# COVID-19:
# The Crown Evolves

Department of Tropical Medicine Seminar

3/25/20

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Queen's Medical Center

# Goals and Objectives

- Discuss the origin and  transmission of COVID -19
- Discuss the clinical presentation of COVID-19 and compare to influenza, MERS and SARS
- Review treatment options
- Discuss basic infection control and prevention strategies for COVID-19

3/24/20

# Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at J…

**Total Confirmed**
**414,277**

**Confirmed Cases by Country/Region/Sovereignty**

- 81,591 China
- 69,176 Italy
- 51,542 US
- 39,676 Spain
- 32,781 Germany
- 24,811 Iran
- 22,605 France
- 9,877 Switzerland
- 9,037 Korea, South
- 8,164 United Kingdom
- 5,578 Netherlands
- 5,137 Austria
- 4,269 Belgium
- 2,779 Norway
- 2,581 Canada
- 2,362 Portugal

Admin1


Cumulative Confirmed Cases | Active Cases

169

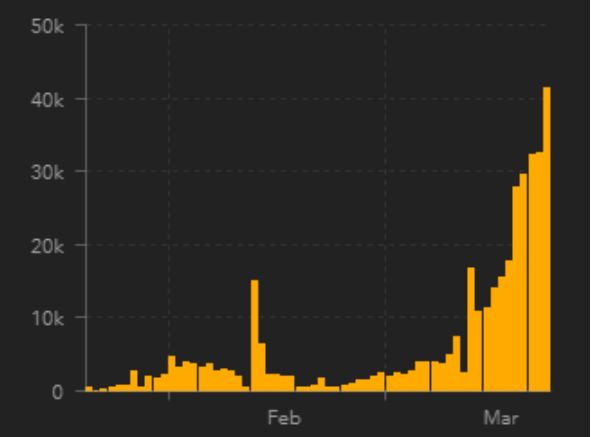
*Lancet Inf Dis* Article: Here. Mobile Version: Here. Visualization: JHU CSSE. Automation Support: Esri Living Atlas team and JHU APL. Contact US. FAQ.
Data sources: WHO, CDC, ECDC, NHC, DXY, 1point3acres

**Total Deaths**
**18,557**

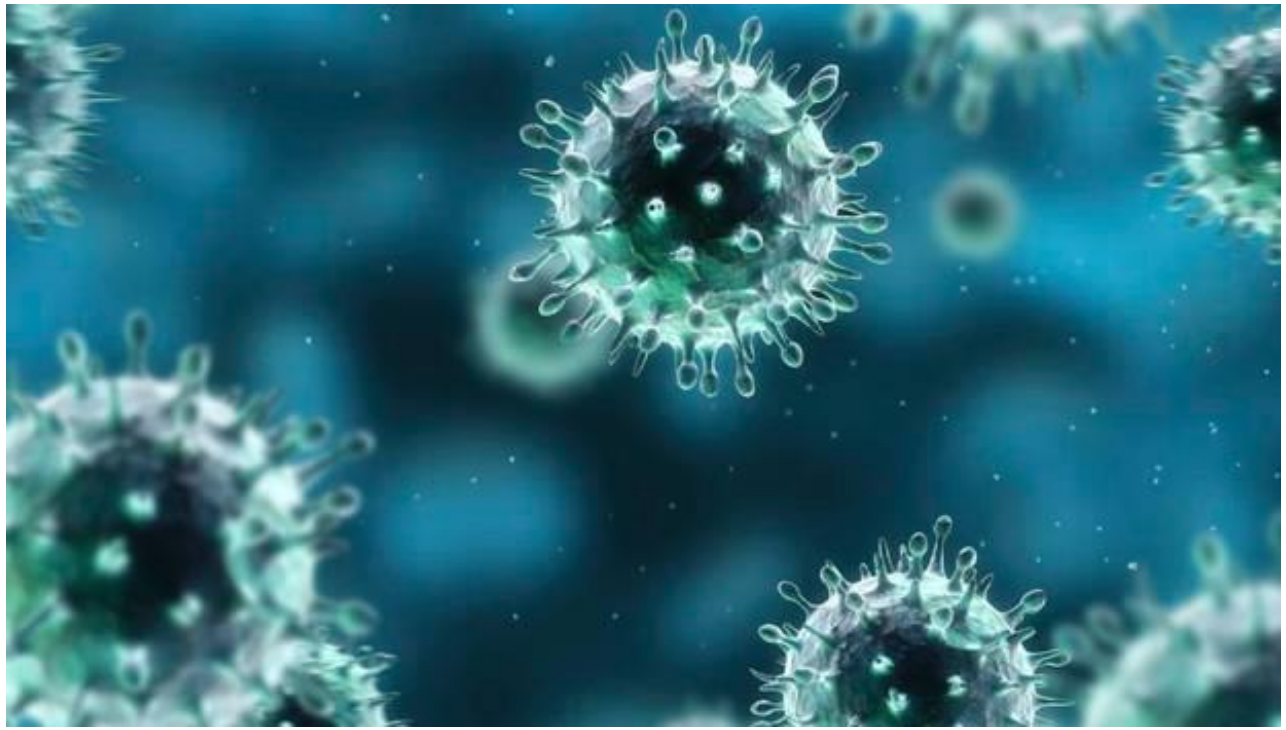
- 6,820 deaths Italy
- 3,160 deaths **Hubei** China
- 2,800 deaths Spain
- 1,934 deaths Iran
- 1,100 deaths France
- 422 deaths United Kingdom
- 276 deaths Netherlands
- 156 deaths Germany
- 125 deaths

**Total Recovered**
**107,806**

- 60,324 recovered **Hubei** China
- 8,913 recovered Iran
- 8,326 recovered Italy
- 3,794 recovered Spain
- 3,507 recovered Korea, South
- 3,281 recovered France
- 3,243 recovered Germany
- 1,333 recovered **Guangdong** China
- 1,250 recovered

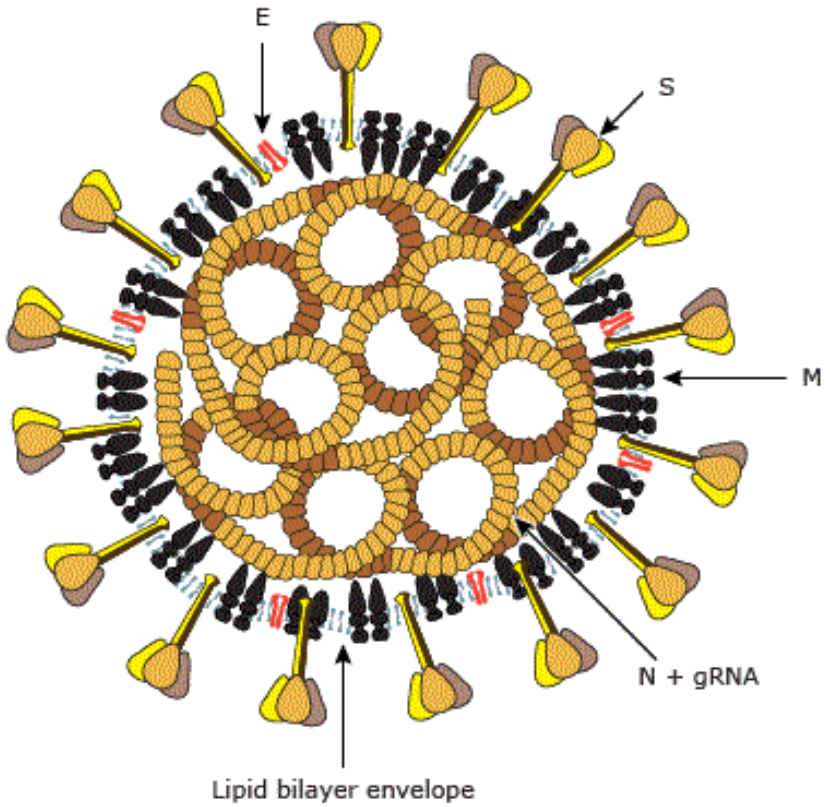


# Coronaviruses



*Nidovirus family
*Name derives from crown-like appearance
*medium-sized, enveloped
*positive-stranded RNA viruses
*have the largest known viral RNA genomes, with a length of 27 - 32 kb
*cause range of disease in animals
*human strains hard to grow in culture

**Model of coronavirus structure: A schematic diagram of virion structure**




Schematic showing the major structural proteins of the coronavirus virion.

S: spike protein; M: membrane protein; E: envelope protein; N: nucleocapsid protein.



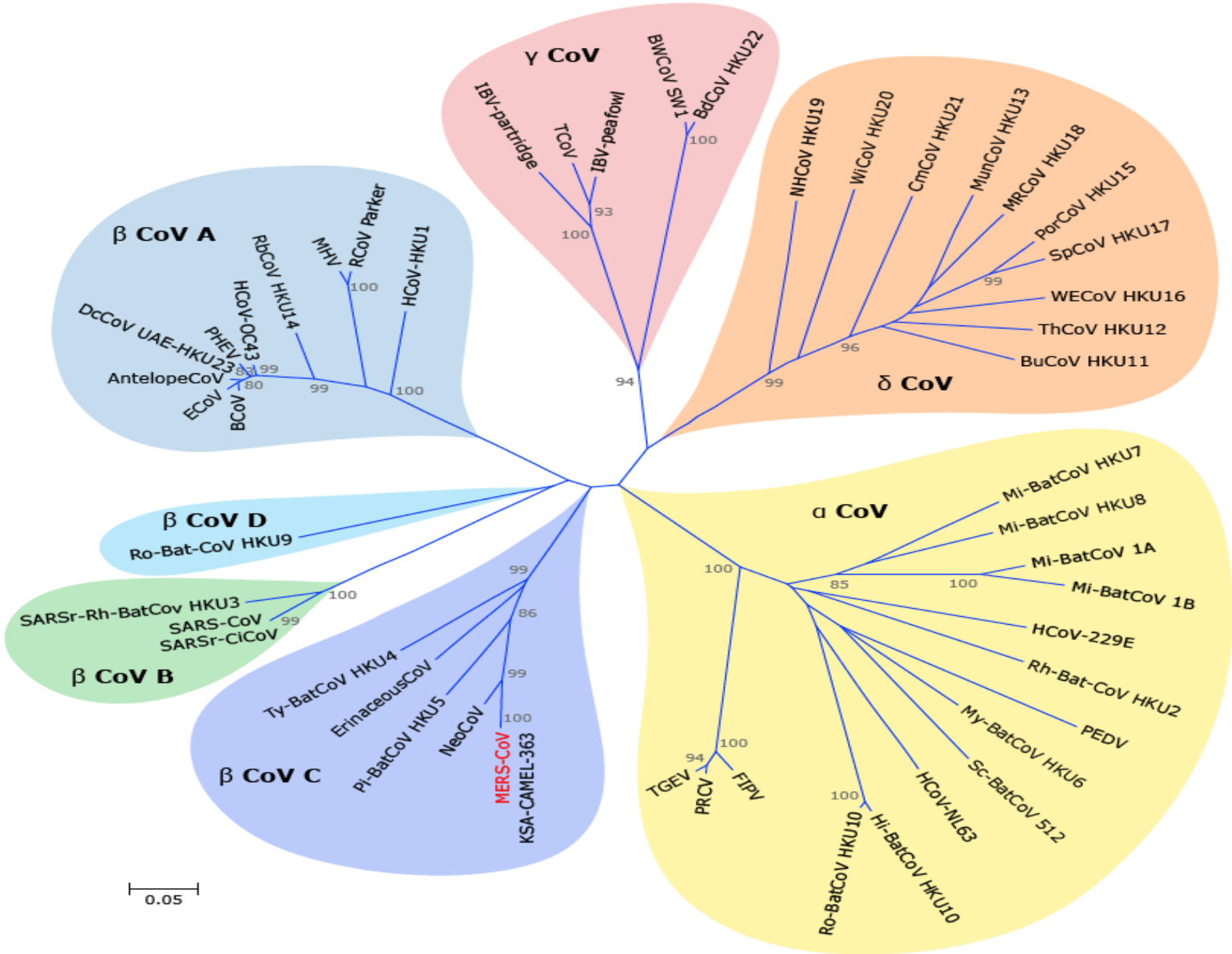
E function is not known, although in the SARS-CoV, the E protein along with M and N are required for proper assembly and release of the virus

S mediates receptor binding and fusion with the host cell membrane; contains major antigens that stimulate neutralizing antibody & important targets of cytotoxic lymphocytes

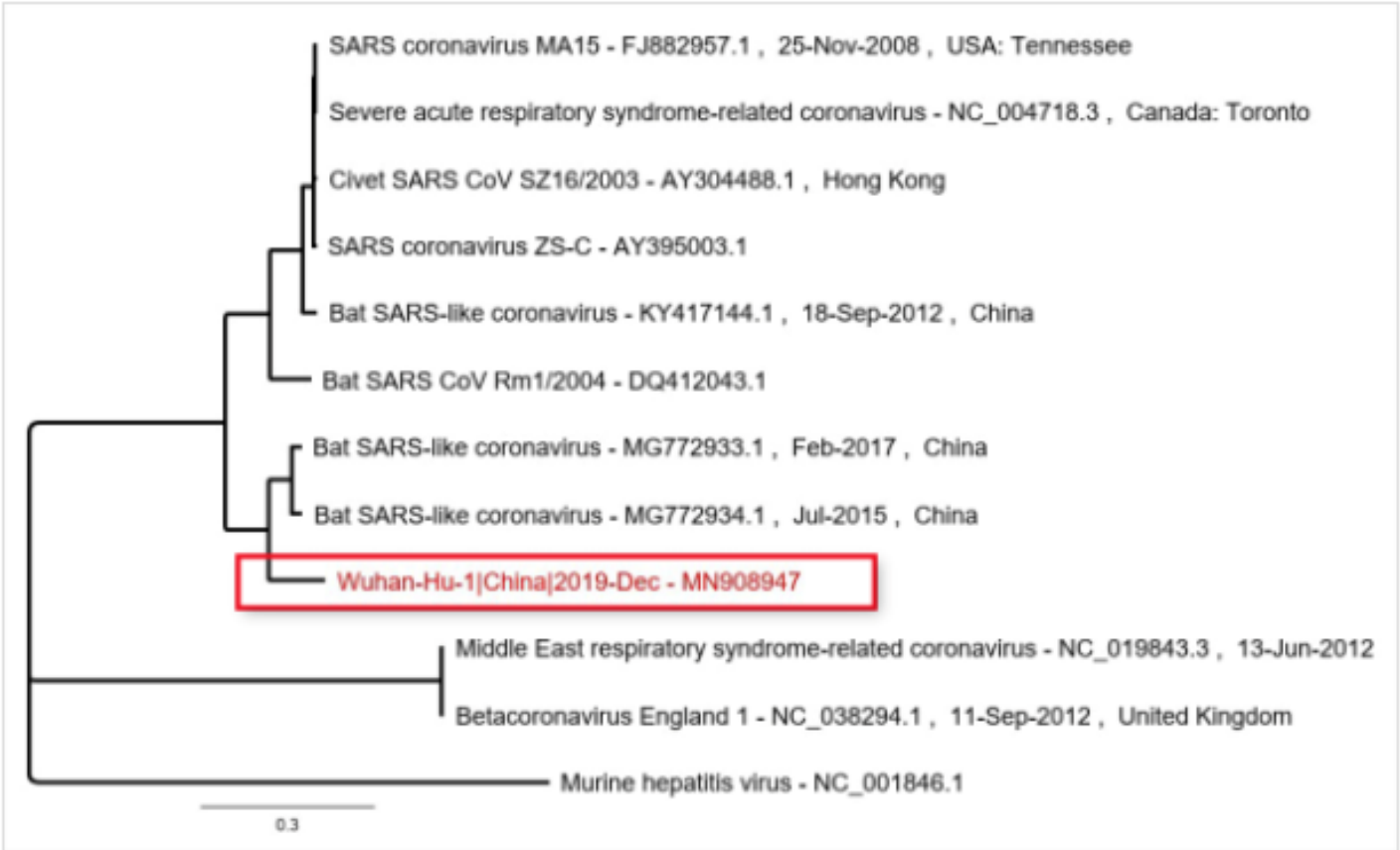
M plays an important role in viral assembly

N associates with the RNA genome to form the nucleocapsid; may be involved in regulation of viral RNA synthesis & interact with M protein during virus budding

## Coronavirus phylogenetic tree



The complete annotated genome sequence of the novel coronavirus associated with the outbreak of pneumonia in Wuhan, China is now available from GenBank for free and easy access by the global biomedical community. Figure 1 shows the relationship of the Wuhan virus to selected coronaviruses.




Posted on National Center for Biotechnology Information Website on Jan 13, 2020

# Coronaviruses

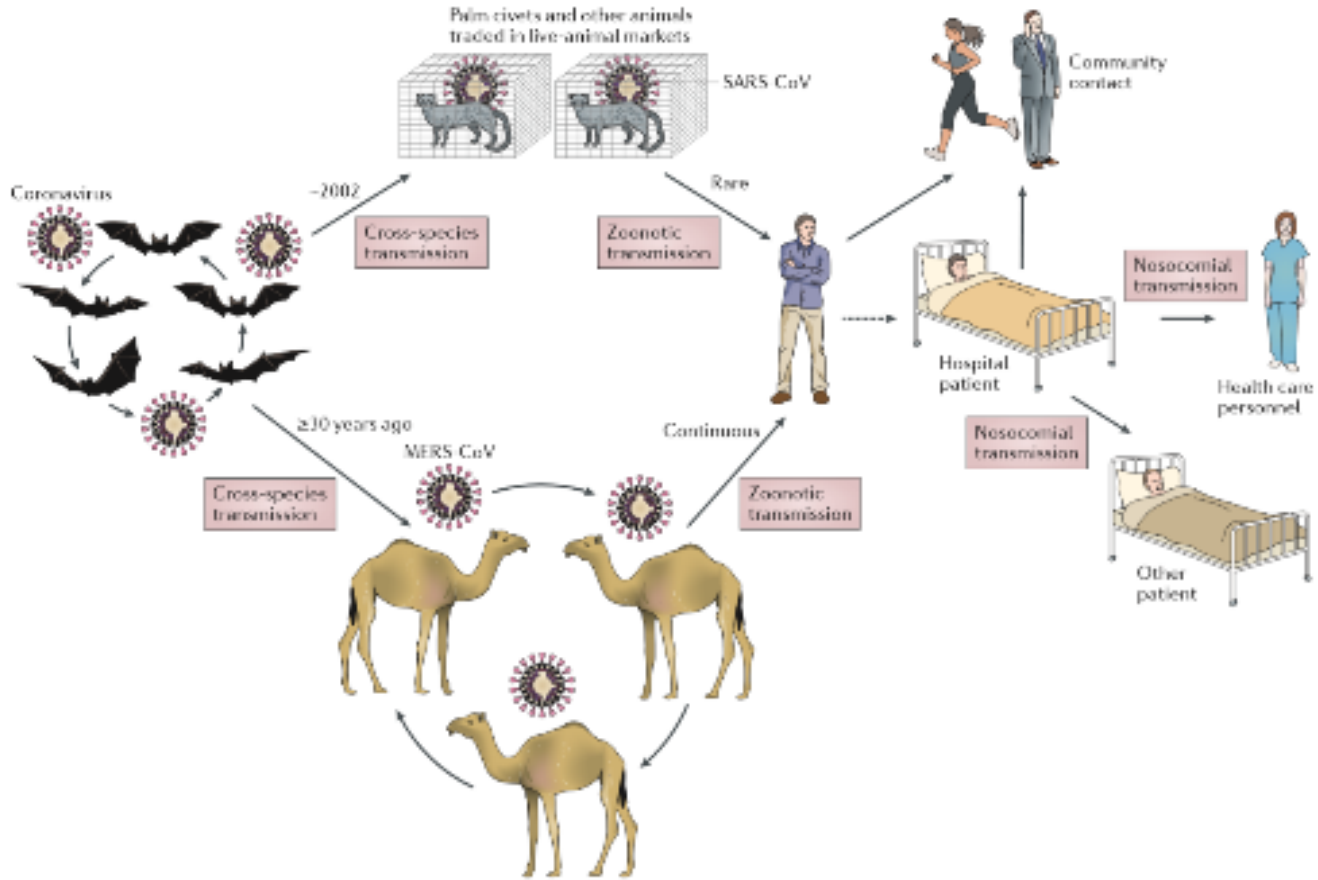
- Ubiquitous, world-wide
- Circulate in winter in temperate climates
- Cause 5-10% of acute upper respiratory infections in adults
- Important cause of viral acute OM in children
- Asymptomatic infection common in children
- Infrequent cause of diarrhea in infants and children hospitalized with diarrhea

# More Severe Manifestations in Adults

- Found in 4% of adults with acute exacerbation of COPD
- Influenza-like illness, acute exacerbation of chronic bronchitis, pneumonia, including in HIV-infected described
- Severe acute respiratory distress syndrome (SARS) 2003
- Middle Eastern respiratory distress syndrome (MERS) 2012
- Novel 2019 Coronavirus

# The Emergence of SARS-CoV and MERS-CoV

- SARS-CoV crossed species from bats into masked palm civets and other animals in live-animal markets in China. Genetic analysis suggests that this occurred in late 2002.
- MERS-CoV ancestral virus crossed the species barrier into dromedary camels. Serological evidence suggests that this happened more than 30 years ago.



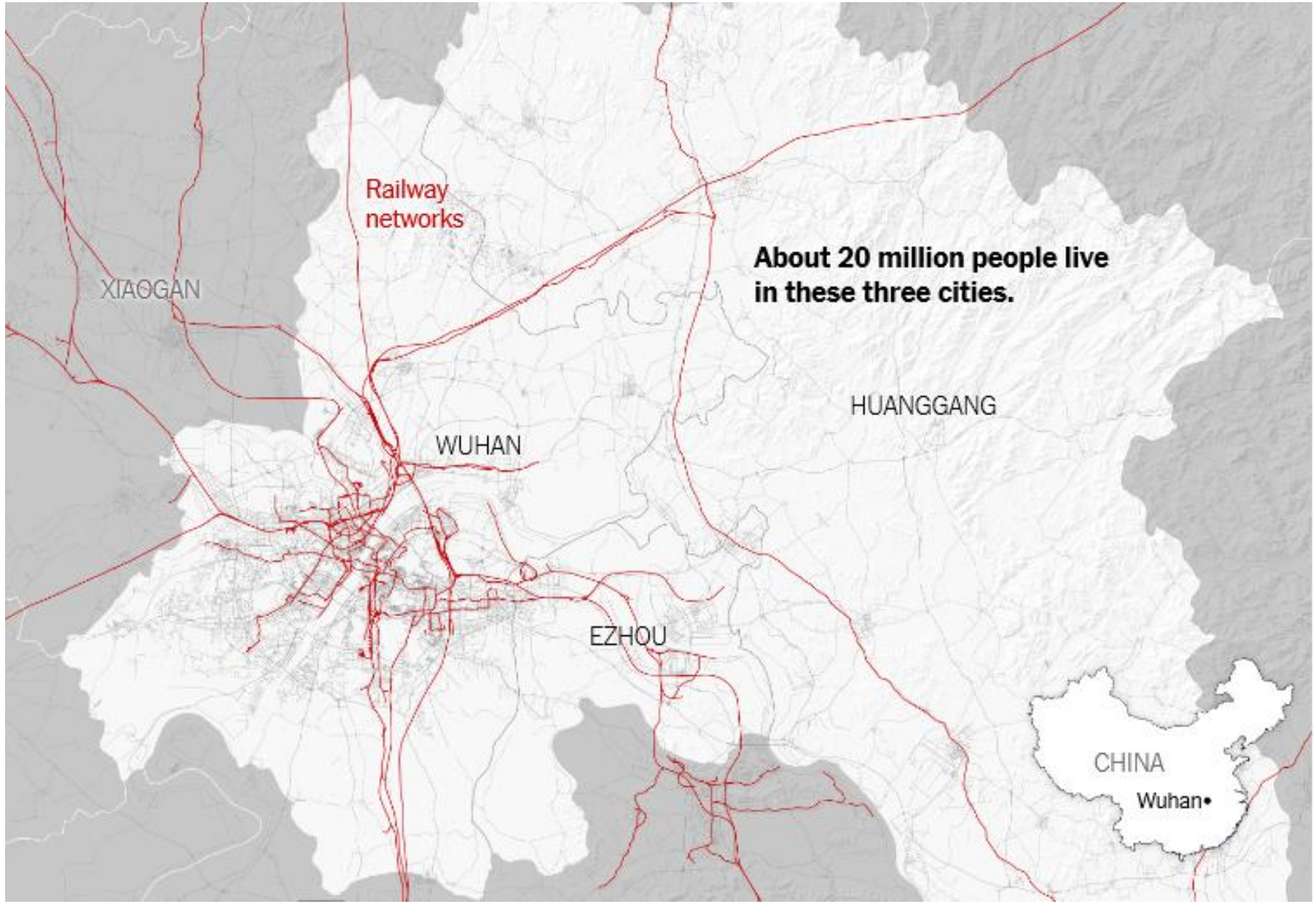

de Wit, E., van Doremalen, N., Falzarano, D. et al. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 14, 523–534 (2016)

# Role of Animals in Coronavirus Transmission

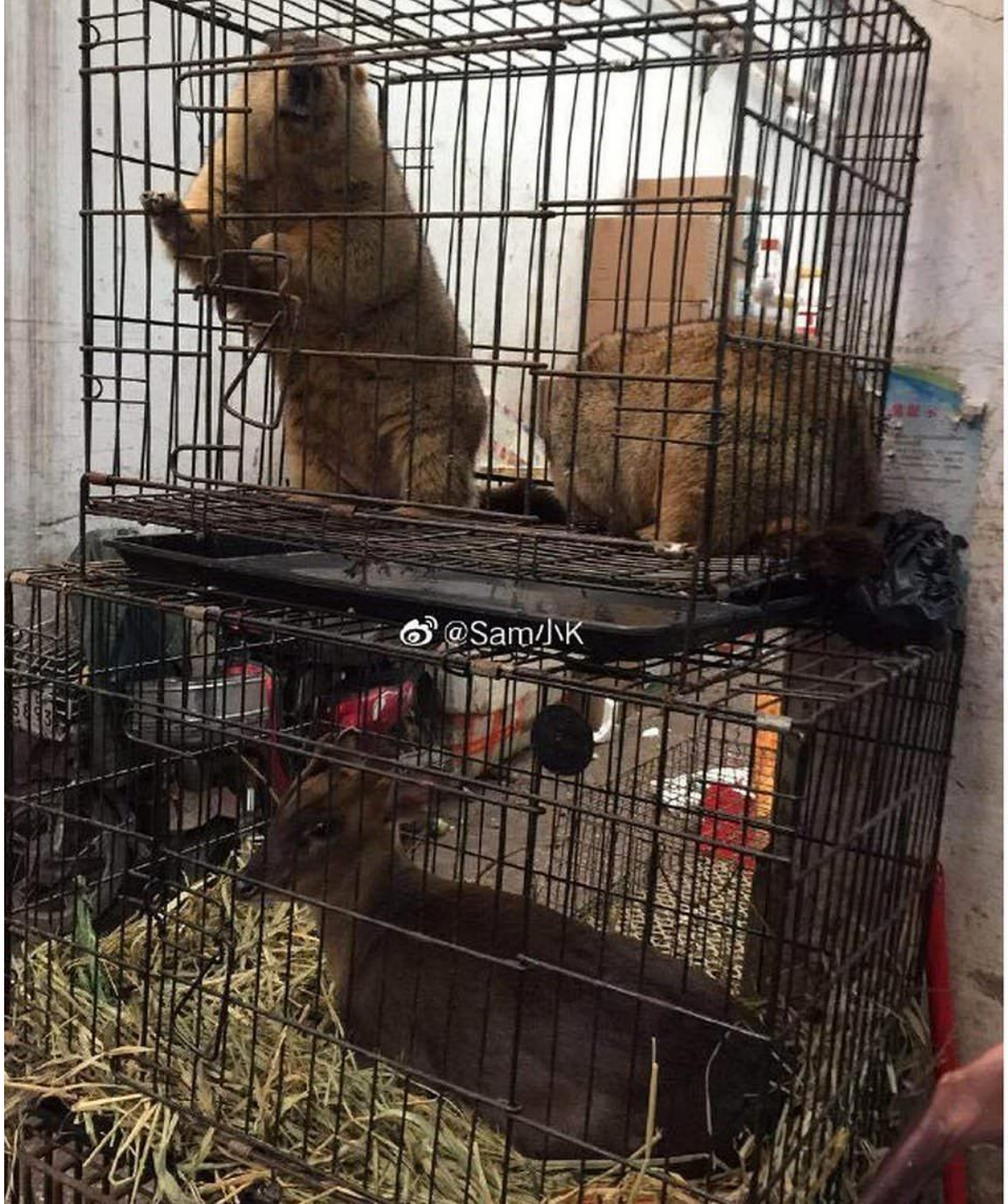
- SARS: bats to civets to human
- MERS: camels to humans
- December 2019 CoV: bats to snakes? Pangolin? mammal? to humans

# Jan 30, 2020 WHO: Novel 2019 Coronavirus GLOBAL Health Emergency

- Identified as new virus in `12/19
- Mainland China :8100 people infected, 171 people dead
- Originated in city of Wuhan, province of Hubei
- Early cases associated with Huanan Seafood Market
- Travelers from Wuhan have spread disease globally


Railway networks
About 20 million people live in these three cities.
XIAOGAN
WUHAN
HUANGGANG
EZHOU
CHINA
Wuhan


Genomic analysis of 9 patients with 2019 nCoV from Wuhan who had common exposure to Huanan Seafood Market


@Sam小K

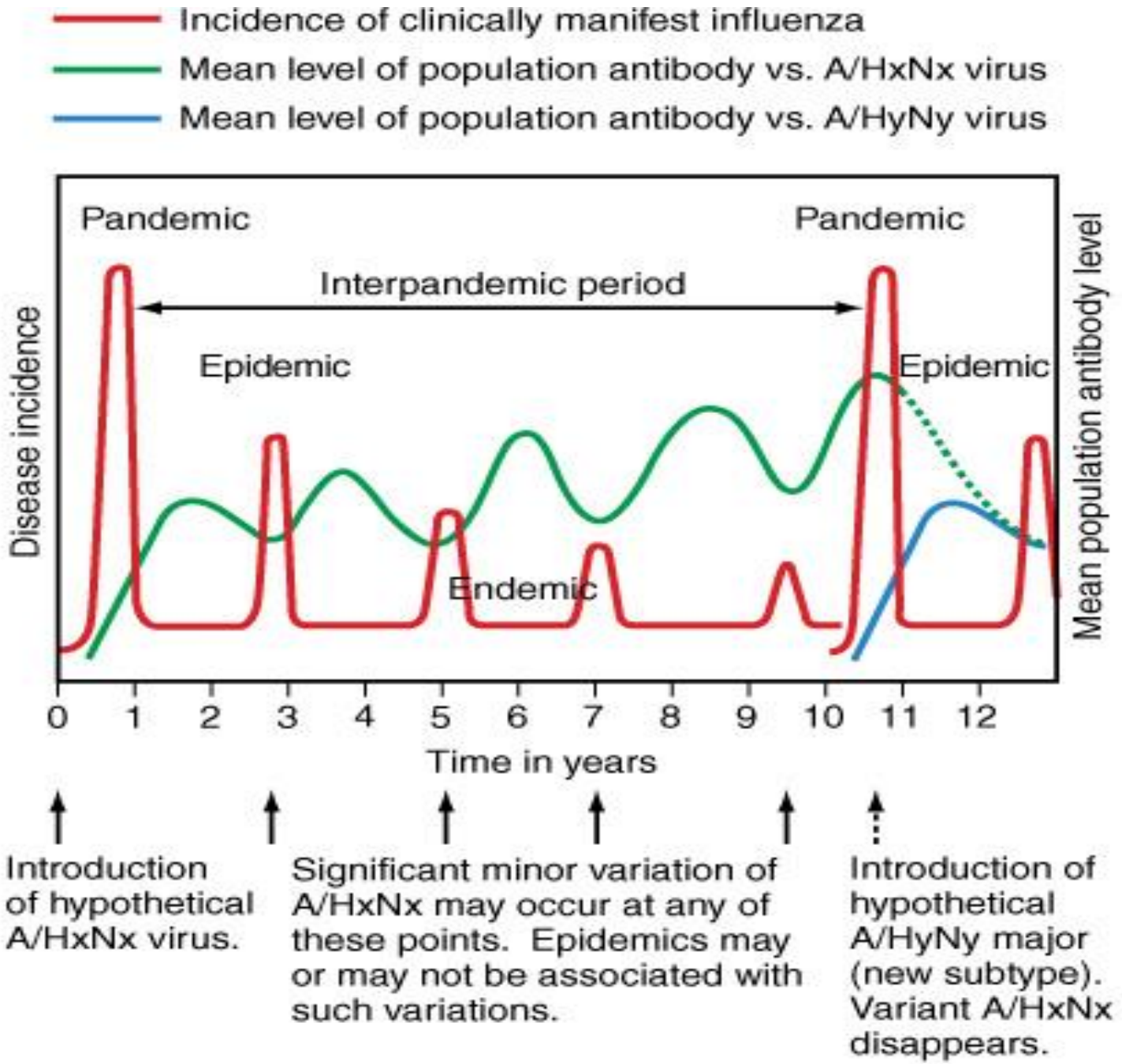

大众畜牧
诚信经营，遵守法


大众畜牧野味
品名 价格 品名 价格 品名 价格 品名 价格 品名 价格 品名 价格 品名 价格
活孔雀 500/只 活鸭豚 活蝎子 500 狐狸肉 45 活豚鼠 40 鹿 脯 38 鳄鱼尾 45
孔雀肉 350/只 活珍珠鸡 活蜗牛 15 活狼仔 75 活荷兰猪 40 鹿 血 100/袋 鳄鱼掌 60
活大雁 170 活贵妃鸡 蜗牛肉 30 狼仔肉 70/45 活藏香猪 30 鹿 筋 100 鳄鱼鞭 40/根
大雁肉 15 鹌 鹑 15/只 蜂 蛹 150 活果子狸 130 活豪猪 45 干鹿筋 150 鳄鱼皮 30
去骨大雁肉 15 土 鸽 18/只 蚕 蛹 15 果子狸肉 70 活湘猪 30 鹿 茸 1500 鳄鱼舌 35
活鸿雁 铁 雀 蚂 蚱 100/斤 活刺猬 18 香猪肉 75 鹿里脊 50 鳄鱼胸 30
活火鸡 78 活白鹅 木 虫 刺猬肉 8/只 牦牛肉 30 袋装鹿肉 30 活鳄鱼龟 75
活斗鸡 500/只 香椿鸟 15/只 竹 虫 75 活狗狸獾 25 牦牛掌 45 鹿 鞭 40/根 活山龟 90
活野鸡 60 活鸵鸟 4000/只 活竹鼠 85 活猪狸獾 28 骆驼肉 30 鹿 排 38 活山瑞甲鱼 55
野鸡肉 25/只 鸵鸟肉 45 竹鼠肉 75 花猪肉 25 骆驼掌 45 活鹿子 55 活水貂 500/条
斑 鸠 18/只/条 鸵鸟掌 80 活麝香鼠 活石头猪 30 骆驼峰 70 鹿子肉 40 活树熊 70
竹 鸡 15/只 鸵鸟肾 45 活青根貂 60 狍子肉 75 活梅花鹿 50 娃娃鱼苗 60/时 带皮乌梢蛇 60
藏 鸡 90/只 鸵鸟蛋 150/个 活海狸鼠 30 条交野猪肉 15 小活鹿 6000/只 活娃娃鱼 65 去皮乌梢蛇 60
线 鸡 野山羊 40/条 袋鼠肉 野猪肚 120 鹿白条 35 活鳄鱼 40 大蛇条肉 40
育槟鸟 15/只/条 毛野兔 75 松鼠肉 活野猪 75 冷鲜鹿肉 38 鳄鱼肉 40 活海蛇 220
蜈 蚣 5/条 金 蝉 70 活狐狸 500/只 野猪肉 26 鹿 腿 40 鳄鱼苗 25/只 活虎纹蛙

# Feb 1, 2020 White House Declares

- National Public Health Emergency
- American citizens in China's Hubei Province in the 2 weeks prior to their re-entry will have to undergo up to 14 days of mandatory quarantine upon returning to the U.S.
- Those returning from mainland China will have to undergo screening upon entry and then will have a monitored self-quarantine.
- No entry of foreign nationals (other than immediate family of U.S. citizens and permanent residents) who've been to China in the past 2 weeks.

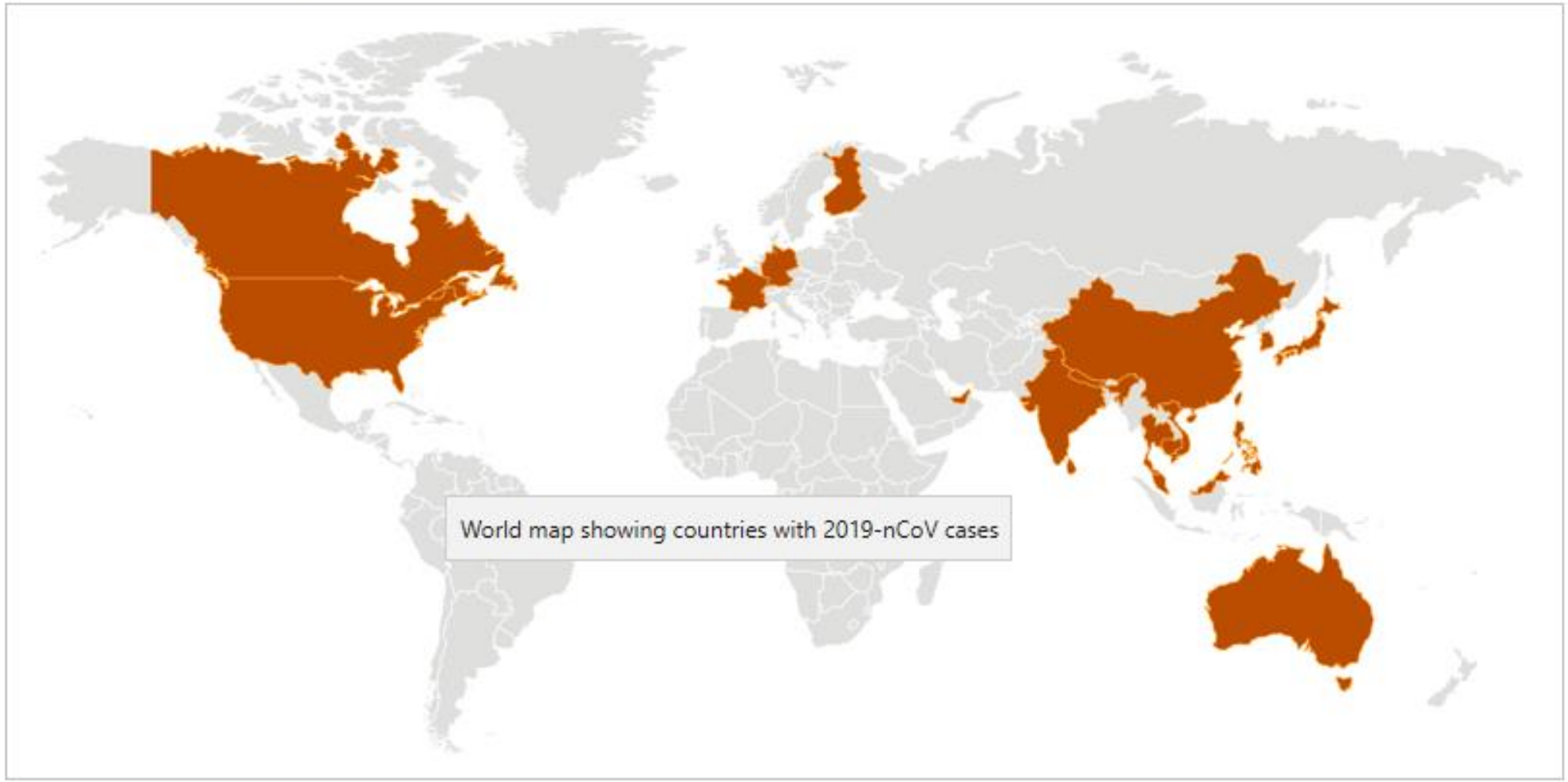
March 11, 2020
WHO declares Pandemic



Jan 29, 2020

# Confirmed 2019-nCoV Cases Globally

## Global Map

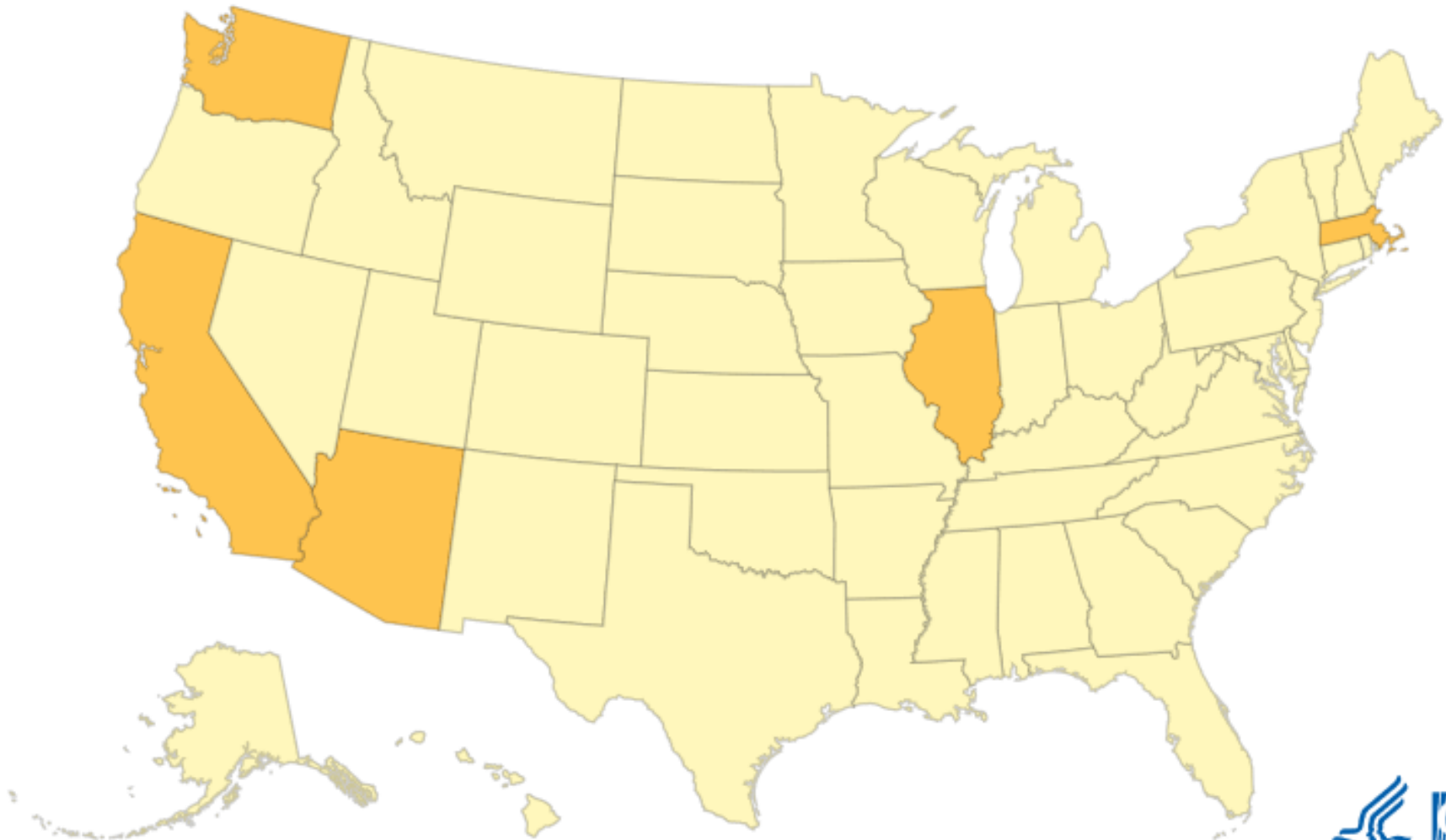


# Confirmed 2019-nCoV Cases Globally

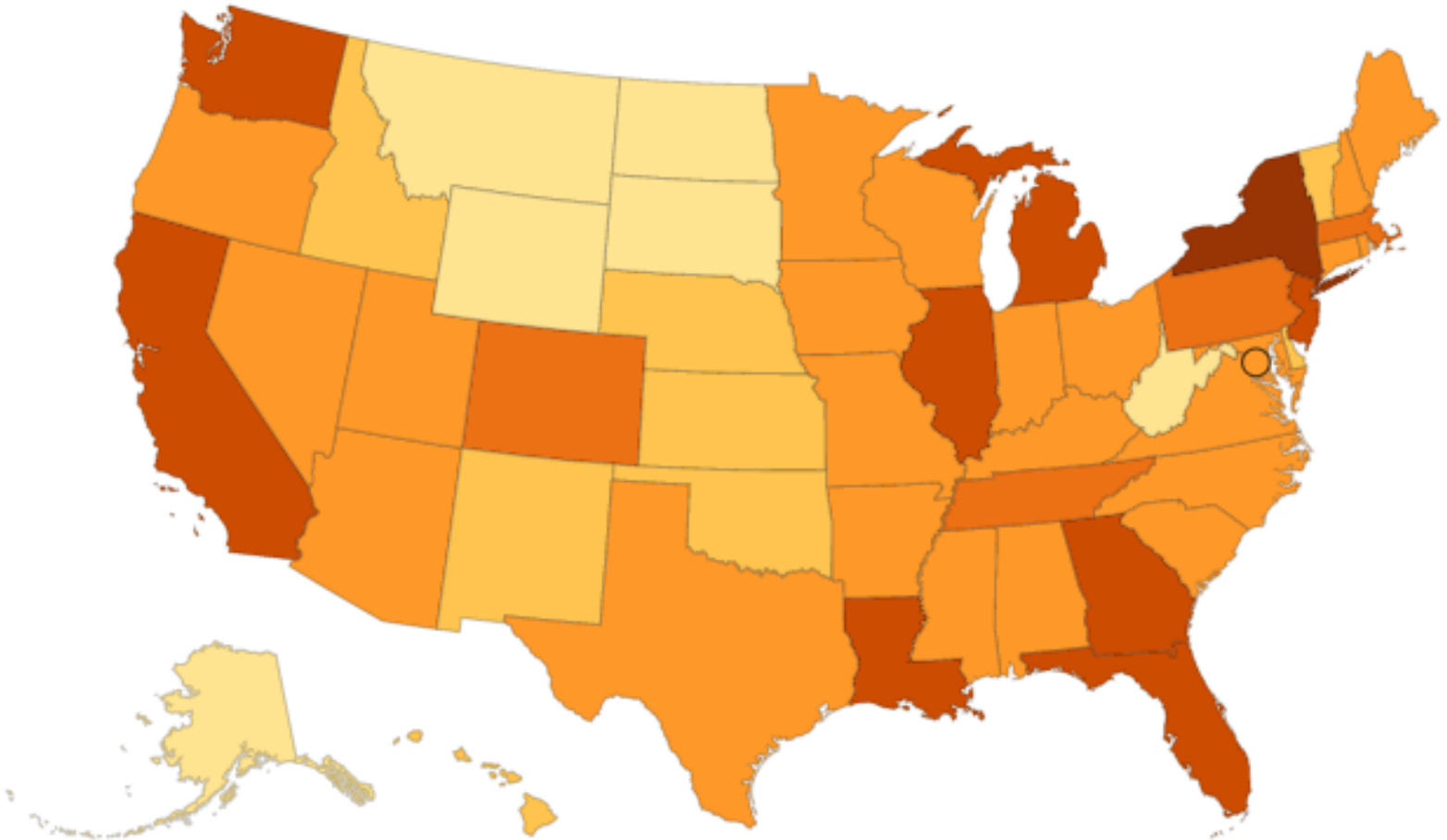
## Global Map

*As of 11:00 a.m. ET January 31, 2020*

# States with confirmed 2019-nCoV cases



CDC, Feb 3, 2020



Territories AS GU MH FM MP PW PR VI

## Reported Cases

(last updated March 24, 2020)

None 6 to 50 51 to 100 101 to 500 501 to 1000 1001 to 5000 5001 or more

# Transmission of Novel 2019 Coronavirus

- Person to person
- Respiratory droplets from coughing, sneezing, talking
- Health care workers, family transmission
- Contact with surfaces
- Asymptomatic transmission documented
- Still lack detailed knowledge

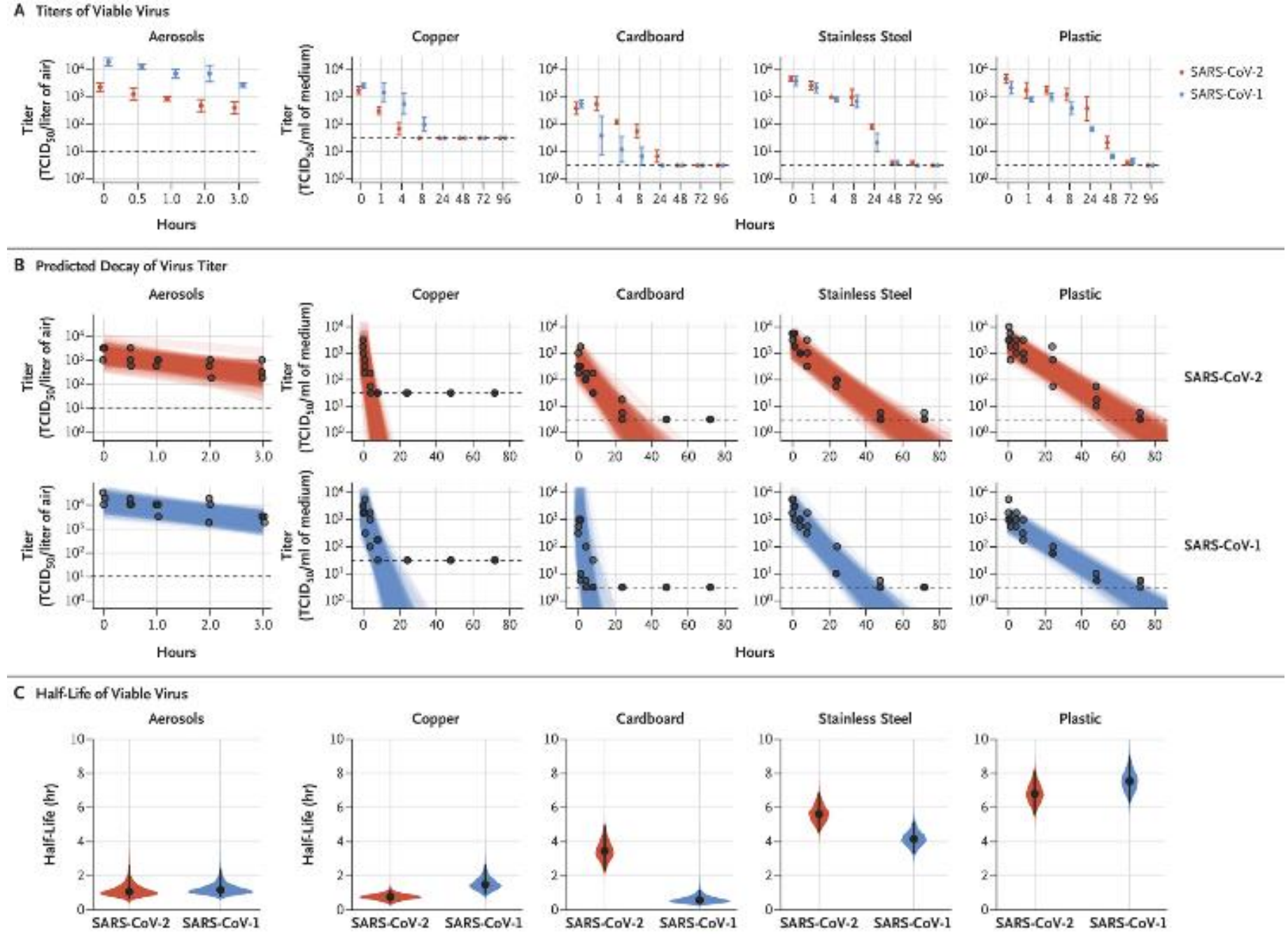
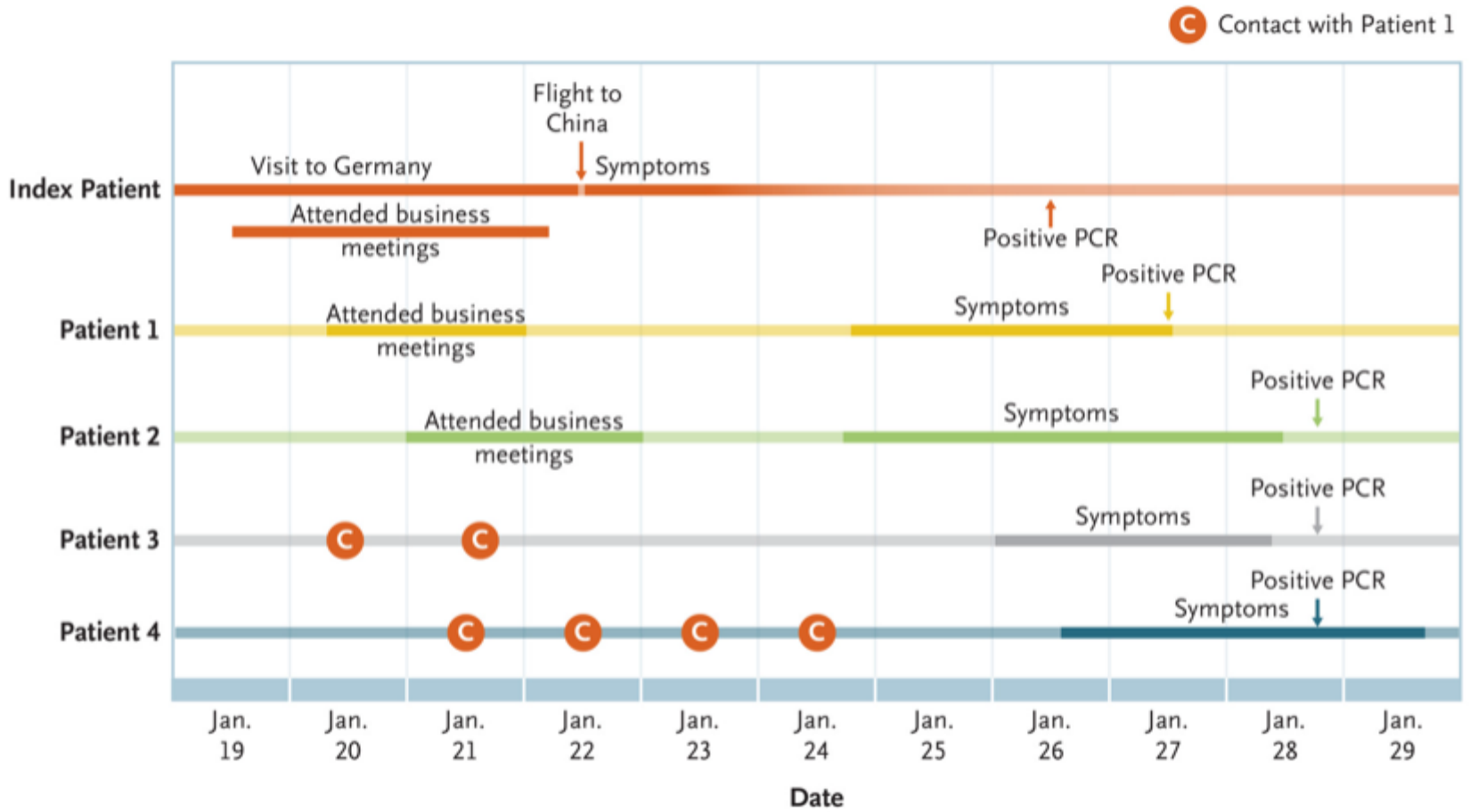
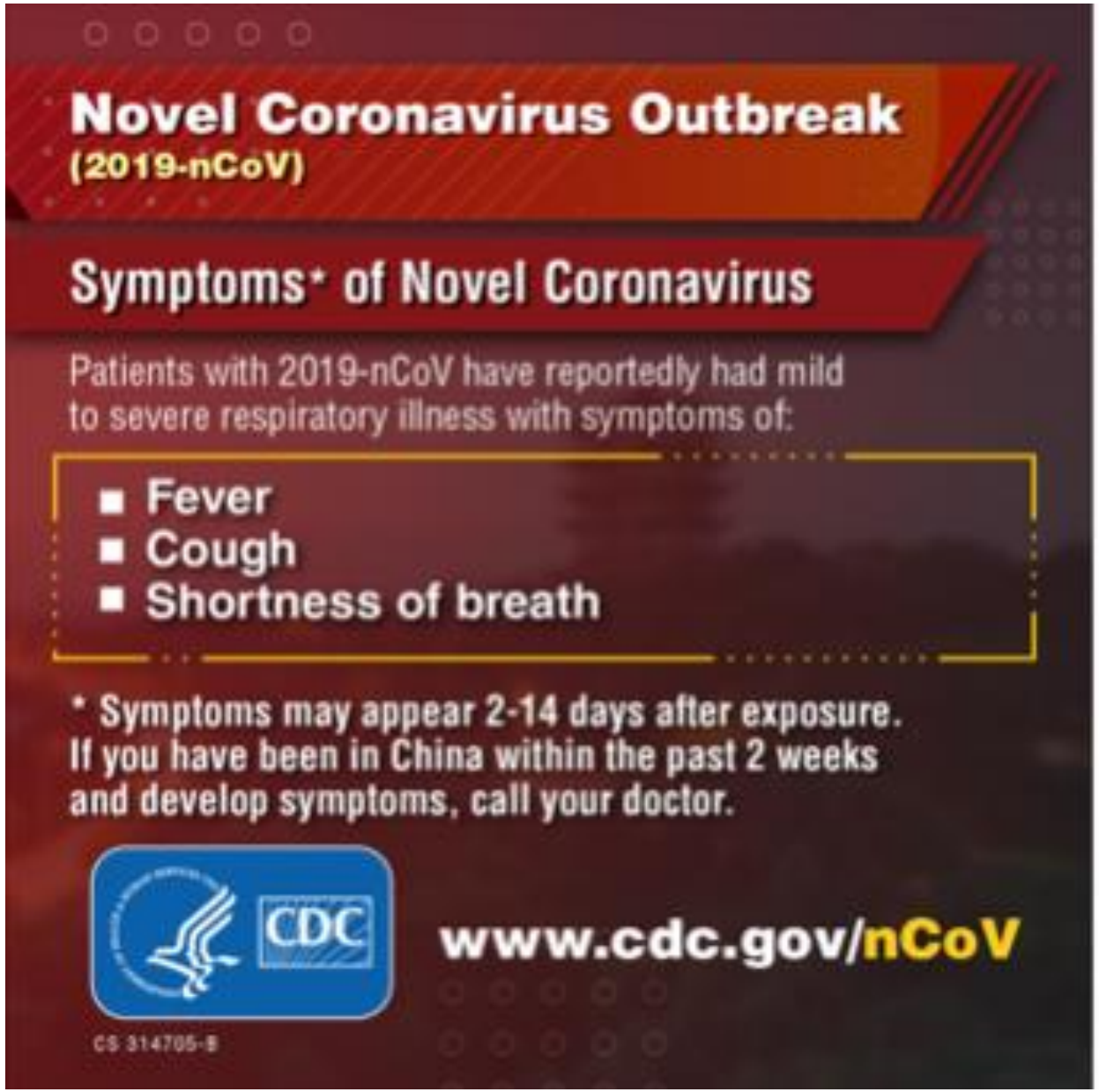
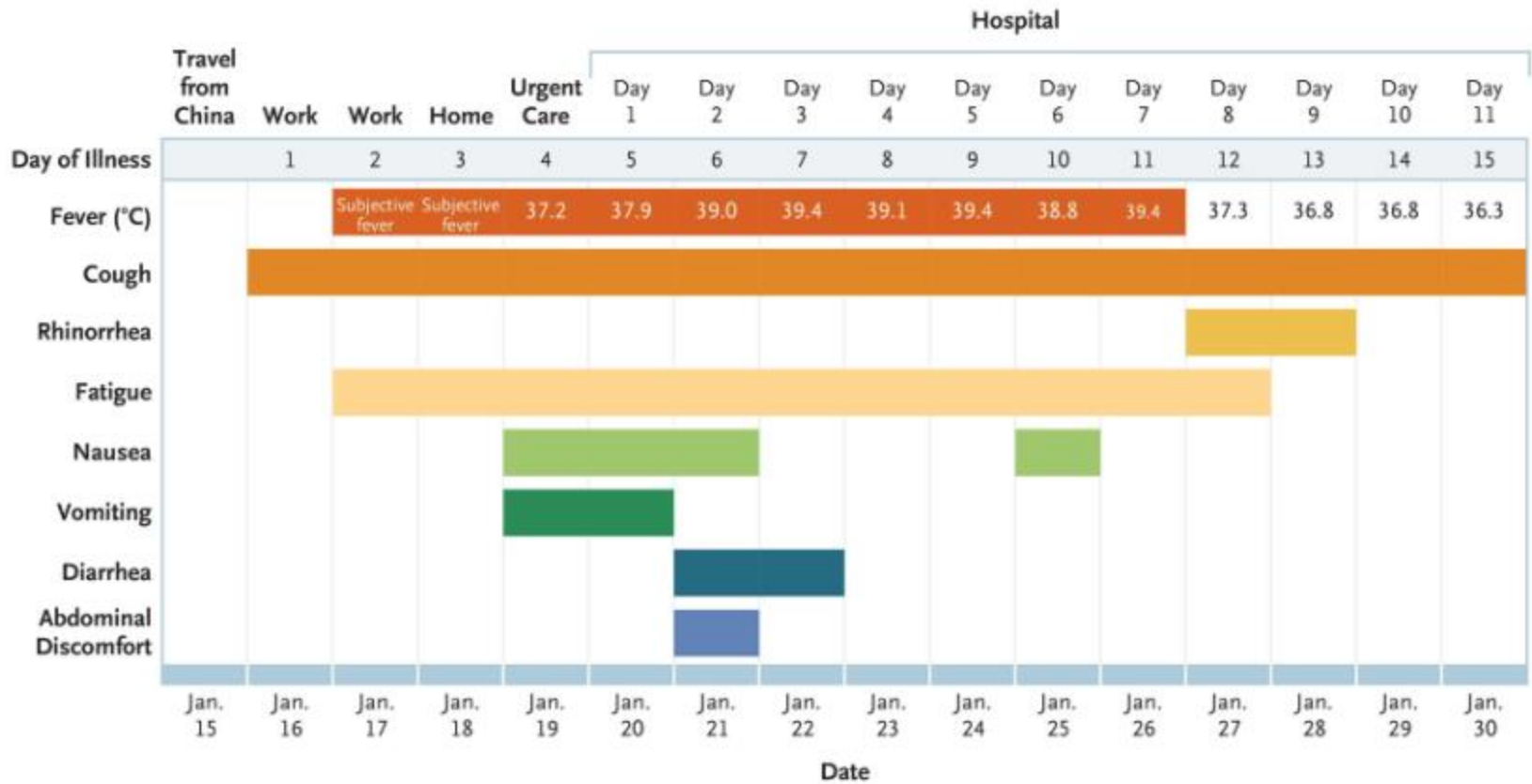

A Titers of Viable Virus
Aerosols
Copper
Cardboard
Stainless Steel
Plastic
Titer (TCID50/liter of air)
Titer (TCID50/ml of medium)
Hours
SARS-CoV-2
SARS-CoV-1
B Predicted Decay of Virus Titer
C Half-Life of Viable Virus
Half-Life (hr)

**Figure 1. Timeline of Exposure to Index Patient with Asymptomatic 2019-CoV Infection in Germany.**




Rothe et all NEJM 1/30/20


Novel Coronavirus Outbreak
(2019-nCoV)
Symptoms* of Novel Coronavirus
Patients with 2019-nCoV have reportedly had mild to severe respiratory illness with symptoms of:
Fever
Cough
Shortness of breath
* Symptoms may appear 2-14 days after exposure.
If you have been in China within the past 2 weeks and develop symptoms, call your doctor.
CDC
www.cdc.gov/nCoV
CS 314705-B


Hospital
Travel from China
Work
Work
Home
Urgent Care
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Day 10
Day 11
Day of Illness
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Fever (°C)
Subjective fever
Subjective fever
37.2
37.9
39.0
39.4
39.1
39.4
38.8
39.4
37.3
36.8
36.8
36.3
Cough
Rhinorrhea
Fatigue
Nausea
Vomiting
Diarrhea
Abdominal Discomfort
Jan. 15
Jan. 16
Jan. 17
Jan. 18
Jan. 19
Jan. 20
Jan. 21
Jan. 22
Jan. 23
Jan. 24
Jan. 25
Jan. 26
Jan. 27
Jan. 28
Jan. 29
Jan. 30
Date

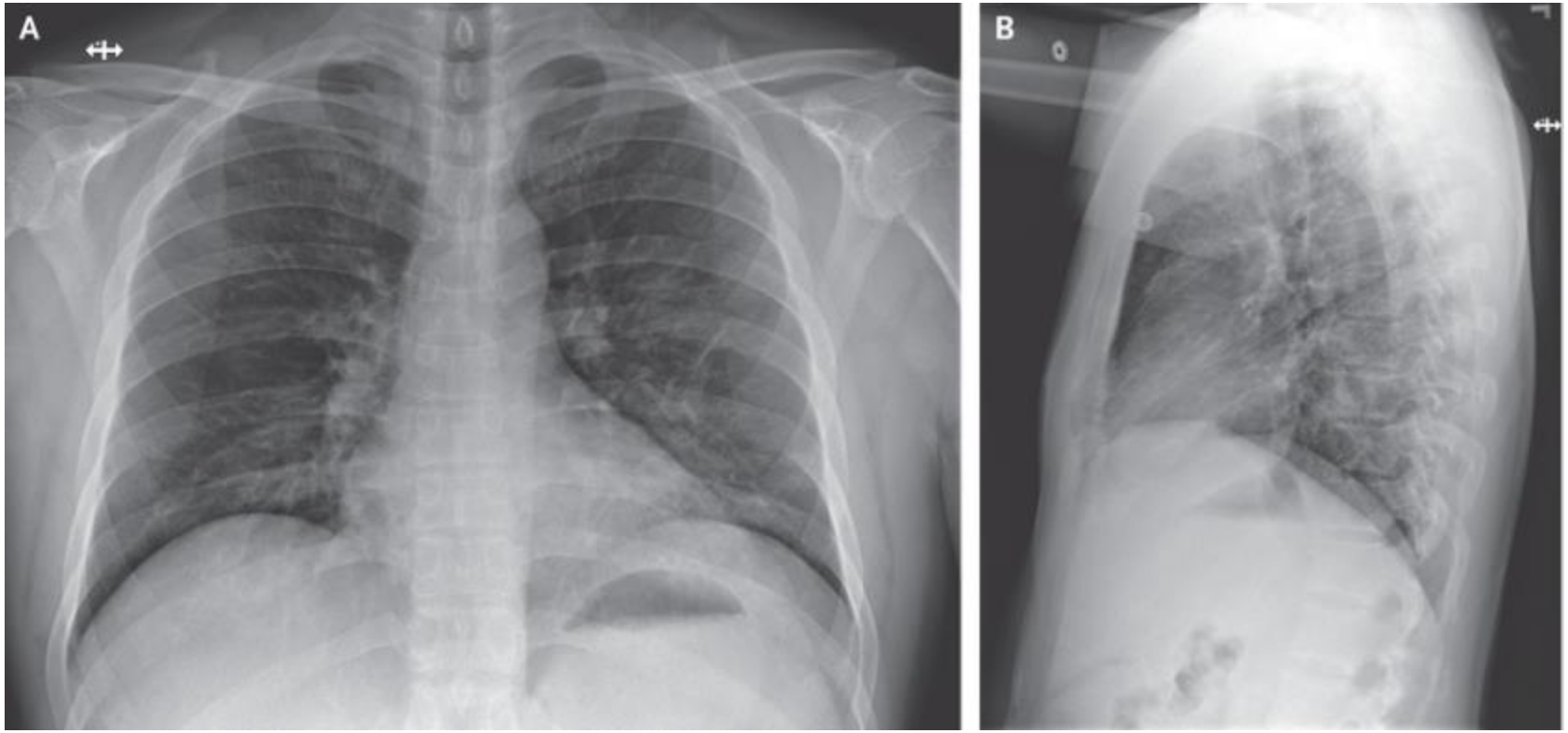



**Figure 5. Anteroposterior and Lateral Chest Radiographs, January 26, 2020 (Illness Day 10, Hospital Day 6).**

Stable streaky opacities in the lung bases were visible, indicating likely atypical pneumonia; the opacities have steadily increased in density over time.

# Clinical Manifestations

- Incubation period : 2-14 days; average 5-6 days
- Anosmia, dysgeusia may be early symptoms in o/w asymptomatic
- Hospitalized patients
  - Fever 77–98% ; may be prolonged, intermittent
  - Cough 46–82%
  - Myalgia or fatigue 11–52%
  - SOB 3-31%

# Less Common Clinical Manifestations

- Sore throat
- Headache
- Productive cough with sputum production
- Hemoptysis
- GI symptoms –may develop prior to fever and lower respiratory symptoms
  - Diarrhea
  - Nausea

The Lancet: 41 admitted hospital patients had been identified as having laboratory-confirmed 2019-nCoV infection
Published:January 24, 2020DOI:https://doi.org/10.1016/S0140-6736(20)30183-5

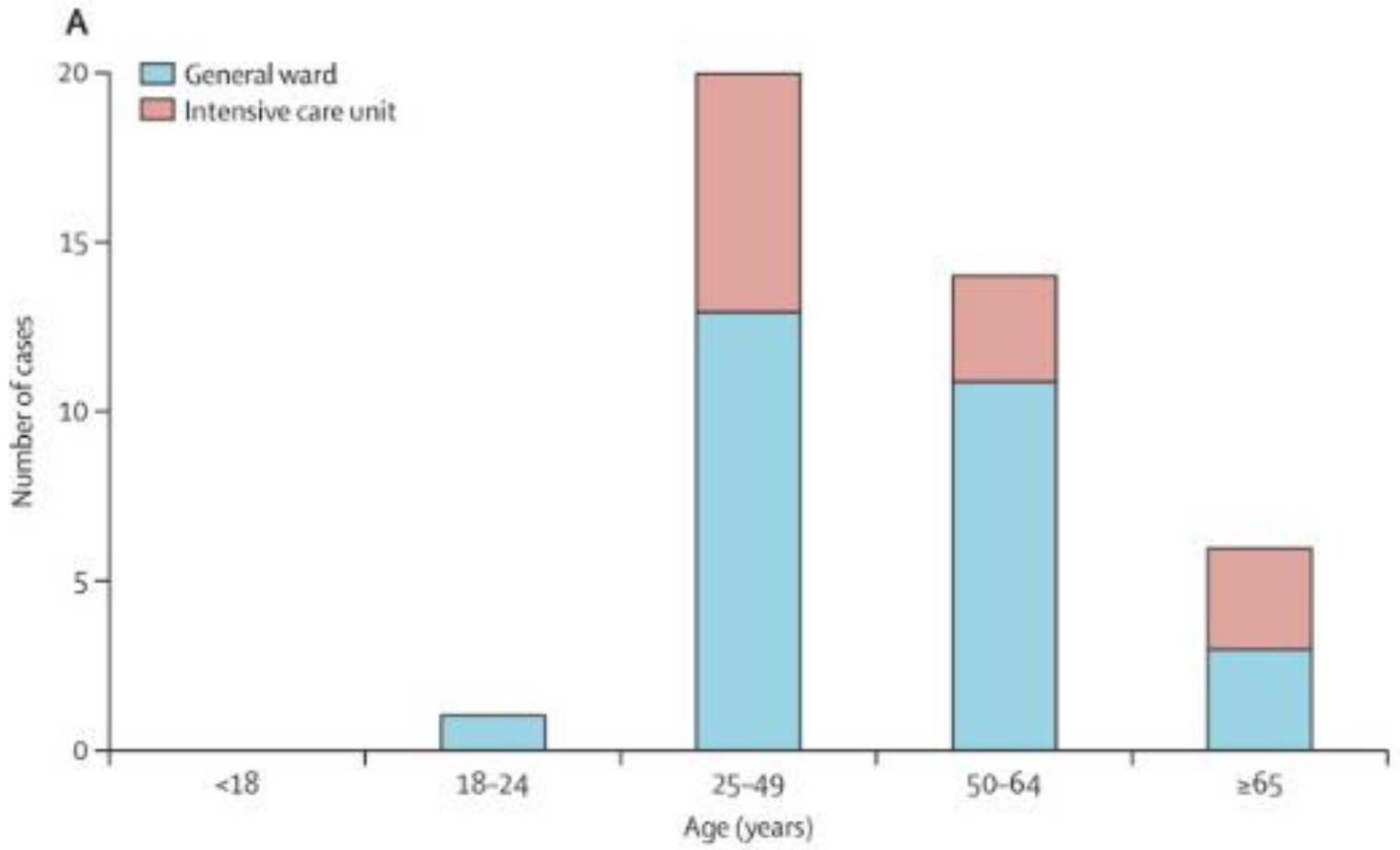


**Table 3 Treatments and outcomes of patients infected with 2019-nCoV**

| | | All patients (n=41) | ICU care (n=13) | No ICU care (n=28) | p value |
|---|---|---|---|---|---|
| Duration from illness onset to first admission | | 7·0 (4·0–8·0) | 7·0 (4·0–8·0) | 7·0 (4·0–8·5) | 0·87 |
| Complications | | | | | |
| | Acute respiratory distress syndrome | 12 (29%) | 11 (85%) | 1 (4%) | <0·0001 |
| | RNAaemia | 6 (15%) | 2 (15%) | 4 (14%) | 0·93 |
| | Cycle threshold of RNAaemia | 35·1 (34·7–35·1) | 35·1 (35·1–35·1) | 34·8 (34·1–35·4) | 0·35 |
| | Acute cardiac injury* | 5 (12%) | 4 (31%) | 1 (4%) | 0·017 |
| | Acute kidney injury | 3 (7%) | 3 (23%) | 0 | 0·027 |
| | Secondary infection | 4 (10%) | 4 (31%) | 0 | 0·0014 |
| | Shock | 3 (7%) | 3 (23%) | 0 | 0·027 |

| Treatment | | all | icu | no icu |
|---|---|---|---|---|
| | Antiviral therapy | 38 (93%) | 12 (92%) | 26 (93%) |
| | Antibiotic therapy | 41 (100%) | 13 (100%) | 28 (100%) |
| | Use of corticosteroid | 9 (22%) | 6 (46%) | 3 (11%) |
| Continuous renal replacement therapy | | 3 (7%) | 3 (23%) | 0 |
| Oxygen support | | .. | .. | .. |
| | Nasal cannula | 27 (66%) | 1 (8%) | 26 (93%) |
| | Non-invasive ventilation or high-flow nasal cannula | 10 (24%) | 8 (62%) | 2 (7%) |
| | Invasive mechanical ventilation | 2 (5%) | 2 (15%) | 0 |
| | Invasive mechanical ventilation and ECMO | 2 (5%) | 2 (15%) | 0 |

| | | | | |
|---|---|---|---|---|
| Prognosis | | .. | .. | .. |
| | Hospitalisation | 7 (17%) | 1 (8%) | 6 (21%) |
| | Discharge | 28 (68%) | 7 (54%) | 21 (75%) |
| | Death | 6 (15%) | 5 (38%) | 1 (4%) |

# Case Fatality Rate

- 60-69 years: 3.6%; 70-79 years: 8%; ≥80 years: 14.8%
- Higher for patients with comorbidities:
  - 10.5% for those with cardiovascular disease
  - 7% for diabetes
  - 6% each for chronic respiratory disease, hypertension, and cancer

  49% for patients who developed respiratory failure, septic shock, or multiple organ dysfunction

**Table 2. Results of Real-Time Reverse-Transcriptase–Polymerase-Chain-Reaction Testing for the 2019 Novel Coronavirus (2019-nCoV).***

| Specimen | Illness Day 4 | Illness Day 7 | Illness Day 11 | Illness Day 12 |
|---|---|---|---|---|
| Nasopharyngeal swab | Positive (Ct, 18–20) | Positive (Ct, 23–24) | Positive (Ct, 33–34) | Positive (Ct, 37–40) |
| Oropharyngeal swab | Positive (Ct, 21–22) | Positive (Ct, 32–33) | Positive (Ct, 36–40) | Negative |
| Serum | Negative | Negative | Pending | Pending |
| Urine | NT | Negative | NT | NT |
| Stool | NT | Positive (Ct, 36–38) | NT | NT |

* Lower cycle threshold (Ct) values indicate higher viral loads. NT denotes not tested.

Guidance Date 3/23/20

# QHS GUIDANCE ON TESTING FOR COVID-19

Testing should be considered for the following individuals:

| | |
|---|---|
| **Symptoms** | Fever (Temp >100.3F) **OR** signs/symptoms of lower respiratory illness (e.g., cough or shortness of breath [**beyond baseline**]) |
| **AND** one (1) of the following | |
| **Exposure** | *Close contact with a confirmed COVID-19 patient within 14 days |
| **Travel** | Travel outside the state in the last 14 days prior to symptom onset |
| **Occupation** | • Occupation that places person in close contact with travelers (flight attendant, hotel worker, cruise ship attendant, bus drivers, firefighters, police)<br>• Health care workers |
| **Comorbidities** | Age>65, diabetes, heart disease, chronic lung disease, chronic kidney disease, immunocompromised |
| **Severity of illness** | Hospitalized patients **without an alternate diagnosis besides COVID-19** |

LA County Public Health Dept: Nursing home, longterm care facility

# Close Contact is defined as:

a) being within approximately 6 feet (2 meters), or within the room or care area, of a 2019-nCoV case for a prolonged period of time while not wearing recommended personal protective equipment or PPE (e.g., gowns, gloves, NIOSH-certified disposable N95 respirator, eye protection); close contact can include caring for, living with, visiting, or sharing a health care waiting area or room with a 2019-nCoV case

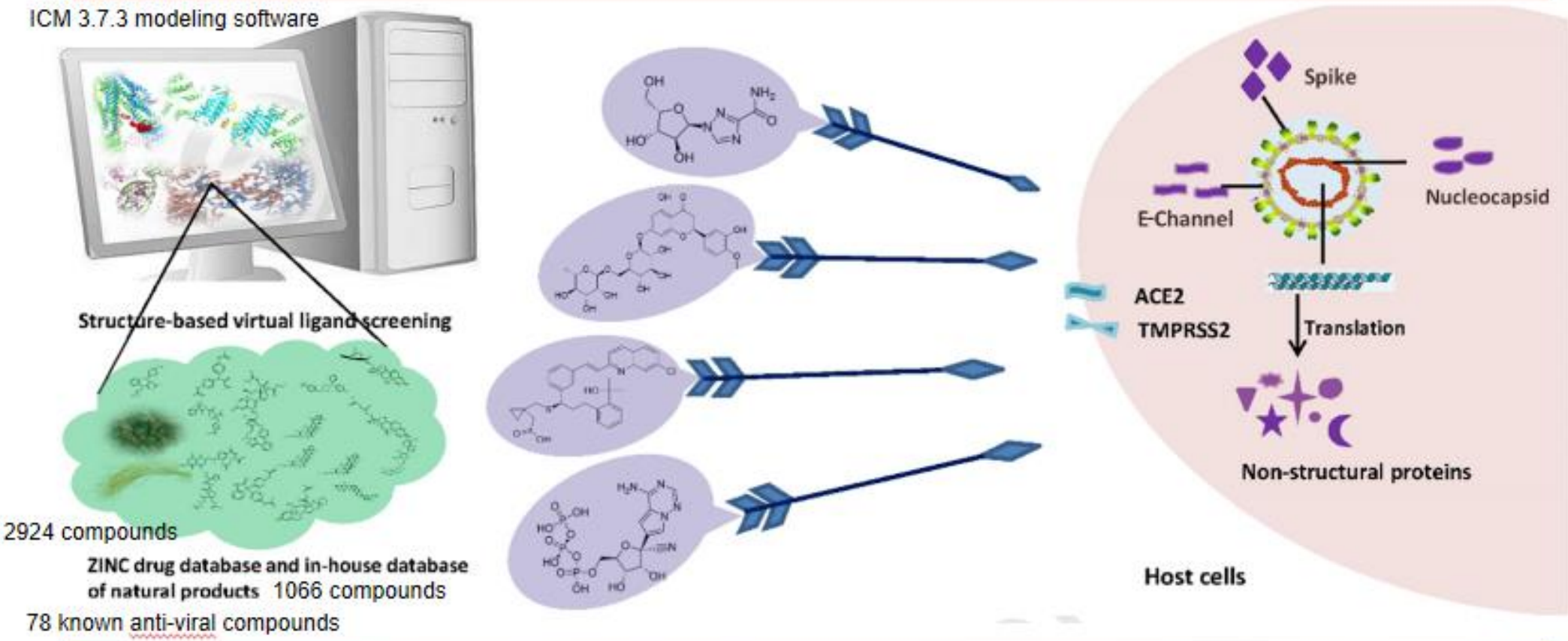
*– or –*

b) having direct contact with infectious secretions of a 2019-nCoV case (e.g., being coughed on) while not wearing recommended personal protective equipment.

# What is Critical Contact Time?

- UNKNOWN
- Hong Kong – 15 minutes
- Singapore – 30 minutes

# Viral and Host Targets



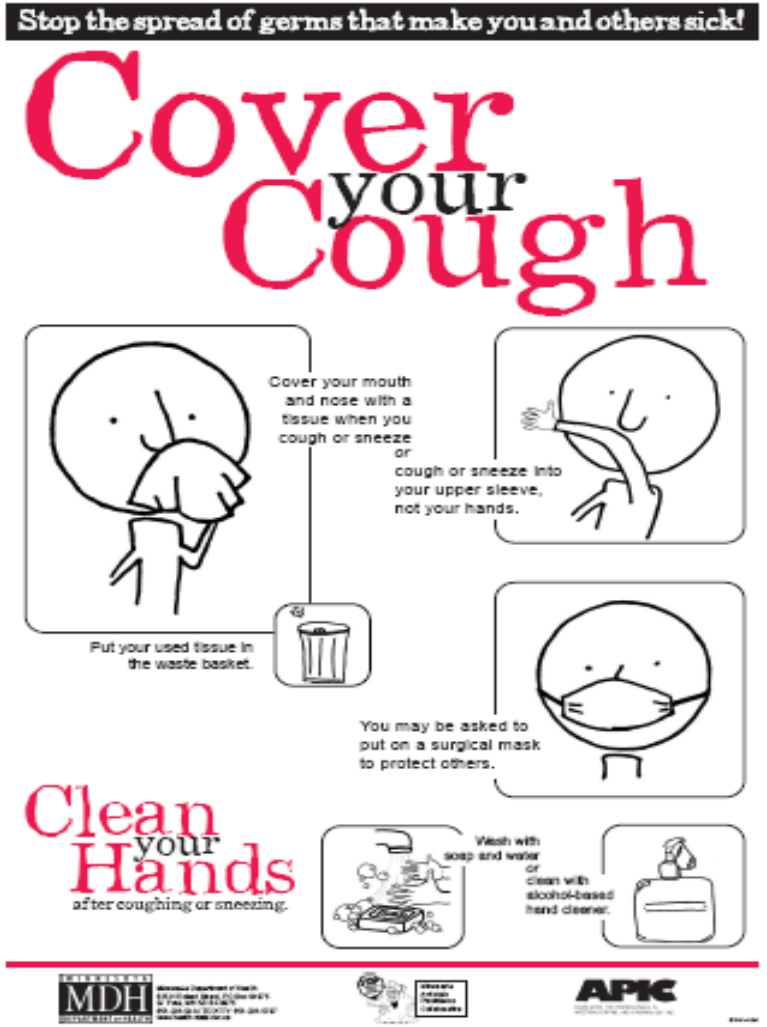

Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Wang Q, Xu Y, Li M, Li X, Zheng M, Chen L, Li H, Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods, Acta Pharmaceutica Sinica B, https://doi.org/10.1016/j.apsb.2020.02.008.

# Treatment

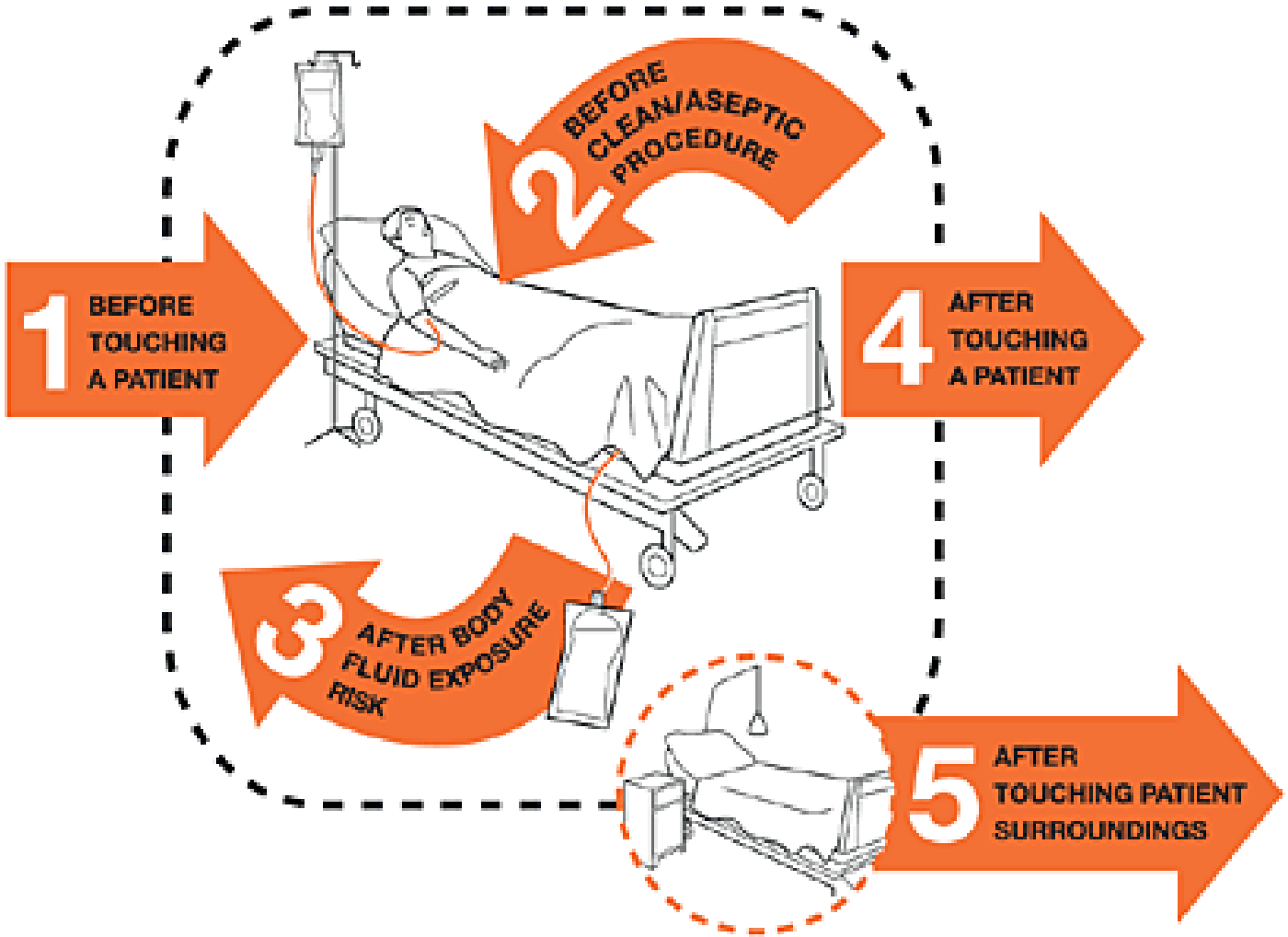
- SUPPORTIVE CARE
- Antivirals: Remdesivir, Lopinavir-ritonavir
- Chloroquine/Hydroxychloroquine
- Monoclonal Ab
- Hyperimmune globulin
- Convalescent plasma
- Receptor Blockers
- At least 12 groups working on vaccine expected to be in Phase I trials in next 3 mos

# Respiratory Hygiene and Cough Etiquette

- Provide mask/tissue to patients who are coughing
- Wear mask for close contacts with patient with respiratory infections
- Place patient in isolation if communicable infectious respiratory infection is suspected.

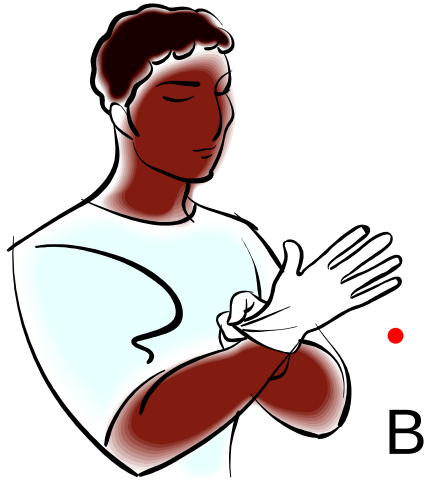


# The WHO Five Moments for Hand Hygiene



# Personal Protective Equipment (PPE)

- All body substances considered potentially infectious.
- Use barriers (i.e. personal protective equipment/PPE) based on potential for contact with body substances:

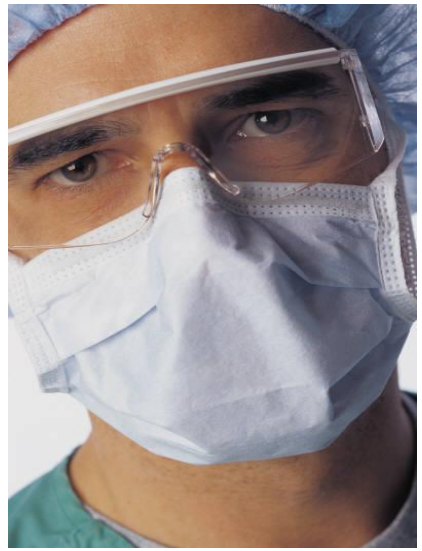


- Gloves
- Gown
- Mask
- Face shield or safety glasses

- PREVENT CONTAMINATION!

Before moving on to next patient:

- Remove and dispose of used PPE
- **Hand Hygiene**
- Disinfect equipment as needed



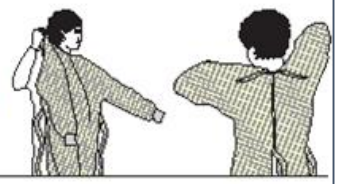
# PPE: Donning and Doffing

## SEQUENCE FOR PUTTING ON PERSONAL PROTECTIVE EQUIPMENT (PPE)

The type of PPE used will vary based on the level of precautions required, such as standard and contact, droplet or airborne infection isolation precautions. The procedure for putting on and removing PPE should be tailored to the specific type of PPE.

### 1. GOWN

- Fully cover torso from neck to knees, arms to end of wrists, and wrap around the back
- Fasten in back of neck and waist



### 2. MASK OR RESPIRATOR

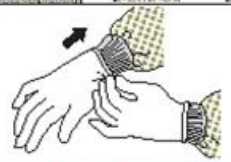
- Secure ties or elastic bands at middle of head and neck
- Fit flexible band to nose bridge
- Fit snug to face and below chin
- Fit-check respirator

### 3. GOGGLES OR FACE SHIELD

- Place over face and eyes and adjust to fit

### 4. GLOVES

- Extend to cover wrist of isolation gown



## USE SAFE WORK PRACTICES TO PROTECT YOURSELF AND LIMIT THE SPREAD OF CONTAMINATION

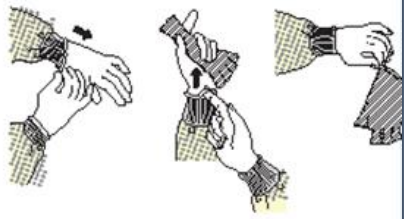
- Keep hands away from face
- Limit surfaces touched
- Change gloves when torn or heavily contaminated
- Perform hand hygiene

## SEQUENCE FOR REMOVING PERSONAL PROTECTIVE EQUIPMENT (PPE)

Except for respirator, remove PPE at doorway or in anteroom. Remove respirator after leaving patient room and closing door.

### 1. GLOVES

- Outside of gloves is contaminated!
- Grasp outside of glove with opposite gloved hand; peel off
- Hold removed glove in gloved hand
- Slide fingers of ungloved hand under remaining glove at wrist
- Peel glove off over first glovet
- Discard gloves in waste container



### 2. GOGGLES OR FACE SHIELD

- Outside of goggles or face shield is contaminated!
- To remove, handle by head band or ear pieces
- Place in designated receptacle for reprocessing or in waste container

### 3. GOWN

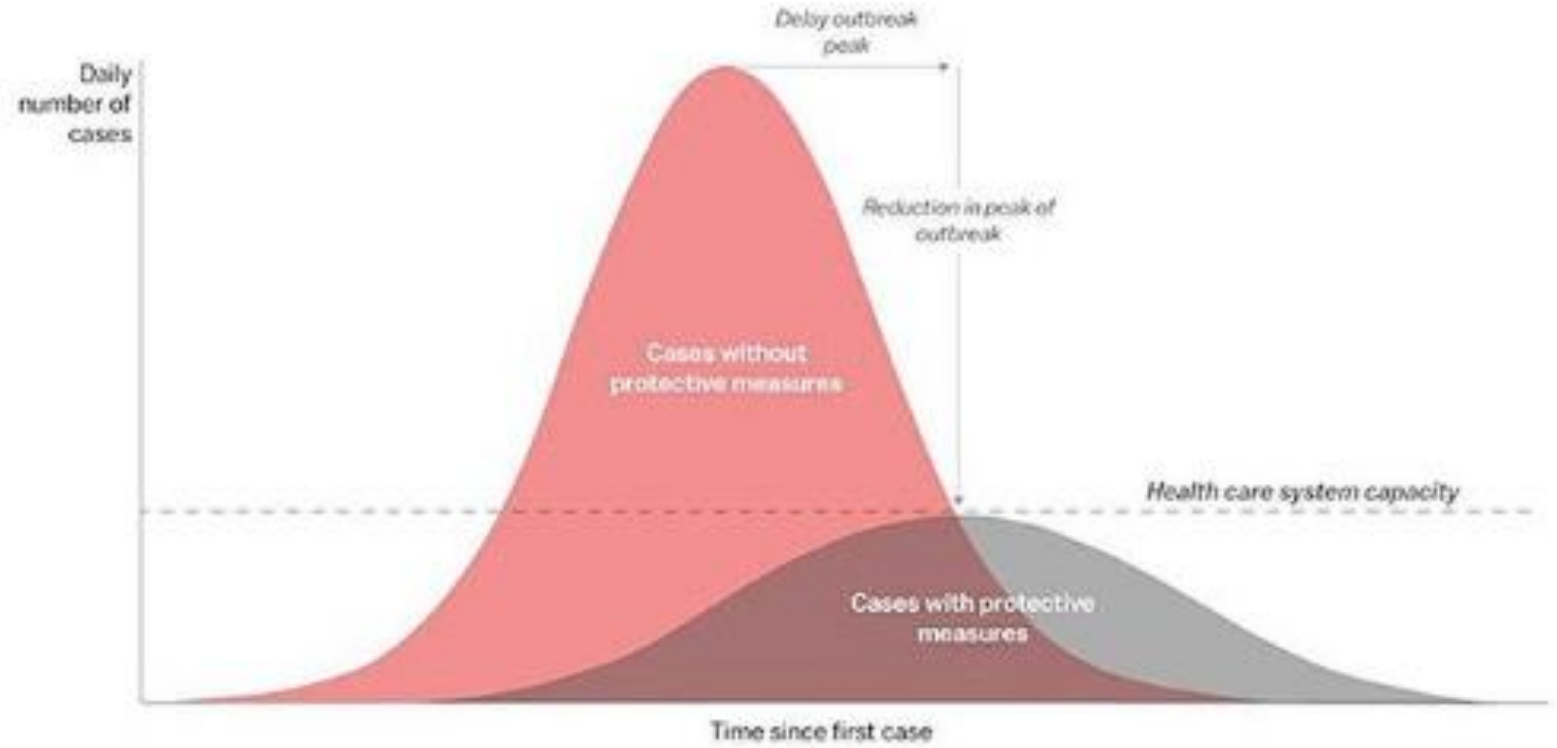
- Gown front and sleeves are contaminated!
- Unfasten ties
- Pull away from neck and shoulders, touching inside of gown only
- Turn gown inside out
- Fold or roll into a bundle and discard

### 4. MASK OR RESPIRATOR

- Front of mask/respirator is contaminated — DO NOT TOUCH!
- Grasp bottom, then top ties or elastics and remove
- Discard in waste container

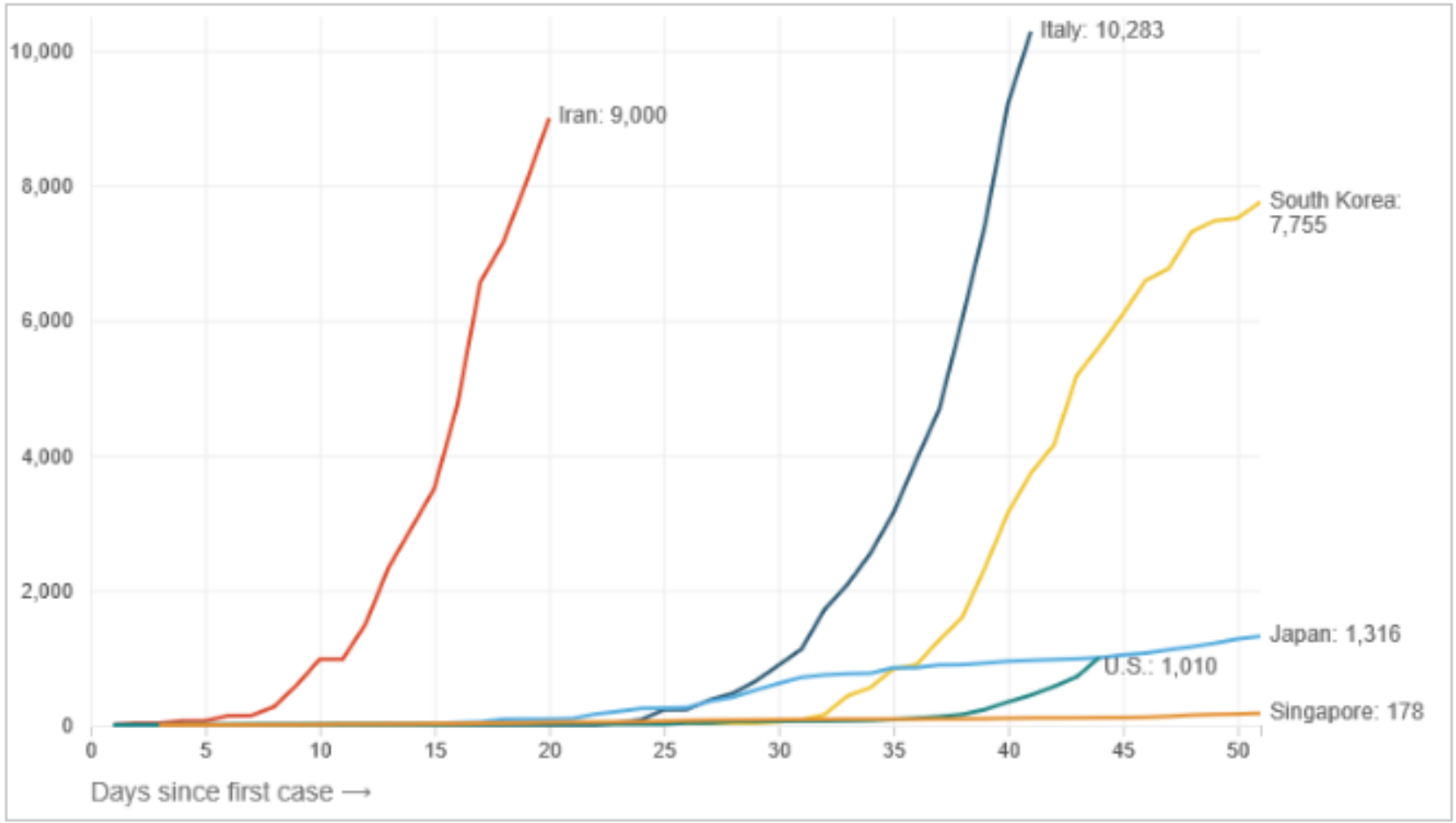
## PERFORM HAND HYGIENE BETWEEN STEPS IF HANDS BECOME CONTAMINATED AND IMMEDIATELY AFTER REMOVING ALL PPE

# “Flattening the Curve”






Source: CDC

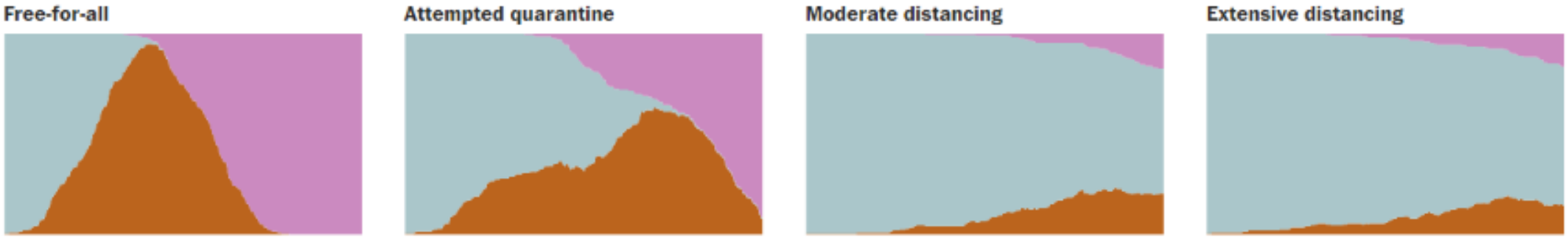



*Source: Humanistic GIS Lab at the University of Washington*
*Credit: Stephanie Adeline/NPR*

# Lessons Learned from Hong Kong & Singapore

- Surgical masks for all patient encounters
- Gloves
- Hand hygiene
- Disinfect surfaces between patient contacts
- Patients with suspicious symptoms or high risk exposures treated in separate locations, separate teams
- Social distancing in clinics and hospitals

# Modeling on Social Distancing




https://www.washingtonpost.com/graphics/2020/world/corona-simulator/?utm_campaign=2cecc5799b-EMAIL_CAMPAIGN_2020_03_17_05_35&utm_medium=email&utm_source=Dog%20Aging%20Project

# What They Did Not Do?

- Use N95 respirators, face protectors, goggles, gowns for other than
  - Aerosol generating procedures
  - Known or suspected COVID-19 pts
- Neglect Intensive contact tracing but well-defined close contact
- Neglect enforcement of quarantine close contacts

# Hospital Strategies

- Manage visitor access and movement in the facility
- Consistent PPE
- Appropriate isolation of PUIs and confirmed
- Temperature and symptom screen at entrances
- Monitor, manage ill and exposed HCP
- Train and educate HCP
- Implement environmental infection control
- Establish reporting structure within facilities and to public health dept
- Disseminate rapidly changing info and policies
- Delay elective surgeries
- Know community prevalence

# What Can People Do To Protect Themselves ?

- DO NOT TRAVEL : cruise ship, plane
- Social distancing: Avoid large group events: meetings, social gatherings, crowds
- Practice cough etiquette
- Frequent hand washing
- Disinfect shared high touch surfaces
- Avoid going to hospitals and clinics unless you are ill or must accompany a dependent or incapacitated family member
- General health measures: healthy diet, sleep and rest, exercise
- Protect elderly, immunocompromised
- Stay informed

*All travelers in 14 day quarantine
*Schools closed
*Home quarantine except for essential workers
*Essential services/businesses open

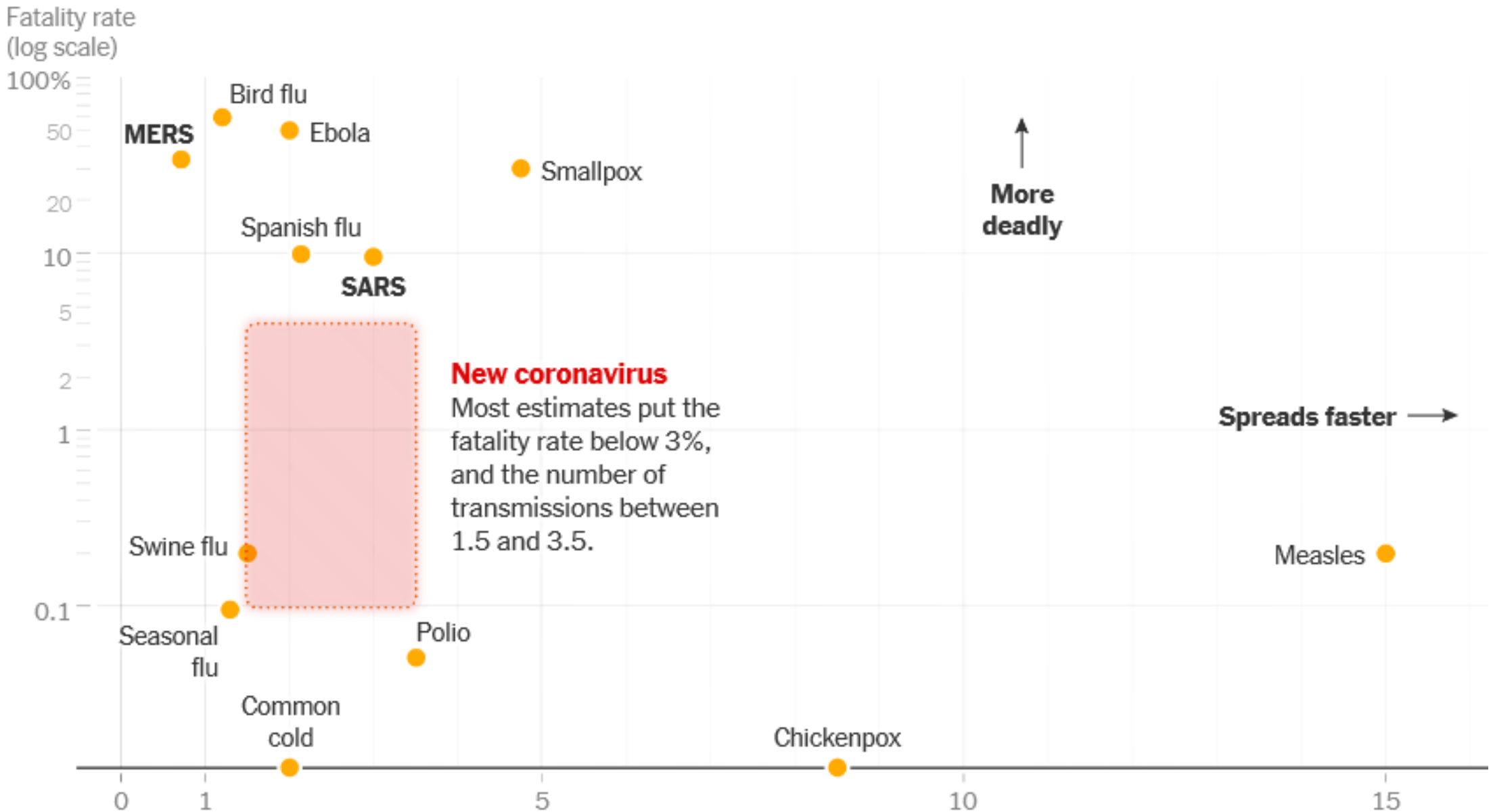
**Novel Coronavirus in Hawaii**

COVID-19 Positive* Cases

*Cumulative totals as of 12:00 noon on March 24, 2020*

| **Total (new)** | 90 (14) |
|---|---|
| *By Residence* | |
| Hawaii | 2 (0) |
| Honolulu | 58 (10) |
| Kauai | 1 (0) |
| Maui | 9 (0) |
| Non-Hawaii Residents | 14 (3) |
| Pending | 6 (1) |
| | |
| Required Hospitalization | 6 (2) |
| Deaths | 1 (1) |

*includes presumptive and confirmed cases, and Hawaii and non-Hawaii residents; data are preliminary and subject to change; note that CDC provides case counts according to states of residence.


Fatality rate
(log scale)
100%
50
20
10
5
2
1
0.1
Bird flu
MERS
Ebola
Smallpox
Spanish flu
SARS
More
deadly
New coronavirus
Most estimates put the
fatality rate below 3%,
and the number of
transmissions between
1.5 and 3.5.
Spreads faster
Swine flu
Measles
Seasonal
flu
Polio
Common
cold
Chickenpox
0
1
5
10
15
Average number of persons infected by each sick person

“Be patient and tough; one day this pain will be useful to you.”

OVID