# SARS-CoV-2/COVID-19

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# Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2)

# COronaVIrusDisease-2019 (COVID-19)



-Data/Statistics/Trends -Epidemiology -Biology -Protection -Prevention -Treatment -Questions



### SARS-CoV-2 update

### <del>08-02;</del> <del>08-19; 09-17; 10-06; 10-16-20</del>, 10-23-20

### Cases

Worldwide – <del>19M 22M 30M 36M 39M</del> 42M USA <del>~5 5.57 6.7 7.5 8.0</del> 8.5M NYS 422 428 451 472 479 495K NYC <del>231 232 243 252 253</del> 261K

Leading countries by <u>total cases</u>: <del>US, Brazil, India, Russia, South Africa, Mexico</del> USA, India, Brazil, Russia, <del>Spain</del>, Argentina, Colombia, Spain

UK and the rest of Europe Peru Columbia have the greatest current rise in rates (doubling roughly every two months) - at current rates, the USA is doubling ~every three months

IL, MN, IA, NE, MI, WI Midwest states currently showing largest rate increases KS, SD, ND, IA, WI, IL

Leading states by <u>total cases</u>: CA, TX, FL, NY, IL, GA CA,FL,TX,NY,GA,IL CA,TX,FL,NY,IL CA,TX,FL,NY,GA,IL

### **SARS-CoV-2** update

08-02; 08-19; 09-17; 10-06; 10-16-20

### **Mortality**

Worldwide <del>700 783 942 1.1</del> 1.2M US <del>160 174 200 210 218</del> 225K NYS <del>31.4 32 32.5</del> <del>32.9</del> 33K NYC <del>23 23.6</del> <del>23.7 23.9</del> 24K Leading states: <del>NY, TX, CA, NJ, FL, MA</del> NY, TX, CA, FL, NJ, MA

Estimates suggest perhaps 10X as many are infected as being reported. Historic death data suggests mortality is almost certainly underreported too.

### **Death certificates**

**WHO:** *"COVID-19 should be recorded on the medical certificate of cause of death for ALL decedents where the disease, or is assumed to have caused, <u>or contributed to death</u>" CDC: <i>"COVID-19 symptoms can be similar to influenza-like illness, thus <u>deaths may be</u> <u>misclassified as influenza</u>. Thus, increases in pneumonia and influenza deaths may be an indicator of excess COVID-19-related mortality."* 



### **Troubling recent Trends**

 An unusual joint CDC and HSS news conference this week discussed a disturbing rise in COVID-19 positive cases in 75% of the country.

weekly average of 75,000 cases/day and 900 deaths

- Chicago: city's average daily case rate increased by >50 percent in the last week
- Europe is seeing a surge of new cases-likely 2<sup>nd</sup> wave

- Spain's prime minister urged citizens to "*step up the fight*" after reporting reporting >1 million cases, a milestone for Western Europe

- The Polish government announced the country will enact strict anti-COVID-19 restrictions starting Saturday.







#### How seasonal flu and Covid-19 compare FLU COVID-19 Bottom of the range **RO** number Estimate of how many people will be infected by an average individual with the disease Top of the range 2-2.5 1.3 DAYS Incubation time The time from exposure to first symptoms 1-4 1-14 Hospitalization rate Average percentage for total cases 2% 19% Case fatality rate Percentage of reported .1% or less 1-3.4% deaths among total cases Vox Sources: CDC, WHO, NCBI



**ENVIRONMENTAL HEALTH SCIENCES** 



Doshi P. Trends in recorded influenza mortality: United States, 1900-2004 Am J Public Health. 2008; 98:939-45.

### Deaths per 100,000 persons



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# Where to find accurate information about COVID-19?



### Johns Hopkins University of Medicine Coronavirus Resource Center



### https://coronavirus.jhu.edu/map.html



#### New York Times Covid World Map: Tracking the Global Outbreak



https://www.nytimes.com/interactive/2020/world/coronavirus-maps.html

### Center for Disease Control and Prevention (CDC) COVID Data Tracker

CDC COVID Data Tracker × +			
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https://covid.cdc.gov/covid-data-tracker/#cases\_totalcases



#### Center for Disease Control and Prevention (CDC) Coronavirus COVID-19



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### https://www.cdc.gov/coronavirus/2019-nCoV/index.html

#### New York State Department of Health Information on Novel Coronavirus



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https://coronavirus.health.ny.gov/home

# **Basic Virus Biology**



### History

- "Virus" originates from the Latin word for "poison".
- The term was originally used by Louis Pasteur to describe the infectious agent for rabies.
- In the early 1900's viruses were first distinguished from bacteria by being *"filterable agents"*.
- By the 1950's the science of "virology" became well established.



### What is a virus? "An infectious particle"





### Properties of a virus

- A virus is a very small, infectious, obligate intracellular parasite
- Virus particles are **not** considered living things
- Viruses cannot reproduce by themselves
- A susceptible cellular host is needed for reproduction. The virus utilizes the host machinery to make copies of itself



## Coronavirus





Called corona because of the "corona" or crown-like shape of the virus and in particular its projecting spikes.



### What Do We Know About Coronaviruses?



Coronaviruses have a crown-like appearance under the microscope

Coronaviruses are a large family of viruses some cause illness in people, and others only infect animals.

Some coronaviruses infect animals then spread to people, and then spread person to person such as:

- Middle East Respiratory Syndrome (MERS)
- Severe Acute Respiratory Syndrome (SARS)
- Coronavirus Disease 2019 (COVID-19)

Common coronaviruses include some that cause mild upper-respiratory illnesses, like the common cold.



### **Corona Facts**

- Most animals and insects have multiple strains of coronaviruses associated with them
- 7 coronaviruses infect humans 4 cause common, cold-like symptoms
  - These 4 viruses have been repeatedly infecting humans for decades, if not longer
- 3 coronaviruses, SARS, MERS, SARS-CoV2 are associated with severe respiratory distress, in particular in susceptible individuals
  - Age, obesity, diabetes, immunocompromise, cardiovascular disease, lung disease
- Contains RNA as its genetic material. Makes DNA from RNA using an enzyme called reverse transcriptase inside infected cells.
- Contains a fatty outer coat, easily disrupted by soap, alcohol
  - Soap and water hand washing best, 70% alcohol-based hand sanitizers good too



### Which cells does SARS-CoV-2 infect?

- The virus binds to a receptor on the outside of cells called ACE2 (Angiotensin Converting Enzyme - which regulates blood pressure) found in high concentrations in the <u>upper respiratory tract</u> and in the <u>upper intestine</u>.
- ACE2 receptors are also found at lower concentrations in other cells and organs including the brain.



### **Early History**

- News reports of an outbreak of severe respiratory disease in Wuhan, China in early December
- Retrospective data now shoes the first case occurred in Hubei province 400 miles away in November.
- Pathogen first identified as a coronavirus on Jan 10 and by Jan 20 spread to S. Korea, Singapore, Thailand, Japan and the USA.
- New data suggests co-infection of an original bat host by two distinct related corona viruses led to recombination, possible passage through intermediate animal vectors and ultimately SARS-CoV2, which was able to infect and cause disease in humans. "Zoonotic" origin.



### **Transmission**

- Airborne via human to human contact
  - Droplets (large particles that tend to travel only a few feet and quickly drop to the ground in seconds to minutes)
     <u>MOST LIKELY</u>
  - Aerosols (superfine suspended particles that can travel long distances and remain suspended for tens of minutes or longer)
     <u>LESS LIKELY TO OCCUR</u>

### Surfaces

- Liquid or dried viral material (Fomites), from saliva, respiratory tract, tears, mucous
- Not considered a primary mode of transmission
   <u>NOT VERY LIKELY</u>



### **Symptoms**

- Some studies suggest up to 25% of individuals may be asymptomatic or mildly symptomatic
- NEVERTHELESS, Asymptomatic individuals ARE still quite capable of spreading virus and may account for a large number of cases
- Number of people subsequently infected by each infected person crucial for predicting severity of epidemics and pandemics
  - **R0** "R naught" ~=2.4 persons but.... Superspreaders likely >50+



### **Symptoms**

- Large numbers of varied symptoms (many common to other respiratory diseases) are reported including:
  - Headache
  - Fatigue/Body aches
  - Fever/Chills
  - Loss of taste and smell
  - GI symptoms (nausea, diarrhea, intestinal distress)
  - Sore throat
  - Congestion
  - Unilateral sudden loss of hearing
  - Difficulty breathing
  - Chest pain
  - Confusion



### Testing

- Gold Standard is Polymerase Chain Reaction (PCR) looking for viral RNA in <u>nasopharyngeal</u> swabs
  - Emergency Use Approval (EAU) also given for saliva, nasal PCR
- Rapid Tests (15 min-1 hr) are also approved under an EUA looking for SARS-CoV-2 protein in saliva or nasal swabs
  - Quick, easy, cheaper, higher false positive rates, less sensitivity
- Antibody tests are also approved under an EUA to detect our subsequent immune response (antibody production) to an earlier infection
  - Assume a positive finding indicates prior infection
  - Antibody levels drop with time
  - Some people do not mount a robust immune response and test negative despite being infected at some earlier time

### Testing

- May NOT detect infection within the first 1-3 days
- Testing is not 100% accurate: Specificity and Sensitivity
  - False negatives and False Positives
  - Somewhere in the range of 90-95% accuracy for the BEST tests
  - Somewhere below 65% for the worst tests



### Sensitivity, specificity accuracy and precision

- Sensitivity identifies the false negative rate, it gives the percentage of truly positive subjects who test positive -for HIV, for example, this number approaches 99-100% for a pregnancy test, it is >97%
- Specificity identifies the false positive rate, it gives the percentage of true negative subjects who test negative -for HIV, this number approaches 99.99% for pregnancy tests, it is 100%
- Accuracy: The total percentage of "true" results, whether positive or negative,
- Precision is similar to sensitivity



### Why is this important?

You want to know the COVID-19 mortality rate and your sensitivity is 95% and your specificity is 95%.

• You test 100 people. Two are truly positive and one of these dies.

### What is the overall mortality?

- 2/100 are truly positive. If sensitivity is 95%, 0.95 x 2 = 1.9% both will show up as a positive.
- 98/100 are truly negative but... if specificity is 95%, 0.95 x 98 = 93%; 5 people who are negative will test positive.
- The <u>true mortality</u> rate is 1 out of 2 or <u>50%</u>. The <u>reported mortality</u> is 1/7 or 14%. Big difference. That's why sensitivity and especially specificity are so important.

Similarly, if you want to know whether you've been exposed and can go back to your life, the true exposure is 2% but reported exposure will be 7%. 5 people who are actually negative for antibodies will think they were infected and are now safe.



### **Prevention and Protection**

- Social Distancing
  - 6 ft minimizes spread of large droplets
- Masks
  - Face coverings protect others from your saliva, mucous
    - 3 ply masks offer somewhere in the range of a 50-60% reduction in your inhalation risk via mouth or nose
    - N95 masks offer 95% protection
- Gloves
  - Protect user from potential fomite transmission (unlikely event)- IF THEY ARE USED CORRECTLY
    - Remove when contaminated/do not used to touch personal items
    - Don't touch face or head with gloved hands
- Face Shields
  - Protect against possible airborne transmission to eyes/upper face


#### Chris Christie says he was in ICU for 7 days battling Covid-19, urges Americans to wear masks

"As a former public official, I believe we have not treated Americans as adults, who understand truth, sacrifice and responsibility," Christie said in a statement.



Chris Christie, from center, talks with guests in the Rose Garden after President Donald Trump introduced 7th U.S. Circuit Court Judge Amy Coney Barrett, 48, as his nominee to the Supreme Court at the White House on Sept. 26, 2020. Chip Somodevilla / Getty Images file

Oct. 15, 2020, 8:43 PM EDT / Updated Oct. 15, 2020, 7:02 PM EDT By Dareh Gregorian

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Former New Jersey Gov. Chris Christie on Thursday urged Americans to wear masks to fight the coronavirus that put him in intensive care for seven days, and warned the virus is "something to take very seriously."



https://www.nbcnews.com/politics/politics-news/chrischristie-says-he-was-icu-7-days-battling-covid-n1243589

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## **Tips for Reducing Risk of Getting COVID-19**







### **Prevention and Protection, cont'd**

- Cleaning surfaces with disinfectant sprays or solutions
  - Reduces likelihood of fomite transmission
- Using UV light to kill virus on surfaces or in air
  - Dose dependent, most germicidal UV light (254 nm) cannot be used when people are present due to cancer risk
  - Popular media promotes UV devices to "disinfect" phones, jewelry, contacts, etc.
  - Early testing of "far-UVC" (222 nm), a type of UV that may be safer.

### Air filters

- Virus particles are very small and require special "Hepa" filters that need frequent replacement
- Not practical for most homes or offices

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### **Prevention and Protection, cont'd**

- Forward and reverse contact tracing (by Public Health Officials)
  - Identify superspreaders
  - Reduce likelihood of further transmission by isolation of potentially infected contacts
  - Identify types of activities and events that pose highest risk for transmission



#### **New CDC recommendations on time of close contact**

- Previously, CDC recommended limiting close contact (<6 ft) to no more than 15 min at one time
- This week, the CDC revised that recommendation to limit close contact to a TOTAL of 15 min every 24 hrs in light of a recent outbreak where an infected asymptomatic individual had repeated, but very short (1 min) contact with a number of other persons who all got infected.

# CDC considering new recommendations on quarantine if you come into close contact with a known COVID-19 positive individual

- Previously, CDC recommended you self quarantine for 14 days
- In light of accumulating data on time to infection, the CDC is considering reducing the quarantine time to 10 or even 7 days



## **Vaccines and Therapeutic Drugs**



### How are vaccines developed?

- 1. Hypothesis
- 2. Lab bench work
- 3. Animal testing
- 4. Human testing
- 5. Phase 1: 20-80 subjects, non-blinded, safety, side-effects, type and extent of immune response. Carefully monitoring, conditions tightly controlled.
- 6. Phase 2: 50-200 subjects, randomized and well controlled, includes placebo. Tests safety, immunogenicity, doses, schedule, delivery method.

#### **Combined phase 1/2-: emergency justification** - *risky*

- 7. Phase 3: 1-10,000 subjects, randomized and double blind. Includes placebo. Vaccine safety in a much larger group of people looking for rare adverse events. (power calculations: if 1/ 10,000, 30K each treated and control to detect a significant difference.) Vaccine efficacy; prevention, reduction in severity, cellular and humoral immune response?
- 8. FDA license application
- 9. Examination, approval, ramp up production, inspection, monitoring.



#### Current coronavirus vaccine development <u>worldwide</u> 09-17 10-06 10-15-20 10-24-20

160+ preclinical <del>18</del> <del>29 30</del> <del>33</del> phase 1 <del>12</del> <del>14</del> <del>15</del> <del>14</del> phase 2 <del>6 11</del> <del>12</del> phase 3 <del>1 5</del> <del>6</del> limited approval (in China, Russia only)</del>



#### Vaccine history suggests that a COVID-19 vaccine will take some time to develop



Front. Pharmacol., 19 June 2020 | https://doi.org/10.3389/fphar.2020.00937



### Multiple types of vaccines are under development

#### Live attenuated virus

#### **Killed virus**

Sinovac Biotech-inactivated

Viral vector: replicating, or non-replicating (antigen presenting)

AstroZeneca: adenovirus Ph2/3

Johnson & Johnson Ph1/2

Novartis/Mass Eye & Ear Ph1

Merck VSV Ph1

Fractionated: Virus protein, polysaccharide (sugar), membrane or other component

Novavax-Ph1. Already completed Ph3 for a flu vaccine

Sanofi-preclinical

Recombinant

Viral particle

Next gen: Viral nucleic acid, lipid nanoparticle vector, multiple doses required - Never tried before!

RNA:	Moderna, never did before, 30K subjects in PH3 just started
	recent news indicates they are behind schedule
	Pfizer, 30K subjects in PH3 just started, some side effects in PH2
	Imperial College/Morningside Ventures, PH1/2
	recent news reported several adverse effects that temporarily
	stopped Moderna , Imperial College and and J&J trials pending further analyses
DNA	Zydus (India) Ph1
	Angus (Japan) Ph1
	Inovio PH1, immune response +



# **Herd Immunity?**



#### Infection transmission if basic reproduction number R<sub>0</sub> = 4



Fine P. Clin Infect Dis 2011; 52:911-6.



### **Threshold concept of herd immunity**



Fine P. Clin Infect Dis 2011; 52:911-6.

Herd Immunity Threshold =  $(1-1/R_0)$ 



# Cumulative lifetime incidence of infection in unvaccinated individuals if R0 = 3. (Assumes a 100% effective vaccine.)



Fine P. Clin Infect Dis 2011; 52:911-6.

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# Therapeutic Approaches Drugs and Biologics





- First FDA approved drug to treat patients with active COVID-19
- Reduces the hospital stays among patients with moderate illness by 4 days, from 15 to 11 days
- <u>No effect on mortality</u>
- Approach has "Biological plausibility". This class of drugs interferes with RNA virus replication and was originally developed to fight EBOLA
- WHO, however, reports no benefit to very sick patients- this drug works best if administered early in the course of disease

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#### **Convalescent Plasma**

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19A Randomized Clinical Trial. JAMA 2020

#### No statistically significant effect 😕

Most US trials are stalled because of lack of patient recruitment (either severe case numbers are down (NYC) or patients are unwilling to participate in a double blind trial.

#### CDC: 10/09/20

*"there are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19."* 



### **Other Drugs and Treatments**

#### No FDA approvals yet-Only emergency use authorizations

Human trials

Hydroxycholoroquine-fuggataboutit

HIV antivirals-studies stopped-no good findings

Favipiravir-same idea as remdesivir, -no good clinical data for this drug yet

**Dexamathasone**-appears to down-regulate aberrant/overactive immune response, reduced mortality in very severe cases but may aggravate less severe cases. Good early results in hospitalized patients in ICU.

**Cytokine inhibitors**-some modest success in decreasing immune flareups in small study -others show no or adverse effects (eg tocilizumab, Regeneron's Kezvara-failed Ph3 trial)

#### Monoclonal antibodies

Regeneron, Eli Lilly

In development. Trying to identify best targets. Ph2 trials underway. Positive but limited initial findings. More subjects needed to clearly identify benefit. Most likely, this may help those who fail to make a robust immune response themselves

#### Lab or animal trials

EIDD-2801: undergoing study, another replication inhibitor ACE2 decoys: benchtop studies Interferons: active investigation-boosts immune system



# **CONCERNS?**



## Antibody-Dependent Enhancement (ADE)

"Antibody-dependent enhancement, sometimes less precisely called immune enhancement or disease enhancement, is a phenomenon in which binding of a virus to suboptimal antibodies enhances its entry into host cells, and sometimes also its replication." Wikipedia



#### **ADE Examples from past vaccine trials**



REVIEW published: 05 December 2018 doi: 10.3389/fmicb.2018.02991



### Viral-Induced Enhanced Disease Illness

Maria K. Smatti, Asmaa A. Al Thani and Hadi M. Yassine\*

Biomedical Research Center, Qatar University, Doha, Qatar

Understanding immune responses to viral infections is crucial to progress in the quest for effective infection prevention and control. The host immunity involves various mechanisms to combat viral infections. Under certain circumstances, a viral infection or vaccination may result in a subverted immune system, which may lead to an exacerbated illness. Clinical evidence of enhanced illness by preexisting antibodies from vaccination, infection or maternal passive immunity is available for several viruses and is presumptively proposed for other viruses. Multiple mechanisms have been proposed to explain this phenomenon. It has been confirmed that certain infection- and/or vaccine-induced immunity could exacerbate viral infectivity in Fc receptor- or complement bearing cells- mediated mechanisms. Considering that antibody dependent enhancement (ADE) is a major obstacle in vaccine development, there are continues efforts to understand the underlying mechanisms through identification of the epitopes and antibodies responsible for disease enhancement or protection. This review discusses the recent findings on virally induced ADE, and highlights the potential mechanisms leading to this condition.

OPEN ACCESS

Edited by:

Keywords: antibody-dependent enhancement, Fc receptors, complement, immune response, viral infections

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## Coronavirus

- Feline infectious peritonitis virus (FIPV)
- Cats vaccinated against FIPV got significantly sicker than cats unvaccinated.
- Virus-specific antibody increased the virus uptake by macrophages.

JOURNAL OF VIROLOGY, Feb. 1992, p. 956–965 0022-538X/92/020956-10\$02.00/0 Copyright © 1992, American Society for Microbiology Vol. 66, No. 2

#### Monoclonal Antibodies to the Spike Protein of Feline Infectious Peritonitis Virus Mediate Antibody-Dependent Enhancement of Infection of Feline Macrophages

CHRISTOPHER W. OLSEN,\* WAYNE V. CORAPI, CHRISTOPHER K. NGICHABE, JOEL D. BAINES,† AND FRED W. SCOTT

Department of Microbiology, Immunology, and Parasitology and Cornell Feline Health Center, New York State College of Veterinary Medicine, Cornell University, Ithaca, New York 14853



## **MERS** Coronavirus

- Human coronavirus with significant mortality
- Rabbit model of infection
- After initial infection, rabbits were MORE susceptible to subsequent challenge than uninfected animals
- Plasma from infected animals recapitulated this phenomena when naïve rabbits were challenged with MERS





## COVID-19?

#### **BMJ Global Health**

### Hypothesis to explain the severe form of COVID-19 in Northern Italy

Luca Cegolon <sup>(b)</sup>, <sup>1,2</sup> Jennifer Pichierri, <sup>3</sup> Giuseppe Mastrangelo, <sup>4</sup> Sandro Cinquetti, <sup>1</sup> Giovanni Sotgiu, <sup>5</sup> Saverio Bellizzi, <sup>6</sup> Giuseppe Pichierri<sup>7</sup>

Prior infections with SARS-CoV-2 (or other viruses/ coronaviruses) may arguably predispose to more severe forms of the disease following re-infection with SARS-CoV-2, with an immunological mechanism known as Antibody-Dependent-Enhancement, already observed with infections sustained by other coronaviruses (MERS-CoV and SARS-CoV) or other viruses such as the West Nile Virus and Dengue.



### **Conclusions and Takeaways**

- COVID-19 is a potentially dangerous respiratory virus with at least 10X greater mortality than the flu
- SARS-CoV-2 infection rates are climbing RAPIDLY in many parts of the USA and world and are unlikely to decrease anytime soon
- Deaths in the USA are likely to approach 300,000 within six months in the absence of an effective, widely distributed vaccine or therapy
- It is unlikely that an effective vaccine will be approved and widely distributed before mid 2021
- We can greatly reduce our risk of infection through a COMBINATION of protective measures
  - it is unlikely that any one thing (vaccine, drug, masks, UV light, warm weather, or Acts of Nature) will significantly reduce our risk
- Use of social distancing, masks, hand washing and awareness of our individual actions and interactions will, together, help to reduce transmission and likelihood of infection



Each individual must make personal decisions about the degree of risk they are comfortable with assuming.

We do this everyday in our normal lives but, when confronted with unexpected or unfamiliar risks (e.g., COVID-19), we are less able to accurately assess relative risk to guide our behaviors.



## This too shall pass....



# Miss Manners' Mask Etiquette

Peter Arden, MS Christine Kuryla, MS Charlotte Michaelcheck, MS





The mystique and appeal of the mask as an accessory is quickly undermined by the gauche, tasteless decision to stand less than six feet apart.





If you must remove your mask to speak, then the content of your speech must be lacking in substance. Those who keep their masks on for witty repertoire are clearly more deserving of a listen.





You would not wear your insides on your outsides, please do not wear your mask's inside on the outside.





Please refrain from exhibitionist behavior whilst donning a mask; do not show your 'under mask' parts.





Do not fall prey to the faux pas of a see-through mask. The substance of the accessory is negated by a flimsy material: Every color and pattern is "in" this season, except see-through.





You wouldn't put your most refined accessories atop your laundry pile or countertop. Please treat your mask with the respect it deserves and give it a clean, isolated space all its own.





For goodness sake, don't pull your mask down to eat whilst out and about.





This refined accessory does not afford you the right to sneeze or cough with reckless abandon. Please dignify the mask by adhering to proper sneezing and coughing decorum.




Protect your sensitive accessory from moisture!

You would not subject your best silk or most coveted suede to undue moisture - apply the same principle to your delicate and stylish mask. Water and excess moisture strip your mask of their power to protect yourself and others.





For most other manners, the rulebook in your own domicile has been tossed for the time being. Feel free to chew with your mouth open, eat entire cartons of ice cream, and attend professional meetings in sweatpants until further notice

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Don't be afraid to raise your hand and share what you've learned.





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## **QUESTIONS?**

