Pathogenesis and transmission of SARS-CoV-2 in golden hamsters

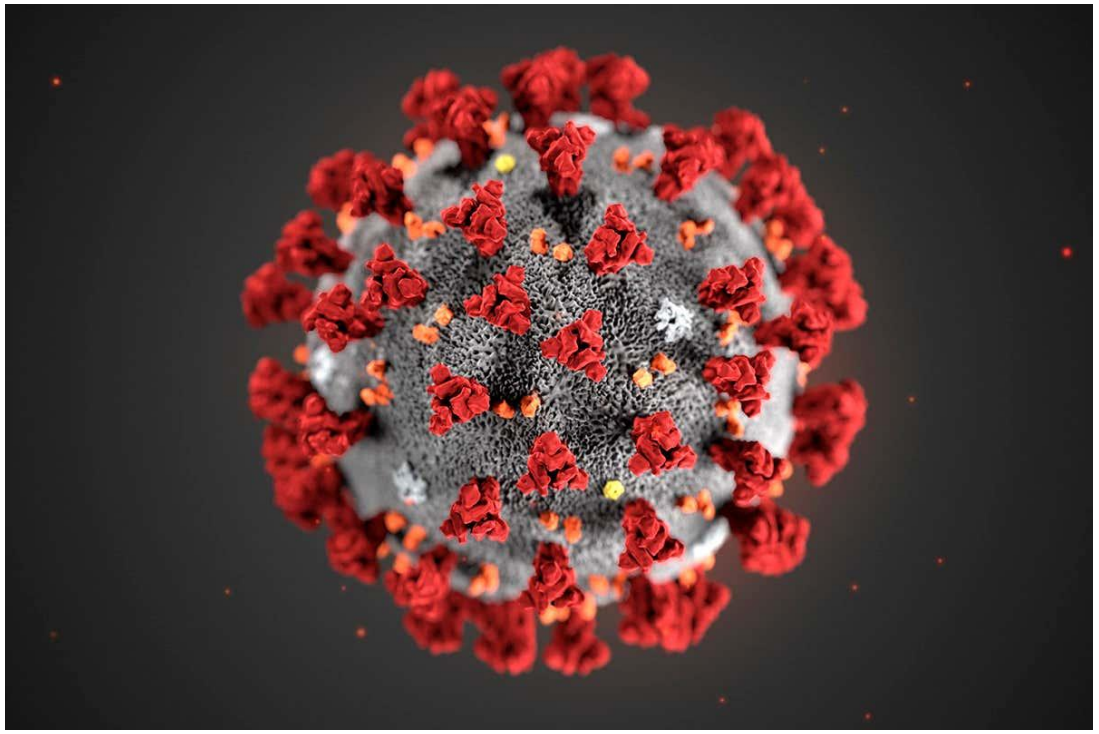
Sin Fun Sia, Li-Meng Yan, Alex W. H. Chin, Kevin Fung, Ka-Tim Choy, Alvina Y. L. Wong, Prathanporn Kaewpreedee, Ranawaka A. P. M. Perera, Leo L. M. Poon, John M. Nicholls, Malik Peiris & Hui-Ling Yen

nature

https://doi.org/10.1038/s41586-020-2342-5

Accelerated Article Preview

SARS-CoV-2



https://www.newscientist.com/term/covid-19/

- Spreads across the world from the end of 2019.
- Causes human to human transmission & incredible high death tolls from an outbreak now.
- A suitable small animal model is needed to support vaccine and therapy development.

Golden Syrian hamsters

Image from BioLasco Biotechnology Inc.

- The spike protein of SARS-CoV-2 utilizes ACE2 receptors that are distributed predominantly in the epithelial cells of the lungs and small intestine to gain entry into epithelial cells for viral replication.
- SARS-CoV-2 showed good binding for human ACE2 but limited binding to murine ACE21, which has limited the use of inbred mice for research.
- The availability of macaques and transgenic ICR mice for the virus infection is limited.
- Golden Syrian hamsters have been wildly utilized for SARS-CoV partly due to the animals are permissive for infection by other respiratory viruses.

Material & Methods

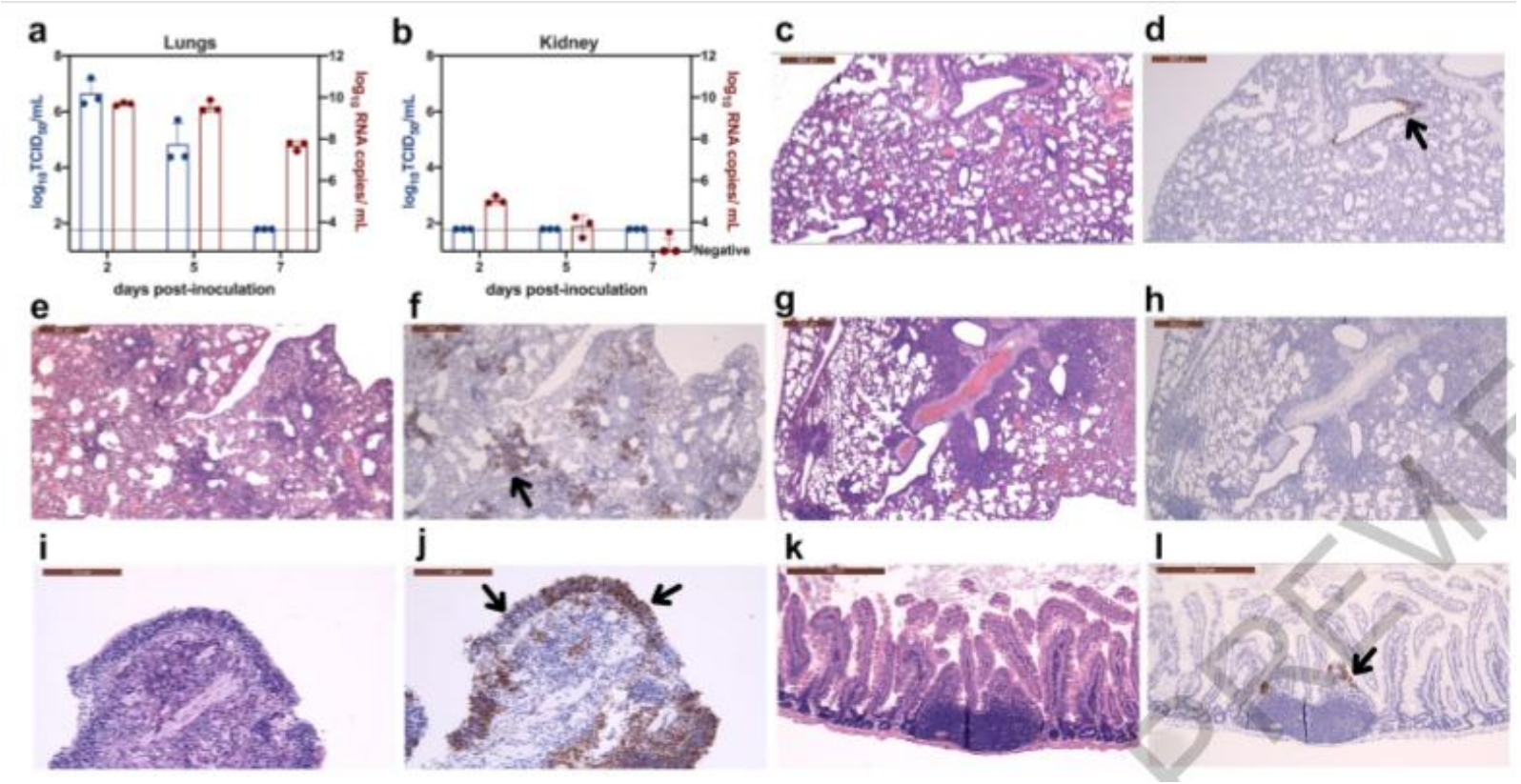
- **All experiments are performed in at the BSL-3 facility.**
- Male golden Syrian hamsters (4 – 5 weeks old) are infected intranasally with 8 x 10^4 TCID50 of the BetaCoV/Hong Kong/VM20001061/2020 virus.
- On days 2, 5, 7 infection, animals are euthanatized, lungs and one kidney are collected for viral load determination and were homogenized in 1mL PBS. Brain, nasal turbinate, lungs, liver, heart, spleen, duodenum, and kidney are subjected to histopathological examination.
- Fecal samples are collected for RT-PCR and TCID50 tests.
- Viral load determination by quantitative real-time RT-PCR
- Plaque reduction neutralization (PRNT) assay.
- For immunohistochemistry, SARS-CoV-2 N protein was detected using monoclonal antibody (4D11)34, CD3 was detected using polyclonal rabbit anti-human CD3 antibodies; neuron-specific beta-III tubulin was detected using 1monoclonal antibody

Experimental designs

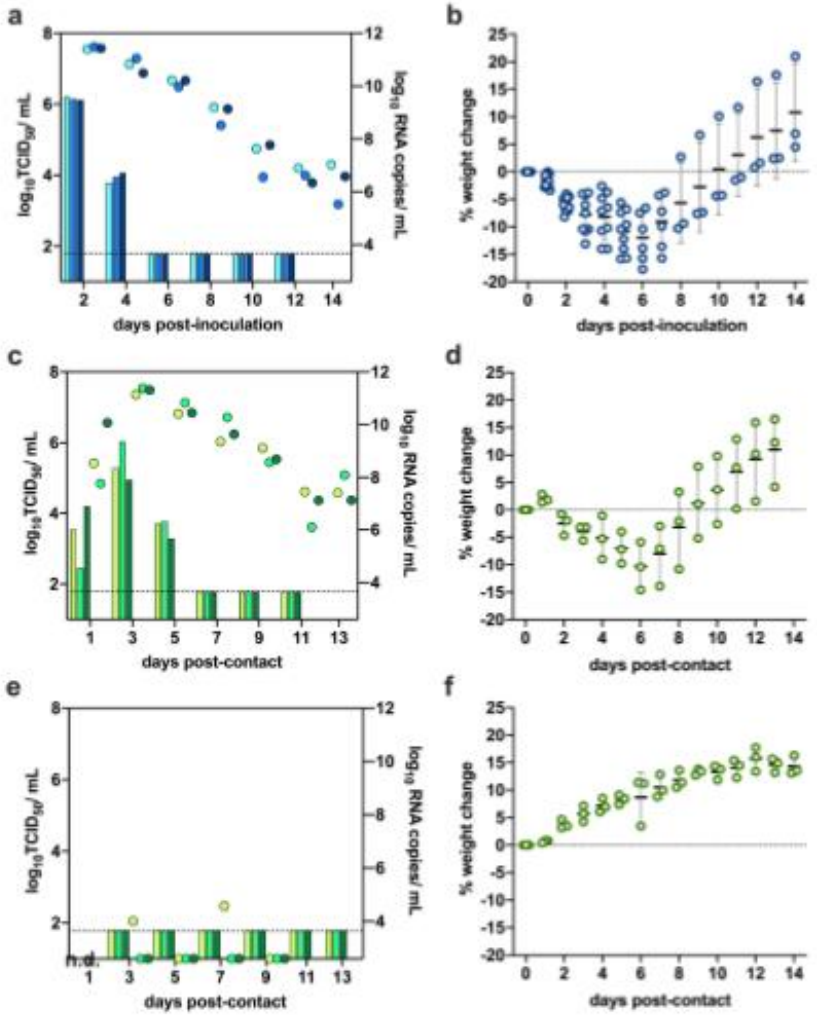
- For characterizing SARS-CoV-2 transmissibility by direct contact, 8 x 10^4 TCID50 of SARS-CoV-2-infected animals are co-housed with one naïve hamster for at least 13 days.
- For characterizing SARS-CoV-2 transmissibility by aerosol, one naïve hamster was exposed to one inoculated donor hamster in two adjacent stainless steel wired cages on 1 dpi for 8 hours.
- To evaluate transmission potential of SARS-CoV-2 virus via fomites, three naïve fomite contact hamsters were each introduced to a soiled donor cage on 2 dpi. The fomite contact hamsters were single-housed for 48 hours inside the soiled cages and then were each transferred to a new cage on 4 dpi of the donor. All animals were continued monitored for 14 days.
- To monitor the level of fomite contamination of SARS-CoV-2 virus in soiled cages, surface samples (5 cm x 5 cm, except that the whole water bottle nozzle was swabbed) were collected using flocked polyester swabs.

Viral load and histopathological changes in golden Syrian hamsters intranasally challenged with SARS-CoV-2

- Virus load in lung and kidney (a,b); Inflammatory cell infiltration in lung tissue (c,d,e,f); viral antigen in bronchial epithelial (d) with progression to pneumocytes (f); an increased consolidation lungs (g); moderate inflammatory cell infiltration in the nasal turbinate (i), and viral antigen in the nasal epithelial cells (j) and in olfactory sensory neurons at the nasal mucosa (j); on 14 dpi, no inflammation was present (k), viral antigen was detected from the epithelial cells of duodenum on 2 dpi (l)

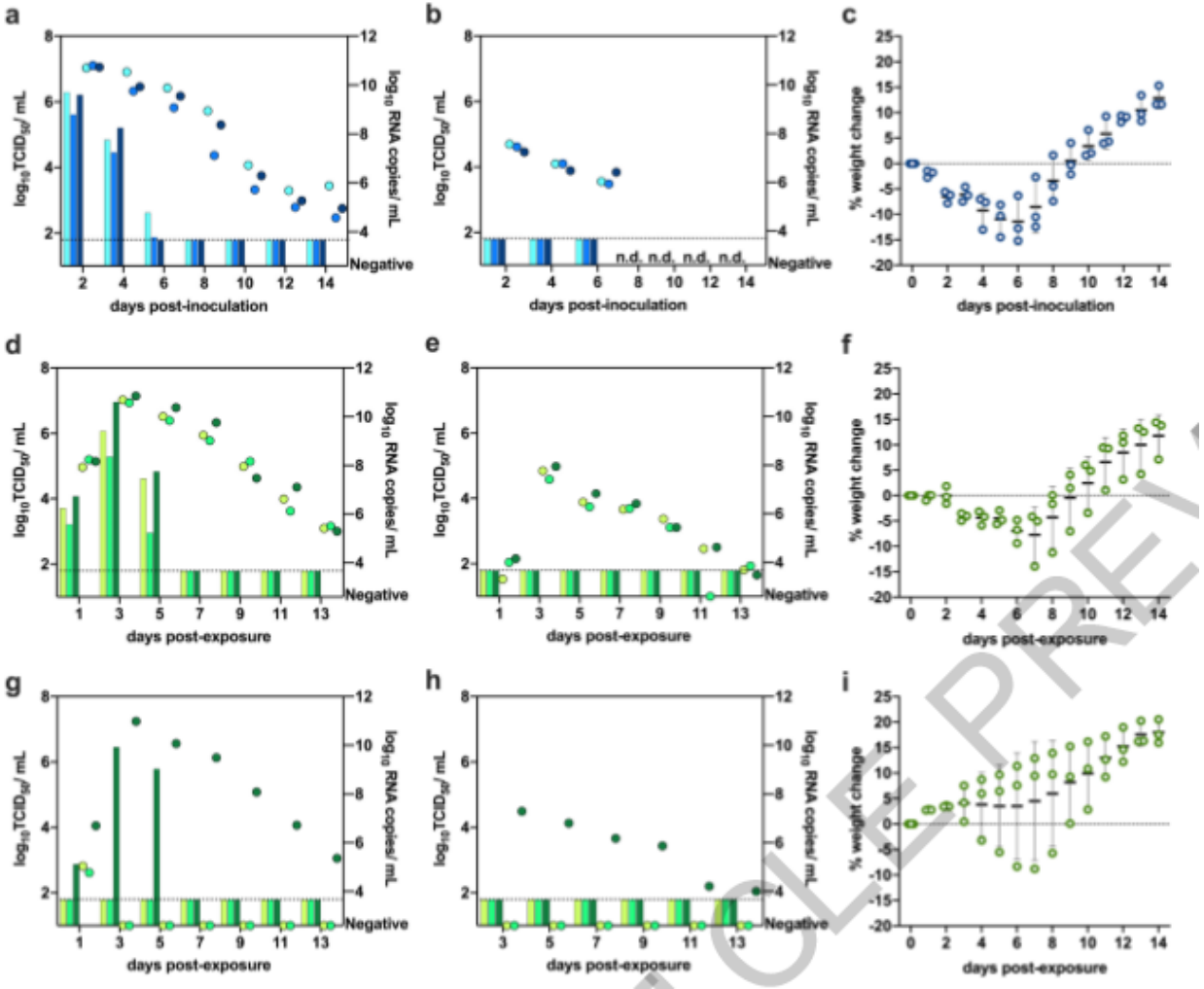


Transmission of SARS-CoV-2 in golden Syrian hamsters by direct contact



- **a**, Infectious viral load and viral RNA copy numbers in the nasal washes of donor
- **b**, Body weight changes (% weight change compared to day 0) of hamsters inoculated with SARS-CoV-2 (N=9).
- **c**, Transmission of SARS-CoV-2 to naïve hamsters (N=3) that were each co-housed with one inoculated donor on 1 dpi; infectious viral load and viral RNA copy numbers detected in the nasal washes of contact hamsters were shown.
- **d**, Body weight changes of contact hamsters (N=3) infected with SARS-CoV-2.
- **e**, Transmission of SARS-CoV-2 to naïve hamsters (N=3) that were each co-housed with one donor on 6 dpi; infectious viral load and viral RNA copy numbers detected in the nasal washes of contact hamsters were shown.
- **f**, Body weight changes of contact hamsters (N=3)

Transmission of SARS-CoV-2 in golden Syrian hamsters via aerosols and fomites



a, Infectious viral load and viral RNA copy in the nasal washes of donor hamsters (N=3) inoculated with SARS-CoV-2.
b, Infectious virus and viral RNA detected in the fecal samples of donor hamsters (N=3).
c, Body weight changes of donor hamsters (N=3).
d, Aerosol transmission to naïve hamsters exposed to donors for 8 hours on 1 dpi; Infectious virus and viral RNA detected in the nasal washes of aerosol contact hamsters.
e, Infectious virus and viral RNA detected in the fecal samples of aerosol contact hamsters (N=3).
f, Body weight changes of aerosol contact hamsters.
g, Fomite transmission to naïve hamsters (N=3) that were single-housed in donors' soiled cages for 48 hours; Infectious virus and viral RNA detected in the nasal washes of fomite contact hamsters.
h, Infectious virus and viral RNA detected in the fecal samples of fomite contact hamsters (N=3).
i, Body weight of fomite contact hamsters (N=3).

Summary

- The golden Syrian hamster is a suitable experimental animal model for SARS-CoV-2 as there is weight loss in the inoculated and naturally-infected hamsters and evidence of efficient viral replication in the nasal mucosa and lower respiratory epithelial cells
- Transmission of SARS-CoV-2 from inoculated donors to naïve hamsters by direct contact or via aerosols.
- Hamsters are easy to handle. The results highlights similarity and differences between the SARS-CoV and SARS-CoV-2 in the hamster model.

What behind the scenes

- The host defense mechanism leading to the rapid viral clearance in the respiratory tissues of the hamsters.
- The transmission dynamics of the virus by aerosols.