

Emerging and re-emerging infections

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Abstract: An emerging infection is defined as an infection that has newly appeared in a population while a re-emerging infection would be one that has existed in the past but its incidence has increased in recent times. The reasons for the emergence or reemergence of an infection are not completely understood but they are multifactorial and complex in the nature of their interactions. These factors may be related to the etiological organism, the host or the environment. Human activity appears to be a major driver. Malaysia had to deal with outbreaks of several emerging infections over the last two decades. They include Nipah virus infection, SARS and avian influenza. Infections like dengue, tuberculosis and leptospirosis are re-emerging in Malaysia. Both human activity and climatic changes appear to be key factors in the emergence and re-emergence of infections in Malaysia. Our country needs to put in place a comprehensive plan to meet the challenge of emerging diseases. A multidisciplinary approach is required and the strategies involved should not merely be confined to medical and health strategies.

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Introduction

An emerging infection is defined as an infection that has newly appeared in a population. This may be a new disease caused by a new pathogen which has not hitherto been described. An example of this would be AIDS due to the human immunodeficiency virus or Nipah encephalitis caused by the Nipah virus.¹ It may be a newly recognised disease like toxic shock syndrome which is due to an old pathogen, *Staphylococcus aureus*. It could be a known disease with a newly recognised pathogen and a good example would be peptic ulcer disease caused by *Helicobacter pylori*.² Finally there could be infections due to well recognised pathogens

but have become increasingly difficult to treat due to the acquisition of antibiotic resistance. A re-emerging infection would be one that has existed in the past but its incidence has increased in recent times. A good example of a re-emerging infection would be tuberculosis.

Reasons for emerging infections

The exact reasons why infections emerge or re-emerge are not completely understood. The reasons are likely to be complex and multi-factorial involving interactions among microbiological, environmental and socioeconomic factors.³ It is convenient to examine these factors based on 3 broad areas (i) pathogen factors (ii) host factors (iii) environmental factors.

The Pathogen

Microbes are extraordinarily resourceful and are constantly able to acquire new virulence factors and to adapt to new environments and new hosts. Bacteria have been on this planet for around 3 billion years. This is evidenced by the existence of structures called stromatolites which are fossilised remains of ancient bacteria.⁴ Stromatolites are particularly abundant in Shark Bay, Western Australia but they have also been found in the Mulu Caves in Sarawak.⁵ Moreover bacteria have a mean generation time of around 20 minutes compared to 30 years in humans. This would imply a much higher mutation rate over a far longer duration. Microbes are also able to constantly change their antigens, thereby confusing the immune systems of their host. The influenza viruses undergo continual minor antigenic changes (referred to as the antigenic drift). Every decade or so, the virus may undergo a major antigenic change, or an antigenic shift resulting in an influenza pandemic.⁶ Microbes also constantly acquire resistance to antimicrobial agents.

The Host

Host factors that affect emergence of infections would include the herd immunity of the population.

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Immunologically naive populations had suffered greatly when infections are introduced into their communities. In 1875 an epidemic of measles in Fiji killed up to 40,000 natives or a quarter of the entire population.⁷ Human activity is a major driver of emerging infections. Migration and travel facilitate the spread of infections globally and with air-travel this can occur with astonishing rapidity. It was estimated that in 2007, there were 898 million international tourist arrivals globally representing a 35-fold increase from 1950.⁸ Social behaviour and economic activities also contribute to the emergence of infections. Sexually transmitted diseases are spread by promiscuous behaviour. Economic activities often lead to deforestation, upsetting the ecosystem and increasing the risks of human contact with animal pathogens. Wars and civil strife result in the breakdown of basic public health infrastructure which will cause outbreaks of infections.⁹ Even changes in medical practice can alter the pattern of infections. The increasing use of intravascular catheters is associated with an increase in catheter-related blood stream infections. Uncontrolled and overuse of antibiotics lead to emergence of antimicrobial resistance. Human activity remains the main driver in the emergence and re-emergence of infections.

The environment

Climatic changes also affect the occurrence of infections. Global warming is expected to affect vector-borne as well as food and water borne infections. Resulting droughts and floods as a result of climate change can also result in outbreaks of infections. A very large outbreak of leptospirosis with over 3000 cases and nearly 250 deaths was reported in the Philippines in 2009 following severe flooding as a result of typhoons.¹⁰ The El Nino phenomenon has been associated with outbreaks of dengue, malaria and Rift Valley fever. The effects of deforestation have been mentioned previously. The building of dams has been shown to affect the population of snails which

act as intermediate hosts for certain parasitic infections and thereby affect the prevalence of these infections. The building of the Aswan High Dam across the Nile led to an increase in the prevalence of schistosomiasis.¹¹ Uncontrolled urbanisation arising from mass rural-to-urban migration creates vast urban slums. Slum dwellings which are overcrowded, poorly ventilated, without proper potable water supplies or sewerage systems are often the foci of outbreaks of respiratory and waterborne infections.

Some recent emerging infections in Southeast Asia and Malaysia

There have been several outbreaks of emerging and re-emerging infections in Southeast Asia including Malaysia in recent years. They include Nipah encephalitis, Chikungunya, hand, foot and mouth disease due to enterovirus 71, dengue and dengue haemorrhagic fever, tuberculosis, severe acute respiratory syndrome (SARS), leptospirosis, avian influenza and health care infections due to multiply resistant organisms.

Dengue and Dengue Haemorrhagic fever (DHF)

In Malaysia dengue and dengue haemorrhagic fever (DHF) is the commonest notifiable infection encountered. In 2011 the incidence rate in Malaysia was 68.65 per 100,000 population.¹² The re-emergence of dengue and DHF can be attributable to several factors. Dengue is an urban disease and Malaysia has witnessed very rapid urbanisation in the past three decades. There is extensive construction of buildings and other public infrastructure. Construction sites however are often not well maintained and provide breeding opportunities for the mosquito vector, *Aedes aegypti*. Although the law allows for fines if mosquito larvae are detected, enforcement is poor and there is general apathy among the population to environmental hygiene. The incidence of the infection also increases whenever there is a change in the serotype of the prevailing virus.

Climatic changes may also play a role. In 1997 the country experienced a severe drought due to the El Nino phenomenon. There was a significant increase in cases that year. Because of the drought, water rationing was imposed and led many households to store water in open containers thus increasing breeding opportunities for the vector. The higher temperatures also increase the proportion of infectious mosquitoes that bite more frequently. These factors may partly contribute to the increase in the number of cases.¹³⁻¹⁵

Nipah virus infection

The first recorded Nipah virus outbreak occurred in Malaysia in 1999.¹ The outbreak was preceded by disease in pigs which suffered from both a respiratory illness as well as encephalitis. Humans were infected as a result of close contact with infected pigs. A total of 265 human cases were reported in Malaysia with 105 deaths, thus giving a case fatality rate of nearly 40%. Eleven cases with 1 fatality were also reported among Singapore abattoir workers as a result of contact with imported pigs from Malaysia.

The Nipah virus is a Paramyxovirus in the genus *Henipavirus*. The principal reservoir of Nipah virus is the bat of the genus *Pteropus*. It is postulated that the virus was transmitted from bats to pigs when the bats foraged for fruit in orchards which were located next to pig farms.¹⁶ In 1997 and 1998 there was a severe drought in South East Asia as a result of El Nino. The ensuing deforestation due to a combination of human activity and massive forest fires probably drove the bats from their natural habitat in the forests to the fruit orchards to forage for food.

Outbreaks of Nipah virus have also been reported in Bangladesh.¹⁷ Several severe outbreaks of nipah encephalitis in humans were documented from the early 2000s, with case fatality rates about 70–90%. Transmission of the virus from bat to man has been traced to consumption of contaminated fruits or drinking of contaminated date palm sap. Human-to-human transmission has also been reported in Bangladesh.

SARS

The severe acute respiratory syndrome (SARS) is caused by a coronavirus. It emerged as a new infection in 2003 in South China and spread globally causing a pandemic from November 2003 – July 2004. In all a total of 8096 cases in 29 countries were reported of which 774 (9.6%) patients died. 1706 cases (21%) occurred in health care workers as a result of health care associated transmission. Hong Kong, China, Singapore, Taiwan, Vietnam and Canada were the worst affected countries. In Malaysia we encountered 5 cases (all imported) with no local transmission.¹⁸⁻¹⁹

The appearance of SARS typifies the complex interactions involved in the emergence of an infection.²⁰ The definitive host of the SARS coronavirus is now established to be the horseshoe bat (*Rhinolophus* sp). The virus was then transmitted from bat to the civet cat and then to man. There is some evidence to support that this transmission occurred in the markets in South China. Both bats and civets are part of the exotic cuisine of the Southern Chinese. The bat droppings are also used in Chinese medicine. Live bats and civets as well as bat droppings can be found in these markets which are often unsanitary.

Bats and emerging infections

In addition to Nipah and SARS, bats are also the principal reservoirs in a number of other emerging infections.²¹ They include Lyssavirus (rabies), the Filoviruses like Marburg and Ebola and the Hendra virus. The reason for bats being a major source of emerging infections could be due to their diversity and global distribution. Being capable of flight, their extensive mobility allows them to transmit infectious materials to many different animal species.

Avian influenza A (H5N1)

The avian influenza A virus (H5N1) was first isolated from geese in Southern China in 1996 and the first human cases reported in Hong Kong in 1997. In mid-

December 2003, eight Asian countries (Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand, and Vietnam) reported epizootics of the virus in their poultry populations. The virus has subsequently spread to Europe and Africa.

Up to August 2012, 608 human cases have been reported in 15 countries.²² 369 cases were fatal giving a case fatality rate (CFR) of around 60%. Indonesia, Vietnam and Egypt have the most number of cases. As a country Indonesia has the highest CFR (83 %).

The H5N1 virus probably originated in wild birds. The virus then spread to poultry. Man is infected through close contact with infected poultry and thus far, man to man transmission is extremely rare. Nonetheless there is the theoretical possibility that if a suitable host like the pig, is co-infected with both human and avian influenza viruses, exchange of genetic material can occur.

This exchange of genetic material may cause a mutant virus to emerge. The new virus could retain the virulence of the H5N1 virus but is also readily transmissible from man to man. Given the high case fatality rate of the H5N1 virus, an influenza pandemic caused by this new influenza virus will have devastating consequences for mankind.

Recently scientists in the Netherlands have successfully modified the wild H5N1 strain into one that can be readily transmitted between mammals (ferrets) through substitutions of 5 amino acids.²³ Scientists in the US have also successfully created a hybrid virus from avian (H5N1) and swine flu (H1N1) with 4 substitutions and 1 reassortment.²⁴ The mutant virus was found to be efficiently transmissible between ferrets. Surveillance data shows that 2 of these substitutions are already common in A/H5N1 viruses and would require only 3 additional substitutions to become readily transmissible between mammals in nature.²⁵

There was some concern as to whether the publication of these two H5N1 studies in ferrets will pose a biosecurity

threat.²⁶ This issue was taken up by an independent federal advisory committee in the United States known as the National Science Advisory Board for Biosecurity (NSABB). Eventually, the findings of the research were deemed sufficiently important to public health and the US government agreed to their publication.

Antibiotic-resistant Healthcare Associated Infections (HAI)

Antibiotic resistant HAIs are increasingly prevalent around the world. There are several reasons for this. There are increasing numbers of immunocompromised patients in hospitals today. In the past, these patients would have succumbed to their illnesses. Today they are being kept alive through medical interventions which often leave them with little or no immune defenses. The lack of antibiotic stewardship in health institutions has led to the overuse of antibiotics which imposes a selection pressure on the bacteria with emergence of antibiotic resistance. Lapses in infection control facilitate the spread of resistant organisms among patients.

Antibiotic-resistant bacteria are prevalent in Ministry of Health hospitals in Malaysia. There is a particular challenge with *Acinetobacter baumannii* isolates. In 2011, the National Surveillance of Antibiotic Resistance found that resistance rates to *Acinetobacter baumannii* were extremely high. The resistance rates to amikacin, ceftazidime, piperacillin-tazobactam and imipenem were 49.9%, 57.0%, 58.2% and 56.6% respectively.²⁷

Antibiotic resistance, once it has emerged, can spread rapidly across national boundaries due to the mobility of patients between countries. A recent example is the New Delhi metallo-beta-lactamase-1 (NDM-1). The gene encoding for the resistance resides on a transmissible genetic element encoding multiple resistance genes. This new metallo-beta-lactamase hydrolyses nearly all beta-lactam antibiotics thus rendering the organism resistant to all penicillins, cephalosporins and

carbapenems.²⁸ The enzyme was first detected in a *Klebsiella* strain from a 59-year old Swedish male of Indian origin who was admitted to a New Delhi hospital in Dec 2008 for a decubital ulcer. He returned to Sweden in 2009 where a urine culture yielded a strain of *Klebsiella* with the NDM-1 gene.

By November 2010, NDM-positive cases have been reported from many countries including Australia, Austria, Belgium, Canada, China, France, Germany, Hong Kong, Israel, Japan, Kenya, Netherlands, Norway, Oman, Pakistan, Singapore, Sweden, Taiwan, UK and US. In most of the cases, patients had been hospitalised in India, Pakistan or Bangladesh, were of South Asian origin or had spent time in that part of the world.²⁹

Bioterrorism

Bioterrorism is the use or threatened use of biological agents against a person, group, or a larger population in order to create fear or illnesses for purpose of intimidation, gaining an advantage, interruption of normal activities, or for ideological objectives. The current geopolitical situation in the world has increased the risk of bioterrorist attacks. The agents which had been used or have potential use as biological weapons are often agents that cause infections which are currently rarely encountered, and in the case of smallpox, an infection which has been eradicated.³⁰ These agents would include the variola virus, *Bacillus anthracis*, *Pastuerella pestis*, *Franciscella tularensis*, *Clostridium botulinum* and other exotic viruses. A genetically engineered organism may also be specifically created as a bioweapon. Possible clues for a bioterrorist attack would include the occurrence of an unusual illness for a specific population, a disease with an unusual geographic or seasonal distribution, simultaneous clusters of similar illness in different areas and an outbreak of infection caused by an unusual, atypical, engineered, or antiquated strain.

The Challenges

There are numerous challenges posed by the emergence or re-emergence of infections. This is particularly so when the infectious outbreak is caused by a novel causative microorganism. The occurrence of morbidity and mortality as a result of an unknown agent often gives rise to irrational fears. Immense pressures are exerted upon the authorities by various groups, each with its own separate agenda. Events are sensationalised and reactions are often based on emotion rather than good science.

To face the challenge there is a need for recognition of the problem and the political will to solve it. The response has to be multidisciplinary in nature. Strategies that are based on medicine and science alone are insufficient. Strategies should also include social and behavioural, economic and political solutions.

Health-based strategies would include improving surveillance, early detection and control of the spread of infectious diseases and the formulation of rapid response plans at national, regional and global levels. Diagnostic and treatment capabilities including isolation facilities for infectious diseases need to be enhanced. The education and training of present as well as future health care professionals is key to meeting these challenges. Research into emerging diseases should be intensified since there is still much that is not understood.

Medical strategies alone are insufficient. Other strategies should include public education and behaviour modification. A good system of risk communication should be established as it is important. Improving basic health amenities and food hygiene, the preservation of the environment and the management and control of urbanisation are all important issues that need to be addressed.

Conclusions

Emerging and re-emerging infections are a very real and major problem. The factors causing emergence and re-emergence are still not well understood and insufficient efforts have been made to meet this challenge. Outbreaks are wholly unpredictable and the next major outbreak is a matter of “when” not “if”. The world needs to be better prepared to face these emerging infections as it is better to be safe than sorry.

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