COVID-19 Vaccines in Older Adults

Challenges in Vaccine Development and Policy Making

Chih-Kuang Liang, MD, PhD[a,b], Wei-Ju Lee, MD, PhD[a,c], Li-Ning Peng, MD, PhD[a,d], Lin-Chieh Meng, BS Pharm[e], Fei-Yuan Hsiao, PhD[e,f,g], Liang-Kung Chen, MD, PhD[a,d,h,*]

KEYWORDS

• COVID-19 • Disability • Frailty • Immunosenescence • Vaccine

KEY POINTS

- Older adults are a vulnerable group with a high need for coronavirus disease 2019 (COVID-19) vaccines, but these individuals are also more prone to the development of vaccine-related adverse events.
- Older adults with frailty, disability, dementia or living in long-term care facilities need special attention in COVID-19 vaccination programs because supporting evidence for the safety and efficacy of COVID-19 vaccines in these individuals is limited.
- The active involvement of geriatricians in vaccine development and related public-policy development is important for the success of adult vaccination strategies against COVID-19 and other communicable and noncommunicable diseases.
- The completion of a primary series of COVID-19 vaccines with a heterologous booster dose remains the best strategy to reduce the impact of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections and transmission.

[a] Center for Healthy Longevity and Aging Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan; [b] Center for Geriatrics and Gerontology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; [c] Department of Family Medicine, Taipei Veterans General Hospital Yuanshan Branch, Yi-Lan, Taiwan; [d] Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan; [e] Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan; [f] School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan; [g] Department of Pharmacy, National Taiwan University, Taipei, Taiwan; [h] Taipei Municipal Gan-Dau Hospital (Managed by Taipei Veterans General Hospital), Taipei, Taiwan
* Corresponding author. Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, No. 201, Sec 2, Shih-Pai Road, Taipei, Taiwan
E-mail address: lkchen2@vghtpe.gov.tw

Clin Geriatr Med 38 (2022) 605–620
https://doi.org/10.1016/j.cger.2022.03.006
geriatric.theclinics.com

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 and was declared a global pandemic on March 11, 2020, by the World Health Organization (WHO). By the end of 2021, there were 288,306,329 confirmed cases and 5,438,835 COVID-19–related deaths according to the WHO Coronavirus Dashboard.[1] The COVID-19 pandemic has substantially affected health care systems and societies across the world, and this impact will last longer than expected. Public health crises such as the COVID-19 pandemic and extreme weather have strong adverse impacts on vulnerable populations, such as children, the disadvantaged, frail older adults, and people with disability or dementia.[2–5] Studies have clearly shown the vulnerability of these populations when encountering a public health crisis (eg, earthquakes, extreme weather, and pandemics), and special attention and care plans are needed to tackle these challenges.[6] Older people are generally considered a high-risk population in clinical services because they are more likely to present atypical symptoms, multimorbidity, geriatric syndromes, functional limitations, and unexpected clinical outcomes.[7,8] The knowledge and clinical experiences in the treatment of older people with acute illnesses can be applied to the COVID-19 pandemic. A recent systematic review and meta-analysis included 13,624 older patients with COVID-19 and identified that approximately half of older patients with COVID-19 had severe illness, one-fifth were critically ill, and one-tenth died.[9] Because of their high disease severity and mortality risk, older people have become the priority in COVID-19 vaccination programs.

The success of COVID-19 vaccine development, together with extensive global public health efforts (face masks, hand hygiene, lockdowns, and many others), brought a glimmer of hope to the control of the COVID-19 pandemic. All countries started their vaccination plans based on the availability and access to COVID-19 vaccines, and most countries prioritized older adults and nursing home residents for vaccination because of their high risk of severe illness and mortality.[10] However, the vaccination strategies also caused some unexpected challenges, because potential vaccine-related deaths negatively influenced the willingness of many people to receive COVID-19 vaccines.[11,12] The challenges of COVID-19 vaccination in older adults involve many different issues, including multimorbidity, frailty, disability, and immunosenescence (a process of immune dysfunction that occurs with age and inflammaging), which are all important factors for COVID-19 severity, complications, and the effectiveness of vaccines.[13] Nevertheless, the proportion of older adults included in the available vaccine clinical trials is usually low. For example, only 24.8% of participants in the Moderna vaccine trial were people aged 65 years and older,[14] and only 5% of participants in the Oxford-AstraZeneca trial were people aged 70 years and older.[15] The safety, efficacy, and vaccination strategies of COVID-19 vaccines in older adults, especially frail older people, have not been well researched. Therefore, this review focuses on the challenges of COVID-19 vaccines and related policy development in older adults, with a special focus on those with frailty, disability, dementia, or living in nursing homes.

CHALLENGES OF VACCINATIONS IN OLDER ADULTS

Although vaccinations have become one of the most widely accepted preventive services in the world, and older adults, as a vulnerable population, need those preventive services most, they are also susceptible to vaccine-related adverse effects.[16] Despite all safety and efficacy concerns, vaccination remains a cost-effective approach to reduce the burden of communicable and associated noncommunicable conditions.

Experiences in vaccinations in older adults may provide some insights for COVID-19 vaccine and policy development. The development of vaccines to prevent viral infections or disease reactivation in older adults, such as influenza or herpes zoster, has shown that older adults with frailty, disability, dementia, or living in nursing homes are more susceptible to vaccine-related adverse events, and the risks may sometimes outweigh the clinical benefits.[17]

The immune systems of older people differ greatly from those of young adults and middle-aged people, especially cellular immunity, so the immunogenicity and efficacy of vaccines usually remain questionable in older people with frailty, disability, and dementia. Most vaccines used in older people are less immunogenic and effective than those used in younger adults,[18] which results from several factors, such as immunosenescence, inflammation, and altered immune responses to infections and vaccines.[19] Hence, older people need special attention in vaccine development. For example, influenza virus is transmitted via direct contact, droplets, and fomites, and particularly increases the burden of disease and mortality in those aged 75 years and older.[20,21] However, the effectiveness of influenza vaccine was found to be only approximately 29% to 48% in elderly individuals.[22] The reduced vaccine effectiveness results in a lower prevention rate of hospital admissions due to influenza among older adults (37%; 95% confidence interval [CI], 30%–44%) than among younger adults aged 18 to 64 years (51%; 95% CI, 44%–58%).[23] However, the effectiveness of influenza vaccine to prevent any influenza-associated deaths was shown to be well preserved (74%; 95% CI, 44.0%–88.4%) for people aged 65 years and older.[24] The reduced vaccine effectiveness in older adults is related to several factors, such as the virus strain, vaccination rates, seasonal factors, geographic demography, infection history, and frailty or multimorbidity. Despite all the factors mentioned earlier, older age is a key player in vaccine effectiveness.[25]

Current strategies to enhance vaccine immunogenicity and efficacy in older adults include increasing the vaccine dose or adding appropriate adjuvants to trigger immunostimulation, which are common in vaccine development for older people.[21,22] A previous meta-analysis suggested that a high-dose influenza vaccine was consistently more effective than a standard-dose influenza vaccine in reducing influenza cases and influenza-associated clinical complications.[26] In addition, the recombinant influenza vaccine using DNA recombination technology to produce influenza hemagglutinin protein in the cell culture instead of growing live influenza virus in embryos has been developed with success. Recombinant influenza vaccines also included high-dose vaccines (3 times the influenza antigens). All 3 types of enhanced influenza vaccines mentioned earlier induced higher antibody responses than standard-dose vaccines, maintained improvements in immunogenicity, and had better protection in people aged more than 75 years and those with chronic diseases (heart or lung conditions).[22]

Similarly, the effects of immune aging have been observed in herpes zoster vaccines. The live, attenuated herpes zoster vaccine was the first vaccine developed for herpes zoster prevention, and it significantly and safely increased varicella zoster virus–specific T cell–mediated immunity (51.3% effective rate in preventing herpes zoster; 66.5% effective rate in preventing postherpetic neuralgia).[27] However, the effectiveness of the herpes zoster vaccine was significantly affected by age. The Shingles Prevention Study[27] demonstrated that the live, attenuated zoster vaccine reduced the herpes zoster burden of illness by 61.1% (65.5% in subjects aged 60–69 years; 55.4% in subjects aged $\geq$70 years), the incidence of clinically significant postherpetic neuralgia by 66.5% (65.7% in subjects aged 60–69 years; 66.8% in subjects aged $\geq$70 years), and the incidence of herpes zoster by 51.3% (63.9% in

subjects aged 60–69 years, but only 37.6% in subjects aged ≥70 years).[28] Another vaccine against herpes zoster is the recombinant subunit herpes zoster vaccine, which consists of recombinant varicella zoster virus glycoprotein E and the AS01B adjuvant system. Varicella zoster virus glycoprotein E is the most abundant glycoprotein in cells infected with varicella zoster virus and thus becomes the main target of varicella zoster virus–specific antibodies and T cells.[29] AS01B adjuvant systems included 2 types of adjuvants, 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and QS-21, which stimulate virus glycoprotein E–specific CD4+ T cell and antibody responses in animal models.[30] The pooled efficacy of the recombinant subunit herpes zoster vaccine was 91.3%, and the vaccine efficacy was similar across ages ranging from 50 to 59 years, 60 to 69 years, and 70 years and older.[31,32] The experiences in herpes zoster vaccine development were similar to those of influenza vaccines and thus may become common challenges in the development of vaccines for older people.

In pneumococcal vaccination, currently, the 23-valent pneumococcal polysaccharide vaccine against *Streptococcus pneumoniae* (PPV23) has been replaced by a 13-valent conjugated pneumococcal vaccine (PCV13).[33] PPV23 successfully induced immunity in older adults against pneumococcal diseases, but the protective effects declined over time. Despite the declining efficacy of PPV23 in older adults, the booster dose of PPV23 was not recommended for various reasons. PCV13 was originally developed for young children to overcome the limitations of T cell–independent polysaccharide antigens, but it protects against pneumonia only approximately 50% of the time.[34] In 2019, the United States Advisory Committee on Immunization Practice removed the recommendation for routine PCV13 use among people aged 65 years and older. In contrast, routine 1-dose PPV23 use for people aged 65 years and older remains in the recommendations, and only those individuals at risk for exposure to PCV13 serotypes are recommended to receive PCV13 vaccinations.[35] If the decision is made to administer a PCV13 vaccine, it should be administered at least 1 year before a PPV23 vaccine. The use of pneumococcal vaccines also reflects the challenges in vaccination for older adults because of the clinical characteristics, immune responses, personal risks in the life course, and the efficacy of vaccines in this population.

CORONAVIRUS DISEASE 2019 VACCINE DEVELOPMENT

The success of COVID-19 vaccine development has been widely recognized as an important key to ending the pandemic. To date, several different platforms of technology have been used to develop COVID-19 vaccines, including DNA, messenger RNA (mRNA), nonreplicating viral vector, protein subunit, and inactivated vaccines.[36–39] Each COVID-19 vaccine platform has its own unique advantages and disadvantages based on cultivation technology, production speed, large-scale production, vaccine safety, storage and transportation requirements, and the effectiveness of the immune response triggered (**Table 1**).

Protein-based vaccines account for the largest proportion of COVID-19 vaccine development (35.9%).[40] The latest update at the end of 2021 showed that the WHO has approved 10 COVID-19 vaccines from 8 original vaccines based on 4 vaccine technological platforms (mRNA, nonreplicating viral vector, inactivated vaccine, and protein subunit platforms).[36,40,41] Recombinant viral vector vaccines consist of replicating and nonreplicating types based on their ability to replicate in host cells. The adenoviral (Ad) vector is the most commonly used viral vector. A safe viral vector is a delivery system that contains antigens and molecules that can induce both

Table 1
Overview of the characteristics of major vaccine technology platforms and vaccines used to prevent severe acute respiratory syndrome coronavirus-2 infections

	Vaccine Platform	Existing Vaccine Examples Approved by the WHO[36,37]	Production Speed[36,37]	Immune Response[36,37]	Advantages[36–39]	Disadvantages[36–39]
Traditional approaches	Live, attenuated	• Under development	Slow	Both cellular and humoral	• Broad antigenic profile • Strong and long-lasting immune response	• Safety issues in immunocompromised and pregnant people • Require dedicated biosafety facilities • Can be complicated to scale up manufacturing
	Inactivated	• Covaxin (Bharat Biotech (India)) • Covilo (Sinopharm (Beijing)) • CoronaVac (Sinovac (China))	Medium	Mostly humoral	• Broad antigenic profile • Safe • Convenient transport and storage	• Reduced immune response • Risk of vaccine-enhanced disease • Antibody titers reduce over time • Requirement for biosafety facilities • Lower purity
	Protein subunit	• Nuvaxovid (Novavax) • COVOVAX (Serum Institute of India [Novavax formulation]) • MVC-COV1901 (Medigen)[a]	Medium	Humoral	• Safe for immunocompromised people • Noninfectious • Simple and less expensive to produce • Targeting key antigens	• Limited capability in inducing cellular immunity • Unstable structure, which may lead to a loss of immunogenicity • Several booster doses and adjuvants are often needed • Challenges in large-scale production
Novel approaches	Viruslike particles	• Under development	Medium	Both cellular and humoral	• Noninfectious • Broad antigenic profile • Safe • Scalability of production	• Limited immunogenicity • Lower purity
	Nonreplicating viral vector	• Ad26.COV2.S (Janssen	Medium	Both cellular and humoral	• Fast to produce • Reusable platform	• Preexisting immunity against the vector

(*continued on next page*)

Table 1
(*continued*)

Vaccine Platform	Existing Vaccine Examples Approved by the WHO[36,37]	Production Speed[36,37]	Immune Response[36,37]	Advantages[36–39]	Disadvantages[36–39]
	[Johnson & Johnson]) • Vaxzevria (Oxford/AstraZeneca) • Covishield (Serum Institute of India [Oxford/AstraZeneca formulation])			• Safe • Strong immune response	• Risk of adverse reactions
Replicating viral vector	• Under development	Fast	Both cellular and humoral	• Fast to produce • Lower doses/single dose • Reusable platform • Strong immune response • Less infectious	• Preexisting immunity against the vector • Risk of adverse reactions
DNA	• Under development	Fast	Both cellular and humoral	• Fast to produce • Robust immune response • Scalable • Noninfectious • Reusable platform • Stable at room temperature	• May need special devices for storage and transport • No DNA-based vaccine has previously been produced • Potential genome integration risk
mRNA	• Spikevax (Moderna) • Comirnaty (Pfizer/BioNTech)	Fast	Both cellular and humoral	• Fast to produce • Strong immune response • Noninfectious • No genome integration risk • Reusable platform • Stimulates strong T-cell response • Simple formulations	• May need extremely low temperatures for storage and transportation • No mRNA-based vaccine has previously been produced

[a] Not approved by WHO until 31 January 2022 (https://covid19.trackvaccines.org/agency/who/) but has been recommended by an independent vaccine prioritization advisory group to be included in the WHO Solidarity Trial Vaccines (STv).

antibody-mediated and cell-mediated immune responses. After invading the host cells, the antigen gene is inserted into the nucleus of the host cells, and the viral protein is produced on the surface of the host cells to induce host immune responses. Inactivated vaccines contain completely inactivated or killed pathogens (a part of the killed pathogen or the whole pathogen) and primarily induce protective antibodies against epitopes on hemagglutinin glycoprotein on the surface of the virus. Compared with live, attenuated vaccines, inactivated vaccines usually induce a weaker immune response, so an adjuvant is usually needed to increase the effectiveness of the immune response. The manufacturing principles of recombinant protein-based (protein subunit) vaccines are to identify the required pathogenic protein from the virus coat, implant the DNA sequence for the target protein into a cell culture, and purify the target protein for the vaccines. The human immune system detects the viral protein when the vaccine is injected and generates an immune response against future infections. Protein-based vaccines are generally safe because they contain noninfectious protein subunits and induce sufficient antibody-mediated immune responses, but they also need adjuvants to induce long-lasting immune responses. The mRNA vaccines include mRNA molecules encoding antigens to induce target protein production without affecting the DNA of host cells. The mRNA vaccine is composed of mRNA encapsulated in lipid nanoparticles, which protects the RNA structure and facilitates host cell absorption. After the mRNA vaccine is injected into muscle, the cells translate it into spike proteins. The produced spike proteins further emerge on the surface of cell membranes and are secreted into body fluids for immunostimulation.

Two mRNA-based COVID-19 vaccines were approved for emergency use authorization (EUA) by the US FDA on 11 December 2020 (BNT162b2) and 18 December 2020 (mRNA-1273) to control the COVID-19 pandemic.[36–39] BNT162b2 is an mRNA-based vaccine encoding the SARS-CoV-2 receptor binding domain that was jointly developed by BioNTech in Germany and Pfizer in the United States. BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that works against the S protein of the SARS-CoV-2. The mRNA in BNT162b2 encodes a SARS-CoV-2 full-length spike protein modified by 2 proline mutations to ensure that the protein remains in the prefusion conformation. BNT162b2 was approved by the WHO on 31 December 2020 and has been approved in 122 countries.[42] mRNA-1273, another mRNA-based vaccine developed by Moderna, was approved by the WHO on 30 April 2021 and has been approved in 83 countries.[42] The mRNA-1273 vaccine contains a lipid nanoparticle-encapsulated nucleoside-modified mRNA that encodes the full-length spike protein of SARS-CoV-2, S(2P), a prefusion protein that is stabilized after replacing S protein residues 986 and 987 with the 2P mutation. The spike glycoprotein is the primary vaccine target, because it is essential for the virus to attach and enter host cells. mRNA-1273 triggers a neutralizing antibody response and eliminates the virus by inducing CD4+ T cell and CD8+ cytotoxic T-cell responses.[43,44]

CORONAVIRUS DISEASE 2019 VACCINE ACCEPTANCE

Although COVID-19 vaccines are an effective strategy to control the COVID-19 pandemic, a significant proportion of people refuse COVID-19 vaccination, even though the benefits of vaccinations have been clearly demonstrated. A global survey of potential acceptance of COVID-19 vaccines from 19 countries in mid-2020 showed that 71.5% of participants reported positive attitudes toward COVID-19 vaccination (ranging from 65.2% in Sweden to 88.6% in China).[45] However, another systematic review included data from 33 countries at the end of 2020 and identified high variability

in COVID-19 vaccine acceptance rates across countries.[46] COVID-19 vaccine acceptance rates were particularly low in the Middle East, Eastern Europe, and Russia (<60%). In contrast, high acceptance rates were noted in east and southeast Asia (>90%).[46] It was estimated that a 60% to 75% vaccination rate of all populations is needed to slow or stop the transmission and community spreading of COVID-19.[47–49] In the older population, the vaccination rate is higher than that in adults or younger populations. In the United States, approximately 99.9% and 98.1% of older adults aged 65 to 74 and 75 years and older, respectively, have received at least 1 dose of a COVID-19 vaccine, and 89.7% and 84.4% of them were fully vaccinated. However, only 74.6% and 82.7% of people aged 25 to 39 and 40 to 49 years have received at least 1 dose of a COVID-19 vaccine.[50] In the United Kingdom, nearly 95% of older adults aged 65 years old and older have received a full dose of a COVID-19 vaccine.[51]

To improve the overall vaccination rates to increase herd immunity against COVID-19, it is important to explore vaccine acceptance in different regions and the reasons for rejection. A systematic review of 15 studies found that ethnicity, working status, religiosity, politics, sex, age, education, and income status were all predisposing factors to accept or refuse COVID-19 vaccination.[52] The most common reasons to decline COVID-19 vaccination were attitudes against vaccinations in general, concerns about safety because of the short development process, beliefs that vaccines were unnecessary because of the harmless nature of COVID-19, general distrust, doubt about the provenience of vaccines, and a lack of faith in vaccine efficacy.[53,54] In addition, the limited number of older individuals in clinical trials is a strong reason to reject COVID-19 vaccination because these individuals are at high risk for severe illness and vaccine-related adverse events.[55] Older adults' decisions for COVID-19 vaccination, especially for those with cognitive impairment, physical disability, frailty, and/or low sociocultural status, may be influenced by their family members or peers. Limited access to facilities for vaccinations is another obstacle for frail older adults to receive COVID-19 vaccines. A well-designed health care system and an effective public health system are critical to identify people in need and provide necessary services. In addition to compulsory measures, effective education and adequate information strategies for the target population are important to improve vaccination rates.[56]

CHALLENGES OF CORONAVIRUS DISEASE 2019 VACCINATION IN OLDER ADULTS

The successful development of COVID-19 vaccines has strengthened pandemic control strategies; the WHO aimed to achieve 70% vaccination coverage by mid-2022, and older people were prioritized for vaccination to reduce mortality, severe morbidity, and related hospitalizations.[57] Most countries prioritized older adults for COVID-19 vaccinations because of their vulnerability and susceptibility to infections.[58] The WHO published a framework to guide mass vaccination policies[59] and to encourage countries to publish and monitor the progress of their vaccination programs.[60] Hasan and colleagues[61] reviewed 15 national policies and summarized critical elements for successful vaccination policies, including equitable access and vaccination scheduling, vaccination locations, coordination with cold chain infrastructure, planning for staff for vaccinations, and community engagement to enhance the efficiency of vaccination strategies.[61] Among these strategies, the capacity to provide COVID-19 vaccinations is the most critical, and creating facilities for and access to mass COVID-19 vaccination should be the priority.[62] In many countries, locations such as large public venues, hospitals, clinics, pharmacies, and even malls are used to increase vaccination accessibility.[61] Incorporating

routine vaccines such as influenza, pneumococcal, or herpes zoster vaccines with COVID-19 vaccines is also an effective approach.[63]

Despite the challenges in public policy for mass COVID-19 vaccination in older adults, special challenges related to the health characteristics of older adults remain. In real-world practice, frail older people or nursing home residents were earmarked as having first priority for COVID-19 immunization, but they were not included in any phase of the clinical trials of COVID-19 vaccine development.[64] A recent review of 12 COVID-19 therapeutic or prophylactic trials showed that the average age of enrolled participants was 20 years younger than the average age of participants in large observational studies, and none of those trials reported on cognitive performance or functional outcomes, the foremost determinants of the health of older people.[65] Concern regarding the underrepresentation of older or frail populations in the trials included that the validity of vaccines for these vulnerable groups may be compromised.[66] Although 42.2% of the Pfizer/BioNTech vaccine trial participants were aged 55 years old and older, less than 5% of individuals were older than 75 years.[67] Approximately one-quarter of Moderna vaccine trial participants were aged 65 years and older,[14] but the Oxford-AstraZeneca vaccine trial enrolled only 5% participants aged 70 years old and older.[15] The Oxford-AstraZeneca vaccine trial further excluded those with cognitive impairment and frailty,[15] the individuals potentially most susceptible to SARS-CoV-2 infections.[68] An observational study on a long-term care facility disclosed that SARS-CoV-2 infection-naive residents showed delayed, lower responses to COVID-19 vaccines, which were less effective in antagonizing the spike protein of viral variants.[69]

Because of the lack of evidence on the safety and efficacy in this special population, postmarket surveillance for COVID-19 vaccines is an important alternative to examine the safety and efficacy of these vaccines. The Norwegian government received 100 reports of suspected vaccine-related deaths after providing BNT162b2 mRNA vaccines for approximately 35,000 nursing home residents,[70] and 10 probable and 26 possible vaccine-related fatal events were concluded after careful cross-examinations by experts. The vaccine-related fatality risk may be related to the existing frailty and disability, instead of older age itself. However, public attention related to postvaccination deaths substantially increased the hesitancy of nursing home staff toward COVID-19 vaccination,[71] as well as the lay public. The vulnerable groups needing vaccines are also those susceptible to adverse reactions. A study reported the favorable effects of BNT162b2 mRNA COVID-19 vaccines in older adults with frailty or living in long-term care facilities,[72] but the small sample size (134 residents from 5 long-term care facilities) and inclusion criteria (58.2% participants infected by SARS-CoV-2) meant that concerns were not completely addressed. In particular, the study concluded that only previous SARS-CoV-2 infection status was associated with vaccine immunogenicity.

A large prospective cohort study based on more than 10,000 care home residents reported that COVID-19 vaccines (BNT162b2 and Oxford-AstraZeneca) significantly reduced the transmission of COVID-19 but did not eliminate the infection risk.[73] Because of the lack of well-designed research, a study used a mathematical model to examine the roles of vaccine coverage in nursing homes and showed that increasing vaccine coverage of the nursing home staff, not vaccination of the residents, was the key to reducing symptomatic cases among nursing home residents.[74] A study of 2501 nursing homes in the United States supported the results of this analysis and showed that vaccinations for both residents and care staff significantly reduced SARS-CoV-2 infections in both residents and nursing staff, especially in nursing homes with fewer certified beds and higher numbers of nursing staff.[75]

Although vaccinations did not entirely prevent postvaccination breakthrough SARS-CoV-2 infections, these breakthrough infections were mostly mild or asymptomatic.[76] More research efforts in COVID-19 vaccine development and vaccination strategies among older persons with frailty, disability, dementia, long-term care facility residence, or home-bound status are needed.[77]

Although the WHO and most countries emphasized the importance of increasing the coverage of primary vaccination series to control the COVID-19 pandemic, breakthrough infections by SARS-CoV-2 variants such as Delta or Omicron triggered the need for booster doses. A recent systematic review and meta-regression analysis showed that the average declines in vaccine effectiveness over 6 months for symptomatic COVID-19 and severe COVID-19 in all age groups were 25.4% and 8.0%, respectively.[78] In particular, among persons aged 50 years old and older, the vaccine effectiveness decreased by 32% for symptomatic COVID-19 and by 10% for severe COVID-19.[78] A booster dose is recommended for individuals who have completed their primary vaccination series because of waning vaccine effectiveness over time, as well as the threats from Omicron and Delta variants. In 2022, an updated revision of the WHO Strategic Advisory Group of Experts summarized 2 key findings to recommend a booster dose. First, within the priority-use group, increasing the primary vaccination series coverage rate had a greater impact on reducing hospitalizations and deaths per dose than the use of an equivalent vaccine supply to increase the booster-dose coverage rate. Second, across priority-use groups, increasing the booster-dose coverage rate for higher priority-use groups yielded greater reductions in severe disease and deaths than the use of an equivalent vaccine supply to increase the primary vaccination series coverage rates of lower priority-use groups.[79]

Although the optimal interval to administer the booster dose has yet to be determined, an interval of 4 to 6 months after the completion of the primary vaccination series is a widely accepted scheme. The next challenge for the booster dose is the choice of using homologous or heterologous vaccines. A phase 1/2, open-label clinical trial conducted at 10 sites in the United States compared the serial use of homologous and heterologous boosters of BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines, and disclosed acceptable reactogenicity and humoral immunogenicity for all combinations except for spike-specific T-cell responses in the homologous Ad26.COV2.S-boosted subgroup.[80] Another study in the Netherlands also found that heterologous regimens significantly increased immunogenicity and reactogenicity compared with homologous regimens in health care workers who received the Ad26.COV2.S vaccine as the initial vaccine.[81] Compared with homologous booster groups, the heterologous booster groups showed superior responses of antispike immunoglobulin G antibodies 28 days after the booster dose among those who had received 2 doses of CoronaVac.[82] In addition, 2 studies also found that participants who received a booster dose of the BNT162b2 vaccine had significantly lower rates of SARS-CoV-2 infections and severe illness than those who did not receive a booster dose.[83,84] The WHO reviewed available evidence and recommended that either homologous or heterologous schedules should be used. They also provided 3 heterologous schedules of primary and booster vaccination series: (1) initial doses of inactivated vaccines, with vectored or mRNA vaccines considered for subsequent doses; (2) initial doses of vectored vaccines, with mRNA vaccines considered for subsequent doses; and (3) initial doses of mRNA vaccines, with vectored vaccines considered for subsequent doses. Similar to the WHO recommendation, the US government recommended an interval of at least 5 months for mRNA vaccine (BNT162b2 and mRNA-1273) boosters.[85] Specifically, a booster can be given at least 2 months after receiving a primary Ad26.COV2.S vaccine.

THE ROLE OF GERIATRICIANS IN VACCINE DEVELOPMENT AND POLICY MAKING

Older people with frailty, disability, dementia, or living in nursing homes need special attention during the COVID-19 pandemic because of their high risk of infections, severe illness, mortality, lower vaccine responses, and vaccine adverse events, as well as their reduced access to health care services, reduced daily activities, and adverse impacts from activity restriction and lockdowns.[86] Some unique issues for vaccine development, clinical trial designs, outcome measurements, safety issues, and postmarket surveillance should be addressed to improve vaccine development and related vaccination policy making.[87] Involving geriatricians in COVID-19 vaccine-development and policy-making processes is important because of the special health and socioeconomic characteristics of older people, especially those with frailty, disability, dementia, or living in nursing homes.[88] It may be argued that including frail older people in vaccine clinical trials may delay vaccine development because this would likely lead to poorer safety or efficacy profiles, but these individuals are usually the prioritized group for vaccination. With the active participation of geriatricians in the vaccine-development and policy-making processes, the clinical trial design may be modified to include certain subsamples to examine the safety and efficacy of COVID-19 vaccines in this vulnerable group, and the development of vaccination policies may be improved with input from these professionals.[64]

SUMMARY

The success of COVID-19 vaccine development through various technological platforms has substantially relieved the impacts of the COVID-19 pandemic, because COVID-19 vaccines not only have prevented COVID-19 transmission but also have reduced the rates of severe COVID-19 and mortality. Special attention to older adults with frailty, disability, or dementia or living in nursing homes is needed in vaccine development, clinical trial designs, and vaccination policies. Despite the abovementioned concerns, the completion of a primary series of COVID-19 vaccines with heterologous booster doses in intervals of 4 to 6 months remains the best strategy to reduce the impact of SARS-CoV-2 infections and to obtain immunity against COVID-19 transmission.

CLINICS CARE POINTS

- Older adults with frailty, disability, dementia, or living in nursing homes are vulnerable to SARS-CoV-2 infections, but are also susceptible to vaccine-related adverse events. More clinical attention should be paid and more thorough explanations should be provided to vaccinees and their families.
- Limited evidence confirms the safety and efficacy of COVID-19 vaccinations for frail older adults in long-term care settings, and all necessary infection controls should be maintained after vaccinations, especially the care staff in long-term care settings.
- The completion of a primary series of COVID-19 vaccines with heterologous booster dose in intervals of 4 to 6 months remains the best strategy to reduce the impact of SARS-CoV-2 infections and to obtain immunity against COVID-19 transmission.
- Active involvement of geriatricians in vaccine development and related public-policy development is important for the success of adult vaccination strategies against COVID-19.

ACKNOWLEDGMENTS

The authors would like to express gratitude to the staff of the Center for Healthy Longevity and Aging Sciences of National Yang Ming Chiao Tung University for all research assistance, the National Health Research Institutes for funding support (NHRI-11A1-CG-CO-01-2225-1), and all researchers dedicated to vaccine development. Moreover, the authors would like to express their condolences to the families of individuals who died of COVID-19 for their loss.

REFERENCES

1. WHO coronavirus disease (COVID-19) dashboard. World Health Organization. Available at. https://covid19.who.int/. Accessed January 28, 2022.
2. Mostaza JM, García-Iglesias F, González-Alegre T, et al. Clinical course and prognostic factors of COVID-19 infection in an elderly hospitalized population. Arch Gerontol Geriatr 2020;91:104204.
3. Rowe TA, Patel M, O'Conor R, et al. COVID-19 exposures and infection control among home care agencies. Arch Gerontol Geriatr 2020;91:104214.
4. Bernabeu-Wittel M, Ternero-Vega JE, Díaz-Jiménez P, et al. Death risk stratification in elderly patients with covid-19. A comparative cohort study in nursing homes outbreaks. Arch Gerontol Geriatr 2020;91:104240.
5. Pranata R, Huang I, Lim MA, et al. Delirium and mortality in coronavirus disease 2019 (COVID-19) - a systematic review and meta-analysis. Arch Gerontol Geriatr 2021;95:104388.
6. Ahmadi S, Khankeh H, Sahaf R, et al. How did older adults respond to challenges after an earthquake? results from a qualitative study in Iran. Arch Gerontol Geriatr 2018;77:189–95.
7. Gómez-Belda AB, Fernández-Garcés M, Mateo-Sanchis E, et al. COVID-19 in older adults: what are the differences with younger patients? Geriatr Gerontol Int 2021;21(1):60–5.
8. Chen LK. COVID-19 vaccination and frailty in older adults. Arch Gerontol Geriatr 2021;96:104487.
9. Singhal S, Kumar P, Singh S, et al. Clinical features and outcomes of COVID-19 in older adults: a systematic review and meta-analysis. BMC Geriatr 2021; 21(1):321.
10. Teo SP. Review of COVID-19 vaccines and their evidence in older adults. Ann Geriatr Med Res 2021;25(1):4–9.
11. Hara M, Ishibashi M, Nakane A, et al. Differences in COVID-19 vaccine acceptance, hesitancy, and confidence between healthcare workers and the general population in Japan. Vaccines (Basel) 2021;9(12):1389.
12. Gallant AJ, Nicholls LAB, Rasmussen S, et al. Changes in attitudes to vaccination as a result of the COVID-19 pandemic: a longitudinal study of older adults in the UK. PLoS One 2021;16(12):e0261844.
13. Chen LK. Older adults and COVID-19 pandemic: Resilience matters. Arch Gerontol Geriatr 2020;89:104124.
14. Voysey LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384(5):403–16.
15. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021; 397(10269):99–111.

16. Farge G, de Wazières B, Raude J, et al. The health professional's view on the inclusion of age in the recommendations for pneumococcal vaccination: results of a cross-sectional survey in France. Geriatrics (Basel) 2021;7(1):4.
17. Wu Q, Dudley MZ, Chen X, et al. Evaluation of the safety profile of COVID-19 vaccines: a rapid review. BMC Med 2021;19(1):173.
18. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012;12(1):36–44.
19. Ciabattini A, Nardini C, Santoro F, et al. Vaccination in the elderly: the challenge of immune changes with aging. Semin Immunol 2018;40:83–94.
20. Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 2018;391(10127):1285–300.
21. Andrew MK, Bowles SK, Pawelec G, et al. Influenza vaccination in older adults: recent innovations and practical applications. Drugs Aging 2019;36(1):29–37.
22. Cunningham AL, McIntyre P, Subbarao K, et al. Vaccines for older adults. BMJ 2021;372:n188. Published 2021 Feb 22.
23. Rondy M, El Omeiri N, Thompson MG, et al. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: a systematic review and meta-analysis of test-negative design case-control studies. J Infect 2017;75(5):381–94.
24. Nichols MK, Andrew MK, Hatchette TF, et al. Influenza vaccine effectiveness to prevent influenza-related hospitalizations and serious outcomes in Canadian adults over the 2011/12 through 2013/14 influenza seasons: a pooled analysis from the Canadian Immunization Research Network (CIRN) serious outcomes surveillance (SOS Network). Vaccine 2018;36(16):2166–75.
25. Lewnard JA, Cobey S. Immune history and influenza vaccine effectiveness. Vaccines (Basel) 2018;6(2):28. Published 2018 May 21.
26. Lee JKH, Lam GKL, Shin T, et al. Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: an updated systematic review and meta-analysis. Vaccine 2021;39(Suppl 1):A24–35.
27. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352(22):2271–84.
28. Oxman MN, Harbecke R, Koelle DM. Clinical usage of the adjuvanted herpes zoster subunit vaccine (HZ/su): Revaccination of recipients of live attenuated zoster vaccine and coadministration with a seasonal influenza vaccine. J Infect Dis 2017;216(11):1329–33.
29. Arvin AM. Humoral and cellular immunity to varicella-zoster virus: an overview. J Infect Dis 2008;197(Suppl 2):S58–60.
30. Dendouga N, Fochesato M, Lockman L, et al. Cell-mediated immune responses to a varicella-zoster virus glycoprotein E vaccine using both a TLR agonist and QS21 in mice. Vaccine 2012;30(20):3126–35.
31. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med 2015;372(22):2087–96.
32. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. N Engl J Med 2016;375(11):1019–32.
33. Juergens C, de Villiers PJ, Moodley K, et al. Safety and immunogenicity of 13-valent pneumococcal conjugate vaccine formulations with and without aluminum phosphate and comparison of the formulation of choice with 23-valent pneumococcal polysaccharide vaccine in elderly adults: a randomized open-label trial. Hum Vaccin Immunother 2014;10(5):1343–53.

34. Wagner A, Weinberger B. Vaccines to prevent infectious diseases in the older population: immunological challenges and future perspectives. Front Immunol 2020;11:717. Published 2020 Apr 23.
35. Matanock A, Lee G, Gierke R, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 Years: updated recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep 2019;68(46):1069–75.
36. Sharma O, Sultan AA, Ding H, et al. A review of the progress and challenges of developing a vaccine for COVID-19. Front Immunol 2020;11:585354.
37. Awadasseid A, Wu Y, Tanaka Y, et al. Current advances in the development of SARS-CoV-2 vaccines. Int J Biol Sci 2021;17(1):8–19.
38. Mathew S, Faheem M, Hassain NA, et al. Platforms exploited for SARS-CoV-2 vaccine development. Vaccines (Basel) 2020;9(1):11.
39. Funk CD, Laferrière C, Ardakani A. A snapshot of the global race for vaccines targeting SARS-CoV-2 and the COVID-19 pandemic. Front Pharmacol 2020;11:937.
40. Li Y, Tenchov R, Smoot J, et al. A comprehensive review of the global efforts on COVID-19 vaccine development. ACS Cent Sci 2021;7(4):512–33.
41. Rawat K, Kumari P, Saha L. COVID-19 vaccine: a recent update in pipeline vaccines, their design and development strategies. Eur J Pharmacol 2021;892:173751.
42. WHO—COVID19 vaccine tracker. Available at. https://covid19.trackvaccines.org/agency/who/. Accessed January 28, 2022.
43. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. N Engl J Med 2020;383(20):1920–31.
44. Umakanthan S, Chattu VK, Ranade AV, et al. A rapid review of recent advances in diagnosis, treatment and vaccination for COVID-19. AIMS Public Health 2021;8(1):137–53.
45. Lazarus JV, Ratzan SC, Palayew A, et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med 2021;27(2):225–8.
46. Sallam M. COVID-19 vaccine hesitancy worldwide: a concise systematic review of vaccine acceptance rates. Vaccines (Basel) 2021;9(2):160.
47. Billah MA, Miah MM, Khan MN. Reproductive number of coronavirus: a systematic review and meta-analysis based on global level evidence. PLoS One 2020;15(11):e0242128.
48. Anderson RM, Vegvari C, Truscott J, et al. Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination. Lancet 2020;396(10263):1614–6.
49. Britton T, Ball F, Trapman P. A mathematical model reveals the influence of population heterogeneity on herd immunity to SARS-CoV-2. Science 2020;369(6505):846–9.
50. Clinic Mayo. US COVID-19 vaccine tracker: see your state's progress. Available at: https://www.mayoclinic.org/coronavirus-covid-19/vaccine-tracker. Accessed January 28, 2022.
51. National flu and COVID-19 surveillance reports: 2021 to 2022 season: 16 December 2021 (week 50). Available at: https://www.gov.uk/government/statistics/national-flu-and-covid-19-surveillance-reports-2021-to-2022-season. Accessed January 28, 2022.
52. Troiano G, Nardi A. Vaccine hesitancy in the era of COVID-19. Public Health 2021;194:245–51.
53. Aw J, Seng JJB, Seah SSY, et al. COVID-19 vaccine hesitancy-a scoping review of literature in high-income countries. Vaccines (Basel). 2021;9(8):900.

54. Biswas MR, Alzubaidi MS, Shah U, et al. A scoping review to find out worldwide COVID-19 vaccine hesitancy and its underlying determinants. Vaccines (Basel) 2021;9(11):1243.
55. Cesari M, Vellas B. Older persons "Lost" to the COVID-19 vaccination: where are they? J Frailty Aging 2021;10(4):308–9.
56. Gallè F, Sabella EA, Roma P, et al. Acceptance of COVID-19 vaccination in the elderly: a cross-sectional study in southern Italy. Vaccines (Basel) 2021;9(11): 1222.
57. Strategy to achieve global Covid-19 vaccination by mid-20222021. World Health Organization. Available at: https://www.who.int/publications/m/item/strategy-to-achieve-global-covid-19-vaccination-by-mid-2022. Accessed December 25 2021.
58. Chakraborty C, Sharma AR, Bhattacharya M, et al. All nations must prioritize the COVID-19 vaccination program for elderly adults urgently. Aging Dis 2021;12(3): 688–90.
59. Framework for decision-making: implementation of mass vaccination campaigns in the context of COVID-19: interim guidance. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/332159. Accessed May 22 2021.
60. Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/EEa. European centre for disease prevention and control at: https://www.ecdc.europa.eu/en/publications-data/overview-implementation-covid-19-vaccination-strategies-and-deployment-plans. Accessed January 31, 2022.
61. Hasan T, Beardsley J, Marais BJ, et al. The implementation of mass-vaccination against SARS-CoV-2: a systematic review of existing strategies and guidelines. Vaccines (Basel) 2021;9(4):326.
62. Chakraborty C, Sharma AR, Bhattacharya M, et al. COVID-19 vaccines and vaccination program for aging adults. Eur Rev Med Pharmacol Sci 2021; 25(21):6719–30.
63. Privor-Dumm LA, Poland GA, Barratt J, et al. A global agenda for older adult immunization in the COVID-19 era: a roadmap for action. Vaccine 2021;39(37): 5240–50.
64. Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. Age Ageing 2021;50(2):279–83.
65. Prendki V, Tau N, Avni T, et al. A systematic review assessing the underrepresentation of elderly adults in COVID-19 trials. BMC Geriatr 2020;20(1): 538. Published 2020 Dec 20.
66. Antonelli Incalzi R, Trevisan C, Del Signore S, et al. Are vaccines against COVID-19 tailored to the most vulnerable people? Vaccine 2021;39(17):2325–7.
67. Wang X. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2021;384(16):1577–8.
68. Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health 2020;5(8):e444–51.
69. Tut G, Lancaster T, Krutikov M, et al. Profile of humoral and cellular immune responses to single doses of BNT162b2 or ChAdOx1 nCoV-19 vaccines in residents and staff within residential care homes (VIVALDI): an observational study. Lancet Healthy Longev 2021;2(9):e544–53.
70. Wyller TB, Kittang BR, Ranhoff AH, et al. Nursing home deaths after COVID-19 vaccination. Dødsfall i sykehjem etter covid-19-vaksine. Tidsskr Nor Laegeforen 2021;141.

71. Harrison J, Berry S, Mor V, et al. Somebody like Me": understanding COVID-19 vaccine hesitancy among staff in skilled nursing facilities. J Am Med Dir Assoc 2021;22(6):1133–7.
72. Salmerón Ríos S, Mas Romero M, Cortés Zamora EB, et al. Immunogenicity of the BNT162b2 vaccine in frail or disabled nursing home residents: COVID-A study. J Am Geriatr Soc 2021;69(6):1441–7.
73. Shrotri M, Krutikov M, Palmer T, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study. Lancet Infect Dis 2021;21(11):1529–38.
74. Kahn R, Holmdahl I, Reddy S, et al. Mathematical modeling to inform vaccination strategies and testing approaches for COVID-19 in nursing homes. Clin Infect Dis 2021;74(4):597-603. ciab517.
75. Domi M, Leitson M, Gifford D, et al. The BNT162b2 vaccine is associated with lower new COVID-19 cases in nursing home residents and staff. J Am Geriatr Soc 2021;69(8):2079–89.
76. Teran RA, Walblay KA, Shane EL, et al. Postvaccination SARS-CoV-2 infections among skilled nursing facility residents and staff members - Chicago, Illinois, December. Am J Transpl 2021;21(6):2290–7.
77. Palermo S. Covid-19 pandemic: maximizing future vaccination treatments considering aging and frailty. Front Med (Lausanne) 2020;7:558835.
78. Feikin D, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet 2022;399(10328):924-944 (Pre-print).
79. WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines. World Health Organization. Available at: https://www.who.int/publications/i/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines. Accessed January 21, 2022.
80. Atmar RL, Lyke KE, Deming ME, et al. Homologous and heterologous Covid-19 booster vaccinations. N Engl J Med 2022;386:1046-1057.
81. Sablerolles RSG, Rietdijk WJR, Goorhuis A, et al. Immunogenicity and reactogenicity of vaccine boosters after Ad26.COV2.S priming. N Engl J Med 2022; 386(10):951-963.
82. Costa Clemens SA, Weckx L, Clemens R, et al. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. Lancet 2022;S0140-6736(22):00094–100.
83. Arbel R, Hammerman A, Sergienko R, et al. BNT162b2 vaccine booster and mortality due to Covid-19. N Engl J Med 2021;385(26):2413–20.
84. Bar-On YM, Goldberg Y, Mandel M, et al. Protection against Covid-19 by BNT162b2 booster across age groups. N Engl J Med 2021;385(26):2421–30.
85. CDC COVID-19 Vaccine Booster Shots. Center for disease control and prevention. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html. Accessed January 21, 2022.
86. Shakespeare T, Ndagire F, Seketi QE. Triple jeopardy: disabled people and the COVID-19 pandemic. Lancet 2021;397(10282):1331–3.
87. Andrew MK, Schmader KE, Rockwood K, et al. Considering frailty in SARS-CoV-2 vaccine development: how geriatricians can assist. Clin Interv Aging 2021;16: 731–8.
88. Andrew MK, McElhaney JE. Age and frailty in COVID-19 vaccine development. Lancet 2021;396(10267):1942–4.