

2020 Spring Regulatory Update and Hot Topics in Clinical Research

COVID-19: The Virus, Preparedness in the time of Crisis, and Clinical Research

WELCOME

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2020 Spring Regulatory Update and Hot Topics in Clinical Research

COVID-19: The Virus, Preparedness in the time of Crisis, and Clinical Research

KEYNOTE

9:15am – 10:15am

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National Institutes of Health (NIH)





Pandemic Coronavirus Disease 2019

CAPT Daniel S. Chertow, M.D., M.P.H.

United States Public Health Service

Critical Care Medicine Department, NIH Clinical Center

and Laboratory of Immunoregulation, NIAID

April 17, 2020



Disclosures

- None

While this pandemic is global,
it is also very personal

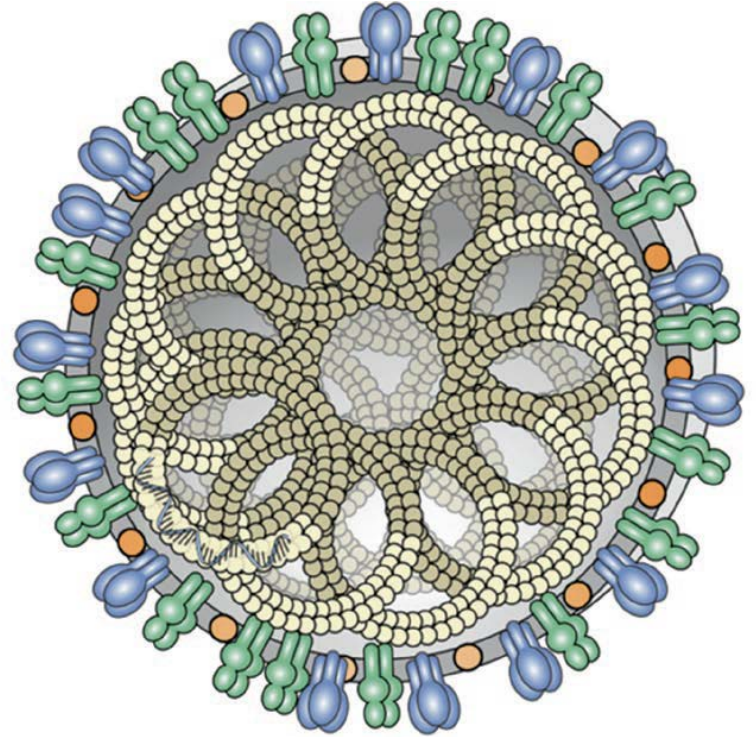
Learning objectives

- Overview biology of coronaviruses (CoVs)
- Discuss coronavirus disease 2019 (COVID-19)
 - Biology, epidemiology, and pathogenesis
 - Clinical manifestations and management
- Planning for the future
 - Public health measures to limit spread
 - Preparing for the next wave of illnesses

Coronavirus biology

Viral structure and diversity

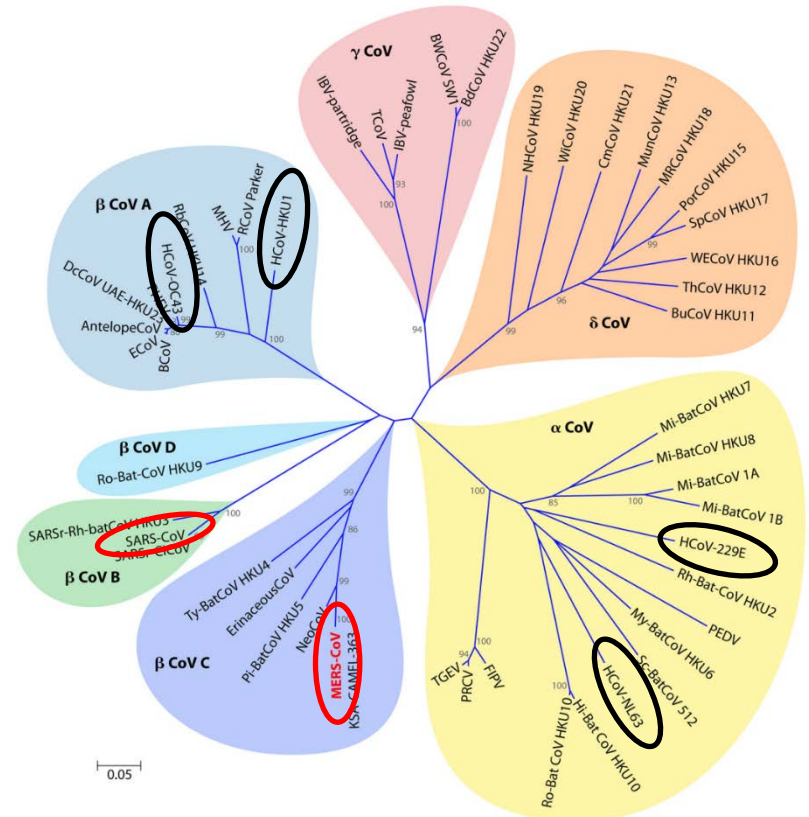
- Spherical enveloped, positive-strand RNA viruses
- 4 genera: **alpha**, **beta**, delta, and gamma
- Wide host range in animals
- Commonly cause respiratory illnesses in humans



Structural proteins:  Spike,  Envelope,  Membrane,  Nuclear

Human coronaviruses

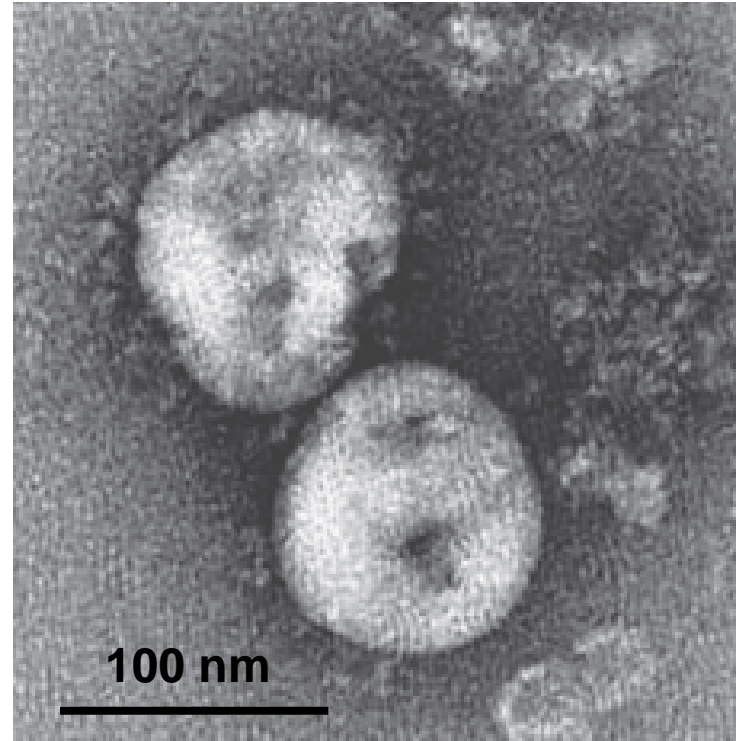
- **Endemic human CoVs**
 - 229E, NL63, OC43, HKU1
 - 15-30% of common colds
- **SARS-CoV**
 - Global epidemic, 2002-2003
 - 8096 cases, 774 deaths (9.6%)
- **MERS-CoV**
 - Recognized in 2012 and ongoing
 - 2494 cases, 858 deaths (34.4%)



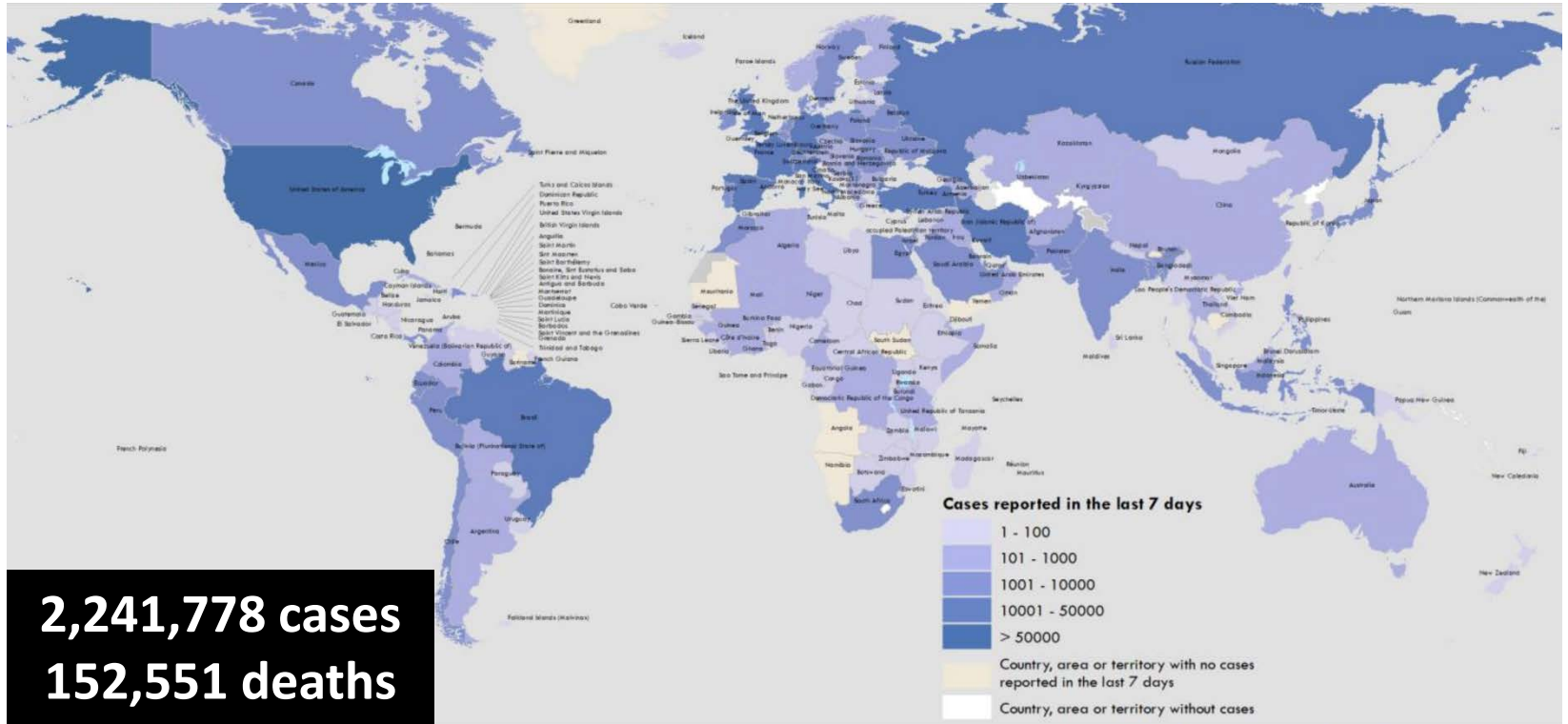
COVID-19 epidemiology

Pneumonia in Wuhan City, China

- Cluster reported to WHO on December 3rd, 2019
- Common exposure to local seafood/animal market
- Novel virus isolated termed SARS-CoV-2
- Genetic sequence is most similar to bat CoVs



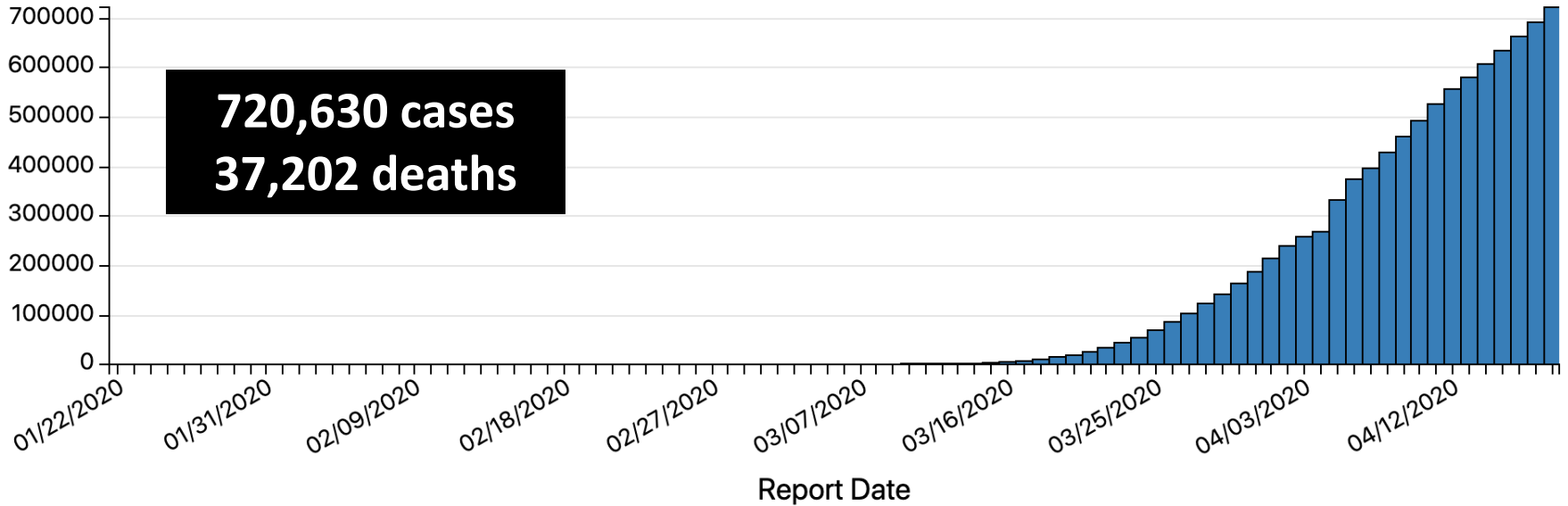
Global distribution of cases



WHO. Coronavirus disease (COVID-2019) situation reports. Accessed **April 20, 2020**.

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>

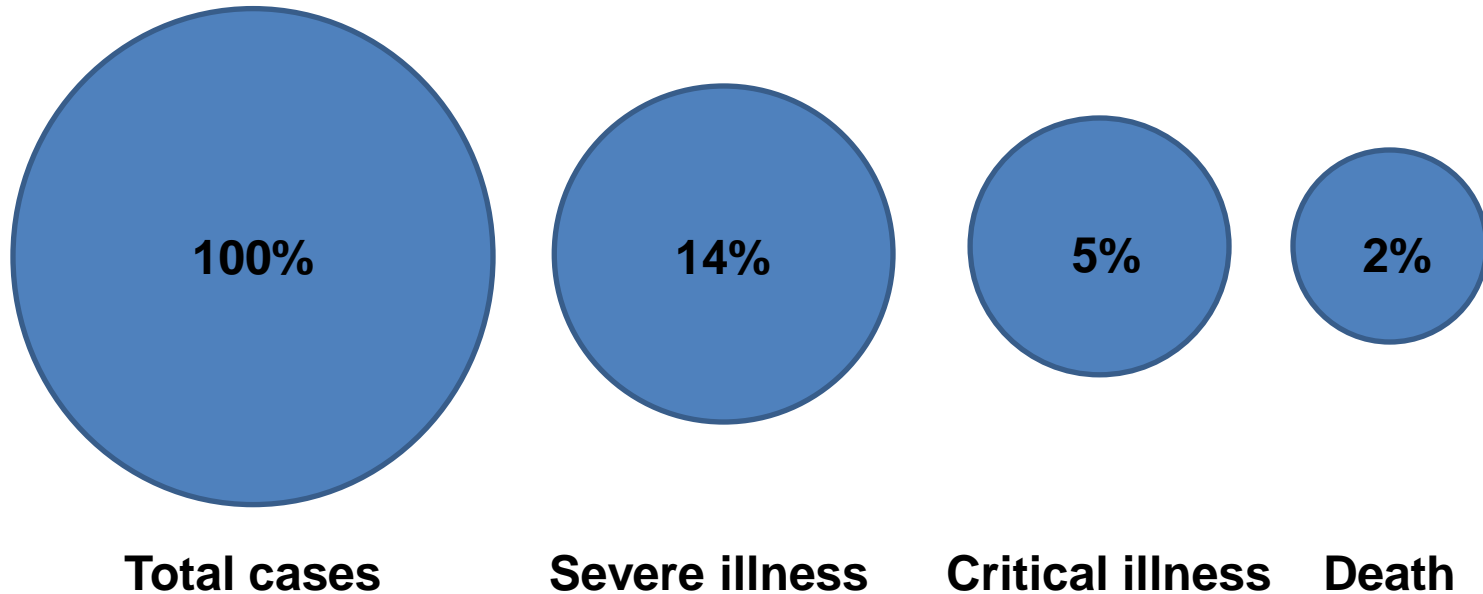
Rapidly rising cases in the United States



CDC. Coronavirus Disease 2019 (COVID-19). Accessed **April 20, 2020**.

<https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html>

Estimated distribution of case severity



Age-specific case fatality ratios

	Confirmed cases, N (%)	Deaths, N (%)	Case fatality ratio, %
Age, years			
0-9	416 (0.9)	0	0
10-39	11,768 (26.3)	26 (2.5)	0.2
40-49	8,571 (19.2)	38 (3.7)	0.4
50-59	10,008 (22.4)	130 (12.7)	1.3
60-69	8,583 (19.2)	309 (30.2)	3.6
70-79	3,918 (8.8)	312 (30.5)	8.0
≥ 80	1408 (3.2)	208 (20.3)	14.8

COVID-19 clinical manifestations

Clinical findings, 1099 hospitalized patients

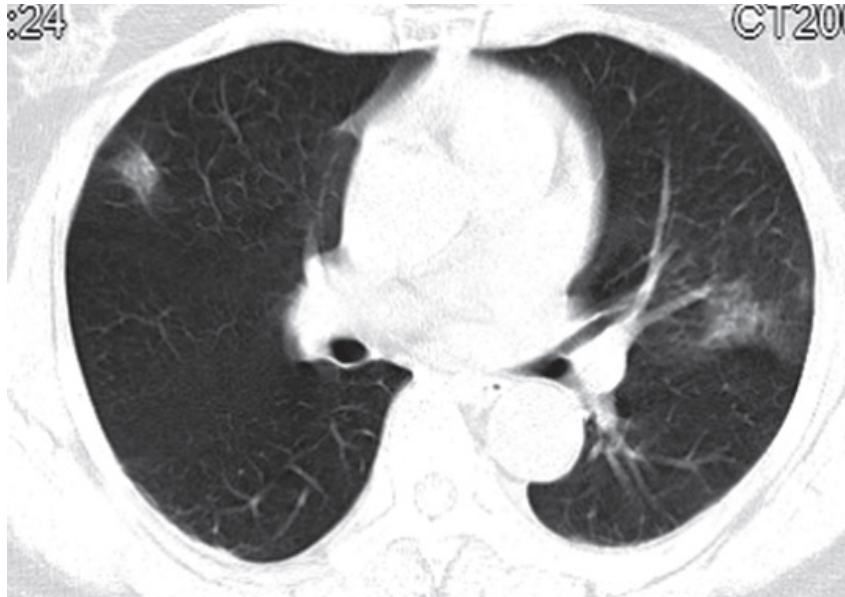
Characteristic	All patients	ICU care	No ICU care
Median age, year	47	52	45
Female	42%	42%	42%
Any comorbidity	24%	39%	21%
Fever	89%	92%	88%
Cough	68%	71%	67%
Fatigue	38%	40%	38%
Dyspnea	18.7%	38%	15%

Common laboratory findings

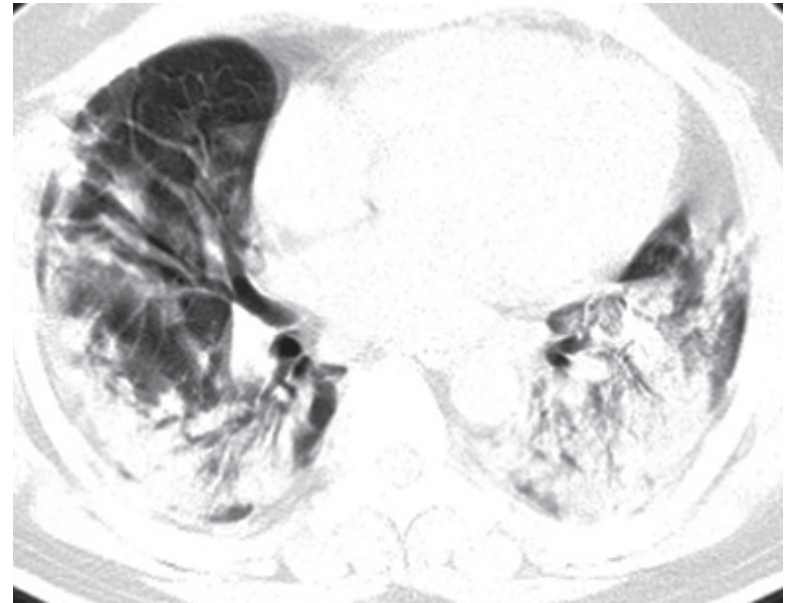
- Leukopenia, lymphopenia, leukocytosis
- Among severe illness
 - Elevated serum creatinine
 - Elevated transaminases and direct bilirubin
 - Elevated cardiac enzymes
 - Disordered coagulation

Rapidly progressive respiratory failure

Illness Day 8

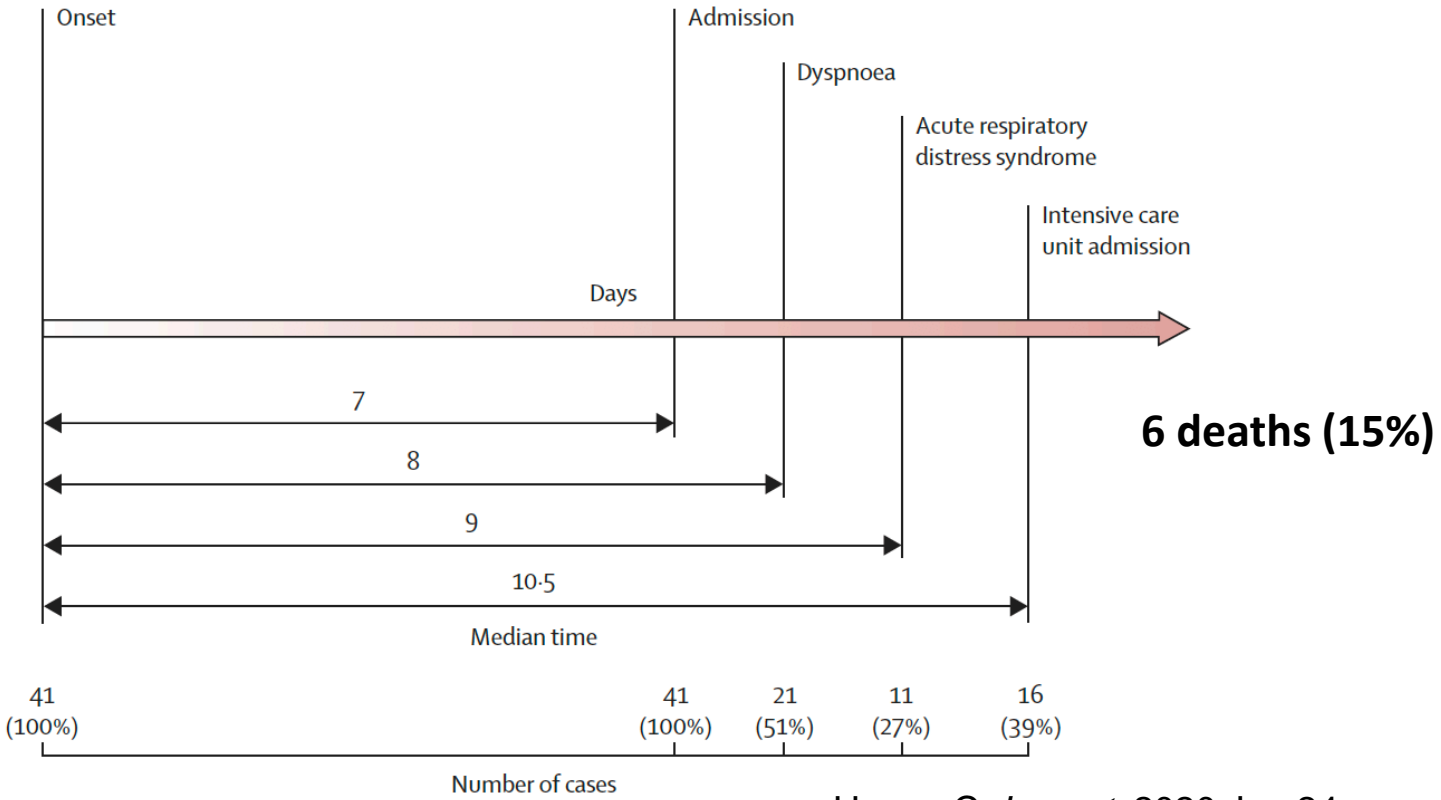


Illness Day 15



Illness timeline, 41 hospitalized patients

**5 day incubation
(range 2-10 days)**

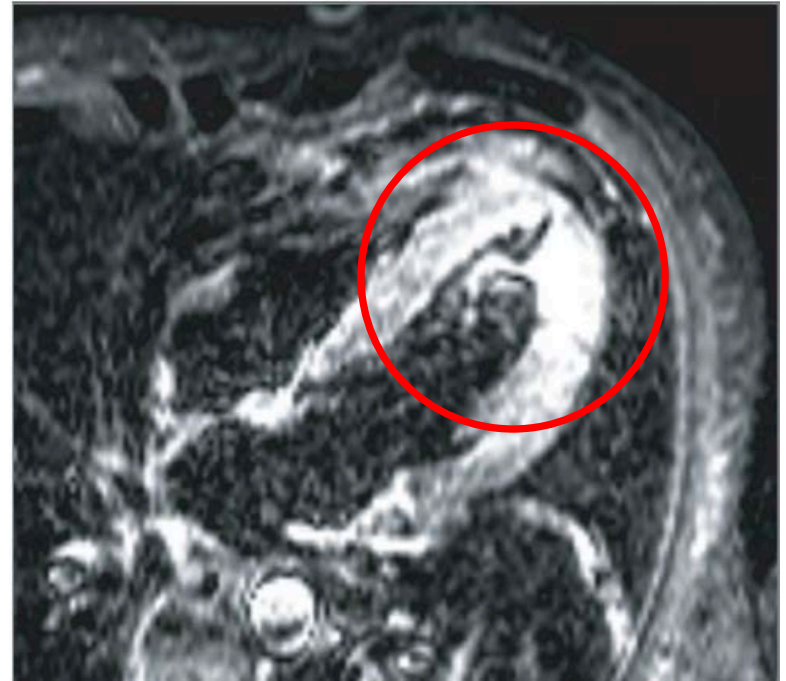


Clinical complications

- ARDS/bacterial co-infection
- Renal insufficiency/failure
- Hepatic injury
- DIC and venous thromboembolism
- Distributive or cardiogenic shock

Acute myo-pericarditis by cardiac MRI

- 53 year-old woman with 1 week fever and cough
- SARS-CoV-2 positive
- HR 100, BP 90/50
- EKG: diffuse ST-segment elevations
- 2D Echo: EF 40%, effusion without tamponade



COVID-19 clinical management

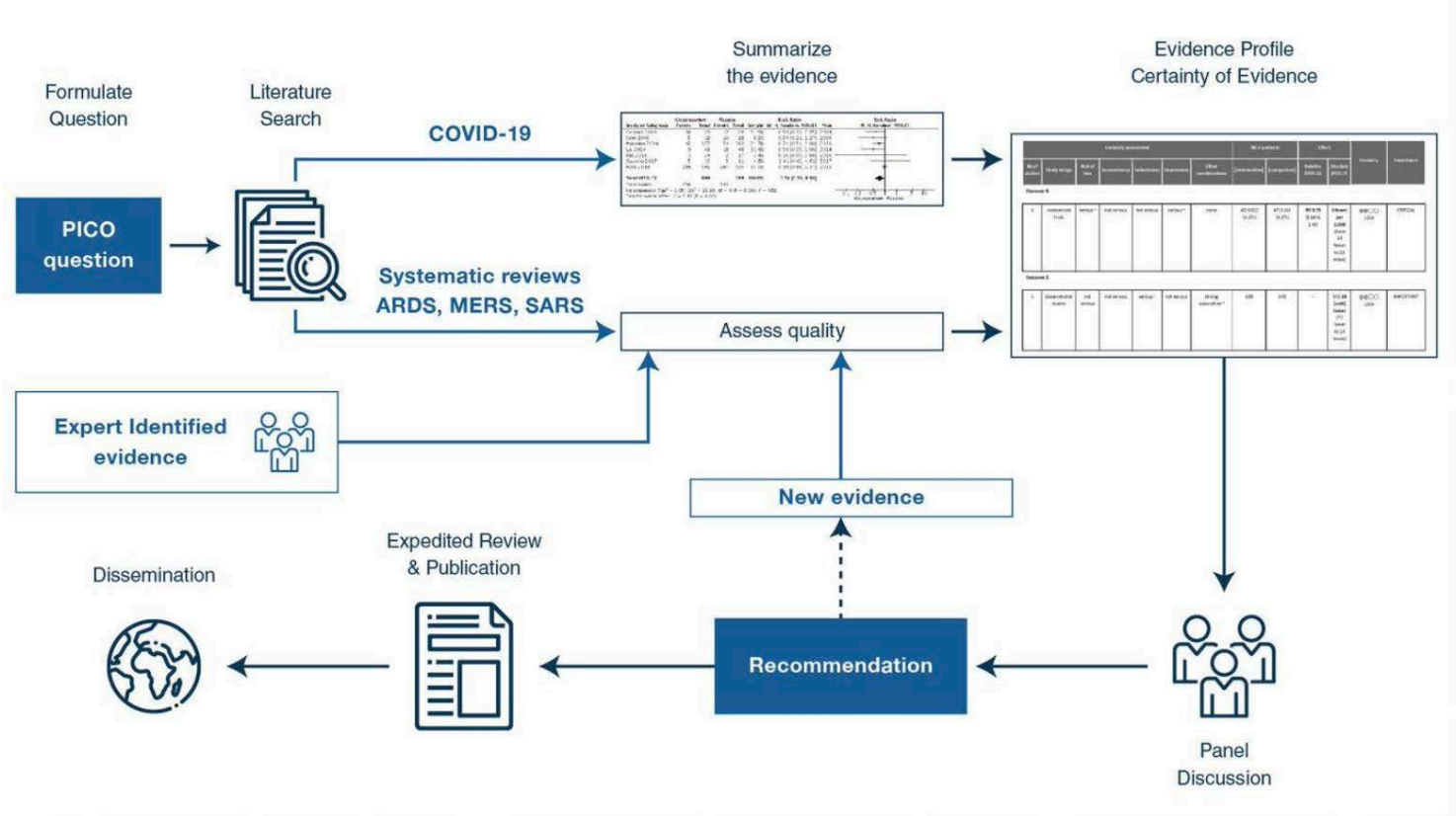
CDC guidance on PPE for healthcare workers caring for COVID-19 patients

- Minimum requirements
 - Gloves, gown, eye protection
 - Medical/surgical face-mask
- N95 respirator mask for aerosol-generating procedures
- Balances risk with potential for scarcity

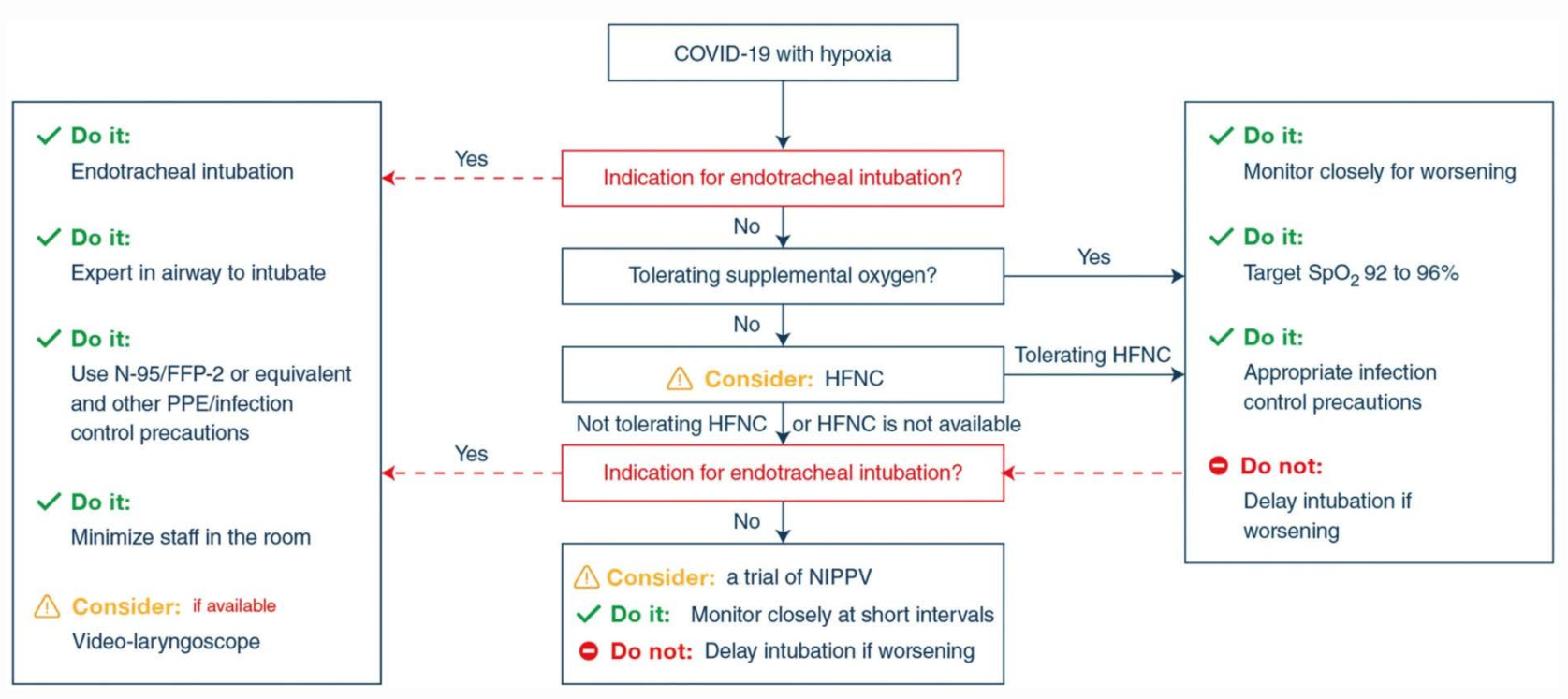
CDC. Coronavirus Disease 2019 (COVID-19). Accessed **March 18, 2020**.

<https://www.cdc.gov/coronavirus/2019-ncov/about/transmission.html>

Surviving sepsis guidelines COVID19



Management of hypoxia



Management of ARDS

COVID-19 with mild ARDS	COVID-19 with Mod to Severe ARDS	Rescue/Adjunctive therapy
<p>✓ Do: Vt 4-8 ml/kg and P_{plat} < 30 cm H₂O</p>	<p>⚠ CONSIDER: Higher PEEP</p>	<p>❓ Uncertain: Antivirals, chloroquine, anti-IL6</p>
<p>✓ Do: Investigate for bacterial infection</p>	<p>⚠ CONSIDER: NMBA boluses to facilitate ventilation targets</p>	<p>⚠ CONSIDER: if proning, high P_{plt}, asynchrony NMBA infusion for 24 h</p>
<p>✓ Do: Target SpO₂ 92% - 96%</p>	<p>⚠ CONSIDER: if PEEP responsive Traditional Recruitment maneuvers</p>	<p>⚠ CONSIDER: Prone ventilation 12-16 h</p>
<p>⚠ CONSIDER: Conservative fluid strategy</p>	<p>⚠ CONSIDER: Prone ventilation 12-16 h</p>	<p>⚠ CONSIDER: STOP if no quick response A trial of inhaled Nitric Oxide</p>
<p>⚠ CONSIDER: Empiric antibiotics</p>	<p>⚠ CONSIDER: if proning, high P_{plt}, asynchrony NMBA infusion for 24 h</p>	<p>⚠ CONSIDER: follow local criteria for ECMO V-V ECMO or referral to ECMO center</p>
<p>❓ Uncertain: Systematic corticosteroids</p>	<p>🚫 Don't do: Staircase Recruitment maneuvers</p>	
	<p>⚠ CONSIDER: Short course of systemic corticosteroids</p>	
	<p>❓ Uncertain: Antivirals, chloroquine, anti-IL6</p>	

COVID-19 pathogenesis

SARS-CoV-2 transmission

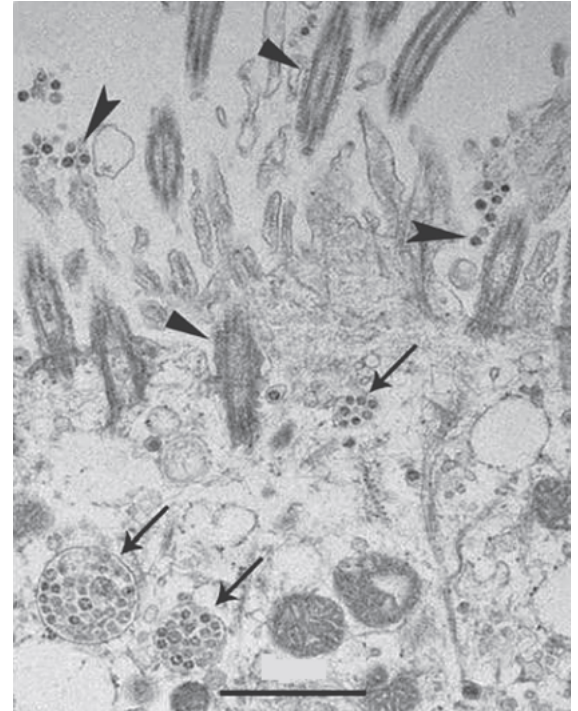
- Initial spillover from animal reservoir or intermediate host (not yet identified)
- Human-to-human spread via
 - Large respiratory droplets (e.g., cough, sneeze)
 - Fomites (e.g., contaminated surfaces)
 - Airborne route possible with aerosol-generating procedures (e.g., intubation)

CDC. Coronavirus Disease 2019 (COVID-19). Accessed **March 18, 2020**.

<https://www.cdc.gov/coronavirus/2019-ncov/about/transmission.html>

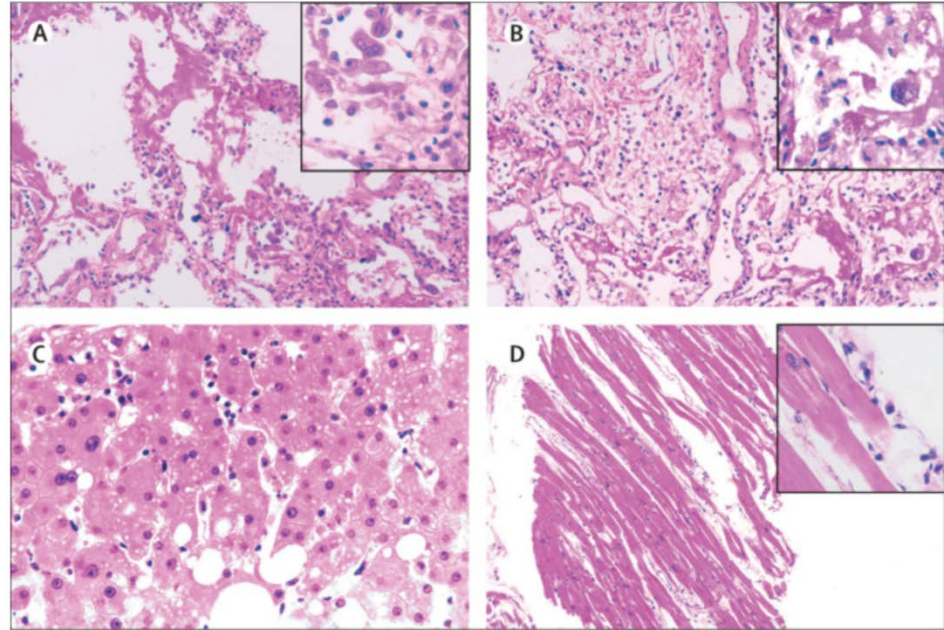
Infection and dissemination

- Infects airway cells (figure)
- Progresses to pneumonia
- Severe lung injury possible
- Disseminates in blood
- Causes direct or indirect organ injury/dysfunction



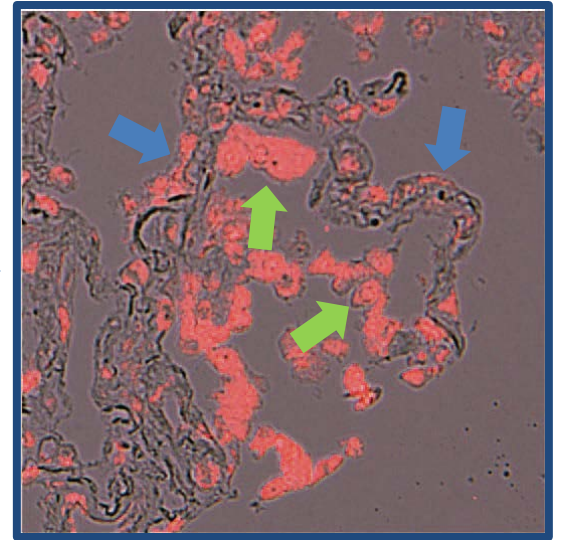
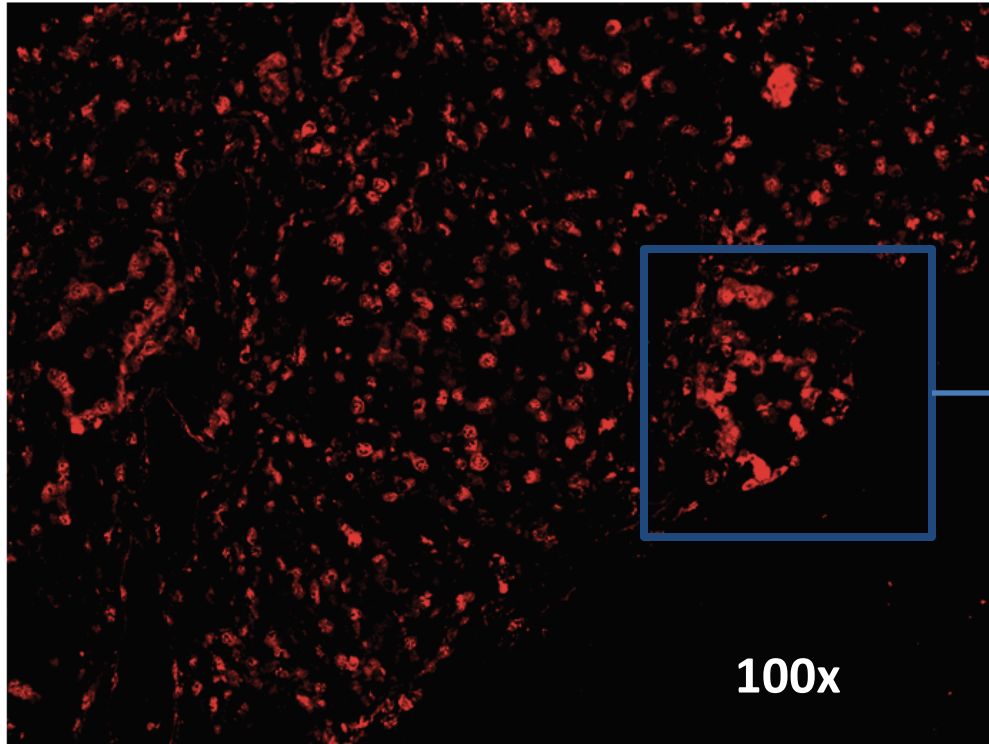
COVID-19 histopathology

- Lung (A, B)
 - Diffuse alveolar damage
 - Lymphocytic infiltrate
 - Viral cytopathic changes
- Liver (C)
 - Microvesicular steatosis
- Heart (D)
 - Few mononuclear infiltrates



Xu Z et al. *Lancet Respir Med.* 2020 Feb 18.

Diffuse immunostaining of SARS-CoV-2 in pneumocytes



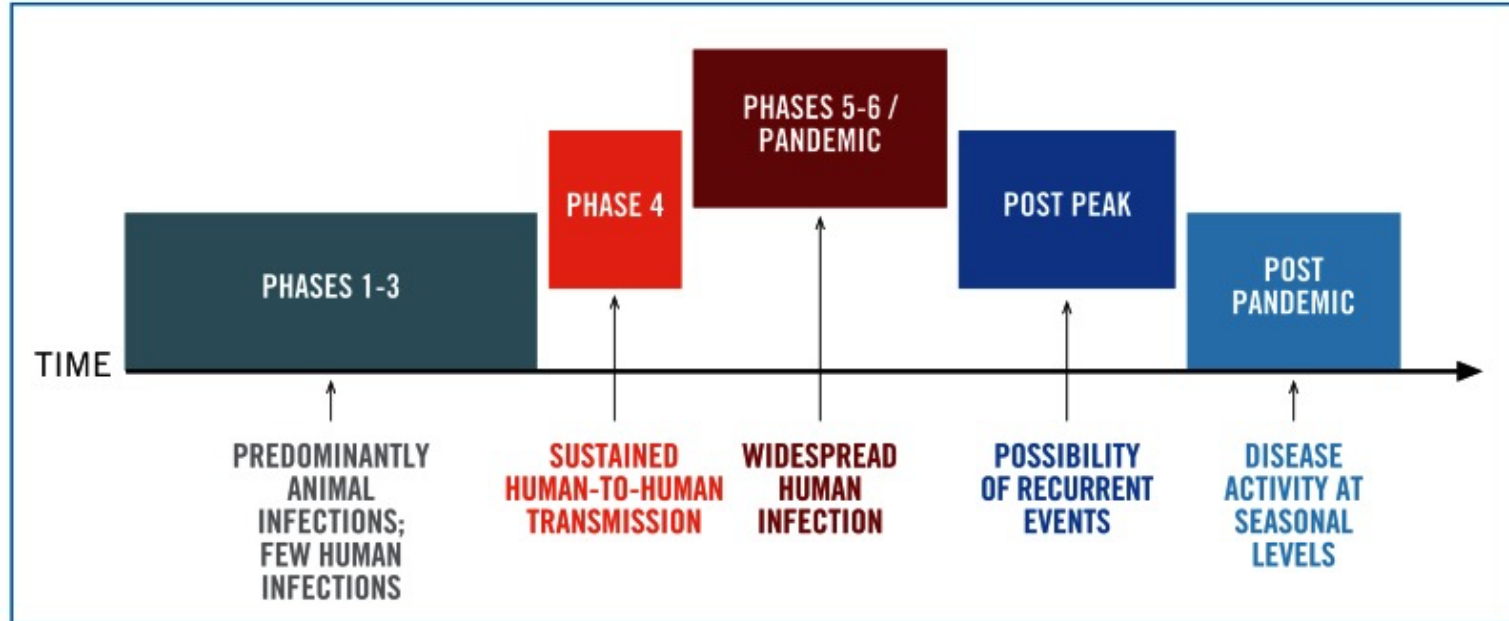
Public health measures

Public health measures to limit spread

- Current measures in the US
 - Restrictions on travel and movement
 - Increased testing, case isolation, contact tracing, and quarantine
- Vaccine and therapeutic development ongoing

Preparing for the next wave

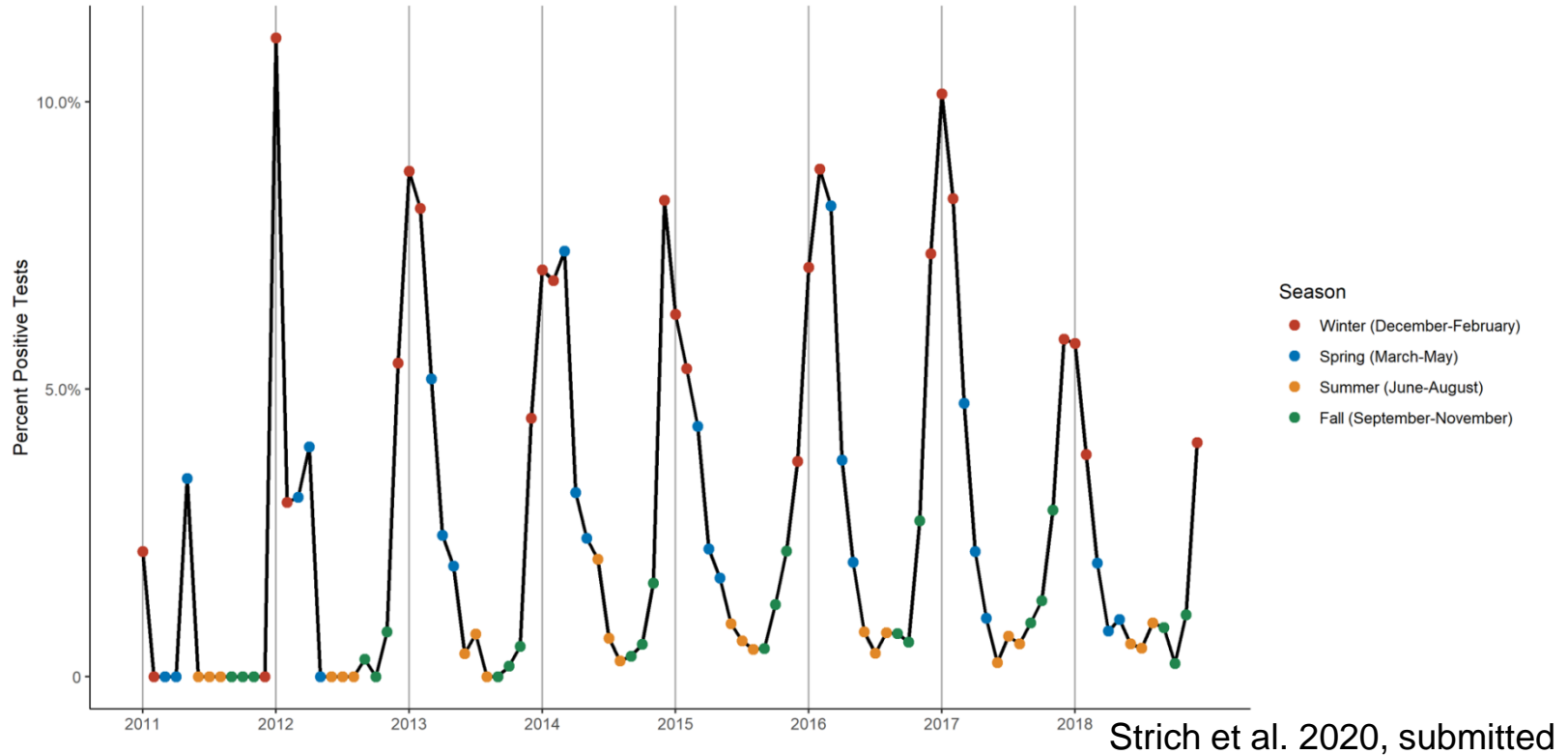
Phases of a pandemic



WHO. The WHO Pandemic Phases. Accessed **April 20, 2020**.

https://www.ncbi.nlm.nih.gov/books/NBK143062/pdf/Bookshelf_NBK143062.pdf

Seasonality of Endemic Human CoVs in the United States, 2011-2018



Summary

- SARS-CoV-2 is a new human coronavirus
 - Spreads efficiently from human-to-human
 - High case-fatality ratio
- This outbreak is evolving
 - Updates on optimal care, therapies, and vaccine can be expected
 - Sustained preparedness and ongoing response from the local to international level is essential