



Review Article

Focused Review: Insight and Updates on COVID-19 from Progress in Microbes and Molecular Biology

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Abstract: COVID-19 Bulletins from various countries have been published as the pandemic hit. This focused review provides an overview of the published COVID-19 cases, including the first case detected in respective countries, preventive measures implemented, and vaccinations available for some countries, depending on the time it was written. The countries that will be covered in this review are the United Kingdom, Spain, Malaysia, Singapore, Thailand, India, Australia, South Africa, and Brunei. This review also discusses the variants of concern (VOCs) that emerged since the start of the pandemic, which include variants: Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), Gamma (P.1), and Omicron (B.1.1.529). COVID-19-associated gastrointestinal manifestations and mental health implications and the application of probiotics as a potential adjunct therapy to psychotropic medications will be addressed in this review. Additional information on COVID-19 will also be reviewed, such as risk factors affecting COVID-19 case fatality rate, positive impacts of public health measures, the cost-effectiveness of public health strategies on COVID-19 control, and the COVID-19 pandemic and diet.

Keywords: COVID-19; SARS-CoV-2; variants of concern (VOCs); vaccines; probiotics

1. Introduction

COVID-19 is a global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This is the third zoonotic human coronavirus that emerged within the past century following the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) ^[1-3]. Covid-19 started in early December 2019 when the news reported a pneumonia outbreak by an unknown aetiology in Hubei province of China. This incident consequently led to closing of

a seafood market on 1st January 2020, and countries with travel links to Wuhan were on high alert for travellers with respiratory diseases potentially linked to the pneumonia outbreak ^[4, 5]. On the 30th January 2020, SARS-CoV-2 was declared a public health emergency by the World Health Organization (WHO) ^[6]. The sequenced SARS-CoV-2 genome was postulated to be of bat origin ^[7], but the intermediate host is uncertain ^[6], and the transmission of COVID-19 had progressed to human-to-human contact. SARS-CoV-2 mainly affects the respiratory system, with the most common clinical symptoms of COVID-19 infection, including fever, cough, dyspnea, fatigue/myalgia, lymphopenia, and pneumonia accompanied by abnormal findings on chest computed tomography (CT) scans were reported in the initial cases from Wuhan, China. Other less common symptoms were sputum production, headache, haemoptysis, and diarrhoea ^[8].

By early April 2020, SARS-CoV-2 had spread worldwide, spawning several mutations in which spike protein amino acid D614G mutation was the dominant form of SARS-CoV-2 variant ^[9]. Simultaneous mutations on the spike proteins consequently led to the emergence of variants of concern (VOCs) which are more transmissible and have immune evasion potentials ^[10]. Although there was a rapid development of vaccines against COVID-19, their efficacy could be affected by the VOCs ^[10]. Despite COVID-19 vaccines being made available and the national vaccination program has been implemented worldwide, the issue on long COVID-19 emerged as the health of many individuals were affected by post-COVID-19 infections ^[1, 3]. As of February 2023, there had been a total of 671,852,527 cases and 6,845,598 deaths recorded worldwide ^[11]. This focused review will consolidate and integrate all pertinent information obtained from COVID-19 related articles published by PMMB, which include COVID-19 bulletins, genomic analysis of SARS-CoV-2 strains isolated in Malaysia, the variants of concern (VOCs) of COVID-19, the available COVID-19 vaccines, COVID-19 gastrointestinal manifestations and complications, and long-COVID-19.

2. The Onset of the COVID-19 Pandemic in Various Countries

2.1. United Kingdom (UK)

The outbreak started at the end of January 2020, and by the middle of March 2020, Europe became one of the countries with the highest number of reported cases and deaths globally, following China. Compared to other European countries excluding France, Italy, and Spain, the United Kingdom (UK) was hit hard in February due to the lack of isolation, quarantine and control tracing, resulting in surging COVID-19 cases as well as critically ill patients, consequently overwhelming the healthcare system. The first confirmed case was on 31st January 2020, involving two members of a family of Chinese nationals staying in a hotel in York ^[12]. These cases were identified without any clear case definition and were purely due to information about the spread of COVID-19 and clinical suspicion ^[13]. In terms of the actions in preparations for and response to COVID-19, the UK government faced heavy criticism. Although the UK government launched the “Contain-Delay-Mitigate-Research” on the 3rd March 2020, it had failed due to the lack of testing in the UK, which led the

government to shift to “Suppress-Shield-Treat-Palliate” [12, 14]. On 23rd March 2020, the UK was officially placed under lockdown [15].

2.2. Spain

Spain was once hit by the 1918 influenza pandemic, known as “Spanish flu”, caused by the H1N1 coronavirus [16–18]. In 2020, along with the rest of the world, Spain was again hit by a pandemic — COVID-19 and had the highest record of confirmed COVID-19 cases in Europe. The first COVID-19 case in Spain was reported on the 31st January 2020, which involved a German tourist in the Canary Islands who had contact with people who had travelled to China. Although the Spanish government took many counter-measures to reduce the spread of COVID-19, including closure of schools, flight controls and gatherings (>1000 people) at closed venues at hardest-hit hit areas, but by the second week of March, Spain has ranked second badly affected country among other European countries [18, 19]. With that, a 15-day national emergency was declared by the government using a royal decree (463/2020) starting 15th March [20]. It was extended to midnight of 12th April as cases continued to increase [21], and subsequent extension to stop the spread of the pandemic. Additionally, the Spanish government also incorporated artificial intelligence as an official channel to provide advice and enquiries about COVID-19 [22]. Furthermore, they also set up research grants to expedite drug and vaccine development [18, 23].

2.3. Malaysia

Malaysia is one of the countries with the highest number of recorded confirmed cases and deaths in Southeast Asia by early May 2020 [24]. The first COVID-19-positive case in Malaysia was reported on the 25th January 2020, and it was an imported case from Wuhan, China [25]. The first COVID-19-positive case involving a Malaysian was reported on the 3rd February 2020. This individual had just returned from a business meeting in Singapore, which was also attended by a delegation from China [26]. Two days later, his younger sister tested positive for COVID-19, making it the first local SARS-CoV-2 transmission case in Malaysia [27]. In March 2020, the COVID-19 cases surged as a result of a mass gathering linked to a religious event held in Sri Petaling, Kuala Lumpur, which involved approximately 16,000 participants with roughly 1,500 foreign participants from other Southeast Asian countries [27, 28]. Subsequently, the government implemented the closure of international borders and started taking strict preventive measures [27].

The initiative taken by the federal government to combat the spread of COVID-19 was the implementation of a movement control order (MCO) for 2 weeks, effective from 18th March 2020. It gradually extended to a total of 8 weeks until 12th May 2020, encompassing a total of 4 phases. Rules were strictest during phase 2 and phase 3 of MCO; for instance, travel distance was limited to within a 10 km radius from home, business hours and delivery times were limited to 8 a.m. – 8 p.m., and only one representative per household is allowed at a time to purchase essentials. Following MCO, midway through phase 4, a conditional MCO (CMCO) was introduced with eased restrictions followed through during phase 5 from

4th May 2020 up until 9th June 2020. Subsequently, a recovery MCO (RMCO) was introduced until 31st August 2020, restrictions were eased, and economic sectors resumed gradually in stages. Nonetheless, strict social distancing and self-hygiene are to be practised [29].

Notably, a standard operating procedure with the use of a mobile app known as “MySejahtera” introduced by the Ministry of Health (MOH) was implemented to monitor COVID-19 outbreaks. Additionally, wearing a face mask in public domains was made mandatory starting 1st August 2020 [29]. COVID-19 has affected the psychosocial aspects of Malaysians, especially during MCO phases, subsequently imposing a new normality [29]. Meanwhile, Ser et al. [24] analysed the phylogenetic evolution of SARS-CoV-2 strains from Malaysia to compare with worldwide SARS-CoV-2 genomes. Based on seven publicly available whole genome sequences of SARS-CoV-2 isolated from patients in Malaysia, they performed the single nucleotide variants (SNV) analysis to investigate the genotype changes during SARS-CoV-2 transmission in Malaysia [24]. The study concluded that the SARS-CoV-2 strains from Malaysia were highly similar to other strains derived from Asia, and more than one subtype was detected.

2.3.1. Vaccination in Malaysia (up until December 2021)

Malaysia started ordering vaccines developed by Sinovac (CoronaVac), Pfizer (Comirnaty), and AstraZeneca (Vaxzevria) since November 2020. In 2021 additional orders were placed to speed up Malaysia’s vaccination process so an 80% immunity can be achieved by February 2022 for its 32 million population. The first batch of Sinovac, Pfizer, and AstraZeneca vaccines arrived on the 27th February 2021, 21st February 2021, and 23rd April 2021 respectively, and more vaccine shipments arrived in the months following the first batch. The COVID-19 vaccines were distributed in three phases via the COVID-19 Immunization Program. The first phase was completed in April 2021 and prioritised front liners. On the other hand, the second phase was scheduled to complete in August 2021. It prioritised individuals in high-risk groups, including those with chronic disease and senior citizens. Lastly, phase 3 prioritised individuals >18 years old [27]. Later, the government approved the use and launched Janssen, CanSino, Sinopharm, and Moderna for the vaccination program. In December 2021, Malaysia has achieved over 60% vaccinated individuals and aims to have nearly 80% of the population fully vaccinated by 4th August 2022 [30].

2.4. Singapore

With a population of 5.7 million, Singapore has often been used as an exemplary for other countries in handling COVID-19 [31,32]. Its first COVID-19 case was an imported case that was reported on the 23rd January 2020. Not too long after that, in early February local transmission was reported resulting in nationwide alert. Consequently, the national assessment level, known as the Disease Outbreak Response System Condition (DORSCON) turned from “yellow” to “orange” [33]. Besides that, TraceTogether, a mobile phone-based tracing application developed by the Government Technology of Singapore (GovTech) was

launched in March 2020 to track interactions between individuals diagnosed with SARS-CoV-2 with their close contacts [33, 34]. However, a surge in cases in March 2020 led to the implementation of a “circuit breaker” with a stringent set of lockdown measures from 7th April 2020 to 1st June 2020 [33]. Additionally, a national cloud-based registration system called SafeEntry was introduced by the government for contact tracing purposes [33, 34]. Furthermore, in May 2021, locally developed breathalysers were provisionally approved as a screening method to detect COVID-19 [33]. In terms of the reopening of Singapore, after 1st June 2020 was phase 1 of reopening, followed by phase 2 on 17th June 2020 and later phase 3 on the 28th December 2020. The different phases of reopening were followed with rules that exhibited a slightly reduced level of strictness compared to the previous guidelines [33, 35]. The governance, transparency, good cooperation between the public and the local government, the enforcement of social responsibility, utilisation of technological advancement, and high vaccination rates have all contributed to the proper control of COVID-19 in Singapore [33].

2.4.1. Vaccination in Singapore (up until November 2021)

In March 2021, Singapore’s mass vaccination began with an estimated 800,000 individuals already receiving at least one dose of the COVID-19 vaccine and the program was set to roll out for younger age group [33, 36]. At that time, the COVID-19 vaccines authorised for use by the Health Sciences Authority in Singapore under the Pandemic Special Access Route (PSAR) were vaccines developed by Pfizer (Comirnaty) and Moderna [33]. In order to achieve herd immunity, on 18th May 2021, COVID-19 vaccine by Pfizer (Comirnaty) was then authorised for individuals 12 to 15 years of age [33, 37].

2.5. Thailand

The first COVID-19 case reported in Thailand was on the 13th January 2020. Prior to mid-March 2020, Thailand’s COVID-19 cases remained relatively low. Still, it surged due to a boxing event on the 6th March 2020 as the people did not comply with the government’s ban on large gatherings implemented just a few days earlier. Nonetheless, the government was able to keep COVID-19 under control for most of the year 2020 [38]. Given that the government took measures to control the spread of COVID-19, including comprehensive infection prevention and control measures, quarantine, travel restrictions, site closures, entry point screening, and contact tracking, nevertheless, the second wave still hit in mid-December 2020 [38]. The second wave of COVID-19 hit Thailand in December 2020 as COVID-19 cases surged up to 7,284 daily new cases due to the incident in a wholesale shrimp market [38, 39]. Later, the third wave in Thailand started in April 2021. The superspreading incidents were identified at entertainment establishments, karaoke lounges, bars, pubs, and gambling venues in different regions. The surge in cases during the third wave was greater than the first and second waves combined [38, 39]. This could be a result of eased restrictions to prevent further economic downturns. Furthermore, the government also permitted inter-provincial travel during the Thai New Year holiday in April 2021 [38].

Thailand aimed to achieve 70% herd immunity by the end of 2021, and in July 2021, it opened its borders for Phuket's tourism industry. Then starting 1st November 2021, it opened its borders to fully-vaccinated individuals. However, on the 6th December 2021, Thailand's Ministry of Public Health reported its first Omicron case, which involved a citizen from the United States (visiting from Spain). Despite the emergence of the new Omicron variant in Thailand, its plan for border reopening continues [38].

2.6. India

India was one of the countries badly affected by COVID-19 [40,41]. The first confirmed COVID-19 case was on the 30th January 2020, involving a patient returning to Kerala from Wuhan [41, 42]. On the 22nd March 2020, the Prime Minister of India announced "Janata curfew" for 14 hours. On the other hand, the Ministry of Health and Family Welfare took precautionary measures to ensure sufficient workers, personal protective equipment, isolation wards, medicines, and test kits. However, with the continuous surge of thousands of COVID-19 cases a day, a nationwide lockdown was implemented starting 25th March 2020, which was extended thrice until 31st May 2020 [41, 43-45]. Among some of the measures taken by the Indian government were improvements in the healthcare system and infrastructures, an increase in Rapid Antigen Test, an increase in labs and the launch of a mobile application called "Aarogya Setu" to aid in contact tracing and surveillance as well as a video consultation program called e-ICU. Later, on the 8th October 2020, "Jan Andolan" was launched to observe behaviours, including wearing of face mask, hand washing and 6-foot social distancing. Despite the decrease in daily new cases and deaths in November 2020, a sudden surge in cases occurred in February 2021, leading to the lockdown in New Delhi. On the 1st May 2021, India became the first country to record >400,000 new COVID-19 cases within 24 hours since the pandemic [41].

2.6.1. Vaccination in India (up until June 2021)

The national vaccination program in India begins on the 16th January 2021, and intends to vaccinate 300 million individuals by July 2021. The National COVID-19 Strategy was divided into 3 phases. Phase I targets healthcare and frontline workers, while phase II's registration and booking started on the 1st March 2021 and was meant for individuals ≥ 60 years old and individuals 45-69 years old with comorbidities, lastly, phase III's vaccination which begun after 1st May 2021 for individuals ≥ 18 years old [41, 46, 47]. At that time, the COVID-19 vaccines granted Emergency Use Authorization were COVISHIELD® (AstraZeneca's vaccine), manufactured by Serum Institute of India (SII) and COVAXIN, manufactured by ICMR in collaboration with Bharat Biotech International Limited (BBIL). Later in mid-April, Russia's Sputnik V was approved as the third COVID-19 vaccine in India [41, 46]. As of 1st May 2021, India had administered a total of 156,816,031 doses of COVID-19 vaccines [48].

2.7. Australia

The first COVID-19 positive case in Australia was reported in Melbourne at the end of January 2020 ^[49]. The first 12 COVID-19 positive cases in Australia were all acquired from China. The first local case was reported in Queensland, whereby the patient had contact with a Chinese tourist in the first week of February 2020 ^[50]. COVID-19 cases surged to over 4,000 by the end of March 2020 ^[51]. Then in late April 2020, Australia launched its contact tracing app, COVIDSafe, which is part of the three key requirements (Test, Trace, Responds) for easing restrictions ^[52]. In July 2020, due to a surge in cases in Victoria resulted in a lockdown implemented in Victoria, Mitchell Shire, and metropolitan Melbourne. Despite implementing mitigation measures by the Australian government, cases continued to increase in August 2020. Therefore, a nightly curfew was implanted together with compulsory face coverings in public, and both businesses and schools were told to close. In October 2020, as COVID-19 cases started to decrease, restrictions were eased, and finally, the 112-day lockdown in Victoria ended, and various sectors were allowed to reopen starting 28th October 2020 ^[51]. However, the lockdown was again implemented on the 19th November 2020 in response to cluster cases in South Australia. It was revoked on the 22nd November 2020, as the outbreak was successfully controlled, leading to eased restrictions ^[51, 53]. The COVID-19 cases in Australia showed a decreasing trend continuing into the year 2021, nevertheless, on the 30th November 2021 as announced by the local government, a total of six Omicron variants of the COVID-19 cases were reported in Australia. The government began implementing travel restrictions, home isolation requirements, and revised quarantine ^[51].

2.7.1. Vaccination in Australia (up until December 2021)

Vaccinations started in late February 2021 and priority was given to frontline healthcare workers, quarantined and border workers, aged and disability care residents, and staff with significantly higher risk of COVID-19. After that, the vaccines were distributed to the mass public. Vaccines approved for use in Australia are Comirnaty (Pfizer), Vaxzevria (AstraZeneca), and SpikeVax (Moderna). By June 2021, >6.5 million vaccine doses had been administered in Australia, but in July 2021, COVID-19 cases started increasing. There are four phases in the national plan to transition Australia's COVID-19 response. On 1st July 2021, Australia entered phase one, known as "Vaccinate, prepare, and pilot" which aimed to vaccinate as many individuals as possible and implement early, stringent, and short lockdowns in outbreak-occurring areas. On 20th October 2021, the phase two vaccination transition phase began. On 3rd December, 87.9% of the population was fully vaccinated. Hence, it has achieved the target (80%) of fully vaccinated individuals, which was part of phase three, the vaccination consolidation phase. Lastly, phase four, the post-vaccination phase was at that time put on hold due to the emergence of the Omicron variant. Additionally, the only approved and preferred COVID-19 booster dose in Australia at that time was Comirnaty ^[51].

2.8. South Africa

The South African government had prepared to face SARS-CoV-2 even before the country's first COVID-19 case was detected by having planned an overlapping eight-stage program^[54]. The first stage of the national COVID-19 response program focuses on COVID-19 preparation which includes surveillance, education on SARS-CoV-2 and methods to prevent the spread^[55]. The first COVID-19 case in South Africa involved a citizen who returned from Italy on 1st March 2020 and was diagnosed on 5th March 2020^[54,56]. Ten days after the first COVID-19 case was diagnosed, stage two of the program begins, and its focus is on COVID-19's primary prevention. The government announced a national state of disaster, promoting social distancing and hand hygiene, prohibiting international travel, closing schools, and restricting gatherings^[54, 55]. Nonetheless, COVID-19 cases continue surging. The first local transmission case documented in South Africa was on the 18th March 2020; by the end of March, COVID-19 had spread to all nine provinces in South Africa^[55, 57]. Then stage three of the national COVID-19 response program was a strict level five (L5) national lockdown that took place to control the spread of COVID-19^[55, 58]. In April 2020, stage four was commenced, and it involved active case-finding through contact tracing. However, in May 2020, the lockdown measures were eased to level four then in June 2020, it was further eased to level three^[55]. Later in July 2020, the COVID-19 cases reached the peak and stage five to eight of the program commenced as hotspots were rapidly identified and medical care were provided promptly. In August 2020, the curve flattened, allowing the lockdown measures to drop to level two, but the national state of disaster was extended for another month^[55]. Additionally, in the same month, the COVID Alert SA app was launched to trace COVID-19 positive individuals^[55, 59]. As COVID-19 in South Africa stabilised, the restrictions were further eased to level one^[55, 60, 61].

The second wave of COVID-19 occurred at the end of the year 2020, which caused a surge in cases, and subsequently, the hotspots for SARS-CoV-2 were put under stricter restrictions^[54, 55]. Furthermore, the VOC-Beta variant (B.1.351) was detected in South Africa, which resulted in >1 million COVID-19 cases recorded on the 27th December 2020. Hence, a partial level three lockdown was implemented for two weeks^[55, 62]. Then in May 2021, the detection of VOC- Alpha (B.1.1.7) and Delta (B.1.617.2) in South Africa led to a surge in COVID-19 cases, resulting in the third wave of COVID-19 and consequently, heightened lockdown restrictions at level two starting 31st May 2021^[55]. However, in June 2021, the lockdown restrictions went up to level four, and as the cases decreases, it went back down to level one in October 2021. Although in December 2021, the VOC-Omicron (B.1.1529) resulted in the fourth wave in South Africa, it subsided quickly by the end of December 2021^[55].

2.8.1. Vaccinations in South Africa (up until February 2022)

The first vaccines delivered to South Africa were Pfizer (Comirnaty), and by the end of May 2021, 960,000 individuals had received one dose of the vaccine^[63]. Up until February

2022, only two vaccines were used in their national vaccination program, namely Pfizer (Comirnaty) and Janssen (Johnson & Johnson) [55].

2.9. Brunei

On the 9th March 2020, Brunei reported its first COVID-19 case involving a citizen returning from a Tablighi Jama'at in Kuala Lumpur, Malaysia, on 3rd March 2020. By the first week of April, 71 COVID-19 cases were reported and acquired in Malaysia [64, 65]. Hence, the start of the first wave of COVID-19 in Brunei. On the 16th May 2020, the government implemented a four-stage de-escalation plan to control the outbreak. The guidelines laid down four operational readiness levels with specific restrictions: Level 0- very high restriction (closure), Level 1- high restriction, Level 2-(medium restriction), Level 3- (low restriction), Level 4- normal operation (pre-normal) [64, 66, 67]. For most of 2020, the COVID-19 outbreak was well-controlled in Brunei until the arrival of the Delta variant [64, 68, 69].

The second wave of COVID-19 in Brunei started on the 7th August 2021, involving a local transmission of the COVID-19 Delta variant. As the Delta variant is a VOC with a high transmission rate, it escalated COVID-19 cases, thereby overwhelming Brunei's healthcare system [70]. With the increasing COVID-19 cases and vaccine shortage, starting 9th August 2021, Brunei went into a two-month partial lockdown [64, 71]. Restrictions imposed include "Operasi Pulih", closure of several non-essential businesses and public facilities, work from home policies, restrictions on gathering, suspension of on-site activities for educational institutions, and dine-in were prohibited [64]. These measures successfully flattened the curve, but they had mental health impact on the people [72, 73]. Thus, there is a need for a plan to ensure a safe transition and stable situation with minimal disruption to the daily activities of the community. On 25th October 2021, the government announced a National COVID-19 Recovery Plan Framework consisting of the containment, preparation, transition, and endemic phases. The commencement of each stage depends on the vaccination coverage status and critical cases. The curve was successfully flattened in November, and on December 2021, the early endemic phase began [64, 71].

However, in late December 2021, the emergence of Omicron variant in Brunei marked the third wave of COVID-19, which peaked in March 2022 [64, 74]. On 1st June 2022, Brunei entered its endemic phase. As of February 2023, Brunei had entered the "new normal" phase of its de-escalation plan [64, 75]. Brunei effectively controlled the COVID-19 pandemic with the help of the whole nation. Like other countries, Brunei's Ministry of Health launched a mobile app in May 2020 called "BruHealth" focused on contact tracing [76]. Then another app called "PremiseScan" was launched to further ensure better accessibility of "BruHealth" by recording customers' entry and exit of business premises [64, 77].

2.9.1. Vaccination in Brunei (up until February 2023)

Brunei's national vaccination program commenced on the 3rd April 2021, in three phases. The first phase was targeted towards frontliners, senior citizens, and students studying abroad; the second phase targeted adults with comorbidities, child care centre staffs, and

teachers; and lastly, the third phase targeted individuals ≥ 18 years old, which began 5th July 2021. To achieve herd immunity, five COVID-19 vaccines have been authorised by the Brunei Darussalam Medicines Control Authority (BDMCA) under Emergency Use Authorisation, namely Pfizer (Comirnaty), Vaxzevria (AstraZeneca), Spike Vax (Moderna), Covilo (Sinopharm), and Janssen (Johnson and Johnson) [64, 78]. On the 19th October 2021, vaccination for children aged 12 to 17 was set to roll out [79]. Then on 3rd April 2022, kids 5-11 years old were administered the first dose of the Pfizer vaccine [80].

Around November 2021, the first booster doses were administered to frontliners, followed by senior citizens. For those who are 12-17 years old, they can receive their booster dose starting April 2022. Later in June 2022, the second booster was offered to healthcare workers and frontliners with high-risk exposure, elderly ≥ 80 years old, adults ≥ 60 years old with chronic disease, and immunocompromised individuals ≥ 18 years old. Lastly, the fourth dose is voluntary and given only to eligible individuals. The government encourages people to receive a booster dose even though it is not mandatory [81-83]. Recently, in late November 2022, the BDMCA authorised and rolled out a bivalent vaccine from Moderna, and soon another bivalent vaccine from Pfizer will be expected to be available in early 2023 [84, 85]. As of 11th November 2022, 78.9% of Brunei's population had received a third COVID-19 vaccine dose [64].

3. Variants of Concern (VOCs)

Variants of concern (VOCs) are variants with evolutionary advantages which are favoured [10, 86, 87]. Since the start of the COVID-19 pandemic, there have been a total of five VOCs since the COVID-19 pandemic started which are variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529). However, it is to note that as of writing, the only VOC is the Omicron variant. These VOCs have similarities in terms of the presence of multiple mutations on their spike protein, contributing to their increased transmissibility and immune evasion potentials. Therefore, this leads to increased virulence. This review will briefly discuss the VOCs in the following sections [10, 30, 88, 89].

3.1. Alpha (B.1.1.7)

The alpha variant was first detected in England on the 20th September 2020, and by February 2021, it had accounted for almost 95 % of England's COVID-19 transmission [90]. The alpha variant has higher transmissibility (43–82% more transmissible), higher viral load, longer duration of infection, higher hospitalisation rate, and higher mortality rate [10, 90-95]. In terms of vaccine efficacy, the impact from the susceptibility of neutralising antibody is minimal, and reinfection was found to be not higher than other earlier strains [10, 96-98]. There are nine mutations on the spike protein (two deletions and seven amino acid substitutions): $\Delta 69-70$ HV and $\Delta 144$ Y deletions; N501Y, D614G, A570D, P681H, T716I, S982A, and D1118H. Additionally, E484K, S494P, and K1191N may be present in some sequences. Nonetheless, mutations N501Y, P681H, A570D, D614G, S982A, $\Delta 144$ Y, and $\Delta 69-70$ HV deletions have been associated with this variant's increase in binding affinity, cell entry,

infectivity, and neutralisation. Details about the mutation affecting the different characteristics of the alpha variant have been discussed by Thye et al. ^[10].

3.2. Beta (B.1.351)

The emergence of the Beta variant is likely from South Africa's first COVID-19 wave that occurred in Nelson Mandela Bay metropolitan area in the Eastern Cape province in October 2020. B.1.351 has higher transmissibility, viral load, reinfection, vaccine escape, hospitalisation rate, and mortality than the progenitor strain ^[10, 94, 99-102]. The beta variant seemed to have a lower vaccine efficacy rate and a higher risk of reinfection ^[10, 101, 103-106]. The Beta variant has three amino acid deletions in the spike protein and eighteen amino acid mutations (seven in the spike protein). Compared to the progenitor strain, the beta variant has ten changes: 3 receptor binding domain (RBD) mutations at E484K, K417N, N501Y; replacements of A701V, D215G, D80A; D614G spike mutation; amino acid L242–244 deletions and R246I and L18F ^[10, 99, 100]. In this variant, mutations that are of great concern are at RBD: E484K, K417N, N501Y and have been associated with increased binding affinity, cell entry, infectivity, resistance to neutralisation, and immune evasion ability that have been discussed in detail by Thye et al. ^[10, 99].

3.3. Delta (B.1.617.2)

Delta variant was first detected in India in December 2020. Based on the articles by Thye et al., at that time of writing, this variant was relatively new, and information was limited ^[10, 107]. Nonetheless, this variant appeared to have higher transmissibility (60% more than the alpha variant), higher risk of hospitalisation and potential to escape the vaccine ^[10, 107, 108]. The delta variant has been reported to possess RBD mutations: D614G, L452R, T19R, T478K, P681R, R158G, G142D, A222V substitution along with 156–157 deletion in the NTD, S2 substitution in D950N ^[10, 107, 109]. However, the mutation G142D is found only in some delta strains ^[10]. Mutations of particular interest, including L452R and P681R, have been further discussed by Thye et al. by associating them with cell infectivity, binding affinity, immune evasion, and resistance to neutralisation ^[10, 107].

3.4. Gamma (P.1)

The gamma variant was first detected on the 6th December 2020 in Manaus Amazonas state, northern Brazil. Its emergence marks the start of Manaus's second COVID-19 wave, and in January 2021, it was associated with 87% of all infections ^[10, 110]. This variant consisted of mutations K417T, E484K, N501Y in the RBD; L18F, T20N, P26S, D138Y, R190S in the NTD; D614G and H655Y at C terminus in S1; and V1176F and T1027I in S2. This variant potentially has higher transmissibility and result in increased hospitalisation. Additionally, this variant seems less resistant than the beta variant to vaccine-induced or naturally-acquired antibody responses ^[10, 111]. More information on the associations of key mutations N501Y, E484K, and K417T with this variant's characteristics have been discussed by Thye et al. ^[10].

3.5. Omicron (B.1.1.529)

Omicron is the latest addition and the only mutant of SARS-CoV-2 that remained a VOC. This variant was detected in Botswana on the 11th November 2021, but it was reported to the WHO in South Africa on the 24th November 2021. Later, B.1.1.529 was designated as a VOC named Omicron by the WHO on the 26th November 2021 [88, 112]. There have been three hypotheses on the origin of Omicron: it could be circulated and evolved from hidden populations, evolved from immunocompromised patients or originated from animal reservoirs [30, 88, 113]. Compared to previous VOCs, Omicron had the most mutations, with over fifty mutations [114]. The mutations include A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969 K, L981F [115]. Importantly, fifteen out of the thirty over mutations occur on the RBD, which has significant implications as the RBD is the key binding site for SARS-CoV-2 entry and a key target for neutralising antibodies [116]. Additionally, Thye et al. [88] showed that compared to previous VOCs, the Omicron variant seemed to have lower severity, lower hospital admission but higher transmissibility and infectivity, and have immune evasion potential.

4. Vaccines and Their Concerns

After the emergence of COVID-19, vaccines were developed rapidly. The different types of vaccines include inactivated viral vaccines, mRNA vaccines, recombinant viral vector vaccines, and protein subunit vaccines. As of January 2021, a few vaccines have been authorised for emergency use and have been administered to countries worldwide. Review by Loo et al. [117] (published March 2021) provided an overview into the vaccines approved for emergency use, vaccine candidates in Phase III trial (as of 30th January 2021), the different types of vaccines and their respective advantages and disadvantages, and strategies used to develop these vaccines.

Nonetheless, there have been concerns regarding COVID-19 vaccines [118, 119]. Pregnant women are among the most vulnerable populations at risk of being infected with severe COVID-19 and consequently experiencing poor pregnancy and neonatal outcomes. Vaccination appeared to be the safest way of stopping the pandemic, and there is reassuring evidence supporting vaccination in pregnant women, but data is limited. Hence, Kwan et al. [118] reviewed the latest evidence on COVID-19 vaccine's safety, immunogenicity, and reactogenicity of these vaccines in pregnant women, the recommendations and guidelines provided by the public health authorities in Southeast Asia countries. They found that most countries in Southeast Asia generally recommend vaccination in pregnant women [118]. On the other hand, a scoping review by Vairavan et al. [119] addresses the concern of autoimmune patients by exploring the safety, outcomes, and effects of COVID-19 vaccines in autoimmune patients, mainly focusing on autoimmune diseases: myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. In conclusion, most autoimmune patients presented with good antibody response to vaccination, particularly after the second dose.

Furthermore, the overall risk of flares and development of severe side effects was low after immunisation ^[119].

The development of booster vaccines was mainly due to the waning protection of COVID-19 vaccines, the reduced protection against COVID-19's VOCs and the inadequate protection of the primary vaccination for some risk groups. Thus, the aim of booster vaccines is to improve and prolong the protection against COVID-19. The review by Thye et al. ^[120] discussed the various booster vaccines being authorised and administered in different countries, the eligibility criteria for the different booster vaccines, and the extent of protection it provides in several countries: UK, United States (US), Israel, Singapore, and Chile.

5. COVID-19 Manifestations

Although the common symptoms upon contracting COVID-19 are respiratory symptoms and fever, it can also involve the gastrointestinal tract, presenting symptoms such as diarrhoea, abdominal pain, nausea and/or vomiting^[121]. Many studies reported the presence of SARS-CoV-2 RNA in stool samples of COVID-19 infected patients ^[122-126]. Besides, the angiotensin-converting enzyme-2 (ACE2) is highly expressed in the gastrointestinal epithelial cells, especially the ileum, duodenum, jejunum, caecum, and colon ^[127]. A review by Thye et al. ^[121] showed the prevalence of SARS-CoV-2 RNA in COVID-19 patients' stool samples and the gastrointestinal manifestations upon being infected with SARS-CoV-2. Additionally, Thye et al. ^[121] also discussed the possible pathophysiology of COVID-19 associated gastrointestinal manifestations, which includes associations with the human-host receptor ACE-2, the intestinal microflora, the use of antibiotics and antiviral medicines, and the direct and indirect inflammatory response as SARS-CoV-2 damages the digestive system. All in all, SARS-CoV-2 could infect and replicate in the gastrointestinal tract, suggesting possible SARS-CoV-2 tissue tropism in the intestinal cells, and it possibly transmits via the faecal-oral route in addition to droplet transmission ^[121].

Another concern would be the issue of long covid-19. Many studies have shown COVID-19 survivors experienced increased mental health consequences than the general population, and some of the mental health implications include depression, anxiety, and post-traumatic stress disorder (PTSD) as presented in reviews by Thye et al ^[1, 3]. The cause may be directly related to the infection via direct and indirect mechanisms, but the underlying aetiology is complex and multifactorial, involving biological, environmental, and psychological factors. Risk factors and the prevalence rate seemed to vary across different studies, however, having a history of mental disorders and the female gender seems to be more consistent risk factors. On the other hand, the possible mechanisms by which SARS-CoV-2 enters the brain may affect the central nervous system, resulting in these mental health implications include via the ACE-2 receptors and through the implications of immune inflammatory signaling on neuropsychiatric disorders ^[1, 3]. Several reviews published in PMMB also discussed using probiotics as a potential adjunct treatment in addition to conventional psychotropic medication to alleviate and prevent COVID-19 mental health implications ^[1, 3, 128, 129].

6. Public Health Related

Various articles associating COVID-19 with public health have also been published in PMMB. A review by Goh et al. ^[130] examined the relationship between various prevailing population-based risk factors in comparison with the mortality rate and fatality rate (CFR) of COVID-19. They found that countries having more older people aged >65 years old have a high risk of CFR due to COVID-19. Additionally, differences in gender and smoking prevalence did not prove a significant association with COVID-19 mortality rate and CFR ^[130].

COVID-19 pandemic has impacted various aspects, including the development of mobile applications to control the pandemic, the implementation of public health measures and public health strategies, and even promoted diet change. A review by Loy et al. ^[131] assessed the features and content of COVID-19 mobile applications accessible in the Apple Appstore. They found that the most popular mobile applications provided knowledge and guidance, contact tracing and hotspot information, and 50% of these evaluated mobile applications were maintained by respective countries' health authorities, allowing the government to disseminate information to the public and collect data for COVID-19 control ^[131].

In a review by Hoo et al. ^[132], the author discussed the unforeseen positive impacts on healthcare as a result of the implementation of public health measures. The positive impacts includes positive environmental effects; increased health consciousness; decreased hospital admissions; more individuals quitting smoking; in some ways, mental health, sexual health, and family relationship were positively impacted; and the global movement towards healthcare innovation and technology development ^[132]. Another systematic review by Rayanakorn et al. ^[133] provided a critical summary of complete economic evaluations to inform decisions regarding adopting public health interventions. They concluded that tight and timely implementation of public health interventions is vital to flatten the COVID-19 curve and that stringency, enforcement, timing, and adherence to interventions are key to the cost-effectiveness of epidemiological control measures. Additionally, compared to non-selective widescale measures or single intervention, the application of a combination approach is more cost-effective. Furthermore, the epidemiological characteristics of the virus, the healthcare capacity, and the local context need to be considered in the adoption of public health interventions ^[133].

Lastly, a review by Loh et al. ^[134] suggested that plant-based diets gained tremendous popularity globally during the COVID-19 pandemic. The drop in meat and seafood sales could be associated with a few reasons; namely, the fear of meat contamination by SARS-CoV-2, rise in price, and ethical reasons. Furthermore, people believe that a plant-based diet can improve immunity, have more health benefits, and be more cost-effective than other diets. During the pandemic, there were more vegan venues and eateries with vegan options. Their review concluded that there is a need for changes regarding the use of livestock and

wild animals to prevent future zoonotic pandemics. Hence, promoting plant-based diets while decreasing animal-based diets are steps needed to prevent future zoonotic pandemics ^[134].

7. Conclusions

PMMB had published many articles on COVID-19, such as bulletins from various countries, emergence of VOCs, COVID-19 vaccines, COVID-19 related public health measures and even genomic analysis of isolated SARS-CoV-2 strain from Malaysia. This focused review compiles all COVID-19 articles published by PMMB, providing a general overview of these articles. Based on the various bulletins, it is clear that the cooperation between the government and people is essential to curb the COVID-19 pandemic successfully and that the development of mobile applications for contact tracing plays a significant role in stopping the spread of the virus. Key strategies used include the national vaccination program, contact tracing applications, and public health measures such as social distancing, wearing of face masks, hand hygiene etc. Despite the pandemic, there are positive impacts from public health measures. In terms of vaccination, even though protection from primary vaccination may be waning, booster vaccines are available, and vaccination remains a key component in curbing the COVID-19 pandemic. Moreover, it is clear that SARS-CoV-2 affects not just the respiratory system but could also affect the gastrointestinal system and have implications on mental health, in which probiotics have shown to be a potential adjunct treatment in addition to psychotropic medications.

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