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Recommendations and guidance for pneumococcal vaccination for adults in Taiwan

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ABSTRACT

Streptococcus pneumoniae remains a global health concern, causing diseases from sinusitis, otitis media, to invasive pneumococcal diseases (IPD), such as bacteremia, bacteremic pneumonia, empyema, and meningitis. Key IPD risk factors include age under five or over 50 years, chronic medical conditions, and lifestyle factors. In Taiwan, IPD incidence has declined following national immunization program. However, morbidity and mortality remain substantial, particularly among older adults. There are two types of pneumococcal vaccines, polysaccharide conjugate vaccines (PCV) and pneumococcal polysaccharide vaccines (PPSV). These vaccines target specific IPD serotypes but may lead to serotype replacement. In Taiwan, the available/forthcoming vaccines include PCV13, PCV15, PCV20, PCV21, and PPSV23, with numbers indicating serotype coverage. This guidance, developed and endorsed by eight national academic societies, serves as an adjunct to the Taiwan Advisory Committee on Immunization Practices recommendations. Using the GRADE framework, it provides evidence-based recommendations for adult pneumococcal vaccination. It emphasizes health promotion to assist healthcare professionals in vaccine selection tailored to current local epidemiology and individual vaccination history. A shared decision-making approach is encouraged, considering individual vulnerabilities, exposure risks, and lifestyle factors. This guidance addresses optimal timing, dosing schedules, coadministration, and safety; grounded in immunological evidence on efficacy, effectiveness, and immunogenicity. In recognition of feasibility of implementation, single-dose PCV20 or PCV21 is proposed as a simplified alternative to complex sequential strategies. However, PCV21 is recommended only where PCV7 serotypes are well controlled or no longer prevalent. This guidance reflects evolving pneumococcal vaccination strategies in response to serotype dynamics and availability of higher-valency conjugate vaccines.

1. Introduction

Pneumococcal infections, caused by *Streptococcus pneumoniae* (commonly known as pneumococcus), remain a major public health concern [1,2]. Pneumococcus commonly colonizes the human respiratory tract and spreads from person to person through direct contact with saliva or respiratory secretions [3]. These infections vary in severity, ranging from non-invasive conditions such as sinusitis, otitis media, and non-bacteremic pneumonia, to invasive pneumococcal diseases (IPD), which include bacteremia, bacteremic pneumonia, empyema, and meningitis [4]. Populations at an increased risk for IPD include children under five years of age [5] and adults over 50 years [6–8], as well as individuals with chronic medical conditions or immunocompromising conditions (Table 1) [9–22]. Additional risk factors include increased exposure, such as residing in nursing homes or long-term care facilities; or increased vulnerability, such as smoking and excessive alcohol consumption [5,11,12,17,19,23]. Pneumococcus remains a leading cause of community-acquired pneumonia in adults, significantly contributing to hospital admissions, morbidity, and mortality worldwide [1,24].

Pneumococci are classified into over 100 serotypes based on their capsular polysaccharides [25]. These polysaccharides serve as both virulence factors and immunogens, making them critical targets for vaccine development [25]. Serotype-specific immunity is elicited through opsonophagocytosis, whereby antibodies facilitate bacterial recognition and elimination by phagocytes [26]. The currently available pneumococcal vaccines include two main categories: polysaccharide conjugate vaccines (PCV) and pneumococcal polysaccharide vaccines (PPSV). Both provide protection against specific serotypes of *S. pneumoniae* and may lead to "serotype replacement", where non-vaccine serotypes become more prevalent [3,5,27,28]. In Taiwan, the currently available and forthcoming vaccines include PCV13, PCV15, PCV20, PCV21, and PPSV23, with the numeric designation indicating the number of pneumococcal serotypes covered by each vaccine (Fig. 1). While expanded vaccine options enhance the prevention of pneumococcal infections, they also introduce greater complexities into clinical decision-making. After more than a decade of implementing the national immunization program (NIP), which included PCV7 and PCV13 for children and PPSV23 for the older adults, and more recently PCV13 for adults in Taiwan, the increasing prevalence of non-vaccine serotypes has emerged as a major challenge to optimizing future vaccine strategies, for both individual protection and population-level public health [3,5,27,28].

This guidance provides evidence-based recommendations and emphasizes the principles of health promotion in order to assist healthcare professionals in navigating these complexities by tailoring immunization strategies to current local epidemiology and individual vaccination history. A shared decision-making approach is encouraged, enabling clinicians to offer recommendations that consider individual vulnerabilities, exposure risks, and lifestyle factors, and also to determine the optimal timing, number of doses, and choice of vaccine. Furthermore, this guidance takes into account the feasibility of implementation in real-world settings.

This guidance was jointly developed by 8 national academic societies as an adjunct to the recommendations provided by the Taiwan Advisory Committee on Immunization Practices (ACIP). It aims to empower healthcare professionals and individuals to select the optimal, individualized vaccination strategy, including timing, number of doses, and choice of vaccine, to ensure that immunization decisions are both personalized and evidence-based.

2. Methods

2.1. Working group and expert panels

The "Working Group on Adult Immunization Practice" of the Infectious Diseases Society of Taiwan (IDSTAIP), established in 2021, is committed to developing updated, evidence-based recommendations and guidance to complement the national vaccination policy issued by the Taiwan ACIP. The working group comprises 25 experts, including 14 adult infectious diseases specialists, 10 pediatric infectious diseases specialists, and one pharmacist, representing 14 hospitals across Taiwan. Members conducted comprehensive literature reviews and jointly drafted the guidance document. The draft underwent a rigorous review process, including a series of consensus meetings with expert panels comprising IDST members and representatives from seven additional national academic societies: Taiwan Association of Family Medicine, Taiwan Society of Pulmonary and Critical Care Medicine, Taiwan Association of Gerontology and Geriatrics, Taiwan Society of Cardiology, Hematology Society of Taiwan, Transplantation Society of Taiwan, and Taiwan AIDS Society.

Table 1
Target populations and indications for pneumococcal vaccination in adults.

Target population	Description	Supporting evidence	Vaccination schedule
Age group	50 years or older	[7,8], Fig. 2B	Table 2
High-risk conditions	- Cerebrospinal fluid leak - Cochlear implant	[9,10]	Table 2
Immunocompromising conditions	- Chronic renal failure or nephrotic syndrome - Primary or secondary immunodeficiency - Iatrogenic immunosuppression - Generalized malignancy - HIV infection - Hematologic malignancies: Hodgkin disease, leukemia, lymphoma, multiple myeloma - Congenital or acquired asplenia - Sickle cell disease and other hemoglobinopathies	[9–11,13,16–22]	Table 2
	- Hematopoietic stem cell transplant (HSCT) - Solid organ transplant recipients - Chimeric antigen receptor T cell (CAR-T) therapy recipients	[15,22,78,88–94,96]	Table 3
Chronic medical conditions	- Chronic heart disease (including congestive heart failure and cardiomyopathies) - Chronic liver disease - Chronic lung disease (including COPD, emphysema, asthma) - Diabetes mellitus	[11,12,17,19,20]	Table 2
Increased vulnerability or exposure	- Cigarette smoking - Alcohol use disorder - Nursing home or long-term care facility residents - Homelessness	[17,19,23,78]	Table 2

Abbreviations: COPD, chronic obstructive pulmonary disease.

2.2. Process of guidance development

From May to September 2024, the working group convened five monthly online meetings to define key clinical questions using the population, intervention, comparison, and outcome (PICO) framework. These questions were formulated based on expert consensus and extensive literature review, particularly focusing on local IPD epidemiology and vaccine efficacy, effectiveness, and safety. Systematic search strategies were developed for each PICO question, followed by comprehensive evidence appraisal, assessment of recommendation strength, and synthesis of preliminary draft recommendations. A multidisciplinary meeting was convened on December 15, 2024, with expert review panels from the eight academic societies to critically review the draft recommendations. The final version of the guidance was reviewed, approved, and endorsed by all eight societies. To ensure transparency and uphold the integrity of the guidance development process, all committee members disclosed potential conflicts of interest both at the initiation of the guidance development process and upon finalization of the recommendations.

2.3. Search strategy

We conducted a comprehensive literature search across PubMed, Embase, the Cochrane Database, and Clinicaltrial.gov to identify systematic reviews, meta-analyses, randomized controlled trials (RCTs), and observational studies. The search focused on studies comparing specific pneumococcal vaccines in adults, either against a placebo or other pneumococcal vaccines, with particular emphasis on vaccine efficacy, effectiveness, immunogenicity, and safety. The primary outcomes of interest were IPD and pneumococcal pneumonia. English-language articles published up to June 30, 2024, were included, and additional emerging evidence was incorporated throughout the drafting process.

2.4. Immunogenicity measurements

Both real-world cohort and clinical trial data were synthesized to provide comprehensive insights. For newer vaccines lacking established clinical effectiveness data, only immunogenicity results from clinical trials were included. Immunogenicity in these studies was primarily assessed using two key measures: serotype-specific functional antibacterial opsonophagocytic activity (OPA) and serotype-specific anti-polysaccharide antibody levels determined by enzyme-linked immunosorbent assay [26,29]. Antibody concentrations are expressed as geometric mean concentration (GMCs), a standardized metric accepted by the World Health Organization and commonly used as a primary endpoint in pediatric trials. Meanwhile, the OPA assay measures were expressed as geometric mean titers (GMTs), derived from the reciprocal of the highest serum dilution that produced >50% killing, serving as a surrogate outcome for the functional capacity of antibodies to opsonize and kill *S. pneumoniae*. OPA enables comparative evaluation of candidate pneumococcal vaccines against those with established

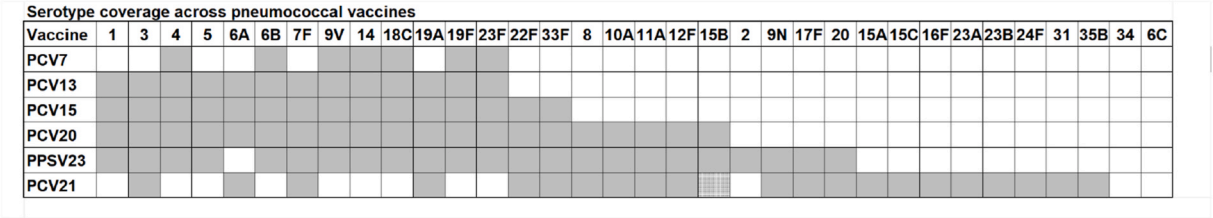

Fig. 1. Serotype coverage of pneumococcal vaccines in Taiwan.
Shaded cells indicate the serotype coverage of the 7-valent (PCV7), 13-valent (PCV13), 15-valent (PCV15), 20-valent (PCV20), and 21-valent (PCV21) pneumococcal conjugate vaccines, as well as the 23-valent pneumococcal polysaccharide vaccine (PPSV23). The hatched cell denotes serotype 15B coverage in PCV21, which is approved for the prevention of IPD caused by serotype 15B based on prespecified criteria, defined as the proportion of participants achieving a fourfold or greater rise in OPA responses [33].

clinical efficacy through immunobridging [29]. Accordingly, it is widely employed as a primary endpoint in adult clinical trials [30–33].

2.5. Evidence assessment by the GRADE framework

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system was applied to assess the quality of evidence and the strength of recommendations [34]. The quality of evidence was categorized as high, moderate, low, or very low, based on factors such as risk of bias, consistency of results, directness of evidence, precision of estimates, and potential publication bias. These categories represent varying degrees of confidence in the estimated treatment effects [35]. While vaccine efficacy was designated a critical outcome, the absence of efficacy data specific for immunocompromised populations did not undermine the assessment for directness of evidence in this guidance. For subgroups with limited evidence, expert consensus played a key role in forming relevant recommendations. The strength of each recommendation was categorized as strong or weak, based on an evaluation of the balance between benefits and harms, resource and cost considerations, patient values and preferences, as well as the feasibility and acceptability of the intervention [36]. The GRADEpro Guideline Development Tool (http://gradepro.org) was employed to generate summary tables facilitating the guidance development process. Final recommendations, including proposed pneumococcal vaccine schedules, are summarized in Table 2.

2.6. Calculation of IPD incidence

Annual IPD case data were obtained from the Taiwan Centers for Disease Control (Taiwan CDC) via the Taiwan National Infectious Disease Statistics System (https://nidss.cdc.gov.tw/en/Home/Index). Corresponding population statistics were retrieved from the Department of Household Registration, Ministry of the Interior, Republic of China (Taiwan) (https://www.ris.gov.tw/app/en), using the dataset *Population by Sex and 5-Year Age Group for Counties and Cities*. Annual IPD incidence rates were calculated by dividing the number of reported cases by the total population for the corresponding year and multiplying by 100,000. Average incidence rates and 95% confidence intervals (CIs) were subsequently calculated. Additionally, the age distribution of annual IPD cases was analyzed to illustrate demographic patterns of disease burden.

3. Epidemiology of pneumococcal disease in Taiwan

PCV7 became available in Taiwan in October 2005. The NIP in Taiwan began implementing pneumococcal vaccines in 2009, initially targeting high-risk children with PCV7. In 2013, a broader PCV13 catch-up program was introduced for children aged 2–5 years, and by 2014, eligibility was expanded to include children aged 1–5 years. The program integrated PCV13 into the routine immunization schedule for all healthy infants in 2015 [37,38]. For the elderly, PPSV23 was provided through private funding beginning in 2008 for those aged 75 and older. From October 2023, both PCV13 and PPSV23 were integrated into the nationally funded immunization program for those aged 65 and older, with eligibility subsequently expanded to high-risk adults aged 19–64 years in March 2025.

The overall incidence of IPD in Taiwan decreased gradually to 1.25 per 100,000 population in 2024, according to the Taiwan CDC [39], with higher rates observed in vulnerable age groups, including children under five years of age and the elderly (Fig. 2A). Specifically, the incidence rate in 2024 was 4.31 per 100,000 in 1-year-olds, 2.77 in children aged 2−4 years, 1.61 in adults aged 65−74 years, and 4.33 in adults aged 75 years and older [39]. This represents a substantial reduction compared to 2008−2017 (Fig. 2A), when incidences among older adults were 6.3 per 100,000 in those aged 65–74 years and 12.4 per 100,000 in those aged 75 years and older [38]. Importantly, the proportion of IPD in patients aged 50 years and older increased substantially from 49% in 2007 to 68% in 2025 (Fig. 2B). In 2023, pneumonia was the diagnosis in 69.3% of reported IPD cases in Taiwan, and 95.1% of reported IPD cases had concurrent bacteremia [6].

Mortality rates reflect the persistent severity of IPD among older adults. During 2008–2017, case fatality rates reached 35.5% in adults aged 75 years and older and 22.3% in those aged 65–74 years, compared with only 3.2% in children aged five years and younger [38]. The overall fatality rate of IPD was 14.7% in 2023. Mortality remained highest among males aged 75 years and older, reaching 28.0% in 2023 [6].

Table 2
Recommended pneumococcal vaccine schedules for the general adult population by prior vaccination status.

Vaccination status	Interval	Pneumococcal vaccines for primary series	Interval	Pneumococcal vaccine for booster	Level of Evidence
Naïve		PCV13 or PCV15	1 year[a]	PPSV23	1A
		PCV20 or PCV21[b]			1A
PPSV23[c]	1 year[c]	PCV20 or PCV21[d]			1B
PCV13 or PCV15	1 year[a]	PCV21 or PCV20[e]			1B
		PPSV23			1B
PCV13 and PPSV23 in any order	1 year[f]	PCV21 or PCV20[f]			2C

Abbreviations: PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PCV21, 21-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.
Level of evidence: 1A, Strong recommendation, High quality of evidence; 1B, Strong recommendation, Moderate quality of evidence; 2B, Weak recommendation, Moderate quality of evidence; 2C, Weak recommendation, Low quality of evidence.

[a] An interval of eight weeks may be considered for individuals with immunocompromising conditions, cochlear implants, or cerebrospinal fluid leaks.

[b] The selection of pneumococcal vaccine should be guided by the most recent epidemiological data from the Taiwan Centers for Disease Control. In settings with high pediatric vaccination coverage with PCV7 or PCV13, PCV21 may be preferred, particularly if serotypes 15A, 15C, 23A, or 35B are prevalent. In contrast, in regions where PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) remain common or where episodic outbreaks are reported, a PCV7-based vaccine, such as PCV13, PCV15, or PCV20, is recommended. For individuals who frequently travel to areas with low pediatric vaccine coverage, PCV20 should also be considered.

[c] Due to concerns regarding vaccine hyporesponsiveness, PPSV23 is no longer recommended as the primary agent for pneumococcal vaccination. For individuals who have received PPSV23, a PCV is recommended at least one year later to avoid hyporesponsiveness.

[d] If PCV20 or PCV21 is not available, administration of PCV13 or PCV15 after PPSV23 with an interval of at least one year may be considered but is not the preferred approach (Level of Evidence 2B).

[e] If the individual has already received PCV13 or PCV15, which cover the PCV7-based serotypes, PCV21 is preferred for subsequent dosing due to its inclusion of emerging serotypes relevant to current local epidemiology.

[f] Under current guidelines, pneumococcal vaccination is considered complete following either a sequential regimen of PCV13 or PCV15 followed by PPSV23, or a single dose of PCV20 or PCV21. Additional vaccination should be determined through shared decision-making. Although previous studies suggest protection lasts at least five years, booster doses given as early as one year apart have been evaluated in clinical trials without reported safety concerns [71,74]. Thus, additional doses of PCV20 or PCV21, preferably PCV21 based on local serotype distribution, may be considered on an individual basis.

Table 3
Special pneumococcal vaccination strategies and schedules in vaccine-naïve adults with selected medical conditions.

Medical condition	Interval between medical condition and vaccination	Pneumococcal vaccines for primary series	Interval between primary series and booster	Pneumococcal vaccines for boosters	Level of Evidence
Autologous or allogeneic HSCT[a] (Day of therapy)	3–6 months	PCV13 or PCV15 3 doses at 1-month interval[a]	6–9 months[b]	PPSV23, or 4th PCV13 or PCV15 for patients with chronic GVHD[a]	1B[c]
		PCV20 3 doses at 1-month interval		4th PCV20, or PCV21	Expert opinion
Solid organ transplant	*Either* pre-transplant (at least 2 weeks prior), *or* post-transplant (3–6 months after)[d]	PCV13 or PCV15 PCV20 or PCV21[d]	At least 8 weeks	PPSV23	1B[c] Expert opinion
CAR-T cell therapy (Day of therapy)[¶]	6 months	PCV13 or PCV15 3 doses at 1- to 2-month intervals[e]	At least 8 weeks[e]	PPSV23	Expert opinion
		PCV20 3 doses at 1- to 2-month intervals		4th PCV20, or PCV21	Expert opinion

Abbreviations: PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PCV21, 21-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; CAR-T, chimeric antigen receptor T cell.
Level of evidence: 1A, Strong recommendation, High quality of evidence; 1B, Strong recommendation, Moderate quality of evidence; 2B, Weak recommendation, Moderate quality of evidence; 2C, Weak recommendation, Low quality of evidence.
[a] A ″3 + 1″ approach with a primary series of three PCV13 or PCV15 doses administered at one-month intervals, beginning 3–6 months post-transplantation, followed by PPSV23 at one year post-transplantation to extend serotype coverage. For HSCT recipients with GVHD, the 4th dose, which is PPSV23, is replaced with an additional PCV dose [89].
[b] At least six months after the third dose of the last vaccine or at least 12 months after HSCT.
[c] Of note, the evidence and recommendations were generated before the availability of PCV20 and PCV21.
[d] Invasive pneumococcal disease is most common within the first three years post-transplantation. While there is currently no recommendation for the optimal timing of pneumococcal vaccination in solid organ transplant recipients, vaccination before transplantation can be considered to provide early protection during the peri-transplant phase. A single dose of PCV20 or PCV21 may offer greater flexibility and ease of implementation than a sequential PCV/PPSV23 regimen.
[e] For patients who have received CAR-T cell therapy, inactivated vaccines may be considered beginning six months after treatment and at least two months following the last immunoglobulin administration, based on expert opinion [99]. Subsequent vaccination with PPSV23, intended to broaden serotype coverage, should be administered at least two months after the third dose of the final conjugate vaccine or at least 12 months after CAR-T cell therapy [98].

In addition to IPD, non-invasive pneumococcal disease (NIPD), particularly mucosal disease and non-bacteremic pneumonia, represents a significant portion of the pneumococcal disease burden [24]. While IPD incidence has been declining, NIPD remains substantial, particularly in children younger than five years, with an incidence of 60–80 per 100,000 population in 2018 [27].

3.1. Serotype distribution and virulence in Taiwan

During 2001−2006, the pre-PCV7 era in Taiwan, pneumococcal serotypes 6B, 14, 19F, and 23F predominated, collectively accounting for a substantial portion of IPD cases. These serotypes harbored high antibiotic resistance, particularly to macrolides and penicillin [40]. Their prevalence decreased significantly following the introduction of PCV7 [41]. Between 2007 and 2014, serotype 19A emerged as the dominant strain, affecting children under five years of age [41,42]. This serotype was of particular concern given its high invasive potential, frequent complications, and multidrug resistance to both β-lactams and macrolides [40,43]. Since the introduction of PCV13 in 2013, the prevalence of serotype 19A decreased from 25.3% in 2012 [42] to 10.1% in 2018 [40], although it remained a leading cause of breakthrough pneumococcal infections in children [44] and continued to represent an important cause of IPD in adults (Fig. 3A).

Since 2015, non-vaccine serotypes have become increasingly predominant, including 15A, 15C, 23A, 35B, and 34 [27,28,45]. Serotype 23A and 15A, in particular, have emerged as leading causes of IPD and are notable for their considerable multidrug resistance [40]. Between 2021 and 2025, serotypes 23A and 15A, and 19A, were the leading causes of IPD-related mortality among adults aged over 65 years (Fig. 3B) [4]. Serotype 3, despite inclusion in PCV13, remains a persistent clinical challenge, largely attributable to its unique capsular structure that enables vaccine escape, resulting in breakthrough infections under the NIP [46]. This serotype has been associated with severe disease, with an overall mortality rate of 9.7%, rising to 18.5% in adults aged 65 years and older; and the majority of cases (75.4%) presents as pneumonia [46].

During 2007–2008, vaccine serotypes in PPSV23 and PCV13 accounted for 77.7% and 76.8% of circulating strains, respectively [41]. Following the NIP, the serotype coverage rates of both PPSV23 and PCV13 have declined markedly (Fig. 3C and D). In 2024, only 39.4% of IPD isolates in adults aged 65 years and older were attributable to serotypes included in PCV13 (Fig. 3D) [39]. Although PPSV23 provided a broader coverage at 47.0% [39], it does not include several of the commonly circulating serotypes such as 15A, 23A, and 35B. This gap in serotype coverage by currently available vaccines underscores the need for higher-valency pneumococcal vaccines to address the evolving serotype landscape.

4. Pneumococcal vaccines

4.1. Differences between conjugate vaccine and polysaccharide vaccine

The efficacy, effectiveness, and immunogenicity of pneumococcal vaccines that are available and forthcoming in Taiwan are summarized in Table S1. Pneumococcal vaccines differ significantly in their immunological mechanisms of action [47,48]. PPSV23 contains capsular polysaccharide antigens derived from 23 serotypes of *S. pneumoniae*, which induce only T cell-independent immune responses with limited immunogenicity in children under two years of age. T cell signals are essential for the generation of B cell memory; therefore, PPSV23 is unable to induce long-term memory B cell immunity [47,48]. In contrast, PCVs employ polysaccharides conjugated to immunogenic carrier proteins [30–33], which enable recognition by both T and B cells, and trigger T cell-dependent immune responses [47,48]. PCV produces a more robust and broader immunogenicity compared to PPSV23 and establishes immunological memory that is reactivated upon subsequent

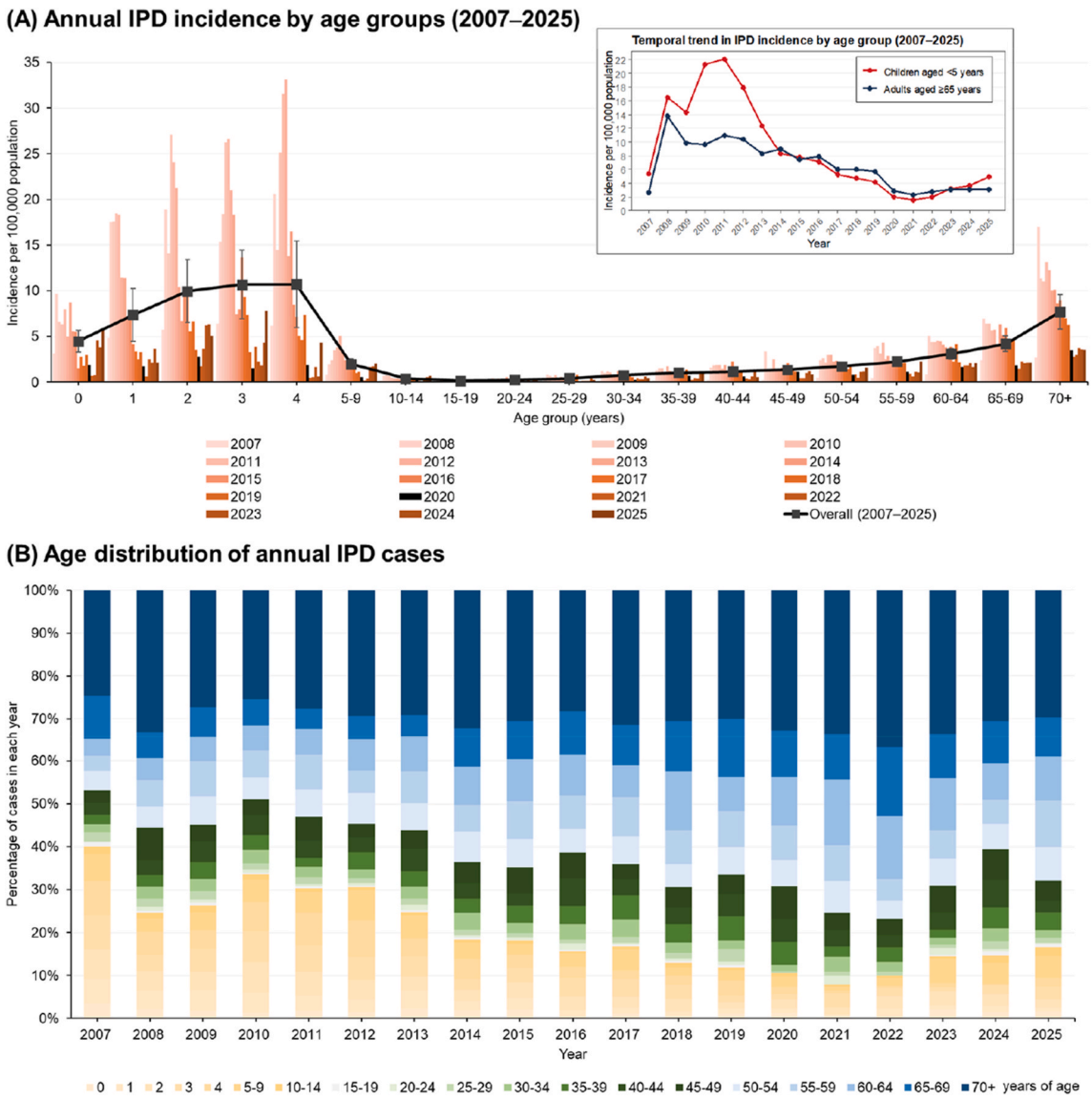

Fig. 2. Epidemiology of invasive pneumococcal disease (IPD) in Taiwan from 2007 to 2025.
(A) Annual incidence of IPD by age group, 2007–2025 (mandatory reporting to Taiwan CDC began in 2007). Bars represent annual incidence per 100,000 population for each year (2007–2025); the black line with square markers indicates the overall mean incidence with 95% confidence intervals. Incidence declined in 2020–2021 during the COVID-19 pandemic (black bars) and showed a mild resurgence after 2021 (inset: temporal trend in children aged <5 years and adults aged ≥65 years). (B) Age distribution of annual IPD cases from 2007 to 2025. The proportion of patients aged 50 years and older increased from 49% to 68% of all IPD cases during this period.
Abbreviations: CDC, Centers for Disease Control; COVID-19, coronavirus disease 2019.

natural exposure or booster vaccination [29]. PCV elicits superior immunogenicity in immunocompromised populations due to its enhanced immunological mechanism [49].

4.2. *PPSV23 (23-valent pneumococcal polysaccharide vaccine)*

PPSV23 was approved in 1983 and registered in Taiwan in 1998 [38,50], and has played a key role in past adult pneumococcal vaccination programs [38,51]. PPSV23 is the pneumococcal vaccine currently available with the broadest serotype coverage (Fig. 1) and has demonstrated moderate effectiveness against IPD in adults (Table S1) [52]. A recent meta-analysis estimated approximately 45% effectiveness (95% CI: 37–51%) against vaccine-type IPD [53]. However, its effectiveness against pneumococcal pneumonia is substantially lower, at 18% (95% CI: −4%–35%) [53]. Variability in study years, vaccine uptake rates, study designs, case definitions, and participant characteristics contributes to the heterogeneity observed in reported outcomes [53,54]. Despite the heterogeneity, real-world data from NIPs in Taiwan continue to support the benefits of PPSV23 in reducing pneumococcal disease burden among individuals with increased IPD risks, such as the elderly and people living with HIV (PLWH) [38,45,51,55].

4.3. *PCV13 (13-valent pneumococcal conjugate vaccine)*

PCV13 has demonstrated substantial efficacy and effectiveness in preventing IPD and pneumococcal pneumonia in adults [29]. The CAPiTA (Community-Acquired Pneumonia Immunization Trial in Adults) trial, a double-blinded RCT enrolling 84,496 adults aged 65 and older, reported that PCV13 resulted in a 75% reduction (95% CI: 41%–91%) in vaccine-type IPD and 46% reduction (95% CI: 22%–63%) in

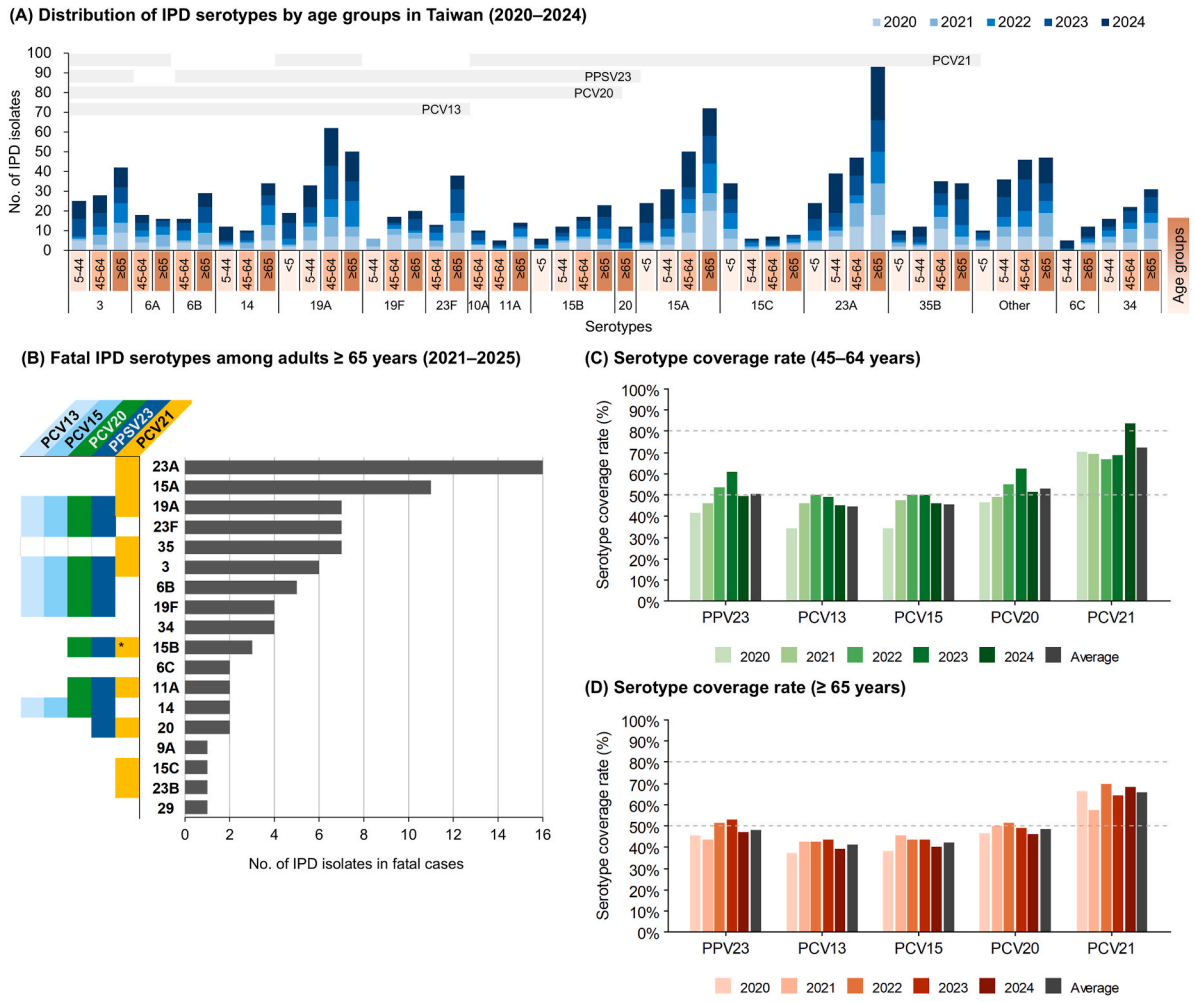

Fig. 3. Invasive pneumococcal disease (IPD) in Taiwan: annual serotype distribution by age (A), serotypes causing mortality in adults ≥65 years (B), and vaccine coverage rates (C–D).

(A) Distribution of pneumococcal serotypes among IPD isolates reported to the Taiwan Centers for Disease Control (CDC), stratified by age group (2020–2024). Horizontal grey bars overlaying the serotype data indicate the coverage of each respective pneumococcal vaccine (PCV13, PCV20, PPSV23, and PCV21) for the serotypes below them.

(B) Fatal IPD serotypes in adults aged ≥65 years (2021–2025), ranked by frequency and color-coded by pneumococcal vaccine. *PCV21 is approved for the prevention of IPD caused by serotype 15B based on prespecified criteria for the proportion of participants with a fourfold or more rise in OPA responses [33]. Figure courtesy of Professor Ching-Tai Huang. Data from the 2025 IPD Quarterly Report (Chinese) [4].

(C–D) Annual serotype coverage rates of different pneumococcal vaccines from 2020 to 2024 among adults aged (C) 45–64 years and (D) ≥ 65 years.

Data of panels (A) and (C–D) were derived from Taiwan CDC research projects conducted by Chuen-Sheue Chiang et al. and supplemented by personal communication (Table S2), including "Molecular epidemiology of vaccine-preventable *Streptococcus pneumoniae*" (Project No.: MOHW109-CDC-C-315-114116, MOHW110-CDC-C-315-124115, MOHW111-CDC-C-315-134114, MOHW112-CDC-C-315-144119) and "Trend analysis of *Streptococcus pneumoniae* in the post-pandemic era" (Project No.: MOHW113-CDC-C-315-114113).

Abbreviations: PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PCV21, 21-valent pneumococcal conjugate vaccine.

vaccine-type pneumococcal pneumonia [56]. Post hoc analyses demonstrated that PCV13 maintained its effectiveness against vaccine-type IPD and pneumococcal pneumonia over five years, with no evidence of waning immunity [57]. Real-world observational studies further supported PCV13 effectiveness, showing effectiveness estimates ranging from 47% to 68% against vaccine-type IPD and from 38% to 68% against vaccine-type pneumococcal pneumonia [53,58]. In older adults with chronic medical conditions, PCV13 retained an efficacy of 40% (95% CI: 11%–60%) against vaccine-type pneumococcal pneumonia over an average follow-up of 3.95 years, indicating sustained immunity despite comorbidities [59]. Although PCV13 may be less immunogenic in immunocompromised adults [60–62], an observational cohort study reported a 45% reduction in the risk of hospitalization for pneumonia or sepsis among patients with hematological malignancies receiving immunosuppressive therapy [63]. These findings highlight the importance of PCV13 in reducing the burden of pneumococcal disease across diverse adult populations with various risk factors.

4.4. PCV15 (15-valent pneumococcal conjugate vaccine)

PCV15 expands the coverage of PCV13 by adding two serotypes (22F and 33F) (Fig. 1). PCV15 is immunogenically comparable to PCV13 for

shared serotypes and elicited higher immune responses for serotypes 3, 22F, and 33F in adults aged 50 years and older, in the PNEU-AGE (PCV15 vs PCV13) and PNEU-PATH (PCV15 vs PCV13; followed by PPSV23) trials (Table S1) [32,64]. Additionally, PCV15 has shown robust immunity in younger at-risk adults and special populations, including those living with HIV and in hematopoietic stem cell transplant (HSCT) recipients [65–67]. In adults who previously received PPSV23, a subsequent dose of PCV15 elicited antibody responses generally comparable to PCV13 for the 13 shared serotypes [68]. PCV15 can be used in sequential vaccination strategies followed by PPSV23 to enhance protection in high-risk populations [64].

4.5. PCV20 (20-valent pneumococcal conjugate vaccine)

PCV20 is a higher-valency conjugate vaccine that includes seven additional serotypes beyond those in PCV13: 22F, 33F, 8, 10A, 11A, 12F, and 15B (Fig. 1). Notably, PCV20 demonstrates cross-reactivity with serotype 15C [69], though it has not received regulatory approval for prevention of serotype 15C-related disease. This immunological cross-reactivity stems from the nearly identical capsular polysaccharide structures of 15B and 15C [69]. Across two phase 3 RCTs, PCV20 demonstrated noninferiority to PCV13 for the 13 shared serotypes, eliciting robust immune responses across all age groups (Table S1) [31,70]. For the seven additional serotypes, PCV20 met noninferiority criteria compared to PPSV23 for six serotypes, except serotype 8. However, secondary immunogenicity endpoints were achieved for all seven additional serotypes [31,70]. PCV20 also demonstrated a safety profile comparable to PCV13 and elicited strong immune responses regardless of prior vaccination history (PPSV23, PCV13, or both) [71]. In real-world effectiveness studies among U.S. adults aged 65 years and older, PCV20 was effective in preventing both IPD and all-cause pneumonia, regardless of prior pneumococcal vaccination status [72]. Overall vaccine effectiveness against IPD was 25.6% (95% CI: 19.5–31.3%) among adults aged 65 years and older. For all-cause pneumonia, overall vaccine effectiveness was 15.2% (95% CI: 14.6–15.8%) (Table S1) [72]. The estimated annual number of PCV20-preventable cases per 100,000 population was 12.5 for IPD and 262.3 for all-cause pneumonia [72]. With its broader serotype coverage and single-dose strategy, PCV20 offers a valuable option for pneumococcal vaccination, particularly among high-risk, vaccine-naïve adults.

4.6. PCV21 (21-valent pneumococcal conjugate vaccine)

PCV21 expands coverage to 21 serotypes, including eight emerging strains not included in prior pneumococcal vaccines, 15A, 15C, 16F, 23A, 23B, 24F, 31, and 35B (Fig. 1). Notably, PCV21 is approved for the prevention of IPD caused by serotype 15B based on prespecified criteria for the proportion of participants with a fourfold or more rise in OPA responses [33], although direct clinical efficacy data remain limited. PCV21 was specifically designed for regions or populations that have achieved high PCV7 coverage among children, and therefore, omits the original PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F). In a phase 3 trial (STRIDE-3) involving vaccine-naïve adults aged 18–49 and those aged 50 years and older, PCV21 demonstrated noninferiority to PCV20 for its ten shared serotypes and elicited strong immune responses to its unique serotypes in older adults (Table S1) [33]. Immunogenicity was comparable between younger and older adults [33]. In the STRIDE-10 trial, PCV21 met noninferiority criteria to PPSV23 for their 12 shared serotypes and was superior for all nine unique serotypes based on OPA responses in vaccine-naïve adults aged 50 years and older [73]. PCV21 consistently induced strong immune responses across all 21 serotypes, regardless of prior pneumococcal vaccination history [74]. Notably, PCV21 induced strong responses to emerging serotypes 23A, 15A, 15C, and 35B in Taiwan (Fig. 3A), which are not covered by PPSV23 or earlier PCVs. This broadened coverage positions PCV21 as a promising strategy to provide enhanced protection against emerging pneumococcal strains in Taiwan. However, the single-dose vaccination strategy of PCV21 is only appropriate in regions such as Taiwan, where classical PCV7 serotypes are already under effective control or no longer prevalent.

4.7. Rationale for choosing different PCVs

Vaccination strategies should be individualized, taking into account factors such as serotype coverage and accessibility of each vaccine type, the individual's risk level, duration of vulnerability of individuals, and the feasibility of implementing various vaccination strategies to ensure timely protection.

The optimal choice between PCV13, PCV15, PCV20 or specialized formulations such as PCV21 depends on several key factors [53,75]:

1. Pneumococcal vaccination history: Prior vaccination history, including the timing of the last dose and the vaccine formulation (serotype coverage), plays a critical role in guiding subsequent immunization strategies. Completion of either a sequential regimen of PCV13 or PCV15 followed by PPSV23 after one year, or a single dose of PCV20 or PCV21, is currently considered sufficient to confer protection against pneumococcal disease. Any additional vaccination beyond these schedules should be based on shared decision-making between clinicians and patients.
2. Local distribution of pneumococcal serotypes: Regional serotype surveillance is essential for identifying dominant or emerging serotypes following routine childhood immunization programs. In regions with high uptake of PCV7 or PCV13 in children, a shift toward non-vaccine serotypes is frequently observed [3,27,28,37], warranting consideration of serotype coverage beyond that included in pediatric vaccines [75,76]. Conversely, if PCV7 serotypes (e.g., 4, 6B, 9V, 14, 18C, 19F, 23F) re-emerge or cause outbreaks, PCV20 may be a more appropriate choice. Therefore, vaccine selection should be guided by the current local epidemiology to ensure optimal protection.
3. Individualized risk considerations: Elderly adults with limited access to vaccination services and immunocompromised individuals often benefit from broader, single-dose coverage rather than sequential vaccination schedules. PCV20 or PCV21 offers the advantage of avoiding the required one-year interval between PCV and PPSV23. PCV20 may be the preferred option for individuals who travel frequently to areas with low pediatric pneumococcal vaccine coverage, where PCV7 serotypes continue to circulate.

5. Summary of recommendations for pneumococcal vaccines in adults

5.1. Who should receive pneumococcal vaccines?

We recommend pneumococcal vaccination for adults aged 50 years or older; for high-risk individuals including those with cochlear implants, cerebrospinal fluid (CSF) leaks, asplenia, or immunocompromising conditions; for at-risk persons with chronic medical conditions; and for those with increased vulnerability or exposure risks, such as cigarette smoking, alcohol use disorder, and residents of long-term care facilities (Table 1). *(Strong recommendation, High quality of evidence) (1A)*.

Rationale

Pneumococcal disease remains a significant public health challenge in Taiwan, particularly among the elderly population. We lowered the recommended vaccination age to 50 years and older, based on local epidemiological data showing that adults aged 50 years and older now account for 61% of IPD cases in Taiwan (Fig. 2B), and this aligns with current U.S. recommendation [77]. Adults with immunocompromising conditions, chronic medical conditions, or social and behavioral risk factors should receive pneumococcal vaccination due to their increased risk of infection, severe complications, and mortality [11,12,14,16,17,19–21]. Social and behavioral risk factors include cigarette smoking,

alcohol use disorder, residence in long-term care facilities, and homelessness [23,78].

5.2. What types and schedule of pneumococcal vaccines are recommended for adults who have not previously received any pneumococcal vaccine?

1. For pneumococcal vaccine-naive adults, we recommend a single dose of PCV20 or PCV21; and additional PPSV23 vaccination is not required. *(Strong recommendation, high quality of evidence) (1A)*
2. For pneumococcal vaccine-naive adults, we recommend a single dose of PCV13 or PCV15 followed by PPSV23 one year later. A shorter interval of 8 weeks may be considered for selected individuals, including those with immunocompromising conditions, cochlear implants, or CSF leaks. *(Strong recommendation, High quality of evidence) (1A)*

Rationale

5.2.1. Sequential versus single dosing

The primary goal of pneumococcal vaccination is to induce broad and durable immunity against diverse *S. pneumoniae* strains, preventing infections and reducing the burden of IPDs. PPSV23, which is currently the vaccine with the widest serotype coverage (Fig. 1), has been used in the elderly since 2007 in Taiwan [38]. However, studies have demonstrated that a prior dose of PPSV23 attenuates the immune response to subsequent administration of PCV13 leading to hyporesponsiveness [29,50,79,80]. Following the introduction of high-valency PCVs which provide potent, broad, and prolonged protection, PPSV23 is no longer considered the single-dose option for broad serotype coverage in vaccine-naïve adults.

The pediatric NIP with PCV13 in Taiwan provided indirect protection in adult populations and contributed to observed serotype shifts. [27,45]According to the epidemiologic data from the Taiwan CDC in 2024 [39], the estimated coverage of PCV13 or PCV15 followed by PPSV23 is less than 50% of the IPD serotypes currently circulating in Taiwan (Fig. 3C and D). A single dose of PCV20 is estimated to cover up to 45% of IPD serotypes, while PCV21 may provide even broader protection, with coverage of up to 80% of circulating serotypes in Taiwan (Fig. 3C and D). Although the sequential vaccine strategy offers the broadest serotype coverage, its effectiveness is challenged by implementation difficulties, successful completion of the full vaccination series, and the need for accurate immunization records or well-maintained registries. Therefore, a single-dose strategy is preferentially recommended, taking into account factors such as compliance, operational feasibility, and the direct and indirect costs of vaccination.

Evidence for PCV20 and PCV21 in immunocompromised individuals, such as recipients of HSCT and CAR-T cell therapy, is currently limited. Furthermore, the relatively lower immunogenicity of PCV20 for selected serotypes, such as serotype 8, compared to PCV13, warrants further evaluation in real-world settings. As for PCV21, concerns have been raised regarding potential breakthrough infections due to its lack of coverage for the original PCV7 serotypes. This is particularly relevant given the episodic surges of IPD caused by PCV7 serotypes in Taiwan (e.g., serotypes 4, 6B, 14, 19F, and 23F; Fig. 3A), and their continued circulation in other regions, posing a concern for international travelers. Therefore, we recommend that vaccination strategies should be individualized.

5.2.2. Shortened interval of eight weeks for select populations

The optimal interval between sequential dosing with PCV and PPSV23 has been extensively studied [50]. Evidence from repeat PPSV23 vaccination and sequential PCV13/PPSV23 studies suggests that extending the interval between PCV and PPSV23 may help to reduce the risk of hyporesponsiveness [29,81]. The evidence supporting a one-year interval between sequential PCV/PPSV23 includes a double-blinded RCT which showed a noninferior immune responses when administering PPSV23 one year after PCV13 in both the general population and individuals with chronic medical conditions [80]. Similarly, PCV15 followed by PPSV23 at a one-year interval elicited comparable immune responses to sequential PCV13/PPSV23 in adults aged 50 years and older, with higher responses for PCV15 unique serotypes (22F and 33F) [64]. Based on this evidence, it is now widely accepted in clinical practice to administer PPSV23 as a booster at one year following PCV13 or PCV15 vaccination.

Several RCTs evaluated shorter intervals in sequential vaccination, particularly in those with medical conditions. A phase 3 RCT comparing either eight or 26 weeks intervals for sequential PCV13/PPSV23 in vaccine-naïve adults aged 50 years and older found comparable immune responses across both intervals, suggesting that shorter intervals may offer earlier protection without compromising immunogenicity [82]. In patients with rheumatoid arthritis (RA), sequential vaccination with PCV13/PPSV23 at a 16 to 24-week interval achieved high response rates to six and more of 12 pneumococcal serotypes at four weeks post-vaccination in those receiving biological or conventional synthetic disease-modifying anti-rheumatic drugs (87% in bDMARDs vs 94% in csDMARDs-treated patients), but notably lower responses were observed in those treated with rituximab (25%) [83]. Low response rates were also observed in RA patients treated with methotrexate and anti-TNF, with only one third achieving a two-fold increase in immunoglobulin G (IgG) GMCs toward at least 70% of serotypes, and with waning of response to below baseline at two years after sequential PCV13/PPSV23 vaccination at an eight-week interval [84]. A phase 3 RCT for at-risk adults aged 18–49 years demonstrated that a sequential PCV15/PPSV23 with a six-month interval induced immune responses comparable to PCV13/PPSV23 [66]. Another phase 3 RCT involving vaccine-naive PLWH receiving sequential vaccines with either PCV13 or PCV15 followed by PPSV23 at an eight-week interval showed comparable serotype-specific OPA GMTs and IgG GMCs between the two groups [65].

Based on the above evidence, we recommend sequential vaccination of either PCV13 or PCV15 followed by PPSV23 with an interval of at least one year. However, for select populations, such as severely immunocompromised patients or individuals scheduled for immunosuppressive therapy, a shortened interval vaccination strategy may be considered to allow early protection against pneumococcal infection. Clinicians need to weigh the benefit of achieving earlier seroprotection against the potential risk of reduced immunogenicity associated with shorter vaccination intervals.

5.3. What patient groups should receive individualized dosing schedules?

1. For vaccine-naïve patients with multiple myeloma (MM), we recommend following the standard pneumococcal vaccination schedule as for the immunocompromised population. *(Strong recommendation, high quality of evidence) (1A)* A repeated three-dose PCV regimen at one-month intervals may offer additional protection. *(Weak recommendation, very low quality of evidence) (2D)*
2. For vaccine-naïve recipients of autologous or allogeneic hematopoietic stem cell transplant (HSCT), we recommend a 3-dose series of PCV13 or PCV15 at 1-month intervals, starting 3–6 months after transplantation, followed by PPSV23 at least 6 months after the last PCV dose or 12 months after transplantation. In patients with chronic graft-versus-host disease (GVHD), we suggest replacing the fourth dose with PCV13 or PCV15. *(Strong recommendation, moderate quality of evidence) (1B)*
3. For vaccine-naïve recipients of autologous or allogeneic HSCT, we recommend a 3-dose series of PCV20 at 1-month intervals, beginning 3–6 months post-transplantation, followed by a fourth PCV20 or PCV21 at least 6 months after the third dose or at least 12 months post-transplantation. *(Expert opinion)*

4. For vaccine-naïve solid organ transplant recipients, we recommend pneumococcal vaccination at least 2 weeks before transplantation, or 3–6 months after transplantation. A single dose of PCV20 is suggested for ease of implementation (*Expert opinion*), while a sequential regimen of PCV13 or PCV15 followed by PPSV23, at least 8 weeks apart, may also be administered. *(Strong recommendation, moderate quality of evidence) (1B)*
5. For vaccine-naïve recipients of chimeric antigen receptor T cell (CAR-T), we recommend a 3-dose series of PCV13 or PCV15 at 1- to 2-month intervals, starting 6 months post CAR-T, followed by PPSV23 at 12 months post CAR-T. *(Expert opinion)*

Rationale

5.3.1. Multiple myeloma

Patients with multiple myeloma (MM) and those with monoclonal gammopathy of undetermined significance exhibit impaired antibody responses to common pathogens, a deficiency more pronounced in MM. This immune dysfunction is further aggravated by lymphopenia, neutropenia, reduced opsonization, impaired phagocytosis and intracellular killing, and myeloma therapies that cause cytopenia, immunosuppression, and disrupt mucosal barriers, and may be exacerbated by immune senescence in older adults [85].

Despite this profound immunosuppression, PCV13 and PPSV23 have shown the potential to elicit immune responses in MM patients [85]. We recommend MM patients adhere to the standard pneumococcal vaccination schedule for the immunocompromised population, with either a single shot of PCV20 or PCV21, or PCV13 or PCV15, followed by PPSV23 as short as eight weeks apart. The pneumococcal antibody titers are known to decline within months, and repeated pneumococcal vaccination may be beneficial. A small, prospective, case-control study (18 per group) found that a three-dose PCV13 regimen administered at one-month intervals between cycles of novel agents (such as bortezomib, lenalidomide, and ixazomib) resulted in an absolute risk reduction of pneumonia by 33.3% at one year in vaccinated patients, demonstrating the effectiveness of three-dose PCV13 administration [86]. However, with this three-dose PCV administration strategy, the optimal timing for a subsequent PPSV23 dose to expand serotype coverage remains unclear. A plausible solution is to administer a three-dose PCV20 or PCV21 regimen directly, as they offer the broadest coverage. If a PPSV23 dose is to follow, the interval (whether as short as two months or 12 months post the latest lymphodepleting therapy) will depend on the patient's condition.

If the patient with MM is scheduled to undergo autologous HSCT, the pneumococcal vaccination schedule should follow the HSCT recommendations in the next section, in alignment with NCCN guidelines [87], with vaccination administered 3–6 months post-transplant.

5.3.2. Hematopoietic stem cell transplant

The risk of IPD is high in allogenic HSCT recipients and remains elevated for many years, with a median onset at one to two years post-transplant [63,88]. Preventing IPD through vaccination is crucial in allogeneic HSCT recipients, yet suboptimal immunogenicity remains a significant challenge in this high-risk population. HSCT recipients exhibit poor immune response to PPSV23, particularly when administered within the first year post-transplantation or in those with chronic GVHD [49]. Previous guidelines recommended a "3 + 1″ approach, with a primary series of three PCV13 doses administered at one-month intervals, beginning three months post-transplantation, followed by PPSV23 at one year post-transplantation to extend serotype coverage [89]. For HSCT recipients with GVHD, the fourth dose, which is PPSV23, is replaced with an additional PCV dose [89].

Evidence for pneumococcal vaccination in HSCT is mainly based on PCV13 and PCV15 trials, with extrapolation to PCV 20 and PCV21. Two studies evaluating vaccination schedules in allogeneic HSCT recipients investigated the addition of a fourth PCV13 dose at six months after the third, while retaining the standard timing for PPSV23 administration (one to two months after the last PCV13) [90,91]. This strategy resulted in significantly higher immune responses to PCV13 serotypes, but immune responses to PPSV23-only serotypes remained suboptimal, especially in those on immunosuppressive therapy [91]. PCV15 elicited immunogenicity comparable to PCV13 in a phase 3 study using the "3 + 1" schedule [67]. Further increasing the number of doses failed to elicit a higher immune response, as shown in a phase 2 RCT using five-dose schedules (including either an additional PCV13 dose before PPSV23 or two PPSV23 booster doses) [88].

Currently, no clinical trial data are available that specifically evaluated the use of PCV20 or PCV21 in HSCT recipients. Based on the immunogenicity of a three-dose regimen of PCV13 or PCV15 with sequential PPSV23 at one year, the U.S. ACIP recommends a series of three PCV20 doses, administered at four-week intervals, starting three to six months post-HSCT. A fourth dose of PCV20 or PCV21 should be given at least six months after the third dose of PCV20 or at least 12 months post-HSCT, whichever is later [78]. The panel's recommendation aligns with the current U.S. CDC guidelines.

5.3.3. Solid organ transplant

Solid organ transplant (SOT) recipients face higher incidence rates of pneumococcal disease compared to the general population; therefore, vaccination is recommended for all SOT candidates and recipients [22]. Immune responses to pneumococcal vaccines in SOT recipients may decline faster than in the general population [22]. While a prime-boost vaccination strategy has been explored to augment vaccine-mediated immunity, results have been variable [92–94]. The administration of pneumococcal vaccines in SOT recipients was demonstrated to be safe and did not result in an increased risk of graft rejection [92].

IPD is most common in the first three years post-transplant, although it can occur at any time [92]. Currently, there is no recommendation for the timing of pneumococcal vaccination in SOT candidates and recipients. Generally, it can be administered both before and after transplant [93]. If administered pre-transplant, it is advised to be given two weeks before the procedure. If administered post-transplant, it is advised to be given three to six months after the procedure [95]. A PCV as a prime vaccine is suggested. This is based on a small study (n = 45) reporting suboptimal vaccine response of PPSV23 in liver transplant recipients [95]. Furthermore, a more recent RCT showed that PCV13 followed by a PCV13 booster induced higher immunogenicity compared to a primary PPSV23 vaccination before kidney transplant, followed by a PCV13 booster six months after transplantation [94]. As sequential administration of PCV followed by PPSV23 has been shown to elicit a booster effect [96], we continue to recommend sequential vaccination with a minimum interval of at least eight weeks. However, with the availability of newer, higher-valency PCVs, we also recommend single-dose administration of PCV20 or PCV21 for its ease of implementation.

5.3.4. CAR-T cell therapy

CAR-T cell therapy induces B cell aplasia and hypogammaglobulinemia, increasing susceptibility to infections caused by encapsulated bacteria, such as *Haemophilus influenzae* type B, *Neisseria meningitidis*, and *S. pneumoniae* [15]. B cell aplasia can persist for up to six months after CAR-T, and the impact of CAR-T on pre-existing vaccine-induced immunity remains uncertain [97]. Patients generally exhibit diminished immune responses to vaccination following CAR-T cell therapy. A small retrospective study in 148 CAR-T recipients found that baseline pneumococcal humoral protection was low, and antibody levels declined further after therapy. Vaccination with PCV13 at 90 days and 180 days post CAR-T failed to restore protective IgG response, and only a minority of patients (8/37, 21.6%) vaccinated at 360 days post CAR-T achieved protective responses [62]. Based on clinical experience and guidelines for immunocompromised hosts [77,89,98], PCV may be considered for patients without plans for further chemotherapy or HSCT, starting six

months post CAR-T therapy and at least two months after the last immunoglobulin treatment [98,99].

5.4. What types and schedule of pneumococcal vaccines are recommended for adults who have received pneumococcal vaccines before?

1. For individuals previously vaccinated with PPSV23, we recommend a single dose of PCV20 or PCV21 at least 1 year after the PPSV23. *(Strong recommendation, moderate quality of evidence) (1B)*. Alternatively, if PCV20 or PCV21 is not available, we recommend a single dose of PCV13 or PCV15 at least 1 year after PPSV23. *(Weak recommendation, moderate quality of evidence) (2B)*
2. For individuals previously vaccinated with PCV13 or PCV15, we recommend a single dose of PCV 21 or PCV20 at least 1 year after the PCV13 or PCV15. *(Strong recommendation, moderate quality of evidence) (1B)* Alternatively, if PCV21 or PCV20 is not available, we recommend a single dose of PPSV23 at least 1 year after the PCV13 or PCV15. *(Strong recommendation, moderate quality of evidence) (1B)* For those with immunocompromising conditions, cochlear implants, or CSF leaks, an interval of 8 weeks may be considered. *(Strong recommendation, High quality of evidence) (1A)*
3. For individuals previously vaccinated with PCV13 and PPSV23 in any order, supplemental vaccination with PCV21 or PCV20 may be considered 1 year after the last PPSV23 dose. This decision should be made on an individualized basis through shared decision-making, taking into account local epidemiology and individual risks. *(Weak recommendation, low quality of evidence) (2C)*
4. Time since last pneumococcal vaccination: a gap of 5 years or more since the last dose may justify consideration of additional vaccination, due to waning immunity over time. *(Weak recommendation, low quality of evidence) (2C)*

Rationale

Since the introduction of PPSV23 vaccination in 2007 in Taiwan, cumulative coverage among adults aged 75 years and older reached approximately 41.9% by June 2016 [38]. For adults previously vaccinated with PPSV23, especially in the elderly population, vaccination strategies should take into account both the time since prior vaccination and the current serotype coverage needs. At the time of drafting this guidance, only PCV13, PCV15, PCV20, and PPSV23 were available in Taiwan; therefore, the recommendations were developed as a transitional framework, incorporating interim strategies based on currently available vaccines while anticipating the future availability of higher-valent vaccine options.

Under current recommendations, pneumococcal vaccination is considered complete after either PCV13 or PCV15 followed by PPSV23 at one-year interval, or a single dose of PCV20 or PCV21. Any additional vaccination should be guided by a shared decision-making approach. Although previous studies suggest protection lasts at least five years [29,57], booster doses given as early as one year apart have been evaluated in clinical trials without reported safety concerns [71,74]. Due to progressively decreasing vaccine coverage and emerging serotype gaps, where only 39.4% of IPD isolates in adults aged 65 years and older were attributable to serotypes included in PCV13 (Fig. 3D) [39], the panel experts identified a need for further vaccination with broader serotype coverage vaccines. Thus, additional doses of PCV20 or PCV21, preferably PCV21 based on local serotype distribution, may be considered on an individual basis. This recommendation differs from the US ACIP guidance, and recommends a single dose of PCV21 or PCV20 five years or more after the last pneumococcal vaccine dose, if a decision to administer these vaccines is made [77].

The administration of PCV13 or PCV15 following prior PPSV23 is given a weak recommendation due to concerns about hyporesponsiveness [79,80]. In contrast, clinical trials of PCV20 and PCV21 have not shown significant blunting of immunogenicity in individuals previously vaccinated with PPSV23, supporting a stronger recommendation for their use [71,74]. The phenomenon of hyporesponsiveness was shown when repeat PPSV23 doses were given less than five year apart [100], but not when the interval was extended to beyond five years, which induced immune responses comparable to those in PPSV23-naïve individuals [50,101].

Revaccination with PCV13 in adults aged 70 years and older who had been previously vaccinated with PPSV23 more than five years earlier resulted in significantly higher OPA titers (PPSV23/PCV13) compared to revaccination with PPSV23 (PPSV23/PPSV23) for ten of the PCV13 serotypes, although baseline OPA titers following the initial PPSV23 dose were not assessed [79]. In an open-label, single-arm, prospective study of HIV-infected adults aged 18 years and older with CD4 cell counts $\leq$200 cells/mm^3 and HIV viral loads <50,000 copies/mL, a single dose of PCV13 administered a mean of 3.7 years after prior PPSV23 significantly increased IgG GMCs and OPA titers at one month post-vaccination across PCV13 serotypes, surpassing responses observed after subsequent PCV13 doses given at six-month intervals [60]. Similarly, in adults aged 65 years and older who were vaccinated with PPSV23 at least one year earlier, both PCV13 and PCV15 induced a $\geq$ 4-fold increase in IgG and OPA titers for the 13 shared serotypes within 30 days post-vaccination [68].

Two phase 3 RCTs evaluated PCV20 and PCV21 in pneumococcal vaccine-experienced adults. In the PCV20 study involving adults aged 65 years and older with prior vaccination with PPSV23, PCV13, or both, PCV20 induced robust OPA responses across all 20 serotypes irrespective of prior pneumococcal vaccination status, supporting PCV20 as an effective booster strategy. PCV20 was administered at an interval of one to five years after prior PPSV23, at least six months after PCV13, or one year after prior PCV13/PPSV23 vaccination [71]. In a separate phase 3 trial of PCV21 in adults 50 years and older who had received pneumococcal vaccination one year before (either PPSV23, PCV13, PCV15, or a combination), PCV21 induced serotype-specific OPA GMTs immune responses comparable to those of PCV15 and PPSV23 for shared serotypes at one month post-vaccination, while eliciting higher responses to PCV21-unique serotypes such as 23A, 15C, and 35B, and was immunogenic across all serotypes regardless of prior vaccination history [74]. Both studies observed that serologic responses were generally lower in previously vaccinated individuals compared to vaccine-naïve adults. Nevertheless, PCV20 and PCV21 still demonstrated safety as well as robust immunogenicity in these populations.

Given the demonstrated immunogenicity of higher-valency vaccines in individuals with varying histories of prior pneumococcal vaccination, the panel recommends PCV20 or PCV21 for pneumococcal vaccine-experienced adults. However, although PCV21 trials included some participants who had received PCV15 [74], the role of administering PCV20 after PCV15 remains uncertain. Nonetheless, PCV20 expands coverage against five additional serotypes not included in PCV15 (8, 10A, 11A, 12F, 15B) and may be considered for individuals unable to receive PPSV23. If PCV20 or PCV21 is not available, we recommend a single dose of PPSV23 following prior PCV13 or PCV15, or conversely, PCV13 or PCV15 may be given at least one year after prior PPSV23 vaccination. Repeated PPSV23 vaccination is not recommended and should be considered only when all PCV options are unavailable.

5.5. Can pneumococcal vaccines be administered to adults concomitantly with other vaccines?

1. Pneumococcal vaccines (PCV13, PCV15, PCV20, PCV21, or PPSV23) can be administered concomitantly with seasonal influenza vaccines or messenger RNA vaccines for COVID-19. *(Strong recommendation, moderate quality of evidence) (1B)*

Table 4
Recommendations and guidance for concomitant vaccinations with pneumococcal vaccines in adults aged ≥18 years.

Recommendation	GRADE Strength of Recommendation/ Quality of Evidence	Comments
Pneumococcal vaccines (either PCV13, PCV15, PCV20, PCV21, or PPSV23) can be given concomitantly with seasonal influenza vaccines or messenger RNA vaccines for COVID-19.	Strong/Moderate (1B)	- In general, inactivated vaccines can be administered concomitantly with other inactive or live attenuated vaccines (Good practice statement). - Currently, comprehensive data on all possible combinations of pneumococcal vaccines with other vaccines is lacking. Only vaccine combinations that have been evaluated in randomized controlled trials are included in this recommendation.
Recombinant zoster vaccine can be administered concomitantly with either PCV13 or PPSV23.	Weak/Moderate (2B)	
Tetanus-diphtheria vaccine can be administered concomitantly with PCV13.	Weak/Moderate (2B)	

Abbreviations: PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PCV21, 21-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; COVID-19, coronavirus disease 2019.
Level of evidence: 1A, Strong recommendation, High quality of evidence; 1B, Strong recommendation, Moderate quality of evidence; 2B, Weak recommendation, Moderate quality of evidence; 2C, Weak recommendation, Low quality of evidence.

2. The recombinant zoster vaccine can be administered concomitantly with either PCV13 or PPSV23. *(Weak recommendation, moderate quality of evidence) (2B)*
3. The tetanus-diphtheria vaccine can be administered concomitantly with PCV13. *(Weak recommendation, moderate quality of evidence) (2B)*

Rationale

5.5.1. Pneumococcal/seasonal influenza and pneumococcal/COVID-19 vaccines coadministration

Several RCTs have demonstrated that pneumococcal vaccines elicit comparable immunogenicity when administered concomitantly or separately with influenza vaccines [102–105]. However, in some trials, a few pneumococcal serotypes did not meet the noninferiority criteria when the vaccines were coadministered [106,107]. In contrast, the immunogenicity of the seasonal influenza vaccine was noninferior when administered concomitantly with pneumococcal vaccines compared with separate administration [102–105]. Most studies administered the vaccines in contralateral limbs; one randomized trial from Korea suggested that ipsilateral administration enhanced immunogenicity for serotype 6B [108]. Although some studies report slightly higher rates of mild adverse effects with concomitant vaccination compared to separate administration [106,108], coadministration of pneumococcal vaccines (PCV13, PCV15, PCV20, PCV21, or PPSV23) with influenza vaccines has generally been safe and well-tolerated across clinical trials [102–104, 107]. Similarly, studies evaluating the coadministration of COVID-19 messenger RNA vaccines with pneumococcal vaccines (PCV15 and PCV20) showed comparable immunogenicity and safety to separate administration [109,110].

Coinfections with bacterial pathogens, particularly *S. pneumoniae*, are not uncommon during influenza and COVID-19 illnesses and can lead to substantial mortality, especially among the elderly [2,111]. Based on these findings, we recommend the concomitant administration of influenza, COVID-19, and pneumococcal conjugate vaccines to reduce disease burden and improve clinical outcomes, particularly in high-risk populations such as older adults and individuals with underlying medical conditions (Table 4).

5.5.2. Pneumococcal vaccines coadministered with other vaccines

Two studies demonstrated that concurrent administration of PPSV23/PCV13 with the recombinant zoster vaccine elicits comparable immunogenicity and safety to separate administration [112,113]. Another RCT showed that coadministration of PCV13 with the tetanus-diphtheria vaccine resulted in similar immunity and safety profiles compared to separate administration [114].

In general, inactivated vaccines can be safely administered concomitantly with other inactivated or live attenuated vaccines (Good Practice Statement), such as respiratory syncytial virus vaccines. However, coadministration of PCV7 with meningococcal vaccine, MenACWY-D, resulted in reduced antibody concentrations of three pneumococcal serotypes (4, 6B, and 18C) [115]. Similarly, coadministration of PCV13 with the hepatitis A virus vaccine resulted in lower protective anti-HAV antibody levels compared to HAV vaccination alone [116]. The clinical significance of this reduced immunogenicity remains unclear. For individuals planning to receive the aforementioned vaccines in combination with pneumococcal vaccines, it is advisable to schedule an interval of at least one month between vaccinations.

6. Safety

PPSV23 has been in use for decades since its approval in the U.S. in 1983. Systematic reviews including various study designs have not reported serious adverse events during the observation periods following primary vaccination or revaccination, respectively [117]. Two post-licensure safety surveillance reports found no safety concerns [118, 119]. A pivotal trial of PCV13 and subsequent systematic reviews demonstrated similar safety profiles compared to placebo or PPSV23 [56,120]. Clinical trials of newer PCV vaccines, including PCV15 [64,68, 103], PCV20 [31,70,71], and PCV21 [33,74] also showed safety outcomes consistent with PCV13 or PPSV23 in vaccine naïve or previously vaccinated adults. The most commonly solicited adverse event was injection-site pain. No vaccine-related serious adverse events or death were reported, except for a report of vaccine-related cellulitis in one participant following PCV21 vaccination [74]. Overall, the safety of all PCV vaccines is well established based on available clinical trial data. Continued post-licensure safety monitoring after extensive use of new PCV vaccines is needed to capture rare adverse events following vaccination.

7. Limitations of evidence

This guidance evaluated the efficacy and safety of pneumococcal vaccines primarily based on published clinical trials. Efficacy assessments mostly reported serotype-specific functional OPA titers, which are widely accepted as surrogate markers of pneumococcal vaccine immunogenicity; however, the correlation between OPA titers and real-world clinical effectiveness remains uncertain and requires further validation through long-term observational studies [26]. Safety data from clinical trials are also limited by short durations of follow-up and relatively small sample sizes, highlighting the importance of continued post-licensure surveillance to capture rare or delayed adverse events, and confirm the safety profile of these vaccines.

The implementation of PCV in children under two years of age has been shown to confer herd immunity, leading to reductions in pneumococcal pneumonia and IPD across other age groups [38]. There are concerns that adults receiving PCV21, a novel high-valency pneumococcal vaccine not containing the original PCV7 serotypes, will rely only

on herd immunity to have sufficient protection against non-vaccine serotypes. Additionally, the possibility of waning immunogenicity with higher-valency vaccines, such as PCV20 and PCV21, will require long-term evaluations for durability and the need for booster doses. Cost-effectiveness analyses incorporating herd immunity effects in Taiwan have demonstrated that PCV13/PCV7 vaccination strategies may be cost-effective [121,122]. Future economic evaluations of newer PCV vaccines should consider local epidemiology and real-world data to guide the NIP policy.

Finally, in view of the dynamic changes in local pneumococcal seroepidemiology, consultation with infectious disease specialists is recommended to ensure optimal vaccine selection and vaccine strategy.

8. Conclusion

This guidance highlights the continual evolution of pneumococcal vaccination strategy in response to changing serotype epidemiology and the introduction and availability of higher-valency conjugate vaccines. The recommendations in this guidance are based on current epidemiological data and available clinical evidence; and are intended to give healthcare providers clear guidance for selecting an optimal vaccine strategy for protecting at-risk adults against pneumococcal disease. Ongoing surveillance and periodic reassessment and updates of these recommendations are necessary to ensure that adult pneumococcal vaccination strategies remain optimal and provide the broadest and most effective protection for vulnerable populations.

CRediT authorship contribution statement

I-Fan Lin: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Kuan-Yin Lin:** Writing – original draft, Data curation, Conceptualization. **Lian-Yi Su:** Writing – original draft, Data curation, Conceptualization. **Wei-Hsuan Huang:** Writing – original draft, Data curation, Conceptualization. **Wen-Chia Tsai:** Writing – original draft, Data curation, Conceptualization. **Ping-Feng Wu:** Writing – original draft, Data curation, Conceptualization. **Ching-Hsun Wang:** Writing – original draft, Data curation, Conceptualization. **Chia-Hsiang Yu:** Writing – original draft, Data curation, Conceptualization. **Miao-Chiu Hung:** Writing – original draft, Data curation, Conceptualization. **Cheng-Hsun Chiu:** Writing – review & editing, Supervision, Conceptualization. **Chien-Hsien Huang:** Writing – review & editing, Supervision, Conceptualization. **Nan-Chang Chiu:** Writing – review & editing, Supervision, Conceptualization. **Chun-Yi Lu:** Writing – review & editing, Supervision, Conceptualization. **Ming-Fang Cheng:** Writing – review & editing, Supervision, Conceptualization. **Szu-Min Hsieh:** Writing – review & editing, Supervision, Conceptualization. **Ning-Chi Wang:** Writing – review & editing, Supervision, Conceptualization. **Ping-Ing Lee:** Writing – review & editing, Supervision, Conceptualization. **Hsiao-Wei Wang:** Writing – review & editing, Supervision, Conceptualization. **Swee Siang Wong:** Writing – review & editing, Supervision, Conceptualization. **Po-Chang Lin:** Writing – review & editing, Supervision, Conceptualization. **Ming-Han Tsai:** Writing – review & editing, Supervision, Conceptualization. **Shun-Cheng Yang:** Writing – review & editing, Supervision, Conceptualization. **Yu-Lung Hsu:** Writing – review & editing, Supervision. **Chuen-Sheue Chiang:** Writing – review & editing, Data curation. **Susan Shin-Jung Lee:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Yee-Chun Chen:** Writing – review & editing, Supervision, Conceptualization. **Feng-Yee Chang:** Writing – review & editing, Supervision, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used ChatGPT-5 (OpenAI, 2025) solely to improve the clarity and fluency of the text. The tool was used exclusively for language refinement and structural organization; it did not generate or alter any scientific data, analyses, or recommendations. All authors have carefully reviewed and edited the AI-assisted output to ensure accuracy and integrity, and we take full responsibility for the final content.

Declaration of competing interest

The authors declare no potential conflicts of interest with regard to the research, authorship, or publication of this article.

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Appendix A. Supplementary data

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