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Recommendation of Vaccine in Elderly

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ABSTRACT

Vaccination is an efficient strategy to prevent infectious diseases. For healthy aging, the immune response of the elderly against various infectious diseases has to be improved. In the elderly, most vaccines are less immunogenic and therefore less efficient because of age-related changes of the innate and adaptive immune system, which is collectively termed as immunosenescence. By using appropriate vaccination that is recommended for elder individuals we can achieve the goal of healthy aging in this population. In this review, we analyze the impact of age-associated factors such as immunosenescence, inflammation, the immune response of the elderly to vaccination and the recommended vaccines for the elderly.

INTRODUCTION:

The increase in the elderly (>65 years) population is largely because of modern medicines, nutrition, and hygiene, so that older adults enjoy greater longevity and greater quality of life. The protection of these patients from infection is of major importance. Vaccination is the most efficient measure to prevent infectious diseases. The rational use of vaccines can contribute clearly to achieve the goal of healthy aging in this population.

As per the WHO definition for healthy aging, it is defined "as the process of developing and maintaining the functional ability that enables well being in older age". With increasing life expectancy, the global population ages, and the number of persons older than 60 years of age is expected to double by 2050, reaching 2.1 billion[1]. The rate of growth in the elderly population is more in low and middle-income countries compared to developed nations [2]. As per the study conducted it is estimated that by 2050 more than two-thirds of the elderly population of the world will reside in developing countries [2]. In the elderly, most vaccines are less immunogenic and therefore less efficient the elderly because of age-related changes of the innate and adaptive immune system, which is collectively termed as immunosenescence [3].

With increasing age, the hematopoietic stem cells differentiate into myeloid progenitors at the expense of lymphoid lineage. Therefore the number of innate immune cells of the myeloid lineage does not decrease with age. The number of natural killer cells is even increased with age, which functions cytotoxicity and cytokine production. Chemotaxis is disturbed in neutrophils, monocytes/macrophages, and dendritic cells and impaired microbicidal function as a consequence of reduced phagocytosis and superoxide production are also observed in neutrophils as wells as monocytes/macrophages. The reduced phagocytic capacity of dendritic cells also leads to impaired antigen presentation and activation of adaptive immune responses. In addition to this, there are also age-related alternations in toll-like receptor (TLR) signaling, which are of particular interest in the context of vaccination, as many novel adjuvants target different TLRs.

One of the indications of immunosenescence is the gradual replacement of functional thymic tissue by fat which leads to a reduction in newly generated naïve T cells in peripheral blood and lymphoid organs. Concomitantly, antigen-experienced T cells accumulate with increasing age, T cell compartment is skewed more towards highly differentiated effector T cells bearing large clonal expansions and thereby limiting the T cell repertoire. Highly

differentiated effector T cells produce less interleukin 2 and more proinflammatory cytokines such as interferonγ and tumor necrosis factor α contributing together with cells of the innate immune system to the low-grade proinflammatory background observed in the elderly. Elderly persons often lack high-affinity antibody responses to infectious agents and vaccination, which can partly be explained by a defect in T cell help but is also the result of intrinsic defects within the B cell pool. It has been demonstrated that B cell generation in the bone marrow is affected at several developmental stages leading to a decreased output and therefore diminished the number of naïve B cells in mice and that antigen-experienced B cells accumulate at the same time. However, changes in B cell subpopulation with age are more controversially discussed for humans. Defects in class- switch recombination and somatic hypermutation have been described and molecularly characterized in old mice, but are mechanistically less clear for humans.

This review will introduce the vaccines that are recommended currently for the elderly with a particular focus on the effect of age on immunogenicity and efficacy and novel vaccines developed specifically for this age group.

Need of vaccines in elderly:

Immune function wanes in all adults, whether healthy or sick- as they age into their fifth decade and beyond. Their bodies become weak at recognizing and stopping pathogens and the ability to develop and maintain immunity declines. Vaccines are an effective way of stimulating and heightening immune response and boosting waning immunity in older adults. Seasonal influenza, pneumococcus infection, and reactivation of varicella-zoster virus are three harmful pathological conditions that cause significant morbidity and mortality in old people more than young adults [4]. Most currently used vaccines are less immunogenic and effective in the elderly compared to young adults [5]. This is due to fact that most of the vaccines are specifically designed for children and young adults with an immune system that is different from the elderly people, where the physiological immunosenescence coexists with the personal history of infections and vaccinations [5].

The value of vaccines for the elderly relies not only on their efficacy but also on effectiveness that is the measure of the capacity of generally improving the health status of the older individual avoiding other related diseases [4]. The two essential characteristics of aging are immunosenescence and inflammaging.

Immunosenescence:

Immunosenescence is defined as the changes in the immune system associated with age. With aging the immune system of the elderly is remodeled with fewer naïve cells and an increase in dysfunctional memory cells, as well as primary lymphoid organ involution and altered innate immune response leading to greater susceptibility to infectious diseases and replaced responses to vaccination [4]. Due to aging, the network of several events results in the complex biological process of different cell types and tissues which include alternation in gene regulation and protein expression signaling pathways and biological networks [4]. Different cell populations such as neutrophils, macrophages, monocytes, and dendritic cells are altered and their functions are reduced [4]. With aging, both the innate and adaptive immune response decreases, leading to reduced response to vaccination [4].

Immunosenescence involves involution of the primary lymphoid organ(bone marrow, thymus) with reduction of B and T cell progenitors, dysfunctional memory cells, due to chronic antigenic stimulation, reduction of phagocyte functions (such as chemotaxis and phagocytosis) with a concomitant increased level of proinflammatory cytokine production. All these changes can result in a decline in the immune response to vaccination [4].

Inflammaging:

Inflammaging is the long term result of the chronic physiological stimulation of the innate immune system, which can become damaging during aging. Inflammaging strongly affects the susceptibility of the elderly subject to communicable disease and on the immune response to vaccination. Therefore it should be taken into consideration for the design of vaccine formulations including adjuvant [4]. Several processes that contribute to inflammation include a variety of organs and tissue damage due to the increase of cell death rate and senescence, mitochondrial dysfunction, inflammasome and NFKB activation, circulating miRNAs, chronic infections such as CMV, hormones and reactive oxygen species(ROS) [6], age related changes of nutrition, metabolism, α-galactosylated N-glycans and host gut microbiota dysbiosis [8].

In recent studies, it has been reported that studies conducted on mouse gut microbiota exert its regulatory effects not only on intestinal immunity but also on systemic immune response and systemic T cell subset populations [4].

Currently recommended vaccines for elderly:

Influenza vaccines:

Influenza is a viral infection, caused by influenza viruses belonging to the orthomyxoviridae family, which contains four genera- influenza virus A, B, C, and the go to viruses [9]. Type A influenza viruses are further classified into subtypes according to the combination of various virus surface proteins [10]. Among many subtypes of influenza A viruses, influenza A/HINI and A/H3N2 circulate among humans [10]. Type C influenza cases occur less frequently than A and B [10]. The data available in the disease burden for influenza are studied well in developed countries. In India and other southeast countries, there is a lack of exact data relating to the impact of influenza [10]. According to WHO surveillance the vaccination for influenza virus is necessary for persons aged 50 years and above annually, which results in a reduction in hospitalization due to seasonal influenza and there is also decreased mortality in vaccinated elderly persons aged 65 years and above. Annual influenza vaccination is considered the most effective strategy to prevent influenza.

Two types of influenza vaccines, killed or inactivated and live attenuated vaccines are available commercially [2]. For vaccination in elderly persons, only inactivated vaccines are recommended. The live vaccine is recommended for healthy persons between 2- 50 years [2]. The inactivated vaccine contains two strains of influenza A virus (H3N2 and H1N1) and one influenza B virus [2]. The strains used for the preparation of vaccines are antigenically equivalent to the currently circulating strains [2]. The trivalent inactivated influenza vaccine (TIV) contains antigens from two subtypes of influenza A strain and one strain from influenza B [4]. The frequent observation of mismatch between the vaccine component and the circulating strain promotes the vaccine manufacturer to produce quadrivalent inactivated influenza vaccine (QIV) which contains two A strain and two B strains [11]. Due to antigenic drift, influenza viruses are constantly changing which results in the modification of surface protein hemagglutinin and neuraminidase [4]. For this reason, the vaccine composition has to be adapted annually to integrate viral strain as similar as possible to the epidemic strain [4].

Administration of TIV: a single dose of 0.5 ml given IM and should be revaccinated every year [12]. It should be stored between 2-8º C and not to be frozen [12]. LAIV should not be used in person with the following condition or situation: the history of severe allergic reaction to any vaccine component or to a previous dose of any influenza vaccine, the person with a cochlear implant, cerebrospinal fluid- oropharyngeal communication, close contacts or

caregivers of severely immunosuppressed persons who require a protected environment, pregnancy, received influenza antiviral medication within the previous 48 hours [13]. Several adverse events are seen after immunization it includes systemic side effects such as fever, malaise, localized pain, tenderness, allergic reactions (hives, angioedema, and anaphylaxis) [12]. Guillain Barre Syndrome is a rare side effect of vaccination [12]. If any patient with a history of Guillain Barre Syndrome within 6 weeks of the previous dose of influenza vaccine, they should not be vaccinated unless vaccination benefits outweigh risks for severe complications from influenza [13].

Several strategies have been applied to improve the influenza vaccine for the elderly. These include the increase of vaccine antigen from 15 to 60 µg of HA protein perdose [14], the administration of vaccine by intradermal versus intramuscular route [15] and the formulation of the inactivated vaccine with oil-in-water emulsion adjuvant [16]. The intradermal vaccination with trivalent IIV stimulates the dermal population of specialized dendritic cells (DC) such as Langerhans cells, that are efficient in antigen presentation [17] and increases also the recruitment of DC and macrophage precursors from the bloodstream [4]. Results collected after the intradermal administration demonstrate that intradermal influenza vaccines can produce better immune response than TIVs at a full antigen dosage in the elderly, and an equivalent response at a lower antigen dose in the healthy adult dose and patient with severe chronic diseases or immunocompromised [18].

The MF59 adjuvant trivalent inactivated vaccine was developed to increase the immune response of the elderly to influenza vaccination; MF59 is an oil-in-water emulsion [4]. The efficacy findings analyzed in younger, healthy seniors may not apply to older and frail seniors because of advanced age and the presence of serious medical conditions associated with immune function decline [4].

Pneumococcal vaccine:

Pneumonia, an infection of lungs affect millions of people, adult, above 65 years and children below 5 years are particularly at risk [2]. Pneumonia can be caused by viruses, bacteria and fungi. A common cause of viral pneumonia is influenza and respiratory syncytial virus and among bacterial pneumonia, a most common cause is *Streptococcus pneumonia* [2]. It is the most commonly isolated agent of community-acquired pneumonia and also causes invasive pneumococcal disease [4]. The presence of comorbidities and immunosenescence increase the susceptibility to community-acquired pneumonia in the elder population [19]. There are

two types of vaccines available for the prevention of pneumococcal pneumonia [2]. Pneumococcal polysaccharide vaccine 23 valent (PPV23) and pneumococcal conjugate vaccine 13 valent (PCV13) [2], the PPV23 contains 25µg of the purified capsular polysaccharide of 23 different serotypes of S.pneumoniae [2]. The immune response is very poor in children less than two years. So they are commonly used in older adults but polysaccharide induces IgM dominated antibody responses without adequate immunological memory, as they are T cell-independent antibody responses and does not show booster effect upon repeated vaccination.

A heptavalent, protein conjugated pneumococcal vaccine (PCV7) which has been used for childhood vaccinations, is also capable of eliciting memory responses in children and allows booster vaccinations [3]. It is more immunogenic in the elderly as compared with PPV and also shows a booster effect in second vaccination [20]. Later conjugate vaccine containing 13 serotypes have been developed and replaced PCV 7. PCV 13 has also been licensed for persons over 50 years of age [21]. PCV 13 can elicit a T-dependent response producing high titers of functional antibodies and thus being recommended in the elderly population [4]. It has proven safe and immunogenic in the elderly in the presence of comorbidities [22].

As per the US Centers for Disease Control and Prevention, routine vaccination in persons with age 65 years or older have to be immunized with 1 dose of PPSV23, if PPSV23 was administered before age 65 years administer 1 dose PPSV 23 at least 5 years after the previous dose [13]. Because the vaccine is reported to be very effective (93%) in preventing disease in immune-competent adults aged below 55 years and also those over 85 years of age [9]. Studies have shown that the vaccine has a protective effect against invasive diseases and reduces the number of hospital admission and overall death in elderly age group [9]. For those who are immunocompetent 1 dose of PCV 13 have to be administered based on shared clinical decision making, if both PCV13 and PCV 23 are to be administered, PCV13 should be administered first [13]. PCV13 and PPSV23 should not be administered during the same visit. In special situations, age 19 through 64 years with chronic medical conditions (chronic heart (excluding hypertension), lung or liver disease, diabetes), alcoholism or cigarette smoking; 1 dose of PPSV23 can be administered [13]. Age 19 years or older with immune compromising conditions or anatomical or functional asplenia, 1 dose PCV 13 followed by 1 dose of PPSV23 at least 8 weeks later, then another dose PPSV23 at least 5 years after previous PPSV23, at age 65 years or older, administer 1 dose PPSV23 at least 5 years after most recent PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older) [13].

Herpes zoster:

Another infection to which the geriatric age group is susceptible is varicella-zoster infection. The primary infection which occurs in childhood and manifests as chickenpox and lives long latency is established afterward [1]. Partial reactivation of the virus probably occurs frequently throughout life, but it is controlled by virus-specific T cell responses. In the absence of sufficient immunological control due to immunosuppression or immunosenescence, viral reactivation can lead to herpes zoster(shingles) [23]. In a fraction of patients, acute episodes of herpes zoster are followed by postherpetic neuralgia (PHN), which is characterized by long-lasting severe pain [1]. The vaccines available for the herpes zoster virus are zoster live (ZVL) and zoster recombinant (RZV) which are used in the elderly as vaccination against herpes zoster. In children variable vaccines (VAR) are used to produce an immune response against chickenpox.

In 2006, a single shot immunization with an attenuated live vaccine against herpes zoster has been licensed for use in older adults [1]. This vaccine induces T cell and antibody responses [24]. The antibody response to the second dose of vaccine more than 10 years after the first dose was similar to the first response, but cellular immune responses were higher after the booster dose [1]. The recommended vaccine has been licensed in 2017 and demonstrated an efficacy of about 97% in preventing herpes zoster in 50 years of age or older adults [25]. The immunological analysis revealed that the recombinant vaccine, containing ASO1B adjuvant, elicits a robust and persistent memory response in older adults [26].

As per the US Centers for Disease Control and Prevention, the routine vaccination of zoster vaccine for age 50 years or older; 2 dose series RZV, 2- 6 months apart (minimum interval; 4 weeks, repeat dose if administered too soon), regardless of previous herpes zoster or history of ZVL vaccination (administer RZV at least 2 months after ZVL) [13]. For age 60 years or older, 2 dose series RZV, 2-6 months apart (minimum interval 4 weeks; repeat if administered too soon) or 1 dose ZVL if not previously vaccinated. RZV preferred over ZVL (if previously received ZVL, administer RZV at least 2 months after ZVL) [13]. In severe immunocompromising conditions (including HIV infection with CD4 count < 200 cell/µL), ZVL is contraindicated; recommended use of RZV under review [13].

Tetanus:

Tetanus is another infection whose incidence is higher among the elderly than the adults and children [10]. In developed countries, tetanus has become a geriatric disease with the majority of cases occurring in persons aged 60 years or older [27]. CDC recommends all elderly adults (older than or equal to 65 years), should have completed a primary series of diphtheria and tetanus toxoids and thereafter should receive a booster dose every 10 years. In India, the API expert group recommends T dap for all adults not immunized earlier [9]. For adults in the age group of 18 to 64 years who have completed their childhood vaccination schedule, a booster dose of Td vaccine is indicated once 10 years till the age of 65 years [9].

As per US CDC, routine vaccination of tetanus, diphtheria, and pertussis vaccine; is recommended for a person who is not receiving Tdap previously at or after age 11 years; 1 dose of Tdap, then Td or Tdap every 10years [13]. In special situations where subjects previously did not receive primary vaccination series for tetanus, diphtheria, pertussis; at least 1 dose Tdap followed by 1 dose Tdap or Td atleast 4 weeks after Tdap and another dose Td or Tdap 6-12 months after last Td or Tdap every 10 years thereafter [13].

Issues regarding immunization in elderly age group:

The elderly population is increasing largely by the use of modern medicines, nutrition and hygiene. These populations are needed to be protected from infectious diseases, due to immunosenescence and inflammation. Geriatric immunization can substantially reduce the burden of disease and mortality in this population. Several barriers to improving the rate of adult vaccination include professional and public education, policy issues, vaccine efficacy and safety measures, cost and reimbursement.

The main factor is the lack of knowledge about immunization and its necessity in the elderly population is the main fact. Several resources are available now like fact sheets, posters, and videos. These CDC materials can be downloaded, copied and distributed to patients. These materials include all the information about the need for vaccine administration, uses, adverse effects, who should use the vaccines, its complications, contraindications. The family members can also play a major role in vaccinating the older population for good health by consulting with the health care professionals. Policy issues are based on issue surveillance to collect data from health facilities regarding incidence, hospitalization, disability and mortality from a given disease. The lacks of epidemiological data on the incidence rate and deaths

attributable to vaccine-preventable disease among the geriatric age group have to be monitored [28]. Vaccine safety and efficacy is another factor that is a barrier for adult vaccination. The safety of a new vaccine is assessed by clinical trials before it is used in post-marketing surveillance. As per the studies conducted, no sufficient data are available from developing countries regarding the effectiveness of several vaccines used in India. Even though the results of published data from developed countries on the effectiveness of these vaccines are also controversial. Therefore more studies are needed for decisions about introducing these vaccines in developing countries.

CONCLUSION:

Immunization is a pillar of healthy aging. Immunosenescence contributes to decreased immune responses after vaccination of elderly individuals. Several vaccines against influenza, *S.pneumoniae*, herpes zoster, tetanus, diphtheria and pertussis are available for the elderly. The first step towards optimal protection of the elderly is the comprehensive use of existing vaccines. Vaccination recommendations for adults and the elderly differ from country to country. Taking regional differences such for example, epidemiological parameters into account are of course necessary for optional vaccine recommendation. However, further studies have to be conducted by the clinicians about the use of vaccination in the elder population and should communicate with the older patients about the threat posed by vaccine-preventable diseases and imperative to accept appropriate vaccinations.

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CONFLICT OF INTEREST:

There is no conflict of interest.

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ABBREVIATION:

Toll-like receptor	TLR
Reactive oxygen species	ROS
Trivalent Inactivated Influenza Vaccine	TIV
Quadrivalent Inactivated influenza Vaccine	QIV
Live Attenuated Influenza Vaccine	LAIV
Dendritic Cells	DC
Pneumococcal Polysaccharide Vaccine 23	PPV23
Pneumococcal Conjugate Vaccine 13	PCV13
Conjugated Pneumococcal Vaccine 7	PCV 7
Zoster Live	ZVL
Zoster Recombinant	RZV
Variable Vaccine	VAR

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