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Ivermectin for the Treatment of COVID-19 Infection

A Technical Report by

The Drug Expert Task Force for Ivermectin (DETF-ivermectin)
Pharmaceutical Services Programme, Ministry of Health Malaysia

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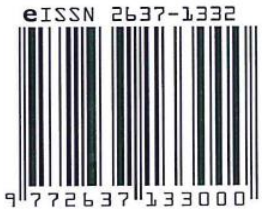
December 2022



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1. Background

In Malaysia, ivermectin is registered for veterinary use, while the use of ivermectin in human is only approved for clinical trial purpose in a proper setting under the close supervision of medical practitioners. During the COVID-19 pandemic, however, ivermectin emerged as an option for COVID-19 treatment in many countries despite inconclusive scientific evidence. Cases involving the unregistered use of ivermectin for the treatment of COVID-19 in Malaysia, with or without the supervision of healthcare providers, were being reported. Therefore, the Drug Expert Task Force for Ivermectin (DETF-ivermectin) was established by the Pharmaceutical Services Programme, Ministry of Health Malaysia in August 2021 to provide recommendations to the policy makers regarding the use of ivermectin for COVID-19 treatment. Members of this task force were selected from various divisions in the Pharmaceutical Services Programme headquarters, Ministry of Health facilities and National Pharmaceutical Regulatory Agency (NPRA). This technical report was prepared by the DETF-ivermectin to summarise the evidence related to ivermectin's use in COVID-19 (literature search as of July 2022).

2. General information

2.1 What is Ivermectin

Ivermectin (IVM) was developed by Merck in the 1970s with its proprietary name Stromectol®. Ivermectin is derived from the avermectins, a class of highly active broad-spectrum anti-parasitic agents isolated from the fermentation products of Streptomyces avermitilis (1).

Ivermectin is a well-known medicine that is approved as an anti-parasitic by the US Food and Drug Administration (USFDA) as well as World Health Organization (WHO). It is included in the WHO list of essential medicines and is considered a very safe drug with few side effects when it is taken properly.

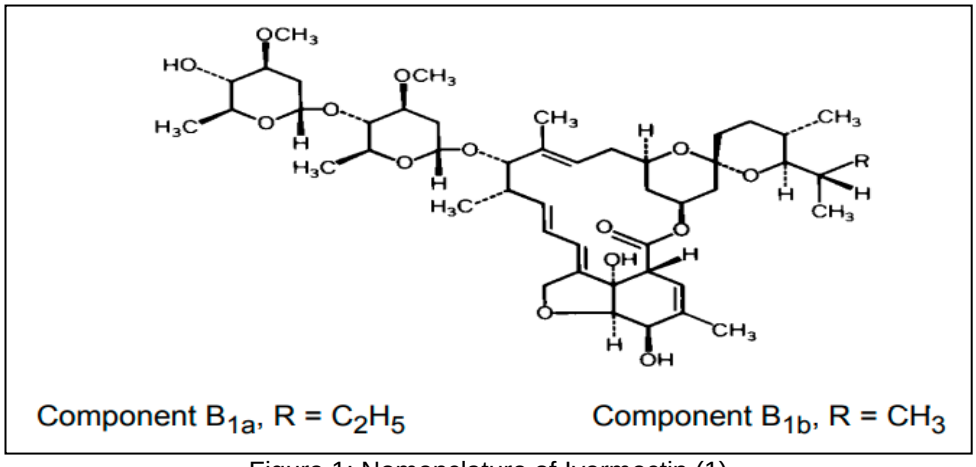

Figure 1: Nomenclature of Ivermectin (1)

2.2 Pharmacokinetic Profiles

- Plasma concentrations are approximately proportional to the dose given.
- High fat meal will increase the bioavailability of ivermectin.
- Does not readily cross the blood-brain barrier in humans.
- Plasma half-life of ivermectin is approximately 18 hours post oral ingestion.
- Metabolised in the liver.
- Excreted almost exclusively in the faeces over an estimated 12 days.
- Less than 1% of the administered dose is excreted in the urine.

2.3 Mechanism of Action

Selectively binds with high affinity to the glutamate-gated chloride ion channels in the invertebrate muscle and nerve cells of the microfilaria. This binding causes increased permeability of the cell membrane to chloride ions and resulting in hyperpolarisation of the cell which will lead to paralysis and death of the parasite.

2.4 Indications Approved by National Regulatory Authorities

Globally, ivermectin is authorised mainly to be used as an antiparasitic and dermatological agent as summarised in Table 1. World Health Organization (WHO) approved indication for ivermectin also only in tablet form for oral intestinal antihelminthics, antifilarials and ectoparasitic infections as listed in their essential medicines list (2). Although several countries have approved ivermectin for human use, Malaysia approved this drug only for animal use (3). Zimbabwe is also another country that approved ivermectin for animal use only (4).

2.5 Pregnancy & Teratogenicity

Ivermectin has shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1, and 4.5 times the maximum recommended human dose:

- Cleft palate; clubbed forepaws.

There are no adequate and well-controlled studies on pregnant women. Therefore, ivermectin should not be used during pregnancy since the safety in pregnancy has not been established.

2.6 Usage among Breastfeeding Mothers

Ivermectin is found to be excreted in human milk in low concentrations. Treatment of mothers who intend to breastfeed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the new-borns.

Table1: List of ivermectin indications approved for human use by respective National Regulatory Authorities

	Authority	Dosage form	Approved indication	Reference
1	US FDA	Oral (Tablet)	• Strongyloidiasis • Onchocerciasis	(5)**
		Topical (Cream)	Topical treatment of the inflammatory lesion of rosacea	
		Topical (Lotion)	Topical treatment of head lice infestations in patients 6 months or older	
2	UK MHRA	Topical (Cream)	Used on the skin to treat pimples and spots found with rosacea / papulopustular rosacea in adult	(6)**
3	Australia TGA	Oral (Tablet)	• Onchocerciasis • Intestinal strongyloidiasis (anguillulosis) • Crusted scabies in conjunction with topical therapy • Human sarcoptic scabies when prior topical treatment has failed or is contraindicated	(7)**
		Topical (Cream)	Topical treatment of inflammatory lesions of rosacea (papulo-pustular)	
4	India CDSCO	Oral (Tablet)	For the treatment of intestinal helminthes and suppression of microfilaraemia especially with bancrofti infections	(8)**
5	China NMPA	Oral (Tablet)	No further information on the approved product	(9)**
6	France ANSM	Oral (Tablet)	• Intestinal strongyloidiasis (strongyloidiasis) • Microfilaria due to lymphatic filariasis. • Skin mites (mange) / scabies	(10)**
		Topical (Cream)	To treat pimples (papules and pustules) associated with rosacea	
7	Slovakia SIDC	Oral (Tablet)	• Gastrointestinal strongyloidiasis • Microfilaraemia especially with bancrofti infections • Human sarcoptic scabies when prior topical treatment has failed or is contraindicated	(11)**
8	Indonesia BPOM	Oral (Tablet)	• Onchocerciasis • Intestinal strongyloidiasis	(12)*
9	Thailand	Oral (Tablet)	• Strongyloidiasis • Onchocerciasis	(13)**
		Topical	• Rosacea • Head pediculosis	
10	Philippines FDA	Topical	• Rosacea • Head Lice	(14)**
11	Peru DIGEMID	Oral (Tablet)	• Strongyloidiasis • Onchocerciasis	(15)**
		Topical	• Rosacea (papulopustular)	

* *Latest accessed on 11 January 2022*

** *Latest accessed on 11 January 2022 (using search term "IVERMECTIN")*

2.7 Adverse Drug Reactions (ADR)

- All indications:
  - Hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, hepatitis, elevation of liver enzymes, and elevation of bilirubin.
- Strongyloidiasis:
  - Body as a Whole: asthenia/fatigue (0.9%), abdominal pain (0.9%).
  - Gastrointestinal: anorexia (0.9%), constipation (0.9%), diarrhoea (1.8%), nausea (1.8%), vomiting (0.9%).
  - Nervous System/Psychiatric: dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), tremor (0.9%).
  - Skin: pruritus (2.8%), rash (0.9%), and urticaria (0.9%).
  - Elevation in ALT and/or AST (2%), decrease in leukocyte count (3%).
- Onchocerciasis:
  - Conjunctival haemorrhage.
  - Arthralgia/synovitis (9.3%).
  - Axillary lymph node enlargement and tenderness (11.0% and 4.4%, respectively).
  - Cervical lymph node enlargement and tenderness (5.3% and 1.2%, respectively).
  - Inguinal lymph node enlargement and tenderness (12.6% and 13.9%, respectively).
  - Other lymph node enlargement and tenderness (3.0% and 1.9%, respectively).
  - Pruritus (27.5%).
  - Skin involvement including oedema, pustular or frank urticarial rash (22.7%).
  - Fever (22.6%).
- Summary of ADR reports from Vigilyze, WHO (as of 24 November 2021). This data only can be assessed by National Pharmaceutical Regulatory Agency (NPRA).
  - There was a total of 6,842 ADRs associated with ivermectin.
  - The top 3 countries reporting the highest number of reports were Peru, the United States of America, and Sierra Leone.
  - Majority of cases involved adults aged 18 and above (73.5%) and females (55.2%).
  - The most common reactions reported were diarrhoea, itchiness, and headache.
  - Main System Organ Classes (SOC) were from General Disorders and Administration Site Conditions, Gastrointestinal Disorder.
  - Serious cases were reactions involving prolonged hospital stay (7.5%) or other medically important conditions (5.0%), death (1.7%), life-threatening incidents (1.3%), and disability (0.6%). For serious cases, there could be one report with more than one serious ADR and concomitant medications such as albendazole, azithromycin, and paracetamol.
  - Out of 6,842 suspected ivermectin ADR reports, 2,036 (29.8%) were reported for COVID-19 indication and 47 of the COVID-19 reports involved serious adverse effects. However, dosages reported were variable and no reasonable conclusion could be made.
- General information of WHO data:
  - WHO global ADR database consists of individual case safety reports (ICSRs) of suspected (not yet confirmed) events collected by contributing countries through passive surveillance. This form of surveillance is subjected to under-reporting and information on indication and prevalence of drug use may not be available. For these reasons, interpretations of adverse event data should be done with caution, particularly comparisons between medicinal products to prevent misleading outcomes.
- In summary, a total of 5 cases of toxicity involving the use of ivermectin in humans were reported to the National Poison Centre in Malaysia as of March 2022, as shown in Table 2.

2.8 Overdosage

- Significant lethality was observed in mice and rats after single oral doses of 25 to 50 mg/kg and 40 to 50 mg/kg, respectively.
- In accidental intoxication with, or significant exposure to, unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, the following adverse effects have been reported most frequently:
  - Rash, oedema, headache, dizziness, asthenia, nausea, vomiting, and diarrhoea.
- Other adverse effects that have been reported include:
  - Seizure, ataxia, dyspnoea, abdominal pain, paraesthesia, urticaria, and contact dermatitis.

2.9 Off-Label Use of Ivermectin in Malaysia (Other than COVID-19)

- Ivermectin is classified as Group B in First Schedule Poisons List under the Poisons Act 1952.
- Ivermectin is approved for animal use, and it is not registered with the Drug Control Authority for human use. As of 14th December 2021, there are 30 registered veterinary products containing ivermectin. Among the indications approved for animals are antiparasitic.
- Therefore, if ivermectin needs to be used in humans in Malaysia, it must comply with Regulation 15(6) of Control of Drugs and Cosmetics Regulations 1984. The process of approval by the Director of Pharmaceutical Services is handled by the Formulary Management Branch, Pharmacy Practice & Development Division, MOH (16):
  - Application for medicines used by the institutions under the Ministry of Health Malaysia:
    In 2020, this division received a total of five applications for the importation of ivermectin from health facilities under MOH Malaysia for various indications not including the treatment of COVID-19, whereas in 2021 (until October), a total of six applications were received.
  - Application to import/manufacture unregistered products for the treatment of life-threatening illnesses (Private/Non-MOH Institutions):
    In 2020, this division received a total of seven applications for the importation of ivermectin from non-MOH / private health facilities for various indications not including the treatment of COVID-19, whereas in 2021 (until October), a total of ten applications were received.
- Registration of ivermectin for human use in Malaysia will be dependent on several factors which include:
  - The willingness of a company to be the product registration holder in Malaysia.
  - The marketability of the drugs in Malaysia.
  - The completeness of safety, efficacy, and quality data dossier in relation to the indication to be evaluated by NPRA Malaysia.

Table 2: Adverse drug reactions (ADR) reports from National Poison Centre, Malaysia (as of March 2022)

Gender / Age[#] / Race:	Female / 35 / Chinese	Male / 65 / Malay	Female / 92 / Chinese	Female / 26 / Chinese	Male / 26 / N/A
Amount:	N/A	3 tablets	180mg	2 Tablets	16 tablets
Type of Poison:	Pharmaceutical	Pharmaceutical	Pharmaceutical	Pharmaceutical	Pharmaceutical
Subtype of Poison:	Unknown	Veterinary drug	Unknown	Unknown	Unknown
Type of Incident:	Intentional	Intentional	Intentional	Intentional	Intentional
Location of Case:	Home and surrounding	Home and surrounding	Home and surrounding	Home and surrounding	Home and surrounding
Clinical Features:	Others	Vomiting	N/A	Chest pain	Itchiness of whole body, restless
Poisoning Comments:	5 days post-ingestion, the patient is negative for COVID-19, and healthy. Developed symptoms after taking 1 dose of ivermectin.	The patient took 2 tablets of ivermectin on Friday 27/8/2021 and 1 tablet on Saturday 28/8/2021 after having a fever. Tablet was given by his daughter who claims to get it from her friend. There is no packaging of the medication to confirm the details of the medication. The patient developed SOB, vomiting, and complaint of poor oral intake. On day 5, lab result in the hospitals detected an increase in creatinine and urea. Initial symptom (vomiting, SOB) resolved. The swab test showed a negative result for COVID-19. Patient also had underlying hypertension and diabetes not under medical follow-up.	Last seen awake and responsive at 5pm, family found grandmother LOC at 8pm. Unsure timing of ingestion. Arrived at ED at 1am the next day. Currently responsive but confused (GCS 9/15 - E2V2M5).	The patient is in close contact with positive COVID-19 case. She was worried and took 2 tablets yesterday and claim developed symptoms today. Her COVID-19 status is still pending, just swabbed.	The patient has positive COVID-19 test. His employee gave him ivermectin to take 2 tablets daily and he has been taking it for 8 days.

[#] Age in years old

(Source: National Poison Centre, Malaysia)

3. Ivermectin for COVID-19 Treatment

3.1 Why was Ivermectin Considered for the Treatment of COVID-19?

Ivermectin is widely used as an anti-parasitic agent. Although it has in vitro activity against some viruses, it has no proven therapeutic utility. In year 2020, a study conducted by Caly L *et al*. demonstrated that ivermectin does have some in vitro activity against SARS-CoV-2 (17). This study reported that ivermectin has antiviral action against the SARS-CoV-2 clinical isolate in vitro with a single dose able to control viral replication within 24–48 hours in human system. The recommended IC50 of ivermectin treatment was determined to be ~2 μM (=1750 ng/mL). This short report raises the possibility that ivermectin could be a useful antiviral to limit SARS-CoV-2 and demonstrates that ivermectin is worthy of further consideration as a possible SARS-CoV-2 antiviral. Ivermectin has demonstrated efficacy in laboratory conditions, but no evidence has yet to be reported among hospitalised patients with COVID-19 (Appendix A).

Hence, subsequent to this publication, it has triggered many clinical trials to study the efficacy of ivermectin in the treatment of COVID-19. However, these findings should be interpreted with caution as pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the antiviral efficacy detected in vitro would require the administration of doses up to 100-fold higher than those approved for use in human.

3.2 Clinical Trials on Ivermectin for COVID-19

Rapid clinical trials on Ivermectin for COVID-19 treatment protocol have been designed to evaluate whether the maximum approved dose and suitable dosage could have an impact on the efficacy of ivermectin towards SARS-COV-2 virus. A review on clinical trials of ivermectin on the COVID-19 treatment from the US National Library of Medicine were conducted (18). Studies were filtered based on the recruitment status. Only studies that were completed, active and still in recruiting were chosen. Further analysis on the list of studies was performed which was then summarised in Table 3. The complete list was available for download as **Supplementary 1**. It was found that randomised controlled trials (RCT) were the most common type of study that has been registered. Other than that, observational studies such as cohort, case-controlled and non-randomised interventional studies have also been registered on the website. As summarised in Figure 2, 73 studies were registered in which 27 studies had been completed and 31 were either on-going or in the recruiting phase. The other 15 studies have not started recruiting any participants.

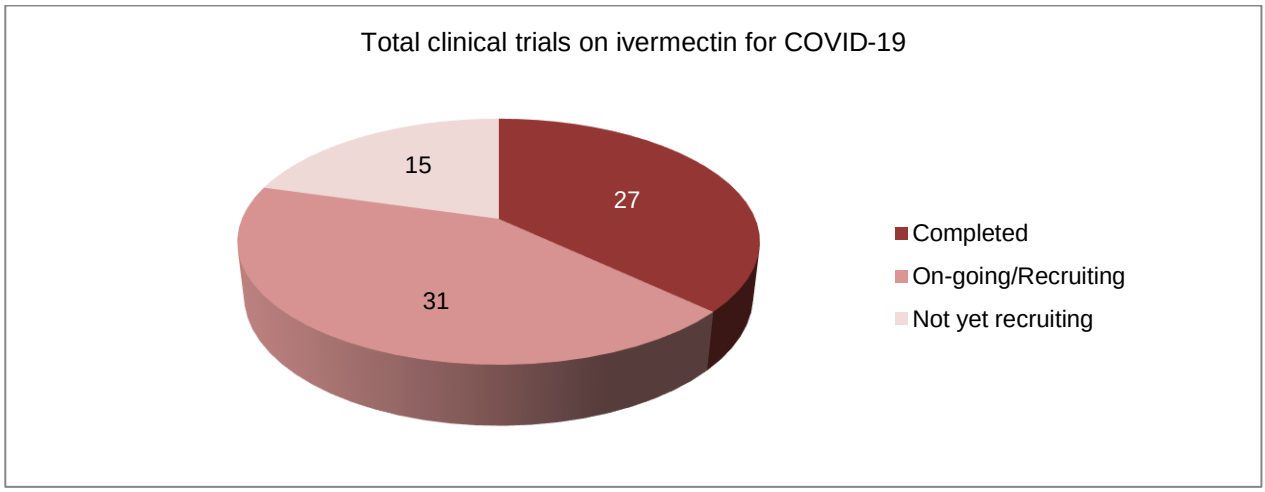

Figure 2: Total clinical trials around the world on ivermectin for COVID-19 (18)
(Data assessed on 18 Nov 2021)

Table 3: The total number of studies registered on Clinical Trial according to the status, study design and study type (18) (Data assessed on 18 November 2021)

Status of Studies	Study Design	Total	Study type	Total	Technique	Total
Completed	Observational	5	Cohort	4		
			Case-only	1		
	Interventional	22	RCT	21	Open-label	8
					Single blind	3
					Double blind	6
					Triple blind	2
					Quadruple blind	2
			Others	1		
On-going/ Recruiting	Observational	0				
	Interventional	31	RCT	28	Open-label	10
					Single blind	4
					Double blind	4
					Triple blind	5
					Quadruple blind	5
			Non-RCT	3	Cross Over	1
					Parallel	2
Not Yet Recruiting	Observational	1	Cohort	1		
	Interventional	14	RCT	14	Open-label	5
					Single blind	1
					Double blind	3
					Triple blind	2
					Quadruple blind	3

3.3 Summary of Scientific Evidence on the Usage of Ivermectin in COVID-19 Patients

Numerous systematic reviews (SR) on the usage of ivermectin in COVID-19 patients had been done to date. Three out of four SR support the use of Ivermectin as part of the treatment guideline for COVID-19 patients. Based on Bryant et al. (2021), SR which is considered the latest SR published and included the highest number of peer-reviewed papers (24 RCTs, 3406 subjects), ivermectin can be considered as part of treatment guideline for mild to moderate COVID-19 (category 2 preferably) (19). In terms of the dose, most reviews did not elaborate much but the accepted range was around 0.2-0.4mg/kg/day which is debatable whether it is sufficient for category 3 and above COVID-19 infections with the involvement of lung. Summary of evidence on systematic reviews paper on ivermectin as compared to standard treatment were explained in detail in Appendix B.

3.4 Randomised Clinical Trials of Ivermectin for COVID-19 Treatment

Based on the real time ivermectin for COVID-19 meta-analysis website, reviews on specifically randomised control trials (RCT) were conducted. Among all the reported studies, only RCT studies were filtered and chosen to be reviewed. Most of the studies were done in the early stage of COVID-19 patients as compared to the study of the usage of ivermectin as the late treatment regime. In terms of dosage form, few studies chose to test ivermectin in suspension form while most of the studies were tested on tablet form (Table 4). It was found that the duration of treatment varies from one day up to four weeks of studies. It was also found that there were variations in terms of dosages.

Specifically, an open-label RCT known as Ivermectin Treatment Efficacy in COVID-19 High-Risk (I-TECH) study was conducted at 20 government hospitals and a COVID-19 quarantine centre in Malaysia between 31 May and 25 October 2021. Based on the results of the I-TECH study which involved 490 patients, ivermectin did not reduce the risk of severe COVID-19 disease (20). The results of I-TECH were in line with other large-scale studies such as IVERCOR-COVID-19 in Argentina and TOGETHER in Brazil, that did not support the routine use of ivermectin in the clinical practice of COVID-19 treatment (21,22).

3.5 Ivermectin as COVID-19 Treatment Globally

Online search was conducted to collect information about the management of COVID-19 globally. It was intended to identify which country had adopted or included ivermectin as treatment for COVID-19 (Table 5). It was found that Egypt was the only country that adopted ivermectin in their national COVID-19 management protocol. India, on the other hand had halted the use of ivermectin from their COVID-19 management country-wide even though it was included in their protocol previously. Meanwhile, in ASEAN there was no country that use ivermectin for COVID-19 treatment.

Table 4: Summary on review of RCT for ivermectin from IVMmeta.com website

Characteristics of trial		Number of clinical trials
Treatment		
	Prophylaxis	3
	Early treatment	16
	Late treatment	7
Dosage Form		
	Tablet	19
	Syrup suspension	3
	Nasal Spray	1
Duration		
	Once/ 1 day	12
	2 days	2
	3 days	3
	5 days	5
	7 days	2
	2 weeks	1
	4 weeks	2
Dosage		
	200ug/kg	5
	300ug/kg	1
	400ug/kg	3
	600ug/kg	1
	1200ug/kg	1
	6mg	3
	12mg	13
	15mg	1
	24mg	4

(accessed on 22 Oct 2021)

Table 5: Inclusion of ivermectin in countries' National COVID-19 Management Protocol

Country	Usage of Ivermectin	National COVID-19 Management Protocol	Ivermectin Adoption	References	Remarks
Argentina	Ivermectin usage is not listed in the national COVID-19 management protocol, but is available as an OTC drug. A nation-wide misuse of ivermectin as home-based therapy in early COVID-19 intervention is hindering the drug clinical trial.	Not included	Scattered mixed-usage	21, 23	Updated Version 3.0, September 2020 Published Correction December 2020
Egypt	Ivermectin usage is listed in the national COVID-19 management protocol as a potential antiviral drug under evaluation for COVID-19 treatment. For moderate cases - patients presenting with pneumonia, Hydroxychloroquine + ivermectin is recommended.	Included	Country-wide	24, 25	MOHP Protocol updated November 2020 Mini-Review on Egypt's COVID-19 happenings. Published 16 August 2021
India	Tab ivermectin (200mcg/kg OD for 3 days) is recommended at the mild stage of disease. As of Oct 2021, The Indian Council of Medical Research-led COVID-19 National Task Force has dropped the use of the drugs ivermectin and hydroxychloroquine (HCQ) from the revised "clinical guidance for management of adult COVID-19 patients".	Previously included, now halted	Country-wide	26, 27	MOHFW Protocol Version 6 25 May 2021 Published online 25 Sept 2021
Japan	Ivermectin is not included in the national COVID-19 management guideline, but the Tokyo Metropolitan Medical Association strongly recommends off-label emergency use to prevent aggravation of disease spread.	Not included	Scattered off-label usage	28, 29	MOH Japan Infographic Updated as of 20 Sept 2021 Article published 19 August 2021

Country	Usage of Ivermectin	National COVID-19 Management Protocol	Ivermectin Adoption	References	Remarks
Brazil	Physicians are free to prescribe off-label drugs to COVID-19 outpatients - backed by the Brazilian Federal Board of Medicine (issued in April 2020) in the name of “physician's autonomy“ - Promotion of "Early Treatment of COVID-19" with the "COVID-19 Kit", supported by Medical Association of Rio Grande do Norte (AMRN).	No specific guidelines	Scattered off-label usage	30–32	Published 5 October 2021
	DETECTCoV-19 study showed that among people with a previous COVID-19 diagnosis, 56% had taken medications as treatment for the disease, usually combining different drugs from the “COVID-19 Kit” - 19% had taken (hydroxy)chloroquine, 55% ivermectin, 8% nitazoxanide, 77% azithromycin, and 26% corticosteroids.				Article published 26 January 2021
	Brazilian Medical Association and the Brazilian Societies of Infectious Diseases and of Pulmonology and Tisiology currently recommend against the use of these drugs for both prophylaxis and treatment of early/mild, non-hospitalised COVID-19 cases.				Published May 2020
Mexico	The Ministry of Health of the Federal Government will update the clinical care guidelines for COVID-19 patients, which are expected to include the use of ivermectin and azithromycin.	Official national clinical guideline not found or yet to be released	Country-wide	33, 34	Article published 3 February 2021
	In Mexico City, health authorities enacted a proactive home outreach program that includes rigorous and repeated testing and early care using a protocol including ivermectin.				Article published 28 August 2021
Brunei	No official COVID-19 treatment guidelines are found online. Published article from KPK, DG Health Malaysia cited in Brunei newsletter.	Not found	N/A	35	-

Country	Usage of Ivermectin	National COVID-19 Management Protocol	Ivermectin Adoption	References	Remarks
Cambodia	Unable to determine the adoption of ivermectin as the national protocol has no English translation, although ivermectin appears to be mentioned in the protocol.	No English translation	N/A	36	Posted date 8 August 2021
Indonesia	Official national guideline updated in March 2020 did not include the usage of ivermectin as COVID-19 treatment algorithm.	Not included	Scattered off-label use	37–41	March 2020 Article published 15 July 2021
	Controversial claims arose in early-July 2021, stating that the Indonesian Food and Drug Monitoring Agency or BPOM granted the Emergency Use Authorization for ivermectin as the therapeutic drug to support the COVID-19 treatment.				Article published 18 July 2021
	The BPOM issued an official statement and ivermectin usage information for the public, against the use of ivermectin for COVID-19 treatment without the supervision of a doctor.				Published 22 June 2021
Laos	COVID-19 treatment algorithm adapted from WHO recommendations. Official national guidelines for COVID-19 treatment are not available online. No articles associating ivermectin use with COVID-19 in Laos were found.	Not found	N/A	-	-
Malaysia	COVID-19 treatment algorithm was adapted from WHO recommendations and open-label use of ivermectin is strictly for the purpose of RCT Studies.	Not included	Scattered off-label usage	42, 43	Updated 13 August 2020 Article published 5 Jun 2021
	Off-label use requires Drug Control Authority approval.				Article published 25 Jun 2021
Myanmar	COVID-19 Case Management Guideline for Home-based Care in Myanmar is developed based on WHO Global Guidelines. Recommendation against the use of ivermectin for treatment or prophylaxis of COVID-19.	Not included	N/A	44, 45, 46	Updated 1 September 2021 Published July 2021
	Management Guidelines for COVID-19 (Updated July 2021) Older version from official government website.				Last updated 23 July 2020

Country	Usage of Ivermectin	National COVID-19 Management Protocol	Ivermectin Adoption	References	Remarks
Philippines	Ivermectin is not recommended in the national CPG as there is insufficient evidence to recommend the use for the treatment of patients with COVID-19 infection. Ivermectin for the treatment of COVID-19 is currently in use for clinical trials, and physicians' prescriptions are subject to doctor-patient relationships.	Not included	Scattered off-label use	47–50	Updated 3 April 2021 Updated 10 April 2021 Article published 2 September 2021 Article published 11 September 2021
Singapore	Ivermectin usage is not listed in the national COVID-19 management protocol. National University Health System concluded an RCT study in 2020 and did not find any significant evidence suggesting that ivermectin has any effect as COVID-19 treatment.	Not included	Isolated use - self-medicated	51–53	Updated 15 April 2021 Article published 5 October 2021 Published 14 April 2021
Thailand	Ivermectin usage is not listed in the national COVID-19 management protocol and no further recommendation for ivermectin at this time. Possible scattered off-label usage but minimal findings.	Not included	Scattered off-label usage	54	Updated 4 August 2021 Internet archive. Posted 28 July 2021
Vietnam	COVID-19 treatment algorithm adapted from WHO recommendations. On 16 January 2020, Vietnamese Government issued the first diagnostic and management guidelines for COVID-19, but official document is not made publicly available.	Not found	N/A	55	Published 24 February 2021

4. Regulation of Ivermectin in Malaysia

In Malaysia, the importation, advertising, manufacturing and compounding of ivermectin for human use are only limited to clinical trials. Currently, ivermectin is only allowed to be imported for the use in clinical trials. This restriction is in line with international advices given by established organisations and regulatory authorities such as WHO, EMA, and USFDA (56, 57).

A strict control over the importation of the active pharmaceutical ingredient (API) of ivermectin into Malaysia had been imposed by the Pharmacy Enforcement Division, MOH. At the entry point, the enforcement officers will investigate the name of the company and the purpose of manufacturing the intended product. The number of ivermectin related products detained at entry points was found to be relatively higher in year 2021 as compared to the previous year (Table 6). Table 6 also showed the number of raids, documented sales, and advertisements related to ivermectin being taken for enforcement action by the Pharmaceutical Services Programme, MOH in 2020 and 2021.

Table 6: Number of ivermectin related products being taken enforcement action by MOH in 2020 and 2021

Item	2020	2021 (as of June)
No. of complaint received	Nil	33
No. of raid and total and value of item seized	No. of raids: 17 No. of items seized:36 items Value of items seized: RM7,193	No. of raids: 4 No. of items seized:9 items Value of items seized: RM4,952
No. and quantity of ivermectin product / raw material detained at entry point	<u>Finished product</u> No. of detention: 1 Quantity: 100 tablets Value: RM237	<u>Finished product</u> No. of detention: 21 Quantity: 11,090 tablets Value: RM13,611 <u>Raw material</u> No. of detention: 1 Quantity: 20 kg Value: RM104,857 No. of pending query: 2 Quantity: 4 kg / 25kg Value: RM6,970 / RM23,165 No. of retour to origin country: 1 Quantity: 50 grams Value: RM1,672
No. of community pharmacy doing ivermectin compounding (if any)	No information	3
No. of advertisement removed from e-commerce platform	6	134 *Note: Warning letter 4B – 2*
No. of advertisement on website being applied for MCMC's blockage and removal of content from social media	0	17

4.1 Compounding of Ivermectin

A guideline on the use of compounding medicines in Malaysia is needed and recognition of any reference country should be detailed out to facilitate the enforcement of ivermectin products.

4.2 Advertisement of Ivermectin

The Medicines (Advertisement and Sale) Act 1956 prohibits certain advertisements relating to medical matters and regulates the sale of substances classified as medicines. Hence, approval by the Medicine Advertisements Board (MAB) is required before any advertisement of medicine is allowed to be published in any mediums. Therefore, any advertisements involving poisons, such as ivermectin, without the approval by MAB is considered illegal,.

As an effort to protect the wellness of consumers, rigorous efforts were made to ensure that advertisements related to ivermectin in various social media were removed. Advertisement removal requests were made to various e-commerce platform operators to remove the content related to ivermectin from the internet. Table 7 showed the number of blockages of ivermectin-related sales and advertisements on the internet in 2020 and 2021.

Table 7: Number of Ivermectin-related online sales and advertisements blocked

Year	No. of Ivermectin-related link blocked			
2020	EC21	Ezbuy	Youtube	Webpage
	0	38	12	1
2021 (as of July)	Facebook	Instagram	Alibaba	Webpage
	6	1	6	4

5. Public Health Awareness on Ivermectin

Numerous public health awareness programmes were organised by the Pharmaceutical Services Programme, MOH to ensure that the public is well informed about ivermectin and its usage for COVID-19. Figure 3 showed the types of consumer awareness activities concerning ivermectin. The details of awareness activities can be found in Appendix C.

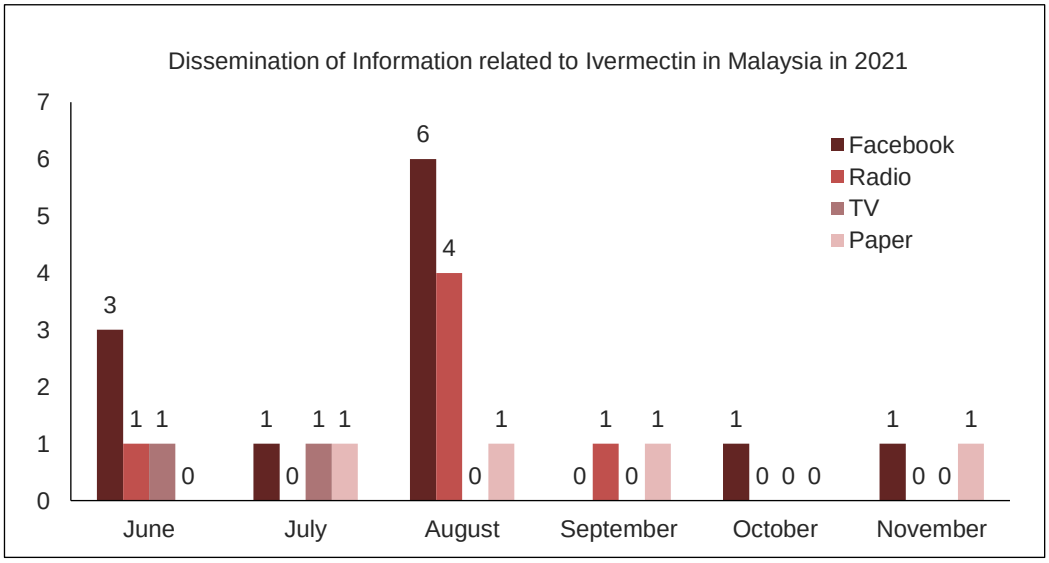

Figure 3: Dissemination of information related to ivermectin in Malaysia (2021)

6. Conclusion

Although some initial studies had shown the effectiveness of ivermectin for treating COVID-19, pharmacokinetic and pharmacodynamic studies suggested that achieving the plasma concentrations necessary for an antiviral efficacy would require much higher doses than those approved for human use. Furthermore, recent randomised clinical trials could not demonstrate ivermectin's efficacy to reduce the risk of severe COVID-19 disease, and thus did not support the routine use of ivermectin for COVID-19 treatment. Based on the evidence gathered to date, the Drug Expert Taskforce for Ivermectin (DETF-IVM) suggested that Ivermectin **should not be included** as a standard treatment for COVID-19 in Malaysia.

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Appendix A: Pharmacokinetic (PK) and/or pharmacodynamic (PD) studies on ivermectin

1) Landmark study of ivermectin PD effect in SARS-COV (from in-vitro data)

Type of study	Method	Observation	Summary	Reference
In vitro	Cells infected with SARS-CoV-2 were treated with serial dilutions of ivermectin 2 h post infection and supernatant and cell pellets collected for real-time RT-PCR at 48 h Vero/hSLAM cells were infected with SARS-CoV-2 isolate Australia/VIC01/2020at a MOI of 0.1 for 2 h, followed by the addition of 5 µM ivermectin Supernatant and cell pellets were harvested at days 0–3 and analysed by RT-PCR for the replication of SARS-CoV-2 RNA To further determine the effectiveness of ivermectin, cells infected with SARS-CoV-2 were treated with serial dilutions of ivermectin 2 h post infection and supernatant and cell pellets collected for real-time RT-PCR at 48 h	Ivermectin inhibited the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2 h post infection with SARS- CoV-2 able to effect ~ 5000-fold reduction inviral RNA at 48 h At 24 h, there was a 93% reduction in viral RNA present in the supernatant (indicativeof released virions) of samples treated with ivermectin compared to the vehicle DMSO. Similarly, a 99.8% reduction in cell- associated viral RNA (indicative of unreleased and unpackaged virions) was observed with ivermectin treatment. By 48 h this effect increased to an ~5000- fold reduction of viralRNA in ivermectin- treated compared to control samples, indicating that ivermectin treatmentresulted in the effective loss of essentially all viral material by 48 h The IC50 of ivermectintreatment was determined to be ~2 µM	The results demonstrated that ivermectin has antiviral action against the SARS-CoV-2 clinical isolate in vitro, with a single dose able to control viral replication within 24–48 h in human system The recommended IC50 of ivermectin treatment was determined to be ~2 µM (= 1750 ng/mL)	17

2) Ivermectin PK and/or PD studies in human

Type of study	Participants	Intervention / Endpoints	Results	Summary	Reference
Population PK study – plasma samples versus DBS samples (conservative technique of sampling versus DBS)	12 healthy volunteers	Single oral dose 12mg ivermectin Peripheral venous andcapillary DBS sample Fasted state, 30-min before dosing given ahigh-fat breakfast, 5hpost dose received high-fat diet to stimulate gallbladderemptying Sampling points: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9,10,11, 12, 24, 36, 48, 72H post dose	Parameter estimatesof pop PK: CL – 7.67 L/h Vc-d – 89.13 L PK of observed data: Tmax - 4.4 h Cmax – 70.7 ng/ml AUC-inf – 1743.5 Vd – 382.6 L Cl – 7.7	PK variability - enterohepatic circulation Cmax in plasma 70.7ng/ml (far less than 1750 from Caly et al)	58
Double-blind, placebo-controlled, dose escalation study	Subjects (healthy volunteers) (n = 68) were assigned to one offour panels (3:1, ivermectin/placebo): 30or 60 mg (three times a week) or 90 or 120 mg (single dose) The 30 mg panel (range: 347 – 594 microg/kg) also received a single dose with food after a 1-week washout	Safety assessments: CNS effects and generaltoxicity, mydriasis PK evaluation	All dose regimens hada mydriatic effect similar to placebo Adverse experiences were similar betweenivermectin and placebo and did not increase with dose. Following single doses of 30 to 120 mg, AUC and Cmax were generally dose proportional, with t(max) approximately 4 hours and t1/2 approximately 18 hours.	This study demonstrated that ivermectin is generally well tolerated at these higher doses and more frequent regimens	59
Open-label, randomized, crossover phase I clinical trial performed under fasting conditions	54 healthy adult volunteers stratified in 3 weight groups Subjects in Group 1, weighing from 51 to 65 kg, in Group 2, weighingfrom 66 to 79 kg and in Group 3, weighing ≥80	Safety and pharmacokinetic profile of 3 dosing regimens ofIVM Single dose, three- period, comprising 3 experimental phases oftreatment with different doses of IVM Each experimental period lasted from at least 12 h prior to drug administration to + 168 h post-dose (7days	Safety: No significant association was found between the distribution of adverse events and the three treatments arms (p = 0.695) Pharmacokinetics: Half-life between 81 and 91 h in the different treatment groups Increase in AUC0t and Cmax for	Fixed-dose regimens (both 18mg and 36 mg) are as safe as the standard dosage and could justify the use of fix dosing regimens rather than the use of current weight-based strategy based on the dosing regimens, the observed Cmax were still far below	60

Type of study	Participants	Intervention / Endpoints	Results	Summary	Reference
		Study drug: IVM 18 mg i) one tablet of IVM 18mg (FD18), ii) two tablets of IVM 18 mg, 36 mg in total (FD36) and iii) IVM 200µg/kg in 6mg tablets Nineteen venous samples of 6 mL (2 and 4 mL for IVMB1a and IVMB1b respectively) were collected into EDTA K2 plastic tubes at baseline and at +0.5 h, +1 h, +2 h, +3 h, +3.5h, +4h, +5 h, +6 h, +8 h, +10 h, +12h, +16 h, +24 h through acannula placed in the arm of the volunteer and at +36 h, +48 h, +72 h, +120 h, and +168 h post-drug administration by direct venipuncture	the two experimental treatments of 18 mg and 36 mg Body mass index (BMI) and weight were associated witht1/2 and V/F – probably reflecting the high liposolubilityof IVM with longer retention times proportional to the presence of more adipose tissue PK data: All study groups Median CMax 0.2mg/kg = 44.52ng/ml Median Cmax fixed-dose 18mg = 38.09 ng/ml Median Cmax fixed-dose 36mg = 65.49 ng/ml Gp 1 (n=18) Median CMax 0.2mg/kg = 45.33ng/ml Median Cmax fixed-dose 18mg = 52.19 ng/ml Median Cmax fixed-dose 36mg = 71.80 ng/ml Gp 2 (n=18) Median CMax 0.2mg/kg = 39.34ng/ml Median Cmax fixed-dose 18mg = 31.72 ng/ml Median Cmax fixed-dose 36mg = 65.49 ng/ml Gp 3 (n=18) Median CMax 0.2mg/kg = 44.52ng/ml Median Cmax fixed-dose 18mg = 37.08 ng/ml Median Cmax fixed-dose 36mg = 75.16 ng/ml	from the PD data by Caly et al in plasma	

Type of study	Participants	Intervention / Endpoints	Results	Summary	Reference
Pilot, multicenter, randomized, open label,outcome assessor blinded, controlled study to assess the antiviral activity and safety of a 5-day regimen of high dose IVM versus no treatment in a 2:1 allocation ratio, in patients with COVID-19	The trial was done at 4 hospitals in the metropolitan area of Buenos Aires, Argentina Eligibility criteria included COVID-19 symptoms onset ≤ 5 days at recruitment, absence of use of drugs with potential activity against SARS-CoV-2 (hydroxychloroquine, lopinavir, remdesivir and azithromycin); and those drugs were not permitted during the first week of the trial Patients in the IVM group received oral treatment for 5 consecutive days with either breakfast or lunch at approximately24 h intervals IVM 6 mg ranurated tablets (IVER P, Laboratorios Elea/Phoenix, Argentina) were used in all cases at a dose of 600 µg/kg/day based on baseline weight rounding to the lower full (6 mg) and half (3mg) dose Blood samples were obtained by venipuncture for plasma IVM concentrations 4 h after drug intake on treatment days 1, 2, 3, and 5 (aiming at measuring peak plasma levels) and on day 7 (aiming to evaluate potential drug accumulation) in the IVM group	The primary outcome measure was the difference in SARS-CoV-2 viral load between baseline and day-5 in both groups Secondary outcomes included clinical evolution at days 7 and30, relationship between IVM plasma concentrations and theprimary outcome, and frequency and severityof adverse events	The difference in viral load between baselineand day-5 was similar between groups and decreasing over time, without significant differences A significant positive correlation was identified between mean plasma IVM concentration levels and reduction in viral load (higher mean plasma concentrations of IVM reaching higher reductions in viral load in nasopharyngeal secretions (r: 0·44; p <0·04)) Mean IVM plasma concentration levels also showed a positive correlation with viral decay rate (r:0·47, p = 0·02). 160 ng/ml as the cutoff plasma concentration (identified as the potential thresholdabove which a significant viral load reduction could be established compared to untreated controls as an indicator of the relationship between ivermectin concentrations in plasma and antiviral activity) Median Cmax was 202ng/ml (IQR: 167–268 ng/ml) in the >160 ng/ml subgroup and109 ng/ml (IQR: 91–141 ng/ml) in the <160 ng/ml subgroup (p < 0·0001)	The observed Cmax still far below from the data by Caly et al (1750 ng/mL) – therefore factors contributed to the reduction of viral load and viral decay rate Baseline characteristics:Age 38.1 (control), 42.3 (ivermectin)	61

3) Ivermectin PK and/or PD modelling or simulation studies

Type of study	Participants	Intervention / Endpoints	Results / Observation	Summary	Reference
Physiologically-based PK model	Ivermectin lung and plasma concentrations from Holstein Calves Human lung and plasma exposure simulations were performed	Holstein Calves (received 0.2 mg/kg using formulation available for cattle) – plasma and lung samples were obtained between 1- and 48-days post treatment (average dose administered = 15mg) Simulation of human lung exposure: Therapeutic and supra- therapeutic single dosesof ivermectin (12, 30 and 120 mg) were evaluated. 12 mg represent typical dose to while 30 and 120 were supratherapeutic dosesin human Target PD index: IC50 = 1750 ng/ml (=2 µM) (based on invitro data from Caly et al. Antiviral Res 2020. 178:104787)	Human lung exposure simulation: Maximum simulatedivermectin concentrations in plasma = 288 ng/ml,lung = 772 ng/ml at 5.1h	Simulated peak lung concentration following a single oral 120mg were well below the targeted PD index for ivermectin against SARS-COV-2 virus (in vitro) Maximum simulated ivermectin concentrations in plasma = 288 ng/ml, lung = 772 ng/ml at 5.1h(less than 1750 by Caly et al) *not considering plasma protein binding, thus free drug concentration in lung could be much lower	62
Population PK model	Data reported from Duthaler et al was simulated using NONMEM • Healthy subjects Receiving single dose of 12mg in the fed state	Plasma ivermectin concentrations of total(bound and unbound) and unbound concentrations were measured Plasma concentration- time profiles were simulated to predict exposure for approved dose of ivermectin (0.2 mg/kg in 3mg increments) and 120 mg Additional simulations were conducted to predict plasma concentrations with weekly dosing and 60 mg3x weekly (every 72 hours) Target PD index: IC50 = 1750 ng/ml (=2 µM) (based on invitro data from Caly et al. Antiviral Res 2020. 178: 104787)	Plasma concentrations of total (bound and unbound) and unbound concentrations do not reach the IC50 targeted, even for dose 10x higher than the approved dose, or repeat dosing Plasma exposures didnot increase substantially after repeat dosing Even with high lung: plasma ratio, Ivermectin unlikely to reach the IC50 of 2µMin the lung after singleoral administration of the approved dose (predicted lung concentration = 0.0873 µM) or at dose120 mg (10x higher) (predicted lung concentration: 0.820 µM)	In vitro experiments of repurposed drugs should be conducted at clinically relevant concentrations Well-controlled clinical dose-response study with ivermectin at a low dose and at a higher dose should be conducted Study need to control for factors affecting variability in exposure; eg administration during fasted state, P- glycoprotein (protein binding), CYP3A4 inhibitors (as ivermectin extensively metabolized by CYP3A4) which could increase ivermectin exposure, and	63

Type of study	Participants	Intervention / Endpoints	Results / Observation	Summary	Reference
			Expected lung accumulation (based on ball-park accumulation ratio which relative to IC50after repeating doses:12mg administer weekly dose – ratio 1.3 (=1/20th of theIC50) 12mg 3x weekly – ratio 2.2 (= 1/10th ofthe IC50) 12mg daily – ratio 5.35 (=1/4th of theIC50) Higher doses (60mg 3xweekly or 120 mg once weekly) – 1/5th of the IC50	concentration at site of infection	

4) Ivermectin PK and/or PD studies in animal

Study findings	Overall highlights from animal PK studies (summarised from reference 64)
Inhibition effect - At a wide range of nanomolar to micromolar concentrations that had no effect on arthropods,ivermectin significantly inhibited infection and/orreplication of Dengue virus in Aedes albopictus (65) - Ivermectin significantly inhibited infection and/or replication of Bluetongue virus in Culicoides sonorensis (66) - Ivermectin significantly inhibited infection and/ or parvovirus of crayfish (67) No inhibition effect - Ivermectin had no effect on infection and/ or dissemination of Zika virus in Aedes aegypti (68) - Ivermectin had no effect on infection and/or dissemination West Nile virus in Culex tarsalis and Epizootic haemorrhagic disease virus in Culicoides sonorensis (69) Mammalian PK study - In mammalian hosts, administration of 0.2 mg/kg of ivermectin for 2–6 days inhibited the replication of Porcine circovirus in visceral organs including the brain,liver, heart, kidneys, spleen and lymph nodes over 21 days in piglets (70) - A single ivermectin dose of 0.2 mg/kg did not prevent infection but it inhibited replication of Suid herpesvirusin the brain and kidneys, and mortality at day 7 post-infection in mice (71) - One study showed that administration of 4 mg/kg of ivermectin for 2 days before infection and ~~at~~ on days 1, 2 and 4 after infection did not prevent the infection or mortalities caused by Zika virus in mice (72)	In vitro studies showed that ivermectin exerts selectivity for some viruses in ex vivo mammalian cell infection model The micromolar concentration range required to inhibitreplication by 50% for most viruses may be a cause for concern Clinically approved formulations of ivermectin can be administered orally, subcutaneously, intramuscularly or topically with a recommended dose range of 150–200 µg/kg in humans and 6–500 µg/kg in animals depending on species and formulation, and the indicated clinical applications With this dose range, pharmacokinetic characterizations have shown that attainable peak plasma concentrationsincrease with dose and may range from 3–48 ng/ml in dogs, 21–82 ng/ml in horses, 7–40 ng/ml in pigs, 9–60 ng/ml in sheep, 12–133 ng/ml in cattle and 20–81 ng/ml in humans even with extremely high doses of ivermectin, attainablepeak plasma concentrations would remain markedly lower than established EC50 concentrations for most viruses in vitro, albeit significantly higher than 0.5–1 ng/ml that is optimal for the anthelmintic activity The use of extremely high doses of ivermectin would increase the prospect of adverse drug-drug interactionsin patients requiring polypharmacy, as is often the case in viral infections If ivermectin is to be repurposed as an antiviral agent, established antiviral properties based on in vitro experiments should be critically evaluated in validated models of infection in animals in vivo Caution should be exercised in interpreting these data asthe applicability will depend on broader questions such as which viral and animal species should be targeted, what would be the optimal dosing regimen and whatcosts or benefits would ensue.

Appendix B: Summary of evidence on systematic review of ivermectin for the treatment and prevention of SARS-CoV-2

No.	Name of Systematic Review	No. of studies / patients	Outcome Measure	Results	Limitation & Interpretation
1	Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines (19)	- Authors contacted for missing data - 24 RCT involved, 3406 participants - Sample size ranging from 24 – 476 - Treatment trial: ➢ 16 mild tomoderate ➢ 6 for severe - Prophylaxis trial: 3 trials, 738 participants - Country of trials: ➢ Bangladesh=4 ➢ Egypt=3 ➢ Iran=3 ➢ India=2 ➢ Pakistan=2 ➢ Argentina=2 ➢ Nigeria=1 ➢ Spain=1 ➢ Brazil=1 ➢ Mexico=1 ➢ Colombia=1 ➢ Turkey=1 ➢ Bulgaria=1 ➢ Lebanon=1 ➢ Israel=1 - Studies included: Treatment ➢ Ahmed 2020 ➢ Babalola 2020 ➢ Bukhari 2020	• Primary outcome: - Mortality - Presence of COVID-19(for prophylaxis) • Secondary outcome: - time to PCR negativity - clinical recovery - length of hospital stays - admission to hospital (for outpatient treatment) - admission to ICU or requiring mechanicalventilation - duration of mechanical ventilation - severe or serious adverse events - post hoc assessments of improvement and deterioration	<u>TREATMENT</u> A. Mortality i) Mortality (All cause) - Mild to moderate COVID-19 (11 trials; 945 IVM vs 774 control) *RR 0.24 [95%, 0.06, 0.94) - Severe COVID-19 (5 trials;235 IVM vs 304 control) *RR 0.51 (95%, 0.22, 1.14) - Mild, moderate & severe COVID-19 (1 trial; 120 IVM, 60 control) *RR 0.18 (95%, 0.06, 0.55) - Pooled (17 trials; 1300 IVM vs 1134 control) *RR 0.38 (95%, 0.19, 0.73) ii) Mortality (All cause minus outliers to reduce heterogeneity) - Mild to moderate COVID-19 (11 trials; 945 IVM vs 774 control) *RR 0.24 [95%, 0.06, 0.94) - Severe COVID-19 (5 trials; 235 IVM vs 304 control) *RR 0.37 (95%, 0.14, 0.98) - Mild, moderate & severe COVID-19 (1 trial; 120 IVM, 60 control) *RR 0.18 (95%, 0.06, 0.55) - Pooled (17 trials; 1300 IVM vs 1134 control) *RR 0.31 (95%, 0.17, 0.58) iii) Mortality (excluding high risk of bias papers) - Mild to moderate COVID-19 (10 trials; 897 IVM vs 726 control) *RR 0.24 [95%, 0.06, 0.94) - Severe COVID-19 (2 trials; 152 IVM vs	- Several studies not provided fulldescription of method and attempt to contact authors was done - Variability in terms of participants recruited and treatment regimen did subgroup analysis (mild, moderate, severe COVID) and sensitivity analysis to minimise bias - Several meta-analyses were conducted to reduce heterogeneity(I^2) of study included for mortality outcome - Not included pre-print publication One patient developed hyponatremia probably becauseof higher range of Ivermectin being used (0.6mg/kg/d - Krolewiecki et al 2020)

No.	Name of Systematic Review	No. of studies / patients	Outcome Measure	Results	Limitation & Interpretation
		➢ Chaccour 2020 ➢ Chachar 2020 ➢ Chowdhury 2020 ➢ Elgazzar 2020 ➢ Fonseca 2021 ➢ Gonzalez 2021 ➢ Hashim 2020 ➢ Krolewiecki 2020 ➢ Lopez-Medina 2021 ➢ Mahmud 2020 ➢ Mohan 2021 ➢ Niaee 2020 ➢ Okumus 2021 ➢ Petkov 2021 ➢ Podder 2020 ➢ Raad 2021 ➢ Ravikirti 2021 ➢ Rezai 2020 ➢ Schwartz 2021 Prophylaxis ➢ Chahla 2021 ➢ Elgazzar 2020 ➢ Shouman 2020	215 control) RR 0.36 (95%, 0.04, 3.59) - Mild, moderate & severe COVID-19 (1 trial; 120 IVM,60 control) *RR 0.18 (95%, 0.06, 0.55) - Pooled (13 trials; 1169 IVM vs 1001 control) *RR 0.28 (95%, 0.10, 0.78) B. Need for mechanical ventilation (3 trials; 207 IVM, 224 control) RR 0.66 (95%, 0.14, 3.00) C. Improvement (6 trials; 628 IVM, 526 control) - Mild to moderate COVID-19 RR 1.25 (95%, 1.08, 1.45) D. Deterioration (9 trials; 845 IVM, 742 control) - Mild to moderate COVID-19 *RR 0.4 (95%, 0.19, 0.82) - Severe COVID-19 RR 0.31 (95%, 0.08, 1.15) - Pooled *RR 0.35 (95% 0.19, 0.65) E. Adverse Event RR 1.65 (95% 0.44,6.09) <u>PROPHYLAXIS</u> i) Presence of COVID *RR 0.14 (95%, 0.09,0.21) I i) Adverse event 2 trials, 538 participants, no reported case. Conclusion: Support Ivermectin	

No.	Name of Systematic Review	No. of studies / patients	Outcome Measure	Results	Limitation & Interpretation
2	Ivermectin and mortality in patients with COVID: A systematic review, meta-analysis, and meta-regression of randomized controlledtrials (73)	9RCT, 1788 patients Papers included: ➢ Elgazzar 2020 ➢ Galan 2021 ➢ Gonzalez 2021 ➢ Hashim 2020 ➢ Lopez-Medina ➢ Niaee 2020 ➢ Ravikitri 2021 ➢ NCT04523831 ➢ NCT04646109	• Mortality	Mortality a. Overall: *RR 0.39 [95%, 0.20, 0.74] b. Subgroup analysis in patients with severe COVID-19: RR 0.42 [95% 0.18, 1.01] c. Hypertension RR 1.08 [95% 1.03-1.13] Conclusion: Support ivermectin	- Dose varied between studies - Most of the study's pre-print were not peer-reviewed
3	Outcomes of Ivermectin inthe treatment of COVID- 19: a systematic review and meta-analysis (74)	12 RCT for qualitative analysis and 5 were included in quantitativeanalysis			Exclude since is not certified by peer review yet
4	Therapeutic potential of ivermectin as add-on treatment in COVID 19: A systematic review and meta-analysis (75)	- 4 observational studies, 629 patients - 3 observational studies for meta-analyses (2 were notpeer reviewed)	- Clinical improvement • Time to dischargefrom the hospital	a. Clinical Improvement *OR=1.95, (95%; 1.09 to 3.49) b. Time to discharge from thehospital 7.62± 2.75 versus 13.22± 5.90 days, p <0.05 Conclusion: Support ivermectin	- 2/3 papers in meta-analysesnot peer-reviewed - small observational studies with confounders - very low-quality evidence

No.	Name of Systematic Review	No. of studies / patients	Outcome Measure	Results	Limitation & Interpretation
5	Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials (76)	10 RCT, 1173 patients Papers included: ➢ Chachar 2021 ➢ Krolewiecki 2020 ➢ Niaee 2020 ➢ Podder 2020 ➢ Ahmed 2021 ➢ Beltran 2021 ➢ Chaccour 2021 ➢ Karamat 2021 ➢ Lopez-Medina 2021 ➢ Ravikirti 2021	- All-cause mortality - LOS - Adverse Event	- All-cause mortality (28 days) RR 0.37(0.12-1.13) - LOS RR 0.72(-0.86-2.29) - AE RR 0.95(0.85-1.07) - Severe AE RR 1.39 (0.36-5.3) - Viral clearance RR 0.96 (0.79-1.16) Conclusion: Did not support ivermectin	All the papers included has been incorporated in Bryant et al except 2 papers: - Beltran et al 2021 (Mexico) - Karamat et al 2021 (Pakistan)

Appendix C: Consumer awareness programmes about ivermectin carried out by the Pharmaceutical Services Programme, MOH

No.	Date	Title	Platform/ Medium	Remarks
1	08/06/2021	Infografik : Ivermectin	FB Duta Kenali Ubat Anda	Dikongsi daripada FB KKM
2	10/06/2021	Forum : Ivermectin	FB Live Medical Mythbusters Malaysia	Panel : En. Mohd. Dziehan Mustapha
3	23/06/2021	Wawancara Radio : Perbetulkan salah faham tentang vaksin COVID-19	Radio KL FM 97.2 FM	Panel : En. Sean Liew Jia Xen
4	23/06/2021	Kenyataan Akhbar : Tindakan Penguatkuasaan Terhadap Penjualan Produk Ivermectin Tidak Berdaftar dengan KKM di Selangor dan Kuala Lumpur	FB Duta Kenali Ubat Anda	Dikongsi daripada FB KKM
5	24/06/2021	Wawancara TV : Perbetulkan salah faham tentang vaksin COVID-19	Selamat Pagi Malaysia, TV1	Panel : Pn. Sofhatun Nur
6	18/07/2021	Artikel: Ivermectin perlu disokong pembuktian lebih kukuh	Metro Ahad	Penulis: En. Mohd Shahiri Abd Ghapar
7	28/07/2021	Keratan Akhbar : Keputusan kajian ubat Ivermectin September ini	FB Duta Kenali Ubat Anda	Dikongsi daripada Berita Harian
8	28/07/2021	Wawancara TV : Isu Penggunaan Ivermectin	Malaysia Hari Ini, TV3	Panel : Dr. Nur Sufiza binti Ahmad
9	01/08/2021	Infografik : Ivermectin dan kesan sampingan ivermectin	FB Duta Kenali Ubat Anda	Dikongsi daripada FB KKM
10	04/08/2021	Wawancara Radio : Kenapa nak pilih vaksin COVID-19?	Radio Nasional FM 88.5 FM	Panel : En. Mohd. Dziehan Mustapha
11	07/08/2021	Podcast : Salah Faham tentang Rawatan dan Pencegahan COVID-19	Borak Medik Sinar, Podcast Syok	Panel : En. Mohd Shahiri Abd Ghapar
12	09/08/2021	Wawancara TV : Ivermectin Untuk Rawatan COVID-19 Perlu Bukti Lebih Kukuh	Bicara DR RTM / FB Duta Kenali Ubat Anda	Panel : Pn. Sofhatun Nur Subhi
13	11/8/2021	Infografik : Rawatan Kendiri Ivermectin : Boleh atau Tidak?	FB Duta Kenali Ubat Anda	Dikongsi daripada FB KKM
14	16/8/2021	Artikel : Keracunan Ivermectin : Elakkan Pengambilan Dos Kendiri	FB Duta Kenali Ubat Anda	Dikongsi daripada FB Pusat Racun Negara

No.	Date	Title	Platform/ Medium	Remarks
15	17/8/2021	Wawancara Radio : COVID-19 : Usah Melulu Ambil Ivermectin	Radio BERNAMA	Panel : Cik Siti Nurul Fathihah Baharudin
16	19/8/2021	Forum : Ivermectin : Alternatif atau Racun!	Wacana Sinar Harian	Panel : En. Mohd. Dziehan Mustapha
17	23/8/2021	Wawancara Radio : Ivermectin : Antara Fakta dan Falasi	Radio Zayan FM	Panel : Pn. Sofhatun Nur Subhi
18	23/8/2021	Video : Apa itu Ivermectin?	FB Duta Kenali Ubat Anda	Dikongsi daripada FB KKM
19	26/08/2021	Wawancara TV : Salah Faham Tentang Rawatan & Pencegahan COVID-19	Bicara DR RTM / FB Duta Kenali Ubat Anda	Panel : Pn. Sofhatun Nur Subhi
20	6/9/2021	Wawancara Radio : Jangan Ambil Ivermectin Sembarangan	Radio Selangor FM	Panel : En. Mohd. Dziehan Mustapha
21	10/9/2021	Artikel: Salah faham penggunaan ivermectin	MyHealthFor Life Edisi September 2021	Penulis: Cik Siti Nurul Fathihah binti Baharudin
22	27/10/2021	Video: Ubat dan Rawatan COVID-19	FB Duta Kenali Ubat Anda	Panel: Pn. Siti Hawa Mond Noor
23	2/11/2021	Fighting A Pandemic	New Straits Times	Penulis : En Mohd Shahiri bin Abd Ghapar
24	5/11/2021	Infografik : Keberkesanan Rawatan Ivermectin Pada Pesakit Berisiko COVID-19 (Kajian I-TECH)	FB Duta Kenali Ubat Anda	Dikongsi daripada FB KKM

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