Emerging & Re-emerging Infectious Diseases
WHO Warns the Trends

• The World Health Organization warned in its 2007 report that infectious diseases are emerging at a rate that has not been seen before. Since the 1970s, about 40 infectious diseases have been discovered, including SARS, Ebola, Avian flu, and Swine flu. With people traveling much more frequently and far greater distances than in the past, the potential for emerging infectious diseases to spread rapidly and cause global epidemics is a major concern.
• Emerging infectious disease

Newly identified & previously unknown infectious agents that cause public health problems either locally or internationally
• **Re-emerging infectious disease**

Infectious agents that have been known for some time, had fallen to such low levels that they were no longer considered public health problems & are now showing upward trends in incidence or prevalence worldwide or have appeared in areas where they were not previously found.
Epidemiological Triad of Disease

Disease does not occur in a vacuum!!!
Factors Contributing To Emergence

AGENT

• Evolution of pathogenic infectious agents
  (microbial adaptation & change)
• Mutations
• Development of resistance to drugs
• Resistance of vectors to pesticides
Antimicrobial Drug Resistance

- Causes:
  - Wrong prescribing practices
  - Non-adherence by patients
  - Counterfeit drugs
  - Use of anti-infective drugs in animals & plants
  - Loss of effectiveness:
    - Community-acquired (TB, Pneumococcal) & Hospital-acquired (Enterococcal, Staphylococcal)
    - Antiviral (HIV), Antiprotozoal (Malaria), Antifungal
Antimicrobial Drug Resistance

• Consequences
  Prolonged hospital admissions
  Higher death rates from infections
  Requires more expensive, more toxic drugs
  Higher health care costs
Factors Contributing To Emergence

HOST

• Human demographic change (inhabiting new areas)- increase contact with animals and natural environment

• Human behaviour (sexual & drug use- sharing needles, drug abuse, body piercing)

• Human susceptibility to infection (Immunosuppression)- stress and lifestyle changes

• Nutritional changes, more use of pesticides
• Poverty & social inequality
• Wars, civil unrest –
  - creates refugees, food and housing shortages, increased density of living etc.

• Outdoor activity
- Globalization of travel and trade –
- Increased international travel (Influenza)
  - *Aedes albopictus* mosquito eggs in shipments of used tyres \(\rightarrow\) dengue fever
  - Long-distance travel; wild animal trade
    - Monkey Pox
    - West Nile Virus (New York City, 1999)
    - SARS, 2003
- Agricultural practices–
  - Pig farming (Nipah virus), Goose farms, Israel (West Nile virus)
  - **Breakdown of public health measures**–

  - breakdown in vector control
  - increased abundance and distribution of *Aedes aegyptii*,
  - spread of dengue hemorrhagic fever to America.
Transmission of Infectious Agent from Animals to Humans- ZOONOTIC diseases

• >2/3rd emerging infections originate from animals-wild & domestic
• E.g Emerging Influenza infections in Humans associated with Geese, Chickens & Pigs
• Animal displacement in search of food after deforestation/ climate change (Lassa fever)
• Humans themselves penetrate/ modify unpopulated regions- come closer to animal reservoirs/ vectors (Yellow fever, Malaria)
Reforestation in USA

Increased the number of deer & deer ticks

Increased Human contact with deers

Human affection by Lyme disease

Deer ticks are natural reservoir of Lyme diseases
Conversion of grassland to maise cultivation

Rodents come to people

People go to rodents

Rodents are natural reservoir of the virus

Argentine Haemorrhagic fever in humans
Pig Farm -> China 

Duck farm -> China 

China 

Mixing vessels 

Influenza 

Influenza 

Influenza 

Influenza 

Influenza
Increased Rice cultivation in South East Asia

Increased human contact with Field mouse

Field mouse is natural reservoir of Hantaan virus

Introduction of Korean haemorrhagic fever in Humans
• Lack of Political will (the lack of reporting of global infectious diseases of interest for political and economic reasons, such as with SARS in China)

• Technology and industrialization

• Improved diagnosis
Breakdown of public health measures

• Decrease in chlorine in water supplies lead to rapid spread of cholera in South America.
• Non functioning water plant in Wisconsin, USA lead to outbreak of waterborne cryptosporidium.
• Inadequate vaccinations and Diphtheria in former USSR independent countries.
• Discontinued mosquito control efforts and dengue and malaria re-emergence.
Factors Contributing To Emergence

ENVIRONMENT

• Climate & changing ecosystems
• Economic development & Land use (urbanization, deforestation)
• Technology & industry (food processing & handling)
• Changes in agricultural & food production patterns- food-borne infectious agents (E. coli)

Dr. KANUPRIYA CHATURVEDI
Uncontrolled Urbanization & Population Displacement

• Growth of densely populated cities-substandard housing, unsafe water, poor sanitation, overcrowding, indoor air pollution (>10% preventable ill health)

• Problem of refugees & displaced persons

• Diarrhoeal & Intestinal parasitic diseases, ARI
Deforestation forces animals into closer human contact - increased possibility for agents to breach species barrier between animals & humans - e.g. clearing forests in Venezuela has resulted in an increased cane mouse population, the probable reservoir host of the Guanarito virus and an outbreak of Venezuelan hemorrhagic fever
- **El Nino**- Triggers natural disasters & related outbreaks of infectious diseases (Malaria, Cholera)
- Possible increase in frequency of epidemics of diseases linked to El Nino Southern Oscillation (i.e. Rift Valley fever, Sin Nombre Virus)

- **Building Dams-** Emergence of Rift Valley hemorrhagic fever in Egypt. Slowed water flaw AND allowed snails to go south introduced S. mansoni in Upper Egypt. Increased its occurrence in Nile Delta.
• Climate changes –
  - heavy rains can result in increased breeding sites for mosquito vectors and increases in mosquito-borne infectious diseases

• Global warming- spread of Malaria, Dengue, Leishmaniasis, Filariasis
• Global warming- climatologists project temps to increase up to 5.8°C by 2100.
• Elevated rainfall
• creates new breeding habitats for mosquitoes.
• decreases salinity which can increase toxic bacteria.
• increases vegetation which increases rodents.
• increases runoff into drinking reservoirs
Bioterrorism

• Possible deliberate release of infectious agents by dissident individuals or terrorist groups

• Biological agents are attractive instruments of terror- easy to produce, mass casualties, difficult to detect, widespread panic & civil disruption
• Highest potential - B. anthracis, C. botulinum toxin, F. tularensis, Y. pestis, Variola virus, Viral haemorrhagic fever viruses
• Likeliest route - aerosol dissemination
# Emerging Infections in the World

<table>
<thead>
<tr>
<th>Year</th>
<th>Agent</th>
<th>Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>Rotavirus</td>
<td>Enteritis/Diarrhea</td>
</tr>
<tr>
<td>1976</td>
<td>Cryptosporidium</td>
<td>Enteritis/Diarrhea</td>
</tr>
<tr>
<td>1977</td>
<td>Ebola virus</td>
<td>VHF</td>
</tr>
<tr>
<td>1977</td>
<td>Legionella</td>
<td>Legionnaire’s dz</td>
</tr>
<tr>
<td>1977</td>
<td>Hantaan virus</td>
<td>VHF w/ renal flr</td>
</tr>
<tr>
<td>1977</td>
<td>Campylobacter</td>
<td>Enteritis/Diarrhea</td>
</tr>
<tr>
<td>1980</td>
<td>HTLV-1</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>1982</td>
<td>E.coli 0157:H7</td>
<td>HUS</td>
</tr>
<tr>
<td>1982</td>
<td>HTLV-II</td>
<td>Leukemia</td>
</tr>
<tr>
<td>1982</td>
<td>Borrelia burgdorferi</td>
<td>Lyme disease</td>
</tr>
</tbody>
</table>
# Emerging Infections in the World

<table>
<thead>
<tr>
<th>Year</th>
<th>Organism/Pathogen</th>
<th>Disease/Condition</th>
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</thead>
<tbody>
<tr>
<td>1983</td>
<td>HIV</td>
<td>AIDS</td>
</tr>
<tr>
<td>1983</td>
<td>Helicobacter pylori</td>
<td>Peptic ulcer dz</td>
</tr>
<tr>
<td>1988</td>
<td>Hepatitis E</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>1989</td>
<td>Hepatitis C</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>1990</td>
<td>Guanarito virus</td>
<td>VHF</td>
</tr>
<tr>
<td>1991</td>
<td>Encephalitozoon</td>
<td>Disseminated dz</td>
</tr>
<tr>
<td>1992</td>
<td>Vibrio cholerae O139</td>
<td>Cholera</td>
</tr>
<tr>
<td>1992</td>
<td>Bartonella henselae</td>
<td>Cat scratch dz</td>
</tr>
<tr>
<td>Year</td>
<td>Virus/Agent</td>
<td>Disease/Condition</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>1994</td>
<td>Sabia virus</td>
<td>VHF</td>
</tr>
<tr>
<td>1994</td>
<td>Hendra virus</td>
<td>Respiratory dz</td>
</tr>
<tr>
<td>1995</td>
<td>Hepatitis G</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>1995</td>
<td>H Herpesvirus-8</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>1996</td>
<td>vCJD prion</td>
<td>Variant CJD</td>
</tr>
<tr>
<td>1997</td>
<td>Avian influenza (H5N1)</td>
<td>Influenza</td>
</tr>
<tr>
<td>1999</td>
<td>Nipah virus</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>1999</td>
<td>West Nile virus</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>2001</td>
<td>BT Bacillus anthracis</td>
<td>Anthrax</td>
</tr>
<tr>
<td>2003</td>
<td>Monkeypox</td>
<td>Pox</td>
</tr>
<tr>
<td>2003</td>
<td>SARS-CoV</td>
<td>SARS</td>
</tr>
</tbody>
</table>
Emerging Virus

2001 - Nipah Virus (Bangladesh, India)
2003 - SARS Coronavirus
2004 - Avian Influenza (H5N1), Thailand, Vietnam
2006 - Influenza H5N1 (Egypt, Iraq)
   - New Human Rhinovirus (USA)
2007 - Nipah Virus (Bangladesh)
   - LCM like Virus (Australia)
   - Polyoma like virus (Australia)
2009 - Influenza H1N1
2011 - Crimean Congo Hemorrhagic Fever (India)

Re-emerging Virus

- Ebola
- Marburg
- Dengue
- Yellow fever
- Chikungunya
- Chandipura
- West Nile Virus
- Rift Valley Fever
- Human Monkey Pox
<table>
<thead>
<tr>
<th>Emerging Bacteria</th>
<th>Re-emerging Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug resistant MTB - Both MDR and XDR</td>
<td>• Cholera, H. pylori,</td>
</tr>
<tr>
<td>• MRSA</td>
<td>• Neonatal tetanus</td>
</tr>
<tr>
<td>• VRE</td>
<td>• Yersinia pestis</td>
</tr>
<tr>
<td>• CR – GNB esp. Klebsiella</td>
<td>• Rickettsia</td>
</tr>
<tr>
<td>• E. coli O104: H4</td>
<td>• Cl. Difficile</td>
</tr>
<tr>
<td>• <em>Stenotrophomonas</em> spp.</td>
<td>• Cl. Botulinum</td>
</tr>
<tr>
<td>• Extended spectrum beta-lactamase producing pathogens:</td>
<td>• Bacillus anthracis (due to bioterrorim)</td>
</tr>
<tr>
<td></td>
<td>• Fransciella</td>
</tr>
</tbody>
</table>
Emerging bacterial zoonosis in immunocompromised:

- Salmonella, non typhoidal
- Campylobacter
- Bartonella henselae – bacillary angiomatosis
- Fish tank granuloma by M. marinum
- Dog bites: by Capnocytophaga
Antibiotic Resistant Bacteria

• The discovery of penicillin in 1928 and the introduction of other antibiotics such as streptomycin, chloramphenicol, tetracycline in the 1940s raised hopes that cures could be found for all infectious diseases.
• Only one family of antibiotics (quinolones) have been developed since the 1960s.
• Strains of Staphylococcus aureus developed immunity against penicillin in the 1960s. However, methicillin was still effective.
• Methicillin resistant Staphylococcus aureus (MRSA) were found by the 1980s. Vancomycin was used as a last resort.
• Now vancomycin resistant Staphylococcus aureus (VRSA) has been observed in hospitals around the world.
Antibiotic Resistant Bacteria

• Streptococcus A which caused scarlet fever more or less vanished by the 1960s, but it re-emerged in a much more deadly form in the late 1980s.
• Streptoccous pyrogenes (dubbed the ‘flesh eating bug’) causes life threatening necrotizing fasciitis unless stopped by amputation.
• Various strains of Pneumonoccus have resistance to whole classes of antibiotics.
• Hospitals are a major breeding ground for antibiotic resistant bacteria.
Antimicrobial Resistance

• Worldwide problem

• Dramatic increase in antimicrobial-resistant community-acquired and nosocomial pathogens

• Major risk factors:
  Antimicrobial use (misuse)
  Infection control practices (noncompliance)
Evolution of Antimicrobial Resistance

- **Penicillin**
  - **Penicillin-resistant S. aureus** ([1950s])

- **Methicillin**
  - **Methicillin-resistant S. aureus** ([1980s])
  - **Vancomycin-resistant enterococcus (VRE)** ([1997])
  - **Vancomycin-resistant S. aureus** ([?])
  - **Vancomycin (glycopeptide) - intermediate resistant S. aureus**
  - **Vancomycin-resistant S. aureus (MRSA)** ([1990s])
Other Resistant Bacteria

• Penicillin resistant *Pneumococcus* was discovered in Spain in 1980s. Became resistant to cephalosporin antibiotics in US in 1990s. Still responds to vancomycin.

• *Enterococcus faecium* developed a Vancomycin resistant form (VREF) in 1989. It is now resistant to all antibiotics.

• Severe diarrhoea in patients on antibiotics caused by *Clostridium difficile*. At least two fatal epidemics in the community. Developing resistance to quinolones.

• Broad-spectrum antibiotics may also kill commensals (i.e. beneficial bacteria) which help keep the pathogenic bacteria in check (e.g. *Candida albicans*).
Emerging Parasites

- Cryptosporidium
- Drug resistant Malaria
- Cyclospora
- Acanthamoeba Keratitis
- Gnathostoma

Re-emerging parasites

- Amoebiasis
- Schistosomiasis
- Cysticercosis/taeniasis
- Hydatid disease
Emerging Fungi
• Non albicans Candida
• Penicillium marneffii
• Apophysomyces spp.
• Fusarium
• Trichosporon
• Curvularia, Alternaria

Re-emerging fungi
• Zygomycosis
• Aspergillosis
• Penicilliosis
• Histoplasmosis
Examples of recent emerging diseases
<table>
<thead>
<tr>
<th>Disease</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>Human papilloma virus</td>
</tr>
<tr>
<td>Chronic hepatitis, liver cancer</td>
<td>Hepatitis B and C viruses</td>
</tr>
<tr>
<td>Lyme disease (arthritis)</td>
<td><em>Borrelia burgdorferi</em></td>
</tr>
<tr>
<td>Whipple’s disease</td>
<td><em>Tropheryma whippelii</em></td>
</tr>
<tr>
<td>Bladder cancer</td>
<td><em>Schistosoma haematobium</em></td>
</tr>
<tr>
<td>Stomach cancer</td>
<td><em>Helicobacter pylori</em></td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td><em>Helicobacter pylori</em></td>
</tr>
<tr>
<td>Atherosclerosis (CHD)</td>
<td><em>Chlamydiae pneumoniae</em></td>
</tr>
<tr>
<td>Diabetes mellitus, type 1</td>
<td>Enteroviruses (esp. Coxsackie)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td><em>Epstein-Barr v, herpes vv?</em></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td><em>Mycobacterium avium</em> sub-spp.</td>
</tr>
<tr>
<td></td>
<td><em>Paratuberculosis, Yersinia</em></td>
</tr>
</tbody>
</table>
Prevention of Emerging Infectious Diseases

- Surveillance and Response
- Applied Research
- Infrastructure and Training
- Prevention and Control
How to tackle these infections

Public health surveillance & response systems
- Rapidly detect unusual, unexpected, unexplained disease patterns
- Track & exchange information in real time
- Response effort that can quickly become global
- Contain transmission swiftly & decisively
Global Outbreak Alert & Response Network

- Coordinated by WHO
- Mechanism for combating international disease outbreaks
- Ensure rapid deployment of technical assistance, contribute to long-term epidemic preparedness & capacity building
• Surveillance at national, regional, global level
  – epidemiological,
  – laboratory
  – ecological
  – Anthropological

• Investigation and early control measures
• Implement prevention measures
  – behavioural, political, environmental
• Monitoring, evaluation
International Health Regulations 2005

Four major changes in the revision

• Public Health Emergency of International concern
• Epidemic alert and response
• National Focal Point
• Dictates the core requirements for:
  – surveillance and response
  – ports of entry
The Role of the National Epidemic Alert and Response System

Veterinarian Surveillance System → Detection (Early Warning) → National Laboratory System → Notification/Risk Communication → Response

Food Surveillance → Health Care Services → Unofficial (Rumors) Sources

Health Care Services

WHO International

Authorities/Decision Makers

Media, General Public

Public Health Measures

Health Care Services

National Health Emergency Response System
National surveillance: current situation

- Independent vertical control programmes
- Surveillance gaps for important diseases
- Limited capacity in field epidemiology, lab. diagnostic testing, rapid field investigations
- Inappropriate case definitions
• Delays in reporting, poor analysis of data and information at all levels

• No feedback to periphery

• Insufficient preparedness to control epidemics

• No evaluation
• Applied Research

• Integrate laboratory science and epidemiology to increase the effectiveness of public health practice.
• Infrastructure and Training

• Strengthen public health infrastructures to support surveillance, response, and research and to implement prevention and control programs.

• Provide the public health work force with the knowledge and tools it needs.
• Prevention and Control

• Ensure prompt implementation of prevention strategies and enhance communication of public health information about emerging diseases.
- Enhance communication: locally, regionally, nationally, globally
- Increase global collaboration
- Share technical expertise and resources
- Provide training and infrastructure support globally
- Ensure political support
- Ensure judicious use of antibiotics
- Vaccines for all
Prevention Partners
Emerging Infections Network

- In 1995, the CDC granted a Cooperative Agreement Program award to the Infectious Diseases Society of America (IDSA) to develop a provider-based emerging infections sentinel network: the Emerging Infections Network (IDSA EIN).
Emerging Infections Network Works

- IDSA EIN has evolved into a flexible sentinel network composed of over 1,100 infectious disease specialists primarily from North America, with some global members. The overarching goal of the EIN is to assist CDC and other public health authorities with surveillance for emerging infectious diseases and related phenomena.
The Specific goals of the EIN are to:

- Detect new or unusual clinical events;
- Identify cases during outbreak investigations;
- Gather information about clinical aspects of emerging infectious diseases;
- Help connect members to the CDC and other public health investigators; and
- Develop new methods for gathering epidemiological and clinical information.
STRATEGIES TO REDUCE THREATS

• IMPROVE GLOBAL RESPONSE CAPACITY
  – WHO
  – National Disease Control Units (e.g. USCDC, CCDC)

• IMPROVE GLOBAL SURVEILLANCE
  – Improve diagnostic capacity (training, regulations)
  – Improve communication systems (web, e-mail etc.)
  – Rapid data analysis
  – Develop innovative surveillance and analysis strategies
  – Utilize geographical information systems
  – Utilize global positioning systems
  – Utilize the Global Atlas of Infectious Diseases (WHO)
STRATEGIES TO REDUCE THREATS

• **USE OF VACCINES**
  – Increase coverage and acceptability (e.g., oral)
  – New strategies for delivery (e.g., nasal spray administration)
  – Develop new vaccines
  – Decrease cost
  – Decrease dependency on “cold chain”

• **NEW DRUG DEVELOPMENT**
STRATEGIES TO REDUCE THREATS

• DECFAESE INAPPROPRIATE DRUG USE
  – Improve education of clinicians and public
  – Decrease antimicrobial use in agriculture and food production

• IMPROVE VECTOR AND ZOONOTIC CONTROL
  – Develop new safe insecticides
  – Develop more non-chemical strategies e.g. organic strategies

• BETTER AND MORE WIDESPREAD HEALTH EDUCATION
  (e.g., west Nile virus; bed nets, mosquito repellent)

Dr.T.V.Rao MD
ROLE OF THE PUBLIC HEALTH PROFESSIONAL

• Establish surveillance for:
  – Unusual diseases
  – Drug resistant agents
• Assure laboratory capacity to investigate new agents (e.g., high-throughput labs)
• Develop plans for handling outbreaks of unknown agents
• Inform physicians about responsible antimicrobial use
ROLE OF THE PUBLIC HEALTH PROFESSIONAL

• **Educate public about**
  – Responsible drug compliance
  – Emergence of new agents
  – Infection sources
    • Vector control
    • Malaria prophylaxis

• Be aware of potential adverse effects of intervention strategies

• Anticipate future health problems

• Promote health and maximize human functional ability
Role of Microbiology: Crucial link

The importance of Microbiology laboratories rests with prompt identification and reporting can cure with simple remedies, as most of the emerging infections respond to several drugs and choice lies with optimal selection based on Antibiograms, as resistance is not a menace with emerging, newer and uncommon isolates.

- The modern generation of Microbiologists should be familiar with Identification of the Microbes with newer generation of Technological advances.
Today sharing the knowledge on Microbes through World Wide Web (WWW) helps for faster dissemination of Knowledge and many lives in the Developing world can be saved
Need for global help to Developing countries

Commitment to technology transfer and global collaboration is essential if we are to have the agility required to keep pace with emerging infectious diseases. Pathogen surveillance and discovery can promote global interaction via collaborations on matters that know no national or political boundaries but simply reflect our common goals.
CDC Emerging Infections Priority Issues

- Antimicrobial resistance
- Food and water safety
- Vectors and animal health
- Blood safety
- Infections that cause chronic diseases
- Opportunistic infections
- Maternal and child health
- Health of travelers and refugees
- Vaccines
Summary

- Humans, domestic animals and wildlife are inextricably linked by epidemiology of infectious diseases (IDs).

- IDs will continue to emerge, re-emerge and spread.

- Human-induced environmental changes, inter-species contacts, altered social conditions, demography and medical technology affect microbes’ opportunities.
Neglected Diseases

• About 1 billion people are affected by one or more neglected tropical diseases (NTDs).
• They are named neglected because these diseases persist exclusively in the poorest and the most marginalized communities, and have been largely eliminated and thus forgotten in wealthier places.
• The diseases thrive in places with unsafe water, poor sanitation, and limited access to basic health care.
• Despite the severe pain and life-long disabilities they cause, these diseases are often less visible and given a low priority alongside high mortality diseases.
Neglected Diseases

• There are 14 diseases currently listed as NTDs.
• Most can be prevented, eliminated and one, guinea worm, has been eradicated.
• Children are the most vulnerable.
• The 14 NTDs are:

– Buruli ulcer,
– Chagas disease,
– cholera/epidemic diarrhoeal diseases,
– dengue/dengue haemorrhagic fever,
– dracunculiasis (guinea-worm),
– endemic treponematoses (yaws, pinta, endemic syphilis),
– human African trypanosomiasis (sleeping sickness),
– leishmaniasis,
– leprosy,
– lymphatic filariasis,
– onchocerciasis,
– schistosomiasis,
– soil-transmitted helminthiasis, and
– trachoma.
Neglected Diseases

• Since neglected tropical diseases do not travel easily, they pose little immediate threat to wealthier societies.

• Meanwhile, those who are affected have little political voice and are too poor to demand treatment.

• These diseases therefore do not represent a lucrative market for medicines as the underfunding for the development of new drugs shows: Less than 1% of the newer drugs registered are for tropical diseases.
"Knowing is not enough; we must apply. Willing is not enough; we must do."
—*Johann Wolfgang von Goethe, German poet (1749-1832)*