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Unit No. 1

VACCINE-PREVENTABLE RESPIRATORY DISEASES: A CASE FOR ONGOING VIGILANCE IN PRIMARY CARE

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ABSTRACT

Pneumonia is the second-most-common cause-of-death in Singapore; vaccination therefore comprises a significant part of Singapore's strategy to improve population health, and is embedded into primary care at the national level through Healthier SG. Tropical heat and humidity in Singapore predisposes to year-round transmission of respiratory-viral-infection (RVIs), including COVID-19, influenza, and respiratory-syncytial virus (RSV). The list of vaccine-preventable respiratory infections has expanded beyond influenza and pneumococcal vaccination in recent years to include COVID-19 and RSV; however, vaccine-hesitancy is a major obstacle to vaccination uptake and prevention of respiratory infections. Familiarity with the various vaccine-preventable respiratory diseases is essential for the primary care physician.

Key words: RSV, COVID-19, pneumococcal, vaccination

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INTRODUCTION

Pneumonia is the second-most-common cause of death in Singapore; tropical heat and humidity in Singapore predisposes to year-round transmission of respiratory-viral-infection (RVIs).[1] Following the COVID-19 pandemic, significant rebound in transmission of endemic respiratory infections, such as influenza, respiratory-syncytial-virus (RSV) and pneumococcal disease[1,2] has been observed in Singapore.[1,2] Locally, mortality rates of ~5 percent were observed for hospitalisations attributed to various vaccine-preventable-respiratory-infections (VPRIs) amongst older Singaporeans (refer to **Figure 1**).

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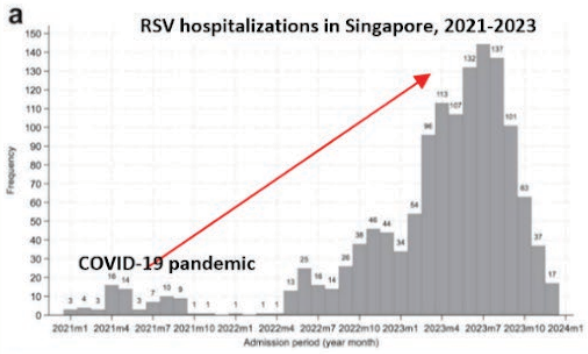
Vaccination against VPRIs, such as influenza/COVID-19/respiratory-syncytial-virus [RSV]/pneumococcal disease, have been shown to confer effective protection against hospitalisations and mortality in clinical trials[3] and other cohort studies.[4-6] However, despite incorporation of vaccination against VPRIs into Singapore's national adult immunisation schedule (NAIS), and the availability of subsidised vaccination at the primary care level, gaps still exist in uptake.

For instance, both influenza and pneumococcal vaccination (23-valent pneumococcal-polysaccharide-vaccine [PPSV-23], and the 13-valent pneumococcal-conjugate-vaccine [PCV-13]) are included in the NAIS and subsidised for older adults (aged ≥65 years) and adults with comorbidities; with the rollout of the Healthier SG (HSG) initiative in Singapore from July 2023 onwards, eligible HSG-enrolled Singaporean citizens are entitled to receive fully-subsidised ($0) vaccinations under the NAIS at their enrolled HSG clinic.[7] These efforts have translated into increases in influenza/pneumococcal vaccination uptake over the years, but room still remains for improvement. Prior to the COVID-19 pandemic, only 32.4 percent of older Singaporean adults received yearly influenza vaccination,[8] a figure substantially below the OECD average of 55 percent influenza vaccination coverage rates for older adults in 2021,[9] and below the World Health Organisation recommendation for 75 percent influenza vaccination coverage amongst older adults aged ≥65 years.[10]

Similarly, while COVID-19 vaccination is also freely available in primary care, differences in vaccination uptake across socioeconomic strata persist into the post-pandemic era,[11] and uptake of updated COVID-19 boosters has significantly dropped post-pandemic, with <5 percent having received an updated COVID-19 booster.[6]

The list of VPRIs has expanded beyond influenza and pneumococcal vaccination in recent years to include COVID-19 and RSV, but vaccine hesitancy remains an issue. Multiple reasons for vaccine hesitancy likely exist in the Singaporean context, including patient/physician factors, and healthcare system gaps. Local studies identified that having a regular family physician was associated with uptake of pneumococcal vaccination,[12] and point-of-care informational interventions carried out by primary care physicians significantly increased influenza/pneumococcal vaccination uptake.[13] This update aims to provide information on the significance of various VPRIs (beyond influenza) in the local context, so that primary care physicians can act as effective advocates for vaccination, particularly amongst at-risk groups. Specifically, we will examine the evidence supporting COVID-19, RSV and pneumococcal vaccination.

Figure 1: Trend in a)RSV; b)influenza hospitalisations amongst adult Singaporeans nationally, 2021-2023.



Sociodemographic and clinical characteristics	Respiratory-syncytial-virus (RSV) hospitalisations,[a] N (%)	COVID-19 hospitalisations, boosted ≥1 year prior with ancestral mRNA vaccines,[b] N (%)	COVID-19 hospitalisations, boosted <1 year prior with updated mRNA vaccines,[b] N (%)	COVID-19 hospitalisations, unboosted,[b,] N (%)	Influenza hospitalisations,[c] N (%)	Total hospitalisations, N (%)
Clinical outcomes and healthcare utilisation						
28-day mortality	72 (5.4)	281 (5.0)	44 (4.5)	82 (9.7)	36 (0.9)	515 (4.0)
Intensive-care-unit (ICU) admission	51 (3.8)	163 (2.9)	23 (2.3)	34 (4.0)	69 (1.7)	340 (2.7)
Total cost of hospitalisation, US$ (median, IQR)[i]	2497.8 (1448.3-4673.9)	3421.7 (1554.3-5990.3)	3414.6 (1577.9-5972.6)	3889.1 (1883.2-7270.3)	2187.8 (1353.7-4215.1)	2821.0 (1461.6-5442.3)

Wee LE, et al. Severity of respiratory syncytial virus versus SARS-CoV-2 Omicron and influenza infection amongst hospitalized Singaporean adults: a national cohort study. Lancet Reg Health West Pac. 2025 Feb 20;55:101494. doi: 10.1016/j.lanwpc.2025.101494.

COVID-19

While the threat of COVID-19 has receded in the public imagination during endemicity, COVID-19 still accounts for a substantial proportion of hospitalisations attributable to acute-respiratory-infection amongst adult Singaporeans. In a modelling study that estimated excess influenza-, RSV-, and SARS-CoV-2-associated hospitalisation in Singapore from 2015–2023, 19.3 percent of hospitalisations for acute-respiratory-infection were attributed to COVID-19.[1] Periodic surges in SARS-CoV-2 transmission are attributed to emergence of new circulating variants; as with other endemic respiratory diseases, periodic COVID-19 waves are expected throughout the year. Studies in other populations during endemicity found that COVID-19 imposed a greater disease burden than influenza, reflecting as higher hospital admission, mortality rates, and more severe illness.[14] During Omicron, mortality amongst adult COVID-19 hospitalisations in Singapore was estimated at 5.0 percent, with 2.9 percent requiring ICU admission.[2]

Comparative severity:

- In Singaporean adults, Omicron COVID-19 was more severe compared to influenza (4.5–9.7 percent 28-day mortality in COVID-19 hospitalisations, versus 0.9 percent 28-day mortality in influenza hospitalisations).[2]

At-risk populations:

- Older adults and individuals with pre-existing comorbidities remain at risk.
- During Omicron, significantly higher risk of infection, hospitalisation, and severe COVID-19 was observed among Singaporean adult patients with asthma and chronic-obstructive-pulmonary-disease (COPD).
- Singaporean adult asthmatics had a 31 percent higher risk of severe COVID-19 versus non-asthmatic population-based controls, while individuals with COPD had a 36 percent higher risk of severe COVID-19, versus controls.[15]
- Singaporean adults with pre-existing heart conditions, including ischaemic heart disease and heart failure, had significantly higher risk of COVID-19 hospitalisation during the Omicron period.[16]
- Individuals with heart failure had a 77 percent higher risk of COVID-19 hospitalisation, while individuals with ischaemic heart disease had a 21 percent higher risk, versus matched controls.[16]

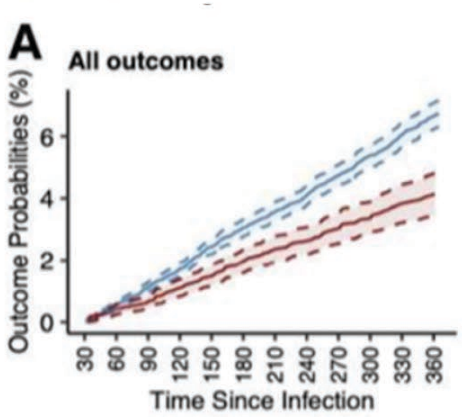
Impact of vaccination:

- Boosted COVID-19 hospitalisations were less severe than unboosted COVID-19 hospitalisations (unboosted: 9.7 percent 28-day mortality; boosted: 4.5–5.0 percent 28-day mortality).[2]
- Updated vaccine formulations confer greater protection against severe COVID-19 compared to ancestral vaccine doses.
- During a JN.1 wave in Singapore, recent receipt of updated boosters conferred protection against SARS-CoV-2 infection and emergency-department (ED) visits/hospitalisations, in both previously infected and uninfected individuals.[6]
- Compared with individuals last boosted ≥1 year earlier with ancestral monovalent vaccines, receipt of an updated XBB.1.5 booster 8-120 days earlier was associated with 40-50 percent lower risk of JN.1

infection, COVID-19-associated ED visits, and COVID-19 hospitalisations (refer to **Figure 2**).[6]

- Updated COVID-19 vaccine doses were also protective against long-term sequelae post-COVID-19 ("long-COVID-19") in the Singaporean population.[17]
- A 40 percent decrease in risk of any post-acute sequelae was observed amongst adult Singaporeans who received prior bivalent COVID-19 boosters, versus those boosted with ancestral COVID-19 vaccines (refer to **Figure 2**).[17]

Figure 2: Comparative vaccine-effectiveness of ancestral versus bivalent COVID-19 vaccines against post-acute and acute infection outcomes in a pandemic



B

mRNA Vaccination Status	aHR (95% CI SARS-CoV-2 Infection
Boosted; ≥1 y since last dose[c]	1.00 (Reference)
Boosted, with last dose a bivalent booster; 8–120 d since last dose	0.77 (.66–.91)
Boosted, with last dose a bivalent booster; 121–365 d since last dose	0.92 (.88–.95)
Boosted, with last dose an XBB 1.5 booster; 8–120 d since last dose	0.59 (.52–.66)

A: Vaccine-effectiveness of ancestral versus bivalent COVID-19 vaccines against any post-acute sequelae at 31-365 days post-SARS-CoV-2 infection, comparing outcome probabilities of any post-acute sequelae in individuals boosted with ancestral versus bivalent COVID-19 vaccines. Red line: bivalent vaccines; blue line: ancestral vaccines; dotted lines: 95% CIs.

B: Vaccine-effectiveness of ancestral versus bivalent COVID-19 vaccines against acute SARS-COV-2 infection; computed using Cox-regression, with adjusted-hazards-ratios (aHR) and 95% CIs

Wee et al. Bivalent Boosters and Risk of Postacute Sequelae Following Vaccine-Breakthrough SARS-CoV-2 Omicron Infection: A Cohort Study. Clin Infect Dis. 2025 Mar 17;80(3):520-528.
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Vaccination recommendations:

- Singaporeans aged six months and above are eligible for COVID-19 vaccination. The persons recommended for COVID-19 vaccination in 2024/2025 are:
  1. Individuals aged 60 years and above
  2. Medically vulnerable individuals aged six months and above
  3. Residents of aged care facilities

Persons living or working with medically vulnerable individuals are also encouraged to consider receiving the vaccine.

RESPIRATORY SYNCYTIAL VIRUS

Often confused with the common cold, respiratory syncytial virus (RSV) can in fact cause serious disease. Previously, awareness of RSV was low due to a lack of testing; however, in tropical Singapore, RSV is most common at the extremes of age,[19] and year-round RSV transmission occurs given the heat and humidity. In a modelling study that estimated excess influenza-, RSV-, and SARS-CoV-2-associated hospitalisation in Singapore from 2015–2023, 4.0 percent of hospitalisations for acute-respiratory-infection were attributed to RSV.[1] Mortality amongst adult RSV hospitalisations in Singapore was estimated at 5.4 percent, with 3.8 percent requiring ICU admission.[2] RSV hospitalisations account for significant morbidity and costs; a systematic review across Asian countries found that the direct inpatient medical costs attributable to a RSV hospitalisation ranged from US$126–$2,448 in low-middle-income countries (LMICs) to US$838–$3,402 in high-income countries.[20]

Comparative severity:

- In Singaporean adults, higher odds of 28-day mortality/intensive-care-unit admission and higher healthcare utilisation were observed in RSV hospitalisations versus influenza (5.4 percent 28-day mortality in RSV hospitalisations, versus 0.9 percent 28-day mortality in influenza hospitalisations).[2]
- RSV was less severe than unboosted COVID-19, with lower odds of 28-day mortality and healthcare utilisation. However, higher odds of intensive-care-unit admission were observed in RSV hospitalisations, versus COVID-19 hospitalisations boosted <1 year prior with updated vaccines.[2]
- Beyond respiratory complications, emerging evidence suggests that RSV is also linked to cardiac events.
- In a large cohort of hospitalised US veterans, nearly one-quarter of hospitalised adults with RSV infection experienced an acute cardiac event (most frequently heart failure).[21]
- In a cohort of almost 33,000 adult Singaporeans hospitalised for RSV, COVID-19, or influenza, slightly more than one in 10 RSV hospitalisations had an acute cardiovascular event; the odds of a cardiac event were significantly higher than patients hospitalised for COVID-19, as well as for patients with vaccine-breakthrough influenza hospitalisations.[22]
- Long-term sequelae may also occur following RSV hospitalisation.[23]

- Within a cohort of 83,000 adults hospitalised for RSV, COVID-19, or influenza, increased risk of long-term cardiovascular and neurological complications was observed up to 300 days post-hospitalisation.[23]

At-risk populations:

- Older age (≥70 years) and diabetes mellitus were associated with greater odds of 28-day mortality amongst Singaporean adults hospitalised for RSV.[2]

Impact of vaccination:

- Vaccines targeting RSV have recently become available for adult populations.
- Two RSV vaccines are currently licensed for use: an AS01-adjuvanted vaccine targeting the RSV fusion F surface glycoprotein of an RSV-A strain (Arexvy), and an unadjuvanted bivalent RSV prefusion F (RSVpreF) vaccine (Abrysvo).
- In clinical trials, vaccine effectiveness of the AS01-adjuvanted vaccine against RSV-related lower respiratory tract disease was 82.6 percent,[24] while vaccine effectiveness of the unadjuvanted bivalent vaccine against RSV-related lower respiratory tract disease was 85.7 percent.[25]
- Emerging data supports real-world effectiveness of RSV vaccination. In a real-world analysis following administration of the RSV vaccine amongst Scottish adults aged 75–79 years, a 62.1 percent reduction in RSV-related hospitalisations was observed amongst the eligible age group, compared with predictions.[26]
- In a real-world analysis of vaccine-effectiveness for the RSVpreF vaccine amongst members of a large US healthcare system aged 60 years and above, vaccine-effectiveness against RSV-related lower respiratory tract disease was estimated at 90 percent.[27]
- A single dose of RSV vaccine prevented RSV-associated hospitalisation across two RSV seasons, although effectiveness was lower in patients with immunocompromising conditions and cardiovascular disease.[28]
- However, the optimal timing for RSV re-vaccination remains unknown, given variations in RSV seasonality.

Vaccine safety:

- Real-world surveillance data supports overall safety of RSV vaccination.
- In a large electronic health record study of more than 4 million vaccinated adults, RSV vaccination was shown to be safe overall, with no excess risk of immune thrombocytopenic purpura (ITP).[29]
- A statistically significant signal for increased risk of Guilain-Barré syndrome (GBS) was observed amongst patients who received the RSVPreF vaccine, though it must be emphasised that this risk was extremely rare (estimated excess of GBS cases: 5.2 per 1,000,000 vaccinations).[29]

Vaccination recommendations:

- In Singapore, RSV vaccines, though not part of the NAIS, are currently licensed for use in the following groups of individuals:
- Adults 60 years of age and older to prevent RSV disease
- Adults 18 through 59 years of age who are at increased risk for RSV disease (e.g., those with chronic heart or lung disease, weakened immune system)
- Pregnant women at 32 through 36 weeks gestational age to protect their infants from birth through six months of age against RSV disease

PNEUMOCOCCAL VACCINATION

Streptococcus pneumoniae remains a major respiratory pathogen and significant cause of pneumonia globally.[30] Two types of pneumococcal vaccines, polysaccharide and conjugate vaccines, are available for prevention of pneumococcal disease in older adults and individuals with comorbidities.[30] Multiple population-based studies have demonstrated real-world effectiveness of the 23-valent pneumococcal-polysaccharide-vaccine (PPSV-23),[31-35] and the 13-valent pneumococcal-conjugate-vaccine (PCV-13),[36-39] respectively, in mitigating risk of pneumococcal-related-disease and hospitalisations for pneumonia in older adults. National surveillance data from 2019-2022 indicated that 44.4–52.3 percent of invasive-pneumococcal-disease cases in adult Singaporeans involved serotypes covered by PCV-13, while 55.5–70.3 percent of cases were covered by PPSV-23, with type 3 the predominant serotype in all years except 2021.[40,41]

At-risk populations:

- Older age and presence of comorbidities were identified as risk factors for invasive pneumococcal disease amongst adult Singaporeans.[42]

Impact of vaccination:

- In a real-world population-wide study of PPSV-23 vaccine effectiveness conducted amongst older Danish adults from 2020-2023, vaccine effectiveness of PPSV-23 was estimated at 32 percent.[35]
- In a much larger population-based study of US Veterans-Health-Administration (VHA) enrollees, sequential PCV-13/PPSV-23 vaccination was associated with lower risk of invasive pneumococcal disease, highlighting the additional benefit of combined pneumococcal vaccination.[43]

Vaccination recommendations:

- In Singapore, the pneumococcal conjugate PCV-20 vaccine was included on the subsidised vaccine list starting September 2025, Singapore being the first country in Asia to get PCV-20.
- PCV-20 covers seven more bacterial serotypes compared to PCV-13.
- Under the NAIS, PCV-20 is recommended for all adults aged 65 years and above, as well as adults aged 18 to 64 years who are at increased risk of developing severe pneumococcal disease. Healthier SG Singaporean enrolees will be fully subsidised for PCV20 at their enrolled clinic.
- Detailed recommendations on pneumococcal vaccines are available in the NAIS (refer to **Figure 3**).

Figure 3: NAIS recommendations for pneumococcal vaccines

Detailed NAIS recommendations on pneumococcal vaccines:
1. All persons aged 65 years or older

Prior vaccines	Option A: PCV20 recommendations	Option B: PCV13 and/or PPSV23 recommendations
None	**PCV20**	**PCV13;** followed by **PPSV23** (interval: ≥1 year*)
Received **PPSV23** only (at any age)	**PCV20** (interval: ≥1 year from PPSV23)	***<<If previous PPSV23 was ≥65 years>>*** **PCV13** (interval: ≥1 year from PPSV23)
		<<If previous PPSV23 was <65 years>> **PCV13** (interval: ≥1 year from PPSV23); **followed by PPSV23** (interval: ≥1 year)
Received **PCV13** only (at any age)	**PCV20** (interval: ≥1 year from PCV13)	**PPSV23** (interval: ≥1 year from PCV13*)
Received **PCV13** (any time) and **PPSV23** (at <65 years)	**PCV20** (interval: ≥5 years†)	**PPSV23** (intervals: see footnote§)
Received **PCV13** (any time) and **PPSV23** (at ≥65 years) or Received **PCV20** (any time)	**No vaccines recommended** Have already completed vaccination series	**No vaccines recommended** Have already completed vaccination series

** For persons with an immunocompromising condition, cochlear implant or CSF leak, a minimum interval of 8 weeks can be considered*
† Interval of at least 5 years from any of the most recent dose of PCV13 or PPSV23
§ Intervals of at least 5 years from PPSV23 and at least 1 year from PCV13, whichever is later

CONCLUSION

Vaccine-preventable respiratory infections remain a year-round problem in Singapore, where a humid tropical climate predisposes to year-round, rather than seasonal, transmission of respiratory viral infections. A large proportion of patients hospitalised with pneumonia in a tropical setting have evidence of a respiratory viral infection on systematic testing. The list of vaccine-preventable respiratory infections has expanded beyond influenza and pneumococcal vaccination in recent years to include COVID-19 and RSV; however, vaccine-hesitancy is a major obstacle to vaccination uptake and prevention of respiratory infections. Physician recommendations are important in educating patients regarding key benefits arising from vaccination against respiratory infections.

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LEARNING POINTS

- **Pneumonia is the second-most-common cause-of-death in Singapore; the list of vaccine-preventable respiratory infections has expanded beyond influenza and pneumococcal vaccination in recent years to include COVID-19 and RSV.**
- **During COVID-19 endemicity, keeping up-to-date with vaccination improves protection against acute and longer-term sequelae of COVID-19.**
- **RSV vaccinations are now available for older adults and individuals at increased risk for RSV disease; with real-world evidence of benefit.**
- **The pneumococcal conjugate PCV-20 vaccine was included on the subsidised vaccine list from September 2025 onwards; multiple real-world studies support effectiveness of pneumococcal conjugate vaccines in protecting against severe disease.**