European Review for Medical and Pharmacological Sciences 2021; 25: 6719-6730

COVID-19 vaccines and vaccination program for aging adults

C. CHAKRABORTY[1], A.R. SHARMA[2], M. BHATTACHARYA[3], G. AGORAMOORTHY[4], S.-S. LEE[2]

[1]Department of Biotechnology, School of Life Science and Biotechnology, Adamas University, Barasat, Kolkata, West Bengal, India
[2]Institute for Skeletal Aging & Orthopedic Surgery, Hallym University-Chuncheon Sacred Heart Hospital, Chuncheon-si, Gangwon-do, Republic of Korea
[3]Department of Zoology, Fakir Mohan University, Vyasa Vihar, Balasore, Odisha, India
[4]College of Pharmacy and Health Care, Tajen University, Yanpu, Pingtung, Taiwan

Chiranjib Chakraborty and Ashish Ranjan Sharma contributed equally

Abstract. – OBJECTIVE: COVID-19 vaccines have developed quickly, and vaccination programs have started in most countries to fight the pandemic. The aging population is vulnerable to different diseases, also including the COVID-19. A high death rate of COVID-19 was noted from the vulnerable aging population. A present scenario regarding COVID-19 vaccines and vaccination program foraging adults had been discussed.

MATERIALS AND METHODS: This paper reviews the current status and future projections till 2050 of the aging population worldwide. It also discusses the immunosenescence and inflammaging issues facing elderly adults and how it affects the vaccinations such as influenza, pneumococcal, and herpes zoster.

RESULTS: This paper recommends clinical trials for all approved COVID-19 vaccines targeting the elderly adult population and to project a plan to develop a next-generation COVID-19 vaccine.

CONCLUSIONS: The review has mapped the COVID-19 vaccination status from the developed and developing countries for the elderly population. Finally, strategies to vaccinate all elderly adults globally against COVID-19 to enhance longevity has been suggested.

Key Words:
Aging adults, COVID-19 vaccines, Vaccination program, Vaccination status, Vaccination strategies.

Introduction

The COVID-19 pandemic has infected over 140 million people worldwide with 3 million deaths, particularly the aging population[1,2]. Vaccination has enabled to contain the spread of various infectious diseases[3]. The immunization procedure has been stated as one of the top achievements of public health in the 1900s. It has eradicated several viral and infectious diseases[4]. Keeping this in mind, the COVID-19 vaccination received a priority throughout the world. Several countries have started the fastest vaccination program to end the pandemic. The vaccination program was rolled out after the end of the clinical trial in December 2020. The USA was the first to initiate the vaccination program[5]. Several Asian countries[6,7] have also followed the vaccination programs, including India, China, etc.. Simultaneously, the vaccine was rolled out in several low to middle-income countries such as Zimbabwe, South Africa, etc.[8,9]. The first shot of the COVID-19 vaccine was given to people in the USA using Moderna developed mRNA vaccine in March 2020, which started the clinical trial for the COVID-19 vaccine[10].

The aging population is vulnerable to several diseases, including infectious diseases. It has been noted that age is a significant risk factor in severe disease, and the elderly are more prone to infections[11]. Infections are the fundamental reason for mortality and morbidity in the aging population[12]. Various studies[13,14] have shown that the aging population is more vulnerable to COVID-19. They are at risk for severe COVID-19 and death. Chen et al[15] hypothesized that inflammaging and immunosenescence play an essential role in augmenting the susceptibility towards the severe COVID-19 in aging adults. The estimat-

Corresponding Authors: Chiranjib Chakraborty, Ph.D; e-mail: drchiranjib@yahoo.com
Sang-Soo Lee, MD, Ph.D; e-mail: 123sslee@gmail.com

ed mortality rate is 18% in aging adults of more than 76 years of age due to the infection of this disease[16]. Koff and Williams[17] asked for more research towards the COVID-19 research aging populations in terms of immunity perspective. Vaccination has emerged as an effective, safe, and valuable procedure for the elderly community[18]. Therefore, COVID-19 vaccination is urgently needed for the aging adults to protect this vulnerable community.

This review presents the current scenarios and future projections of the COVID-19 vaccination program for the aging population.

Regional and Global Trends

The aging population is one of the most discussed health subjects in the world. By 2030, the world expects to have over one billion aging adults accounting 13% of the total global population[19]. Scientists have tried to map the regional and global trends of the aging population. According to the United Nations, the number of aging adults (≥60 years of age) is projected to increase by 116.2% from 2017 to 2050. Over the next few decades, Africa's aging adults will grow threefold from 69 million to 226 million during 2017-2050. The Latin Americas region will follow Africa. Similarly, in Asia, the number of aging adults is expected to amplify two folds (Figure 1)[20]. However, older men and women are changed geographically, and scientists have mapped their mortality pattern and disease burden globally[20,21]. Understanding the present and future projections of an aging population will help proper resource planning and disease prevention strategies, such as vaccination planning.

Aging Population in COVID-19 Scenario

Studies found an age-related gradient for the risk or severity of disease, hospitalization, and mortality[22]. The high mortality rate for the elderly with 83.7% for over 70 years and 16.2% below 69 years in developed countries[23]. In China, over 50% of COVID-19 deaths were reported among people aged above 70 years[24]. In the USA, the case-fatality rate was 27% for people over 85 years[25] (Figure 2). Comorbidities and multimorbidity are other risk factors for the aging population during the COVID-19 infection. It was observed that comorbidities are the signs found in 32 to 60% of the cases in the aging population. It includes the general population having COVID-19 with diabetes (approximately 16% to 20% patients), COVID-19 with hypertension (among about 15-41% patients), and COVID-19 with cardiovascular disease and chronic obstructive pulmonary disease (among approximately

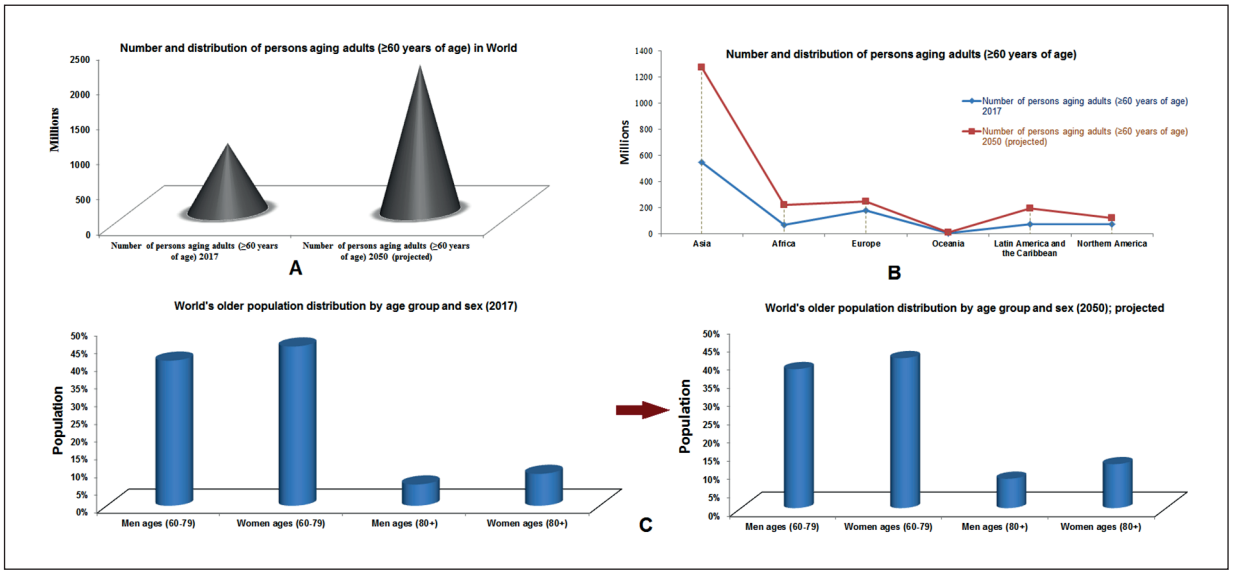

Figure 1. Distribution of aging people (>60 years of age) in the world in 2017 and 2050 (projected). **A,** Aging people in the world in 2017 and 2050 (projected). **B,** Regional distribution of aging people in the world in 2017 and 2050 (projected). **C,** Age and sex-wise distribution of aging people in the world in 2017 and 2050 (projected).

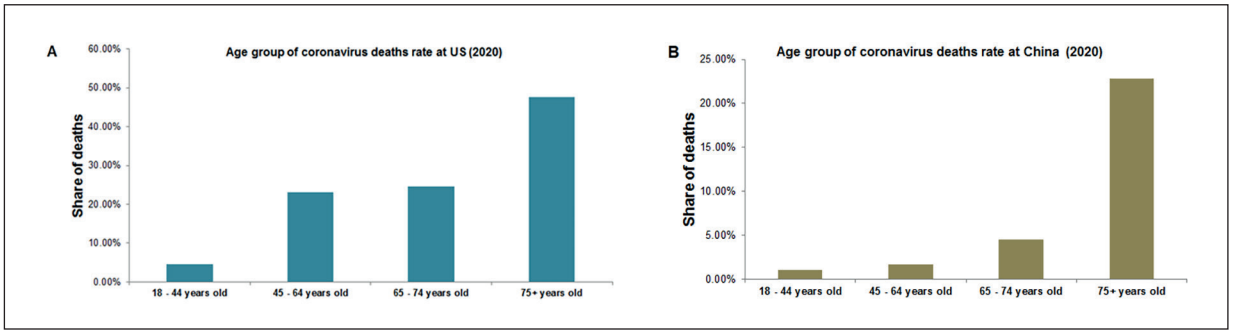

Figure 2. Age-wise COVID-19 death rate in different countries. **A,** Age-wise COVID-19 death rate in the USA. **B,** Age-wise COVID-19 death rate in China.

14-15% patients)[16,26,27]. Multimorbidity is another cause of mortality affecting nearly 75% of the elderly above 70 years in several countries[28]. It is also one of the leading causes of mortality in the aging populations during COVID-19[24].

Immunosenescence and Inflammaging Impact on Vaccination

Immunosenescence is a decline in the different processes of the immune system due to age progression. The immune system of aging people is remodeled. In reality, the physiological and immune system activities decrease and hamper different organs and systems[29,30]. Several complex changes have been observed in the adaptive immune system (Figure 3).

Along with age progression, the subsets of naive T cells (Th0 cell), memory T cells, and effector T cells are affected. At the same time, T regulatory (T reg) is also affected in elderly adults[31,32]. It has been noted that there is a decrease in total naive T cells in elderly adults. Conversely, there is an increase in the memory T cells[33-36]. Memory cell subsets accumulation is noted due to the aging process. Sometimes, memory T cell inflation is noted, which may occur due to chronic viral infections[37]. This phenomenon has been recorded during the infection of Human cytomegalovirus in elderly patients, where the generation of particular CD^{8+} T cells indicates the infection[38].

At the same time, age progression affects B cell responses where the production and efficiency of naïve B cells are decreased. Similarly, the production and efficiency of memory B cells are also reduced[35,39]. Recently, Frasca and Blomberg[39] have reported that aging causes imperfection of B cells, and thus the B cell defect can cause reduce antibody responses after the influenza infection.

Scientists have given the "autoantibodies" production theory due to the losing efficiency

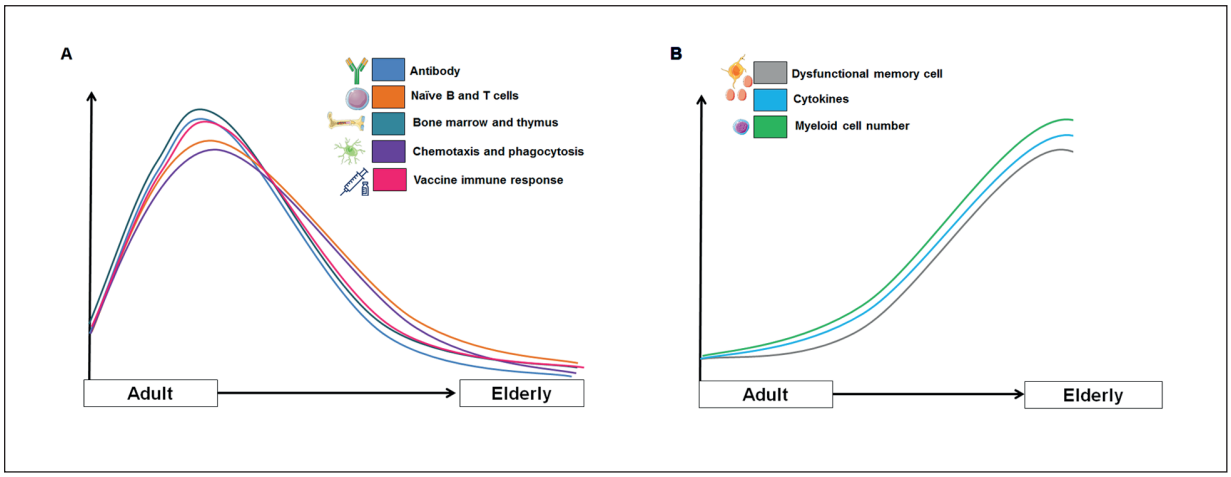

Figure 3. Immunosenescence and inflammaging associated with aging, and it can affect vaccination. **A,** Immunosenescence phenomena in elderly adults. **B,** Inflammaging phenomena in elderly adults.

of the immune system. The production of autoantibodies was observed due to two significant factors: the decline in naïve T cells and the gathering of clonal T cells during the aging process. Like augmented CD^{5+} B lymphocytes, several other age-related factors may play a significant role in autoantibody production in the elderly population[40,41].

Therefore, there is a change in the innate immunity and adaptive immunity associated with aging. The innate immune may overtake the changed adaptive immune system in elderly adults due to immunosenescence[42], leading to the reduced response to the vaccination process. Therefore, the vaccination process is a real challenge for elderly people' inflammaging and immunosenescence. Studies are essential to understand the efficacy and immunity pattern of the vaccine in elderly adults. Therefore, designing and developing a vaccine for elderly adults considering the factors such as inflammaging and immunosenescence are critical.

Present Suggested Vaccines for the Elderly Adults

For the elderly adults, the influenza vaccine, pneumococcal vaccine, and varicella-zoster vaccines have been recommended by different countries (Table I).

Influenza Vaccine

Influenza causes morbidity and mortality in the elderly, especially over 65 years. Annually, 4 to 5 million severe influenza cases leading to mortality have been reported in elderly adults[32,43,44]. There are two types of influenza vaccines, such as the live attenuated and inactivated. An inactivated vaccine is available in the market entitled trivalent form – it contains antigens from three different strains. It uses antigens from two subtypes of influenza A strain and one influenza B strain, and the two subtypes of influenza A are H1N1 and H3N2. Hence, the trivalent vaccine uses strain-A/H1N1, strain-A/H3N2, and strain-B[32,45], and it has been licensed by different countries and used for elderly adults. Based on WHO surveillance data, quadrivalent vaccines were developed using two different influenza B strains along with two subtypes of influenza A[45,46]. However, the composition of the influenza vaccine alters concerning the currently circulating influenza strains.

The trivalent inactivated vaccine was evaluated in the age group of 65 years or more with a randomized clinical study in Italy. It showed a much lower rate of (25%) hospitalization due to adjuvant used in the vaccine[46,47]. However, the influenza vaccination for elderly adults is still debatable, and for example, Trucchi et al[48] doubt the benefits of influenza vaccination in adults.

Table I. Different recommended vaccines for elderly adults by different countries.

Vaccine name	Different country	Remarks
Pneumococcal vaccine	Finland	Vaccine suggested for above 65 years old people
	Germany	Vaccine recommended for above 60 years old individuals
	Denmark	Vaccine acclaimed for individualsage above 65 years
	Hungary	Vaccine for Individuals having age above 50 years
	Spain	Vaccine suggested for the peoples of age above 65 years
	Italy	Vaccine for the aged elderly having above 65 years age
Herpes zoster vaccine	Austria	Vaccine for the persons having age above 50 years
	France	Vaccine for the age groups 65-75 years older
	Sweden	Vaccine for the individuals having age above 65
	Italy	Vaccine acclaimed for personsabove 65 years older age
	USA	Vaccine recommended for above 60 years old persons
	UK	Vaccine for the aged elderly above 70 years
Influenza vaccine	Belgium	Vaccine suggested for above 65 age groups
	Czech Rep.	Vaccine for all adults individuals
	Hungary	Vaccine for peoples with age above 60 years
	Netherlands	Vaccine recommended for above 60 years old individuals
	Portugal	Vaccine acclaimed for individualsage above 65 years
	Spain	Vaccine suggested for above 65 age groups

Pneumococcal Vaccine

It has been observed that pneumococcal disease affects the elderly causing morbidity and mortality[49]. The chance of occurrence of this disease increases with chronic medical conditions, especially in immune-compromised older patients. Different reports[50] have been published to support this from the UK and the USA. Due to the high burden of this disease among elderly adults, the pneumococcal vaccine is recommended[51-53]. There are two types of pneumococcal vaccines: pneumococcal polysaccharide vaccine (PPV) and pneumococcal conjugate vaccine (PCV). Four kinds of PPV were developed and marketed, which are PCV7, PCV9, PCV10 and PCV13[53,54]. In the USA, two vaccines are marketed: Prevnar 13 (PCV13) and Pneumovax 23 (PPSV23). PCV13 is a 13-valent pneumococcal conjugate vaccine that contains five serotypes found in PPSV23, seven serotypes in PCV7, and one specific serotype that is not available neither in PCV7 nor PPSV23. PCV13 has each polysaccharide type of 2.2 μg quantity other than the serotype 6B, and the amount of serotype 6B is about 4.4 μg, which contains conjugated to the CRM197 (nontoxic mutant of diphtheria toxin) and adjuvant (aluminum phosphate with a quantity of 0.125 mg)[32,54].

Similarly, the PPSV23 or 23-valent pneumococcal polysaccharide vaccine was developed in 1983, protecting 80-90% against pneumococcal disease (capsular serotype). The PPSV23 formulation contains different 23 capsular serotypes of the bacteria, and it contains 25 μg purified polysaccharide (pneumococcal polysaccharide) from every serotype[55,56]. Recently, some countries have recommended PPV23 (23-valent pneumococcal conjugate vaccine) for high-risk persons, such as elderly adults and children. However, researchers have raised controversy about the vaccination in high-risk groups of persons. For example, Papadatou and Spoulou have urged more research on these vaccines, such as PCV13/PPV23, to vaccinate high-risk individuals[57]. However, low to moderate effectiveness using PPV23 against pneumococcal pneumonia in elderly adults (65 years or more aged population) has been observed. The PPV23 has shown little functional activity with comparatively low antibody titers and weak immunogenic[58].

On the other hand, PCV13 has also been recommended in elderly adults since it shows proficiency in producing high titers of functional antibodies and can elicit a T-dependent response[54]. However, there is a decrease in the pneumococcal disease observed after the pneumococcal vaccination among elderly adults[59].

Herpes Zoster Vaccine

Herpes zoster (HZ) affects many elderly adults, and millions are infected worldwide[60,61]. Two-thirds of the infections occur above the age of 50 in Australia and USA[62,63]. Two different HZ vaccines have been approved, which include the live attenuated vaccine and the subunit vaccine. Merck markets the live attenuated vaccine in the brand name, Zostavax.

Similarly, the subunit zoster vaccine has been marketed by GSK in the brand name of Shingrix. The US-FDA has approved the attenuated active virus HZ vaccine for older adults. In the live attenuated vaccine, the Oka strain (approximately 20.000 PFU) is used to manufacture the vaccine, and the strain (VZV strain) was initially isolated in Japan. The vaccine has been tested in sizeable elderly adult populations.

Another recombinant subunit vaccine contains the recombinant VZV glycoprotein E (gE) (approximately 50 μg) – it is a significant component of the viral surface glycoprotein. To formulate this vaccine, a liposome-based AS01B adjuvant has been used[64,65]. In 2017, this recombinant vaccine was licensed, and the efficacy was demonstrated to be 97% against HZ (among the age group of 50 years and above)[66]. A recombinant zoster vaccine was applied in the USA among adults aged 50 and above in a recent clinical trial, and it showed 90% efficacy in the clinical trial[67].

Approved COVID-19 Vaccines' Efficacy

Several COVID-19 vaccines have been approved and authorized for users from different countries, and they include Pfizer-BioNTech vaccine, Oxford-AstraZeneca vaccine, Moderna vaccine, Sputnik V, BBIBP-CorV, Johnson & Johnson vaccine, CoronaVac, Ad5-nCoV, BBV152, EpiVacCorona, ZF2001, CoviVac, and WIBP-CorV. It is essential to understand the vaccine's impact on elderly adults. Also, the efficacy of all the approved vaccines in the older population has to be investigated to document B and T cell responses. Therefore, rapid clinical trials should be performed using the vaccines for the elderly[68]. All studies should emphasize evaluating the vaccine efficacy for older people due to immunosenescence and their adaptive

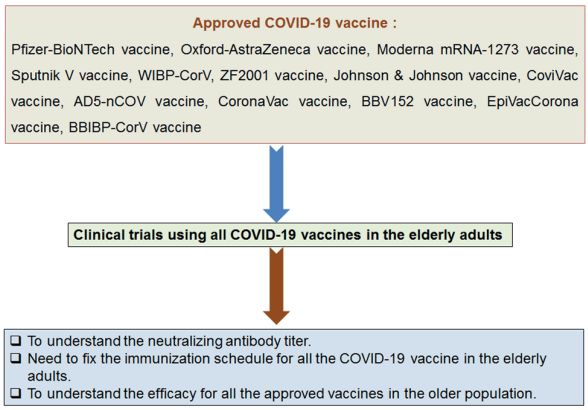

Figure 4. A plan to understand the efficacy and other factors of approved COVID-19 vaccines in elderly adults.

immune response decline. We need to understand the neutralizing antibody titer and fix the immunization schedule and the booster dose for all the COVID-19 vaccines in elderly adults (Figure 4). It is also necessary to unfold the immunity condition during COVID-19 in aging populations. COVID-19 vaccination may decrease hospitalization, morbidity, and mortality. At the same time, COVID-19 vaccination will provide a healthier life for elderly adults while increasing life expectancy[17]. Reports show that vaccines are less protecting against diseases faced by the elderly adults than younger adults, especially in the case of Influenza vaccines[69,70]. Therefore, the COVID-19 vaccination protectiveness in the elderly population has to be thoroughly investigated. Sadarangani et al[71] tried to understand COVID-19 effectiveness of possible vaccines through activity and age-structured mathematical model formation to stop the infection or disease in the elderly population. They performed simulations in an infectious class (0.01% of the population) and used SEIR (susceptible-exposed-infected recovered) model with two infectious and two exposed compartments. They have recommended performing the trials of COVID-19 vaccine candidates using elderly adults to monitor the vaccine effectiveness. The US-CDC performed a survey with the 417 participants using the Pfizer-BioNTech and Moderna vaccine to understand the effects of vaccination. Among them, 230 people were taken as the control group and 187 people were case-patients. In this study, it was noted that half of the patient age were more than 75 years old. The survey found that the elderly above 65 years who were fully vaccinated had 94% less chance for hospitalization once infected with COVID-19[72]. However, more studies are needed in this direction.

Some clinical trials of BCG vaccines have been performed among elderly adults to understand the vaccine's immunogenicity and safety in elderly adults for the COVID-19, and the clinical trials include NCT04383574, NCT04475302, NCT04417335, and NCT04441047 NCT04470609.

Several countries have tried to vaccine their most vulnerable community using different COVID-19 vaccines. Dhama et al[73] described the risk factors associated with the elderly for the infection of this virus and the progress of COVID-19 vaccinations in other countries, especially developing countries.

Need to Develop a Next-Generation COVID-19 Vaccine for Elderly Adults

Scientists need to develop the next-generation COVID-19 vaccine considering different factors such as proper antigen selection for the COVID-19 vaccine, adjuvant selection considering biological and immunological aging, and next-generation vaccine delivery for the elderly and unfold the immune responses of older people as shown in Figure 5.

Role of Immunoinformatics, Bioinformatics, and Vaccine Genomics in Antigen Selection

For the next-generation COVID-19 vaccine development work, immunoinformatics and bioinformatics will play a crucial role. Using immunoinformatics, bioinformatics and bioinformatic tools, scientists have developed COVID-19 vaccine contracts using significant epitopes from S protein and other structural proteins. The immunoinformatics can help identify the B cell epitopes and T cell epitopes and common epitopes selection and design the successful vaccine construct[74-76].

Proper Adjuvant Selection for Elderly

An adjuvant can enhance and adequately titillating the immune responses to the vaccine antigen[77,78]. It is essential to select the vaccine adjuvant for the elderly during vaccine design because specific adjuvant needs to be tailored for older adults. Several vaccine adjuvants are currently using vaccines that are highly used for elderly

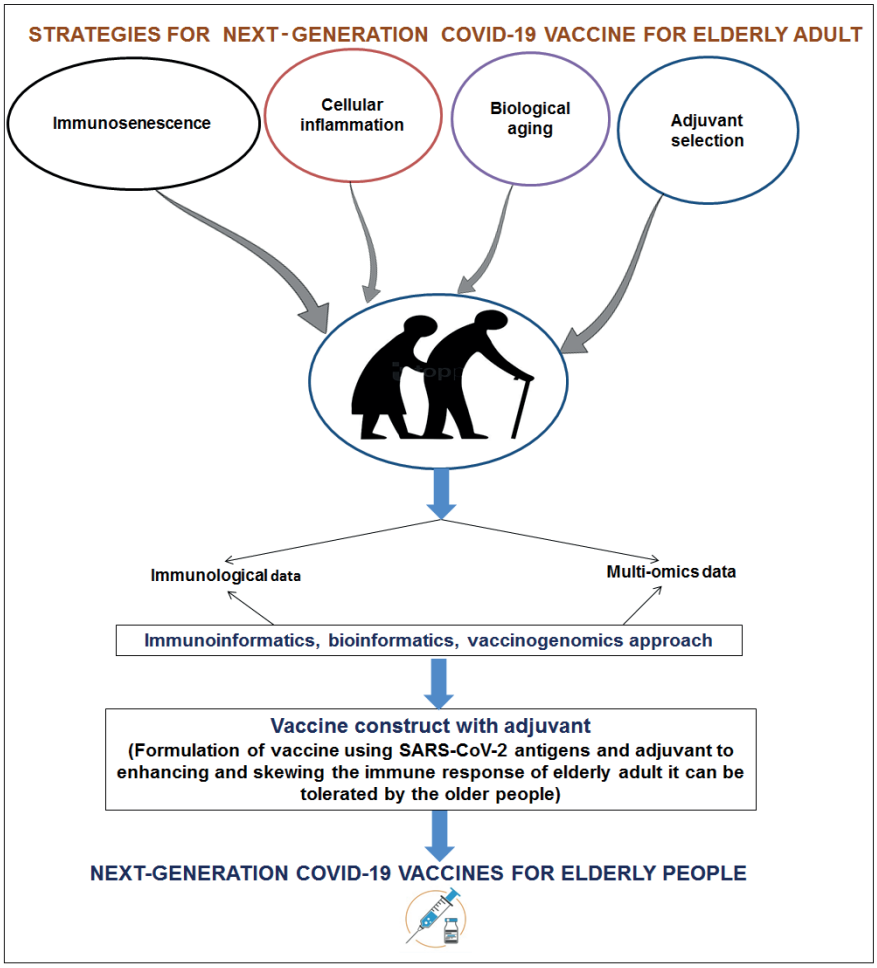

Figure 5. A graphical representation that illustrates the next-generation COVID-19 vaccine development for older people.

people, such as influenza vaccines, HZ vaccine, and pneumococcal vaccine. Influenza vaccines use AS03 and MF59 adjuvant, while the recombinant HZ vaccine uses AS02 adjuvant. Also, the pneumococcal vaccine uses aluminum phosphate as an adjuvant[32]. It has been noted that AS03 can strongly induce the regulatory genes, which are programming chemokines and inflammatory cytokines[79]. Similarly, AS01 contains two immunostimulant molecules which are the QS-21 and MPL. This is a liposome-based vaccine adjuvant[80]. Therefore, it is crucial to select a proper adjuvant for the next-generation COVID-19 vaccine, balancing the immune system's inflammatory status and immune stimulation for elderly people.

Antigen Delivery System For Next-Generation Vaccine

Scientists have to select proper antigen delivery for the next-generation COVID-19 vaccine. Several novel adjuvants can be used as the delivery system, such as ASO2A ASO4, GM-CSF, and CPG 7907. These molecules are in a clinical trial[81]. This type of adjuvants-based antigen delivery system can be used. The elderly vaccine can utilize other delivery systems that are in use. One example is virosomes. It is used for influenza vaccines. Virosomes are small round lipid membrane vesicles and unilamellar[82], and this type of delivery system can be used for the next-generation COVID-19 vaccine.

Unfold the Immune Responses of Older People

It is necessary to understand the immune responses of older people while developing the next-generation vaccine. The next-generation vaccine should stimulate a broad range of B cell and T cell responses among this population. It is necessary to understand the neutralizing an-

tibody titer by the next-generation vaccine and fix the immunization schedule for older people.

COVID-19 Vaccination Status Among Elderly Adults

The COVID-19 vaccination program has started throughout the world. All countries have started to vaccinate their populations along with elderly adults. The Kaiser family foundation (KFF.org) has reported the vaccination progress in elderly adults in the USA, showing that about 22 states have vaccinated at least one-third of the elderly adults. North Carolina and Florida have immunized more elderly adults (aged 65 and above). These two states have 45 to 49% of elderly adults who have been immunized fully. Arizona and South Carolina states have also fully vaccinated 44% of the elderly adults[83].

Until 21 March 2021 in the UK, over 25% are fully vaccinated above the age of 80, and nearly 3.5% in the age group of 75-79[84]. In Phase 1, the elderly adults are the priority groups for vaccination[85]. India, China, and Singapore have also started to vaccinate elderly adults on a priority basis. Every low and middle-income country needs to vaccinate them on an urgent basis. However, vaccination status report for this population is not available for elderly adults both from the developed and under-developed countries, which need to be updated regularly by the WHO.

COVID-19 Vaccination Strategies for the Elderly Adults

COVID-19 pandemic has created global urgency of immunization programs against the virus, especially elderly adult immunization. In a recent article, Chakraborty et al[68] appealed for COVID-19 vaccination to elderly adults urgently, and all nations should take necessary steps in this direction. Soiza et al[86] also appealed for vaccinating the elderly adults, and a national vaccination program should be earmarked for this population as the earliest recipients of COVID-19 vaccines. They have noted that most of the COVID-19 vaccine trials have usually excluded older people. Therefore, safety and efficacy are still needed to understand COVID-19 vaccines in elderly adults. Privor-Dumm et al[87] develop a roadmap for an action plan of the COVID-19 for elderly adults. The immunization roadmap for the action plan includes creating a framework for COVID-19 vaccine immunization and then refining the framework. Moreover, we need to understand the burden of disease in elderly adults and the impact of adult immunization. The researchers appealed to evaluate the social, economic benefits of COVID-19 vaccination for older adults.

Scientists must assess the capabilities of the country and the approaches to support COVID-19 immunization policies for older adults. The manufacturers should develop the COVID-19 vaccine adequately to address the needs of COVID-19 immunization for older adults. It is also needed

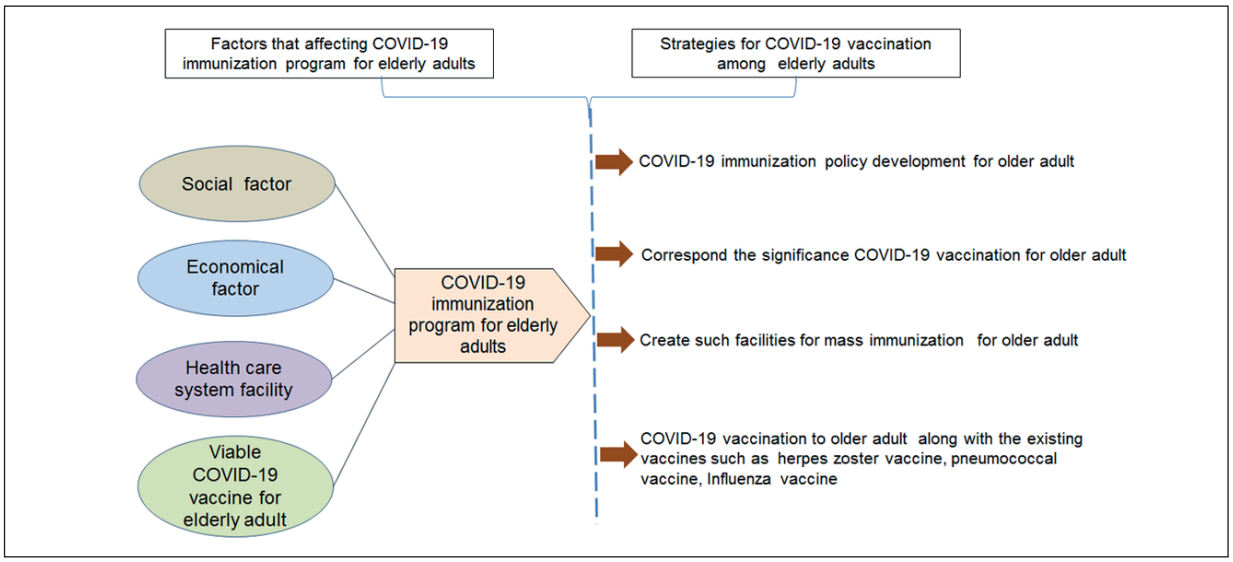

Figure 6. A schematic diagram that shows the COVID-19 vaccination strategies among elderly adults.

that the healthcare workers, policymakers, public workers, and politicians correspond to the significance of COVID-19 vaccination for older adults. Many low and middle-income countries do not have adequate facilities for COVID-19 vaccination for older adults. So, they must create such facilities on an emergency basis for immunization. At the same time, COVID-19 immunization programs for older adults can be included immediately for COVID-19 vaccination along with the existing vaccines such as herpes zoster vaccine, pneumococcal vaccine, and influenza vaccine (Figure 6).

Conclusions

Elderly adults are more vulnerable to COVID-19 and are more prone to hospitalization and deaths than other age groups. People with co-morbid conditions, such as heart diseases, lung problems, and diabetes are more prone to death. Therefore, vaccination is urgently needed for this group of people. It has been noted that developed countries have already started to vaccinate them. Nevertheless, agewise, vaccination data for older adults are not available, so they should publish the data immediately.

An immunoinformatics approach can provide the next-generation vaccine for elderly adults. This approach can offer a new next-generation vaccine with alternative epitopes using the Wuhan SARS-CoV-2 strain and the major variants of concerns (VOC), stimulating the immune system for the elderly adults against COVID-19. Immunologists, immunoinformaticians, and vaccinologists should work in this direction to develop a next-generation vaccine for elderly adults. The world should not delay and must protect the elderly first in the battle of the pandemic. Every nation can prepare an immediate action plan for vaccine-induced protection to the elderly from the next wave of the COVID-19 pandemic. In this way, society can protect them with healthier extended life.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

This study was supported by Hallym University Research Fund and by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2020R1C1C1008694 & NRF-2020R1I1A3074575).

Data Availability Statement

All the data, score and model are generated or used during the study appear in the submitted article.

Authors' Contribution

Chiranjib Chakraborty: Conceptualization, investigation, writing- original draft preparation, reviewing and editing, and supervision. Ashish Ranjan Sharma: Validation, formal analysis, visualization, reviewing and editing. Manojit Bhattacharya: Validation, formal analysis, visualization. Govindasamy Agoramoorthy: Review & editing. Sang-Soo Lee: Review and funding acquisition.

References

1) Morens DM, Fauci AS. Emerging pandemic diseases: How we got to COVID-19. Cell 2020; 182: 1077-1092.
2) Saha A, Sharma AR, Bhattacharya M, Sharma G, Lee SS, Chakraborty C. Response to: Status of Remdesivir: Not Yet Beyond Question! Arch Med Res 2021; 52: 104-106.
3) Kabir KA, Tanimoto J. Dynamical behaviors for vaccination can suppress infectious disease–A game theoretical approach. Chaos Solitons Fractals 2019; 123: 229-239.
4) Greenwood B. The contribution of vaccination to global health: past, present and future. Philos Trans R Soc Lond B Biol Sci 2014; 369: 20130433.
5) Painter EM, Ussery EN, Patel A, Hughes MM, Zell ER, Moulia DL, Scharf LG, Lynch M, Ritchey MD, Toblin RL, Murthy BP, Harris LQ, Wasley A, Rose DA, Cohn A, Messonnier NE. Demographic characteristics of persons vaccinated during the first month of the COVID-19 vaccination program--United States, 14 December, 2020-14 January, 2021. MMWR Morb Mortal Wkly Rep 2021; 70: 174-177.
6) Bagcchi S. The world's largest COVID-19 vaccination campaign. Lancet Infect Dis 2021; 21: 323.
7) Leng A, Maitland E, Wang S, Nicholas S, Liu R, Wang J. Individual preferences for COVID-19 vaccination in China. Vaccine 2021; 39: 247-254.
8) Choi EM. COVID-19 vaccines for low-and middle-income countries. Trans R Soc Trop Med Hyg 2021; 115: 447-456.
9) Dzinamarira T, Nachipo B, Phiri B, Musuka G. COVID-19 Vaccine Roll-Out in South Africa and Zimbabwe: Urgent Need to Address Community Preparedness, Fears and Hesitancy. Vaccines 2021; 9: 250.
10) Cohen J. With record-setting speed, vaccinemakers take their first shots at the new coronavirus. Science 2020; 31 March. doi: 10.1126/science.abb9996
11) Kline KA, Bowdish DM. Infection in an aging population. Curr Opin Microbiol 2016; 29: 63-67.

12) Esme M, Topeli A, Yavuz BB, Akova M. Infections in the elderly critically-Ill patients. Front Med (Lausanne) 2019; 6: 118.

13) Mahase E. Covid-19: Why are age and obesity risk factors for serious disease? BMJ 2020; 371: m4130.

14) Clark A, Jit M, Warren-Gash C, Guthrie B, Wang H, Mercer SW, Sanderson C, McKee M, Troeger C, Ong KL, Checchi F, Perel P, Joseph S, Gibbs PH, Banerjee A, Eggo RM. Centre for the Mathematical Modelling of Infectious Diseases COVID-19 working group. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. Lancet Glob Health 2020; 8: e1003-e17.

15) Chen Y, Klein SL, Garibaldi BT, Li H, Wu C, Osevala NM, Li T, Margolick JB, Pawelec G, Leng SX. Aging in COVID-19: Vulnerability, immunity and intervention. Ageing Res Rev 2021; 65: 101205.

16) Dhama K, Patel SK, Kumar R, Rana J, Yatoo MI, Kumar A, Tiwari R, Dhama J, Natesan S, Singh R, Harapan H. Geriatric population during COVID-19 pandemic: problems, considerations, exigencies and beyond Head Title: Geriatrics during COVID-19 pandemic. Front Public Health 2020; 8: 54198.

17) Koff WC, Williams MA. Covid-19 and immunity in aging populations—a new research agenda. N Engl J Med 2020; 383: 804-805.

18) Verma R, Khanna P, Chawla S. Vaccines for the elderly need to be introduced into the immunization program in India. Hum Vaccin Immunother 2014; 10: 2468-2470.

19) Dobriansky PJ, Suzman RM, Hodes RJ. Why population aging matters: A global perspective. National Institute on Aging, National Institutes of Health, US Department of Health and Human Services, US Department of State. 2007; 1-32.

20) GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis 2018; 18: 1191-210.

21) Mathers CD, Loncar D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. PLOS Med 2006; 3: e442.

22) Holt NR, Neumann JT, McNeil JJ, Cheng AC, Unit HE, Prahan V. Implications of COVID-19 in an ageing population. Med J Aust. 2020; 382: 2081-2090.

23) Abbatecola A, Antonelli-Incalzi R. COVID-19 spiraling of frailty in older Italian patients. J Nutr Health Aging 2020; 24: 453-455.

24) Polidori MC, Sies H, Ferrucci L, Benzing T. COVID-19 mortality as a fingerprint of biological age. Ageing Res Rev 2021: 101308.

25) CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)--United States, 12 February–16 March, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 343-346.

26) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Li H, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

27) Chu DK, Pan Y, Cheng SM, Hui KP, Krishnan P, Liu Y, Ng DY, Wan CK, Yang P, Wang Q, Peiris M, Poon PL. Molecular diagnosis of a novel coronavirus (2019-nCoV) causing an outbreak of pneumonia. Clin Chem 2020; 66: 549-555.

28) Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, Glynn L, Muth C, Valderas JM. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PloS one 2014; 9: e102149.

29) Avery P, Barzilai N, Benetos A, Bilianou H, Capri M, Caruso C, Franceschi C, Katsiki N, P Mikhailidis D, Panotopoulos G, Sikora E, Tzanetakou IP, Kolovou G. Ageing, longevity, exceptional longevity and related genetic and non genetics markers: panel statement. Curr Vasc Pharmacol 2014; 12: 659-561.

30) Aiello A, Farzaneh F, Candore G, Caruso C, Davinelli S, Gambino CM, Ligotti ME, Zareian N, Accardi G. Immunosenescence and its hallmarks: how to oppose aging strategically? A review of potential options for therapeutic intervention. Front Immunol 2019; 10: 2247.

31) Fessler J, Felber A, Duftner C, Dejaco C. The impact of aging on regulatory T-cells. Front Immunol 2013; 4: 231.

32) Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D, editors. Vaccination in the elderly: the challenge of immune changes with aging. Semin Immunol 2018; 40: 83-94

33) Sridharan A, Esposo M, Kaushal K, Tay J, Osann K, Agrawal S, Gupta S, Agrawal A. Age-associated impaired plasmacytoid dendritic cell functions lead to decreased CD4 and CD8 T cell immunity. Age 2011; 33: 363-376.

34) Gupta S, Bi R, Su K, Yel L, Chiplunkar S, Gollapudi S. Characterization of naıve, memory and effector CD8+ T cells: effect of age. Exp Gerontol 2004; 39: 545-550.

35) Frasca D, Blomberg BB. Aging affects human B cell responses. J Clin Immunol 2011; 31: 430-435.

36) Salam N, Rane S, Das R, Faulkner M, Gund R, Kandpal U, Lewis V, Mattoo H, Prabhu S, Ranganathan V, Durdik J, George A, Rath S, Bal V. T cell ageing: effects of age on development, survival & function. Indian J Med Res 2013; 138: 595-608.

37) Snyder CM, Cho KS, Bonnett EL, van Dommelen S, Shellam GR, Hill AB. Memory inflation during chronic viral infection is maintained by continuous production of short-lived, functional T cells. Immunity 2008; 29: 650-659.

38) Wertheimer AM, Bennett MS, Park B, Uhrlaub JL, Martinez C, Pulko V, Currier NL, Nikolich-Žugich

D, Kaye J, Nikolich-Žugich J. Aging and cytomegalovirus infection differentially and jointly affect distinct circulating T cell subsets in humans. J Immunol 2014; 192: 2143-2155.

39) Frasca D, Blomberg BB. Aging induces B cell defects and decreased antibody responses to influenza infection and vaccination. Immun Ageing 2020; 17: 1-10.

40) Prelog M. Aging of the immune system: a risk factor for autoimmunity? Autoimmun Rev 2006; 5: 136-139.

41) Watad A, Bragazzi NL, Adawi M, Amital H, Toubi E, Porat B-S, Shoenfeld Y. Autoimmunity in the elderly: insights from basic science and clinics-a mini-review. Gerontology 2017; 63: 515-523.

42) Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, Witkowski JM, Franceschi C. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? Front Immunol 2018; 8: 1960.

43) Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, Fukuda K. Influenza-associated hospitalizations in the United States. JAMA 2004; 292: 1333-1340.

44) Ahmad FB, Cisewski JA, Miniño A, Anderson RN. Provisional mortality data—united states, 2020. MMWR Morb Mortal Wkly Rep 2021; 70: 519.

45) 45. Weinberger B. Vaccines for the elderly: current use and future challenges. Immun Ageing 2018; 15: 1-8.

46) Trucchi C, Alicino C, Orsi A, Paganino C, Barberis I, Grammatico F, Canepa P, Rappazzo E, Bruzzone B, Sticchi L, Ansaldi F. Fifteen years of epidemiologic, virologic and syndromic influenza surveillance: a focus on type B virus and the effects of vaccine mismatch in Liguria region, Italy. Human vaccines & immunotherapeutics. Hum Vaccin Immunother 2017; 13: 456-463.

47) Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, Boldori L, Caramaschi F, Gattinoni A, Malchiodi G, Rothman KJ. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. Am J Epidemiol 2012; 176: 527-533.

48) Trucchi C, Paganino C, Orsi A, De Florentiis D, Ansaldi F. Influenza vaccination in the elderly: why are the overall benefits still hotly debated? J Prev Med Hyg 2015; 56: E37.

49) Melegaro A, Edmunds W, Pebody R, Miller E, George R. The current burden of pneumococcal disease in England and Wales. J Infect 2006; 52: 37-48.

50) van Hoek AJ, Andrews N, Waight PA, Stowe J, Gates P, George R, Miller E. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect 2012; 65: 17-24.

51) Koul PA, Chaudhari S, Chokhani R, Christopher D, Dhar R, Doshi K, Ghoshal A, Luhadiya SK, Mahashur A, Mehta R, Nene A, Rahaman M, Swarnakar R. Pneumococcal disease burden from an Indian perspective: Need for its prevention in pulmonology practice. Lung India 2019; 36: 216-225.

52) Van Buynder P, Booy R. Pneumococcal vaccination in older persons: where are we today? Pneumonia 2018; 10: 1-5.

53) Malik A, Taneja D. Conjugate pneumococcal vaccines: Need and choice in India. Indian J Community Med 2013; 38: 189-191.

54) van Deursen AM, van Houten MA, Webber C, Patton M, Scott DA, Patterson S, Sidhu M, Drews W, Gruber WC, Emini EA, Grobbee DE, Bonten MM, Sanders EAM. Immunogenicity of the 13-valent pneumococcal conjugate vaccine in older adults with and without comorbidities in the community-acquired pneumonia immunization trial in adults (CAPiTA). Clin Infect Dis 2017; 65: 787-795.

55) Green C, Moore CA, Mahajan A, Bajaj K. A simple approach to pneumococcal vaccination in adults. J Glob Infect Dis 2018; 10: 159-162.

56) Daniels CC, Rogers PD, Shelton CM. A review of pneumococcal vaccines: current polysaccharide vaccine recommendations and future protein antigens. J Pediatr Pharmacol Ther 2016; 21: 27-35.

57) Papadatou I, Spoulou V. Pneumococcal vaccination in high-risk individuals: are we doing it right? Clin Vaccine Immunol 2016; 23: 388-395.

58) Suzuki M, Dhoubhadel BG, Ishifuji T, Yasunami M, Yaegashi M, Asoh N, Ishida M, Hamaguchi S, Aoshima M, Ariyoshi K, Morimoto K. Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study. Lancet Infect Dis 2017; 17: 313-321.

59) Plotkin S, Jackson LA, Janoff EN. Pneumococcal vaccination of elderly adults: new paradigms for protection. Clin Infect Dis 2008; 47: 1328-1338.

60) John AR, Canaday DH. Herpes zoster in the older adult. Infect Dis Clin North Am 2017; 31: 811-826.

61) Schmader K. Herpes zoster in older adults. Clin Infect Dis 2001;32:1481-1486.

62) Yawn BP, Saddier P, Wollan PC, Sauver JLS, Kurland MJ, Sy LS, editors. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc 2007; 82: 1341-1319.

63) Cunningham AL, McIntyre P, Subbarao K, Booy R, Levin MJ. Vaccines for older adults. BMJ. 2021; 372: n188.

64) Gagliardi AM, Andriolo BN, Torloni MR, Soares BG. Vaccines for preventing herpes zoster in older adults. Cochrane Database Syst Rev 2016; CD008858.

65) Gagliardi AM, Silva BNG, Torloni MR, Soares BG. Vaccines for preventing herpes zoster in older adults. Sao Paulo Med J 2014; 132: 255.

66) Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang S-J, Levin MJ, McElhaney JE, Poder A, Puig-Barberà J, Vesikari T. Efficacy of an adjuvanted herpes zoster subunit

vaccine in older adults. N Engl J Med 2015; 372: 2087-2096.

67) Sun Y, Kim E, Kong CL, Arnold BF, Porco TC, Acharya NR. Effectiveness of the recombinant zoster vaccine in adults aged 50 and older in the United States: a claims-based cohort study. Clin Infect Dis 2021; ciab121.

68) Chakraborty C, Sharma AR, Bhattacharya M, Agoramoorthy G, Lee SS. All Nations Must Prioritize the COVID-19 Vaccination Program for Elderly Adults Urgently. Aging Dis 2021; 12: 688-690.

69) Andrew MK, Bowles SK, Pawelec G, Haynes L, Kuchel GA, McNeil SA, McElhaney JE. Influenza vaccination in older adults: recent innovations and practical applications. Drugs Aging 2019; 36: 29-37.

70) Dhakal S, Klein SL. Host factors impact vaccine efficacy: implications for seasonal and universal influenza vaccine programs. J Virol 2019; 93: e00797-19.

71) Sadarangani M, Raya BA, Conway JM, Iyaniwura SA, Falcao RC, Colijn C, Coombs D, Gantt S. Importance of COVID-19 vaccine efficacy in older age groups. Vaccine. 2021;39:2020-2023.

72) CDC. Fully Vaccinated Adults 65 and Older Are 94% Less Likely to Be Hospitalized with COVID-19. 2021; 404: 639-3286

73) Dhama K, Patel SK, Natesan S, Vora KS, Iqbal Yatoo M, Tiwari R, Saxena SK, Singh KP, Singh R, Malik YS. COVID-19 in the elderly people and advances in vaccination approaches. Hum Vaccin Immunother 2020; 16: 2938-2943.

74) Bhattacharya M, Sharma AR, Patra P, Ghosh P, Sharma G, Patra BC, Lee SS, Chakraborty C. Development of epitope-based peptide vaccine against novel coronavirus 2019 (SARS-COV-2): Immunoinformatics approach. J Med Virol 2020; 92: 618-631.

75) Bhattacharya M, Sharma AR, Patra P, Ghosh P, Sharma G, Patra BC, Saha RP, Lee SS, Chakraborty C. A SARS-CoV-2 vaccine candidate: In-silico cloning and validation. Inform Med Unlocked 2020; 20: 100394.

76) Chakraborty C, Sharma AR, Bhattacharya M, Sharma G, Lee S-S. Immunoinformatics approach for the identification and characterization of T cell and B cell epitopes towards the peptide-based vaccine against SARS-CoV-2. Arch Med Res 2021; 52: 362-370.

77) Coffman RL, Sher A, Seder RA. Vaccine adjuvants: putting innate immunity to work. Immunity 2010; 33: 492-503.

78) Pulendran B, Arunachalam PS, O'Hagan DT. Emerging concepts in the science of vaccine adjuvants. Nat Rev Drug Discov 2021; 20: 454-475.

79) Sarkar I, Garg R, van Drunen Littel-van den Hurk S. Selection of adjuvants for vaccines targeting specific pathogens. Expert Rev Vaccines 2019; 18: 505-21.

80) Margherita C, Collignon C, Hervé C, Aurélie C, Iain W, Sophie D, van Helden Mary J, Sheetij D, Genito CJ, Waters NC, van den Berg Robert A. Cellular and molecular synergy in AS01-adjuvanted vaccines results in an early IFNγ response promoting vaccine immunogenicity. NPJ Vaccines 2017; 2: 25.

81) Pichichero ME. Improving vaccine delivery using novel adjuvant systems. Hum Vaccin 2008; 4: 262-270.

82) Saroja C, Lakshmi P, Bhaskaran S. Recent trends in vaccine delivery systems: a review. Int J Pharm Investig 2011; 1: 64-74.

83) Meredith Freed JC, Nancy Ochieng , and Tricia Neuman. Vaccinating Older Adults in the US Against COVID-19: A Work in Progress 2021 [cited 2021]. Available from: https://www.kff.org/coronavirus-covid-19/issue-brief/vaccinating-older-adults-in-the-us-against-covid-19-a-work-in-progress/.

84) Ian Jones P. Latest UK Covid-19 vaccine figures by nation and age group 2021. Available from: https://ca.movies.yahoo.com/latest-uk-covid-19-vaccine-181631190.html.

85) Assets.publishing.service.gov.uk. UK COVID-19 vaccines delivery plan 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/951928/uk-covid-19-vaccines-delivery-plan-final.pdf.

86) Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. Age Ageing. 2021; 50: 279-283.

87) Privor-Dumm LA, Poland GA, Barratt J, Durrheim DN, Knoll MD, Vasudevan P, Jit M, Bonvehí PE, Bonanni P. A global agenda for older adult immunization in the COVID-19 era: a roadmap for action. Vaccine 2020; 39: 5240-5250.