Emerging Infections: A Perpetual Challenge

Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
January 9, 2018
White House Holds Disaster-Response Exercise with Trump Officials
Dr. Anthony Fauci, Expert on Immunity and AIDS, Named Director of Nat'l. Institute of Allergy and Infectious Diseases

Dr. Anthony S. Fauci has been named Director of the National Institute of Allergy and Infectious Diseases, effective Nov. 2.

NIAID conducts and supports research to better understand the causes of allergic, immunologic and infectious diseases, and to develop better means of preventing, diagnosing and treating such illnesses.

Dr. Fauci, 43, an internationally renowned expert on the immune system, has been chief of NIAID's Laboratory of Immunoregulation since 1980 and deputy clinical director of the Institute since 1977.

"I am extremely pleased that Dr. Fauci will take over the leadership of this important institute," HHS Secretary Margaret M. Heckler said in announcing the appointment. "His unique background, particularly in the fields of immunology and infectious diseases, will be of key importance in maintaining and accelerating our momentum in these crucial areas of research.

Dr. Fauci is internationally renowned for his expertise on the immune system.
Testimony before the House Appropriations Subcommittee for NIH – 1980s
Global Examples of Emerging and Re-Emerging Infectious Diseases

- Newly emerging
- Re-emerging/resurging
- “Deliberately emerging”
Global Examples of Emerging and Re-Emerging Infectious Diseases
Global Examples of Emerging and Re-Emerging Infectious Diseases

- Antimicrobial-resistant threats
  - CRE
  - MRSA
  - *C. difficile*
  - *N. gonorrhoeae*
- H3N2v influenza
- Cyclosporiasis
- *E. coli* O157:H7
- Measles
- Human monkeypox
- Listeriosis
- Bourbon virus
- 2009 H1N1 influenza
- Adenovirus 14
- Anthrax bioterrorism
- Chikungunya
- Hantavirus pulmonary syndrome
- Dengue
- Zika virus
- Human African trypanosomiasis
- Cholera
- Yellow fever
- Marburg hemorrhagic fever
- MDR/XDR tuberculosis
- Plague
- HIV
- Akhmeta virus
- Rift Valley fever
- Typhoid fever
- SFTSV bunyavirus
- *E. coli* O157:H7
- H10N8 influenza
- H7N9 influenza
- H5N1 influenza
- Nipah virus
- Hendra virus
- Enterovirus 71
- Human monkeypox
- Ebola virus disease
- Zika virus

Legend:
- Red circle = Newly emerging
- Blue circle = Re-emerging/resurging
- Black circle = “Deliberately emerging”

September 2017
Five Administrations and Emerging Infectious Diseases


William J. Clinton 1993-2001

Barack H. Obama 2009-2017


George W. Bush 2001-2009
Ronald W. Reagan
1981-1989
June 5, 1981

Pneumocystis Pneumonia – Los Angeles

July 3, 1981

Kaposi’s Sarcoma and Pneumocystis Pneumonia Among Homosexual Men – New York City and California
"...because we do not know the cause of this syndrome, any assumption that the syndrome will remain restricted to a particular segment of our society is truly an assumption without scientific basis."
This political scandal must be investigated!

54% of people with AIDS in NYC are Black or Hispanic. AIDS is the No. 1 killer of women between the ages of 24 and 29 in NYC.

By 1991, more people will have died of AIDS than in the entire Vietnam War. What is Reagan's real policy on AIDS?

Genocide of all Non-whites, Non-males, and Non-heterosexuals.

Silence = Death
In 2016:
- 36.7 million living with HIV
- 1.8 million infected with HIV
- 1.0 million deaths from AIDS-related illnesses

Since start of the pandemic
- 76.1 million infected with HIV
- 35.0 million deaths from AIDS-related illnesses
HIV/AIDS

George H. W. Bush
1989-1993
NIH HIV/AIDS Research Funding, FY 1982 to FY 1993

- Treatment
- Prevention
- Pathogenesis
- Diagnosis
- Etiology
- Virology
- Natural History
- Epidemiology
- Vaccine Development

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

- Median survival of AIDS patients: ~8-15 months
## FDA-Approved Antiretroviral Drugs

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>Multi-Class Combinations</th>
<th>Integrase Inhibitors</th>
<th>Fusion Inhibitor</th>
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<tbody>
<tr>
<td>5 multi-drug combinations</td>
<td>Delavirdine</td>
<td>Atazanavir</td>
<td>Atripla</td>
<td>Dolutegravir</td>
<td>Enfuvirtide</td>
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<td>Stavudine</td>
<td>Nevirapine</td>
<td>Darunavir</td>
<td>Complera</td>
<td>Raltegravir</td>
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<td>Tenofovir (TDF, TAF)</td>
<td>Rilpivirine</td>
<td>Fosamprenavir</td>
<td>Genvoya</td>
<td>Elvitegravir</td>
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<td>Abacavir</td>
<td>Indinavir</td>
<td>Lopinavir/ Ritonavir</td>
<td>Odefsey</td>
<td>Dolutegravir</td>
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<td>Didanosine</td>
<td>Nelfinavir</td>
<td>Nelfinavir</td>
<td>Stribild</td>
<td>Raltegravir</td>
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<td>Emtricitabine</td>
<td>Saquinavir</td>
<td>Ritonavir</td>
<td>Triumeq</td>
<td>Elvitegravir</td>
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<td>Lamivudine</td>
<td>Tipranavir</td>
<td>Tipranavir</td>
<td>Juluca</td>
<td>Maraviroc</td>
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</tbody>
</table>

Source: FDA, 11/2017
Life Expectancy for 20-Year-Old Newly Diagnosed with HIV, 1980s and Today

1980s (no ART)  1-2 years from AIDS diagnosis

Today (on ART)  ~53 years

Source: JL Marcus et al., JAIDS, 2016.
Combination HIV Prevention

- HIV Testing/Counseling
- Treatment as Prevention
- Medical Male Circumcision
- STI Treatment
- Microbicides
- Treatment/Prevention of Drug/Alcohol Abuse
- Clean Syringes
- Education/Behavior Modification
- Condoms
- Blood Supply Screening
- PrEP
- PMTCT
William J. Clinton
1993-2001
Meeting at the White House to Discuss AIDS Research, Dec. 3, 1996
"If America commits to find an AIDS vaccine and we enlist others in our cause, we will do it... Today I'm pleased to announce the National Institutes of Health will establish a new AIDS vaccine research center dedicated to this crusade."
VRC Research: From HIV to Zika

- HIV
- West Nile virus
- Chikungunya
- Ebola/Marburg
- Influenza
- Malaria
- MERS-CoV
- RSV
- Tuberculosis
- Venezuelan, Eastern, and Western equine encephalitis viruses
- Zika
Global Examples of Emerging and Re-Emerging Infectious Diseases

West Nile virus

- N. gonorrhoeae
- H3N2v influenza
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- Cholera
- Marburg hemorrhagic fever
- MDR/XDR tuberculosis
- Plague
- HIV
- Ebola virus disease
- Drug-resistant malaria
- Diphtheria
- MERS-CoV
- Akhmeta virus
- Rift Valley fever
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- Enterovirus 71
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- Ebola virus disease

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

September 2017
Global Distribution of West Nile Virus, 1999

Source: CDC
U.S. West Nile Virus Cases & Deaths, 1999-2017

Source: CDC

*As of Dec. 19, 2017; includes probable cases
A West Nile Virus DNA Vaccine Utilizing a Modified Promoter Induces Neutralizing Antibody in Younger and Older Healthy Adults in a Phase I Clinical Trial

JE Ledgerwood, BS Graham et al. for the VRC 303 Study Team
George W. Bush
2001-2009

- HIV/AIDS
- Anthrax
- H5N1 Influenza
- SARS
Juxtaposition of Events of September 11, 2001 and the Deliberate Release of Anthrax
Bioterrorism: A Clear and Present Danger

HC Lane, J La Montagne and AS Fauci
NIAID Strategic Plan for Biodefense Research

Responding Through Research

NIAID Biodefense Research Agenda for CDC Category A Agents

Responding Through Research

National Institute of Allergy and Infectious Diseases
NATIONAL INSTITUTES OF HEALTH
Category A Select Agents: Key Achievements

- Smallpox
  - Dryvax; MVA; antiviral drug

- Anthrax
  - Next-generation 2-dose vaccine; antitoxins

- Botulinum
  - Antitoxins; mAbs

- Plague
  - Antibiotics

- Ebola
  - First human vaccine trials; therapeutics; diagnostics
February 5, 2002

President GW Bush: “Tony, what scares you the most among potential microbial threats that a terrorist might use?”

Fauci: “Mr. President, I worry more about the natural occurrence of an influenza pandemic and the ongoing plague of HIV than I do about a bioterror attack.”
Newsday
November 18, 2001

The Worst Bioterrorist May Be Nature Itself
REVIEW ARTICLE

Avian Influenza A (H5N1) Infection in Humans

The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5
Pandemic Influenza Preparedness
Strategy and Implementation

- International Surveillance
- Domestic Surveillance
- Vaccines
- Antivirals
- Communications
- State and Local Preparedness
Global Examples of Emerging and Re-Emerging Infectious Diseases

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September 2017
SARS: A New Challenge to Global Health
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 in Hong Kong

Sources: MMWR, March 28, 2003; WHO, 2003
Cumulative Reported Cases of SARS
November 1, 2002 to July 31, 2003

8,096 cases (774 deaths)

Source: WHO
SARS Characterization and Vaccine Development

2003
- March 24, 2003: SARS CoV Discovered

2004
- April 14, 2003: SARS CoV Sequenced
- March 31, 2004: 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
- December 13, 2004: SARS Phase 1 Clinical Trial Initiated at NIAID VRC
WHO Declares Victory over SARS: Taiwan Last Country to Be Taken off List of Infected Areas
The Birth of the President’s Emergency Plan for AIDS Relief (PEPFAR)
Addressing HIV/AIDS: Visits to 11 Countries in Sub-Saharan Africa
The President’s Emergency Plan for AIDS Relief – $15B Over 5 Years

Goals:
- Prevent 7 million new infections
- Treat 2 million HIV-infected people
- Care for 10 million HIV-infected people, orphans and other vulnerable children
State of the Union Address, January 28, 2003

President Bush announces the President’s Emergency Plan for AIDS Relief (PEPFAR)
Selected PEPFAR Accomplishments

As of 9/30/2017:

- 13.3 million people on antiretroviral therapy
- 2.2 million perinatal HIV infections averted
- 85.5 million people received HIV testing services in FY 2017
- 25-40% decline in new HIV diagnoses among adolescent girls and young women through comprehensive HIV prevention interventions – DREAM partnership
Global Examples of Emerging and Re-Emerging Infectious Diseases

Antimicrobial-resistant threats
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- C. difficile
- N. gonorrhoeae

H3N2v influenza
Cyclosporiasis
E. coli O157:H7
Measles
Human monkeypox

West Nile virus
Cryptosporidiosis
Powassan virus
E. coli O104:H4
Drug-resistant malaria

Diphtheria
MERS-CoV
Akhmeta virus
Rift Valley fever
Typhoid fever
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Marburg hemorrhagic fever
MDR/XDR tuberculosis
Plague

2009
H1N1 influenza

Red Circle: Newly emerging
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September 2017
Beginning of Global H1N1 Influenza as of March, 2009

Source: WHO
Global H1N1 Influenza Cases, as of April 29, 2009

Confirmed or suspected cases

Source: WHO
Countries with Confirmed Pandemic (H1N1) 2009 Influenza Cases as of Sept. 30, 2009

Source: WHO
Vaccine Lags Behind 2009 H1N1 Influenza Pandemic

- Percent of ILI Visits Reported by Sentinel Providers, Weeks 30-50 2009
- H1N1 Vaccine Doses Available
- Children Return to School
- 6 months after virus isolation (April 2009), first vaccine doses become available
House Oversight and Government Reform Committee Hearing on H1N1 Influenza Vaccines, Sept. 29, 2009
Global Examples of Emerging and Re-Emerging Infectious Diseases

Ebola virus disease

- Newly emerging
- Re-emerging/resurging
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Reported Ebola Virus Disease Cases in Guinea, Liberia, and Sierra Leone, 2014-2016

**Guinea**
3,814 cases / 2,544 deaths

**Sierra Leone**
14,124 cases / 3,956 deaths

**Liberia**
10,678 cases / 4,810 deaths

*Confirmed, probable and suspected cases*

Source: WHO, 12/2016

**Total***:
28,616 cases
11,310 deaths

40% mortality
Phase 2 Placebo-Controlled Trial of Two Vaccines to Prevent Ebola in Liberia

SB Kennedy, HC Lane et al. for the PREVAIL I Study Group

- Randomized, placebo-controlled Phase 2 trial of ChAd3-EBO-Z (GSK) and rVSVΔG-ZEBOV-GP (Merck)
- By 1 month, vaccines had elicited immune responses that were largely maintained through 12 months
- Trial rapidly initiated and completed; showed that rigorous research can be conducted during an outbreak
First Case Diagnosed in the U.S.: Timeline

- **Sept 19**: Subject departs Monrovia
- **Sept 20**: Arrives and departs Brussels, Belgium
- **Sept 20**: Arrives in Dallas
- **Sept 24**: Develops symptoms
- **Sept 26**: Presents to ER, sent home
- **Sept 28**: Patient transferred by ambulance, admitted
- **Sept 30**: Tests positive for Ebola
- **Oct 8**: Patient dies
First Two Ebola Transmissions Within the U.S.

The New York Times

October 12, 2014

Texas Health Worker Tests Positive for Ebola

2nd Ebola Case in U.S. Stokes Fears of Health Care Workers
Fear Spreads Faster than Ebola: Our View

By USA Today Editorial Board
NIH Special Clinical Studies Unit: Designated Ebola Treatment Facility

*As of Oct. 2014, three Designated Ebola Treatment Facilities existed in the U.S.*
Nina Pham, Nurse Who Contracted Ebola, is Now Free of Virus and Leaves NIH
March 12, 2015

U.S. Ebola Patient Headed to NIH
Patient Admitted With Ebola Virus Disease Discharged From NIH Clinical Center
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- Dengue
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- Human African trypanosomiasis
- Cholera
- Marburg hemorrhagic fever
- MDR/XDR tuberculosis
- Plague
- HIV

**Zika virus**

- Newly emerging
- Re-emerging/resurging
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Zika Virus Spread, 1947-2017

1952: First human cases described
1947: Discovered in Uganda
1977-78: Pakistan, Malaysia, Indonesia
2007: Yap, Micronesia
2013: French Polynesia
2015: Brazil
2016: United States

Source: Lancaster University
Symptoms of Zika Virus Infection

4 in 5 individuals asymptomatic

- Incubation: 3-12 days
- Mild symptoms: 2-7 days

- Rash
- Headache/Malaise
- Non-purulent conjunctivitis/Conjunctival hyperemia
- Elevated body temperature (Above 99°F)
- Arthralgia/Myalgia
- Peripheral edema/gastrointestinal disturbance have also been observed

Source: BMJ.com, 2/2016
Suspected and Confirmed Zika Cases in the Americas, 2015-2017

Marked Increase in Microcephaly Cases in Brazil

Associated Press
November 30, 2015

Brazil Links Mosquito-Borne Zika Virus to Microcephaly Birth Defect

Microcephaly cases in Brazil 2010-14; suspected/confirmed cases 2015-2017

- Number of cases:
  - 2010: 153
  - 2011: 139
  - 2012: 175
  - 2013: 167
  - 2014: 147
  - 2015-2017: 5,889

- Suspected cases (3,236)
- Confirmed cases (863 confirmed Zika+ by PCR)

*does not include cases investigated and discarded

Source: Brazilian MOH; data as of April 26, 2017
Baby Born With Microcephaly
Congenital Zika Syndrome is a Pattern of Birth Defects in Babies Infected with Zika During Pregnancy

- Small head size (microcephaly)
- Problems with vision and hearing
- Problems moving limbs and body
- Damage to the brain
- Seizures
- Problems with feeding (difficulty swallowing)

Source: CDC
NIH Zika Countermeasure Research and Development

- Therapeutics
- Novel Vector Control
- Vaccines
- Diagnostics
- Expansion of Research Capacity
- Basic Research
- Genomics
- Clinical Research
NIH Zika Countermeasure Research and Development

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- Therapeutics
- Novel Vector Control
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- Expansion of Research Capacity
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- Basic Research
- Genomics
NIH Zika Vaccine Candidates

- DNA vaccine (NIAID VRC)
- Zika purified inactivated vaccine (WRAIR/NIAID/BARDA and Sanofi Pasteur)
- Live-attenuated Zika/dengue chimeric virus (NIAID intramural/Butantan)
- mRNA vaccine candidate (NIAID VRC, GSK)
- Vesicular Stomatitis Virus vectored vaccine (NIAID extramural)
NIH Zika Vaccine Candidates

- DNA vaccine (NIAID VRC)

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VRC DNA Vaccines for Emerging Infections

Sequence Selection to 1st Human Injection

- **SARS**
  - 4-14-2003
  - 20 months

- **2005 H5N1**
  - 2-11-2006
  - 11 months

- **2009 H1N1**
  - 4-27-2009
  - 4 months

- **ZIKA**
  - 4-24-2016
  - 3.25 months

Courtesy: J Ledgerwood/NIAID VRC
Phase 2/2b Clinical Trial of VRC Zika DNA Vaccine

- **Part A (non-placebo controlled)**
  - Launched 3/31/2017
  - Fully enrolled – n=90

- **Part B (placebo-controlled)**
  - Launched 7/19/2017
  - Target n=2,400 to 5,000
Five Administrations and Emerging Infectious Diseases


William J. Clinton 1993-2001
George W. Bush 2001-2009

Barack H. Obama 2009-2017
Six Administrations and Emerging Infectious Diseases


William J. Clinton 1993-2001

George W. Bush 2001-2009

Barack H. Obama 2009-2017

Donald J. Trump 2017-present
What's Next?
Health Officials Brace for Return of Zika
Will Mayaro Virus Be Responsible for the Next Outbreak of an Arthropod-borne Virus in Brazil?

DLO Esposito, BAL daFonseca

Oropouche Virus Could Emerge and Cause a Public Health Problem

Vector is no longer confined to villages in the Amazon but is spreading to major cities throughout Brazil, researcher warns
Examples of Recently Emergent Influenza Viruses

- H7N9 influenza
- H5N1 influenza
- SARS
- Nipah virus
- Hendra virus
- Human monkeypox
- Ebola virus disease
- MDR/XDR tuberculosis
- Plague
- Zika virus

Key:
- Red dot: Newly emerging
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September 2017
Waves of Human H7N9 Influenza Infections in China, February 2013–present

- 1,623 confirmed human cases, 620 deaths
- 5th wave: >50% of cumulative cases

Source: FAO, 12/19/17
The Pathway to a Universal Influenza Vaccine

CI Paules, HD Marston, RW Eisinger, D Baltimore, AS Fauci
Selected Targets for “Universal” Influenza Vaccines

Conserved epitopes of NA

Conserved epitopes of HA

1. PB2
2. PB1
3. PA
4. HA
5. NP
6. NA
7. M1+M2
8. NS1+NS2

M2

NP

Source: Subbarao/Murphy
Influenza A Hemagglutinin (HA)

- Head region
- Stem region
- Neuraminidase
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 area in the stem region.

H1N1 Sequence conservation

| ≤98% | 100% |

Courtesy Jeffrey Boyington
Evolution of Technologies for Influenza Vaccines

Egg-based → Cell-based → Recombinant DNA Technologies
New Platforms for Seasonal and Pandemic Influenza Vaccines

- Recombinant subunit
- Synthetic peptide
- Microbial vector
- Nanoparticle-based
- Virus-like particles (VLPs)
- DNA-based
- Novel delivery systems (e.g., microneedles)
Selected Approaches to Universal Influenza Vaccines

Chimeric HA

Stem only

Nanoparticle

Virus-like particle
February 9, 2017

What Three Decades Of Pandemic Threats Can Teach Us About The Future

Anthony S. Fauci

“If history has taught us anything, it is that the new administration is likely to experience at least one infectious disease crisis of significance.”
Lessons Learned from Previous Pandemics

- Global surveillance
- Transparency and communication
- Infrastructure and capacity building
- Coordinated and collaborative basic and clinical research
- Adaptable platform technologies for vaccines, diagnostics and therapeutics
- Stable funding mechanism – “Public Health Emergency Fund”
Emerging Infections: A Perpetual Challenge

DM Morens, GK Folkers & AS Fauci