COVID-19: KEEPING UP WITH A MOVING TARGET

Paul Auwaerter, MD

Clinical Director, Division of Infectious Diseases

Sherrilyn and Ken Fisher Professor of Medicine

Fisher Center for Environmental Infectious Diseases

Johns Hopkins University School of Medicine

Baltimore, Maryland

Thank You

This program is brought to you through the generous support of DKBmed, Postgraduate Institute for Medicine, the Institute for Johns Hopkins Nursing, ArcheMedX, and FreeCME.

CME Information

Jointly provided by Postgraduate Institute for Medicine and DKBmed, LLC.

Disclosure of Conflicts of Interest

Postgraduate Institute for Medicine (PIM) requires instructors, planners, managers, and other individuals who are in a position to control the content of this activity to disclose any real or apparent conflict of interest (COI) they may have as related to the content of this activity. All identified COI are thoroughly vetted and resolved according to PIM policy. PIM is committed to providing its learners with high quality activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

The faculty reported the following financial relationships or relationships they or their spouse/life partner have with commercial interests related to the content of this continuing education activity:

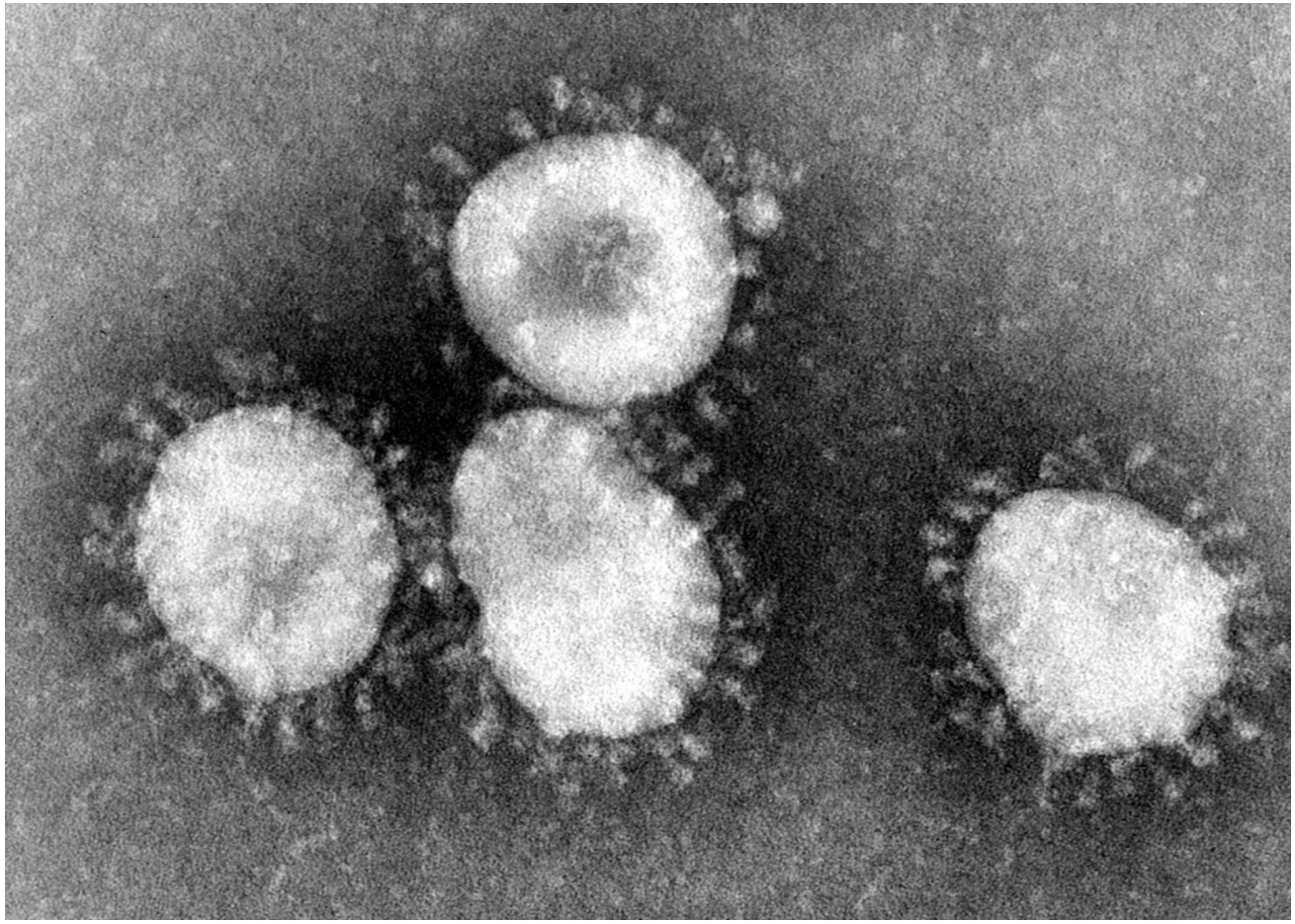
Name of Faculty or Presenter	Reported Financial Relationship
Paul G. Auwaerter, MD, MBA, FIDSA	Scientific Advisor: DiaSorin, Shionogi Inc. JNJ: Ownership equity

There will be no references to the unlabeled/unapproved uses of any drugs or products in today's discussion. All activity, content, and materials have been developed solely by the activity directors, planning committee members, and faculty presenters, and are free of influence from a commercial entity.

For complete accreditation information, please visit covid19.dkbmed.com

Learning Objectives

- Discuss symptoms and transmission of COVID-19.
- Discuss risks, management, and precautions associated with COVID-19.
- Describe natural history of COVID-19 illness.



Coronaviruses Four Routine

- HCoV seen in
  - 10% hospitalized children RTIs
    - < 2 yrs > older
  - 10% asx controls
  - Co-infection seen
- Seasonal
  - Winter predominance
  - Some year round

Norwegian Peds Hosp Study

	HCoV Detections, Total and Subtypes, No. (%)				
	Total HCoV (N = 313)	OC43 (n = 146)	NL63 (n = 101)	HKU1 (n = 50)	229E (n = 18)
Respiratory viruses					
Rhinovirus	78 (25.0)	35 (24.0)	21 (20.8)	16 (32.0)	7 (38.9)
Respiratory syncytical virus	73 (23.4)	33 (22.7)	28 (27.8)	10 (20.0)	2 (11.2)
Enterovirus	52 (16.7)	23 (15.8)	14 (13.9)	12 (24.0)	4 (22.3)
Human bocavirus	35 (11.2)	17 (11.7)	10 (10.0)	6 (12.0)	2 (11.2)
Parainfluenza virus types 1–4	31 (10.0)	12 (8.3)	9 (9.0)	7 (14.0)	3 (16.7)
Human parechovirus	22 (7.1)	9 (6.2)	7 (7.0)	5 (10.0)	1 (5.6)
Adenovirus	20 (6.4)	13 (9.0)	4 (4.0)	2 (4.0)	1 (5.6)
Human metapneumovirus	15 (4.8)	6 (4.2)	2 (2.0)	6 (12.0)	1 (5.6)
Influenzavirus A/B	8 (2.6)	3 (2.1)	5 (5.0)		
No. of detections					
Single HCoV detection	100 (32)	50 (34.3)	32 (31.7)	12 (24.0)	6 (33.4)
HCoV + 1 codetection	132 (42.2)	60 (41.1)	45 (44.6)	22 (44.0)	6 (33.4)
HCoV + ≥2 codetections	81 (25.9)	36 (24.7)	24 (23.8)	16 (32.0)	6 (33.4)

Relationship Between HCoV and RTI, Comparing Children With RTI (n = 313) and Asymptomatic Controls (n = 38)

	Univariate analysis			Adjusted analysis		
	OR	(95% CI)	*P* value	OR	(95% CI)	*P* value
HCoV viral load						
Ct value <28	2.59	(1.21–5.54)	.010	3.12	(1.24–7.86)	.016
Ct value >28 (reference)						

dkbmed

Heimdal et al. J Infect Dis 2019;219(3):1198-1206

Where did SARS-CoV-2 come from?

Bat SARS-like coronavirus (genus Betacoronavirus, subgenus Sarbecovirus)

Pangolin

SARS-2-CoV or 2019 nCoV

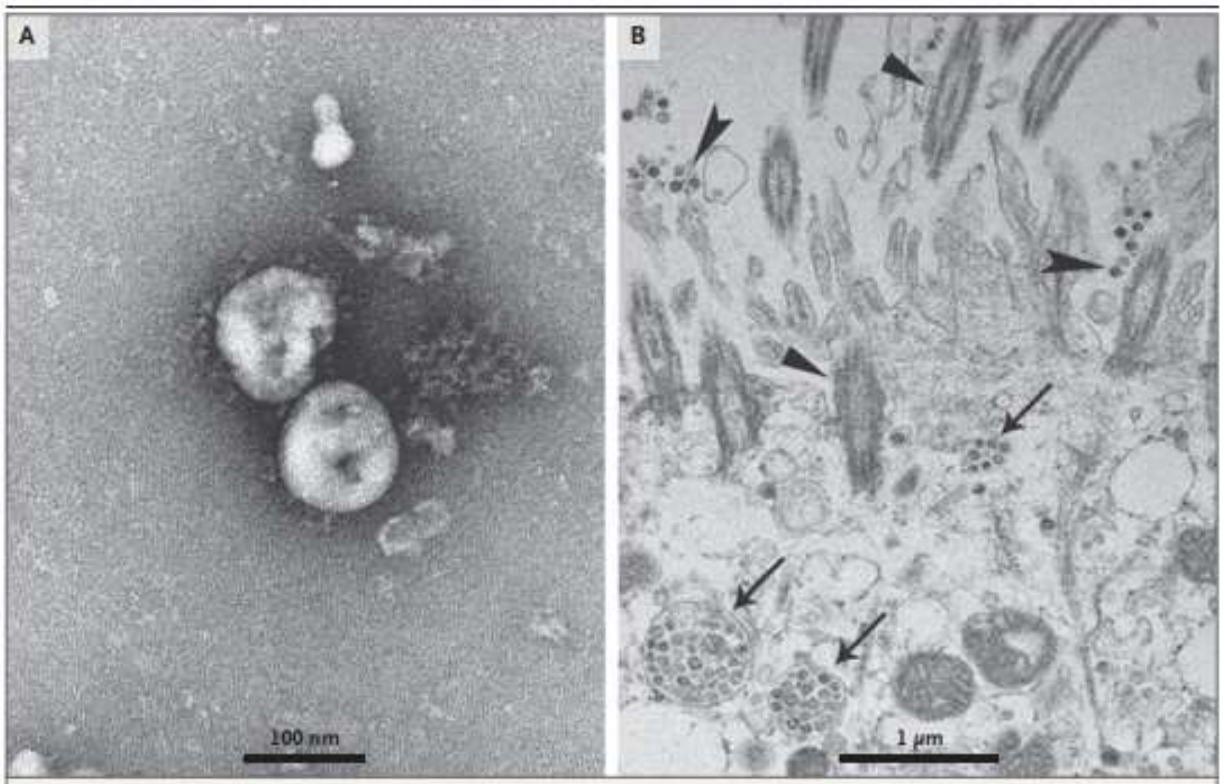


Figure 3. Visualization of 2019-nCoV with Transmission Electron Microscopy.

Negative-stained 2019-nCoV particles are shown in Panel A, and 2019-nCoV particles in the human airway epithelial cell ultrathin sections are shown in Panel B. Arrowheads indicate extracellular virus particles, arrows indicate inclusion bodies formed by virus components, and triangles indicate cilia.

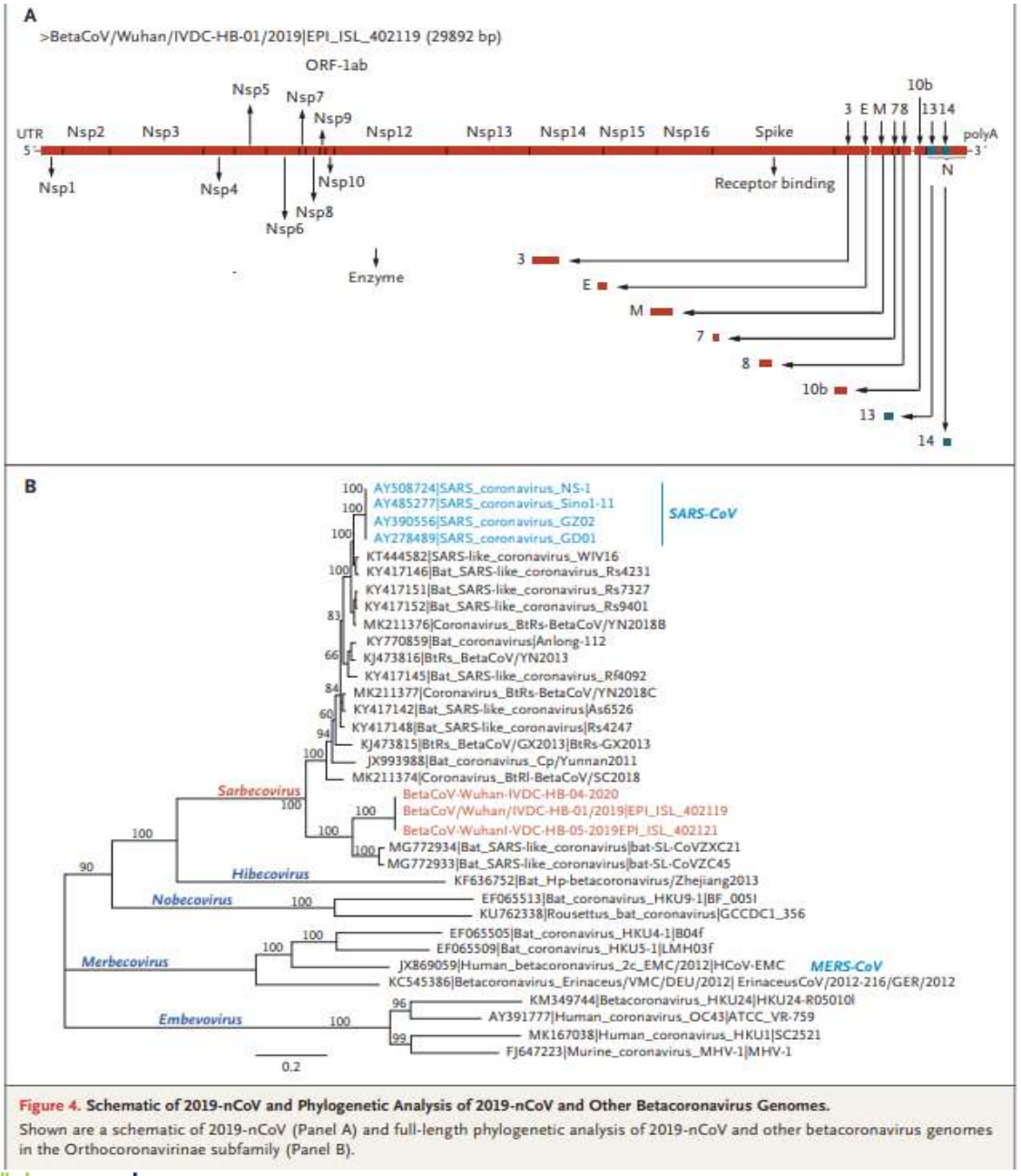
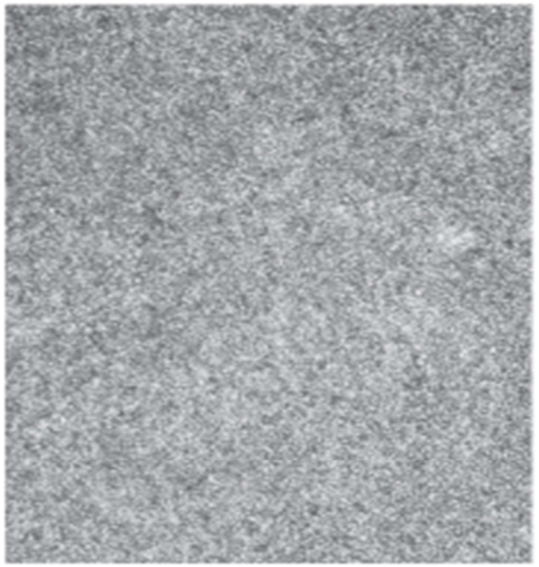
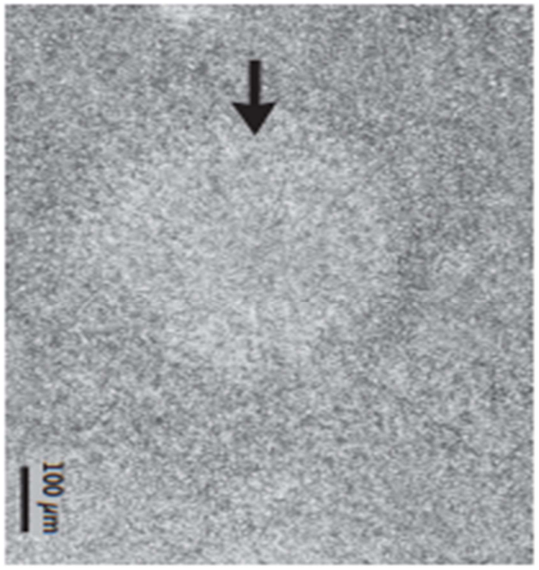


Figure 4. Schematic of 2019-nCoV and Phylogenetic Analysis of 2019-nCoV and Other Betacoronavirus Genomes.

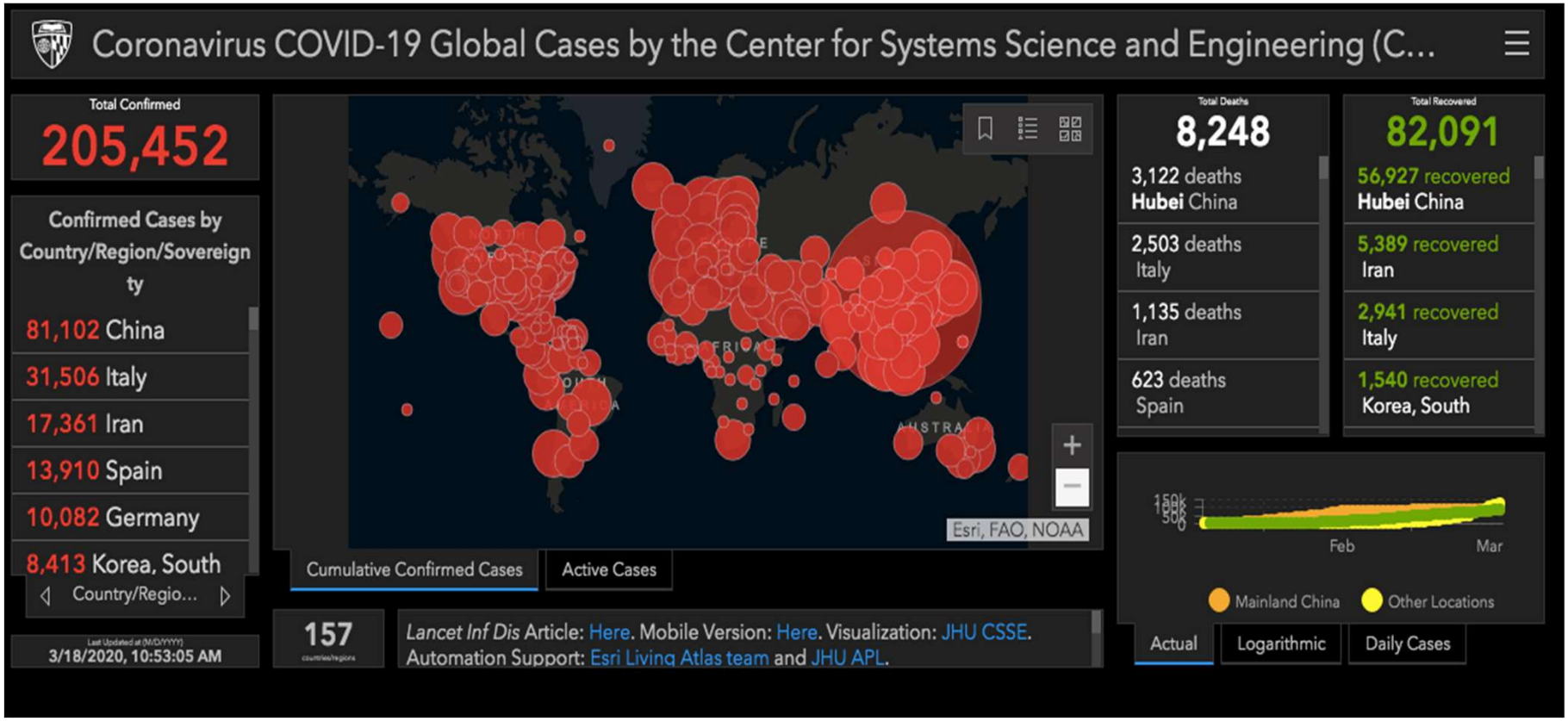
Shown are a schematic of 2019-nCoV (Panel A) and full-length phylogenetic analysis of 2019-nCoV and other betacoronavirus genomes in the Orthocoronavirinae subfamily (Panel B).





COVID-19 (As of March 18, 2020)

COVID-19
KEEPING UP WITH A MOVING TARGET



https://coronavirus.jhu.edu/map.html Accessed March 18, 2020

Transmission

- Predominantly droplet
  - Sneeze travels 3-6 feet
  - Surface contamination
    - 2-3 d on metal or plastic at room temperature, 40% humidity
    - 6-12 hrs fabric
  - Airborne likely but infrequent
    - Suctioning respiratory secretions

Infectious Comparisons

Virus	R	Transmission	Case Fatality Rate⁺	Comments
p09H1N1	1.4-1.6	droplet	< 0.1%	Co-morbidities ↑
SARS-2-CoV	1.4-6.6*	droplet	< 2.3-4.6%	Co-morbidities ↑
MERS-CoV	0.3-0.8 to 8.1*	droplet	< 26.5-55.5%	Co-morbidities ↑
SARS-CoV	2.0-5.0*	droplet	11%	Co-morbidities ↑
Measles	5.0-7.0	airborne	1.0-3.0%	In developing countries
Ebola	1.5-2.0	body fluids	83-90%	Early supportive care improves outcomes
Pertussis	3.0-5.5	droplet	<1.0%, 3.7% (infants)	
Polio	5.0-7.0	fecal-oral	2-5% (children) 15-30% (adult)	

R = basic reproduction number, *super-spreader issues
⁺if untreated, if pertinent

Personal Protection for HCP: CDC

Hospital Healthcare Personnel should adhere to Standard, Contact, and Airborne Precautions:

- Eye protection when caring for patients
  - Goggles or a face shield
- PPE
  - Including NIOSH-approved N95 respirators
- Gowns
- Gloves
- Face shield/eye protection, etc.
- Includes, but not limited to, surgical N95 respirators

https://www.cdc.gov/coronavirus/2019-ncov/hcp/healthcare-supply-ppe-index.html Accessed March 18, 2020

Personal Protection for HCP: WHO

Setting	Activity	PPE or Procedure
Inpatient room	Direct care to COVID-19 patient	Medical mask, gown, gloves, eye protection (goggles or face shield).
Inpatient room	Aerosol-generating procedures performed on COVID-19 patients.	Respirator N95 or FFP2 standard, or equivalent. Gown, gloves, eye protection, apron
Inpatient triage	Preliminary screening not involving direct contact	Maintain spatial distance of ≥1 m. No PPE required
Outpatient consultation room	Physical examination of patient with respiratory symptoms.	Medical mask, gown, gloves, eye protection (goggles or face shield).
Outpatient consultation room	Physical examination of patient without respiratory symptoms	PPE according to standard precautions and risk assessment.

https://apps.who.int/iris/bitstream/handle/10665/331215/WHO-2019-nCov-IPCPPE_use-2020.1-eng.pdf
Accessed March 18, 2020

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China

Dawei Wang, MD; Bo Hu, MD; Chang Hu, MD; Fangfang Zhu, MD; Xing Liu, MD; Jing Zhang, MD; Binbin Wang, MD; Hui Xiang, MD; Zhenshun Cheng, MD; Yong Xiong, MD; Yan Zhao, MD; Yirong Li, MD; Xinghuan Wang, MD; Zhiyong Peng, MD

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019

Na Zhu, Ph.D., Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xingwang Li, M.D., Bo Yang, M.S., Jingdong Song, Ph.D., Xiang Zhao, Ph.D., Baoying Huang, Ph.D., Weifeng Shi, Ph.D., Roujian Lu, M.D., Peihua Niu, Ph.D., Faxian Zhan, Ph.D., Xuejun Ma, Ph.D., Dayan Wang, Ph.D., Wenbo Xu, M.D., Guizhen Wu, M.D., George F. Gao, D.Phil., and Wenjie Tan, M.D., Ph.D., for the China Novel Coronavirus Investigating and Research Team

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Chaolin Huang, Yeming Wang*, Xingwang Li*, Lili Ren*, Jianping Zhao*, Yi Hu*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†*

Summary

Background A recent cluster of pneumonia cases in Wuhan, China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV). We report the epidemiological, clinical, laboratory, and radiological characteristics and treatment and clinical outcomes of these patients.

Lancet 2020; 395: 497–506
Published Online
January 24, 2020
https://doi.org/10.1016/

A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster

Jasper Fuk-Woo Chan, Shuofeng Yuan*, Kin-Hang Kok*, Kelvin Kai-Wang To*, Hin Chu*, Jin Yang, Fanfan Xing, Jieling Liu, Cyril Chik-Yan Yip, Rosana Wing-Shan Poon, Hoi-Wah Tsoi, Simon Kam-Fai Lo, Kwok-Hung Chan, Vincent Kwok-Man Poon, Wan-Mui Chan, Jonathan Daniel Ip, Jian-Piao Cai, Vincent Chi-Chung Cheng, Honglin Chen, Christopher Kim-Ming Hui, Kwok-Yung Yuen*

Summary

Background An ongoing outbreak of pneumonia associated with a novel coronavirus was reported in Wuhan city, Hubei province, China. Affected patients were geographically linked with a local wet market as a potential source. No data on person-to-person or nosocomial transmission have been published to date.

Lancet 2020; 395: 514–23
Published Online
January 24, 2020
https://doi.org/10.1016/

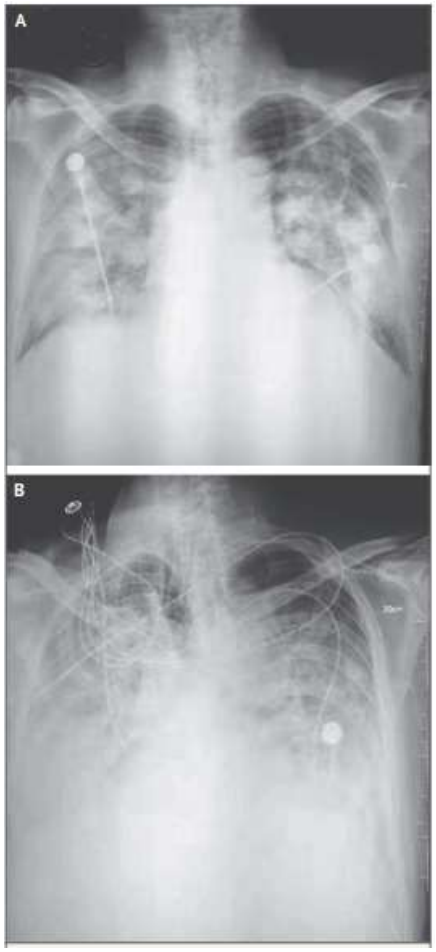
COVID-19

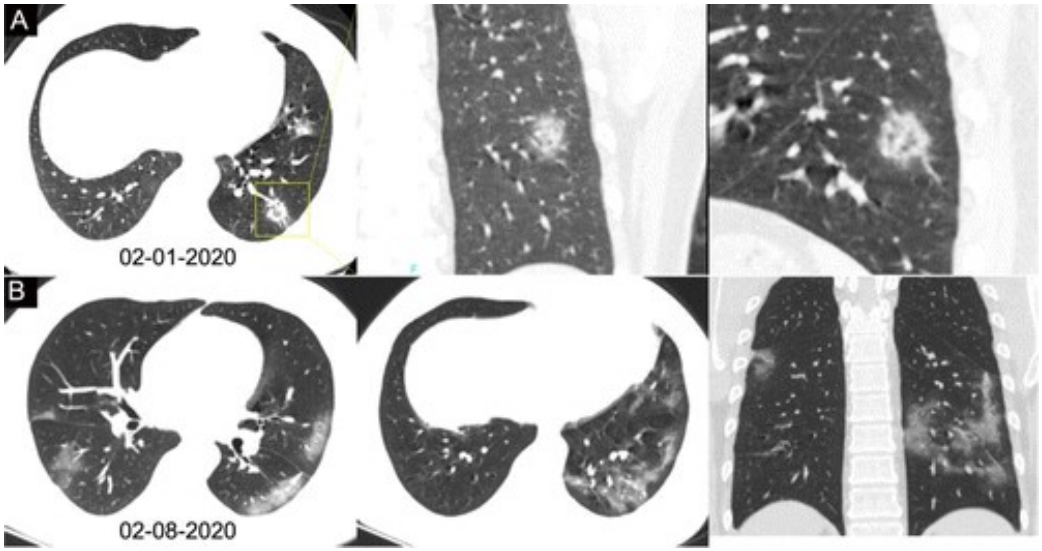
- Range of illness:
  - Asx to mild to severe
  - Incubation period:
    - Early data suggests 2-12d, mean 6.4d
    - Report of up to 24d
  - Wuhan experience
    - Hospitalized pts more male, mid-late fifties
    - Higher mortality than elsewhere

Clinical Presentation

- Descriptions mostly limited to hospitalized patients
- Signs, symptoms & labs
  - Fever (83-98%)
  - Cough (46-82%, usually dry)
  - Myalgia or fatigue (11-44%)
  - Shortness of breath at onset (31%)
  - Less common symptoms:
    - Pharyngitis
    - Headache
    - Productive cough
    - GI symptoms
    - Hemoptysis
  - Leukopenia in ~ 70% hospitalized pts.
  - LDH often elevated

Imaging





CT superior to CXR for early diagnosis
Ground glass opacities or consolidation
May progress to ARDS
Peak findings d10 of illness
Resolution starting ~ d14

Zhu et al. NEJM Feb 2020
Tao et al, Radiology 2020;200643 DOI

Diagnostics

- FDA-approved assays (e.g., Film Array) ≠ SARS-2-CoV detection
- Molecular:
  - CDC, US local health departments and qualified labs (NOT hospitals, clinics, etc.)
    - CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panel.
  - Many labs now authorized by FDA or state health depts
    - Quest, LabCorp, hospitals
  - Many testing for Influenza/RSV first then reflex to SARS-CoV-2.
- Serology:
  - China, CDC and others, developing assays

CDC Detection Kit

SARS-CoV-2

Disease Course

- Hospitalized patients, limited studies
  - ~50% develop hypoxemia by d8
  - ARDS 17-29%
  - ICU patients
    - Non-invasive ventilation 42%
    - Mechanical ventilation 47%
    - High-flow O2 11%
    - ECMO 2-5%

Huang Lancet 2020; Wang NEJM 2020; Chen Lancet 2020

Monthly Rates

- Early Wuhan experience: 4.3%
  - Early epidemics, sickest seen/prioritized
- China estimates: ~ 2%
  - Outside of China: lower is some countries
  - Italy high
- Reality: not known, likely lower
  - Need serological testing

Mortality Rates: All But Varies in Different Countries

Age (yrs)	Case Fatality Rate (%)
80	14.8
70-79	8.0
60-69	3.6
50-59	1.3
40-49	0.4
30-39	0.2
20-29	0.2
10-19	0.2
0-9	None

Pre-existing conditions	Case Fatality Rate (%)
Cardiovascular disease	10.5
Diabetes	7.3
Chronic respiratory disease	6.3
Hypertension	6.0
Cancer	5.6
No pre-existing conditions	0.9

Age, Sex, Existing Conditions of COVID-19 Cases and Deaths. Available at https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/#pre-existing-conditions Accessed March 18, 2020

Therapeutics

- Supportive care
- Investigational: Remdesivir (GS-5734) IV
  - Developed for Ebola/Marburg but less effective than mAbs
  - Coronaviruses (MERS-CoV, SARS-CoV)
    - Good *in vitro* activity
    - Rhesus/MERS-CoV
      - ❖**Effective when given 12h post-inoculation**
      - ❖**Preventive when given prophylactically**
  - Used in one American patient (survived)
- Await late, early use trials from China

deWit, PNAS 2020

Agents Under Study

- **List of medications currently under investigation (US, China):**
  - ASC09/ritonavir, lopinavir/ritonavir with or without umifenovir
  - ASC09/oseltamivir, ritonavir/oseltamivir, oseltamivir
  - Azvudine
  - Baloxavir marboxil/favipiravir and lpv/rtv in combination(s)
  - Camostat mesylate
  - Chloroquine, hydroxychloroquine
  - Darunavir/cobicistat alone or with lpv/rtv_and thymosin α1 in combination(s)
  - Remdesivir
  - Chloroquine or hydroxychloroquine
  - Interferon alfa-2b alone or in combination with lpv/rtv + ribavirin
  - Methylprednisolone
  - Camrelizumab and thymosin
  - Tocilizumab

LVP/RTV (Kaletra)

- Thought to inhibit SAR-2-CoV 3-chymotrypsin-like protease
- SARS: some benefit
- Difficult to obtain in US
  - IC50 coronavirus < 100x wild-type HIV-1
  - Clinical trial (non-RCT, China), results pending

Chloroquine/Hydroxychloroquine

- Mechanism may be by interfering with cellular acidification, interfering with endosomal pH ◆ viral/cell fusion and/or glycosylation of ACE2 (SARS-2-CoV receptor)
- Reported to have some efficacy in vivo and in COVID-19 pneumonia
  - SARS (in vitro, Vincent J Virol 2005)
  - MERS-CoV (NO EFFECT in vitro, Cong Y, PLoS One 2018)
  - SARS-2-CoV (in vitro, Wang Cell Res 2020)
- Chloroquine phosphate listed in Chinese GL
  - "Superior" in trial of 100 pts, faster resolution lung imaging, cessation of viral shedding

http://www.nhc.gov.cn/xcs/yqfkdt/202002/f12a62d10c2a48c6895cedf2faea6e1f.shtml Accessed March 18, 2020
Audio transcript, State Council China (in Chinese, 2/28/2020)

Chloroquine/Hydroxychloroquine

- Only in vitro data and some animal model with other coronaviruses
  - No COVID published experience
  - Study in influenza + HIV showed increased HIV VL
  - Mixed data with non-coronaviruses for efficacy
    - Ebola
    - Influenza
- Some centers using, others not

Prevention of Fibrosis/Irreversible Lung Damage

- Autopsy findings (China, preliminary)
- Reports of two lung transplants (China)

Xinhuanet, March 4, 2020

Monoclonal Abs to IL-6 Receptor (IL-6R)

- China COVD-19 Guideline for c19-related “cytokine storm”
  - Extensive lung disease, severe illness + documented elevated IL-6 levels
- Two FDA approved drugs
  - Tocilizumab (Actemra, Genentech/Roche)
  - Sarilumab (Kevzara, Sanofi Genzyme)
- FDA indications (Tocilizumab)
  - RA, GCA, Juvenile idiopathic rheumatoid arthritis
  - Cytokine Release Syndrome (CRS)
    - Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome
- No published data yet, Chinese Press releases said to be effective in severe disease

Off-label FDA-Approved Drugs for COVID-19

- Scant evidence of effectiveness to date
- Chinese Coronavirus Guidelines list
  - Chloroquine (antimalarial, US)
  - Favilavir (Influenza, China approved only)
  - Tocilizumab (anti-IL6R, US)
  - Traditional Chinese Medications

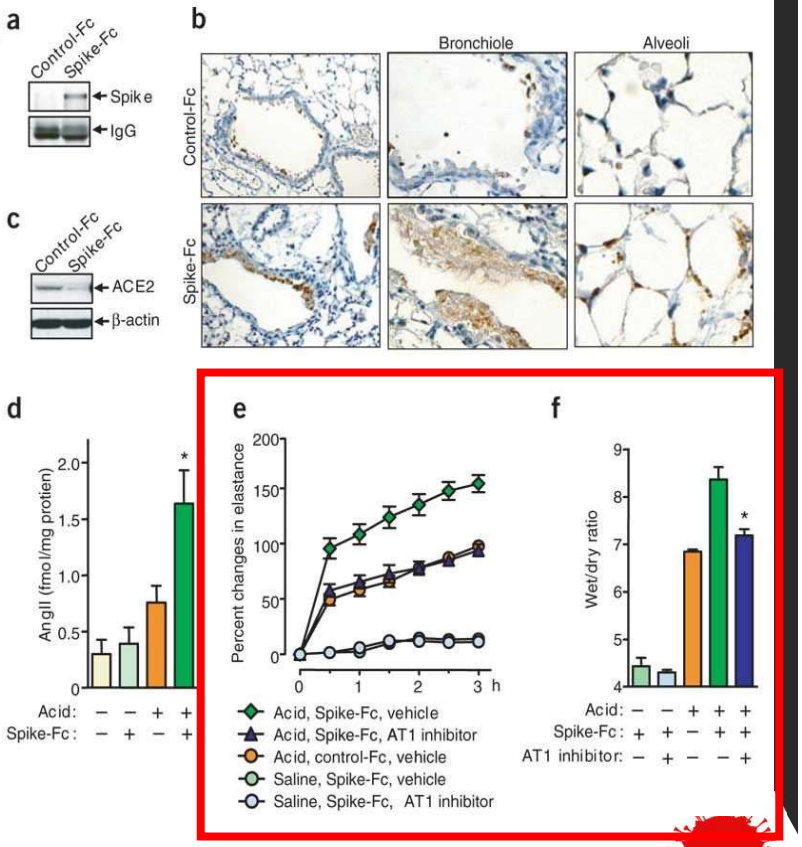
LETTERS

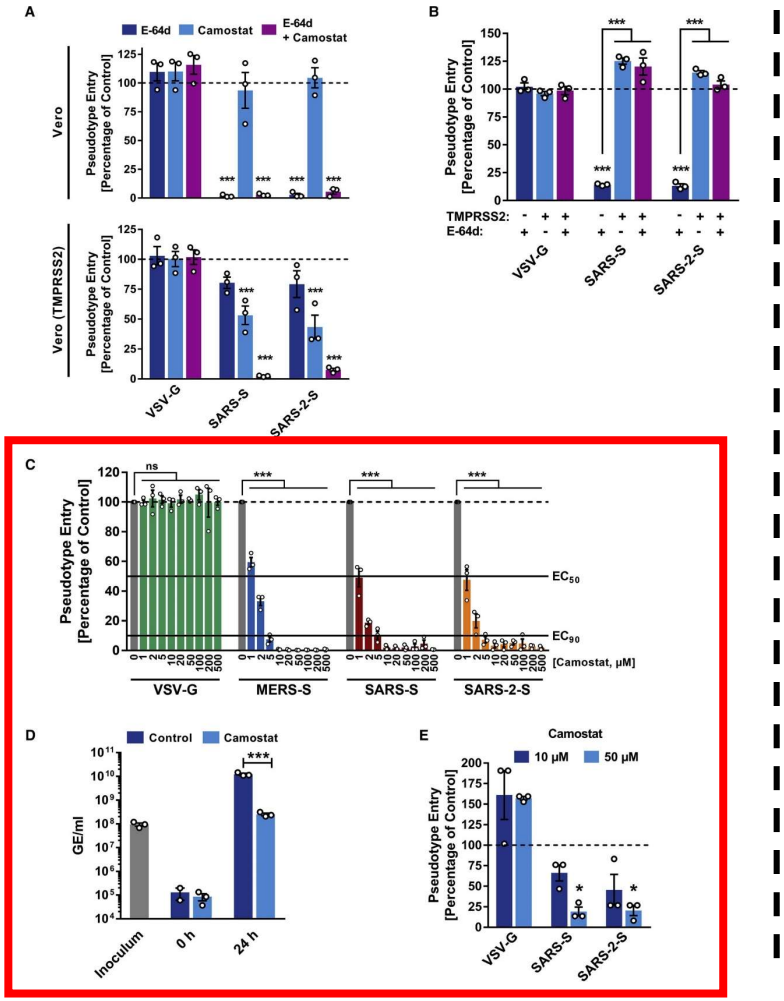
nature medicine

A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury

Keiji Kuba[1,7], Yumiko Imai[1,7], Shuan Rao[2,7], Hong Gao[3], Feng Guo[2], Bin Guan[2], Yi Huan[2], Peng Yang[2], Yanli Zhang[2], Wei Deng[3], Linlin Bao[3], Binlin Zhang[3], Guang Liu[2], Zhong Wang[4], Mark Chappell[5], Yanxin Liu[2], Dexian Zheng[2], Andreas Leibbrandt[1], Teiji Wada[1], Arthur S Slutsky[6], Depei Liu[2], Chuan Qin[3], Chengyu Jiang[2] & Josef M Penninger[1]

During several months of 2003, a newly identified illness termed severe acute respiratory syndrome (SARS) spread rapidly through the world[1–3]. A new coronavirus (SARS-CoV) was identified as the SARS pathogen[4–7] which triggered severe pneumonia and acute, often lethal, lung failure[8]. Moreover, among infected individuals influenza such as the Spanish flu[9,10] and the emergence of new respiratory disease viruses[11,12] have caused high lethality resulting from acute lung failure[13]. In cell lines, angiotensin-converting enzyme 2 (ACE2) has been identified as a potential SARS-CoV receptor[14]. The high lethality of SARS-CoV infections, its enormous economic and social impact, fears of renewed outbreaks as well as the potential misuse of such viruses as biologic weapons make it paramount to understand the pathogenesis of SARS-CoV. Here we provide the first genetic proof that ACE2 is a crucial SARS-CoV receptor *in vivo*. SARS-CoV infections and the Spike protein of the SARS-CoV reduce ACE2 expression. Notably, injection of SARS-CoV Spike into mice worsens acute lung failure *in vivo* that can be attenuated by blocking the renin-angiotensin pathway. These results provide a molecular explanation why SARS-CoV infections cause severe and often lethal lung failure and suggest a rational therapy for SARS and possibly other respiratory disease viruses.

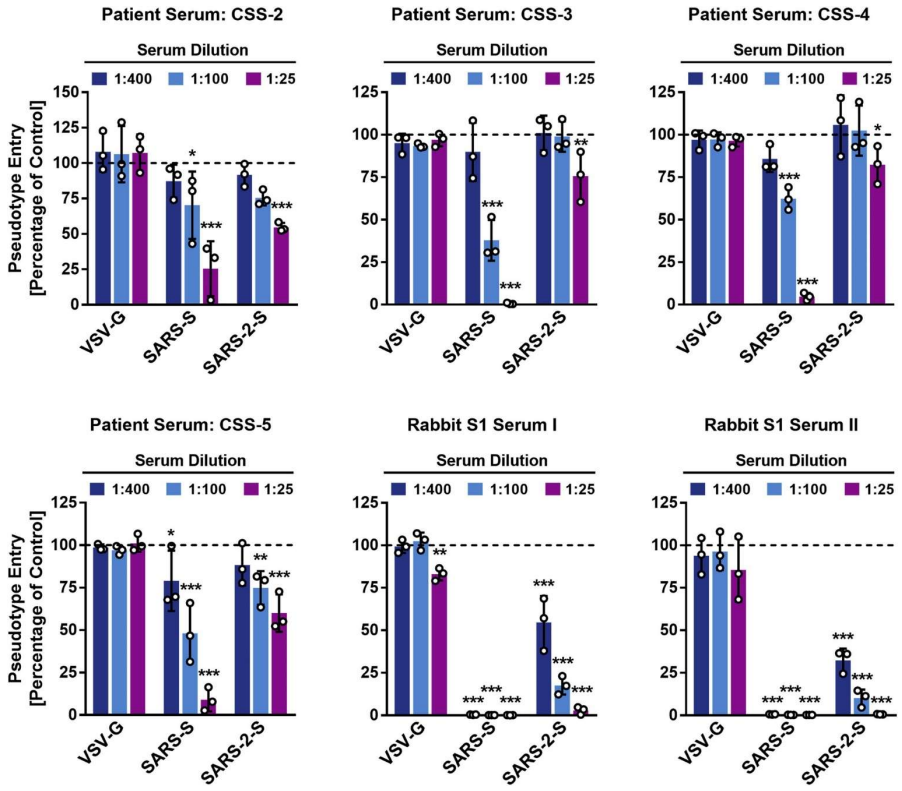




Cell PRESS

SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor

Markus Hoffmann, Hannah Kleine-Weber, Simon Schroeder, Nadine Krüger, Tanja Herrler, Sandra Erichsen, Tobias S. Schiergens, Georg Herrler, Nai-Huei Wu, Andreas Nitsche, Marcel A. Müller, Christian Drosten, Stefan Pöhlmann



COVID Vaccine

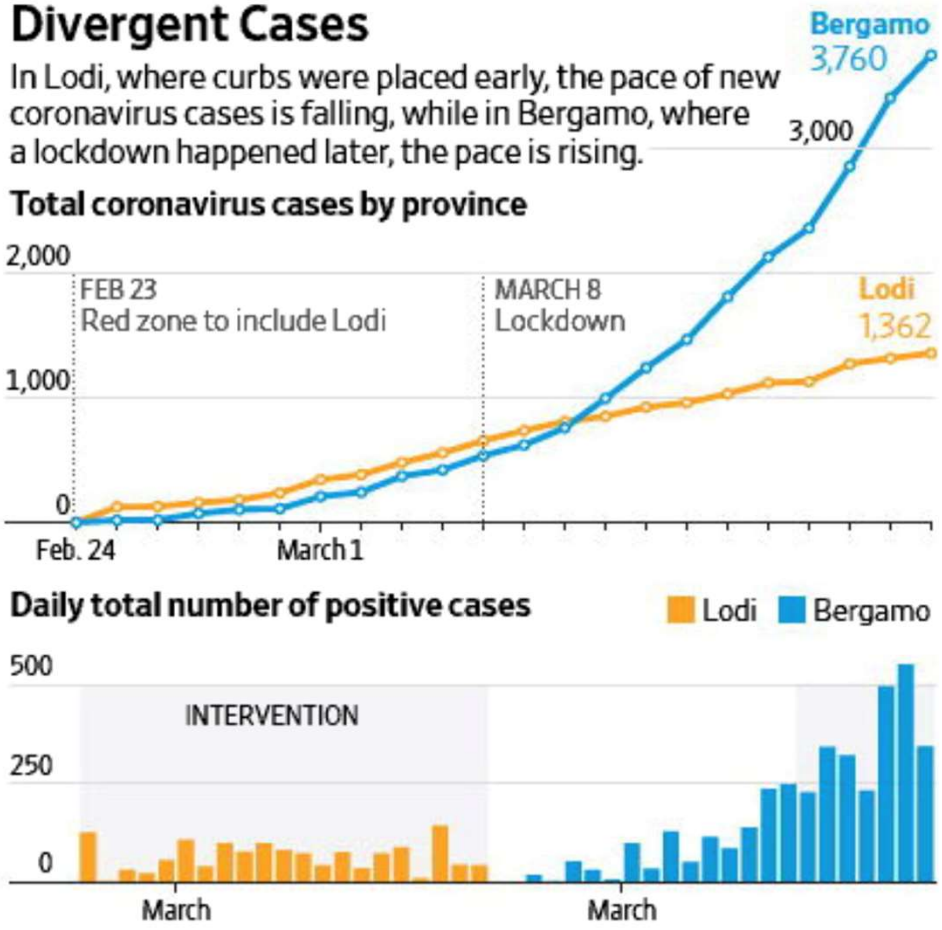
- NIH-sponsored Phase I trial
- First enrolled patient 3/16/2020
  - Experimental COVID-19 vaccine mRNA-1273 (Moderna)
  - Kaiser Permanente Washington Health Research Institute
    - 45 healthy adults, 18 to 55 years
    - Study over six weeks, dose ranging
    - Goals:
      - Safety
      - Immune response

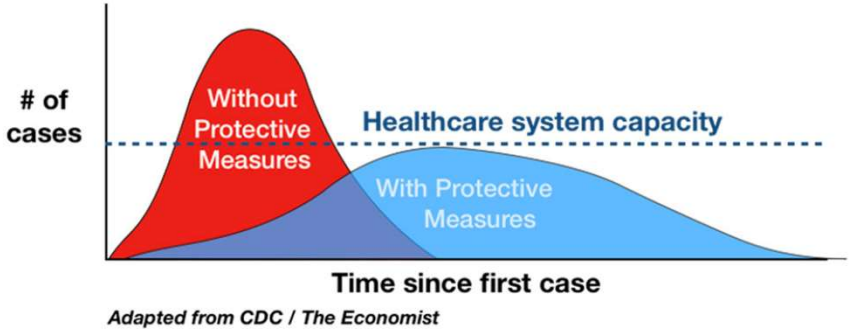
Sometimes Hollywood gets it right, sort of:
R = 2.0, CFR = 20% ≠ 70M (rather 2 Billion!)

Fake Medical News – Unverifiable Sources Help Your Family, Friends & Patients

- Be wary
- Looks at website sources
  - ufoconspiracyexperts.com or aliensarereal.net ??
- Sensational claims, definitive statements, old data repurposed
- Check out authors

Rationale for Social Distancing





Adapted from CDC / The Economist

Summary

- COVID-19 is a moving target
- Recommendations likely to change, frequently
- Fear/panic likely spreading faster than disease
- Medical impact
  - Potential multiplier of severe seasonal influenza?
- Societal/economic impact
  - Potentially greater than medical?