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Development and Application of A Markov Chain Model for Predicting Influenza Exposure in Indoor Environments

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Built Environment Research Group | http://built-envi.com

INTRODUCTION

- Exposure to airborne pathogens such as influenza remains a significant threat to public health

Li, Yiping, et al. "Role of ventilation in airborne transmission of infectious agents in the built environment–a multidisciplinary systematic review." *Indoor air* 17.1 (2007): 2-18.

Iowa State University Gym during the influenza epidemic of 1918
http://www.public.iastate.edu/~isu150/history/quick.html

- Influenza routes of transmission
  - Fomite
  - Inhalation
  - Inspiration
  - Direct spray

ASHRAE. ASHRAE Position Document on Airborne Infectious Diseases. American Society of Heating, Refrigerating and Air-Conditioning Engineers; 2009.

- Influenza A virus (IAV) exposure and transmission risk associated with each route in indoor environments is a function of many variables

BACKGROUND and MOTIVATIONS

- Azimi & Stephens (2013) used a modified version of the Wells-Riley model to predict transmission risk of infectious disease in 4 climate conditions, and investigate the effect of building characteristics on probability of infection

Azimi, P., Stephens B. "HVAC filtration for controlling infectious airborne disease transmission in indoor environments: Predicting risk reductions and operational costs." *Building and Environment* 70 (2013): 150-160.

- Wells-Riley is a simple model to use but it cannot consider parameters such as:
  - Different routes of infection transmission
  - Human activity
  - Some building characteristics
  - Not well-mixed conditions

- Markov chain method is a powerful mathematical system that undergoes transitions from one state to another
  - More parameters can be considered in this method
  - It has been successfully used in influenza transmission studies

Nicas, Mark, and Gang Sun. "An Integrated Model of Infection Risk in a Health-Care Environment." Risk Analysis 26.4 (2006): 1085-1096.
Chen, Chun, et al. "Predicting transient particle transport in enclosed environments with the combined computational fluid dynamics and Markov chain method." Indoor air 24.1 (2014): 81-92.

BACKGROUND and MOTIVATIONS

- Markov chain methods can estimate the exposure to and intake dose of IAV

- A dose-response model can then be used to calculate the IAV probability of infection corresponding to the intake dose

Sze To, G. N., et al. "A methodology for estimating airborne virus exposures in indoor environments using the spatial distribution of expiratory aerosols and virus viability characteristics." *Indoor air* 18.5 (2008): 425-438.

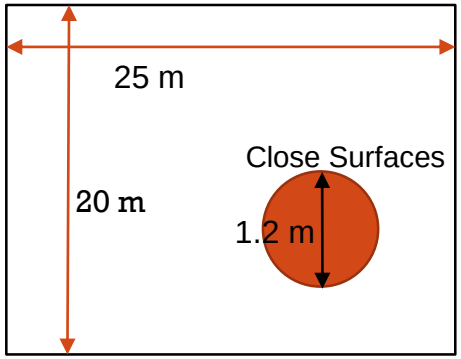
- Monte Carlo simulation can provide a statistical distribution for probability of infection

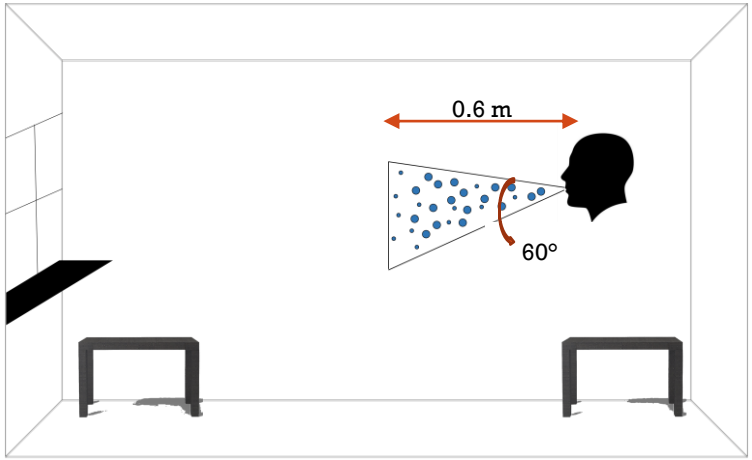
- The combination of Markov chain method and dose-response model with Monte Carlo simulation has been used recently to predict probability of infection in complex conditions

Jones, R. M., Adida E. "Influenza infection risk and predominate exposure route: uncertainty analysis." Risk Analysis 31.10 (2011): 1622-1631.
Jones, Rachael M., et al. "Characterizing the risk of infection from Mycobacterium tuberculosis in commercial passenger aircraft using quantitative microbial risk assessment." Risk Analysis 29.3 (2009): 355-365

- In the existing Markov chain models some parameters have not been considered yet
  - Deposition rate of particles
  - Effects of building ventilation system characteristics such as outdoor air (OA) ratio and HVAC filters removal efficiency (RE)
  - Human activity

METHODS (Defining The Case Study)





A 500 m^2 hypothetical office environment
3 meter ceiling height
25 occupancies
1 infector
1 susceptible individual
8 hours exposure time

Azimi, P.,Stephens B. "HVAC filtration for controlling infectious airborne disease transmission in indoor environments: Predicting risk reductions and operational costs." *Building and Environment* 70 (2013): 150-160.

- Per ASHRAE Standard 62.1, the minimum outdoor air ventilation rate is 0.5 per hour

ASHRAE. Standard 62.1: Ventilation for acceptable indoor air quality. American Society of Heating, Refrigerating and Air-Conditioning Engineers; 2010.

- We assumed that emitted particles with d_a >10 μm travel 0.6 m

Nicas M, Sun G. An integrated model of infection risk in a health care environment. Risk Analysis, 2006; 26:1097–1108.

- Therefore, a circle with radius of 0.6 m around the infector considered as close surfaces

METHODS (Infectious Particle Transmission Parameters)

- **We assumed**
- Surface area of each finger strip is 2 cm^2
- Surface area of mucous membranes (i.e. eyes, noise, lips) is 15 cm^2
- Just one finger touches the mucous membranes in each touch

Nicas, M., Jones. R. M. "Relative contributions of four exposure pathways to influenza infection risk." *Risk Analysis* 29.9 (2009): 1292-1303.

- Contact rates of hand to surfaces and face are 1.5 per minute
- Average number of coughs in influenza infected individuals is 38 per hour

Jones, R. M., Adida E. "Influenza infection risk and predominate exposure route: uncertainty analysis." Risk Analysis 31.10 (2011): 1622-1631.

- Pulmonary ventilation of an adult is 0.67 (m^3/hr)
- Average breathing rate for adults is 17 per minute
- 99% of infectious particles injected to the office environment are settle down very fast on close surfaces

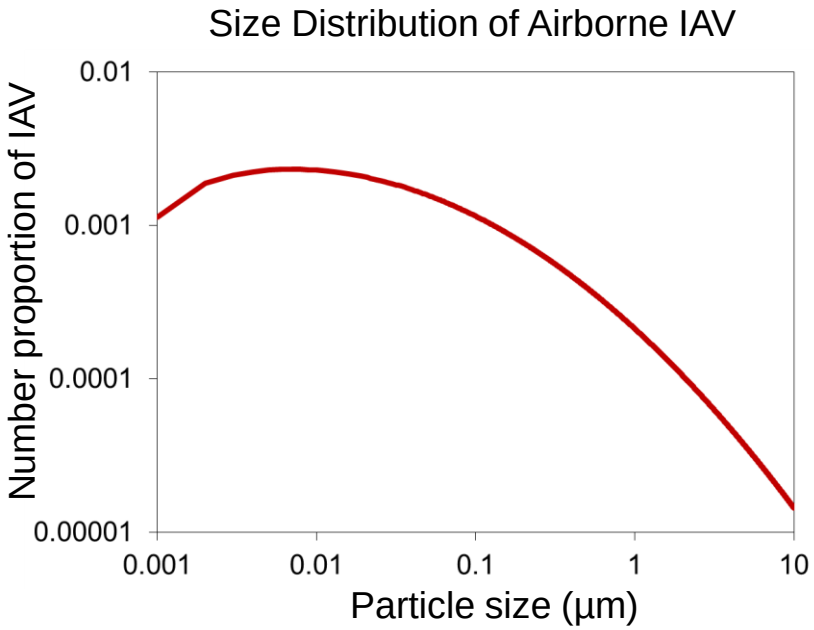
Chao, C. Y. H., et al. "Characterization of expiration air jets and droplet size distributions immediately at the mouth opening." *Journal of Aerosol Science*40.2 (2009): 122-133.
Lidwell OM. The microbiology of air. Topley and Wilson's Principles of Bacteriology, Virology and Immunity, 8th ed. London: Hodder Arnold; 1990. p. 226-40.

METHODS (Size Distribution of IAV In The Air)

- Reported infectious particle size distribution is varied in different studies

Cumulative percentage of IAV in each particle size bin

Ref.	< 0.25 μm	<0.5 μm	< 1 μm	< 2.5 μm	< 4 μm	< 5 μm	< 10 μm	Total
[1]			4%		53%			100%
[2]			20%		95%			100%
[3]			11%		43%			100%
[4]			32%			48%		100%
[5]			42%		65%			100%
[6]		70%	87%			100%		100%
[7]	19%	82%	97%	97%			100%	100%
[8]	18%	31%	41%	68%				100%



[1] Blachere F.M. et al., “Measurement of airborne influenza virus in a hospital emergency department,” Clinical Infectious Diseases, vol. 48, no. 4, pp. 438–440.

[2] Noti, J. D. et al., “Detection of infectious influenza virus in cough aerosols generated in a simulated patient examination room,” Clinical Infectious Diseases, vol. 54, no. 11, pp. 1569–1577, 2012.

[3] Lindsley WG,et al. Distribution of Airborne Influenza Virus and Respiratory Syncytial Virus in an Urgent Care Medical Clinic. Clinical Infectious Diseases 2010a.

[5] Lindsley WG, et al. Measurements of Airborne Influenza Virus in Aerosol Particles from Human Coughs. PLoS ONE 5(11) 2010b.

[6] Fabian, et.al. "Influenza virus in human exhaled breath: an observational study." PloS one 3, no. 7 (2008).

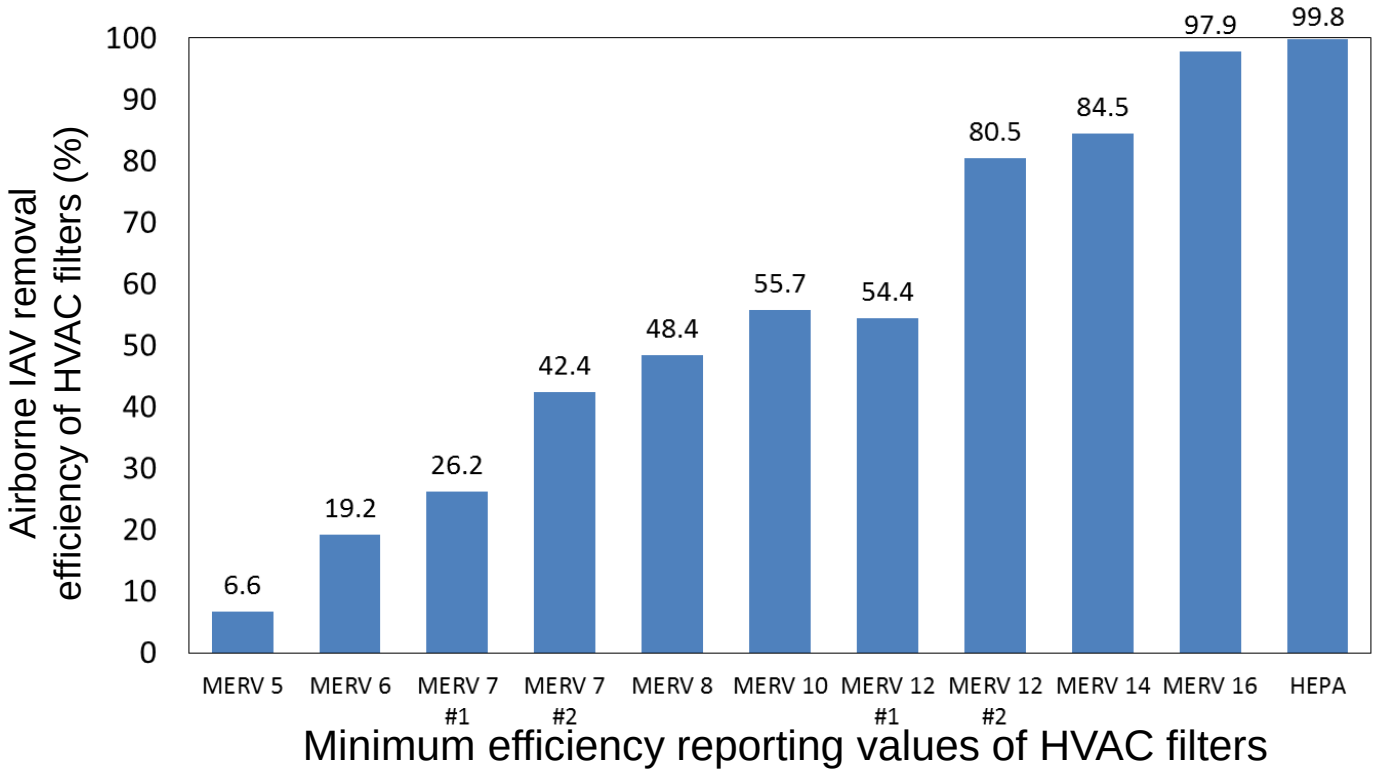
[7] Lednicky, et.al.. "Detection and Isolation of Airborne Influenza A H3N2 Virus Using a Sioutas Personal Cascade Impactor Sampler."Influenza research and treatment 2013.

[8] Yang W,et.al 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 ;8(61):1176–84, 2011.

METHODS
(HVAC Filters RE and Deposition of Infectious Particles)

- We mapped the CDF of IAV in the air to the existing size-resolve removal efficiency of HVAC filters (Azimi et.al. 2014) and size-resolve deposition loss rate coefficient (Riley et.al. 2002)

Riley, W. J., et al. "Indoor particulate matter of outdoor origin: importance of size-dependent removal mechanisms." Environmental science & technology 36.2 (2002): 200-207.



- The average deposition rate of IAV particles was calculated 0.9 per hour

METHODS (Monte Carlo Simulation)

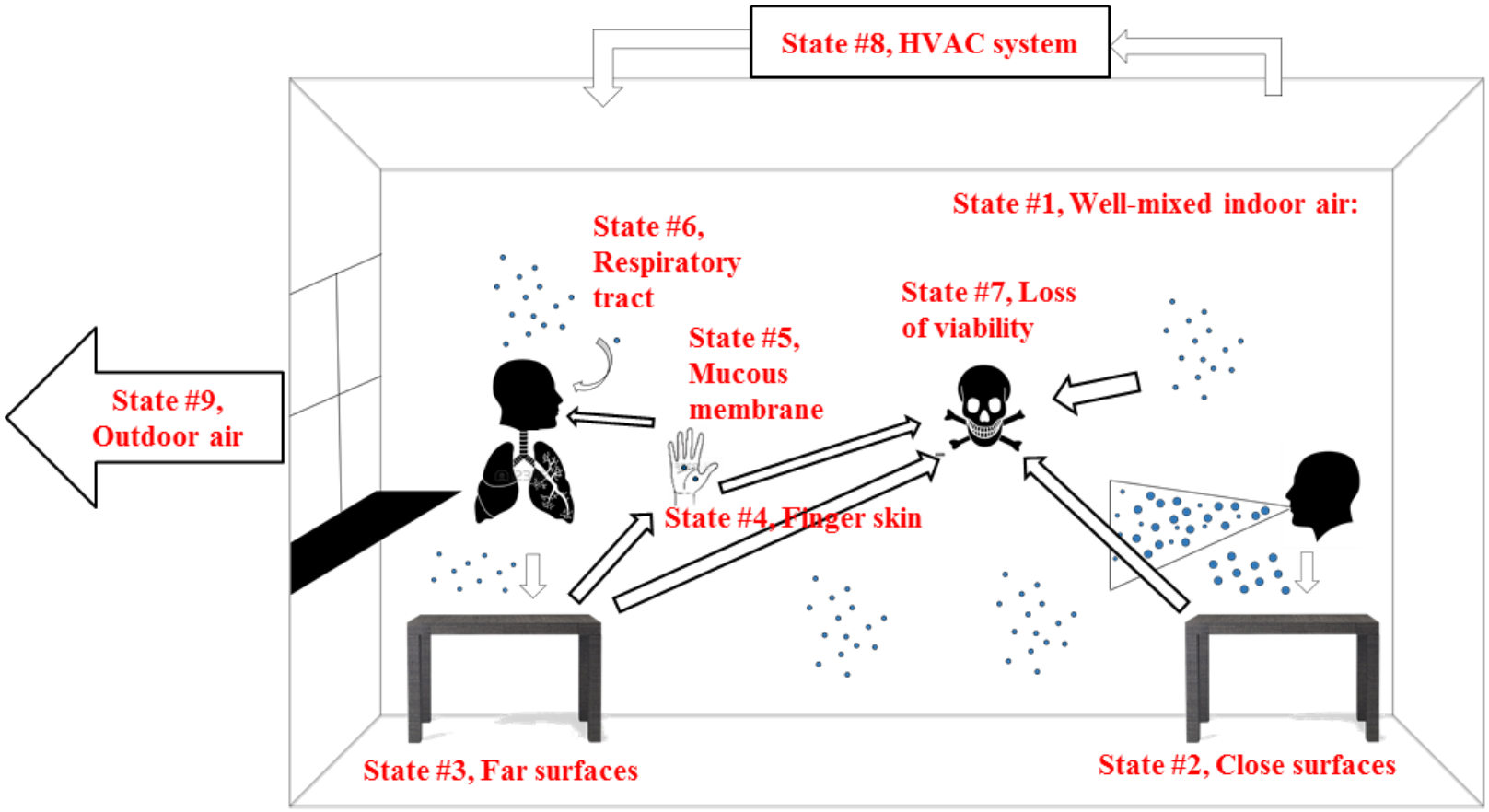
- We defined probability distributions for the parameters used in Monte Carlo simulation

Variable		Distribution	Distribution characteristics		Ref.
Inactivation rate (hour)	Air	Log-normal	GM = 0.50	GSD = 1.51	[1]
	Surfaces	Log-normal	GM = 1.44	GSD = 1.17	[1]
	Skin	Normal	Mean = 71.9	STD = 23.4	[2]
Transfer efficiency	Surface-Skin	Log-normal	GM = 0.014	GSD = 1.4	[2]
	Finger-Face	Log-normal	GM = 0.046	GSD = 1.4	[2]
Number of IAV injected to indoor air ($TCID_{50}$)	Per breath	Stair-step (three)	71.4%	of time is zero	[3]
			21.6%	of time is 0.05	[4]
			7%	of time is 0.71	[5]
	Per cough	Normal (Concentration of IAV)	Mean = 3.21 (TCID50/ml)	STD = 0.16 (TCID50/ml)	[1]
		Uniform (Fluid Volume)	from 4.0×10^{-4} to 4.4×10^{-2} (ml)		[2]
HID_{50} ($TCID_{50}$)	Lower respiratory tracts	Uniform	from 0.6 and 3		[6]
	Mucous membranes	Uniform	from 127 to 320		[7] [8]

[1] Jones, Rachael M. "Critical review and uncertainty analysis of factors influencing influenza transmission." *Risk Analysis* 31.8 (2011): 1226-1242.
[2] Jones, Rachael M., and Elodie Adida. "Influenza infection risk and predominate exposure route: uncertainty analysis." Risk Analysis 31.10 (2011): 1622-1631.
[3] Fabian, Patricia, et al. "Influenza virus in human exhaled breath: an observational study." *PloS one* 3.7 (2008).
[4] Martin, K. E. L. S. E. Y., and A. Helenius. "Transport of incoming influenza virus nucleocapsids into the nucleus." *Journal of virology* 65.1 (1991): 232-244.
[5] Wulff, Niels H., Maria Tzatzaris, and Philip J. Young. "Monte Carlo simulation of the Spearman-Kaerber TCID50." *J. Clinical Bioinformatics* 2 (2012): 5.
[6] Alford, Robert H., et al. "Human influenza resulting from aerosol inhalation."*Experimental Biology and Medicine* 122.3 (1966): 800-804.
[7] Couch, R. B., ey.al. 1971 Correlated studies of a recombinant influenza-virus vaccine. 3. Protection against experimental influenza in man. J. Infect. Dis. 124, 473–480.
[8] Couch, R. B et.al.. 1974 Induction of partial immunity to influenza by a neuraminidase-specific vaccine. J. Infect. Dis. 129, 411–420

METHODS (Markov Chain Method)

- We assumed 9 states for the hypothetical office environment
- We estimated IAV number in each state by 10^{-7} hour time steps
- By repeating Markov chain procedure, we calculated number concentration of IAV after 8 hours exposure time in each state



METHODS (Dose Response Model)

- We used a non-threshold dose-response model that assumes a single virus can infect the host with probability α.

- For a non-integer expected dose, E[D], the dose-response function is

$$R = 1 - \exp(-\alpha \times E[D])$$

  - R: Probability of infection

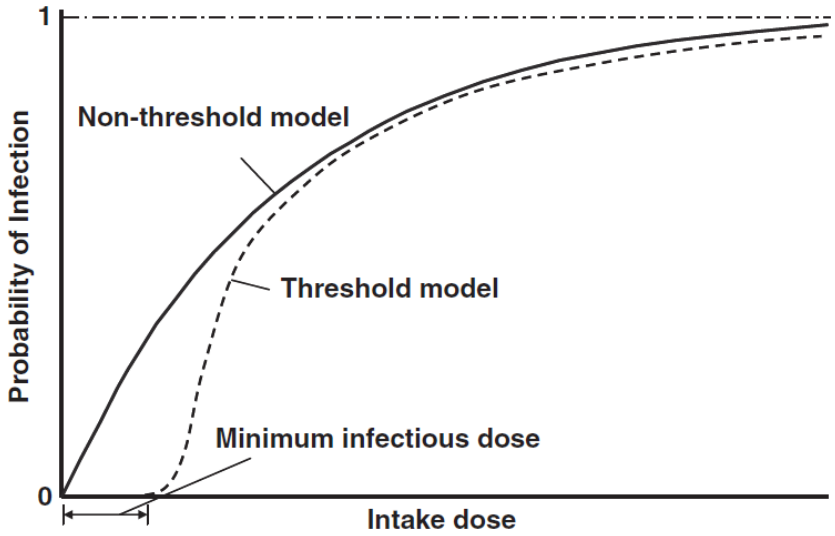
- Also α can be estimated from HID_{50}

(50% Human Intake Dose)

$$\alpha = \ln(2) / HID_{50}$$

Nicas, Mark, and Gang Sun. "An Integrated Model of Infection Risk in a Health-Care Environment." *Risk Analysis* 26.4 (2006): 1085-1096.

An illustration of the difference between a non-threshold model and a threshold model

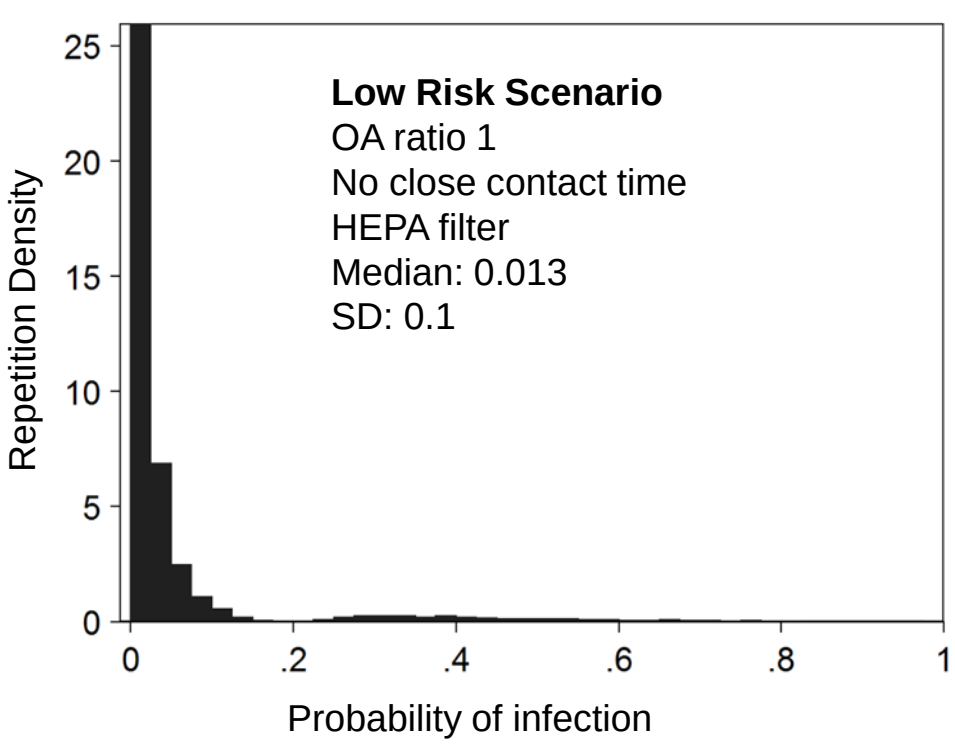


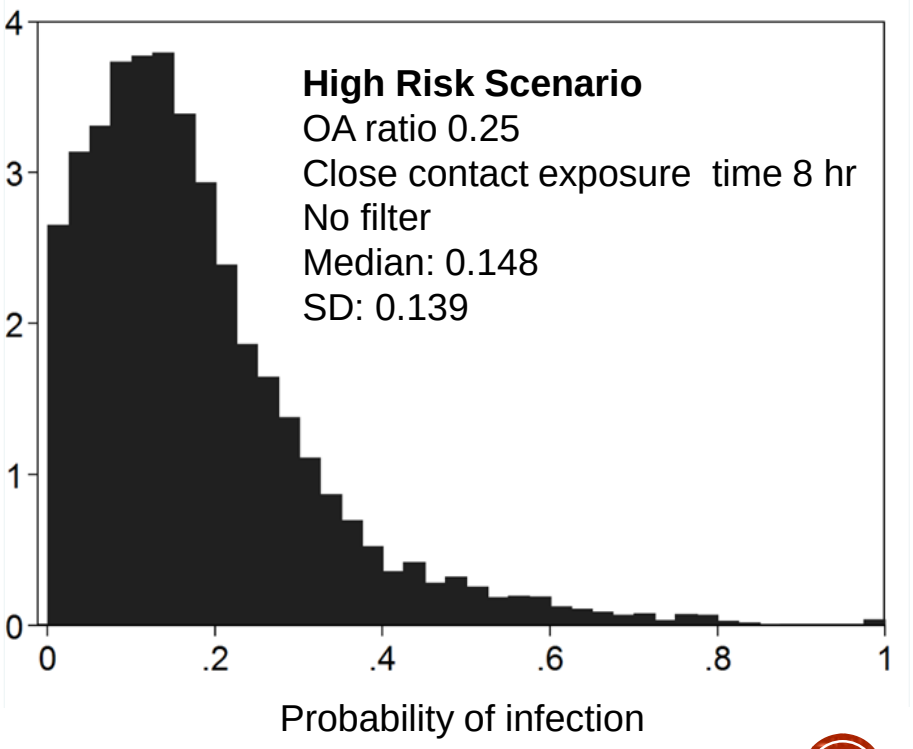
Sze To, G. N., and C. Y. H. Chao. "Review and comparison between the Wells–Riley and dose-response approaches to risk assessment of infectious respiratory diseases." *Indoor Air* 20.1 (2010): 2-16.

- We considered different **α** values for lower respiratory tracts and mucous membrane

RESULTS (Infectious Probability Histograms)

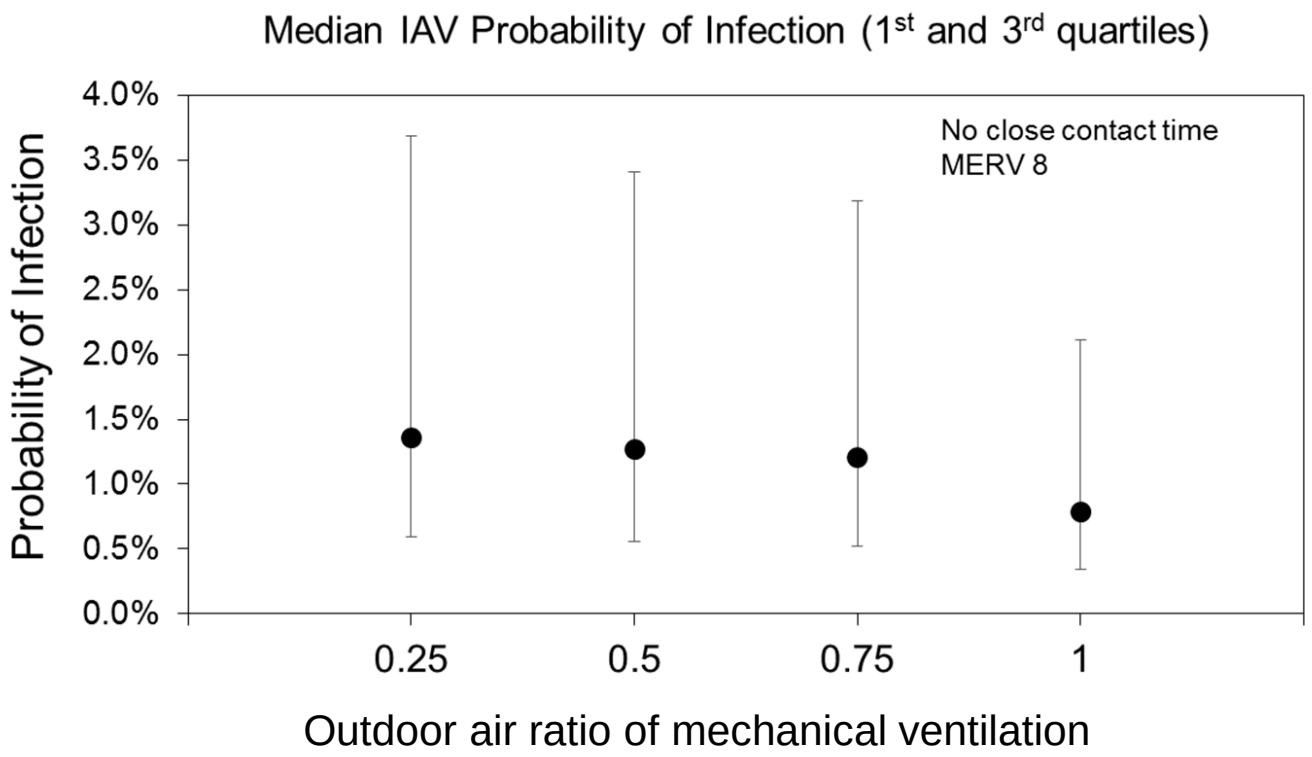
- We ran a Monte Carlo simulation with 10,000 repetitions to predict the statistical distribution of probability of infection
- Typical histograms for low and high infection risk scenarios are shown below





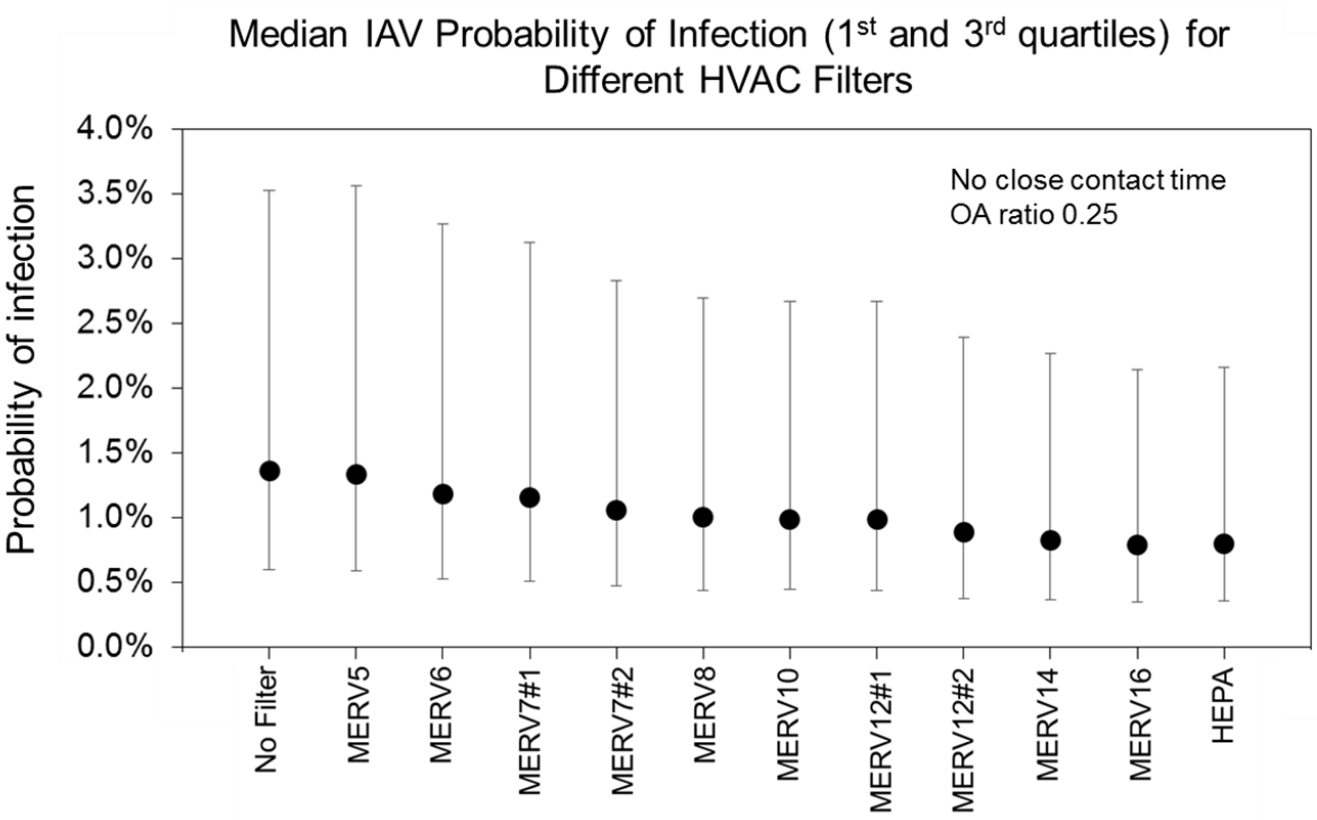
RESULTS (Effect of Outdoor Air Ratio)

- We explored effect of office ventilation system characteristic (OA ratio and HVAC filters RE) on probability of infection



- In sensitivity analysis, corresponding to 100% increase in OA ratio from 0.25 to 0.5, median probability of infection decreases 4%

RESULTS (Effect of HVAC Filters RE)

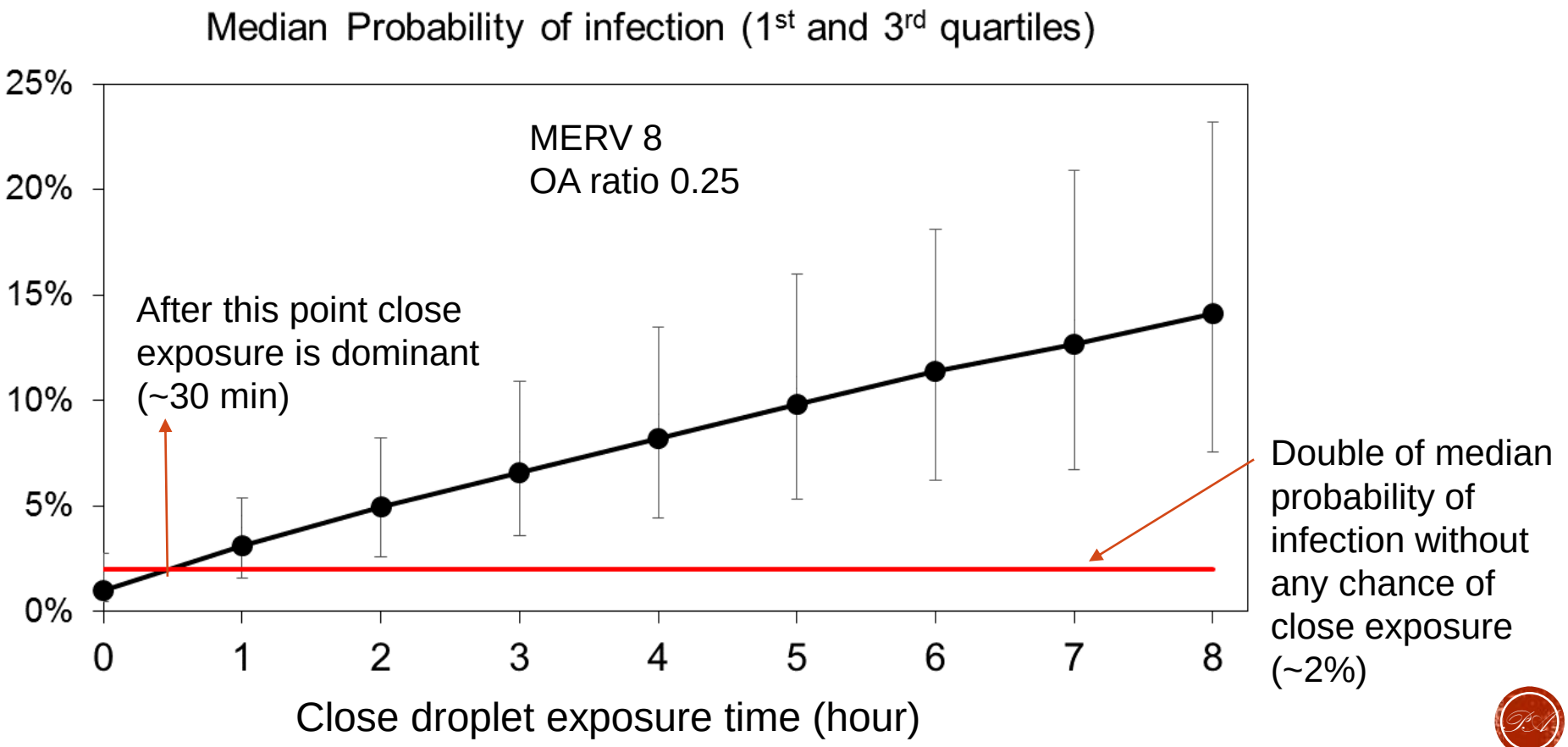


Minimum efficiency reporting values of HVAC filters

- In sensitivity analysis, corresponding to ~100% increase in removal efficiency of HVAC filters from 48% for MERV8 to 97% for MERV16 filters, median probability of infection decreases 9%

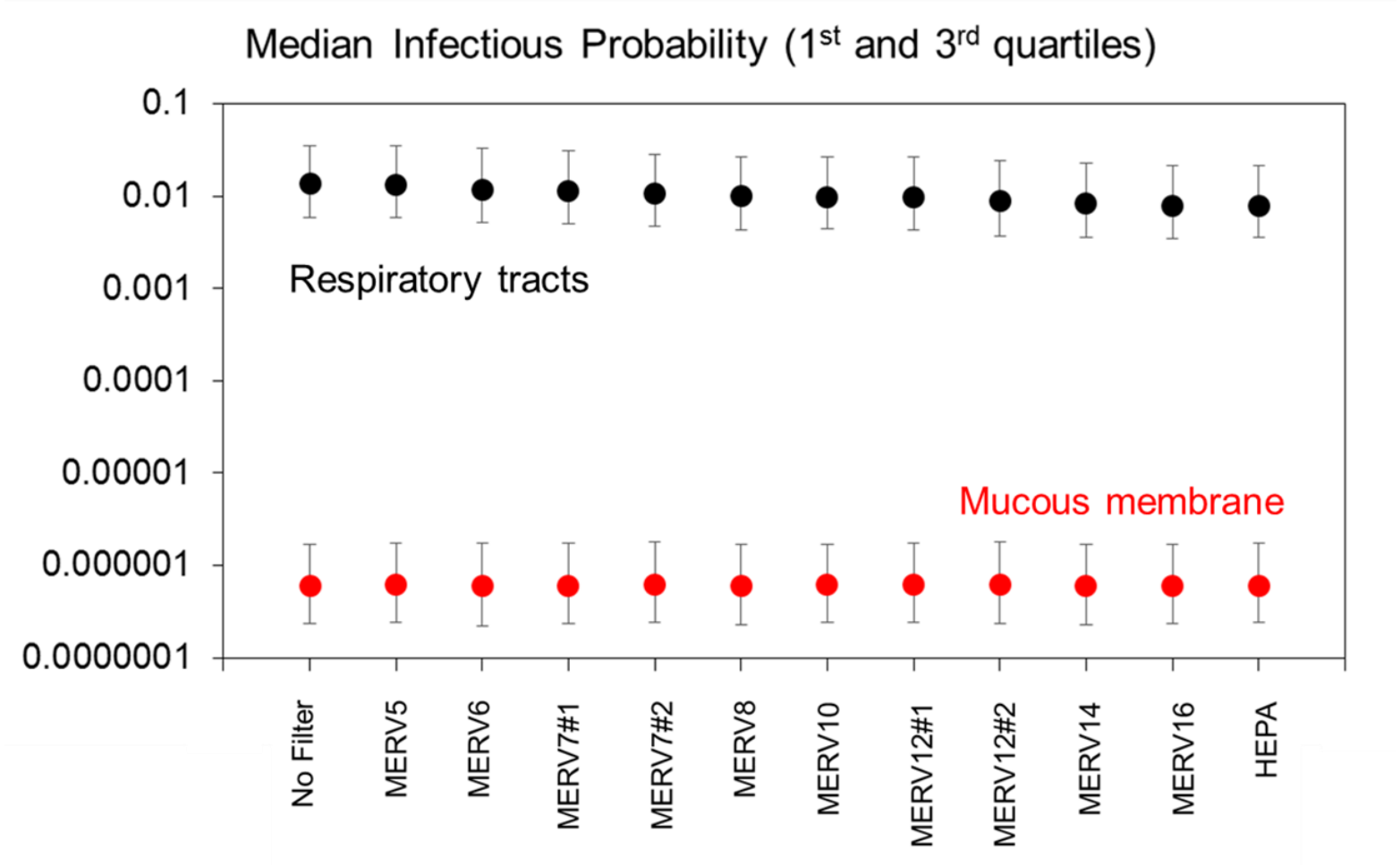
RESULTS (Effect of Close Droplet Exposure Time)

- We assumed the close droplet exposure is dominate pathway of IAV transmission after the time in which the median probability of infection considering close exposure is higher than double of median probability of infection without any chance of close exposure



RESULTS (Dominate Pathway of Infection Transmission)

- We also explored the dominate route of infection transmission assuming there is no chance of close droplet exposure



RESULTS (Compare to Wells-Riley Model)

- For comparison, we back calculated quanta generation rate, q (1/hr), from a modified transient Wells-Riley model

$$P_{\text{infection}} = 1 - e^{-\frac{pIq}{V} \times \frac{Ct + e^{-Ct} - 1}{C^2}}$$

Gammaitoni, Laura, and Maria Clara Nucci. "Using a mathematical model to evaluate the efficacy of TB control measures." *Emerging infectious diseases* 3 (1997): 335-342.

I = number of infector individuals
p = pulmonary ventilation rate of a person (m^3/hour)
t = exposure time (hr)
C = the total loss/disinfection rate (e.g., $\lambda_{\text{ventilation}} + k_{\text{filtration}} + k_{\text{deposition}} + k_{\text{inactivation}}$, 1/hr)

- Quanta generation rate is typically back calculated from epidemiological studies and for Influenza it is varied ~15 to ~500 per hour (67 and 100 per hour are both commonly used)

Azimi, P.,Stephens B. "HVAC filtration for controlling infectious airborne disease transmission in indoor environments: Predicting risk reductions and operational costs." *Building and Environment* 70 (2013): 150-160.

- The calculated mean value for quanta generation rate was from 30 to 113 per hour which is completely in line with the existing data in the literature

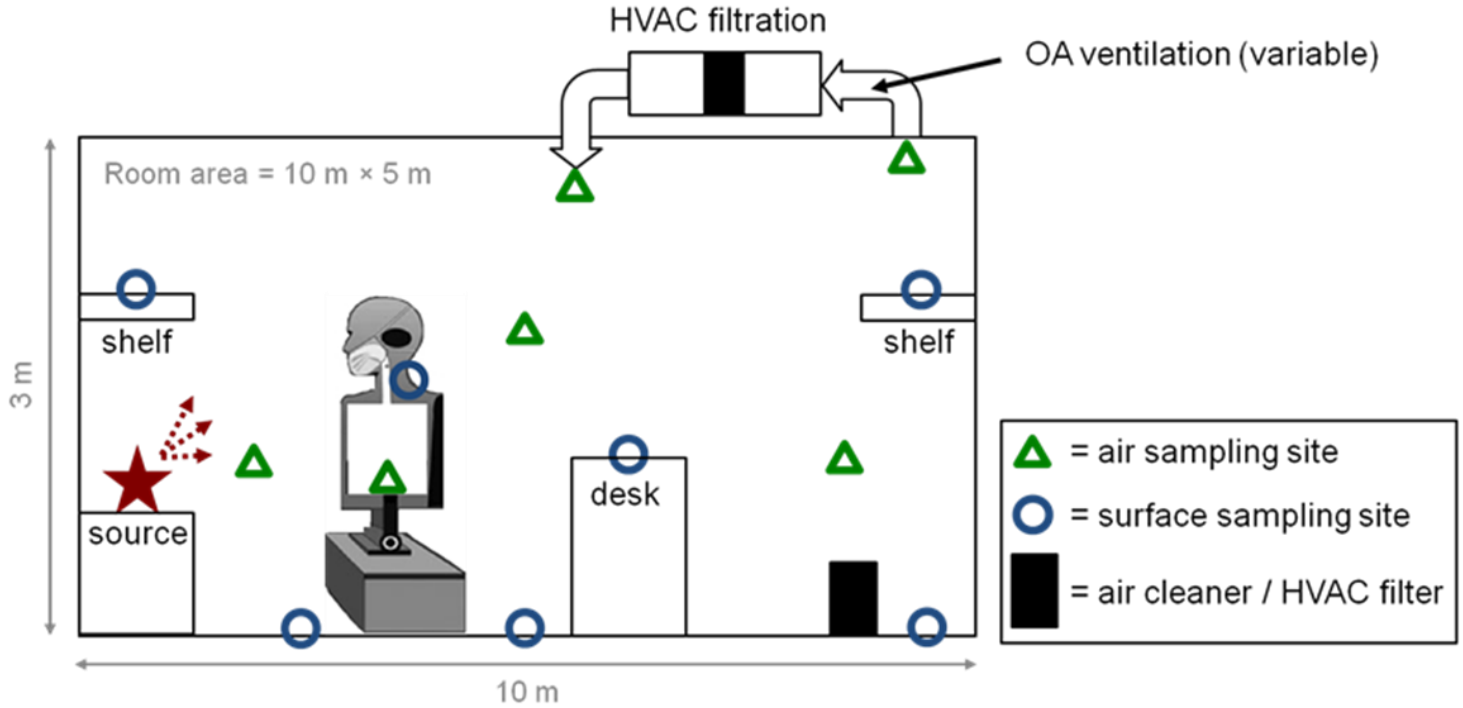
CONCLUSION

- The probability of infection can be varied as a function of many parameters including OA ratio of ventilation system, size-resolve RE of HVAC filters, and close range droplet exposure time
- Increasing OA ratio, from 0.25 to 1 decreases the median probability of infection up to ~30%
- HVAC filters with higher MERV rate usually provide lower probability of infection (HEPA filters with 99.7% bulk RE for infectious particles decreases the median chance of getting infected up to ~40% compare to no filter scenario)
- 8 hours of close range droplet exposure time increases the median chance of getting infected up to ~1300% compare to no close exposure
- Dominate pathway of infection transmission is close range droplet contact for exposure time above ~0.5 hour
- Without any chance of close droplet exposure, inhalation is the dominate pathway
- The mean calculated value for quanta generation rate is ranged from 30 to 113 per hour which is completely in line with the existing data from the literature.

THANK YOU FOR YOUR ATTENTION

LIMITATIONS AND FUTURE WORKS

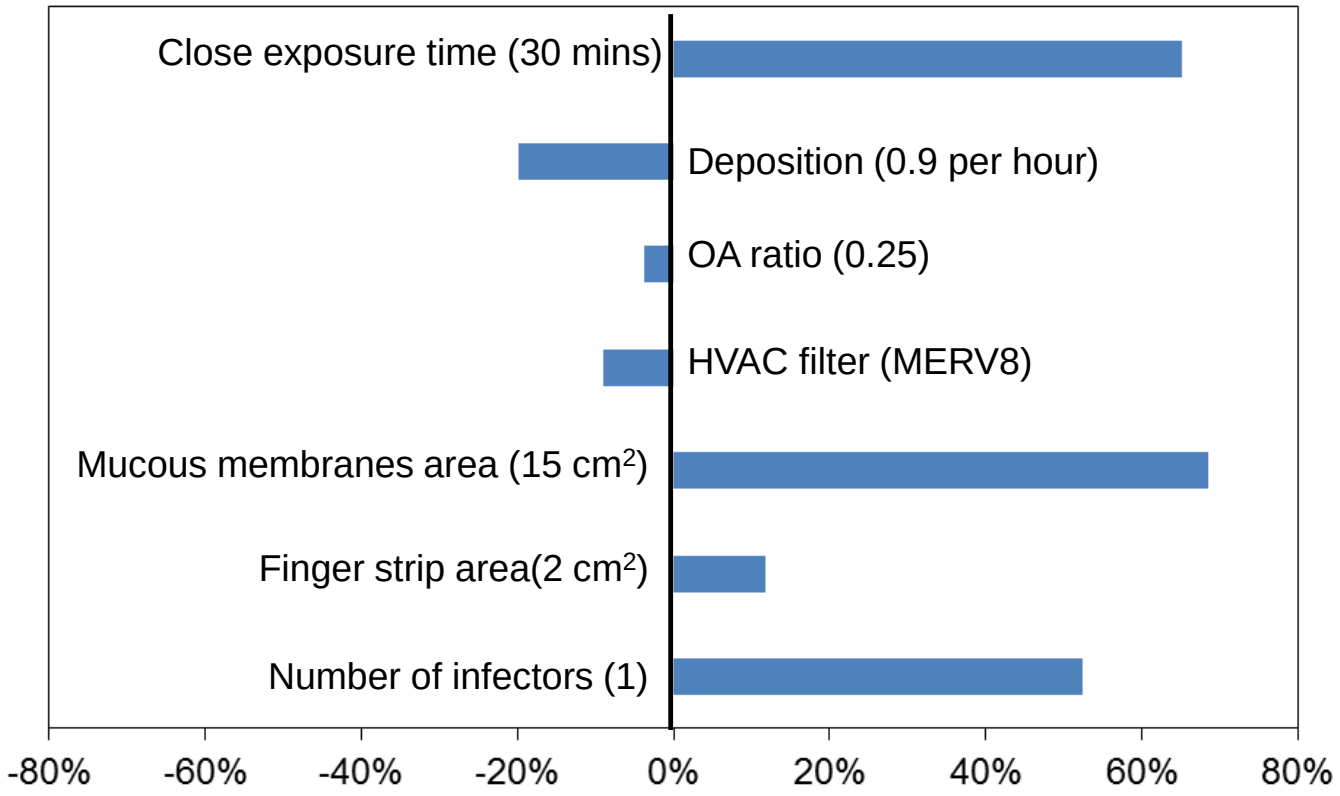
- The main limitation of this work is the uncertainty around the model parameters
- We decide to clarify the model input values by doing a controlled experiment
  - Measuring size-resolved concentration of bioaerosols and the impact of building characteristics
  - Estimate airborne infectious particle concentration in each state and compare with measured data



RESULTS (Sensitivity Analysis)

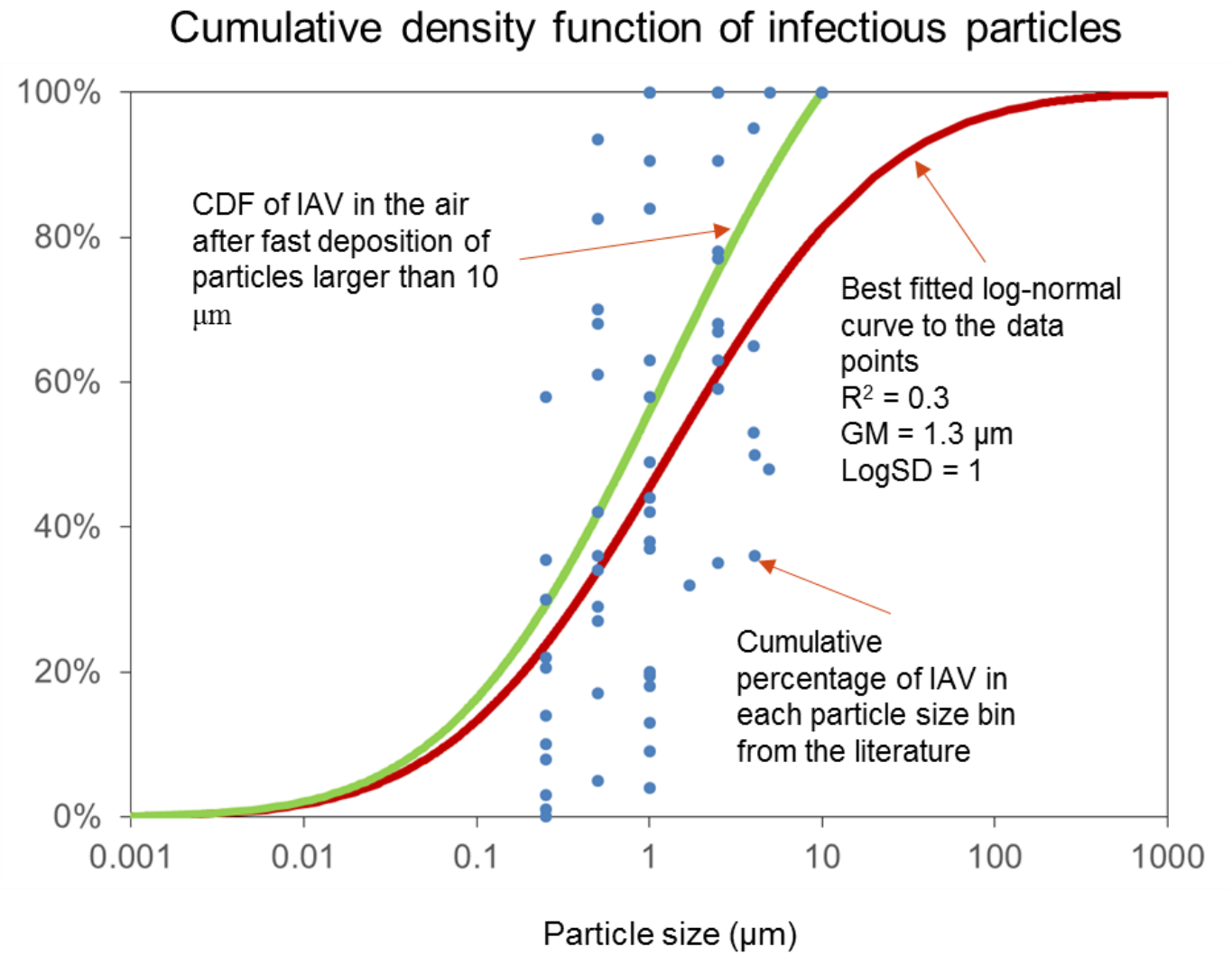
- We explored the change in probability of infection after each of the model parameter values increased 100% in comparison to the base scenario.

Change in median probability of infection (parameter base values)



METHODS (Size Distribution of IAV In The Air)

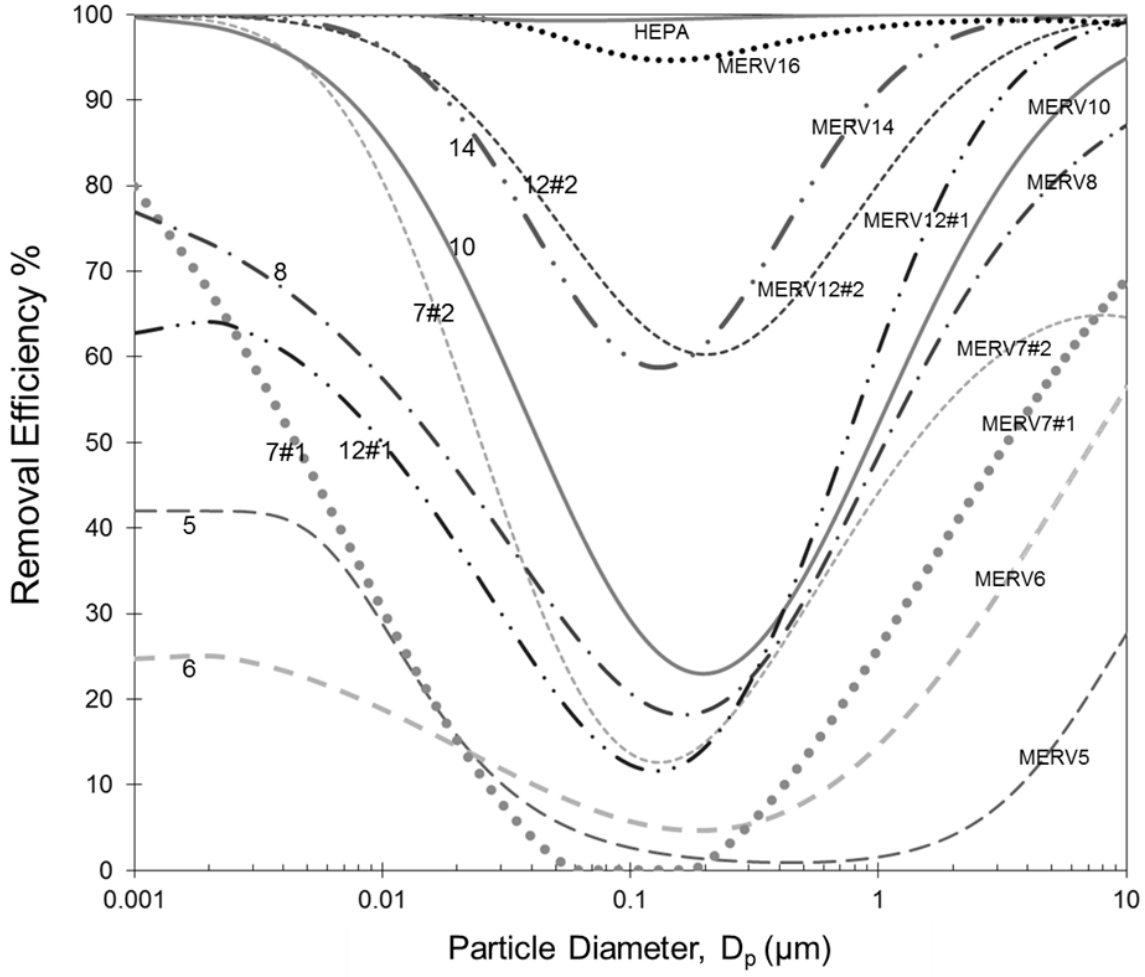
- Reported infectious particle size distribution is varied in different studies



METHODS (HVAC Filter Removal Efficiency)

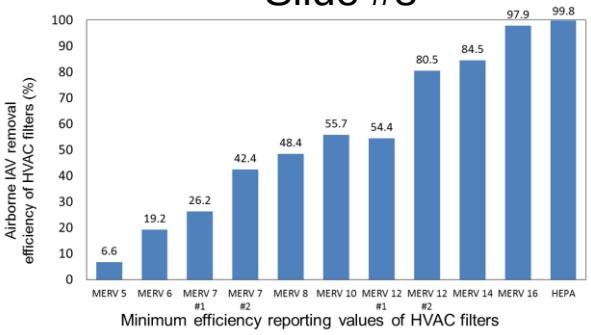
- We mapped the CDF of IAV in the air to the existing size-resolve removal efficiency of HVAC filters

Size-resolved removal efficiency of various MERV designations



Azimi, P., et.al "Estimates of HVAC filtration efficiency for fine and ultrafine particles of outdoor origin." Atmospheric Environment (2014).

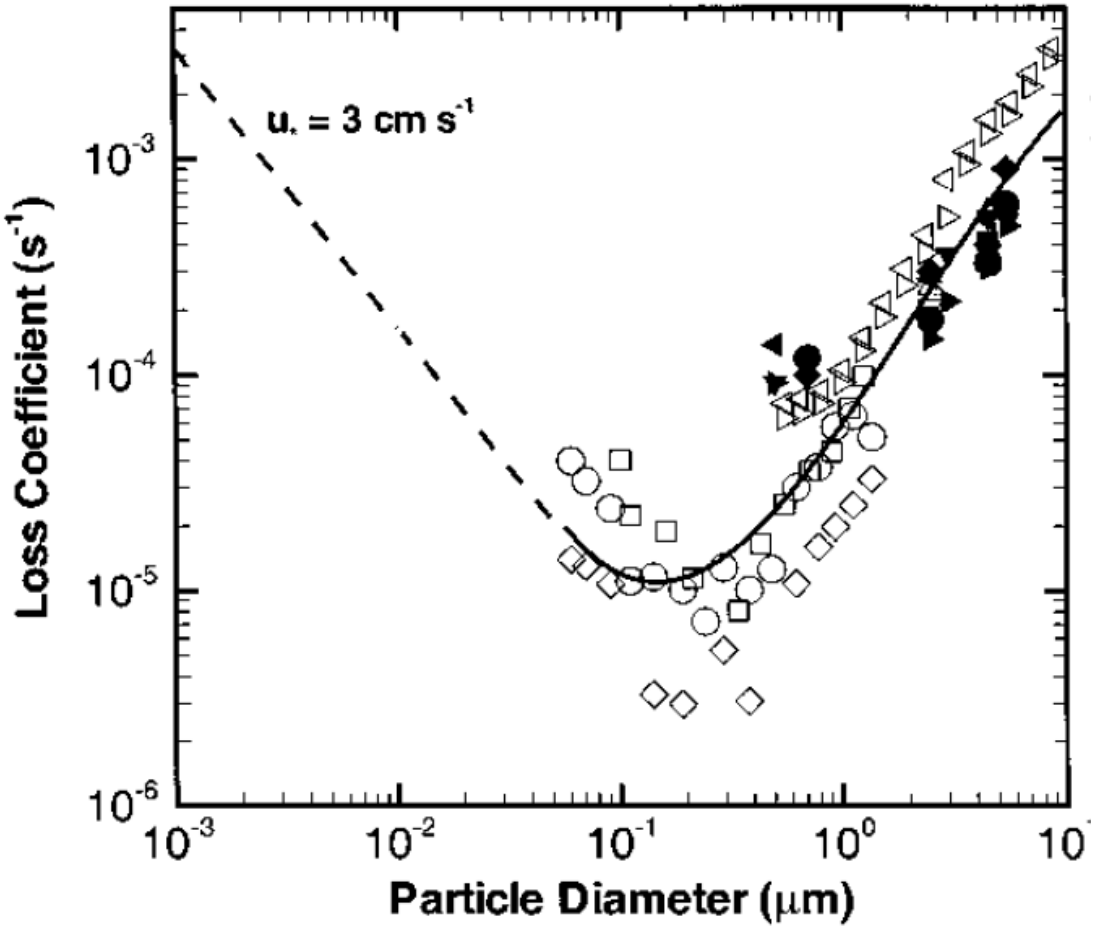
Slide #8



METHODS (Deposition of Infectious Particles)

- We mapped the CDF of IAV in the air to the existing size-resolve deposition loss rate coefficient

Deposition loss rate coefficient (β) vs particle size



Riley, W. J., et al. "Indoor particulate matter of outdoor origin: importance of size-dependent removal mechanisms." Environmental science & technology 36.2 (2002): 200-207.

- The average deposition rate of IAV particles is calculated 0.9 per hour

METHODS (Markov Chain Method)

- A 9×9 single-step transition **probability matrix** for the model system is provided
- Most of influenza A viruses (IAV) injected from infector in each cough or breath drop down instantaneously on **close surfaces**, smaller portion of them suspend in the **indoor air**
- There is a chance of **close range droplet exposure** during coughing

IAV injected matrix

per cough per breath

	per cough	per breath
Indoor air	N_{1c}	N_{1b}
Close surf.	N_{2c}	N_{2b}
Far surf.	0	0
Finger Skin	0	0
Mucous m.	N_{5c}	0
Respiratory tr.	0	0
Inactivation	0	0
HVAC system	0	0
Outdoor air	0	0

or ×

9×9 single-step transition probability matrix

	S 1	S 2	S 3	S 4	S 5	S 6	S 7	S 8	S 9
Indoor air	P_{11}	P_{12}	P_{13}	0.0	0.0	P_{16}	P_{17}	P_{18}	P_{19}
Close surf.	0.0	P_{22}	0.0	P_{24}	0.0	0.0	P_{27}	0.0	0.0
Far surf.	0.0	0	P_{33}	P_{34}	0.0	0.0	P_{37}	0.0	0.0
Finger Skin	0.0	P_{42}	P_{43}	P_{44}	P_{45}	0.0	P_{47}	0.0	0.0
Mucous m.	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0
Respiratory tr.	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0
Inactivation	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0
HVAC system	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0
Outdoor air	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0

P_{ii}: probability of remaining in the same state i

P_{ij} : probability of moving from state i to j

N_{ic}: IAV number injected to state i per cough

N_{ib}: IAV number injected to state i per breath

METHODS (Dose Response Model)

- Total probability of getting infected was calculated as the following

$$P_{total} = 1- \exp(-\alpha_{MM} \times (E_{MM\text{-}Cough}[D]+E_{MM\text{-}Breath}[D]) -\alpha_{RT} \times (E_{RT\text{-}Cough}[D]+E_{RT\text{-}Breath}[D]))$$

- α_{MM} and α_{RT} :

  Alpha values for mucous membrane and respiratory tracts respectively

- $E_{MM\text{-}Cough}[D]$ and $E_{MM\text{-}Breath}[D]$:

  Expected doses of IAV in mucous membrane because of coughing and breathing

- $E_{RT\text{-}Cough}[D]$ and $E_{RT\text{-}Breath}[D]$:

  Expected doses of IAV in respiratory tracts because of coughing and breathing