Something in the Air

December 5, 2014

Mark Russi, MD, MPH
Professor, Medicine and Public Health
Yale University

Medical Director, Wellness and Employee Population Health
Yale-New Haven Health System
Disclosures

• I, Mark Russi, hereby declare that the content for this activity, including any presentation of therapeutic options, is well balanced, unbiased, and to the extent possible, evidence-based.

• I have no financial relationships with commercial entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients relevant to the content I am presenting, or evaluating.
Outline

• New Haven
• Jos, Nigeria
• Meschede, Germany
• Hong Kong
• Atlanta
• Aerosols
• Public Health Guidance
• Implications for EVD
Definitions

• Airborne Transmission occurs when an individual releases infectious particles by coughing or sneezing which are small enough to remain suspended in the air for long periods of time, and capable of being carried for long distances on air currents. Examples of diseases that require Airborne Precautions are tuberculosis (TB), varicella (chickenpox, shingles), and measles.

• Droplet Transmission occurs when an individual coughs or sneezes and releases large respiratory droplets into the air. Unlike airborne particles, these droplets are heavy and fall to surfaces rapidly, usually falling within 3 feet of the patient. They are too heavy to remain in the air and to be carried on air currents. Examples of agents that require Droplet Precautions are Neisseria meningitidis, adenovirus, and Bordetella pertussis.
New Haven
Deadly virus at Yale

Researcher infected; public risk low

By Abram Katz
Register Science Editor

NEW HAVEN — A Yale researcher accidentally contracted a deadly new virus early this month, and now federal and state health officials are tracking almost 200 people in Connecticut and Massachusetts whom he may have infected before being hospitalized Saturday.

The unidentified male researcher was studying the Sabin alenavirus from Brazil, where it has caused two cases of hemorrhagic fever. One woman died, while a man recovered.

The Yale researcher was reported to be in stable but quarantined condition in an isolation unit at Yale-New Haven Hospital Sunday. He is receiving well being anti-viral drug, physicians said at a press conference.

The man's name is being withheld to protect doctor-patient confidentiality, a hospital spokesman said.

High-level officials of the U.S. Centers for Disease Control and Prevention in Atlanta met with state health officials and top Yale physicians and administrators late Sunday night to discuss the case.

Federal and state health officials said there is little risk to the general public.

Dr. Clifton J. Peters, chief of the CDC's special pathogens branch, said Sunday, "It's very unlikely anyone else was infected. We want the risk as low as we can get it."

Please see Virus, A4.
Clinical History

• August 16, 1994
  – Scientist developed myalgias, mild headache, stiff neck and fever while driving home from Boston
  – Symptoms persisted despite ibuprofen

• August 19, 1994
  – Scientist called Tropical Medicine Clinic for “malaria treatment”
  – Hx. of P. vivax malaria contracted many years previously with recrudescences, never treated with primaquine
  – No hx. of tick bites, recent travel overseas, or significant spills in laboratory work.
Clinical Presentation

- Mildly toxic appearing male
- BP 130/80, pulse 90, RR 12, temp 99.8 F (on ibuprofen)
- Skin: no rash
- HEENT: mild conjunctival injection
- LNs: shotty anterior cervical nodes
- Lungs: clear
- Heart: no murmurs
- Abdomen: no hepatosplenomegaly
- Extremities: no edema
Laboratory Values, August 19

- WBC 2600, Hct 42
- Platelet count 138,000
- UA 2+ protein
- Malaria smear negative
- Ehrlichial inclusions negative
- ALT 53
Further History

- Laboratory accident 11 days prior to presentation, BSL-3.
- 250 cc cracked centrifuge bottle leaked during 10,000 rpm spin.
- Sabia virus cultures: 100,000 - 10,000,000 viral particles/ml.
- Tube and rotor were transferred to safety hood and disinfected immediately.
- The virologist wore a surgical mask, gown, and gloves during procedure.
Biosafety issues

- Centrifuge cups not opened in a biosafety hood.
- Virologist did not immediately leave room.
- Spill cleaned by pouring bleach into rotor.
- Bearded virologist wore gloves, gown, surgical mask.
- Lab supervisor not informed of the spill.
A new arenavirus, called Sabia, was isolated in Brazil from a fatal case of hemorrhagic fever initially thought to be yellow fever. Antigenic and molecular characterization indicated that Sabia virus is a new member of the Tacaribe complex. A laboratory technician working with the agent was also infected and developed a prolonged, non-fatal influenza-like illness. Sabia virus is yet another arenavirus causing human disease in South America.
Jos

Sequence of Events

• January 27, 1970: notification of case cluster.
• Paired sera tested, confirmatory viral isolation
• 23 patients, all but three treated at Evangel
• Two patient groups, January and February
Epidemiological Investigation

• Geographical analysis.
• Other common experiences.
• Identification of probable index case.
• First 17 patients in hospital at time of her treatment.
• Index patient found in Lagos one year later, interviewed.
Possible means of transmission

- Bedpans and emesis basins
- Nurses and ward personnel
- Food supply
- Persistent surface contamination
- Potential animal hosts trapped and tested
- Airborne spread
• PCR confirmed Sabia.
• Negative pressure isolation, strict patient isolation.
• Anteroom, hepa masks, gowns, gloves.
• All laboratory work discontinued.
Handling and Processing of Lab Specimens

- Tubes double bagged, hand carried to labs.
- Protocols developed for processing of chemistry tests, hematology and coagulation tests, microbiology samples.
Respiratory Protection

- Emergent HEPA mask fit testing of immediate caregivers
- Urgent fit testing for anticipated caregivers
- Limitation of healthcare worker contact
Enhanced Personal Protection

- Contingency plan for intensive care
- Enhanced precautions with PAPRs for profuse bleeding.
Changes to CDC Guidance

• Patients in a hospital outpatient or inpatient setting should be placed in a private room. A negative pressure room is not required during the early stages of illness, but should be considered at the time of hospitalization to avoid the need for subsequent transfer of the patient. Nonessential staff and visitors should be restricted from entering the room. Caretakers should use barrier precautions to prevent skin or mucous membrane exposure to blood and other body fluids, secretions, and excretions. All persons entering the patient's room should wear gloves and gowns to prevent contact with items or environmental surfaces that may be soiled. In addition, face shields or surgical masks and eye protection (e.g., goggles or eyeglasses with side shields) should be worn by persons coming within approximately 3 feet of the patient to prevent contact with blood, other body fluids, secretions (including respiratory droplets), or excretions. An anteroom for putting on and removing protective barriers and for storing supplies would be useful, if available.

• For patients with suspected VHF who have a prominent cough, vomiting, diarrhea, or hemorrhage, additional precautions are indicated to prevent possible exposure to airborne particles that may contain virus. Patients with these symptoms should be placed in a negative-pressure room (9). Persons entering the room should wear personal protective respirators as recommended for care of patients with active tuberculosis (high efficiency particulate air {HEPA} respirators or more protective respirators).


The Precautionary Principle

• Better safe than sorry. -Samuel Lover
• Look twice before you leap. -Charlotte Bronte
• An ounce of prevention is worth a pound of cure. -Benjamin Franklin
• The requirement that decision-makers anticipate harm before it occurs. Within this element lies an implicit reversal of the onus of proof: under the precautionary principle it is the responsibility of an activity proponent to establish that the proposed activity will not (or is very unlikely to) result in significant harm.
• The establishment of an obligation, if the level of harm may be high, for action to prevent or minimize such harm even when the absence of scientific certainty makes it difficult to predict the likelihood of harm occurring, or the level of harm should it occur. The need for control measures increases with both the level of possible harm and the degree of uncertainty.
In September 2008 an outbreak of unexplained hemorrhagic fever was reported in South Africa. The index patient was airlifted in critical condition from Zambia on September 12 to a clinic in Sandton, South Africa, after infection from an unidentified source. Secondary infections were recognized in a paramedic (case 2) who attended the index case during air transfer from Zambia, in a nurse (case 3) who attended the index case in the intensive care unit in South Africa, and in a member of the hospital staff (case 4) who cleaned the room after the index case died on September 14. One case of tertiary infection was recorded in a nurse (case 5) who attended case 2 after his transfer from Zambia to Sandton on September 26, one day before barrier nursing was implemented. The course of disease in cases 1 through 4 was fatal; case 5 received ribavirin treatment and recovered.
Meschede
Meschede, West Germany, 1970
Sequence of Events

- 20-year old German man, living on streets of Karachi, Pakistan.
- Arrives Germany, Dec 31, 1969.
- Febrile, 10 days later.
- Admitted to Meschede Hospital.
- Develops rash on 4th hospital day.
- Transferred to “isolation hospital” on 6th hospital day.
- Contacts vaccinated, patients quarantined, wing closed to visitors.
- 17 additional cases, none had direct contact with index case.
Figure 2. Meschede Hospital

View of back of hospital

Floor plan

Meschede Hospital
Smallpox Guidance

- WHO: Medical care givers, attendants, and mortuary workers, even if vaccinated, should wear gloves, caps, gowns, and surgical masks.
- CDC: Use Standard Precautions for all patient care. In addition, use Contact and Airborne Precautions (i.e., disposable gowns and gloves to enter the contaminated area, disposal of used gowns and gloves before leaving the area, and fit-tested N95 masks) for patient care until a vaccine take has been confirmed in the care provider. Following the vaccine take, the care provider is no longer required to wear an N95 mask. Standard Precautions and Contact Precautions should be maintained.

Hong Kong
Epidemiology

- World total (revised 9/26/03):
  - 8098 cases
  - 774 deaths
  - Case fatality rate 9.6%
  - 1707 HCWs affected. (21% of all cases.)
  - Elevated HCW transmission rates in Viet Nam (57%), Singapore (41%), Canada (43%).
SARS Transmission: Global Spread from Hotel M

- Guangdong Province, China
- Hong Kong SAR: 95 HCW
  >100 close contacts
- Vietnam: 37 HCW
  21 close contacts
- Singapore: 34 HCW
  37 close contacts
- United States: 1 HCW
  11 close contacts
- Ireland: 0 HCW

Hotel M Hong Kong

- A: Hong Kong SAR
- H, J: Hong Kong
- B: Vietnam
- C, D, E: Singapore
- F, G: Canada
- K: United States
- I, L, M: Ireland

SARS Transmission: Global Spread from Hotel M
Amoy Gardens

Potential route of contamination to adjacent apartment blocks

Operation of the bathroom extract fan creates a negative pressure - drawing the foul gases from the sewer

Virus-laden water droplets enter the upper apartment

Dry floor drain
Airborne Transmission of SARS

- Extremely high concentrations of the SARS-associated coronavirus found in the feces and urine of the index patient, coupled with the aerosolization due to hydraulic action inside the drainage pipes most likely generated huge numbers of virus-laden aerosols.

- Virus-laden aerosols generated in the vertical soil stack of unit 7 in building E returned to the bathroom through the dried up seals of the floor-drain traps and then entered the air shaft, probably by means of suction from an exhaust fan. Aerosols moved upward owing to the buoyancy of the warm, humid air within the air shaft and could enter apartment units that bordered the air shaft on the upper floors because of the negative pressure created by the exhaust fans or the action of wind flows around the building.

SARS Guidance


Atlanta

- Plane held in Alaska for three hours.
- Ventilation shut down.
- 72% of passengers contracted influenza.
- Passengers free to move about cabin.
- Index patient seated at back of plane near closet, buffet and restroom.

- Study suggested that ventilation system impacted influenza transmission.
- Newest building provided 100% outside air, 1.6% of patients infected.
- Two buildings providing 70% outside air had infection rates of 15.8% and 9.3%.
- Building providing 30% outside air had 13.8% infected.
- But, attack rates the following season were similar among the buildings.

- Hospital housing TB patients during the 1957 flu epidemic.
- 2% of patients became infected with influenza on ward with upper air UV disinfection.
- 19% of patients became infected on ward without UV disinfection.

- 30-bed open medical ward, 59 patients, 29 healthcare personnel.
- Index patient treated with non-invasive ventilation for 16 hours.
- Nine inpatients and two healthcare workers subsequently developed influenza.
- Seven of the secondary cases occurred within 2-4 days of ventilation of index case.
- Air conditioning outlet in ceiling above index patient’s head, net flow of air from Bay C to Bay B, verified by tracer testing and computer modeling.
- Attack rate 20% on Bay C, 22.2% on Bay B, 0% on Bay A, which did not receive airflow from Bay C.
- Aerosol generating procedure, net airflow.
Computational Fluid Dynamics Modeling

The spatial distribution of normalized concentration of hypothetical virus-laden aerosols (modeled as gaseous tracer) in the outbreak ward at a height of 1.1 m. The flow rates used in this model were those described in Figure 3. All high-efficiency particulate absorbing (HEPA) filters were assumed to function with 100% filtration of the modeled droplet nuclei. The 3 HEPA air purifiers are shown as black boxes, the 4 diffusers are shown by a square with an X, and the 4 returns are shown as a small rectangular filled box. Affected patients are represented by white ovals (the index patient is marked as a red oval).

- U.S. tour group, 30 members, 4-day China trip, 4 flights.
- Index patient and 10 secondary cases.
- Attack rate for >2 minutes talking with index patient at <2 meters 56% vs 0% for those who did not speak with pt.
- Talking >10 minutes 5-fold higher risk than 2-9 minutes.
Aerosols
Stokes’ Law

\[ v_s = \frac{2}{9} \frac{(\rho_p - \rho_f)}{\mu} g R^2 \]

- \( v_s \) is the particle’s settling velocity (m/s)
- \( \rho_p \) is the density of the particles (kg/m\(^3\)), and
- \( \rho_f \) is the density of the fluid (kg/m\(^3\)).
- \( g \) is the gravitational acceleration (m/s\(^2\)),
- \( \mu \) is the dynamic viscosity (N s/m\(^2\)),
- \( R \) is the radius of the spherical object (in meters)
Additional Background on Aerosols

- Stokes Law: 3-meter fall: 4 minutes for 20-micron particle, 17 minutes for 10-micron, 67 minutes for 5-micron particle.
- Desiccated particles termed droplet nuclei. Evaporation of sub-20 micron particles to less than half original size within one second.
- 30% penetration of 5-micron particles to alveoli.
- 50% of 10-micron particles to tracheobronchial region.
- Essentially no penetration of 20-micron or greater particles beyond trachea.
- Definitions vary. 5 micron or less are aerosols. 5-20 sometimes termed “intermediate”. 20 microns and greater are droplets.
• Can influenza virus be detected on particles of aerosol dimension?

- Forty-nine percent of PCR-detectable influenza virus particles in a hospital ED waiting room are in the 1-4 micron fraction.
- Four percent in sub 1-micron fraction.
• Of 33 aerosol samples collected from a pediatric emergency room, 8 (24%) positive for influenza A.

• Size distribution not reported.

- Seventeen percent of stationary samplers and 19 percent of personal samplers contained influenza A.
- Forty-two percent of influenza A RNA in particles <4.1 um.
- Positive samples correlated well with number and location of patients with influenza.
Yang W, Elankumaran S, Marr LC. Concentrations and size distributions of airborne influenza A viruses measured indoors at a health centre, a day-care centre and on aeroplanes. J.R. Soc. Interface 2011, published online.

• Half of 16 samples positive for influenza A, 5800 – 37000 genome copies per cubic meter.
• Average of 64% of viral genome copies associated with particles smaller than 2.5 um.
• Inhalation dose over one hour estimated at 30-fold the TCID\textsubscript{50}. 

- Patients with confirmed influenza in 3 Hong Kong clinics
- Exhaled breath analyzed with optical particle counter, qPCR for influenza A and B.
- Influenza virus RNA detected in one-third of all subjects while breathing quietly.
- Subjects exhaled from 67 to 8500 particles per liter of air.
- >87% of exhaled particles were <1 micron in diameter.
• Does influenza virus remain viable on particles of aerosol dimension?
Viability of flu virus in aerosols

- Viable flu virus detectable for up to 24 hours in artificially generated aerosols. (multiple studies, 1960s and 1970s)
- Detectable and infectious to chick embryos, mice, ferrets.
- Survival of virus influenced by relative humidity.
• Have animal studies demonstrated long range transmission?
Animal Studies

- Transmission between guinea pigs in separate cages separated by 90 cm. (Lowen et al 2006).
- Probable aerosol transmission between ferrets. (Andrews and Glover, 1941)
- Transmissions between source and exposed animals when separated by 2.5-meter-long S-shaped and U-shaped ducts, with airflow from source to exposed. (Andrews and Glover 1941)
- Transmissions between guinea pigs enhanced at low relative humidity (Lowen et al 2007)
- H1N1 seasonal and novel strains equally transmissible between ferrets in adjacent cages. (Munster et al 2009).
• Have human experimental studies suggested transmission by the aerosol route?
Human Experimental Studies

- Influenza in 17-19% of human subjects exposed to aerosolized virus by facemask. (Smorodintseff et al 1937, Alford et al 1966).
- Particle size distribution of artificial aerosols differs from naturally produced aerosols.
- Intranasally infected college students had less severe disease than college students who acquired influenza naturally. (Little et al 1979).
• Do studies of personal protective equipment suggest aerosol range transmission?
Studies of Masks and Respirators

- Randomized trial, ’08 – ’09 flu season: 225 nurses used surgical masks, 221 fit tested N95 respirators.
- Infection with influenza virus in 50 nurses assigned to surgical masks (23.6%), in 48 assigned to N95S (22.9%)
- Similar vaccination rates (30%), similar spouse/roommate/child exposures.
- Audits showed good compliance with assigned protection.
- 9 nurses in surgical mask group vs. 2 in N95 group met criteria for IILI.
- 65-70% of nurses remained asymptomatic despite positive serology.
- Loeb M, Dafoe N, Mahony J, et al. Surgical mask vs N95 respirator for preventing influenza among health care workers: a randomized trial. JAMA. Published online Oct 1, 2009

- Assigned to face mask use, face masks with hand hygiene, or control for 6 weeks.
- Significant reductions in ILI during weeks 4-6 in the mask and hand hygiene group (35-51%)
- No significant reduction for cumulative ILI over entire period.

- Radiolabeled aerosol, generating and receiving heads 3 feet apart.
- 1% reached receiving head with no masking.
- Masking of generating head resulted in sWPF of 172 to 317. No difference between N95 and surgical mask.
- Masking of receiving head did not significantly reduce exposure.
- Masking had no effect in absence of environmental air flow.
Public Health Guidance


- Russi M, Buchta W, Swift M, Budnick L, Hodgson M, Berube D, Kelafant G. ACOEM Guidance for Occupational Health Services in Medical Centers JOEM 2009; 51(11) 1e.

- May 13, 2009, Centers for Disease Control and Prevention (CDC) issued Interim Guidance for Infection Control for Care of Patients with Confirmed or Suspected Novel Influenza A (H1N1) Virus in Healthcare Setting.

- Justification for heightened level of protection.
Public Health Response

- Many state health departments departed from CDC guidance spring, 2009.
- HICPAC endorsed return to droplet precautions for standard patient care, airborne precautions for aerosol-generating procedures, July 23, 2009.
  - *Updated Isolation Precaution Recommendations for Care of Patients with Confirmed or Suspected Novel Influenza A (H1N1) Virus in Healthcare Settings. Recommendations of the HICPAC Influenza A (H1N1) Virus Infection Control Working Group.*
- President’s Council of Advisors on Science and Technology released report August 7, 2009.
  - Consult with relevant professional societies and health care organizations to ensure that guidance for protection of health care workers from the effects of 2009-H1N1 is supported by the evidence, feasible to implement, and is harmonized among multiple sources. Relevant societies include the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and, where recommendations concern children, the American Academy of Pediatrics (AAP).
- SHEA, IDSA, APIC issue position statement endorsing droplet precautions.
- CDC and OSHA commission IOM to examine issue and develop recommendation without regard to finances or implementation barriers.
- IOM issues statement September 3, 2009, endorsing use of N95 respirators for healthcare workers caring for patients with 2009 H1N1 influenza.
- Updated CDC guidance issued October 14, 2009.
- 2010 CDC guidance endorses droplet precautions, N95 respirators for aerosol-generating procedures.
State of California OSHA Airborne-Transmissible Disease Standard.

• Issued 2009.
• As of September, 2010, PAPR required for high risk procedures with airborne transmissible agents.
  – Intubation
  – Bronchoscopy
  – Aerosolized delivery of medication
  – Pulmonary function testing
• Concerns regarding lack of adaptability.
What next?

• H5N1
• H7N9
• MERS
• Ebola
Ebola in Africa

[Map showing Ebola outbreaks in Africa]

<table>
<thead>
<tr>
<th>Species</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaire-ebolavirus</td>
<td>1-10</td>
</tr>
<tr>
<td>Sudan-ebolavirus</td>
<td>11-100</td>
</tr>
<tr>
<td>Taï-forest-ebolavirus</td>
<td>101-415</td>
</tr>
<tr>
<td>Bundibugyo-ebolavirus</td>
<td></td>
</tr>
</tbody>
</table>

[Legend for map markers]

[Scale bar for miles]

[Map of Africa highlighting areas with Ebola outbreaks]
Case Counts (November 14)

- Guinea: 1878 cases. 1142 deaths
- Liberia: 6822 cases. 2836 deaths
- Sierra Leone: 5368 cases. 1169 deaths
- Mali: 4 cases. 4 deaths
- Senegal: 1 case. 0 deaths
- Nigeria: 20 cases. 8 deaths
- Spain 1 case. 0 deaths
- United States: 4 cases. 1 death
Transmission of Ebola

- More than 20 African outbreaks suggest direct contact required.
- Dowell study of family members.
- Bausch study of surface contamination.
- Roels study of unidentified source contacts.
- Role of short-range aerosols
  - Reston virus outbreak – Jaax
  - Transmissions in animal labs – Jaax et al
  - Experimental aerosols – Johnson et al
Hazmat Suits
Isolation Suite
Personal Protective Equipment
Conclusions

• Opportunistic airborne transmission occurs under some conditions with a variety of agents.

• The Precautionary Principle dictates the initial imposition of enhanced levels of protection when virulence and transmission characteristics of a novel agent are incompletely understood. This takes on heightened priority when populations are unprotected by vaccine and when potential for mortality is high.

• Influenza virus is contained in particles of aerosol dimension, animals can be infected by such aerosols, transmissions over longer ranges have been documented in animals and may be possible in humans.

• Both short- and longer-range transmissions may occur primarily via droplet nuclei (aerosols).

• Implications for EVD.

• Need for further research.
To fear the worst oft cures the worse.
-Shakespeare
Thank you.