Emerging and Re-Emerging Viral Diseases: A View from NIAID

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National Institute of Allergy and Infectious Diseases
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March 18, 2014
NIAID Research: A Dual Mandate

Maintain and “grow” a robust basic and applied research portfolio in microbiology, infectious diseases, immunology and immune-mediated diseases

Respond rapidly to new and emerging disease threats

New/Improved Interventions
Plagues and Peoples

“A book of the first importance, a truly revolutionary work.”

The New Yorker

By the Author of The Rise of the West

William H. McNeill

Guns, Germs, and Steel

The Fates of Human Societies

Jared Diamond

Author of The Third Chimpanzee
Progress in the Control of Infectious Diseases

- Recognition that microbes cause many serious diseases
- Improvements in sanitation, hygiene, vector control
- Discovery and development of antimicrobials
- Development of vaccines and implementation of vaccination programs
- Advances in detecting and monitoring infectious diseases
Crude Infectious Disease Mortality Rate, United States, 1900 to 1996

Source: GL Armstrong et al., JAMA 281:61, 1999
A Premature Declaration of Victory Over Infectious Diseases

"We can look forward with confidence to a considerable degree of freedom from infectious diseases at a time not too far in the future. Indeed... it seems reasonable to anticipate that within some measurable time... all the major infections will have disappeared."

Infectious Diseases Cause ~19% of All Deaths Worldwide

Total Deaths (2010): ~52.8 Million

Source: Lozano, Murray et al., Lancet, 2012
Global Health and Infectious Diseases

Established Infectious Diseases

+ 

Emerging and Re-Emerging Infectious Diseases
Global Health and Infectious Diseases

Established Infectious Diseases

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Emerging and Re-Emerging Infectious Diseases
# Selected Established Infectious Diseases of Global Public Health Importance

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated Annual Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Infections</td>
<td>&gt;2,000,000</td>
</tr>
<tr>
<td>Diarrheal Infections</td>
<td>1,800,000</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1,600,000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1,300,000</td>
</tr>
<tr>
<td>Hepatitis (A, B, C, E)</td>
<td>900,000-1,200,000</td>
</tr>
<tr>
<td>Malaria</td>
<td>600,000</td>
</tr>
<tr>
<td>Vaccine Preventable Childhood Diseases (measles, pertussis, tetanus, etc.)</td>
<td>400,000</td>
</tr>
<tr>
<td>Neglected Tropical Diseases*</td>
<td>320,000-700,000</td>
</tr>
</tbody>
</table>

Global Health and Infectious Diseases

Established Infectious Diseases

+ 

Emerging and Re-Emerging Infectious Diseases
Global Trends in Emerging Infectious Diseases

KE Jones, Peter Daszak, et al.

“In the global human population, we report the emergence of 335 infectious diseases between 1940 and 2004.”
Global Examples of Emerging and Re-Emerging Infectious Diseases

Antimicrobial resistant threats
- CRE
- MRSA
- C. diff
- N. gonorrhoeae

Cryptosporidiosis
E. coli O104:H4
Drug-resistant malaria

Hepatitis C
vCJD

H3N2v influenza
Cyclosporiasis
E. coli O157:H7
Human monkeypox
Listeriosis
2009 H1N1 influenza
Adenovirus 14

Anthrax bioterrorism
Chikungunya

Hantavirus pulmonary syndrome
Dengue
Yellow fever
Human African trypanosomiasis

West Nile virus
Lyme disease

Ebola hemorrhagic fever
Drug-resistant malaria

Diphtheria
MERS-CoV
Rift Valley fever
Typhoid fever

SFTSV bunyavirus
E. coli O157:H7
H7N9 influenza
H5N1 influenza
SARS
Nipah virus
Hendra virus

Lassa fever
MDR/XDR tuberculosis
HIV

Human monkeypox
Plague

○ Newly emerging ○ Re-emerging/resurging ● “Deliberately emerging”

March 2014
Emerging Infectious Diseases

Newly Emerging

Re-Emerging or Resurging
Global Examples of Emerging and Re-Emerging Infectious Diseases

- Antimicrobial resistant threats
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- Ebola hemorrhagic fever
- Drug-resistant malaria

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- Typhoid fever

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- E. coli O157:H7
- Human monkeypox
- Listeriosis
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- Dengue
- Yellow fever
- Human African trypanosomiasis
- Cholera
- Marburg hemorrhagic fever
- MDR/XDR tuberculosis

- HIV

- Lassa fever
- Lyme disease
- vCJD

- Plague
- Human monkeypox

- Enterovirus 71
- Hendra virus

- SARS
- H5N1 influenza
- H7N9 influenza
- Nipah virus

- March 2014

- Newly emerging
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- “Deliberately emerging”
June 5, 1981

Pneumocystis Pneumonia – Los Angeles

July 4, 1981

Kaposi’s Sarcoma and Pneumocystis Pneumonia Among Homosexual Men – New York City and California
Current Status of the Global HIV/AIDS Pandemic

- >70 million total HIV infections
- 36 million total AIDS deaths
- 35.3 million people living with HIV
- 1.6 million AIDS deaths in 2012
- 2.3 million new HIV infections in 2012
The Science of HIV/AIDS: Much Accomplished

- Natural History
- Etiology
- Virology
- Diagnosis
- Epidemiology
- Pathogenesis
- Prevention
- Treatment
- Vaccine Development
Rounds at NIH Clinical Center,
Early 1980s – AIDS Patient

- Median survival of AIDS patients: ~6-8 months
FDA-Approved Antiretroviral Drugs

**NRTI**
- Zidovudine
- Didanosine
- Zalcitabine*
- Stavudine
- Lamivudine
- Abacavir
- Tenofovir
- Emtricitabine
- 4 multi-drug combinations

**NNRTI**
- Nevirapine
- Etravirine
- Delavirdine
- Rilpivirine
- Efavirenz

**PI**
- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir*
- Lopinavir + Ritonavir
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

**Fusion Inhibitor**
- Enfuvirtide (T-20)

**Entry Inhibitor**
- Maraviroc

**Integrase Inhibitors**
- Raltegravir
- Elvitegravir**
- Dolutegravir

**Multi-Class Combinations**
- Atripla
- Complera
- Stibrild

*no longer marketed  **currently approved only as part of combination tablet

Source: FDA, 2013
Closing the Gap: Increases in Life Expectancy among Treated HIV-Positive Individuals in the United States and Canada

H. Samji et al. for The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

- 22,937 individuals, 82,022 person-years

A 20-year-old HIV-infected individual on ART in the U.S. or Canada is expected to live into their early 70s, a life expectancy approaching that of the general population
Scale-up of Antiretroviral Treatment in Low- and Middle-Income Countries

- President’s Emergency Plan for AIDS Relief (PEPFAR)
- Global Fund to Fight AIDS, Tuberculosis and Malaria
- Philanthropies and NGOs – e.g., BMGF, MSF, Clinton Foundation
- Host country programs
Current Status of the Global HIV/AIDS Pandemic

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- 36 million total AIDS deaths
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- 1.6 million AIDS deaths in 2012
  ↓ 30% since 2005
- 2.3 million new HIV infections in 2012
Combination HIV Prevention

- ARVs for PMTCT, PEP, PrEP
- Treatment as Prevention
- Medical Male Circumcision
- STI Treatment
- Microbicides
- Treatment/Prevention of Drug/Alcohol Abuse
- Clean Syringes
- Education/Behavior Modification
- Condoms
- Blood Supply Screening
- HIV Testing/ Counseling
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- 35.3 million people living with HIV
- 1.6 million AIDS deaths in 2012

- 2.3 million new HIV infections in 2012
  \[\downarrow \text{33\% since 2001}\]
Modeling the End of the HIV/AIDS Pandemic

- Status quo
- Scale-up of non-vaccine combination prevention
Too Soon for a Victory Lap!

Much to do with regard to:

- Implementation
- Discovery
Remaining Challenges in HIV Discovery

- Vaccine
- Cure
Global Examples of Emerging and Re-Emerging Infectious Diseases

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Diphtheria
MERS-CoV
Rift Valley fever
Typhoid fever
HRSV
Hendra virus
Nipah virus
Enterovirus 71
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March 2014
Early Cases of SARS: Guangdong Province, China

Nov 16, 2002: first known cases of atypical pneumonia in Foshan

Feb 11-12, 2003: China reports 305 cases of acute respiratory syndrome in Guangdong Province
2003 Spread of SARS from Hotel Metropole

Sources: MMWR, March 28, 2003; WHO, 2003
Cumulative Reported Cases of Severe Acute Respiratory Syndrome (SARS), Sept. 26, 2003

8,098 Cases (774 deaths)

Source: WHO
SARS Characterization and Vaccine Development

SARS CoV Discovered
March 24, 2003

SARS CoV Sequenced

2003

April 14, 2003

SARS Vaccine Developed
A DNA Vaccine Induces SARS Coronavirus Neutralization and Protective Immunity in Mice
Zhi-yong Yang, Wing-pui Kong, Yue Huang, Anjeanette Roberts, Brian R. Murphy, Kanta Subbarao and Gary J. Nabel

2004

March 31, 2004

December 13, 2004

SARS Phase I Clinical Trial Initiated at NIAID VRC
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- MERS-CoV

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March 2014

Total: 189 cases/82 deaths
(~43% case fatality rate)

Source: WHO, March 12, 2014
Report: NIAID MERS-CoV Expert Consultation

June 24, 2014

Bethesda, MD

NIAID MERS-CoV Research Response

- Rapid research response capability, similar to SARS
- Basic research
- Animal model development
- Vaccines
- Therapeutics
- Animal reservoirs
MERS-CoV Animal Models: Selected Examples of NIAID-Supported Work

Pneumonia from Human Coronavirus in a Macaque Model
VJ Munster, E de Wit and H Feldmann

Rapid Generation of a Mouse Model for Middle East Respiratory Syndrome
J Zhao, S Perlman et al.
MERS-CoV Vaccines: Selected Examples of NIAID-Supported Work

Candidate Vaccines

- DNA/gene-based
- Purified protein subunit
- Multivalent nanoparticle
MERS-CoV Therapeutics: Selected Examples of NIAID-Supported Work

Inhibition of Novel β Coronavirus Replication by a Combination of Interferon-α2b and Ribavirin
D Falzarano, H Feldmann et al.

Cell Host Response to Infection with Novel Human Coronavirus EMC Predicts Potential Antivirals and Important Differences with SARS Coronavirus
L Josset, M Katze et al.

Treatment with Interferon-α2b and Ribavirin Improves Outcome in MERS-CoV-infected Rhesus Macaques
D Falzarano, H Feldmann et al.
MERS-CoV Animal Reservoirs: Selected Examples of NIAID-Supported Work

Middle East Respiratory Syndrome Coronavirus Infection in Dromedary Camels in Saudi Arabia
AN Algaili, WI Lipkin et al.

MERS Coronavirus in Dromedary Camels, Egypt
DKW Chu, G Kayali et al.
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Dengue

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NIAID Dengue Research

- Basic research
- Vector biology
- Tools, resources, and services
- Translational research (vaccines, therapeutics, diagnostics)
NIAID-Supported Dengue Vaccine Development: Selected Examples

- **TetraVax-DV live-attenuated tetravalent**
  - NIAID-developed
  - Phase I, II trials underway
  - Technology licensed to companies in Brazil, India, Vietnam, and U.S.

- **Tetravalent, recombinant dengue vaccine**
  - Developed by CDC and InViragen
  - Phase I trials conducted in NIAID Vaccine and Treatment Evaluation Units
  - Acquired by Takeda in 2013 for late-stage development

- **Chimeric dengue vaccine with tetravalent yellow fever 17D virus backbone**
  - NIAID supported early R&D
  - Phase III trials underway (Sanofi Pasteur)
Chikungunya Virus (CHIKV)

- *Aedes* mosquito-borne alphavirus
- Causes rash, fever, debilitating arthritis, generally not fatal
- No licensed vaccines or specific treatments
- Recent outbreaks have posed significant public health impact
- Risk of spread from outbreak areas due to broad vector range
Chikungunya Virus: An Emerging Threat

- Crossed Atlantic in December 2013
- >10 countries in Region of the Americas report cases
- >12,000 probable or confirmed cases

Source: ECDC, March 14, 2014
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NIAID CHIKV Vaccine Development: Basic Through Clinical Research

A Virus-Like Particle Vaccine for Epidemic Chikungunya Virus Protects Nonhuman Primates Against Infection

W Akahata, GJ Nabel, et al.

- Phase I trial completed in November 2013
- Data suggest vaccine is safe and immunogenic
The Threat of Influenza

Seasonal Influenza – annual burden:

- USA
  - up to 49,000 deaths
  - more than 200,000 hospitalizations
  - $27 billion in medical costs plus lost earnings

- Global
  - 250,000 to 500,000 deaths

Pandemic Influenza

- 1918, 1957, 1968, and 2009

- 1918 “Spanish Flu” pandemic caused 50 to 100 million deaths worldwide
Issues Related to Influenza Vaccines

- Lack of life-long immunity following infection and/or vaccination
- Invariable “drift” of seasonal influenza strains requiring “timetable” approach to vaccine development
- Imprecision in predicting seasonal strain
- Cost ($2-4 billion) to prepare seasonal influenza vaccines de novo each year
- Inability to stockpile vaccines for several years
- Potential for emergence of pandemic strain
Induction of Unnatural Immunity: Prospects for a Broadly Protective Universal Influenza Vaccine

GJ Nabel and AS Fauci
Influenza A Hemagglutinin (HA)
Generating Broadly Neutralizing Antibodies: Targeting the Stem

- Most antibodies bind to epitopes of highly variable head region
- Antibodies that neutralize multiple strains bind to a highly conserved region (red) in the stem region

Source: Doms, Science 329:1021, 2010
DNA Priming and Influenza Vaccine Immunogenicity: Two Phase 1 Open Label Randomized Clinical Trials

J.E. Ledgerwood, G.J. Nabel, B.S. Graham, et al. and the VRC 306 Study Team

Initial immunization with DNA vaccine boosts effectiveness of traditional influenza vaccine and could help prepare for future pandemics
Generating a More Potent Immune Response Using Nanoparticles

- Ferritin self assembles into nanoparticles to which hemagglutinin can be affixed
- Offers the ability to show more antigen on stable platform

Emerging Infections: A Perpetual Challenge

DM Morens, GK Folkers & AS Fauci