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Consistency of dose-response models and outbreaks – the case of SARS

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SARS and its causal pathogen

- ✓SARS =
  - **S**evere
  - **A**cute
  - **R**espiratory
  - **S**yndrome

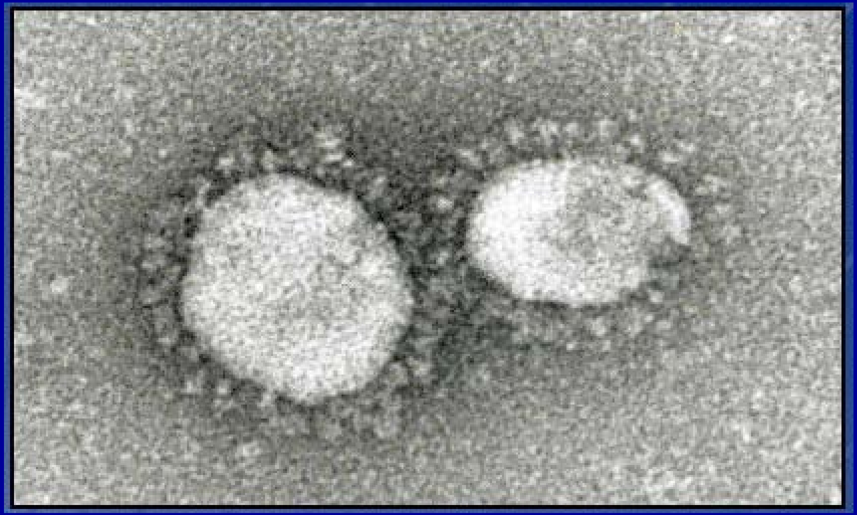


Photo by C. Humphrey, Pathology Activity Program, CDC

- ✓This severe pneumonia is caused by a newly isolated coronavirus (SARS-CoV) which first appeared in late 2002 in China.

SARS pandemic in 2003

- ✓In the spring 2003, a large outbreak of SARS occurred in Hong Kong and rapidly spread throughout the world.
- ✓Ultimately 8,096 cases of SARS were identified in 29 countries/areas and 774 patients reportedly died.
- ✓The rapid transmission and high mortality rate made SARS a global threat for which no efficacious therapy was available.

Objectives

- ✓To develop a dose-response model for SARS-CoV based on the available datasets.

- ✓To apply the developed model to the analysis of the epidemiological data of the SARS outbreak that occurred at an apartment complex in Hong Kong.

Procedures for this study

1. Collecting dose-response datasets from a variety of medical/biomedical journals

2. Fitting dose-response models to the datasets with the maximum likelihood method

3. Choosing the best-fit model based on their deviances (goodness-of-fit)

4. Model application to the analysis of SARS outbreak in Hong Kong

SARS-CoV and other coronaviruses

✓Coronaviruses are generally restricted in their host range.

✓SARS-CoV can infect and replicate in mice, ferrets, hamsters, cats and several species of non human primates.

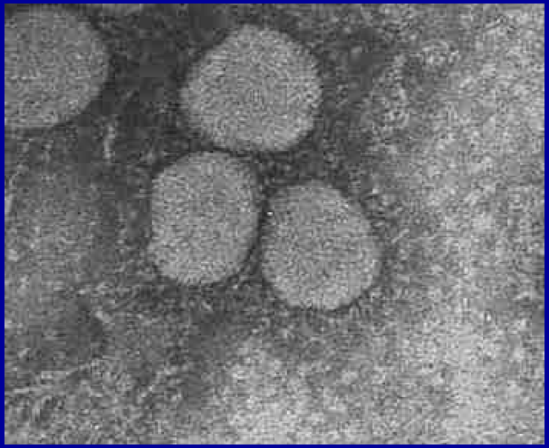


Photo by Dept of Microbiology, The Univ of Hong Kong and the Government Virus Unit, Dept of Health, Hong Kong , China

SARS-CoV and other coronaviruses (cont'd)

✓Most attempts to reproduce completely human clinical disease and pathological findings in these animals failed.

✓*It was so tough to find the dose-response dataset for SARS-CoV!*

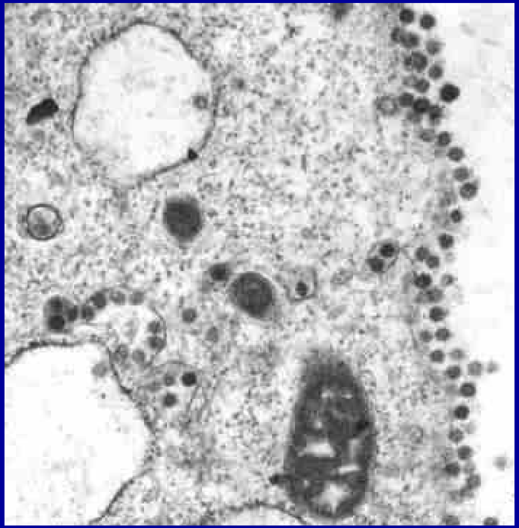
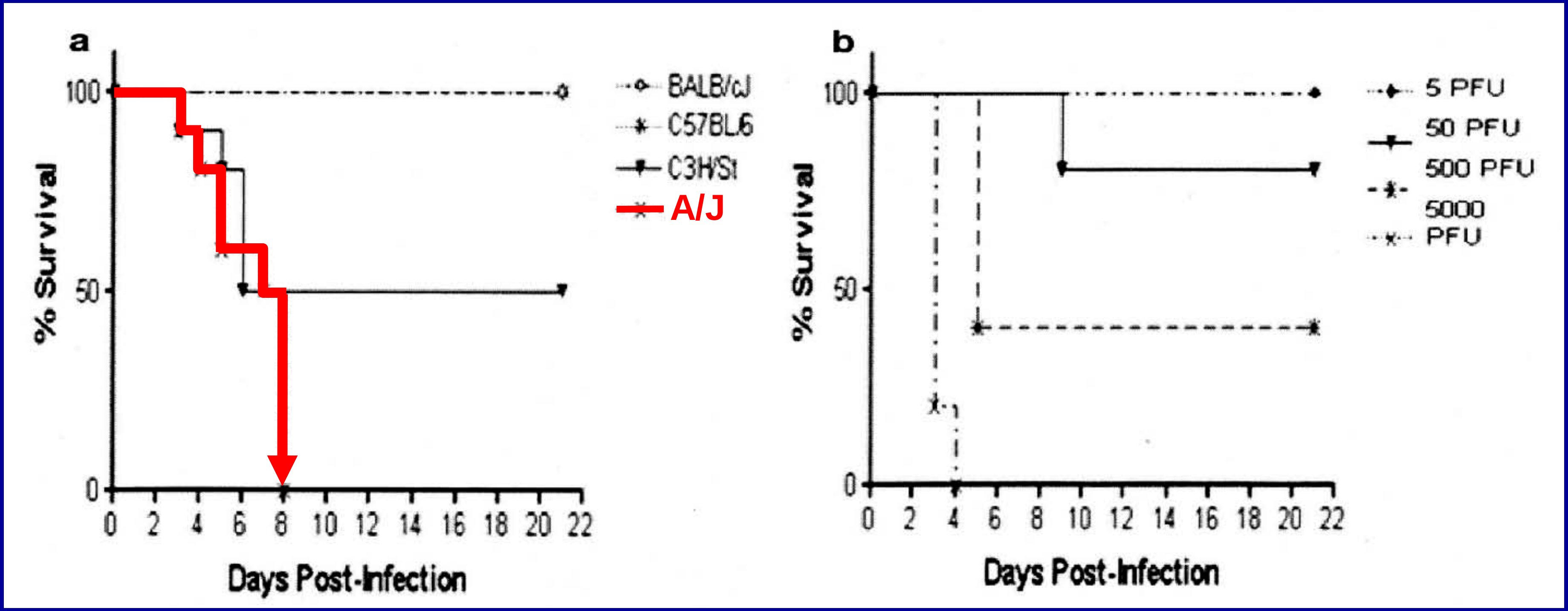


Photo by Dept of Microbiology, The Univ of Hong Kong and the Government Virus Unit, Dept of Health, Hong Kong , China

Infection of A/J mice with MHV-1



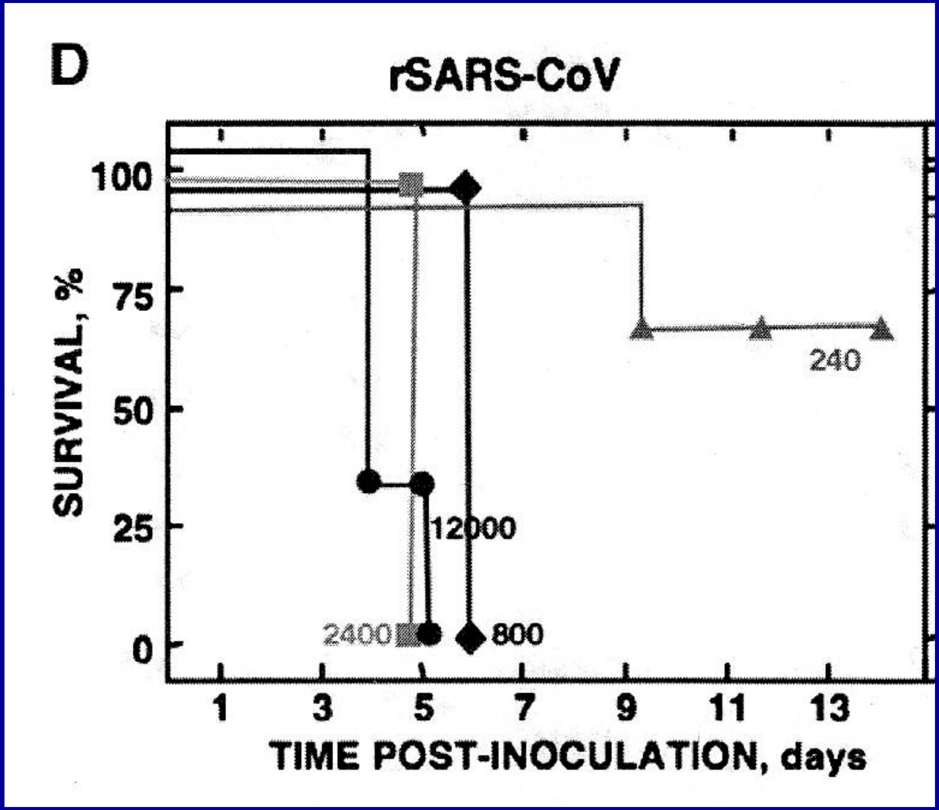
✓All MHV-1-infected mice developed progressive interstitial pneumonitis and died by day 8 post infection.

✓The infected mice would be a potentially useful small animal model of human SARS.

Ref.) De Albuquerque *et al.*, *J. Virol.* (2006)

Tg mice susceptible to SARS

✓Transgenic (tg) mice expressing the human receptor for SARS-CoV were infected with recombinant SARS-CoV.



Ref.) DeDiego *et al.*, *Virology* (2008)

Fitting models to dataset

These datasets were successfully pooled as a surrogate dataset for human SARS-CoV infection.

Dose-response models fitted to the pooled datasets.

$$p(d) = 1 - \left[1 + \frac{d}{280}\left(2^{1/670} - 1\right)\right]^{-670}$$

Beta-Poisson model
(deviance=1.74, p=0.94)

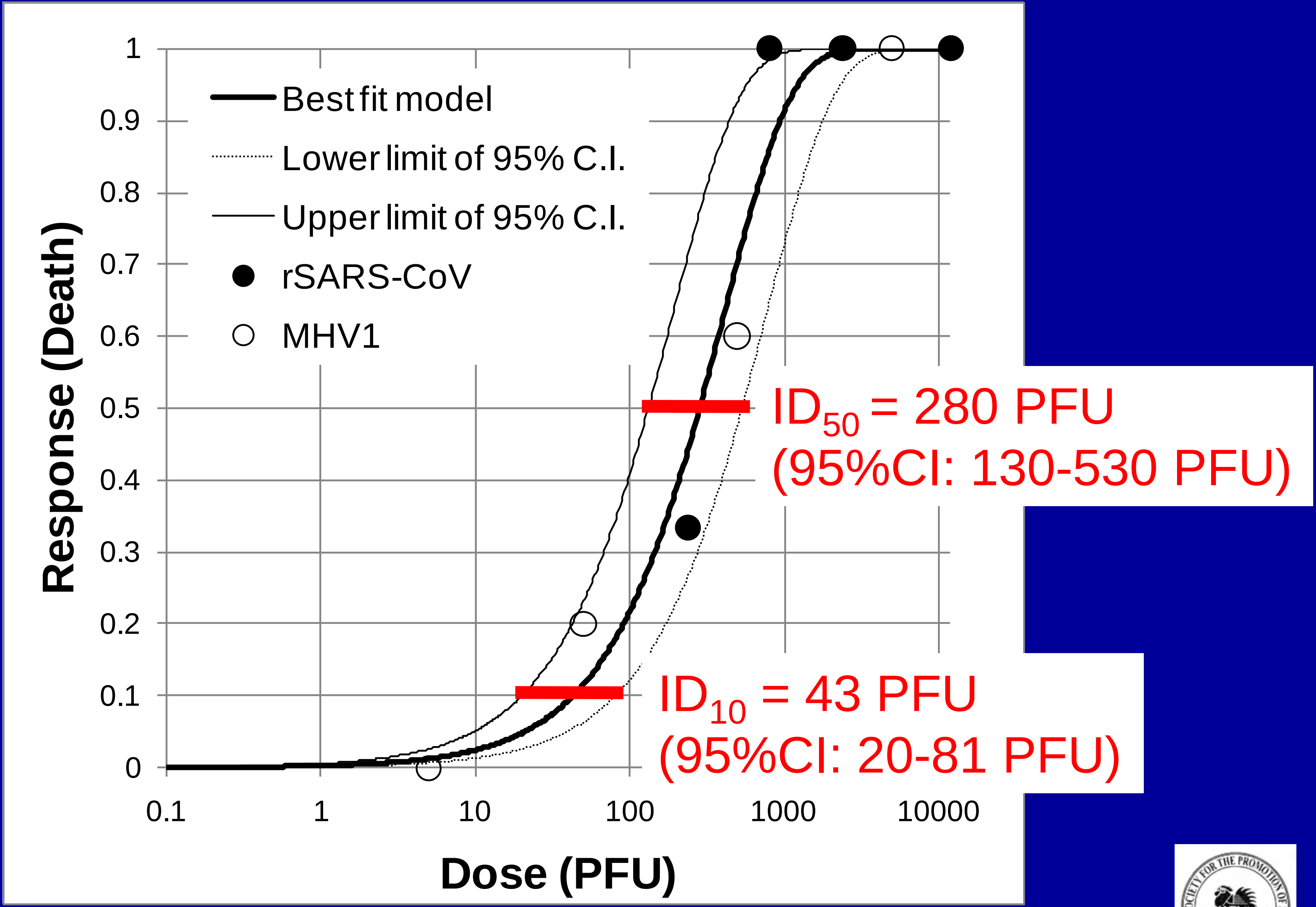
$$p(d) = 1 - \exp\left(-\frac{d}{410}\right)$$

Exponential model
(deviance=1.75, p=0.97)

where, d is a dose and p(d) is the probability of infection.

Beta-Poisson model did not provide a statistically significant improvement in fit to the pooled datasets rather than exponential model

D-R model for SARS-CoV

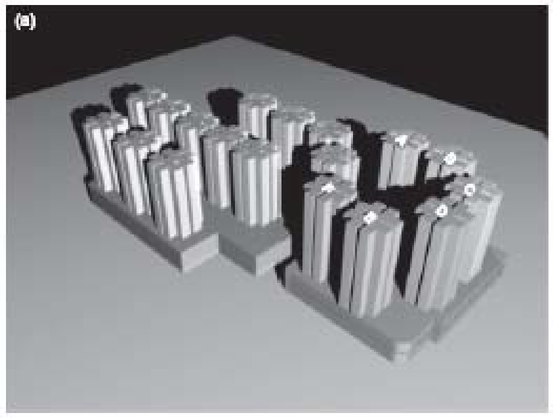


95% confidence intervals were based on 10,000 times bootstrap trials.

4. Model application

Back-calculation of dose of SARS coronavirus to residents at an apartment complex in Hong Kong

✓More than 300 among 20,000 residents were affected in the early stage of the outbreak in Hong Kong



Ref.) Li *et al.*, *Indoor Air* (2004)

Cause of the SARS outbreak

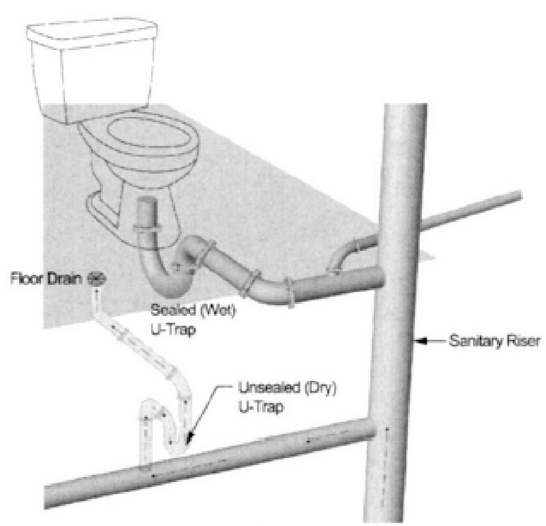
✓The outbreak was begun with an index case who visited his family in Building E.

✓*He stayed overnight and used toilet there.*

✓*Sewage contamination associated with the index case excreting SARS-CoV that gained entry to households through the bathroom floor drain with dried U-trap was the primary cause of the outbreak.*

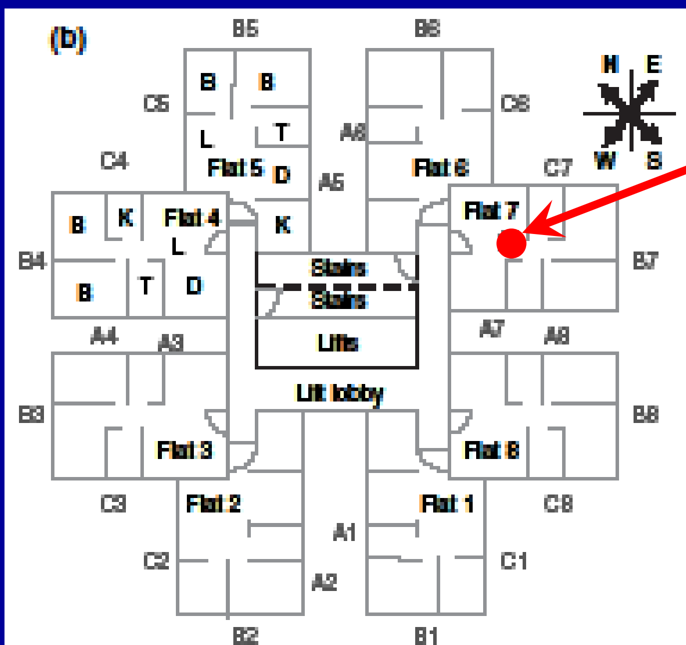
FIGURE 2

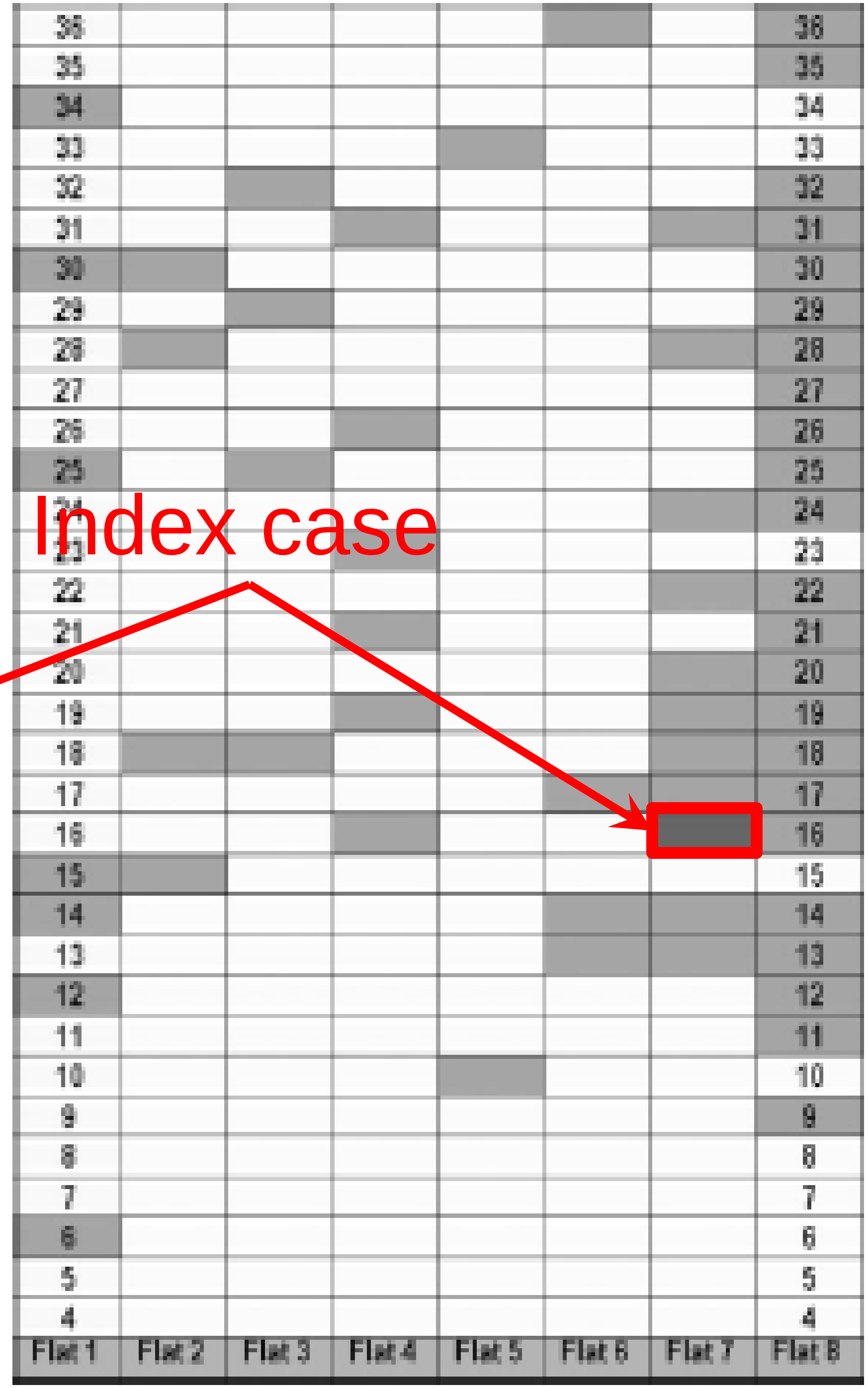
Typical Sanitary Plumbing Configuration



Ref.) Report by Department of Health, Hong Kong SAR (2003)

Distribution of infected flats for the first 99 confirmed cases in Building E





Ref.) Li *et al.* (2004)

How to estimate dose of SARS-CoV to residents

- ✓While number of cases in each flat was reported, number of residents wasn't done.
- ✓Attack rate defined as the ratio of number of cases to number of residents is unknown.
- ✓Alternatively attack rate was calculated on the assumption that every flat had four residents which was the largest number of cases in any one flat.

How to estimate dose of SARS-CoV to residents (cont'd)

✓Dose (d) of SARS-CoV to residents was estimated with the dose-response model by substituting the probability of infection (p(d)) by the attack rate.

(a) Estimation based on the assumed number of resident.

Floor (level)	Number of reported cases	Number of residents*	Attack rate	Estimated dose (PFU)
Lower (4-13)	12	320	0.038	16
Middle (14-23)	46	320	0.144	63
Upper (24-36)	41	416	0.099	42
Overall	99	1056	0.094	40

* Assumed that each flat has four residents.

→ Underestimation because number of residents in some flats would be below four and there were possibly unoccupied flats.

How to estimate dose of SARS-CoV to residents (cont'd)

✓Attack rate was also calculated as the ratio of number of flats having at least one case to total number of flats. The dose of SARS-CoV to residents was estimated in the same manner.

(b) Estimation based on the number of affected flats.

Floor (level)	Number of affected flats**	Total number of flats	Attack rate	Estimated dose (PFU)
Lower (4-13)	9	80	0.113	49
Middle (14-23)	26	80	0.325	160
Upper (24-36)	26	104	0.250	117
Overall	61	264	0.231	107

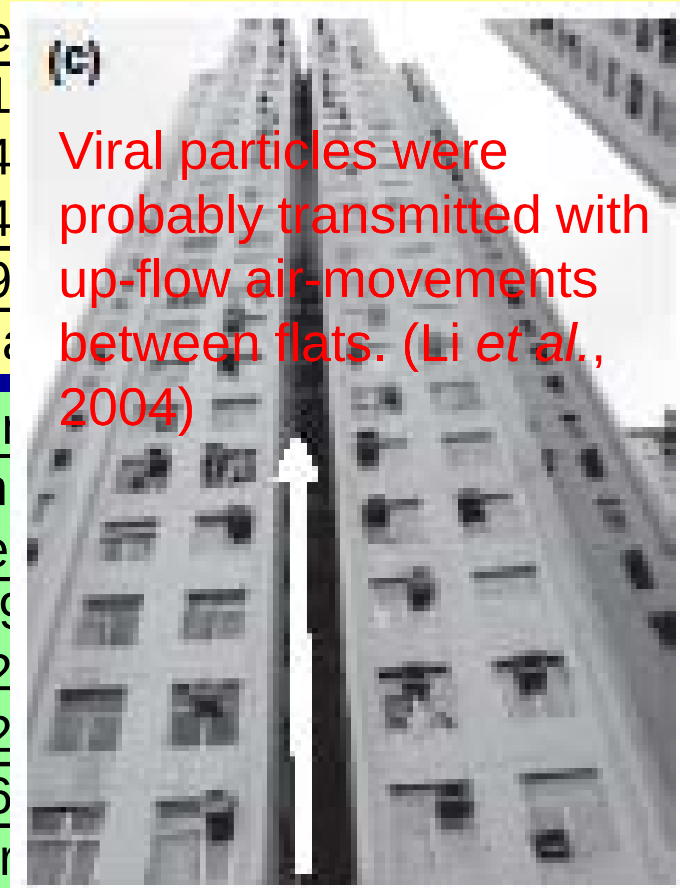
** Number of flats where at least one case was reported.

Estimated dose of SARS-CoV

(a) Estimation based on the assumed number of resident.

Floor (level)	Number of reporte…	Number of …	Attack rate	Estimated dose (PFU)
Lower (4-13)	1…		…038	16
Middle (14-23)	4…		…144	63
Upper (24-36)	4…		…099	42
Overall	9…		…094	40

* Assumed that each fl…



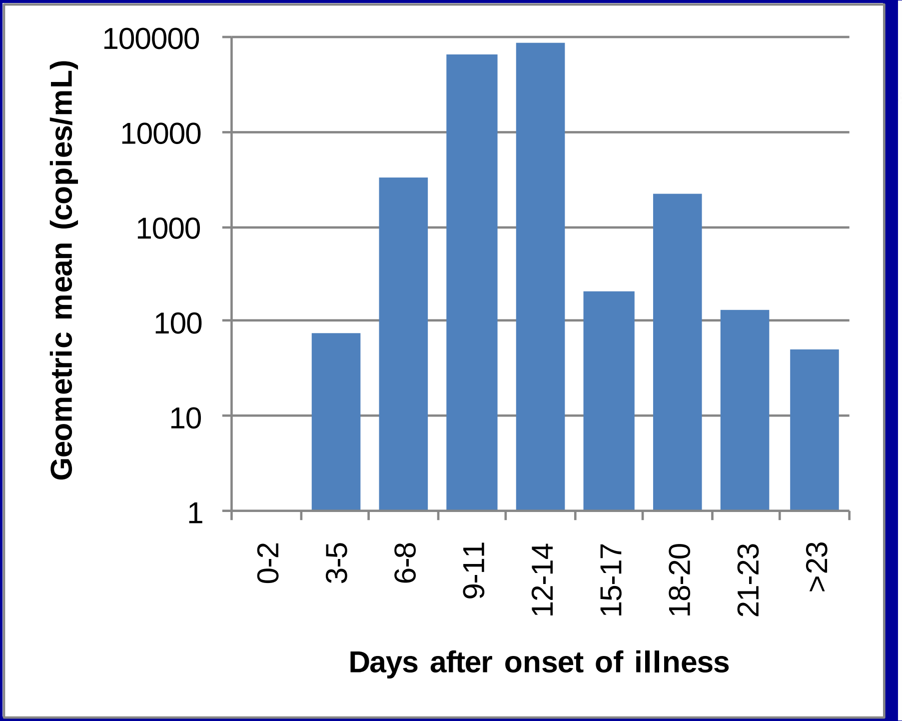
(b) Estimation based o… …

Floor (level)	Num… affecte…		…ck rate	Estimated dose (PFU)
Lower (4-13)	9…		…113	49
Middle (14-23)	2…		…325	160
Upper (24-36)	2…		…250	117
Overall	6…		…231	107

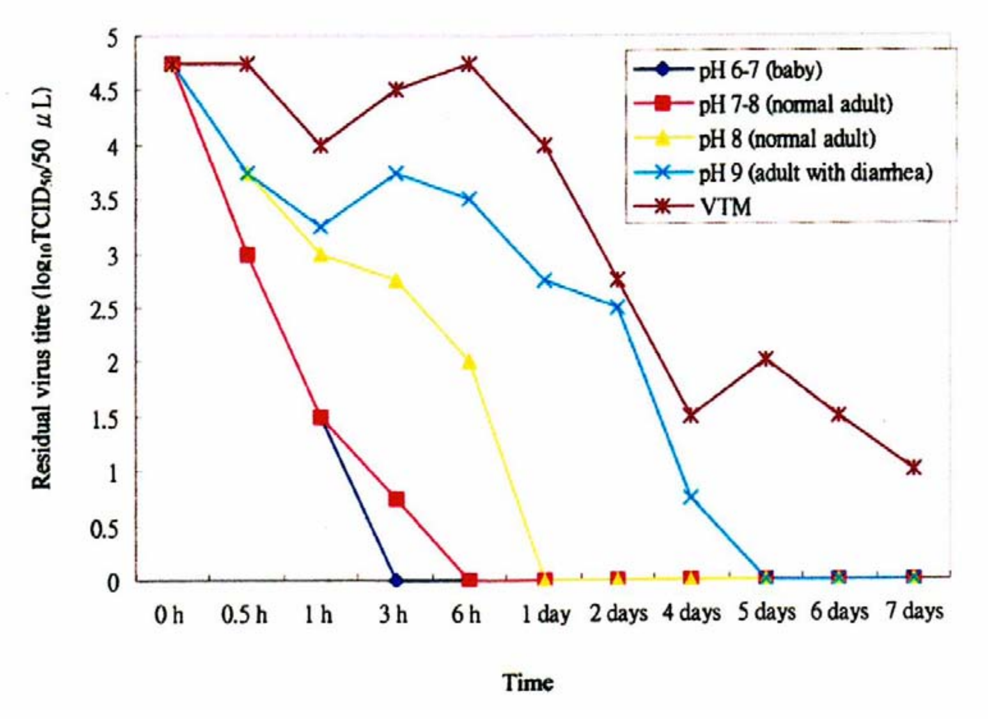
** Number of flats wher… …rted.

Real doses were in the range between those estimated in above two assumptions.

Validation of estimated dose



Virus concentration in feces of SARS patients (Cheng *et al.*, 2004)



Survival of SARS-CoV in stool specimens at room temperature (Lai *et al.*, 2005)

If index case's feces of 1mL contained 90,000 copies of virus, 900 copies (1%) could survive during the first day. Estimated dose (16-160 PFU) is equivalent to the copies of viruses in only 20-200 μl of feces.

Drexel

Conclusions

- ✓We proposed the exponential model ($k = 4.1 \times 10^2$) for SARS-CoV infection via intranasal route.
- ✓It was revealed that the residents were exposed to the dose of SARS-CoV between 16 and 160 PFU/person, depending on the floor, during the outbreak in an apartment complex in Hong Kong, 2003

Uncertainty factors

- ✓Species dependency (mouse=human?)
- ✓Infection route (intranasal vs aerosol)
- ✓Time-to-response

Significance & impact

✓The developed model is the sole dose-response model for SARS-CoV at the present and would help us predict the reemergence of SARS in the future.

Thank you for your kind attentions!