An Update on Influenza Research at NIOSH

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Aims

Transmission of influenza virus: focus on aerosol transmission
How to protect healthcare workers exposed to influenza virus

Airborne Influenza Virus in Healthcare Facilities

Goal: Determine amount and size of airborne particles containing influenza A virus (qPCR only)

Ruby Hospital Emergency Dept

(4 days of 2008 flu season; 3-5 flu patients/day)

- 74 stationary samplers (2 waiting rooms, 2 exam rooms, reception area, triage room) + 7 personal samplers

Results:

- Virus detected in all but exam rooms (~15 virus/L room air)
- 46% virus (>4 µm), 49% virus (1-4 µm), 4% virus (<1 µm)
- Virus detected in 3 personal samplers

Blachere et al. Clin Inf Dis 2009

WVU Urgent Care Clinic

(11 days of 2009 flu season; 1-4 flu patients/day)

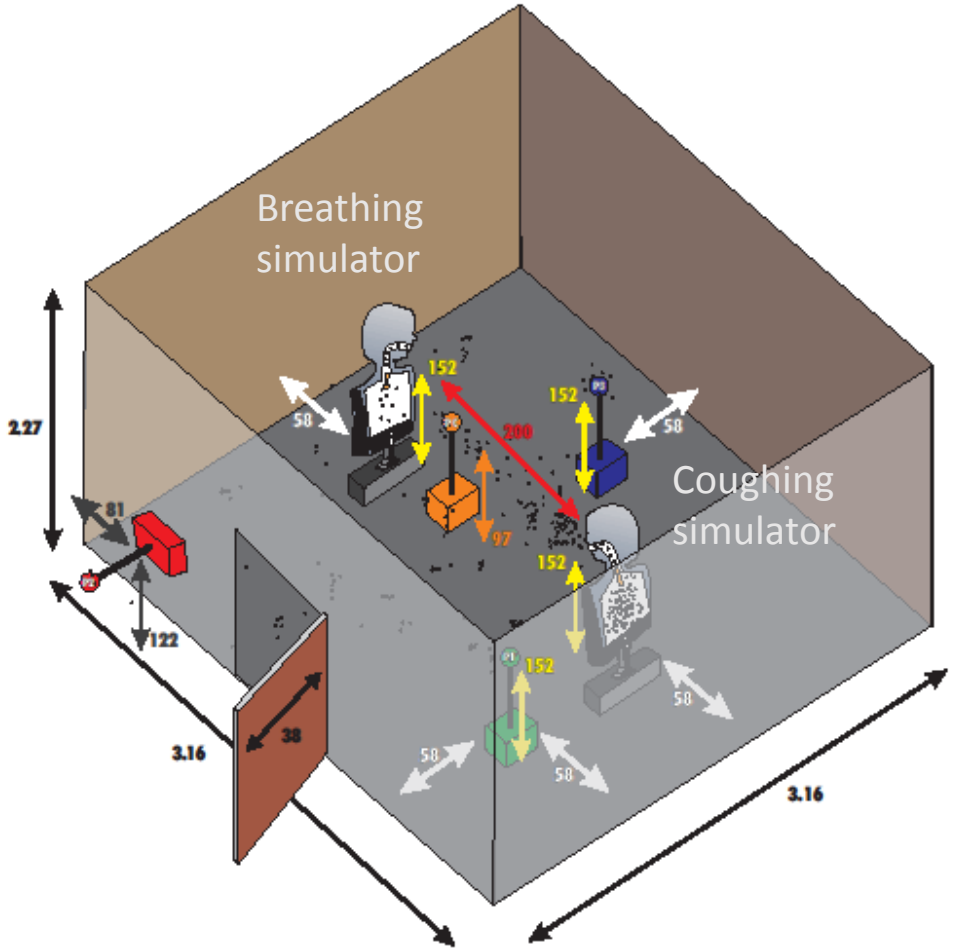
- 264 stationary samplers (1 waiting room, 6 exam rooms, 2 procedure rooms) + 21 personal samplers

Results:

- Virus detected in all rooms, highest in exam rooms)
- 46% virus (>4 µm), 42% virus (1-4 µm), 11% virus (<1 µm)
- Virus detected in 4 personal samplers

Lindsley et al. Clin Inf Dis 2010

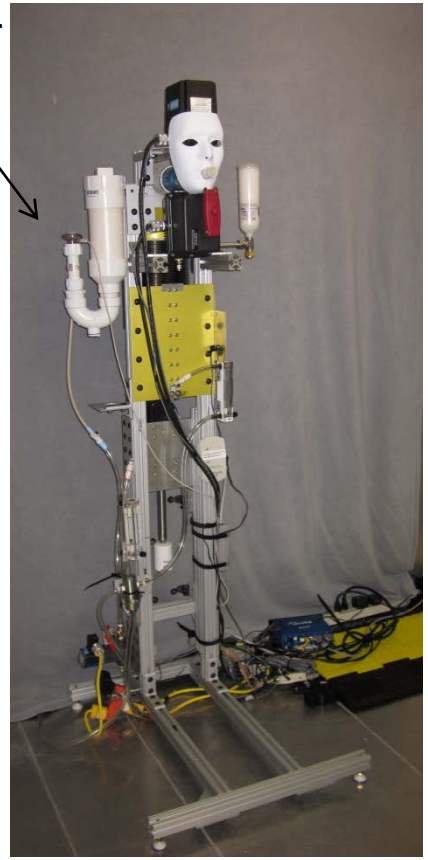
3D View of the Simulated Examination Room

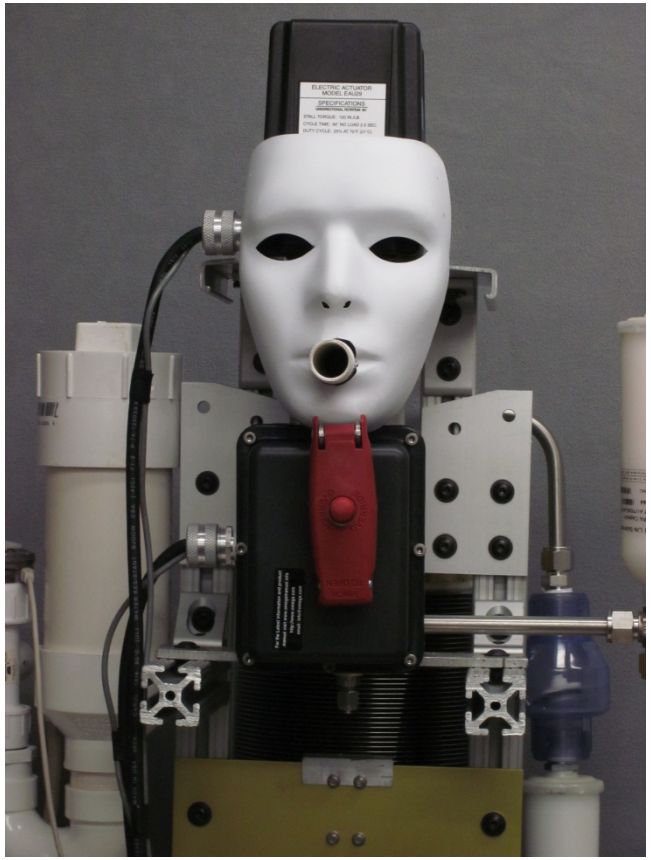


NIOSH samplers collect air from the mouth and at various positions (P1,P2,P3) within the room. Particle counter (orange sketch). Dimensions in meters (outside) or centimeters (inside)

“Homer”
Cough Aerosol Simulator

nebulizer



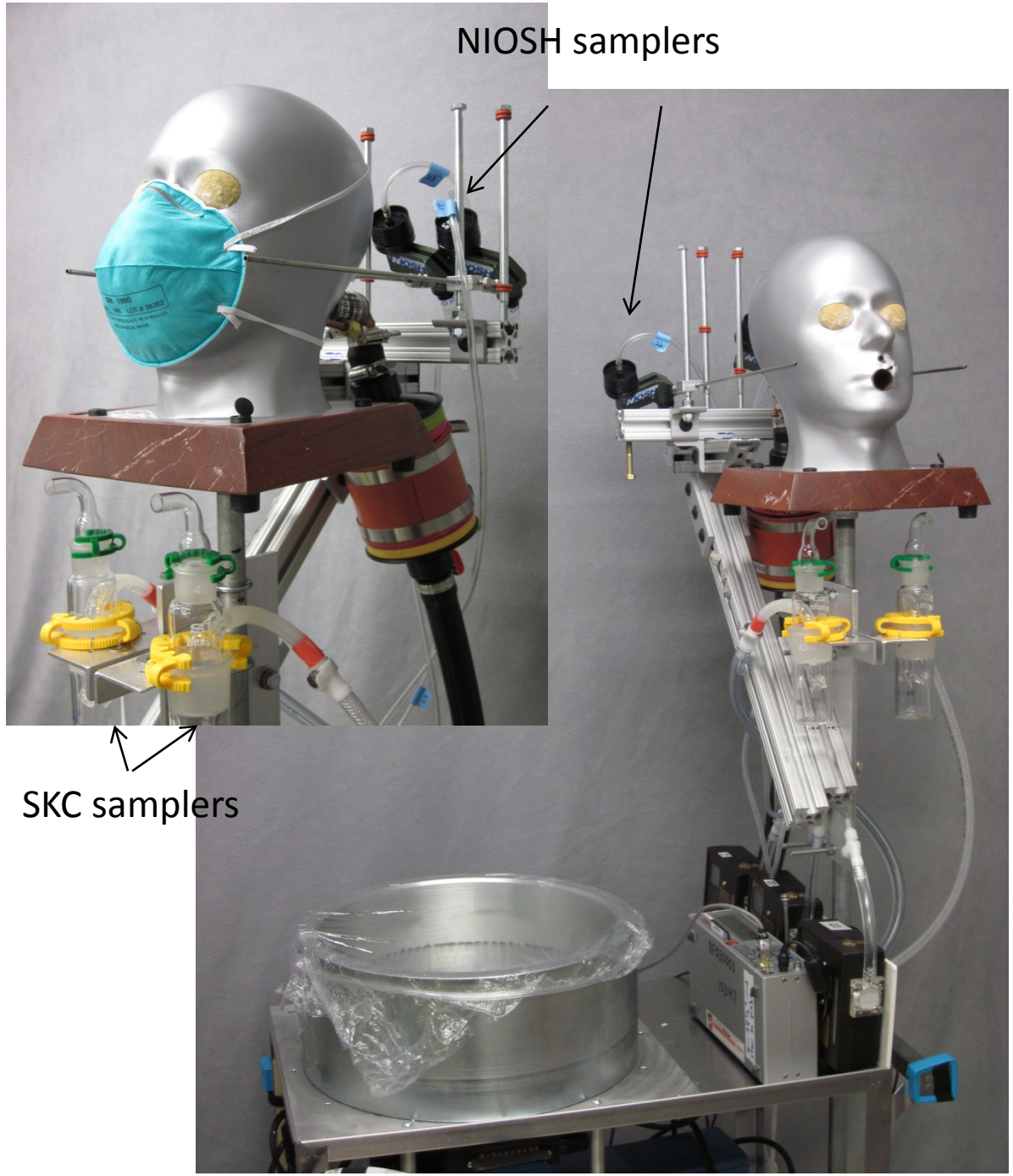


Mixing chamber

Lindsley et al. Aerosol Sci Technol 2013

“Marge” Breathing simulator

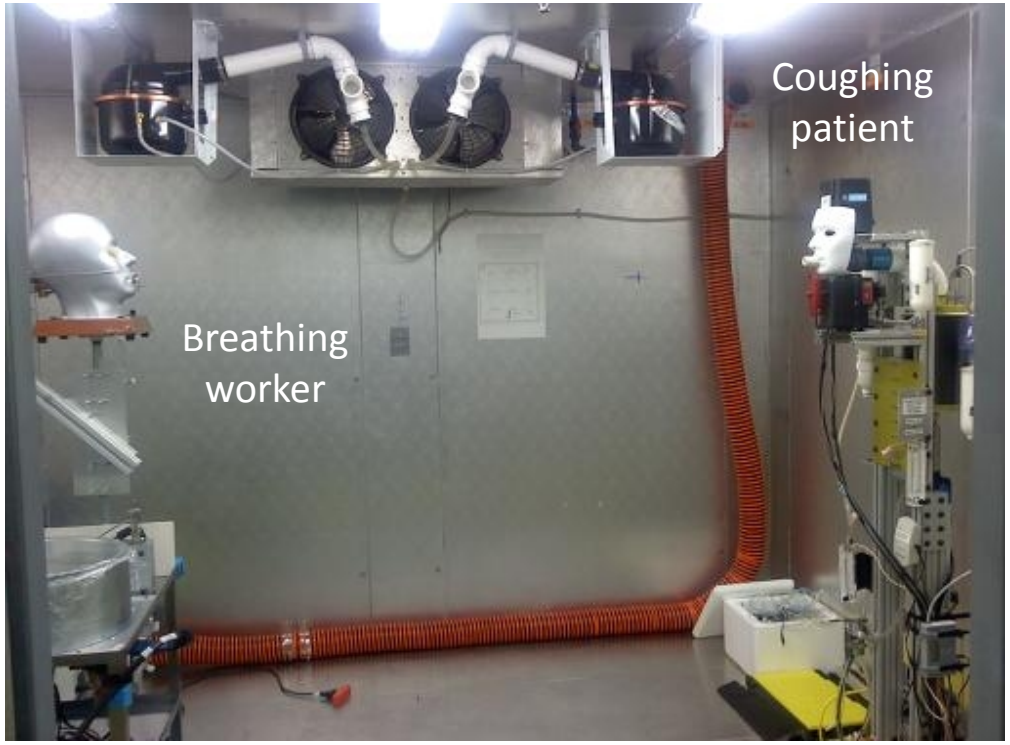
NIOSH samplers

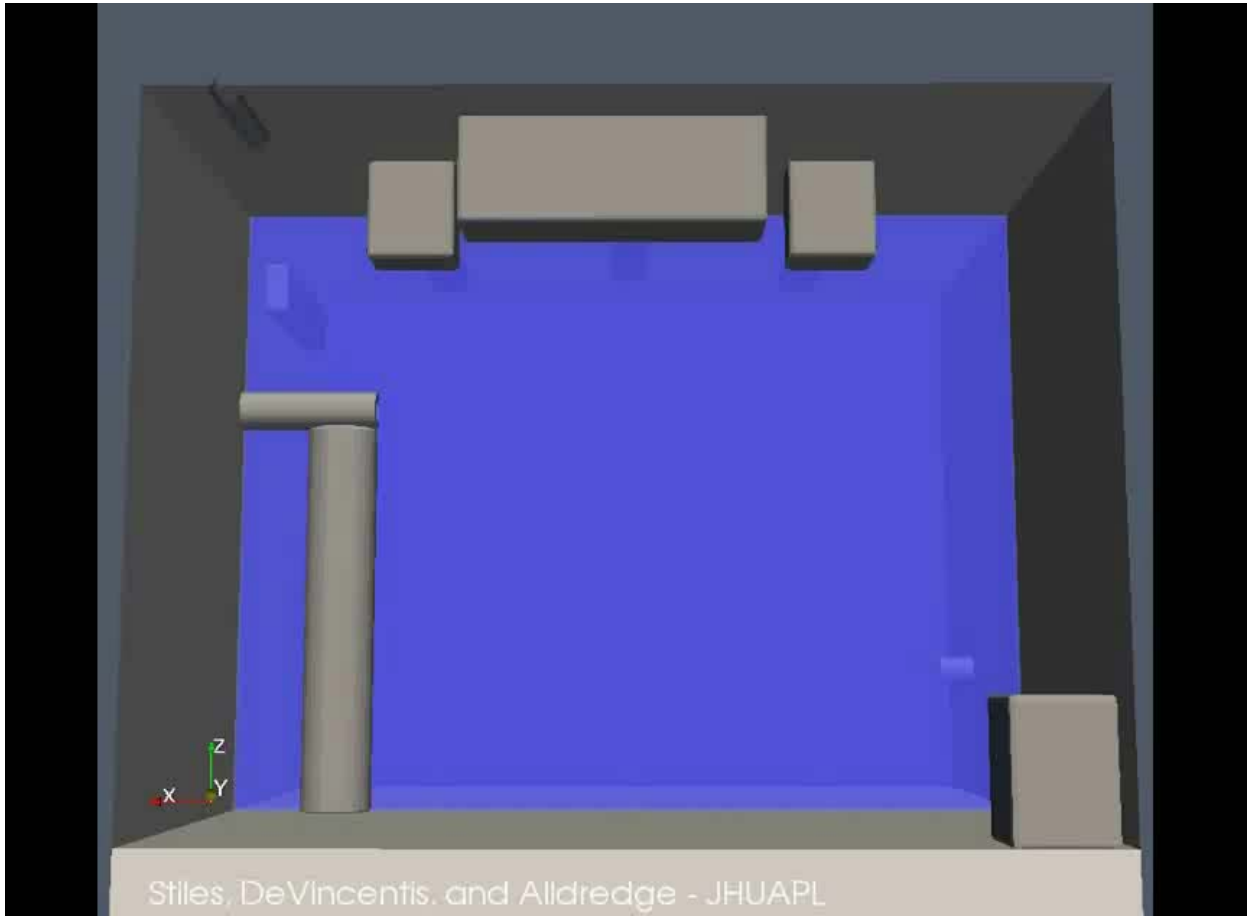


SKC samplers

Particle counters

Simulated Particle Flow of a Cough Aerosol



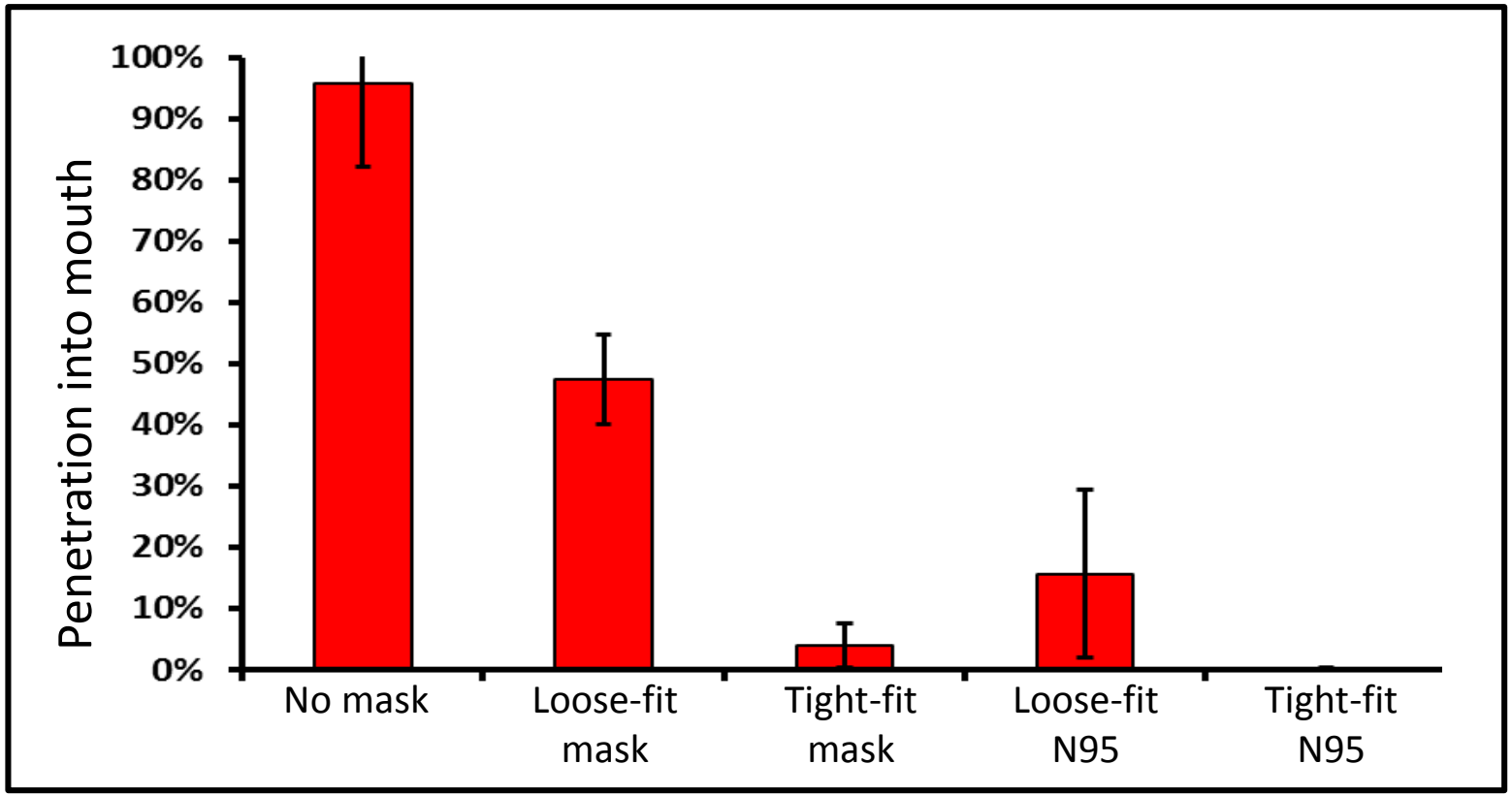


- Coughed KCl particles impact directly on breather
- Within minutes aerosols spread throughout room
- N95 blocks >99% KCl aerosol particles; mask blocks 86%
- Coughed live influenza virus and detected in all 3 fractions of the NIOSH sampler
- Infectivity detected up to 5 h after coughing but drops over time

Courtesy of Johns Hopkins University Applied Physics Laboratory

Lindsley et al. J Occup Environ Hyg 2012
Noti et al. Clin Inf Dis 2012

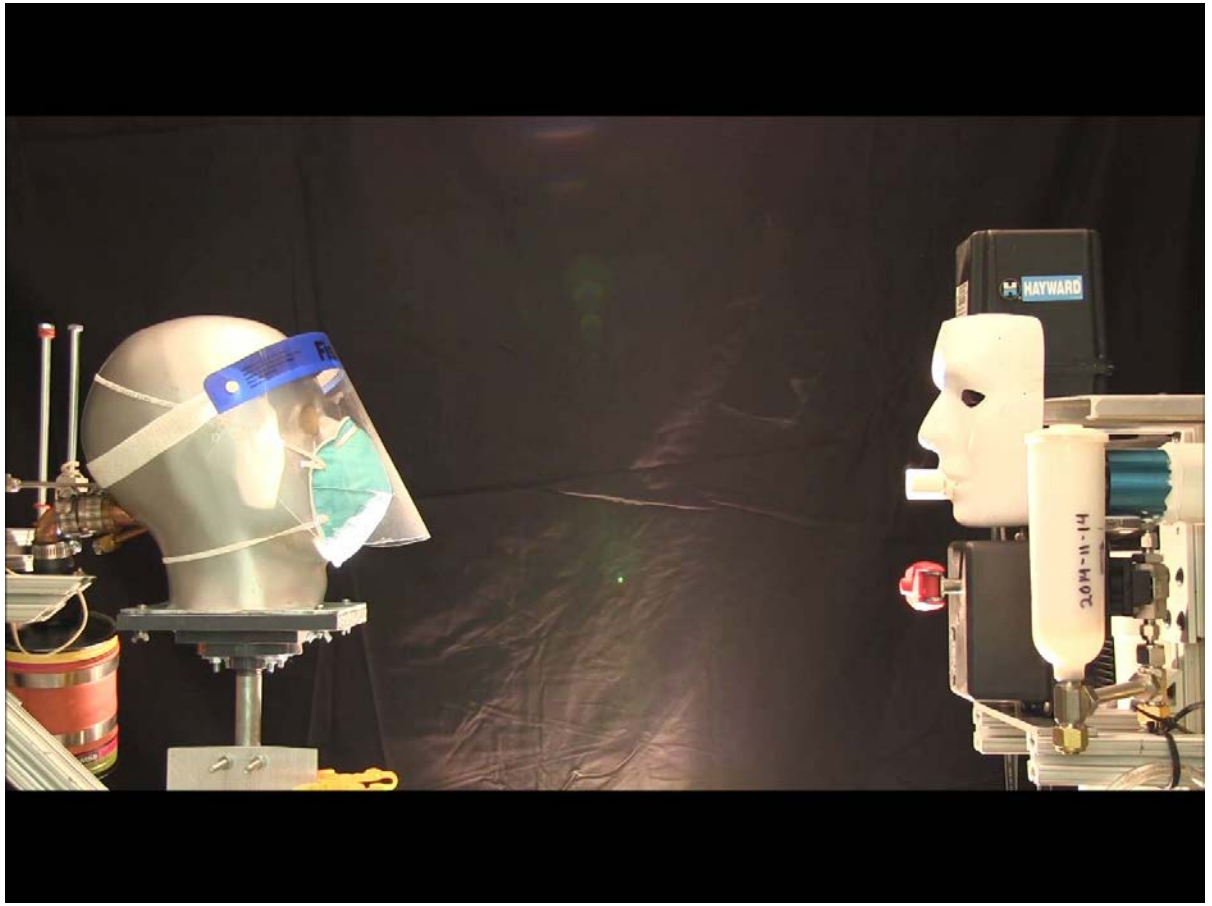
Effectiveness of Respirators and Masks: Preventing Inhalation of Infectious Airborne Influenza Virus



- Infectious virus was coughed into simulated exam room.
- Loose-fit mask (as normally worn by workers) blocks about 50% .
- Loose-fit N95 (poorly fitted) blocks about 80%.
- Tight-fit N95 (properly fitted) blocks >99% of infectious influenza virus.
- Note: Tight-fit mask blocks about 95%, potential for new product-"BREATHE"

Noti et al. Clin Inf Dis 2012

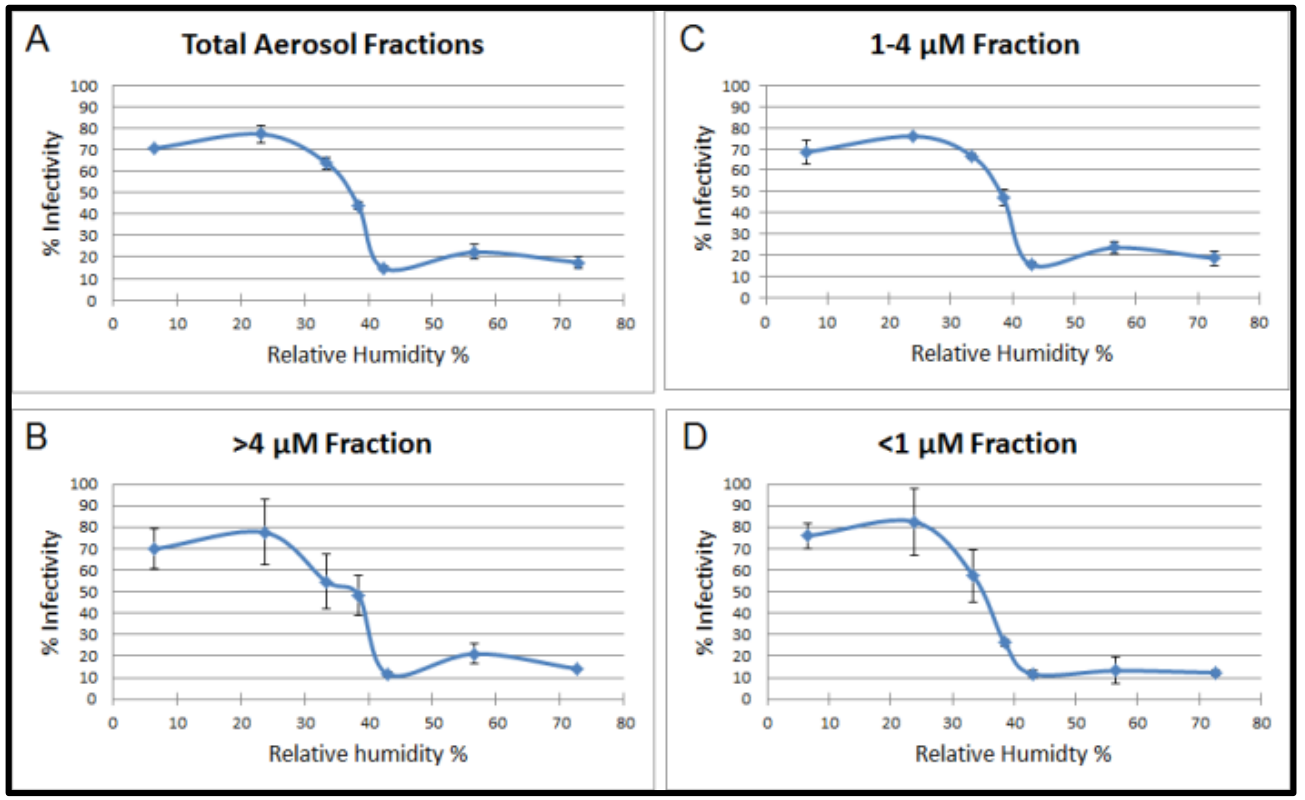
Face Shield Reduces Exposure to Infectious Influenza Virus



- Face shield blocked 95% of the infectious virus from reaching the mouth
- Some smaller viral particles can circumvent the face shield
- Significantly more smaller particles reach the mouth as distance between cougher and breather gets larger

Lindsley et al. J Occup Environ Hyg 2014

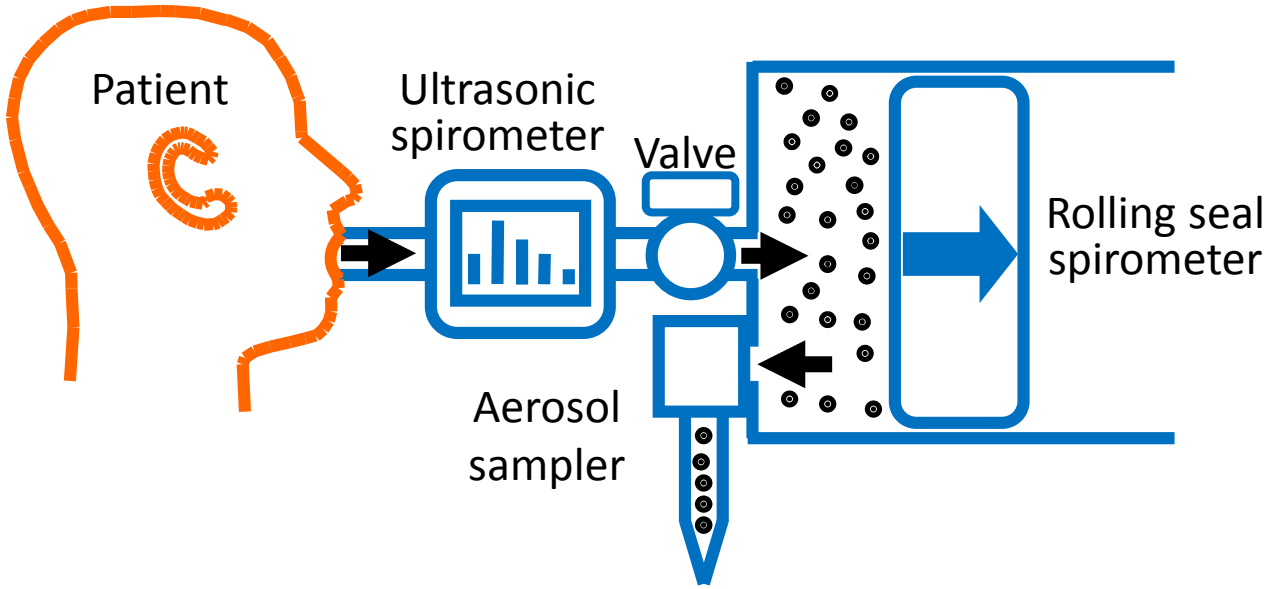
Effect of Humidity on Virus Infectivity



- Infectious virus was coughed into the simulated exam room.
- The relative humidity in the simulated exam room was varied over 7-73% at 20^{O}C.
- Similar losses of infectivity with increasing humidity regardless of aerosol fraction size.
- Significant loss of infectivity occurs within 0-15 min after coughing.

Noti et al. PLOS ONE 2013

Infectious Influenza Virus Emitted in Coughs



- Patients cough out larger aerosol volumes when infected with influenza virus
- 65% of the virus detected by PCR was in the respirable (≤4 µm) size fraction
- Infectious virus was cultured from the coughs and exhaled breath

Lindsley et al. PLOS ONE 2010
Lindsley et al. J Occup Environ Hyg 2012
Lindsley et al. J Occup Environ Hyg 2015
Lindsley et al. Influenza Other Resp Viruses 2016

Why Hospital Staff Catch the Flu (WHSCF) Study

- Ron Shaffer (PI) NIOSH NPPTL
- Project involves NIOSH (NPPTL, HELD, DSHEFS) and Johns Hopkins
- Goals to (1) measure influenza levels on healthcare workers PPE (gloves, masks, N95s) and in air and surface samples to gauge actual worker exposure; (2) determine the potential for direct-contact transmission from doffing of contaminated PPE

Lab Study

- Use the simulated exam room to cough low levels of virus and refine protocols to detect the virus on PPE
- Contaminate PPE with MS2 (surrogate for influenza) and determine how much virus is transferred to a volunteer's hand when doffing the contaminated PPE

Clinical Study

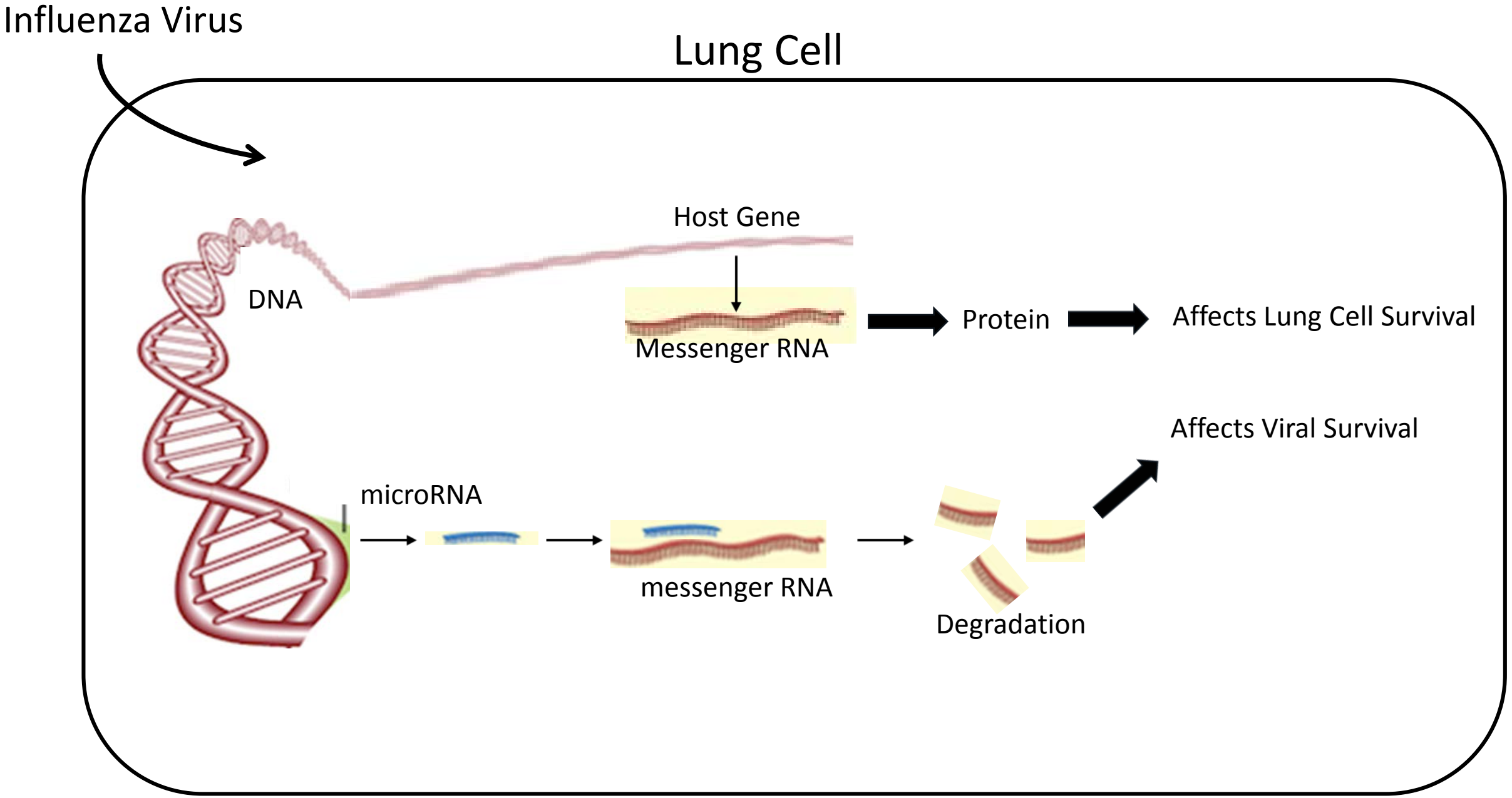
- Two week pilot study to assess the feasibility of the study
- Eight week study to assess virus in aerosol samples and in personal aerosol samplers worn by the healthcare workers, and on masks/N95s
- Assay for a panel of 17 other respiratory viruses

Fisher et al. Risk Anal 2014
Blachere et. In preparation
Ahrenholtz et al. In preparation
Rule et al. In preparation

Evaluating Modes of Influenza Transmission using a Human Challenge Model (EMIT)

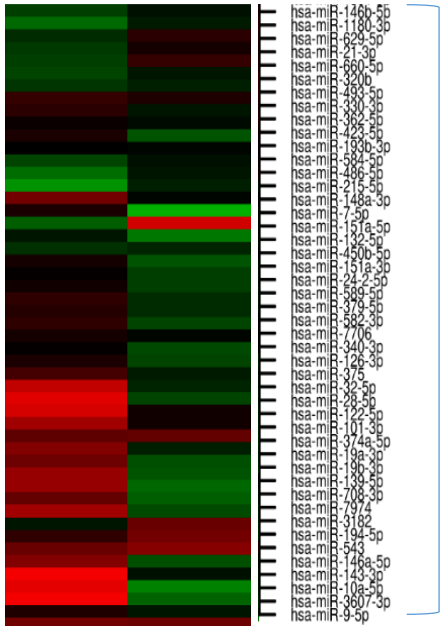
- Funded by CDC
  - Principle investigator: Jonathan Nguyen-Van-Tam, University of Nottingham
- Goal: To assess the relative contribution of influenza transmission by droplet spray, contact, and aerosol
- Recipients were exposed to donor volunteers experimentally infected with H3N2
- Recipients randomized to either a control arm (no intervention- allowing all modes of transmission) or an intervention arm (face shield and hand hygiene – allowing only transmission by aerosol)
- Air samples were collected with NIOSH samplers and processed for influenza (qPCR and VPA) by HELD
- Conclusion: no virus detected in aerosol samplers and no transfer of virus to study recipients

MicroRNAs Regulate Host Gene Expression



Expression of Lung Cell Non-Structural-1 Binding Protein is Modulated by microRNA-548

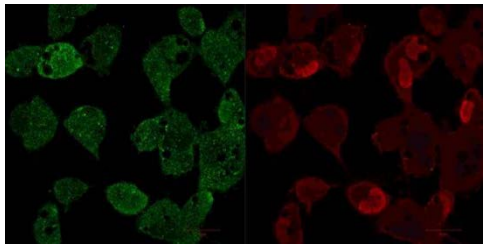
Influenza infection alters microRNA expression patterns in lung cells



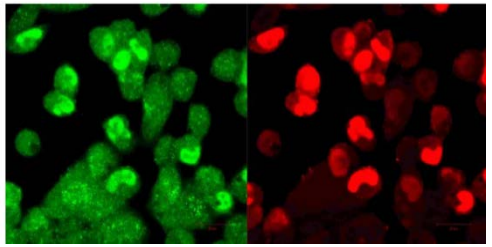
microRNA-548 is **lowered** after infection

Lung Cell NS1ABP | Viral Nucleoprotein

High microRNA-548 decreases NS1ABP and limits viral survival



Low microRNA-548 increases NS1ABP and viral survival



Conclusions

- NS1ABP binds influenza NS1 protein to alter the ability of NS1 to induce apoptosis, and inhibit cytokine release, and cytoplasmic export of host messenger RNAs
- Findings suggest the development of safe and effective intervention strategies to block influenza infection through the delivery of synthetic microRNAs

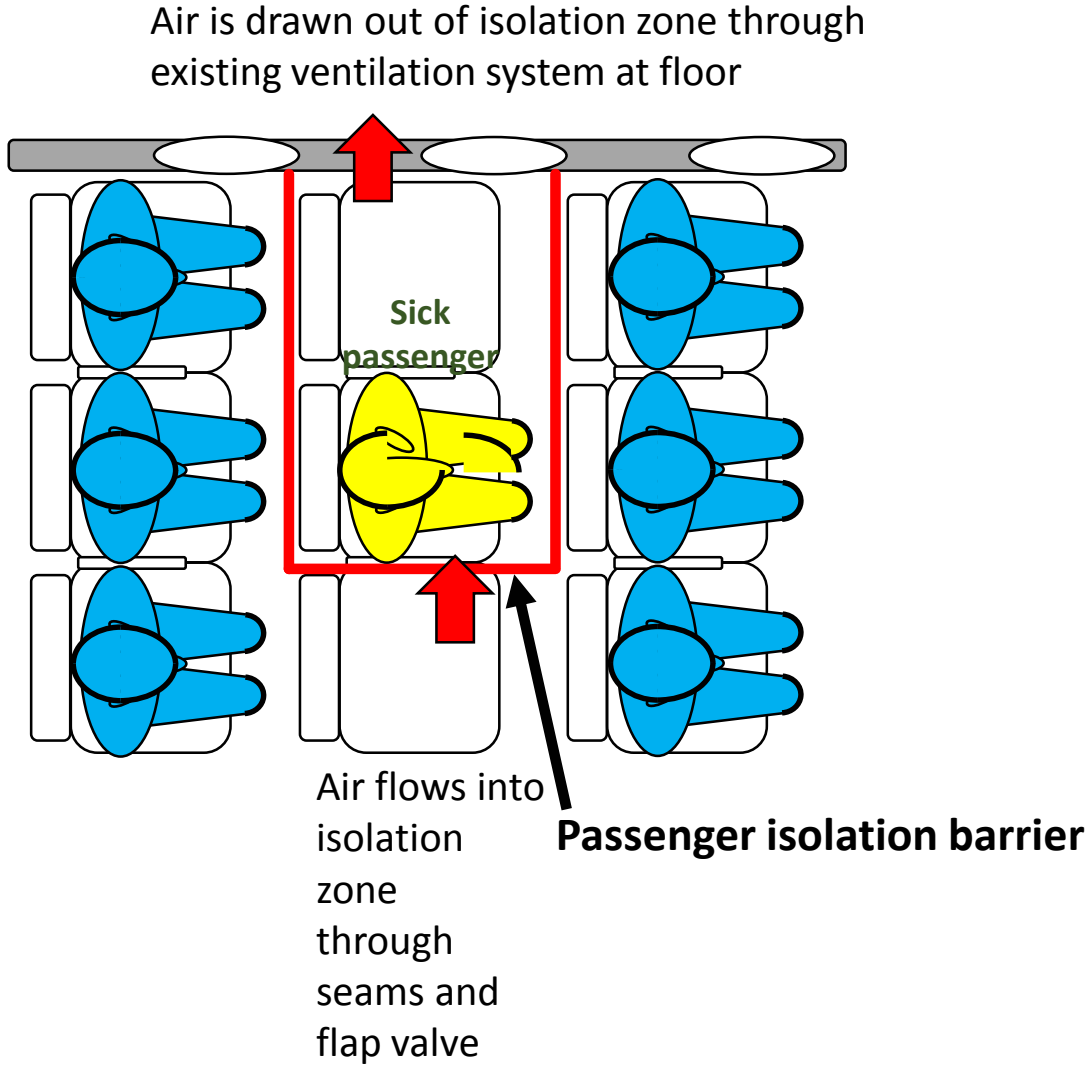
Othumpangat et al. Virology 2013
Othumpangat et al. Virology 2014
Othumpangat et al. Virology 2016

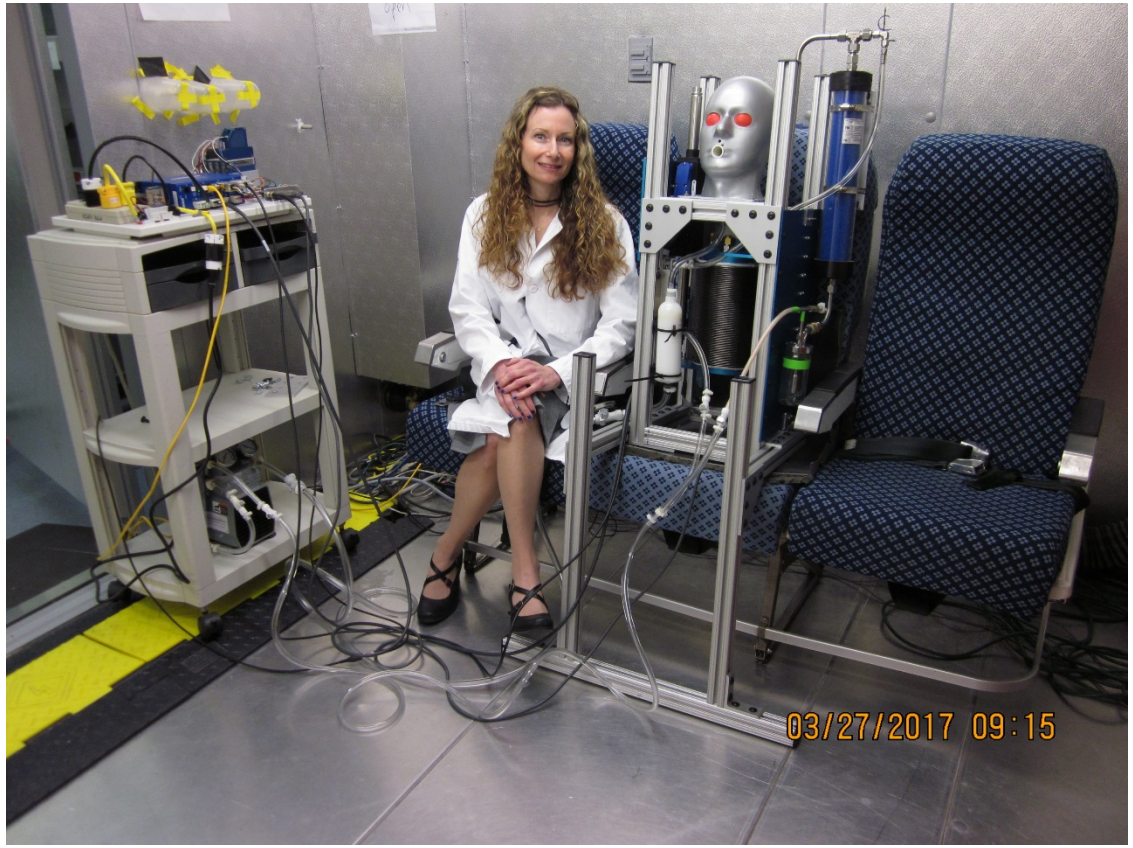
Application of In-Flight Engineering Controls to Reduce Risk of Infectious Disease Transmission on Commercial Airline Flights

- Ken Mead , DART, (PI)-funded through the OPHPR
  - HELD, RHD collaborators
- Recent years have seen an increase in the amount of air traffic, particularly international traffic
- Travel occurs in confined spaces over long periods
- Passengers and cabin-crew may potentially be exposed to infectious diseases (Ebola, flu variants) originating from other plane occupants
- Options for reducing airborne and droplet exposures are limited
- AFA recommends that airlines develop "realistic procedures and/or engineering controls for isolating symptomatic passengers if the incident aircraft is too full to permit isolating an unoccupied radius around the symptomatic individual(s) consistent with WHO and/or CDC recommendations"

The FAA's Boeing 747 test aircraft used to do a 3-D scan of the cabin and create a lab mock-up cabin

IsoPass
Airline passenger isolation system





- First generation prototype is designed to cover just 2 seats (leaving aisle seat outside the enclosure) so that someone can sit outside IsoPass and observe/assist the sick passenger

- A seated passenger manikin capable of producing a cough aerosol of tracer gas particles or surrogate microorganisms will be used to evaluate containment and removal in the IsoPass

Ambulance Disinfection using UV Germicidal Irradiation

The Problem

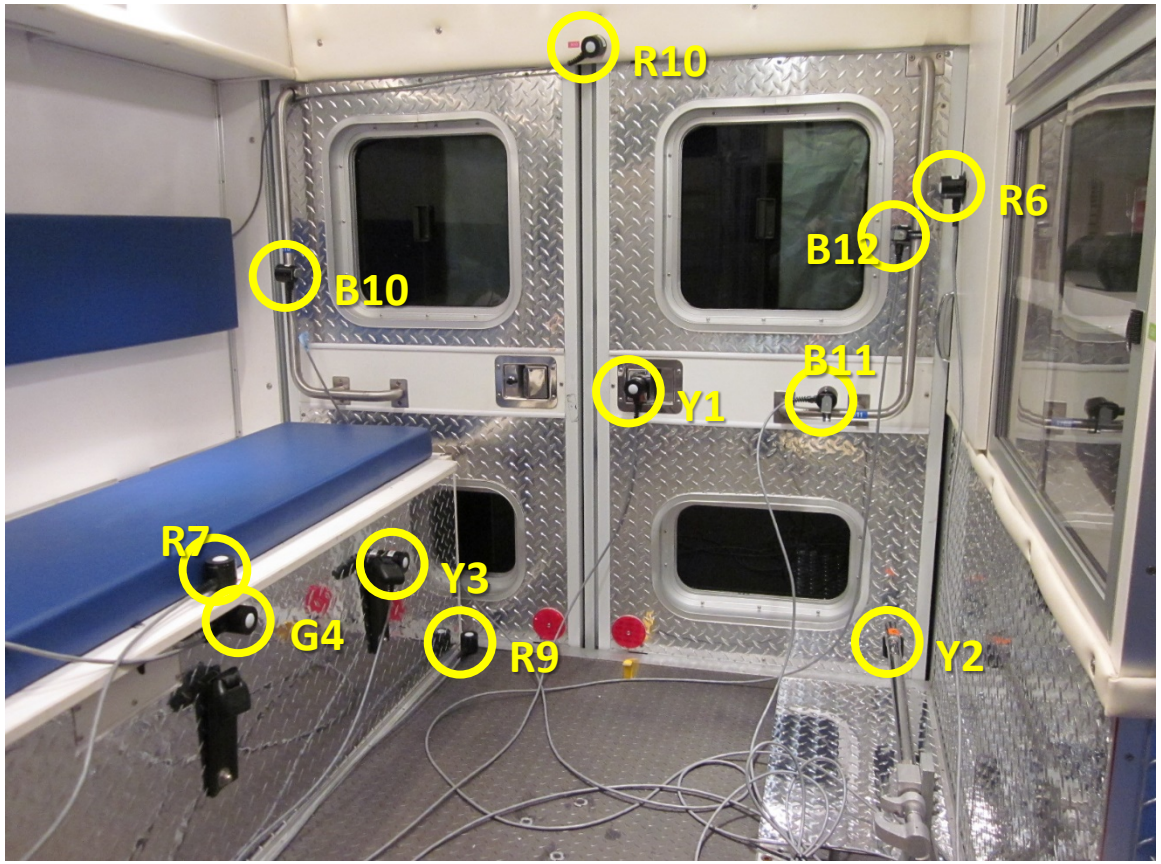
- Ambulances are frequently contaminated with pathogenic microorganisms shed by patients during transport
- These microorganisms can potentially be transferred to subsequent patients and the EMS workers
- Risk for transmission increases during a disease pandemic

The Experiment

- An ambulance was outfitted with UV sensors at 49 locations
- A UV fixture was placed in the front, middle or back of the patient compartment
- Disinfection tests were conducted using *Bacillus subtilis* spores as a surrogate for pathogens

Conclusions

- Changing the position of the UV fixture and increasing the surface reflectivity with aluminum tiles and UV-reflective paint reduced the disinfection time from 16.5 hours to 59 minutes



Lindsley et al. American Journal of Infection Control. Submitted

Other Collaborations

H7N2 outbreak in cats

- In Jan 2017, responded to an outbreak of avian H7N2 in NYC shelter cats
- Coordinated with NIOSH Disaster Science Responder Relief (DSRR), ASPCA, & NYC Health Dept to collect air/surface samples

Airborne influenza detection in live animal markets, public spaces, and healthcare facilities

- Dr. Ben Cowling at U of Hong Kong is conducting a number of studies to detect influenza with NIOSH samplers

Modeling airflow in a hospital room

- Johns Hopkins Applied Physics Lab conducting research to validate a hospital room airflow model with NIOSH cough simulator

Air sampling in China, Malaysia and Vietnam

- Duke One Health Training Program at Duke Univ using NIOSH samplers to assess transmission risk in developing countries

Mycobacterium abscessus and Influenza Air Sampling

- Kevin Fennelly, MD, at National Heart, Lung and Blood Institute at NIH to use NIOSH samplers for M. abscessus and pilot studies of influenza challenges, intervention strategies

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Questions/Future Direction

What clinical trials are still needed to assess influenza transmission?

- What human challenge trials would better assess aerosol vs contact/droplet spray transmission?
- We are a small team-can we contribute to a larger trial?

What host factors that increase/decrease risk of infection should we assess?

Is there a need to assess the risk of infection to responders to influenza outbreaks?

Can UV disinfection systems be exploited more to reduce influenza infection?

- Can UV disinfection be incorporated into HVACs, used on buses, trains, hospital rooms?
- Is a large scale study needed?
- Can adjustments like humidity and temperature control be incorporated in planning?