REVIEW

Vaccination in Older Adults in Singapore: A Summary of Recent Literature

Minh Ha Nguyen[1], *MBBS, MRCP*, Li Li Chen[2], *CGP*, Kiat Wee Lim[2], *BSc (Pharm)*, Wei Terk Chang[2], *BPharm*, Kaysar Mamun[1], *ABIM, ABGM, FAMS*

[1]Department of Geriatric Medicine, Singapore General Hospital, Singapore

[2]Department of Pharmacy, Singapore General Hospital, Singapore

ABSTRACT

Singaporeans are living longer and not having enough babies to replace themselves, with projected 20% of the population aged 65 years and above by 2030. These worrying trends can exert significant pressure on Singapore's economy and society. Health-resource utilisations are increasing as our population ages, with increase in hospitalisations, emergency room visits and consumption of pharmaceutical drugs. Interventions such as vaccinations in older people are well-studied approaches to prevent infections and the related complications. The Advisory Committee on Immunization Practice (ACIP) by the US Centers for Disease Control and Prevention (CDC) recommends routine immunisation against influenza, tetanus, pneumococcal pneumonia as well as herpes zoster infections in all people aged 65 years and above. The administrations of other vaccines (meningococcal, hepatitis A and B, varicella and *Haemophilus influenzae* type b) are recommended only in older people with certain risk factors. Despite the benefits of vaccination in older people, the data in the West shows that the rate of vaccination in this age group remains lower than targets recommended by the World Health Organisation (WHO). The main barriers to vaccinations exist in the healthcare system, health care providers, patients and caregivers. Interventions are warranted to increase awareness among physicians, to engage the involvement of the pharmacist/nurse to provide standing orders and reduction in cost of vaccination; this potentially improves vaccination uptake to protect our increasing elderly population.

Keywords: Vaccination, Older adults, Influenza, Tetanus, Pneumococcal, Herpes zoster

INTRODUCTION

Improved living standards and current advancements in healthcare system have increased life expectancy, leading to a rapidly aging population in developed countries. It is projected globally that the number of older adults (age 60 years old and above) would be more than double, from 841 million people in 2013 to more than 2 billion by 2050[1]. In Singapore, the national data showed that 11.2% of local population are 65 years old and above in 2014[2], with this figure expected to increase to 20% in 2030[3].

In comparison to the younger population, older adults are more vulnerable to infectious diseases with a higher rate of morbidity and mortality[4]. As such, the aging population poses a major challenge to the public healthcare system with increased hospitalisations and length of stay. Studies have shown that vaccination is an effective alternative to protect older adults from preventable infections, hence the subsequent serious complications[5,6].

AGEING AND IMMUNITY

Increasing age significantly decreases both innate and adaptive immune system's responses to infection, and this phenomenon was termed "immunosenescence". There are several proposed mechanisms involved in this gradual deterioration of the immune system which affect the ability to respond to infections and the development of long-term immune memory, especially by vaccination. The innate immune system provides the first-line barrier to protect human body from micro-organisms. The main components include 1) epithelial barrier; 2) phagocytic cells (neutrophils,

macrophages, dendritic cells); 3) natural killer cells; and 4) circulating plasma proteins. The number and the function of these cells and proteins diminished with age, causing a decrease in inflammatory responses of the innate system[7,8].

Alternatively, the adaptive immune system consisting of T-cells and B cells plays a major role in recognition and generation of a series of immunity responses to neutralise or eliminate the evading micro-organisms. Maturation of T cells happens in the thymus, which is located behind the sternum, and in front of the heart. One of the hallmarks of immunosenescence is the reduction in thymus gland size, with gradual replacement of its functional cortex and medulla by fat tissue[7,9]. As a result, production of mature naive T-cells and their number in the peripheral blood is significantly reduced. Similar to T-cell systems, the number of naive B-cells also decreases in older adults[7,9]. On the other hand, the number of memory T-cells and B-cells appears to be well preserved with aging[10]. These increased effector T-cells and B-cells number together with their age-related alterations in cytokines and antibodies production cause restriction in the diversity of the immune cell repertoire[6]. As a consequence, the effectiveness and diversity of the adaptive immune response are impaired, which lead to increased susceptibility to infectious diseases as well as decreased immune responses to vaccination in older adults[7,10]. This phenomenon has been demonstrated in a meta-analysis by Goodwin *et al.*, which showed that seroprotection against influenza virus strains was only 29%–46% in persons aged 75 years, compared with 41%–58% in persons 60–74 years of age[11].

These changes in the immune system potentially affect successful vaccination in the older population. Therefore, optimisation of immunisation schedules and modes of administration, using new adjuvants and vaccines that specifically address the issues of immunosenescence phenomenon will help to improve protection in this vulnerable population.

VACCINE RECOMMENDATIONS FOR OLDER ADULTS

Since the establishment of the Advisory Committee on Immunization Practice (ACIP) by the US Centers for Disease Control and Prevention (CDC) in 1964, ACIP makes recommendations for adult vaccination program every two years[12]. In the last 15 years, a number of new vaccines have been introduced, including varicella, hepatitis A, pneumococcal, and human papillomavirus vaccines. The latest recommendations on adult vaccinations by the ACIP were published in October 2013[13,14]. The ACIP recommends routine immunisation against influenza, tetanus, pneumococcal pneumonia as well as herpes zoster (HZ) infection in all adults above 65 years of age. The administrations of other vaccines (meningococcal, hepatitis A and B, varicella and *Haemophilus influenzae* type b) are recommended only in older adults with high risk factors (Table 1). Currently, there is no specific vaccination guideline for adults in Singapore.

Influenza

Influenza is a disease caused by highly contagious influenza viruses: type A, type B or type C. Among these, influenza A viruses are the most pathogenic and accounted for more severe illnesses and complications. The Ministry of Health (MOH) in Singapore has a national surveillance program for influenza which monitors the attendance of upper respiratory tract infections (URTI) at government clinics. The months from April to July and November to January are the traditional "influenza seasons" with a distinct peak in reported cases. More than 5,000 cases of acute respiratory infection are reported in polyclinics, hospitals and tertiary care centres across Singapore each year[15]. Although influenza affects people of all ages, older adults (age 65 and above) are at the highest risks of influenza–related hospitalisations and deaths[16,17].

Influenza vaccination has been shown to be clinically effective in reducing the rate of hospitalisations as well as influenza-related mortality in older population[18–20]. The ACIP recommends annual influenza vaccination starting from age 6 months and above. Older adults should receive inactivated formulation (not the live, intranasal influenza vaccine), either intramuscularly or subcutaneously (depending on the brands). The side effects are rare, mostly limited to local reactions at the injection sites which typically last for less than 48 hours.

Pneumococcal Pneumonia

Pneumococcal disease (PD), caused by the bacterium *Streptococcus pneumoniae*, is a leading cause of morbidity in children and adults worldwide[21]. The bacteria can attack different body systems, causing pneumonia, meningitis, bacteraemia or other life-threatening conditions. The incidence of invasive pneumococcal disease

Table 1. The ACIP recommendations on vaccines and immunisation schedule in elder people

Vaccines	Indications in Elder People	Brand Available in Singapore (Manufacturer)	Route	Type of Vaccine	Vaccination Schedule	Potential Benefits in Elder People	Possible Side Effects
1, Influenza A&B	Adults aged 65 years or older can receive the standard-dose Influenza, Inactivated Vaccine (IIV) or the high-dose IIV	Fluarix™ (GSK) Vaxigrip® (Sanofi Pasteur) Agrippal™ S1 (Novartis)	IM/SC	Inactivated, Whole Viral or Fractional (Protein-based)	1 dose annually	Reduce risks of influenza illness, influenza-related hospitalisation and death	Local reactions: pain, swelling at injection site Systemic reactions (rare): fever, malaise, myalgia, headache
2, Tetanus, diphtheria, pertussis (Td/Tdap) DTaP: InfanrixTM (GSK) is indicated for age 6 weeks through 6 years of age	Older adults who have not received Tdap(a) vaccine or who vaccination status unknown People with tetanus prone wound(s) if the last Tdap/Td vaccination was more than 5 years ago	Tdap: BoostrixTM (GSK)	IM	Inactivated, Fractional (Bacterial Toxoids)	Adults ≥19 years (including adults ≥65 years) Unvaccinated adults should complete a 3-dose primary vaccination series with Td-containing vaccines: A single dose of Tdap should be given first, followed by Td vaccine for routine boosters (first 2 doses at least 4 weeks apart and the third dose 6 to 12 months after the second dose) The following patients, who have not yet received Tdap or for whom vaccine status is not known, should receive a single dose of Tdap as soon as feasible: • Close contacts of children <12 months of age; Tdap should ideally be administered at least 2 weeks prior to beginning close contact • Healthcare providers with direct patient contact Give Td (b) booster every 10 years after the primary series has been completed People with tetanus prone wound should receive a dose of Tdap/Td if his/her last vaccination was more than 5 years ago.	Reduce incidence of Tetanus infection, Tetanus-related hospitalisation and death	Local reactions:pain, erythema, swelling at injection site Systemic reactions (rare): Brachial neuritis, Guillain-Barré syndrome (GBS)
3, Herpes zoster (shingles)	Routine vaccination of older adults ≥60 years of age, including patients who report a previous episode of zoster; patients with chronic medical conditions (eg, chronic renal failure, diabetes mellitus, rheumatoid arthritis, chronic pulmonary disease) unless those conditions are contraindications;	Zostavax™ (MSD)	SC	Live, Attenuated	1 dose (no data available on additional dose yet; current data suggests that duration of protection is up to 6 years)	Reduce incidence of Herpes Zoster Infection and Post-herpetic neuralgia	Local reactions:pain, erythema, swelling, pruritus at injection site Systemic reactions (rare): Increased Cardiovascular events in patients who received Herpes Zoster Vaccine has been reported

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Table 1. The ACIP recommendations on vaccines and immunisation schedule in elder people (continued)

Vaccines	Indications in Elder People	Brand Available in Singapore (Manufacturer)	Route	Type of Vaccine	Vaccination Schedule	Potential Benefits in Elder People	Possible Side Effects
	and residents of nursing homes and other long-term care facilities ≥60 years of age without contraindications						
4, Pneumococcal pneumonia	All adults aged 65 years or older	PPSV 23-Pneumovax® 23 (MSD)	IM/SC	Inactivated, Fractional (Polysaccharide-based)	Pneumococcal vaccine naive people: 1 dose of PCV13 followed by 1 dose of PPSV23 at 6 to 12 months later People who has received ≥ 1 dose of PPSV23, 1 dose of PCV 13 should be given 1 year or more after the most recent PPSV23 dose	Protect against invasive pneumococcal diseases such as bacteremia, pneumonia with bacteremia, and meningitis	Local reactions: pain, swelling, erythema at injection site Systemic reactions (rare): fever, myalgia
Prevanar 7® (PCV7 Pfizer) is no longer available in Singapore		PCV 13-Prevanar 13® (PCV13 Pfizer)	IM	Inactivated, Fractional (Conjugate)			
5, Meningococcal	Adults ≥56 years: Meningococcal polysaccharide vaccine (MPSV4) is preferred for meningococcal vaccine-naive persons in this age group who are at increased risk of meningococcal infection and require a single dose (eg, travelers or during a community outbreak). Persons previously vaccinated with a quadrivalent meningococcal conjugate vaccine (MenACWY) and who require revaccination or for whom multiple doses are anticipated, MenACWY-D is preferred (eg, persons with asplenia or microbiologists).	MenACWY-D (MCV4): Menactra® (Sanofi Pasteur)-Meningococcal and Diphteria toxoid conjugate vaccine	IM	Inactivated, Fractional (Polysaccharide-based)	Give 2 initial doses of MCV4 separated at 2 months interval to people with functional or anatomic asplenia or persistent complements components deficiency Give booster dose every 5 years to those with persistent risk exposure		Local reactions: pain, erythema at injection site Systemic reactions (rare): fever, diarrhoea
		MenACWY (MCV4): Menveo® (Novartis)	IM		There is limited data on individuals aged 56-65 and there is no data on individuals aged >65 years The need for, and timing of, a booster dose of Menveo has not yet been determined		
		MenACWY (MPSV4): Mencevax® (GSK)	SC		MPSV4 preferred in elder people ≥ 56 years old and required single dose Give booster dose every 5 years to those with persistent risk exposure		
6,Varicella zoster (chickenpox)	All people without evidence of immunity Highly recommended in healthcare personnel; household contact of immunocompromised persons; people living or working in environments where transmission is likely e.g. resident of institutional settings; adolescents and adults in households with children; international travellers	Varilrix™ (GSK)	SC	Live, Attenuated	2 doses at 4 to 8 weeks interval		Local reactions: pain, erythema at injection site Systemic reactions: hepatitis, severe rash

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Table 1. The ACIP recommendations on vaccines and immunisation schedule in elder people (continued)

Vaccines	Indications in Elder People	Brand Available in Singapore (Manufacturer)	Route	Type of Vaccine	Vaccination Schedule	Potential Benefits in Elder People	Possible Side Effects
7, Hepatitis A Avaxim® (Sanofi Pasteur) is available as a pediatric vaccine	Homosexual men; illicit drugs users Persons working with HAV infected patients or with HAV in laboratory setting Persons with chronic liver disease; persons who receive clotting factor concentrates Persons travelling to or working in country with high or intermediate endemicity of Hepatitis A	Havrix® Adult (GSK)	IM	Inactivated, Whole Virus	2 doses at 6 to 12 months interval (6 to 18 months if other brand)		Local reactions: pain, erythema at injection site Systemic reactions (rare): fever, headache
8, Hepatitis B (Patients >65 years may have lower response rates to hepatitis B vaccine)	People with high risks of Sexually Transmitted Diseases Household contacts and sex partners of Hep B carrier patients Health care personnel People with End-stage renal failure; HIV infection; chronic liver diseases	Engerix-B™ (GSK) HBvaxPRO® (MSD) Twinrix™ Adult (GSK) - Hepatitis A & B vaccine	IM	Inactivated, Fractional (Protein-based)	3 doses of 1ml at 0-, 1- and 4- or 6-month Booster may be given whenever anti-HBsAb <10 mIU/mL in select populations 3 doses of 1ml at 0-, 1-, and 6-month schedule No booster dose recommended		Local reactions: pain, erythema at injection site Systemic Reactions (rare): fever
9, *Haemophilus Influenzae* type b (Hib)	People with functional or anatomic asplenia; sickle cell disease People who undergoing elective splenectomy and haven't received Hib vaccine previously Recipients of haematopoietic stem cell transplant	Hiberix™ (GSK)	IM	Inactivated, Fractional (Polysaccharide-based	1 dose For transplant recipients, 3 doses at 6 to 12 months after a successful transplant, regardless of vaccination history; at least 4 weeks apart		Local reactions: pain, erythema, swelling at injection site Systemic Reactions (rare): fever, dizziness

IM: intramuscular; SC: subcutaneous

(a)Tdap: Tetanus, Diptheria, Acellular Pertussis

(b)Td: Tetanus, Diptheria

Source of available vaccines in Singapore: Singapore Health Sciences Authority. PZ4970 INFOSEARCH - Medicinal Products. Available Online at http://eservice.hsa.gov.sg/prism/common/enquirepublic/SearchDRBProduct.do?action=load. Accessed on November 14, 2014.

(IPD) increases with age, with the highest mortality rate among older adults[22]. A study in USA reported an overall case-fatality rate of 7.4 deaths per 100,000 patients aged 65–79 years old and 17.4 deaths per 100,000 patients aged ≥80 years[23].

In an analysis of 4,275 patient records with PD from 1995–2004 in Singapore, the mean annual hospitalisation rate from PD was 10.9 per 100,000 population but considerably higher among the older adults (>75 years; 95/100,000). The overall mortality rate was 3.2%; with meningitis mortality and pneumococcal pneumonia mortality rates were 23.3% and 2.9% respectively[24].

There are currently two types of pneumococcal vaccines available: the pneumococcal polysaccharide vaccine (PPV) and the pneumococcal conjugate vaccines (PCV). A Cochrane review in 2013, which included both RCT and non-RCT trials, supported the use of PPV for IPD in the elderly[25]. However, the meta-analysis did not provide the evidence to support the use of PPV to prevent all cause pneumonia or mortality. Vaccine efficacy was also poorer in adults with chronic illness. A second study by Jackson *et al.* concluded that although vaccination with PPV seems to be effective against pneumococcal bacteraemia, there was no association between PPV vaccination and community acquired pneumonia of any cause (including non-invasive pneumococcal pneumonia) among older adults[26]. The study also found an unexplained increased risk of hospitalisation for community acquired pneumonia for vaccinated patients. Recently, CAPiTA (Community Acquired Pneumonia Immunization Trial in Adults), a randomised placebo controlled double-blind trial was conducted in the Netherlands from 2008 to 2013 among approximately 85,000 patients age 65 and older to study the efficacy of PCV13 (funded by Pfizer). It is the first trial to show efficacy of a vaccine against not only vaccine-type IPD (75% efficacy, CI of 41.4–90.8%) but also vaccine-type non-bacteraemic pneumococcal disease (45% efficacy, CI of 14.2–65.3%) in the elderly population[27].

After the release of the CAPiTA result, the ACIP endorsed the routine use of both PCV13 and PPSV23 in adults aged ≥65 years since August 2014[28]. The two vaccines should not be co-administered, and the minimum acceptable interval between PCV13 and PPSV23 is 8 weeks. The ACIP recommends that PCV13 should be given first, followed by PPSV23 after 6–12 months. However, if PPSV23 has already been given, PCV13 should only be given after 1 year. While local adverse reactions including pain, redness and swelling at the injection site are common, systemic reactions are rare.

Herpes Zoster

Herpes zoster is caused by the reactivation of the varicella-zoster virus (VZV). The clinical manifestations include development of painful vesicular rash along one or two dermatomes. The infection is commonly complicated by post-herpetic neuralgia (PNH), which is presented as persistent neuropathic pain along the affected dermatome. The incidence of HZ rises with age due to aging related weakening of T cell-mediated immunity, and the reported rate is around 10 cases per 1,000 U.S. populations annually among adults age 60 years and above[29].

The Shingles Prevention Study (SPS) has illustrated that a highly potent live attenuated VZV vaccine could potentially reduce the overall incidence of HZ infection as well as PNH in adults age 60 years and above[30]. However, a follow-up study, Short Term Persistence Substudy (STPS) for Shingles Prevention Study indicated possible waning of protection against HZ overtime[31]. In the STPS as compared to the SPS, vaccine efficacy for HZ burden of illness decreased from 61.1% (95%CI: 51.1–69.1) in the years 0.0–4.9 to 50.1% (95%CI: 14.1–71.0) in the years 3.3–7.8, vaccine efficacy for the incidence of PHN decreased from 66.5% (95%CI: 47.5–79.2) in the years 0.0–4.9 to 60.1% (95%CI: −9.8 to 86.7) in the years 3.3–7.8, and vaccine efficacy for the incidence of HZ decreased from 51.3% (95%CI: 44.2–57.6) in the years 0.0–4.9 t to 39.6% (95%CI: 18.2–55.5) in the years 3.3–7.8. Nonetheless, the most recent cost benefit analysis in 2014 by ACIP revealed that targeted HZ vaccination by age group (age 70 instead of age 50) can result in an eight-fold savings in costs. The costs for each Quality Adjusted Life Year (QALY) saved by vaccination using the high dose live attenuated zoster vaccine for age group 60, 70 and 50 were US$37,000, US$86,000, and US$287,000 respectively[32].

In conclusion, the ACIP recommends the use of vaccine against VZV (causing HZ) in all older adults ≥60 years old, with or without any previous episode of HZ. It can be given subcutaneously and it is contraindicated in immunocompromised persons.

Table 2. Barriers to vaccinations in older adults.

	Issues that affect vaccination uptake rate
Systems	Factors affecting the supply and distribution of vaccines Factors affecting the storage of vaccines Funding and costs
Health care providers	Lack of knowledge about diseases and vaccines Failure to assume the responsibility for vaccination Incomplete or inaccessible documentation of previous vaccinations Concern about the efficacy and side effects of vaccines
Patient and caregiver	Lack of knowledge on diseases and vaccines Concern about the efficacy and side effects of vaccines Time consuming, especially vaccines that require booster dosage Confusion on vaccination schedule

Tetanus, Diptheria, Acellular Pertussis

Tetanus booster dose is recommended routinely every 10 years for older adults who have completed a primary series. Adults with an unknown or incomplete history of primary tetanus vaccination series should complete their primary vaccination series which includes a Tdap (tetanus, diptheria, acellular pertussis) dose. Tdap products for boostering adolescents were licenced in 2005 in Singapore. The ACIP also recommends administering Td/Tdap-containing vaccine as prophylaxis in tetanus-prone wound management[33].

BARRIERS TO VACCINATIONS IN OLDER ADULTS

Despite the encouraging evidence of vaccination in the older population, the rate of vaccination in this age group remains lower than targets recommended by the World Health Organisation (WHO). In the United States, the National Health Interview Survey in 2013 reported that only 66.2% of older adults were vaccinated against influenza during the 2012–2013 season[34]. The percentage for older adults who were vaccinated against pneumococcal pneumonia, tetanus and HZ were 59.9%, 55.1% and 20% respectively[35]. Similar findings were also reported in another study in England[36]. However, there is a dearth of such data in Singapore.

Studies were conducted to investigate the barriers of low vaccination rate in adults[37–40]. The three main barriers identified to vaccinations in older adults can be classified under barriers in system, health care provider and patient or caregiver (Table 2). Several factors were recognised to improve the uptake of vaccinations in older adults, which includes physician recommendation, previous history of the illness, self-reported bad health conditions, perception on the efficacy of vaccination and family influences[41–43]. A number of strategies have been shown to improve vaccination rate in older adults, which consists of:

(1) Implementation of a reminder/recall system for patients and health care providers;

(2) Reduction in vaccination costs;

(3) Expansion of access to vaccinations in medical or public health settings; and

(4) Implementation of standing orders (the use of a nurse-led or pharmacist-led immunisation program)[44–47].

CONCLUSION

Vaccination is potentially the most cost-effective public healthcare measure, providing significant protection against infectious diseases and their complications for older adults with age-related decline in their immune system. Further investigations are required to show reproducibility in efficacy of vaccines in older patients, as the viral load and local immunity may not be the same as that in published studies. There are also opportunities for more studies on vaccination efficacy in a subgroup of elderly that are above 80 years of age with frailty, multiple co-morbidities and that are not community-ambulant. Further research on the mechanisms of immunosenescence, the development of new adjuvants and other immunotherapy, coupled with initiatives to improve immunisation uptake in the elderly, will definitely help to achieve better protection for the increasing elderly population in Singapore.

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