# Practice recommendations for respiratory syncytial virus prophylaxis among children in Hong Kong

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A B S T R A C T

Hong Kong has a high burden of hospitalisations associated with respiratory syncytial virus (RSV) infection in young children. Most international guidelines concerning RSV prophylaxis are based on studies conducted in temperate climates and may not fully apply to subtropical locations such as Hong Kong. In July 2022, a group of nine experts in neonatology, paediatric intensive care, paediatric respiratory medicine, and paediatric cardiology in Hong Kong convened to formulate recommendations for RSV prophylaxis. The recommendations were based on literature review and expert discussion. Each expert reviewed evidence specific to a particular area and formulated consensus statements. The expert panel reached a consensus on 11 statements, which addressed the epidemiology of RSV infection in Hong Kong, the goals and outcomes of RSV prophylaxis in preterm infants and infants with congenital heart disease or bronchopulmonary dysplasia, safety, and cost. Because there is no clear seasonality pattern for RSV infection in Hong Kong, panel members emphasised using gestational age, rather than season, to guide prophylaxis recommendations. The experts agreed that RSV prophylaxis should be considered for 5 to 6 months after hospital discharge among preterm infants born at <29 weeks gestational age; it should also be considered for children aged <1 year with haemodynamically significant congenital heart disease or bronchopulmonary dysplasia.

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## Introduction

Acute lower respiratory tract infections associated with respiratory syncytial virus (RSV) are a common cause of hospitalisation among young children.[1,2] In Hong Kong, RSV infection is the leading reason for hospitalisation among children aged <5 years with respiratory viral infections, causing 50% of deaths in this age-group.[3] A study conducted at a paediatric intensive care unit (ICU) in Hong Kong revealed that paramyxovirus infections, predominantly RSV, caused 5% of all paediatric ICU admissions and were associated with significant morbidity.[4] Among the RSV-infected patients, 39.4% needed mechanical ventilation and 21.1% needed inotropic support.[4] Treatment for viral bronchiolitis is mainly supportive because no pharmacological treatment or novel therapy has been shown to improve outcomes compared with supportive care.[5]

Although numerous vaccines, therapeutic antibodies, and antiviral drugs for the prevention and treatment of RSV infection are in development,[6] the only available prophylactic agent is palivizumab,[7] a humanised immunoglobulin G1 monoclonal antibody that targets the fusion protein of RSV.[8] Palivizumab is effective in reducing the rate of RSV hospitalisation (RSVH) among high-risk children.[9] International guidelines recommend palivizumab prophylaxis in groups such as preterm infants, former preterm infants with chronic lung disease/bronchopulmonary dysplasia (BPD), and children aged <2 years with haemodynamically significant congenital heart disease (hsCHD).[7,10]

 

In Hong Kong, local healthcare practices regarding palivizumab prophylaxis are informed by data from international studies and guidance statements.[10-12] However, these international publications do not reflect the local treatment landscape. Palivizumab is reimbursed by the government for preterm infants born at <34 weeks gestational age (wGA) who have chronic lung disease requiring home oxygen therapy or medication at discharge, up to a chronological age of 6 to 9 months (maximum of five doses). The perception among clinicians is that palivizumab use varies across hospitals. Furthermore, international guidance is predominantly derived from studies in regions with temperate climates and may not fully apply to subtropical locations such as Hong Kong, particularly with respect to the seasonality of RSV infection.[13,14] In this article, we summarise RSV prophylaxis recommendations developed by a group of experts in Hong Kong, with the aim of assisting physicians engaged in treating children at risk of RSV infection, both locally and internationally.


## 預防香港兒童感染呼吸道合胞病毒的實踐建議

韓錦倫、張蔚賢、李民瞻、馮寶姿、林樹仁、李淑嫻、李誠仁、梁平、吳國強

在香港，與呼吸道合胞病毒（RSV）感染相關的住院常見於幼童，為醫院造成沉重負擔。大部分關於預防RSV的國際指引都是按於温帶地區進行的研究而制訂，因此未必完全適用於亞熱帶地區（例如香港）。2022年7月，九位來自新生兒科、兒童深切治療科、兒童呼吸科及兒童心臟科的香港醫生組成專家小組，召開會議制訂預防RSV的建議。小組根據文獻回顧，進行討論提出相關建議，並由每位專家檢視其範疇的證據及制訂共識聲明。小組最終就11項聲明達成共識，涵蓋本港RSV感染的流行病學、預防早產嬰兒及患有先天性心臟病或支氣管肺部發育不良的嬰兒感染RSV的目標及結果，以及預防感染RSV措施的安全性及成本。由於本港的RSV感染沒有明顯的季節性模式，因此小組成員著重使用妊娠年齡而非季節來制訂預防感染RSV的建議。各成員同意應考慮為以下兒童採取預防感染RSV的措施：（1）早於29週出生的早產嬰兒（在出院5至6個月內）；及（2）患有具血流動力學意義的先天性心臟病或支氣管肺部發育不良的1歲以下兒童。


## Methods

A meeting was convened in July 2022 to formulate evidence-based recommendations for RSV prophylaxis among children in Hong Kong. The panel comprised experts in neonatology, paediatric intensive care, paediatric respiratory medicine, and paediatric cardiology, representing both private and public healthcare sectors. A set of clinical questions was established, and selected panel members screened the results of a series of focused literature reviews. These reviews were centred around the following topics: the epidemiology of RSV infection (including seasonality), the burden of RSV infection in vulnerable paediatric populations, international guidance concerning RSV prophylaxis, and the efficacy and safety of prophylaxis. Literature searches were performed using PubMed to identify relevant English-language publications, with an emphasis on studies published in the past 10 years (up to April 2022). Proposed statements were drafted and evaluated during the meeting using a modified Delphi method. Panel members rated the statements using a Likert scale (1–Agree completely; 2–Agree with reservation; 3–Disagree with reservation; 4–Disagree completely). Consensus was defined as ≥75% of panel members responding '1–Agree completely' or '2–Agree with reservation'. In the absence of consensus, the relevant statements were revised and re-evaluated until consensus was reached. Where applicable, the quality of evidence supporting each statement was evaluated according to the Oxford Centre for Evidence-Based Medicine's 2011 Levels of Evidence.[15] Treatment recommendations were assigned a subjective strength (strong, moderate, or weak) based on the level of evidence and degree of consensus.

This manuscript was prepared in accordance with the AGREE (Appraisal of Guidelines for Research and Evaluation) Reporting Checklist.[16]

## Consensus statements

Eleven statements were formulated and met the consensus criteria during the meeting. These statements, including their level of evidence, strength of recommendation and agreement, are summarised in the Table.[15]

*Statement 1: The disease burden of respiratory syncytial virus is high in Hong Kong; infants are most affected.*

Data concerning RSV epidemiology in Hong Kong are scarce, but two studies provided important insights. A single-centre study conducted from 1998 to 2012 revealed that the annual rate of RSVH among children aged <5 years was 157.7 per 10 000; most hospitalisations involved infants aged <1 year.[3] This RSVH rate was higher than the rates reported in a 2015 systematic review and modelling study, which estimated that RSVH rates in high-income countries were 26.3, 11.3, and 1.4 per 1000 in children aged ≤5 months, 6 to 11 months, and 12 to 59 months, respectively[2]; corresponding mortality rates were 0.2%, 0.9%, and 0.7%.[2] Almost half of the hospitalisations and hospital deaths attributed to RSV-associated acute lower respiratory tract infection occurred in children aged <6 months.[2] More recent local epidemiological data were provided by a multicentre case-control study conducted in four hospitals from 2013 to 2015, which included 3538 admissions for paediatric

TABLE. Summary of consensus statements concerning respiratory syncytial virus prophylaxis

| No. | Statement | Evidence level[15] | Strength of recommendation | Agreement |
|---|---|---|---|---|
| 1 | The disease burden of RSV is high in Hong Kong; infants are most affected. | 1 | N/A | 100% |
| 2 | RSV infection does not demonstrate a clear seasonal pattern in Hong Kong, but its incidence tends to peak from March to April and again during the summer (July to August). | 3 | N/A | 100% |
| 3 | Although RSV incidence decreased during COVID-19 lockdown periods, some countries experienced a resurgence after social restrictions had been lifted, with altered epidemiological patterns. The exact impact on RSV prevalence in Hong Kong remains unknown. | 3 | N/A | 100% |
| 4 | The goals of RSV prophylaxis are to reduce adverse effects on the lungs and circulation, while decreasing hospitalisations and ICU stays, in vulnerable infants. | 1 | Strong | 100% |
| 5 | RSV prophylaxis should be considered for 5 to 6 months after hospital discharge among preterm infants born at <29 weeks gestational age. | 1 | Strong | 89% |
| 6 | Children aged <1 year with BPD are vulnerable to serious lower respiratory tract illness and have a higher risk of hospitalisation compared with healthy children after RSV infection; RSV prophylaxis should be considered for these children. | 1 | Strong | 100% |
| 7 | RSV prophylaxis reduces the number and duration of RSV-related hospitalisations among children aged <2 years with haemodynamically significant CHD. | 1 | Moderate | 100% |
| 8 | A 6-month prophylaxis regimen (six doses) in the first year of life is suggested for children with hsCHD. | 1 | Moderate | 78% |
| 9 | Current evidence indicates that the use of palivizumab as RSV prophylaxis is safe and well-tolerated, with minimal risk of adverse reactions. | 1 | N/A | 100% |
| 10 | The only contraindication to the use of palivizumab is a previous history of confirmed hypersensitivity reaction to palivizumab. | 1 | N/A | 100% |
| 11 | The cost-effectiveness of palivizumab prophylaxis in Hong Kong is unclear. | N/A | N/A | 100% |

Abbreviations: BPD = bronchopulmonary dysplasia; CHD = congenital heart disease; COVID-19 = coronavirus disease 2019; hsCHD = haemodynamically significant congenital heart disease; ICU = intensive care unit; N/A = not applicable; RSV = respiratory syncytial virus

RSV infection.[17] The mortality rate was 0.14%, and 44.6% of hospitalisations involved infants aged ≤12 months[17]; this rate is lower than comparable data from Western countries (ie, 75%-90% in infants aged ≤12 months).[18] Meta-analysis data from China indicate that RSV is the leading cause of viral acute respiratory tract infections, present in 18.7% of cases overall and 26.5% of cases among infants aged ≤1 year.[19] The actual burden of RSV infection in China may be higher, due to the limited sensitivity of diagnostic methods used during studies included in the meta-analysis.[19] Although differences in study designs may explain the discrepancies between international and local data, there is no doubt that RSV is associated with a substantial disease burden among infants in Hong Kong.

*Statement 2: Respiratory syncytial virus infection does not demonstrate a clear seasonal pattern in Hong Kong, but its incidence tends to peak from March to April and again during the summer (July to August).*

In Western European countries, laboratory-confirmed RSV infections generally exhibit a well-defined seasonal pattern, with peaks in winter and spring; few cases occur in summer and autumn.[20] In Hong Kong, an analysis of RSVH across all age-groups at a single centre over 15 years showed annual peaks of approximately 12 cases per week occurring around March and September; moderate levels of cases (5-10 cases per week) were observed from May to August, and the lowest rate of hospitalisation (<5 cases per week) occurred from October to February.[3] A multicentre study of paediatric RSV admissions across four Hong Kong hospitals from 2013 to 2015 revealed a similar pattern of peaks in hospitalisation from March to April and July to August, separated by moderate inter-peak levels during the summer; the lowest levels of hospitalisation were observed from October to February.[17] Similar seasonality patterns

were observed both overall and among a subset of patients with heart disease.[17] Most infections (87.7% in the entire cohort and 91.1% in the heart disease group) occurred between January and September.[17] The same study showed that RSV incidence was positively correlated with relative humidity, whereas it was negatively correlated with wind speed and atmospheric pressure.[17] Despite differences in populations, the pattern of RSVH seasonality was consistent between these two studies; both demonstrated that RSVH in Hong Kong mainly occurs in warmer months.[3,17]

*Statement 3: Although respiratory syncytial virus incidence decreased during coronavirus disease 2019 lockdown periods, some countries experienced a resurgence after social restrictions had been lifted, with altered epidemiological patterns. The exact impact on respiratory syncytial virus prevalence in Hong Kong remains unknown.*

Data from Australia,[21] France[22] and Japan[23] show that strict infection control measures implemented during the coronavirus disease 2019 (COVID-19) pandemic led to a substantial reduction—up to 98%—in RSV cases during 2019 and 2020. In Australia, after the relaxation of physical distancing measures in late 2020, the usual incidence peak in autumn was replaced by a peak in summer[21]; RSV incidence was higher in the 2020 summer peak than it had been in winter peaks from 2012 to 2019.[21] Furthermore, the median patient age after COVID-19 restrictions were lifted in 2019 to 2020 was 18.4 months, significantly older compared with previous years (7.3-12.5 months from 2012 to 2019; P<0.001)[21]; this shift likely resulted from decreased prior exposure and declining collective immunity. Data from Hong Kong suggest that measures adopted during the COVID-19 pandemic (eg, social distancing, face masks, and enhanced personal hygiene) reduced the incidence of RSV infection; the surge in RSV cases during late 2021 coincided with the relaxation of these measures.[24] However, the overall impacts of measures adopted during the COVID-19 pandemic on RSVH rates, affected populations, and seasonality in Hong Kong are unclear.

*Statement 4: The goals of respiratory syncytial virus prophylaxis are to reduce adverse effects on the lungs and circulation, while decreasing hospitalisations and intensive care unit stays, in vulnerable infants.*

Various international studies have demonstrated that the risk of severe illness from RSV infection increased among at-risk children, namely preterm infants and those with CHD or BPD. A retrospective cohort study in the US (1989-1993; 248 652 child-years) showed that children with BPD had a higher rate of RSVH in the first year of life compared with children who lacked underlying medical conditions (388 vs 30 per 1000, respectively).[25] The same study also revealed that preterm infants with CHD had a RSVH rate of 120.8 per 1000 from 0 to 6 months after birth (vs 44.1 in low-risk infants); this rate declined in the second year of life to 18.2 per 1000 (vs 3.7 for low-risk infants).[25] A multicentre study in Korea (n=1140) demonstrated that BPD increased the risk of re-admission to neonatal ICUs among preterm infants born at <34 wGA compared with similar preterm infants who did not exhibit BPD (odds ratio [OR]=2.95, 95% confidence interval [CI]=1.44-6.04; P=0.003).[26] The results of a retrospective database study in Australia (2001-2010; n=870 314) indicated that BPD had the largest effect on RSVH risk among various risk factors.[27] Furthermore, a meta-analysis of 29 studies by Chaw et al[28] assessed RSVH risk and other measures of severe illness from RSV infection among young children with BPD. In addition to an increased risk of hospitalisation (OR=2.6, 95% CI=1.7-4.2; P<0.001), children with BPD had an increased risk of ICU admission (OR=2.9, 95% CI=2.3-3.5; P<0.001), increased need for oxygen supplementation (OR=4.2, 95% CI=0.5-33.7) and mechanical ventilation (OR=8.2, 95% CI=7.6-8.9; P<0.001), and longer median length of stay (7.2 days vs 2.5 days) compared with children who did not exhibit BPD.[28] Overall, these studies have shown that children with BPD experience higher risks of hospitalisation and severe illness from RSV infection relative to children without BPD.

Illustrative data concerning the impact of prematurity on RSV infection burden were provided by SENTINEL1, an observational cohort study conducted in the US involving preterm infants (29-35 wGA, <12 months old) who did not receive prophylaxis and were hospitalised for RSV during peak season (2014-2015).[29] Infants aged <6 months experienced 78% of hospitalisations and 87% of ICU admissions; they comprised 92% of cases requiring invasive mechanical ventilation.[29] Among infants aged <3 months who had been born at 29 to 32 wGA, the ICU admission rate was 68%; 44% of these infants required invasive mechanical ventilation.[29] Regression analysis demonstrated that earlier gestational age at birth and younger chronological age at the time of RSV infection were factors associated with ICU admission and the need for invasive mechanical ventilation.[29] A pooled analysis of seven prospective observational studies conducted in the Northern Hemisphere (2000-2014) assessed the burden of RSV infection in preterm infants who had been born at 33 to 35 wGA, lacked co-morbidities, and were not receiving immunoprophylaxis (n=7820).[30] The pooled incidence rate of RSVH was 3.41%; among the infants, 22.2% required neonatal

ICU admission and 70.4% required supplemental oxygen.[30] Although these two studies are not directly comparable due to differences in design and population—notably the infants' gestational age at birth—they consistently demonstrate a high burden of severe illness in preterm infants with RSV infection.[29,30]

Similar to preterm infants, infants with CHD have an increased risk of severe disease.[12] The local burden of RSV infection among children with CHD is unclear, but the multicentre study by Lee et al[17] assessing paediatric RSVHs included a subset of children with heart disease (not limited to CHD). Relative to children without heart disease, children with heart disease had a longer median hospital stay (4 days vs 2 days; P<0.001), higher complication rate (28.6% vs 9.8%; P<0.001), and higher rates of intensive care (11.6% vs 1.4%; P<0.001) and mechanical ventilation (3.6% vs 0.4%; P=0.003).[17] Based on the local and international data summarised above, and in alignment with guidelines from the American Academy of Pediatrics (AAP),[11] we recommend that RSV prophylaxis should focus on reducing the disease burden in preterm infants and young children with BPD or heart disease.

*Statement 5: Respiratory syncytial virus prophylaxis should be considered for 5 to 6 months after hospital discharge among preterm infants born at <29 weeks gestational age.*

The AAP published guidance in 2009 recommending palivizumab prophylaxis at the start of RSV season among infants born at <31 wGA, as well as among infants born at 32 to 35 wGA who have risk factors for increased exposure (eg, attending a day-care facility or living with young siblings).[7] The AAP made a substantial change to the guidance in 2014 by narrowing the intended population to infants aged <12 months who had been born at <29 wGA.[11] An observational study in Italy compared the RSVH rates among infants aged <2 years before (up to 2016) and after changes in palivizumab reimbursement criteria that aligned with the changes in AAP recommendations.[31] The study identified a reduction in RSVH rates from 6.3 per 1000 (95% CI=6.0-6.7) to 5.5 per 1000 (95% CI=5.0-5.9) after the change.[31] These data suggest that 29 wGA is an appropriate age cut-off for palivizumab prophylaxis; our recommendation for this age threshold concerning prophylaxis in preterm infants aligns with the AAP's 2014 guideline.[11]

As noted above, the seasonality of RSV incidence is less distinct in Hong Kong than in Europe,[3,17,20] but local data indicate that gestational age is a key determinant of RSVH risk. One study showed that the cost-effectiveness of palivizumab prophylaxis was higher among infants born at <27 wGA than among infants born at <29 wGA, regardless of the season.[32] Therefore, gestational age, rather than season, should be a primary factor guiding prophylaxis recommendations in Hong Kong.

*Statement 6: Children aged <1 year with bronchopulmonary dysplasia are vulnerable to serious lower respiratory tract illness and have a higher risk of hospitalisation compared with healthy children after respiratory syncytial virus infection; respiratory syncytial virus prophylaxis should be considered for these children.*

In the IMpact-RSV study, preterm children aged ≤6 months who had been born at ≤35 wGA or children aged ≤24 months with BPD were randomly assigned to receive five monthly doses of palivizumab or placebo.[9] Overall, RSVH rates were reduced by 55% in the palivizumab group compared with the placebo group (P<0.001); palivizumab treatment also led to a 39% reduction in RSVH (vs placebo) among children with BPD.[9] These results were subsequently reinforced by a meta-analysis of three randomised studies (n=2831) showing favourable efficacy of palivizumab, with a 51% reduction in RSVH (vs placebo) among preterm children and children born with BPD.[33] In the US, a registry study of infants receiving palivizumab (n=2116, predominantly born at ≤35 wGA) demonstrated an RSHV rate of 2.9%,[34] which compares favourably to the 4.8% hospitalisation rate observed in the pivotal trial.[9] Based on these data, we recommend palivizumab prophylaxis for 5 to 6 months after hospital discharge among children aged <12 months who are receiving medication for BPD, irrespective of prematurity.

*Statement 7: Respiratory syncytial virus prophylaxis reduces the number and duration of respiratory syncytial virus–related hospitalisations among children aged <2 years with haemodynamically significant congenital heart disease.*

*Statement 8: A 6-month prophylaxis regimen (six doses) in the first year of life is suggested for children with haemodynamically significant congenital heart disease.*

We define hsCHD based on the population included in the study by the Cardiac Synagis Study Group.[35] This included cyanotic patients (oxygen saturation <85%, either unoperated or partially corrected by surgery or interventional catheterisations), patients with hypercyanotic episodes (paroxysmal hypoxic events characterised by severe reductions in pulmonary blood flow lasting from minutes to several hours), patients receiving cardiac medications, patients with congestive heart failure (requiring treatment with two medications), patients with pulmonary hypertension (mean pulmonary artery pressure >25 mm Hg for >3-4 months of life) and patients with increased

pulmonary blood flow.[35]

Prophylaxis for children aged ≤12 months with hsCHD is widely supported by international guidelines, but recommendations for prophylaxis among children aged 12 to 24 months vary.[12] In Hong Kong, an individualised approach should be taken; prophylaxis should be considered for children aged ≤12 months with hsCHD, congestive heart failure, or pulmonary hypertension, especially at the start of the local RSV season. Prophylaxis for children aged 12 to 24 months may be considered after corrective surgery if residual defects are present, but prophylaxis beyond 6 months post-surgery should be carefully considered on a case-by-case basis. Currently, there are insufficient data to recommend prophylaxis for children aged >24 months with hsCHD.

The evidence supporting these statements was collected from randomised clinical trials and real-world studies. A placebo-controlled randomised clinical trial of palivizumab prophylaxis, delivered as five monthly injections, among young children (aged ≤24 months; n=1287) with hsCHD demonstrated a 45% relative reduction in RSVH (P=0.003) and a 56% reduction in total days of RSVH per 100 children (P=0.003), compared with placebo.[35] The same study revealed a 73% reduction in total RSVH days requiring increased supplemental oxygen per 100 children (P=0.014).[35] The efficacy of six doses of palivizumab prophylaxis among children aged ≤12 months with hsCHD is also supported by findings from an observational study in Taiwan (n=1556), which showed a 49% reduction in RSVH and a 57% reduction in admission days compared with propensity-matched controls.[36] A database study from the US that included 2518 children with hsCHD demonstrated a decline of 36% in RSVH among children with hsCHD between pre- and post-palivizumab guideline eras, compared with an 8% decline among children without hsCHD (P<0.001).[37] Additional data confirming the efficacy of palivizumab prophylaxis against RSVH among children with hsCHD have been acquired through real-world studies in Spain[38] and Australia.[39] In Spain, a prospective, multicentre study of children aged ≤24 months with hsCHD (n=2613) showed that those with adequate palivizumab prophylaxis (n=2366) had a lower rate of RSVH than those with inadequate prophylaxis (n=247; 3.3% vs 7.9%, respectively).[38] An observational cohort study in Australia compared RSHV rates among infants aged ≤12 months with haemodynamically significant cardiac disease between 2008-2009, when palivizumab prophylaxis was administered in a coordinated manner, to the rates during 2005-2007, when prophylaxis was given on an ad hoc basis.[39] Admission rates for RSV bronchiolitis in 2008-2009 (2% per year) were significantly reduced compared with the rates in 2005-2007 (5%-9% per year; P<0.03).[39] These findings support our recommendation for prophylaxis among children aged ≤24 months with hsCHD; our suggested duration of dosing is based on the above studies and the limited seasonality of RSV observed in Hong Kong.

Clinical experience regarding palivizumab prophylaxis for other special populations in Hong Kong (eg, immunocompromised children and children with Down syndrome, cystic fibrosis, or neuromuscular disorder) is extremely limited. For cases involving these children, clinicians should refer to international recommendations.[11]

*Statement 9: Current evidence indicates that the use of palivizumab as respiratory syncytial virus prophylaxis is safe and well-tolerated, with minimal risk of adverse reactions.*

*Statement 10: The only contraindication to the use of palivizumab is a previous history of confirmed hypersensitivity reaction to palivizumab.*

The favourable safety profile of palivizumab has been demonstrated in clinical trials and observational studies. In the pivotal IMpact-RSV trial, which involved premature infants with BPD, adverse event rates were similar in the palivizumab and placebo groups (10%-11%).[9] Discontinuations due to palivizumab-related adverse events were rare (0.3%), as were reports of injection site reactions (1.8% [placebo] vs 2.7% [palivizumab]) and fever (3.0% vs 2.8%).[9] Observational data from several studies suggest that palivizumab is well-tolerated in at-risk children. The prospective observational CARESS study from Canada included 13 025 infants treated with palivizumab (63.1% born at ≤35 wGA, 11.1% aged <2 years with hsCHD, and 7.5% exhibiting BPD) and monitored serious adverse events from 2008 to 2013.[40] Hospitalisations for respiratory illness unrelated to palivizumab were reported in 915 patients.[40] Other than these hospitalisations, 62 serious adverse events were reported in 52 patients.[40] Of these 62 adverse events, 14 hypersensitivity episodes in six patients (2.8 per 10 000 patient-months) were deemed possibly or probably related to palivizumab.[40] The events experienced by these six patients included erythema or urticaria, difficulty swallowing, vomiting, nasal congestion, bronchospasm, and acute respiratory distress; two patients required hospitalisation.[40] All six patients discontinued palivizumab, and their symptoms resolved after 30 days of monitoring with no immediate life-threatening consequences.[40] In a prospective study involving 100 high-risk children in Russia, 94 children completed their palivizumab dosing schedule; there were no reported RSV-related hospitalisations or deaths.[41] Three non-serious adverse events were considered palivizumab-related: rhinitis and acute intermittent

rhinitis (both occurring in one patient) and atopic dermatitis.[41] Data concerning palivizumab use in immunocompromised children (n=167) and children with Down syndrome (n=138) were obtained during a post-marketing surveillance study in Japan.[42] Adverse drug reactions occurred in 25 patients (8.22%), including 11 patients (3.62%) who experienced palivizumab-related serious adverse drug reactions.[42] Further support for palivizumab safety in immunocompromised children was presented in a Japanese study of children aged ≤2 years; of the 30 included participants, 26 (92.9%) completed the study.[43] Most adverse events were mild to moderate; only two patients experienced serious adverse events, none of which were considered palivizumab-related.[43] Overall, these data indicate that in routine clinical practice, palivizumab-related adverse effects and hypersensitivity reactions are rare; palivizumab is well-tolerated in various patient populations.

*Statement 11: The cost-effectiveness of palivizumab prophylaxis in Hong Kong is unclear.*

International studies regarding the cost-effectiveness of palivizumab prophylaxis yielded mixed results. For example, a systematic review of 28 studies suggested that the incremental cost-effectiveness ratio for preterm infants (born at 29-35 wGA) ranged from US$5188 to US$791 265 per quality-adjusted life-year, with 90% of estimates below US$50 000 per quality-adjusted life-year.[44] The authors concluded that prophylaxis was cost-effective for preterm infants and infants born with lung complications.[44] However, another systematic review (also comprising 28 studies) by Hussman et al[45] concluded that the overall cost-effectiveness of palivizumab prophylaxis was inconsistent: some studies showed favourable outcomes, whereas others showed unfavourable outcomes or inconclusive results. A cost-effectiveness study conducted in Hong Kong concluded that palivizumab was more cost-effective among preterm infants born at <27 wGA than among those born at <29 wGA, but the authors advised careful interpretation of the results because patient selection was biased towards individuals with more severe lung disease.[32] Another Hong Kong study, a retrospective analysis by Chen et al,[46] assessed the cost-effectiveness of palivizumab prophylaxis using data from 236 patients aged <12 months with hsCHD, 26 of whom had RSVH. The study, which assumed no local seasonality of RSV, concluded that palivizumab prophylaxis was not cost-effective for this population in Hong Kong[46]; this result contrasts with our suggested regimen in Statement 8. This study, identified after our main literature review and consensus meetings, provides an alternative local opinion. For this reason, Statement 8 is presented as a suggestion with moderate strength, rather than a recommendation. As noted above, the study by Chen et al[46] assumed no local RSV seasonality, despite the existence of peaks in March to April and July to August; its applicability is limited by its reliance on relative risk reductions in RSVH from studies conducted in temperate regions.[46] Our opinion is that further cost-effectiveness studies of palivizumab in Hong Kong and other tropical locations are required. Furthermore, because reimbursement policies and healthcare costs considerably vary among locations, and because we aim to provide consensus statements that are useful to healthcare professionals elsewhere in Asia, decisions regarding the cost-effectiveness of prophylaxis must be guided by local data.

## Conclusion

The burden of RSVH in Hong Kong is high, and children aged <1 year experienced more than half of all hospitalisations.[3] Respiratory syncytial virus infections generally peak in the summer months in Hong Kong, although the seasonality pattern is less distinct compared with temperate regions.[3,17,20] Therefore, our recommendations place greater emphasis on patient populations, rather than seasonality.

Our criteria for prophylaxis would lead to a substantial increase in the number of infants eligible for palivizumab prophylaxis in Hong Kong, relative to current practice. Consistent with guidance from the AAP, we recommend prophylaxis for preterm infants born at <29 wGA.[11] Although the <29 wGA cut-off may appear to be more restrictive than the current Hospital Authority limit (<34 wGA), most premature infants are discharged without oxygen or medication and therefore do not meet the existing criteria for palivizumab prophylaxis.

Our guidance statements aim to identify the populations for which RSV prophylaxis is appropriate and to summarise the efficacy and safety data supporting palivizumab prophylaxis. Although a high level of consensus was reached for these statements, all recommendations should be tailored to the needs of individual patients, ideally using a multidisciplinary clinical approach.

As of early 2025, three RSV vaccines have been approved for medical use in the US.[47] In June 2024, the US Centers for Disease Control and Prevention recommended that people aged ≥75 years and people aged 60 to 74 years who are at increased risk of severe RSV receive the RSV vaccine.[48] One of the RSV vaccines, Abrysvo, is indicated for active immunisation for the prevention of lower respiratory infection caused by RSV in people ≥60 years of age, high-risk individuals aged 18 years through 59 years, and pregnant individuals at 32 through 36 weeks gestational age to prevent severe disease in their infants from birth through 6

months of age.[49] However, currently in Hong Kong, the Scientific Committee on Vaccine Preventable Diseases under the Centre for Health Protection does not recommend universal RSV vaccination for elderly persons or pregnant women.[50] Recommendations about childhood RSV immunisation by local expert panel should be called for in the not-so-remote future.

## Author contributions

Concept or design: GPG Fung, KL Hon, AM Li, MSH Lee, DKK Ng.
Acquisition of data: EWY Cheung, KL Hon, DSY Lam, MSH Lee.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: EWY Cheung, KL Hon, RSY Lee, AM Li, MSH Lee, DKK Ng.
Critical revision of the manuscript for important intellectual content: All authors.

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.

## Conflicts of interest

MP Leung, AM Li and DKK Ng have received an honorarium for this consensus meeting from AstraZeneca Hong Kong. EWY Cheung has received an honorarium for lectures from AstraZeneca Hong Kong. As an editor of the journal, KL Hon was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

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