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Epidemiology of COVID-19 cases and vaccination coverage in Seremban District, Malaysia, 2021

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Objective: Malaysia's first case of coronavirus disease (COVID-19) was reported in January 2020, with the first case in the state of Negeri Sembilan diagnosed on 17 February 2020. The National COVID-19 Immunisation Programme commenced in early March 2021 in Negeri Sembilan. This study describes the COVID-19 cases and vaccination coverage in Seremban District, Negeri Sembilan, during 2021.

Methods: The demographic and clinical characteristics of COVID-19 cases and the district's vaccination coverage were described. Vaccination coverage was plotted against COVID-19 cases on the epidemic curve. The chi-square test was used to examine the differences between the vaccination status of COVID-19 cases and severity category, hospitalization status and mortality.

Results: In Seremban District, there were 65 879 confirmed cases of COVID-19 in 2021. The data revealed that the 21–30-year age group had the highest proportion of cases (16 365; 24.8%), the majority of cases were male (58.3%), and most cases were from the sub-district of Ampangan (23.1%). The majority of cases were Malaysian. Over half (53.5%) were symptomatic, with fever (29.8%) and cough (22.8%) being the most frequently reported symptoms. COVID-19 vaccination status was significantly associated with severity category, hospitalization and mortality ($P < 0.001$ for all categories).

Discussion: This is the first study to describe two-dose vaccination coverage and the trend in COVID-19 cases in Seremban District. It was observed that COVID-19 cases had been reduced following more than 60.0% vaccination coverage.

In Malaysia, the first case of coronavirus disease (COVID-19) was diagnosed on 25 January 2020. In the urban city of Seremban, which is the state capital of Negeri Sembilan with a population of 636 400, the first case was diagnosed on 5 February 2020.[1] Malaysia initiated the National COVID-19 Immunisation Programme on 24 February 2021, which commenced in Negeri Sembilan on 3 March 2021.[2] The programme provided free COVID-19 vaccines across three phases: Phase 1 targeted front-line health-care workers; Phase 2 commenced on 19 April 2021 for elderly adults and high-risk groups; and Phase 3 began on 12 July 2021 for all eligible people over the age of 18.

Herd immunity for COVID-19 was estimated to require 50–66% of the population to be immunized, either spontaneously or artificially,[3] and the Ministry of Health Malaysia projected a herd immunity threshold of 70–80% vaccination coverage.[4] To the best of our knowledge, there has been no local study on COVID-19 vaccination in Negeri Sembilan; therefore, the objective of this study is to describe the characteristics of COVID-19 cases and two-dose vaccination coverage in Seremban District during 2021.

METHODS

A descriptive analysis of all COVID-19 cases registered in Seremban was undertaken from 1 January to 31 December 2021. A confirmed case of COVID-19 was defined as a person with a positive rapid antigen test in predetermined areas with an incidence of COVID-19

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greater than 10% OR a person (alive or dead) with a positive reverse transcription polymerase chain reaction test.[5] COVID-19 severity was classified into five categories: category 1, asymptomatic; category 2, symptomatic without pneumonia symptoms; category 3, symptomatic with pneumonia symptoms; category 4, requiring intensive care and supplemental oxygen; and category 5, critical illness with multiple organ involvement.[6]

Telephone interviews for every case were conducted by employees of the Seremban District Health Office to gather data on demographics, symptoms, onset date, date of exposure, travel history, comorbidities and vaccination status. Vaccination coverage for Seremban District from March to July 2021 was obtained from data compiled manually in Microsoft Excel® from each health-care facility and the Malaysia Vaccine Administration System. From 23 July to 31 December 2021, vaccination coverage was obtained through an automated system.[7] Vaccination coverage was plotted against COVID-19 cases on an epidemic curve (**Fig. 1**).

All verified data were recorded in a line list, and Microsoft Excel® was used for data analysis. The demographic and clinical characteristics of confirmed COVID-19 cases and district vaccination coverage were tabulated and analysed using descriptive statistics. The chi-square test was used to examine the differences between the vaccination status of COVID-19 cases and severity category, hospitalization status and mortality.

RESULTS

There were 65 879 confirmed cases of COVID-19 in Seremban District in 2021, giving an incidence rate of 10 358 per 100 000 population. The cases were distributed unevenly among the eight sub-districts. Sub-district Ampangan recorded the highest number of cases (15 213; 23.1%), while sub-district Pantai had the lowest (362; 0.5%). A plurality of cases were aged 21–30 years (16 365; 24.8%), and a majority were male (38 421; 58.3%), Malaysian nationals (54 023; 82.0%) and symptomatic (35 262; 53.5%). Fever (19 602; 29.8%), cough (15 049; 22.8%) and loss of smell and taste (5448; 8.3%) were the most frequently observed symptoms. The majority of cases had no comorbidities (55 981; 85.0%) and had a history of close contact with at least one other confirmed case (47 480; 72.1%). Almost all of the reported cases (65 642; 99.6%) were locally acquired, 23 333 (35.4%) were hospitalized for isolation and treatment, and 561 died (0.9%) (**Table 1**).

The number of COVID-19 cases per week increased between March and August 2021, declined in early August 2021, and then plateaued until December 2021. On 8 August 2021, two-dose vaccination coverage for adults reached 56% (**Fig. 1**).

Before the vaccination programme, from 1 January to 20 March 2021, there were 7149 confirmed COVID-19 cases including 31 deaths. Most of these cases were in severity categories 1 (4807; 67.2%) and 2 (2297; 32.2%), while 14 cases (0.2%) were in category 3. None were in categories 4 and 5 (**Table 2**).

From the start of the vaccination programme on 21 March 2021 until 60.0% coverage was reached on 15 August 2021, 43 375 patients were registered with COVID-19, of whom 37 937 (87.5%) were unvaccinated. Of the 476 deaths, 431 (90.5%) were unvaccinated. In terms of severity, 23 265 were category 1 (21 316 unvaccinated vs 1949 vaccinated), 18 970 were category 2 (15 679 unvaccinated vs 3291 vaccinated), 656 were category 3 (507 unvaccinated vs 149 vaccinated), 7 were category 4 (4 unvaccinated vs 3 vaccinated), and 1 was category 5 (vaccinated) (**Table 2**).

For the period of 15 August to 5 September 2021 (with vaccination coverage of 60.0–84.0%), 4965 COVID-19 cases were reported. With regard to COVID-19 severity, 3048 cases were category 1 (1389 unvaccinated vs 1659 vaccinated), 1771 were category 2 (693 unvaccinated vs 1078 vaccinated), 82 were category 3 (31 unvaccinated vs 51 vaccinated), 12 were category 4 (5 unvaccinated vs 7 vaccinated), and 3 were category 5 (2 unvaccinated vs 1 vaccinated) (**Table 2**). Twenty of the 49 COVID-19 deaths (40.8%) during this period were unvaccinated. There was a large decline in cases once vaccination coverage of more than 60.0% was reached (**Fig. 1**). It was also found that the case fatality rate was higher when vaccine coverage was less than 60.0% (1.1%) compared to when it was 60.0–84.0% (0.3%).

There was a significant difference in the distribution of unvaccinated and vaccinated (two doses) cases by severity category, hospitalization and mortality ($P < 0.001$;

Fig. 1. **Number of COVID-19 cases by week and vaccination coverage in Seremban District, Malaysia, 1 January to 31 December 2021**

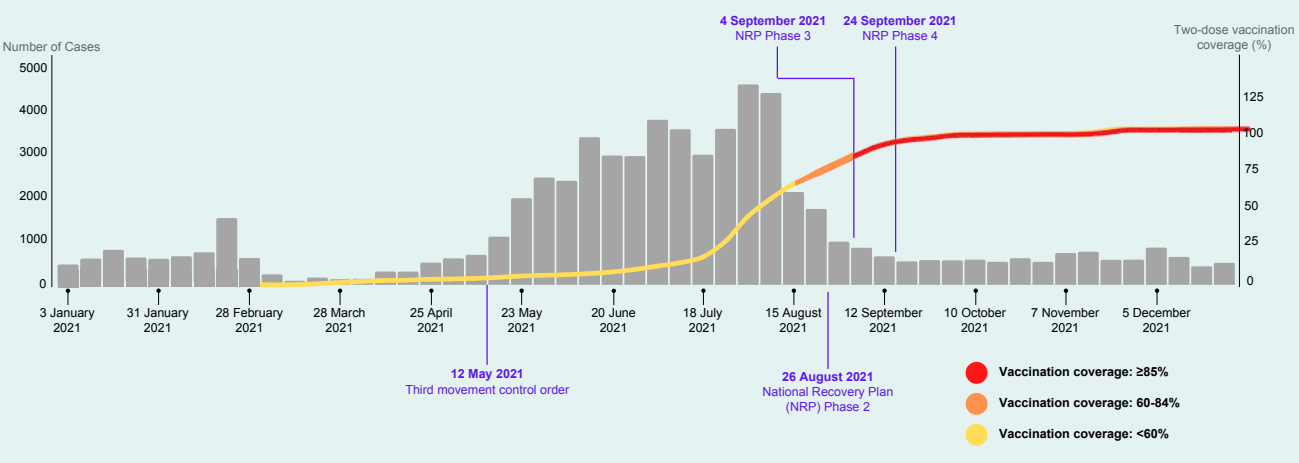

Table 3). The proportion of cases being hospitalized or dying who received two vaccine doses was lower compared to those who were unvaccinated (**Table 3**).

DISCUSSION

This study describes the demographic and clinical characteristics of 65 879 cases of COVID-19 from the most densely populated district in the state of Negeri Sembilan. It demonstrated that the number of cases per week declined after the district vaccination coverage reached 60.0%.

The 21–30-year age group had the highest proportion of COVID-19 cases, possibly due to rapid housing development and a growing workforce in this district.[8] The fact that there were more cases among the male population could be due to their being less compliant with preventive measures such as frequent hand washing, face-mask use and stay-at-home orders.[9] The high proportion of cases registered among Malaysian nationals is most likely due to international travel restrictions. The high urbanization and population density in Ampangan sub-district[10] may also account for the elevated number of cases. Most COVID-19 cases were asymptomatic and detected through contact tracing. The high proportion of young cases may have contributed to the increased number of asymptomatic individuals, as younger individuals tend to have mild or no symptoms.[11] Compared to vaccinated cases, unvaccinated cases had higher proportions of cases in the higher severity categories, hospitalizations and deaths, similar to a previous study from Malaysia, which reported that vaccination could prevent severe COVID-19 illness, hospitalization, intensive care unit admission and death.[12]

Our data showed that the number of COVID-19 cases per week was decreasing when two-dose vaccination coverage reached 60.0%. While vaccination has been shown to reduce COVID-19 outbreaks,[13,14] the impact of other response components also needs to be considered. Malaysia was under its third movement control order from 12 May 2021 to 1 April 2022, during which international, inter-state and inter-district travel, as well as economic, social, educational, sports and business operation hours, were restricted. Physical distancing and mask use were enforced nationwide under the Prevention and Control of Infectious Diseases Act 1988. Personal hygiene practices including hand washing were continuously promoted by the Ministry of Health through various media platforms. During this period, COVID-19 variants Alpha and Beta were mostly circulating in Malaysia before the Delta variant emerged in July 2021.[15]

Another intervention for COVID-19 was the establishment of the Greater Klang Valley Special Task Force on 12 July 2021. This task force was a multi-agency collaboration for COVID-19 management in the Klang Valley (covering the federal territories of Kuala Lumpur and Putrajaya and the state of Selangor) and Seremban District. The task force's objectives included organizing strategic actions to improve health-care delivery, lessening the transmission of infectious diseases, and assisting both the general public and health-care professionals.[16]

Table 1. **Characteristics of COVID-19 cases in Seremban District, Malaysia, 1 January to 31 December 2021 (*N* = 65 879)**

Characteristic	*n*	%
Age group		
0–10	9075	13.8
11–20	8236	12.5
21–30	16 365	24.8
31–40	12 576	19.1
41–50	7190	10.9
51–60	4965	7.5
>60	3947	6.0
No information	3525	5.4
Sex		
Male	38 421	58.3
Female	27 458	41.7
Nationality		
Malaysian	54 023	82.0
Other	11 856	18.0
Symptomatic		
Yes	35 262	53.5
No	30 617	46.5
Sub-district		
Ampangan	15 213	23.1
Labu	13 445	20.4
Setul	10 761	16.3
Rantau	9286	14.1
Rasah	7278	11.0
Seremban	6558	10.0
Lenggeng	2038	3.1
Bandar Seremban	938	1.4
Pantai	362	0.5
Symptoms		
Fever	19 602	29.8
Cough	15 049	22.8
Loss of smell and taste	5448	8.3
Sore throat	3572	5.4
Myalgia	2760	4.2
Headache	2096	3.2
Stomach pain	1155	1.8
Comorbidities		
None	55 981	85.0
Hypertension	5508	8.4
Diabetes mellitus	3731	5.7
Asthma	1408	2.1
Heart disease	652	1.0
Dyslipidaemia	477	0.7
History of close contact with confirmed COVID-19 case		
Yes	47 480	72.1
No	18 399	27.9
Source of infection		
Local	65 642	99.6
Imported	237	0.4
Hospitalized		
Yes	23 333	35.4
No	42 546	64.6
Status		
Alive	65 318	99.1
Dead	561	0.9

To our knowledge, this is the first study to describe two-dose vaccination coverage and the trend of COVID-19 cases in Seremban District. It was observed that COVID-19 cases decreased once 60.0% vaccination coverage had been reached. The strength of this study is in the use of large datasets acquired from the Seremban District Health Office, which may reflect the real number of COVID-19 cases in other districts. These data are managed systematically, making their source more reliable.

This study has limitations, the first of which is that it is a descriptive observational study of one area in Malaysia. A more sophisticated statistical analysis is needed to compare vaccination coverage and the number of COVID-19 cases. Given that only symptomatic patients were screened for COVID-19,[15] a potentially large number of individuals with asymptomatic infection may have remained undiagnosed, thus contributing to the lower number of reported COVID-19 cases. Other limitations include: the lack of data on disease progression and on the use of the severity categories during diagnosis; the unavailability of COVID-19 vaccine for the different variants; and the fact that case data on COVID-19 variants were not obtained during field investigations as they were not a priority for the primary management of COVID-19. The findings of this study need to be interpreted with caution.

In summary, this study describes the epidemiology of COVID-19 cases in 2021 in Seremban District, Malaysia. Although we show that the COVID-19 case

Table 2. **COVID-19 cases by severity category before and after the vaccination programme started in Seremban District, Malaysia, 1 January to 31 December 2021 (*N* = 65 879)**

Before vaccination programme, 1 January to 20 March 2021		
Severity category	**Cases (*N* = 7149)**	
	n	**%**
1	4807	67.2
2	2297	32.2
3	14	0.2
4	0	0
5	0	0
Deaths	31	0.4

Vaccination coverage <60.0%, 21 March to 14 August 2021					
Severity category	**Cases (*N* = 43 375)**	**Unvaccinated (*n* = 37 937)**		**Vaccinated (*n* = 5438)**	
		n	**%**	***n***	**%**
1	23 265	21 316	91.6	1949	8.4
2	18 970	15 679	82.7	3291	17.3
3	656	507	77.3	149	22.7
4	7	4	57.1	3	42.9
5	1	0	0	1	100
Deaths	476	431	90.5	45	9.5

Vaccination coverage 60.0–84.0%, 15 August to 5 September 2021					
Severity category	**Cases (*N* = 4965)**	**Unvaccinated (*n* = 2140)**		**Vaccinated (*n* = 2825)**	
		n	**%**	**n**	**%**
1	3048	1389	45.6	1659	54.4
2	1771	693	39.1	1078	60.9
3	82	31	37.8	51	62.2
4	12	5	41.7	7	58.3
5	3	2	66.7	1	33.3
Deaths	49	20	40.8	29	59.2

Vaccination coverage >85.0%, 6 September to 31 December 2021					
Severity category	**Cases (*N* = 10 390)**	**Unvaccinated (*n* = 2353)**		**Vaccinated (*n* = 8037)**	
		n	**%**	***n***	**%**
1	4976	1450	29.1	3526	70.9
2	5244	886	16.9	4358	83.1
3	144	12	8.3	132	91.7
4	18	3	16.7	15	83.3
5	3	2	66.7	1	33.3
Deaths	5	0	0	5	100

Category 1: asymptomatic.

Category 2: symptomatic without pneumonia symptoms.

Category 3: symptomatic with pneumonia symptoms.

Category 4: requiring intensive care and supplemental oxygen.

Category 5: critical illness with multiple organ involvement.

Table 3. **Factors associated with vaccination status in COVID-19 cases in Seremban District, Malaysia, 1 January to 31 December 2021 (*N* = 65 874)[a]**

Variable	Unvaccinated (*n* = 49 579)		Vaccinated (n = 16 295)		*P*
	n	%	*n*	%	
Severity category					
1	29 109	58.7	7155	43.9	<0.001
2	19 819	40.0	8763	53.8	
3	633	1.3	345	2.1	
4	12	0.02	26	0.2	
5	6	0.01	6	0.04	
Hospitalized					
Yes	20 075	40.5	3258	20.0	<0.001
No	29 504	59.5	13 037	80.0	
Outcome					
Alive	49 097	99.0	16 216	99.5	<0.001
Dead	482	1.0	79	0.5	

[a] Five of the total 65 879 COVID-19 cases are excluded for lack of information on vaccination status.

Category 1: asymptomatic.

Category 2: symptomatic without pneumonia symptoms.

Category 3: symptomatic with pneumonia symptoms.

Category 4: requiring intensive care and supplemental oxygen.

Category 5: critical illness with multiple organ involvement.

numbers decreased as vaccination coverage increased, other control measures such as movement control orders, physical distancing, mask use and regular hand washing are likely to have also contributed to the decrease in cases. Additional analyses are needed to confirm an association between COVID-19 cases and vaccination coverage.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

The study protocol was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-22-01171-6AR).

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Involvement and readiness of fellows from Papua New Guinea's Field Epidemiology Training Programme in the COVID-19 response, 2020–2021

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Problem: Fellows of the Papua New Guinea Field Epidemiology Training Programme (FETP) were part of the national coronavirus disease (COVID-19) response. However, the specific activities and challenges experienced by fellows in the field were unknown.

Context: The advanced FETP cohort commenced just prior to the COVID-19 pandemic and all fellows were involved in the response. The advanced fellows participating in this review represented a cross-section of the country's public health workforce.

Action: A review was conducted to better understand the scope of activities undertaken by FETP fellows, identify the challenges experienced and assess how well the programme prepared fellows for their COVID-19 response roles. A facilitated discussion based on the World Health Organization COVID-19 intra-action review methodology and an online survey was conducted with advanced FETP fellows.

Outcome: The fellows made important contributions to the national COVID-19 response by assuming leadership positions at all levels of government, leading training activities and applying core field epidemiology competencies in surveillance and response activities. The programme had prepared them well for the response, giving them the confidence and skills to undertake a diverse range of response roles.

Discussion: The FETP review of the COVID-19 response in Papua New Guinea highlighted the role and influence of the fellows during the pandemic response. Fellows were able to apply core field epidemiology competencies across a range of roles. The recommendations derived from this review will be instructive for the FETP specifically and the COVID-19 response generally.

PROBLEM

Graduates and fellows of the Field Epidemiology Training Programme of Papua New Guinea (FETPNG) were part of the national coronavirus disease (COVID-19) response. However, the specific activities and challenges experienced by FETP fellows in the field were not known. Given the important role of field epidemiologists in emergency response, the FETP faculty conducted a review to understand what worked well, what worked less well, the scope of activities undertaken by fellows during the COVID-19 response, how prepared fellows felt, their confidence in performing key field epidemiology tasks during the response and what FETPNG could do better to prepare fellows for future infectious disease emergencies.

CONTEXT

The COVID-19 pandemic has tested public health emergency response capacity across the world. The first case of COVID-19 was confirmed in Papua New Guinea (PNG)

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on 6 March 2020 and the country has experienced multiple waves since that time, relying heavily on international and domestic border control measures as well as contact tracing, quarantine and isolation to suppress transmission and preserve health systems.[1,2] As of 22 August 2022, 44 861 confirmed cases of COVID-19, including 664 deaths, were reported in PNG.[3]

FETPs are supervised, on-the-job, competency-based training programmes for public health professionals. They train field epidemiologists to collect, analyse and interpret public health information, using evidence to take action and save lives. The skills of locally trained field epidemiologists are well suited to support public health emergency response activities.[4] As health security concerns have grown globally, FETPs have become increasingly recognized in global, regional and national preparedness and response mechanisms.[5] Field epidemiologists are identified as important human resource requirements for implementation of the International Health Regulations (2005), or IHR (2005).[6,7] The Global Health Security Agenda, launched in 2014 to support IHR (2005) implementation, highlights workforce training as a key element in strengthening health security.[8] FETPs are a key part of training this health security workforce. Regionally, the Asia Pacific Strategy for Emerging Diseases (APSED III) has identified the importance of FETPs in progressing IHR (2005).[9]

PNG has been running an intermediate level (9-month) FETP since 2013[10] and recently initiated an extended 18-month programme, known as the advanced FETPNG (aFETPNG). As of July 2022, there were 94 intermediate FETP graduates working across all 22 provinces of the country and 17 fellows enrolled in aFETPNG.

The aFETPNG cohort commenced in 2019 just prior to the COVID-19 pandemic, and work in 13 of PNG's 22 provinces (59%). They represent all levels of the government's public health workforce, with fellows recruited from district (n = 7), provincial (n = 9) and national levels (n = 1). The substantive roles of fellows included surveillance officers, health extension officers, district health managers, disease programme managers, provincial disease control officers, the FETP convenor and a provincial deputy director of public health.

ACTION

Facilitated discussion

A 1-day review was held with aFETPNG fellows during their second face-to-face training workshop. We adapted the World Health Organization (WHO) COVID-19 intra-action review methodology,[11] framing discussions with FETP fellows around WHO's emergency response pillars which were used to guide a country's COVID-19 response.[12] The pillars we focused on were:

- Risk communications and community engagement (pillar 2);
- Surveillance, case investigation, laboratory (pillars 3 and 5);
- Case management and infection prevention and control (pillars 6 and 7); and
- Operational support and logistics (pillar 8).

Facilitated discussions identifying what went well and what went less well during the COVID-19 response were held, which included a root cause analysis.[11,13] Findings from the root cause analysis were used to develop recommendations for action.

Online survey

Understanding the contribution of aFETPNG fellows during the COVID-19 response, their role, how well prepared they felt and their confidence in performing key field epidemiology tasks during the response was carried out through an online survey.[13] The survey also asked how FETPNG could better prepare fellows for future infectious disease emergency responses.

OUTCOME

Facilitated discussion

The findings from the facilitated discussion and key recommendations derived from root cause analysis were organized into four groups based on the WHO pillars (**Table 1**).

Online survey

Fifteen (88%) aFETPNG fellows responded to the survey. All 15 (100%) were involved in the COVID-19 response in PNG. When asked about their involvement in COVID-19 throughout 2021, just over half (53%; *n* = 8) reported working full time on the response. Of those not in a full-time role, 13% (*n* = 2) worked on the response 3–4 days per week and 33% (*n* = 5) 1–2 days per week.

The most common COVID-19 response roles undertaken included leading surveillance activities, providing advice to stakeholders, leading rapid response teams (RRTs), contact tracing and conducting training. The majority (80%; *n* = 12) of fellows received specific training to support them in their COVID-19 response roles. Almost all fellows (93%; *n* = 14) were involved in training others in support of the COVID-19 response, with fellows conducting an average of four training activities (range 1–15) in 2021. The 14 fellows collectively trained over 700 individuals.

Table 1. **Summary of what worked well, what worked less well and key recommendations for the advanced Field Epidemiology Training Programme of Papua New Guinea, based on root cause analysis, April 2022**

Risk communications and community engagement		
Worked well	**Worked less well**	**Recommendations**
• Using established systems and community structures • Partnerships with key stakeholders • Community leaders trained and engaged in COVID-19 awareness • Risk communications training for health-care workers (HCWs) at provincial and district levels • Good political influence in the community • Other partners helped develop information, education and communication (IEC) materials that were easy to understand by the community	• Misinformation about COVID-19 vaccination and the impact this has on COVID-19 vaccination and routine immunization • HCWs spreading false rumours about the virus and COVID-19 vaccination • Lack of established partnerships with communities affected communication and engagement efforts • Provincial communication officers not always available • Limited use of local languages in IEC materials	• Establish and maintain strong working relationships with community leaders and partners • Establish high-quality training-of-trainers strategies to ensure HCWs at all levels are knowledgeable across response needs • Establish recruitment strategy at provincial level to ensure adequate professional health staff to raise public health awareness alongside risk communication experts • Continue to work with and build relationships with partners
Surveillance, case investigation, laboratory		
Worked well	**Worked less well**	**Recommendations**
• Roll out of rapid antigen test kits • Provincial-level management support for surveillance activities • Opportunities afforded to Field Epidemiology Training Programme (FETP) fellows to apply surveillance skills • Purchase of two-way radios for surveillance teams • Training of health extension officers at district level to collect specimens • Capitalizing on COVID-19 surveillance to strengthen other reporting systems • Proactive response supported by appropriate legislation	• Turnaround time for polymerase chain reaction (PCR) results (2–4 weeks) • Turnaround time for whole genome sequencing • Lack of training in data management • No dedicated data management officers at provincial or district levels for COVID-19	• Roll out COVID-19 rapid antigen tests at all facilities, including aid posts • Ensure supply of rapid antigen tests is adequate • Develop a sensitization programme to highlight the value of surveillance to management within the province

Case management and infection prevention and control		
Worked well	**Worked less well**	**Recommendations**
• When available, rapid antigen tests helped with timely case detection/ diagnosis • Improved health facilities (e.g. construction of new wards and isolation facilities, instalment of incinerators, etc.) • Creation and dissemination of treatment protocols • Engagement of mental health counsellors	• Limited or no patient transport available • No expertise to deal with mental health problems • Standard treatment protocols not always available, confusion around the use of ivermectin • Insufficient human resources for case management and infection prevention and control • Poor coordination and cooperation between clinical and public health response • Poor compliance with case isolation	• Direct funding and resources to boost health-care workforce • Provide staff incentives for additional responsibilities • Target educational resources to promote vaccination among HCWs • Build new isolation facilities or separate COVID-19 wards with dedicated staff to work in them • Ensure resources are allocated to home isolation monitoring • Strengthen and invest in sustainability of call centres in all provinces (for example, integrate the call centre with the disaster office) • Offer staff incentive packages and infection prevention and control training for those who work with COVID-19 patients

Response, operational support and logistics		
Worked well	**Worked less well**	**Recommendations**
• Integration of COVID-19 response with other programmes • Establishment of rapid response teams (RRTs) to support the response • Strengthened emergency operations centres at the provincial level • Coordination of funding available for COVID-19 response • Involvement of partners/ commercial properties to support response needs	• Staff shortage – inadequate staffing resulted in multi-tasking, exhaustion and mental stress • Waste management issues (e.g. non-functional incinerators) • Delay in receiving funds for the response • Disruption to routine services, including routine childhood immunization • Funding impacts on other programmes • Poor compliance with control measures (mask wearing, physical distancing, isolation, quarantine, vaccination)	• Establish and allocate funding for a RRT in every province; use existing workforce to formulate RRTs • Ensure there is a provincial budget for COVID-19 response and outbreaks with programme-based budgeting • Establish processes at provincial level to facilitate rapid mobilization of financial and human resources in response to public health emergencies (with minimal impact on routine services) • Provide targeted education and incentives to promote vaccination of HCWs at all levels

Core FETP competencies, such as disease surveillance, outbreak response and data analysis, were all highlighted as being useful in preparing fellows for the COVID-19 response. Fellows also identified that the FETP provided them with confidence, enabling them to fill leadership roles, conduct public speaking and influence decision-makers.

"Decision makers have confidence in me presenting analysed data on COVID-19."

"As an FETP fellow, I have been appointed incident manager – I took a lead in surveillance, contact tracing, risk communication and community engagement."

"There is respect for the [FETP] course."

"There is recognition of FETP grads who are identified to take lead roles in the response."

"From the FETP training – we could actively participate as a team lead in RRT, conduct contact

tracing, case investigation and surveillance – across all areas of response."

Fellows felt most confident supporting or leading case investigation and contact tracing activities, and least confident supporting or leading risk communication, community engagement, specimen handling and shipping, and infection prevention and control activities (**Supplementary Table 1**).

Areas for strengthening the response capacity of graduates included further training on tools to support surveillance, data management, analysis and interpretation, risk communications and community engagement, psychological first aid, management and leadership during public health emergencies, and the establishment of RRTs. Fellows highlighted a need for more careful consideration and inclusion of gender issues when responding to emergencies and commented on connectivity challenges associated with virtual training.

Most fellows (93%; $n = 14$) reported that the intermediate and advanced FETPs were very helpful in preparing them for the COVID-19 response, while one respondent (7%) indicated the programmes were moderately helpful. Half ($n = 7$) of the fellows indicated that their manager was very aware of their skills as a field epidemiologist, 36% ($n = 5$) of managers were somewhat aware and 14% ($n = 2$) were not aware. Most of the fellows (79%; $n = 11$) indicated that their skills in field epidemiology were well utilized by their managers during the COVID-19 response.

When asked what could be done to improve the use of FETP graduates and fellows by management, the following themes emerged: (i) the need for management to recognize the potential of field epidemiologists and make use of them in leadership positions; (ii) the creation of designated field epidemiology positions within the public service; (iii) FETP sensitization training for managers; and (iv) the need for FETP fellows and graduates to appropriately manage up, including proactively presenting their surveillance and project findings to management.

DISCUSSION

The COVID-19 review highlighted the role and influence of aFETPNG fellows during the pandemic response. Fellows were able to apply core field epidemiology competencies across a range of roles. The diversity of their roles highlights the value and versatility of field epidemiologists in public health emergencies. While the majority of fellows found the FETP training very helpful in preparing them for a pandemic response, they identified areas for improvement.

Based on the findings from the facilitated discussion and the online survey, the faculty prioritized the following actions:

- revise the intermediate and advanced FETPNG curricula to include additional training on areas highlighted by fellows, especially risk communication and community engagement;
- develop supplementary training, tools and resources to enable fellows and graduates to master core FETP competencies; fellows identified eLearning modules (provided in both offline and online formats), further refresher training opportunities, and a written technical manual with PNG examples;
- develop mechanisms to support graduates in the ongoing application of FETP knowledge and skills in the workplace through activities such as individual and group-based projects for graduates and ongoing mentorship (including during outbreak response activities);
- develop and deliver a sensitization training programme for senior management to promote the best utilization of field epidemiology graduates in the workplace; and
- advocate for the creation of designated field epidemiology positions within the public health service, providing a clear career pathway for graduates.

This FETP COVID-19 review was limited to fellows enrolled in the advanced FETP and did not include feedback from fellows or graduates of the intermediate FETP. Thus, these findings are not representative of all FETP fellows and graduates and cannot be generalized to the whole FETPNG population.

This COVID-19 review supports a culture of ongoing reflection and evaluation. The recommendations are

instructive for FETPNG specifically and the COVID-19 response generally. Findings from this review support previous work focusing on workforce issues during emergency responses.[4,14,15] This review has highlighted the important contribution of the FETP fellows during the COVID-19 response, and the need for the programme to adapt to better prepare PNG's field epidemiology workforce for future challenges.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

This activity met the University of Newcastle's requirements for a Quality Assurance project and did not require review by the Human Research Ethics Committee.

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Ensuring access to novel COVID-19 therapeutics in Pacific island countries and areas

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Problem: As of November 2022, over 417 397 confirmed cases and 2631 deaths related to coronavirus disease (COVID-19) were reported in Pacific island countries and areas (PICs). Most PICs have faced challenges accessing therapeutics recommended for the treatment of COVID-19 due to their high demand worldwide and supply chain constraints.

Context: The World Health Organization (WHO) coordinates and provides tailored technical and operational support to 21 PICs. Since the start of the pandemic, WHO has worked with partners to establish a mechanism to ensure equitable access to three novel COVID-19 therapeutics (tocilizumab, molnupiravir and nirmatrelvir/ritonavir) for lower-income countries, including 11 eligible PICs.

Action: WHO coordinated the requests, procurement and distribution of the three novel therapeutics. In addition, WHO supported PICs by providing trainings in clinical management of COVID-19, developing critical supply needs estimates, and facilitating regulatory approval of clinical therapeutics, including emergency use authorization.

Lessons learned: The main barriers to procurement of novel COVID-19 therapeutics were identified as prolonged negotiations with licence holders, sourcing funding, the high cost of therapeutics and limited capacity to provide safety monitoring.

Discussion: Uninterrupted supply and availability of essential medicines in the Pacific region is dependent on external and local sourcing. To overcome procurement barriers and ensure access to novel COVID-19 therapeutics in PICs, WHO's pandemic support to Member States focused on strengthening regulatory requirements, safety monitoring and supply chain activities.

The first case of coronavirus disease (COVID-19) in the Pacific was reported in March 2020 in French Polynesia.[1] Since then, a total of 417 397 cases and 2631 deaths have been reported across the Pacific (data as of mid-November 2022).[1] Among the Pacific island countries and areas (PICs), Nauru has had the highest incidence rate, with 42 551 cumulative cases per 100 000 population.[1]

Several novel therapeutics for the treatment of patients with COVID-19 have been recommended by the World Health Organization (WHO).[2,3] While many high-income countries have the resources to procure and implement pharmaceutical interventions, most PICs have faced difficulties in accessing and delivering COVID-19 therapeutics to their populations, largely due to high worldwide demand and supply chain constraints. This report describes the challenges experienced by WHO and partnering organizations at national and local levels in relation to ensuring access to novel COVID-19 therapeutics in PICs and the progress that has been made in overcoming those challenges.

CONTEXT

The WHO Division of Pacific Technical Support (DPS) coordinates and provides tailored technical and operational support to 21 PICs (**Fig. 1**), which collectively are home to 3.2 million people spread across an ocean that covers 30% of Earth's surface.[4] According to the

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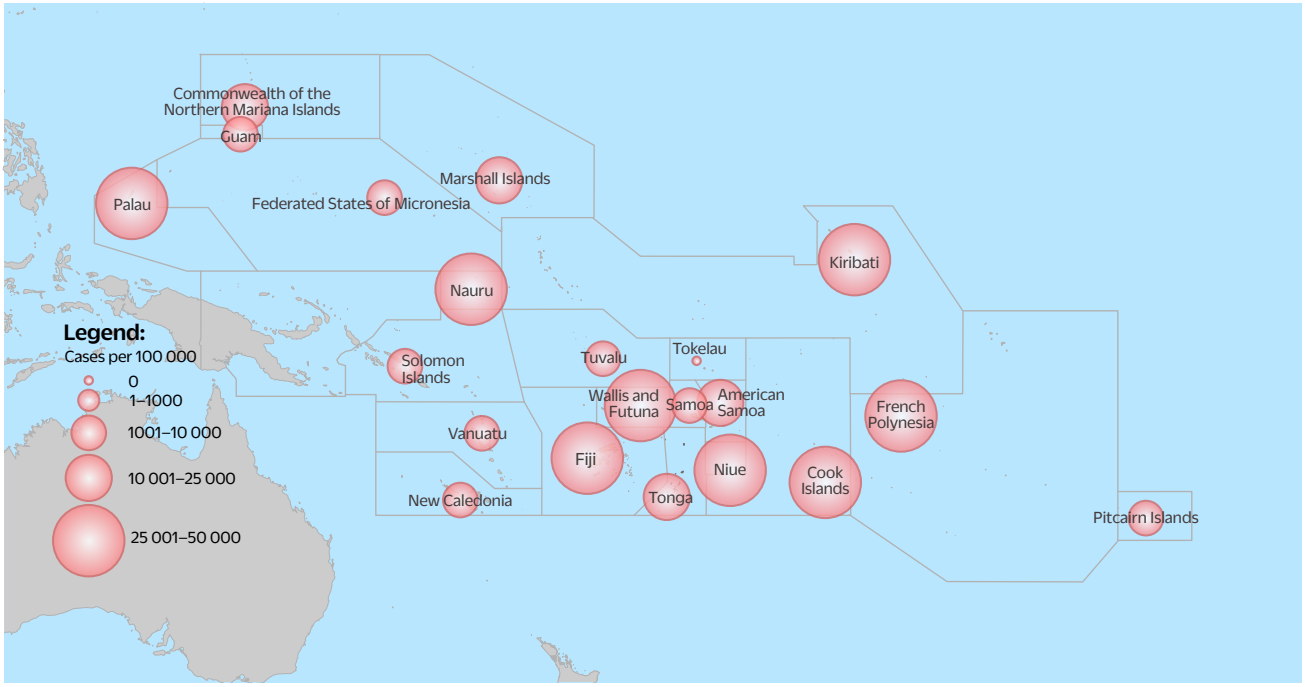
Fig. 1. **Map of Pacific island countries and areas, by corresponding cumulative COVID-19 cases per 100 000 population**



World Bank, French Polynesia, New Caledonia and the Commonwealth of the Northern Mariana Islands (CNMI) are categorized as high-income nations, while American Samoa, Kiribati, the Federated States of Micronesia (FSM), Samoa, Solomon Islands and Vanuatu are ranked as low-income countries. The remaining countries and areas are classified as upper-middle-income nations.[5]

Owing to their limited resources, dependence on international trade, remote location and fragile ecosystems, PICs are highly susceptible to the threats to national and regional health security posed by emerging and re-emerging infectious diseases and climate change.[4] In addition, the Pacific region is prone to natural disasters such as floods, cyclones and volcanic eruptions that can disrupt health systems. Although the geographical remoteness of PICs provides some advantages in isolating and preventing transmission of infectious disease outbreaks, few escaped the impacts of the COVID-19 pandemic. Fiji, French Polynesia, Guam, FSM and New Caledonia all experienced outbreaks of widespread community transmission due to the Delta and Omicron variants.[1]

Pharmaceutical interventions such as vaccines and therapeutics have proven effective against COVID-19 and are a vital part of national strategies to prevent SARS-CoV-2 from circulating and threatening health and economic security. However, COVID-19 therapeutics are subject to stringent approval processes by regulatory authorities, such as WHO, the United States (US) Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Therapeutic Goods Administration of Australia, as well as the New Zealand Medicines and Medical Devices and Safety Authority (MEDSAFE). At the time of writing, only tocilizumab, molnupiravir and nirmatrelvir/ritonavir were available for WHO procurement under the emergency use listing.[6] However, other authorities have approved the use of alternative therapeutics for COVID-19 such as sotrovimab, casirivimab/imdevimab, cilgavimab/tixagevimab and tofacitinib in some PICs.

During 2020 and 2021, WHO, together with partners, responded to the surge in COVID-19 cases in the Pacific by assisting PICs in accessing essential medicines such as dexamethasone and heparin, as well as oxygen.[2,3] In 2022, the three novel therapeutics recommended in WHO's Therapeutics and COVID-19: Living Guideline[2] (tocilizumab for hospitalized patients, and molnupiravir and nirmatrelvir/ritonavir for non-severe cases) were also made available through WHO's Access to COVID-19 Tools (ACT) Accelerator, a global mechanism that ensures appropriate allocation and equitable distribution of limited supplies of expensive novel COVID-19 therapeutics.[6]

ACTION

Novel COVID-19 therapeutics need to be properly regulated and distributed as prescription medication with appropriate information provided to health-care workers and patients to minimize potential adverse events.[2] During 2020–2022, WHO DPS supported its Pacific Member States in accessing and distributing recommended novel COVID-19 therapeutics of assured quality by:

1. coordinating requests, procurement and distribution of tocilizumab, molnupiravir and nirmatrelvir/ritonavir through the ACT-Accelerator;
2. developing and updating clinical management guidelines and standard operating procedures and delivering trainings in the clinical management of COVID-19;
3. facilitating regulatory approval of COVID-19 therapeutics, including emergency use authorization; and
4. developing estimates of critical supply needs.

Coordination of requests, procurement and distribution

As COVID-19 spread globally, many PICs mounted a multisectoral response to the pandemic – introducing border closures, mandatory isolation, and quarantine for suspected and confirmed cases – in a bid to contain cases to one geographical cluster and to buy time until pharmaceutical interventions could be implemented. PICs have had access to tocilizumab since May 2022 and molnupiravir since November 2022. Eight PICs have recently accepted allocations of nirmatrelvir/ritonavir.

During 2022, WHO DPS received requests for COVID-19 therapeutics from the 11 PICs that were eligible for support through the WHO ACT-Accelerator platform. By October 2022, WHO had procured 1155 doses of tocilizumab injections at an estimated cost of US$ 317 900 to PICs (**Table 1**), and six countries were on track to take delivery of their allocated 2016 courses of molnupiravir. In November 2022, eight PICs opted-in to access 2736 courses of nirmatrelvir/ritonavir; procurement has entered the distribution phase with delivery carried out in March–May 2023. Some PICs (American Samoa, the Marshall Islands, FSM and Palau) were able to access COVID-19 therapeutics in early 2022 through the support of other partners including the US Centers for Disease Control and Prevention.

Clinical management support

As part of its pandemic support to PICs, WHO DPS developed and updated treatment algorithms and standard operating procedures for the clinical management of COVID-19. Trainings in clinical management, prescription and administration of novel therapeutics were delivered via in-person deployments and face-to-face trainings for health managers and clinicians across the PICs.

Between July and October 2022, four webinar sessions on the implementation of COVID-19 therapeutics contextualized for clinical practice in the PICs were delivered via Zoom (Zoom Video Communications, Inc., San Jose, CA, USA). The webinars covered topics such as indications for use, storage conditions, care pathways, therapeutic management of severe and non-severe cases, and safe and appropriate use, as well as country experiences. Trainers comprised experts and clinicians from WHO DPS, the WHO Regional Office for the Western Pacific, the Australian Therapeutic Goods Administration, the Central and Northern Adelaide Local Health Networks (Adelaide, Australia) the Royal Alfred Hospital (Melbourne, Australia), the University of South Australia (Adelaide, Australia), New Zealand MEDSAFE, the WHO Global Outbreak Alert and Response Network, Fiji, the Marshall Islands, FSM and Palau. More than 150 health-care professionals including nurses, medical doctors, pharmacists and health advisers attended the webinars. Attendees represented 12 PICs – Fiji, Kiribati, the Marshall Islands, FSM, Nauru, Niue, Papua New Guinea, Solomon Islands, Tokelau, Tonga, Tuvalu and Vanuatu. The webinars provided a platform not only for participants to learn lessons from countries such as Australia and New Zealand (who were also represented among the attendees), but also for neighbouring countries to share information and their experiences of therapeutics and clinical management of COVID-19 cases.

Regulatory approvals

In the Pacific, the level of regulatory systems development for medicines is either non-existent or very limited.[7] Many

Table 1. **Procurement and supply of COVID-19 therapeutics in 11 Pacific island countries and areas by October 2022**

Country or area	Tocilizumab (vials)	Molnupiravir (courses)	Nirmatrelvir/ritonavir (courses)
American Samoa	105	NA	NA
Fiji	105	360	96
Kiribati	105	432	576
Marshall Islands	105	216	240
Micronesia (Federated States of)	105	NA	336
Nauru	105	NA	192
Samoa	105	432	384
Solomon Islands	105	NA	NA
Tonga	105	NA	240
Tuvalu	105	72	672
Vanuatu	105	504	NA
Total	**1155**	**2016**	**2736**

NA: not applicable.

PICs have a legal basis for pharmaceutical activities, such as registration of medicines, regulation and control of dangerous drugs and poisons, licensing of establishments, regulation of the pharmacy profession and reporting of adverse events. However, in many cases, the existence of national legislation does not necessarily translate into implementation and enforcement. The main barriers are a lack of human and technical capacity, as well as limited financial resources of the regulatory authorities.[7]

WHO's pandemic response thus included facilitating regulatory approval of COVID-19 therapeutics in PICs with limited technical capacity and resources. In addition to conducting literature reviews and disseminating emerging evidence on novel therapeutics, WHO assisted countries in navigating the necessary regulatory processes and systems that precede the approval of novel medical products by the relevant regulatory authorities, including product registration and licensing, and post-marketing surveillance activities. Based on the information and support provided by WHO, regulatory approvals – in the form of emergency use authorizations and adaptive licensing mechanisms – were issued for COVID-19 therapeutics by the relevant stakeholders, on average within 4 weeks of the initial request. In the majority of cases, approvals were granted by established regulatory authorities and mechanisms such as prequalification by WHO, US FDA,[8] EMA,[9] the Australian Therapeutic Goods Administration[10] and New Zealand MEDSAFE.[11]

Critical supply estimates for COVID-19 therapeutics

To forecast the quantity of essential medicines and therapeutics required to treat COVID-19 cases in PICs, WHO DPS developed a series of critical supply estimates. Initially, these supply estimates were based on a single COVID-19 wave and on current treatment guidelines.[2] Estimates thus allowed for the treatment with oral antivirals of those non-severe cases at increased risk for severe disease. As molnupiravir and nirmatrelvir/ritonavir have the same target population, the demand for these therapeutics was assumed to be the same to avoid double-counting.

WHO DPS's critical supply estimates were used as the basis for expressions of interest or requests for COVID-19 therapeutics by PICs eligible for support through WHO's ACT-Accelerator. Such requests require countries to submit information on important factors such as minimum amount to meet their needs, time period, supply availability and prioritization criteria.[6] The final allocation of COVID-19 therapeutics was performed by WHO in partnership with Wellcome and Tous Unis pour Aider (UNITAID),[6] and was based on (a) demand, (b) the epidemiological situation in each country and (c) the global supply of therapeutics for populations in low- and middle-income countries. The allocation mechanism

also considered treatment goals, the target population (according to WHO treatment guidelines) and rate-limiting criteria as appropriate.

LESSONS LEARNED

Securing access to novel COVID-19 therapeutics in the PICs has been challenging for a number of reasons. The limited availability of evidence for the use of novel therapeutics was an early problem not just in PICs but around the globe. In the PICs, a lack of local capacity for developing national guidelines and standard operating documents governing the use of novel therapeutics was a major barrier to early implementation; other challenges have included the lengthy and protracted nature of procurement negotiations with manufacturers, licence holders and funding sources, and the high cost of therapeutics. Significant mark-up costs, other additional charges, and the costs associated with logistics and transportation of therapeutics were all factors that contributed to the high cost of therapeutics for PICs. Recognizing these key barriers to access, WHO DPS support to PICs was targeted at identifying funding partners and facilitating discussions between suppliers and counterparts across the Pacific. Moreover, procurement of COVID-19 therapeutics through the WHO ACT-Accelerator enabled high-cost medicines to be supplied to eligible PICs at an affordable cost.

In terms of the distribution of novel COVID-19 therapeutics within countries, several important lessons were learned. Several PICs, notably the US-affiliated Pacific islands including the Marshall Islands and FSM, set up community-based "test-to-treat" centres where patients could be tested and, if found positive, could be prescribed an oral antiviral straightaway (if they were eligible for antiviral treatment, i.e. in a high-risk category for severe COVID-19 disease).[12] The success of this "one-stop-shop" test-to-treat initiative suggests that similar strategies could be adopted and implemented across the Pacific.

WHO-recommended treatments for severe or critical COVID-19 infection, which include interleukin-6 receptor blockers (tocilizumab or sarilumab) and corticosteroids,[2,3] were implemented in PICs, as elsewhere, in clinical settings only. However, when evidence emerged that patients treated with corticosteroids who were coinfected with *Strongyloides stercoralis*,[13] an intestinal roundworm, were at higher risk of developing hyperinfection,[14] it became apparent that specific guidance for the treatment of severe COVID-19 in the Pacific was needed, especially in those tropical and subtropical PICs where *Strongyloides stercoralis* is prevalent. WHO continues to provide support to address specific clinical issues common in the Pacific.

Several PICs experienced difficulties in procuring an adequate supply of some essential medicines required for treatment of moderate-to-severe COVID-19, in particular dexamethasone,[2,3] which is not manufactured in the Pacific. Shortages in other essential drugs were also reported, including saline solution, which is needed to dilute medicines such as tocilizumab.[3] Alongside delivering ongoing technical support, WHO DPS also successfully procured and supplied dexamethasone injections to 10 Member States in response to emergency requests.

In addition to supply chain issues, the COVID-19 pandemic highlighted the limited capacity of PICs to conduct safety monitoring activities for novel therapeutics. Although existing data suggest that newly introduced COVID-19 therapeutics were generally well tolerated,[2] the effects of long-term use have yet to be studied, and thus there is a need for ongoing safety monitoring. It was also noted that while several PICs had existing legal provision for monitoring adverse drug events and adverse events following immunization, none had a robust pharmacovigilance system in place prior to the pandemic.[15] Historically, reporting was undertaken at the health service provider level but was not routinely shared nationally or with other countries.[15] During the pandemic phase, WHO DPS assessed PICs' needs and demands for establishing and strengthening post-marketing surveillance systems and provided continuous technical guidance and trainings. Supported by WHO DPS, Fiji has recently renewed its full membership in the WHO Programme for International Drug Monitoring. Members of this programme work nationally and collaborate internationally to monitor and identify any potential medicine-induced harms.

Finally, the pandemic phase focused attention on the potential risk to public health posed by the general absence of robust quality control and assurance systems for medical products that exist across the Pacific. The identification of batches of falsified COVID-19 therapeutics in countries of neighbouring regions[16] in particular highlighted the lack of sufficient laboratory testing capacity in many PICs. While countries such as the Cook Islands, Fiji, Kiribati, the Marshall Islands,

FSM, Nauru, Palau, Papua New Guinea, Tonga, Tuvalu and Vanuatu have laws that mandate the regulation of medical products,[15] during the pandemic most relied on the quality supply chain of wholesalers or the limited laboratory support provided by WHO to ensure that their COVID-19 therapeutics were safe, effective and of assured quality.[15] Going forward, WHO plans to extend its laboratory support to PICs by providing a wider range of laboratory tools, technical advice and training. For example, quality assurance trainings are scheduled to take place in Solomon Islands.

Limitations

This report has some inevitable limitations. As it describes the experience of PICs, due to the huge diversity in social systems, health-care provision, economic factors and geography, the findings might not be generalizable to all countries in the Pacific. Likewise, each PIC is unique in its culture and customs, and therefore even within the group of PICs, the responses and lessons learned may not apply universally. Nevertheless, in a field with a paucity of literature, this report not only contributes to new knowledge but also provides some important lessons for countries that share similar characteristics, namely geographical isolation and limited regulatory systems, in terms of the management of future infectious disease outbreaks in which novel therapeutic interventions are required.

CONCLUSION

Throughout the COVID-19 pandemic, WHO DPS, in collaboration with partners, has delivered tailored support to PICs. This support has taken the form of assistance with procurement and emergency use authorization of novel therapeutics; provision of clinical management guidance and technical support; and regulatory system strengthening, in particular building capacity in safety monitoring and quality assurance programmes. Looking ahead, WHO DPS support should continue to be focused on strengthening regulatory requirements, safety monitoring and supply chain activities to ensure access to and implementation of novel COVID-19 therapeutics in all PICs. To ensure sustainable access to quality-assured therapeutics in the event of future pandemics, it will be important to continue to develop methodologies to estimate critical supply needs and demands.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

Not applicable

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Responding to COVID-19 vaccine-related safety events: WHO Western Pacific regional experience and lessons learned

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Problem: Novel vaccines were developed in an unprecedentedly short time in response to the global coronavirus disease (COVID-19) pandemic, which triggered concerns about the safety profiles of the new vaccines. This paper describes the actions and outcomes of three major adverse events of special interest (AESIs) reported in the World Health Organization's (WHO's) Western Pacific Region: anaphylaxis, thrombosis with thrombocytopenia syndrome (TTS) and post-vaccination death.

Context: During the large-scale introduction of various novel COVID-19 vaccines, robust monitoring of and response to COVID-19 vaccine safety events were critical.

Action: We developed and disseminated information sheets about anaphylaxis and TTS; provided tailor-made training for anaphylaxis monitoring and response, webinars about TTS and AESIs, and an algorithm to support decision-making about AESIs following immunization; as well as provided country-specific technical support for causality assessments, including for possible vaccination-related deaths.

Outcome: Each major vaccine event and situation of high concern was responded to appropriately and in a timely manner with comprehensive technical support from WHO. Our support activities have not only strengthened countries' capacities for vaccine safety surveillance and response, but also enabled countries to decrease the negative impact of these events on their immunization programmes and maintain the confidence of health-care professionals and the general population through proactive delivery of risk communications.

Discussion: This paper summarizes selected, major AESIs following COVID-19 vaccination and responses made by WHO's Regional Office for the Western Pacific to support countries. The examples of responses to vaccine safety events during the pandemic and unprecedented mass vaccination campaigns could be useful for countries to adopt, where applicable, to enhance their preparation for activities related to monitoring vaccine safety.

PROBLEM

The World Health Organization (WHO) declared a global coronavirus disease (COVID-19) pandemic in March 2020.[1] Novel COVID-19 vaccines were developed in an unprecedentedly short time, with WHO listing the first COVID-19 vaccine, the Comirnaty (Pfizer-BioNTech) COVID-19 mRNA vaccine, for emergency use in December 2020.[2] This was followed by other COVID-19 vaccines that utilized various platforms, including an adenovirus vector–based vaccine, an inactivated vaccine and a protein subunit vaccine.

Large-scale vaccination campaigns were conducted globally, which triggered concerns about the safety profile of the vaccines, particularly about rare serious adverse events of special interest (AESIs). AESIs, a subset of serious adverse events following immunization (AEFIs), are defined as preidentified and predefined events that are medically significant and have the potential to be causally associated with a vaccine product and that need to be carefully monitored and confirmed or discounted by further specific studies. AESIs require careful monitoring – ideally through an active surveillance system – in order to determine whether the event is truly associated with a vaccine or vaccination.[3]

This paper describes the actions taken by WHO's Regional Office for the Western Pacific and the outcomes associated with three major high-impact AESIs reported

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in the Region, as well as public and programme managers' concerns about them: anaphylaxis, thrombosis with thrombocytopenia syndrome (TTS) and post-vaccination death.

CONTEXT

Various novel COVID-19 vaccines have been introduced globally since late 2020 as part of the public health emergency response to the pandemic. Before the COVID-19 vaccine roll out, countries in WHO's Western Pacific Region started preparing for COVID-19 vaccine safety surveillance. COVID-19 vaccination has been the largest mass vaccination programme in immunization history, covering wide age groups across all geographical regions. The delivery of millions of COVID-19 vaccine doses within less than 2 years led to a large number of reported serious AEFIs and AESIs.

Anaphylaxis

Anaphylaxis is a rare but serious allergic reaction that is occasionally fatal, if not treated quickly and properly.[4] It is a well-known serious AEFI of many vaccines used for routine immunization, including the hepatitis B vaccine, human papillomavirus vaccine and measles-containing vaccines. The expected anaphylaxis rate of these non-COVID-19 vaccines is approximately 1–6 per 1 million doses.[4] During the early stage of the COVID-19 vaccination roll out, there was concern about the relatively high reporting rates of anaphylaxis observed globally and in the Western Pacific Region. For example, 21 cases of anaphylaxis were reported following administration of approximately 1.9 million doses of the Pfizer-BioNTech COVID-19 vaccine in the United States of America (11.1/1 million doses) during 2 weeks in December 2020.[5] Based on internal data from the Regional Office for the Western Pacific from four countries' weekly AEFI reports, as of April 2021, the reporting rate for anaphylaxis ranged from approximately 3.2 to 127.9 per 1 million doses for four different COVID-19 vaccines, including those by Vaxzevria (AstraZeneca), Pfizer-BioNTech, CoronaVac (Sinovac) and BBIBP-CorV (Sinopharm).

The high number of anaphylaxis diagnoses may be largely due to increased awareness of anaphylaxis and a high index of clinical suspicion among health-care workers. Overdiagnosis of anaphylaxis is not uncommon and has been reported for both COVID-19 vaccines and routine immunizations.[6,7] Some countries in the Western Pacific Region have suboptimal capacity, particularly at the subnational level, for emergency responses and management of anaphylaxis following immunization. Both overdiagnosis and underdiagnosis of anaphylaxis are concerns. Overdiagnosis is safer than underdiagnosis, which can lead to a potentially fatal outcome due to a delay in providing the proper treatment. However, overdiagnosis can negatively impact a vaccination programme and result in declining vaccine acceptance. The overuse of adrenaline for treating suspected anaphylaxis is another concern, which can also cause adverse health outcomes.[8]

Thrombosis with thrombocytopenia syndrome

TTS was one of the earliest AESIs reported during the post-authorization phase of COVID-19 vaccines. As of 31 August 2021, TTS reporting rates ranged from 0.2 in Asian countries to 17.6 in Nordic countries per 1 million doses.[9] This newly reported rare AESI following administration of COVID-19 adenovirus vector–based vaccines (e.g. AstraZeneca and Ad26.COV 2-S [Johnson & Johnson] vaccines) has raised great concern not only within the Western Pacific Region but also globally because TTS can be fatal and has many unknown characteristics in the context of novel COVID-19 vaccines. Particularly during the early stage of the COVID-19 vaccination roll out, in many low- and middle-income countries with limited capacity for diagnosing and assessing potential TTS cases, detection and reporting were challenging, primarily due to the uncertainty of pathogenesis, the complicated clinical and laboratory presentations, and the lack of a clear case definition. Potential TTS cases might not be detected and reported in resource-limited settings, considering there is a significant gap in diagnostic capacity between high-income countries and low- and middle-income countries.

Post-vaccination deaths

The WHO Strategic Advisory Group of Experts on immunization has recommended that elderly people and people with comorbidities should be among the highest-priority groups for COVID-19 vaccination to minimize disease severity and mortality.[10] Considering the high risk of mortality among these groups following any medical condition, it would be anticipated that deaths in these groups following COVID-19 vaccination could be falsely

attributed to the vaccine or vaccination. This highlights the importance of using caution when interpreting reporting rates of deaths following immunization as well as the importance of conducting thorough investigations followed by comprehensive causality assessments for all post-vaccination deaths. The availability of background mortality rates, particularly cause-specific rates, is important and necessary to ensure a valid population-based causality assessment can be conducted at the country level.

ACTIONS

Anaphylaxis

Timely diagnosis and management are critical to avoid fatal anaphylaxis following COVID-19 vaccination. Therefore, we focused on increasing awareness of and facilitating preparedness for managing anaphylaxis, even in limited-resource settings. We developed and distributed an anaphylaxis information sheet tailored to the COVID-19 vaccination response to country focal points for COVID-19 vaccination and to WHO Country Office teams; the information sheet included the case definition, clinical features, expected rates after vaccination and information about basic initial treatment. We also periodically shared updated anaphylaxis rates and trends to help inform the safety profiles of the COVID-19 vaccines.

In addition, to enhance country-specific capacity for anaphylaxis response and management, we provided online refresher training that focused on proper diagnosis and appropriate and timely clinical management, although anaphylaxis is not a new AEFI. During November–December 2021, clusters of anaphylaxis cases following administration of various COVID-19 vaccines were reported from multiple provinces in Viet Nam. Investigations revealed there was a likelihood of overdiagnosis of anaphylaxis. In response to these reported clusters of cases, we facilitated a comprehensive training course in December 2021 for clinicians at the national and provincial levels, conducted by the Ministry of Health, about managing anaphylaxis, with particular focus on differential diagnosis and the rational use of adrenaline.

Thrombosis with thrombocytopenia syndrome

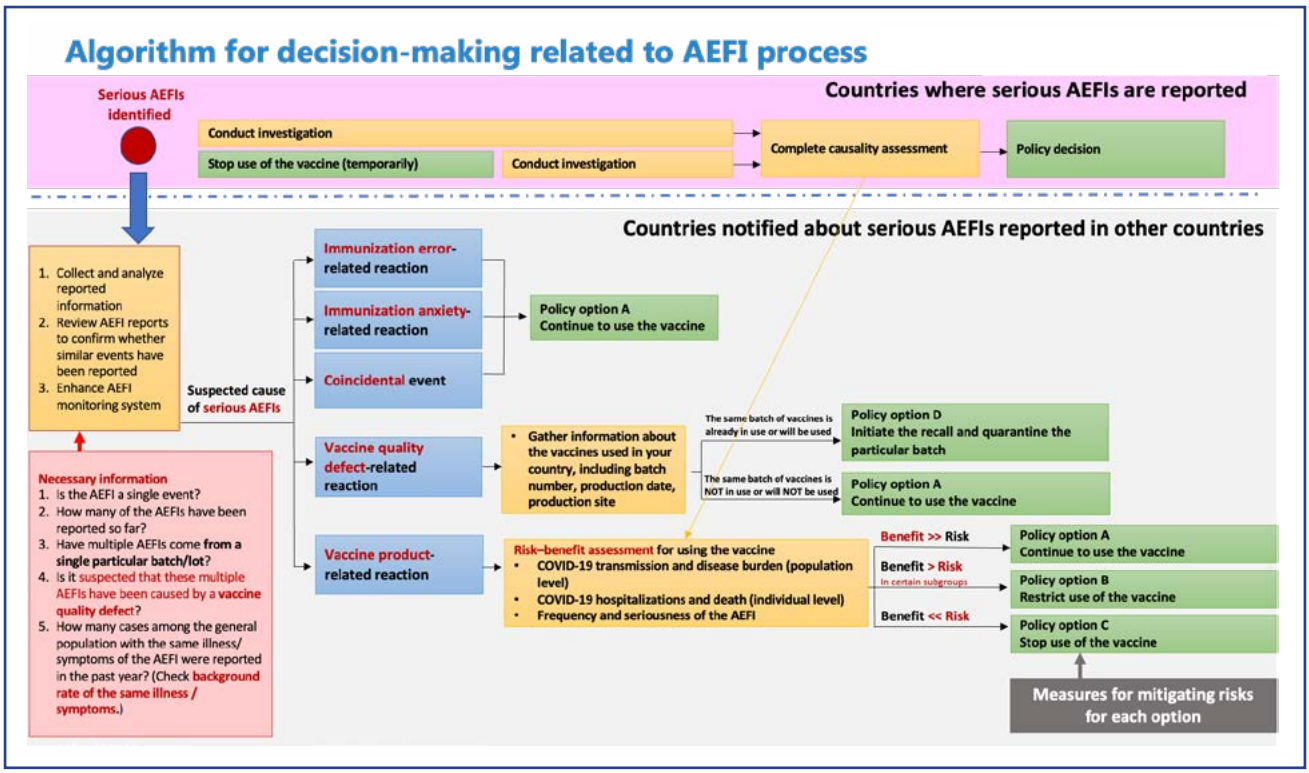
We provided an information sheet on TTS, similar to the one for anaphylaxis, which included a technical guide to diagnosis and management. In addition, with the support of the National Centre for Immunisation Research and Surveillance in Australia, we held a webinar on AESIs related to COVID-19 vaccination, including TTS, to provide the most updated information to enable health-care workers to detect and report potential cases early. Particularly for Pacific island countries and areas, where clinical specialists and diagnostic tools are limited, we provided joint virtual trainings and telemedicine consultations for clinical assessment of individual AESI cases in collaboration with WHO Country Offices and relevant external partners, including the National Centre for Immunisation Research and Surveillance.

We also developed an algorithm to support the decision-making process at the country level for when a rare but serious AESI was reported. The simplified algorithm (**Fig. 1**) displayed possible policy options (A–D) for countries that were vigilant about AESIs reported in other countries although not necessarily detected in their own. These options were primarily based on a risk–benefit assessment. For example, policy option A, which is to continue using the vaccine with risk mitigation measures, describes a situation in which the benefits of continued vaccination outweigh a potential risk even if there is a possible association between a vaccine and an AESI. This proactive development of the algorithm enabled countries to continue COVID-19 vaccination without unnecessary suspension of the use of a given vaccine.

Post-vaccination deaths

We have provided ongoing technical assistance to investigations and causality assessments of AESIs and deaths since the COVID-19 vaccination roll out in 2021. This was done through workshops and consultations for members of national AEFI committees in countries including Brunei Darussalam, the Lao People's Democratic Republic, Malaysia, the Philippines and Pacific island countries and areas.

Fig. 1. **Algorithm for decision-making related to AEFIs following COVID-19 immunization, WHO Western Pacific Region, July 2022**



AEFI: adverse event following immunization; COVID-19: coronavirus disease.

We conducted an in-depth analysis of a subset of post-vaccination deaths reported in the Philippines from March to May 2021 to further support the assessments of the national AEFI committee looking into deaths possibly related to a specific batch of vaccines.

OUTCOMES

Anaphylaxis

The tailor-made tools disseminated in a timely manner to countries triggered staff awareness and have contributed to better preparedness for detecting and managing anaphylaxis. Intensive awareness of possibly high observed reporting rates has led to more confidence among immunization staff and clinicians in being cautious in interpreting and responding to them. Based on the authors' observations and continuous communication with WHO Country Offices, the periodic sharing of monitoring and updates of anaphylaxis rates and trends appears to have significantly contributed to avoiding unwarranted concerns from national stakeholders.

By March 2022, anaphylaxis reporting rates following the administration of various COVID-19 vaccines in countries in the Western Pacific Region had gradually declined to 0.3–13.7 cases per 1 million doses. Despite the very high reporting rates for anaphylaxis observed early on during COVID-19 vaccination, the more stable rates reported by March 2022 offer reassurance that they are comparable to those of many other vaccines used globally in immunization programmes.[3] This is an important observation and a lesson learned: during the period when any new vaccine is introduced, there is a possibility of higher-than-expected reaction rates or rates that are even higher than the background rates for AESIs. However, over time the rates will return to the expected range as a result of the high number of doses being administered (i.e. with a larger denominator) for any given vaccine. Thus, caution should be used when interpreting and responding to the observed rates of serious AEFIs or AESIs during the early stage of a vaccine roll out.

Additionally, during November–December 2021, clusters of anaphylaxis cases were reported after

administration of various COVID-19 vaccines in multiple provinces in Viet Nam. The WHO-supported investigations revealed the likelihood of overdiagnosis of anaphylaxis. The situation was improved promptly and rectified by providing comprehensive training for clinicians at the national and provincial levels.

Thrombosis with thrombocytopenia syndrome

Our tools were extensively used to update the knowledge of health-care workers, COVID-19 vaccination focal points and policy-makers, all of whom needed specific information about the diagnosis, clinical management and safety profile of this new AESI identified after authorization of the vaccines. Collaborative telemedicine consultations provided real-time support to clinicians, who could be reassured of their ability to clinically manage this complex adverse event and avoid or minimize any potential serious consequences.

Post-vaccination deaths

After providing technical assistance to the Philippines, we conducted an analysis of a subset of deaths reported there following COVID-19 vaccination occurring from March to May 2021, and we were able to support the conclusion of the national AEFI committee that cause-specific death rates following COVID-19 vaccination were significantly lower than the background rates in the Philippines. This analysis reassured stakeholders by ruling out a possible safety signal for a certain batch of vaccines. Further, after causality assessments, these deaths were determined not to be causally associated with the vaccines.

These country-support activities have not only strengthened countries' capacities for causality assessment, but also enabled them to decrease the negative impact of these events on their immunization programmes and maintain the confidence of health-care professionals and the general population by delivering proactive risk communications.

DISCUSSION

This paper summarized a few major adverse events that occurred following COVID-19 vaccination and the responses by WHO's Regional Office for the Western Pacific to support countries when specific vaccine safety events occurred. Lessons learned from these experiences were (i) the importance of ensuring correct interpretation of observed AESI rates over time (e.g. anaphylaxis) when a new vaccine is being introduced; (ii) the importance of being prepared to provide appropriate management of and responses to newly reported AESIs (e.g. TTS) in a timely manner; and (iii) a need to implement evidence-based decision-making following serious AEFIs, AESIs and post-vaccination deaths after thorough and scientific investigation and causality assessment to sustain the public's trust in vaccination. However, this paper has shared only limited quantitative data and instead has focused primarily on sharing the lessons learned, which it is hoped will benefit future preparedness activities for manging safety events when new vaccines are introduced.

The examples presented in this paper about COVID-19 vaccine safety events and responses during the pandemic and the associated unprecedented mass vaccination campaigns could be useful for countries seeking to strengthen their surveillance of and response to events possibly related to vaccine safety. Countries' capacities and preparedness for vaccine and immunization safety monitoring and responses are important to ensure continuing large-scale introduction of new vaccines. Moreover, if COVID-19 vaccination is to continue as part of a life-course approach – that is, to be integrated with regular immunization programmes – these responses will be useful guiding examples to aid in planning and implementing effective risk communication strategies to prevent vaccine hesitancy, particularly pertaining to vaccine safety concerns, and maintain trust in and demand for regular immunization.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

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Antimicrobial use in patients with confirmed COVID-19 infection in the Philippines: a cross-sectional study

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Objective: The ongoing coronavirus disease (COVID-19) pandemic is exacerbating optimal antibiotic stewardship and the promotion of bacterial resistance due to the over-prescribing of antibiotics for patients with COVID-19. This study aimed to determine the prevalence of antibiotic therapy in patients with COVID-19 infection and explore the association of antibiotic prescribing with patients' demographics and clinical characteristics.

Methods: A retrospective analytical cross-sectional study was conducted at a tertiary hospital and training institution in Baguio City, the Philippines from March 2020 to March 2021. Univariate and multivariable logistic regression was used to compare COVID-19 patients who were prescribed antibiotics with those who were not.

Results: Of the 157 patients hospitalized with COVID-19 infection, 90 (57.3%) received antibiotics, with only three (1.9%) having confirmed bacterial coinfection. Among those prescribed antibiotics, azithromycin was the most frequently prescribed antibiotic (43.3%), followed by ceftriaxone (33.1%), piperacillin-tazobactam (15.3%), ceftazidime (5.1%), moxifloxacin (1.3%), amikacin (0.6%), ampicillin and sulbactam (0.6%), cefuroxime (0.6%), metronidazole (0.6%) and penicillin (0.6%). Antibiotic use was associated with factors such as having bilateral infiltrates on chest X-ray, the severity of COVID-19 infection and high white blood cell counts.

Discussion: Antibiotic use was high among patients with confirmed COVID-19 despite a low prevalence of confirmed bacterial coinfection. This may be due to the similarities in the clinical manifestations of both viral and bacterial infections. Judicious use of antibiotics in the treatment of COVID-19, as well as other viral infections (for example, influenza), is required to prevent antibiotic resistance in accordance with the principles of antimicrobial stewardship.

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first documented in Wuhan, Hubei Province, China in December 2019.[1] According to the World Health Organization (WHO), as of April 2023, there have been 762 million COVID-19 cases with over 6.8 million deaths worldwide. In the Philippines, there have been over 4 million confirmed cases with over 66 000 deaths.[2] The global incidence has steadily declined in 2023 after a peak in December 2022.[2] However, severe and critical disease remains a concern; in one study from the United States of America, 5.3% of cases infected with the Omicron variant were hospitalized, with 3% requiring oxygen.[3] Internationally[4] and in the Philippines,[5] severe and critical infections usually affect older patients and those with multiple comorbidities.

Respiratory viral infections are a risk factor for bacterial coinfections, which may increase disease severity and mortality.[6] Bacterial coinfections are defined as suspected bacterial pneumonia in addition to COVID-19 within 48–72 hours of hospital admission for COVID-19,[7] and are relatively common in patients with severe and critical disease.[8] Secondary bacterial infections are defined as suspected bacterial pneumonia after 72 hours of hospitalization for COVID-19,[7] and are diagnosed when patients present with the symptoms and signs of pneumonia and a pathogen is isolated from sputum, blood, endotracheal aspirate or

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bronchoalveolar lavage cultures following admission.[1] There are limited cues for differentiating bacterial and viral respiratory infections.

Despite the viral origin of COVID-19, physicians tended to start treatment with antibiotics since cough, fever and infiltrates on chest imaging are markers of bacterial community-acquired pneumonia requiring antibiotics.[9] The uncertainty of the COVID-19 pandemic and the absence of antiviral treatments with proven efficacy probably also contributed to the widespread and excessive use of antibiotics,[10] especially in the first year of the pandemic. This prescriber behaviour threatens antimicrobial stewardship, which is defined as "an organizational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness."[11] WHO recommends that antimicrobials be used for severe COVID-19 cases at increased risk for secondary bacterial infection and death.[12]

The main objective of this study is to describe antibiotic use in patients with confirmed COVID-19 infection at a tertiary hospital in Baguio City, Philippines. More specifically, the study aims to: (1) determine the prevalence of antibiotic use in patients with confirmed COVID-19 infection; (2) verify the prevalence of bacterial coinfection; (3) ascertain the most frequently prescribed antibiotics; and (4) explore the associations of variables with antibiotic use, specifically, age, sex, comorbidities, severity of COVID-19 infection, chest X-ray findings, white blood cell count, differential count, procalcitonin, blood culture, and sputum and endotracheal aspirate culture.

METHODS

Study design

A retrospective analytical cross-sectional study was conducted at a tertiary hospital and training institution in Baguio City, Philippines.

Study population

All adult patients (≥19 years old) with mild, moderate, severe and critical confirmed COVID-19 infection who were seen, diagnosed and eventually hospitalized from March 2020 to March 2021 were included in the study. Patients who were asymptomatic, regardless of the presence or absence of comorbidities, as well as patients who developed hospital-acquired infection during the course of their hospital stay, were excluded.

Data collection

Charts of confirmed COVID-19 patients who met the inclusion criteria were reviewed. Data collected were: antibiotic usage (use or non-use, type of antibiotic); age (19–59 years old or ≥60 years old); presence or absence of comorbidities; disease severity (mild, moderate, severe or critical); results of chest X-ray (normal, unilateral infiltrates or bilateral infiltrates); white blood cell count (<5000, 5000–10 000 or >10 000); differential count (neutrophilia or lymphocytosis); procalcitonin (≤2 ng/mL or >2 ng/mL); and blood, sputum and/or endotracheal aspirate cultures (with or without growth) (**Table 1**).

The severity classification of patients with COVID-19 was based on the Unified COVID-19 Algorithms (**Table 2**).[13] The comorbidities included were diabetes, hypertension, coronary artery disease, rheumatic heart disease, asthma, chronic obstructive pulmonary disease, chronic kidney disease, cancer, arrhythmia and stroke. Patients were diagnosed with a bacterial coinfection if there was growth in culture samples conducted within the first 48 hours of admission to hospital.

Data analysis

Data were encoded and analysed using SPSS v24 (IBM Corp., Armonk, NY, United States of America). Frequencies and percentages were used to describe the prevalence of antibiotic use in patients with COVID-19. To determine the association between antibiotic use and the variables of interest (age, sex, comorbidities, severity of COVID-19 infection, chest X-ray findings, white blood cell count, differential count, procalcitonin, blood culture, and sputum and endotracheal aspirate culture), univariate and multivariable logistic regression was used. Imputation of missing variables for some patients at hospital admission was considered if <20% of values were missing, and imputation based on the expectation–maximization algorithm method was used to replace missing values. A *P* value of <0.05 was considered statistically significant.

Table 1. **Characteristics of hospitalized COVID-19 cases at a tertiary hospital in Baguio City, the Philippines, March 2020 to March 2021 (*N* = 157)**

Characteristic	Number	%
Age (years)		
19–59	106	67.5
≥60	51	32.5
Sex		
Male	96	61.1
Female	61	38.9
Comorbidities[a]		
Yes	97	61.8
No	46	29.3
Severity		
Mild	64	40.8
Moderate	36	22.9
Severe	50	31.8
Critical	7	4.5
Chest X-ray		
Normal	80	51
Unilateral	20	12.7
Bilateral	57	36.3
White blood cell count[a]		
<5000	28	17.8
5000–10 000	99	63.1
>10 000	26	16.6
Differential count[a]		
Neutrophilia	149	94.9
Lymphocytosis	4	2.5
Procalcitonin		
≤2 ng/mL	77	49
>2 ng/mL	5	3.2
Not requested	75	47.8
Bacterial coinfection		
Yes	3	1.9
No	77	49
Not requested	77	49

[a] Values are missing from some patients for comorbidities (n = 14), white blood cell count (n = 4) and differential count (n = 4).

Table 2. **Severity classification of COVID-19 cases, the Philippines, 2020**

Classification	Signs and symptoms
Mild	Fever, cough, diarrhoea, change in taste or smell, or fatigue; no signs of hypoxia on pulse oximetry or arterial blood gas, or pneumonia on physical examination and chest X-ray
Moderate	Symptomatic with clinical or radiographic evidence of lower respiratory tract disease (infiltrates on chest X-ray, presence of crackles) and oxygen saturation >94% on room air
Severe	Symptomatic with oxygen saturation ≤94% on room air and lung infiltrates on chest X-ray
Critical	Respiratory failure not fully explained by cardiac failure or fluid overload (acute respiratory distress syndrome), septic shock or multiple organ dysfunction

Source: Unified COVID-19 Algorithms.[13]

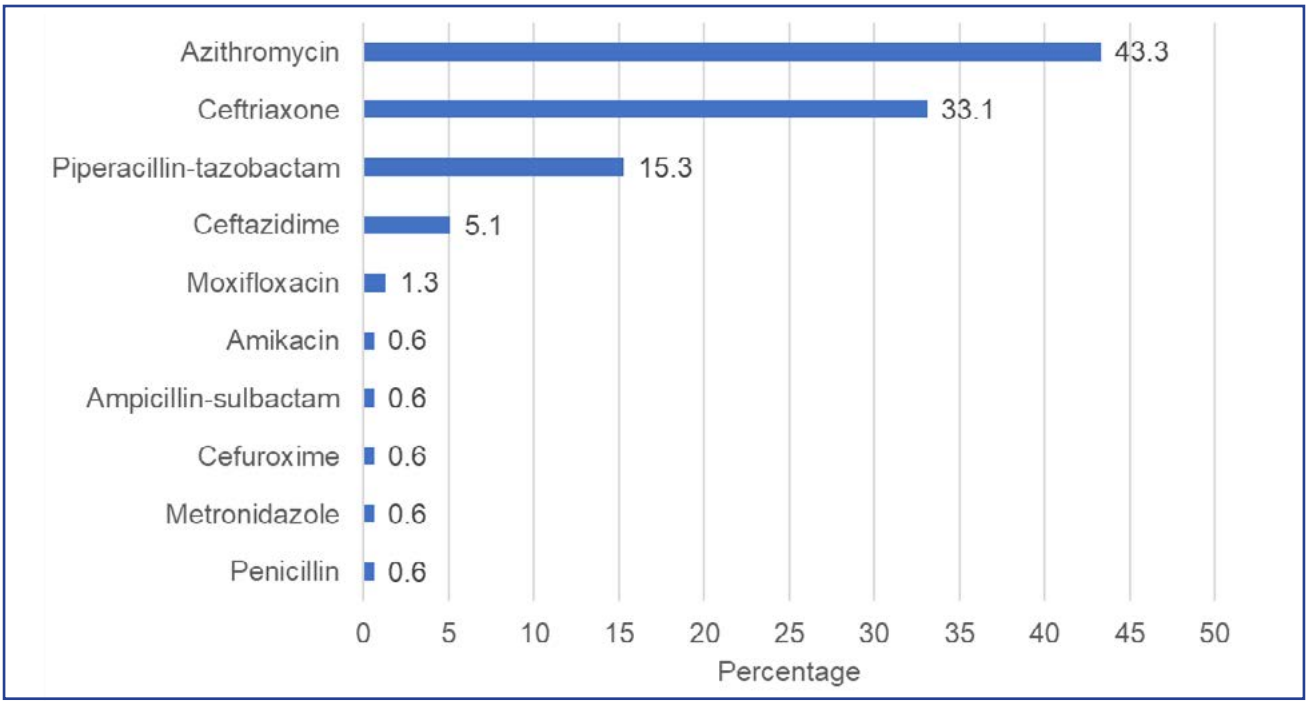
RESULTS

The charts were reviewed of all 157 hospitalized COVID-19 patients, of whom 90 (57.3%) received antibiotics and three (1.9%) had confirmed bacterial coinfection. Among the 90 patients who were given antibiotics, azithromycin was the most frequently prescribed antibiotic (43.3%), followed by ceftriaxone (33.1%) and piperacillin-tazobactam (15.3%) (**Fig. 1**).

There were 106 patients (67.5%) aged 19–59 years and 51 (32.5%) aged ≥60 years. There were more males (61.1%) than females (38.9%). Comorbidities were reported for 97 patients (61.8%). They included diabetes mellitus, hypertension, cancer, chronic kidney disease, coronary artery disease, bronchial asthma and chronic obstructive pulmonary disease. With regards to the severity of COVID-19 infection, 64 patients (40.8%) were mild, 36 (22.9%) were moderate, 50 (31.8%) were severe and seven (4.5%) were critical (**Table 1**).

Eighty patients (51.0%) had a normal chest X-ray, 20 (12.7%) had unilateral infiltrates and 57 (36.3%) had the presence of bilateral infiltrates on chest X-ray. Twenty-eight patients (17.8%) had white blood cell counts of <5000, 99 (63.1%) had counts of 5000–10 000 and 26 (16.6%) had counts of >10 000. Regarding differential counts, neutrophilia was noted in 149 patients (94.9%), while only four patients (2.5%) had lymphocytosis. Of the 157 patients, procalcitonin was measured in only 82 patients, of whom 77 (49%) had results of ≤2 ng/mL and five (3.2%) of >2 ng/mL (**Table 1**).

Fig. 1. **Frequency of antibiotics prescribed to hospitalized COVID-19 patients at a tertiary hospital in Baguio City, the Philippines, March 2020 to March 2021 (*N* = 90)**



Factors significantly associated with antibiotic use in multivariable analysis were: having bilateral chest X-ray infiltrates (odds ratio [OR] 48.11, 95% confidence interval [CI] 11.24–205.88, $P < 0.001$); severity of COVID-19 infection (moderate: OR 8.98, 95% CI 2.833–28.477, $P < 0.001$; severe: OR 4.81, 95% CI 1.38–16.71, $P = 0.014$; critical: OR 0.24, 95% CI 0.07–0.81, $P = 0.021$); and having elevated white blood cell count (5000–10 000: OR 7.85, 95% CI 1.28–48.29, $P = 0.026$; >10 000: OR 7.12, 95% CI 1.48–34.36, $P = 0.015$) (**Table 3**).

DISCUSSION

The prevalence of empiric antimicrobial use at this tertiary hospital in Baguio City, the Philippines was 57.3%, which is high considering that the prevalence of bacterial coinfection was 1.9%. However, similar studies have reported higher antibiotic use in patients with COVID-19 from rates of 70–90%.[14–17] In a cohort study from Wuhan, China in 2020,[1] all patients with laboratory-confirmed COVID-19 were given empiric antibiotic therapy. Prescribing antibiotics for COVID-19 patients was based on the WHO interim guidelines to treat for possible bacterial infection.[18,19] In two smaller studies from Jiangsu and Wuhan, antibiotics were prescribed to almost all patients.[20,21] In a study conducted by Rawson et al.,[14] 72% of patients with COVID-19 received antimicrobial therapy, though only 8% of patients were reported to have bacterial coinfection. This may be due to difficulty ruling out bacterial coinfection during patients' admission since viral and bacterial pneumonia have similar clinical manifestations. In a 2020 global survey of antibiotic-prescribing practices for patients with COVID-19, respondents reported that their decision to use antibiotics was based more on clinical presentation and less on laboratory or radiologic markers.[22] Many of these studies were from 2020, early in the COVID-19 pandemic, when antiviral treatments for COVID-19 were not available.

Almost half of the patients included in this study had mild COVID-19 infection and, therefore, as per local practice guidelines, sputum and bacterial cultures were not indicated.[23] This could account for the low prevalence of bacterial coinfection in this study. Rates of bacterial coinfection in patients with COVID-19 have been low, as confirmed by several studies.[14–17,24] In contrast, a study from Wuhan, China revealed a higher bacterial coinfection rate of 25.5% in patients admitted for COVID-19.[25] In a study from a secondary-care setting in the United Kingdom of Great Britain and Northern Ireland, blood cultures were positive in 3.2% of patients during the first 5 days of admission; after

Table 3. **Factors associated with antibiotic use in hospitalized COVID-19 cases at a tertiary hospital in Baguio City, the Philippines, March 2020 to March 2021**[a]

Factors	Univariate		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)				
19–59	Ref		Ref	
≥60	2.0 (1.0–4.0)	**0.049**	0.3 (0.1–1.2)	**0.116**
Sex				
Male	Ref		Ref	
Female	0.8 (0.4–1.6)	0.644	1.7 (0.3–8.8)	0.507
Comorbidities				
No	Ref		Ref	
Yes	0.5 (0.2–1.0)	0.069	0.4 (0.7–3.0)	0.438
Severity of COVID-19 infection				
Mild	Ref		Ref	
Moderate	22.5 (9.7–52.0)	**<0.001**	8.9 (2.8–28.4)	**<0.001**
Severe	10.7 (4.4–25.9)	**<0.001**	4.8 (1.3–16.7)	**0.014**
Critical	0.1 (0.0–0.2)	**<0.001**	0.2 (0.0–0.8)	**0.021**
Chest X-ray				
Normal	Ref		Ref	
Unilateral	3.1 (0.5–17.2)	0.180	1.9 (0.3–11.8)	0.454
Bilateral	57.7 (16.2–206.0)	**<0.001**	48.1 (11.2–205.8)	**<0.001**
White blood cell count				
<5000	Ref		Ref	
5000–10 000	8.8 (2.1–36.3)	**0.003**	7.8 (1.2–48.2)	**0.026**
>10 000	6.6 (1.8–23.6)	**0.003**	7.1 (1.4–34.3)	**0.015**
Differential count				
Neutrophilia	Ref		Ref	
Lymphocytosis	0.2 (0.0–2.2)	0.209	0.1 (0.0–1.8)	0.149
Procalcitonin				
≤2 ng/mL	Ref		Ref	
>2 ng/mL	1.5 (0.1–14.2)	0.724	0.6 (0.0–11.9)	0.794
Bacterial coinfection				
No	Ref		Ref	
Yes	3.7 (0.3–45.9)	0.297	4.8 (0.1–127.6)	0.346

[a] Statistically significant *P* values (<0.05) are in bold.

5 days of confinement, the positivity rate increased to 6.1%. The same study revealed that pathogenic bacteria were identified at a higher rate (34.8%) from respiratory samples.[26]

Azithromycin, ceftriaxone, piperacillin-tazobactam and ceftazidime were the most commonly used antibiotics in this study. The distribution of antibiotics used follows the Philippine Clinical Practice Guidelines on the management of community-acquired pneumonia[27] and the antibiogram of the hospital. This finding was similar to that of a retrospective cohort study done at a COVID-19 referral hospital in the Philippines by Abad et al.[28] In contrast, a study from a German university hospital revealed that the most commonly used antibiotics were fluoroquinolones, carbapenems and third-generation cephalosporins;[6] however, this may be due to different antibiotic protocols in Europe.

The presence of bilateral pulmonary infiltrates on chest X-ray was the most significant predictor of antibiotic use in this study. Such radiologic findings increase the probability of bacterial infection. Cheng et al.[24] reported a similar finding in a hospital in Hong Kong Special Administrative Region (China). This study also showed that the severity of illness was associated with antibiotic use, suggesting that disease severity had a potential role in the decision to prescribe antibiotics to COVID-19 patients. Patients who are severely to critically ill develop a systemic inflammatory response that may lead to lung injury and organ dysfunction, ultimately increasing the risk of bacterial coinfection. A study by Nasir et al.[29] showed that patients with severe to critical COVID-19 infection on admission had 4.42 times higher risk of bacterial infection. Langford et al.[30] reported that the percentage of antibiotic use was especially high in patients in the intensive care unit and for those requiring mechanical ventilation. However, in a scoping review of the first 6 months of the pandemic, antibiotics were prescribed to COVID-19 patients regardless of severity of illness, with similar proportions prescribed to patients with severe or critical illness (75.4%) and patients with mild or moderate illness (75.1%).[31] Chedid et al.[32] suggested that although antibiotic treatment was more prevalent in more severe patients, half of the patients who received antibiotics were not severe, suggesting a tendency to extend indications of antibiotic therapy to non-severe patients.

Antibiotic use was also influenced by elevated white blood cell counts in the present study. COVID-19 patients usually have normal white blood cell counts. A study by Huang et al.[18] reported that white blood cell counts in patients with COVID-19 on admission indicated leucopenia (25%) with lymphocytic predominance (64%). Leucocytosis with neutrophilic predominance alerts physicians to the presence of bacterial coinfection. A study by He et al.[33] showed that antibiotic prescription was significantly more common in patients with leucocytosis. In contrast, the study by Cheng et al.[24] demonstrated that antibiotics were commonly ordered even if routine blood tests showed normal white blood cell count.

The limited number of patients in this study restricts the generalization of the results to a broader population, as does the lack of a comparison group, such as antibiotic prescription rates prior to the COVID-19 pandemic, to determine if antibiotic-prescribing habits changed or increased during the COVID-19 pandemic. Therefore, we recommend that a similar study be conducted with a larger and more diverse sample size that could include other provinces in the country to obtain a better understanding of trends in antimicrobial use in patients with confirmed COVID-19 infection.

Antibiotic use was high among patients with confirmed COVID-19 in the tertiary hospital in the Philippines during the first year of the pandemic despite a low prevalence of confirmed bacterial coinfection. Similarly, the high rates of prescribing antibiotics for COVID-19 patients were observed globally, especially in the first year of the pandemic, for both severe and non-severe cases. Factors associated with antibiotic use were radiologic evidence of bilateral infiltrates, severity of COVID-19 pneumonia and leucocytosis. The similarities in the clinical manifestations of both viral and bacterial infections may have contributed to the increased use of antimicrobials during this period, as well as there being no antiviral treatment for COVID-19 available at that time. Judicious use of antibiotics in the treatment of COVID-19, as well as other viral infections (e.g. influenza), is required to prevent antibiotic resistance in accordance with the principles of antimicrobial stewardship.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics approval

Permission to conduct this study at the hospital was obtained from the Medical Director and Vice President for Hospital Affairs. Research ethics approval was obtained from the University Research Ethics Committee. All charts were identified by code number and did not contain the names of the participants. All data were coded and were kept confidential and anonymous. Charts were reviewed within the hospital premises.

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School outbreak of hand, foot and mouth disease in Balungao, Pangasinan Province, Philippines, October 2022

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Objective: On 24 September 2022, the Regional Public Health Unit in Ilocos received a report of a cluster of suspected hand, foot and mouth disease (HFMD) in one school in Balungao, Pangasinan Province, the Philippines. On 4 October 2022, the public health unit sent a team from the Field Epidemiology Training Program – Intermediate Course to conduct an outbreak investigation.

Methods: Active case-finding was conducted at the school. A suspected case was defined as any student or staff member with mouth ulcers and papulovesicular or maculopapular rash on the palms, fingers, soles of the feet or buttocks occurring from 1 September to 5 October 2022. We interviewed school officials about possible sources of infection and students' activities. We collected oropharyngeal swab samples for testing. Findings were used for descriptive analysis.

Results: Nine suspected cases of HFMD were detected, with the highest number of cases (6, 67%) occurring in children in grade 1. The majority of cases (7, 78%) were 6 years old, and five cases (56%) were male. Seven (78%) of the cases had been exposed to a confirmed case of HFMD, as reported by their parents or guardians and teachers. Six cases (67%) were positive for coxsackievirus A16 and two (22%) for enterovirus.

Discussion: The causative agents of this outbreak were coxsackievirus A16 and other enteroviruses. Direct contact with a confirmed case was the source of transmission, with a lack of physical distancing in classrooms likely contributing to transmission. We recommended that the local government implement measures to control the outbreak.

On 24 September 2022, the Regional Public Health Unit in Ilocos received a report of a cluster of suspected hand, foot and mouth disease (HFMD) cases in one school in Balungao, Pangasinan Province, the Philippines, from the Development Management Officer of the municipality. The outbreak was verified through the event-based surveillance and response system. On 4 October 2022, a team from the Field Epidemiology Training Program – Intermediate Course in Northern Luzon was dispatched to conduct an outbreak investigation.

HFMD is a common viral illness that usually affects infants and children younger than 5 years, although it can sometimes occur in older children and adults. Symptoms include low-grade fever, mouth sores and skin rashes. The rash is commonly found on the hands and feet, and sometimes on the genitals and buttocks.[1] A case is most contagious during the first week of the illness, but can be contagious for weeks after symptoms resolve. People without symptoms can still spread the virus.[2] HFMD is not transmitted to or from pets or other animals.[2]

Balungao municipality has an estimated population of 30 004, as per the 2020 census.[3] The school involved in the outbreak has 565 students enrolled from kindergarten to grade 6, ranging in age from 5 to 12 years.

METHODS

Active case-finding was conducted at the school. A suspected case was defined as any student or staff member with mouth ulcer and papulovesicular or maculopapular rash on the palms, fingers, soles of the feet or buttocks occurring from 1 September to 5

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October 2022. A confirmed case was a suspected case who tested positive for a human enterovirus that causes HFMD. Findings were used for descriptive analysis.

Face-to-face interviews were conducted with the parents or guardians of cases and teachers, using a standard questionnaire to collect information about demographic characteristics, clinical symptoms and exposure history. The medical records of cases who consulted with or were admitted to the local medical clinic or regional medical and trauma centre from 1 September to 5 October 2022 were also reviewed, as was 5-year HFMD surveillance data from the local health unit and the provincial epidemiology and surveillance unit of Pangasinan Province. From this, we developed a line list using Microsoft Excel that included the name, age, sex, address, grade level, date of onset and admission, signs and symptoms, possible source of infection and laboratory results of each case. The descriptive analysis included information about time (i.e. the scope of the study), place and person, with the frequencies and percentages of HFMD characteristics calculated using Microsoft Excel. An epidemic curve was created by date of onset to describe the epidemiological linkage of cases.

Interviews were also conducted using a guided questionnaire with the Municipal Health Officer, Disease Surveillance Officer, other health staff and school staff to determine possible sources of infection and to understand the activities and practices of students in the school and other relevant information. A site visit to school classrooms and grounds was conducted at the same time.

Oropharyngeal swab samples were collected and specimens placed in viral transport medium before being sent for testing to the Research Institute for Tropical Medicine in Alabang Muntinlupa City. Semi-nested polymerase chain reaction (PCR) was used for enterovirus detection, and an enterovirus multiplex reverse transcription–PCR was used to detect enterovirus 71, coxsackievirus A6 (CV-A6) and CV-A16.

A transmission pattern was observed and key areas contributing to the spread of the disease were identified.

RESULTS

Descriptive analysis

Nine HFMD cases were recorded at the investigated school during 1 September–5 October 2022. The number of cases peaked during 16–20 September 2022 (**Fig. 1**). The first case had a rash on their hands and feet on 12 September 2022. During the epidemiological investigation, two additional cases manifested signs and symptoms of rash on their hands and feet, as well as having fever and mouth ulcers. It was reported that they had contact with a confirmed HFMD case who is their relative.

The highest number of cases occurred among students in grade 1 (6, 67%), with the majority of cases (7, 78%) occurring in students who were aged 6 years, and five cases (56%) in males. Aside from maculopapular and papulovesicular rashes and mouth ulcers, some cases also developed fever (5, 56%). Rash manifested predominantly on the palms (9, 100%) and fingers (7, 78%). Seven (78%) of the cases reported exposure to a confirmed case of HFMD (**Table 1**). There were no suspected cases among school staff. Surveillance data showed that no HFMD cases were reported in the municipality of Balungao during 2021.

Key informant interviews

The mother of the index case reported having no known exposure prior to the onset of illness. His teacher noticed he had a cough from 5 to 9 September, but assumed it was just an allergic cough. On 12 September 2022, he developed a papulovesicular rash on his hand; his mother took him to the local medical clinic where he was diagnosed with HFMD.

According to the Municipal Health Officer, no outbreaks of HFMD had been reported in the municipality. The reported cluster of cases at the investigated school was the municipality's first recorded HFMD event in a school.

The principal, school administrators and teachers reported being aware of a number of students with HFMD at the school during the outbreak, but noted that

Fig. 1. **Epidemiological curve of cases of hand, foot and mouth disease (*N* = 9) by date of onset at a school in Balungao, Pangasinan Province, the Philippines, 1 September–5 October 2022**

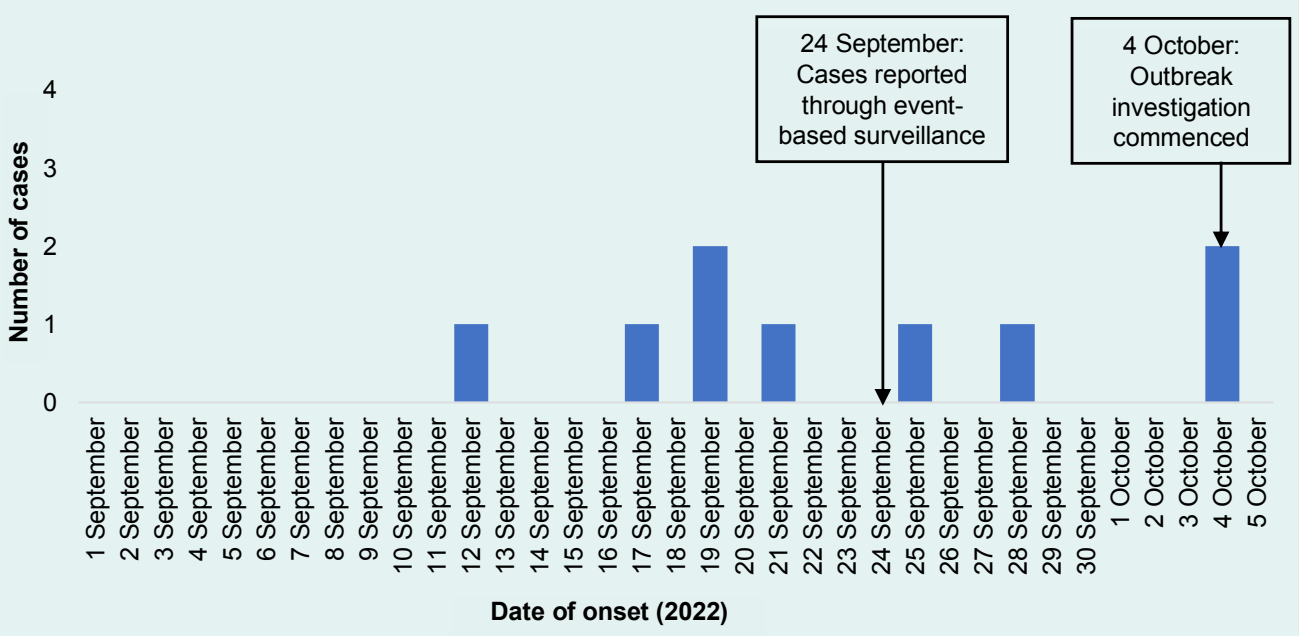

Table 1. **Characteristics of cases of hand, foot and mouth disease (*N* = 9) at a school in Balungao, Pangasinan Province, the Philippines, 1 September–5 October 2022**

Characteristics	No. (%) of cases
Sex	
Male	5 (56)
Female	4 (44)
Age (years)	
6	7 (78)
8	2 (22)
Grade level	
Kindergarten	1 (11)
Grade 1	2 (22)
Grade 3	6 (67)
Reported exposure to a case	7 (78)
Signs and symptoms[a]	
Rash	9 (100)
Mouth ulcers	9 (100)
Fever	5 (56)
Loss of appetite	1 (11)
Site of rash[a]	
Palms	9 (100)
Fingers	7 (78)
Soles of feet	1 (11)
Buttocks	1 (11)

[a] Multiple responses were allowed.

these were the school's first reported cases of HFMD. After the first case, teachers began monitoring students for signs and symptoms. At the same time, hybrid learning was implemented in the classroom for grade 1 students because case clustering was identified. Teachers observed that the students did not always wash their hands properly before and after eating.

Environmental survey

Cases occurred in three grades: kindergarten, grade 1 and grade 3. The school has two washing areas: a common bathroom for each grade level and two common eating areas. The washing area was two to three classrooms away from the classrooms with reported cases of HFMD. The bathroom for grade 1 students was not functional, and the other bathroom was not being properly cleaned.

Laboratory results

Throat swabs were collected from each of the nine cases. Six (67%) tested positive for CV-A16, two (22%) tested positive for enterovirus and one (11%) was negative for enterovirus RNA.

DISCUSSION

This outbreak of HFMD in a school in Pangasinan Province, the Philippines, had two causative agents: CV-A16 and enterovirus. Similar studies in a day-care centre in Sydney, Australia, and in Viet Nam also identified CV-A16.[4,5] The signs and symptoms of the cases were similar to those in other HFMD outbreaks. The mild signs and symptoms reported by the cases concur with the mild and self-limiting signs and symptoms of coxsackievirus infection compared with infection with other types of enterovirus.[6] A records review showed that no cases of HFMD had been previously reported in the school or the municipality.

Direct contact with a confirmed case was the source of transmission, and a lack of physical distancing in the classrooms may have contributed to transmission. A study conducted in Beijing, China, found that being in close proximity to someone exhibiting signs and symptoms of HFMD plays a significant role in disease transmission.[7] HFMD is spread from person to person by direct contact with the infectious viruses that cause this disease. These viruses are found in nose and throat secretions (i.e. in saliva, sputum and nasal mucus), blister fluid and stool of infected persons.[8]

The unknown exposure of the index case may be due to asymptomatic transmission. A study in Bangkok, Thailand, discovered that HFMD can be transmitted by exposure to asymptomatic individuals.[9] Although further evidence is needed, the presence of asymptomatic transmission may indicate that this municipality is already prone to HFMD epidemics.

Poor hand-washing practices and minimal disinfection of commonly touched surfaces at the school may have played roles in transmission. The viruses can be spread when infected persons touch objects and surfaces that are then touched by others.[8] Ruan et al. discovered that hand-washing by caregivers and children attending preschool significantly reduced the risk of HFMD in the community.[10]

This study is only descriptive and is limited in its ability to test a hypothesis and determine risk factors. Despite these limitations, the study was able to identify the pathogen and source of this outbreak. While no additional cases were reported at this school after the outbreak, new cases were recorded at another elementary school and a day-care centre and in one village, suggesting further community spread. We recommended that the local government of Balungao, Pangasinan, engages in health-promotion activities, that schools encourage self-isolation at the onset of symptoms, and that hand-washing facilities are functional and accessible.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

The activities conducted for this study were part of routine surveillance and response work, and standard procedures to protect personal information were taken. Therefore, ethics committee approval for the study was deemed unnecessary.

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COVID-19 vaccine-related adverse events following immunization in the WHO Western Pacific Region, 2021–2022

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The speed at which new vaccines against coronavirus disease (COVID-19) were developed and rolled out as part of the global response to the pandemic was unprecedented. This report summarizes COVID-19 vaccine-related safety data in the World Health Organization Western Pacific Region. Data for 1 March 2021 to 31 March 2022 from 36 out of 37 countries and areas in the Western Pacific Region are presented. More than 732 million doses of eight COVID-19 vaccines were administered; reporting rates of adverse events following immunization (AEFIs) and serious AEFIs were 130.1 and 5.6 per 100 000 doses administered, respectively. Anaphylaxis, thrombosis with thrombocytopenia syndrome, and myocarditis/pericarditis were the most frequent COVID-19 adverse events of special interest (AESIs) reported. The reported rates of AESIs in the Western Pacific Region were within the range of expected or background rates. Vaccine benefits far outweigh the risk of reported serious adverse reactions and serious outcomes of COVID-19. Continued AEFI surveillance is recommended to better understand and ensure the safety profiles of novel COVID-19 vaccines.

The global coronavirus disease (COVID-19) immunization campaign was unprecedented in its scale, speed and specificities.[1,2] The first COVID-19 vaccine was granted emergency use listing (EUL) by the World Health Organization (WHO) in December 2020.[3] By 31 March 2022, nine COVID-19 vaccines had received EUL,[4] eight of which have been used in the WHO Western Pacific Region.

While the development and EUL approval processes of COVID-19 vaccines were accelerated, the quality and safety of COVID-19 vaccines were not compromised, as evidenced by the clinical trials conducted in the development phase[5] and the robust vaccine and immunization safety monitoring mechanisms that were established post-licensure. The latter are an essential part of ensuring the safety of vaccines and were especially important in the case of COVID-19 given the large target population (which included different age groups and high-risk individuals) and the simultaneous use of different COVID-19 vaccines.

Many countries expanded their existing surveillance systems for adverse events following immunization (AEFIs) to include the monitoring of COVID-19 vaccine safety events. Data collected by these systems on AEFIs with COVID-19 vaccines were routinely reported to WHO. This paper reviews the available surveillance data on COVID-19 vaccine-related AEFIs from countries and areas in the Western Pacific Region during 1 March 2021–31 March 2022.

METHODS

Definitions

An AEFI is defined as any untoward medical occurrence that follows immunization; AEFIs do not necessarily have a causal relationship with the use of a vaccine. A serious AEFI is defined as an event that is life-threatening or results in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect or death.[6] Adverse events of special interest (AESIs) are a subset of AEFIs and are defined as a pre-specified medically significant condition that has the potential to be causally associated with a vaccine product and that

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needs to be carefully monitored and/or confirmed by further studies.[7]

Data sources

Data were obtained from 36 of the 37 countries and areas in the WHO Western Pacific Region; no data were available from China (**Table 1**). COVID-19 vaccination and safety data for the period, 1 March 2021 to 31 March 2022, were collated from weekly reports provided by WHO country offices and countries; for countries that did not provide weekly reports, safety data were obtained from publicly available data published on official government websites (e.g. websites of ministries or departments of health or national regulatory agencies). For some countries and areas, both weekly reports and data from official government websites were used (**Table 1**). Inconsistent and incomplete data were followed up with the corresponding WHO country offices or government focal points for COVID-19 vaccine data.

Data reported through the Regional event-based surveillance (EBS)[8] system were used to supplement the analysis. The EBS system was established as an early warning mechanism to rapidly capture publicly reported safety events related to COVID-19 vaccination, including AESIs reported by regional and global sources such as media International Health Regulations (2005) reports, and government agency reports and publications. It was established by, and functions with, the guidance of the Health Emergencies Programme team at the WHO Regional Office for the Western Pacific.

Four categories of AESIs are included in this report: anaphylaxis, thrombosis with thrombocytopenia syndrome (TTS), myocarditis/pericarditis and Guillain-Barré syndrome (GBS). Although WHO's COVID-19 safety surveillance manual defines anaphylaxis as a severe immediate (within 1 hour) allergic reaction leading to circulatory failure with or without bronchospasm and/or laryngospasm/laryngeal oedema,[7] the case definitions and diagnostic criteria[9] used by countries for anaphylaxis varied across the Region.

TTS was defined as the presence of a thrombosis/thromboembolism, generally in uncommon anatomical locations (such as cerebral venous sinus or splanchnic veins) and marked thrombocytopenia following vaccination with a COVID-19 non-replicant adenovirus vector-based vaccine.[10] At the start of 2021, the detection and reporting of TTS was compromised by uncertainty in the pathogenesis, complicated clinical and laboratory presentations and the lack of a clear case definition for TTS. However, TTS surveillance quickly improved as new evidence became available and guidelines evolved during May and June 2021. Only rates of TTS following immunization with the Vaxzevria (AstraZeneca) COVID-19 vaccine were reported; despite reports of TTS following administration of the Ad26.COV2.S (Janssen or Johnson & Johnson) COVID-19 non-replicant adenovirus vector-based vaccine globally, and although 14 countries and areas in the Region had introduced this vaccine, disaggregated data were not available to assess TTS rates for the Johnson & Johnson vaccine in the Western Pacific Region.

Myocarditis is an inflammation of the heart muscle, and pericarditis is an inflammation of the lining that surrounds the heart. In July 2021, the COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) issued a statement regarding reports of myocarditis and pericarditis following administration of COVID-19 mRNA vaccines and encouraged reporting of these two conditions.[11]

GBS is a rare, serious neurological autoimmune disorder that affects the peripheral nervous system and can lead to weakness and paralysis. GBS has been observed following some viral and bacterial infections and, more rarely, following the use of some vaccines including influenza vaccines.[12] In July 2021, the WHO GACVS COVID-19 subcommittee issued a statement regarding reports of GBS following administration of adenovirus vector-based COVID-19 vaccines.[13]

Data analysis

Data were used to calculate rates of reported AEFIs and AESIs (anaphylaxis, TTS, myocarditis and/or pericarditis and GBS) per 1 million doses administered. Reporting rates were calculated separately for Pacific island countries and areas (PICs) and non-PICs. Where either the numerator (number of adverse events) or the denominator (number of administered doses) was not available separately, i.e. disaggregated by vaccine, these data were excluded from the computation of AEFI rates.

Table 1. **Sources of COVID-19 safety data, by country and area in the Western Pacific Region**

Data source	Country and area[a]
Weekly reports	Non-PICs: Brunei Darussalam, Cambodia, Hong Kong SAR (China), Lao People's Democratic Republic, Macao SAR (China), Malaysia,[b] Mongolia, New Zealand,[b] Papua New Guinea, the Philippines, Viet Nam
	PICs: American Samoa, Cook Islands, Fiji,[b] Guam, Kiribati, Marshall Islands, Federated States of Micronesia, Nauru, Niue, Commonwealth of the Northern Mariana Islands, Palau, Pitcairn Islands, French Polynesia,[b] Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Wallis and Futuna
Official government websites	Non-PICs: Australia, Japan, Malaysia,[b] New Zealand, Republic of Korea, Singapore
	PICs: New Caledonia, Fiji,[b] French Polynesia[b]

PICs: Pacific island countries and areas; SAR: Special Administrative Region.

[a] There are 27 countries and 10 areas in the Western Pacific Region.

[b] Safety data were obtained from both weekly reports and data published on official government websites.

RESULTS

Vaccines used in the Western Pacific Region

Between 1 March 2021 and 31 March 2022, more than 732 million doses of the seven WHO EUL-granted COVID-19 vaccines – Comirnaty (Pfizer-BioNTech), Spikevax (Moderna), AstraZeneca, Johnson & Johnson, BBIBP-CorV (Sinopharm), CoronaVac (Sinovac) and Nuvaxovid (Novavax) – and one non-WHO EUL COVID-19 vaccine, Gam-Covid-Vac (Gamaleya) – were administered across 36 countries and areas in the Region. The most widely used vaccine was the Pfizer-BioNTech vaccine (433.7 million doses administered in 29 countries and areas), followed by the Moderna vaccine (101.8 million doses administered in 17 countries and areas). Although the Sinovac vaccine was administered in relatively few countries in the Region, it ranked third in terms of number of doses administered (**Table 2**).

Adverse events following immunization in the Western Pacific Region

The reporting rates of total AEFIs and serious AEFIs were 130.1 and 5.6 events per 100 000 doses administered, respectively. For both total AEFIs and serious AEFIs, reporting rates in non-PICs and PICs were similar to that for the Western Pacific Region overall (**Table 3**). Rates differed according to vaccine type, with the AstraZeneca vaccine having the highest reporting rate for both total AEFIs and serious AEFIs (**Table 4**).

Adverse events of special interest in the Western Pacific Region

Anaphylaxis

Reporting rates for anaphylaxis by vaccine type ranged from 0.3 (Sinopharm) to 13.7 (Pfizer-BioNTech) cases per 1 million doses administered (**Table 5**). Anaphylaxis reporting rates in non-PICs were higher for most COVID-19 vaccines at the start of the reporting period; these rates then declined and stabilized over the course of the reporting period (**Fig. 1**). The stabilization of anaphylaxis reporting rates coincided with the rise in the number of vaccine doses administered and thus an increase in the size of the denominator.

Thrombosis with thrombocytopenia syndrome

Of the 21 countries and areas that introduced the AstraZeneca vaccine, 12 (10 non-PICs and two PICs) provided data on the number of cases of TTS, of which six (five non-PICs and one PIC) reported no cases. In total, there were 178 suspected and/or confirmed TTS cases following administration of 42.1 million doses of the AstraZeneca vaccine, which equates to a reporting rate of 4.2 cases per 1 million doses administered. Among the six countries that reported TTS cases following the AstraZeneca vaccine, the lowest rate was 0.2 cases per 1 million doses administered and the highest was 17.2 cases per 1 million doses administered.

Table 2. **COVID-19 vaccine introductions during 1 March 2021–31 March 2022, by country and area in the Western Pacific Region**

Country and area	Vaccine							
	Pfizer-BioNTech BNT162b2	Moderna mRNA-1273	Sinovac	AstraZeneca-Oxford University AZD1222	Sinopharm COVID-19 vaccine BIBP	Johnson & Johnson Janssen Ad26.COV2.S	Gamaleya Gam-COVID-Vac[a]	Novavax NVX-CoV2373
Non-PICs								
Australia	Y	Y	N	Y	N	N	N	Y
Brunei Darussalam	Y	Y	N	Y	Y	N	N	N
Cambodia	Y	Y	Y	Y	Y	Y	N	N
Hong Kong SAR (China)	Y	N	Y	N	N	N	N	N
Japan	Y	Y	N	Y	N	N	N	N
Lao People's Democratic Republic	Y	N	Y	Y	Y	Y	Y	N
Macao SAR (China)	N	N	N	N	Y	N	N	N
Malaysia	Y	N	Y	Y	Y	N	N	N
Mongolia	Y	N	N	Y	Y	N	Y	N
New Zealand	Y	N	N	Y	N	N	N	Y
Papua New Guinea	N	N	N	Y	Y	Y	N	N
Philippines	Y	Y	Y	Y	Y	Y	Y	N
Republic of Korea	Y	Y	N	Y	N	Y	N	Y
Singapore	Y	Y	Y	N	Y	N	N	N
Viet Nam	Y	Y	N	Y	Y	N	Y	N
PICs								
American Samoa	Y	Y	N	N	N	Y	N	N
Cook Islands	Y	N	N	N	N	N	N	N
Fiji	Y	Y	N	Y	N	N	N	N
French Polynesia	Y	N	N	N	N	Y	N	N
Guam	Y	Y	N	N	N	Y	N	N
Kiribati	N	N	N	Y	Y	N	N	N
Marshall Islands	Y	Y	N	N	N	Y	N	N
Micronesia, Federated States of	Y	Y	N	N	N	Y	N	N
Nauru	Y	N	N	Y	N	N	N	N
New Caledonia	Y	N	N	N	N	Y	N	N
Niue	Y	N	N	N	N	N	N	N
Northern Mariana Islands, Commonwealth of the	Y	Y	N	N	N	Y	N	N
Palau	Y	Y	N	N	N	Y	N	N
Pitcairn Islands	N	Y	N	Y	N	N	N	N
Samoa	Y	N	N	Y	N	N	N	N
Solomon Islands	Y	N	N	Y	Y	N	N	N
Tokelau	Y	N	N	N	N	N	N	N
Tonga	Y	N	N	Y	N	N	N	N
Tuvalu	N	N	N	Y	N	N	N	N
Vanuatu	N	N	N	Y	Y	Y	N	N
Wallis and Futuna	N	Y	N	N	N	N	N	N
Total number of countries and areas	**29**	**17**	**6**	**21**	**13**	**14**	**4**	**3**
Total number of doses administered (millions)	**433.7**	**101.8**	**97.4**	**68.7**	**18.5**	**10.6**	**1.2**	**0.3**

SAR: Special Administrative Region.

[a] Includes Sputnik V and Sputnik light.

Table 3. **Total and serious AEFI reporting rates for COVID-19 vaccines in non-PICs and PICs in the Western Pacific Region, 1 March 2021–31 March 2022**

	Total number of doses administered (millions)	Total AEFIs		Serious AEFIs	
		Number of events reported	Rate (per 100 000 doses administered)	Number of events reported	Rate (per 100 000 doses administered)
Non-PICs	730.2	950 031	130.1	40 704	5.6
PICs	2.1	2679	129.8	117	5.7
Total	732.3	952 710	130.1	40 821	5.6

AEFI: adverse event following immunization; PICs: Pacific island countries and areas.

Table 4. **Total and serious AEFI reporting rates for COVID-19 vaccines in non-PICs and PICs in the Western Pacific Region by vaccine type,[a] 1 March 2021–31 March 2022**

Vaccine		Total AEFIs n (rate per 100 000 doses)			Serious AEFIs n (rate per 100 000 doses)		
		Total	Non-PICs	PICs	Total	Non-PICs	PICs
mRNA vaccine	Pfizer-BioNTech	465 901 (107.7)	465 272 (107.7)	629 (80.3)	23 163 (5.9)	23 100 (5.9)	63 (8.1)
	Moderna	191 009 (187.7)	190 894 (188.1)	115 (42.0)	4078 (4.2)	4059 (4.2)	19 (6.9)
Adenovirus vector-based vaccine	AstraZeneca	229 331 (333.9)	227 717 (335.3)	1614 (209.1)	7401 (13.5)	7374 (13.6)	27 (3.5)
	Johnson & Johnson	13 621 (128.1)	13 405 (126.9)	216 (324.1)	1135 (10.7)	1128 (10.7)	7 (10.9)
	Gamaleya	875 (71.3)	875 (71.3)	0	37 (3.0)	37 (3.0)	0
Inactivated vaccine	Sinopharm	8575 (46.3)	8470 (45.9)	105 (155.4)	107 (0.6)	106 (0.6)	1 (1.5)
	Sinovac	42 670 (43.8)	42 670 (43.8)	0	4885 (5.0)	4885 (5.0)	0
Protein subunit	Novavax[b]	728 (281.3)	728 (281.3)	0	15 (8.6)	15 (8.6)	0

AEFI: adverse event following immunization; PICs: Pacific island countries and areas.

[a] In cases where either the numerator (number of events) or the denominator (number of doses administered) was not available separately (i.e. disaggregated by vaccine), or where there were no available data, data were excluded from computation of the AEFI rates.

[b] The rollout of the Novavax vaccine in the Western Pacific Region started in mid-February 2022, and by the end of March 2022, three countries were using the vaccine (cumulative total number of doses administered = 258 834).

Myocarditis/pericarditis

Seventeen countries and areas (nine non-PICs and eight PICs) used the Pfizer-BioNTech vaccine and reported on myocarditis/pericarditis; of these 17 countries, two non-PICs and six PICs reported zero cases. In the remaining nine countries, there were a total of 5784 reported cases of myocarditis/pericarditis, giving a reporting rate for the Pfizer-BioNTech vaccine in the Western Pacific Region of 15.2 cases per 1 million doses administered. Ten countries and areas (six non-PICs and four PICs) used the Moderna vaccine and also reported on myocarditis/pericarditis. Among this group of countries, half (one non-PIC and all four PICs) reported zero cases; the other five reported a total of 921 cases following the administration of 98.6 million doses. This translates to a reporting rate of myocarditis/pericarditis for the Moderna vaccine of 9.3 cases per 1 million doses administered.

Cases of myocarditis and/or pericarditis were more frequently reported after the second dose of mRNA

Table 5. **Reporting rates[a] of suspected and/or confirmed anaphylaxis following COVID-19 vaccination in non-PICs and PICs in the Western Pacific Region, 1 March 2021–31 March 2022**

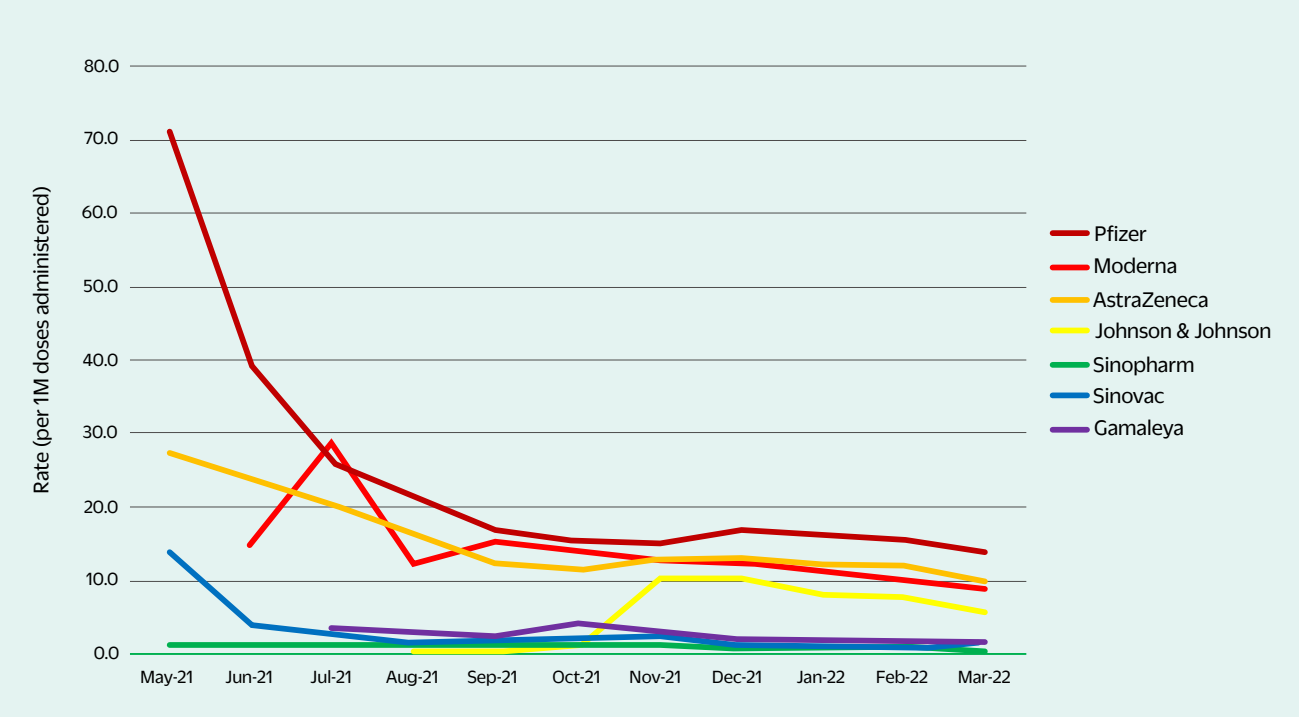
	Non-PICs	PICs	Total
No. of reporting countries	14	17	31
No. of anaphylaxis cases	7563	3	7566
COVID-19 vaccine[b]	**Anaphylaxis reporting rate (cases per 1 million doses administered)**		
Pfizer-BioNTech	13.7	1.3	13.7
Moderna	8.9	0.0	8.9
AstraZeneca	10.0	2.6	9.9
Johnson & Johnson	5.7	0.0	5.6
Gamaleya	1.6	NA	1.6
Sinovac	1.5	NA	1.5
Sinopharm	0.3	0.0	0.3

NA: not applicable; PICs: Pacific island countries and areas.

[a] In cases where either the numerator (number of events) or the denominator (number of doses administered) was not available separately (i.e. disaggregated by vaccine), or where there were no available data, data were excluded from computation of the AEFI rates.

[b] Novavax is not included as its rollout only began in February 2022. By the end of March 2022, 14 cases of anaphylaxis had been reported.

Fig. 1. **Anaphylaxis reporting rates following administration of COVID-19 vaccines[a] in non-PICs, 1 May 2021–31 March 2022**



PICs: Pacific island countries and areas.

[a] Novavax is not included as its rollout only began in February 2022. Data are only available for two non-PICs and only for February and March 2022.

Table 6. **Reporting rates of likely myocarditis following Pfizer-BioNTech and Moderna COVID-19 vaccines in Australia, by age and sex (as of 27 March 2022)[a]**

Age group[b] (years)	Pfizer-BioNTech (number of events per 100 000 doses)[c]				Moderna (number of events per 100 000 doses)[c]			
	Both doses		2nd dose		Both doses		2nd dose	
	Male	Female	Male	Female	Male	Female	Male	Female
12–17	7.6	1.4	12.2	2.3	10.8	3.0	20.5	5.1
18–29	4.2	1.2	4.5	2.0	8.6	1.1	17.8	2.4
30–39	1.6	0.6	2.0	0.7	2.4	0.6	5.1	0
40–49	0.7	0.5	1.0	1.0	1.4	0.3	1.7	0
50–59	0.4	0.3	0.1	0.3	0.3	0.9	0	2.5
60–69	0.1	0.3	0	0.4	0	0.3	0	0
≥70	0	0.1	0	0.4	0	0.2	0	0
Total	2.0	0.7	3.9	1.1	3.2	0.8	9.6	1.9

[a] Likely myocarditis includes cases classified as levels 1–3. Level 1 cases are confirmed to be myocarditis based on strong clinical evidence including the patient's symptoms, and results of tests and imaging indicating a diagnosis of myocarditis. Level 2 cases are probable myocarditis based on a combination of symptoms and routine tests for heart conditions. Level 3 cases are possible myocarditis based on symptoms and a doctor's report that myocarditis is the most likely diagnosis in the absence of medical tests and investigations. For all cases of suspected myocarditis, where possible, other known causes of the patient's symptoms or test results are ruled out before cases are classified.

[b] As of 27 March 2022, no likely cases of myocarditis had been reported in children aged 5–11 years.

[c] The rate includes cases of myocarditis that occurred after vaccination but may not be vaccine-related. In order to comply with the Therapeutic Goods Administration's copyright, the rates are expressed per 100 000 doses administered. In order to comply with the Therapeutic Goods Administration's copyright, the rates are expressed per 100 000 doses administered.

Source: Data are reproduced with permission from the Therapeutic Goods Administration, Australian Government.[19]

Table 7. **Rates of confirmed myocarditis following Pfizer-BioNTech and Moderna COVID-19 vaccines in the Republic of Korea, by age and sex (as of 31 January 2022)**

Age group (years)	Pfizer-BioNTech (number of events per 1 million doses)				Moderna (number of events per 1 million doses)			
	1st dose		2nd dose		1st dose		2nd dose	
	Male	Female	Male	Female	Male	Female	Male	Female
12–17	12.9	4.3	23.6	3.7	–	–	–	–
18–19	14.6	8.2	14.7	8.3	13.9	0.0	47.5	15.6
20–29	4.7	4.7	5.4	1.3	10.0	10.4	37.2	4.8
30–39	10.4	5.7	2.2	3.3	12.3	9.4	7.8	6.4
40–49	2.1	2.5	2.9	2.9	4.3	7.6	3.3	3.9
50–59	1.2	4.0	1.9	2.3	1.9	8.6	1.9	0.0
≥60	0.0	0.0	0.7	0.4	0.0	0.0	0.0	0.0
Total	4.8	3.5	5.0	2.4	6.4	8.4	11.5	3.5

Source: Data are reproduced with permission from the Korea Disease Control and Prevention Agency, WHO Global Advisory Committee on Vaccine Safety meeting, unpublished presentation, January 2022.

COVID-19 vaccines in young males aged 12–39 years. Given the clinical and safety importance of myocarditis, particularly among young age groups, a more detailed breakdown of case numbers is provided, by age, sex and dose, for a number of countries for which such data were available, including Australia, Japan and the Republic of Korea (**Tables 6–8**). In all three countries, the highest reported rates of myocarditis were observed in young males following the second dose of the vaccine; reporting rates were higher for the Moderna vaccine than for the Pfizer-BioNTech vaccine. Reported myocarditis rates were generally lower in older adults (i.e. those

Table 8. **Reporting rates of suspected myocarditis following Pfizer-BioNTech and Moderna COVID-19 vaccines in Japan, by age and sex (as of 5 December 2021)**

Age group (years)	Pfizer-BioNTech (number of events per 1 million doses)				Moderna (number of events per 1 million doses)			
	Both doses		2nd dose		Both doses		2nd dose	
	Male	Female	Male	Female	Male	Female	Male	Female
10–14	13.4	1.5	21.6	1.1	42.3	0	89.8	0
15–19	12.9	2.5	21.9	1.7	50.6	1.3	86.5	2.5
20–24	8.2	0.6	12.2	0	27.9	1.1	51.9	1.1
25–29	6.0	0.9	10.2	1.2	19.7	1.4	34.7	2.9
30–34	2.4	0.8	3.0	0	5.9	1.6	10.9	0
35–39	1.3	1.5	2.0	0.9	1.5	1.5	2.0	1.6
40–44	2.1	0.9	3.8	0.4	3.0	1.5	4.0	1.5
45–49	0.8	0.6	0.7	0.6	2.6	2.6	4.4	2.6
50–54	0.8	0.9	1.0	0.3	0.5	2.2	1.0	3.0
55–59	1.1	0.3	1.1	0.7	1.3	0	2.6	0
60–64	0.4	0.8	0.7	1.3	0	0	0	0
65–69	0.9	0.4	0.6	0	2.1	2.9	4.3	0
70–74	0.4	0.8	0	0.2	0	0	0	0
75–79	0.7	0.1	0.4	0	0	0	0	0
≥80	1.0	0.9	0.8	0.9	0	0	0	0

Data include Brighton Collaboration level 1–5 cases.

Source: Data are reproduced with permission from the Ministry of Health, Labour and Welfare, Japan.[26]

aged ≥30 years); in this age group, rates exhibited little difference between males and females and between the first and second doses for either vaccine.

Guillain-Barré syndrome

Of the 21 countries and areas in the Western Pacific Region using the AstraZeneca vaccine, 11 (nine non-PICs and two PICs) reported on GBS. Eight of these 21 countries (six non-PICs and two PICs) reported that they had no cases of GBS in the period covered by this study. There were a total of 172 reported suspected and/or confirmed GBS cases in the other 13 countries, suggesting a reporting rate for the AstraZeneca vaccine of 4.1 cases per 1 million doses administered. There was a marked difference in reporting rates between countries, the lowest being 0.93 cases per 1 million doses administered and the highest being 11.59 cases per 1 million doses administered. The Republic of Korea reported two confirmed cases of GBS in people given the Johnson & Johnson vaccine.

DISCUSSION

This regional analysis summarizes data on AEFIs and AESIs following COVID-19 vaccination as reported by 36 of the 37 countries and areas in the Western Pacific Region during the period of 1 March 2021 to 31 March 2022. The total and serious AEFI reporting rates were used to monitor the functionality of vaccine safety surveillance systems.[7]

The total AEFI reporting rate in the Western Pacific Region during the study period was 130.1 cases per 100 000 doses administered; the serious AEFI reporting rate was 5.6 cases per 100 000 doses administered. For both categories of adverse events, total AEFIs and serious AEFIs, reporting rates in non-PICs and PICs were similar, suggesting that all countries and areas in the Western Pacific Region had a basic functional surveillance system for monitoring vaccine safety during the COVID-19 vaccination programme. This is a significant improvement compared with 2018, when

only 12 countries met the WHO AEFI reporting rate of 10 cases per 100 000 surviving infants, the indicator recommended by the Global Vaccine Action Plan 2011–2020 for monitoring the functionality of countries' AEFI surveillance systems.[14]

Vaccine safety data have been monitored and shared by WHO with countries in the Region through various platforms; however, the findings need to be interpreted with caution. Across the Western Pacific Region, there was a wide variation in the capacity of countries to detect, diagnose, report, investigate and establish causality of AESIs. Although efforts were taken to ensure completeness and accuracy of the aggregated data provided by countries, it was not possible to verify or validate individual cases of reported AESIs. This limitation is expected when cases of AESIs are reported through passive surveillance systems and because of the large scale of the COVID-19 vaccination rollout, which resulted in a high volume of reports within a relatively short period.

The reported rates of anaphylaxis following COVID-19 vaccination in countries and areas in the Region ranged from 0.3 to 13.7 cases per 1 million doses administered, depending on the type of vaccine. This is in line with the mean anaphylaxis rate of 10.7 cases per 1 million doses administered associated with four COVID-19 vaccines (Moderna, Pfizer-BioNTech, AstraZeneca and Johnson & Johnson) reported by the United States Vaccine Adverse Event Reporting System and the European EudraVigilance,[15] and also with anaphylaxis rates for the most commonly administered non-COVID-19 vaccines (which ranged from 1 to 10 cases per 1 million doses administered depending on the vaccine).[15] The anaphylaxis reporting rate for all COVID-19 vaccines was ranked fifth compared with non-COVID-19 vaccines.[15]

The high reporting rates for anaphylaxis that were observed in the early period of the COVID-19 vaccination programme and at the start of our study period were not inconsistent with reporting rates for non-COVID-19 vaccines used in global immunization programmes. For any new vaccine there is a possibility of higher-than-expected rates for anaphylaxis; however, over time the rates tend to return to the expected range due to the high number of doses being administered. In the Western Pacific Region, as the number of vaccines being administered increased as the COVID-19 immunization programme was rolled out, the reporting rates of anaphylaxis stabilized over time. This is an important observation, and one that provides reassurance of the safety of COVID-19 vaccines.

Reports of TTS following COVID-19 vaccination raised concerns across the Region and globally. In the Western Pacific Region, there were 4.2 reported cases of TTS following immunization with AstraZeneca vaccines per 1 million doses administered (range, 0.2–17.2 cases per 1 million doses administered). According to the WHO interim recommendations for use of the AstraZeneca COVID-19 vaccine and data from the global safety database, TTS reporting rates ranged from 0.2 cases per 1 million doses administered in Asian countries to 17.6 cases per 1 million doses administered in European countries.[16] This wide range may be a reflection of country variation in TTS detection and/or reporting capacities, as well as a lack of well-defined case definitions of TTS in the early period of the COVID-19 vaccination programme.[10] Furthermore, as the diagnosis of TTS requires several tests, including imaging and laboratory tests, countries with fewer clinical specialists such as radiologists and haematologists and where diagnostic facilities are more limited may have reduced capacity to detect and report TTS cases. It is also possible that as TTS appears to be age-specific (more commonly reported in people aged <50 years),[17] the age restrictions for obtaining COVID-19 vaccinations implemented by some countries in 2021 (which tended to favour the older age groups) may have affected the reporting rates.

The global COVID-19 vaccination programme also flagged myocarditis/pericarditis as a potential AESI following administration of COVID-19 mRNA vaccines. In the Western Pacific Region, the reported rate of myocarditis/pericarditis for the Moderna vaccine was 9.3 cases per 1 million doses administered, while for the Pfizer-BioNTech vaccine, the rate was 15.2 cases per 1 million doses administered. This compares with reported rates of 104.5 and 97.7 cases per 1 million doses, respectively (as of 27 March 2022), in Australia;[18] 29.7 and 22.7 cases per 1 million doses, respectively, in Canada;[19] 26.8 and 15.9 cases per 1 million doses, respectively, in the United Kingdom of Great Britain and Northern Ireland;[20] and 7.7 and 5.9 cases per 1 million doses, respectively (as of 24 March 2022), in the Republic of Korea.[21] Myocarditis and pericarditis data from countries in the Western Pacific Region (**Tables 6–8**) and several other WHO regions have also shown that for both vaccines, reporting rates were highest in young males and higher

after the second dose than after the first.[22] These data suggest that reporting rates stratified by age and sex would be useful for the monitoring of safety profiles of mRNA COVID-19 vaccines in the future.

Overall, 4.1 cases of GBS were reported for every 1 million doses of the AstraZeneca vaccine that were administered in countries and areas in the Western Pacific Region (range, 0.9–11.6 cases per 1 million doses). This is consistent with the reporting rate published by the European Medical Agency (4.4 cases per 1 million doses administered)[13] but lower than that in the United States of America (8.2 cases per 1 million doses administered of the Johnson & Johnson vaccine, as of June 2021).[23] In July 2021, WHO reviewed the reports of GBS following administration of adenovirus vector-based vaccines, the AstraZeneca and Johnson & Johnson vaccines, and found no evidence to suggest that use of these vaccines was associated with an increase in GBS case rates.[13] The reporting rates of GBS for the AstraZeneca and Johnson & Johnson vaccines are lower than that of the 1976 inactivated influenza vaccine (10 cases per 1 million doses administered) but higher than that for seasonal influenza vaccines (1–2 cases per 1 million doses administered).[24] This warrants further monitoring of GBS following COVID-19 vaccines and more studies to properly evaluate the potential association of GBS with COVID-19 vaccines.

The COVID-19 vaccination programme provided the opportunity for countries in the Western Pacific Region to expand and strengthen their vaccine and immunization safety surveillance programmes to provide timely detection, reporting and response to safety events, and to ensure the safety of vaccine recipients. The data included in this report suggest that there were functional vaccine safety surveillance systems throughout the Region. In general, high-income countries and areas have greater capacities for surveillance and response to vaccine and immunization safety events than low- and middle-income countries (LMICs) and PICs, particularly in the case of new AESIs. The vaccine and immunization surveillance capacities of many LMICs, particularly at the subnational level and in PICs, are still limited, particularly in the investigation and causality assessment of AESIs. During the course of the pandemic, WHO has provided technical support to several countries in the form of new guidelines, tools and training of country staff.

It is anticipated that the reporting rates presented in this paper will be useful for evaluating the safety performance of COVID-19 vaccines as part of future programmatic and policy decision-making, particularly if COVID-19 vaccines are to be used in a life-course approach and integrated with routine immunization programmes. However, as most of the data stem from passive or enhanced passive surveillance systems, interpretation of the reported AEFI and AESI rates requires caution, as passive surveillance systems are subject to detection and reporting bias. Furthermore, the effect of confounding factors (e.g. age and sex), which are not accounted for in the reporting of some AESIs, cannot be ruled out.

With uncertainty around the continuation of the COVID-19 pandemic, planning and implementing strategies to build resilience for routine immunization programmes beyond COVID-19 vaccination will remain a challenge for many countries. Vaccine benefits far outweigh the risk of reported serious adverse reactions and serious outcomes of COVID-19.[25] Adopting a transparent approach to identifying AESIs helps build public trust and can be part of effective risk communication strategies aimed at preventing vaccine hesitancy, which is often grounded in vaccine safety concerns. Thus, in order to maintain trust in and demand for regular immunization and improve their management of serious AEFI response, countries should sustain the enhancements to their AEFI surveillance programmes made at the national level during the pandemic and further strengthen subnational capacities in AEFI investigation and causality assessment.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

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