

Serology surveillance of anti-SARS-CoV-2 antibodies among asymptomatic healthcare workers in Malaysian healthcare facilities designated for COVID-19 care

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Abstract

Introduction

Healthcare workers (HCW) are presumed to be at increased risk of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection due to occupational exposure to infected patients. We aim to determine the prevalence of anti-SARS-CoV-2 antibodies among asymptomatic HCW.

Methods

We prospectively recruited HCW from the National Public Health Laboratory and two COVID-19 designated public hospitals in Klang Valley, Malaysia between April 13th and May 12th, 2020. Quota sampling was applied to ensure adequate representation of the HCW involved in provision of care for patients directly and indirectly. All participants had worked in the respective healthcare facility for at least 30 days prior study enrollment. HCW who were previously confirmed with COVID-19 infection or listed as "patient under investigation" were excluded. A self-administered questionnaire was used to capture sociodemographic information, history of contact with COVID-19 cases within the past month, clinical signs and symptoms and adherence to universal precautions. Blood samples were taken to test for anti-SARS-CoV-2 antibodies by surrogate virus neutralization test.

Results

A total of 400 HCW were recruited, comprising 154 (38.5%) nurses, 103 (25.8%) medical doctors, 47 (11.8%) laboratory technologists and others (23.9%). The mean age was 35 ± 7.8 years, with females predominant (74%). A majority (68.9%) reported direct contact with COVID-19 patients, body fluids of COVID-19 patients and/or contaminated objects and surfaces in the past month within their respective workplaces. Nearly all claimed to adhere to personal protection equipment (PPE) guidelines (97%-100% adherence) and hand hygiene practice (91%-96% adherence). None (95% CI: 0, 0.0095) of the participants had anti-SARS-CoV-2 antibodies detected, despite 135 (33.8%) reporting respiratory symptoms one month prior to study recruitment. One hundred and fifteen (29%) participants claimed to have contact with known COVID-19 persons outside of the workplace.

Conclusion

Our finding of zero seroprevalence among asymptomatic HCW suggests a low risk of asymptomatic COVID-19 infection in our healthcare setting; which is at expected levels for a country with an incidence of 26 per 100,000. The adequacy of PPE equipment and strict adherence to infection prevention and control measures offers considerable protection during contact with COVID-19 cases and should be ensured to prevent future nosocomial transmission.

Introduction

On 25th January 2020, Malaysia had its first confirmed case of coronavirus disease 2019 (COVID-19),^[1] a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^[2] Initially, confirmed cases were mainly imported and daily reported cases remained relatively low. However, local transmission began to emerge, following a mass religious event that was held in Kuala Lumpur between late February and early March 2020. This event was attended by an estimated 16,000 people from all over Asia, of whom 14,500 were Malaysians.^[3] Since then, massive spikes in local cases and exportation of cases to other countries had been observed. As of 16th June 2020, over 8,500 COVID-19 positive cases and 121 deaths have been reported in Malaysia. With a population of 31 million, this gives an incidence of about 26 per 100,000. Klang Valley, which comprises Selangor state, the Federal Territory (and capital) of Kuala Lumpur and the Federal Territory of Putrajaya, contributed about half of the national COVID-19 burden.^[4]

The spectrum of COVID-19 severity ranges from mild to critical. According to the Chinese Center for Disease Control and Prevention, about 80% of confirmed COVID-19 patients suffered from mild disease.^[5] Asymptomatic COVID-19 infections have been well documented, but its proportion within total COVID-19 cases remains unclear.^[6] Nevertheless, current evidence suggests that asymptomatic and presymptomatic COVID-19 individuals can transmit the infection to others.^[7]

As of 6th May 2020, the World Health Organization (WHO) reported that a total of 22,073 HCW from 52 countries had contracted COVID-19 infection.^[8] In Malaysia, the first case of COVID-19 infection among HCW was reported in early March 2020,^[9] followed by further clusters.^[10-12] As they manage suspected and confirmed COVID-19 patients, HCW are presumed to have higher risk for COVID-19 infection and, if infected, can possibly transmit the virus to vulnerable patients and other co-workers. With the uncertainties of the proportion and transmission risk of asymptomatic cases, and ongoing HCW concern about the adequacy of infection control procedures, understanding the true prevalence of COVID-19 infection among HCW is vital. Seroprevalence studies are useful to provide information on the proportion of people with past symptomatic or asymptomatic infection. We conducted a serology surveillance of anti-SARs-CoV-2 antibodies among asymptomatic HCW from designated COVID-19 healthcare facilities.

Methods

Study Setting and Participants

A cross-sectional study of HCW from Kuala Lumpur Hospital, Sungai Buloh Hospital and National Public Health Laboratory (NPHL) was conducted from April 13th to May 12th, 2020. These represent two of the three public hospitals which were designated to manage confirmed COVID-19 patients in Klang Valley, Malaysia; with NPHL being a referral laboratory for diagnostic reverse transcription polymerase chain reaction (RT-PCR) testing for suspected COVID-19 cases. Quota sampling was applied to ensure the recruited study samples were representative of the HCW involved in provision of care for patients directly (e.g. doctors, nurses and assistant medical officers), and indirectly (e.g. laboratory technologists,

pharmacists, drivers, clerks and so on). Participation in the study was voluntary. All participants had worked in the respective healthcare facility for at least 30 days prior study enrollment, and were asymptomatic at the point of study recruitment. HCW who were previously confirmed with COVID-19 infection or listed as “patient under investigation” for COVID-19 were excluded from this study. A “patient under investigation” has presented with acute respiratory infection (sudden onset of respiratory infection with at least one of shortness of breath, cough or sore throat) with or without fever; and had history of travel to or residence in a foreign country within 14 days prior to the onset of illness, close contact with a confirmed case of COVID-19 within 14 days before illness onset, or who had attended any event associated with a known COVID-19 outbreak. HCW with active symptoms upon study recruitment were excluded as they would have been seen by Occupational Safety and Health team for further management.

Data Collection Procedure

Each HCW who consented to participate in this study was given a self-administered questionnaire to capture sociodemographic characteristics, adherence with recommended infection prevention and control (IPC) measures, history of exposure to SARS-CoV-2 and clinical signs and symptoms in the past month prior to study entry. The questionnaire was modified from the protocol “Assessment of potential risk factors for 2019-novel coronavirus (2019-nCoV) infection among HCW in a healthcare setting”, published by WHO.^[13] For each participant, 5 mL of peripheral venous blood was collected for anti-SARS-CoV-2 antibody serology testing.

Definitions and Personal Protection Equipment (PPE) Guidelines

The history of close contact and prolonged face-to-face exposure with COVID-19 patients were captured in the questionnaire. Close contact was defined as contact between HCW and patient within one meter distance, with or without PPE. Prolonged face-to-face exposure was defined as face-to-face exposure within one meter distance which lasted at least 15 minutes.

According to local guidelines, use of PPE should be guided by risk assessment concerning anticipated contact during routine patient care. For inpatient facilities, HCW are required to wear full PPE which includes an N95 mask, an isolation gown, gloves, eye protection and a head cover when providing care to PUI or confirmed COVID-19 patients who are intubated, or those who are not intubated but unable to wear a surgical mask. For patients who can wear a surgical mask, HCW may opt for a surgical mask instead of an N95 mask. Full PPE should be worn when collecting oropharyngeal or nasopharyngeal swabs.^[14]

Anti-SARS-CoV-2 Antibodies Serological Test

Total circulating neutralizing antibodies against SARS-CoV-2 were tested by using the cPass SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) kit, according to the manufacturer's instructions (GenScript Biotech, USA).^[15] This test is based on antibody-mediated blockage of virus-host interaction between the receptor binding domain of the viral spike glycoprotein and the angiotensin converting enzyme-2 receptor protein. Its ability to detect total antibodies in COVID-19 patient sera with different level of anti-SARS-CoV-2 IgM/IgG was demonstrated in previous study.^[16] It has a sensitivity of 95%-100% and specificity of 100%, and is capable of distinguishing antibody responses from other known human coronaviruses.^[16] To confirm assay performance in our laboratory, the test was first performed on 20 serum samples from recovered patients with PCR-confirmed SARS-CoV-2 infection, and 20 archived serum samples from July 2019, well before the pandemic emerged.

Sample Size and Statistical Analysis

In view of the uncertainty about seroprevalence of antibodies against SARS-CoV-2 among the HCW, we used 50% as the prevalence to provide the most conservative sample size. Hence, with a 95% confidence interval, precision of 5% and 5% non-responses, we estimated we would need at least 383 HCW for this study.

The analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM, USA). Categorical variables were expressed in frequency and percentage. As for continuous variables, mean and standard deviation were used. Seroprevalence of anti-SARS-CoV-2 antibodies was calculated as a proportion, and confidence intervals were calculated using Wilson score interval.

Results

Baseline Characteristics

A total of 400 HCW from National Public Health Laboratory (N=38), Kuala Lumpur Hospital (N=201) and Sungai Buloh Hospital (N=161) were recruited for this study. The three departments with the most participants were the medical (32.3%), emergency (17.5%) and pathology departments (13.5%) (Supplementary 1). This cohort consisted of 154 (38.5%) nurses, 103 (25.8%) medical doctors, 47 (11.8%) laboratory technologists and other professions (Table 1). The mean age was 34.9 ± 7.8 years old, with female predominance (74.3%).

Table 1: Sociodemographics of Study Participants

Sociodemographic Characteristics		Result (N = 400)
Age in years, mean (\pm SD)		34.9 (7.8)
Sex, n (%)		
	Female	297 (74.3)
	Male	103 (25.8)
Ethnicity, n (%)		
	Malay	291 (72.8)
	Indian	62 (15.5)
	Chinese	29 (7.3)
	Others	18 (4.5)
Professional category, n (%)		
	Nurse	154 (38.5)
	Doctor	103 (25.8)
	Laboratory technologist	47 (11.8)
	Assistant medical officer	39 (9.8)
	Health attendant	32 (8.0)
	Others*	25 (6.3)

*Includes 7 drivers, 3 clerks, 3 assistant food technologists, 2 dentists, 2 physiotherapists, 2 speech therapists, 2 dental surgeon assistants, 1 entomologist, 1 research officer, 1 science officer and 1 pharmacist.

There were 135 (33.8%) HCW who reported respiratory symptoms between March 2020 and May 2020. The most common reported respiratory symptoms were sore throat (70.4%), followed by runny nose (43%), cough (40.7%) and breathlessness (8.1%). Only 12 reported fever ($\geq 38^{\circ}\text{C}$). All the symptoms had resolved upon study entry.

Exposure History to SARS-CoV-2

Overall, 115 of HCW claimed to have contact with known COVID-19 cases outside of their workplace in the month prior to study enrollment. Among them, 81 (70.4%) reported the contact as more than 14 days prior to study entry, while five (4.3%) did not specify how recent the contact occurred.

The majority (68.9%) of participants had potential exposure to SARS-CoV-2 at their workplace, within the month prior to study entry (Table 2). The source of exposure at the workplace included contact with COVID-19 patients and their bodily fluids, as well as contaminated objects and surfaces. A higher proportion of doctors and nurses were found to have various types of exposure compared to other professional categories, ranging from 45-65% and 51-76%, respectively. Laboratory technologists who were not involved in provision of care directly, had contact with patients' body fluids most of the time.

Table 2: Exposure History to SARS-CoV-2 among Healthcare Workers

History of Exposure to SARS-CoV-2 [‡]		Total	Professional Category, n (%)				
			Doctor	Nurse	Assistant Medical Officer	Laboratory Technologist	Others
Setting							
	Outside of workplace ^a	115 (28.8)	15 (14.6)	84 (54.5)	11 (28.2)	1 (2.1)	4 (7.0)
	At workplace ^b	275 (68.8)	72 (69.9)	130 (84.4)	14 (35.9)	39 (83.0)	20 (35.1)
Type of exposure at workplace							
	Close contact with infected patients	201 (50.3)	67 (65.0)	117 (76.0)	7 (17.9)	1 (2.1)	9 (15.8))
	Prolonged face-to-face exposure with infected patients	137 (34.3)	48 (46.6)	79 (51.3)	5 (12.8)	0 (0.0)	5 (8.8)
	Handled / contact with body fluids of infected patients	196 (49.0)	54 (52.4)	90 (58.4)	5 (12.8)	38 (80.9)	9 (15.8)
	Contact with contaminated objects	166 (41.5)	47 (45.6)	104 (67.5)	5 (12.8)	2 (4.3)	8 (14.0)
	Contact with contaminated surfaces	198 (49.5)	62 (60.2)	117 (76.0)	8 (20.5)	0 (0.0)	11 (19.3)

[‡]Exposure history in the past month upon study entry; ^a4 respondents did not answer this question; ^b1 respondent did not answer this question and 51 respondents were unsure if they had had any exposure in the workplace

Adherence to Infection Prevention and Control Measures

Generally, adherence of the study participants to infection prevention and control (IPC) measures was found to be satisfactory. High compliance with PPE usage (>97%) were reported by HCW who had prolonged face-to-face exposure with COVID-19 infected patients and contact with infected patients' body fluids, contaminated objects and surfaces (Table 3). Among them, the level of compliance towards hand hygiene was satisfactory (Table 4).

Table 3: Adherence of Healthcare Workers to Personal Protection Equipment Usage

Type of Exposure at Workplace	Total	Adherence to PPE*, n (%)
Prolonged face-to-face exposure with infected patients	137	134 (97.8)
Handled / contact with body fluids of infected patients	196	196 (100.0)
Contact with contaminated objects	166	163 (98.2)
Contact with contaminated surfaces	198	192 (97.0)
*PPE = Personal protection equipment		

Table 4: Level of Compliance with Hand Hygiene among Healthcare Workers

Hand Hygiene	Total	Level of Compliance, n (%)			
		Always	Most of the time	Occasionally	Rarely
After close contact with infected patients	201	187 (93.0)	12 (6.0)	1 (0.5)	1 (0.5)
After handling / contact with body fluids of infected patients	196	188 (95.9)	6 (3.1)	1 (0.5)	1 (0.5)
After contact with contaminated objects ^a	166	157 (95.2)	8 (4.8)	0 (0.0)	(0.0)
After contact with contaminated surfaces ^b	198	180 (90.9)	12 (6.1)	3 (1.5)	1 (0.5)
^a 1 respondent did not answer this question; ^b 2 respondents did not answer this question					

When the analysis was stratified by professional categories, nurses reported good compliance to hand washing across all components, ranging from 94% to 98% (Supplementary 2). Comparatively, doctors and assistant medical officers had poorer hand hygiene compliance (<90%) after direct contact with contaminated objects and surfaces. Among the seven assistant medical officers who had close contact with COVID-19 infected patients, one (14.3%) reported poorer hand hygiene compliance.

Seroprevalence of Total Antibodies Against SARS-CoV-2

The sVNT was found to detect antibodies in all 20 samples from convalescent COVID-19 cases, and did not detect antibodies in any of the 20 pre-pandemic samples. None of the study participants had anti-SARS-CoV-2 antibodies detected (95% confidence interval (CI): 0, 0.0095).

Discussion

In Malaysia, the massive SARS-CoV-2 transmission started since the end of February and peaked in mid-March to mid-April 2020 (Fig. 1).^[17] During this period, both medical resources and healthcare workers around the country were redirected to combat the disease. Healthcare staff from various hospitals of different departments were deployed to manage suspected and confirmed COVID-19 patients in designated healthcare facilities. This study was conducted during the post-peak period. Our finding of zero seroprevalence among asymptomatic HCW suggests that there is a low risk of asymptomatic COVID-19 infection in our healthcare setting. Another Malaysian study of 310 HCW at a non-COVID designated healthcare facility in Sarawak showed a seroprevalence rate of 4.5%, using a rapid antibody test kit, and its seroprevalence among the asymptomatic HCW was 2.7%. However, the authors reported that two study subjects with faint IgM positive results were actually false positives.^[18] The sVNT used in our study is likely to have a higher specific than a rapid antibody test kit, thus reducing the risk of false positives.^[19] Besides, we hypothesized HCW from designated COVID-19 hospitals would have a better perception of the potential risk of infection involved due to higher occupational exposure, which would lead to better adherence to IPC measures and reduce the transmission risk within the facility itself.

A similar study in China reported zero serological response among 420 HCW who were deployed to Wuhan during this pandemic.^[20] The study coupled with our finding and suggest that appropriate PPE

usage protects HCW from contracting the infection while caring for patients. However, studies conducted in other countries observed higher seroprevalence rates among HCWs. A study of 316 employees in a German tertiary hospital showed that 1.6% were seropositive for antibody against SARS-CoV-2.^[21] In Kyoto, seroprevalence of anti-SARS-CoV-2 antibody among HCW were reported to be as high as 5.4%.^[22] An even higher seropositivity rate was observed in an otolaryngology unit in Italy, where 5/58 (8.6%) HCW tested seropositive for IgG.^[23] In a tertiary hospital in Barcelona, 45 (9.3%) out of 578 HCW were seropositive for antibody against SARS-CoV-2.^[24] We postulate the discrepancy between our study and others could be multifactorial. First of all, Malaysia had a relatively low COVID-19 incidence compared to these countries during the study period. As of 17th June 2020, the incidence of COVID-19 in these countries were about 8 to 23 times higher than Malaysia, except Japan which had a lower incidence.^[25] HCW seroprevalence may correlate with wider community circulation.^[26, 27] Secondly, the variation of participants' eligibility criteria between the studies may also contribute to the discrepancy. Our study focused only on asymptomatic HCW, but studies from Italy and Spain included both symptomatic HCW and those who were infected with COVID-19 previously.^[23, 24] The testing method was not standardized across all studies. Any differences between the performances of each testing method can also affect the seroprevalence result.

In terms of the history of SARS-CoV-2 exposure, more than a quarter of participants claimed to have contact with known COVID-19 person outside of workplace. The participants may assume any contact with infected co-workers within hospital compound (i.e. pantry, praying area, etc.), but outside of ward as a form of contact beyond workplace. On the other hand, we observed a connection between professional categories and history of SARS-CoV-2 exposure at the workplace. This study found that doctors and nurses have more exposure to SARS-CoV-2 through all types of contact, from patients to respiratory droplets, objects and surfaces. This was in line with the nature of their work, which involves direct provision of care to patients. Laboratory technologists whose main job scope is to process patient specimens were found to have contact with patients' body fluids most of the time.

As of early May 2020, 359 HCW from Malaysian MOH had been diagnosed with COVID-19. Of these, 73% had acquired COVID-19 from the community, including from coworkers who were infected in the community, 19% had acquired the virus from patients, and the remaining 8% were still under investigation.^[28] Public fear of hospitals and HCW remains high. Many countries observed that patients have avoided seeking medical care for other health problems during this pandemic, thus resulting in late presentation with adverse outcomes.^[29-32] Stigmatization and abuse of HCW has also been reported.^[33-36] A study from Spain in March 2020 observed no difference in the COVID-19 infection rate of HCW by professional categories and risk of exposure in respective work departments. Other studies in Spain^[24], Italy^[23] and Netherlands^[37] also suggested the risk to a HCW of contracting COVID-19 infection in a healthcare facility is minimal. Although our study was unable to fully rule out additional risks of COVID-19 infection in a healthcare facility, zero seroprevalence of anti-SARS-CoV-2 antibody among asymptomatic HCW should reassure the public that the risk of being infected by a HCW is very low.

Numerous studies have stressed the critical importance of strict adherence to IPC measures to prevent patient-to-HCW infections,^[21, 23, 38-40] but few have investigated HCW compliance with IPC measures. Interestingly, Barrett et al. did not find any significant association between usage of PPE and COVID-19 infection rate among the HCW in United States.^[41] However, our findings of high adherence to infection control guidelines and zero seroprevalence of anti-SARS-CoV-2 antibody in HCWs reinforces the importance of strict infection control and PPE usage to reduce the risk of SARS-CoV-2 transmission within healthcare facilities.

SARS-CoV-2-specific IgM and IgG antibodies start to appear during the first week of illness, and peak between two to three weeks.^[42] After taking into consideration the timeline of seroconversion, serostatus of the HCW in this study most likely reflects COVID-19 transmission in Malaysia between middle of March and April 2020. This period corresponds to the second wave of COVID-19 outbreak in Malaysia following the mass religious event held in Kuala Lumpur^[43], with a doubling time of confirmed COVID-19 cases ranging from two to 110 days.^[44] Folgueira et al. found a close link between the driving forces of transmission in the community and HCW infection, which suggested that the rates of SARS-CoV-2 infection among HCW could be an indicator of transmission dynamics in the community.^[27] If we adopt a similar principle, this study shows that the proportion of the general public in Malaysia infected as of mid-March to April could be very low, and PPE for HCW have been effective in preventing nosocomial transmission. This also signifies Malaysia's successful public health efforts in combating this pandemic via extensive contact tracing and early admission of confirmed COVID-19 cases for isolation and close monitoring.

This study has several limitations. Firstly, this study was limited to selected healthcare facilities, so its findings may not be generalizable to HCW in other workplaces, especially non-COVID designated healthcare facilities. Secondly, we acknowledge the existence of selection bias. Participation in the study was voluntary and all participants were sampled by a non-probabilistic sampling method. HCW who refused to participate or were not sampled might be seropositive for antibody against SARS-CoV-2. As the study only recruited asymptomatic HCW, we could have potentially missed out symptomatic individuals with SARS-CoV-2 infection. Nevertheless, the literature shows that a substantial proportion of COVID-19 infected individuals can remain asymptomatic.^[45-49] Thirdly, detection of anti-SARS-CoV-2 antibody in a single sample may potentially miss any SARS-CoV-2 infected HCW yet to seroconvert, although the number is likely to be minimal.

Conclusion

This study suggested a low risk of asymptomatic COVID-19 infection in our healthcare setting, even at facilities designated to handle COVID-19 patients and specimens for suspected cases. The adequacy of PPE equipment and strict adherence to IPC measures offers considerable protection during contact with COVID-19 cases and should be ensured to prevent future nosocomial transmission.

Declarations

Ethics Approval and Consent to Participate

This study was registered under National Medical Research Register (NMRR-20-575-54382) and approved by the Medical Research Ethics Committee, Ministry of Health Malaysia. Written consent was taken from all study participants.

Consent for Publication

During the process of consent taking, all participants were informed regarding the need of publishing the results. All participants' personal information were anonymized during the write up, and none of them will be identified when the findings of this study are published.

Availability of Data and Materials

The dataset analyzed during the current study available from the corresponding author on reasonable request.

Competing Interest

None of the authors have any conflict of interest

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Authors Contribution

YLW, YLL, ICS, HMH, CLL, SKC, KP and PPG conceptualized the study. All authors participated in the design of the study. YLL, NAA, SLK, JFWL, RSK, RKS, AR and CHH involved in blood taking and data collection. YMC, YFC and ICS performed laboratory testing. NAA, SLK, JFWL, RSK, RKS, AR, CHH, YMC and YFC involved in data management. YLW and YLL performed statistical analysis. YLW, YLL, NAA, SLK, JFWL, RSK, RKS, AR and CHH involved in interpretation of data. YLW, YLL and YMC wrote the original draft. YFC, ICS, HMH, CLL, SKC, KP and PPG reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Figures

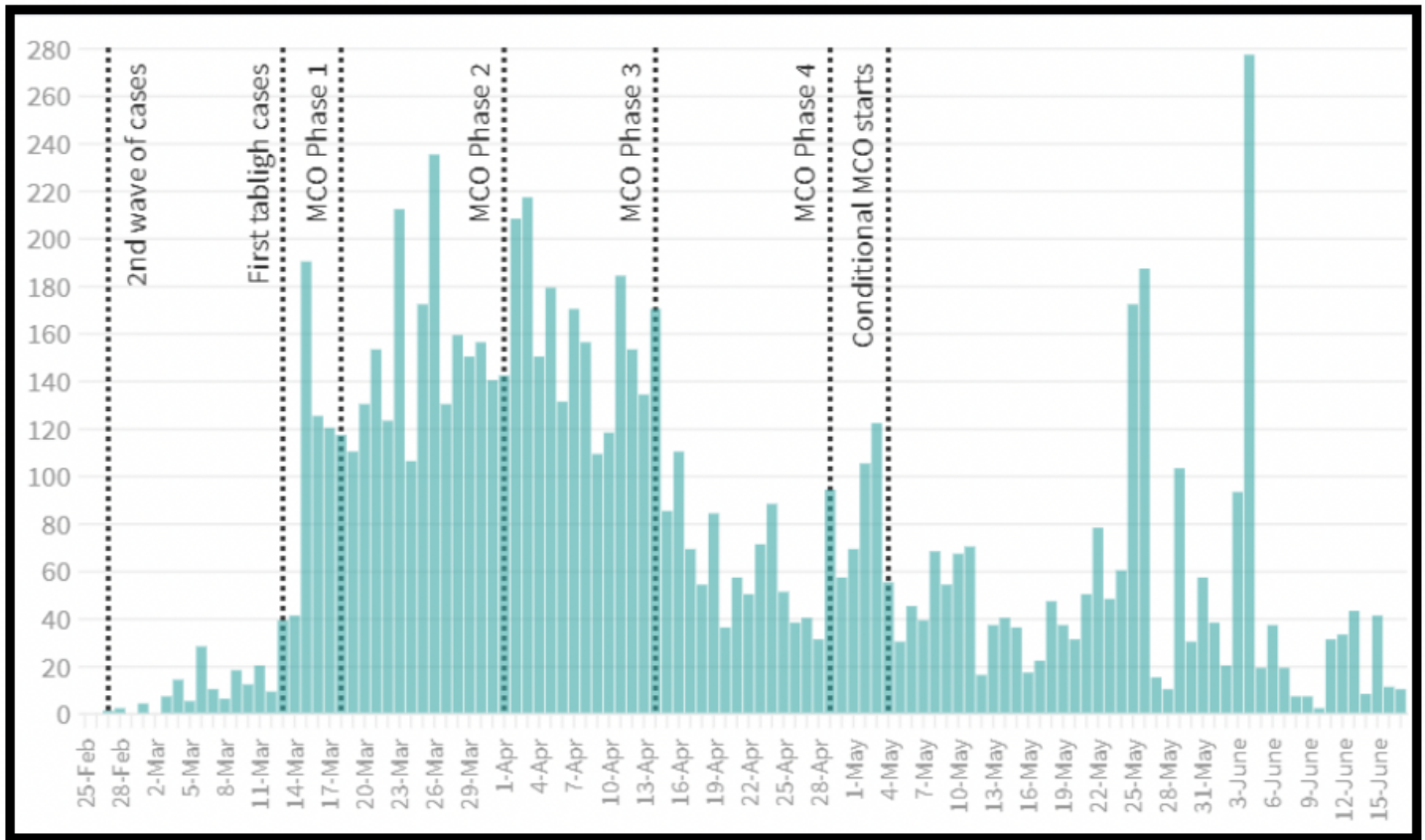


Figure 1

Number of New Cases in Malaysia. Adapted from Covid-19: current situation in Malaysia (updated daily), by D. Pfordten, 2020. Retrieved June 18, 2020, from <https://www.thestar.com.my/news/nation/2020/03/23/covid-19-current-situation-in-malaysia-updated-daily>. Copyright 2020 by The Star online.

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