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Asia Pacific perspectives on the second year of the COVID-19 pandemic: A follow-up survey

Ruby Pawankar[1] | Bernard Yu-Hor Thong[2] | Marysia Tiongco-Recto[3] | Jiu-Yao Wang[4] | Amir Hamzah Abdul Latiff[5] | Ting Fan Leung[6] | Philip Hei Li[7] | Rommel Crisenio M. Lobo[8] | Michela Lucas[9,10] | Jae-Won Oh[11] | Wasu Kamchaisatian[12] | Mizuho Nagao[13] | Iris Rengganis[14] | Zarir F. Udwadia[15] | Raja Dhar[16] | Sonomjamts Munkhbayarlakh[17] | Logii Narantsetseg[18] | Duy Le Pham[19] | Yuan Zhang[20] | Luo Zhang[21]

[1]Department of Pediatrics, Nippon Medical School, Tokyo, Japan

[2]Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore, Singapore

[3]Division of Allergy and Immunology, Department of Pediatrics, University of the Philippines-Philippine General Hospital, Manila, Philippines

[4]Allergy, Immunology, and Microbiome (A.I.M.) Research Centre, China Medical University Children's Hospital, Taichung, Taiwan

[5]Allergy & Immunology Centre Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

[6]Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong, Hong Kong

[7]Division of Rheumatology and Clinical Immunology, Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, Hong Kong

[8]Philippine Childrens Medical Center Hospital of Infant Jesus Medical Center, Fe del Mundo Medical Center, Quezon City, Philippines

[9]Department of Clinical Immunology, Sir Charles Gairdner Hospital, Perth Children's Hospital, Perth, WA, Australia

[10]Medical School, University of Western Australia, Perth, WA, Australia

[11]Department of Pediatrics, Hanyang University Guri Hospital, Guri, South Korea

[12]Pediatric Allergy and Immunology, Samitivej Children's Hospital, Bangkok, Thailand

[13]National Hospital Organization Mie National Hospital, Institute for Clinical Research, Tsu, Japan

[14]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Cipto Mangunkusumo General Hopsital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

[15]P.D. Hinduja National Hospital and Medical Research Centre, Breach Candy Hospital, in Mumbai, Mumbai, India

[16]CMRI Hospital, Kolkata, India

[17]Department of Pulmonology and Allergology, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

[18]Department of Biochemistry, School of Biomedicine, National University of Medical Sciences, Ulaanbaatar, Mongolia

[19]Faculty of Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam

[20]Department of Allergy, Beijing TongRen Hospital, Capital Medical University, Beijing, China

[21]Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing, China

Correspondence
Ruby Pawankar, Department of Pediatrics, Nippon Medical School, Tokyo, Japan.
Email: pawankar.ruby@gmail.com

Abstract

Background: The Coronavirus disease 2019 (COVID-19) pandemic is currently in its third year. This follow-up survey was commissioned by the Asia Pacific Association of Allergy Asthma and Clinical Immunology (APAAACI) Task Force on COVID-19 to compare and contrast changes in the epidemiology, clinical profile, therapeutics and public health measures of the pandemic in the Asia Pacific region.

Ruby Pawankar and Bernard Yu-Hor Thong have contributed equally to this work and manuscript.

Methods: A questionnaire-based survey comprising 32 questions was electronically sent out to all 15 member countries of APAAACI using Survey Monkey® from 1 December 2021 to 28 February 2022.

Results: Seventeen responses were received from 14/15 (93.4%) member countries and 3 individual members. Mild-to-moderate COVID-19 predominated over severe infection, largely contributed by COVID-19 vaccination programmes in the region. The incidence of vaccine adverse reactions in particular anaphylaxis from messenger ribonucleic acid (mRNA) vaccines was no longer as high as initially anticipated, although perimyocarditis remains a concern in younger males. Novel therapeutics for mild-to-moderate disease including neutralizing antibodies casirivimab/imdevimab (REGEN-COV®) and sotrovimab (Xevudy®), anti-virals Paxlovid® (nirmatrelvir and ritonavir) and Molnupiravir pre-exposure prophylaxis for high-risk persons with Tixagevimab and Cilgavimab (Evusheld) are now also available to complement established therapeutics (e.g., remdesivir, dexamethasone and baricitinib) for severe disease. In the transition to endemicity, public health measures are also evolving away from containment/elimination strategies.

Conclusions: With access to internationally recommended standards of care including public health preventive measures, therapeutics and vaccines among most APAAACI member countries, much progress has been made over the 2-year period in minimizing the morbidity and mortality from COVID-19 disease.

KEYWORDS
anaphylaxis, endemic diseases, prophylaxis, therapeutics, vaccination

1 | INTRODUCTION

The World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) following its initial emergence in Wuhan, China, in December 2019, and its global spread, a pandemic on 11 March 2020. In the first year of the pandemic, the Asia Pacific Association of Allergy Asthma and Clinical Immunology (APAAACI) carried out a questionnaire survey among all its national member societies in May 2020 to assess the impact of the pandemic in the Asia Pacific region.[1] Lessons learnt from the first year provided crucial information for public health, infection prevention and control and vaccination policies including risk stratification and safe implementation of vaccines with a view towards disease control and economic recovery for the region. By the end of the second year of the pandemic in February 2022, many countries in our region have gradually achieved beyond 80%–90% COVID-19 full vaccination rates (completion of primary COVID-19 vaccine series) across all age groups, and initiated mRNA vaccination with Pfizer–Comirnaty vaccine in the 5- to 11-year-old age group as the benefits of vaccination against severe disease appear to outweigh the risks of adverse reactions, including allergic reactions and anaphylaxis.[2,3] Enhanced primary vaccination with a third dose in immunocompromised persons[4,5] and booster vaccination programmes[6] have also been initiated to address the problems of incomplete or waning immunity respectively. Self-testing using antigen rapid tests has begun to replace polymerase chain reaction (PCR) testing for border controls and screening of symptomatic individuals as a public health measure.[7] After the surge with the delta variant, many countries worldwide have seen as many as 10,000 to 100,000 new cases per day, albeit with milder disease among predominantly vaccinated populations with the more transmissible Omicron variant of concern.[8] New therapies including neutralizing monoclonal antibodies (NAbs), e.g., casirivimab and imdevimab, sotrovimab;[9] and oral anti-virals, e.g.,

Key Messages

- Anaphylaxis from messenger ribonucleic acid (mRNA) vaccines is not as high as initially anticipated.
- Neutralizing antibodies and anti-virals for mild-to-moderate disease complement established therapeutics for severe disease.
- In the transition to endemicity, public health measures are gradually evolving away from containment/elimination strategies in the majority of countries, although some in East Asia are still trying to maintain a "zero-COVID" policy.

Paxlovid® (nirmatrelvir and ritonavir) and Molnupiravir[10] are now approved for the treatment of mild-to-moderate COVID-19.

The objective of this follow-up survey in the second year of the pandemic was to compare and contrast differences between the first and second year of the pandemic in the region, and comparisons with global trends as the world transitions towards endemicity and "living with COVID."

2 | METHODS

A questionnaire comprising 32 questions was electronically sent out to all 15 member countries of APAAACI using Survey Monkey® from 1st December 2021 to 28th February 2022. A reminder was sent out at the end of the survey period. The questions covered the following areas: demographic and clinical features of COVID-19 diseases, diagnostics, treatment, preventative and public health measures in both children and adults. The questionnaire was sent out to a single point of contact of all 15 APAAACI member countries using Survey Monkey® from 1st December 2021 to 28th February 2022. The point-of-contact was either a national representative of the member country's COVID-19 Task Force, or was involved in the country's COVID-19 operations at his/her institutional, member society or professional society level. Data for the region were obtained from information available in the public domain of the respective country's health, foreign affairs ministry or COVID-19 Task Force. Hence, each member country had one consolidated response representative of the situation in his/her own country's population. Results were collated and reported based on a denominator of the number of respondents who answered the respective questions. A similar methodology was used for our first survey.[1]

3 | RESULTS

3.1 | Demographic profile of respondents

Seventeen responses were received from 14/15 (93.3%) member countries comprising Australia, China, India, Hong Kong, Indonesia, Japan, Korea, Malaysia, Mongolia, Philippines, Vietnam, Singapore, Taiwan and Thailand. Among 17 respondents, 7 (41.2%) looked after adult patients, 4 (23.6%) paediatrics and 6 (35.3%) both adult and paediatric patients. The denominator for each question varied as some respondents did not answer specific questions.

3.2 | Epidemiology of COVID-19 infection among respondents' countries

The median number of cases in the respondents' countries was 2.25 million (interquartile range, IQR 144,358–3.37 million), median number of recovered cases 2.83 million (IQR 2.33–3.27 million) and median number of deaths 98,464 (IQR 51,762–373,320). The predominant variant of concern in the community during the period of the survey was delta (15, 93.8%) followed by alpha (4, 25%), beta and gamma (1, 6.3% respectively). All viral PCR samples were gene sequenced in only 6/16 (37.5%) respondents' countries. Serological tests available comprised Roche-Cov-2 anti-spike protein (anti-S) antibody (16, 100%), the Elecsys Roche total IgG (11, 68.8%) and cPass neutralizing antibody test (11, 68.8%) among respondents.

3.3 | COVID-19 severity

In terms of COVID-19 disease severity, respondents ranked a series of 5 adult and 6 paediatric phenotypes from 1 (most common) to 5 (least common) on a 5-point Likert scale. Among adults, asymptomatic/pre-symptomatic COVID-19 infection (10/17, 58.8%), mild COVID-19 acute respiratory infection (ARI) (9/17, 52.9%) and moderate COVID-19 lower respiratory tract infection (clinical/imaging/oxygen saturation $SpO_2 \geq 94\%$ on room air) (15/17, 88.2%) were ranked as the top 3 most common presentations among respondents. Severe disease was defined using objective parameters including oxygen saturation (SpO_2) and arterial oxygen partial pressure/fraction of inspired oxygen (PaO_2/FiO_2) or P/F ratio. Severe COVID-19 requiring oxygen [$SpO_2 < 94\%$ on room air, or P/F ratio <300 mmHg, respiratory rate >30 breaths/minute or lung infiltrates occupying ≥50% of lung fields] (10/17, 55.8%), or requiring intensive care [respiratory failure, septic shock and/or multi-organ dysfunction] (10/17, 55.8%) were ranked as the least common presentations.

Among the paediatric population (age: 16 years and below), asymptomatic/pre-symptomatic COVID-19 infection (12/16, 75%), mild COVID-19 acute respiratory infection (ARI) (11/15, 73.3%) and moderate COVID-19 lower respiratory tract infection (10/14, 71.4%) were similarly ranked as the top 3 most common presentations. Severe COVID-19 requiring oxygen (6/13, 46.2%) or requiring intensive care (8/14, 57.1%) were ranked as the least common presentations. Multisystem inflammatory syndrome in childhood (MIS-C) was ranked as the top 3 most common presentations in only 3/14 (21.4%) respondents.

Among patients with moderate-to-severe COVID-19 disease, the most common comorbidities among respondents were diabetes mellitus (15, 83.3%), obesity (12, 66.7%), cardiac disease (11, 61.1%) and hypertension (10, 55.6%). Biomarkers commonly used to assess severe disease among respondents comprised C-reactive protein and D-Dimer (16, 94.1% respectively), lymphopenia (15, 88.2%) and serum interleukin-6 (10, 58.8%). These were most commonly used for the diagnosis of severity and prognosis (11, 68.8%).

3.4 | Therapeutics and monoclonal antibodies

The range of therapeutics available for severe/critical COVID-19 patients requiring oxygen and/or intensive care is summarized in

Table 1. Dexamethasone or equivalent steroid and remdesivir were the most commonly used within the region (12, 75%), followed by dexamethasone plus tocilizumab (8, 50%) and prophylactic anticoagulation (8, 50%). For mild COVID-19 at risk of progression, the monoclonal antibodies casirivimab/imdevimab (REGEN-COV®) were available in the countries of 10/17 (58.8%) respondents, and sotrovimab (Xevudy®) in 4/17 (23.5%) and none available for the remaining 7/17 (41.2%). Among 13 respondents, other commonly used therapeutics for treatment/prophylaxis included other non-steroid immunomodulators (6, 46.2%), interferon preparations (5, 38.5%), lopinavir/ritonavir (4, 30.8%), favipiravir (4, 30.8%) and ivermectin (3, 23.1%).

3.5 | COVID-19 vaccines and adverse events

The median number of the population fully vaccinated (completed primary series) in each country was 50.3 million (IQR 10.9 million-107.1 million), translating to a median of 67.3% (IQR 58.8%–79.7%) of the population. Among 16 respondents, there was a wide range of vaccines using different platforms available in the region with the most frequently available being Pfizer/Comirnaty mRNA vaccine (13, 81.3%), AstraZeneca (12, 75.0%) and Moderna mRNA vaccine (10, 62.5%). Among the inactivated virus vaccines, the most widely available were Sinopharm (8, 50.0%), Sinovac/CoronaVac (7, 43.8%) and Covaxin (2, 12.5) as these are manufactured in the region. The whole range of COVID-19 vaccines available are summarized in Figure 1. Pfizer/Comirnaty mRNA vaccine was available for young people aged 12–18 years among 14/17 (82.4%) respondents during the survey period. The highest risk group for developing severe/critical COVID-19 was deemed to be the unvaccinated elderly among all (17, 100%) respondents compared to unvaccinated children below 12 years old (2, 11.8%).

mRNA vaccine contraindications most commonly comprised definite allergy to polyethylene glycol or polysorbate (11, 64.7%), anaphylaxis to other non-COVID-19 vaccines (9, 52.9%), anaphylaxis to other injectable drugs, severe facial/oropharyngeal/laryngeal angioedema and severe cutaneous adverse reaction (5, 29.4% respectively). The contraindications among respondents' countries are summarized in Figure 2.

The incidence of anaphylaxis to mRNA vaccines in each country was less than 1 per 100,000 doses among the majority of respondents (15, 88.2%). The remaining non-anaphylaxis serious adverse events encountered are summarized in Figure 3; of which myocarditis/pericarditis was the most common (12, 70.6%), followed by drug-induced hypersensitivity syndrome (DiHS). Among the adverse events of special interest (AESI), Guillain–Barre syndrome (10, 71.4%), thrombocytopenia (10, 71.4%), Bell's palsy (9, 64,3%) and vasculitis (8, 57.1%) were the most commonly reported. Figure 4 summarizes the series of AESI reported.

For persons who developed mRNA vaccine allergy, the most commonly used diagnostic tests were skin prick test (SPT) and intradermal tests (IDT) using the COVID-19 vaccine (8, 47.1%), serum tryptase (7, 41.2%), SPT and IDT to polyethylene glycol or polysorbate containing surrogate drugs (6, 35.3%), basophil activation tests (5, 29.4%) and measurement of serum complement levels (3, 17.7%).

3.6 | Public health measures

The public health measures still in place at the time of the survey included home isolation (12, 70.6%), community lockdowns (11, 64.7%), modified quarantine (8, 47.1%), enhanced community quarantine (7, 41.2%) and community swabbing (5, 29.4%). The wearing of face mask or face shield remained mandatory among 16 (94.1%) of respondents.

3.7 | Chronic/long COVID-19

Among 15 respondents who identified patients in their population with chronic COVID-19, symptoms were most commonly constitutional or respiratory (14, 93.3% respectively) followed by neurological (12, 80.0%), musculoskeletal (11, 73.3%) and cardiovascular (9, 60.0%). The details are summarized in Figure 5.

TABLE 1 Therapeutics for severe/critical COVID-19 patients requiring oxygen and/or intensive care ($n = 16$ respondents)

Therapy	Number	Percentage
Dexamethasone or equivalent steroid (severe/critical)	12	75.0%
Dexamethasone + Remdesivir (severe)	12	75.0%
Remdesivir (severe)	9	56.3%
Dexamethasone + Tocilizumab (severe/critical)	8	50.0%
Prophylactic anticoagulation	8	50.0%
Tocilizumab (severe/critical)	6	37.5%
Therapeutic anticoagulation	6	37.5%
Dexamethasone + Baricitinib (severe)	3	18.8%
Baricitinib (severe)	3	18.8%
Remdesivir + Baricitinib (severe)	1	6.3%

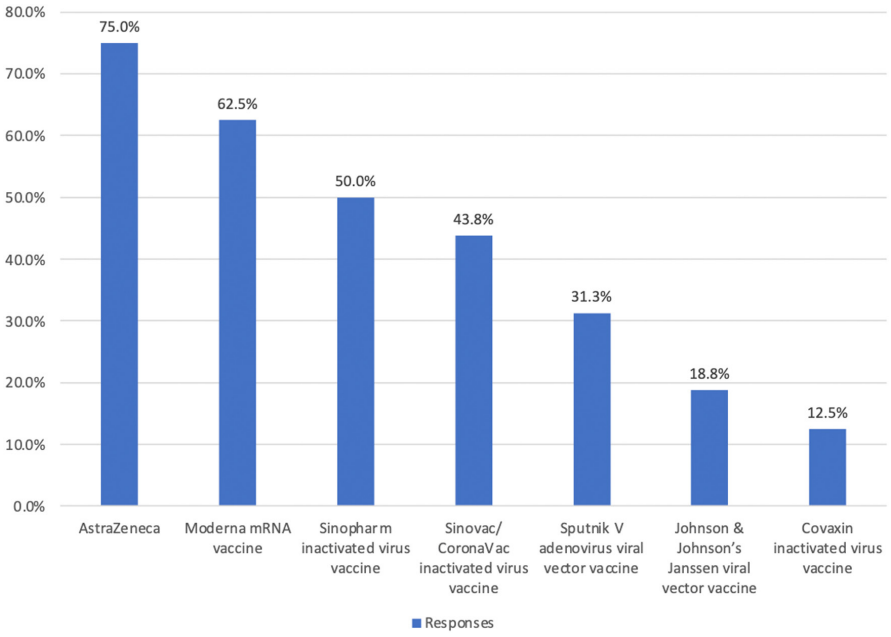

FIGURE 1 Vaccines available among respondents' countries

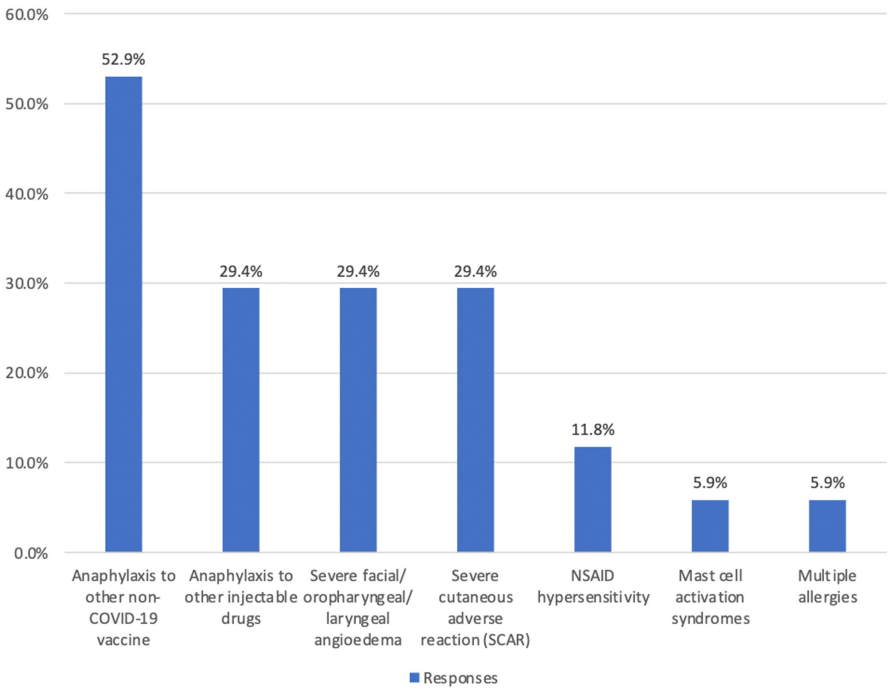

FIGURE 2 mRNA vaccine contraindications in respondents' country

4 | DISCUSSION

The Asia Pacific region is a large geographical region comprising countries with diverse cultural, economic and political profiles. The region's pandemic response plan in terms of access to diagnostics, therapeutics, vaccination and public health strategies differs among countries. The survey provides a cross-sectional analysis of the similarities and differences and summarizes the COVID-19 response in the region for future reference and guidance, facilitating co-learning and collaboration should there be a resurgence or new pandemics. Different COVID-19 vaccination strategies and levels of public acceptance, "zero-COVID" versus "Living with COVID" public health strategies also contrast with the policies and outcomes of strategies in Europe and North America.

Vaccination rates in the region averaged 60%–80% across most countries in the Asia Pacific, with variations in the types of vaccines available depending on different countries' procurement policies, their regulatory agencies' evaluation of prevailing clinical trials on vaccine efficacy and adverse effects and rate of increase in community cases and variants of concern. For instance, mRNA vaccines were recommended as first line followed by inactivated virus vaccines in some countries (e.g., Singapore), non-mRNA vaccines manufactured locally in others (e.g., China and India) or either platform as and when they were made available

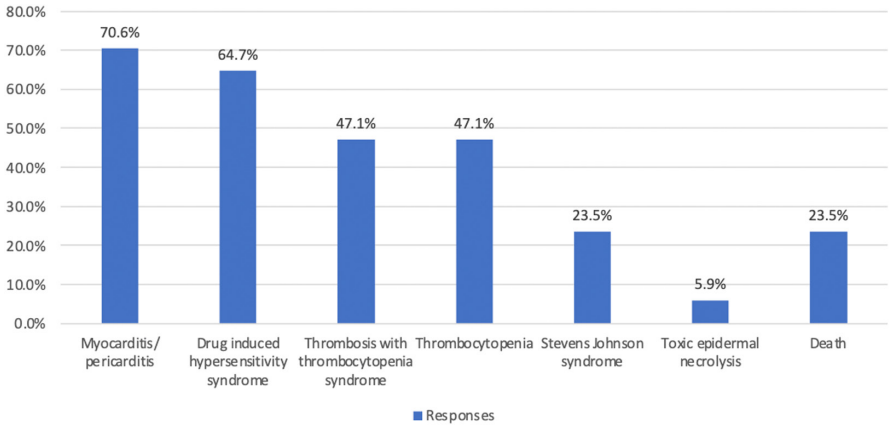

FIGURE 3 Serious vaccine adverse events ($n = 17$ respondents)

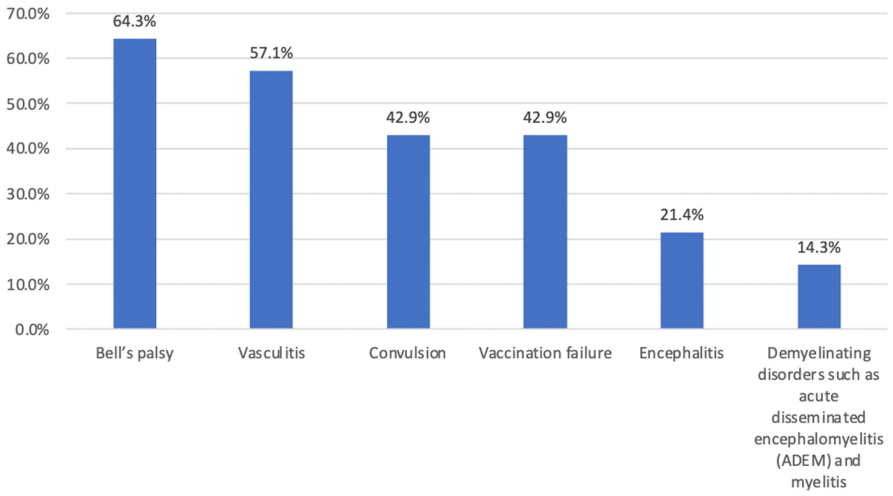

FIGURE 4 Adverse events of special interest (AESI) ($n = 14$ respondents)

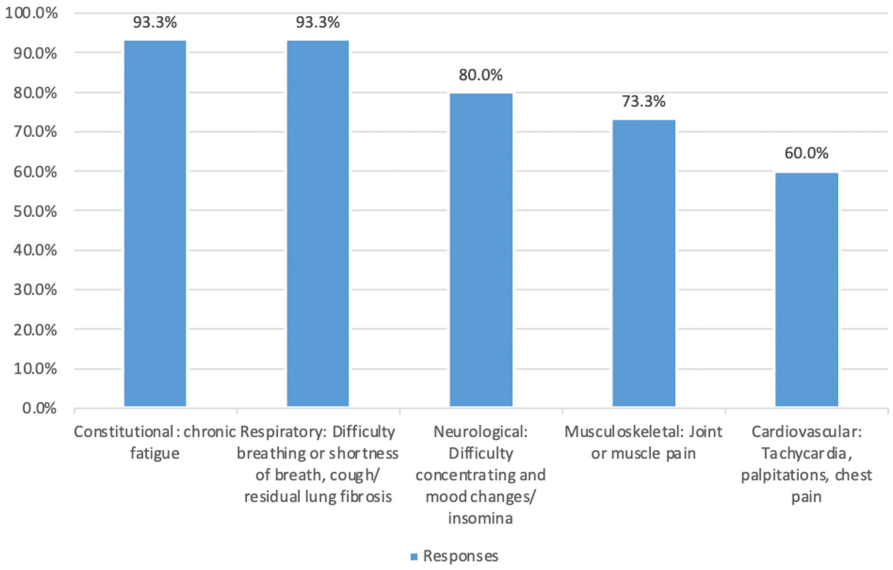

FIGURE 5 Chronic/long COVID-19 symptoms ($n = 15$ respondents)

(e.g., Malaysia and Philippines). The initial concern about risks of anaphylaxis with mRNA vaccines was subsequently also seen in non-mRNA vaccines. Different incidence rates were further confounded by different classification criteria used by different countries' regulatory agencies (Brighton Classification Criteria versus others).

In contrast to our previous survey in the first year of the pandemic, there were several key findings from this survey during the

second year of the pandemic, particularly in relation to the field of clinical immunology and allergy.

Firstly, although there have been increasing numbers of cases worldwide, the incidence of severe cases overall appears to be declining. Omicron appears to be a milder disease limited predominantly to the upper respiratory tract than originally feared.[11]Omicron variants were first detected in the last week of November 2021, and thus were not specifically asked for in the questionnaire survey which opened from 1 December 2021. Although more children below the age of 18 years are increasingly being infected through school and other contacts, the disease course remains generally mild, with MIS-C remaining relatively uncommon.[12] COVID-19 continues to circulate in healthcare facilities and the community. Long COVID or post-acute sequelae of COVID-19 (PASC) [13] is a clinical entity that will need to be longitudinally followed up in different populations with regards to biological mechanisms and potential interventions and preventive measures. Fatigue, respiratory symptoms and forgetfulness appear to be the most common clinical manifestations that persist for up to 6–8 months following acute COVID-19 infection.[14]

Secondly, the pandemic COVID-19 primary vaccination programmes across all age groups, [15–17]including additional primary doses for the immunocompromised[18] and boosters[18–20] appear to have been a major game changer, modifying the COVID-19 disease course. There was initially much concern about vaccine safety in December 2020 when COVID-19 mRNA vaccines were first approved for emergency use. However, the risk of mRNA vaccine-induced anaphylaxis[21,22] in both adults and children, even with boosters, appears to be overall low in relation to the benefit of vaccine protection from severe disease. Other than a definite allergy to polyethylene glycol, there are no other contraindications to mRNA vaccinations.[22,23] Increasing evidence shows that non-IgE-mediated mechanisms, e.g., IgG-mediated anaphylaxis and complement activation-related pseudoallergy (CARPA), may be involved in some of these cases who develop anaphylaxis reactions, [24] limiting the role of skin tests and other in vitro diagnostic tests.[25] Some patients with previous immediate reactions to mRNA vaccinations are able to tolerate subsequent doses without recurrence of a similar reaction [3] following specialist allergy evaluation and risk stratification.[26] Finally, some of these reactions may have been immunization stress-related responses (ISRRs) due to vaccination-related psychologic reactions which occur due to anxiety or stress mimicking acute allergic reactions.

Certain vaccine-induced AESI appears to have certain epidemiological patterns. mRNA vaccine-induced perimyocarditis affects predominantly younger persons below the age of 30 years old, with no increased risk so far in the 5- to 11-year-old paediatric population.[27,28] Vaccine-induced thrombotic thrombocytopenia (VITT), although predominant in recipients of adenovirus vector vaccines,[29] does not appear to recur with the second dose regardless of the type of vaccine and remains rarely, if at all, associated with mRNA vaccines.[30]

Thirdly, diagnostic tests like antigen rapid tests (ART)[31] do have increased sensitivity of early diagnosis of asymptomatic or mildly symptomatic persons when community prevalence is high. They appear to be able to pick up variants like Omicron with high sensitivity, although results differ depending on different test kits.[32] This allows for early self-detection, short test turnaround time and reduction in manpower and infrastructure needed to administer and run PCR tests. These tests are increasingly also being used in the monitoring of infected persons and discharge of those with resolved infections.

Fourthly, in the field of therapeutics, Nabs, e.g., casirivimab and imdevimab, sotrovimab, are now available for the treatment of non-hospitalized patients with mild/moderate COVID-19 infection considered at high risk of progression to severe COVID-19. Risk factors include age >65 years, obesity, pregnancy, chronic kidney disease, diabetes mellitus, immunocompromised, cardiovascular disease (including congenital heart disease) and hypertension, chronic lung disease and sickle cell disease.[9] Oral antivirals, e.g., Paxlovid® (nirmatrelvir and ritonavir) and Molnupiravir[10] are also available for outpatient treatment of early-onset mild disease within 5 days of symptom onset to prevent progression requiring hospitalization and onward transmission to close contacts. Remdesivir,[33] dexamethasone[34] and other immunomodulatory drugs[35] like baricitinib continue to be used for those with severe disease, requiring oxygen to avoid progression to mechanical ventilation (where possible) and reduce the risk of dying. Management strategies are increasingly guided by the use of objective risk assessment measures of disease severity in both vaccinated and unvaccinated to prognosticate outcomes, e.g., the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) score.[36,37]

Pre-exposure prophylaxis using Tixagevimab and Cilgavimab (Evusheld) is now also available.[38] It is administered as intramuscular injections as SARS-CoV-2 pre-exposure prophylaxis (PrEP) for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection and who are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination; or are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe adverse reaction to a COVID-19 vaccine or any of its components. COVID-19 treatment guidelines are updated at https://www.covid19treatmentguidelines.nih.gov/overview/.

Finally, public health measures have evolved between the first and second years of the pandemic, increasingly recommending self-isolation rather than massive lockdowns and use of quarantine facilities which incur high manpower and economic and infrastructural costs. Elimination strategies intended to buy time to develop COVID-19 therapies and vaccines, strengthen health systems and for informed decision-making are not sustainable in the long-term response for many countries in our region which are interdependent on our economic well-being.[39,40]

5 | CONCLUSION

The results of the survey represent a cross-sectional overview of the situation in each member country at the time of the survey. These

results are not intended to replace the outcomes of epidemiological studies and clinical trials on COVID-19 which provide evidence-based perspectives on various clinical, therapeutics and public health aspects of the pandemic.

To end the pandemic and for the region to transit to COVID-19 endemicity requires a multi-pronged approach including continuation of public health infection control and safe management measures, ongoing community vaccinations and research and development into diagnostics and therapeutics across all age groups. The short-term and long-term medical and psychosocial sequelae to the COVID-19 survivor and community, and other therapeutic interventions including vaccinations in children and adults will also need to be longitudinally followed-up long-term. With access to internationally recommended standards of care including public health preventive measures, therapeutics and vaccines among most APAAACI member countries, much progress has been made over the 2-year period in minimizing the morbidity and mortality from COVID-19 disease.

AUTHOR CONTRIBUTIONS

RP conceived the idea for the survey, contributed to the writing of the survey questions, oversaw the dissemination of the survey and collation of survey results as well as writing and review of this manuscript. BT contributed to writing of the survey questions, analysis of the results and writing and review of the manuscript. The remaining authors oversaw the administration of the survey in their respective countries including engaging the appropriate experts involved in COVID-19 diagnosis and management, reviewed the final results and the final manuscript.

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CONFLICT OF INTEREST

Nil.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Bernard Yu-Hor Thong https://orcid.org/0000-0002-6338-8482
Jiu-Yao Wang https://orcid.org/0000-0003-4540-9822
Luo Zhang https://orcid.org/0000-0002-0910-9884

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