation programmes are progressively targeting the elderly. However, immunosenescence blunts the immune response to many vaccines (Refs 19, 20).

This review aims to summarise recent reliable data on age-associated changes in immunity and to highlight their implications for vaccination in the elderly. Improving our understanding of immune ageing is a necessary step toward identifying ways to treat the underlying causes of immunosenescence and to upgrade immune responses of the elderly population to vaccination.

Age-related changes within the immune system

In animal models as well as humans, the immune system undergoes profound alterations during ageing. Those alterations are complex and widespread, extending from haematopoietic stem cells and lymphoid progenitors to mature lymphocytes in secondary lymphoid organs (Ref. 21). Although intensive research over the past decades has attempted to clarify the basic mechanisms of age-related immune dysfunctions, the underlying causes of the defects of the aged immune system are not fully understood yet. However, as a result of coordinated efforts by many laboratories worldwide focusing on immunosenescence, and the advancing knowledge of immune-system biology, a convincing and clear-cut picture has started to emerge.

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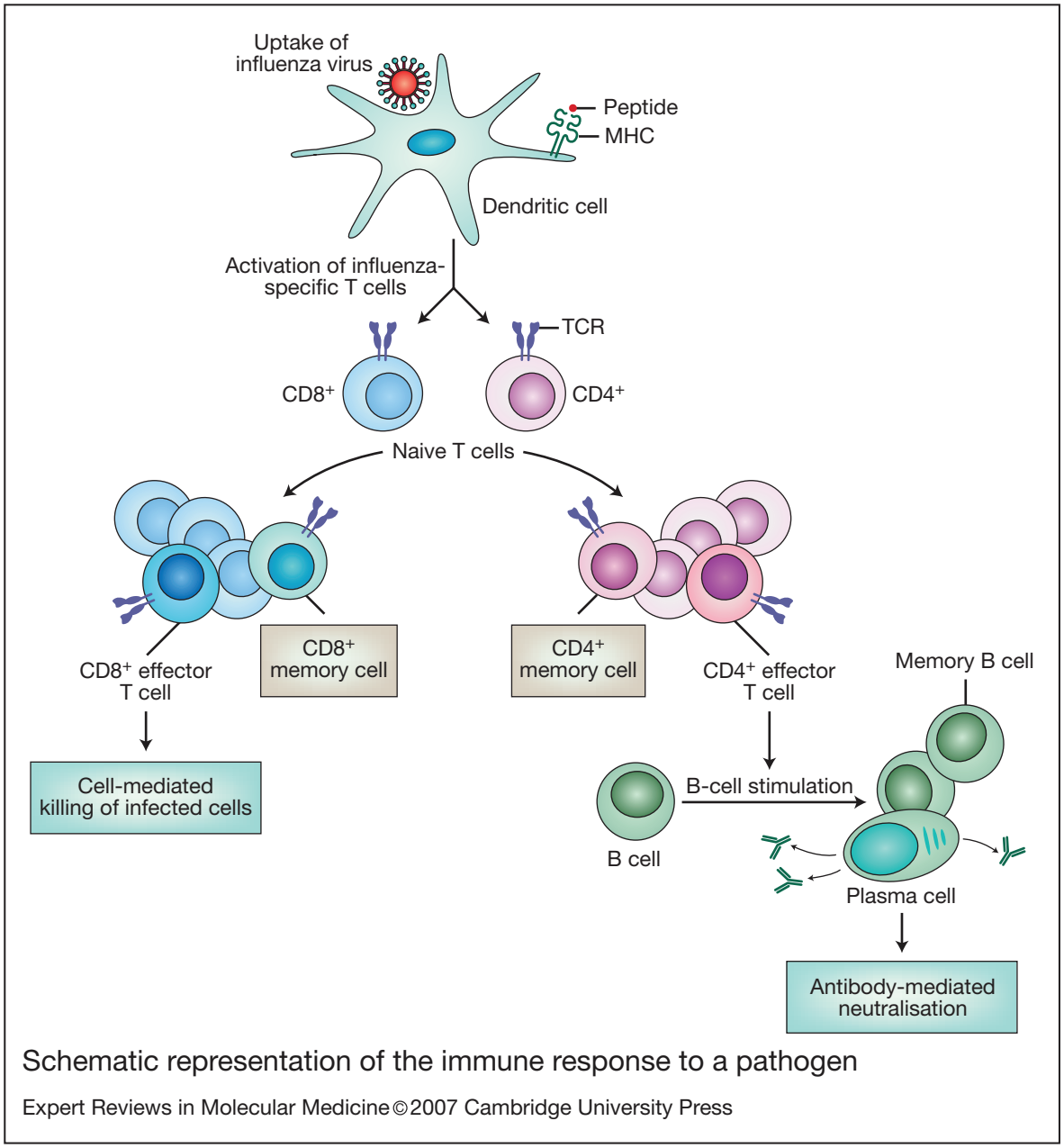


Figure 1. Schematic representation of the immune response to a pathogen. After invading the body, the pathogen is phagocytosed by antigen-presenting cells, such as monocytes and dendritic cells. Peptides derived from pathogen proteins are presented by the major histocompatibility complex (MHC) molecules at the surface of the antigen-presenting cell. T cells recognise these peptide–MHC complexes via their specific T-cell receptor (TCR) and are activated. Activated $CD4^+$ (effector $CD4^+$) T cells can stimulate B cells, which will consequently differentiate into plasma cells and produce antibodies. Activated $CD8^+$ (effector $CD8^+$) T cells can mediate the killing of tumour cells and host cells that have been infected by the pathogen. The activation of $CD4^+$ and $CD8^+$ T cells also leads to the formation of long-lasting immunological memory, which is the aim of vaccination.

Innate immunity and ageing

Innate immunity represents the first line of host defence and provides the basis for an adequate response to pathogens. Ageing is associated with a breakdown of the epithelial barriers of the skin, lung and gastrointestinal tract,

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which enables pathogenic organisms to invade mucosal tissues and thus results in an increased challenge for the aged innate immune system (Ref. 22).

Age-associated alterations have also been observed in the cells responsible for innate immunity. Neutrophilic granulocytes produce reduced amounts of superoxide anion in response to granulocyte–macrophage colony-stimulating factor and Gram-positive bacteria in old age. Furthermore, changes in membrane fluidity, in chemotaxis to selected chemoattractants and in various signal transduction pathways have been detected, although, interestingly, the number of this cell type is not affected by ageing (Ref. 23). An overwhelming body of evidence indicates that, similar to granulocytes, ageing macrophages have an impaired respiratory burst and a reduced capacity to produce superoxide anion and nitric oxide (Refs 24, 25, 26). They are also unable to upregulate the expression of major histocompatibility complex (MHC) class II, thus impairing their capacity to present antigen and to trigger $CD4^+$ T-cell responses (Ref. 27). Defects at the level of Toll-like receptor expression and function may increase susceptibility to and severity of bacterial, mycotic and viral infections in the elderly population (Ref. 28).

Although the number of natural killer (NK) cells increases with age, NK cell cytotoxicity and the production of cytokines in response to activation are impaired on a per cell basis (Refs 29, 30). It is still unclear whether and to what extend dendritic cells (DCs) are affected by ageing. Experiments in mice suggest that the density of DCs in the skin, the expression of MHC class II and other cell-surface molecules, and the capacity of DCs to present antigen can all be altered with increasing age (Ref. 31); however, only a few studies have been carried out to analyse these effects in humans (Ref. 32).

Adaptive immunity and ageing

T cells

One of the most pronounced changes of the ageing immune system is a direct consequence of thymic involution (Ref. 33). The thymus, a central lymphoid organ that lies in the upper anterior thorax just above the heart, is responsible for the development, selection and output of mature naive T cells into the periphery in a process called thymopoiesis. With progressive ageing, the thymus involutes. As a result, the output of naive T cells declines dramatically with age. The reduced thymic output together with a life-long exposure to antigens leads to a shrinkage of the naive T-cell pool in elderly persons (Ref. 34) and consequently to limitations in the host's ability to respond to new antigens. This is particularly disturbing when old individuals contract newly emerging diseases, such as the severe acute respiratory syndrome (SARS), which killed 50% of infected persons over 50 years of age (Ref. 35).

Additionally, the naive T cells found in old age have resided for decades in the periphery and have been exposed to a series of factors, such as oxidative stress and limited concentrations of survival factors, that may have a negative impact on cell function (Refs 36, 37). Naive $CD4^+$ T cells from aged animals, compared with cells from young mice, produce significantly less IL-2, expand poorly and give rise to fewer effectors, with a less activated phenotype and reduced ability to produce cytokines (Ref. 38). However, newly generated $CD4^+$ T cells in old animals respond strongly to antigens in vivo and in vitro, are able to expand, produce IL-2 and exhibit cognate helper function. Thus, age-related defects in response to antigenic stimulation may, at least in part, be due to the chronological age of $CD4^+$ T cells (Ref. 37).

The age-associated reduction in the number of naive cells is accompanied by a parallel increase in the number of antigen-experienced memory or effector cells (Refs 6, 39). This results in a shift of the phenotype of circulating T cells from early to later differentiation stages. Cells of later differentiation stages are characterised by the loss of the costimulatory molecule CD28. $CD28^-$ T cells are long-lived lymphocytes with a limited proliferative capacity. $CD28^-CD8^+$ T cells may be $CD27^+$ or $CD27^-$ (Ref. 40); by contrast, $CD28^-CD4^+$ T cells are strictly $CD27^-$ (Refs 41, 42, 43). $CD28^-CD8^+$ as well as $CD28^-CD4^+$ T cells produce large amounts of interferon (IFN)-γ and perforin and express a variety of killer cell Ig-like receptors (KIRs) normally found on NK cells (Refs 44, 45). Due to their tissue-damaging properties, it is believed that they contribute to the development and perpetuation of age-related diseases. $CD28^-$ T cells frequently exhibit

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specificity for persistent viruses – mainly for cytomegalovirus (CMV), but also for Epstein–Barr virus (EBV) or hepatitis C virus (HCV) (Ref. 46). Loss of CD28 in $CD4^+$ T cells is accompanied by a concomitant defect in CD154 (CD40L) expression; hence, they provide little cognitive help for the induction of humoral responses, leading to reduced B-cell expansion, reduced differentiation to a germinal-centre (GC) phenotype and reduced IgG production (Refs 36, 47, 48). A high frequency of $CD28^-$ T cells has been correlated with a low humoral immune response to influenza vaccination in elderly persons (Refs 49, 50).

A typical feature of the aged immune system is the presence of oligoclonal expansions of nontransformed T-cell populations. In most aged mice and almost all humans over the age of 40, expanded clones of $CD8^+$ T cells exist that are large enough to distort the αβ T-cell repertoire (Refs 21, 51, 52). Outgrowth of $CD4^+$ T-cell clonotypes might also occur but is believed to be much less common. The development of tetramer technology enabled the identification of $CD8^+$ T cells carrying receptors for single peptide epitopes. Although the aetiology of clonally expanded populations is not thoroughly understood, evidence is accumulating that repeated viral infections or the establishment of chronic infections drive the $CD8^+$ T-cell repertoire towards oligoclonality (Ref. 53). It has been hypothesised that chronic antigenic stimulation by CMV leads to an increasing prevalence of senescent, dysfunctional T cells, and therefore contributes to more general alterations in the immune system, which are associated with earlier mortality (Ref. 54). In order to connect the occurrence of CMV clones with immunosenescence, it has been suggested that the accumulation of highly differentiated T cells consisting of a few expanded clones directed to a restricted number of epitopes leads to filling up of the immunological space, resulting in a more restricted repertoire. This results in the inability of $CD8^+$ T cells from elderly individuals to respond to new antigens and they might also lose the ability to respond to secondary antigenic challenge because $CD8^+$ memory T cells might be lost through competition with expanded clonal populations for survival signals (Ref. 55).

Memory $CD4^+$ T cells are pivotal in controlling humoral and cellular responses, and so their longevity and response to vaccination are critical for the maintenance of protective immunity (Ref. 17). Memory T cells generated from aged naive T cells survive and persist well in vivo but they are markedly defective in their proliferation and cytokine secretion during recall responses, whereas memory cells generated in young individuals retain function for extended periods of time as their host ages (Ref. 56). These data, from animal studies, have recently been confirmed in humans. Healthy elderly individuals are able to mount a $CD4^+$ T-cell response comparable to that observed in younger individuals when vaccinated against influenza, but they exhibit an impaired long-term $CD4^+$ T-cell immune response to the influenza vaccine (Ref. 57). The defects at the $CD4^+$ T-cell level have in part been attributed to the age-related increase in cholesterol content within lipid rafts affecting the formation of immunological synapses with APCs. This leads to perturbations in the recruitment of key signalling molecules such as $p56^{Lck}$ and LAT ('linker for activation of T cells') to lipid rafts (Refs 58, 59, 60, 61, 62) and consequently impairs the priming of naive $CD4^+$ T cells.

B cells

As for T cells, the peripheral blood B-cell pool appears to 'fill up' with memory cells, as a result of concurrent displacement of naive cells. The percentage of naive B cells, which are defined by the absence of CD27, is significantly lower in aged individuals than in the young. The opposite is true for memory cells. In addition, memory B cells from aged individuals show a decreased susceptibility to apoptosis (Ref. 63). The kinetics of the peripheral blood B cells are similar between elderly and young subjects, although there may be a trend towards a slower rate of proliferation in the elderly (Ref. 64). Similar to T cells, ageing is associated with the appearance of B-cell clonal expansions. This limits the diversity of the B-cell repertoire and may very likely induce monoclonal serum immunoglobulins and B-cell neoplasms (Ref. 65). Additionally, there is a shift from B2 to B1 cells. Most foreign protein antigens stimulate B2 cells in the presence of T-cell help, while carbohydrate antigens do not depend on T-cell help and stimulate B1 cells (Ref. 66).

Age-related changes in the B-cell pool result in impaired humoral immunity in the elderly.

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Specific antibody responses in humans to virtually all vaccines, including vaccines against influenza and encephalitis viruses as well as vaccines against tetanus and pneumococcal bacteria, decrease with age (Refs 67, 68). Primary antibody responses in aged humans are specifically weak and short-lived, and the antibodies produced bind with lower affinity.

Although age-related changes in humoral immunity might be the result of intrinsic defects in B cells, the lack of regulatory control of T cells on B cells also contributes to the low-level and brief production period of specific antibodies to foreign antigens in the elderly. It is well established that $CD4^+$ T-cell help is crucial for GC formation (Ref. 69). Cognate help from $CD4^+$ T cells drives the formation of GCs, thus enabling isotype switching and affinity maturation of antibodies (Ref. 70). The study of GC reactions in healthy elderly humans is impractical for obvious reasons. However, a severe reduction (60–95%) in GC reactions has been reported in mice of greater than 22 months of age, correlating reduced GC reactions with declining humoral responses in ageing. The reduction of GC reactions occurs gradually, and both the number and the volume of GCs diminish progressively (Refs 39, 48).

Efficacy of vaccines to protect elderly persons from infectious diseases

To date, approximately 26 different infectious diseases can be prevented by vaccinations, and influenza is one of them (Ref. 13). However, influenza immunisation of young adults provides 65–80% protection against illness caused by a virus present in the vaccine, whereas vaccination of the elderly confers only 30–50% protection against disease (Ref. 71). Murasko et al. (Ref. 72) performed a four-year study to evaluate the consistency of immune responses across multiple years in young and elderly individuals. It was demonstrated that both young and elderly persons consistently produce significant antibody and T-cell proliferative responses to influenza vaccine after annual immunisation, but both responses of the elderly are significantly lower than those of the young. However, each year both young and elderly persons demonstrated a significant increase in the percentage of individuals who achieved a haemagglutinin inhibition (HI) IgG antibody titre $\geq$40, which is generally considered to be protective (Ref. 73). Finally, the risk of developing influenza disease after immunisation was higher among the elderly. Recently, Goodwin et al. (Ref. 74) reviewed 31 studies of the production of antibodies in response to vaccination, conducted from 1986 to 2002, and concluded that the antibody response to influenza vaccine in the elderly is considerably lower than in young adults. Other studies, which have focused on antibody production in response to vaccination against *Streptococcus pneumoniae*, hepatitis A, encephalitis, diphtheria, tick-borne encephalitis and tetanus, have shown that the efficacy of vaccinations is greatly decreased with age (Refs 13, 36, 68, 75, 76). The early involution of the thymus and the consequent loss of naive T cells may especially hamper the protective effect of vaccinations of elderly persons with new antigens, such as those for typhoid and yellow fever, hepatitis A and/or rabies virus, which are currently recommended when travelling to tropical and subtropical countries.

The evaluation of vaccine efficacy is mainly based on serologic responses (concentration of neutralising antibodies). Seroconversion, seroprotection and antibody titres following vaccination represent standard measures of vaccine response. Seroconversion can be defined as the percentage of subjects with a fourfold increase in antibody titres. Seroprotection can be estimated by the percentage of subjects with antibody titres higher than a certain value that is considered to be protective (Ref. 74). However, other components of the immune system are also required for achieving long-term protection. Eliciting cell-mediated immunity in addition to an antibody response is extremely important (Ref. 15). Cytotoxic T lymphocytes, for example, play a primary role in clearing influenza from the lungs but are poorly stimulated by the current killed-virus vaccines (Ref. 77). Hence, many elderly people remain at risk for influenza illness despite influenza vaccination. McElhaney et al. (Ref. 78) concluded that measures of ex vivo cellular immune response to influenza are correlated with protection against influenza whereas serum antibody responses might be limited as a sole measure of vaccine efficacy in older people, since pre- and post-vaccination antibody titres could not distinguish between subjects who subsequently developed influenza illness from those who did not. A study by

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Kang et al. (Ref. 57) demonstrated that healthy elderly persons are able to mount a $CD4^+$ T-cell response similar to that observed in younger individuals when vaccinated against influenza. However, they exhibit impaired long-term $CD4^+$ T-cell immune response to the influenza vaccine, probably due to alterations of the frequency of $CD4^+$ central and effector memory T cells in the elderly.

Although vaccines are less protective in the elderly, it needs to be stressed that vaccination of people over 65 years of age has been effective in reducing adverse events. Vaccination against influenza reduces the risk of serious complications or death by 70–80% among the elderly (Ref. 79). Influenza vaccination is associated with a reduction in the incidence of sudden cardiac death, acute myocardial infarction and ischaemic stroke (Ref. 80). Additionally current influenza vaccination programmes reduce hospitalisation rates by 30–40% (Ref. 81). Therefore, despite the current scientific debate about the efficacy of vaccinations of elderly persons, this population group should continue to get vaccinated every year.

Strategies to improve vaccine efficacy in the elderly

Age-related alterations in the function of the immune system are held responsible for the increased frequency and severity of infectious diseases and for the reactivation of quiescent diseases (e.g. caused by the VZV or *Mycobacterium tuberculosis*) in elderly persons. Additionally, the protective effect of vaccinations – considered a constitutive pillar of health care and a highly effective medical procedure for preventing morbidity and mortality caused by infectious diseases – may be abrogated in old age. A two-pronged approach, aimed at developing vaccines to overcome the defects of the ageing immune system and designing age-specific vaccination strategies, is of extreme priority. Performing a comprehensive estimation of the population group at risk for a given disease is of paramount importance. Important parameters to consider are the age of the individuals, medical risk factors [such as respiratory, cardiovascular, diabetes, human immunodeficiency virus (HIV) infection or AIDS and transplantations] and living situation (living independently in the community, in institutions dependent on care, or in mixed settings). A recent study suggested that even racial background might be important when drawing conclusions about cell-mediated responses to influenza vaccine (Ref. 12). Nutritional status is an additional parameter that should not be omitted when designing vaccination strategies that specifically target the elderly population. Randomised controlled studies have shown that supplementation of vitamin E for 4 months improved certain clinically relevant indices of cell-mediated immunity in healthy elderly persons. Delayed-type hypersensitivity and antibody titres to hepatitis B were significantly increased, as were antibody titres to tetanus vaccinations (Ref. 82). It is possible that the inability of elderly individuals to respond adequately to some vaccines is due to a poor diet that fails to provide them with sufficient vitamins, trace elements and minerals to trigger an adequate immune response.

Several strategies are being pursued to increase immunogenicity, induce long-lasting memory T, B and plasma cells, minimise adverse side effects, and enhance vaccine acceptance by developing needle-free injection devices. Whereas live attenuated vaccines (e.g. against varicella, measles or yellow fever) are highly immunogenic and commonly lead to long-lasting protection, inactivated and subunit vaccines (e.g. against influenza) display less side effects but are also less immunogenic, especially in elderly persons (Table 1). To enhance the immunogenicity to the antigen delivered by subunit vaccines, adjuvants can be added. Based on their principal mode of action, adjuvants can be divided into antigen-delivery systems [e.g. aluminium salts, MF59® (microfluidised emulsion), microparticles, immunostimulatory complexes (ISCOMs) and liposomes] and immunostimulatory adjuvants [e.g. QS21, 3-deacetylated monophosphoryl lipid A (MPL), oligodeoxynucleotides containing CpG motifs (CpG-ODNs) and cytokines] (Table 2).

Antigen-delivery systems convert soluble protein antigens into particulate material, which is more readily ingested by antigen-presenting cells such as macrophages (Fig. 2). For example, the antigen can be adsorbed to the adjuvant (e.g. aluminium salt), made particulate by emulsification in mineral oils, or incorporated

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Table 1. Attributes of different vaccine types[a]

Category	Advantages	Disadvantages
Live attenuated vaccines	Booster immunisations usually not required; high antibody levels and strong CTL responses	Safety concerns for immunocompromised persons
Live vector vaccines	Booster immunisations usually not required; high antibody levels and strong CTL responses	Moderate safety concerns for immunocompromised persons
Inactivated whole-virus vaccines	High antibody levels	Higher probability of adverse side effects compared with subunit or conjugate vaccines (which contain highly purified antigens)[b]
Conjugate vaccines	High clinical tolerability	Booster immunisations usually required; no CTL responses
Subunit vaccines	High clinical tolerability because of the high purity of single immunogenic peptides	Moderate immunogenicity can be enhanced by supplementation of an adjuvant or DNA
DNA vaccines	Specific manipulation of the cellular immune response; increased efficiency when added to subunit vaccines	Low immunogenicity
Antigen-delivery systems (e.g. virosomes, liposomes, virus-like particles)	High clinical tolerability; higher antibody levels and moderate CTL responses; delivery of a variety of purified antigens but also DNA	Biostability?

[a]For more detailed information see Refs 92 and 93.
[b]For example, replacement of whole-cell pertussis vaccine by acellular pertussis vaccine.

Abbreviation: CTL, cytotoxic T lymphocyte.

into colloidal particles (microparticles or liposomes). However, immunogenicity is more enhanced by immunostimulatory adjuvants such as the lipopolysaccharide derivative MPL or the triterpene glycoside QS21, a saponin component derived from the bark of the tree *Quillaja saponaria*. QS21 is currently being tested as an adjuvant in a pneumococcal polysaccharide vaccine (Phase II) and in a GM2-KLH (ganglioside GM2 vaccine) immunotherapeutic product for melanoma (Phase III). In mice, QS21 stimulated the production of IgG2a and IgG2b antibodies and induced antigen-specific $CD8^+$ T-cell responses to subunit vaccines. MPL is being tested in an experimental hepatitis B vaccine (HB-AS04® by GlaxoSmithKline) to enhance the immune response to hepatitis B surface antigen (HBsAg). Immunomodulatory adjuvants might overcome the age-related functional decline of innate immune responses by targeting evolutionary conserved receptors that recognise pathogens, such as Toll-like receptors or NOD ('nucleotide-binding oligomerisation domain') proteins, which induce the production of inflammatory cytokines (Ref. 13) (Fig. 2). The combination of both adjuvant systems (e.g. microparticles that contain the antigen as well as the DNA of a cytokine) might lead to a more targeted immune response, overcome immunodominance and also allow the mucosal delivery of vaccines (Ref. 83).

In addition to improving vaccine efficacy, the design of vaccination strategies for elderly

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Table 2. Assortment of approved and potential future vaccine adjuvants

Type of adjuvant	Description
Antigen-delivery systems	
Aluminium hydroxide [$Al(OH)_3$][a] or aluminium phosphate [$AlPO_4$][a]	These are the most commonly used adjuvants. The antigen is adsorbed to the aluminium salt. However, these adjuvants do not improve immunogenicity of influenza vaccines (Ref. 94).
Immunostimulatory complex (ISCOM)	ISCOM is a noncovalently bound complex of Quil-A, cholesterol and antigen. ISCOMs are used in veterinary vaccines but because of the side effects of Quil-A, a saponin component, ISCOMs have not been approved for human vaccines yet (Ref. 95).
Liposomes	Liposomes are lipid membrane particles that serve as vehicles or delivery systems for vaccine antigens. However, phospholipid liposomes have some limitations, such as sensitivity to phospholipases, high cost of manufacture and difficulty in scale-up for production. Recently, it has also been demonstrated that membrane vesicles from dendritic cells can efficiently prime T cells and may also be a valuable tool for tumour immunology (Ref. 96).
MF59®[a]	This oil-in-water (squalene/H_2O) emulsion is stabilised by the sorbitan oleate surfactants Tween 80 and Span 85. MF59 is an approved adjuvant in an influenza vaccine and is currently being tested for use in other vaccines (Ref. 97).
Immunostimulatory adjuvants	
AS02A®	AS02A® is an oil-in-water-based adjuvant consisting of monophosphoryl lipid A (MPL) and QS21. MPL is a nontoxic derivative of lipopolysaccharide that activates innate immunity by targeting Toll-like receptor 4 (Ref. 98).
CpG-ODNs	CpG-ODNs induce strong type 1 cellular immune responses. However, some CpG-ODNs might have side effects because they induce systemic production of pro-inflammatory cytokines (Refs 99, 100, 101).
IC31®	IC31® is a combination of a synthetic oligodeoxynucleotide (ODN1a) and the an 11-mer antimicrobial peptide (KLK), which induced potent cellular and humoral immune responses in mice (Ref. 102). It is currently being tested in Phase I clinical trials as a subunit vaccine candidate against tuberculosis.
Cytokines	The use of recombinant human cytokines, such as IL-2 or IL-12, might prove useful in combination with other adjuvants to induce tailored immune responses and might, in the case of IL-15, enhance the function and longevity of $CD8^+$ T cells (Ref. 103).

[a]Adjuvants that are currently licensed for use in humans.

Abbreviations: CpG-ODN, oligodeoxynucleotides containing CpG motifs; IL, interleukin; MF59®, microfluidised emulsion 59; QS21, Quillaja saponaria component 21.

persons needs consideration. Several vaccination trials have indicated benefits of modifying vaccination strategies. For instance, a decreased response and therefore a shortened duration of protective immunity following booster immunisation is a characteristic feature of old age; thus, shortened vaccination intervals might be another strategy to counteract the accelerated

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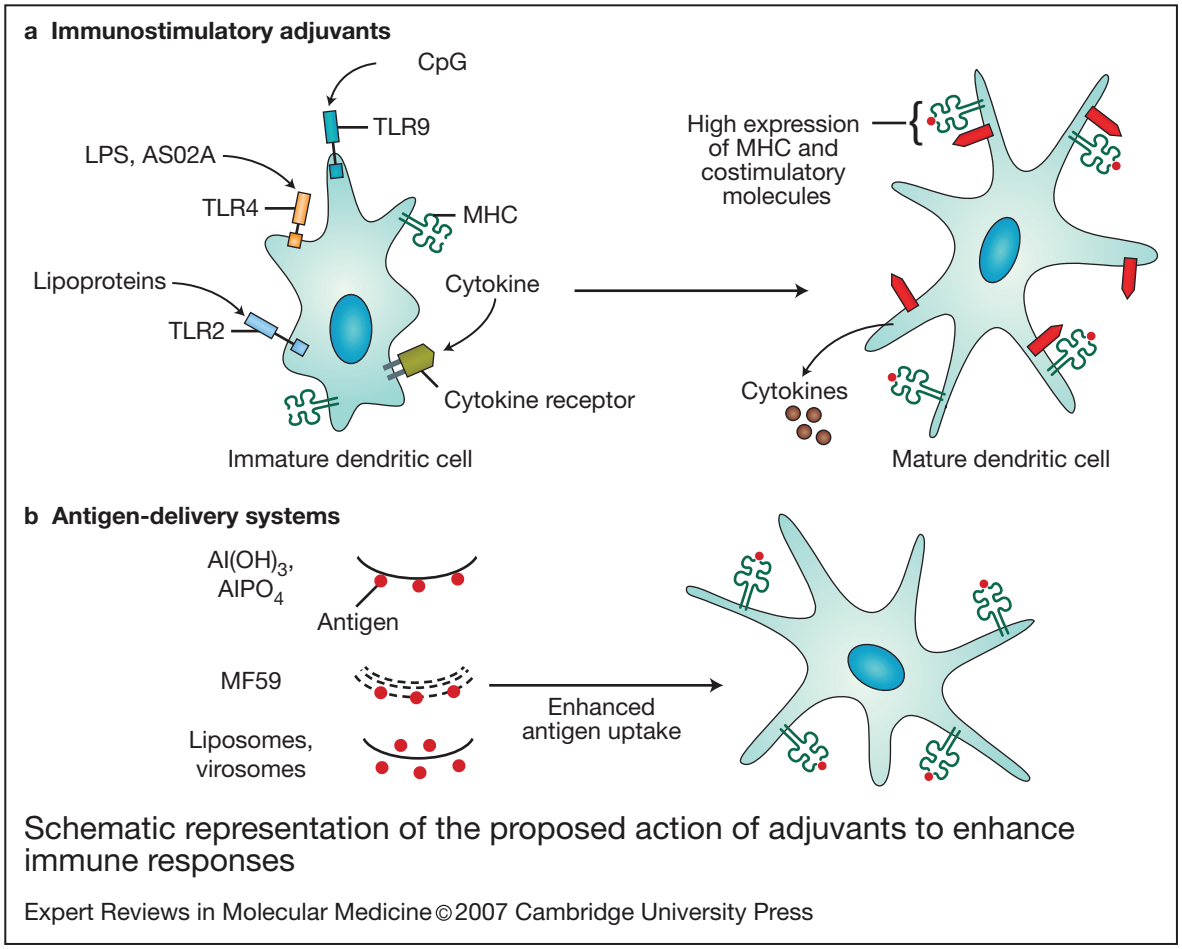


Figure 2. Schematic representation of the proposed action of adjuvants to enhance immune responses. (a) Several immunostimulatory adjuvants induce Toll-like receptor (TLR)- or cytokine-receptor-mediated signalling of immature dendritic cells (DCs). This leads to the development of mature DCs, which produce distinct cytokines and have a high expression of major histocompatibility complex (MHC) and costimulatory molecules. The antigen delivered with the vaccine is therefore potently presented, which leads to strong B- and T-cell responses (not shown). (b) By contrast, aluminium salts, MF59® and liposomes enhance antigen presentation in the absence of costimulatory molecules. This leads to strong B-cell and type 2 T-cell responses (not shown). Abbreviations: LPS, lipopolysaccharide; MF59, microfluidised emulsion 59.

loss of protective antibody levels after vaccination in elderly persons (Fig. 3). Moreover, vaccination coverage among elderly persons is still low in many European countries (Ref. 84).

Some significant progress has been made in vaccination of the elderly, such as the development of adjuvanted influenza vaccines (Ref. 85) or a live attenuated herpes zoster vaccine (Ref. 86) that show an increased immunogenicity in elderly persons. There are also several conjugated pneumococcal vaccines, improved live attenuated tuberculosis vaccines as well as live attenuated and cell-culture-based influenza vaccines in different clinical trials. Some vaccines that target new pathogens have also entered clinical trials such as a conjugated vaccine against *Staphylococcus aureus* and live attenuated or adjuvanted subunit vaccines against CMV.

The decreased protective effect of vaccination in elderly persons has been correlated with the presence of CMV latency. CMV infection is ubiquitous in nature and seroprevalence rates are high in adults, particularly in the developing world. Olsson et al. (Ref. 87) reported a strong correlation between CMV carrier status and the deterioration of immune system observed in old age. Trzonkowski et al.

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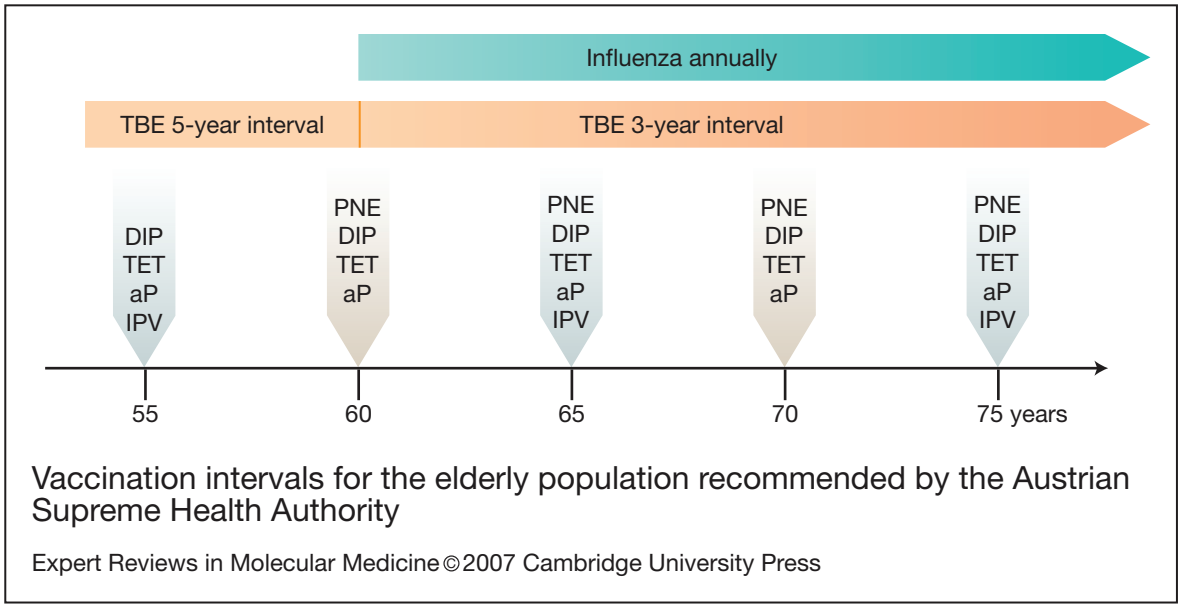


Figure 3. Vaccination intervals for the elderly population recommended by the Austrian Supreme Health Authority. As a result of the high age-associated morbidity and mortality from influenza and pneumonia, annual influenza vaccination and 5-yearly pneumonia (PNE) vaccination is recommended in Austria for all persons over 60 years of age. In light of the age-related alterations in immunity, in persons of more than 60 years of age, booster vaccinations for diphtheria (DIP), tetanus (TET) and pertussis (aP) are recommended at 5-year intervals, tick-borne encephalitis (TBE) at 3-year intervals, and polio (IPV) at 10-year intervals (Refs 20, 68, 70).

(Ref. 88) assessed the association between prior CMV infection and effectiveness of vaccination against influenza and concluded that CMV carrier status might contribute to unresponsiveness to influenza vaccine in elderly individuals. It has been suggested that vaccination against CMV could prevent chronic CMV infection, which may be a cause for the accelerated exhaustion of the T-cell repertoire. Other parameters such as sex (Ref. 89), obesity (Ref. 90) and the composition of the T-cell repertoire (Refs 49, 50, 91) have also been proposed to contribute to the decline of the protective effect of vaccination in old age and therefore could be potential targets for increasing vaccine efficacy.

Concluding remarks

Average life expectancy is continuously rising in all developed countries, but is accompanied by an incremental burden of age-associated illnesses, which lead to disability, loss of mobility and independence. Among them, infectious diseases are becoming an increasingly important issue, especially given the challenge to public health from newly emerging and re-emerging infectious diseases. As a result of age-related changes in the immune system, the frequency of infectious diseases is characteristically increased in the elderly population. Additionally, infections are more severe and have distinct features with respect to clinical manifestation and treatment in this age group.

Vaccinations constitute the most cost-effective medical procedure for preventing morbidity and mortality caused by infectious diseases, but age-related alterations within the immune system hamper vaccine efficacy. A proper understanding of immunological memory and how it is affected by the ageing process could provide the basis for the development of effective vaccination programmes that are able to fully protect the elderly population from infectious diseases and thus reduce the incidence of infectious diseases as well as their consequences within this fragile age group. A reduction of the incidence and severity of infectious diseases is expected to have a strong impact not only on the quality of life of individuals but also on society, by reducing the number of hospitalisations and subsequently the demand for specialised medical care.

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Further reading, resources and contacts

Publications

Welsh, R.M. et al. (2004) Immunological memory to viral infections. Annu Rev Immunol 22, 711-43
This review provides an excellent overview of how T- and B-cell memory is generated in response to virus infections and how these cells respond when the host is infected again by similar or different viruses.

Hodes, R.J. (2005) Aging of the immune system. Curr Opin Immunol 17, 455-456
Editorial overview of a themed issue on ageing and the immune system. The concept papers presented in this issue provide highly informed perspectives from leaders in the field of immunological ageing.

Linton, P.J. and Dorshkind, K. (2004) Age-related changes in lymphocyte development and function. Nat Immunol 5, 133-139
This review provides an excellent overview of age-related changes in lymphocyte development and function.

Kovaiou, R.D. and Grubeck-Loebenstein, B. (2006) Age-associated changes within $CD4^+$ T cells. Immunol Lett 107, 8-14
This summarises cellular and molecular aspects of ageing $CD4^+$ T cells.

Herndler-Brandstetter, D. et al. (2006) Immunizations in the elderly: do they live up to their promise? Wien Med Wochenschr 156, 130-141
This review outlines the impact of infectious diseases on the aged population and summarises the progress made in the field of vaccinations of the elderly.

Jefferson, J. et al. (2005) Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet 366, 1165-1174
Here the authors extensively review the evidence of efficacy and effectiveness of influenza vaccines in individuals aged 65 years and older.

Van Loveren, H. et al. (2001) Vaccine-Induced antibody responses as parameters of the influence of endogenous and environmental factors. Environmental Health Perspect 109, 757-64
A review of the factors that affect responses to vaccination.

Levine, M.M. and Sztein, M.B. (2004) Vaccine development strategies for improving immunization: the role of modern immunology. Nat Immunol 5, 460-464
This commentary on preventive vaccines against infectious agents identifies the desirable characteristics a vaccine should have and discusses strategies to achieve them.

Westendorp, R.G. (2006) What is healthy aging in the 21st century? Am J Clin Nutr 83 (Suppl), 404S-9S
This is a comprehensive review of the current issues influencing healthy ageing.

Websites

The World Health Organization (WHO) site on ageing:

http://www.who.int/ageing/en/

The work of the WHO department of Immunization, Vaccines and Biologicals ranges from vaccine research to immunisation services delivery:

http://www.who.int/immunization/en/index.html

The Centers for Disease Control and Prevention (CDC) of the Department of Health and Human Services (HHS) is the principal agency in the US government for protecting the health and safety of Americans. Useful information on vaccines and immunisations can be found in the health and safety topics:

http://www.cdc.gov/

The Institute for Biomedical Aging Research (IBA) of the Austrian Academy of Sciences aims to prevent age-related functional losses and diseases by analysing the ageing process at a cellular and molecular level:

http://www.iba.oeaw.ac.at/

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Features associated with this article

Figures

Figure 1. Schematic representation of the immune response to a pathogen.
Figure 2. Schematic representation of the proposed action of adjuvants to enhance immune responses.
Figure 3. Vaccination intervals for the elderly population recommended by the Austrian Supreme Health Authority.

Tables

Table 1. Attributes of different vaccine types.
Table 2. Assortment of approved and potential future vaccine adjuvants.

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