

Emerging and re-emerging infections

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Abstract: Since time immemorial, infectious diseases have been, and continue to be, the leading cause of death worldwide. The discovery of various antimicrobials kindled the hope of eradication of these diseases. However, new infections continue to be discovered, leading to increasing morbidity and mortality. Emerging infections are defined as new, re-emerging, or drug-resistant infections whose incidence in humans has increased within the past two decades or threatens to increase in the near future. The reasons for their emergence include international travel, overcrowded cities, intensive food production and new food-processing methods, poverty, sexual practices, increasing immunosuppression due to new treatment modalities and global warming.

The sudden acute respiratory syndrome (SARS) outbreak caught the attention of the media, leading to panic around the world last year, reinforcing the important lesson that we continue to remain vulnerable to unexpected microbial threats. Not only did a new infectious disease emerge, but it also spread rapidly throughout the world, in spite of our astounding technological advances or perhaps because of them. Many new infectious diseases are likely to emerge over the next 25 years unless we acquire an ecological perspective on infectious diseases rather than seeing microbes as simply an invading entity that should be blindly attacked with antibiotics or used as a tool for biological warfare.

The Institute of Medicine, USA has defined emerging infectious diseases as 'new, re-emerging, or drug-resistant infections whose incidence in humans has increased within the past two decades or whose incidence threatens to increase in the near future'.¹

There are some noticeable patterns in the emergence of new diseases. No person, community or country is insulated from the potential introduction of an unfamiliar microbial pathogen. The infected cases can travel around the world within the incubation period of almost any infectious disease and thereby unknowingly disseminate pathogens. The rise in international travel, overcrowded cities, intensive food production, sexual practices, poverty and global warming are some of the causes for the emergence, maintenance and spread of new infectious diseases, as well as the resurgence of older diseases such as cholera, tuberculosis and malaria.

Infectious diseases have a significant impact on the global economy. The estimates of direct and indirect costs of infectious diseases exceed US \$ 120 billion annually. Major epidemics can be devastating to national economies, particularly those of developing nations. The estimated cost of the outbreak of plague in India, in 1994, was between US \$ 1-2 billion. The cholera epidemic in Peru in 1991 resulted in an estimated loss of US \$ 700 million.²

Like other living organisms, infectious agents are subject to genetic change and evolution. This is manifested by their ability to infect new hosts, alterations in their susceptibility to antimicrobial drugs and changes in their response to host immunity. At the same time, the human host has also changed. We have adopted new behaviour, international travel has increased and new food-processing methods are being adopted, which may enhance transmission of some microbes. New diseases as well as modern medical treatment may also lead to immunosuppression and thus increase the susceptibility to pathogens.

Developments in agriculture, urbanization and deforestation have changed ecosystems and allowed the emergence of infections. Lyme disease, first identified in 1976, is spread by ticks; forest fragmentation, loss of predators and the shift of habitation closer to woodlands were the factors that led to its emergence.

Sudden acute respiratory syndrome probably originated from the Guangdong province of China in late 2002 and came into public prominence in February 2003. By July 2003, it had been reported from 32 countries globally, affecting 8098 people with 774 deaths (9.6% case fatality) (Fig.1). The measures used for the management of cases included isolation, ribavirin, corticosteroids,

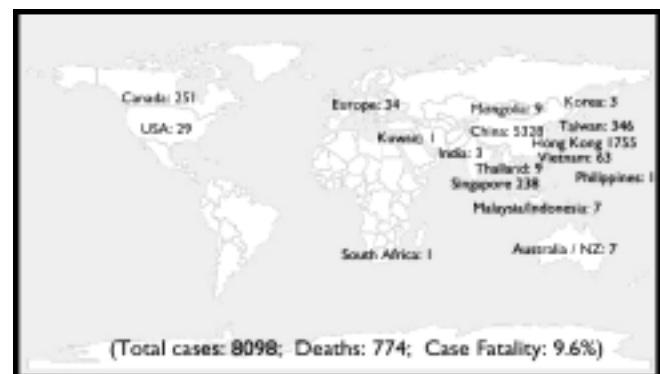


Fig 1. : SARS cases worldwide reported by WHO as of July 31, 2003; revised September 26, 2003. The numbers in the figure indicate cases.

teroids and mechanical ventilation.^{3,4}

In the past two decades, several new human pathogens have been recognized, including those causing hepatitis C, hepatitis E and, recently, SARS. Other diseases that were thought to be under control have re-emerged, often as a result of drug resistance. Some infections that are emerging internationally are listed in Table 1, and those in India in Table 2. The major aetiological agents and infectious diseases, identified since 1983, are given in Table 3.

Table 1. Emerging infections (International)

Emerging infections	Country
Ebola haemorrhagic fever	Zaire, Gabon
Dengue haemorrhagic fever	Western hemisphere, India
Venezuelan equine encephalitis	Venezuela and Colombia
Cholera	Cape Verde
Meningococcal meningitis	Africa
Lassa fever	Sierra Leone
<i>Streptococcus iniae</i> infection	Canada
Variant Creutzfeldt-Jakob disease	United Kingdom, France
<i>Escherichia coli</i> O157:H7 haemorrhagic colitis	Japan
Vancomycin intermediate-sensitive and resistant <i>Staphylococcus aureus</i> (VISA/VRSA)	USA

Table 2. Emerging and re-emerging infections in India

Year	Infections	Location
1990	Multidrug-resistant (ACCo) <i>Salmonella typhi</i>	Most Indian states
1991	<i>Vibrio cholerae</i> 0139	South India, West Bengal
1994	Plague	Maharashtra and Gujarat
1996	Dengue haemorrhagic fever	North India
2000	Fasciolopsiasis	Azamgarh, UP
2001	<i>Acinetobacter baumannii</i>	Manipal, Delhi
2001	<i>Pichia anomala</i>	Chandigarh
2001	Rotavirus G4P8	Kolkata
2001	Low level penicillin resistance in <i>Streptococcus pneumoniae</i>	Pondicherry, Delhi, Vellore
2002	West Nile virus infection	Maharashtra, Rajasthan, Goa, Orissa
2003	Nalidixic acid-resistant <i>Salmonella typhi</i>	Delhi, Mumbai

The human immunodeficiency virus (HIV) was first discovered in 1983, and has successfully transited from an emerging into an established infection. The acquired immunodeficiency syndrome (AIDS) epidemic claimed an estimated 3.1 million lives worldwide in 2002, and an estimated 5 million people acquired HIV in 2002, bringing the estimated number of people globally infected with the virus to 42 million. With the current disease burden, HIV will emerge as the largest cause of adult mortality in this decade, along with an additional 1 million tuberculosis (TB) cases. India, with 1.027 billion people, has an estimated HIV/AIDS infection rate estimated at 0.7% in the adult population, affecting about 3.8-4.6 million.^{5,6}

The Nipah virus, which killed 100 people in Malaysia in 1999, was normally carried by the forest fruit bat and had not previously seemed to pass to humans. However, because of deforestation and agricultural techniques, the bat's normal habitat and food source were changed. This forced the bats to encroach into fruit plantations that were in close proximity to pig

farms. The bats infected the pigs, which in turn infected the farmers.

Identified in 1989, hepatitis C virus is known to be the most common cause of post-transfusion hepatitis worldwide. Up to 3% of the world population is estimated to be infected, among which 170 million are chronic carriers at risk of developing liver cirrhosis and/or liver cancer. Measures to control its spread include its inclusion into routine testing of blood prior to transfusion.

Mycobacterium abscessus and other atypical mycobacterias such as *M. chelonae* and *M. fortuitum*, are responsible for a number of infections, and their incidence and reporting is increasing in the recent years as causes of soft tissue infections, chronic ear infections, bacteraemia associated with haemodialysis and peritoneal dialysis.⁸

Multidrug-resistant (MDR) *Acinetobacter baumannii* is an important cause of hospital associated infections and is known to infect patients with major burns and cancer.⁹

The increasing incidence of *Cryptosporidium* and *Aeromonas* as a cause of diarrhoea has been reported across the world. Enteroggregative *Escherichia coli* (EAEC) is another emerging pathogen linked to acute and persistent diarrhoea in both developing and industrialized countries. Recent sporadic cases and outbreaks of a foodborne illness due to EAEC have been recognized.^{10,11}

Vibrio cholerae 0139 was first detected in 1992 in India and has since spread to seven countries in Asia. The emergence of a new serotype permits the organism to continue to spread and cause disease even in populations protected by antibodies generated in response to previous exposure to other serotypes of the same organism. The upsurge in the worldwide incidence of *V. parahaemolyticus* infection in the past 8 years has been attributed to the appearance of 3 serotypes (03:K6, 04:K68 and 01:KUT) causing the first pandemic across eight countries.^{12,13}

In 1994, the plague epidemic in India caused worldwide concern. The Centers for Disease Control and Prevention (CDC) developed and implemented an enhanced surveillance system to supplement the then existing regulations concerning imported plague.¹⁴

The World Health Organization (WHO) estimates that there are 50 million cases of dengue infection worldwide. Nearly 2500 million people are at risk for dengue. An estimated 500 000 cases of dengue haemorrhagic fever (DHF) require hospitalization every year. The first major outbreak of DHF/dengue shock syndrome (DSS) in India occurred in 1996 in and around Delhi. This was caused by dengue virus type 2, with around 8900 reported cases with a fatality rate of 4.2%.¹⁵

Viral conjunctivitis has also emerged as an important infection affecting large numbers in the Indian subcontinent. An outbreak of acute haemorrhagic conjunctivitis caused by enterovirus type 70 occurred in Delhi in 1996 during the rainy season, which is the season associated with most of the infectious diseases in the subcontinent.¹⁶

Table 3. Major etiological agents and infectious diseases identified since 1983

Year	Agent	Type	Disease
1983	Human immunodeficiency virus (HIV)	Virus	Acquired immunodeficiency syndrome
1983	<i>Helicobacter pylori</i>	Bacteria	Gastric ulcers
1985	<i>Enterocytozoon bieneusi</i>	Parasite	Persistent diarrhoea
1986	<i>Cyclospora cayatanensis</i>	Parasite	Persistent diarrhoea
1988	Human herpesvirus-6 (HHV-6)	Virus	Roseola subitum
1988	Hepatitis E virus	Virus	Enterically transmitted non-A, non-B hepatitis
1989	<i>Ehrlichia chaffeensis</i>	Bacteria	Human ehrlichiosis
1989	Hepatitis C	Virus	Parenterally transmitted non-A, non-B hepatitis
1991	Guanarito virus	Virus	Venezuelan haemorrhagic fever
1992	<i>Vibrio cholerae</i> 0139	Bacteria	New strain associated with epidemic cholera
1992	<i>Bartonella (Rochalimaea) henselae</i>	Bacteria	Cat-scratch disease; bacillary angiomatosis
1993	Sin Nombre virus	Virus	Hantavirus pulmonary syndrome
1994	Equine morbillivirus	Virus	Human pneumonia
1994	Sabia virus	Virus	Brazilian haemorrhagic fever
1995	Hepatitis G virus	Virus	Parenterally transmitted non-A, non-B hepatitis
1995	Human herpesvirus-8 (HHV-8)	Virus	Associated with Kaposi's sarcoma (AIDS)
1996	Transmissible spongiform encephalopathy (TSE)	Prion	New variant Creutzfeldt-Jacob disease
1997	Avian Influenza-type A (H5N1)	Virus	Influenza
1998	Nipah virus	Virus	Encephalitis
2003	SARS-associated coronavirus	Virus	Sudden acute respiratory syndrome

Leptospirosis is another infection emerging across northern India (Chandigarh, Delhi and Varanasi) with a reported seroprevalence varying from 9% to 43% in episodes of acute febrile illness.¹⁷

West Nile virus infection has emerged as an important public health problem causing epidemics in the USA, and has also been reported from western states in India.¹⁸

The growing threat of antimicrobial resistance is of great concern globally. It is of paramount importance that the microbiology laboratory provides accurate and timely quantitative results on antibiotic sensitivity, and the microbiologist manages the results and disseminates the information gathered.

Pathogens developing resistance to antimicrobial agents may also cause public health problems. Chloroquine-resistant *falciparum* malaria, persistence of methicillin-resistant *Staphylococcus aureus* (MRSA) and emergence of glycopeptide-resistant enterococci (GRE, earlier known as vancomycin-resistant enterococci or VRE) in hospitals, and (MDR) tuberculosis and enteric fever are clinical problems which are getting more difficult to manage.

Staph aureus is the most frequently isolated Gram-positive pathogen and is an important cause of hospital-associated infections. MRSA has emerged as an important pathogen not only in the hospital setting but also as a cause of skin and soft tissue infections in the community. In a surveillance study at 3 centres in India, the incidence of MRSA was found to be around 32%, varying from 27% to 47%.¹⁹ The emergence of GRE, vancomycin intermediate-sensitive and resistant *Staph aureus* (VISA/VRSA) have added to the problem of treating Gram-positive infections. Similarly, extended spectrum beta-lactamases (ESBL) and device-associated infections due to staphylococci and *Candida* have compounded the problem of treating MDR Gram-negative infections, particularly in intensive care settings.

Salmonella typhi is endemic in developing countries with an

estimated incidence of 33 million cases every year. The occurrence of MDR isolates of *S. typhi* along with the emergence of decreased susceptibility to quinolones (especially ciprofloxacin) is an important harbinger of increasing treatment failures in enteric fever. Nalidixic acid-resistant *S. typhi* with decreased susceptibility to ciprofloxacin has been responsible for outbreaks in Tajikistan and Viet Nam. Despite the low level of resistance to ciprofloxacin, treatment failures are increasingly being reported and have led to a demand for revised breakpoints for quinolones against *Salmonella*.^{20,21}

Microorganisms have survived ecological change for millions of years because of their rapid rate of replication, mutation, and genetic recombination and exchange, and they will continue to do so as the global ecology changes. Surveillance is the key to recognize new or emerging infectious diseases, and to track the prevalence of more established ones. A well-designed, well-implemented surveillance programme can detect unusual clusters of disease, document the geographical and demographical spread of an outbreak, and estimate the magnitude of the problem. It can also help to describe the natural history of a disease, identify factors responsible for its emergence, facilitate laboratory and epidemiological research, and assess the success of specific intervention efforts.

The microbiology laboratory plays a critical role in recognizing new, emerging and re-emerging infectious diseases by identifying specific causes for the disease syndromes seen by clinicians, and by reporting new or unusual pathogens that they encounter. The laboratory may also serve as a key surveillance point for information gathering and dissemination, as is the case for antimicrobial resistance data. Appropriate specimen collection involves an attending medical staff that is knowledgeable about the samples to be obtained and availability of proper containers, especially if the specimens are to be transported outside the hospital or clinic setting.

Future challenges certainly include antimicrobial-resistant infections, the threat of another influenza pandemic, and the likeli-

hood of increasing problems with DHF and the risk of urban yellow fever in new areas. The global HIV epidemic will put a large number of people at risk for currently recognized and new opportunistic infections. The roles of hepatitis B and C viruses in chronic liver disease and hepatocellular carcinoma, of human papillomaviruses in cervical cancer, and of *Helicobacter pylori* infection in peptic ulcer disease and gastric cancer are now well-established. It is quite likely that more chronic diseases may be found to have an infectious aetiology.

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Drug Profile

DUTERSTERIDE

Dutasteride, 4 azasteroid is a selective and potent inhibitor of type 1 and 2 isoforms of 5 α reductase. This drug is used in the treatment of BPH (Benign prostatic hyperplasia) current medical treatments of BPH include the use of after X-adrenoceptor antagonists and 5 α reductase inhibitors to relieve symptoms and improve urinary flow. How X-adrenoceptor antagonists acts directly on smooth muscle to decrease muscle tone; 5X reductase inhibitors decrease the size of the prostate.

Mechanism of action : Dutasteride is a dual 5X reductase inhibitor. The enzyme 5X reductase is central to the conversion of testosterone to DHT. Daily doses of dutasteride result in a dose dependent reduction of serum DHT that is greater than finasteride.

Pharmacokinetics : Following single dose of 0.5 mg, peak serum concentration occurs within 1-3 hours. It is well absorbed, with bioavailability of approximately 60%. It is highly bound to plasma proteins (>99.5%). The volume of distribution is large (app. 300-500l). Drug is extensively metabolised in the liver by the human cytochrome P450, isoenzyme-CYP3A4 & CYP3A5. Single doses of <5.0 mg are eliminated more rapidly than doses of more than 5.0 mg by both concentration-dependent and independent elimination pathways and have a half life of 3-9 days. Dutasteride and its metabolites are mainly excreted in faeces.

- **Pharmacokinetics in special patient groups** Dutasteride is contraindicated for use in children and adolescents; elderly patients-no dose adjustment is required.

- **In renal failure patients**-No adjustment in dosage is anticipated for these patients as less than 0.1% of unchanged drug is excreted in urine.

- **In hepatic impairment** patients-caution should be exercised in administering to patients with mild to moderate hepatic impairment. Drug is contraindicated in patients with severe hepatic impairment.

Drug interactions : Blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4 such as ritonavir, ketoconazole, verapamil, diltiazem, ciprofloxacin. There are no pharmacokinetic or pharmacodynamic interactions between dutasteride and tamsulosin, terazosin, warfarin, digoxin and cholestyramine.

Indications and Usage - Dutasteride is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men to i) improve symptoms, and (ii) reduce the risk of acute urinary retention (iii) reduce the risk of the need for BPH related surgery.

Contraindication - The drug is contraindicated for use in women and children and in patients with known hypersensitivity to drug.

Warnings - Dutasteride is absorbed through the skin; therefore women who are pregnant or may be pregnant should not handle because of the possibility of absorption of dutasteride and the potential risk of a congenital anomaly in the male fetus.

Men being treated with dutasteride should not donate blood until at least months have passed following their last dose.

Dosage and administration : The recommended dose of Dutasteride is 0.5 mg daily orally. The capsules should be swallowed whole, can be given with or without food.

Effect on PSA-PSA levels decrease following dutasteride treatment. To interpret PSA value in a man treated with dutasteride for 6 months or more, the PSA value should be doubled for comparison with normal values in untreated man.