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Animal Models for Emerging Infectious Diseases

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EMA Non-Clinical Data for Regulatory Decision-Making on the Efficacy of Medical Countermeasures Workshop

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With respect to animal models of infectious disease…

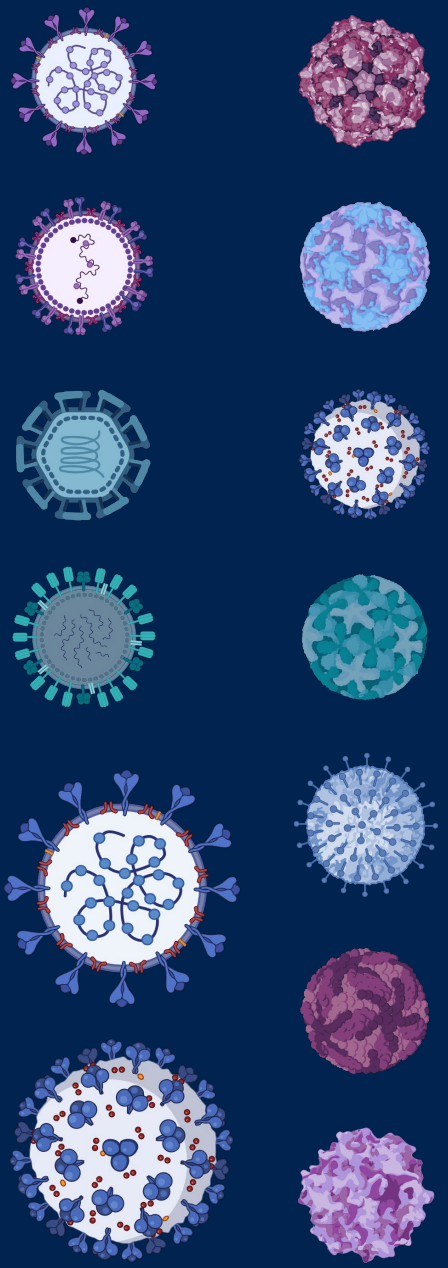
- Certain models are considered "good" in that they recapitulate human disease and have been critical toward the development of medical countermeasures:
  - Nonhuman primate (macaque) models of HIV/AIDS (SIV)
  - Nonhuman primate (macaque) Ebola virus challenge models
  - Ferret influenza challenge models

With respect to animal models of infectious disease…

- Other models are considered "good enough" or "acceptable" in that they serve as valuable tools for studying disease mechanisms as well as developing medical countermeasures:
  - Nonhuman primate (grivet and macaque) models of COVID-19
  - Other nonhuman primate (macaque) filovirus challenge models, including Sudan virus, Marburg virus, and others
  - Nonhuman primate (grivet) Nipah virus challenge models
  - Nonhuman primate (macaque) Mpox challenge models
  - Various rodent models:
    - Hamster models of COVID-19
    - Lassa and Junin virus guinea pig challenge models
    - A very long list of mouse models

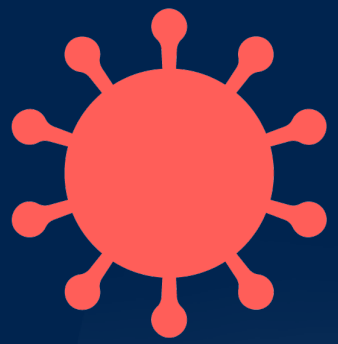
For some infectious diseases, however…

- Establishment of "good", "good enough" and/or "acceptable" animal models has proven challenging:
  - Smallpox
  - Newest variants of SARS-CoV-2
  - Other coronaviruses (e.g., 229E, OC43, HKU1, etc.)
  - MERS-CoV
  - CCHFV
- In general, the difficulty of creating good animal models is often due to fundamental biological differences between species, especially with humans




How do we develop animal models with limited knowledge of the disease and/or when a pathogen may have evolved specifically to infect humans?

2019-nCoV



2019-nCoV (SARS-CoV-2, COVID-19)

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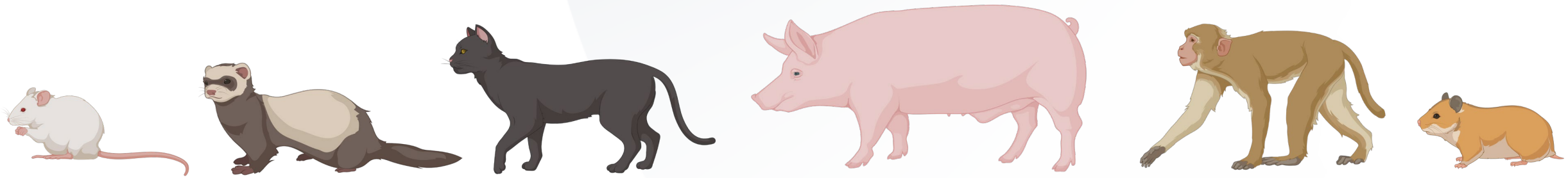
2019-nCoV (SARS-CoV-2, COVID-19)

- Animal model development:
  - Initiated using what we learned during the 2003 SARS-CoV outbreak
  - Mouse (hACE2 Tg)
  - Ferret
  - Cat
  - Swine
  - Nonhuman primates
    - Supply was depleted to the point where individual NHP costs reached upwards of $60K USD
  - Hamster



What did we learn?

Review

Animal models for COVID-19

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Check for updates

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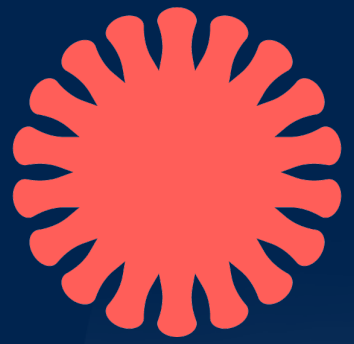
Table 1 | SARS-CoV-2 infection in humans and in animal models

Trait	Organism
Virus replication	
Upper respiratory tract	Humans, mice, ferrets, non-human primates, mink, cats and bats
Lower respiratory tract	Humans, mice, hamsters, ferrets and non-human primates
Other organs	Humans (GI tract, CNS and kidney), hACE2 mice (CNS), hamsters, ferrets and non-human primates (GI tract)
Clinical signs	
Fever	Human and ferrets
Nasal discharge	Humans and ferrets
Laboured breathing	Humans and hamsters
Pneumonia	
Bilateral lung involvement	Humans, hamsters and non-human primates
Ground-glass opacities	Humans, hamsters and non-human primates
Focal oedema and inflammation	Humans, hamsters, ferrets and non-human primates
ARDS	Humans
Transmission	Humans, hamsters, ferrets, cats and bats
Immunology	
Seroconversion	Humans, mice, hamsters, ferrets, non-human primates and bats
Neutralizing antibody titres	Humans, mice, hamsters, ferrets and non-human primates
T cell immunity	Humans, mice, ferrets and non-human primates
Pro-inflammatory cytokines	Humans, mice and non-human primates
Demographics	
More severe disease in males	Humans, hamsters
More severe disease in older individuals	Humans, hamsters and non-human primates

Comparison of SARS-CoV-2 infection in animal models and humans. CNS, central nervous system; GI, gastrointestinal; ARDS, acute respiratory distress syndrome.

The "everything but the kitchen sink" approach was critical during the initial phase of COVID-19; however, as we move beyond the pandemic, addressing other health challenges, including possible future Disease X outbreaks, will demand more refined and targeted strategies.

MERS-CoV

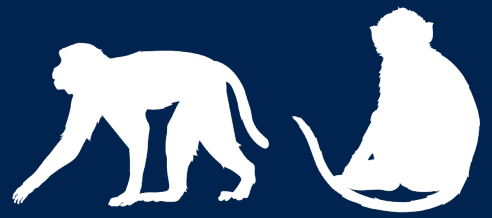


Mouse Models
(*Various*)

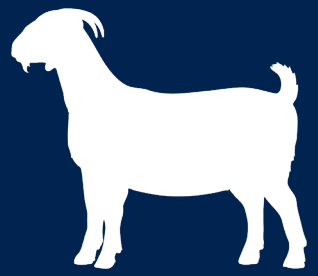
Hamster Model

Rabbit Model

Ferret Model

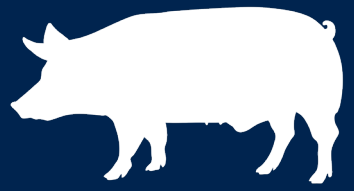


Macaque Models

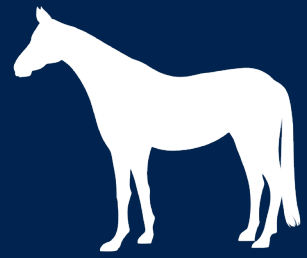


Goat Model

Sheep Model

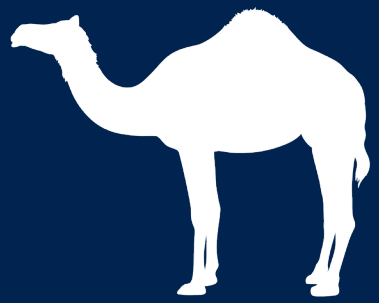


Pig Model



Horse Model

Grivet Monkey
Model



Camel Model

Alpaca Model

Bat Model

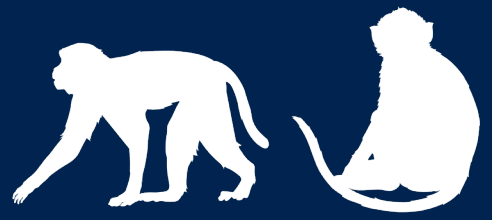
Marmoset Model

Mouse Models
(*Various*)

hDPP4

Rabbit Model

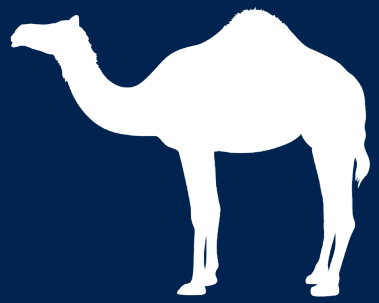
Minimal to no clinical disease



Macaque Models

Grivet Monkey Model

Viral load, but mild clinical symptoms
Challenging logistics



Camel Model

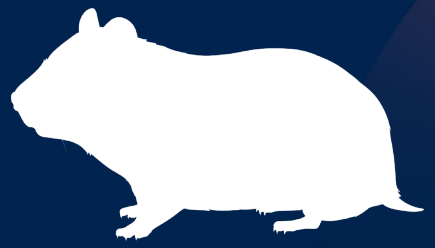
Alpaca Model

Marmoset Model

MERS-CoV Model Development and Use

- Current efforts in the CEPI Preclinical Model Network include:
  - Rodent studies:
    - Refinement of transgenic hDPP4 mouse model
      - Model refinement: dose response and challenge routes (IN and IT)
        - EMC/2012, Jordan/2012, and Riyadh/2018
      - Vaccine efficacy testing
    - Development of hDPP4-transduced hamster model
      - Proof-of-concept (England-1/2012, IN)
    - Development of transgenic hDPP4 hamster model
      - Proof-of-concept
        - EMC/2012, Jordan/2012, and Riyadh/2018 (IN and IT)

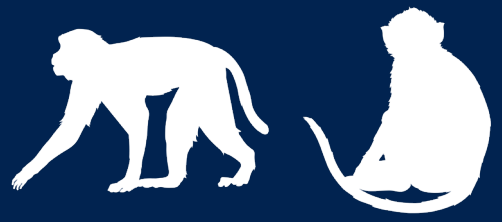
hDPP4 Tg and Transduced Mouse Models



hDPP4 Tg Hamster Model

MERS-CoV Model Development and Use

- Current efforts in the CEPI Preclinical Model Network include:
  - Nonhuman primate studies:
    - Refinement of rhesus and cynomolgus macaque models
      - Dose response and disease pathogenesis
      - Rhesus
        - England-1/2012 and Riyadh/2018
      - Cynomolgus
        - England-1/2012 and Riyadh/2018
    - Refinement of marmoset aerosol challenge model
      - Model refinement via dose response
        - Jordan/2012
        - Challenges due to high virus titer required for nebulizer suspension



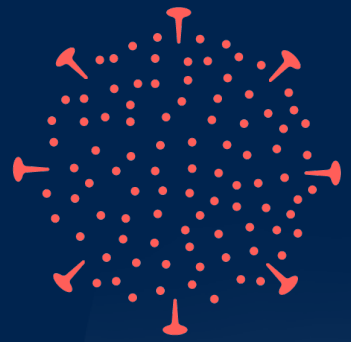
Rhesus and Cynomolgus Macaque Models

Marmoset Model

What have we learned?

- Available animal models for MERS-CoV are limited, but are still valuable:
  - The hDPP4 Tg mouse model is sensitive and presents neurological disease not seen in humans, however it has proven very useful for early screening (e.g., vaccine down-selection) and vaccine efficacy studies
  - Macaque models present with limited disease but are useful for assessing vaccine efficacy in context of febrile responses, viral load, and pathology
    - Similar to SARS-CoV-2
- Early (and often) discussions with regulators is critical to define the model(s) and endpoints to be used for vaccine development and regulatory submission packages

CCHFV



CCHFV

viruses

MDPI

Review

Animal Models for Crimean-Congo Hemorrhagic Fever Human Disease

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"An in-depth understanding of CCHFV-mediated pathogenesis has been hampered by the lack of animal models."

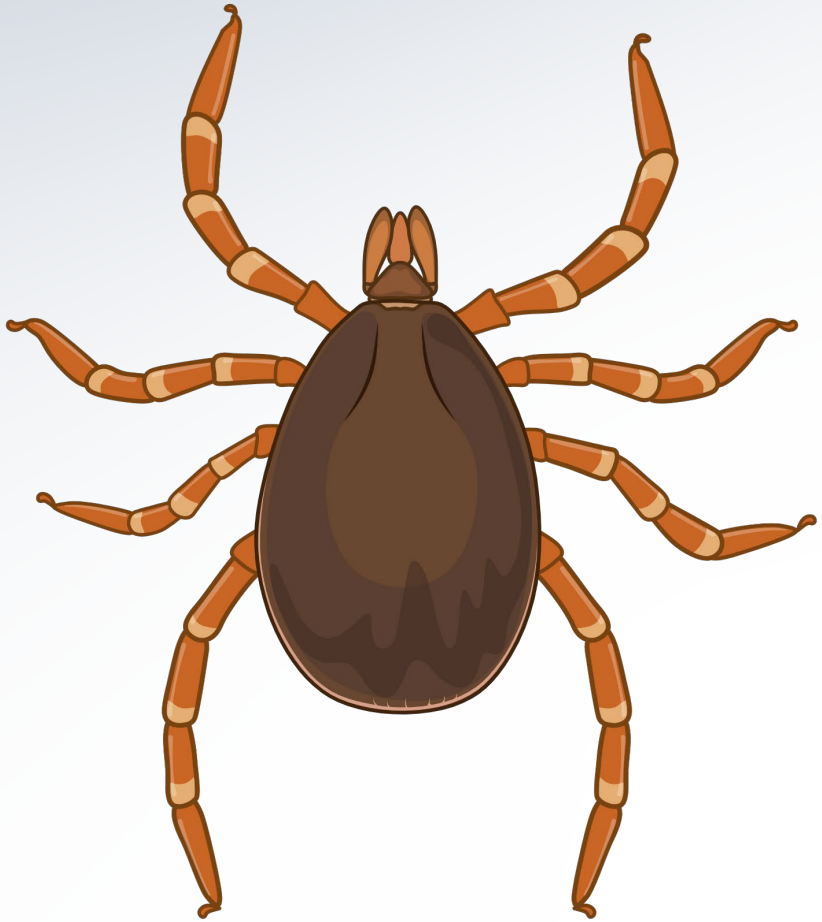
CCHFV

- Animal model development:
  - Various mouse models exhibit lethal disease and have been useful
    - Suckling mice (early studies)
    - IFNAR$^{-/-}$
    - STAT1$^{-/-}$
    - Mouse-adapted CCHFV
  - Hamster (hACE2 Tg)
    - STAT2 KO
  - Nonhuman primates
    - Cynomolgus macaques
      - Mild disease with measurable viral load and clinical pathology alterations, however…
      - Poorly reproducible

CCHFV

- Animal model development:
  - Is there value in establishing/standardizing animal models using ticks given that they are the primary vector and reservoir?
  - What role does the tick play in establishing infection?
  - Does tick saliva enhance infection?

- These types of approaches are often dismissed because of logistical challenges, but efforts to establish standard models have been minimal
  - Should we invest more in models like this?



Disease X

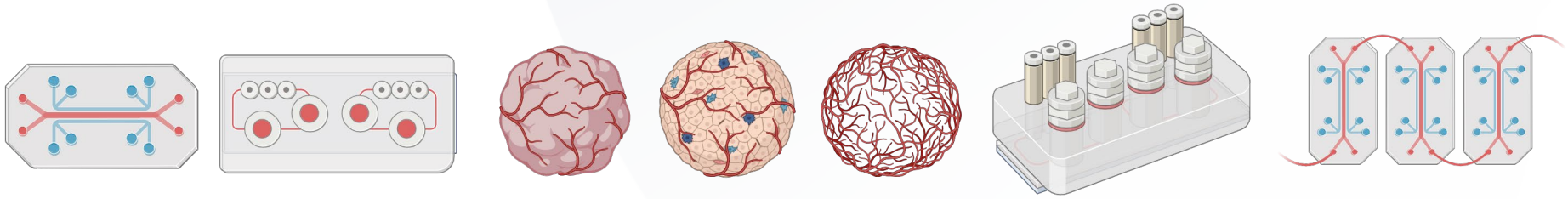
Disease X

- What should our approach be?
  - The “kitchen sink” approach?
  - Strategic selection based on virus family attributes?
  - Should we invest in novel models/approaches?
  - Can we use generative artificial intelligence (GenAI)?

  - What about not using animal models at all?

Non-animal models of infectious disease

- Can we use non-animal systems to help inform model selection or as early screening tools prior to performing studies in animals?
- Microphysiological systems (MPS) are advanced, complex *in vitro* platforms that replicate the functional features of human or animal tissues or organs (*more on this on Day 2, Session 5*)
  - Organoids
  - Organ-on-a-chip
  - Precision-cut tissue slices
- FDA and EMA are actively promoting further development and use as New Approach Methodologies
- In alignment with the 3Rs, we have an obligation to refine and standardize these technologies



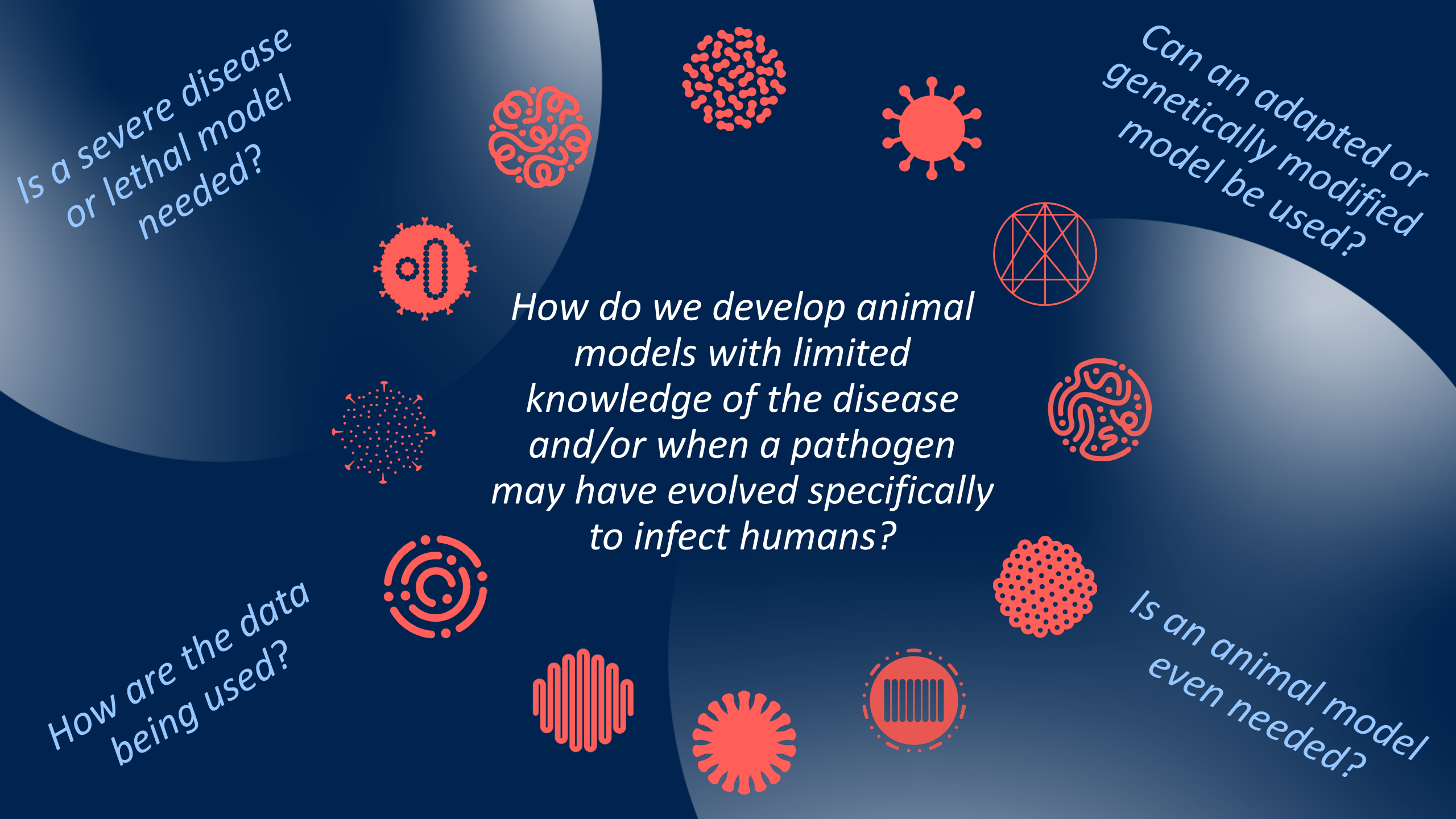
Is a severe disease or lethal model needed?

Can an adapted or genetically modified model be used?

How do we develop animal models with limited knowledge of the disease and/or when a pathogen may have evolved specifically to infect humans?

How are the data being used?

Is an animal model even needed?



A note on quality

Quality

- Animal model development for infectious diseases is a critically important, yet sensitive area
- Scrutiny is increasing and public perception will continue to pose challenges
- Quality implementation is the responsibility of those conducting and sponsoring studies involving animals
- At minimum, these studies should include:
  - Study protocol
  - SOPs
  - Good Documentation Practices
  - Data QC
  - Final Report

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