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Emerging and Re-emerging Infectious Diseases: The Challenge to Global Health

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Infectious diseases have been an ever-present threat to mankind. From the Biblical plagues and the Plague of Athens in ancient times, to the Black Death of the Middle Ages, the 1918 "Spanish Flu" pandemic, and more recently, the HIV/AIDS pandemic, infectious diseases have continued to emerge and re-emerge in a manner that defies accurate predictions. About 15 million (more than 25 %) of the 57 million deaths worldwide are estimated to be related directly to infectious diseases[1].

Definitions

The following are the definitions as given by WHO[2]. (www.who.int/inf-fs/en/fact097.html):

Emerging infectious diseases are defined as those 'resulting from newly identified and previously unknown infections, which cause public health problems either locally or internationally.' SARS is an example of an emerging (new) infectious disease.

Re-emerging infectious diseases are defined as those that are 'due to the reappearance of, and an increase in, the number of infections from a disease, which is known, but which had formerly caused so few infections that it had no longer been considered a public health problem.' Anthrax is an example of a reemerging infectious disease.

In considering how infectious diseases emerge or re-emerge, a division of infections into those that are resident within a species and those that are new to a species is useful. For infections resident in a species, determining what factors increase the incidence or change the characteristics of the infection in order to cause more disease is important. For example, what changes in host ecology or genetics result in shifts from an endemic to an epidemic state, and what genetic changes in the pathogen result in differences in virulence or transmission?

For infections that are new to a species, understanding the factors conducive to a successful host-shift and the genetic changes needed to achieve such a shift is essential. These factors may include enhanced contact opportunities, immigration, or changes in social structure, the relatedness of the species, and the characteristics of the new disease (e.g. respiratory, diarrheal etc.). The factors which contribute to the emergence of new infections and re-emergence of infections are shown in Fig. 1[1].

- Microbial adaptation to change
- Human susceptibility to infection
- Climate and weather
- Changing ecosystems
- Human behavior and demographics
- International travel and commerce
- Technology and industry
- Breakdown of public health measures
- Poverty and social inequality
- War and famine
- Lack of political will
- Intent to harm

Fig. 1: Factors contributing to emergence of infectious diseases

Contributions of Different Factors Towards Development of an Infection and to its Spread

It is important to note that our current ability to predict when a micro-organism will or will not be a

problem to human health, is limited. What factors are needed or not needed, and the magnitude of the impact of specific factors on emergence or re-emergence of an infectious disease, are often not known. However, some of the common factors which could influence the development of an infection and its spread are as below:

Persistent infectious stages: The persistence of the pathogen in infectious forms between or within hosts and the persistence of the pathogen in the environment of humans will enhance the possibility of emergence and re-emergence of infections.

Mechanism of transmission: The specific mechanism of transmission of a pathogen is a key factor in the potential of a pathogen to emerge. Vector-borne[3] and air-borne infections have high secondary attack rates.

Capacity for genetic and structural variability by the pathogen: This capacity permits escape from immune - protective mechanisms, creates functional diversity, and may change host or tissue tropisms. This characteristic also provides the pathogen with the potential to undergo rapid change in response to other selective pressures (e.g. antimicrobials). A limited capacity may cause constraints on emergence (e.g. the emergence of chlorine-tolerant or resistant *Vibrio cholerae* could have a dramatic impact on incidence of cholera).

Case morbidity and mortality caused by an infection: An infection may still be a major threat even if the pathogen causing the infection has a low secondary attack rate, if it kills a large percentage of those infected.

Latency: Latency is defined as a prolonged period between infection and recognizable disease (as occurs in AIDS). Delayed onset of symptoms affects the ability of individuals to change their behavior in a timely fashion. Delayed onset of symptoms may also impair the ability of public health officials to issue alerts and manufacture vaccines[3].

Role of Environment, Pathogen and Host

Emergence and re-emergence of infectious diseases can result from changes that affect the environment, the pathogen, the host, or a combination.

Role of Environmental Change in Host-Parasite Associations

The vast literature on genetic basis of pathogenicity, alongwith a resurgence of interest in the evolution of virulence might suggest that genetic characteristics of pathogens lie at the heart of infectious disease emergence. However, for many emerging and re-emerging infectious diseases, changes in the pathogen and host ecology probably play the primary role[4]. Seemingly minor ecological changes (e.g. the implementation of a new farming technique or long-distance travel of infected hosts) may significantly alter transmission and exposure patterns leading to sudden proliferation of disease. Exposure of pathogens to new environments may also result in disease emergence. For example, even if mutants with greater virulence arise frequently, if such mutations are negatively associated with the ability to survive, they will be rapidly eliminated. In addition, evolutionary changes resulting in new disease often require ecological "co-factors." A microbe that evolved an expanded host range cannot emerge in a new host unless it is able to reach that host.

Changes in population density or, for sexually transmitted diseases, changes in sexual behavior and practices, shifts in climate or nutritional status, and, for vector-transmitted diseases, changes in environments affecting vector abundance, may alter host/micro-organism ecologies and result in shifts from endemic to epidemic states. For example, some of the resurgence of tuberculosis is related to social change[5]. Increased crowding in metropolitan areas, immigration, and the breakdown of public health infrastructures for control of tuberculosis are among the social factors which account for the recent increases in active and latent infection with *M tuberculosis* in certain populations.

Role of Micro-organism (Pathogen) Evolution

The expanding tools of molecular biology (e.g., nucleotide sequencing) now allow us to better evaluate how genetic change affects structural and functional properties of pathogens. However, what specific genetic changes (if any) are needed to result in an emerging or re-emerging infection are often not clear.

Genetic change may result in:

New species or tissue tropisms which may allow pathogens to cross species barriers to cause new human infectious diseases (e.g., plague[6] [frame shift in Yop protein leading to pneumonic plague], HIV, swine influenza viruses) or for micro-organisms to acquire new tissue-specificity.

Enhanced invasiveness or survival results in new or more severe clinical diseases caused by previously recognized infectious agents (certain strains of *Haemophilus influenzae* biogroup *aegyptius* now cause an invasive and often fatal syndrome known as Brazilian purpuric fever, whereas most strains cause only conjunctivitis).

Antigenic shifts and drifts leading to epidemic outbreaks of known pathogens (e.g., *Influenza A*, meningococci, 0139 cholera[7] or within-host shifts that can occur within a patient. AIDS has been proposed to be the result of continuous selection for antigenic variants within a host, leading to gradual immune system breakdown under the weight of a wide diversity of HIV variants[8]. A similar phenomenon may occur in malaria. In these cases, the ability of a disease-causing organism to genetically change rapidly within the host may, in itself, be the factor that makes the infectious agent a threat.

Role of Host Factors

Hospitalized and immunocompromised humans are "Breeding Grounds" for evolution of new pathogens. Hospitals and medical treatment create environments for antimicrobial selection pressures that have lead to the emergence of resistant clones[9]. These resistant clones (e.g. vancomycin-resistant enterococci) are increasingly difficult to treat in any host. In addition, there are concerns about greater recombination opportunities between virulent strains in hospital environments, the occasional genetic linkage of virulence factors and determinants of antibiotic resistance, and the acquisition of new infectious agents in hospitals and medical practices (e.g., cadaver transplants,[10] xenotransplants, infections such as HIV acquired by artificial insemination).

Immunocompromised patients, whose numbers are rapidly increasing in both developed and developing populations, have higher rates of transmissible infections and may serve as reservoirs for infectious agents. Such reservoirs may cause increased disease in other immunocompromised patients and in normal hosts. Immunocompromised patients, whether hospitalized or not, may represent an expanding intermediate habitat, i.e., they provide an opportunity for adaptation of a pathogen to aspects of host biology that it would normally not get a chance to encounter. This allows the subsequent circumvention of the immune system in normal individuals to be easier.

Approaches to Emerging and Re-emerging Infections

Anticipating, Preventing, and Limiting Emergence and Re-emergence

The goals of such efforts should be:

- To predict when and where infections will emerge or reemerge;
- To recognize infections in the early stages of emergence; and
- To control their spread once they emerge.

Each of these goals is associated with financial, social, and environmental costs. The process should involve the development of general and mathematical models to predict and evaluate infectious disease dynamics, the development of improved surveillance systems for the detection of infectious pathogens, and the selection of strategies for limiting the spread of an emerging or reemerging infection. These include sanitary measures, quarantines, distribution of antibiotics or vaccines, distribution of treatment protocols and education. Each of these steps requires a thorough understanding of the pathogenesis of the infection and such efforts should involve a multidisciplinary team including clinicians, epidemiologists, microbiologists, statisticians, immunologists, veterinarians, entomologists, vector-borne disease experts, population biologists, evolutionary biologists, behaviorists, anthropologists, and sociologists.

It is clear that both ecological and evolutionary changes are likely to be important in disease emergence and that they are likely to interact. We need to be able to predict the effects of environmental change, to know what kinds of traits change genetically, and whether some environments favor genetic change more than others.

Role of Models in Understanding Emerging Diseases

The development of general and mathematical models to address emerging and re-emerging infections allows the creation of testable hypotheses. Modeling may provide a conceptual framework for integrating relevant information and identifying deficits, as well as answering practical questions in clinical medicine (eg, given pathogen X, what drug regimen is best) and public health (e.g., optimum vaccination program, outbreak response, potential for emergence etc.).

Mathematical models have also been used successfully to design human vaccination programs-particularly in the United Kingdom[11] ; also in the United States to predict the spread of rabies, and more recently, to explore the dynamic consequences of HIV transmission early in the course of infection, long before AIDS is manifest[12].

A distinction between use of models for emerging and for re-emerging diseases must be made. Modeling approaches will probably work better for re-emerging diseases than emerging diseases. With re-emerging

diseases, we may have a well-established set of model parameters that can be refined to existing parameter estimates. New emerging diseases, by contrast, are much more difficult to model. Critical life-history parameters and life-history characteristics of the pathogen are often unknown. Distinguishing between models that are "predictive" (i.e., too true to be good) and models that are "heuristic" (i.e., too good to be true) is also important. Heuristic models provide a basis for generalizations that can then be a launching point for investigation of specific cases. The empirical basis for such generalizations are comparative studies of broad classes of infections. Our ability to identify a set of characteristics unique to a class of infectious disease allows us to construct general models incorporating (and focusing on) those features, which are relevant to infections. We can use such models to ask how combinations of features interact to influence both population and genetic dynamics, and evolution of transmission.

Research Needs

Critical for new research in emerging infectious disease is the exchange of information between diverse scientists interested in emerging infections. A major and pervasive problem has been the gap in communication between physicians and epidemiologists, and population and evolutionary biologists. A coordinated effort to develop useful databases would be invaluable. Such efforts ideally would include comparative and phylogenetic studies, theoretical models, and empirical studies to test theoretical ideas where possible. While we cannot do experiments on human populations, almost certainly the same generalities and principles will apply to diseases in wild animal or plant populations. Integrative databases on diseases in natural populations of animals and plants would be useful to researchers with a wide variety of purposes. Moreover, the process of developing such databases will not only help us to identify what is known but also what is unknown about a specific infection.

Better methods and global efforts (e.g., ICD10 codes of organisms associated with disease) are needed to identify emerging and re-emerging infections through surveillance. Surveillance systems for the early detection, tracking, and evaluation of emerging infections are needed, including the development of effective inter-nation networks. Rapid clinical diagnosis, detection and containment in populations and environment are the key elements in controlling emerging infections. World Health Organization, US Center for Disease Control and Prevention, along with National, state and local health departments and other agencies have played key roles in containing many of the emerging and reemerging infections[13-14].

Programs to monitor and control vector-borne and zoonotic infections should be included. New technologies such as remote sensing and geographical information systems should be evaluated for their usefulness. In addition, revision of the ICD-10 codes for infectious diseases to reflect the micro-organism responsible for the disease would be useful. Surveillance should include risk assessment in order to recognize the increased susceptibility of populations and accomplish prevention strategies.

Emphasis should be placed on applications of new technologies to emerging and re-emerging infections. For example, new techniques of the polymerase chain reaction (PCR), nucleotide sequencing, and genetic mapping can revitalize our ability rapidly to detect virulence determinants, epidemiologic markers, and infectious disease-causing organisms.

The usual prevention strategies, as well as new and improved countermeasures i.e., improved surveillance tools, diagnostic tests, therapeutic measures and vaccines need to be continually tested, refined and upgraded if we have to meet the challenges of emerging and re-emerging infectious diseases. This requires a strengthened relationship between the public health and basic and clinical sciences[1].

Joshua Lederberg, a noted champion of the war on emerging infections has aptly summarized the challenge presented by the ongoing conflict between the pathogenic organisms and the mankind. He said, ''The future of microbes and the mankind will probably unfold as episodes of a suspense thriller that could be titled *Our Wits Versus Their Genes*[15].''

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