

## Tropical diseases in Malaysia: Past, present and the future

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### The Past

In reminiscing tropical medicine research in Malaysia, it will be a great injustice if the history of the Institute for Medical Research (IMR) is not mentioned. The history began when Sir Patrick Mansor, the father of Tropical Medicine, then the medical adviser to the British Secretary of State for the colonies, pledged the aid of Colonial Office for scientific research into the causes of tropical diseases and announced the intention to establish schools of tropical medicine in the United Kingdom in 1898<sup>1</sup>. Within months, in 1899, the Liverpool and the London Schools of Tropical Medicine were open. The following year in 1900, the first research outpost of the London School of Tropical Medicine was established in Kuala Lumpur, the Kuala Lumpur Pathological Institute, which became the foundation and renamed as it stands now, the Institute for Medical Research (IMR) in 1901.

In the words of Sir Frank Swettenham in his congratulatory message, the IMR work will be devoted towards a scientific and sustained research into the causes and the means of preventing and curing scourges such as beri-beri and all forms of malaria fever. Indeed, the establishment of the IMR was the landmark occasion that propelled the IMR to glory in tropical disease research. Many early studies before independence, contributed to our understanding of the biology, ecology, transmission dynamics, diagnosis and treatment of many tropical diseases such as malaria, lymphatic filariasis, beri-beri and scrub typhus.

Dr Hamilton Wright was the first Director who wasted no time in studying the twin scourges of beri-beri and malaria. Within two years, the Institute's first two Study Series were published. The first was on the malaria fevers of British Malaya and the second was on the aetiology and pathology of beri-beri published in 1902.<sup>2,3</sup> The Institute is also the training ground of the early local legends in various disciplines of tropical medicine in the likes of Dr Lim Boo Liat (zoology) and Dr Nadchatram (acarology) and the recent past outstanding researchers

such as Prof Emeritus CP Ramachandran and Prof Emeritus Mak Joon Wah.

With regards to Malaysian Society for Parasitology and Tropical Medicine (MSPTM) and Southeast Asian Ministers of Education Organisation Network on Tropical Medicine (SEAMEO-TROPMED), two names were legendary. Prof AA Sandosham, was the co-author of the book "Malariology: With special reference to Malaya" which remains a relevant reference text till today.<sup>4</sup> MSPTM was officially established in 1964 and Prof Sandosham was elected as its first President. Prof Sandosham was with the University of Singapore and they were part of Malaysia then. The address of the Society has not changed since then, which is the IMR. Prof. Dato' Dr. Ungku Omar was the first Malay to become a Director of the IMR, an eminent pathologist with public health close to his heart, highlighting the close link between poverty and health. He was instrumental in getting the IMR into the Regional grouping of SEAMEO-TROPMED and enhancing collaboration with international bodies such as the World Health Organisation (WHO). However, the nation had a tragic loss with his passing at a young age of 38 years old in 1969. Nevertheless, he laid the foundation and the IMR was the WPRO Regional Centre for Training and Research in Tropical Medicine and Nutrition for many years and has remained a SEAMEO-TROPMED Centre for Microbiology, Parasitology and Entomology. IMR is also currently a WHO Collaborating Centre for Vectors of Malaria, Filariasis and Dengue.

In the more recent past, we also have two great names in tropical medicines who were closely associated with IMR. Prof Emeritus CP Ramachandran, who started his career in the IMR, is an accomplished scientist and scientist diplomat. As Chief Scientist of WHO Filariasis Programme, he was instrumental in getting research carried out globally on ivermectin as a safer alternative to treat and control onchocerciasis, the major cause of blindness in Africa. The discoverers of ivermectin, Prof Toshi Imura and Prof William Campbell were awarded the Nobel Prize in 2015. He is a scientist diplomat

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*par excellence* because he could put together a Global Programme to Eliminate Lymphatic Filariasis (GPELF) through a World Health Assembly Resolution in 1997.<sup>5</sup> On top of that, he was able to galvanise the support of the global community, pharmaceutical industries and philanthropists in supporting the implementation of this strategy. The biggest component of GPELF is the donated medicines by the pharmaceutical industries for the mass drug administration (MDA) strategy. The impact is simply remarkable. After 13 years in 55 countries, the global prevalence of lymphatic filariasis (LF) was calculated to have fallen by 59% from 3.55% to 1.47%. In the same study, it is estimated that 96.71 million LF cases, 18.73 million hydrocele cases and a minimum of 5.49 million lymphedema cases have been prevented or cured during this period.<sup>6</sup> The prospect of interrupting LF transmission looks bright. LF has been eliminated in Peninsular Malaysia with remaining as isolated foci in Sabah and Sarawak. Ramachandran was awarded the Marry Kingsley Medal by the London School of Tropical Medicine in 1999, placing him among the list of international distinguished leaders of tropical medicine and public health.

Prof Emeritus Mak Joon Wah is also a great son of the nation in tropical medicine particularly in malaria and filariasis. He was the first in the world to culture the larval stage of *Brugia malayi* to immature adult stage *in-vitro*,<sup>7</sup> opening the floodgates to the study of the life cycle, biology, immunology and pathology of the infection. He is a world recognised expert, having served as a WHO consultant to 17 countries. His contribution to the science and body of knowledge on parasitology and tropical medicine is exemplary, having published more than 350 scientific papers. He co-authored an Atlas of Medically Important Parasites with Dr Choong Mooi Fai, his wife. The book is now in its 3rd Edition with more than 5,000 copies sold worldwide. He was the joint recipient of the National Science Award in 1985 and the winner of the Merdeka Award in 2011 for his outstanding scholastic achievement.

The IMR has continued to do well in some areas of tropical medicine research and recently during the World Health assembly in May 2018, an IMR team of young scientists won a prestigious WHO award, the Dr Lee Joon Wook Memorial Prize for Public Health, for their home grown innovation of maggot therapy for difficult skin ulcers.

### Current Situation

Although Malaysia is experiencing a clear shift in the health burden from acute infectious diseases to chronic non-communicable diseases, the challenges of the unfinished agenda and the unexpected of tropical diseases are considerable and cannot be ignored. We are very vulnerable to damaging zoonotic infections, which can cause severe pandemic and tremendous socio-economic loss. Since 1940, 60% of emerging infections were zoonotic in nature.<sup>8</sup> Predicting zoonotic infections as what is next to come, is difficult and almost impossible. While the source of the infection is the animals and humans are at the receiving end, lack of ownership and shifting of responsibility between and among various stakeholders, is a major issue undermining effective and efficient management of the risk and control of emerging zoonotic infections. What more, Malaysia and the South and Southeast Asian countries are in the hotspots of emerging zoonotic infection, where the known drivers include human population density, change in human population density and wildlife diversity.<sup>9,10</sup>

While we are at risk of facing newly emerging pathogens, we are still grappling with the existing endemic zoonotic infections of public health importance in Malaysia. In order to get a better picture of the situation, the Ministry of Health Malaysia (MOH) has decided to make leptospirosis a notifiable disease under the Prevention and Control of Infectious Diseases Act in 2010. Since then the incidence of leptospirosis continues to rise peaking in 2015 with an incidence rate of 27.2 per 100,000 population. Comparison between countries is difficult because of differences in notification

practices and diagnostic criteria used. It is nevertheless much higher than the reported incidences in Philippines (4.8) and Singapore (2.0) but lower than Thailand (48) and Seychelles (432).<sup>11</sup> The incidence is also highly fluctuating on a weekly basis but it generally peaks at the end and the beginning of the year, coinciding with the monsoon season and the risk of flooding which is a common contributing factor. In contrast to the popular belief that the problem is mainly in natural recreational areas such as waterfalls, it is interesting to note that reported outbreaks mostly occurred in urban residential areas as well as in rural community settlements such as the long houses, detention centres and the Orang Asli villages (MOH and Personal Communication).

This drives the important point that leptospirosis in Malaysia and everywhere else, has gone beyond the occupational hazard to become a living hazard. It boils around the issue of environmental cleanliness and hygiene, as well as issues of food wastage and waste management. While individual habits of food wastage are deplorable, the management of waste and urban sanitation is also much to be desired. No city in the world is free from rats. In developed nation cities, rats are confined to the sewage system to source for food and thus have minimal contact with humans, therefore minimising the risk of leptospirosis. But in Malaysia especially in the wet markets and popular outdoor eating outlets, the rats are bigger than the cats and environmental samples tested are heavily contaminated with *Leptospira*.<sup>12</sup> Management of environmental sanitation in Malaysia is under the local government and unless they take the ownership of leptospirosis problem as part of the overall environmental sanitation and waste management performance indicator, we will continue to live with this risk.

Malaysia has a fair share in contributing to the list of newly emerging infections in the form of Nipah virus encephalitis, which some of us here had the opportunity of experiencing first-hand the excitement, turbulence, drama, chaos, initial sense of helplessness and final relief in managing this severe devastating outbreak. Looking back, the emergence of Nipah virus is a classic example

of how anthropogenic factors drive the emergence and how unprepared we were in facing such as a severe health threat.<sup>13</sup>

But do we learn from this terrible incidence? Based on the author's 8 years helming the disease control and public health programme of the Ministry of Health Malaysia, he personally felt that many have forgotten the lesson learnt. The level of inter-sectoral cooperation and information sharing is much more to be desired. Malaysia's resources with regards to laboratory support are still fragmented and the Centre for Disease Control project mooted by the then Prime Minister in 2002 during the ASEAN Summit has yet to take off because of competing priorities.

Interestingly, it will be much more challenging now to do what was thought was the right thing to do then, with regards to managing the affected animals. In a recently published article, it is becoming much more difficult now to justify for the culling of animals in the light of another Nipah event.<sup>14</sup> The same challenge was faced by the Malaysian authority when trying to manage stray dogs in responding to an outbreak of rabies in the northern states of Penang, Perlis and Kedah last year in 2017.

Malaysia had a crude shock with regards to rabies, a fatal infection if not treated correctly and early. The official statistics of the Disease Control Division, MOH showed that there is no rabies case for the last 10 years until 2016. In fact, the Department of Veterinary Services (DVS) had submitted an official declaration in 2012 that Malaysia is free from rabies among its animal population. Barely 3 years from that rabies-free declaration, Malaysians were caught by surprise in 2015 of an outbreak of suspected rabies in the northern states of Perlis, Penang and Kedah. Clinical cases conforming to rabies with history of dog bites were admitted to hospitals but no human confirmed cases were notified and registered with MOH. MOH was frantically looking for the information of the infection in the dogs from the DVS counterpart, to provide the epidemiological link to the suspected human cases, but it was not forthcoming,

despite rumours that dogs were found to be positive. The problem created a huge policy decision gap on the part of MOH in managing the suspected human cases outbreak and in carrying out risk communication to the public.

As mentioned earlier, it is almost impossible to predict a new emerging zoonotic pathogen but for endemic diseases such as rabies, there are tell-tale signs that we need to pay attention to. Rabies is still largely endemic in neighbouring countries of Malaysia that share the land border, namely Thailand to north of Peninsular Malaysia and Indonesia to the south of north Borneo states of Sabah and Sarawak. Cross border control of dog movement and rabies virus surveillance programme in dogs are supposed to prevent the re-introduction of rabies to Malaysia but how much does the border patrol appreciate the importance of such border control and how extensive and comprehensive is the virus surveillance, remains a question.

And two years later, last year 2017, the stark reality faced the Malaysian public, when the first confirmed rabies death after 20 years was reported in Sarawak.<sup>15</sup> The war against rabies still continues to this day and Malaysia will continue to record unnecessary casualties; the eighth death was reported on 3 May 2018. While vaccinating all dogs is the main strategy, the question still remains as to what is the actual implementation plan that the state government is implementing, especially in dealing with stray dogs.

While public assurance and risk communications are critical in managing the outbreak, a question remains as to why MOH must continue to take the ownership and leadership in this issue, as apparent by the various press releases made by the Ministry. Licensing the dogs and requirement for vaccination is under the purview of the Local Authority and maybe the Department of Veterinary Sciences (DVS). Managing stray dogs, which is a public nuisance, is also the responsibility of the Local Authority. As with leptospirosis, unless the root problem is resolved, which is the issue with the Local Authority, our efficiency and effectiveness in managing

such an outbreak and our ability to maintain the state of control, will be compromised.

Malaysia has done well in managing malaria as a public health problem. There is a strong sense of optimism among the global community too that Malaysia can now talk about eliminating the local transmission of malaria. WHO announced the global agenda during the World Malaria Day of 2016. The optimism stems from the fact that we already have all the effective tools to tackle the four components of the malaria transmission dynamics namely, protecting the host, treating the infecting agents and thus removing the source of infection to the mosquito vector, managing the vectors and manipulating the environment to minimise vector breeding. Indeed, we are progressing well too in the local context. Human malaria incidence continues to decline steadily in Malaysia and many states are now malaria free. We can even eliminate *Plasmodium vivax* from many areas without any resurgence.

But our concern is the increasing trend of *P. knowlesi* infection. It is now the most dominant species infecting humans in Malaysia. The proportion is higher in Sarawak and Sabah where it constitutes to about two thirds of the total reported malaria cases annually. As such, an important question was raised, will simian malaria impact on the global programme to eliminate malaria? The infection can impact on global elimination if human-to-human transmission occurs, and so far we are lucky as there is no evidence of human-to-human transmission of *P. knowlesi*. Indeed, the infection foci for human and simian malaria are quite distinct even in Sabah and Sarawak where most of the cases are being reported (Figure 1).

With the restricted distribution of the natural host and the absence of compelling evidence of human-to-human transmission, the impact on the global elimination programme is considered as not significant at this stage. Furthermore, the distribution of *P. knowlesi* follows closely the distribution of its natural hosts which are the two macaques, *Macaca nemestrina* and *M. fascicularis*,

which are practically restricted to the Southeast Asian region.<sup>16</sup> Despite the wide distribution of the natural host in the region, *P. knowlesi* in humans is practically reported only from Malaysia. There are imported cases from Indonesia and Thailand although the one imported from Papua New Guinea is a misnomer since the country is outside the normal distribution of the natural hosts. An imported case from Indonesia was also reported by Australia.<sup>17</sup> This contention that simian malaria will not impact on the elimination of human malaria is further supported by the work of Imai *et al.*, 2014. They described a comprehensive modelling study and it indicated that simian malaria should not be a major problem to local programme managers because existing strategies like the use of bed-net and early diagnosis and early treatment should be able to provide positive impact on the prevalence of the infection.<sup>18</sup>

However, the problem of simian malaria brought about a bigger challenge in managing the eco-system, in promoting the balance between socio-economic needs through commodity crop plantation and the impact on natural eco-system, which borders the overall national policy decision-making process. Nevertheless, at the population level, better understanding of the behaviour of the natural primate hosts as well as the mosquito vectors and the interaction with human behaviour in disease transmission, would provide better solutions to the problem, and this would entail a multi-disciplinary approach in the study design.

Currently the biggest challenge is with dengue. It is the most rapidly increasing infectious disease burden in world and also in Malaysia, rising exponentially over the years. In Malaysia, dengue outbreak is cyclical with the major outbreak occurring every 4-5 years. What is most obvious is that not only are the cycles getting closer, the peak of each outbreak cycle is getting higher and higher exponentially too, with the last highest peak in 2015 with more than 120,000 confirmed cases. And this cyclical pattern of dengue is occurring on a weekly basis and within a year, it is quite common to see two or more peaks of dengue outbreak. Selangor, the greater

Klang Valley for that matter, contributed about 60% of the total reported cases. Considering the limitation in access to diagnosis, the estimated minimum number of dengue cases is 2000 cases a week. We seem to be not able to suppress it any further, to such an extent that the MOH has been questioned for not doing the right thing.

### The Future

With the current persistent challenges of tropical diseases of public health importance, elements of uncertainty and the unknown risk of emerging infections in the future and threat of cross border health security, it is reckoned that tropical medicine is still an important medical discipline which warrants continued investment in human resource development, research and development. Unlike malaria, dengue is still largely an unfinished agenda not only for Malaysia but also regionally and globally. With climate change and global warming, the risk of geographical spread into the temperate countries is real. In fact, sporadic local outbreaks in some of these countries are already occurring.

The real problem with dengue, unlike malaria, lies in the fact that we do not have enough effective tools to attack all the four components of the transmission dynamics, compounded by the super-efficient *Aedes* vector and the lackadaisical attitude of the community that contribute to the breeding of the mosquito. We do not have an effective vaccine to protect the host and the use of bed-net is impractical and ineffective. There is no drug to clear the infecting virus and the environment is difficult to manage because of the *Aedes* cryptic breeding behaviour and human behaviour in littering. A systemic review and meta-analysis evaluated the evidence of the effectiveness of vector control intervention and found that among others, there is strong evidence that community-based campaign can impact on vector abundance, moderate evidence that house screening can reduce vector abundance and no robust studies on the impact of fogging on dengue transmission.<sup>19</sup>

MOH continues to explore new technologies and methods in trying to find sustainable solutions to the dengue menace. Malaysia participated in the multi-centre Phase II/III clinical trial of candidate vaccine. Malaysia also experimented on transgenic mosquito but had to abandon it half-way through for various reasons. Currently the IMR with its international partner is conducting field trial on *Wolbachia* infected *Aedes* in the control of dengue. At the same time, the IMR is exploring the use of Sterile Insect Technique for the same purpose. In adopting any new intervention technology, it is important to be guided by the principle that it must be scientifically sound, feasible, practical and affordable to ensure sustainability over time.

The risk of another Nipah virus-like outbreak is real. The natural reservoir flight range, the fruit bats of the Pteropodidae family, is huge and expanding across continents. Recent studies showed that repeated introduction of the virus, prime the persistence and emergence of Nipah virus, refuting earlier hypothesis that the El-Nino phenomena drives the emergence of the virus. The seroprevalence rates of Hepanivirus infection among sampled fruit bats were also relatively high.<sup>20</sup> In Bangladesh, the risk of human infection has been persistent and human cases and mortality have been reported almost every year for the last 15 years since its first introduction in 2001, two years after the only outbreak in Malaysia in 1999.<sup>21</sup>

Malaysia being centrally located and a popular destination for economic migrants, both legal and illegal, is at high risk of importing exotic and severe tropical infections thus compromising its national health security (Figure 2). With an estimated number of 4 million illegal migrants, the risk is real. For example, we do have the vector for bancroftian filariasis which is *Culex quinquefasciatus* which is abundant in most urban areas and lymphatic filariasis is not in the list of infections screened under the Foreign Workers Medical Screening programme. MOH surveillance activities showed that microfilaraemia is prevalent among migrant workers from South Asia. Visceral leishmaniasis has

been diagnosed in an aboriginal patient several years ago in Malaysia. Importation of multi-drug resistant malaria and tuberculosis may cause a huge economic burden and compromise their elimination effort as well as may threaten national health security.

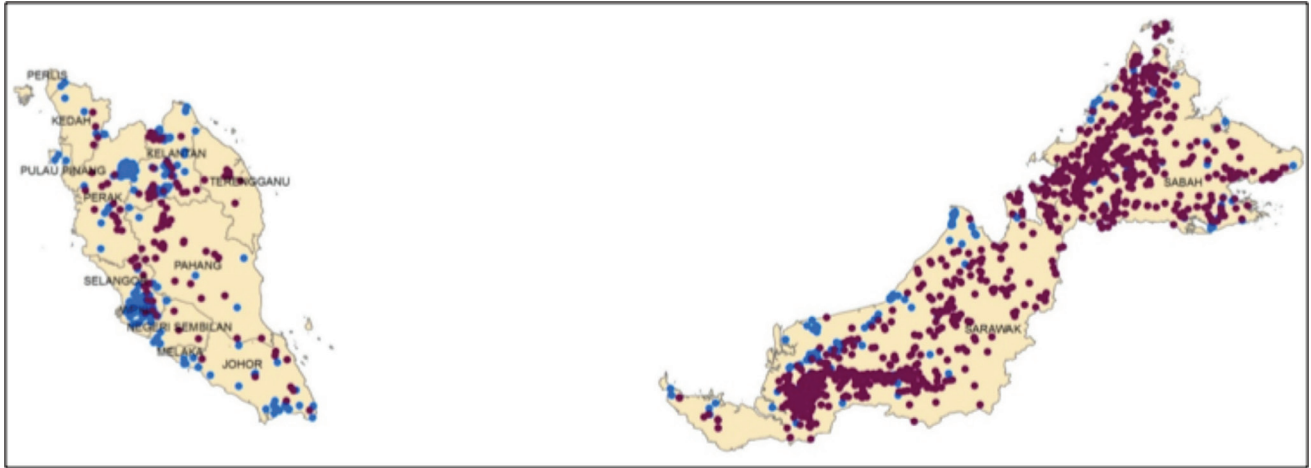
## Conclusion

In conclusion, Malaysian scientists are still very actively engaging in tropical diseases research with significant impact globally as evidenced by some of the recent awards received. For her outstanding work on intestinal helminthiasis, another much neglected tropical disease area, Prof Yvonne Lim, Deputy Dean (Research), Medical Faculty, University of Malaya and an active member of MSPTM, was listed by Nature as one of the Science Stars of East Asia in the recent News Feature. With two international accolades received by Malaysian researchers within the month by Dr Nazni and Prof Yvonne, it proves that Tropical Medicine research is still very much alive in Malaysia. Interestingly, the areas that brought fame to Malaysia recently are the two probably most unpopular fields – maggot and intestinal worms!

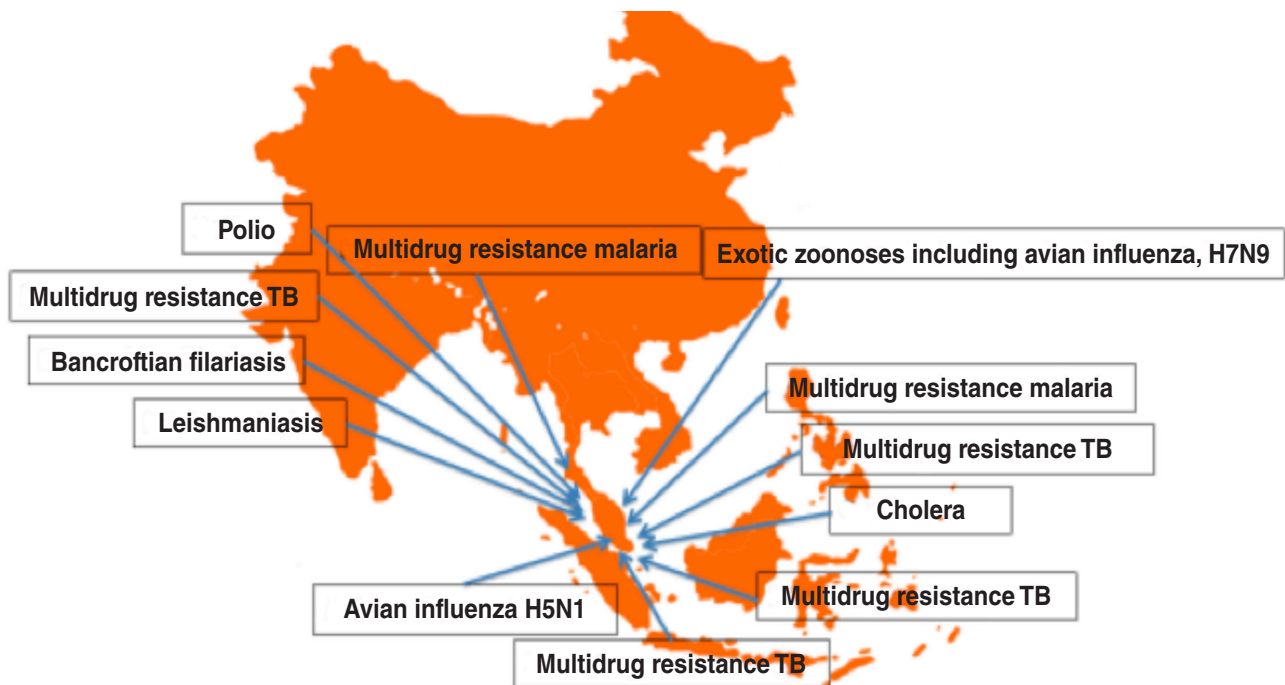
During her inaugural lecture as Fellow of the Academy of Science titled “Debunking the myth about gut worms by unlocking the secrets of gut microbiota”, Prof Yvonne has described a new frontier in understanding the relationship between our human co-existence which the much frowned creature called the gut worms. Who knows one day because of her team’s effort, we might be swallowing capsules of *Ascaris lumbricoides* and *Trichuris trichiura* eggs to treat inflammatory bowel diseases.

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**Figure 1:** Spatial distribution of human & zoonotic malaria cases in Malaysia in 2016 (Source: MOH). The red dots represent *P. knowlesi* cases whereas the blue dots represent other human malaria infections.



**Figure 2:** Human (economic) migration: Risk of importation of exotic infection and national health security.