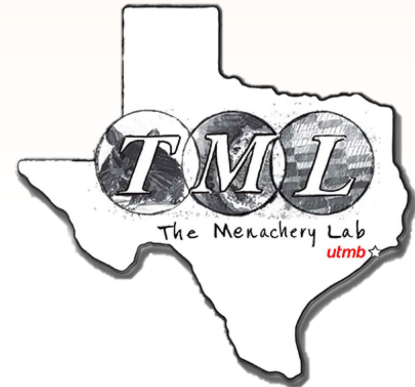


Disease Severity of CoV as a Function of Dose, Age, & Genetic Background

Vineet D. Menachery

Airborne Transmission of SARS-CoV-2

Workshop Session 4



Why the “who” might matter as much as the “how much”?

Vineet D. Menachery

Airborne Transmission of SARS-CoV-2

Workshop Session 4



Overview

- The range of disease observed with COVID-19 reveals complexity
- The amount of virus likely matters for disease outcome based on CoV *in vivo* models
- The specifics on the “who” are a main arbiter of disease and damage

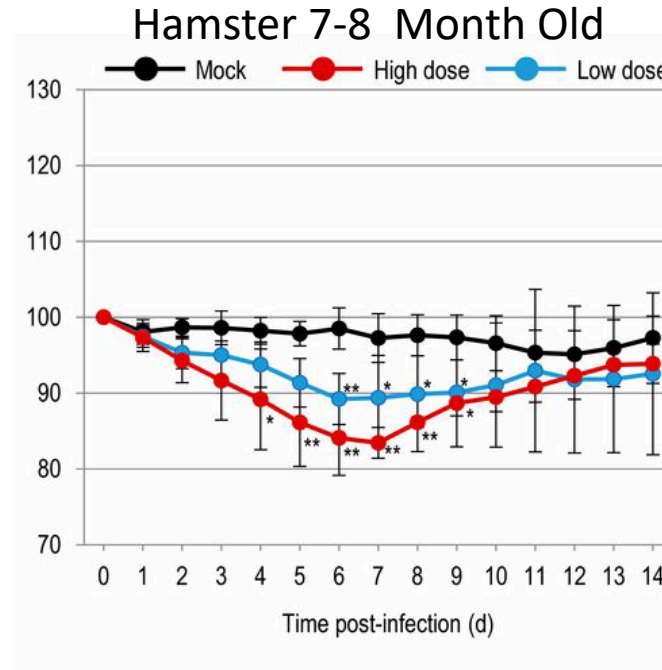
In Vivo CoV Models

- A variety of models exist for SARS-CoV-2
- Work from SARS-CoV & MERS-CoV mouse-models
- Mouse models allow evaluation of host “factors” that influence disease outcome

Dose Response

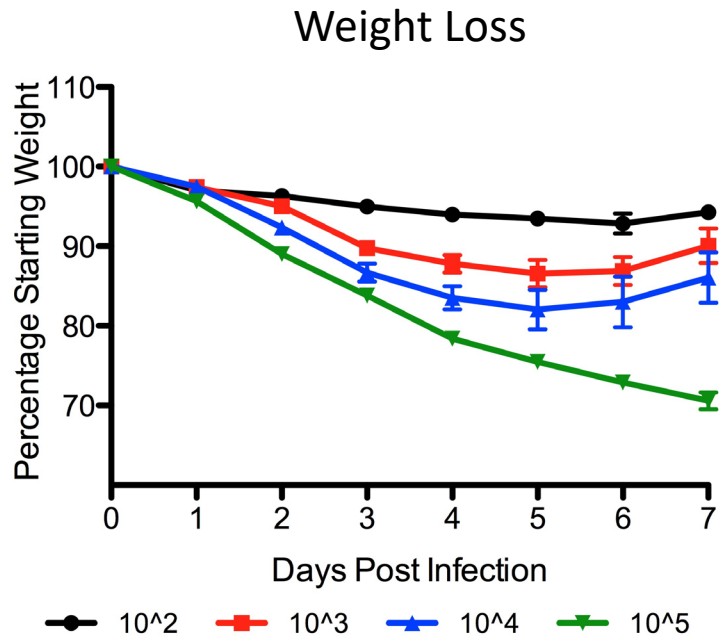
- What is the relationship between dose and disease?
- Limitations: *In vivo* models rarely use a natural infection approach

Dose Response- SARS-CoV-2



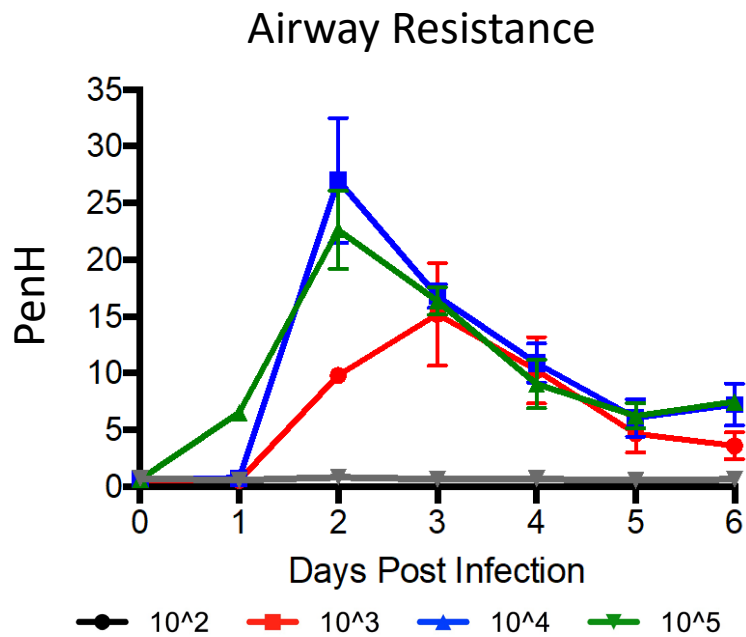
- Data argues for SARS-CoV-2, dose alters disease

Dose Response



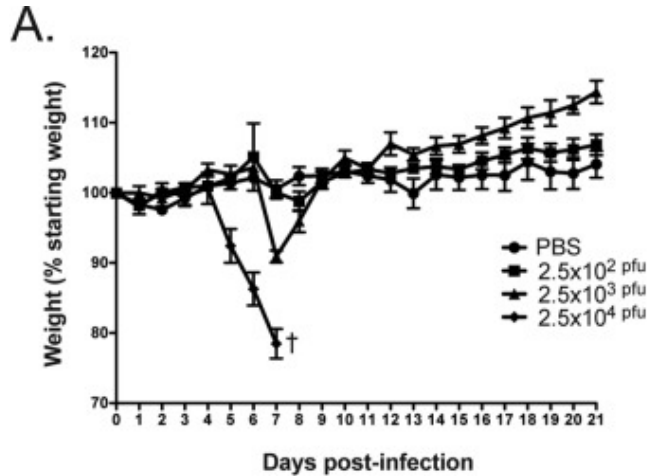
- Young C57/B6 mice infected with mouse adapted SARS-CoV
- Dose dependent changes in disease

Dose Response



- Young C57/B6 mice infected with mouse adapted SARS-CoV
- Dose dependent changes in disease

Dose Response



- Similar findings with the MERS-CoV mouse models
- Results demonstrate impact of dose on CoV mediated disease

Coleman J Virol. 2017 Jan 1; 91(1): e01825-16.

Li Proc Natl Acad Sci U S A. 2017 Apr 11; 114(15): E3119–E3128.

Cockrell Nat Microbiol. 2017; 2(2): 16226.

Disease and Host Conditions

- Even if dose is equal, disease varies based on host conditions
 - Genetic Background
 - Health Status/Condition
 - Age

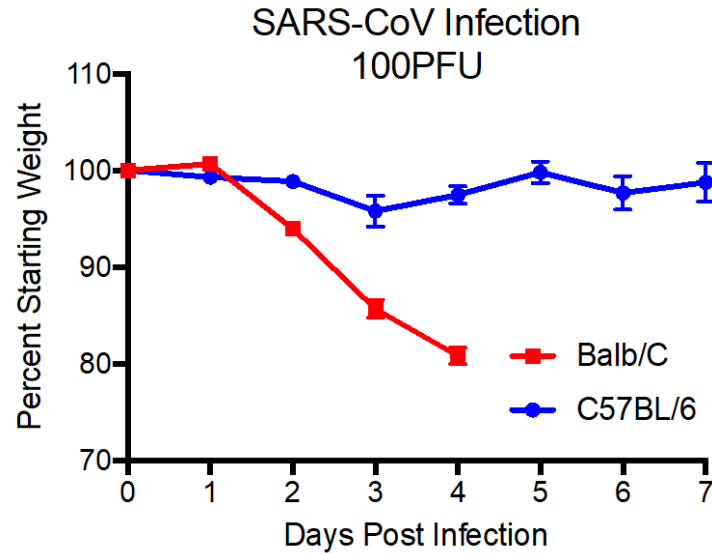
Disease and Host Conditions

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Genetic Background and Disease



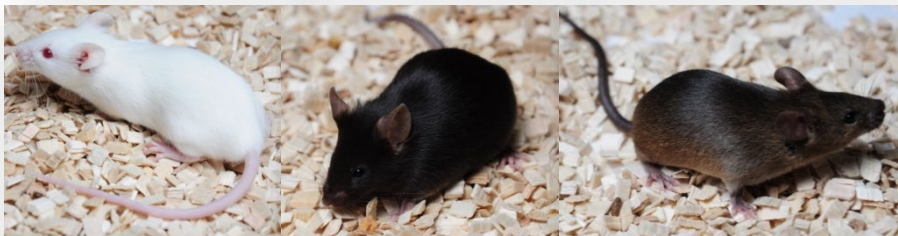
C57BL/6



BALB/C

- Changes in strains alters disease/outcomes

The Collaborative Cross (CC)



lab strains



L/6J

129S1/SvImJ

- Broad genetic resource
- Community-driven effort
- Started in 2002



HLtJ



CAST/EiJ

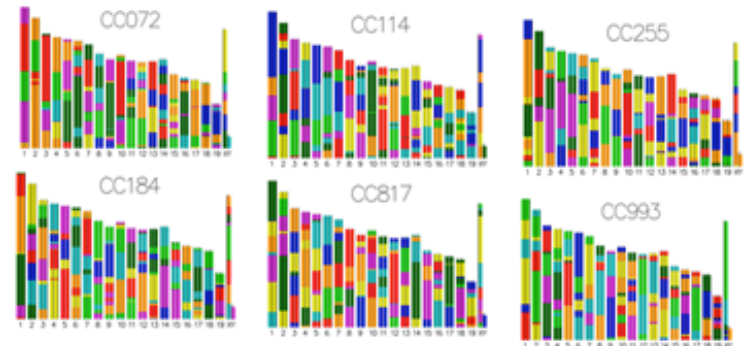
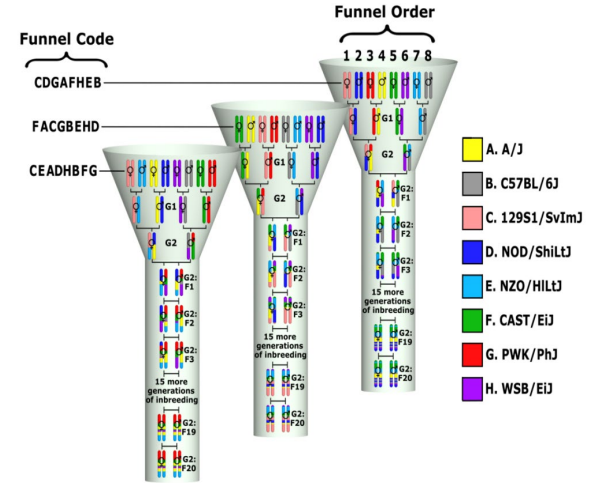
PWK/PhJ

WSB/EiJ

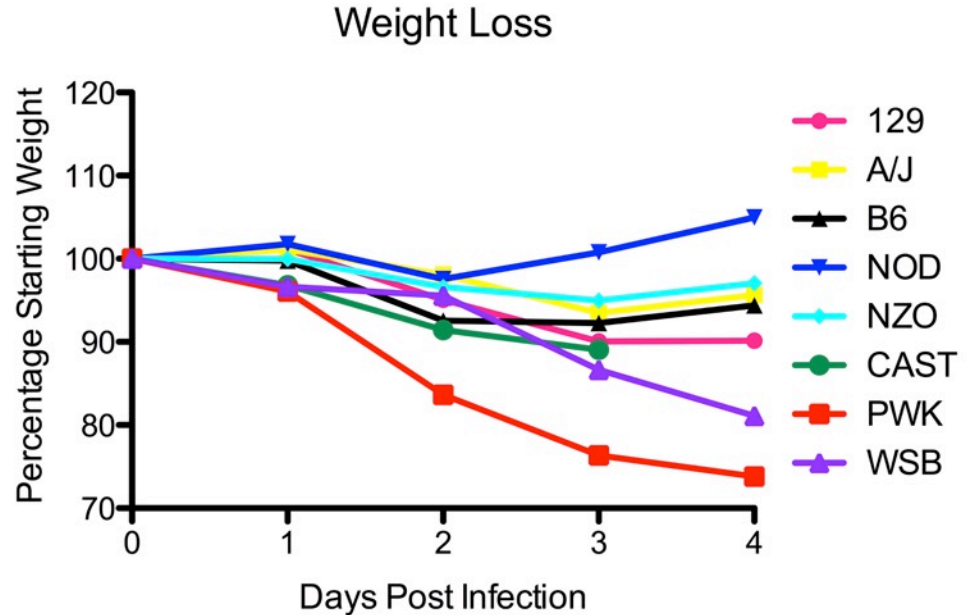
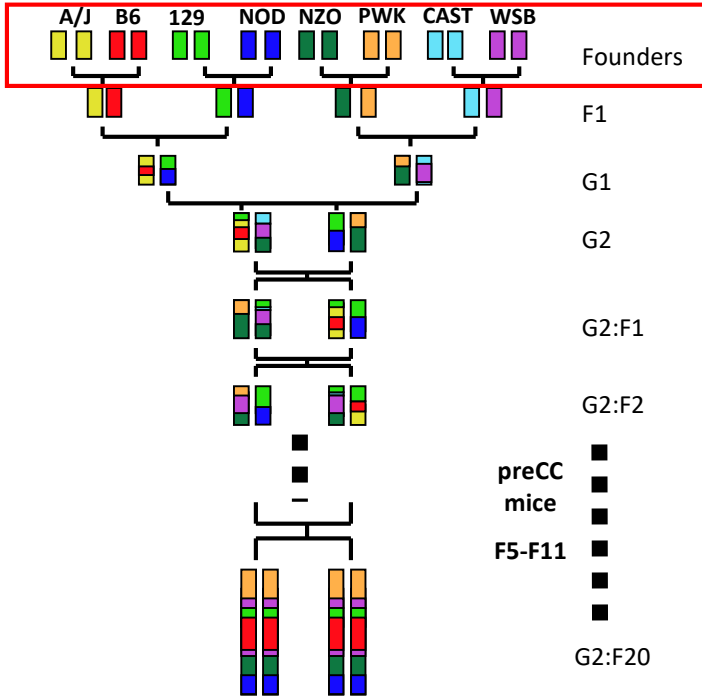
strains

Genetic Background and Disease

- The Collaborative Cross
 - Founders funnel bred to make genetically distinct lines
 - Variation randomly distributed throughout
 - Lines inbred, reproducible, and are large enough to support statistical analysis

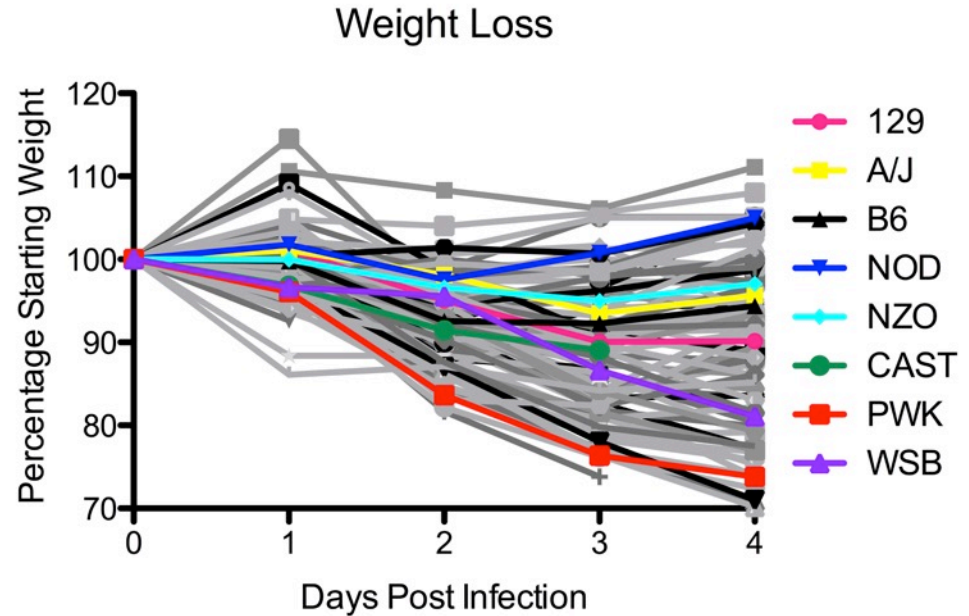
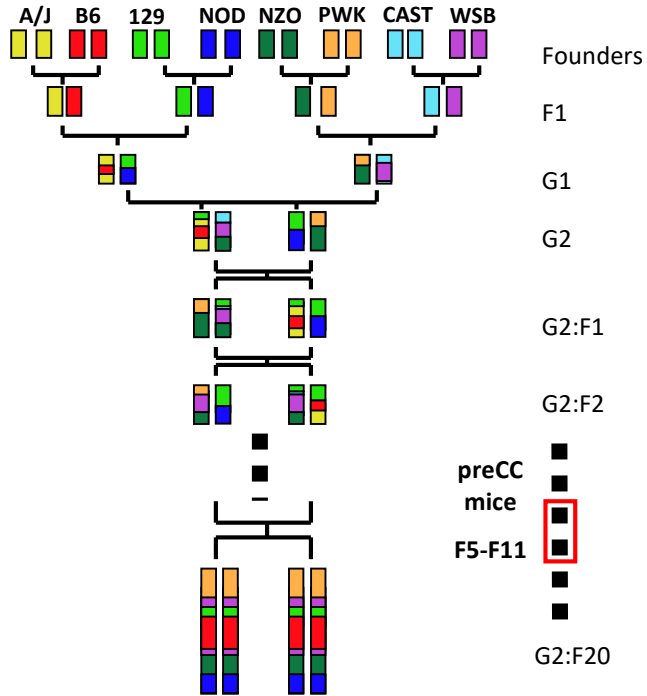


Genetic Background and Disease



Infected with Mouse adapted SARS-CoV

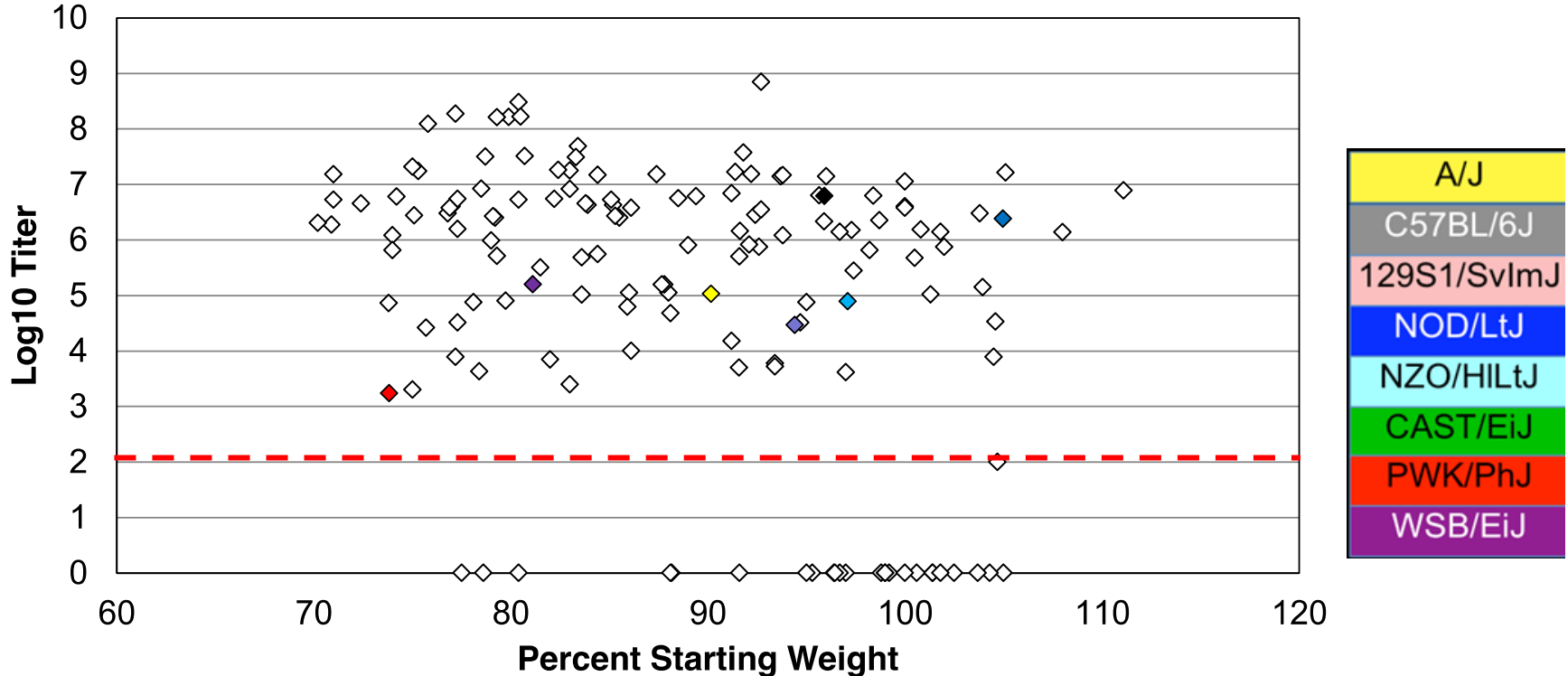
Genetic Background and Disease



Infected with Mouse adapted SARS-CoV

Genetic Background and Disease

Percent Starting Weight vs. Titer



Genetic Background and Disease

- Differences in host genetics alters disease
- Changes can be independent of viral dose indicating importance of host response

Disease and Host Conditions

- Even if dose is equal, disease varies based on host conditions
 - Genetic Background
 - Health Status/Condition
 - Age

Health Condition and Disease

- Obesity, diabetes, and high blood pressure have been associated with more severe disease for SARS-CoV-2
- Work with Influenza has shown exacerbated disease in obese *in vivo* models

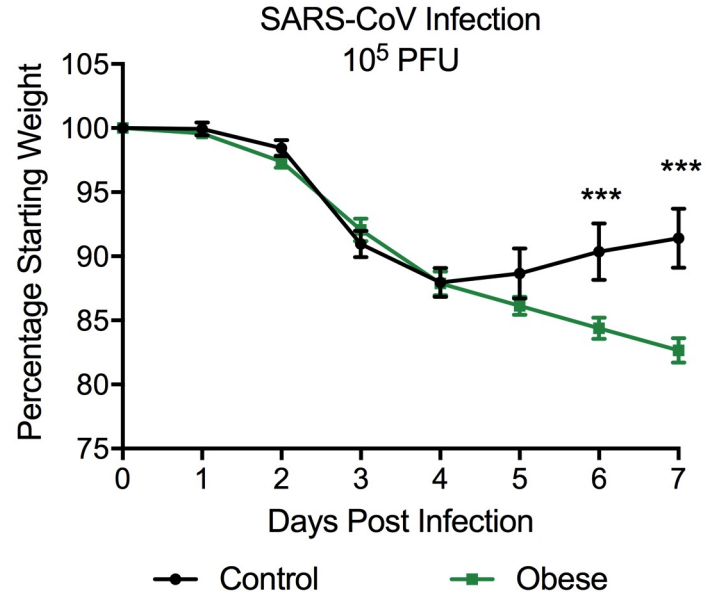
Health Conditions and Disease



Normal



Obese



- Diet-induced obesity model shows exacerbated SARS-CoV disease versus standard

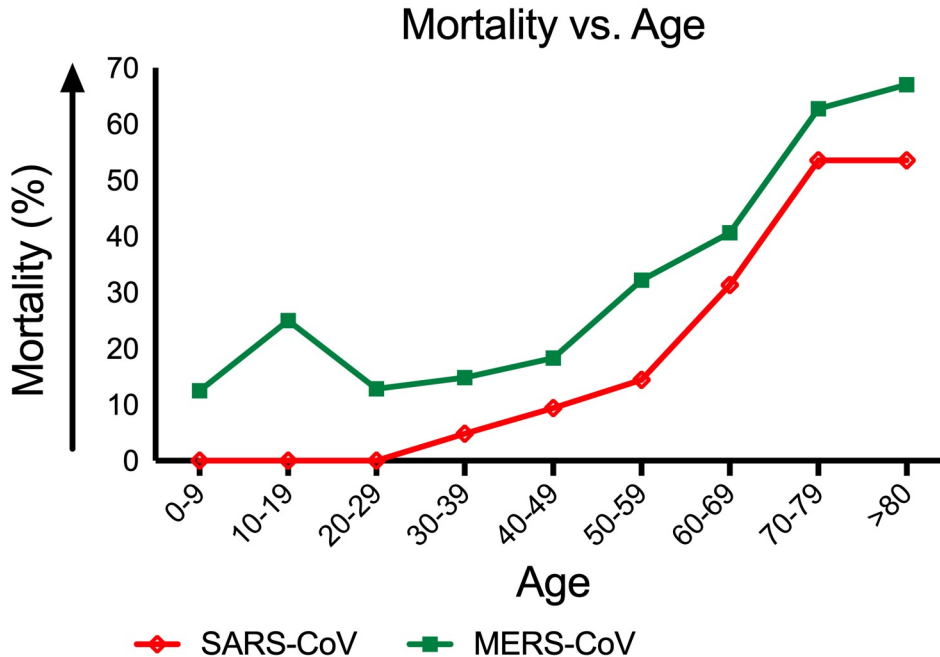
Health Condition and Disease

- Clear impact of obesity on disease in context of same dose
- Other groups exploring other parameters including diabetes, hypoxia, and other conditions that may exacerbate disease

Disease and Host Conditions

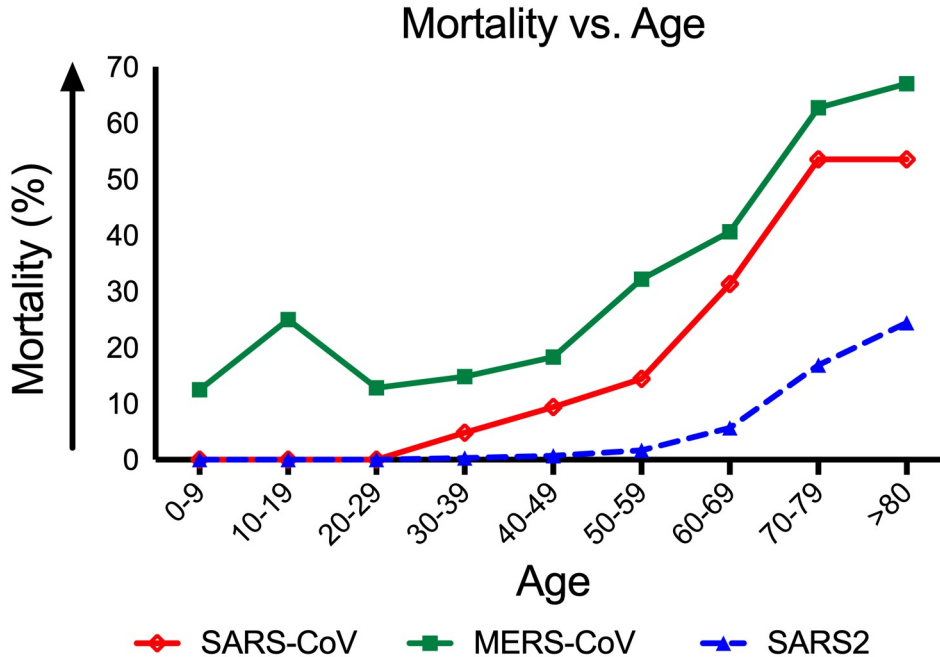
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Aging & Disease



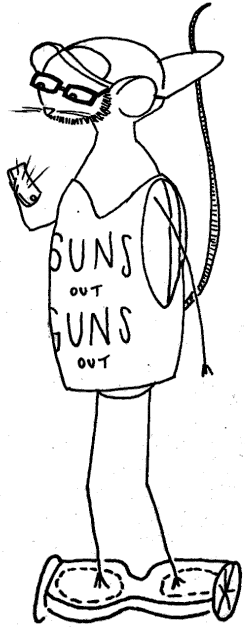
- Major age dependent disease with CoVs in humans

Aging & Disease



- Major age dependent disease with CoVs in humans

Aging & Infection



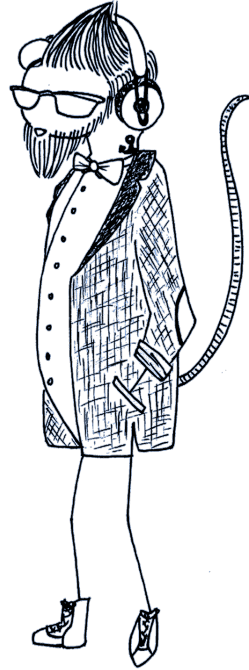
2.5 Month

Human Age: 18-22



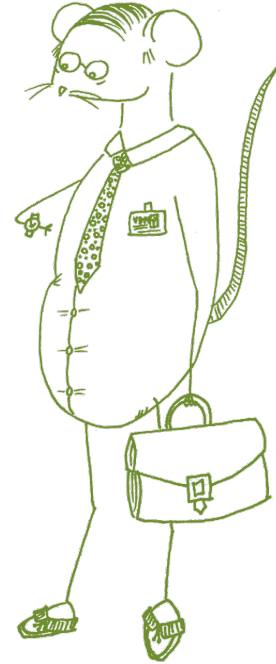
>20 Month Old

Human Age: Early 70s



5 Month Old

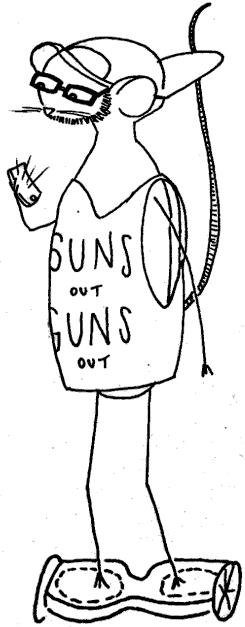
Human Age: 28-34



12 Month Old

Human Age: late 50s

Aging & Infection



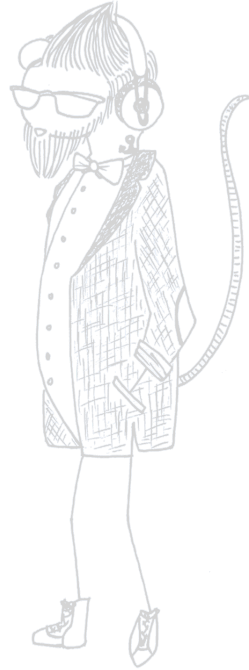
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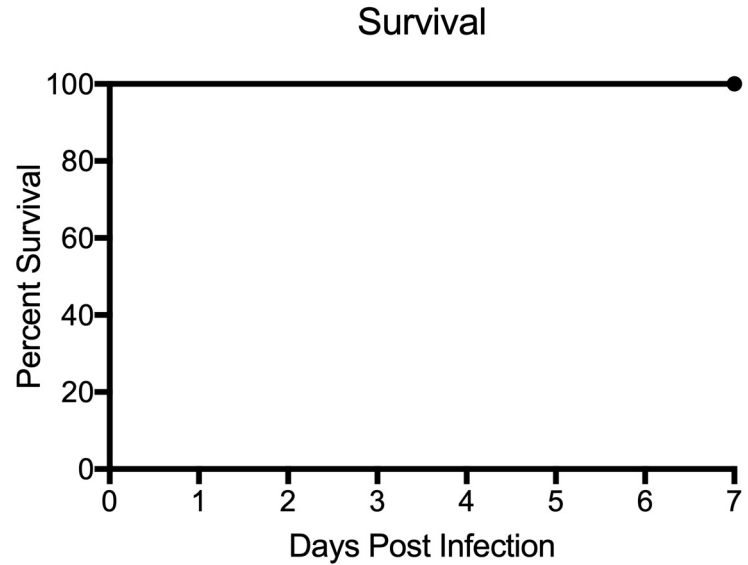
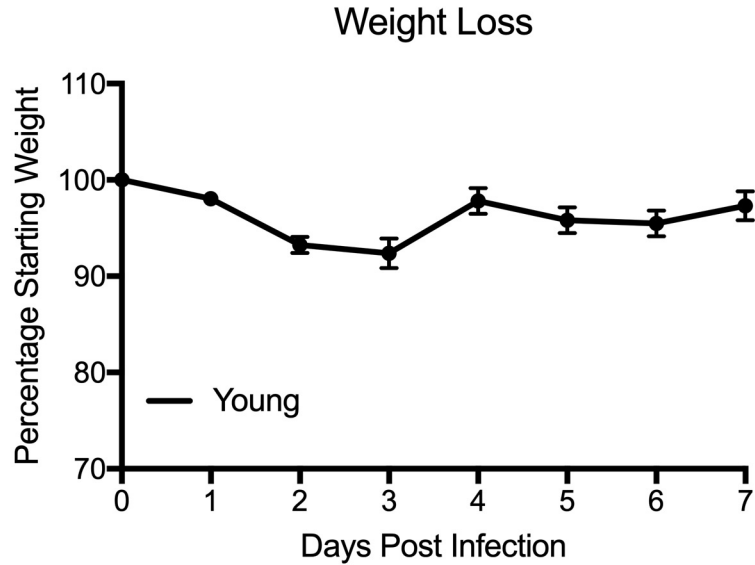
Human Age: 28-34



12 Month Old

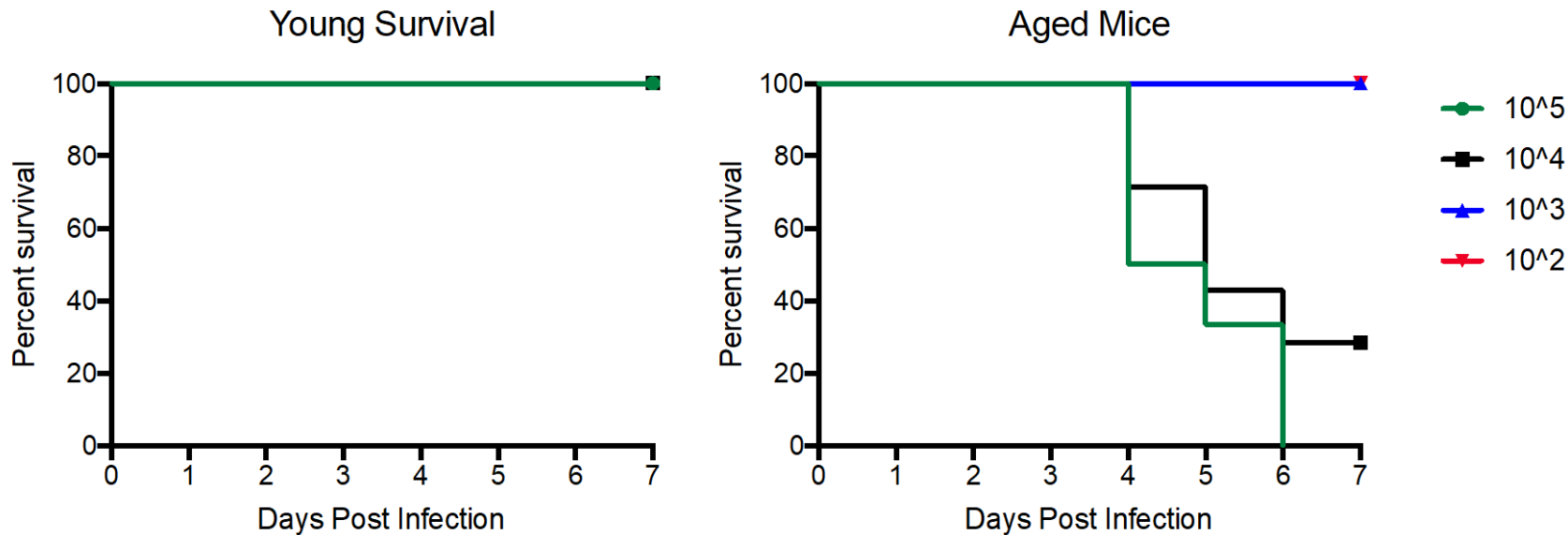
Human Age: late 50s

Aging & Disease



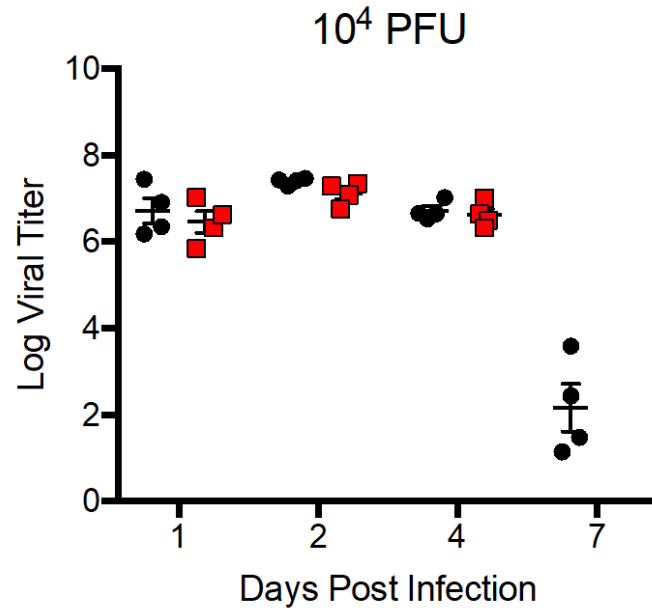
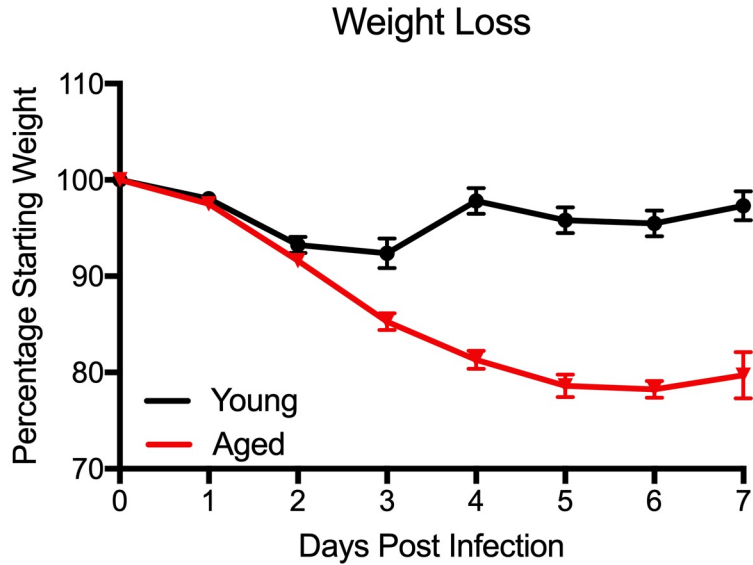
- SARS-CoV age-dependent disease conserved in mice

Aging & Disease



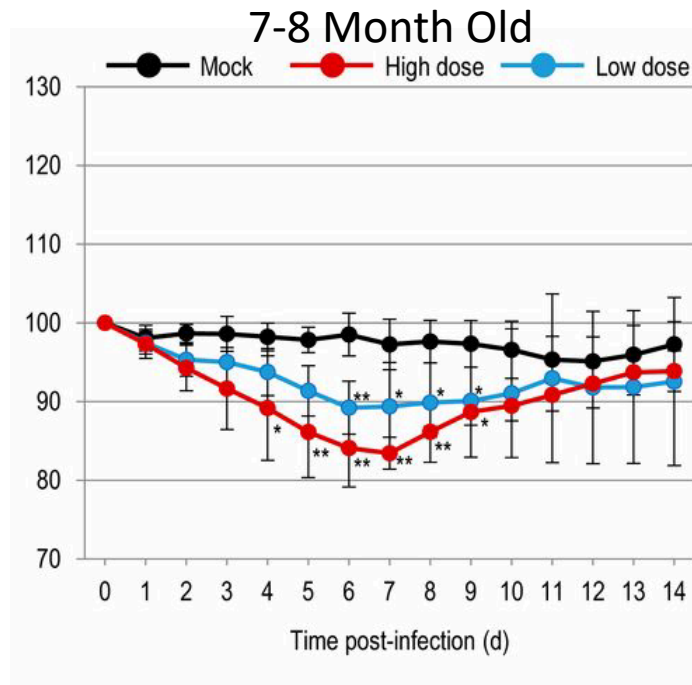
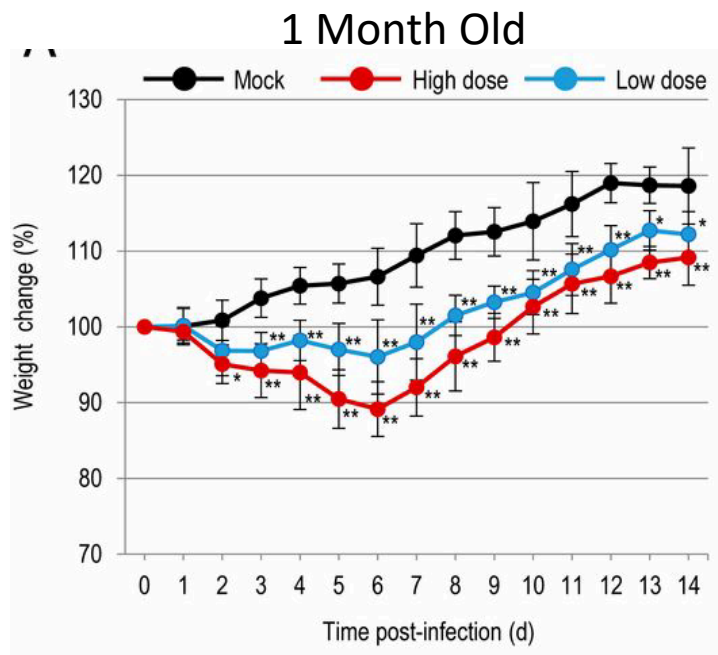
- Dose is major driver of lethality in aged mice

Aging & Disease



- Enhanced disease not due to increase in viral replication

Aging & Disease



- Age-dependent disease observed in SARS-2 hamster model

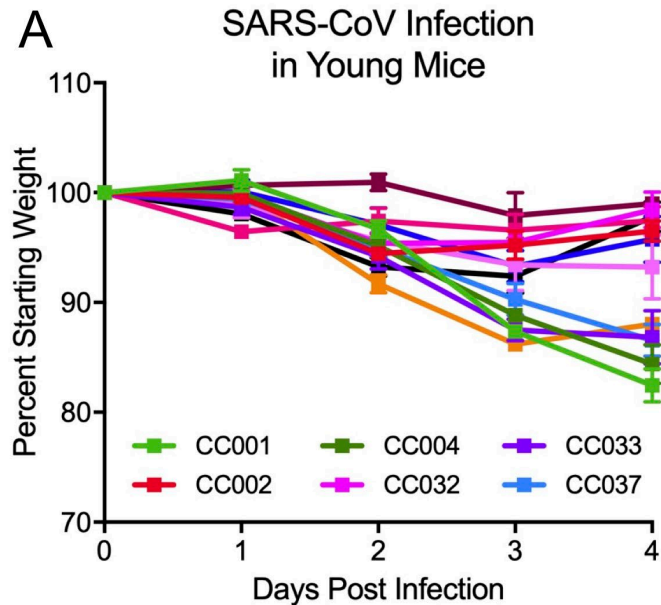
Aging & Disease

- Older mice are more susceptible to SARS-CoV and SARS-2 disease
- Age-related disease is a spectrum rather than binary in terms of damage by age

Disease and Host Conditions

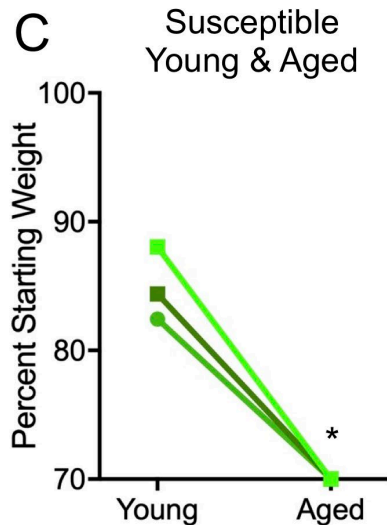
- Disease varies based on host conditions
- The combination of host conditions alters the outcomes in not always expected ways

Host Combinations and Disease



- Examined genetic diversity (CC) and aging following SARS-CoV infection

Host Combinations and Disease



- While aged mice are generally more susceptible, the genetic can shift/alter outcome

Host Combination and Disease

- Combining host conditions does not always lead to predictable outcomes
- Other combinations may offer better understanding of complexity of outcomes

Conclusions

- Dose “how much” matters in the *in vivo* models of CoV disease
- The “who” matters in terms of genetics, health status, and age
- Infectious dose is linked to disease but is not the only variables driving outcome