Aerosols and Transmission of Respiratory Viruses 101

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Acknowledgments

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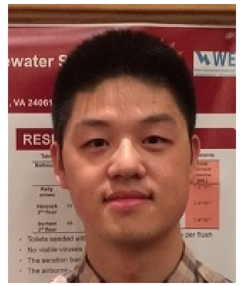





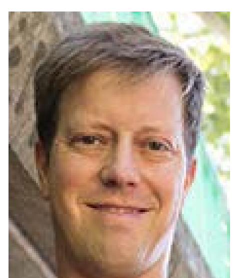
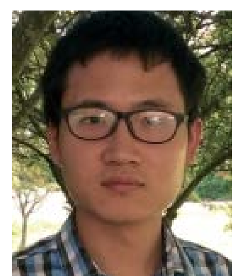


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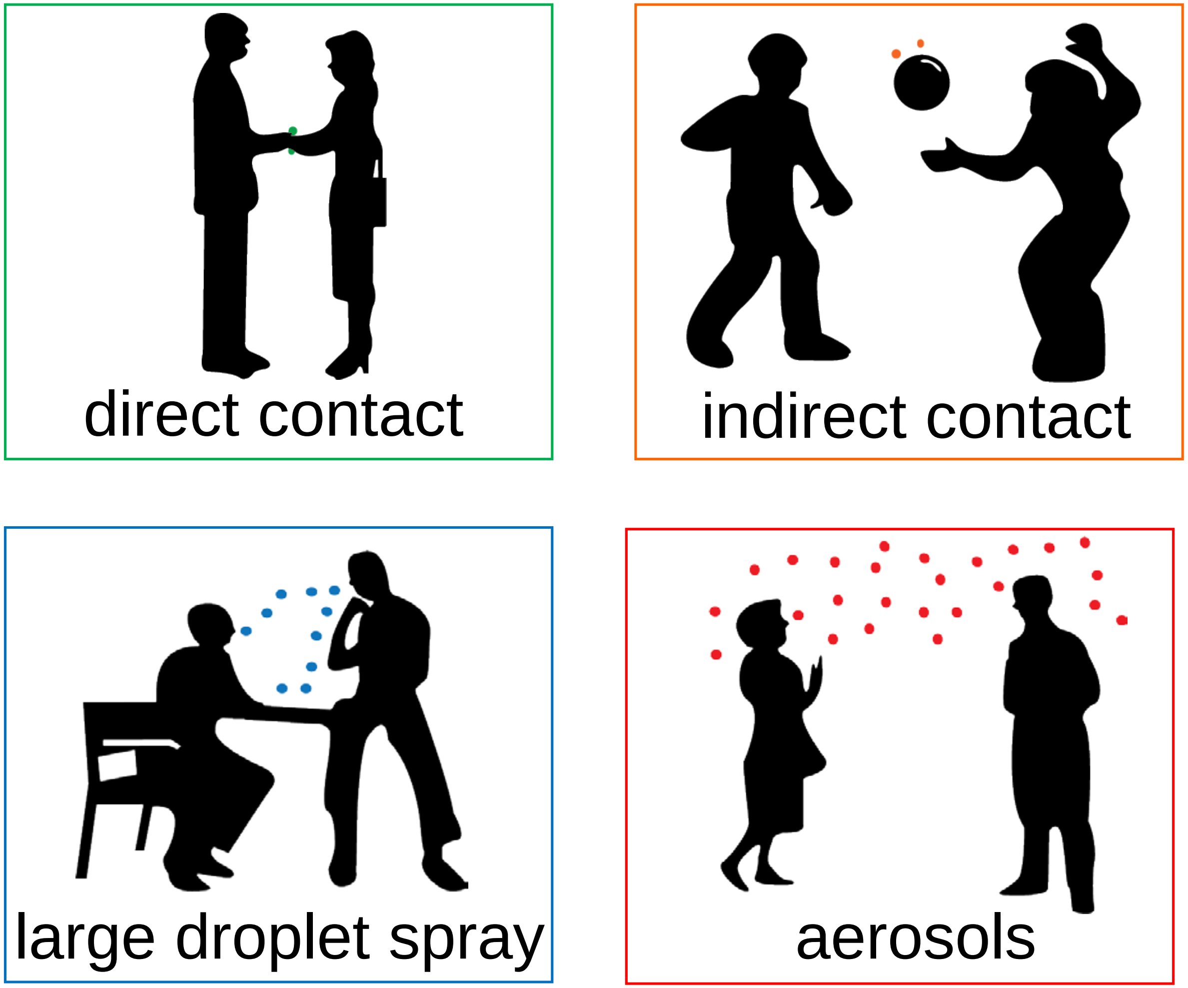
NIH DIRECTOR'S NEW INNOVATOR AWARD

Topics

1. Transmission routes
2. Importance of size
3. Journey of viruses through the air
    1. Emission (takeoff)
    2. Transport and transformation (cruising)
    3. Deposition (landing)
4. Evidence for SARS-CoV-2
5. Interventions

https://phil.cdc.gov/Details.aspx?pid=11160

Transmission Routes



Traditionally defined as >5 μm and happening at close-range only (<2 m)

Traditionally defined as <5 μm and happening mainly at long-distance (>2 m)

The origin of the 5-μm cutoff is not clear. This cutoff is not supported by modern aerosol science. This distinction has hampered our understanding of transmission.

Adapted from http://www.phac-aspc.gc.ca/cpip-pclcpi/annf/v2-eng.php

Terminology

Term	WHO/Infectious Disease	Aerosol Science	Public
Airborne	 Measles	In the air	

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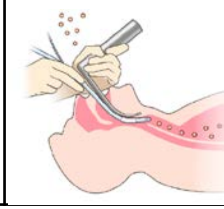
Aerosol	 < 5 µm	Collection of solid or liquid particles suspended in a gas	

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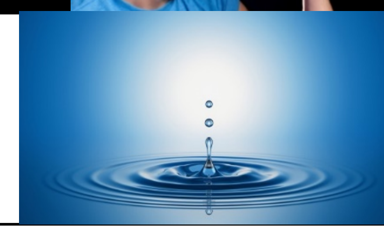
Droplet	 > 5 μm	Liquid particle	

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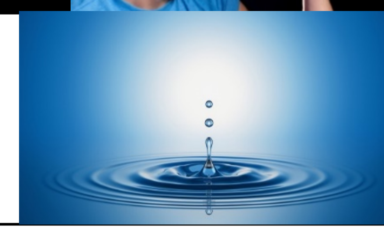
Droplet	 > 5 μm	Liquid particle	
Droplet nuclei	Residue of a droplet that has evaporated to < 5 μm	Is this like cloud condensation nuclei?	?

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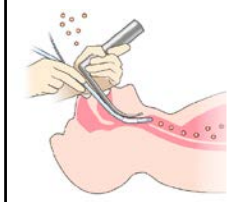
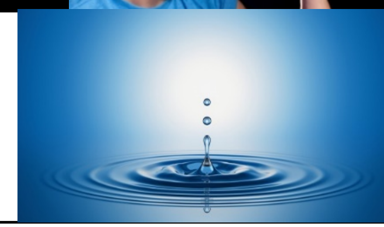
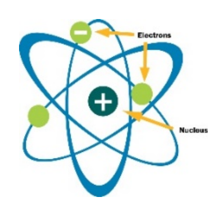
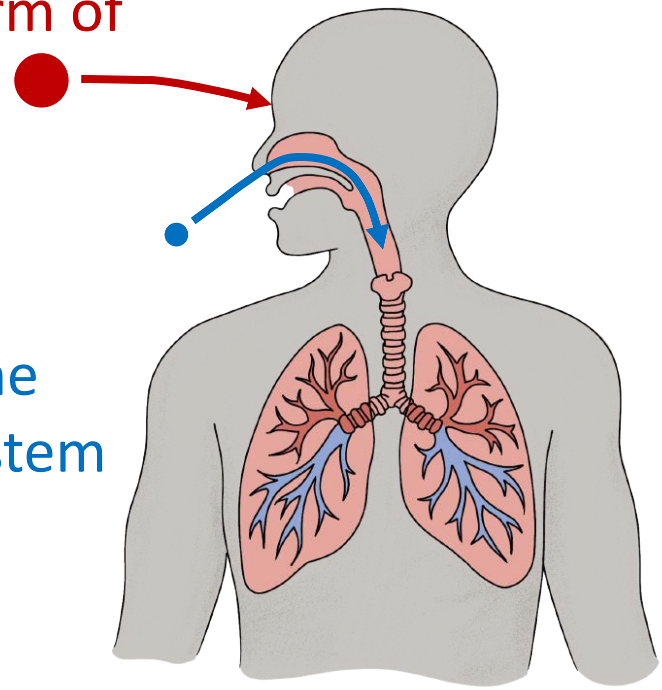
Aerosol	 < 5 μm	Collection of solid or liquid particles suspended in a gas	
Droplet	 > 5 μm	Liquid particle	
Droplet nuclei	Residue of a droplet that has evaporated to < 5 μm	Is this like cloud condensation nuclei?	?
Particle	Virion	Particulate matter	

Defining Transmission by Exposure Path

LARGE DROPLETS are sprayed onto the body, a form of contact transmission

AEROSOLS are inhaled into the respiratory system



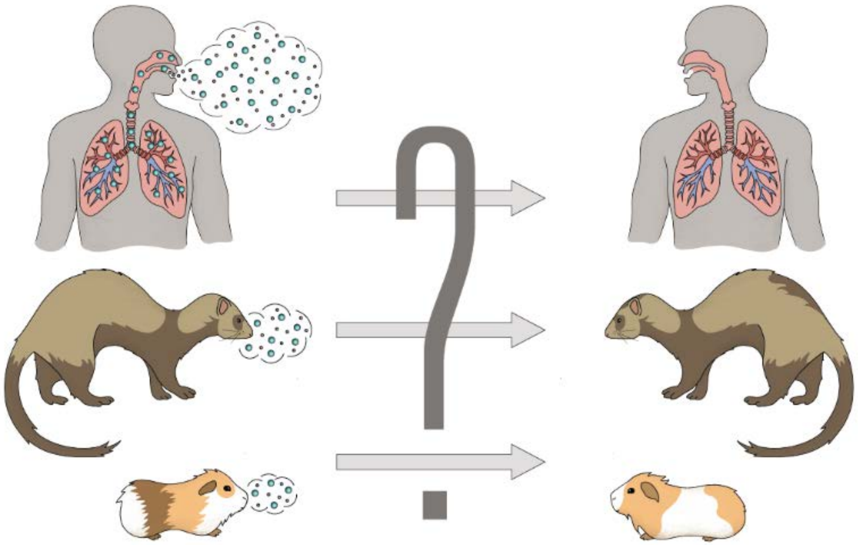
This distinction drives

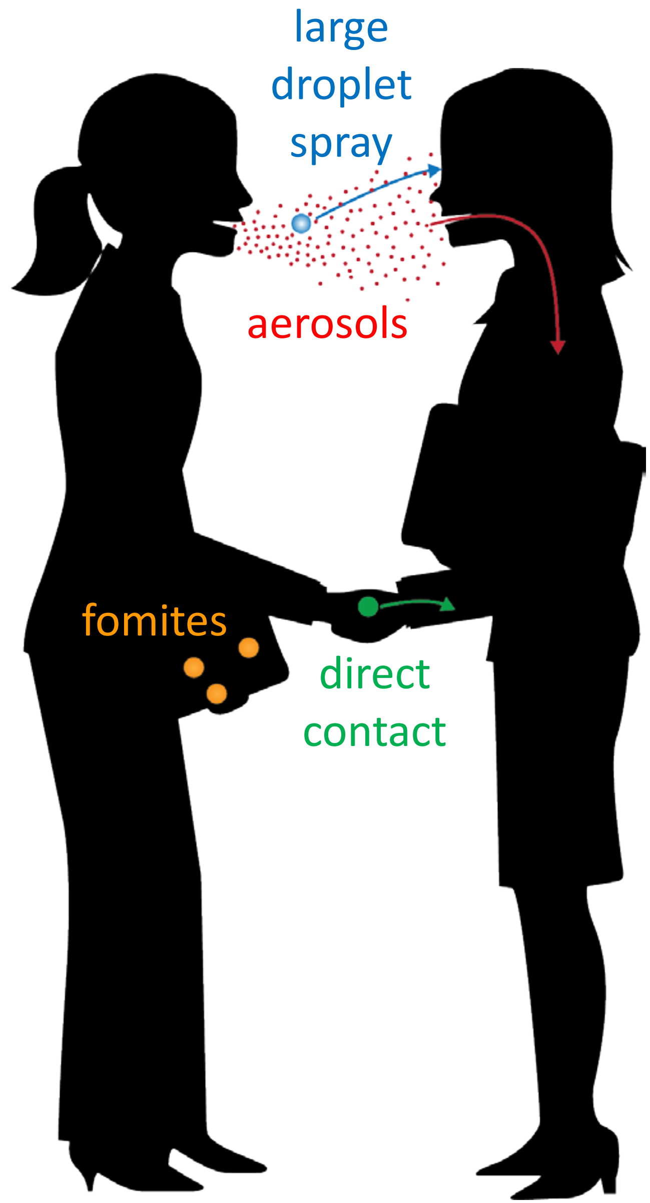
- Control strategies
- Infectious dose
- Severity of disease

(The physics-based cutoff is 60-100 μm)

(1) Wells, W.F., 1934, On air-borne infection. Study II. Droplets and droplet nuclei, *Am J Epidemiol* (2) Xie, X., Li, Y., Chwang, A.T.Y., Ho, P.L., Seto, W.H., 2007, How far droplets can move in indoor environments – revisiting the Wells evaporation–falling curve, *Indoor Air* (3) Tellier, R., Li, Y., Cowling, B.J., Tang, J.W., 2019, Recognition of aerosol transmission of infectious agents: a commentary, *BMC Infect Dis* (4) Lindsley, W.G., Noti, J.D., Blachere, F.M., et al., 2015, Viable influenza A virus in airborne particles from human coughs, Journal of Occupational and Environmental Hygiene

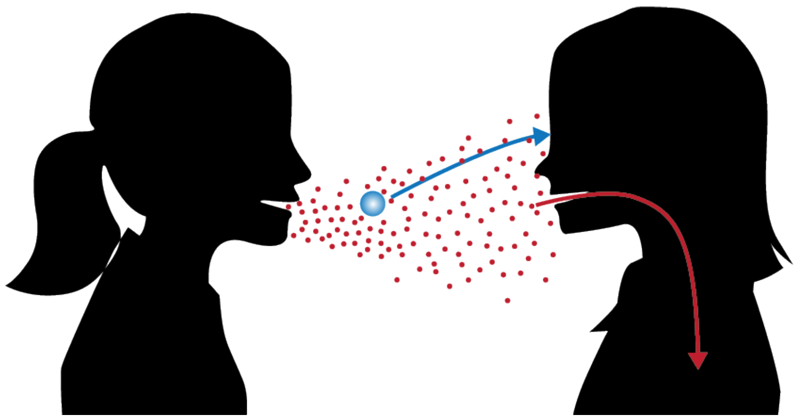
A Mechanistic Perspective





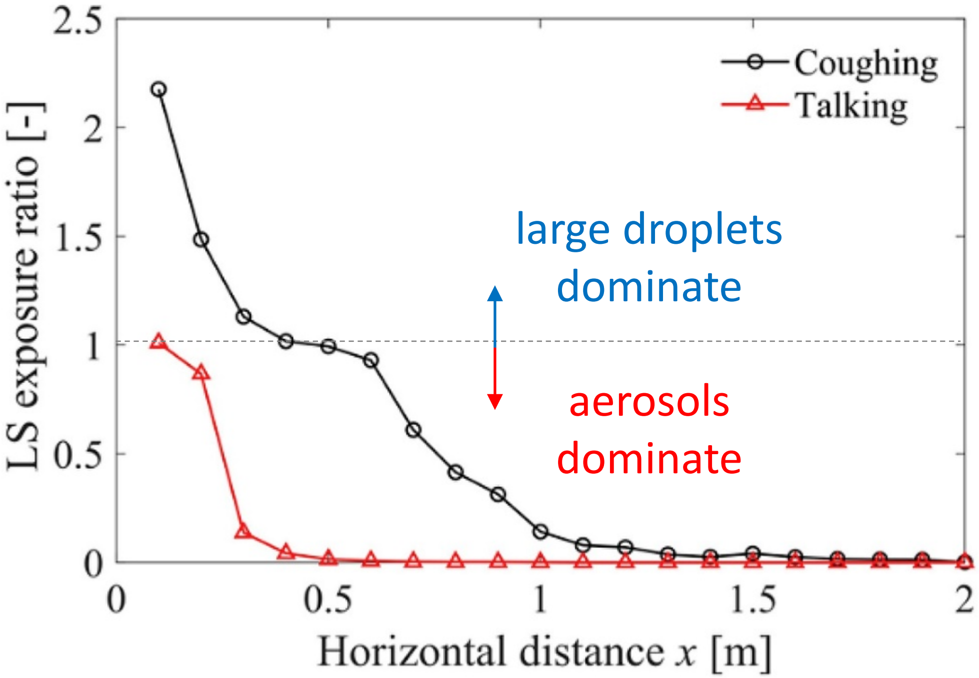
In many studies, a transmission event is observed, but we do not know the path of the virus through the environment.

Close Contact: Droplets vs. Aerosols



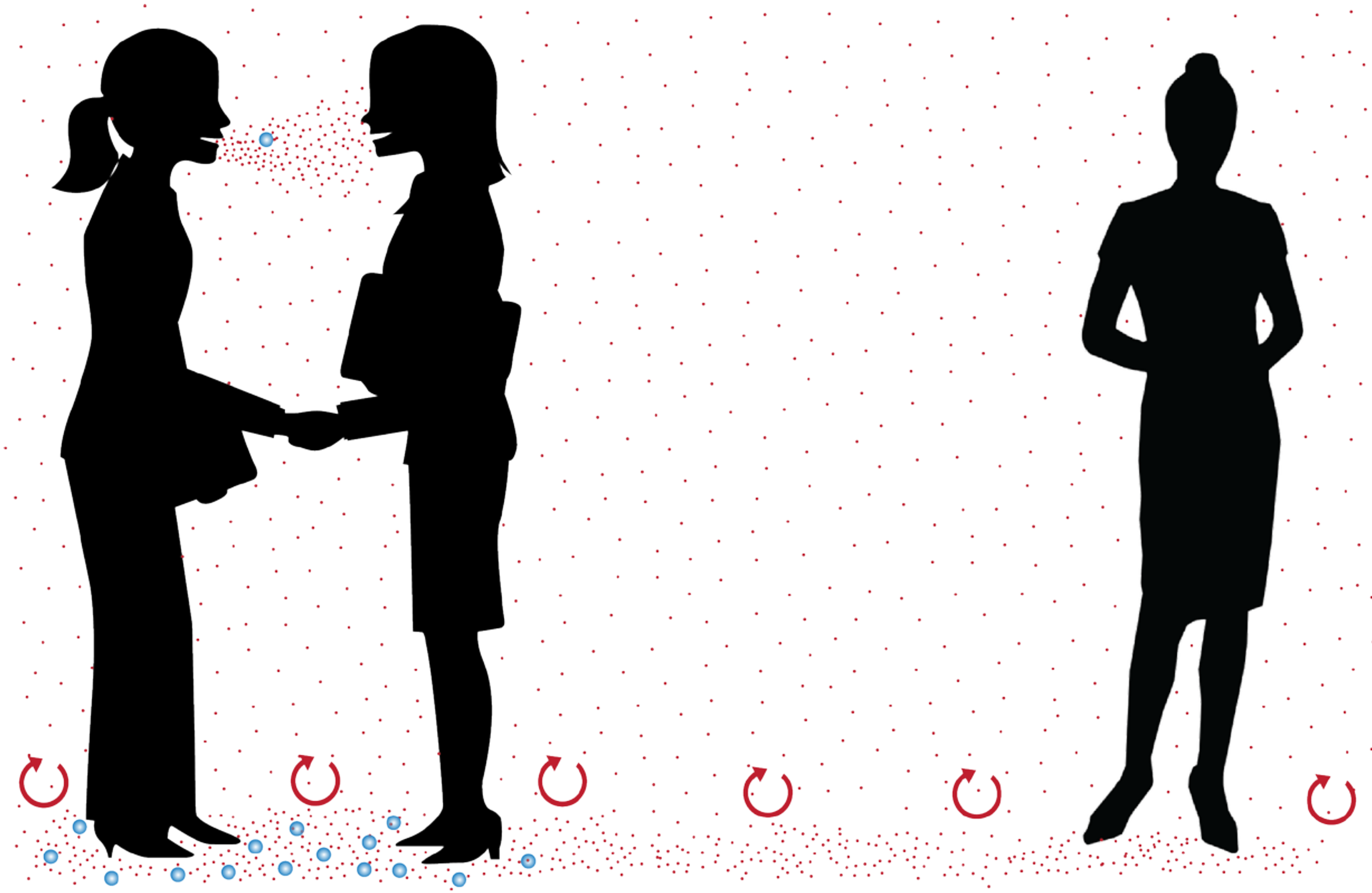
Physics-based model of large droplet spray and aerosols in jets produced by talking and coughing

Ratio of exposure by large droplet spray (L) to inhalation of short-range aerosols (S)



(1) Chen, W., Zhang, N., Wei, J., et al., 2020, Short-range airborne route dominates exposure of respiratory infection during close contact, *Build Environ*

Spread, Dilution, Resuspension

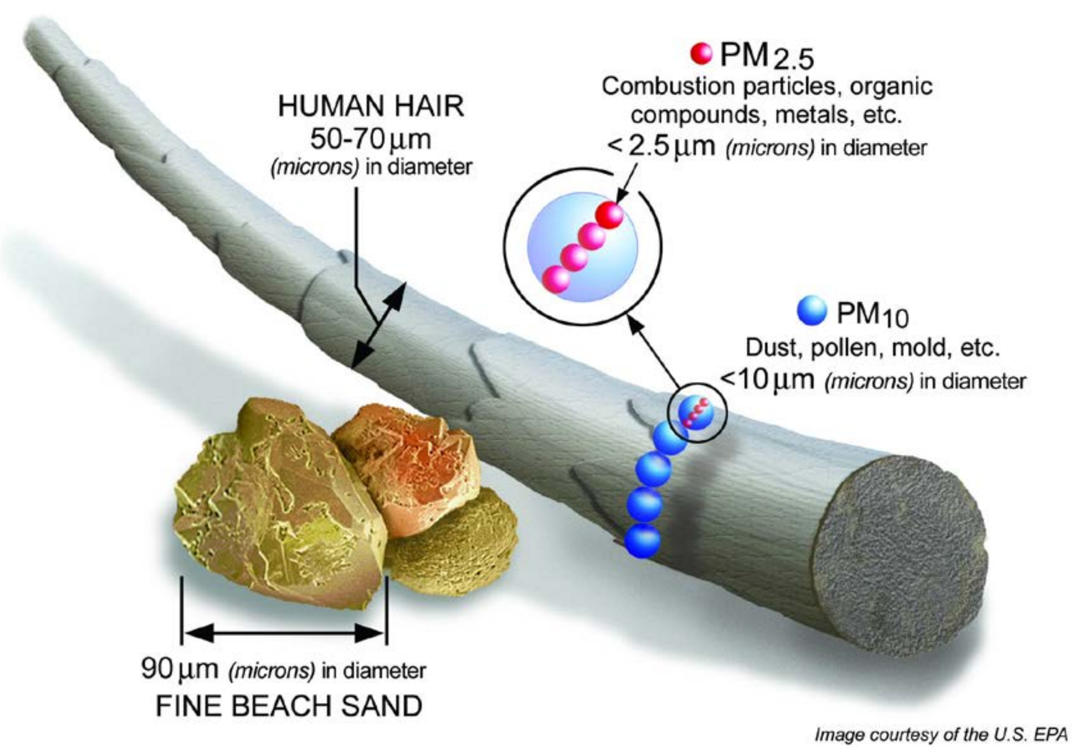


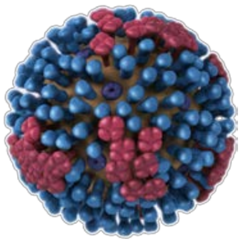
(1) Khare, P., Marr, L.C., 2015, Simulation of vertical concentration gradient of influenza viruses in dust resuspended by walking, *Indoor Air* (2) Asadi, S., Gaaloul ben Hnia, N., Barre, R.S., et al., 2020, Influenza A virus is transmissible via aerosolized fomites, *Nature Comm*

Transmission by inhalation of aerosols can happen at short and long range.

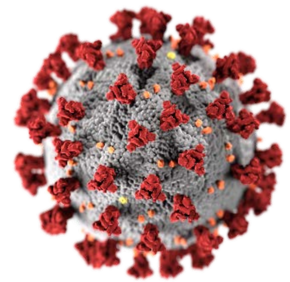
Why is size so important?

Virus Size

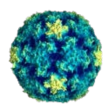




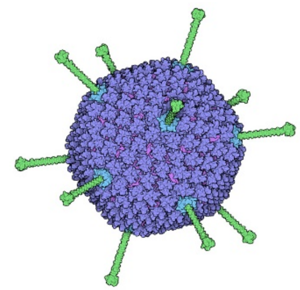
influenza
0.1 µm



SARS-CoV-2
0.12 µm



rhinovirus
0.03 µm

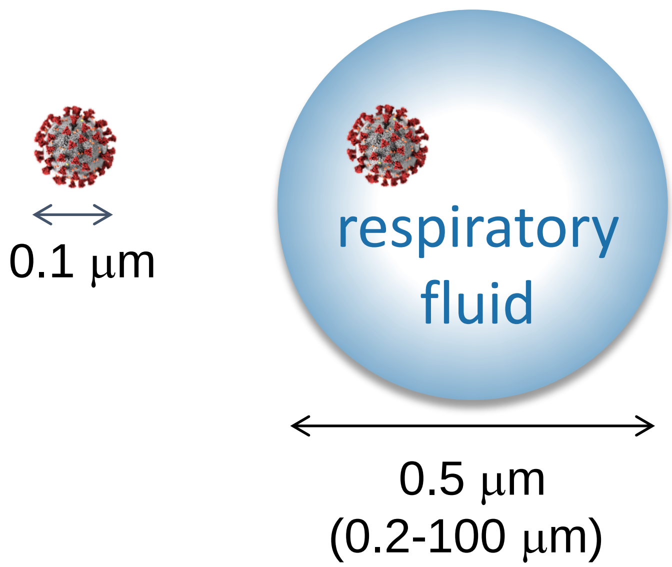


adenovirus
0.1 µm

https://www.cdc.gov/flu/resource-center/freeresources/graphics/images.htm, http://solutionsdesignedforhealthcare.com/rhinovirus, https://phil.cdc.gov/Details.aspx?pid=23312, https://pdb101.rcsb.org/motm/132

Size of Droplet/Aerosol is Critical

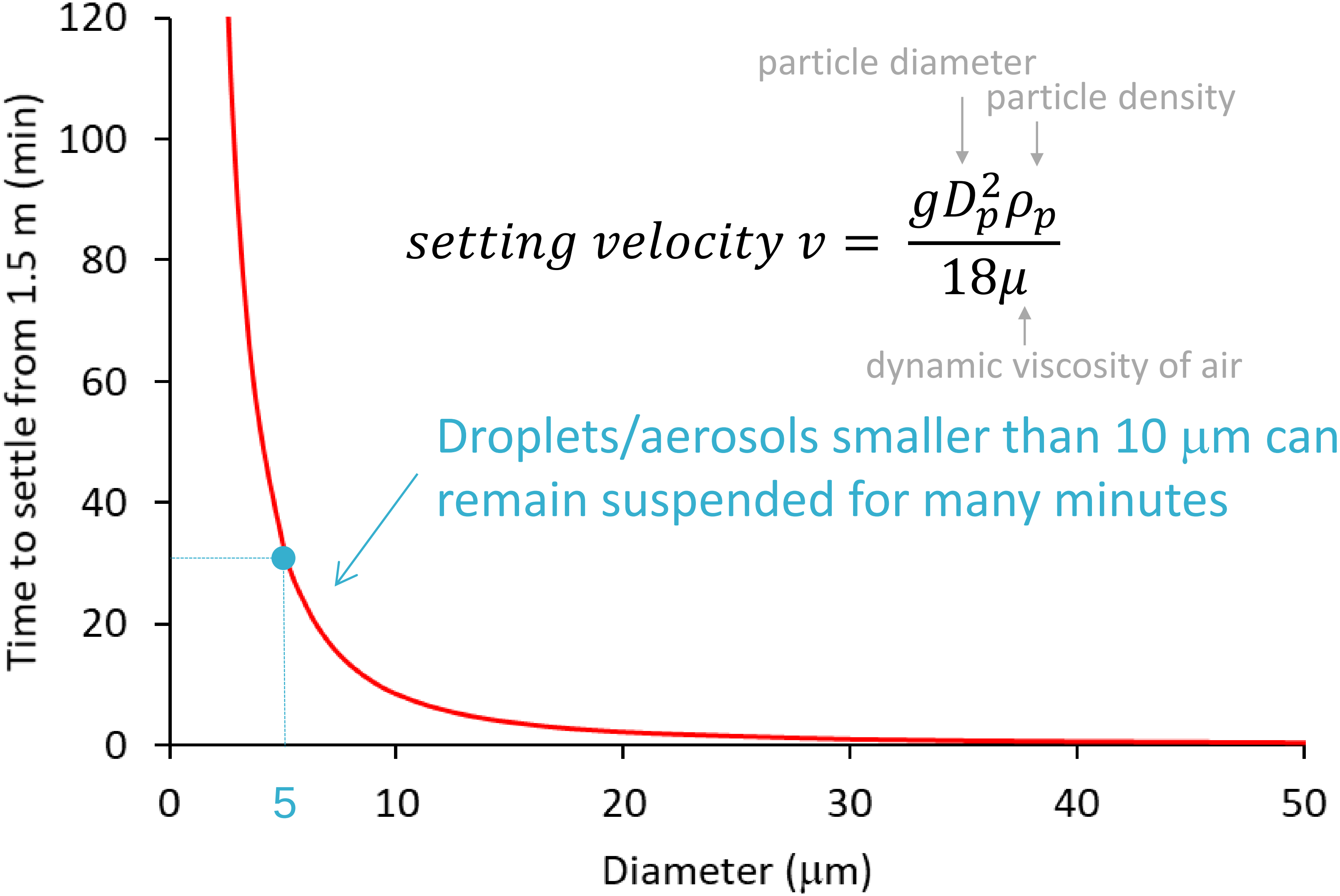
1. Airborne virus is not naked
2. Size of carrier droplet/aerosol defines transport



- How long it stays aloft
- How far it can travel
- How quickly it falls to surfaces
- Where it deposits in the respiratory system
- How efficiently it is removed by masks and filters
- Physics is the same for all viruses

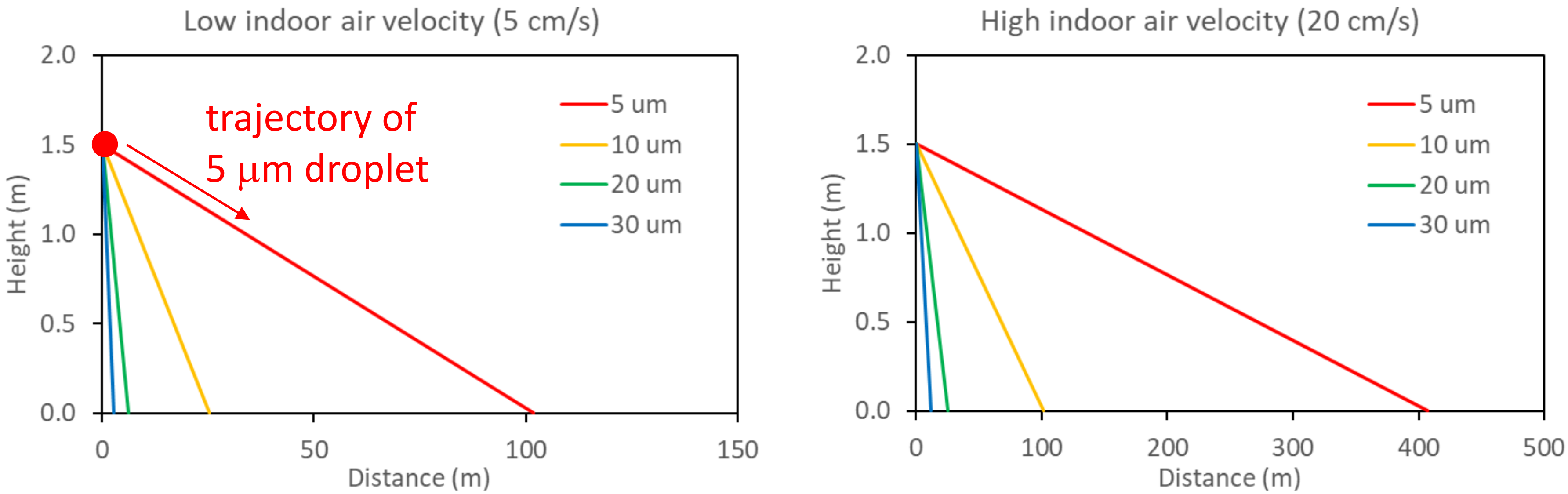
3. SARS-CoV-2 vs. measles vs. other viruses: (1) viral load in different size droplets/aerosols, (2) inactivation rate in droplets/aerosols, (3) location and dose to initiate infection

Settling Velocity and Time



Droplets Can Travel More Than 2 m

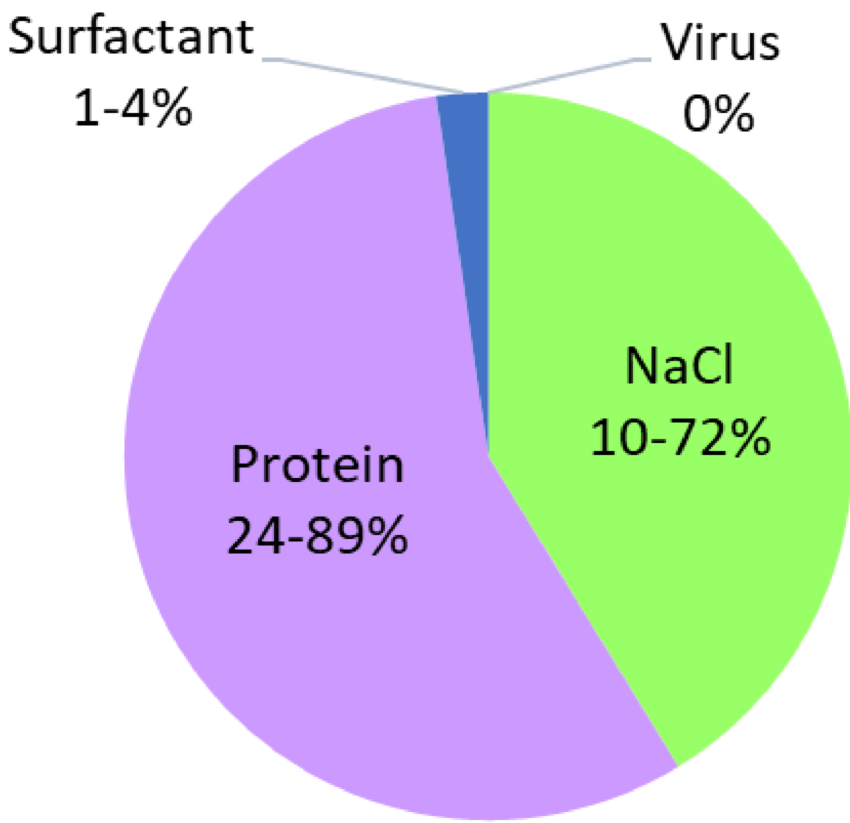
Position of droplets released from a height of 1.5 m



(1) Nazaroff, 2020, personal communication (2) Matthews, T.G., Thompson, C.V., Wilson, D.L., et al., 1989, Air velocities inside domestic environments: An important parameter in the study of indoor air quality and climate, *Environ Internat* (3) Baldwin, P.E., Maynard, A.D., 1998, A survey of wind speeds in indoor workplaces, *Ann Occup Hyg*

Chemical Composition

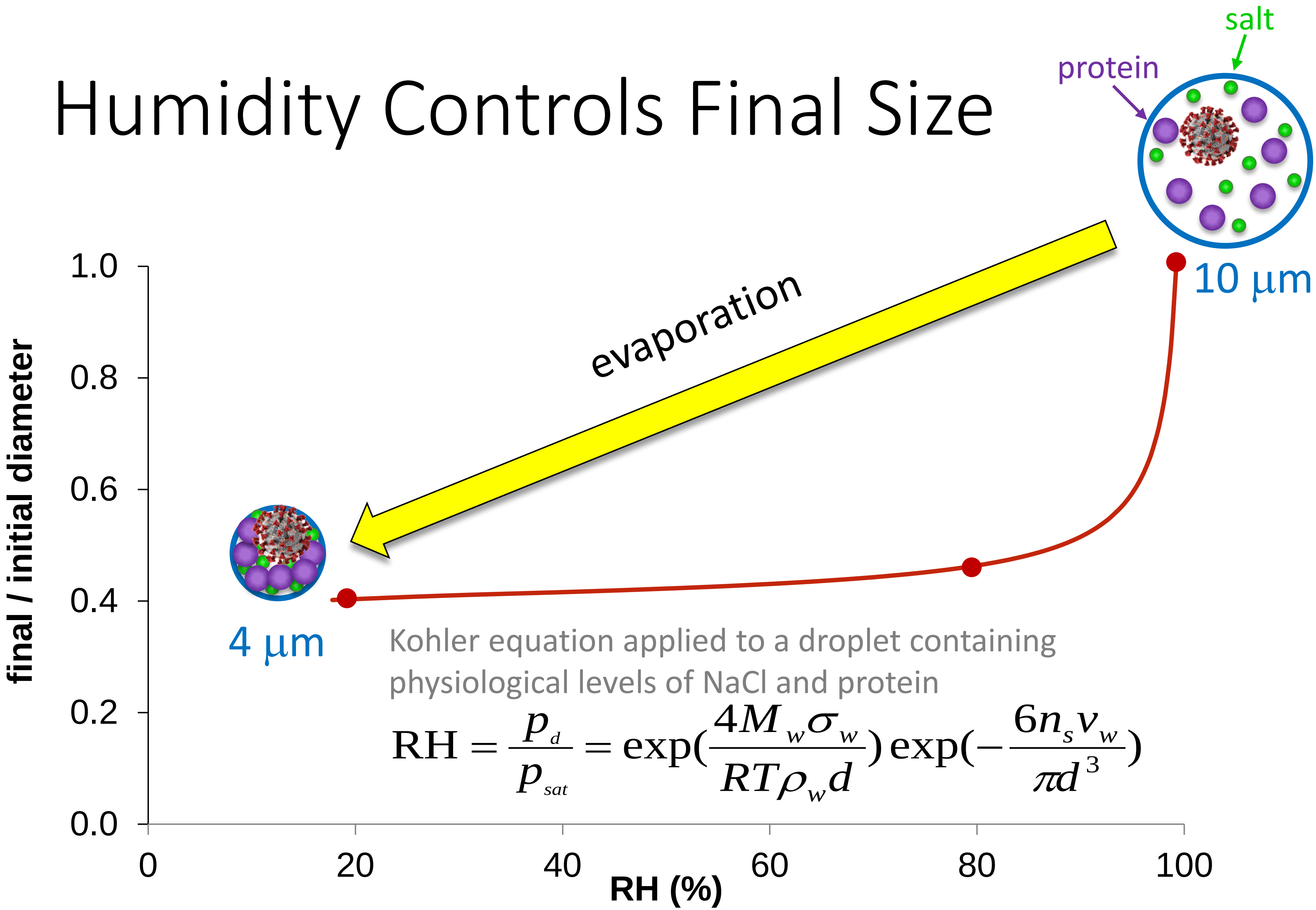
Non-volatile solutes are 1-9% of initial mass



EDX: K, Ca, Cl, C, S

(1) Vejerano, E.P., Marr, L.C., 2018, Physico-chemical characteristics of evaporating respiratory fluid droplets, , *J Roy Soc Interface* (2) Marr, L.C., Tang, J.W., Van Mullekom, J., et al., 2019, Mechanistic insights into the effect of humidity on airborne influenza virus survival, transmission and incidence, *J Roy Soc Interface* (3) Papineni, R.S., Rosenthal, F.S., 1997, The size distribution of droplets in the exhaled breath of healthy human subjects, *J Aerosol Med*

Humidity Controls Final Size



Kohler equation applied to a droplet containing physiological levels of NaCl and protein

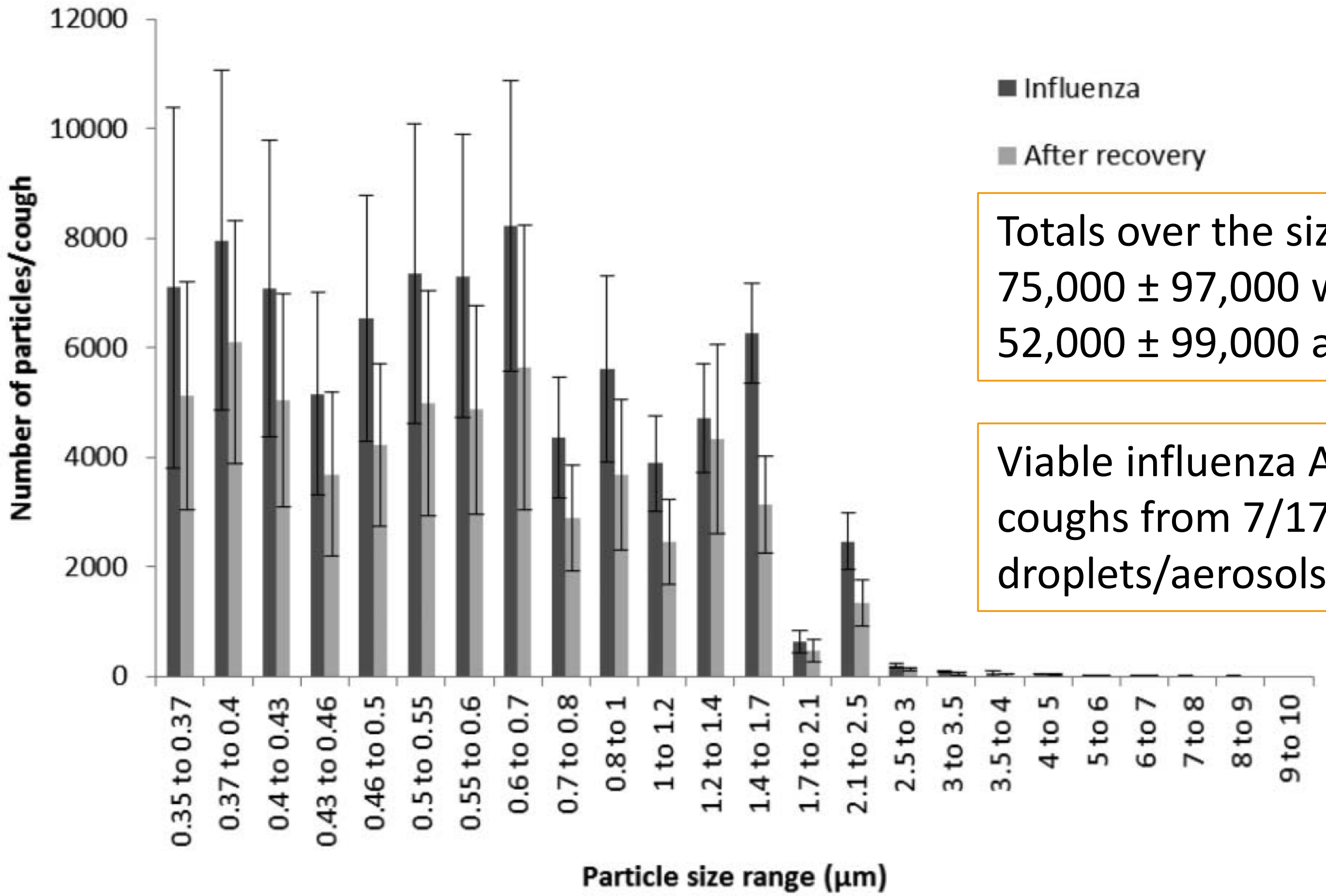
$$RH = \frac{p_d}{p_{sat}} = \exp\left(\frac{4M_w\sigma_w}{RT\rho_w d}\right)\exp\left(-\frac{6n_s v_w}{\pi d^3}\right)$$

(1) Mikhailov, E., Vlasenko, S., Niessner, R., et al., 2004, Interaction of aerosol particles composed of protein and salts with water vapor: hygroscopic growth and microstructural rearrangement, *Atmos Chem Phys* (2) Marr, L.C., Tang, J.W., Van Mullekom, J., et al., 2019, Mechanistic insights into the effect of humidity on airborne influenza virus survival, transmission and incidence, *J Roy Soc Interface*

Droplets >5 μm can travel more than 2 meters, and humidity affects size and chemistry.

How do they get into the air in the first place?

Coughing Produces Aerosols

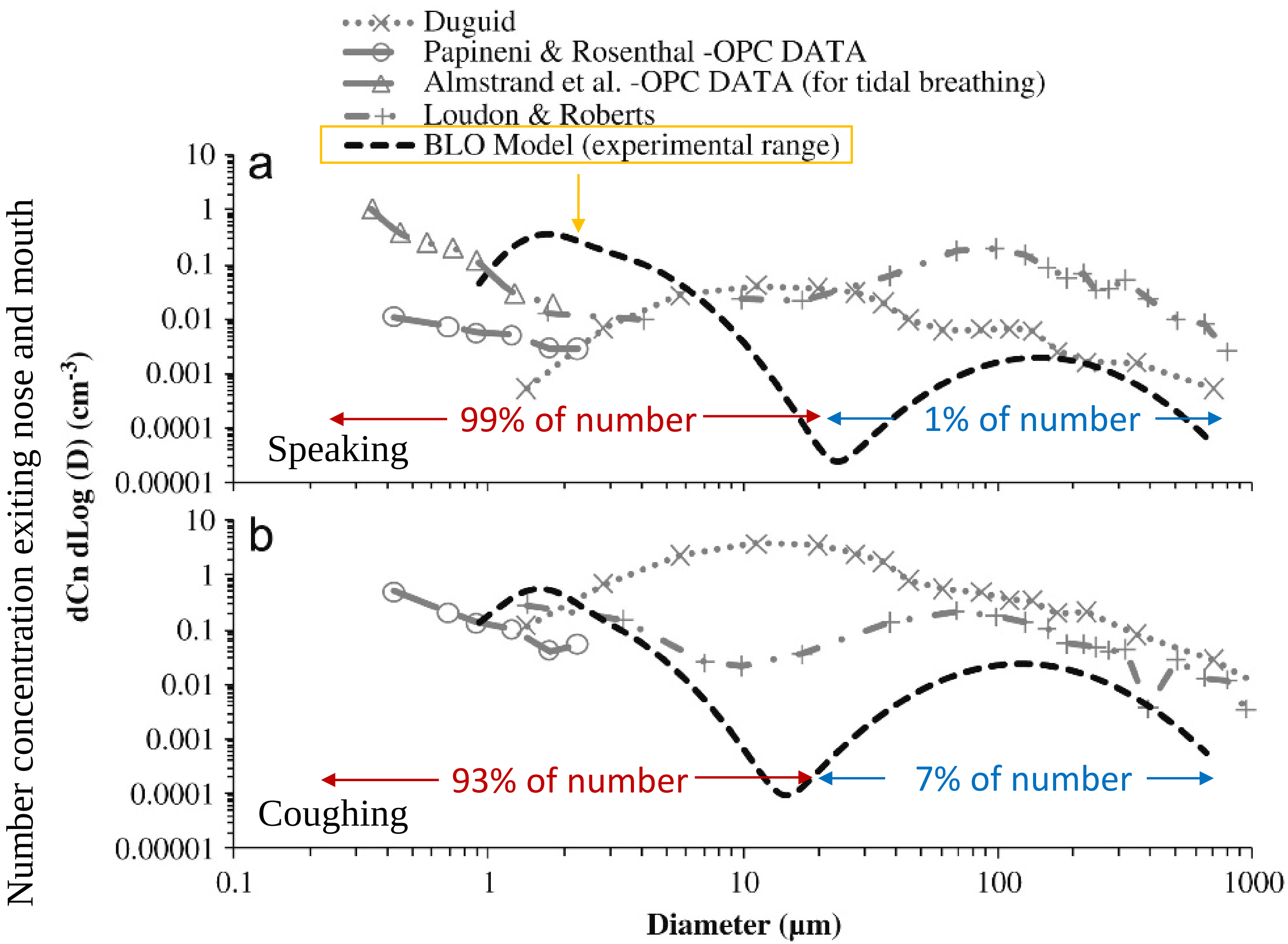


Totals over the size range 0.35-10 µm:
75,000 ± 97,000 when sick
52,000 ± 99,000 after recovery

Viable influenza A virus was found in coughs from 7/17 subjects, in droplets/aerosols 0.3-8 µm

(1) Lindsley, W.G., Pearce, T.A., Hudnall, J.B., et al., 2012, Quantity and size distribution of cough-generated aerosol particles produced by influenza patients during and after illness, *J Occup Environ Hyg* (2) Lindsley, W.G., Noti, J.D., Blachere, F.M., et al., 2015, Viable influenza A virus in airborne particles from human coughs , *J Occup Environ Hyg*

Speaking Produces Aerosols



5 nl and 30 viral RNA copies from saying "Hello, World!"

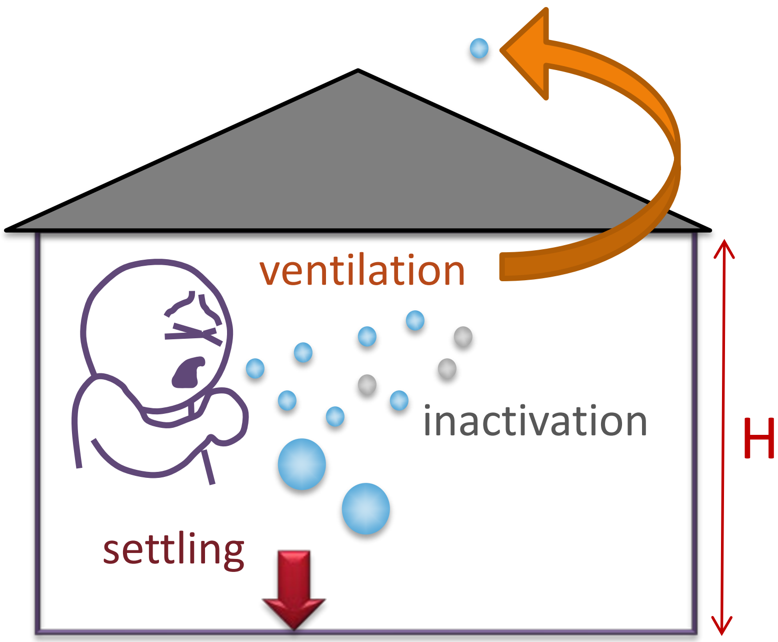
125 nl and 900 viral RNA copies from one cough

(1) Johnson, G.R., Morawska, L., Ristovski, Z.D., et al., 2011, Modality of human expired aerosol size distributions, *J Aerosol Sci*, 42, 839-851 (2) Wölfel, R., Corman, V.M., Guggemos, W., et al., 2020, Virological assessment of hospitalized patients with COVID-2019, *Nature*

Breathing, talking, and coughing release droplets and aerosols that range from submicron to millimeter in size. They may contain virus.

What happens to them in the air?

Virus Removal in Indoor Air



settling ventilation (air-exchange) inactivation

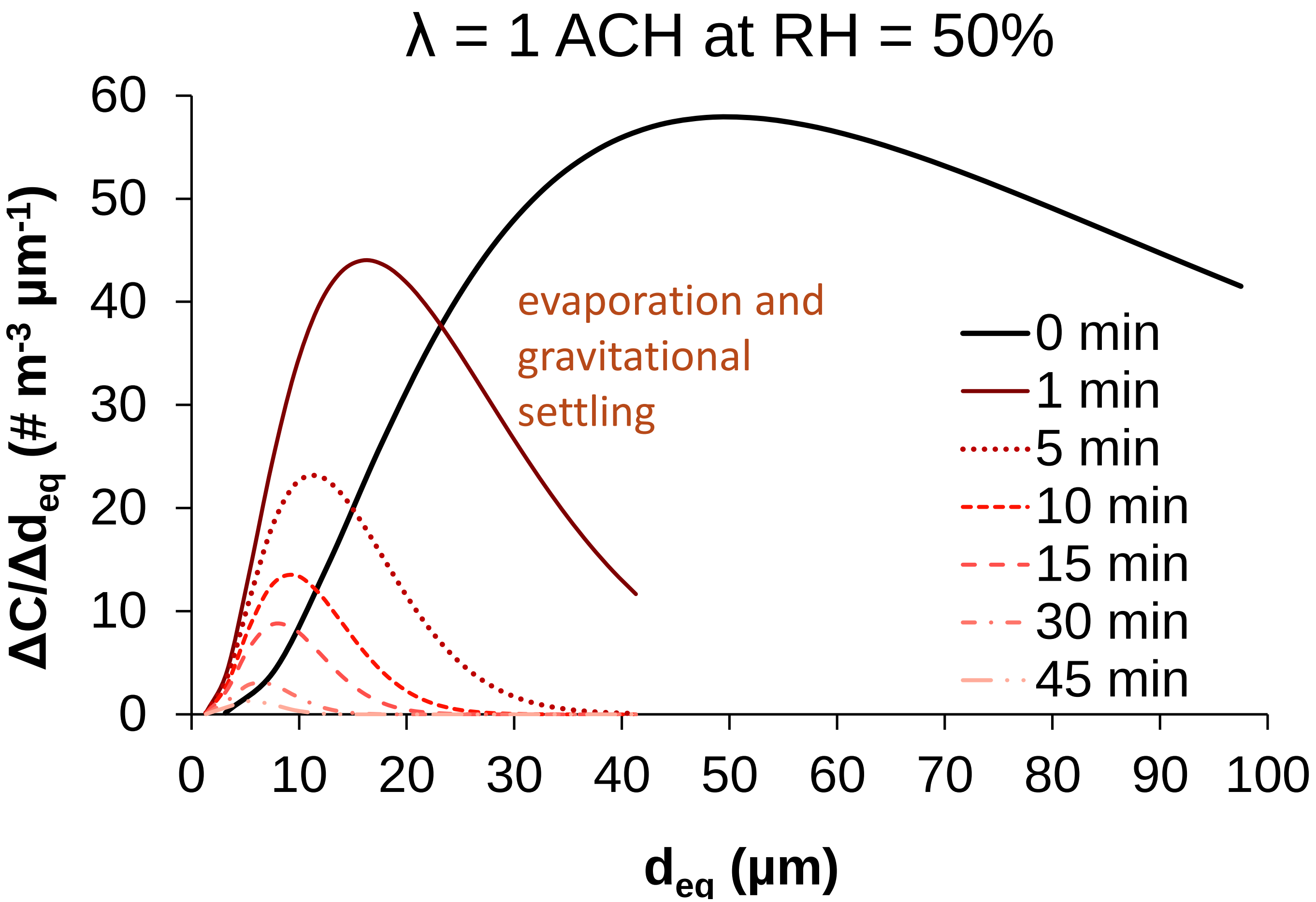
$$\frac{dC_d}{dt} = -\left(\frac{v}{H} + \lambda + k\right)C_d$$

↑

concentration of infectious virus in droplets/aerosols of <u>diameter *d*</u>

(1) Yang, W., Marr, L.C., 2011, Dynamics of airborne influenza A viruses indoors and dependence on humidity, *Plos One* (2) Nazaroff, W.W., 2016, Indoor bioaerosol dynamics, *Indoor Air*

Dynamics of Virus in Air

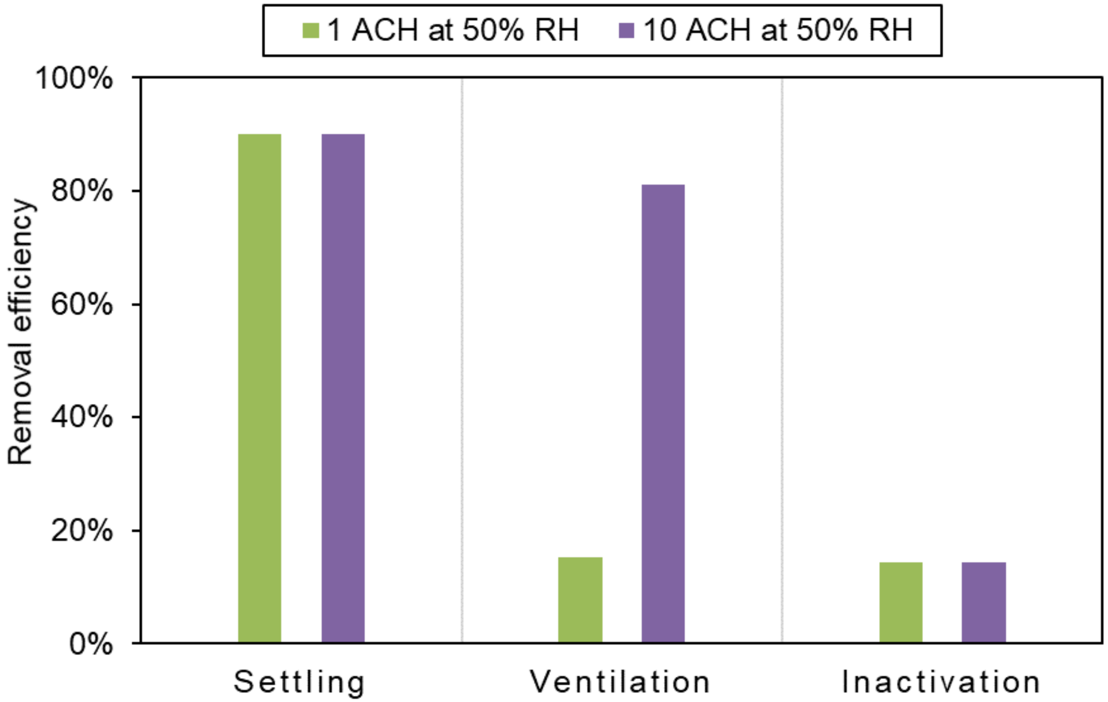


There is a size shift due to loss of larger droplets by gravitational settling.

(1) Yang, W., Marr, L.C., 2011, Dynamics of airborne influenza A viruses indoors and dependence on humidity, *Plos One*

Removal Mechanisms

- Settling: main removal mechanism, efficient for large but not small droplets
- Ventilation: effective for all sizes, important in public buildings
- Inactivation: depends on the virus, may depend on humidity

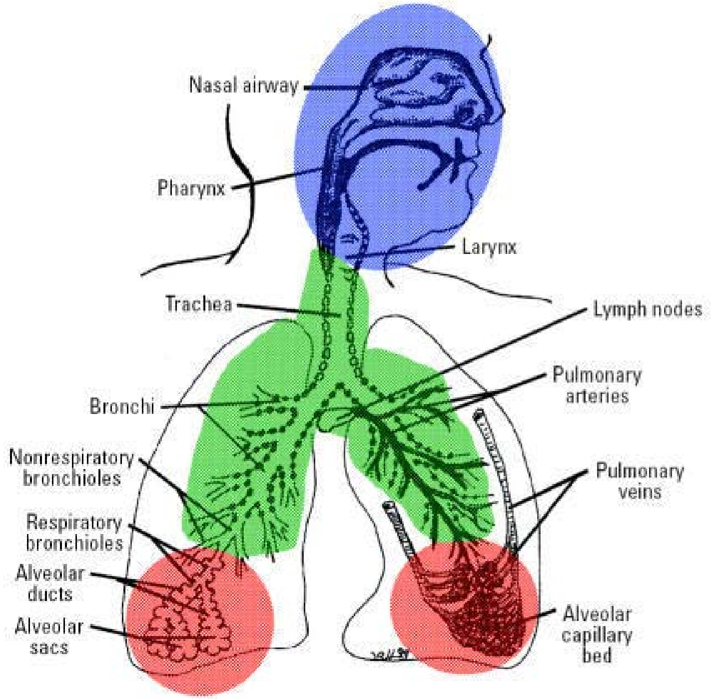


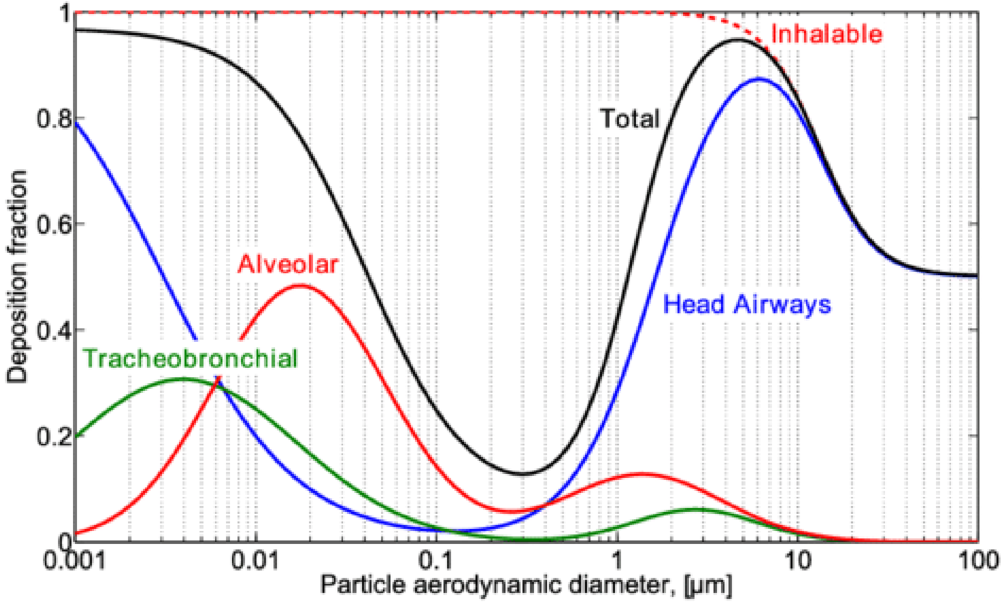
(1) Yang, W., Marr, L.C., 2011, Dynamics of airborne influenza A viruses indoors and dependence on humidity, *Plos One*, 6, e21481 (2) Kormuth, K.A., Lin, K., Prussin II, A.J., et al., 2018, Influenza virus infectivity is retained in aerosols and droplets independent of relative humidity, *J Infect Dis* (3) Kormuth, K.A., Lin, K., Qian, Z., et al., 2019, Environmental persistence of influenza viruses is dependent upon virus type and host origin, *mSphere*

Viruses can be removed from indoor air by settling, ventilation, and inactivation.

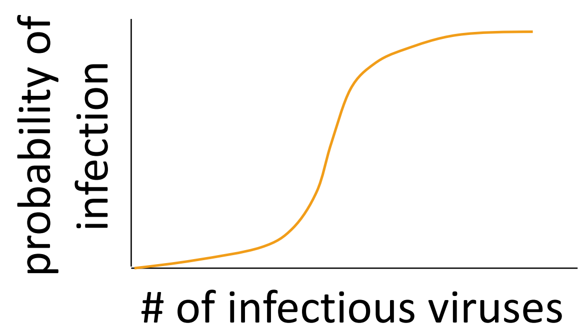
What happens if we breathe them in?

Deposition and Dose





Dose-response curve

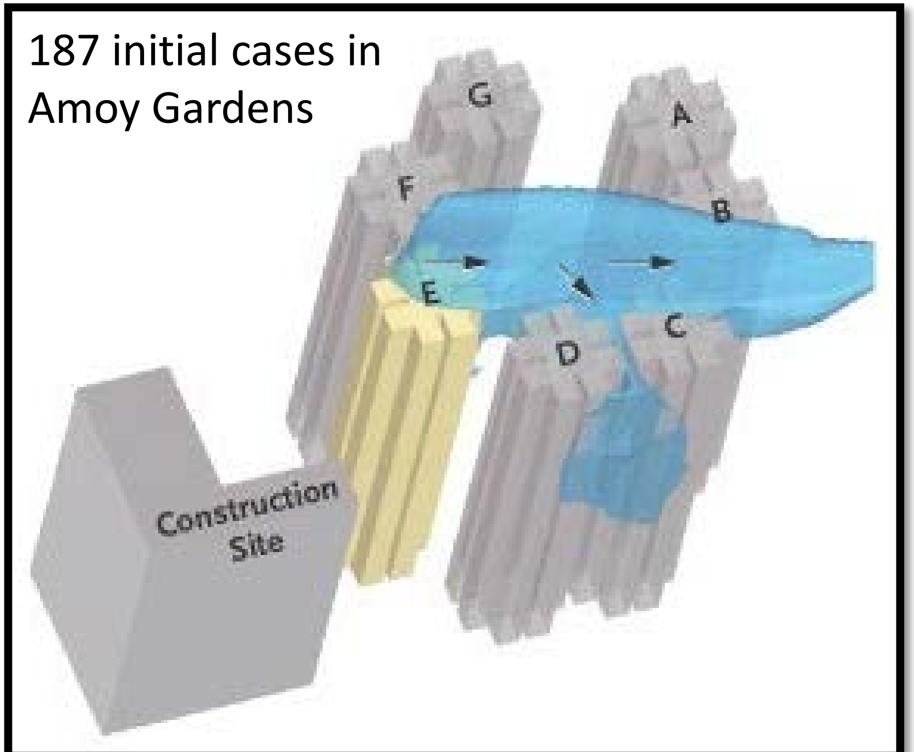


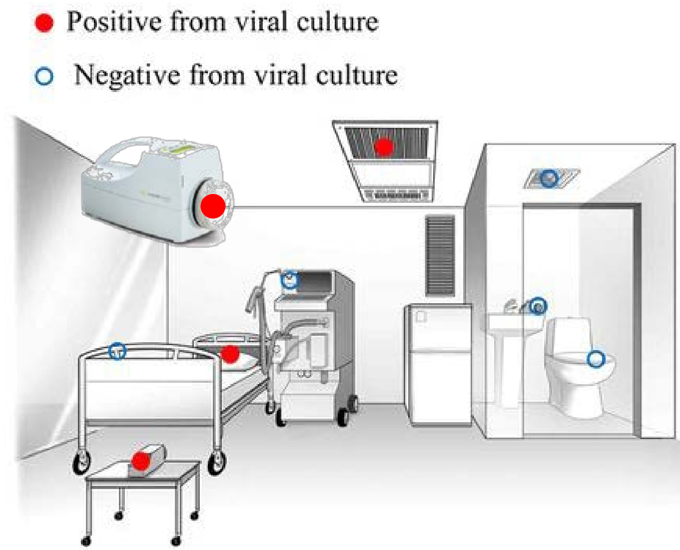
(1) Oberdörster, G., Oberdörster, E., Oberdörster, J., 2005, Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles, *Environ Health Persp*, 113, 823-839 (2) Kovisto, A.J., 2013, Source specific risk assessment of indoor aerosol particles, Ph.D. dissertation (3) Watanabe, T., Bartrand, T.A., Weir, M.H., et al., 2010, Development of a Dose-Response Model for SARS Coronavirus, *Risk Anal*

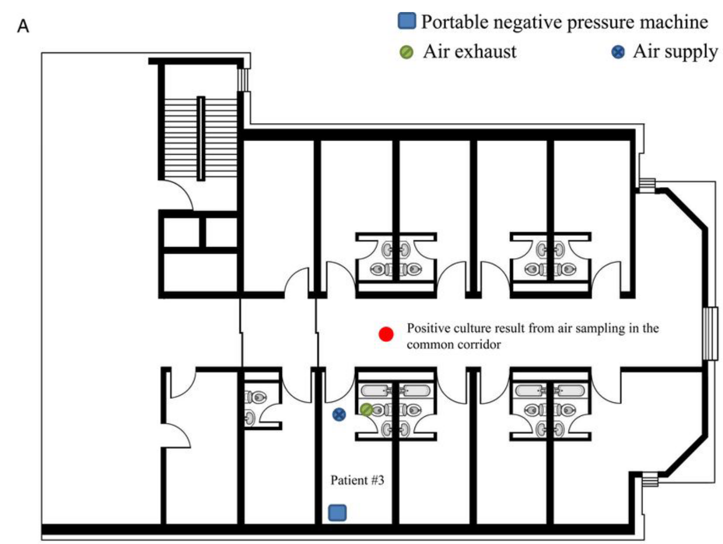
Viruses can deposit in different parts of the respiratory system, depending on the size of the carrier aerosol.

What do we know about SARS-CoV-2?

SARS and MERS



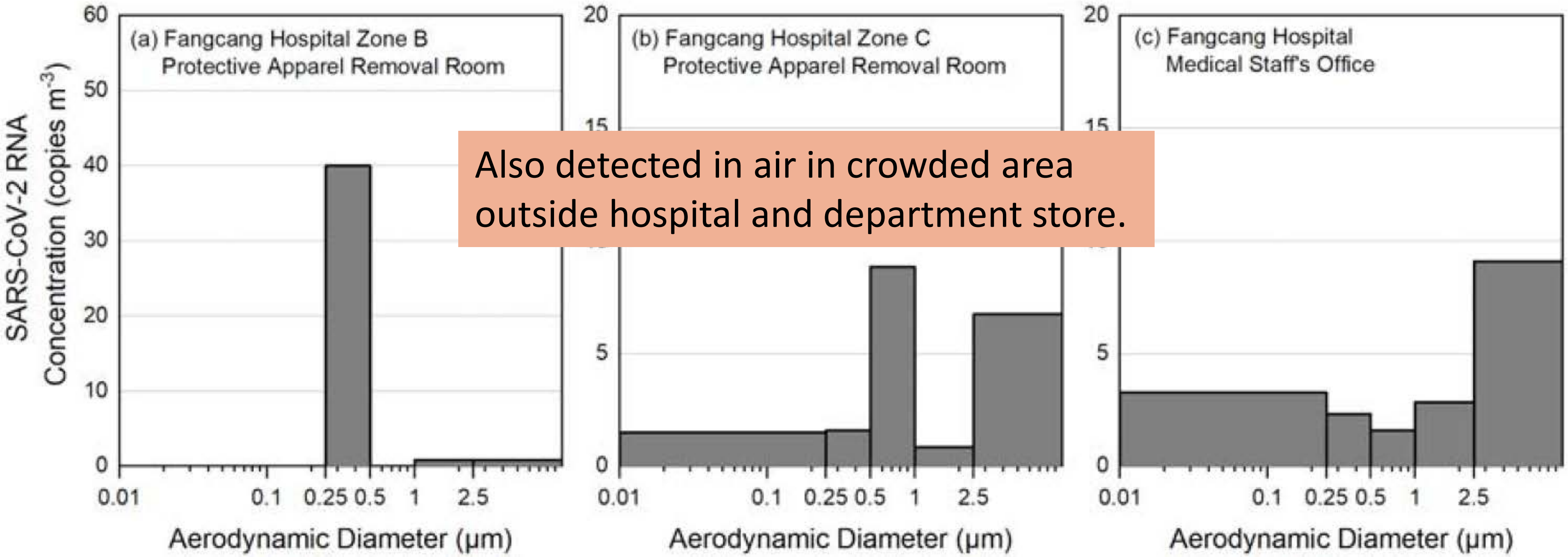




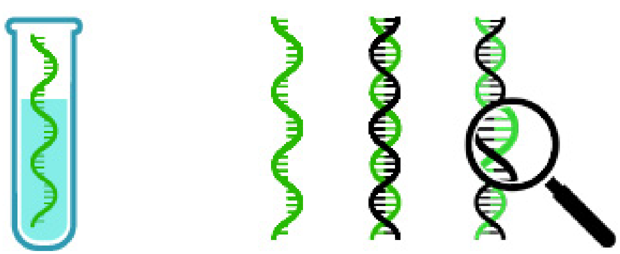
"fear of panic and political blame led to the reluctance of various health authorities in admitting airborne spread of SARS in the community" (2)

(1) Yu, I.T., Li, Y., Wong, T.W., et al., 2004, Evidence of airborne transmission of the severe acute respiratory syndrome virus, *N Engl J Med*, 350, 1731-1739 (2) Yu, I.T.-S., Qiu, H., Tse, L.A., et al., 2013, Severe Acute Respiratory Syndrome Beyond Amoy Gardens: Completing the Incomplete Legacy, *Clin Infect Dis*, 58, 683-686 (3) Kim, S.-H., Chang, S.Y., Sung, M., et al., 2016, Extensive Viable Middle East Respiratory Syndrome (MERS) Coronavirus Contamination in Air and Surrounding Environment in MERS Isolation Wards, *Clin Infect Dis*, 63, 363-369

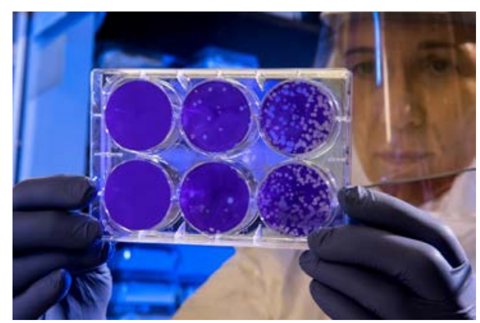
SARS-CoV-2 in Aerosols by Size



Also detected in air in crowded area outside hospital and department store.



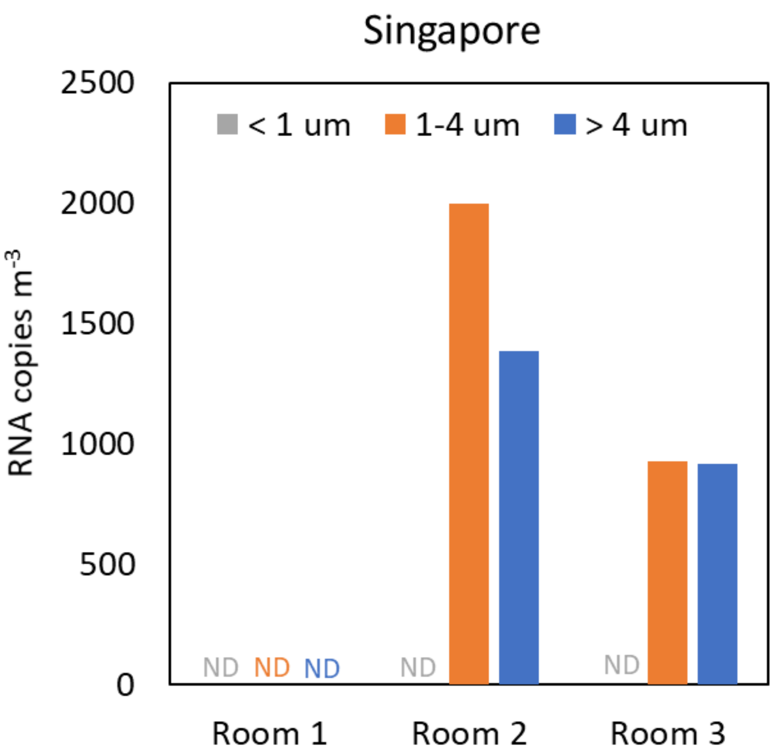
viral RNA gene copies

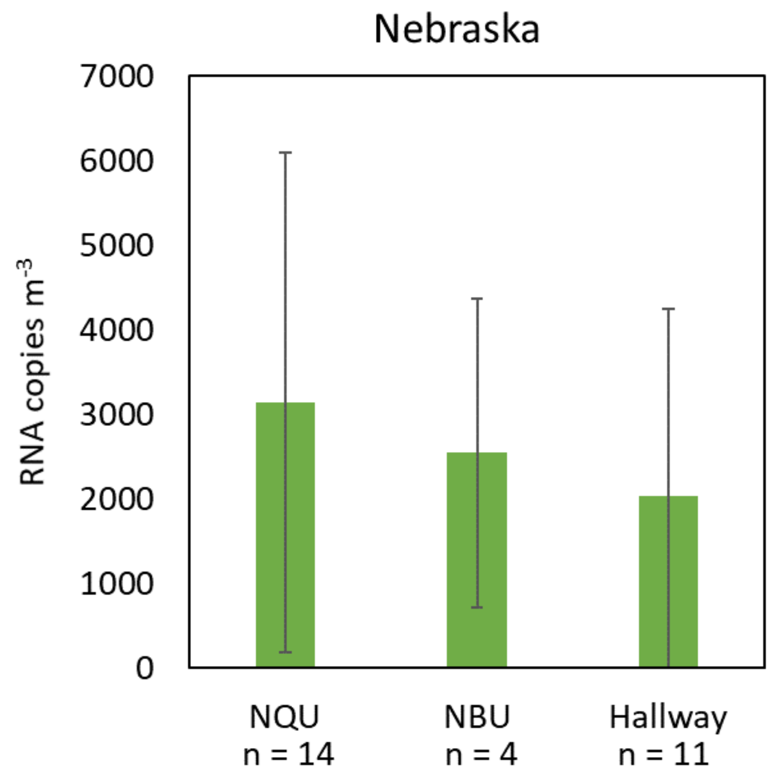


culture for infectious virus

(1) Liu, Y., Ning, Z., Chen, Y., et al., 2020, Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals, *Nature*

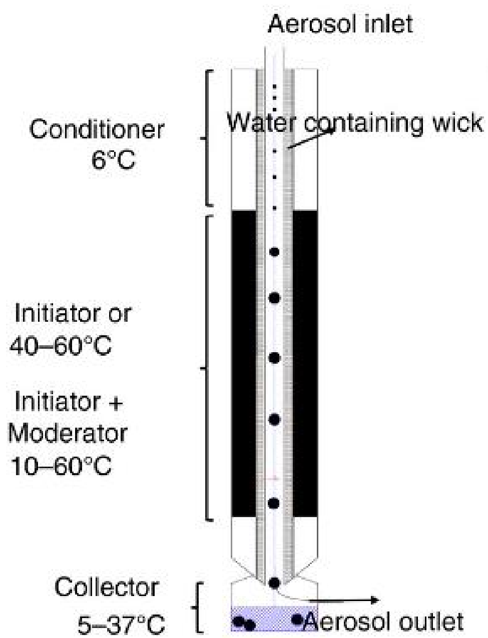
SARS-CoV-2 in Air Samples



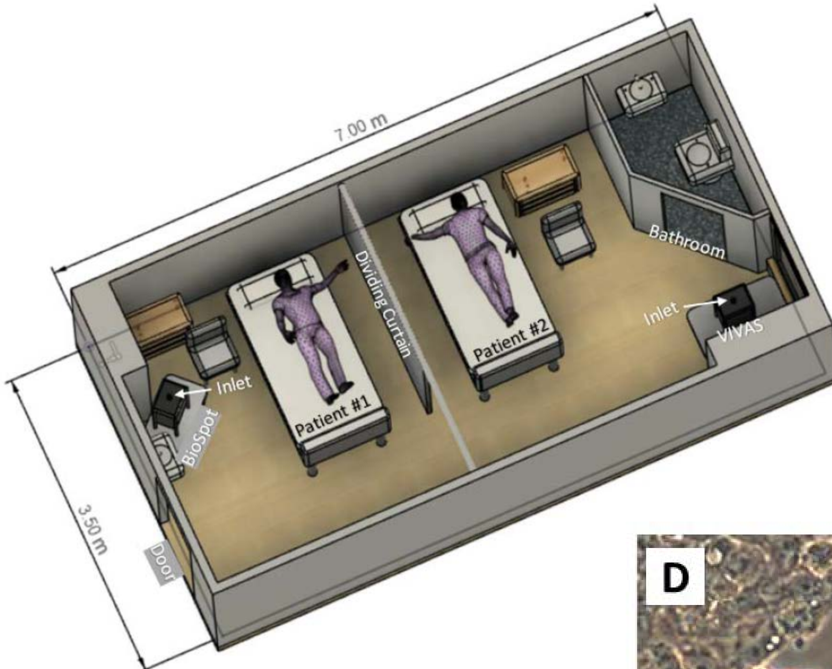


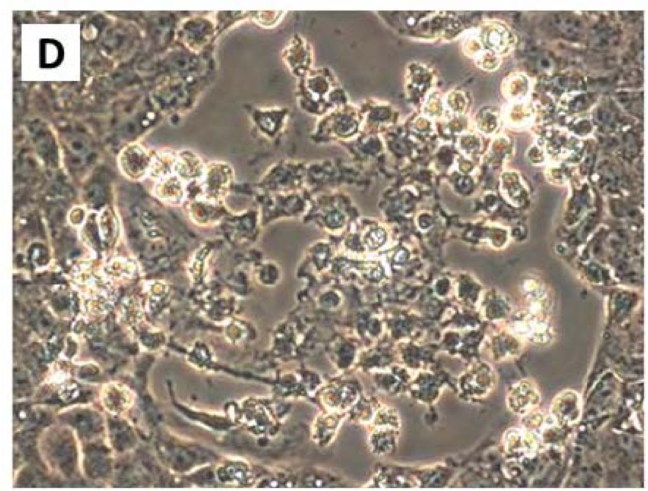
(1) Chia, P.Y., Coleman, K.K., Tan, Y.K., et al., 2020, Detection of air and surface contamination by SARS-CoV-2 in hospital rooms of infected patients, *Nature Comm* (2) Santarpia, J.L., Rivera, D.N., Herrera, V.L., et al., 2020, Aerosol and surface contamination of SARS-CoV-2 observed in quarantine and isolation care, *Sci Rep*

Infectious SARS-CoV-2 in Aerosols



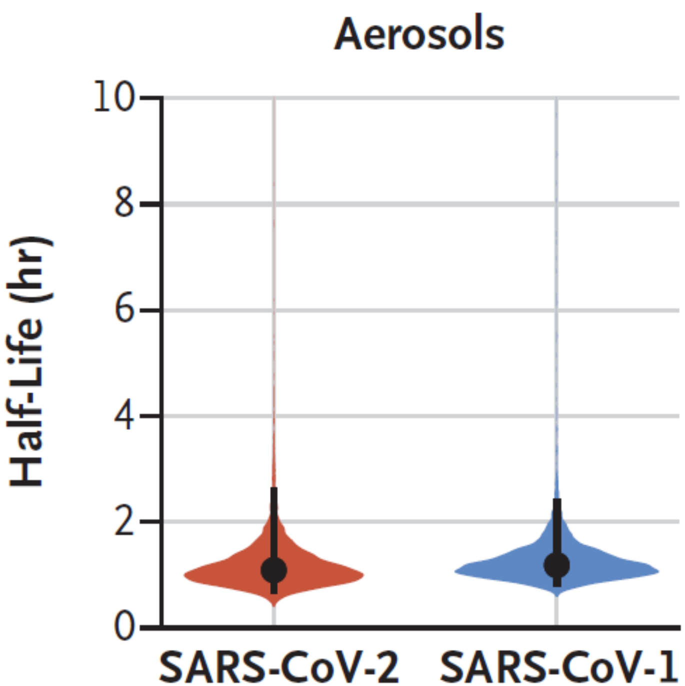
Water-based growth tube collector

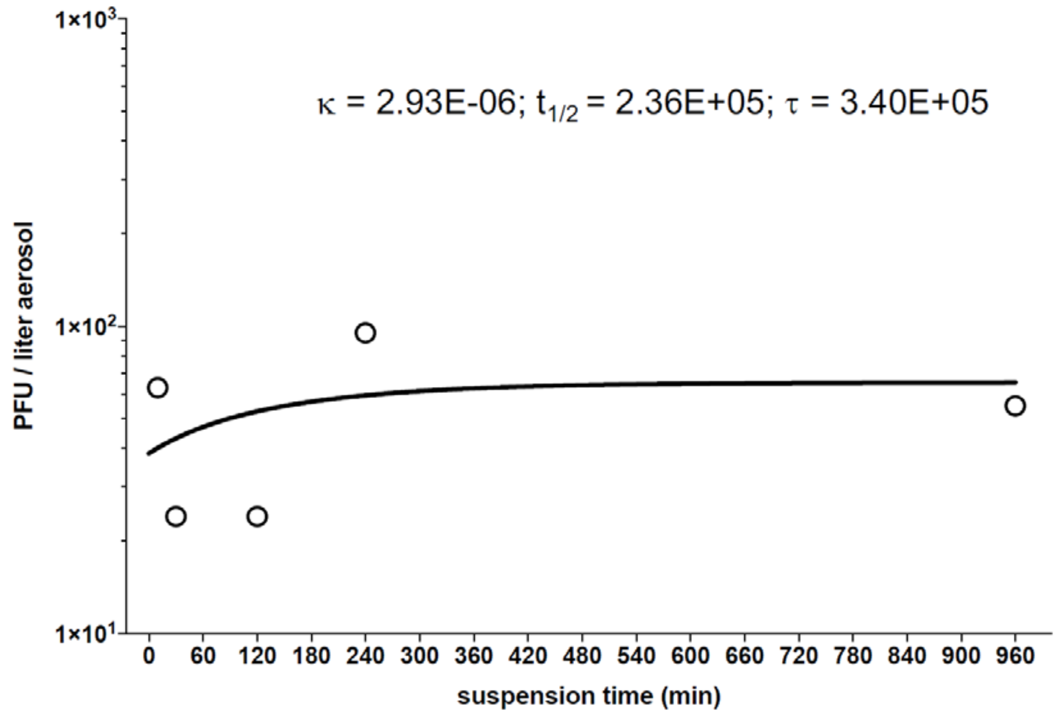




(1) Lednicky, J.A., Lauzardo, M., Fan, Z.H., et al., 2020, Viable SARS-CoV-2 in the air of a hospital room with COVID-19 patients, *medRxiv* (2) Pan, M., Lednicky, J.A., Wu, C.-Y., 2019, Collection, particle sizing and detection of airborne viruses, *J Appl Microbiol*

SARS-CoV-2 Survival in Aerosols



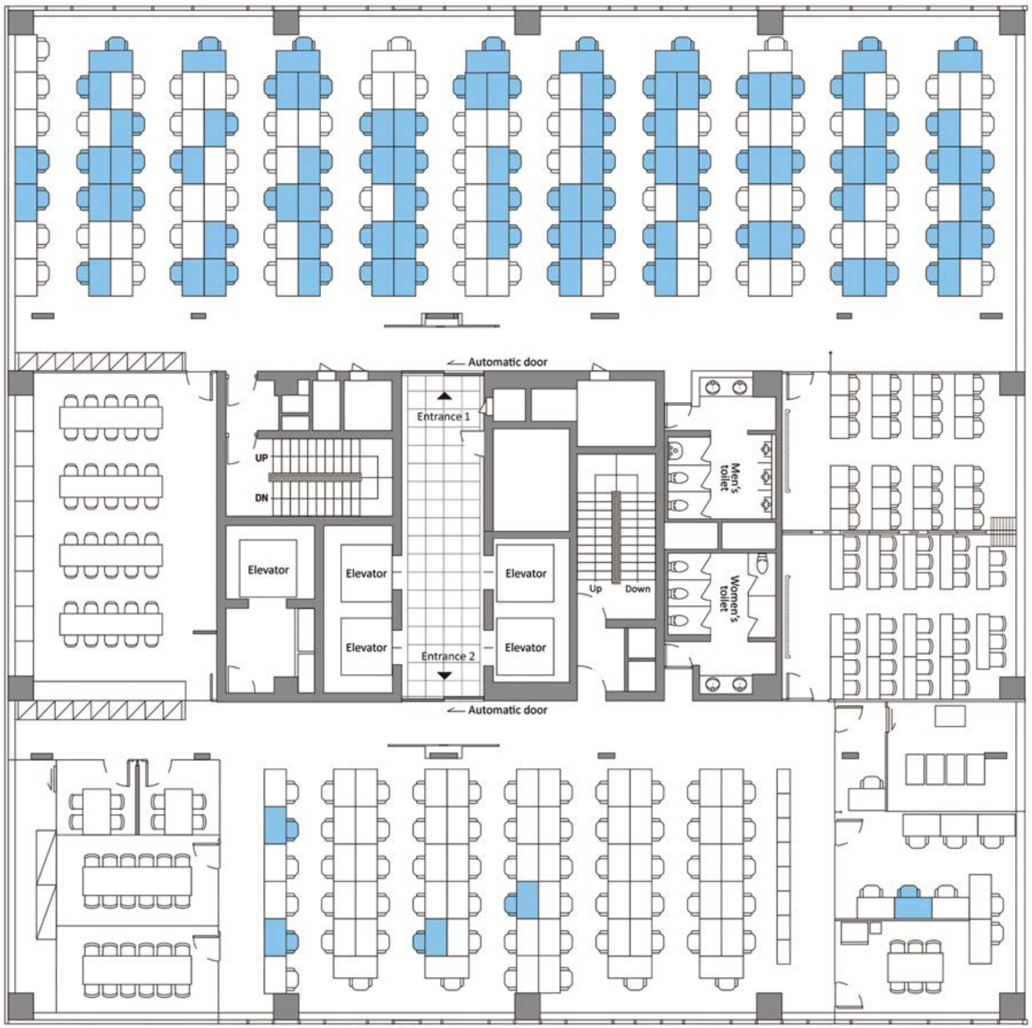


Half-life is 1.1 hours at 65% RH

Virus survives 16 hours at 53% RH

(1) van Doremalen, N., Bushmaker, T., Morris, D.H., et al., 2020, Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1, *New Engl J of Med*, 382, 1564-1567 (2) Fears, A.C., Klimstra, W.B., Duprex, P., et al., 2020, Persistence of Severe Acute Respiratory Syndrome Coronavirus 2 in aerosol suspensions, *Emerging Infect Dis*

Outbreaks Implicate Aerosols

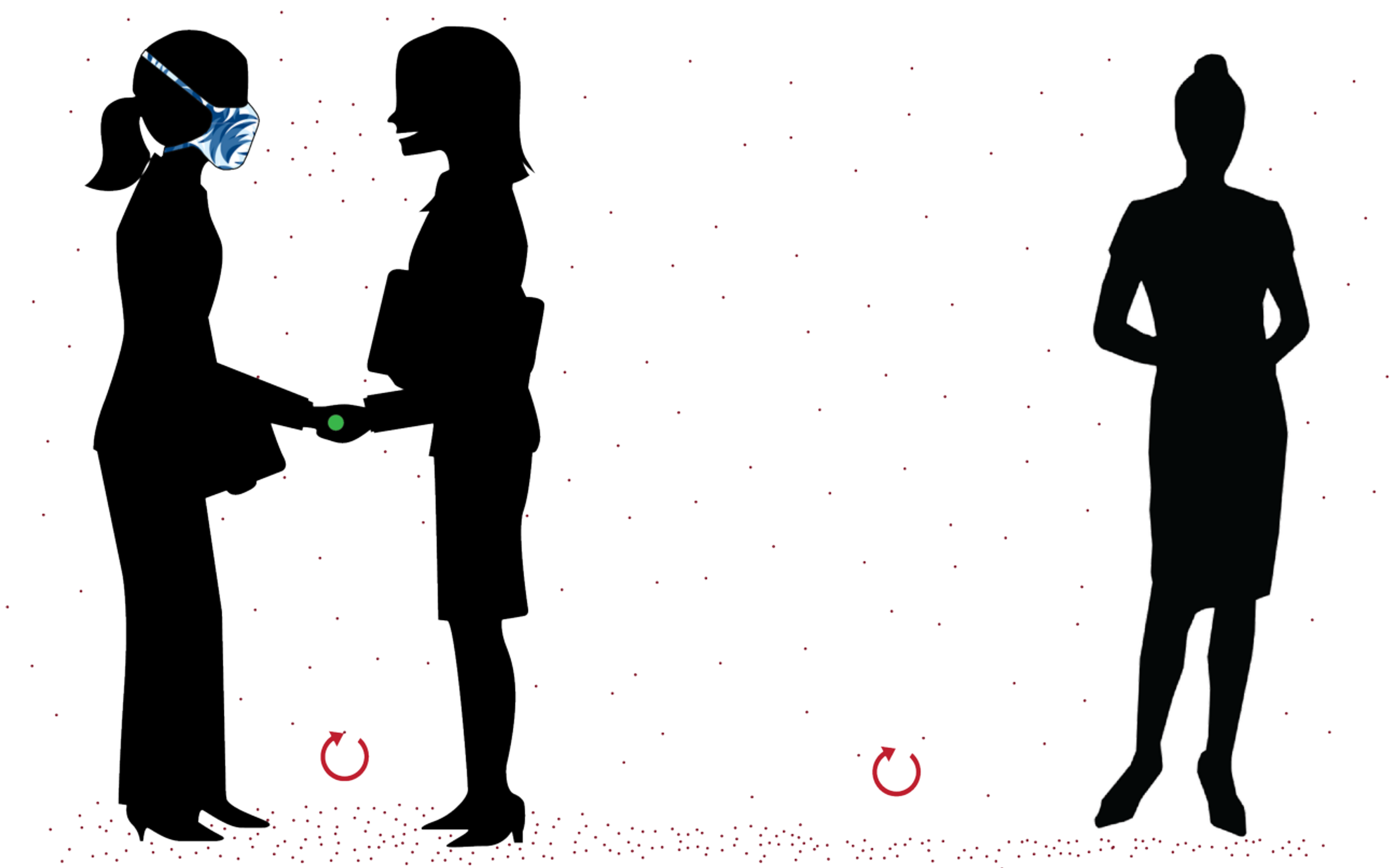


- Harder to explain by other routes of transmission
- Commonalities of many super-spreading events
  - Crowded
  - Vocalization
  - Insufficient ventilation
  - No masks

(1) Park, S.Y., Kim, Y.-M., Yi, S., et al., 2020, Coronavirus Disease Outbreak in Call Center, South Korea, *Emerg Infect Dis*

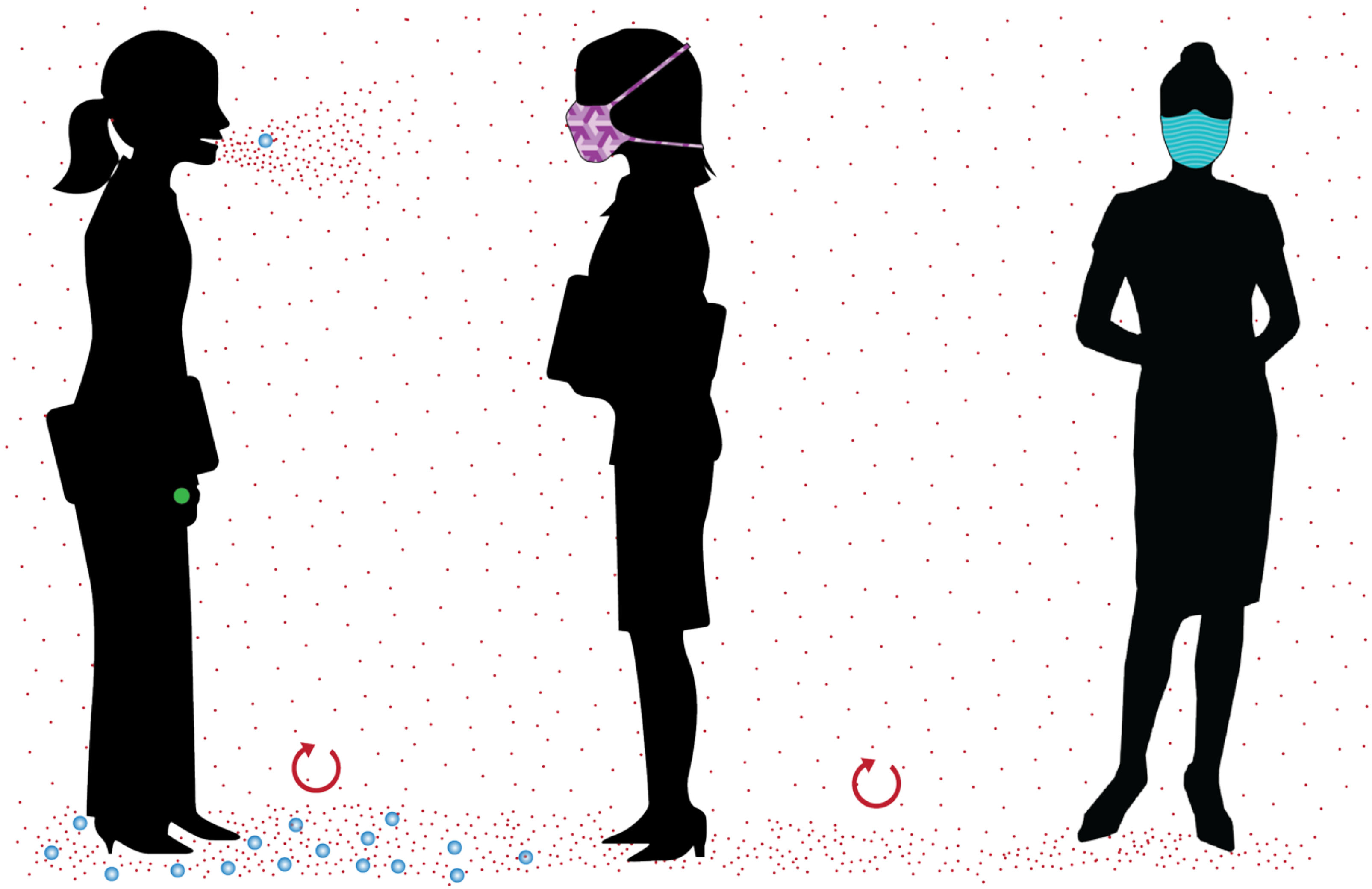
Interventions

1. Source control



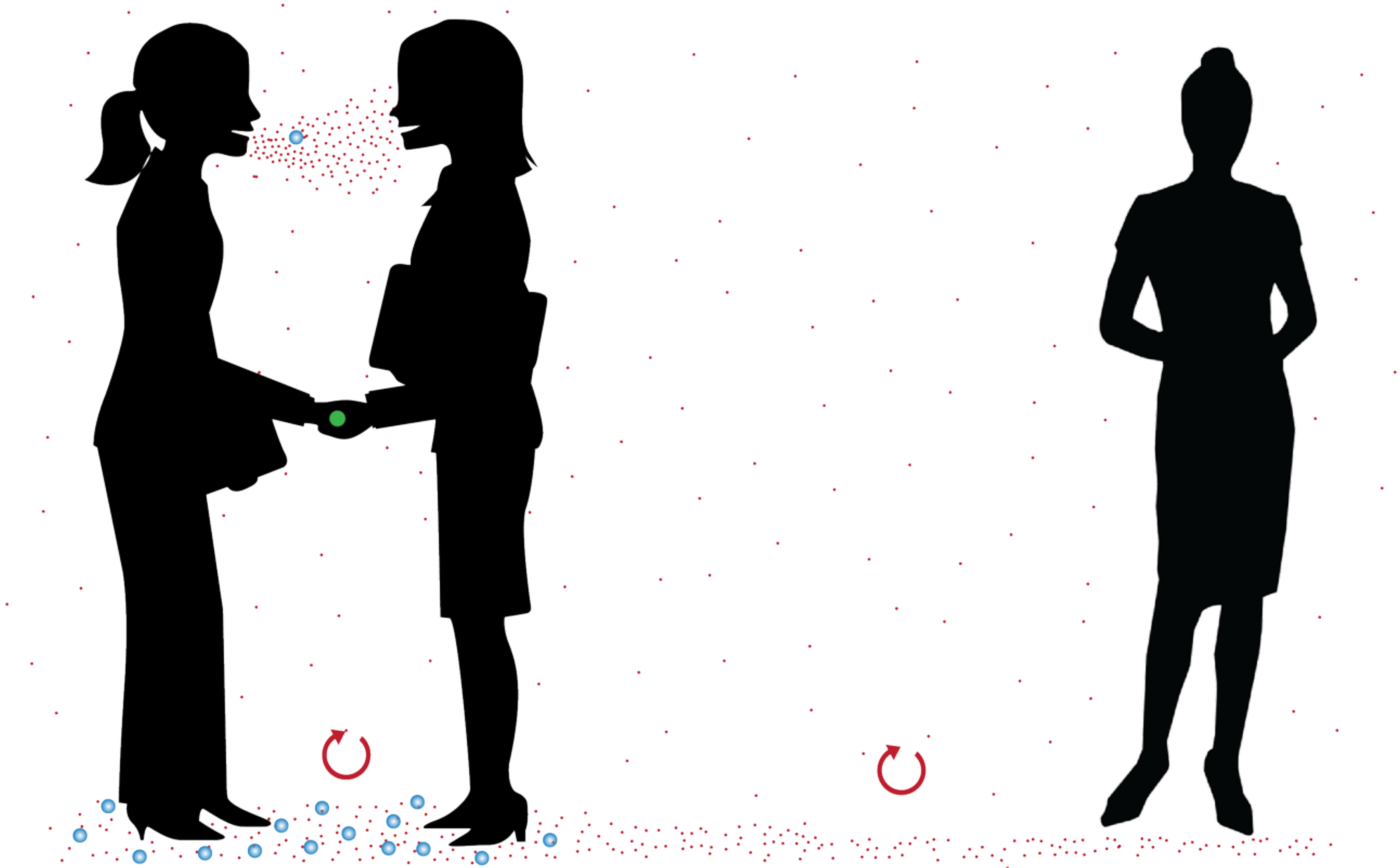
Interventions

2. Distance and PPE



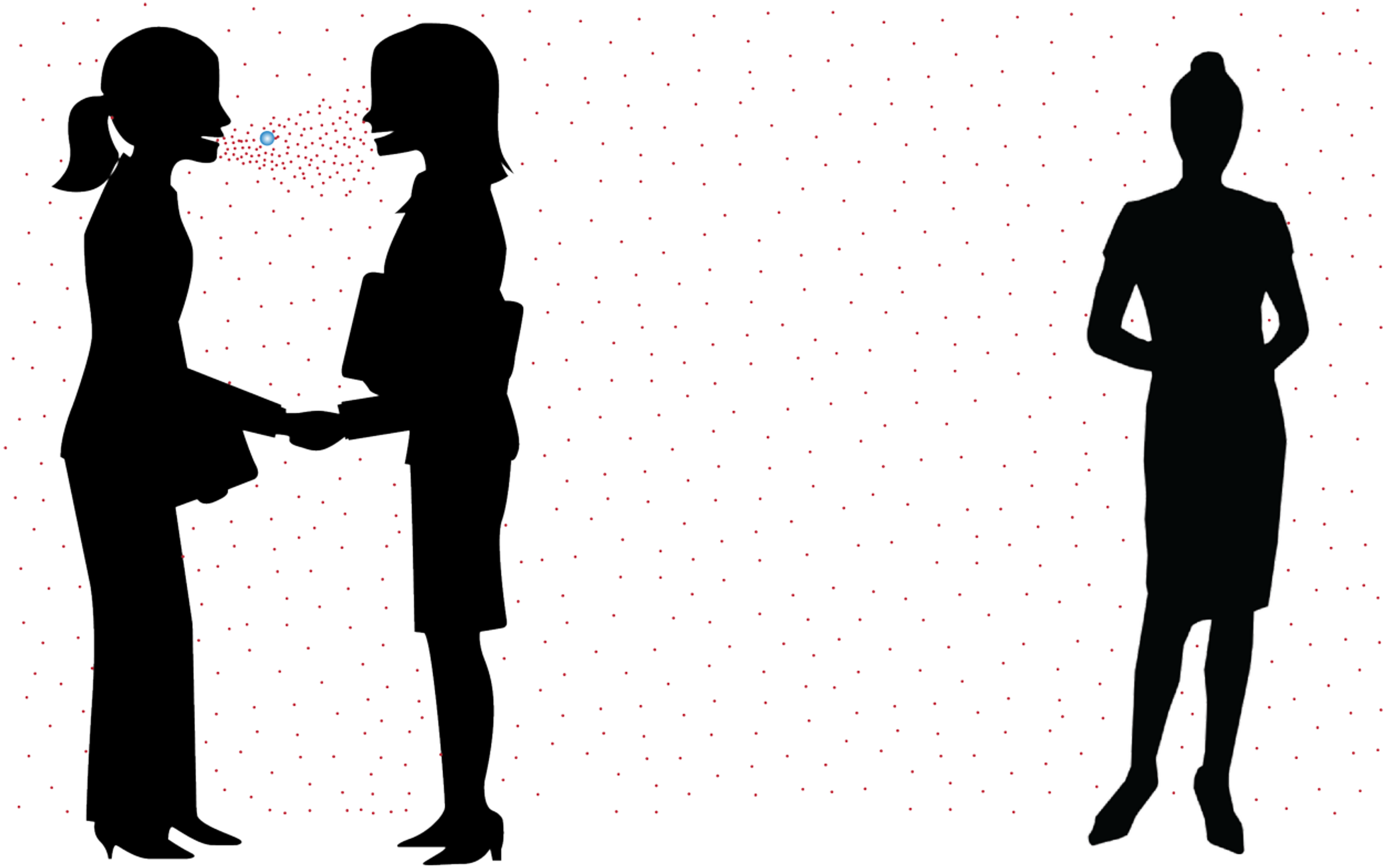
Interventions

3. Ventilation and filtration



Interventions

4. Hygiene



Interventions

1. Source control 2. Distance and PPE 3. Ventilation and filtration 4. Hygiene

Summary

- Breathing, talking, coughing, and other activities produce ~100x more aerosols than large droplets.
- Aerosols may contain infectious viruses that remain suspended in air for hours and can be transported many meters from the source.
- For SARS-CoV-2 and asymptomatic hosts, the aerosol route is especially important in conversation at close distances and in crowded, poorly ventilated rooms.

(1) Allen, J.G., Marr, L.C., 2020, Recognizing and controlling airborne transmission of SARS-CoV-2 in indoor environments, *Indoor Air* (2) Fennelly, K.P., 2020, Particle sizes of infectious aerosols: implications for infection control, *Lancet Resp Med* (3) Morawska, L., Milton, D.K., 2020, It is time to address airborne transmission of COVID-19, *Clin Infect Dis* (4) Prather, K.A., Wang, C.C., Schooley, R.T., 2020, Reducing transmission of SARS-CoV-2, *Science* (5) Wilson, N., Corbett, S., Tovey, E., 2020, Airborne transmission of covid-19, *BMJ*