

## REVIEW

# Perspectives of public health laboratories in emerging infectious diseases

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The world has experienced an increased incidence and transboundary spread of emerging infectious diseases over the last four decades. We divided emerging infectious diseases into four categories, with subcategories in categories 1 and 4. The categorization was based on the nature and characteristics of pathogens or infectious agents causing the emerging infections, which are directly related to the mechanisms and patterns of infectious disease emergence. The factors or combinations of factors contributing to the emergence of these pathogens vary within each category. We also classified public health laboratories into three types based on function, namely, research, reference and analytical diagnostic laboratories, with the last category being subclassified into primary (community-based) public health and clinical (medical) analytical diagnostic laboratories. The frontline/leading and/or supportive roles to be adopted by each type of public health laboratory for optimal performance to establish the correct etiological agents causing the diseases or outbreaks vary with respect to each category of emerging infectious diseases. We emphasize the need, especially for an outbreak investigation, to establish a harmonized and coordinated national public health laboratory system that integrates different categories of public health laboratories within a country and that is closely linked to the national public health delivery system and regional and international high-end laboratories.

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## INTRODUCTION

Infectious diseases have affected humans since the first recorded history of man. Infectious diseases remain the second leading cause of death worldwide despite the recent rapid developments and advancements in modern medicine, science and biotechnology. Greater than 15 million (>25%) of an estimated 57 million deaths that occur throughout the world annually are directly caused by infectious diseases. Millions more deaths are due to the secondary effects of infections. Moreover, infectious diseases cause increased morbidity and a loss of work productivity as a result of compromised health and disability, accounting for approximately 30% of all disability-adjusted life years globally.<sup>1,2</sup>

Compounding the existing infectious disease burden, the world has experienced an increased incidence and transboundary spread of emerging infectious diseases due to population growth, urbanization and globalization over the past four decades.<sup>3–8</sup> Most of these newly emerging and re-emerging pathogens are viruses, although fewer than 200 of the approximately 1400 pathogen species recognized to infect humans are viruses. On average, however, more than two new species of viruses infecting humans are reported worldwide every year,<sup>9</sup> most of which are likely to be RNA viruses.<sup>6</sup>

Emerging novel viruses are a major public health concern with the potential of causing high health and socioeconomic impacts, as has occurred with progressive pandemic infectious diseases such as human immunodeficiency viruses (HIV), the recent pandemic caused by the novel quadruple re-assortment strain of influenza A virus (H1N1), and more transient events such as the outbreaks of Nipah

virus in 1998/1999 and severe acute respiratory syndrome (SARS) coronavirus in 2003.<sup>10–14</sup> In addition, other emerging infections of regional or global interest include highly pathogenic avian influenza H5N1, henipavirus, Ebola virus, expanded multidrug-resistant *Mycobacterium tuberculosis* and antimicrobial resistant microorganisms, as well as acute hemorrhagic diseases caused by hantaviruses, arenaviruses and dengue viruses.

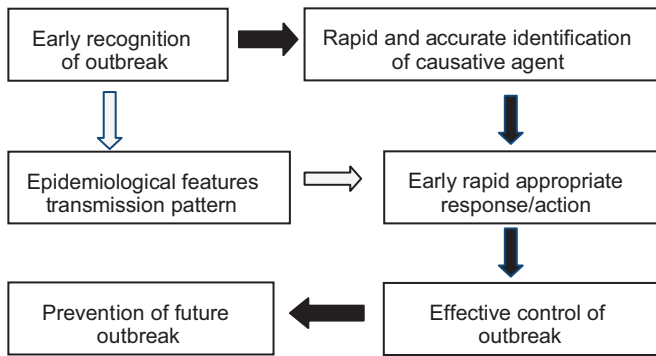
To minimize the health and socioeconomic impacts of emerging epidemic infectious diseases, major challenges must be overcome in the national and international capacity for early detection, rapid and accurate etiological identification (especially those caused by novel pathogens), rapid response and effective control (Figure 1). The diagnostic laboratory plays a central role in identifying the etiological agent causing an outbreak and provides timely, accurate information required to guide control measures. This is exemplified by the epidemic of Nipah virus in Malaysia in 1998/1999, which took more than six months to effectively control as a consequence of the misdiagnosis of the etiologic agent and the resulting implementation of incorrect control measures.<sup>15,16</sup> However, there are occasions when control measures must be based on the epidemiological features of the outbreak and pattern of disease transmission, as not all pathogens are easily identifiable in the early stage of the outbreak (Figure 1). Establishing laboratory and epidemiological capacity at the country and regional levels, therefore, is critical to minimize the impact of future emerging infectious disease epidemics. Developing such public health capacity requires commitment on the part of all countries in the region. However, to develop and establish such an effective national

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**Figure 1** Generic approach to emerging infectious disease outbreak response.

public health capacity, especially the laboratory component to support infectious disease surveillance, outbreak investigation and early response, a good understanding of the concepts of emerging infectious diseases and an integrated country and regional public health laboratory system in accordance with the nature and type of emerging pathogens, especially novel ones, are highly recommended.

Traditionally, emerging infectious diseases are broadly defined as infections that: (i) have newly appeared in a population; (ii) are increasing in incidence or geographic range; or (iii) whose incidence threatens to increase in the near future.<sup>6,17</sup> Six major factors, and combinations of these factors, have been reported to contribute to disease emergence and re-emergence: (i) changes in human demographics and behavior; (ii) advances in technology and changes in industry practices; (iii) economic development and changes in land use patterns; (iv) dramatic increases in volume and speed of international travel and commerce; (v) microbial mutation and adaptation; and (vi) inadequate public health capacity.<sup>6,17</sup>

From the perspective of public health planning and preparedness for effective emerging infectious disease surveillance, outbreak investigation and early response, the above working definition of emerging infectious disease and its associated factors that contribute to infectious disease emergence are too broad and generic for more specific application and for the development of a national public health system, especially in the context of a public health laboratory system in a country. Thus, in this article, emerging infectious diseases are divided into four categories based on the nature and characteristics of pathogens or infectious agents causing the emerging infections; these

categories are summarized in Table 1. The categorization is based on the patterns of infectious disease emergence and modes leading to the discovery of the causative novel pathogens. The factors or combinations of factors contributing to the emergence of these pathogens also vary within each category. Likewise, the strategic approaches and types of public health preparedness that need to be adopted, in particular with respect to the types of public health laboratories that need to be developed for optimal system performance, will also vary greatly with respect to each category of emerging infectious diseases. These four categories of emerging infectious diseases and the factors that contribute to the emergence of infectious diseases in each category are briefly described below.

### CATEGORY 1: 'KNOWN' INFECTIOUS PATHOGENS/AGENTS OCCUR IN NEW 'NICHE'S'

Emerging infectious diseases under this category were subcategorized into 1a, 1b and 1c. Subcategory 1a covers known pathogens that occur in new ecological niches/geographical areas. A few past examples belonging to this subcategory are the introduction and spread of West Nile virus in North America; chikungunya virus of the Central/East Africa genotype in Reunion Island, the Indian subcontinent and South East Asia; and dengue virus of different serotypes in the Pacific Islands and Central and South America.<sup>18–23</sup> Factors that contributed to the occurrence of emerging infectious diseases in this subcategory include population growth; urbanization; environmental and anthropogenic driven ecological changes; increased volume and speed of international travel and commerce with rapid, massive movement of people, animals and commodities; and deterioration of public health infrastructure. Subcategory 1b includes known and unknown infectious agents that occur in new host 'niches'. Infectious microbes/agents placed under this subcategory are better known as 'opportunistic' pathogens that normally do not cause disease in immunocompetent human hosts but that can lead to serious diseases in immunocompromised individuals. The increased susceptibility of human hosts to infectious agents is largely due to the HIV/acquired immune deficiency syndrome pandemic, and to a lesser extent, due to immunosuppression resulting from cancer chemotherapy, anti-rejection treatments in transplant recipients, and drugs and monoclonal antibodies that are used to treat autoimmune and immune-mediated disorders. A notable example is the increased incidence of progressive multifocal leukoencephalopathy, a demyelinating disease of the central nervous system that is caused by the polyomavirus 'JC' following the

**Table 1** Emerging infectious diseases are categorized based on the nature and characteristics of infectious agents that cause the emerging infections

Category	Nature and characteristics of pathogens	Past examples
1	<b>Known pathogens occur in new niches</b>	
1a	Known pathogens occur in new ecological niches/geographical areas	West Nile virus, chikungunya virus
1b	Known pathogens occur in new host niches	Opportunistic pathogens in immunosuppressed hosts
1c	Emerging infections associated with iatrogenic modalities	<i>Exserhillum rostratum</i> , rabies, Acanthamoeba
2	<b>Known pathogens of new biologic phenotypes</b>	Drug-resistant strains
3	<b>Novel infectious pathogens</b>	New subtype or strain of influenza A virus
4	<b>Known disease of unknown etiology due to 'unrecognized' pathogens</b>	Ebola virus, Marburg virus, Hendra virus, Nipah virus, SARS coronavirus
4a	Acute human diseases	Human metapneumovirus, human bocavirus, Melaka virus, Saffold virus
4b	Chronic human diseases	<i>Helicobacter pylori</i> , human herpesvirus 8, hepatitis virus C and G

increased use of immunomodulatory therapies for anti-rejection regimens and for the treatment of autoimmune diseases.<sup>24–26</sup> Subcategory 1c includes known and unknown infectious agents causing infections associated with iatrogenic modalities. Some examples of emerging infections under this subcategory include therapeutic epidural injection of steroids that are contaminated with *Exserhillum rostratum* and infectious agents transmitted from donor to recipients through organ transplantation, such as rabies virus, West Nile virus, Dandenong virus or *Acanthamoeba*.<sup>27–31</sup>

## CATEGORY 2: 'KNOWN' INFECTIOUS PATHOGENS/AGENTS OF A 'NEW BIOLOGIC' PHENOTYPE (NEW SUBTYPES OR STRAINS)

Examples of past emerging infectious diseases under this category are antimicrobial resistant microorganisms (e.g., *Mycobacterium tuberculosis*, *Plasmodium falciparum*, *Staphylococcus aureus*) and pandemic influenza due to a new subtype or strain of influenza A virus (e.g., influenza virus A/California/04/2009(H1N1)).<sup>9,32–35</sup> Factors that contribute to the emergence of these novel phenotype pathogens are the abuse of antimicrobial drugs, ecological and host-driven microbial mixing, microbial mutations, genetic drift or re-assortment and environmental selection. Accidental or potentially intentional release of laboratory manipulated strains resulting in epidemics is included in this category.

## CATEGORY 3: 'NOVEL' INFECTIOUS PATHOGENS/AGENTS

Some examples of novel pathogens causing epidemics are Ebola virus, Marburg virus, Hendra virus, Nipah virus, SARS coronavirus and HIV.<sup>13,14,36–39</sup> Most, if not all, novel pathogens under this category are spillovers of zoonotic pathogens. These spillovers are directly or indirectly due to an enhanced intensity and increased frequency of mixing at the interface between wild-life animal reservoirs carrying the 'novel' zoonotic pathogens and humans or peri-domestic animals. Factors that lead to the spillovers and emergence of these novel pathogens are human population expansion, economic development, changes in land use patterns, modifications to natural habitats, and changes in agricultural practices and animal husbandry. Human behavior, such as wildlife trade and translocations, live animal and bush meat markets, consumption of exotic foods, development of ecotourism, access to petting zoos and ownership of exotic pets, also plays a significant role in the transfer of pathogens between species.<sup>19,40</sup>

## CATEGORY 4: 'OLD/KNOWN' DISEASES OF 'UNKNOWN' ETIOLOGY DUE TO 'UNRECOGNIZED' PATHOGENS

Currently, there are many acute and chronic diseases that affect humans in which the causes are still unknown but the etiologies may be of infectious origin. Regarding etiological discovery approaches for these diseases, category 4 is further classified into two subcategories: category 4a covers acute illnesses, and category 4b focuses on chronic sickness. Some recent examples of infectious diseases that affect humans under category 4a include acute respiratory illnesses due to human metapneumovirus, human bocavirus, human coronaviruses (NL63, HKU1), new human polyomaviruses (KI, WU), novel orthoreoviruses (Melaka virus, Kampar virus, HK23629/07) and Saffold virus.<sup>41–46</sup> Examples of infectious diseases under category 4b are gastritis and peptic ulcers due to *Helicobacter pylori*, Kaposi sarcoma due to human herpesvirus 8 and chronic hepatitis due to hepatitis virus C and G.<sup>47–50</sup> Advances in scientific knowledge and technology have contributed substantially to the discovery of these infectious etiological agents.

Regardless of the category, with some exception for category 4b, effective early detection, identification, characterization, containment, control and ultimately prevention of the emerging infectious diseases will require a good, functional national public health surveillance system. The system needs to be well supported by a network of primary public health and clinical/medical diagnostic laboratories that are coordinated by a national public health reference laboratory with real-time and harmonious communication between the laboratories and epidemiological surveillance units.

Confronted with the great diversity of these emerging pathogens and the equally diverse mechanisms and factors that are responsible for their emergence, there is an urgent need to develop a network of diagnostic laboratories, especially in countries where epidemic infectious diseases are likely to emerge. This network should include local laboratories with basic clinical laboratory capabilities, provincial and national public health diagnostic laboratories with greater capability to diagnose known pathogens and support effective laboratory-based surveillance, and a centralized national reference laboratory that can provide laboratory training and quality control for diagnostic assays for the network of diagnostic laboratories in the country. Ideally, the national reference laboratory should have state-of-the-art laboratory technology and be able to identify and characterize novel pathogens with specialized university laboratories and foreign institutes that can provide backup capability, but more importantly, the national reference laboratory should be able to conduct research for the development of new diagnostic technologies to detect and identify novel pathogens, especially those classified as category 4. The US system, which includes local and state public health laboratories that conduct diagnoses of known pathogens, the Centers for Disease Control and Prevention and university laboratories that provide research and reference activities, is a good model.

Disease or pathogen-specific public health diagnostic laboratories established to support world health organization (WHO)-specific disease surveillance programs and vaccine-preventable diseases, e.g., national influenza, poliovirus and measles laboratories, led to the 'compartmentalization' of laboratory diagnostic services, segregation of functions, and duplication of facilities and equipment. The situation is further complicated by the siting of various pathogen-specific diagnostic laboratories in different buildings or institutes or different locations within a country, thus preventing more cost-effective measures of sharing common equipment and reagents, clinical samples, information and human resources. Finally, the problem is compounded by policy makers and laboratory managers lacking flexibility and not allowing these disease or pathogen-specific laboratories to adopt a more generic approach in the investigation of infectious disease outbreaks.

Past incidents have shown that misdiagnosis or delay in the diagnosis of epidemics can cause substantial economic losses and social disruption and prevent containment or control as a result of the implementation of inappropriate control measures or a delay in implementing the appropriate control measures. The proposed integrated system of public health laboratories is not entirely new; public health laboratories are already in existence in most countries, but most are poorly equipped and are not adequately funded or staffed with trained professional staff. Moreover, a lack of knowledge and coordination has led to ineffective operation in the support of infectious disease surveillance. The basic concept of realigning and harmonizing public health laboratories to optimize their roles and functions can be drawn from the system of medical practices. Due to rapid and vast expansion of medical knowledge,

technology and demand of specialized skills and therapy, medical practices have evolved into a number of specialties and subspecialties, such as infectious disease, cardiology, gastroenterology, neurology, radiology, anesthesiology and oncology. An excellent aspect of the medical system is the continual retention of the general physician (family physician) or general pediatrician as the initial or first entry point for patients seeking consultation for any medical problem before being subsequently referred to the appropriate specialist, if deemed necessary. It is not uncommon for patients, especially older individuals, to have more than one disease or pathology at the time of presentation to the doctor. In a similar manner, in outbreaks of infectious diseases, 'background' endemic pathogens are often present that are capable of similar disease manifestations. Thus, public health analytical diagnostic laboratories (both primary and clinical) should adopt a generic approach and serve as the initial or first entry point for the investigation of the causative pathogens in the event of an infectious disease outbreak or the occurrence of any fatal illness with clinical suspicion of infectious etiology.

In addition, public health laboratories must have the capability to support the expanded scope and sophistication of public health activities brought about by a rapid increase in population and social, demographic and ecological changes, in addition to the factors mentioned above. Despite the presence of several types of health laboratories, they can be classified into three main categories: (i) public health research laboratories; (ii) public health reference laboratories; and (iii) public health analytical diagnostic laboratories. Public health analytical diagnostic laboratories can be further subcategorized into primary public health (community-based) and clinical/medical (hospital and clinic-based) analytical diagnostic laboratories.

A proposed organizational model to establish an integrated system of public health laboratories within a country to coordinate and link health laboratories under different ministries and in both public and private institutions based on their functional roles is shown in Figure 2. The broken lines indicate the diagnostic laboratories that are not directly regulated by the ministry of health. A schematic flow chart illustrating the functional relationships and linkages between various types of public health laboratories in a country was described previously.<sup>51</sup> A defined and harmonious linkage and collaboration will not only avoid duplication and redundancy, but also enhance and complement the function and output quality of each laboratory. Bearing in mind that not all countries in the world have similar resources (financial, man-power and expertise), demography, geopolitical structure, needs and commitment, the proposed model can be appropriately modified to tailor each country's immediate needs with a provision for future upgrading and expansion. Ultimately, it is recommended that all countries establish an integrated system covering all three categories of public health laboratories, with a cohesive centralized national public health reference laboratory.

In countries with limited resources, an interim centralized national public health diagnostic laboratory can take on some of the roles and functions of a national reference laboratory, especially in supporting laboratory training and quality assurance. For countries without such an idealistic centralized public health reference laboratory, an in-place system of networking should be developed to link to regional and international high-end laboratories or WHO Collaborative Centers to rapidly identify and characterize novel pathogens and provide other specialized laboratory diagnostic reagents, assays or validation. In addition, each region should have a regional center for reference

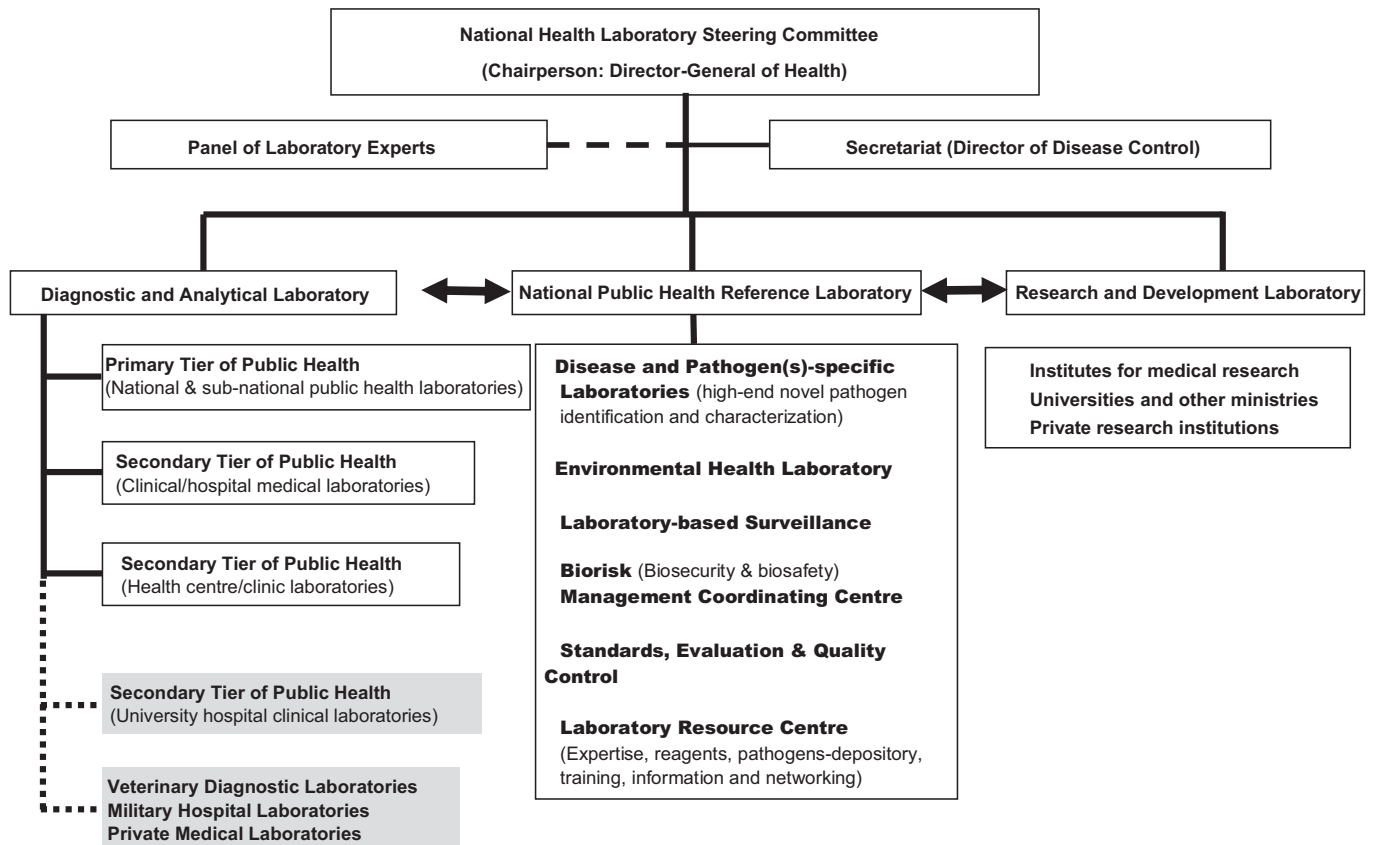


Figure 2 A proposed organizational interrelationship and linkages of public health diagnostic, reference and research laboratories within a country.

and research to help the national reference and/or diagnostic laboratories train and maintain laboratory quality control. The US Centers for Disease Control and Prevention is a major WHO collaborative partner and provides laboratory service not only for the American region, but also for many other countries in the world. Investigations into the diagnosis of Nipah virus, SARS coronavirus, pandemic influenza A virus and hemorrhagic fever viruses are just a few examples illustrating its worldwide function. The placement of the centralized reference laboratory under the National Center for Disease Control strengthens close communication and coordination among public health specialists, epidemiologist and laboratory personnel and serves as an important coordinating center to support the functions and activities pertaining to biorisk issues, centralized pathogen characterization and storage, laboratory-based surveillance and laboratory quality assurance, as shown in Figure 2.

A national reference laboratory will also be able to play an important role as part of a regional laboratory network to strengthen regional public health laboratory capacity in providing specific referral functions for public health diagnostic laboratories in other countries that do not have a reference laboratory. The public health research laboratories within the research institutes of ministries of health and universities or even private research institutions are best suited and can play a crucial role in collaborating with the national public health reference and diagnostic laboratories to discover novel pathogens of many human diseases under category 4, especially in subcategory 4b. The proposed network scheme will provide more cost-efficient laboratory services and ensure a regular flow of laboratory work to maintain the competency of technical staff to produce quality output. Because of the increased likelihood of epidemic diseases caused by novel pathogens, diagnostic laboratories serving as the primary entry point of investigation should be able to take a more generic approach in pathogen detection, isolation and identification. The traditional existing system of 'compartmentalization' of national disease/pathogen-specific diagnostic laboratories should thus be reviewed and integrated into the national public health infectious disease diagnostic laboratory system. This proposed model would improve cost-efficiency and allow a more appropriate approach to infectious disease outbreak investigation and control.

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