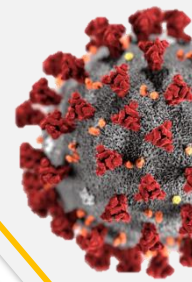




Povidone-Iodine for Disinfection of SARS-CoV-2



INTRODUCTION

The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2). It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. The SARS-CoV-2 is an enveloped virus with single-stranded RNA genome.¹ Genetic sequencing of the virus suggests that it is a beta coronavirus closely linked to the severe acute respiratory syndrome (SARS) virus. Enveloped viruses are susceptible to disinfectants² and sensitive to ultraviolet rays and heat.¹ Furthermore, these viruses can be effectively inactivated by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for chlorhexidine.¹ The virus is transmitted through respiratory droplets, direct contact with infected persons, or by contact with contaminated objects and surfaces harboring the pathogens. Shedding of SARS-CoV-2 is highest in the upper respiratory tract (nose and throat) within the first three days from the onset of symptoms.³

Povidone-iodine (PVP-I) is a well-known broad spectrum antiseptic. The antimicrobial action of PVP-I occurs after free iodine (I₂) dissociates from the polymer complex. Once in the free form, iodine rapidly penetrates microbes and disrupts proteins and oxidises nucleic acid structures.⁴ The PVP-I products have been used as a disinfectant due to its bactericidal and virucidal activity, including towards severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Administration of PVP-I as topical nasal and oral solutions has shown to be safe.

In COVID-19 outbreak, PVP-I has been proposed for nasal spray, gargle/mouthwash and skin cleanser application to the patients and healthcare workers, and also as disinfectant solution for intubation instruments, endoscopy and bronchoscopy equipment. Hence, this rapid review was conducted.

The proposal was based from Kirk-Bayley et al. (2020) protocol on the usage of intra-nasal and oral application of PVP-I for both patients and their attendant healthcare workers (HCWs) during COVID-19 pandemic. The aim is to reduce the viral load via droplets and aerosols. The first cohort includes patients with presumed/confirmed COVID-19 and the healthcare personnel in close contact with the patients. The second cohort includes all patients having procedures in or around the mouth and nose or procedures that transit those areas and the healthcare professional carrying out those procedures. All patients and HCWs will received 0.5% PVP-I solution (0.55 mg/mL available iodine) applied to the oral, oropharyngeal and nasopharyngeal mucosa. The 0.5% PVP-I solution is administered in a dose of 0.28-0.3 ml into each nostril with a total dose of 0.33 mg of iodine. The oral cavity solution used 9 mL of the 0.5% PVP-I solution as mouthwash. The solution is distributed throughout the oral cavity for 30 seconds and then gently gargled at the back of the throat for another 30 seconds before spitting out. It is assumed that 1 mL of solution

will be retained with a maximum dose of 0.55 mg of iodine. The first cohort undertaken intranasal and oral PVP-I every 6 hours for patients, while HCWs prior to contact with patient up to four times a day. As for the second cohort, intranasal and oral PVP-I solution performed to patient prior undergoing procedures and the HCWs prior to contact with the patient. The HCWs can repeat every 2-3 hours, up to four times a day if seeing multiple patients. For unconscious patients, a routine mouth care with an oral care sponge soaked in 2 mL of 0.5% PVP-I solution wiped around the oral mucosal surfaces, giving a maximal dose of 1.1 mg iodine. The authors acknowledged that the proposed protocol for disinfection of the oral and nasal cavities were extrapolated from in vitro finding into the in vivo environment.⁴

EVIDENCE ON EFFECTIVENESS AND SAFETY

The systematic search for new evidence from the scientific databases such as Medline, EBM Reviews, EMBASE via OVID, Pubmed and from the general search engines [Google Scholar and US Environmental Protection Agency (US EPA)], did not retrieved any articles to demonstrate the efficacy, safety or cost-effectiveness of povidone-iodine for COVID-19. However, there were six ongoing clinical trial on PVP-I and COVID-19, three in vitro studies on SARS-CoV-2, three in vitro studies on other coronaviruses and one safety article on PVP-I and coronavirus.

Povidone-iodine and SARS-CoV-2

Currently, there are six ongoing clinical trials to evaluate the efficacy of PVP-I against SARS-CoV-2.

Table 1: Overview of ongoing clinical trials and estimated completion date

ClinicalTrials.gov Identifier	Location	Study design	Intervention	Estimated completion
NCT04341688 ⁵	Aga Khan University, Pakistan	A quadruple blind randomised controlled trial <ul style="list-style-type: none"> • 50 participants 	0.2% Povidone-Iodine (BETADINE®) gargle and nasal lavage	March 2021
NCT04344236 ⁶	NYU Langone Health, New York, United States of America (USA)	Randomised controlled open label trial, parallel design <ul style="list-style-type: none"> • 48 participants 	0.5% PVP-I oral gargle and 0.5% PVP-I nasal rinse	May 2020
NCT04371965 ⁷	Poitiers University Hospital, France	Randomised controlled open label trial, parallel design <ul style="list-style-type: none"> • 24 participants 	1% PVP-I gargle, 1% PVP-I nasal spray and application 10% PVP-I cream in each nostril	August 2020
NCT04347954 ⁸	Stanford Health Care, Stanford, California, USA	A double blind randomised controlled trial <ul style="list-style-type: none"> • 45 participants 	PVP-I 2% nasal spray and PVP-I 0.5% nasal spray	October 2020
NCT04364802 ⁹	University of Kentucky, USA	Non-randomised open label trial, parallel design <ul style="list-style-type: none"> • 250 participants 	PVP-I nasal spray and gargle (10% diluted 1:30)	May 2021
NCT04410159 ¹⁰	Universiti Kebangsaan Malaysia Medical Centre, Malaysia	Randomised open label trial, parallel design <ul style="list-style-type: none"> • 20 patients 	10 ml PVP-I 1% gargle (Betadine®)	August 2020

Bidra et al. (2020) in their in vitro study investigated the optimal contact time and concentration for virucidal activity of oral PVP-I preparations against SARS-CoV-2. The **PVP-I solutions of 0.5%, 1.0% and 1.5% concentrations** and virus were tested in test media [2% fetal bovine serum (FBS) and 50µg/ml gentamicin] at room temperature ($22 \pm 2^\circ\text{C}$) for 15 and 30 seconds. Ethanol (70%) was tested in parallel as a positive control and water as a virus control. Viral titres were calculated as 50% cell culture infectious dose (CCID₅₀/ml). All the PVP-I concentrations showed virus reduction of $>3 \log_{10}$ CCID₅₀ (from $3.67 \log_{10}$ CCID₅₀/0.1 ml to $0.67 \log_{10}$ CCID₅₀/0.1 ml) at 15 seconds. For contact time of 30 seconds, all PVP-I solutions were effective at reducing $>3.33 \log_{10}$ CCID₅₀ (from $4.0 \log_{10}$ CCID₅₀/0.1 ml to $0.67 \log_{10}$ CCID₅₀/0.1 ml or less) infectious virus. The 70% ethanol did not inactivate SARS-CoV-2 completely at 15 seconds but has inactivated the virus after 30 seconds of exposure. This study demonstrated that oral solutions of 0.5% PVP-I and at minimum contact of 15 seconds has virucidal activity.¹¹

Another in vitro study by Liang et al. (2020) was conducted to evaluate the virucidal efficacy of PVP-I in-situ gel forming formulations against SARS-CoV-2 along with the safety assessment in animal toxicology studies. The formulations tested were **1.0% PVP-I gel forming ophthalmic eye drop (IVIEW-1201)** and **0.6% PVP-I gel forming nasal spray (IVIEW-1503)**. Each formulation was tested at different concentrations and treatment time. Ethanol (4%) was tested in parallel as the positive control and water only to serve as the virus control. Higher concentrations (0.9% PVP-I of IVIEW-1201 and 0.54% PVP-I of IVIEW-1503) completely inactivated SARS-CoV-2 at two minutes. At 30 seconds, the half concentration of IVIEW-1201 (0.5%) and IVIEW-1503 (0.3%) able to reduce the virus to near or below the detection level. However, the lowest concentration of 0.09% IVIEW-1201 and 0.05% IVIEW-1503 formulations did not reduce virucidal activity significantly with increased contact time. The authors concluded that dose-dependent and time-dependent exposure of both PVP-I gel forming formulations have demonstrated virucidal activity.¹²

A preprint article by Anderson et al. (2020) on an in vitro study conducted to evaluate the virucidal activity of four PVP-I products against SARS-CoV-2. The products: **BETADINE® Antiseptic Solution (PVP-I 10% x/v)**, **BETADINE® Antiseptic Skin Cleanser (PVP-I 7.5% w/v)**, **BETADINE® Gargle and Mouth Wash (PVP-I 1.0% w/v)** and **BETADINE® Throat Spray (PVP-I 0.45% w/v)**, mixed with virus stocks were tested with phosphate buffered saline (PBS) containing 0.3 gm/l bovine serum albumin (BSA) at defined contact time. Viral titres were measured as 50% tissue culture infectious dose (TCID₅₀/ml). This study demonstrated all PVP-I products tested were effective in reduction of viral titre $\geq 4 \log_{10}$ (corresponding to a $\geq 99.99\%$ viral count reduction) compared to control at 30 seconds exposure. It was stated that the viral titre values ranged from 1.5×10^7 to 1×10^8 TCID₅₀/ml however detailed results were not specified.¹³

Hassandarvish et al. (2020) in their letters to the editor informed an in vitro study conducted in Malaysia to demonstrate virucidal activity on oral PVP-I product against SARS-CoV-2. Two concentrations of **BETADINE Gargle and Mouth Wash**, undiluted (**PVP-I 1.0% w/v**) and a 1:2 dilutions (**PVP-I 0.5% w/v**), were tested. The study showed undiluted PVP-I achieved $>5 \log_{10}$ reduction in the virus titres at 15, 30 and 60 seconds exposure. The 1:2 dilution demonstrated $>4 \log_{10}$ kill at 15 seconds and $>5 \log_{10}$ kill at 30 and 60 seconds.¹⁴ A pilot study was conducted by Nurul A Mohamed to assess the ability of regular gargling to eliminate SARS-CoV-2 in the throat and nasopharynx. A total of 20 patients were enrolled into four groups receiving **oral gargle PVP-I 1.0%**, essential oils gargle, tap water gargle and a control group.¹⁰ Oropharyngeal and nasopharyngeal swabs were taken on day 4, 6, and 12 post-interventions. The swabs were

subjected to detection of SARS-CoV-2 by real-time reverse transcriptase-polymerase chain reaction (rt RT-PCR). Unpublished results showed that subjects in the PVP-I 1.0% gargle were 100% PCR negative at day 4 post-intervention and continued to be negative at day 6 and 12. Whereas patients in essential oils group, tap water group and control group demonstrated 80%, 20% and 0% viral clearance, respectively. The sample size of this study was small.

Povidone-iodine and other coronaviruses

Eggers et al. (2018) conducted an in vitro study of bactericidal and virucidal efficacy of **PVP-I 7% gargle/mouthwash** against relevant oral and respiratory tract pathogens. PVP-I 7% gargle/mouthwash was diluted 1:30 with water to a concentration of 0.23% and tested at room temperature under clean conditions [0.3 gm/l bovine serum albumin (BSA)] and dirty conditions (3.0 gm/l BSA + 3.0 ml/l erythrocytes) with defined contact time. The results showed PVP-I concentration of 0.23% has effective bactericidal activity against *Klebsiella pneumoniae* (5.35 log₁₀/ml) and *Streptococcus pneumoniae* (>5.20 log₁₀/ml) under dirty conditions after 15 seconds of contact time which corresponded to reduction of bacterial count $\geq 99.999\%$. While, the virucidal activity showed reduction between 4.40 and 6.00 log₁₀ TCID₅₀/ml (corresponding to a reduction in viral titre of $\geq 99.99\%$) of **SARS-CoV, MERS-CoV, influenza virus A (H1N1) and rotavirus** after 15 seconds of exposure with PVP-I gargle at 0.23% concentration in the dirty condition. After 30 seconds, SARS-CoV and MERS-CoV were found to be inactivated. The authors suggested that PVP-I gargle/mouthwash at concentration of 0.23% may benefit high risk individuals as a measure of protective oropharyngeal hygiene from oral and respiratory pathogens.¹⁵

Another in vitro study by Eggers et al. (2015) evaluated the efficacy of three formulations of PVP-I against a reference virus (Modified vaccinia virus Ankara, MVA) and **MERS-CoV**. The three antiseptic products: **4% PVP-I skin cleanser, 7.5% PVP-I surgical scrub and 1% PVP-I gargle/mouthwash formulation**, were tested under clean conditions (0.3 gm/l BSA) and dirty conditions (3.0 gm/l BSA + 3.0 ml/l erythrocytes) with defined contact time. The MERS-CoV viral titers were reduced between 4.30 and 4.97 log₁₀ TCID₅₀/mL after 15 seconds of treatment with each undiluted PVP-I products, which corresponded to reduction of $\geq 99.99\%$.²

Kariwa et al. (2004) conducted an in vitro study to evaluate the antiviral efficacy of several PVP-I products, physical (heating and ultraviolet light) and chemical inactivation conditions against **SARS-CoV**. Results showed that treatment of SARS-CoV with **Isodine Scrub, Isodine Palm and Isodine Nodo Fresh** for one minute reduced the virus infectivity from 1.17×10^6 TCID₅₀/ml to below the detection limit. At one minute, **Isodine solution and Isodine Gargle** did not completely eliminate the virus infectivity. However, the virus infectivity completely inactivated after two minutes of treatment with all PVP-I products. This study also demonstrated treatment with 70% ethanol for one minute also reduced the viral infectivity under the detectable level (<10). SARS-CoV-infected cells treated with fixative including formalin, glutaraldehyde, methanol and acetone at five minutes were effective in inactivating the virus. Heating the virus at 56°C for 60 minutes or more reduced the infectivity from 2.6×10^7 TCID₅₀/ml to undetectable levels. While irradiation with ultraviolet light at 134 $\mu\text{W}/\text{cm}^2$ for 15 minutes reduced the virus infectivity from 3.8×10^7 to 180 TCID₅₀/ml. The SARS-CoV seemed to be resistant to UV irradiation as virus still detected (18.8 TCID₅₀/ml) even after 60 minutes of exposure.¹⁶

Povidone-iodine and procedural guidelines during COVID-19

The standard precautions in preventing the spread of COVID-19 including social distancing, appropriate use of personal protective equipment and hand hygiene practices, are highly recommended. However, in ensuring safe delivery of medical services, several interim guidelines have been developed. There is no published evidence regarding the clinical effectiveness of preprocedural mouth rinses (PPMRs) to reduce SARS-CoV-2 viral loads or to prevent transmission of COVID-19.¹⁷ The US Centers for Disease Control and Prevention (CDC) in their guidance for dental settings stated PPMRs with an antimicrobial product (chlorhexidine gluconate, essential oils, **povidone-iodine** or cetylpyridinium chloride) may reduce the level of oral microorganisms in aerosols and spatter generated during dental procedures.¹⁷ American Dental Association also suggested use of 1.5% hydrogen peroxide or **0.2% povidone** as a PPMR.¹⁸ These were considered, as SARS-CoV-2 may be vulnerable to oxidation inferring from the above in vitro studies.

Dexter et al. (2020) adopted an evidence-based approach from the anaesthesia view for optimisation of perioperative (preoperative, intraoperative, and postoperative) infection control and operating room management during COVID-19 pandemic. The authors recommended preprocedural chlorhexidine wipes, two doses of **nasal povidone-iodine** within one hour of incision, and chlorhexidine mouth rinse as steps of patient decolonisation.¹⁹

Chisari et al. (2020) outlined suggested action in preventing the spread of SARS-CoV-2 to be taken by arthroplasty surgeons when elective arthroplasties are resumed. The aim is to reduce the potential viral load and disrupting the chain of pathogen transfer. The procedure performed releases aerosolised materials containing blood, bone and fat tissue. Hence, one of the area proposed by the authors is each room used should be cleaned between cases with solutions such as **dilute povidone-iodine** and alcohol.²⁰

Safety

A literature review by Frank et al. (2020) explored the safety of povidone-iodine applied in the nasal and oral cavities along with the efficacy against SARS-CoV-2. Povidone-iodine has been used as preoperative nasal decontamination to reduce surgical site infections and postoperative contaminations. While PVP-I gargle has been utilised as antisepsis for oral surgical procedures and to prevent respiratory infections. Based on the review, the authors recommended usage of 0.5 to 2.0 ml of 1.25% PVP-I as nasal mucosal decontamination and up to 10 ml of 2.5% PVP-I for oral rinse. Povidone-iodine nasal and oral use should be avoided in patients with thyroid disease, pregnant patients, and patients receiving radioactive iodine therapy. Care should be taken if used in unconscious patients for risk of aspiration. In vitro studies showed PVP-I is effective against SARS-CoV and MERS-CoV at 0.23% after 15 seconds of exposure. Supported by a report that SARS-CoV-2 has shown up to 82% homology with SARS-CoV, PVP-I may be effective against SARS-CoV-2. However, till the review was published, there was no existing data evaluating the efficacy of PVP-I on SARS-CoV-2.²¹

Povidone-iodine is not listed as surface disinfectant in the United States Environmental Protection Agency (EPA) List N: Disinfectants for use against SARS-CoV-2.²²

CONCLUSION

Based on the review above, there was no retrievable evidence on the effectiveness, safety and cost-effectiveness of povidone-iodine for disinfection of SARS-CoV-2 from the scientific databases. There was an unpublished study that showed promising results. However, further study with bigger sample size is required.

REFERENCE

1. Cascella M, Rajnik M, Cuomo A, et al. Features, evaluation and treatment coronavirus (COVID-19). InStatpearls [internet] 2020. StatPearls Publishing. Available at <https://www.ncbi.nlm.nih.gov/books/NBK554776/> (accessed on 21 May 2020)
2. Eggers M, Eickmann M, Zorn J. Rapid and Effective Virucidal Activity of Povidone-Iodine Products Against Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Modified Vaccinia Virus Ankara (MVA). *Infect Dis Ther.* 2015;4(4):491-501. doi:10.1007/s40121-015-0091-9
3. World Health Organization. Clinical management of Covid-19. Interim guidance 27 May 2020. Available at [file:///C:/Users/user/Downloads/WHO-2019-nCoV-clinical-2020.5-eng%20\(1\).pdf](file:///C:/Users/user/Downloads/WHO-2019-nCoV-clinical-2020.5-eng%20(1).pdf) (accessed on 27 May 2020).
4. Kirk-Bayley J, Sunkaraneni V, and Challacombe S. The Use of Povidone Iodine Nasal Spray and Mouthwash During the Current COVID-19 Pandemic May Reduce Cross Infection and Protect Healthcare Workers. 2020. Available at SSRN: <https://ssrn.com/abstract=3563092> or <http://dx.doi.org/10.2139/ssrn.3563092> (accessed on 21 May 2020).
5. A Clinical Trial of Gargling Agents in Reducing Intraoral Viral Load Among COVID-19 Patients. *Clinical trials.gov.* Available at <https://clinicaltrials.gov/show/NCT04341688> (accessed on 24 June 2020).
6. Gargling and Nasal Rinses to Reduce Oro- and Nasopharyngeal Viral Load in Patients With COVID-19. *Clinical trials.gov.* Available at <https://clinicaltrials.gov/show/NCT04344236> (accessed on 24 June 2020).
7. Povidone Iodine Mouthwash, Gargle, and Nasal Spray to Reduce Naso- Pharyngeal Viral Load in Patients With COVID-19. *Clinical trials.gov.* Available at <https://clinicaltrials.gov/show/NCT04371965> (accessed on 24 June 2020).
8. PVP-I Nasal Sprays and SARS-CoV-2 Nasopharyngeal Titers (for COVID-19). *Clinical trials.gov.* Available at <https://clinicaltrials.gov/show/NCT04347954> (accessed on 24 June 2020).
9. COVID-19: Povidone-Iodine Intranasal Prophylaxis in Front-line Healthcare Personnel and Inpatients (PIIPPI). *Clinical trials.gov.* Available at <https://clinicaltrials.gov/ct2/show/study/NCT04364802> (accessed on 27 May 2020).
10. Povidone-Iodine Vs Essential Oil Vs Tap Water Gargling For COVID-19 Patients (GARGLES). *Clinical trials.gov.* Available at <https://clinicaltrials.gov/ct2/show/NCT04410159> (accessed on 3 July 2020).

11. Bidra AS, Pelletier JS, Westover JB, et al. Rapid In-Vitro Inactivation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Using Povidone-Iodine Oral Antiseptic Rinse. *J Prosthodont*. 2020. doi: 10.1111/jopr.13209.
12. Liang B, Yuan X, Wei G, et al. *In-Vivo* Toxicity Studies and *In-Vitro* Inactivation of SARS-CoV-2 by Povidone-iodine *In-situ* Gel Forming Formulations. *bioRxiv [Preprint]*. 2020. doi: 10.1101/2020.05.18.103184.
13. Anderson DE, Sivalingam V, Kang AEZ et al. Povidone-iodine demonstrates rapid in-vitro virucidal activity against SARS-CoV-2, the virus causing COVID-19 disease. *Research Square [Preprint (Version 2)]*. 2020. Available at <https://doi.org/10.21203/rs.3.rs-34544/v2>.
14. Hassandarvish P, Tiong V, Sazaly AB, et al. Povidone iodine gargle and mouthwash. *British Dental Journal*. 2020;228(12):900.
15. Eggers M, Koburger-Janssen T, Eickmann M, Zorn J. In Vitro Bactericidal and Virucidal Efficacy of Povidone-Iodine Gargle/Mouthwash Against Respiratory and Oral Tract Pathogens. *Infect Dis Ther*. 2018;7(2):249-259. doi:10.1007/s40121-018-0200-7
16. Kariwa H, Fujii N, Takashima I. Inactivation of SARS coronavirus by means of povidone-iodine, physical conditions, and chemical reagents. *Jpn J Vet Res*. 2004;52(3):105-112.
17. Centers for Disease Control and Prevention. Guidance for Dental Settings: Interim Infection Prevention and Control Guidance for Dental Settings during the COVID-19 Response. Updated May 19, 2020. Available at <https://www.cdc.gov/coronavirus/2019-ncov/hcp/dental-settings.html> (accessed on 21 May 2020).
18. American Dental Association. ADA Interim Guidance for Minimizing Risk of COVID-19 Transmission. Updated April 1st, 2020. Available at http://success.ada.org/~media/CPS/Files/COVID/ADA_COVID_Rapid_Advice_Treat_Pts.pdf (accessed on 27 May 2020).
19. Dexter F, Parra MC, Brown JR, et al. Perioperative COVID-19 Defense: An Evidence-Based Approach for Optimization of Infection Control and Operating Room Management [published online ahead of print, 2020 Mar 26]. *Anesth Analg*. 2020;10.1213/ANE.0000000000004829. doi:10.1213/ANE.0000000000004829
20. Chisari E, Krueger CA, Barnes CL, et al. Prevention of Infection and Disruption of the Pathogen Transfer Chain in Elective Surgery [published online ahead of print, 2020 Apr 22]. *J Arthroplasty*. 2020;S0883-5403(20)30436-8. doi:10.1016/j.arth.2020.04.049
21. Frank S, Capriotti J, Brown SM, et al. Povidone-Iodine Use in Sinonasal and Oral Cavities: A Review of Safety in the COVID-19 Era [published online ahead of print, 2020 Jun 10]. *Ear Nose Throat J*. 2020. doi:10.1177/0145561320932318
22. United States Environmental Protection Agency. List N: Disinfectants for Use Against SARS-CoV-2. Available at <https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2-covid-19> (accessed on 21 May 2020).

Based on available evidence up to 3 July 2020

Disclosure: The authors of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

Disclaimer: This rapid assessment was prepared to provide urgent evidence-based input during COVID-19 pandemic. The report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.

Malaysian Health Technology Assessment Section (MaHTAS),
Medical Development Division,
Ministry of Health, Malaysia.

