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Integrating One Health research in Sarawak, Malaysia: Addressing emerging and *re*-emerging infectious disease through international collaboration☆

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ABSTRACT

Comprising much of the northern side of the Island of Borneo, the Malaysian region of Sarawak is unique for its dense rainforests, diverse wildlife, and a human population that interacts closely with nature. One Health research in Sarawak, particularly that conducted by the Duke-SEGi-CRC Laboratory in the town of Sibu, has led to discoveries that are improving the health of Sarawakians. One Health research has resulted in the discovery of a novel canine-feline recombinant alphacoronavirus (genotype II), highlighting the potential for zoonotic transmission of respiratory viruses. Other One Health research has helped to determine the etiologies of human encephalitis and diarrheal illnesses, and specially improved the understanding of Japanese encephalitis (JE), *Plasmodium knowlesi* malaria, and melioidosis in Sarawak. This paper highlights the recent impact of international One Health collaborations in emerging and re-emerging infectious disease surveillance in this region. The collaborations have markedly improved local diagnostic capacity, identified previously unrecognized pathogens, and provided public health officials with a better understanding regarding the epidemiology of a number of infectious diseases.

1. Introduction

The Malaysian region of Sarawak comprises much of northern side of Borneo Island. It has a human population of around 2.5 million that is widely dispersed across markedly rugged terrain [1]. Sarawak is well known for its rich cultural and wildlife diversity, with approximately 46 % of populations residing in rural settings (Fig. 1), relying on traditional livelihoods and facing unique health challenges [2]. These areas are often surrounded by mangroves and river systems, or near the rain forest jungle. Sarawak's diverse ecosystems impact human health supporting diseases which have complex life cycles or complex ecology that often require One Health-oriented study for their mitigation. These diseases include, rabies, leptospirosis, *Plasmodium knowlesi* malaria, and Japanese encephalitis (JE), dengue, and melioidosis. The high degree of interactions between people and wildlife, frequent deforestation, and the movement of human habitats into jungle areas, have significantly increased zoonotic spillover risks in Sarawak, further underscoring the value of One Health approach [3].

Sibu, located in central Sarawak, is the gateway to the hinterland, with populations living in the interiors of Sarawak along the Rejang river converging in Sibu for trade and commerce. Sibu Hospital, a major referral hospital in Sibu, experiences many of the healthcare difficulties experienced in rural Malaysia. With heavy patient loads, challenging geographical barriers for gaining medical supplies, it has reduced medical diagnostic capabilities compared to nearby Singapore and big cities in West Malaysia. Up until several years ago, Sibu Hospital did not

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have the local laboratory capacity to diagnose a single viral illness.

Sarawak's researchers have recently increased their emphasis on One Health research and expanded their international collaborations. This has resulted in a stronger focus upon interdisciplinary research, increased diagnostic capabilities, and better healthcare delivery. This paper highlights the significance of Sibu Hospital's international One Health research collaborations. It illustrates how One Health research has improved healthcare services as well as helped to mitigate emerging and re-emerging infectious diseases threats.

2. Opportunities for international One Health research in Sarawak

In 2017, Sibu Hospital Clinical Research Centre, SEGi University, and Duke University constructed and equipped a molecular research laboratory in SEGi University's buildings on the Sibu Hospital campus. This Duke-SEGi-CRC Laboratory was a significant milestone in fostering international One Health research in Sarawak [4]. The level II biosafety laboratory supported multiple research collaborations and graduate student exchanges that paved the way for new diagnostic capabilities at Sibu Hospital. These molecular diagnostics also played a crucial role during the COVID-19 pandemic. This laboratory became the first Sarawak facility outside of Sarawak's capital of Kuching to perform polymerase chain reaction (PCR) testing, establishing local molecular testing capacity and enhancing public health preparedness [5,6]. The laboratory's role as central Sarawak's only laboratory conducting COVID-19 testing during the pandemic (until the Sibu Hospital Pathology Department established its molecular service in June 2020) underscored the value of this international One Health research collaboration [7].

During the pandemic, the Duke-SEGi-CRC Lab continued its One Health research activities despite the additional responsibilities of conducting COVID-19 diagnostic support. Over a period of several years, the laboratory adopted more than 30 unique molecular diagnostic tests for specific pathogens. These assays have resulted in improved clinical care and also yielded multiple scientific advances which have been published in international journals. These successes have won enthusiastic support from senior administrators in the Ministry of Health Malaysia and US Embassy [4] for future One Health research at Sibu Hospital.

3. Research findings and emerging pathogens

3.1. Respiratory viruses

Some of the first research collaborations documented a high prevalence of respiratory viruses among Sarawak's hospitalized pneumonia patients, with respiratory syncytial virus (RSV) and adenovirus being the most prevalent [8,9]. Co-infections were frequent, emphasizing the need for comprehensive diagnostic testing to guide treatment decisions [10,11]. The high burden of respiratory viral infection triggered an interest in further research, particularly regarding the characterization of frequently prevalent viruses and the possibility of cross-species infection. Important in characterizing respiratory viruses in Sarawak has been the application of pan-species respiratory virus diagnostics upon patients' specimens [12]. This led to the discovery of novel viruses where traditional clinical molecular diagnostics would miss their detection. One such pan-species diagnostic for coronavirus was developed at Duke University [13,14]. This pan-coronavirus assay was designed to detect α-, β-, γ-, and δ-coronaviruses and led to the isolation and characterization of a novel canine-feline recombinant alphacoronavirus (genotype II) in a patient hospitalized in Sarawak with pneumonia [15].

This novel coronavirus, named CCoV-HuPn-2018, likely represents the eighth unique coronavirus known to cause human disease, as some months after the virus' detection in Sarawak, a very similar virus was discovered in people with acute respiratory illness returning to the United States from Haiti [16]. Viral evolutionary studies suggest that the CCoV-HuPn-2018 virus likely departed from its animal origins around 60 years ago [17]. CCoV-HuPn-2018 and other novel coronaviruses detections in Haiti, Thailand, and USA [18], reinforce the position that animal coronaviruses likely cross species more often than we recognize.

After CCoV-HuPn-2018's discovery, subsequent research has been performed in Sarawak with a goal of determining if the virus is a human pathogen and how prevalent it might be among human pneumonia patients and healthy adults. Future study plans include surveillance for this virus among dogs in Sarawak. Additional studies are planned to examine potential shared transmission pathways. Such studies are necessary to determine if this novel coronavirus is a serious public health or veterinary health problem requiring intervention.

Fig. 1. A rural village in Daro, Sarawak, Malaysia, reflecting the challenges and resilience of communities living in remote settings (photograph taken and provided by Amrita Chandradas with permission).

3.2. Japanese encephalitis

Japanese encephalitis (JE) is a potentially fatal mosquito-borne viral disease endemic in Southeast Asia, characterized by severe neurological complications such as seizures and paralysis [19,20]. Sarawak established a hospital-based surveillance system and found that from 1997 to 2006, 92 % of cases occurred in children under 12 years of age, highlighting their vulnerability to the disease [21]. A successful JE vaccination program for children was initiated in Sarawak in 2001. This program has significantly decreased JE cases and their associated morbidity and mortality [21]. Similar findings have been demonstrated in other endemic countries in East Asia and the Indian subcontinent [22]. However, ongoing evaluation of the JE vaccination program is essential to monitor the program's effectiveness and to identify areas for improvement, such as implementing a catch-up program to address gaps in immunity.

JE exhibits a seasonal peak during the rainy season in Sarawak and is chiefly reported in central Sarawak [21]. Mosquito vectors responsible for transmitting this virus are expanding their range due to warmer temperatures and altered rainfall patterns, making previously considered low-risk areas like Australia vulnerable [23]. In contrast to Sarawak, Sabah, a neighboring state in Borneo, does not employ JE vaccination, and relatively little is known about JE there. Nearly 20 years of JE surveillance data in Sabah suggest a much lower JE incidence. The limited JE detections in Sabah have not correlated with pig farming, or changes in rainfall, leading researchers to posit that JE cases are markedly under reported in Sabah [24].

Thus, effective JE control in both Sarawak and Sabah requires One Health-like interdisciplinary collaborations between human healthcare providers, veterinarians, and entomologists. These assessments need to be periodic such that public health officials may respond to dynamic changes in JE epidemiology, enhancing public health education programs and JE vaccine use. There is also a very real need to assess the impact of deforestation on JE and to determine which geographical areas and human age groups are at highest priority for future vaccination [21,22].

3.3. Herpes simplex and other viral causes of encephalitis

Viral encephalitis remains a significant public health concern in Sarawak, with JE being a major contributor [20]. A number of other viruses, including herpes simplex (HSV), herpes zoster (HZV), enteroviruses, and dengue, also cause encephalitis [20,25,26], especially among children [27]. It has been reassuring to know that other emerging arboviruses threats such as chikungunya virus and Zika virus, have not yet been detected in a recent surveillance effort in Sarawak [28].

For HSV encephalitis, detecting the virus in the cerebrospinal fluid (CSF) is crucial because effective antiviral treatment is available, and early initiation can reduce mortality of HSV encephalitis by 28 % [29]. However, the treatment is only effective against HSV and has multiple side effects, particularly renal compromise. International guidelines recommend that acyclovir should be empirically initiated in all cases of encephalitis but should be discontinued if a molecular assay for HSV is negative (especially from the CSF) within 72 h of illness [25–27]. Nevertheless, the decision to start or discontinue acyclovir is challenging for clinicians practicing in areas with limited molecular diagnostic capability. Clinicians in this setting have little choice but to diagnose HSV encephalitis presumptively. This often result in unnecessary antiviral treatment or inappropriate discontinuation of other treatments. This challenge was addressed with the establishment of the Duke-SEGi-CRC molecular laboratory in 2017 through a successful international research collaboration. The availability of a regional molecular diagnostic facility has significantly reduced antiviral usage and its adverse events [30]. The regional molecular laboratory also helped to demonstrate the low incidence of HSV and HZV among encephalitis patients in Sarawak, with a 0.76 per million population per year incidence for both, lower than previously reported [20,26,27,31]. The low incidence of HSV [30] and relatively frequent encephalitis morbidity and mortality highlight the need for encephalitis etiology and pathogen discovery efforts. The low incidence of HSV among encephalitis patients was the first study to provide information on the incidence of HSV encephalitis in Sarawak.

A strong collaboration between healthcare providers, public health authorities, and research institutions is essential for understanding, diagnosing, managing, and preventing encephalitis in this region. Hence, a comprehensive One Health approach that emphasizes human, animal, and environmental health is crucial to address the viral encephalitis challenges in Sarawak. Future niche research could focus on aspects related to diagnostics, clinical management, epidemiology, and unique challenges faced by healthcare systems in Sarawak. Given the limited data on infectious encephalitis in Sarawak, comprehensive studies are needed to understand the prevalence and incidence of HSV infections and other viral causes in different population groups in Sarawak: urban vs. rural populations, pediatric vs. adult patients, and people with weakened immune systems (e.g., HIV patients), and the relationship of encephalitis causes with the environment and possibility of zoonotic nature. One Health collaboration is critical in this research, as it will require the expertise of various medical and public health professionals, veterinarians and environmental experts. Given the vast land size of Sarawak, research into the development and deployment of point-of-care diagnostic tests for HSV and viral causes of encephalitis cases will be especially valuable in rural areas where PCR-based diagnostics are not readily available. Long-term studies on the neurological and cognitive outcomes of patients who survive HSV encephalitis in Sarawak, especially children, are crucial to identify gaps in post-infection care and inform rehabilitation strategies to improve quality of life.

3.4. Influenza D virus (IDV)

Poultry farms represent a critical human-animal interface, increasing the risk of zoonotic transmission. In a One Health research study, Bailey et al. [32] detected IDV in bioaerosol samples from poultry farms in Sarawak. The study highlighted the potential for airborne transmission routes from the poultry to farm workers and the surrounding community. The unique genetic sequence of the IDV strain detected in Sarawak indicated viral evolution and diversity. This finding highlights the need for continuous surveillance for this potential human health threat, which can be achieved through meaningful collaborations with the agriculture sector through the One Health approach. IDV surveillance in both animals and human populations should focus on prevalence, genetic diversity, and evidence for cross-species infections. By adopting a One Health approach incorporating surveillance, occupational health interventions, and collaborative research, we can effectively mitigate the risks posed by IDV and other emerging zoonotic threats in Sarawak and globally.

3.5. Respiratory and diarrheal pathogens at the human-pig interface

Another meaningful One Health collaboration in Sarawak led to the discovery of overlapping respiratory and diarrheal pathogens in humans and pigs, suggesting another potential zoonotic transmission [33]. Humans and pigs in areas with pig farming activities and human settlements from different locations in Sarawak were sampled. The study strikingly demonstrated the potential of pathological viruses, such as influenza and adenovirus, to cross species barriers. These findings again demonstrated the interconnectedness of human and animal health, necessitating a holistic approach to infectious disease management. Preventative measures, such as vaccination and hygiene practices in both settings and minimizing human-animal contact, are crucial to reducing zoonotic transmission risks. Collaborative efforts between human and animal health sectors are essential to address these risks

effectively, including data sharing, developing joint surveillance strategies, and coordinating interventions.

3.6. *Plasmodium knowlesi malaria*

Malaria, caused by *Plasmodium knowlesi*, was first reported in humans in Sarawak [34]. It is considered an emerging zoonotic disease of increasing concern with high prevalence in Southeast Asia, particularly Sarawak [35]. In Sibu, the incidence rate of *P. knowlesi* malaria fluctuated between 20 and 40 cases per 100,000 population over a ten-year period from 2012 to 2021 (Fig. 2). This trend saw a notable decline after 2022, likely due to reduced hunting and selling of wild boar. The stricter laws and enforcement implemented in response to concerns over African swine fever [36] appear to have played a role in curbing these activities, thereby contributing to the decrease in malaria transmission, demonstrating the inter-connectedness of human activities and zoonosis. The zoonotic nature of the disease, with macaque monkeys serving as a reservoir host, underscores the interconnectedness of human and animal health. Collaborations between human health services, veterinary professionals, environmental agencies, forest management departments, and local communities are key to successfully implementing One Health control strategies. Continuous surveillance efforts to monitor the prevalence, geographic distribution, and seasonal patterns of *P. knowlesi* and developing rapid and accurate diagnostic tools for detecting *P. knowlesi* in both human and animal populations, particularly in remote rural settings, are essential [37].

An important knowledge gap to fill towards the control of *P. knowlesi* malaria is to study the behavior of mosquito vectors in Sarawak, as they differ from mosquitoes in other regions of Borneo [38,39]. Specific data needs include gaining knowledge where mosquitoes breed, how their behavior differs from other species, and what environmental factors affect malaria transmission. A greater understanding of vector behavior will contribute to developing more targeted vector control strategies with a goal of interrupting *P. knowlesi* transmission cycles. Research is also required to investigate the potential impact of global warming, land-use change, human activities, and the interrelatedness of parasites, vectors, reservoirs, and humans in agricultural and deforested areas [40].

Finally, future collaborations should also explore the possibility of creating a *P. knowlesi* malaria vaccine. To date, only two vaccines are available against malaria and both seek to prevent disease from *Plasmodium* falciparum [41]. As *P. knowlesi*'s nonhuman primate reservoirs make it especially difficult to control, vaccines against *P. knowlesi* are important to produce. A vaccine against *P. knowlesi* malaria administered to nonhuman primates or humans could markedly improve *P. knowlesi* malaria control efforts [42].

3.7. *Melioidosis*

Burkholderia pseudomallei is a soil-dwelling, potentially fatal causative agent of melioidosis. This disease is particularly important in Southeast Asia, including Sarawak [43]. The incidence rate for melioidosis in Sibu fluctuated between 0.3 and 2.6 per 100,000 populations in the last 10 years (Fig. 3). The disease causes a wide range of clinical manifestations which make clinical diagnosis challenging. Often, clinicians fail to consider the disease in their evaluation of patients and miss diagnosis [44]. Even when the disease is considered, diagnosis requires specialized laboratory techniques, which may not be readily available in resource-limited settings [45]. Hence, this neglected bacterial infection is frequently under-reported in areas like Sarawak, making its true prevalence unknowable [44].

Hence, studies are needed to assess the environmental reservoirs for *B. pseudomallei.* A One Health research approach that captures the geographical distributions of human and animal morbidity is greatly needed. Mapping high risk geographical areas and determining what environmental factors (e.g., pH levels, rainfall) are supporting high bacterial prevalence are first steps in reducing morbidity. The development of rapid, point-of-care diagnostic tools for melioidosis are sorely needed, especially in under-resourced districts in Sarawak. The potential public health impact of such research could be quite significant.

3.8. *Other diseases of importance in Sarawak*

Although zoonotic diseases such as dengue, rabies, and leptospirosis are not unique to Sarawak, they are major causes of mortality and morbidity and considered of high public health importance [46–48]. Like the previously mentioned diseases, stronger collaboration between healthcare providers, public health authorities, veterinarians and research institutions, with input from international experts, is essential for understanding, diagnosing, managing, and preventing these pathogens of concern.

One Health collaboration plays a crucial role in addressing emerging and re-emerging infectious diseases in Sarawak. In line with this, we have illustrated the importance of integrated surveillance and response systems that bridge human, animal, and environmental health sectors through various studies and efforts. Below, we outline a proposed One

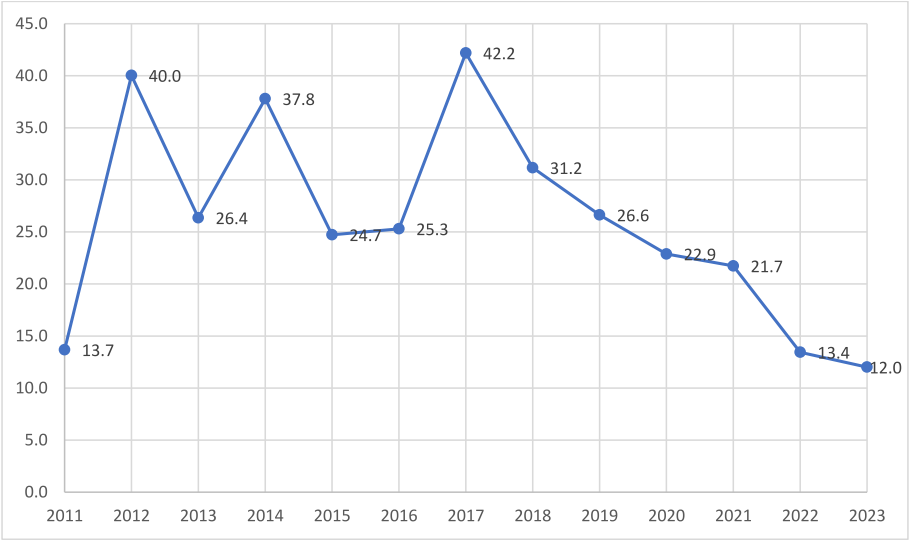

Fig. 2. Incidence rates of *P. knowlesi* in Sibu (per 100,000 populations) between 2011 and 2023.

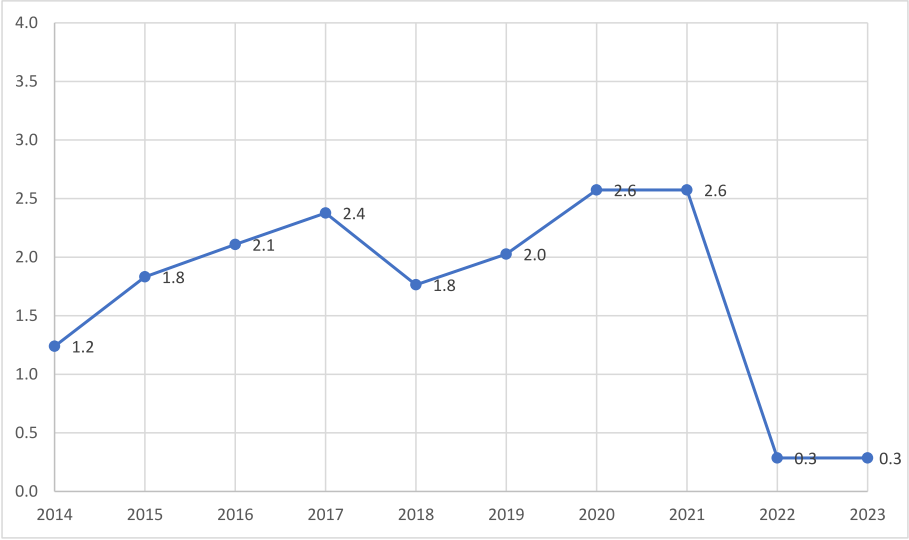

Fig. 3. Incidence rates of Melioidosis in Sibu (per 100,000 populations) between 2014 and 2023.

Health framework to mitigate future public health threats, ensuring rapid detection, collaboration, and response across all relevant sectors.

4. One Health collaborative framework

The One Health Collaborative Framework for Sarawak should be built on four key pillars: Coordination, Surveillance, Response, and Support, as follow:

4.1. Cross-sectoral coordination

A multifaceted approach is required to effectively address emerging and re-emerging diseases. This will likely require the establishment of a permanent One Health Taskforce comprised of representatives from health departments, veterinary services, environmental agencies, academic institutions, local government departments, and international experts. This taskforce would periodically and regularly convene to plan research, share findings and coordinate responses to disease outbreaks. Fostering such multi-sectoral and international collaborations could markedly improve disease surveillance and response.

To be successful, the Taskforce will need to involve leaders from various geographical areas, particularly areas where human-wildlife interaction is frequent. These community representatives will be critical in educating the public, promoting disease prevention efforts, and winning support for Taskforce interventions. Examples of community activities might include reducing mosquito breeding habitats, conducting human and animal vaccine drives, and dispelling inaccurate social media information that might derail Taskforce programs. Existing community volunteers such as the Village Health Promoters [49] could be utilized and trained in One Health concepts and assist the Taskforce on the ground.

4.2. Integrated surveillance systems

A comprehensive and integrated surveillance system is urgently needed in our efforts to effectively prevent and respond to emerging and re-emerging zoonotic diseases. This system should encompass the integration of human and animal health surveillance. It should strengthen and facilitate unusual disease reporting in human healthcare settings, veterinary facilities, livestock farms, and wildlife sectors. In addition, data-sharing mechanisms need to be established for real-time data exchange between sectors. Such real-time data sharing is fundamental to rapid assessment and timely response to a potential emerging disease event.

4.3. Rapid response mechanisms

Effective mitigation of the threat of emerging diseases requires proactive preparedness measures, such as developing and practicing contingency plans for responding to outbreaks. Plans must include clear responsibilities between the various sectors involved and especially how investigations will be supported with interdisciplinary response teams, vehicles, supplies, and laboratory diagnostics. We propose the formation of a Sarawak Multidisciplinary Rapid Response Team to mobilize rapidly upon notification of a potential outbreak of zoonotic disease. Establishing such interdisciplinary response teams and planning for their swift mobilization is paramount. Regularly conducting mock emergencies or outbreak response will instill confidence in various participating sectors.

4.4. Continuous support for innovative one health research

Finally, in Sarawak, we need to continue to support innovative One Health research that seeks to improve the health of humans and animals. Some of the most pressing disease needs are those we have discussed here. They include mitigating our high prevalence of viruses causing respiratory and diarrheal diseases, JE, *P. knowlesi* malaria, and melioidosis. The proposed One Health framework should support long-term collaborations for the development of diagnostics, vaccines, and therapeutics tailored to local needs.

5. Conclusion

Sarawak's unique environment, characterized by dense rainforests, diverse wildlife, and close human-animal interaction, offers a unique opportunity for One Health research. Due to the complex relationship between humans, animals, and the environment, a holistic, interdisciplinary, and global approach is required to address healthcare challenges and prevent future emerging disease outbreaks. We have proposed a One Health framework that seems appropriate for tackling these complex challenges and promoting sustainable health outcomes in this remarkable region. In adopting the proposed integrated framework, Sarawak will be better equipped to respond to current health threats and also have the necessary infrastructure to adapt to future challenges. This comprehensive One Health approach ensures a resilient public health system capable of addressing emerging and re-emerging pathogens.

Future research on emerging and re-emerging pathogens, developing new diagnostic tools, and implementing effective prevention strategies can significantly impact public health, preserve biodiversity, and promote more sustainable development in Sarawak.

CRediT authorship contribution statement

Teck-Hock Toh: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Jeffrey Soon-Yit Lee:** Writing – review & editing, Conceptualization. **Kamilah Dahian:** Writing – review & editing, Conceptualization. **Aw-Zien Toh:** Writing – review & editing, Writing – original draft, Conceptualization. **Jo-Hun Teh:** Conceptualization, Writing – review & editing. **Mohd Raili Suhaili:** Writing – review & editing, Supervision. **Gregory Charles Gray:** Writing – review & editing, Supervision.

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Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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