PREPARING FOR EMERGING INFECTIOUS DISEASES OF THE 21ST CENTURY
The Challenge of Ebola

Dennis G. Maki, MD
Divisions of Infectious Diseases
and Pulmonary-Critical Care Medicine
Department of Medicine
University of Wisconsin School of Medicine

dgmaki@medicine.wisc.edu

CONFLICTS OF INTEREST?
None
EMERGING INFECTIOUS DISEASES OF THE 21st CENTURY

Goals -- to understand:
1. History and the NAS/NIM definition of an emerging infectious disease.
3. Why have EIDs emerged?
4. Preparing for EIDs at the global, national, state and local levels.
5. Ebola: history, the virus, epidemiology, uncontrolled Ebola in 2014-5, clinical features, treatment, protecting healthcare workers and secondary spread, a vaccine, is panic justified...what does the future hold?
6. Future global threats that could dwarf Ebola.
VACCINE-PREVENTABLE INFECTIOUS DISEASES

- Anthrax
- Cervical Cancer (HPV)
- Diphtheria
- Hepatitis A
- Hepatitis B
- Liver Cancer (HBV)
- *Haemophilus influenzae* type b
- Human Papillomavirus
- Influenza
- Japanese encephalitis
- Lyme disease
- Measles
- Meningococcal
- Mumps
- Pertussis
- Pneumococcal
- Polio
- Rabies
- Rotavirus
- Rubella
- Shingles
- Smallpox
- Tetanus
- Typhoid
- Tuberculosis
- Varicella
- Yellow Fever

MAJOR PARENTERAL ANTIBIOTICS

*Penicillin G*
- Ampicillin
- Ampi-Sulbactam

*Methicillin*
- Nafcillin
- Oxacillin

*Carbenicillin*
- Ticarcillin
- Mezlocillin
- Piperacillin
- Azlocillin

*Ampicillin-Sulbactam*

*Ticarcillin-Clavulinic Acid*
- Piperacillin-Tazobactam

CDC 2014
In 1970, William Stewart, the Surgeon General of the United States said that the U.S. was “ready to close the book on infectious disease as a major health threat.”

His optimism resulted from his firm belief that modern antibiotics, vaccination, and sanitation methods seemed to have defeated most of the infectious diseases.

THE ANTIBIOTIC ERA

Infection remains a major problem
Deaths by Cause, World-Wide

- Infectious & Parasitic Diseases
- Cardiovascular Diseases
- Cancer
- Perinatal Causes
- Chronic Obstructive Pulmonary Diseases
- Maternal Causes
- Other Diseases

Number (Millions)

INSTITUTE OF MEDICINE
DEFINITION OF
EMERGING INFECTIONS

(1) *New*, (2) *reemerging* or
(3) *drug-resistant* infections whose
incidence in humans has increased within
the past two decades or whose incidence
threatens to increase in the near future.

*Institute of Medicine Report, 1992

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EMERGING INFECTIOUS
DISEASES OF THE 21st CENTURY

Goals -- to understand:
1. History and the NAS/NIM definition of an
   *emerging infectious disease*.
EMERGING INFECTIOUS DISEASES
1975 - 2015

- Legionella pneumonia
- *C. difficile*-associated colitis
- HTLV I/II
- *Staph aureus* TSS
- Lassa Fever, Marburg and Ebola viruses
- *Campylobacter jejuni*
- HIV and AIDS
- *Helicobacter pylori*, PUD
- Parvovirus
- Norwalk Virus
- HPV genital warts and cancer
- *Borrelia burgdorferi* and Lyme
- *E. coli* 0157 and HUS, TTP
- *Bartonella hensalae*
- Creutzfeldt-Jakob Disease, Mad Cow Disease (BSE) and vCJD
- Hepatitis C
- MDR Tuberculosis
- Erhlichiosis, Anaplasmosis
- Overwhelming blastomycosis...ARDS
- Return Measles, Pertussis, Diphtheria
- Cholera O139 in South America
- Cryptosporidiosis
- Streptococcal TSS
- HHV-8 (Kaposi Sarcoma Virus)
- Sin Nombre Virus (Hantavirus)
- Nipah Virus, Hendra Virus
- Monkeypox
- SARS-CoV
- H1N1 Influenza A
- Asian H5N1, H7N9 Influenza A
- Dengue, Chikungunya Fever
- MERS-CoV
- D68 Enterovirus
- Ebola 2014


EMERGING INFECTIOUS DISEASES OF THE 21st CENTURY

Goals -- to understand:
1. History and the NAS/NIM definition of an *emerging infectious disease*.
3. Why have EIDs emerged?
FACTORS CONTRIBUTING TO EMERGENCE OF NEW INFECTIOUS DISEASES

<table>
<thead>
<tr>
<th>Categories</th>
<th>Specific examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Societal events</strong></td>
<td>War or civil conflict; population growth and migration; urban decay; economic impoverishment</td>
</tr>
<tr>
<td><strong>Health care</strong></td>
<td>Medical devices; organ transplantation; immunosuppression; widespread use of antibiotics</td>
</tr>
<tr>
<td><strong>Food production</strong></td>
<td>Globalization of food supplies; changes in food processing, packaging, and preparation</td>
</tr>
<tr>
<td><strong>Human behavior</strong></td>
<td>Sexual behavior; drug use; travel; diet; outdoor recreation; day-care for children</td>
</tr>
<tr>
<td><strong>Environmental changes</strong></td>
<td>Deforestation/reforestation; changes in water ecosystems; flood/drought; famine; global warming</td>
</tr>
<tr>
<td><strong>Public health infrastructure</strong></td>
<td>Curtailment or reduction of prevention programs; inadequate communicable disease surveillance; inadequate trained personnel (epidemiologists, laboratory scientists, vector/rodent control specialists)</td>
</tr>
<tr>
<td><strong>Microbial adaptation and change</strong></td>
<td>Genuine <em>new pathogen</em> and no population immunity; changes in virulence; antiinfective drug resistance; Bioterrorism</td>
</tr>
</tbody>
</table>

EMERGING INFECTIOUS DISEASES OF THE 21st CENTURY

Goals -- to understand:

1. History and the NAS/NIM definition of an *emerging infectious disease*.
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4. Preparing for EIDs at the global, national, state and local levels.
CDC’s Emerging Infectious Disease Threats Plan and Its Terrorism Preparedness and Response Strategy

- **Addressing New Emerging Infectious Disease Threats**
  - Surveillance and response—detect, promptly investigate, and monitor emerging pathogens, the diseases they cause, and the factors influencing their emergence
  - Applied research—integrate laboratory science and epidemiology to optimize public health practice
  - Prevention and control—enhance communication of public health information about emerging diseases and ensure prompt implementation of prevention strategies
  - Infrastructure—strengthen local, state, and federal public health infrastructures to support surveillance and implementation of prevention and control programs

- **Terrorism Preparedness and Response Strategy**
  - Timely, effective and integrated detection and investigation
  - Sustained prevention and consequence management programs
  - Coordinated public health emergency preparedness and response
  - Qualified, equipped and integrated laboratories
  - Competent and sustainable workforce
  - Protected workers and workplaces
  - Innovative, relevant and applied research and evaluation
  - Timely, accurate and coordinated communications
  - Achieving Shared Goals Through Partnerships
  - Integrated and secure information systems
  - Creative and effective management services

PREPARATION FOR BIOTERRORISM AND EMERGING ID THREATS

- A strong national resolve and defense
- Greatly strengthened national, state and local programs, better networks for communication and reporting
- Primary care providers, Emergency HCWs and intensivists can immediately recognize anthrax, smallpox, other infections and toxin-chemical exposure syndromes
- Vigorous international condemnation / isolation of countries with offensive BW programs
- Consistant and effective international inspections
- Ample stockpiles of critical vaccines and anti-infectives, especially Smallpox and anthrax vaccines
- Research to develop safer and better vaccines, more rapid and reliable diagnostic techniques, highly sensitive “biodetectors”
EMERGING INFECTIOUS DISEASES OF THE 21st CENTURY

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PREPARING FOR EBOLA

History
THE EBOLA VIRUS

One of the hemorrhagic fever viruses:
- Lassa fever virus
- Marburg virus
- Ebola virus
- Rift valley fever virus
- Crimean-Congo fever virus
- Yellow fever virus
- Dengue virus
- Korean Haantan virus
- U.S. Hanta virus

EBOLA: THE BEGINNING

Outbreak of hemorrhagic fever in in southern Sudan and northern Zaire in 1976, with 284 afflicted and 151 dying (53%). Of 230 hospital personnel, 76 became infected from patients and 41 died.

Brit Med J 1977

A new filovirus, distinct from Marburg virus, was isolated and characterized.

EBOLA: THE BEGINNING

Outbreak of hemorrhagic fever in southern Sudan and northern Zaire in 1976, with 284 afflicted and 151 dying (53%). Of 230 hospital personnel, 76 became infected from patients and 41 died.

Brit Med J 1977

EBOLA: 1976 - 2013

Since then, until the 2014 outbreak, there have been 19 additional major African outbreaks of Ebolavirus infection in Sudan (3), Zaire (3), Congo (7), Gabon (3), Uganda (3), with 1-2 introduced cases or laboratory-acquired infections in the UK, S. Africa, Spain, the U.S. and Russia.
EBOLA: THE BEGINNING

......... and outbreaks of subclinical *Ebolavirus Reston* infection in the Phillipines (2) and the U.S. (1).

THE 2014-15 WEST AFRICAN OUTBREAK OF EBOLAVIRUS ZAIRE INFECTION

- Initial case 2 year-old in Guinea in December 2013
- Person-to-person spread to *Liberia, Sierra Leone*, Nigeria, Senegal and Mali...U.S., Europe
THE 2014-15 WEST AFRICAN OUTBREAK OF EBOLAVIRUS ZAIRE INFECTION

- Initial case 2 year-old in Guinea in December 2013
- Person-to-person spread to Liberia, Sierra Leone, Nigeria, Senegal and Mali...U.S., Europe
- By July 16, 2015:
  27,698 cases, 11,268 deaths (41%)

>600 cases in healthcare workers,
~50% fatal
THE 2014-15 WEST AFRICAN EBOLA EPIDEMIC

• Initial case 2 year-old in Guinea in December 2013
• Person-to-person spread to Liberia, Sierra Leone, Nigeria, Senegal and Mali...U.S.
• By July 16, 2015:
  27,698 cases, 11,268 deaths (41%)
• Nigeria had an introduced case with 13 secondary cases but totally contained further spread.
• U.S. had 2 endogenous cases in exposed nurses in Dallas, further spread contained.
THE 2014-15 WEST AFRICAN OUTBREAK OF EBOLAVIRUS ZAIRE INFECTION

• An important aside: during the ongoing huge 2014 outbreak in Guinea-Liberia-Sierra Leone, there has been an unrelated outbreak of Ebolavirus Zaire infection in Congo since August 2014, which appears to have wound down but has afflicted 66 persons to date, with a 74% mortality.

PREPARING FOR EBOLA

The Ebola Virus
THE EBOLA VIRUS

One of the hemorrhagic fever viruses:
- Lassa fever virus
- Marburg virus
- Ebola virus
- Rift valley fever virus
- Crimean-Congo fever virus
- Yellow fever virus
- Dengue virus
- Korean Hatan virus
- U.S. Hanta virus

Ebolavirus is a Filovirus
Unique thread-like structure

Enveloped single-strand RNA virus

Five species:
- Ebolavirus Zaire
- Ebolavirus Sudan
- Ebolavirus Tai Forrest (Ivory Coast)
- Ebolavirus Bundibugyo
- Ebolavirus Reston

PREPARING FOR EBOLA

Epidemiology
EPIDEMIOLOGY OF EBOLAVIRUS INFECTION

• The reservoir of Ebolavirus between outbreaks remained a mystery for decades but the best recent evidence indicates it is like its sister filovirus, Marburgvirus, fruit bats.  
  Leroy et al. Nature 2005

EPIDEMIOLOGY OF EBOLAVIRUS INFECTION

• The reservoir of Ebolavirus between outbreaks remained a mystery for decades but the best recent evidence suggests it is like its sister filovirus, Marburgvirus, is fruit bats.
• Bats defecate on vegetation eaten by primates and duikers, and infect them.
• African natives become infected when they eat these animals and bats as “bushmeat.”
EPIDEMIOLOGY OF EBOLAVIRUS INFECTION

• Virtually all spread thereafter, *initiating, perpetuating and amplifying the epidemic*, is by *person-to-person spread*, and in Africa by the cultural practice of *washing and touching the body of the deceased*. 

EPIDEMIOLOGY OF EBOLAVIRUS INFECTION

Enzootic Cycle
New evidence strongly implicates bats as the reservoir hosts for ebolaviruses, though the means of local enzootic maintenance and transmission of the virus within bat populations remains unknown.

Ebolaviruses:
- Ebola virus (formerly Zaire virus)
- Sudan virus
- Tai Forest virus
- Bundibugyo virus
- Reston virus (non-human)

Epidemic Cycle
Epidemics caused by ebolaviruses appear sporadically, producing high mortality among non-human primates and squirrels and may provide human reservoirs. Epidemics caused by ebolaviruses produce acute disease among humans, with the exception of Reston virus which does not produce detectable disease in humans. Little is known about how the virus first passes to humans, triggering waves of human-to-human transmission, and an epidemic.

Human-to-human transmission is a predominant feature of epidemics.

Following initial human infection through contact with an infected bat or other wild animal, human-to-human transmission often occurs.
PREPARING FOR EBOLA

Why has Ebola spread uncontrolled in 2014?

THE RURAL SOCIETY OF SUBSAHARA AFRICA OF 30 YEARS AGO
PREPARING FOR EBOLA

Clinical Features of Ebolavirus Infection

INCUBATION PERIOD OF EBOLAVIRUS INFECTION

CDC.gov
CLINICAL FEATURES OF EBOLAVIRUS INFECTION

Initial (days 5-8)

Headache  Leptospirosis? Typhus? Q Fever?
Weakness*  Leishmaniasis? Trypanosomiasis?
Dizziness*  Measles? Meningococcemia?
Myalgias
Nausea, vomiting
Diarrhea*
Rash

N Engl J Med 2014 x2 CDC.gov

* Predictors of fatality

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CLINICAL FEATURES OF EBOLAVIRUS INFECTION

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Nausea, vomiting
Diarrhea*
Rash

Fullblown illness (days 7-10)

High fever
Hypotension.....shock*
Vomiting, Diarrhea
Profound lassitude, stupor or coma*
Hemorrhage (10-15%)*
Gingival, conjunctival, skin, GI

LAB

Leukopenia, lymphocytopenia
Thrombocytopenia, features DIC
Elevated AST, BUN/Creatinine

N Engl J Med 2014 x2
CDC.gov

* Predictors of fatality
PREPARING FOR EBOLA
Why does EVD kill?

PATHOGENESIS OF EBOLAVIRUS INFECTION AND DISEASE

PROGNOSTIC FACTORS FOR FATAL OUTCOME

- Age > 40-45 yrs, especially > 60 yrs
- High fever, dizziness, diarrhea at outset
- Initial EBOV load > 100,000, > 10 million /mm3
- Hemorrhage
- Shock
- Coma

Most die in shock and MODS within first 8-10 days.

Sadek et al. J Infect Dis 1999

PREPARING FOR EBOLA

Management of possible Ebolavirus infection and proven EVD
MANAGEMENT OF THE POTENTIAL EBOLA VIRUS-INFECTED PATIENT

- Adequate training and adequate PPE for all HCWs having direct contact with the patient, their secretions or lab specimens.
- Limited no. designated Ebola-care HCWs
- Rigorous training in donning and doffing PPE.
- PPE should cover all skin, double gloves, boot covers, fluid-resistant gowns or coveralls, single-use disposable hoods covering head and neck, single-use disposable face shields, PAPR or N95 respirators.
- Frequent disinfection gloved hands with alcohol-based hand rub, immediately disinfect visibly contaminated PPE.
- Trained colleague (“buddy”) actively observes and supervises donning and doffing PPE.
MANAGEMENT OF THE POTENTIAL EBOLAVIRUS-INFECTED PATIENT

- Adequate training and adequate PPE for all HCWs having direct contact with the patient, their secretions or lab specimens.
- Isolation room with environmental controls.
- Determine level of risk:

High risk
- Percutaneous (eg, needle stick) or mucous membrane exposure to blood or body fluids of a person with EBV.
- Exposure to the blood or body fluids without appropriate PPE.
- Processing blood or other body fluids without appropriate PPE or biosafety precautions.
- Direct contact with a dead body without appropriate PPE in a country with EVD.
- Having lived in the immediate household and provided direct care to a person with symptomatic EVD.
**Some risk**

- In countries with widespread EVD, direct contact while using appropriate PPE with a person with EVD.

- Close *non*direct contact with a person with EBV, within ~3 feet of the infected person for prolonged period while not wearing PPE.

**Low risk**

- **Having been in a country with widespread EBV over past 21 days, but without known exposures.**

- Having brief direct contact (eg, shaking hands) without PPE with a person with EBV in early stage.

- Brief same room exposure to a person with EVD.

- In countries without widespread EVD, direct contact while wearing PPE with a person with EVD.

- Travel on an airplane with a person with EVD, without direct physical contact.
MANAGEMENT OF THE POTENTIAL EBOLAVIRUS-INFECTED PATIENT

- Adequate training and adequate PPE for all HCWs having direct contact with the patient, their secretions or lab specimens.
- Isolation room with environmental controls.
- Determine level of risk:
  - Any risk + symptoms $\rightarrow$ RT-PCR testing
  - Any risk + asymptomatic $\rightarrow$ No testing but monitor closely in quarantine, test if become symptomatic
  - No risk + asymptomatic $\rightarrow$ No testing

TESTING FOR EBOLAVIRUS INFECTION

- Culture (sensitive, hazardous, impractical)
- Serology (variably sensitive early and even late)
- Electron Microscopy (impractical)
- Antigen (not standardized or widely available)
- Real-time RT-PCR (Highly sensitive and specific, quick, + within 3 days of infection)

Kits with primers and QA materials must be made widely available to allow timely testing and optimal management.

Huang. Viral Sin 2012
Ebola Doctors Are Divided on IV Therapy in Africa

By DONALD G. McNEIL Jr.  JAN. 1, 2015

Medical experts seeking to stem the Ebola epidemic are sharply divided over whether most patients in West Africa should, or can, be given intravenous hydration, a therapy that is standard in developed countries. Some argue that more aggressive treatment with IV fluids is medically possible and a moral obligation. But others counsel caution, saying that pushing too hard would put overworked doctors and nurses in danger and that the treatment, if given carelessly, could even kill patients.

The debate comes at a crucial time in the outbreak. New infections are flattening out in most places, better-equipped field hospitals are opening, and more trained professionals are arriving, opening the possibility of saving many lives in Africa, rather than a few patients flown to intensive care units thousands of miles away.

The World Health Organization sees intravenous rehydration, along with constant measuring of blood chemistry, as the main reason that almost all Ebola patients treated in American and European hospitals have survived, while about 70 percent of those treated in West Africa have died.

Severe Ebola virus disease with vascular leakage and multiorgan failure: treatment of a patient in intensive care

Toni Wolf, Gernot Klein, Stephan Bolker, Christoph Steppeken, Harald Hemmer, Philip A. E. L. N. J. M. Veenendaal, Philip F. A. E. L. M. Veenendaal

Summary

Background. The current epidemic of Ebola virus disease in western Africa, nurses and workers have become infected. Some of these aid workers have been transferred to specialized hospitals in Europe and the USA for intensive treatment, providing the potential for unique insight into the clinical course of Ebola virus disease under optimized supportive measures in isolation units.

Methods. A 42-year-old male doctor who had contracted an Ebola virus infection in Sierra Leone was admitted to University Hospital Frankfurt, Germany, on day 5 after disease onset. Within 72 h of admission to the hospital's intensive care unit, the patient developed signs of severe multiorgan failure, including lungs, liver, and gastrointestinal tract. In addition to clinical parameters, the diagnostic work-up included radiography, ultrasonography, pulse contour cardiac output technology, and microbiological and clinical chemistry analyses. Renal failure with polyclonal elevations of alanine aminotransferase and creatine kinase levels and leukopenia was noted. The patient received a 3-day treatment course with F2bM (WE-849), Vaxero, a Ebola-virus-specific peptide under clinical development for vascular leak syndrome. After F2bM administration and reversed detection of Ebola virus-specific antibodies and a fold in viral load, vascular leak syndrome and respiratory parameters substantially improved. We give broad-spectrum empiric antimicrobial therapy and the patient needed intermittent renal replacement therapy. The patient fully recovered.

Findings. This case report shows the feasibility of delivery of successful intensive care therapy to patients with Ebola virus disease under intensive level 3 conditions.

Interpretation. The effective treatment of vascular leakage and multiorgan failure by combination of ventilatory support, antimicrobial treatment, and renal replacement therapy can maintain a patient with severe Ebola virus disease until virological remission. F2bM could potentially be a valuable agent in combination to supportive therapy.
MANAGEMENT OF SYMPTOMATIC PRESUMABLY INFECTED PATIENTS

- Adequate training and adequate PPE for all HCWs having direct contact with the patient, their secretions or lab specimens.
- Isolation room with environmental controls.
- Log all HCWs having contact with patient.
- Limit aerosol-generating procedures.

- Treat dehydration and electrolyte deficiencies.

IV FLUID RESUSCITATION
EBOLA CASES TREATED INJ THE U.S. AND OUTCOME

Cases contracted in the U.S.  2
Cases first diagnosed in U.S.  4
Cases evacuated to U.S. from other countries  6
Total cases  10
Deaths  2
Recoveries from Ebola  8
Active cases  0

EFFECTIVENESS OF PROTOCOL MANAGEMENT WITH IV REHYDRATION

The Sierra Leone Hastings Ebola Treatment Center has recently adopted a new protocol emphasizing IV rehydration:

- **IV RL 500 cc + D5/NS 500 cc Q8-12 hours x3 days**
- **Liberal oral rehydration solution, as tolerated**
- Vit K 10 mg and Artemether 160 mg IV on arrival
- Metaclopramide 10 mg IV, prn, for nausea/vomiting
- Zinc 20 mg po daily
- Ceftriaxone + Metronidazole IV x3 days → **cefuroxime + Metronidazole po x5 days**
- Artesunate-Lumefantrine po daily x3
- Ibuprofen 400 mg po Q12 hours x3 days

Basal reported Sierra Leone mortality ~75%. Mortality among Hastings patients arriving alive treated with the protocol has dropped to 48%, now to 23%.

MANAGEMENT OF SYMPTOMATIC PRESUMABLY INFECTED PATIENTS

• Adequate training and adequate PPE for all HCWs having direct contact with the patient, their secretions or lab specimens.
• Isolation room with environmental controls.
• Log all HCWs having contact with patient.
• Limit aerosol-generating procedures.
• Treat dehydration and electrolyte deficiencies.
• Experimental antiviral therapies.

EXPERIMENTAL THERAPIES FOR EBOLAVIRUS INFECTION

• Convalescent plasma (harvested from survivors) Has been used in Africa for decades, efficacy unproven, CPT now approved/advocated by WHO.
• Experimental rMonoclonal antibodies (ZMapp)
• Interfering RNA (TKM-Obola)
• Brincidofovir

JAMA 2014
Nature 2014
J Infect Dis 2014
BMJ 2014
http://apps.who.int/iris/bitstream/10665/135591/1/WHO
IV FLUID RESUSCITATION

100 centers throughout West Africa that could do timely electrolyte measurements and rehydrate critically ill victims with inexpensive sterile IV IV solutions would save more lives than all the costly novel agents being trialed.

PREPARING FOR EBOLA

Protecting Healthcare Workers
WHAT BODY FLUID OR SITES CONTAIN POTENTIALLY INFECTIOUS EBOLAVIRUS BY RT-PCR?

<table>
<thead>
<tr>
<th></th>
<th>Acute Phase Infection</th>
<th>Convalescence &gt;12 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>++++</td>
<td></td>
</tr>
<tr>
<td>Vomitus</td>
<td>++++</td>
<td></td>
</tr>
<tr>
<td>Saliva</td>
<td>+++</td>
<td>0/86</td>
</tr>
<tr>
<td>Feces</td>
<td>++</td>
<td>0/79</td>
</tr>
<tr>
<td>Tears</td>
<td>++</td>
<td>0/85</td>
</tr>
<tr>
<td>Breast milk</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Skin/sweat</td>
<td>+</td>
<td>0/84</td>
</tr>
<tr>
<td>Urine</td>
<td>+</td>
<td>0/95</td>
</tr>
<tr>
<td>Semen</td>
<td>+++</td>
<td>6/8 (&gt;3 mo)</td>
</tr>
<tr>
<td>Environment</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>


CDC.gov

HOW DOES EBOLAVIRUS GAIN ACCESS AND INFECT THE EXPOSED?

Study of transmission in 27 households during outbreak, 173 HH members exposed to an initial index case.

28 (16%) became secondarily infected, _all had direct physical contact_ with the index case (RR >1000), _none of 73 HH contacts without direct physical contact became infected_ (P<0.001). _Contact with a bodily fluid_ further increased risk (RR 3.6, P<0.01)

Adults were much more susceptible to infection than children.

_Dowell. J Infect Dis 1999_
HOW DOES EBOLAVIRUS GAIN ACCESS AND INFECT THE EXPOSED?

• Risk of transmission from exposure during the acute phase infection >>> convalescence.

• Exposure to blood > vomitus or stool > saliva > intact skin (unless dead person) >>> urine, environmental sources

• Airborne spread documented with experimental infection in pigs and primates but evidence for human transmission in household studies is nil.

WHEN DOES THE INFECTED PATIENT BECOME INFECTIOUS?

• Considerable epidemiologic data suggests infectiousness is minimal before the onset of symptomatic EVD.
Any American hospital should be able to treat an Ebola patient...

Tom Frieden
Director, CDC

U.S. designates 35 hospitals to treat Ebola patients

PREPARING FOR EBOLA

Controlling Ebola In Africa
CONTROLLING ENDEMIC AND EPIDEMIC EBOLAVIRUS INFECTION IN AFRICA

- Protective apparel for HCWs, bleach disinfection
- Identify potentially infected to quarantine + treat
- Identify exposed and quarantine in homes
- Prompt burial or cremation of dead
- Disinfect homes of cases
- Discourage eating of dead animals, cook bushmeat well
- Limit travel AMAP, quarantine involved villages...
- Deploy widely an effective Vaccine ASAP

CONTROLLING EBOLAVIRUS WITH A VACCINE

Experimental vaccines, showing promise in primate models, entering Phase 1→2 clinical trials among West African HCWs and in high-risk areas:
  - A complex DNA-rAdenovirus vaccine
  - rVSV vector encoding Ebola virus surface protein
  - rAdenovirus vaccine
  - rVesicular stomatitis virus vaccine
  - New inactivated Rabies-like vaccine

Expert Opin Biol 2012
J Infect Dis 2014
Ann Intern Med 2014
JAMA 2014
Single-dose attenuated Vesiculovax vaccines protect primates against Ebola Makona virus

Chad E. Mire1,2,*, Demetrius Mataisyov1,*, Jean H. Geisbert1,3, Therese E. Latham1, Krystle N. Agami2,3, Rong Xu4, Ayako Ota, Svetlana Michael A. Egger1, Karla A. Fenton1,2, David K. Clarke5, John H. Elderidge5,6 & Thomas W. Geisbert1,2

The family Filoviridae contains three genera, Ebola virus (EBOV), Marburg virus, and Cairensis virus. Some members of the EBOV genus, including Zaire ebolavirus (ZEBOV), can cause lethal hemorrhagic fever in humans. During 2014 an unprecedented ZEBOV outbreak occurred in West Africa and is still ongoing, resulting in over 10,000 deaths, and causing global concern of uncontrolled disease. To meet this challenge a rapid-acting vaccine is needed. Many vaccine approaches have shown promise in being able to protect nonhuman primates against ZEBOV. In response to the current ZEBOV outbreak several of these vaccines have been fast-tracked for human use. However, it is not known whether any of these vaccines can provide protection against the new outbreak strain of ZEBOV. One of these approaches is a first-generation recombinant vesicular stomatitis virus (rVSV)-based vaccine expressing the ZEBOV glycoprotein (GP) in VSV-ZEBOV. To address safety concerns associated with this vector, we developed two candidate, further-attenuated rVSV-ZEBOV vaccines. Both attenuated vaccines produced an approximately tenfold lower viral dose in monkeys compared to the first-generation vaccine, and both provided complete, single-dose protection of macaques from lethal challenge with the Makona outbreak strain of ZEBOV. Clinical trials of the rChAd5-ZEBOV vaccine were challenging with a ZEBOV seed stock containing a large viable population encoding furin (Fur) at a critical transcriptional editing site in the GP gene. This specific genetic feature typically arises following prolonged passage of ZEBOV in Vesicular stomatitis virus (VSV) in vitro and results in higher levels of expression of full-length GP. In contrast, low-passage ZEBOV isolates retain 7U at the GP editing site, resulting in higher levels of secreted GP (sGP) expression, which is associated with greater virulence. Our neutralizing studies have shown that rAd-based ZEBOV vaccines that completely protect NHPs against ZEBOV stocks containing high populations of 7U virus are not able to completely protect inoculated macaques challenged with ZEBOV stocks containing high populations of 7U virus.

The first-generation rVSV/ZEOBOV vaccine that replaces the VSV glycoprotein with the ZEBOV GP (rVSV/ZEBOVAD) originally developed by Dr. Feldmann and Geisbert and currently licensed by Nabi, has demonstrated solid single-dose NHP protection against a lethal challenge with ZEBOV stock. The rVSV/ZEBOVAD vaccine has also provided 100% of NHPs when administered shortly after ZEBOV challenge, and has demonstrated safety in a NHP neurovirulence model. However, there is a robust post-vaccination viremia in

Aerosolized Ebola vaccine protects primates and elicits lung-resident T cell responses

Michelle Meyer1,2,3, Tania Garron1,2,4, Ndongala M. Lubaki1,2,3, Chad E. Mire2,3,4, Karla A. Fenton2,3,4, Curtis Klages2,3,5, Gene G. Olinger6, Thomas W. Geisbert2,3,4, Peter L. Collins7, and Alexander Bukreyev1,2,3,4,8

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PREPARING FOR EBOLA

Important questions that need research answers ASAP

Important Questions About Ebolavirus that Need Research Answers ASAP

- Is there subclinical Ebolavirus infection?
- Does airborne transmission occur?
- How long does the virus remain infectious on environmental surfaces? Does transmission occur from the environment?
- Does seropositivity correlate with immunity? To all species? Lifelong?
- Is an infected person ever infectious before they become symptomatic? If so, how long before?
- Does EVD produce any chronic residual disease?
- Would EVD treatment centers that could provide early and adequate fluid and electrolyte repletion, guided by lab testing, materially improve survival?
- Does hyperimmune plasma therapy truly improve survival?
- How soon can we have an effective vaccine?
- Might EBOV Reston be worth trialing as a live-virus vaccine to provide protection against infection by virulent EBOV Sudan and Zaire?
PREPARING FOR EBOLA

Why the Panic?

WHY ALL THE PANIC?

- It’s the media, the media and the media.
- Ebola has been sensationalized, far beyond the actual domestic threat it poses or is ever likely to pose.
- 1 million Africans, most small children, die from malaria each year.
- 40,000 Americans die from influenza each year, most adults >65 years, now more children and pregnant women.
- A smoker is millions of times more likely to die from a smoking-related disease or an unimmunized child from a vaccine-preventable disease than from Ebolavirus infection!
- The mortality of MRSA endocarditis or septic shock, 25-40%, exceeds that of Ebolavirus infection with comparable high-quality medical care.
WHAT DOES THE FUTURE HOLD FOR THE 2014 EBOLAVIRUS PANDEMIC?

Big big ifs.....I believe that:

- *If* neither occur, the epidemic will probably spread beyond West Africa and devastate wide swathes of the poorest developing world, but less likely beyond Africa.

- I do not think Ebolavirus infection will ever become a true major threat to the developed countries but the costs of protecting our citizens and healthcare workers could become prohibitive.
WHAT DOES THE FUTURE HOLD FOR THE 2014 EBOLAVIRUS PANDEMIC?

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WHAT CAN WE AS U.S. CITIZENS DO TO CONTROL EBOLA?

• Support public health initiatives and major U.S. aid to the afflicted countries.
• Donate to *Doctors Without Borders* (FMF) and other charitable organizations providing service on the ground in West Africa.
• If feasible, consider volunteering in Africa, especially if you’re a healthcare provider.
EMERGING INFECTIOUS DISEASES OF THE 21st CENTURY

Goals -- to understand:

1. History and the NAS/NIM definition of an emerging infectious disease.
3. Why have EIDs emerged?
4. Preparing for EIDs at the global, national, state and local levels.
5. Ebola: history, the virus, epidemiology, uncontrolled Ebola in 2014-5, clinical features, treatment, protecting healthcare workers and secondary spread, a vaccine, is panic justified…what does the future hold?
6. Future global threats that could dwarf Ebola.
H5N1 AVIAN FLU OUTBREAK
2003-present

Countries (22) reporting bird/animal H5N1 infection:
Cambodia, China, Hong Kong, Indonesia, Japan,
Laos, South Korea, Thailand, Vietnam,
China...Egypt, UK
(U.S. flocks have tested positive for milder form of
H5N1 avian flu)

Human H5N1 infections (as of Mar 31, 2015):
Laboratory-confirmed cases 826
Deaths 440 (60%)
Median age of victims 13 years (range 4-58 years)


MERS-CoV INFECTION

Agent: New human Coronavirus discovered in September 2012
Highly virulent, through July 2015: >1300 cases from 302 Middle
East countries (Saudi Arabia 75%) and Korea, 36% fatal
(CONTRAST: Mortality SARS 12% in 9000 cases in 2003-4)

Epidemiology: Low infectiousness unless prolonged close contact
Reservoir: bats → camels → humans
Humanity has but three great enemies: fever, famine and war; of these, by far the greatest, by far the most terrible, is fever.

William Osler 1925