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# Medical Virology in Malaysia

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**Abstract:** Virology is a branch of biological science dealing with the study of viruses, and medical virology focuses on the study and control of diseases due to viruses that is of medical importance. The development of medical virology in Malaysia has its beginning in the Institute for Medical Research (IMR), following the establishment of the Division of Medical Zoology and Virus Research in the institute on 23 March 1953. The second institution in the country to establish diagnostic and research work in medical virology was Department of Medical Microbiology, Faculty of Medicine, University Malaya. This was followed by University Kebangsaan Malaysia, University Sains Malaysia and University of Sarawak Malaysia. The National Public Health Laboratory (NPHL) is the latest institution to establish a laboratory in 2003 for virus isolation and services to support country surveillance and outbreak investigation of infectious diseases due to viruses. In the field of medical virology, Malaysia contributed substantially in the areas of virus diagnostic services, development and research ranging from survey and documentation on the existence and prevalence of viruses causing diseases in Malaysia, clinical presentation and epidemiological features of virus diseases, evaluation of new diagnostic tests to pathogenesis of viral diseases. Malaysia contributed to the discoveries of at least 12 new viruses in the world. ASEAN plus Three (China, Japan, Republic of Korea) Emerging Infectious Programme was established to overcome the challenges and impact of emerging and re-emerging infectious diseases in this region. Malaysia as the co-ordinator of the laboratory component of the programme, contributed to strengthen the regional laboratory capability, capacity, laboratory-based surveillance and networking. The future of medical virology in Malaysia in terms of integration of diagnostic, reference and research to support the country's need will be enhanced and strengthened with the on-going development of the National Centre for Disease Control and Prevention (CDC Malaysia) which also incorporates a futuristic Special Diagnostic and Reference Laboratory.

**Key words:** Medical Virology; Malaysia

Viruses are submicroscopic, obligate intracellular "parasitic" biomedical entities or particles. They are essentially non-living but parasitizing all known groups of living organisms including those microbes such as bacteria, yeasts and protozoa. In contrast to living organisms, they lack the biochemical or genetic potential to generate the energy that is necessary to

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drive all biological processes, especially in macromolecular synthesis. Thus, they use the biological system of the living organisms to synthesize their necessary components based on the genetic information encoded in their genomes. They are subsequently produced from the assembly of the preformed components synthesized by the hosts' biosynthetic machinery (2, 57).

## DEVELOPMENT OF VIROLOGY IN THE WORLD

Virology is a branch of biological science dealing with the study of viruses, and medical virology focuses on the study and control of diseases due to viruses that is of medical importance. Virology, as a discipline of life sciences, has had a remarkable history although it is only slightly more than a century old. Its development lagged behind that of bacteriology by at least 2 decades. The "germ theory' of disease and scientific principles applicable to bacteriology coupled with the lack of appropriate instrument and technology accounted for the delay in the development of virology. By the last half of the $19^{th}$ century, the existence of a diverse microbial world of bacteria, fungi, and protozoa was already well established. As early as 1840, Jacob Henle, the renowned German anatomist hypothesized the existence of infectious agents that were too small to be observed with the light microscope but were able to cause specific diseases. However, in the absence of any direct evidence for such entities, his hypothesis failed to be accepted. In 1879, a German scientist trained in the field of chemical technology conducted his research on diseases of tobacco plants which he named "tobacco mosaic disease" after the dark and light spots on infected plant leaves. He was able to reproduce the disease in healthy plants with the sap extracted from the diseased plants. The study established the infectious nature of the disease but neither a bacterial nor a fungal agent could be consistently cultured or detected in the juice extract to satisfy Koch's postulates. In 1890, Dimitri Ivanofsky, a Russian scientist, took the experiment a step forward by demonstrating that the sap of infected plants retained its infectious properties even after passing through Chamberland filter (unglazed porcelain) that blocked the passage of bacteria. The third scientist to play a key role in the development of the concept of viruses was Martinus Beijerinck, a Dutch soil microbiologist. He extended the studies on tobacco plant disease by showing that the filtered sap from a diseased plant could be diluted and then regained its "strength" after replication in living, growing tissues of healthy plants, that is, *the agent could reproduce itself only in living tissue and not in cell-free sap of plant*. Beijerinck named this agent a "contagium vivum fluidum" or a contagious living fluid. Thus, the three great scientists, Mayer, Ivanofsky and Beijerinck, each contributed greatly to the development of a new concept: a filterable agent too small to observe in the light microscope but able to cause disease by multiplying in living cells. The term "Virus" (Latin word for slimy liquid or poison) was at that time used interchangeably for any infectious agent, besides its application to tobacco mosaic virus. Subsequently, Loeffler and Frosch described and isolated the first filterable agent, the foot and mouth disease virus, from animals in 1898, and Walter Reed and his team working in Cuba soon recognized the first human filterable agent, yellow fever virus in 1901. The debate on whether viruses were liquids or particles was

only laid to rest when Felix d'Herelle developed the plaque assay in 1917, and when the electron microscope was developed in 1933 with the first electron micrograph of tobacco mosaic virus taken in 1939 (2, 35, 39, 57).

## DEVELOPMENT OF MEDICAL VIROLOGY IN MALAYSIA

The development of medical virology in Malaysia has its beginning in the Institute for Medical Research (IMR) following the establishment of the Division of Medical Zoology and Virus Research in the institute on 23 March 1953, though the institute was set up earlier in 1900 (19, 49, 68). The division was headed by Dr J R Audy and assisted by a talented medical officer Dr Gordon Smith who subsequently took over as the head of the division. The main focus of the virus laboratory was on the isolation and identification of viruses causing diseases in man and animals inclusive of study of the distribution of antibodies to viruses as an index of their importance and prevalence in the community. The first research project carried out was on the effectiveness of yellow fever vaccine in a community who has been exposed to other flaviviruses. During that period, extensive serosurveys conducted on animals and human confirmed that dengue virus and Japanese encephalitis virus were endemic in Malaya (peninsular Malaysia). It was also during this period that a pioneer attempt was made to isolate viruses from various species of bats especially those roosting in caves but no virus was isolated. A few new arboviruses were isolated in the mid of field research to ascertain wild animals and arthropod as potential reservoir of virus diseases (19, 49, 68).

Dr A Rudnick took over as the head of the virus division in the1960s and research into dengue and other arboviruses was enhanced following joint collaboration with scientists from the University of California-International Centre for Medical Research, USA, under the Hooper Foundation initiatives in 1960. In 1977, Dr Dora S K Tan became the head of the virus division who established and strengthened a number of serological studies inclusive of enteroviruses, Australia antigen, Q-fever, Toxoplasmosis and congenital infectious diseases (TORCHES). Dr S Mangalam was appointed as the head of the division in 1988 who contributed substantially in establishing molecular diagnostics in the virus division. Under her dynamic leadership, IMR-JICA Research Programme in Tropical Diseases with special reference to dengue, JE, malaria and filarial was established in 1993. Dr Norshahidah Khairullah who took over as the head of the virus division in 2001 focused on laboratory diagnosis of high risk viruses and biosafety. At the time of SARS coronavirus outbreak, the virus division of IMR was designated as the national laboratory for SARS coronavirus diagnosis (19, 49, 68).

The second institution in Malaysia to establish diagnostic and research work in medical virology was the Department of Medical Microbiology, Faculty of Medicine, University Malaya. The department was established initially as Department of Bacteriology in 1964 with the main focus on teaching medical undergraduates following the separation of Singapore from Malaysia in 1963. In 1964, an arbovirus research unit was seconded from IMR to the department to assist in the development of a virus diagnostic and research laboratory with special focus on dengue virus (49). Dr H B Maitland was the first director of this dengue research unit as well as the head of the Medical

Microbiology Department. The main function of the virus unit then also focused on undergraduate student teaching which subsequently expanded into limited virologic diagnostic services (mainly serodiagnostics) following the completion and commissioning of the University Hospital Kuala Lumpur in 1969. In 1975, Dr Violet J L How established the serodiagnostics for human infections due to hepatitis viruses and subsequently expanded the serodiagnostic service to cover human immunodeficiency viruses in 1985. Following the return of the seconded scientific team back to IMR in 1986, the dengue virus diagnostic services and research unit which had attained the status of World Health Organization (WHO) Arbovirus Research and Reference Centre was continued under the directorship of Dr S K Lam. During that period, extensive research work was carried out on the immunology and pathogenesis of dengue virus infection in human and animals by Dr Tikki Pang and his team of co-workers. The milestone contribution then was the development of an improved method on dengue virus isolation from patients' serum specimens by intra-cerebral inoculation of mosquito larvae (32). The method was an adaptation from the original method described by Rosen and Gubler in 1974, using adult mosquitoes as the living system for the isolation of dengue virus from patients' serum specimens (21, 22). Dr Hamimah Hasan subsequently became the head of the department in 2000 followed by Dr Sazaly Abubakar in 2005.

The medical virology unit in the University Kebangsaan Malaysia was started by Dr Illina Isahak in 1984 and strengthened in 1986 by Dr Yasmin Malik who introduced the improved method of human cytomegalovirus isolation and identification. Dr Jane Cardosa was credited for the development of medical virology in the University Sains Malaysia in 1985. She contributed significantly to the development of excellent dengue virus and Japanese encephalitis virus IgM-capture ELISA and dot-blot tests which provided diagnostic services for all hospitals in Penang and government hospitals in the state of Perak. In 1995, she was appointed as a professor in the Department of Child Health and Community Medicine, University Sarawak Malaysia, and continued her research into viruses that cause infections of the central nervous system.

The National Public Health Laboratory (NPHL) is the latest institution to develop a laboratory in 2003 for virus isolation and services to support the country surveillance and outbreak investigation of infectious diseases due to viruses though the institute was established as early as 1999. Prior to the establishment of NPHL, the infectious disease diagnostic services for the Ministry of Health Malaysia were supported by the Institute for Medical Research. The idea of setting up an institute (National Medical and Health Laboratory Service including a National Blood Transfusion Service) to relieve IMR of the burden of diagnostic services for infectious diseases so as to focus on high end research was mooted as early as 1966 by the sixteenth director of IMR, Dr Ungku Omar Ahmad (49). Unfortunately, the proposal for such institute failed to take off following the early demise of Dr Ungku Omar on 15 February 1969 at an early age of 38 years old. The notion of the need to establish a public health laboratory was re-visited by the former director-general of health, Dr Abu Bakar Suleiman in 1992. Subsequently, three public health laboratories, NPHL and two regional public health laboratories

(one in Ipoh in the north and the other in Johore Bahru in the south), were established simultaneously by November 1999 in peninsular Malaysia. In the early period, the core role of the public health laboratories focused on food safety monitoring and legal enforcement with a small unit for biochemistry (screening of congenital hypothyroidism). Diagnostic bacteriology unit, diagnostic serology unit and diagnostic unit for *Mycobacterium tuberculosis* were subsequently added in 2002. Following the outbreak of Nipah virus in Malaysia in 1999, the government of Malaysia realized the need for a high containment laboratory to handle high risk infectious pathogens and subsequently approved funding for the building of three biosafety level 3 (BSL3) laboratories in the country and one of which was gazetted to be built in the NPHL. Since its approval in late 1999, the planning and construction of the stated BSL3 in NPHL only started to take off in early 2003 following the recruitment of Dr K B Chua as the consultant virologist for the institution. Since NPHL did not even have the BSL2 laboratory for virus isolation and its supportive work on virology (cell culture, electron microscopy and molecular diagnostic facilities), Chua converted the original plan to just building a modular BSL3 laboratory to the state-of-the-art BSL3 Laboratory Complex. This complex, which will be renamed as the Microbial Diagnostic Complex, houses an enhanced BSL3 laboratory for diagnostic virology, a basic BSL3 laboratory for diagnostic bacteriology, BSL2 laboratories for diagnostic virology, bacteriology, parasitology and mycology, an electron microscopy suit and four specifically designed molecular laboratories for each of the four intended purposes. Prior to the completion of the complex, Chua rapidly established a fully operational BSL2 diagnostic virology unit (cell culture facility with virus isolation and identification capability) to solve a number of outbreaks of infectious diseases due to viruses in the country within 6 months of joining the NPHL in early 2003. The diagnostic capability and capacity for infectious diseases in the country were greatly expanded and strengthened following the completion of the BSL3 Laboratory Complex in 2007. As a follow through, he is assisting the Ministry of Health Malaysia to develop a diagnostic virology unit in the newly completed regional public health in Kota Kinabalu, Sabah and a special diagnostic and reference laboratory complex within the future National Centre for Disease Control and Prevention.

## CONTRIBUTIONS TO MEDICAL VIROLOGY

### Virus diagnostic services

In addition to teaching and providing in-house training, all the medical virology laboratories mentioned in the above institutions provide some forms of diagnostic virology services inclusive of virus isolation and serology for laboratory diagnosis of patients' illnesses. Prior to the establishment of diagnostic virology unit in NPHL, the support for country surveillance and outbreak investigation of infectious diseases due to viruses was mainly provided by IMR with periodic contribution from the Department of Medical Microbiology, University Malaya. With the exception of arboviruses, all the country national virus reference laboratories are based in IMR or NPHL under the Ministry of Health.

### Virus Research and Development

Besides diagnostic services, all medical virology laboratories carry out operational research. The main

thrust of operational research in the early period was in the Division of Virology, Institute for Medical Research. Extensive survey and documentation on the existence and prevalence of viruses causing diseases in Malaysia, inclusive of search for their reservoir hosts, were carried out in the institute (9, 21-23, 25, 38, 41, 53-55, 58-64, 70). Evaluation of the performance of commercial diagnostic kits, documentation of clinical manifestations and epidemiological features of diseases due to viruses were actively carried out by institutions such as IMR, Department of Medical Microbiology (University Malaya), Department of Child Health and Community Medicine (University Sarawak Malaysia) and NPHL (4, 6, 7, 26-28, 30, 33,34). Development and improvement of diagnostic tests for laboratory diagnosis of infections due to viruses of local importance was actively undertaken by the institutions (3, 5, 56). Operational research to improve and overcome problems associated with virus diagnostic inclusive the development of Jui Meng's (JM) cell culture tube, a new innovation, to improve biosafety and reduce cost in work for virus isolation (14). A new approach to collect specimens from bats was also introduced to study viruses of bats (12). Limited studies into the pathogenesis of viral diseases were carried out locally by IMR, University Malaya and University Sarawak Malaysia (8, 44, 45, 51, 69). In-depth research into the pathogenesis of diseases due to viruses of medical importance in Malaysia was also actively pursued by scientists in Faculty of Science and Institute of Higher Learning in the University Malaya (24, 40, 43, 50, 65, 66 ).

**Virus Discoveries**

The discovery of viruses in Malaysia occurred in two waves. The first wave occurred following the development of facilities for virus isolation in IMR. Dengue virus was isolated for the first time in Malaysia during an outbreak of dengue fever in Kuala Lumpur in 1954, and influenza A virus, the second virus to be isolated in Malaysia in the same year. Subsequently, influenza B virus was isolated in 1955 and poliovirus was isolated in 1959. Research into the epidemiology and ecology of dengue virus in the 1950s and 1960s led to the discoveries of a number of novel arboviruses, namely Langat virus, Batu Cave virus, Carey Island virus, Tembusu virus, Jugra virus, Bebaru virus and Getah virus (1, 20, 31,37, 46, 47,52). Lanjan virus was described as a new virus agent isolated from tick (*Dermacentor auratus*) found in Malaya which was published in 1967 but its authenticity needs further verification (67).

The second wave of virus discoveries has its beginning in the Department of Medical Microbiology, Medical Faculty of Medicine, University Malaya, in 1996 and subsequently shifted to the National Public Health Laboratory, Ministry of Health Malaysia from 2003 onwards. In the Department of Medical Microbiology, Faculty of Medicine, a substantial number of viruses were isolated, some of which were isolated for the first time in Malaysia (human herpesvirus 6, human herpesvirus 7, enterovirus 71, echovirus 7) and a few of these were isolated for the first time in the world (Nipah virus, Tioman virus, Pulau virus) (10，11，13，16-18, 36, 48). Following the establishment of cell culture facility and virus isolation unit in the National Public Health Laboratory in mid-2003, measles virus, mumps virus, rubella virus and chikungunya virus were isolated for the first time in the country and the aetiologies of a number of outbreaks of infectious diseases due to viruses were

rapidly solved (29, 42). With an improved and expanded cell culture facility, Melaka virus and Kampar virus, two more novel orthoreoviruses were isolated from patients with influenza-like respiratory illness (15).

**Strengthening regional laboratory capability, capacity and networking**

Following the outbreak of Nipah virus in peninsular Malaysia with subsequent spread to Singapore, the concern on the emergence of novel pathogen causing outbreak and trans-boundary spread in this region took centre stage during the 1999 interministerial meeting among the ASEAN health ministers and senior officers of health held in Hanoi, Viet Nam. Three expert groups on infectious diseases (*Mycobacterium tuberculosis*, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), and communicable diseases) were established. In the following year, three projects (strengthening regional information exchange–coordinated by Indonesia, strengthening regional epidemiological surveillance–coordinated by Thailand, and strengthening regional laboratory-based surveillance–coordinated by Malaysia) were formulated under the expert group on communicable diseases with the focus to strengthen regional surveillance and response to emerging and reemerging infectious diseases. Following the outbreak of severe acute respiratory syndrome due to SARS coronavirus, the laboratory component was re-aligned, under the name "strengthening laboratory capacity and quality assurance for infectious disease surveillance among ASEAN countries", and included three more countries (China, Japan, Republic of Korea) to strengthen the laboratory capability, capacity, quality and networking in this regional so as to meet the challenges and reduce the health, socioeconomic impact of emerging and re-emerging infectious diseases. In 2004, the three projects were harmonized into the ASEAN+3 Emerging Infectious Disease Programme. The laboratory component coordinated by Malaysia planned and carried out a number of workshops and activities, namely: i) an inventory of country laboratory capacity (establish member country existing laboratory capability and capacity in the region), ii) bilateral twinning process to develop or strengthen national diagnostic virology laboratory in member countries such as Brunei, Cambodia, Laos PDR, Myanmar and Viet Nam, iii) strengthen regional laboratory biosafety and quality, iv) establish regional laboratory-based surveillance on selected pathogens, and v) strengthen regional laboratory networking and co-operation via establishment of country National Laboratory Contact Point (NLCP) and ASEAN+3 Partnership Laboratories (APL). The NLCP in each member country serves as the country focus point of contact for matters related to laboratory, information resource centre for country laboratory capability, capacity and quality assurance, and country coordinating centre for regional laboratory-based surveillance. The APLs serve as the system of regional laboratory networking and co-operation for high end pathogen ( especially emerging novel infectious agent) identification and characterization, co-ordination and harmonization of regional laboratory quality assurance scheme including provision of "standards" for proficiency testing, collaboration on regional laboratory biosafety and biosecurity practices, provision of laboratory training and information sharing, and collaboration in research and development on infectious pathogens in this region.

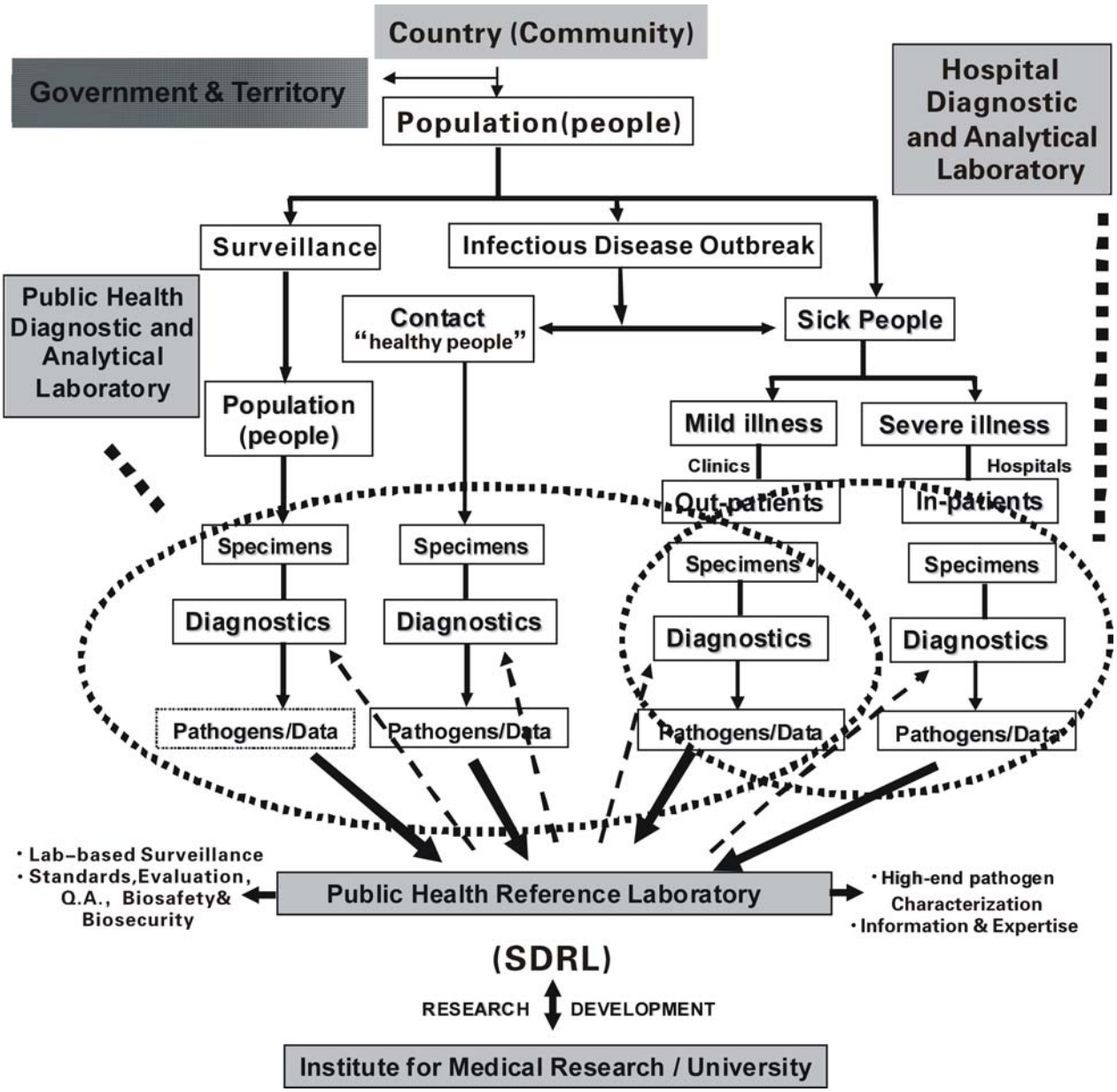


Fig.1. Proposed Interrelationship and Linkages of Health Diagnostic, Medical Diagnostic, Reference and Research Laboratories in Malaysia.

## FUTURE DIRECTION OF MEDICAL VIROLOGY IN MALAYSIA

The Ministry of Health Malaysia is now adequately prepared for good surveillance, investigation and response to infectious disease outbreaks due to currently known and new pathogens, especially viruses, following the establishment of the BSL3 Complex in the National Public Health Laboratory with its linkage of the three existing regional public health laboratories in the country. The diagnostic capacity for infectious diseases is set to be expanded and strengthened with another soon to be completed regional public health laboratory in the north-eastern part of Peninsular Malaysia (Kota Baru, Kelantan State) and future development of a regional public health laboratory in the state of Sarawak (East Malaysia). The future of medical virology in Malaysia in term of diagnostic, reference and research will be

strengthened and integrated with the on-going development of the National Centre for Disease Control and Prevention (CDC Malaysia). The CDC Malaysia will incorporate a futuristic Special Diagnostic and Reference Laboratory (SDRL). The futuristic SDRL will serve not only as the country institution to centralize and co- ordinate all infectious disease reference (pathogens characterization, expertise, information), it will also serve as the co-ordinating centre for national laboratory- based surveillance, national laboratory quality assurance scheme, national laboratory biosafety and biosecurity as exemplified in a proposed model (Fig.1)

A proposed integrated country infectious disease laboratory system linking all institutions (or laboratories) based on their respective functional roles such as diagnostic and analytical, reference or research works is shown in the Figure 1. A clearer separation of respective functions but yet with close linkages will enhance and compliment each infectious disease laboratory in providing respective laboratory diagnostic support, reference function and research in the areas of infectious diseases especially due to novel pathogens. For a country with small population, a unified diagnostic and analytical laboratory (fusion of two oval broken circles in Fig. 1) will probably be adequate and also more cost-efficient to provide both hospital (medical) diagnostics and public health diagnostics. As for the resource (financial and/or expertise) disadvantage country in the ASEAN, some of the reference functions will be provided by the system of ASEAN+3 Partnership Laboratories in the region.

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