The role of a single-shot higher-valency pneumococcal vaccine in overcoming challenges regarding invasive pneumococcal disease in Hong Kong

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Invasive pneumococcal disease (IPD), a major public health problem worldwide (including in Hong Kong),[1-3] is a severe and potentially life-threatening infectious disease caused by the gram-positive bacterium, *Streptococcus pneumoniae*.[1,2] The clinical manifestations of acute IPD vary among organ systems involved; they include severe and potentially fatal infections such as community-acquired pneumonia, meningitis, and sepsis.[2] In Hong Kong, pneumonia has consistently been the second leading cause of death since 2012[4]; it is associated with higher rates of hospitalisation and higher healthcare costs, particularly among older adults.[5,6] Despite appropriate treatment, up to 50% of IPD survivors experience long-term complications, including respiratory, cardiovascular, and neurological sequelae.[7] Invasive pneumococcal disease is associated with substantial healthcare and economic burdens; thus, it represents an acute public health problem in Hong Kong, particularly amid the coronavirus disease 2019 (COVID-19) pandemic. There is an urgent need to develop effective strategies that can mitigate the potential threat of an IPD outbreak.

Burden of invasive pneumococcal disease in Hong Kong

Invasive pneumococcal disease has been a statutorily notifiable disease in Hong Kong since January 2015.[8] Between 2015 and 2019, the Centre for Health Protection recorded a median of 187 (range: 162-190) IPD cases per year; the emergence of COVID-19 in 2020 led to a dramatic decrease in the number of IPD cases in Hong Kong (Fig 1).[3] However, the current IPD burden is severely underestimated because of underdiagnosis, and a high index of suspicion for IPD is a central aspect of differential diagnosis. Because the clinical symptoms of IPD overlap with the symptoms of other respiratory illnesses, inexperienced physicians may experience challenges regarding specimen collection (ie, samples may be inappropriately or inadequately collected); such challenges contribute to the underutilisation of diagnostic tests and underreporting of IPD.

Because *S pneumoniae* is transmitted by direct contact with respiratory secretions from patients with IPD and from healthy carriers,[2,9] public health measures (eg, mask wearing, social distancing, travel restrictions, and quarantine) that were implemented to prevent the transmission of severe acute respiratory syndrome coronavirus 2 also reduced the spread of *S pneumoniae*; thus, the number of IPD cases has decreased since the beginning of 2020 (Fig 1).[3] As Hong Kong emerges from the COVID-19 pandemic, the gradual relaxation of public health intervention measures is expected to result in an increased number of IPD cases. Moreover, seasonality could contribute to a sudden increase in IPD cases because respiratory diseases (eg, pneumococcal infection and influenza) are generally more prevalent during winter and early spring.[10,11] Notably, Israel experienced a nationwide outbreak of *S pneumoniae* serotype 2 between 2015 and 2019, despite the availability of vaccination programmes.[12] Such outbreaks highlight the need to formulate effective strategies for early disease prevention.

Pneumococcal vaccination in Hong Kong

Two types of pneumococcal vaccines are available to prevent IPD: pneumococcal polysaccharide vaccines

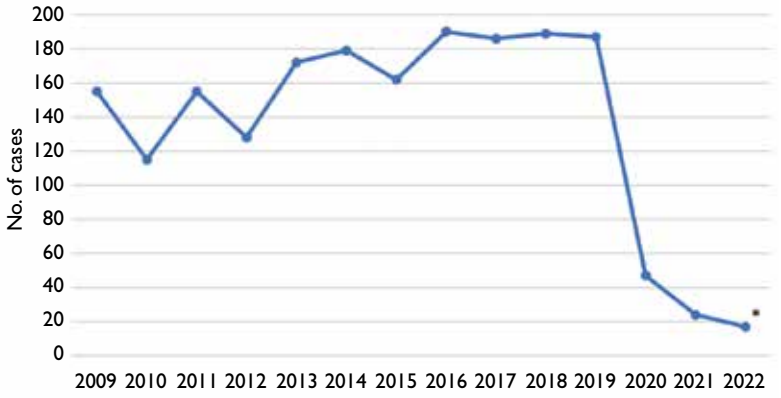


FIG 1. Number of invasive pneumococcal disease cases in Hong Kong, 2009-2022[3]
* Data for 2022 were only available for January through September

(PPSVs) and pneumococcal conjugate vaccines (PCVs). The 23-valent PPSV (PPSV23) contains purified capsular polysaccharide antigens from 23 distinct *S pneumoniae* serotypes, whereas PCVs—including PCV13, PCV15, and PCV20—contain purified capsular polysaccharide antigens from 13, 15 or 20 serotypes of *S pneumoniae* conjugated to a nontoxic variant of diphtheria toxin (CRM197), along with aluminium phosphate as an adjuvant.[13,14] In contrast to PPSVs, the conjugated complexes contained in PCVs exert long-term protection because they are able to stimulate T-cell-dependent immune response to generate immune memory for the specific *S pneumoniae* serotypes covered by the vaccine.[15] Importantly, clinical trials and real-world evidence have consistently demonstrated the effectiveness of PCV13 in providing serotype-specific protection against IPD.[2,13,16] Although IPD can occur at any age, an increased risk of onset is associated with various factors; mortality is substantially higher in children <2 years and adults aged ≥65 years.[10,13] In Hong Kong, the current recommendations for pneumococcal vaccination by the Centre for Health Protection prioritise adults aged ≥65 years with high-risk conditions,[17] consistent with recommendations from the United States Advisory Committee on Immunization Practices.[18] Specifically, pneumococcal vaccine-naïve individuals with high-risk conditions are recommended to receive one dose of PCV13, followed by one dose of PPSV23 at 1 year after PCV13 vaccination.[17]

Since 2017, the Hong Kong government has provided free or subsidised pneumococcal vaccination to eligible individuals through the Government Vaccination Programme (GVP) and the Vaccination Subsidy Scheme (VSS).[19] Despite this governmental support, rates of vaccine uptake and participation in GVP and VSS remain low.[19] Concerns regarding vaccine efficacy, poor understanding of the disease, and lack of clarity regarding vaccine schedules are some of the major challenges that limit pneumococcal vaccination among adults in Hong Kong.[19] Another limiting factor is vaccine hesitancy related to perceived vaccination burden and fatigue.[20]

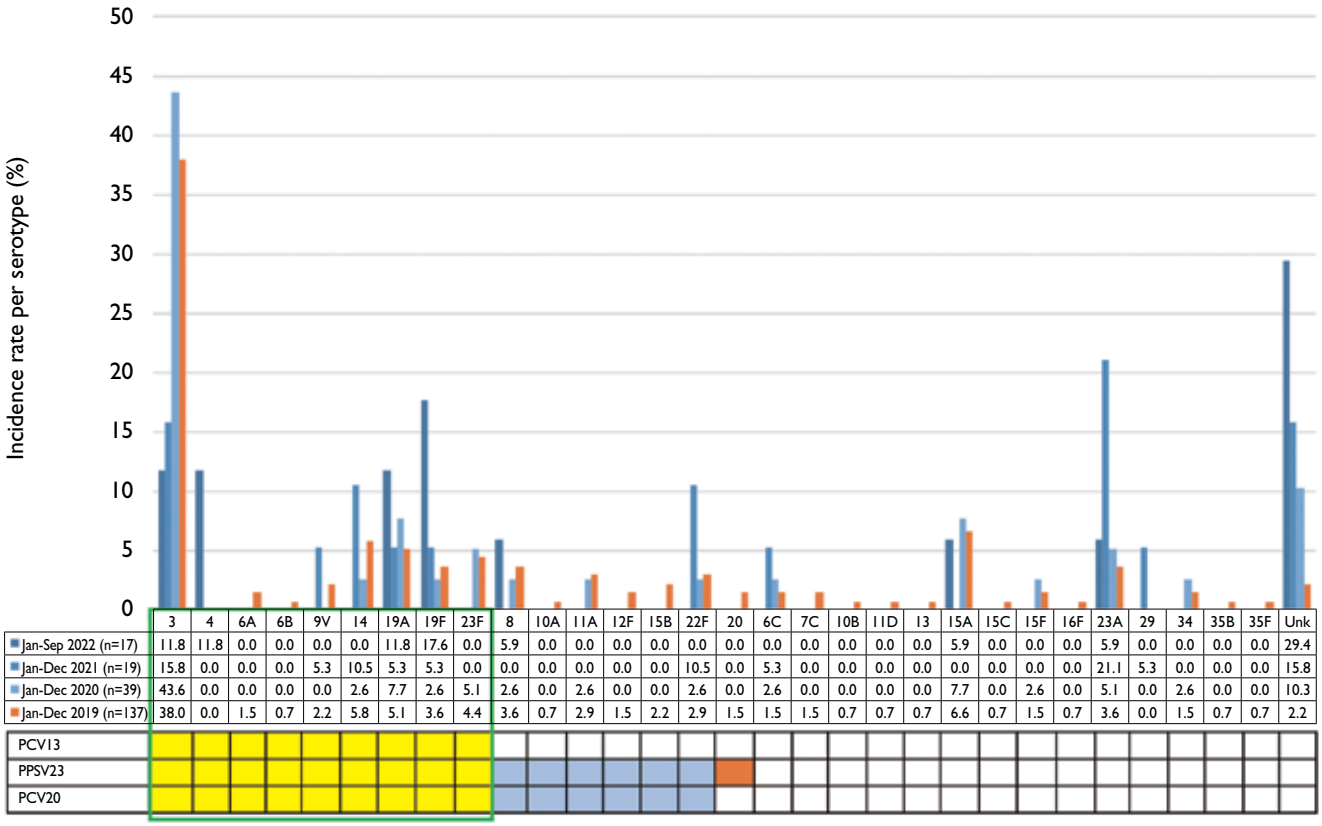
Current serotype burden in Hong Kong

Data from continuous surveillance of pneumococcal serotypes have facilitated analyses of serotypes isolated from the community, which have yielded insights regarding the effectiveness and limitations of pneumococcal vaccination programmes. Since the implementation of pneumococcal vaccination in Hong Kong, the incidence of IPD involving vaccine-covered serotypes has considerably decreased. However, because of low vaccination rates in recent years, PCV13-covered serotypes (including serotypes 3, 19F, and 19A) have been identified in half of all reported IPD cases (Fig 2).[3,21-23] Importantly, although it is covered by PCV13 and PPSV23, serotype 3 remains a major cause of IPD because its unique polysaccharide capsule resists detection by vaccine-induced antibodies.[24] Moreover, the emergence of non-vaccine serotypes (Fig 2; ie, serotype replacement) also poses a public health threat.[23,25]

A higher-valency vaccine for broader protection against invasive pneumococcal disease

Considering the current challenges in Hong Kong, a higher-valency PCV (eg, PCV20) could partly address the potential public health problem associated with serotypes that are not covered by the Hong Kong vaccination programme. The 20-valent PCV provides broader protection against IPD; a single dose contains seven new serotypes, in addition to the serotypes covered by PCV13.[26] Phase 3 studies of clinical efficacy have demonstrated that PCV20 is noninferior to PCV13 and PPSV23 across a subset of age-groups, regardless of pneumococcal vaccination history and high-risk conditions.[27,28] Importantly, PCV20 can be concurrently administered with influenza and COVID-19 vaccines.[26]

In October 2021, the Advisory Committee on Immunization Practices recommended one dose of PCV20 alone, or serial immunisation (PCV15, followed by PPSV23), for all PCV/PPSV-naïve adults aged ≥65 years and PCV/PPSV-naïve adults aged 19-64 years with high-risk conditions.[26] The implementation of a PCV20 single-shot vaccination programme could be a cost-effective strategy to address the current burden of IPD cases that involve serotypes covered by PCV13 and serotypes unique to PCV20.[29] Furthermore, the convenience of a simplified vaccination schedule could improve vaccine uptake.



	3	4	6A	6B	9V	14	19A	19F	23F	8	10A	11A	12F	15B	22F	20	6C	7C	10B	11D	13	15A	15C	15F	16F	23A	29	34	35B	35F	Unk
Jan-Sep 2022 (n=17)	11.8	11.8	0.0	0.0	0.0	0.0	11.8	17.6	0.0	5.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.9	0.0	0.0	0.0	5.9	0.0	0.0	0.0	0.0	29.4
Jan-Dec 2021 (n=19)	15.8	0.0	0.0	0.0	5.3	10.5	5.3	5.3	0.0	0.0	0.0	0.0	0.0	0.0	10.5	0.0	5.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	21.1	5.3	0.0	0.0	0.0	15.8
Jan-Dec 2020 (n=39)	43.6	0.0	0.0	0.0	0.0	2.6	7.7	2.6	5.1	2.6	0.0	2.6	0.0	0.0	2.6	0.0	2.6	0.0	0.0	0.0	0.0	7.7	0.0	2.6	0.0	5.1	0.0	2.6	0.0	0.0	10.3
Jan-Dec 2019 (n=137)	38.0	0.0	1.5	0.7	2.2	5.8	5.1	3.6	4.4	3.6	0.7	2.9	1.5	2.2	2.9	1.5	1.5	1.5	0.7	0.7	0.7	6.6	0.7	1.5	0.7	3.6	0.0	1.5	0.7	0.7	2.2
PCV13																															
PPSV23																															
PCV20																															

FIG 2. Number of reported pneumococcal serotypes among IPD patients aged ≥18 years in Hong Kong, 2019-2022[3]*

Abbreviations: IPD = invasive pneumococcal disease; PCV = pneumococcal conjugate vaccine; PPSV = pneumococcal polysaccharide vaccine; Unk = Unknown

* Coloured boxes indicate the coverage of each vaccine: yellow corresponds to serotypes covered by PCV13, PPSV23, and PCV20; blue corresponds to serotypes covered by PPSV23 and PCV20 but not PCV13; orange corresponds to serotypes covered only by PPSV23; and white corresponds to serotypes not covered by any vaccine. Area outlined in green indicates PCV13-covered serotypes and corresponding annual incidences

Overcoming challenges in Hong Kong and implementing preventive strategies against invasive pneumococcal disease

The government and physicians play key roles in promoting pneumococcal vaccination and improving vaccine uptake, particularly among older adults. Because the perceived low burden of IPD may reduce the rate at which physicians recommend vaccination for their patients,[30] there is a need to improve physician awareness regarding IPD and the benefits of pneumococcal vaccines for individuals with an increased risk of IPD.

Continuing medical education programmes for physicians could cover periodic updates regarding the IPD burden in Hong Kong, current pneumococcal vaccine schedules, proper sample collection methods, and appropriate diagnostic tests for confirmation of IPD in patients with relevant symptoms. These initiatives can improve early diagnosis and treatment of IPD, facilitate accurate data collection regarding IPD incidence, and help to manage the underestimated burden of IPD. Additionally, government-led public education campaigns that focus on bridging knowledge gaps with respect to (i) the public health impact of IPD (a vaccine-preventable disease), and (ii) vaccine accessibility through GVP and VSS, could help to overcome vaccine hesitancy and improve vaccine uptake in Hong Kong.

Conflict of interest

All authors declare no conflict of interest.

Author contributions

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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