How to fight the coronavirus SARS-CoV-2 and its disease, COVID-19

Michael Lin, PhD-MD

Lin Lab Briefing 2020-03-13

Warning: Contains facts

Bonus: Hand sanitizer recipe

This is not a pretty powerpoint

- This is an informational document.

- This is not a TED talk. It is not meant to entertain or dazzle or push an idea with beautiful graphics.

- So there will be a lot of text, because there is a lot of info that needs to be explained. Graphics will be used as data primarily. You will have to do some reading.

Some context for the numbers you will see

- Total population
  - 330,000,000 USA
  - 40,000,000 CA

- Traffic fatalities per year
  - 30,000 USA
  - 3,000 CA

- Flu (influenza) deaths this season
  - 40,000 USA, range 22,000 to 55,000 (www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm)
  - 5,000 CA, estimated. From a population of 40,000,000, if half got the flu virus, this means an infection fatality rate (IFR) of 0.025%. If 25% got the flu virus, this means an IFR of 0.05%.
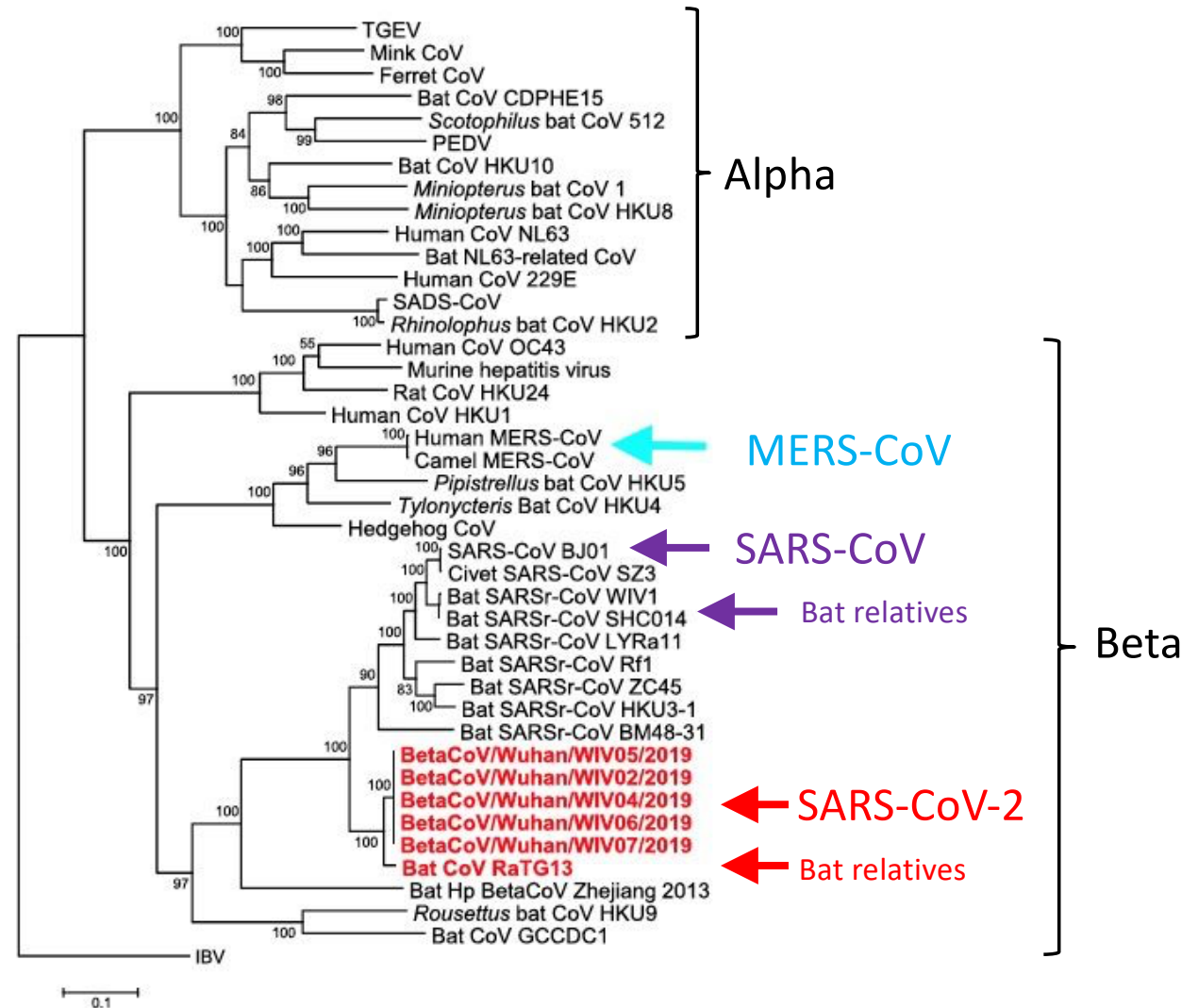
Some definitions

- <u>COVID-19</u> refers to the disease, which in practice is used to refer to having a positive 2019 coronavirus laboratory test regardless of disease signs or symptoms
  - WHO introduced the disease name COVID-19 with great fanfare (after weeks of discussions) at a time when there was no virus name, so it got picked up by the press as the virus name, incorrectly.
  - An example of a mis-use is "COVID-19 can survive on surfaces" (https://abcnews.go.com/Health/covid19-days-surfaces-experiment-findings/story?id=69569397), which is a nonsensical statement.
  - In addition, COVID-19 is a terrible name for a disease, because you can't append the word "virus" to describe the pathogen, as "COVID-19 virus" would mean "coronavirus disease 2019 virus", which sounds silly and indeed reveals the disease name to lack any informational value whatsoever.
  - Previously we named diseases by some sort of description of signs/symptoms, e.g. severe acute respiratory syndrome = SARS. WHO could have named the disease simply "SARS2" and it would have been both accurate and descriptive.

Some definitions

- <u>2019-nCOV</u> was the initial name given by some infectious disease organization for the virus, where nCOV stands for novel coronavirus. But this name is hard to remember because it starts with a generic term (the year). It is also inconsistent with coronavirus naming conventions. It is also misleading, because it gives the misimpression that the virus is especially novel. It's not. In fact it's the least novel of the respiratory disease-causing viruses isolated in the molecular age. It's defining feature is it's NON-novelty...

- <u>SARS-CoV-2</u> is the Genbank name for the virus, because it is 96% identical in nucleotide sequence to SARS-CoV, the cause of SARS in 2003.
  - We will use this name because it is accurate and informative, revealing the high similarity between these two pathogens. This name thus reminds us that we can infer a lot about SARS-CoV-2 from existing data on SARS-CoV.
  - Ironically, the WHO decided not to name the virus SARS-CoV-2 for *precisely this reason* – to obscure the relationship between the two viruses (www.vox.com/2020/2/14/21135208/coronavirus-wuhan-china-covid-19-name-sars-cov-2). However we are scientists, we want clarity not obfuscation.

Coronaviruses (CoVs)

- Positive-strand RNA viruses with large genomes (≥27,000 bases).
- Alpha and beta types cause disease in humans.
- Both types already known to cause the common cold, account for 10-30% of cases (Pubmed 31971553).
- Very stable – CoV OC43 isolates from 1960s and 2001 had only 2 amino acid differences (Pubmed 15280490)!
- Many CoVs in bats.
- Easily hops between species
  - MERS-CoV hopped from camels to humans
  - SARS-CoV hopped from bats to humans and civets
  - SARS-CoV-2 hopped from bats to humans
  - It looks like humans with colds gave mice hepatitis, or vice versa).

https://www.sciencemag.org/news/2020/01/mining-coronavirus-genomes-clues-outbreak-s-origins

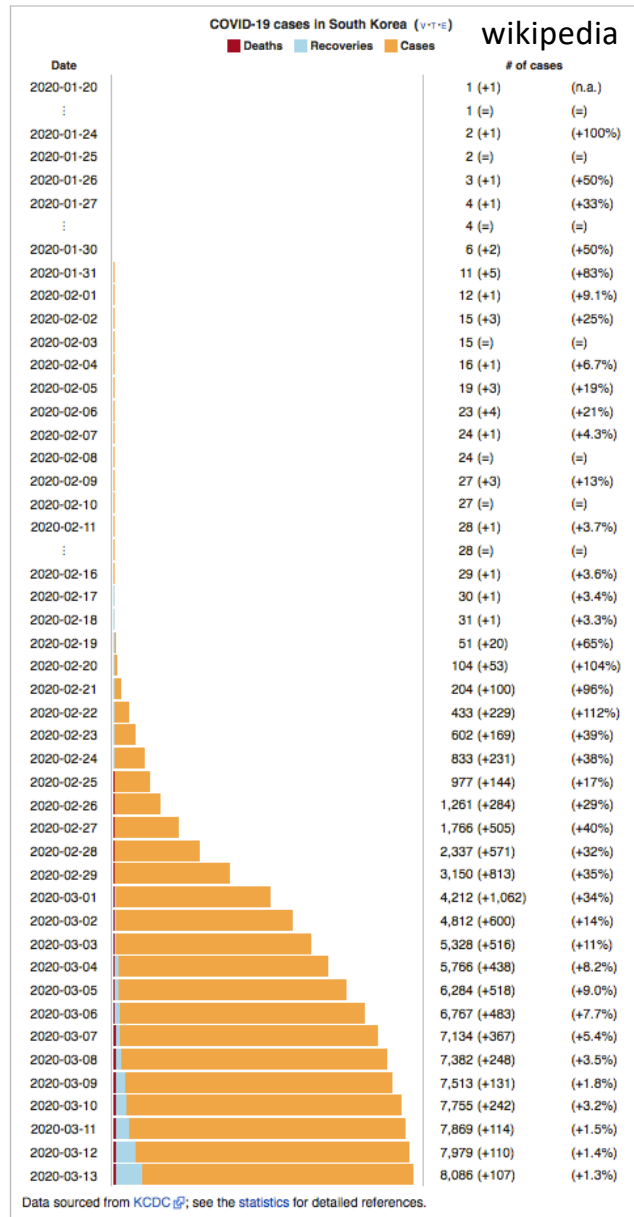3/19/20

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How do you kill SARS-CoV-2?

- It's an enveloped virus (with a thin plasma membrane)
  - Killed by soap/detergents, 60-80% ethanol or isopropanol, Windex (which has detergents), bleach.
- SARS-CoV-1 is sensitive to temperature, so SARS-CoV-2 is likely to be, too (left, Pubmed 22312351).
- SARS-CoV-1 killed by 30min 75ºC=167ºF heat (Pubmed 14631830), SARS-CoV-2 should be similar.
- Survival of SARS-CoV-2 depends on the surface (right, doi.org/10.1056/NEJMc2004973)
  - Drop of virus applied, allowed to dry. 1mL cell-culture media pipetted on and off and tested (roughly the equivalent of licking the surface).
  - On steel and plastic, 10-fold drop in ~12h. On cardboard (porosity/type unclear, source = "local supplier"), 4–8h.
  - On a napkin, the survival should be like on cardboard or lower. Virus should be better trapped by the fluffier napkin fibers, but I still would not wipe my mouth with a napkin that someone just gave me.
- Survival of SARS-CoV-2 in direct sunlight is probably 10% after 2–3h exposure
  - 90% of flu virus dies after 6h sunlight at spring equinox (3/21) at Bay Area latitude (Pubmed 17880524).
  - Coronaviruses are 2–3x more sensitive to UV than flu virus (Pubmed 16254359).

SARS-CoV-1 dried on tissue-culture plastic, y-axis is log reduction
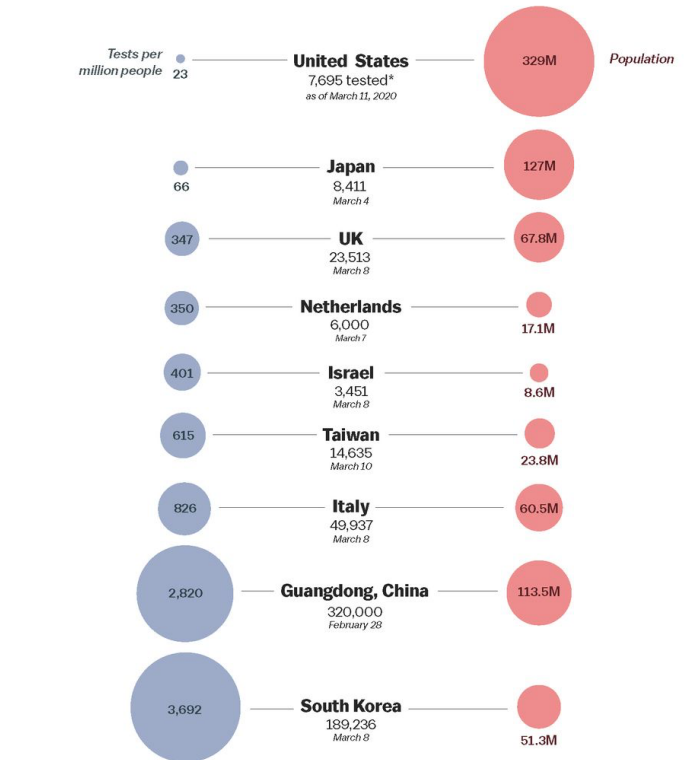
SARS-CoV-2 and SARS-CoV-1
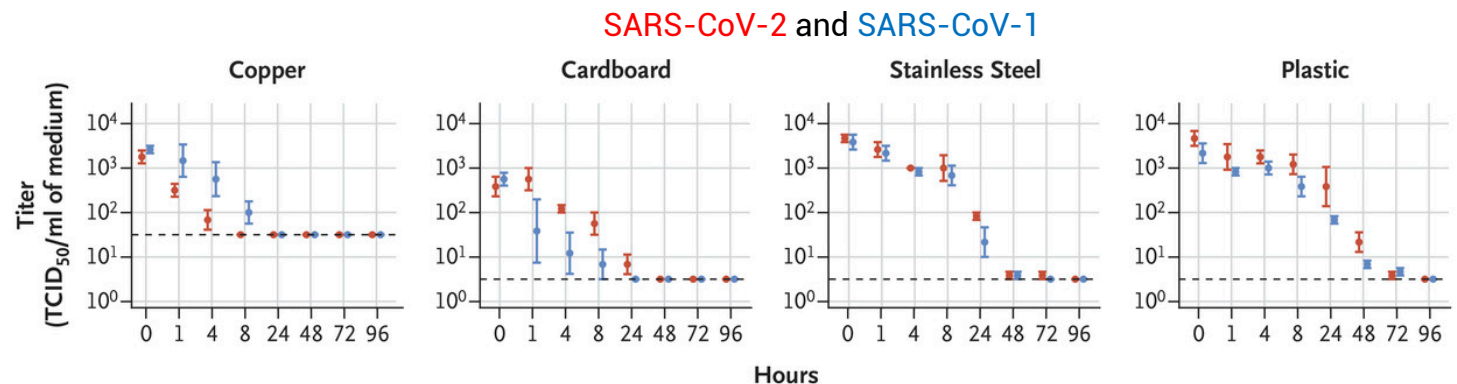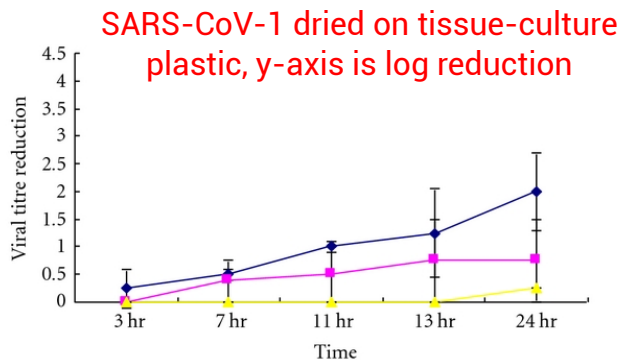
Estimating infection (not disease) numbers

- SARS-COV-2 infection numbers matters more than COVID-19 case (diagnosed) numbers, because it determines transmission and immunity rate: The higher it is, the more transmission risk but also the more immunity.
- South Korea (SK) has done the most testing per capita.
- In SK, known diagnoses = 8162 on 3/14, new diagnoses ~100 daily now (en.wikipedia.org/wiki/2020_coronavirus_pandemic_in_South_Korea).
- Deaths on average will lag diagnosis by 2 weeks (infections by 3 weeks, wwwnc.cdc.gov/eid/article/26/6/20-0320_article). This is consistent with the shapes of case and death curves, which are updated daily here: (www.worldometers.info/coronavirus/country/south-korea/).
- Thus current total deaths (~75 total on 3/14) occurred from cases diagnosed on 2/29 or earlier, when cumulative number ~ 4000. This means case fatality rate (CFR) ~ 75/4000 = 1.9%
- However infections > diagnosed cases, so IFR < 1.9%, depending on what fraction of infections were diagnosed on 2/29,

3/19/20

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COVID-19 cases in South Korea (V·T·E)

Deaths · Recoveries · Cases

Date	# of cases	
2020-01-20	1 (+1)	(n.a.)
⋮	1 (=)	(=)
2020-01-24	2 (+1)	(+100%)
2020-01-25	2 (=)	(=)
2020-01-26	3 (+1)	(+50%)
2020-01-27	4 (+1)	(+33%)
⋮	4 (=)	(=)
2020-01-30	6 (+2)	(+50%)
2020-01-31	11 (+5)	(+83%)
2020-02-01	12 (+1)	(+9.1%)
2020-02-02	15 (+3)	(+25%)
2020-02-03	15 (=)	(=)
2020-02-04	16 (+1)	(+6.7%)
2020-02-05	19 (+3)	(+19%)
2020-02-06	23 (+4)	(+21%)
2020-02-07	24 (+1)	(+4.3%)
2020-02-08	24 (=)	(=)
2020-02-09	27 (+3)	(+13%)
2020-02-10	27 (=)	(=)
2020-02-11	28 (+1)	(+3.7%)
⋮	28 (=)	(=)
2020-02-16	29 (+1)	(+3.6%)
2020-02-17	30 (+1)	(+3.4%)
2020-02-18	31 (+1)	(+3.3%)
2020-02-19	51 (+20)	(+65%)
2020-02-20	104 (+53)	(+104%)
2020-02-21	204 (+100)	(+96%)
2020-02-22	433 (+229)	(+112%)
2020-02-23	602 (+169)	(+39%)
2020-02-24	833 (+231)	(+38%)
2020-02-25	977 (+144)	(+17%)
2020-02-26	1,261 (+284)	(+29%)
2020-02-27	1,766 (+505)	(+40%)
2020-02-28	2,337 (+571)	(+32%)
2020-02-29	3,150 (+813)	(+35%)
2020-03-01	4,212 (+1,062)	(+34%)
2020-03-02	4,812 (+600)	(+14%)
2020-03-03	5,328 (+516)	(+11%)
2020-03-04	5,766 (+438)	(+8.2%)
2020-03-05	6,284 (+518)	(+9.0%)
2020-03-06	6,767 (+483)	(+7.7%)
2020-03-07	7,134 (+367)	(+5.4%)
2020-03-08	7,382 (+248)	(+3.5%)
2020-03-09	7,513 (+131)	(+1.8%)
2020-03-10	7,755 (+242)	(+3.2%)
2020-03-11	7,869 (+114)	(+1.5%)
2020-03-12	7,979 (+110)	(+1.4%)
2020-03-13	8,086 (+107)	(+1.3%)

Data sourced from KCDC ⊠; see the statistics for detailed references.

wikipedia

A snapshot of early Covid-19 testing per capita

Tests per million people

|	Tests	Population
United States — 7,695 tested* as of March 11, 2020	23	329M
Japan — 8,411 March 4	66	127M
UK — 23,513 March 8	347	67.8M
Netherlands — 6,000 March 7	350	17.1M
Israel — 3,451 March 8	401	8.6M
Taiwan — 14,635 March 10	615	23.8M
Italy — 49,937 March 8	826	60.5M
Guangdong, China — 320,000 February 28	2,820	113.5M
South Korea — 189,236 March 8	3,692	51.3M

*Test counts do not include full reporting from all US labs
Source: Covid Tracking Project, Business Insider, the Atlantic, Taiwan CDC

Vox

Estimating infection (not disease) numbers

- An analysis of China and the Diamond Princess (DP) gave an IFR of 0.5% for all-China and 1.2% for DP (cmmid.github.io/topics/covid19/severity/diamond_cruise_cfr_estimates.html).
- Note on the DP, some patients may have been helped with the antiviral medication remdesivir (www.wsj.com/articles/experimental-drug-helps-some-americans-ride-out-coronavirus-nih-doctor-says-11584094955) but then DP passengers skewed old.
- How would US IFR compare to 0.5% for China and <1.9 for Korea? USA is in between Korea (more) and China (less) in % of population over 60, so we can guesstimate IFR = 1.0%. An estimate based on age-adjusted data from China arrived at a similar IFR = 0.9% (possible range 0.4−1.4) (www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf).
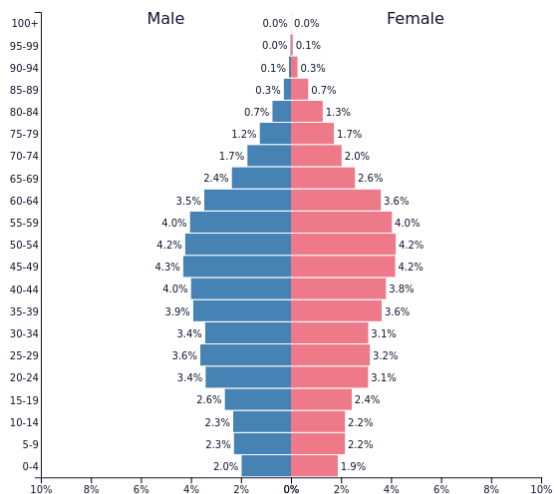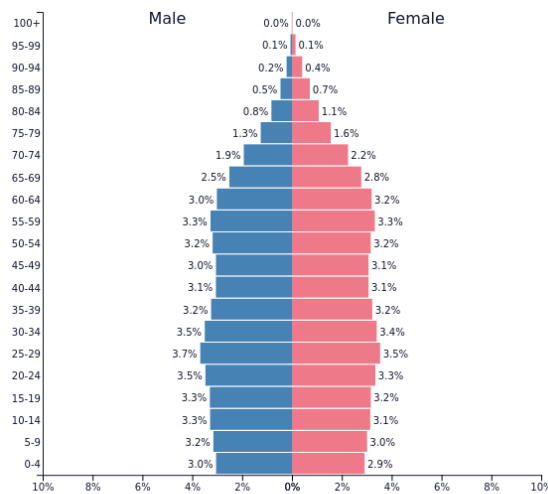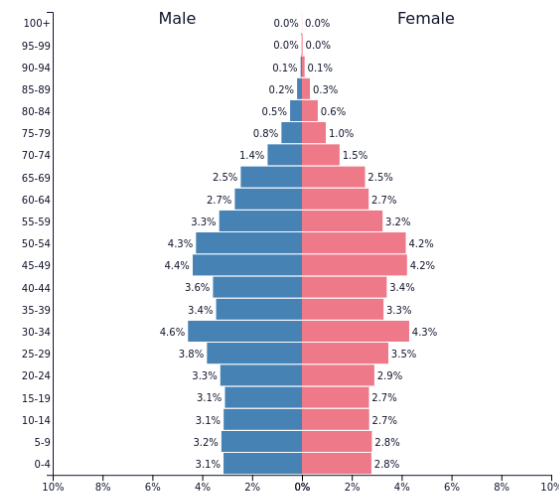
Deaths are mostly in older patients

This is true for both flu and COVID-19

Flu and COVID-19 death rates by age
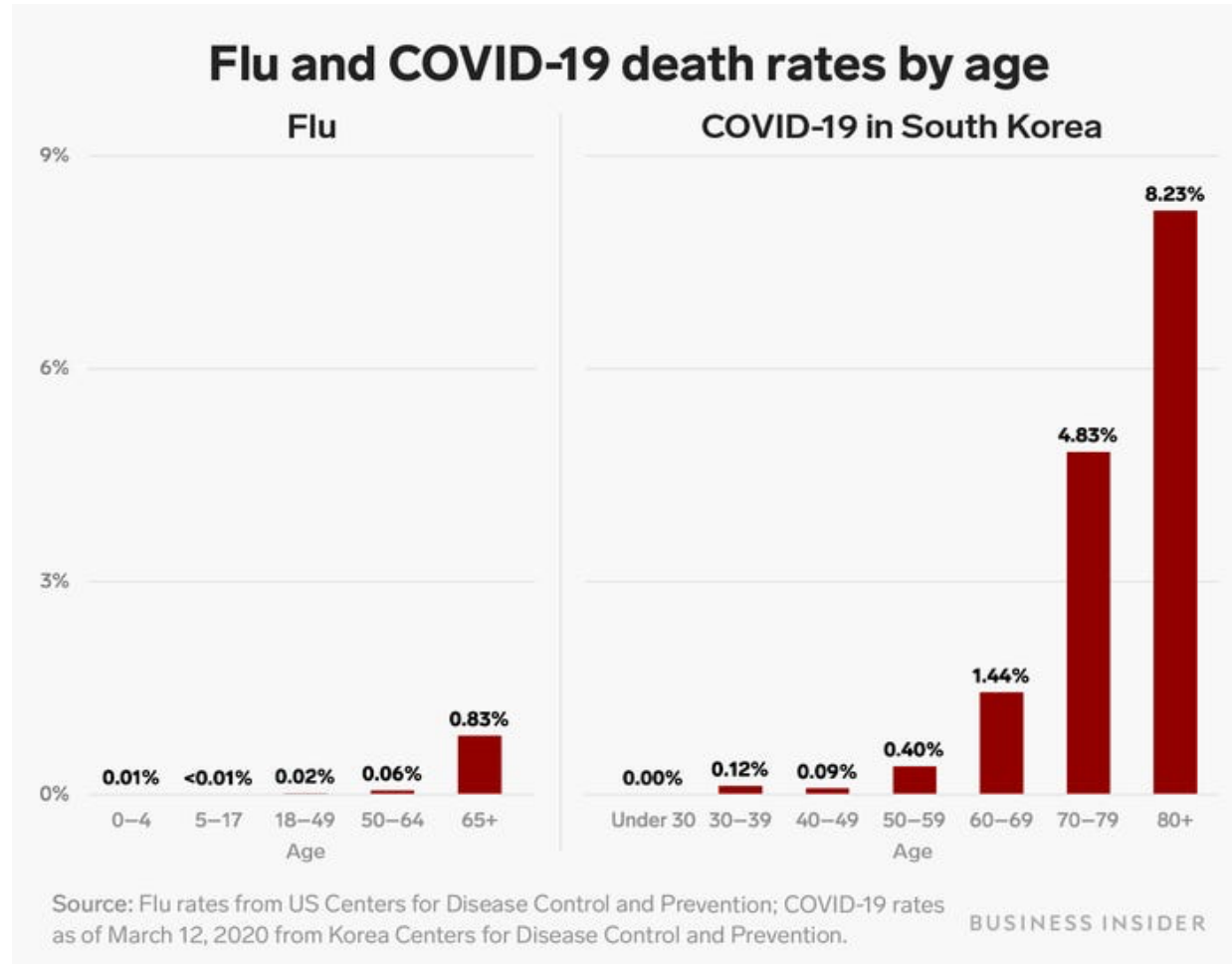
We are still early in the process

Estimating new case rates in CA and Bay Area (updated 2020/3/18)

- 598 confirmed cases and 12 deaths cumulative: 7 this week (Sat-Wed), 4 last week, 1 two weeks ago (weeks defined Sat-Friday) (www.kcra.com/article/coronavirus-covid19-california-sacramento-latest-information/31406140#).

- 5678 cases in US, so CA is ~1/9th of US, proportional to population.

- Deaths will lag infections by 3-4 weeks (18 days from symptoms but that occurs 3-10 days after infection per www.medrxiv.org/content/10.1101/2020.03.09.20033357v1).

- Assuming constant IFR = 1% with 3- to 4-week delay, there were ~400 infected people 4 weeks ago in CA.

- Assuming doubling in new infections each week (average of countries outside China, wwwnc.cdc.gov/eid/article/26/5/20-0146_article), there are now 6400 weekly infections in CA, which is 1 in 6250 people.

- Let's assume 3100 (1/2) are in Bay Area. Popn 8,000,000 (1/5 of state) means 1 in 2560 got infected this week in the Bay Area.

We are still early in the process

What should we do when 1 in 2560 in the Bay Area have the virus?

- 1/2560 means 8 new infections in Stanford popn of 20,000 this week, 4 last week, 2 two weeks ago, 1 three weeks ago. 4 have been reported as suspected or confirmed cases, so that's consistent. Thus there may be ~8 who got it this week but may not know yet.

- About 50% of patients will be asymptomatic, based on experience with the Diamond Princess (cmmid.github.io/topics/covid19/severity/diamond_cruise_cfr_estimates.html), an estimate from Wuhan data (www.medrxiv.org/content/10.1101/2020.03.03.20030593v1), and an estimate from passengers on evacuation flights (www.medrxiv.org/content/10.1101/2020.03.09.20033357v1).

- Average incubation period is ~7 days. Transmission may begin 2 days before symptoms, so on average at 5 days after infection (www.medrxiv.org/content/10.1101/2020.03.15.20036707v2).

- Thus the ~8 on campus who just got the virus this week will start spreading virus and then develop symptoms over the next week (obviously not synchronized but continuously over time).

- We can protect ourselves against any undetected spreaders by keeping our hands and common surfaces clean, and maintaining distance when we talk (and use of face masks if you'd like).

- Risk is 1/2560 from direct personal contact; higher from touching fomites in proportion to the number of people touching them between cleanings.

- Take action to reduce a currently low risk of acquiring/transmitting the virus to as low as possible.

How bad could this be?

- If we did nothing and doubling rate remains 1 week, then in worst case, deaths and infections will grow exponentially until virus runs out of people to infect (using CA-only numbers now):

week ending	weekly deaths	cum deaths	new infection rate (1/n)	new infection rate (%)	cum infection rate (%)	notes
2020-03-13	4	3	6250	0.02%	0.02%	
2020-03-20	8	11	3125	0.03%	0.05%	
2020-03-27	16	27	1563	0.06%	0.11%	
2020-04-03	32	59	781	0.13%	0.24%	
2020-04-10	64	123	391	0.26%	0.50%	
2020-04-17	128	251	195	0.51%	1.01%	
2020-04-24	256	507	98	1.02%	2.03%	
2020-05-01	512	1019	49	2.05%	4.08%	
2020-05-08	1024	2043	24	4.10%	8.18%	
2020-05-15	2048	4091	12	8.19%	16.37%	
2020-05-22	4096	8187	6	16.38%	32.75%	Cumulative deaths exceed flu
2020-05-29	8192	16379	3	32.77%	65.52%	
2020-06-05	16384	32763				
2020-06-12	32768	65531				Virus has run out of people to infect, the highest cumulative infection rate I have seen is 70%, deaths continue as they result from infections 3 weeks earlier
2020-06-19	65536	131067				
2020-06-26	131072	262139				

- For US numbers, multiply by 8: ~2M (million) cumulative deaths.
- The above is not meant to be numerically accurate, it is just for illustration.
- Professional models: 100M cumulative infections (30%), 0.5M cumulative deaths (IFR 0.5%, a "conservative" estimate) (www.nytimes.com/2020/03/13/us/coronavirus-deaths-estimate.html).
- You can follow cases (not infection) and fatality numbers at www.worldometers.info/coronavirus/country/us.
- Compare to Spanish flu of 1917-1918: Cumulative infection rate 27%, IFR 2%. Spanish flu might have higher IFR than COVID-19, but medical care was much worse then (no ventilators, no drugs). In reality COVID-19 is likely the more severe disease. In any case, Spanish flu was devastating.

We need to 'flatten the curve' now

- Estimated 5% of total infected (not diagnosed cases) require hospitalization and 2.5% require ICU. Average hospital stay is 3 weeks, and starts 2 weeks after infection (1 week after diagnosis) (www.vox.com/2020/3/12/21176783/coronavirus-covid-19-deaths-china-treatment-cytokine-storm-syndrome, www.nytimes.com/2020/03/13/us/coronavirus-deaths-estimate.html).

- Wuhan numbers are 15%/5% of cases, but that is with smoking (60% of males) and pollution (everyone), also infection rate underdetected by 50% (www.medrxiv.org/content/10.1101/2020.03.03.20030593v1).

- Biggest infection surge occurs in the weeks of 5/15, 5/22, and 5/29, when 8%, 17%, and 33% of population = 26M, 53M, and 106M get infected. This will result in 1.3M, 2.7M, and 5.3M needing hospitalization starting 6/7, 6/13, and 6/20. As patients need to stay ~3 weeks, 9.3M will overlap on the week starting 6/20.
  - <1M hospital beds in US (www.statnews.com/2020/03/10/simple-math-alarming-answers-covid-19).
  - So we must slow down doubling time from 1 week to ~10 weeks, so hospitalizations peak at <1M.

Possible spread of COVID-19 with and without protective measures

Without protective measures

Healthcare system capacity

With protective measures

Number of cases

Time since first case
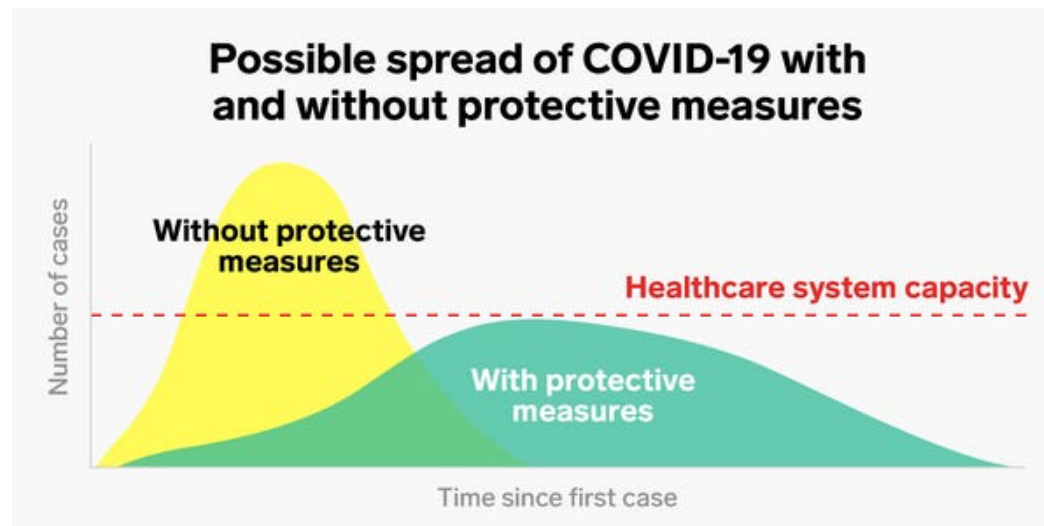
We need to 'flatten the curve' now

The next month is critical: March 16 to April 16. We must do whatever we can to reduce R0 or increase doubling time. It will take several weeks to know if it's working.

If we are still doubling each week on April 16, we have only another month to get a second chance.

If that doesn't work by May 16, there will be no third chance. We would have to immediately clamp down to avoid hospital overflow. This would require Wuhan-like measures such as central quarantine for sick and enforced home-isolation for everyone else.

What can flatten the curve?

- Weather: Maybe 10 ºF increases the doubling time 2x (steady-state reduction in exterior virus levels by 50% per Pubmed 22312351, plus reducing time × concentration of people indoors).

- Goal is to reduce the reproductive number R_0 (how many people infected by each patient).
  - Current R_0 rate ~ 2 (one person infects 2 others. If they do this in 7 days, it explains doubling time of 1 week).
  - Drop R_0 to 1.5: Doubling time would increase ~2-fold.
  - Drop R_0 to 1.25: Doubling time would increase ~4-fold.
  - Drop R_0 to 1.125: Doubling time would increase ~8-fold.
  - Drop R_0 to 1.0: Doubling time would become infinite (constant rate of new cases).

- Social distancing, wide testing and tracing, and strict hygiene (face masks, hand sanitizer): This is the approach in SK, Taiwan, Singapore, HK. This seems to have dropped R_0 to 1.0 (constant rate of new cases).

- Complete household isolation, immediate quarantining of symptomatic, strict hygiene: This was the approach in Wuhan. R_0 dropped from 3.9 to 0.32.

- Is presymptomatic or asymptomatic transmission a factor? Yes, but how much is unclear.
  - In Wuhan, R_0 fell from 1.3 when symptomatic patients stayed at home to 0.32 when they were centrally quarantined. This suggests only 24% (0.32/1.3) of transmission events occurred before symptoms (www.medrxiv.org/content/10.1101/2020.03.03.20030593v1). But another study estimates 44% of transmission is in presymptomatic period (www.medrxiv.org/content/10.1101/2020.03.15.20036707v2).
  - How about asymptomatics? Undiagnosed carriers estimated to be ~55% as infectious as diagnosed cases (doi.org/10.1126/science.abb3221). As undiagnosed carriers are more likely asymptomatic than diagnosed cases, this suggests asymptomatics are not as infectious as symptomatics.

It's not easy, but social distancing, fast testing, and immediate quarantining can be enough!

COVID-19 Cases - 2020-03-07
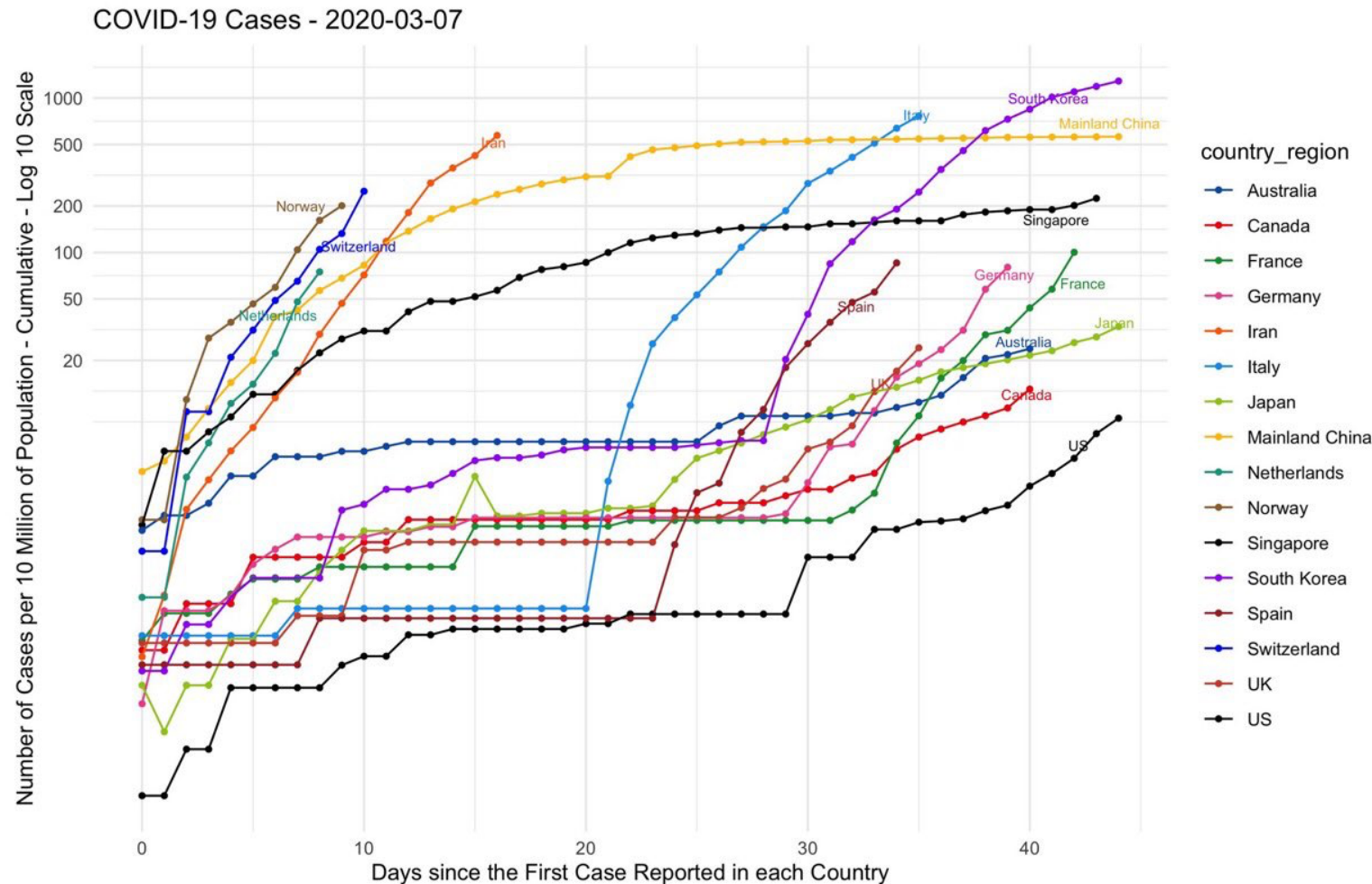
Quality of data here varies a lot – cases are from testing and testing rates vary. Best test data are from China, Singapore, South Korea.

Note log scale, so straight line = exponential growth

@berooz_hm - Data: Tim Churches (UNSW) & John Hopkins University

Thanks to earlier research, we already have drugs with activity against the virus

Camostat

- Coronavirus known to require activity of the cellular protease TMPRSS2 for entry, camostat blocks it.
- Inhibits SARS-CoV-2 cell entry with EC50 = 1000 nM (left, from doi.org/10.1016/j.cell.2020.02.052).
- Also helps prevent death in mice with SARS-CoV-1 (right, Pubmed 25666761).
- Camostat approved in Japan for pancreatitis, off-label use possible already.
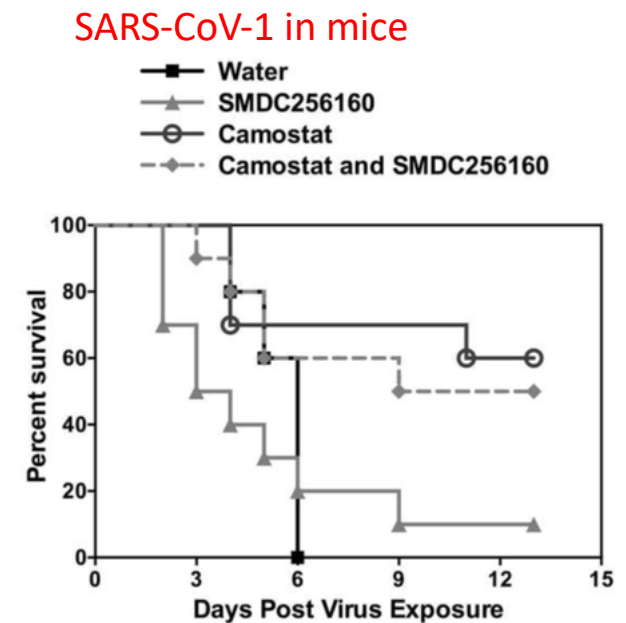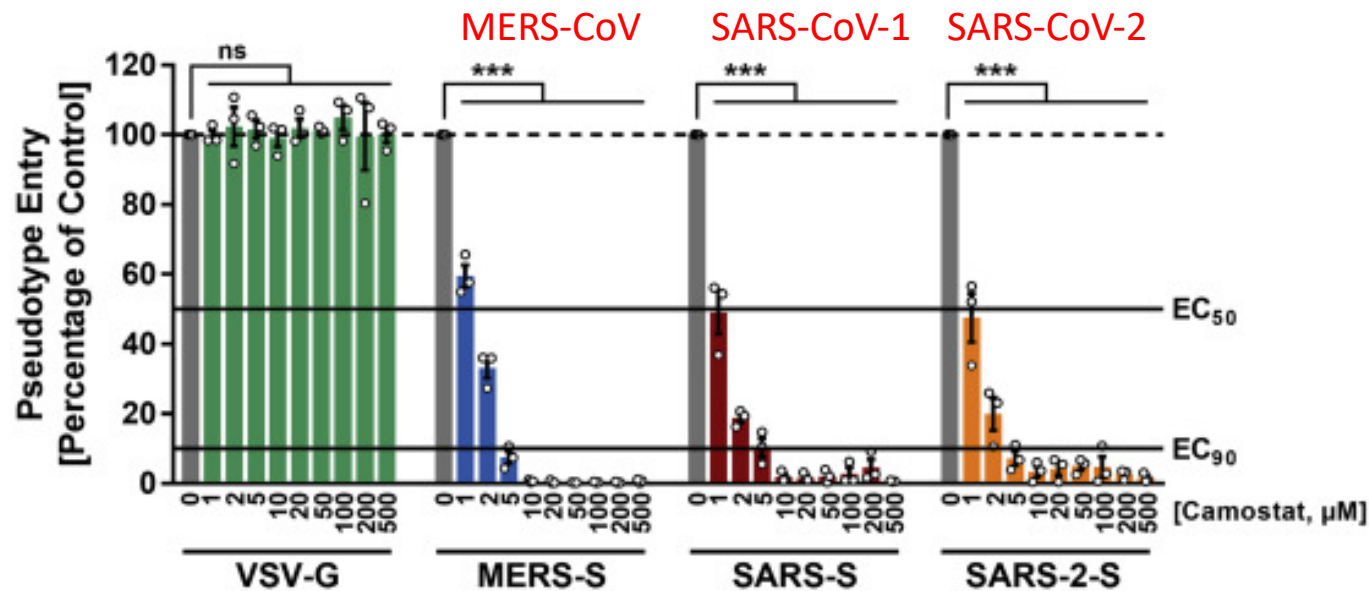
Thanks to earlier research, we already have drugs with activity against the virus

Favipiravir/favilavir/Avigan/T-705 (Fujifilm Toyama)

- Purine analog, gets conjugated to ribose to make a ribonucleoside analog, broad activity against RNA viruses
- Works against SARS-CoV-2 in human cells, EC50 = 61.88 µM (below, Pubmed 32020029). This sounds like relatively poor potency, but Cmax = 400 µM in humans with just oral dosing! (Pubmed 26798032).
- Works in people!
  - On 3/17, Chinese authorities announced that favipiravir is effective against COVID-19 in controlled trials, with 8% favipiravir patients vs 17% control requiring ventilators, and 91% vs 62% improving on lung imaging (asia.nikkei.com/Spotlight/Coronavirus/China-says-Japan-developed-drug-Avigan-works-against-coronavirus, www.chinadaily.com.cn/a/202003/17/WS5e708666a31012821727fcbd.html).
  - Already approved and stockpiled for influenza outbreaks in Japan (huh, maybe we need to learn from Japan).

SARS-CoV-2 in human cells
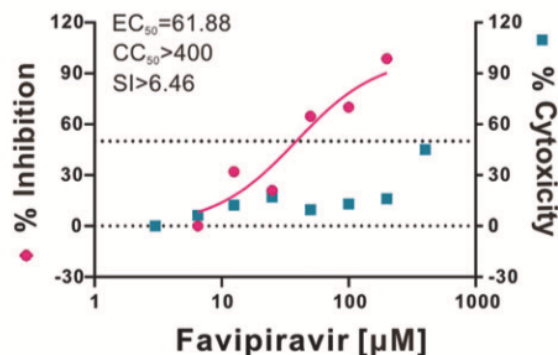
Kaletra (lopinavir+ritonavir)

- HIV protease inhibitor approved in multiple countries
- Being used based on clinical experience in China, and in formal trials (www.the-scientist.com/news-opinion/flu-and-anti-hiv-drugs-show-efficacy-against-coronavirus-67052).
- However MOA is unknown as there is nothing like HIV protease in the SARS-CoV-2 genome.

Thanks to earlier research, we already have drugs with activity against the virus

<u>Chloroquine</u>

- Works against SARS-CoV-2 in human cells, EC50 = 1130 µM (below-left, Pubmed 32020029).

- Works against distantly related cold virus CoV OC43 in mice (Pubmed 19506054).

- Works in people!

  - 2020-2-17: Per Chinese health ministry news briefing: "results from more than 100 patients have demonstrated that chloroquine phosphate is <u>superior to the control treatment</u> in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus- negative conversion, and shortening the disease course" but no data shown (Pubmed 32074550).

  - 2020-03-17: Reported effective in reducing viral titers in patients in open-label trial in France: (bottom-right, www.mediterranee-infection.com/hydroxychloroquine-and-azithromycin-as-a-treatment-of-covid-19).

  - In trials for preventing infection in China and US (www.startribune.com/university-of-minnesota-to-test-three-drugs-for-covid-patients/568766632/).

  - Side-effects can be serious, but it has been safely used for malaria prevention: www.drugs.com/mtm/chloroquine.html.

SARS-CoV-2 in human cells
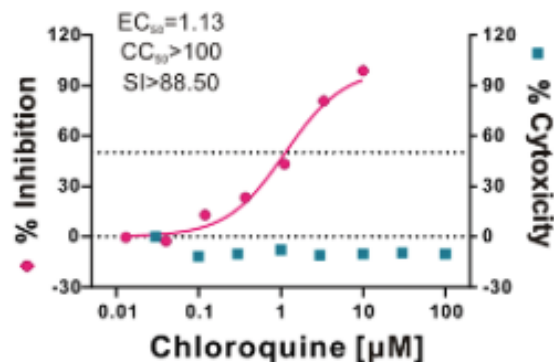
SARS-CoV-2 in humans
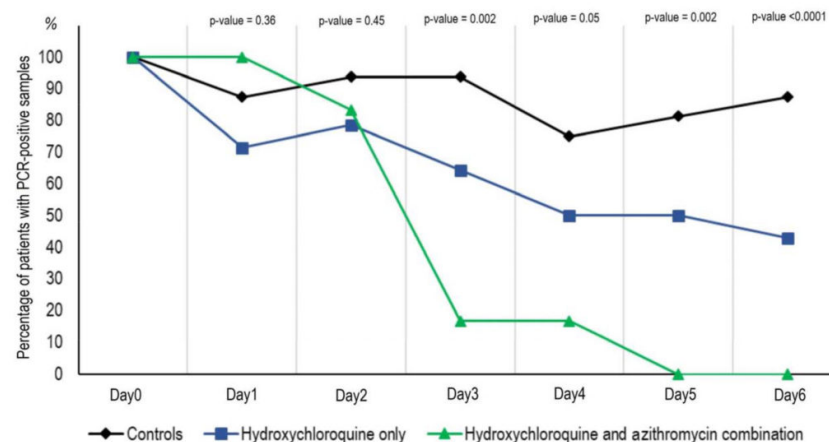
Thanks to earlier research, we already have drugs with activity against the virus

SARS-CoV-1 query vs SARS-CoV-2

Remdesivir (Gilead)

- Designed to inhibit Ebola RNA-dependent RNA polymerase (RdRp).
  - SARS-CoV-1 RdRp (P0C6X7/R1AB_CVHSA) and SARS-CoV-2 RdRp (YP_009725307) are 96% identical (left).
- Works against SARS-CoV-2 in cells, EC50 = 0.77 µM (middle, PMID 32020029).
- Already known to inhibit replication of SARS-CoV-1 in mice (right).
- Being tested in humans
  - Dosed to >11 US patients on compassionate basis, with good anecdotal results (www.wsj.com/articles/experimental-drug-helps-some-americans-ride-out-coronavirus-nih-doctor-says-11584094955).
  - In randomized controlled trials in China, data due mid-April.

SARS-CoV-2 in human cells

SARS-CoV-1 in mice
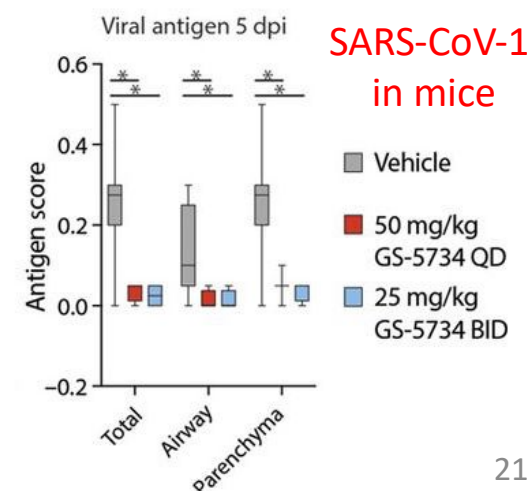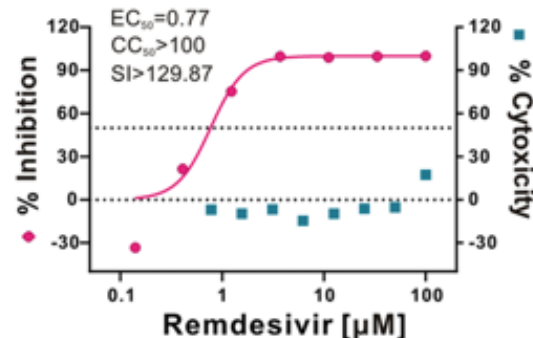
Drugs for reducing disease lethality

- Death is often from cytokine release syndrome (cytokine storm) treatment: once virus replicates to high levels in the lungs, the large release of cytokines causes multi-organ failure (www.vox.com/2020/3/12/21176783/coronavirus-covid-19-deaths-china-treatment-cytokine-storm-syndrome).
    - Anti-IL-6 mAb Actemra (Roche) was approved for CRS in COVID-19 by China (www.pharmaceutical-technology.com/news/roche-actemra-coronavirus-complications).
    - COX-2 inhibitors had been suggested for preventing CRS in SARS but this hasn't been brought up recently.
    - Treating CRS is of course good, but not as good as preventing patients from getting to this point to begin with.

- AT1R blocker losartan is being tested based on a proposal that it will upregulate the SARS-CoV-2 receptor ACE2, preventing loss of ACE2 function which may be protective against the acute respiratory distress syndrome that is one cause of death by COVID-19 (Pubmed 32129518) (www.startribune.com/university-of-minnesota-to-test-three-drugs-for-covid-patients/568766632/).
    - This comes from an old hypothesis (2005) that SARS lethality was due to downregulation of ACE2 (www.nature.com/articles/nrd1830) whose validity I'm not too confident about, since it was based on injecting massive amounts of viruses into mice (who can differ from humans in their cardiovascular regulation).
    - Others have suggested that upregulating the receptor for the virus with losartan might increase susceptibility to the initial infection (www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30116-8/fulltext). This probably doesn't matter either because a virus particle won't to care if the cell surface it's swimming on has 100 or 300 receptor molecules to bind to.
    - This only deals with lung injury secondary to viral replication, not the virus itself. I think it's better to concentrate on specific antiviral medications and not worry about the complex ACE2/AT1R pathway.

- More clinical trials here: www.statnews.com/2020/03/19/an-updated-guide-to-the-coronavirus-drugs-and-vaccines-in-development

New treatments and vaccines

- Specific anti-viral antibodies (Vir Biotechnology): made by cloning Ig genes from recovered patients.

- I expect there are already patents filed on synthetic antibody-like molecules isolated against the SARS-CoV-2 envelope proteins by phage display.

- I also expect there are already remdesivir analogues designed for higher potency on the SARS-CoV-2 polymerase by virtual docking. This is because the SARS-CoV-1 polymerase structure was recently solved by cryo-EM, so the SARS-CoV-2 structure can then be easily predicted (www.nature.com/articles/s41467-019-10280-3).

- There are likely many other drugs being designed based on virtual screens, e.g. www.drugdiscoveryonline.com/doc/stonewise-ai-driven-drug-discovery-polymerase-inhibitors-covid-infection-treatment-0001

- Many vaccines in development, fastest are RNA-based (CureVac, Moderna) www.chemistryworld.com/news/rna-vaccines-are-coronavirus-frontrunners/4011326.article

- Some more summary and speculation here: doi.org/10.1021/acscentsci.0c00272

- Why not vaccinate with formalin inactivated virus like the first polio vaccine?
    - An inactivated SARS-CoV-1 vaccine was protective in monkeys (Pubmed 15837221).
    - This has been proposed for SARS-CoV-2 (www.nature.com/articles/s41541-020-0170-0); I hope someone is trying it. If CDC is doing their job, they should already be making such vaccines in-house AND TELLING US ABOUT IT. Which gets me to the next point…

How CDC and FDA failed

- CDC was initially inflexible on testing guidelines (e.g. needed travel or exposure history).

- CDC created a test requiring a slow RT-PCR reaction on a specific model of machine, designed poor primers, and didn't realize this for a month. This was both strategically (using 30-year-old technology) and tactically (designing bad primers) incompetent. I would expect most graduate students to do better.

- FDA was inflexible on tests: approved only the (initially flawed) CDC test, refused working tests from WHO and other countries (www.cnn.com/2020/03/12/asia/coronavirus-south-korea-testing-intl-hnk/index.html), even required CDC to retest results of other labs (www.propublica.org/article/the-fda-is-forcing-the-cdc-to-waste-time-double-testing-some-coronavirus-cases)
  - Finally allowed academic labs to develop their own tests on 2/29 (www.aamc.org/news-insights/coronavirus-testing-how-academic-medical-labs-are-stepping-fill-void)
  - Finally approved rapid Roche test on 3/13 (www.fiercebiotech.com/medtech/fda-grants-roche-coronavirus-test-emergency-green-light-within-24-hours)

How CDC and FDA failed

- Being too restrained when discussing treatments and vaccines
  - FDA will never say a drug is looking good; they only approve once randomized blinded trials meet pre-set criteria, so it's up to others to say something.
  - CDC wants to promote social distancing because this is required, and fear is a good motivator, and perhaps feel they are not the drug authority.
  - They figure doctors would know what to do for therapy anyway, so no need to broadcast it.
  - But maybe patients need to know before seeing their doctors that something can be done, so they can seek care and isolation earlier instead of just waiting at home and getting worse, then infecting relatives and caregivers.
  - Quack treatments will gain traction because people are under the false impression scientists can't do anything about it.

How CDC and FDA failed

- Providing non-information in place of information. Example from (www.cdc.gov/coronavirus/2019-ncov/specific-groups/children-faq.html)
  - Q: What is the risk of my child becoming sick with COVID-19?
  - A: "Based on available evidence, children do not appear to be at higher risk for COVID-19 than adults. While some children and infants have been sick with COVID-19, adults make up most of the known cases to date. You can learn more about who is most at risk for health problems if they have COVID-19 infection on CDC's current Risk Assessment page."
  - Better answer: "Children have milder disease courses than adults, although they may still transmit the disease at low efficiency to adults." It's clear that kids get less sick if at all. Why doesn't the CDC say so? It won't hurt to tell the truth! If you provide such lousy information, people will stop trusting you.

How POTUS and VPOTUS failed

- Not learning the facts well enough to make useful decisions such as ordering FDA to approve other tests and CDC to expand testing guidelines.
- Not learning the facts well enough to become trustworthy to the public.
- Not explaining to the public why social distancing is necessary to protect the elderly.
- Not explaining to the public that social distancing does NOT mean disruption to food and supplies as long as people don't hoard.
- Not motivating people to do their part by (1) stepping up hygienic habits, (2) limiting non-essential activities that can spread the disease, and (3) not hoarding resources. Instead the press and local officials have taken the initiative to do this, but this creates the problem of too many information sources.
- Hogging the spotlight instead of naming a trusted doctor or scientist to be the face of policy. Should have made sure the surgeon general or Fauci was given the most attention by the press.

Recommendations - health

- At the first sign of CoVID19 symptoms (right), stay away from others and get tested. Put on a mask and keep your hands clean in the presence of others until you know your test results.

- Recall the worry is about transmitting virus to older people, even if you have mild symptoms you do not want to transmit the virus to others.

COVID-19 compared to other common conditions

SYMPTOM	COVID-19	COMMON COLD	FLU	ALLERGIES
Fever	Common	Rare	Common	Sometimes
Dry cough	Common	Mild	Common	Sometimes
Shortness of breath	Common	No	No	Common
Headaches	Sometimes	Rare	Common	Sometimes
Aches and pains	Sometimes	Common	Common	No
Sore throat	Sometimes	Common	Common	No
Fatigue	Sometimes	Sometimes	Common	Sometimes
Diarrhea	Rare	No	Sometimes*	No
Runny nose	Rare	Common	Sometimes	Common
Sneezing	No	Common	No	Common

*Sometimes for children

Sources: CDC, WHO, American College of Allergy, Asthma and Immunology

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Recommendations - hygiene

- Don't shake hands and stay 6 ft away from people outside your household – these are easy.
- But "wash your hands often" and "don't touch your face" are confusing without context – how often is often? Why can't I touch my face? Should I ask someone to scratch my itchy nose for me? Shouldn't I also worry about what I'm touching, not just my hands? If so, what cleaning solutions should I use?
- I'll provide some details. I treat hands and objects similarly, and I am pretty strict:
  - To protect yourself, sanitize your hands right before eating and right after touching things touched by others.
  - To protect others, use clean hands to touch others' things or when handling things to others.
  - Sanitize objects you get, and only give out sanitized objects. For example, I have hand sanitizer open and ready to clean my credit card right after I get them back from cashiers, before I put it back in my wallet.
  - Sanitize smooth surfaces you will touch directly with your hands (e.g. tables and chair edges, wherever you put your phone and computer). Use paper towels to turn off faucets and open bathroom doors.
  - To keep the number of times I have to sanitize, I keep track of whether clean objects and hands stay clean. As long as my hands or my objects have not encounted unknown/dirty things after their last cleaning, they don't need to be recleaned. This is why I suggest immediate sanitation of hands after touching things of unknown cleanliness, so you can resume using your clean things without worry.
  - Create clean zones – your house, your office, your car.
  - Sanitization can be done by soap and water (hands) or hand sanitizer (hands or objects) or Windex (objects).
  - "Disinfectants" like bleach or quarternary amines are for large areas for which soap (due to the need to rinse) or alcohol (due to fumes, expense) are not practical. If you can use soap or alcohol, you don't need them.
  - Open doors with your body or foot whenever possible.
  - Finally, if your hands are clean, you can touch your face! But remember to sanitize them before you touch other people's stuff.

Recommendations − face masks

Face masks: yes or no?

- You will see news articles saying that you don't need face masks as they are largely ineffective, or that you shouldn't buy face masks because caregivers need them.

- These statements cannot both be true! If face masks are ineffective why do caregivers need them?

- Well, they are effective (www.nytimes.com/2018/03/23/well/live/face-masks-work-healthy-colds-flu-immunity-prevention.html)

  – In addition to spreading through contact and then ingestion, SARS-CoV-2 also spreads through inhalation of airborne droplets.

  – Disposable masks are filters, causing bacteria and droplets to be caught in a meshwork of polypropylene. They are not rated for completely filtering out aerosolized viruses, i.e. individual viruses in a small water shell. There is some evidence SARS-CoV-2 can be aerosolized, but its mode of spread is mostly through larger droplets.

  – Masks absorb 95% of exhaled droplets from infected people (Pubmed 23505369).

  – Masks also absorb droplets during inhalation; this is harder to quantify but certainly substantial, as masks cut transmission within households by 60-80%, a situation with lots of viral droplets around (Pubmed 19193267) .

  – Both surgical masks and N95 respirators are effective (Pubmed 19797474), although it's assumed the N95 are better.

Recommendations – face masks

- My recommendations for mask usage are based on <u>relative risks</u>
  - At current infection rates and in normal activities, most people would be wasting masks.
  - However masks would be useful in confined places with strangers (airplane, train, Uber/Lyft, and especially hospital or clinic).
  - They are warranted for at-risk people, i.e. the immunocompromised or elderly, in public.
  - If the infection rates climb then they would be useful for everybody out in public.
  - They are absolutely recommended for people who are sick for avoid transmitting viruses.

- Mask use is controversial because of limited supply
  - To assure those who need masks most get them, try to conserve them, and buy a small supply.
  - It is better to do social distancing without masks than social crowding with masks. In Asia, where most people take public transport, masks are considered a necessity and are handed out by authorities.
  - Given the different risk levels that different people can tolerate, I think there should be no stigma/shaming of people wearing masks.
  - I can share tips for how to conserve masks if anyone wants to know.

Recommendations – face masks

- How to use masks
  - Make sure to clean your hands well before putting on or taking off masks.
  - For the soft surgical masks, make sure you know which side faces out (usually colored side).
  - For the surgical masks, bend the hard edge to fit your nose, put on your nose and pull the straps over your ears, then stretch the mask down to cover your chin.
- How to conserve face masks
  - I might get some flak from my colleagues who are uncomfortable breaking the old rules which assumed unlimited supply, but I think we should use our understanding of the virus and decontamination methods to adapt resourcefully to the limited supply of masks.
  - Disposable masks are meant to be worn "once" then throw away, but once is not defined. To conserve, I think it's reasonable to use one mask one day. In Taiwan, which has controlled the epidemic very well, authorities hand out 3 masks per week per person, so people have been using one mask all day.
  - For a quick drink, you can just use clean hands to lower the mask to your chin. Eating is trickier because you don't want stuff dropping from the mask onto your food. Use clean hands to remove the mask, fold in half to shield the inside, and set in a clean place. As the outside of the mask is potentially dirty, you might clean your hands again before eating, or you can have your hands wet with hand sanitizer the whole time you handle the mask.
  - Clean and reuse: Place in oven at 70ºC = 160ºF for 30-60min, or expose both sides in a UV sterilizer. Alcohol is not recommended (mp.weixin.qq.com/s/3QYVWO4kj5qwuSHnhcM9uQ).

Recommendations - activities

- It's okay to go out to buy essentials, get takeout, but assume anything can be carrying virus, so <u>practice good hygiene</u> as above, i.e. maintain 6ft separation, sanitize hands in between touching others' things and your own things, pass only clean objects, and treat objects you acquire as dirty. Visiting the workplace should be fine if you work mostly alone and can take the same hygiene steps above. (*3/17 update:* Bay Area citizens cannot go to workplaces except for some essential jobs.)

- It's okay to see relatives who are not sick to provide help, but <u>again only if you can practice good hygiene</u>. Limit duration and closeness of visits to elderly or immunocompromised relatives.

- I have reversed my allowance for social visits to friends, given that many feel it's uncool to practice good hygiene such as wearing face masks, not touching common objects.

- Buy groceries online. Ironically stay-in orders increase transmission risk at grocery stores, which are now packed. My estimate is 1 in 1000 will carry infections in early April. That number can pass through one store daily. If you must go, stay 6ft from others and sanitize hands and purchases!

- I suggest not purchasing prepared salads or sandwiches, and retoasting pastries.

- Don't share food, obviously.

- Go outside – sunlight is the best disinfectant.

- Do safer activities – this is not the time you want to break a leg and have to go to the hospital.

Recommendations – travel

- Large meetings that bring people from around the country are obviously a big risk:
  - Large numbers of people who might breath the same air and touch the same things (e.g. at Biogen meeting, attendants used the same serving utensils at a buffet, and 70 got infected)
  - These people tend to travel many times so they can spread viruses further
  - Viruses can be collected from many locations and transmitted to many others (e.g. Biogen)
  - Thus non-urgent meetings should be cancelled (as of 3/16 this has been widely implemented)
- Travel if you must, e.g. to help care for family (updated 3/17 to remove nonessential activities in compliance with most health officials' directives). Students also need to go home! But due to the many points when exposure from strangers can occur, travel requires <u>high vigilance.</u> For example, sanitizing items that others give to you now includes your ID at the TSA checkpoint and the can of soda from the flight attendant. Sanitizing surfaces you touch now include tray tables, seat belts, armrests. Keeping your hands clean when touching your own things now means washing hands after closing the airplane bathroom door (because you don't want germs on your zippers) and, after washing hands after finishing, opening the same door with your elbow (or a napkin). Make sure the ventilation nozzle is on full blast (it puts out HEPA-filtered air) – after you clean the nozzle of course.
- Similar hygienic tips apply to trains and buses and cars that are not your own.
- A face mask would be useful in cars with others, trains, planes, crowded waiting areas.

No need to worry about supplies

- 50% of people with virus have no symptoms but will become immune, just like most symptomatic people
- 95% don't need to go to the hospital
- The workforce is not threatened
- Farmers and truck drivers and store workers will be available for work
- You don't need to buy everything in sight
- This is not the zombie apocalypse

Hand sanitizer recipe

- Hand sanitizer is just 60-70% ethanol with moisturizers.
- The ethanol you want to use is 95% non-denatured ethanol
  - 95% denatured ethanol has toxic additives to prevent drinking (will have a health hazard logo).
  - 100%/dehydrated/absolute/anhydrous ethanol has benzene, also toxic, from the purification process.
- Isopropanol can be substituted for ethanol, but just takes longer to evaporate
  - 60-70% isopropanol is just as effective as 60-70% ethanol as a disinfectant.
  - 99-100% isopropanol (rubbing alcohol) can be purchased by the consumer as a cleaning and disinfecting agent.
- The moisturizer can be aloe vera gel (as home recipes suggest, but hard to find) or glycerol (a common ingredient in moisturizers and makeup).

Lin Lab recipe: Mix two parts 95% non-denatured ethanol or 99-100% isopropanol with 1 part 90-100% glycerol. That's it!

(Thanks to Yichi Su for testing, and Michael Westberg for the safety tips)