COVID-19 vaccines and vaccination program for aging adults

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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 for aging 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. Vaccination has enabled to contain the spread of various infectious diseases. 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. 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. Several Asian countries 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. 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.

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. Infections are the fundamental reason for mortality and morbidity in the aging population. Various studies 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. hypothesized that inflammaging and immunosenescence play an essential role in augmenting the susceptibility towards the severe COVID-19 in aging adults. The estimat-
ed mortality rate is 18% in aging adults of more than 76 years of age due to the infection of this disease. Koff and Williams 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. 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. 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). However, older men and women are changed geographically, and scientists have mapped their mortality pattern and disease burden globally. 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. The high mortality rate for the elderly with 83.7% for over 70 years and 16.2% below 69 years in developed countries. In China, over 50% of COVID-19 deaths were reported among people aged above 70 years. In the USA, the case-fatality rate was 27% for people over 85 years. 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).](image-url)
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14-15% patients). Multimorbidity is another cause of mortality affecting nearly 75% of the elderly above 70 years in several countries. It is also one of the leading causes of mortality in the aging populations during COVID-19.

**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. Several complex changes have been observed in the adaptive immune system (Figure 3).

Along with age progression, the subsets of naïve 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. It has been noted that there is a decrease in total naïve T cells in elderly adults. Conversely, there is an increase in the memory T cells. 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. This phenomenon has been recorded during the infection of Human cytomegalovirus in elderly patients, where the generation of particular CD8+ T cells indicates the infection.

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. Recently, Frasca and Blomberg 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
of the immune system. The production of auto-
antibodies was observed due to two significant
factors: the decline in naïve T cells and the gath-
ering of clonal T cells during the aging process.
Like augmented CD5+ B lymphocytes, several
other age-related factors may play a significant
role in autoantibody production in the elderly
population40,41.

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 immunosenescence42, leading to
the reduced response to the vaccination pro-
cess. Therefore, the vaccination process is a real
challenge for elderly people’s inflammaging and
immunosenescence. Studies are essential to un-
derstand the efficacy and immunity pattern of the
vaccine in elderly adults. Therefore, designing
and developing a vaccine for elderly adults con-
sidering 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 vac-
cines have been recommended by different coun-
tries (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
adults32,43,44. There are two types of influenza
vaccines, such as the live attenuated and inacti-
ved. An inactivated vaccine is available in the
market entitled trivalent form – it contains anti-
gen from three different strains. It uses antigens
from two subtypes of influenza A strain and one
influenza B strain, and the two subtypes of influ-
enza A are H1N1 and H3N2. Hence, the trivalent
vaccine uses strain-A/H1N1, strain-A/H3N2, and
strain-B32,45, 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
A45,46. However, the composition of the influenza
vaccine alters concerning the currently circulat-
ing influenza strains.

The trivalent inactivated vaccine was evalu-
ated 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 vaccine46,47. However, the
influenza vaccination for elderly adults is still
debatable, and for example, Trucchi et al48 doubt the
benefits of influenza vaccination in adults.

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<thead>
<tr>
<th>Vaccine name</th>
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<tr>
<td>Pneumococcal vaccine</td>
<td>Finland</td>
<td>Vaccine suggested for above 65 years old people</td>
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<td>Germany</td>
<td>Vaccine recommended for above 60 years old individuals</td>
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<td>Denmark</td>
<td>Vaccine acclaimed for individuals age above 65 years</td>
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<td>Vaccine suggested for the peoples of age above 65 years</td>
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<td>Italy</td>
<td>Vaccine for the aged elderly having above 65 years age</td>
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<td>Herpes zoster vaccine</td>
<td>Austria</td>
<td>Vaccine for the persons having age above 50 years</td>
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<td></td>
<td>France</td>
<td>Vaccine for the age groups 65-75 years older</td>
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<td>UK</td>
<td>Vaccine for the aged elderly above 70 years</td>
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<td>Influenza vaccine</td>
<td>Belgium</td>
<td>Vaccine suggested for above 65 age groups</td>
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<td>Czech Republic</td>
<td>Vaccine for all adults individuals</td>
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<td>Spain</td>
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Pneumococcal Vaccine

It has been observed that pneumococcal disease affects the elderly causing morbidity and mortality\(^5\). The chance of occurrence of this disease increases with chronic medical conditions, especially in immune-compromised older patients. Different reports\(^5\) 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\(^5\). 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\(^5,54\). In the USA, two vaccines are marketed: Prevnar 13 (PCV13) and Pnuemovax 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)\(^3,54\).

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\(^5,56\). 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\(^5\). 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 immunogenicity\(^58\).

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\(^5,54\). 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\(^5,64,65\). 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
免疫反应的下降。我们需要理解中和抗体滴度，固定所有 COVID-19 疫苗在老年人中的免疫程序和加强剂量。对于所有 COVID-19 疫苗，图 4 中还必须解开老年群体的免疫力。COVID-19 疫苗可能减少住院、发病率和死亡率。同时，COVID-19 疫苗将为老年人提供更健康的生活，提高寿命 17。据报道，疫苗对老年人的保护作用低于年轻人，尤其是在流感疫苗方面 69,70。因此，COVID-19 疫苗在老年人群体的保护性需要彻底研究。Sadarangani et al71 尝试通过活动和年龄结构化的数学模型来理解 COVID-19 可能的疫苗的有效性。他们在感染群体（0.01% 的人口）中进行了模拟，并使用 SEIR（易感-暴露-感染-康复）模型，包含两个传染病和两个暴露 compartment。他们建议在老年人中进行 COVID-19 疫苗候选者的临床试验，以监测疫苗的有效性。

美国 CDC 进行了一项调查，参与者有 417 名使用 Pfizer-BioNTech 和 Moderna 疫苗来了解接种后的效果。其中，230 人作为对照组，187 人为病例。在这项研究中，值得注意的是，超过 75 岁的患者中，一半以上的人发现了 COVID-19 病毒。调查发现，65 岁以上的完全接种者在感染 COVID-19 后，医院住院率降低了 94%。72 然而，还需要更多的研究来支持这个方向。

一些 BCG 疫苗的临床试验在老年人中进行了，以了解疫苗的免疫原性和安全性在老年人中，COVID-19 和临床试验包括 NCT04383574, NCT04475302, NCT04417335, and NCT04441047 NCT04470609。大多数国家试图用不同类型的 COVID-19 疫苗来接种其最脆弱的社区。Dhama et al73 描述了老年人感染这种病毒的风险因素以及在其他国家，尤其是发展中国家的 COVID-19 疫苗接种的进度。
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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. It has been noted that AS03 can strongly induce the regulatory genes, which are programming chemokines and inflammatory cytokines. Similarly, AS01 contains two immunostimulant molecules which are the QS-21 and MPL. This is a liposome-based vaccine adjuvant. 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 AS02A ASO4, GM-CSF, and CPG 7907. These molecules are in a clinical trial. 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, 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-

Figure 5. A graphical representation that illustrates the next-generation COVID-19 vaccine development for older people.
COVID-19 Vaccine Immunization 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. appealed for COVID-19 vaccination to elderly adults urgently, and all nations should take necessary steps in this direction. Soiza et al. 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. 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.
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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, age-wise, 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.

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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.

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