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OPTIONS IX *for* THE CONTROL OF INFLUENZA

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Exposure to Influenza in the Healthcare Environment

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I have financial relationship(s) with:
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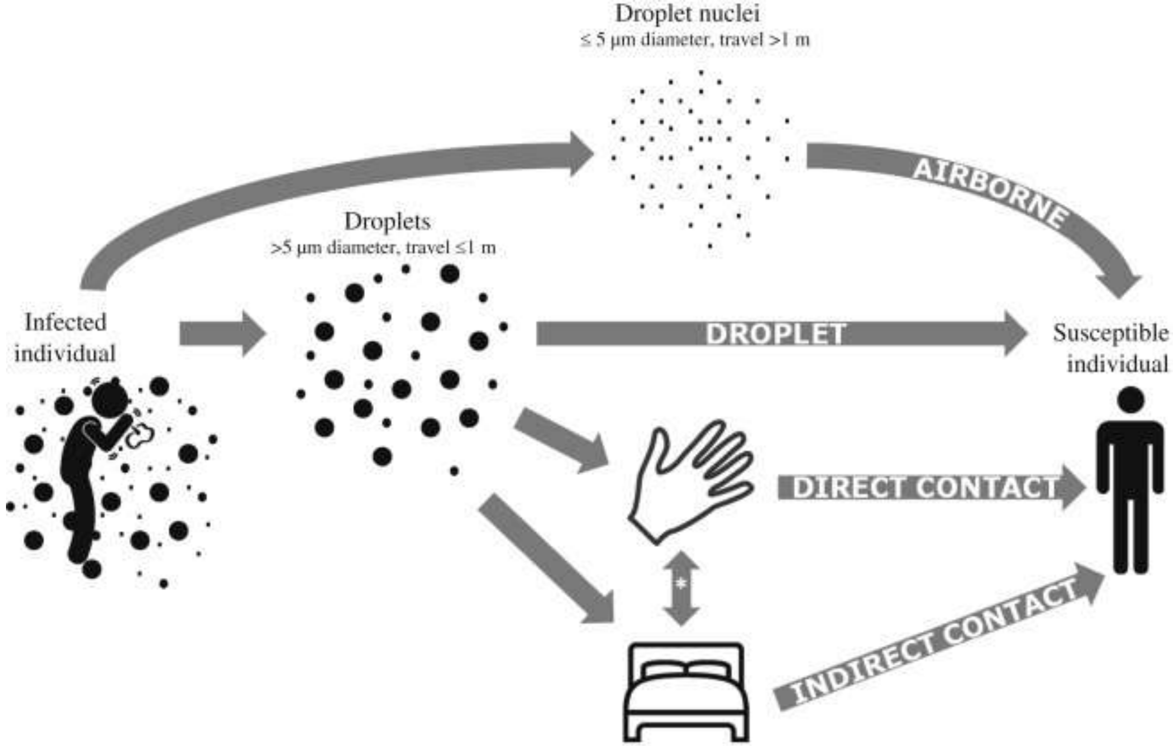
Background

- Millions have lost their lives to influenza in pandemics
- Epidemics of varying severity occur worldwide each year.
- Novel Influenza strains are the latest threats
- Current Recommendations (CDC, WHO):
  - Droplet/Contact Precautions since Influenza transmission has been thought to primarily occur by large-particle respiratory droplets.
  - Only during aerosol-generating procedures such as bronchoscopies are fit-tested respirators required.
  - New Influenza Strains – airborne plus contact plus eye-protection

Influenza Transmission



* Transmission routes involving a combination of hand & surface = indirect contact.

Transmission routes: droplet, airborne, direct contact, and indirect contact.[1]

1. Otter JA et al. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination. Journal of Hospital Infection, Volume 92, Issue 3, 2016, 235–250

Exposure Factors

Environmental Conditions:
- Temperature, Humidity
- Seasonality
- Surface Materials (fomite survival)
- Settings: Indoor, Outdoor

Infector:
- Symptoms
- Infectious Heterogeneity
- Co-Infections
- Microbiome
- Social Interactions

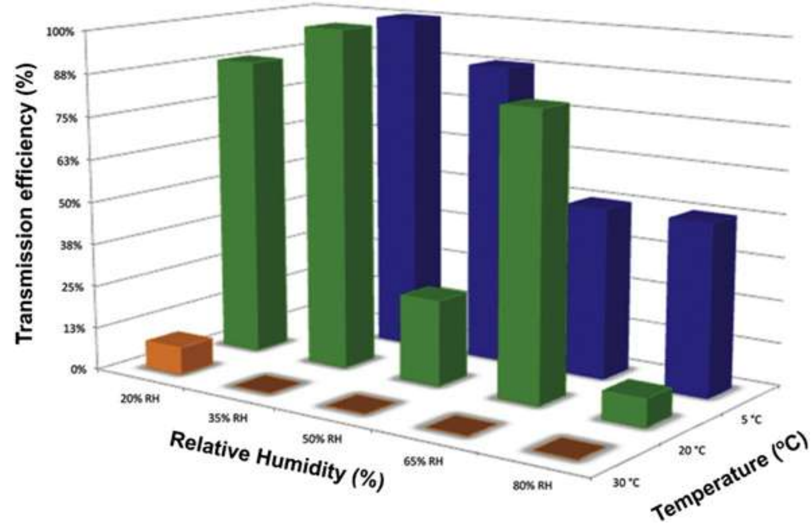
Infectee:
- Entry Route
- Co-Infections
- Microbiome
- Social Interactions
- Immunity

Viral Factors:
- Infectious Dosage
- Carrier Substrate (aerosols)

Modified after Killingley B, Nguyen-Van-Tam J. Routes of influenza transmission. Influenza Other Respir Viruses. 2013 Sep;7 Suppl 2:42-51.

Environmental Conditions

- Temperature/Humidity/Solar Irradiation/Air Exchange:
  - Cold, dry conditions appear to favor Influenza transmission[1,2]
  - High humidity leads to loss of infectious influenza virus from simulated coughs.[3]
  - Solar irradiation (Influenza infectivity reduction [log_{10}/day] summer = 4.9, winter 0.3 [Washington, DC])[4]
  - Air Exchange: dilution effect[5,6]

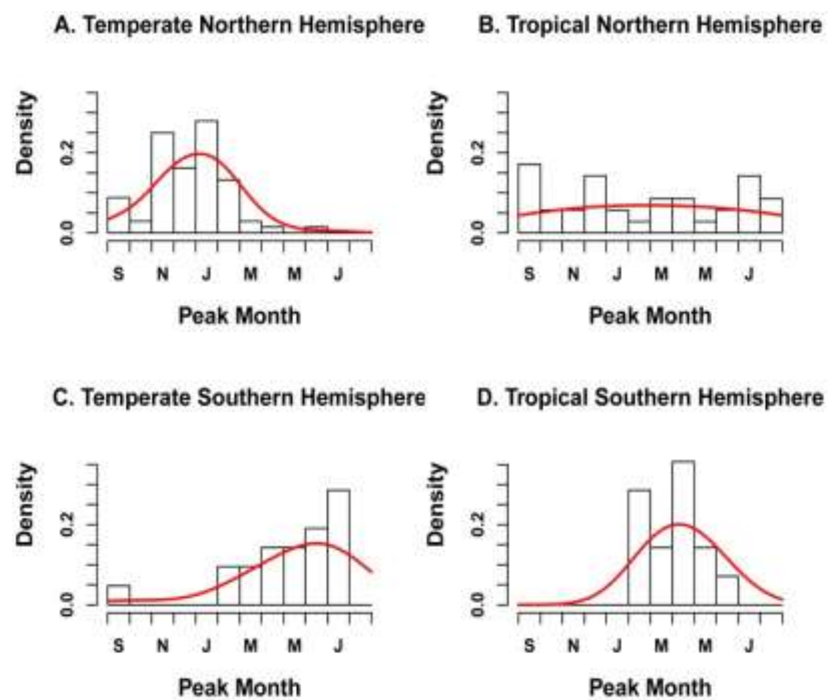


Transmission efficiency of influenza A/Panama/2007/1999 [H3N2], as a function of temperature and relative humidity, in the guinea pig model. Drawn from data presented in Lowen et al. (2007, 2008) and Steel et al. (2011).[2]

1. Lowen AC, Steel J. Roles of humidity and temperature in shaping influenza seasonality. J Virol 2014
2. Thangavel RR, Bouvier NM. Animal models for influenza virus pathogenesis, transmission, and immunology. J Immunol Methods. 2014 Apr 4. pii: S0022-1759(14)00112-4.
3. Noti JD et al. High humidity leads to loss of infectious influenza virus from simulated coughs. PLoS One. 2013;8(2):e57485.
4. Sagripanti JL, Lytle CD. Inactivation of influenza virus by solar radiation. Photochem Photobiol. 2007;83:1278-82
5. Nielsen PV. Control of airborne infectious diseases in ventilated spaces. J R Soc Interface. 2009 Dec 6;6 Suppl 6:S747-55.
6. Bunyan D, Ritchie L, Jenkins D, Coia JE. Respiratory and facial protection: a critical review of recent literature. J Hosp Infect. 2013;85:165-9.

Environmental Conditions

- Seasonality:
  - Seasonal changes in virus survival
  - Host susceptibility
  - Dehydration of mucus membranes
  - Vitamin D deficiency
  - Change in social behavior

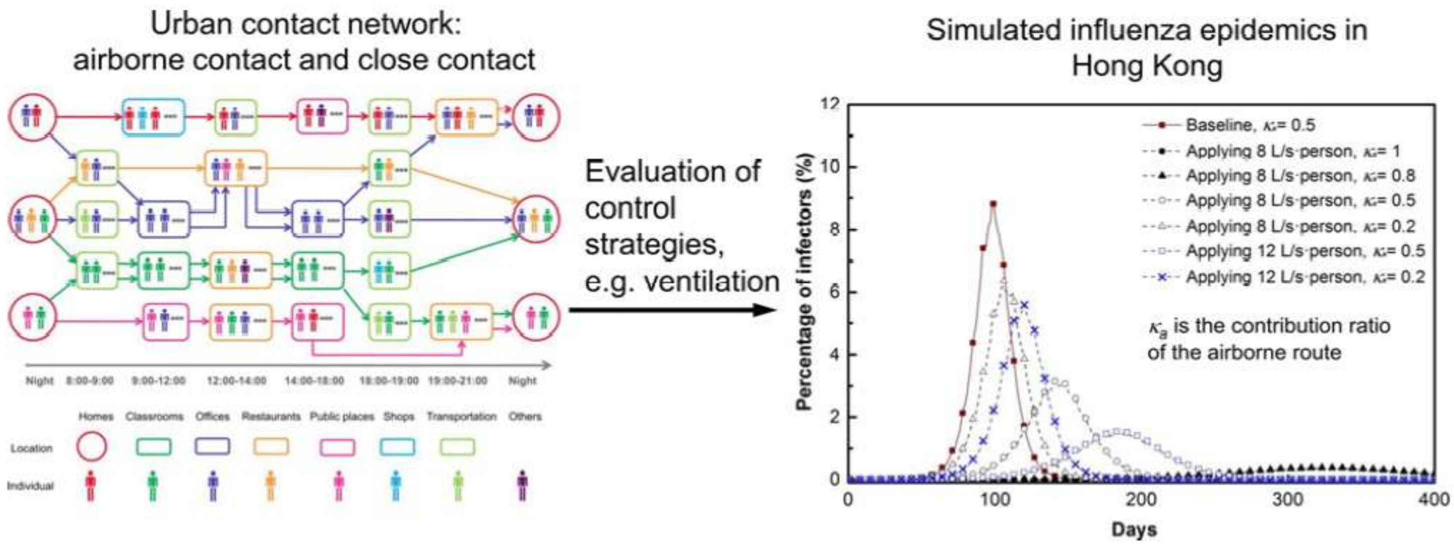


Distribution of influenza peak month by geographic zone (n=77 locations).[1]

1. Bloom-Feshbach K, et al. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PLoS One. 2013;8(2):e54445.

Environmental Conditions

- Setting:
  - Indoor: Crowding[1]; Ventilation rates[2]



rtions[2]

1. Rainey JJ et al. Mass Gatherings and Respiratory Disease Outbreaks in the United States - Should We Be Worried? Results from a Systematic Literature Review and Analysis of the National Outbreak Reporting System. PLoS One. 2016 Aug 18;11(8):e0160378. doi: 10.1371/journal.pone.0160378.
2. Gao X et al. Potential impact of a ventilation intervention for influenza in the context of a dense indoor contact network in Hong Kong. Sci Total Environ. 2016 Nov 1;569-570:373-81. doi: 10.1016/j.scitotenv.2016.06.179.

Environmental Conditions

- Surface Materials – Fomites (Contact Transmission):
  - Duration of infectivity porous (fabric) vs. non-porous (non-fabric)[1-3]:

Pathogen	Porous	Non-Porous
Influenza	8-12 hrs	7 days
RSV	Up to 1 hrs	6 hrs
Parainfluenza	4 hrs	10 hrs

  - No detectable contamination of environment by Influenza positive patients.[4]
  - Ferret Model: '*From animals with a mixed infection of viruses that were resistant and sensitive to the antiviral drug oseltamivir, resistance was propagated through contact transmission but not by air.*'[5]

1. Perry KA, et al. Persistence of Influenza A (H1N1) Virus on Stainless Steel Surfaces. Appl Environ Microbiol. 2016 May 16;82(11):3239-45.
2. Sze-To, et al. Effects of surface material, ventilation, and human behavior on indirect contact transmission risk of respiratory infection. Risk Analysis 2014;34:818-830
3. Goins WP, et al. Health care-acquired viral respiratory disease. Infect Dis Clin N Am 2011;25:227-244
4. Killingley B et al. The environmental deposition of influenza virus from patients infected with influenza A(H1N1)pdm09: Implications for infection prevention and control. J Infect Public Health. 2016 May-Jun;9(3):278-88.
5. Frise R, et al. Contact transmission of influenza virus between ferrets imposes a looser bottleneck than respiratory droplet transmission allowing propagation of antiviral resistance. Sci Rep. 2016 Jul 19;6:29793. doi: 10.1038/srep29793.

Environmental Conditions

- Implications for Successful Exposure:
  – Macro Environment:
    - Seasonality can affect indoor environment and determines timing of vaccination campaigns (Influenza)
  – Micro Environment:
    - Changes in Indoor Climate (Temperature, Humidity, Air Exchange)
    - Selection of Surface Materials – Contact transmission
    - Crowding

Exposure Factors

Environmental Conditions:
- Temperature, Humidity
- Seasonality
- Surface Materials (fomite survival)
- Settings: Indoor, Outdoor

Infector:
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- Co-Infections
- Microbiome
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Viral Factors:
- Infectious Dosage
- Carrier Substrate (aerosols)

Modified after Killingley B, Nguyen-Van-Tam J. Routes of influenza transmission. Influenza Other Respir Viruses. 2013 Sep;7 Suppl 2:42-51.

Exposure Risk – Viral Factors

- Human Infectious Dosage:
  - Definition of Exposure Risk
  - Limited Data available:
    - Influenza - "volunteers" (n = 23)[1]
    - Antibody levels measured
    - Aim HID_{50}
    - Aerosolized virus from culture (1-3 micron, RH 45-55%)
    - 10 Liters of aerosol administered by mask
    - Aerosol (airborne): HID_{50} = 0.6 to 3 $TCID_{50}$
    - Intranasal (large droplet): HID_{50} = 127 to 320 $TCID_{50}$
    - Other respiratory viruses: RSV – 1.0×10^4 $TCID_{50}$[2], Rhinovirus – 0.032 $TCID_{50}$[3]

1. Alford RH, et al. Human influenza resulting from aerosol inhalation. Proc Soc Exp Biol Med 1966;122:800-4.
2. Hall CB, et al. Infectivity of respiratory syncytial virus by various routes of inoculation. Infection and immunity 1981;33:779-783
3. Gwaltney JM, et al. Hand-to-hand transmission of rhinovirus cold. Annals of Internal Medicine, 1978;88:463-467

Exposure Risk – Viral Factors

- Virus Carrier Substrate:
  - Protection through mucus[1,2], appropriate acidity and salinity[3,4]
  - Volume extends virus survival on hands[5]

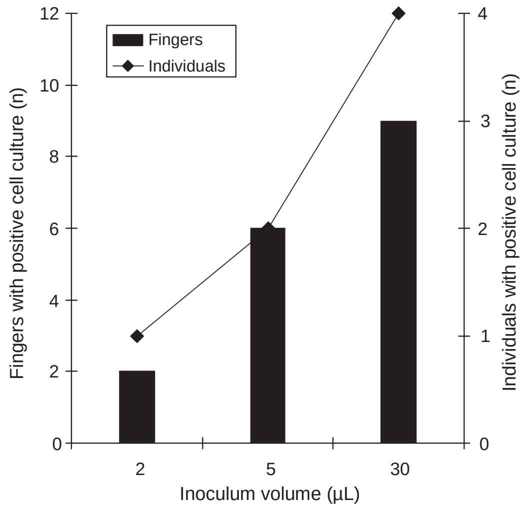


FIG 3. Influenza A (H3N2) viral survival on fingers according to the volume of the contaminated droplet. Four individuals (three fingers each) participated in this experiment, in which viral concentration was fixed. The number of fingers (bars) and individuals (curves) from whom infectious virus could be isolated after 15 min is represented according to the volume of the contaminated droplet (X axis).

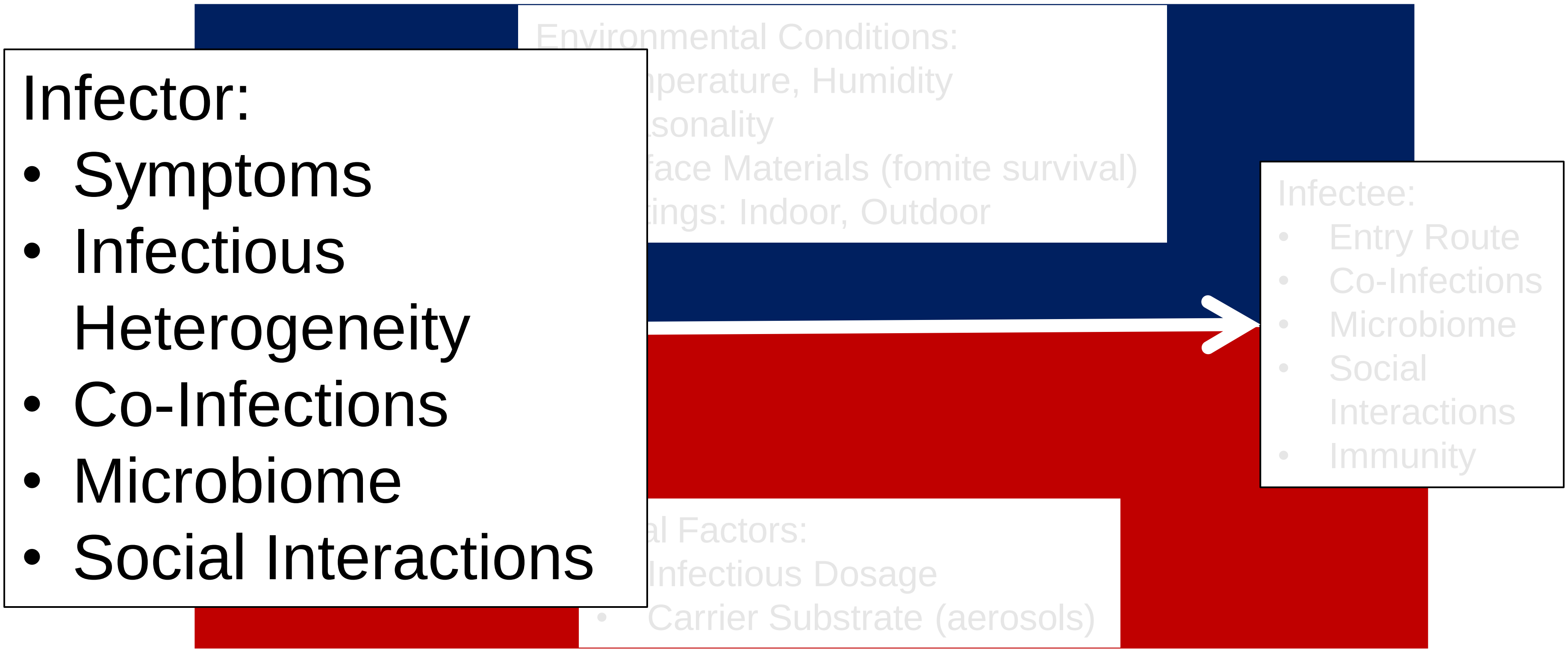
1. Parker ER, Dunham WB, Mac Neal WJ. Resistance of the Melbourne strain of influenza virus to desiccation. J Lab Clin Med 1944; 29: 37–42.
2. Bean B, Moore BM, Sterner B, Peterson LR, Gerding DN, Balfour HH. Survival of influenza-viruses on environmental surfaces. J Infect Dis 1982; 146: 47–51
3. Stallknecht DE, Shane SM, Kearney MT, Zwank PJ. Persistence of avian influenza viruses in water. Avian Dis 1990; 34: 406–411.
4. Lebarbenchon C, Sreevatsan S, Lefevre T et al. Reassortant influenza A viruses in wild duck populations: effects on viral shedding and persistence in water. Proc Biol Sci 2012; 279: 3967–3975.
5. Thomas Y, Boquete-Suter P, Koch D, Pittet D, Kaiser L. Survival of influenza virus on human fingers. Clin Microbiol Infect. 2014;20:O58-64

Exposure Risk – Viral Factors

- Implications for Successful Exposure
  - Human Infectious Dosage – Key to Determine Exposure Risk:
    - Variation by virus/strain?[1]
    - Relative significance of the transmission route (contact, aerosol [small, large])?
    - Variation by entry (nose, mouth, eyes)?
    - Variation by host?
    - Variation by environmental conditions?
  - Viability of Respiratory Viruses:
    - PCR vs Cell Culture – detection dilemma

1. Richard M, Fouchier RA. Influenza A virus transmission via respiratory aerosols or droplets as it relates to pandemic potential. FEMS Microbiol Rev. 2016;40:68-85.

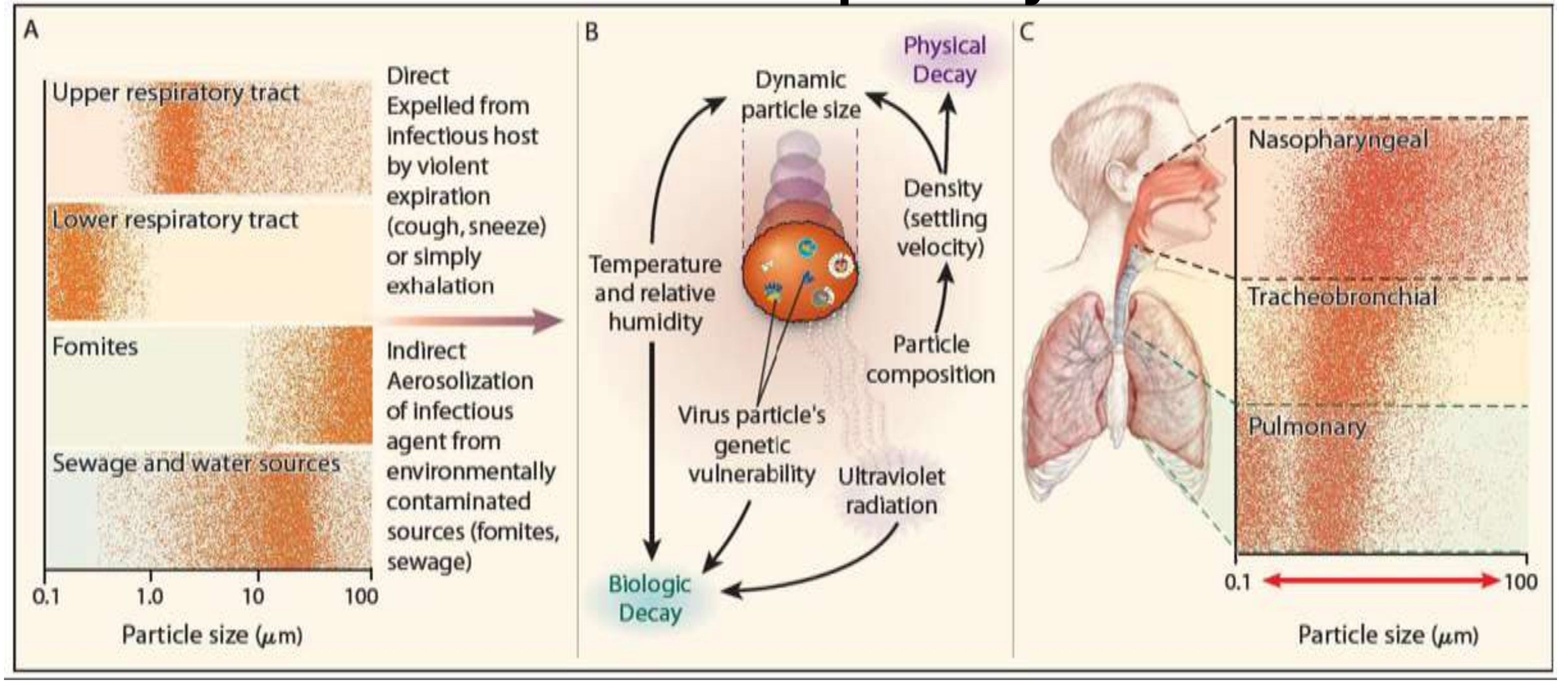
Exposure Factors



Modified after Killingley B, Nguyen-Van-Tam J. Routes of influenza transmission. Influenza Other Respir Viruses. 2013 Sep;7 Suppl 2:42-51.

Exposure Risk - Infector

The Aerobiological Pathway for Transmission of Communicable Respiratory Disease



A: Source, B: Transport and Dispersion, C: Deposition

By Roy C and Milton DK, New Engl J Med, 2004

Exposure Risk - Infector

- Evidence of Influenza Aerosols - Locations:
    - Emergency Rooms (Peds and Adult)[1,3,6]
        - Waiting Areas
        - Examination Rooms
    - Urgent Care Settings[2]
        - Waiting Areas
        - Examination Rooms
        - Procedure Rooms
    - Healthcare Center/Outpatient Clinics[3,5]
    - Inpatient Rooms[4,6,7]
  - Personnel Samplers (HCWs in ER and Urgent Care)[1,2]

1. Blachere et al. CID 2009:48: 438-440; 2. Lindsley et al. CID 2010;50: 693-698; 3. Tseng et al. J Environ Health 2010; 73: 22-28; 4. Leung et al. Plos ONE 11(2): e0128669. doi:10.1371/jounral.pone.0148669; 5. Yang W. et al. J.R. Soc. Interface (2011) 8, 1176-1184; 6. Bischoff WE et al. J Infect Virol 2013;207:1037-46; 7. Muberka et al. J Clin Virol 2015;73:105-107

Exposure Risk - Infector

- Evidence of Influenza Aerosols - Burden:
  - Blachere et al.: up to 16,278 viral RNA copies/m^3 air (Infl. A)[1]
  - Lindsley et al.: 0.7 – 75.4 pg RNA/m^3 air (Infl. A)[2]
  - Tseng et al.: 167.6 – 5,020 viral RNA copies/m^3 air (Infl. A)[3]
  - Leung et al.: 94 – 383 viral RNA copies/m^3 air (Infl. A)[4]
  - Yang et al.: 1.6 + 0.9 x 10^4 viral RNA copies/m^3 air[5]
  - Bischoff et al.: 0.9 - >200 viral RNA copies/m^3 air[6]

Alford et al.: HID_{50} 0.6-3 $TCID_{50}$ = RNA load of 90-1,950 viral copies[7]

1. Blachere et al. CID 2009:48: 438-440; 2. Lindsley et al. CID 2010;50: 693-698; 3. Tseng et al. J Environ Health 2010; 73: 22-28; 4. Leung et al. Plos ONE 11(2): e0128669. doi:10.1371/jounral.pone.0148669; 5. Yang W. et al. J.R. Soc. Interface (2011) 8, 1176-1184; 6. Bischoff WE et al. J Infect Virol 2013;207:1037-46; 7. Alford RH, et al. Proc Soc Exp Biol Med 1966;122:800-4

Exposure Risk - Infector

- Evidence of Influenza Aerosols – Particle Size:
    - Blachere et al.: 53% in particles < 4.1 µm (Infl. A)[1]
    - Lindsley et al.: 53% in particles < 4.1 µm (Infl. A)[2]
    - Yang et al.: 64% < 2.5 µm (Infl. A)[3]
    - Bischoff et al.: up to 89% < 4.7 µm (Infl. A and B)[4]

Viral recovery higher in larger particle sizes (93% > 4 µm vs. 7% in 1-4 µm particles)[5]

1. Blachere et al. CID 2009:48: 438-440; 2. Lindsley et al. CID 2010;50: 693-698; 3. Yang W. et al. J.R. Soc. Interface (2011) 8, 1176-1184; 4. Bischoff WE et al. J Infect Virol 2013;207:1037-46; 5. Leung et al. Plos ONE 11(2): e0128669. doi:10.1371/jounral.pone.0148669;

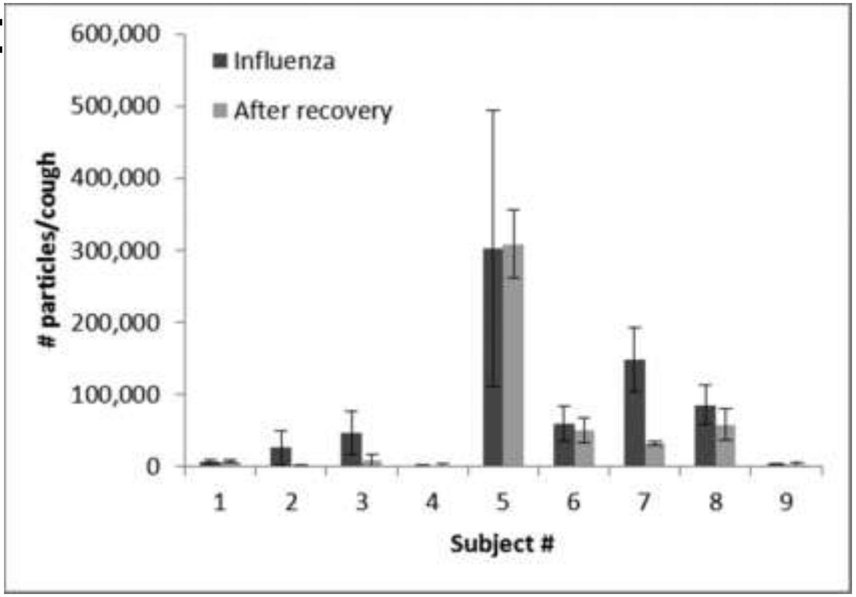
Exposure Risk - Infector

- Evidence of Influenza Aerosols – Contributing Factors:
  - Correlation between Influenza positive patients and virus detection in room.[1]
  - Correlation between patients with LRI and Influenza A detection.[2]
  - Deposition of aerosolized Influenza on surface (13+7 genome copies m-2h-1) unlikely to produce infections.[3]
  - No correlation between mid-turbinate swabs and air sample virus recovery.[4]

1. Lindsley et al. CID 2010;50: 693-698; 2. Tseng et al. J Environ Health 2010; 73: 22-28; 3. Yang W. et al. J.R. Soc. Interface (2011) 8, 1176-1184; 4. Muberka et al. J Clin Virol 2015;73:105-107

Exposure Risk - Infector

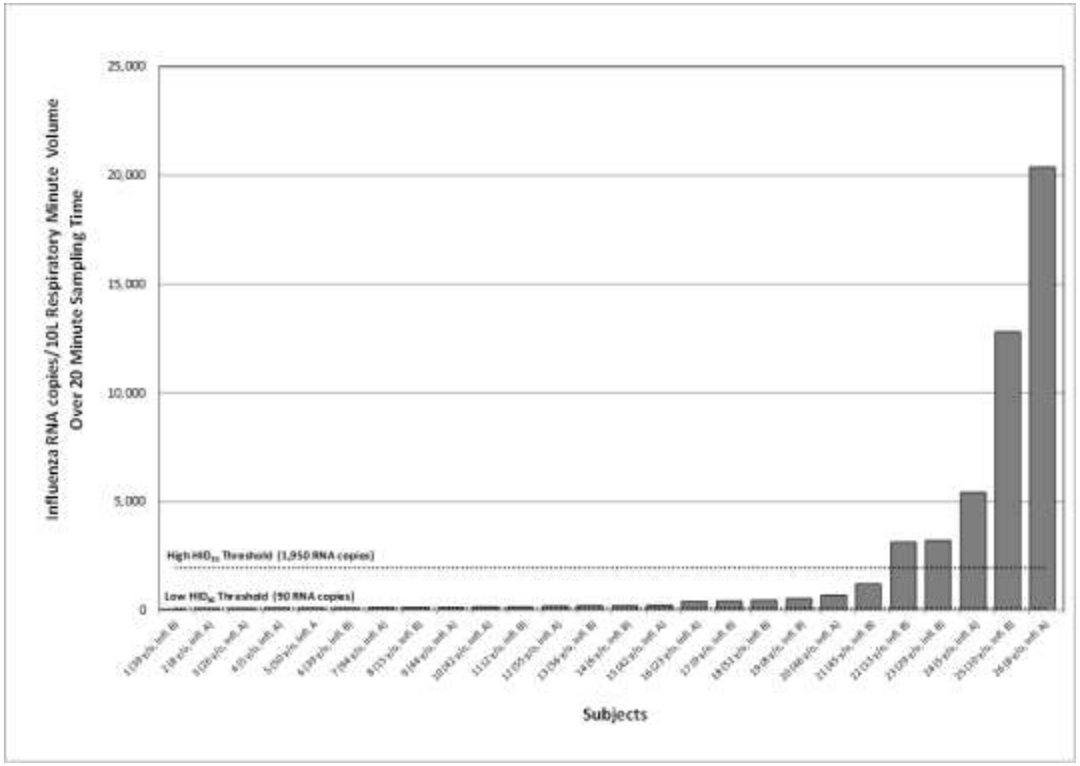
- Symptoms:
  - Breathing, coughing, sneezing increase Influenza virus emission[1-5]:



1. Stelzer-Braid S, et al. Exhalation of respiratory viruses by breathing, coughing, and talking. J Med Virol 2009;81:1674–1679.
2. Lindsley WG, et al. Quantity and size distribution of cough-generated aerosol particles produced by influenza patients during and after illness. J Occup Environ Hyg. 2012;9(7):443-9.
3. Milton DK, et al. Influenza virus aerosols in human exhaled breath: particle size, culturability, and effect of surgical masks. PLoS Pathog. 2013;9:e1003205.
4. Bischoff WE, et al. Exposure to influenza virus aerosols during routine patient care. J Infect Dis 2013;207:1037–1046.
5. Lindsley WG et al. Viable influenza A virus in airborne particles expelled during coughs versus exhalations. Influenza Other Respir Viruses. 2016 Sep;10(5):404-13.

Exposure Risk – Infector

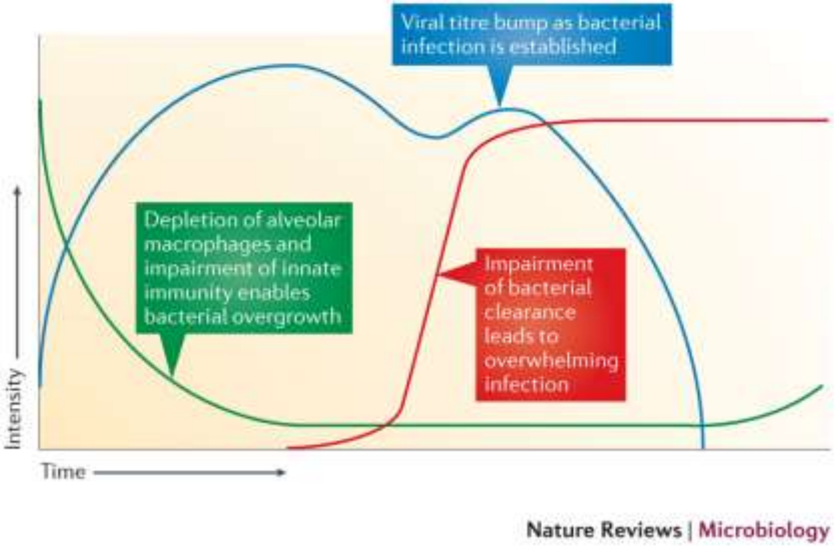
- Infectious Heterogeneity (super-emitters)



Bischoff WE, et al. Exposure to influenza virus aerosol during routine patient care. JID 2013;207:1037-1046

Exposure Risk - Infector

- Co-Infections:
  - Viral-bacterial interactions (influenza pandemics[1])
  - Multiplex respiratory virus assays – 10-50% viral co-infections detected[2]
- Effect on Transmission?



Co-pathogenesis of Influenza virus with bacteria in the lung[1]

1. McCullers JA. The co-pathogenesis of influenza viruses with bacteria in the lung. Nat Rev Microbiol. 2014;12:252-62.
2. Villiers E, Renaud C. Clinical and economical impact of multiplex respiratory virus assays. Diagn Microbiol Infect Dis. 2013;76:255-61.

Exposure Risk - Infector

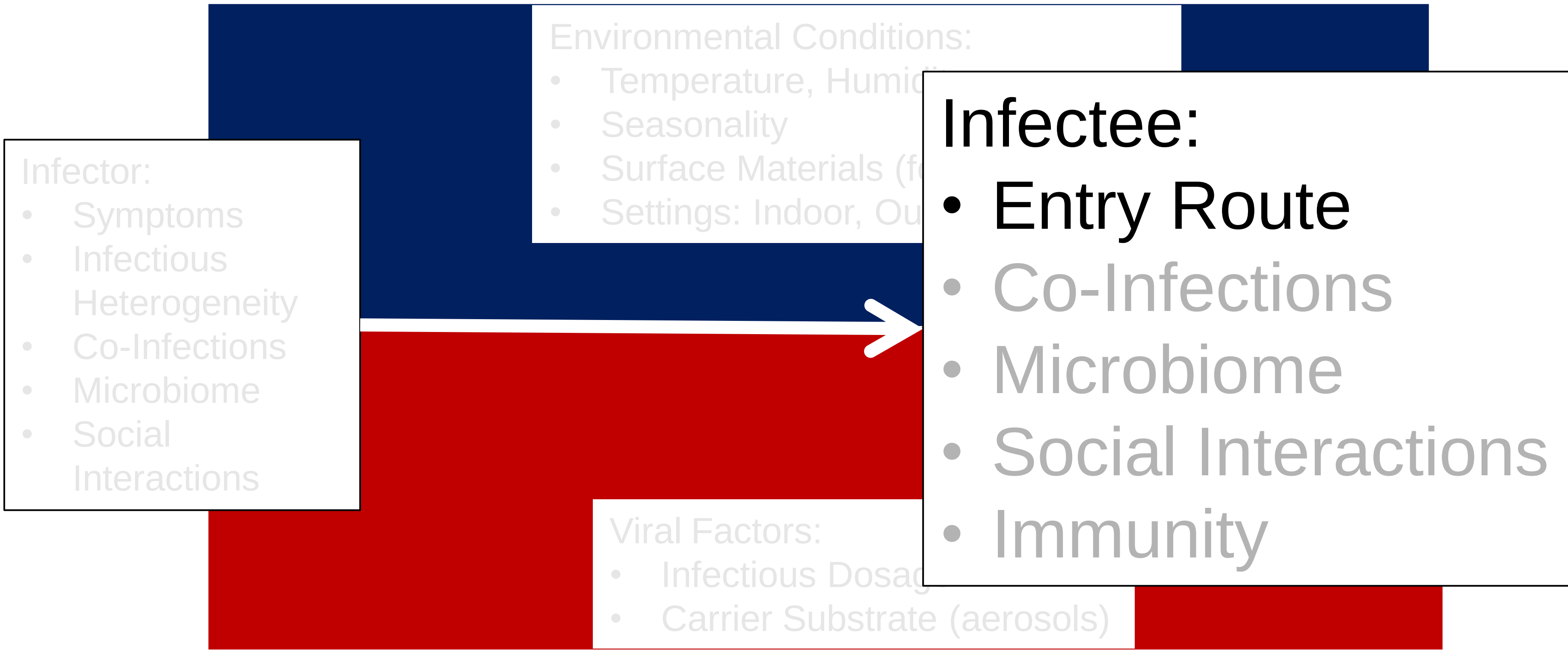
- Microbiome[1-5]:
  - Vast, unknown community of viruses (virobiota) in the human body
  - Highly personlized virus communities
  - Mucosal barrier host defence (bacteriophage part of a non-host-derived innate immunity)
  - Oral viral ecology:
    - Gender associated
    - Household specific
  - Respiratory tract viral ecology:
    - Differences in virobiota between Cystic fibrosis patients and healthy controls
    - Presence of eukaryotic viruses (picornaviruses, coronavirus)
- Role of Virobiota in transmission?

1. Abeles SR, Pride DT. Molecular Bases and Role of Viruses in the Human Microbiome. J Mol Biol. 2014 Jul 11. pii: S0022-2836
2. Abeles SR, et al. Effects of Long Term Antibiotic Therapy on Human Oral and Fecal Viromes. PLoS One. 2015 Aug 26;10(8):e0134941.
3. Chen HW et al. Nasal commensal Staphylococcus epidermidis counteracts influenza virus. Sci Rep. 2016 Jun 16;6:27870.
4. Bellinghausen C et al. Exposure to common respiratory bacteria alters the airway epithelial response to subsequent viral infection. Respir Res. 2016 Jun 3;17(1):68.
5. Deriu E et al. Influenza Virus Affects Intestinal Microbiota and Secondary Salmonella Infection in the Gut through Type I Interferons. PLoS Pathog. 2016 May 5;12(5):e1005572.

Exposure Risk – Infector

- Implications for Infectivity
  - Symptoms/Infectious Heterogeneity/ Co-Infections and Virobiota:
    - Possible explanations of different emission patterns?
  - Open Questions:
    - Variation by virus/strain?
    - Impact on different transmission routes (contact, aerosol [small, large])?
    - Variation by environmental conditions?

Exposure Factors



Modified after Killingley B, Nguyen-Van-Tam J. Routes of influenza transmission. Influenza Other Respir Viruses. 2013 Sep;7 Suppl 2:42-51.

Exposure Risk - Infectee

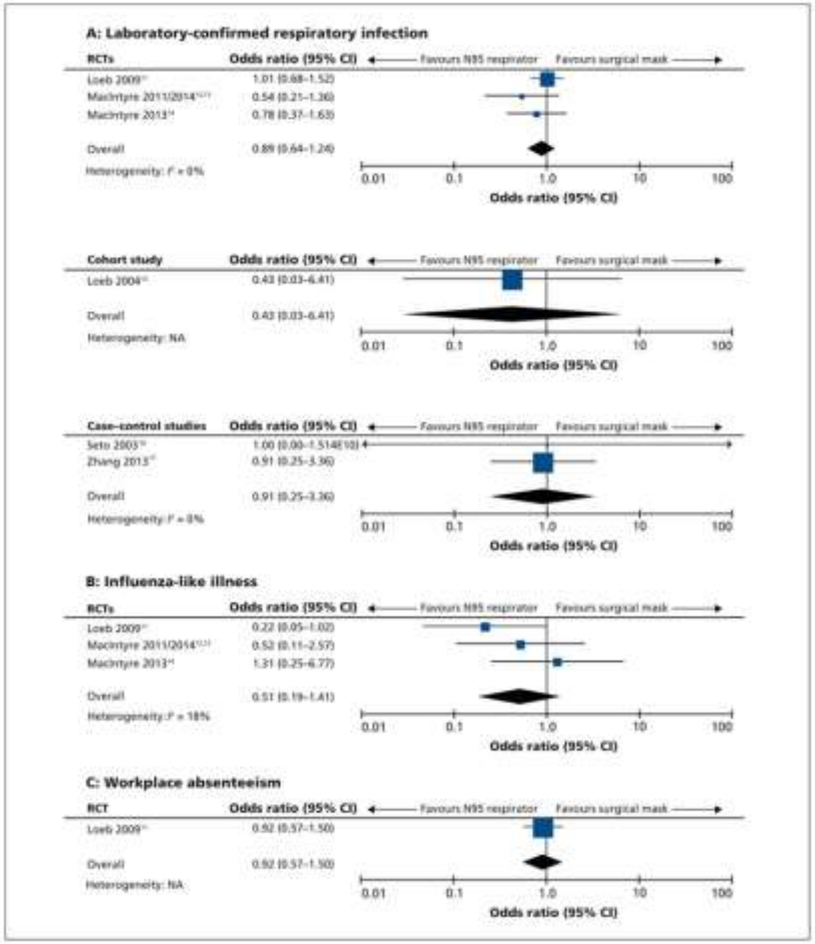
- Entry Routes:
  - Mouth, Nose:
    - Surgical/Medical Masks:
      - Oberg et al. – nine masks tested, none with adequate protection[1]
      - Aiello et al., MacIntyre et al. – no clear protection in community or health care settings[2,3]
      - Bischoff et al. – no protection against LAIV[4]
    - Patients:
      - Johnson et al.[5] – no difference in mask type in preventing aerosol particles emission in patients
      - Diaz et al.[6] – bench model demonstrating successful deflection of exhaled particles

1. Oberg T, Brosseau LM. Surgical mask filter and fit performance. Am J Infect Control. 200836:276-82
2. Aiello AE, et al. Facemasks, hand hygiene, and influenza among young adults: a randomized intervention trial. PLoS One. 2012;7(1):e29744.
3. MacIntyre CR et al. Face mask use and control of respiratory virus transmission in households. Emerg Infect Dis. 2009;15:233-41
4. Bischoff WE et al. Transocular entry of seasonal influenza-attenuated virus aerosols and the efficacy of n95 respirators, surgical masks, and eye protection in humans. J Infect Dis. 2011;204:193-9.
5. Johnson DF, et al. A quantitative assessment of the efficacy of surgical and N95 masks to filter influenza virus in patients with acute influenza infection. Clin Infect Dis. 2009;49:275-7.
6. Diaz KT, Smaldone GC. Quantifying exposure risk: surgical masks and respirators. Am J Infect Control. 2010;38:501-8.

Exposure Risk - Infectee

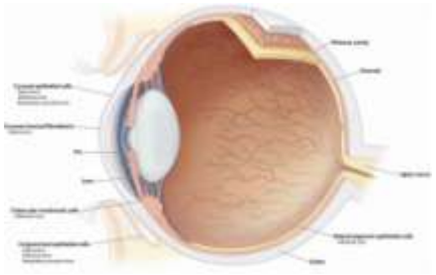
- Entry Routes – Mouth, Nose

Results of meta-analysis to determine effectiveness of N95 respirators versus surgical masks in protecting health care workers against acute respiratory infection.



Smith JD et al. CMAJ 2016;188:567-574

Exposure Risk - Infectee



- Entry Route:
  - Eyes:
    - Replication of influenza, adenovirus, RSV within ocular tissue[1]
    - Influenza – successful ocular-only aerosol inoculation in ferrets[2],
    - Influenza – trans-ocular entry of seasonal influenza virus vaccine in volunteers detected[3]
- **Should ocular protection be considered besides respiratory protection?**

1. Belser JA, et al. Ocular tropism of respiratory viruses. Microbiol Mol Biol Rev. 2013 Mar;77(1):144-56
2. Belser JA, et al. Influenza Virus Infectivity and Virulence following Ocular-Only Aerosol Inoculation of Ferrets. J Virol. 2014 Sep 1;88(17):9647-54
3. Bischoff WE, et al. Transocular entry of seasonal influenza-attenuated virus aerosols and the efficacy of n95 respirators, surgical masks, and eye protection in humans. J Infect Dis. 2011;204:193-9.

Exposure Risk – Infectee

- Implications for Successful Exposure
  - Entry Routes:
    - Entry Routes determine PPE needs
    - Nose, and mouth - classic entry points
    - Role of eyes? – eye protection?
    - Different HIDs for nose, mouth, and eyes?
    - Different effective particle sizes for nose, mouth, and eyes?

Conclusion:

- Environmental Burden:
  - Air (airborne, droplet or combination)
  - Surface (direct and indirect contact)
- Transmission Routes:
  - Dominant
  - Most effective
- Infector/Infectee Factors:
  - Emitter/Recipient characteristics (co-infections, immunity, microbiome)
  - Superspreaders

Thanks