What Do We Know About the Infectious Dose and Disease Relationship for SARS-CoV-2?

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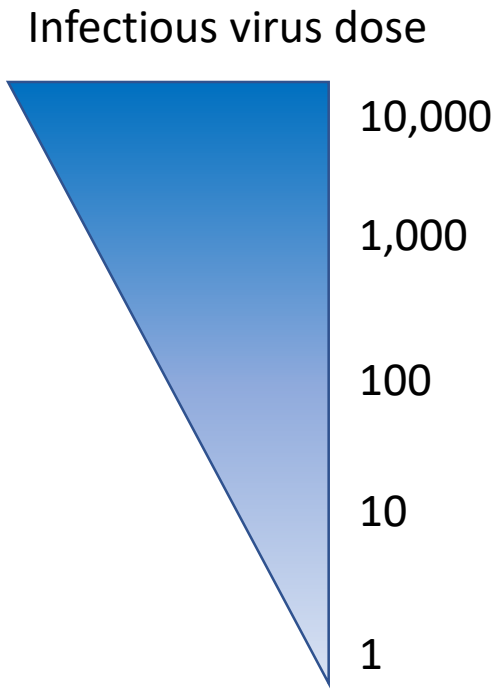
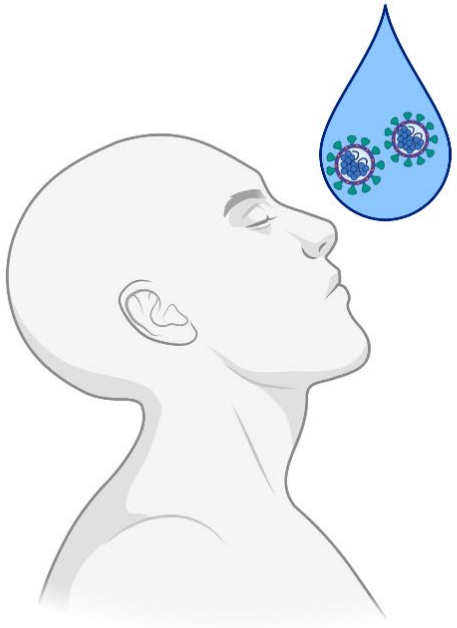
How is Infectious Dose Typically Determined?

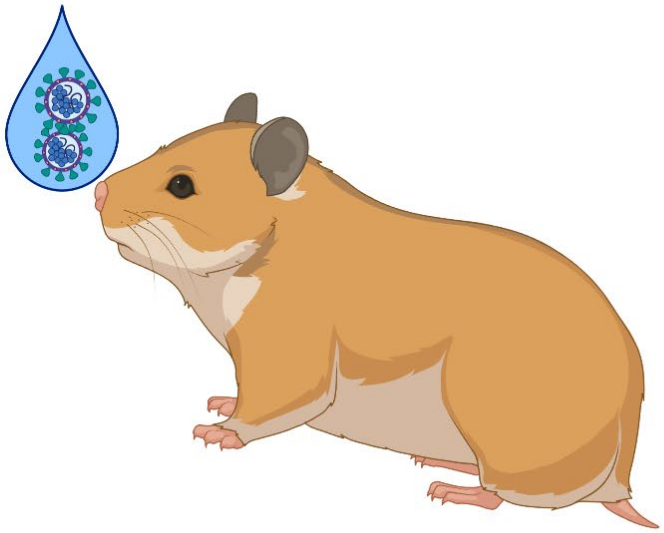
Quantified from dose response experiments – typically inferred from infectious dose 50 (ID_{50}) = the amount of virus to infect 50% of recipients.



Human Challenge Studies



Experimental Studies in Animal Models



Figures created with BioRender.com

Human Challenge Studies with Coronaviruses

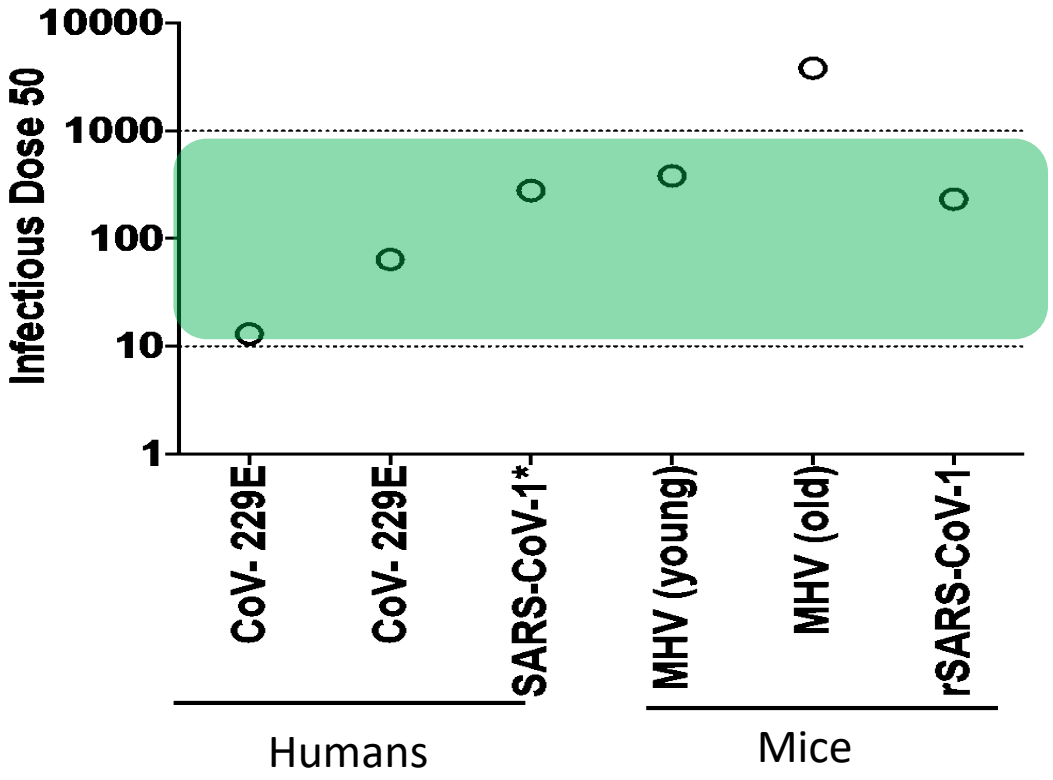
- Common cold causing coronaviruses were identified in 1960's and circulate each season.
- Human challenge studies for non-SARS coronaviruses (229E) :
  1. Bradburn et al 1967 -> Range of doses 5-30 infectious virus ($TCID_{50}$)
     ID_{50} = 13 infectious virus ($TCID_{50}$)

  2. Callow et al 1990 -> 15 volunteers received 100 $TCID_{50}$
     10 became infected
     ID_{50} = 63 $TCID_{50}$

(1) Bradburne, Bynoe, Tyrell "Effects of a 'new' human respiratory virus in volunteers" **British Medical Journal** 1967; (2)Callow, Parry, Sergeant, Tyrrell "Time Course of the immune response to experimental coronavirus infection in man" **Epidemiol Infect** 1990

Infectious Dose Range of Coronaviruses

Infectious Dose 50 data from Animal and Human studies for non-SARS CoV and SARS-CoV-1



Range of 10 to 1000 infectious virus to infect 50% of recipients

(1) Bradburne, Bynoe, Tyrell "Effects of a 'new' human respiratory virus in volunteers" **British Medical Journal** 1967; (2) Callow, Parry, Sergeant, Tyrrell "Time Course of the immune response to experimental coronavirus infection in man" **Epidemiol Infect** 1990; (3) Watanabe, Bastard, Weir, et al "Development of a dose-response model for SARS coronavirus" **Risk Anal** 2010; (4) DeDiego, Pewe, Alvarez, et al "Pathogenicity of severe acute respiratory coronavirus deletion mutants in hACE-2 transgenic mice" **Virology** 2008; (5) Taguchi, Aiuchi, Fujiwara "Age-dependent response of mice to a mouse hepatitis virus, MHV-S" J**apanese Journal of Experimental Medicine** 1977

Infectious Dose for SARS-CoV-2?

- No experimental human challenge studies
- Animal studies using Syrian Hamsters have used as little as 1000 infectious viruses with 100% infection rate.
- Similar for SARS-CoV-1.

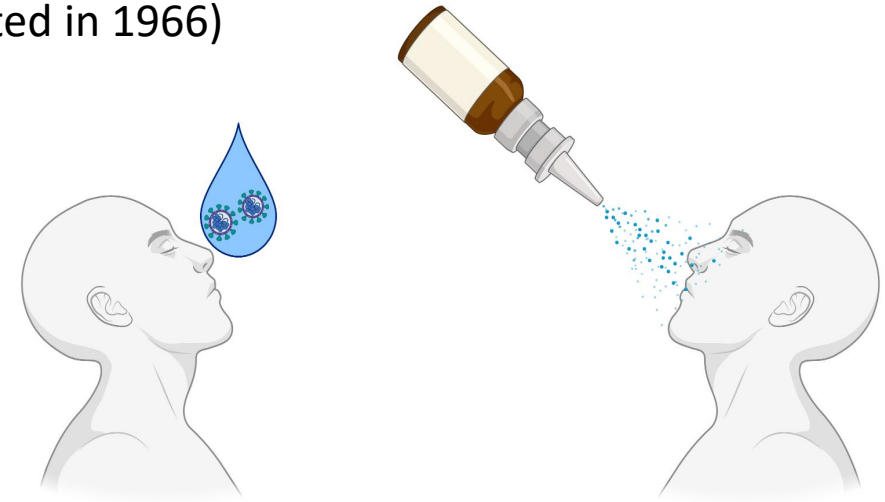
ID_{50} = <1000 infectious virus (PFU)

(1) Imai, Iwatsuki-Horimoto, Hatta et al "Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development" **PNAS** 2020;
(2)Roberts, Vogel, Guarner et al "Severe Acute Respiratory Syndrome Coronavirus Infection of Golden Syrian Hamsters" **J. of Virology** 2005

Factors that Impact Infectious Dose and Relationship to Disease Outcome

1. Route of inoculation matters

Data from human challenge studies of influenza A virus (reported in 1966)



ID_{50} = 100 $TCID_{50}$

ID_{50} = 10 $TCID_{50}$

2. Prior immunity of recipients

Human challenge studies of H1N1 influenza A viruses (reported in 2015)

ID_{50} = 383,000 $TCID_{50}$

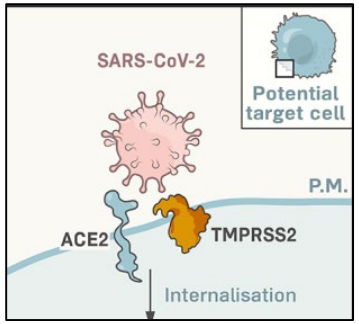
(1) Alford, Kasel, Gerone, Knight "Human Influenza Resulting from Aerosol Inhalation" **Experimental Biology and Medicine** 1966; (2) BR Murphy "Use of live attenuated cold-adapted influenza A reassortant virus vaccines in infants, children, young adults, and elderly adults" **Infectious Disease in Clinical Practice** 1993
(3) Memoli, Czajkowski, Reed, et al "Validation of the Wild-type Influenza A Human Challenge Model H1N1pdMIST…." **Clinical Infectious Diseases** 2015

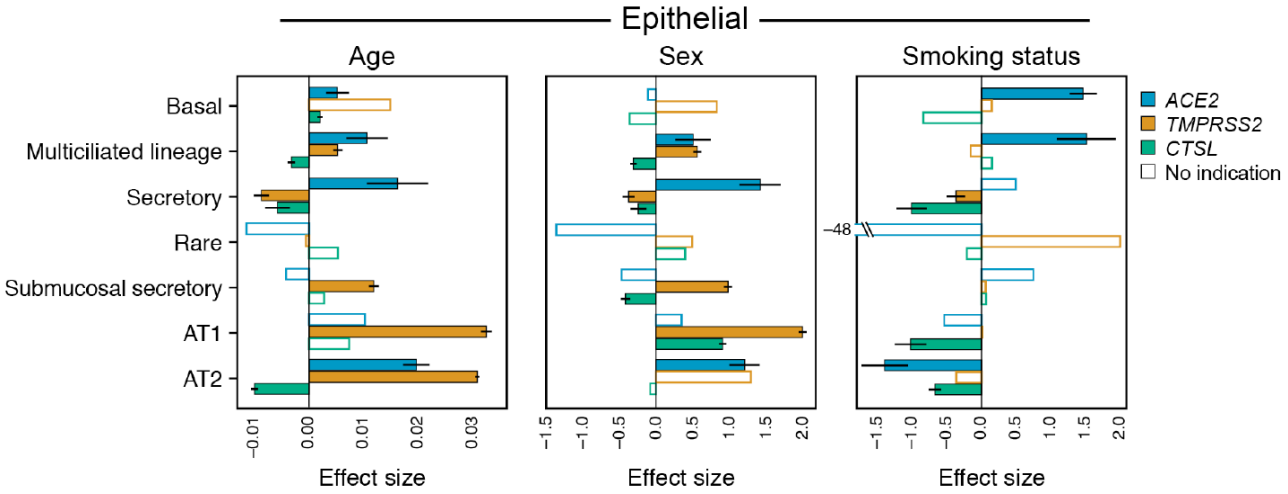
Factors that Impact Infectious Dose and Relationship to Disease Outcome

3. Age of the recipient

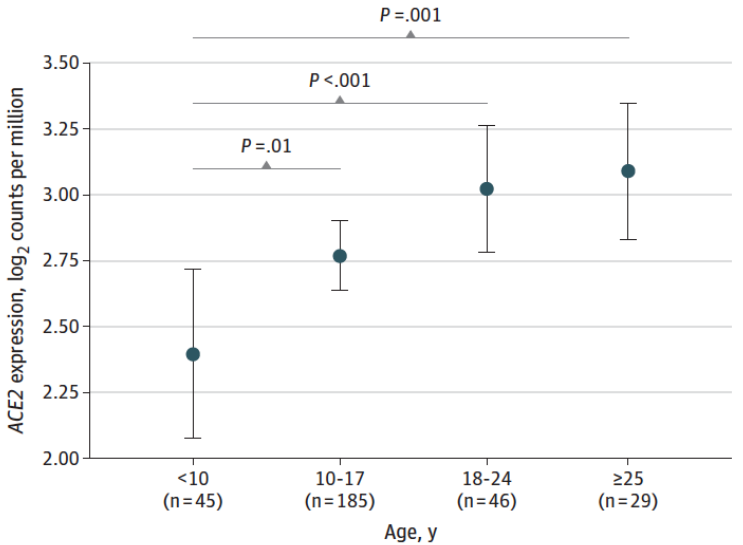
4. Sex of the recipient

5. Receptor abundance and distribution



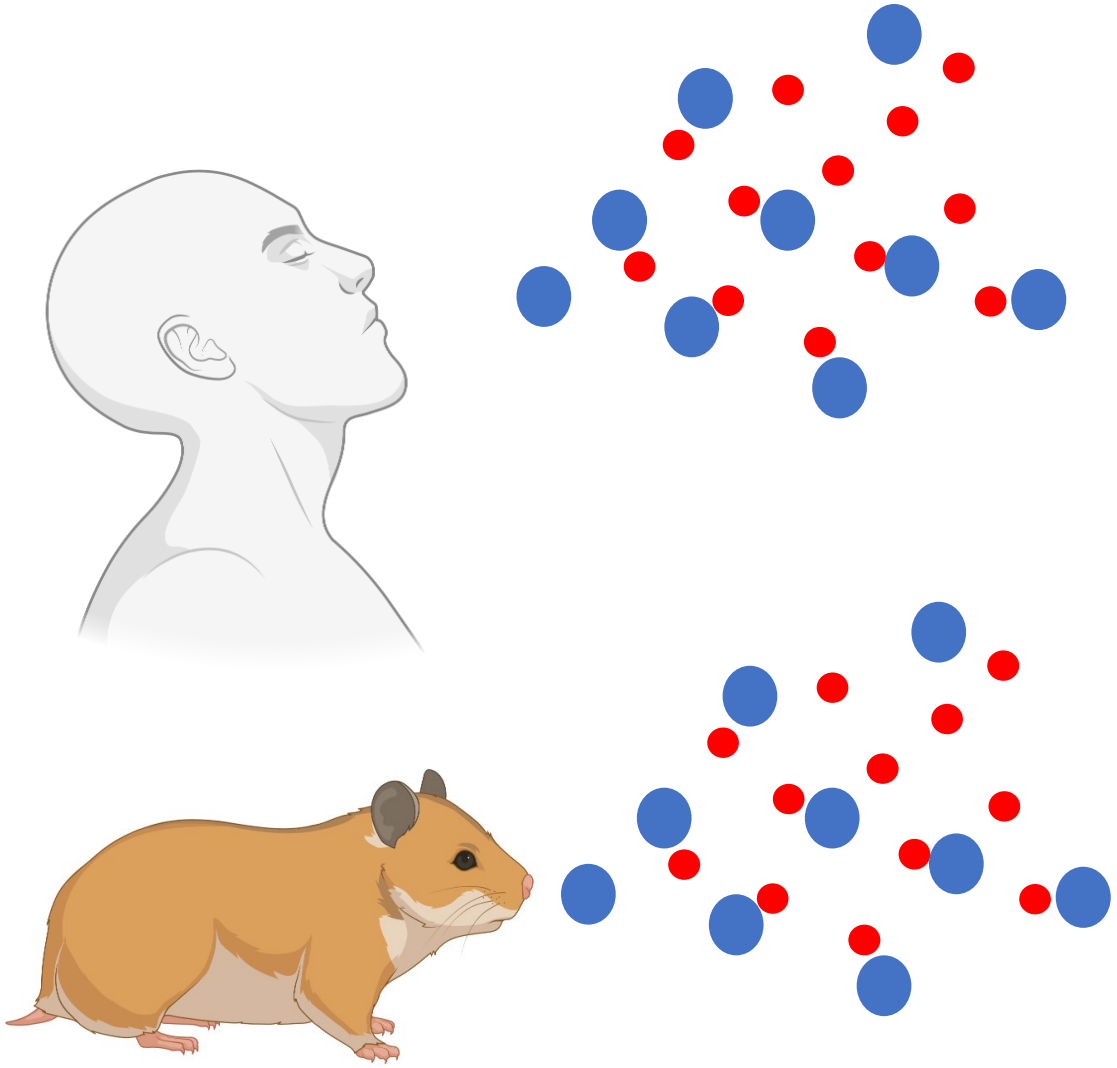


Banked Nasal Swab Samples 2015-2018



(1) C. Baraniuk "Receptors for SARS-CoV-2 Present in Wide Variety of Human Cells" The Scientist; Apr 29 2020; (2) Muus, Luecken, Eraslan et al "Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific …" bioRxiv Apr 2020; (3) Ziegler, Allon, Nyquist et al "SARS-CoV-2 Receptor Ace2 is an interferon-stimulated gene in human airway epithelial cells…" Cell May 2020; (4) Bunyavanich, Do, and Vicencio "Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults" JAMA June 2020.

How to Define SARS-CoV-2 Infectious Dose?



- Human challenge studies ???
- Animal experimental studies
- Air sampling
- Epidemiology