

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

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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](http://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

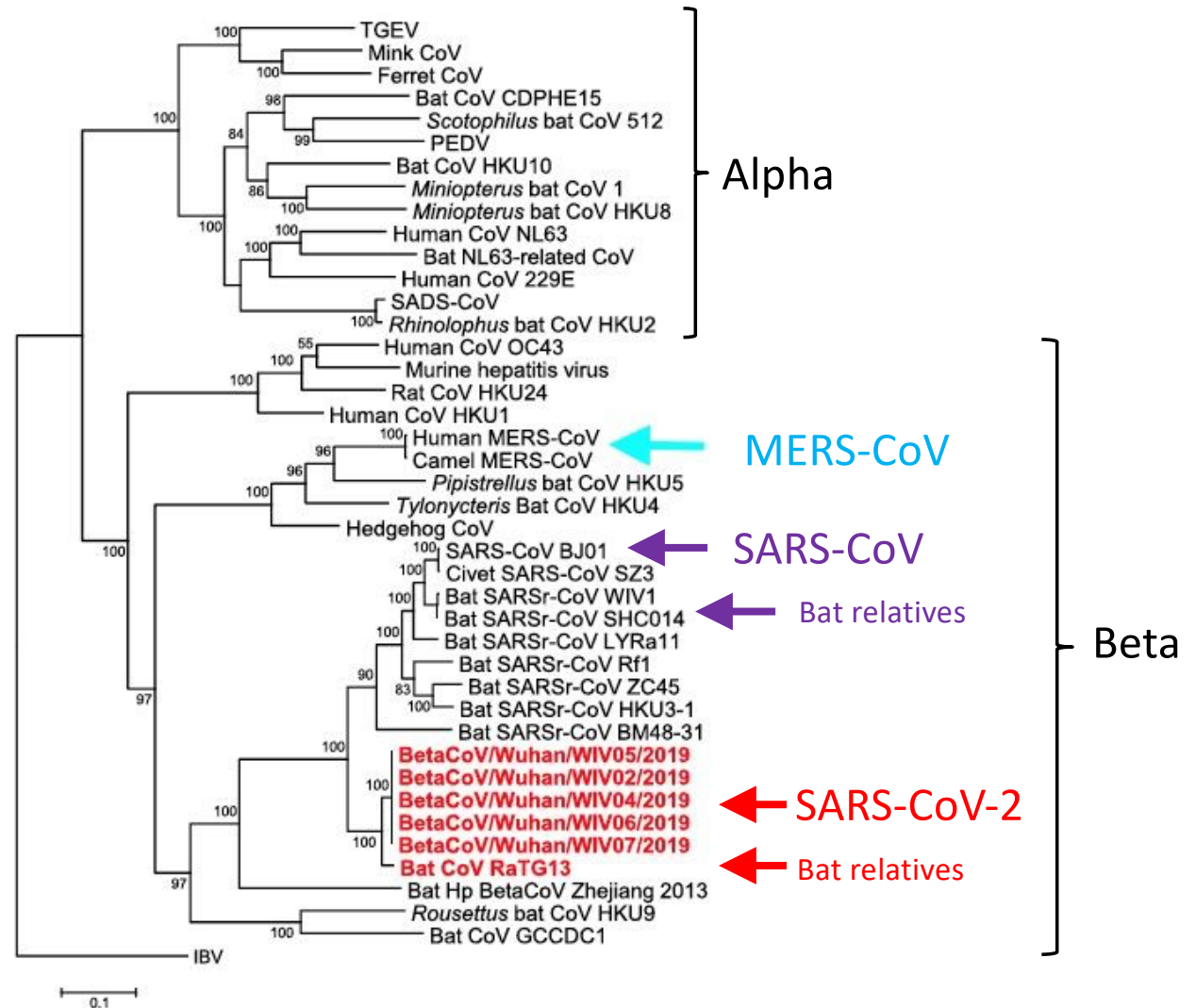
- COVID-19 refers to the disease, which in practice is used to refer to having a positive 2019 coronavirus laboratory test regardless of disease signs or symptoms
  - WHO introduced the disease name COVID-19 with great fanfare (after weeks of discussions) at a time when there was no virus name, so it 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

- 2019-nCoV 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...
- SARS-CoV-2 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](http://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 ( $\geq 27,000$  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).



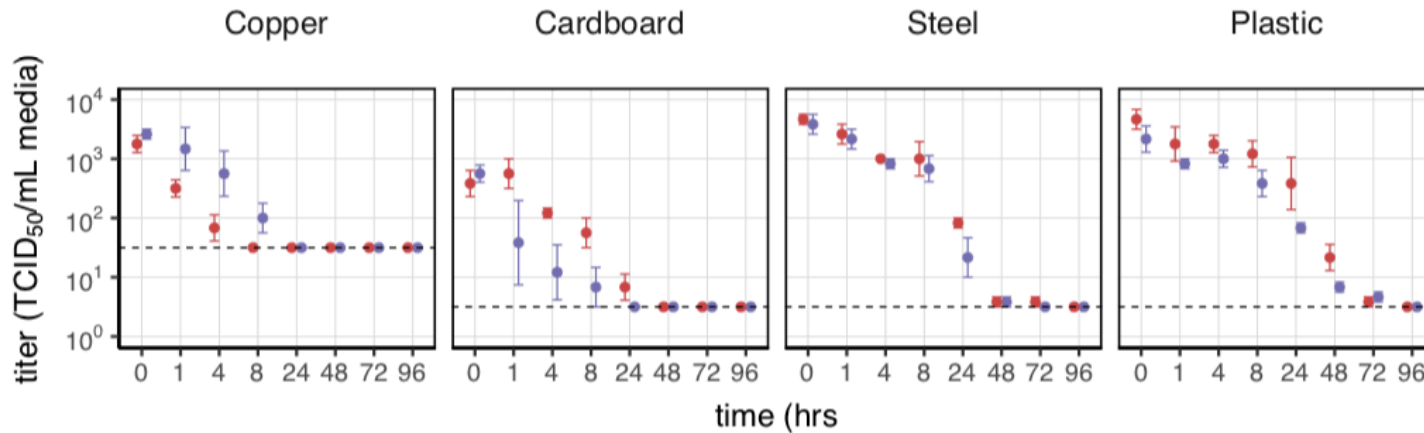
<https://www.sciencemag.org/news/2020/01/mining-coronavirus-genomes-clues-outbreak-s-origins>



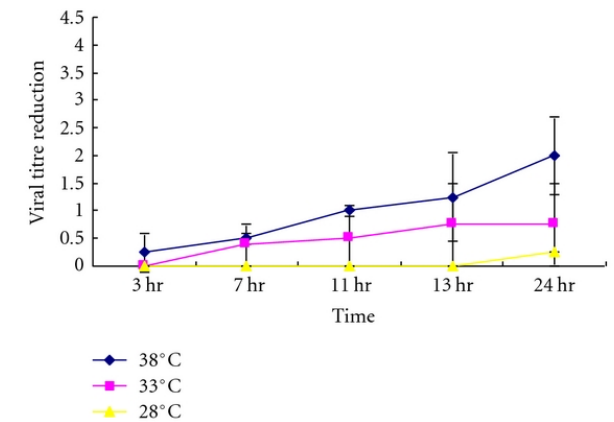
# How do you kill SARS-CoV-2?

- It's an enveloped virus (with a plasma membrane) so it's killed by soap/detergents, ethanol, Windex (which contains detergents), bleach.
- Survival of SARS-CoV-2 depends on the surface (below-left, [doi.org/10.1101/2020.03.09.20033217](https://doi.org/10.1101/2020.03.09.20033217))
  - On steel and plastic, 10-fold drop in ~12 hours
  - On cardboard, 1 hour
  - SARS-CoV-1 is sensitive to temperature, so SARS-CoV-2 is likely to be, too (below-right, Pubmed [22312351](https://pubmed.ncbi.nlm.nih.gov/22312351/)).
- On a napkin, the survival should be like on cardboard or lower, and the virus will get trapped by the paper fibers. That said, I would not wipe my mouth with a napkin that someone just handed to me.

SARS-CoV-1 and SARS-CoV-2 applied to surfaces  
(how exactly not described)

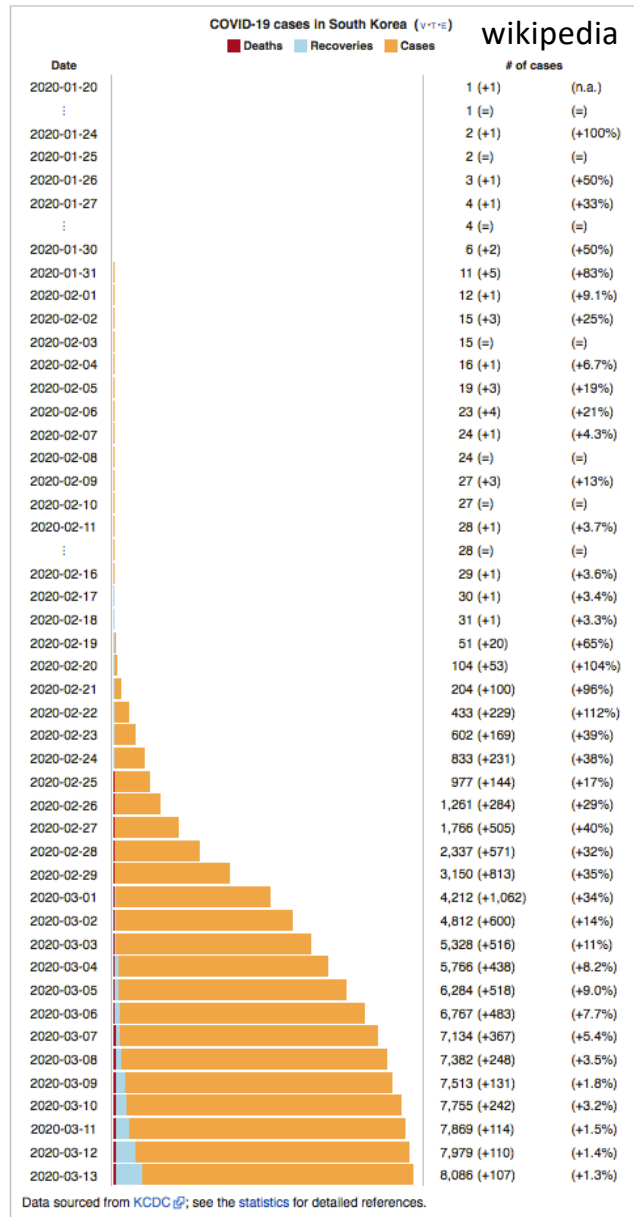


SARS-CoV-1 dried onto tissue-culture plastic, y-axis is log reduction

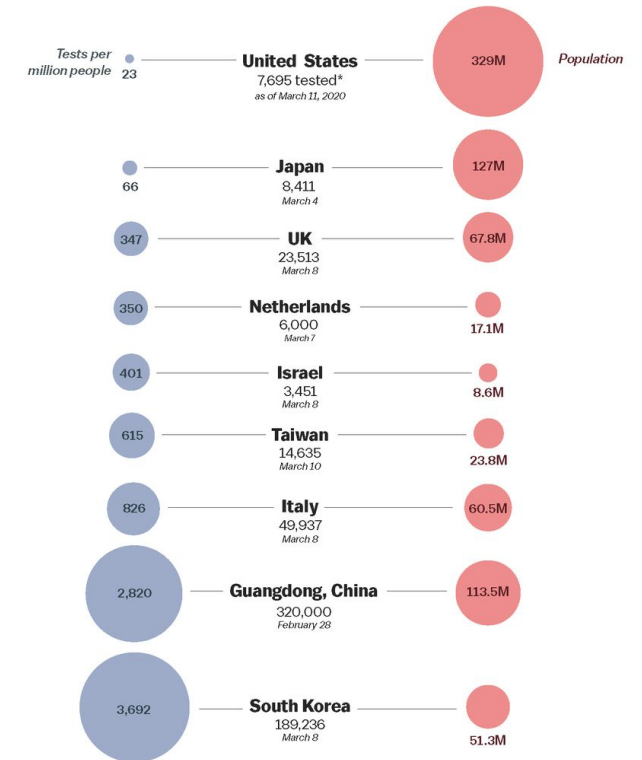


# Estimating infection (not disease) numbers

- Actual SARS-COV-2 infection number matters more than 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](https://en.wikipedia.org/wiki/2020_coronavirus_pandemic_in_South_Korea)).
- Deaths on average will lag diagnosis by 2 weeks ([wwwnc.cdc.gov/eid/article/26/6/20-0320\\_article](https://wwwnc.cdc.gov/eid/article/26/6/20-0320_article)). This is consistent with the shapes of case and death curves ([www.worldometers.info/coronavirus/country/south-korea/](https://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 CFR ~  $75/4000 = 1.9\%$
- However infections > diagnosed cases, so IFR < 1.9%, depending on what fraction of infections were diagnosed on 2/29,



## A snapshot of early Covid-19 testing per capita



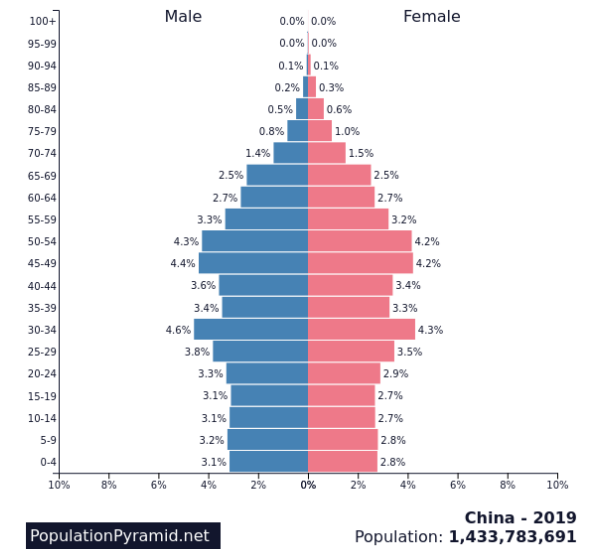
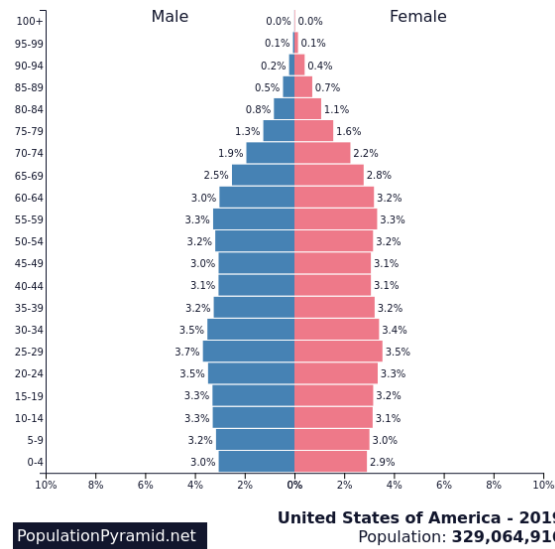
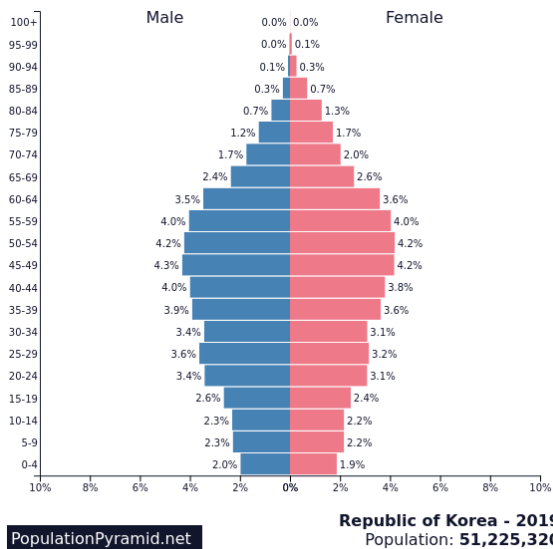
\*Test counts do not include full reporting from all US labs  
Source: Covid Tracking Project, Business Insider, the Atlantic, Taiwan CDC





# Estimating infection (not disease) numbers

- An analysis of China and the Emerald Princess (EP) gave an IFR of 0.5% for all-China and 1.2% for EP ([https://cmmid.github.io/topics/covid19/severity/diamond\\_cruise\\_cfr\\_estimates.html](https://cmmid.github.io/topics/covid19/severity/diamond_cruise_cfr_estimates.html))
- Note on the EP, 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](http://www.wsj.com/articles/experimental-drug-helps-some-americans-ride-out-coronavirus-nih-doctor-says-11584094955)) but then EP passengers may have 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.



# We are still early in the process

Estimating new case rates in CA and Bay Area on 3/12

- 198 confirmed cases cumulative, 4 deaths (CFR = 2%) with 1 death 2 weeks ago, 3 deaths in last week <https://www.kcra.com/article/coronavirus-covid19-california-sacramento-latest-information/31406140#>
- 2000 cases in US, so CA is 1/10<sup>th</sup> of US at the moment
- Death rates will lag infection rates by 3-4 weeks (2 weeks from diagnosis but that's 1 week from infection time on average with current testing practices)
- Assuming constant IFR = 1% with 3- to 4-week delay, there were ~300 infected people 4 weeks ago in CA.
- Assuming doubling in new cases each week (average of countries outside China, [https://wwwnc.cdc.gov/eid/article/26/5/20-0146\\_article](https://wwwnc.cdc.gov/eid/article/26/5/20-0146_article)), there are now 4800 weekly cases in CA, which is 1 in 8333 people.
- Let's assume 2400 (1/2) are in Bay Area. Popn 8,000,000 (1/5 of state) means 1 in 3333 got infected this week in the Bay Area.

# We are still early in the process

What should we do when 1 in 3333 in the Bay Area have the virus?

- 1/3333 means 6 new infections in Stanford popn of 20,000 this week, 3 last week, 1 or 2 two weeks ago. 4 have been reported as suspected or confirmed cases, so that's consistent. Thus there may be ~6 who got it this week who may not know yet.
- About 50% of patients will be asymptomatic. This was the observation with the Emerald Princess ([https://cmmid.github.io/topics/covid19/severity/diamond\\_cruise\\_cfr\\_estimates.html](https://cmmid.github.io/topics/covid19/severity/diamond_cruise_cfr_estimates.html)) and an estimate from Wuhan data ([www.medrxiv.org/content/10.1101/2020.03.03.20030593v1](http://www.medrxiv.org/content/10.1101/2020.03.03.20030593v1)).
- Most transmission correlates with coughing symptoms, according to WHO ([www.who.int/news-room/q-a-detail/q-a-coronaviruses](http://www.who.int/news-room/q-a-detail/q-a-coronaviruses)). Anecdotally, people can spread 1-2 days before having symptoms (e.g. first Germany cases). This makes biological sense; the first replication cycles won't create enough tissue damage to be noticed.
- Thus of the ~6 on campus who just got the virus this week, ~3 of these will start spreading virus and then develop symptoms over the next week (obviously not synchronized but continuous in 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 1/3333 from direct personal contact; higher from touching fomites in proportion to the number of people touching them between cleanings
- Take action to reduce a low risk of acquiring/transmitting the virus to even lower

# However, we need to 'flatten the curve' now

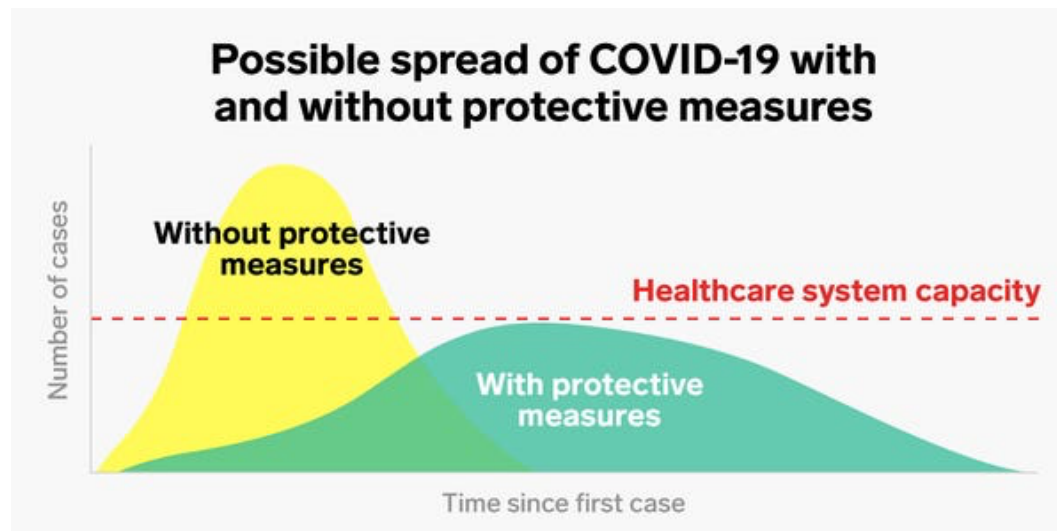
- If we did nothing and doubling rate remains 1 week, then in worst case, deaths and infections will grow exponentially until virus runs out of people to infect (using CA-only numbers now):

week	weekly deaths	cum deaths	new infection rate (1/n)	new infection rate (%)	cum infection rate (%)	notes
2020-03-13	3	3	8333	0.01%	0.01%	
2020-03-20	6	9	4167	0.02%	0.03%	
2020-03-27	12	21	2083	0.05%	0.08%	
2020-04-03	24	45	1042	0.10%	0.18%	
2020-04-10	48	93	521	0.19%	0.37%	
2020-04-17	96	189	260	0.38%	0.75%	
2020-04-24	192	381	130	0.77%	1.52%	
2020-05-01	384	765	65	1.54%	3.06%	
2020-05-08	768	1533	33	3.07%	6.13%	
2020-05-15	1536	3069	16	6.14%	12.27%	
2020-05-22	3072	6141	8	12.29%	24.56%	Cumulative deaths exceed flu
2020-05-29	6144	12285	4	24.58%	49.14%	Virus stops doubling because most people have become immune. I kept new infection rate constant for the last week to reach ~70% cumulative infections as this is the highest projection I've heard. Deaths continue as they are
2020-06-05	12288	24573	4	24.58%	73.72%	1% of infections from 3 weeks earlier
2020-06-12	24576	49149				
2020-06-19	49152	98301				
2020-06-26	49152	147453				

- For US numbers, multiply by 8: ~1,100,000 cumulative deaths
- The above is not meant to be numerically accurate, it is just for illustration
- Professional models: 100,000,000 cumulative infections (30%), 500,000 cumulative deaths (IFR 0.5%, a "conservative" estimate) ([www.nytimes.com/2020/03/13/us/coronavirus-deaths-estimate.html](http://www.nytimes.com/2020/03/13/us/coronavirus-deaths-estimate.html))
- 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.

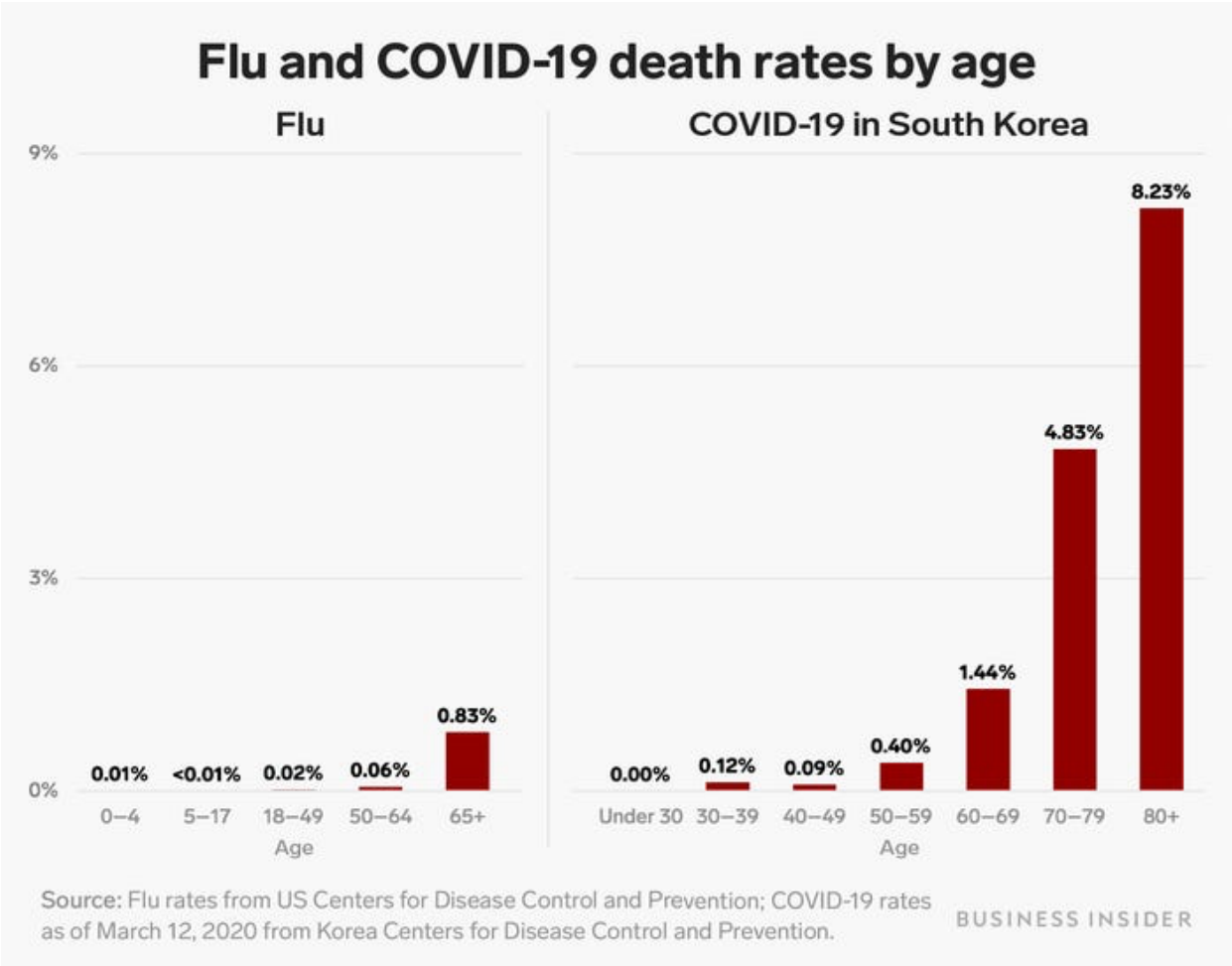
# How bad could this be?

- 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.nytimes.com/2020/03/13/us/coronavirus-deaths-estimate.html](http://www.nytimes.com/2020/03/13/us/coronavirus-deaths-estimate.html), [www.vox.com/2020/3/12/21176783/coronavirus-covid-19-deaths-china-treatment-cytokine-storm-syndrome](http://www.vox.com/2020/3/12/21176783/coronavirus-covid-19-deaths-china-treatment-cytokine-storm-syndrome))
- Wuhan numbers are 15%/5%, but that is with the effects of smoking (60% of males) and pollution (everyone), also infection rate likely underdetected by 50% ([www.medrxiv.org/content/10.1101/2020.03.03.20030593v1](http://www.medrxiv.org/content/10.1101/2020.03.03.20030593v1))
- Biggest surge in infections occurs in the weeks of 5/29 and 6/5, when 25% of population = 80,000,000 gets infected each week. This will result in 4,000,000 needing hospitalization starting 6/12 and another 4,000,000 starting 6/19.
  - Only 1,000,000 hospital beds in US <https://www.statnews.com/2020/03/10/simple-math-alarming-answers-covid-19/>
  - So we must slow down doubling time from 1 week to >8 weeks, so at peak it is <500,000 hospitalizations in a week



# Deaths are mostly in older patients

This is true for both flu and COVID-19





# What can flatten the curve?

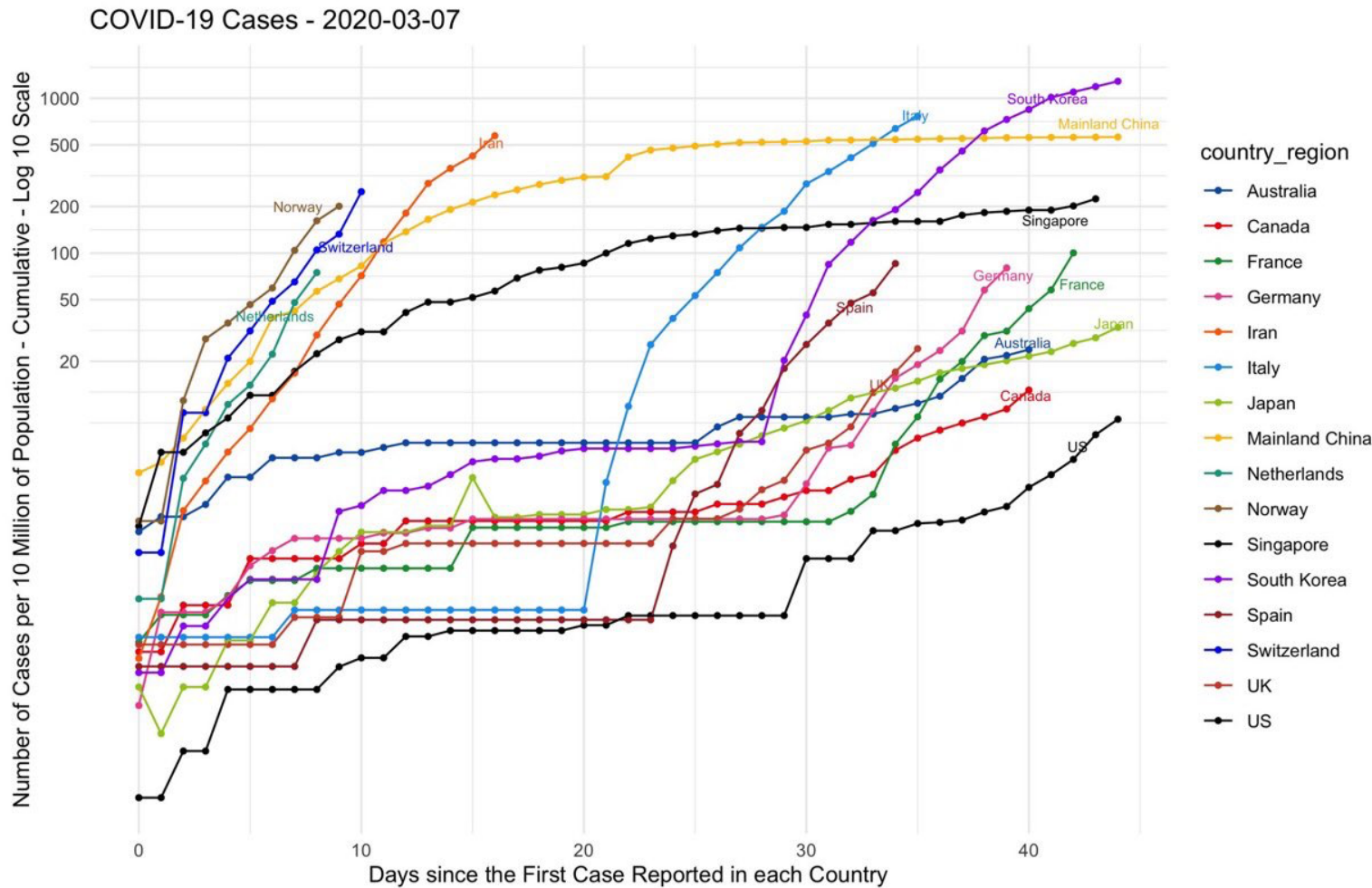
- Social distancing: Could have wide range of effects.
  - Current R0 rate ~ 3 (one person infects 3 other people. If they do this in ~10 days, it would account for doubling time 1 week).
  - Drop R0 to 1.5: Doubling time would increase ~4-fold.
  - Drop R0 to 1.25: Doubling time would increase ~8-fold.
  - Drop R0 to 1.0: Doubling time would become infinite (constant rate of new cases).
- Facility/hospital quarantine: in Wuhan study, changed R0 from 3.4 to 0.32 ([www.medrxiv.org/content/10.1101/2020.03.03.20030593v1](http://www.medrxiv.org/content/10.1101/2020.03.03.20030593v1)).
- Weather: Maybe 10 °F increases the doubling time 2x (steady-state reduction in exterior virus levels by 50% per Pubmed [22312351](https://pubmed.ncbi.nlm.nih.gov/22312351/), plus reducing time × concentration of people indoors).

The next month is critical: March 16 to April 16. It's not so dangerous in terms of getting infected personally, but important in terms of demonstrating we can reduce R0 or increase doubling time.

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 would 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.

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



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

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

## Remdesivir (Gilead)

- Works against SARS-CoV-2 in cells, EC50 = 770nM (left, PMID [32020029](https://pubmed.ncbi.nlm.nih.gov/32020029/)).
- 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](https://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.
- Designed to inhibit Ebola RNA-dependent RNA polymerase (RdRp).
- Already known to inhibit replication of SARS-CoV-1 in mice (middle).
- SARS-CoV-1 RdRp (P0C6X7/R1AB\_CVHSA) and SARS-CoV-2 RdRp (YP\_009725307) are 96% identical (right).

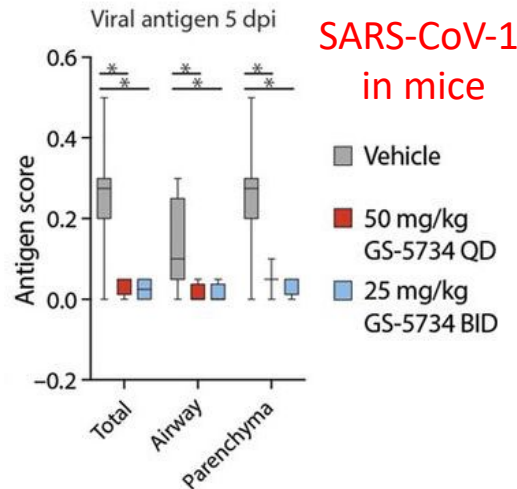
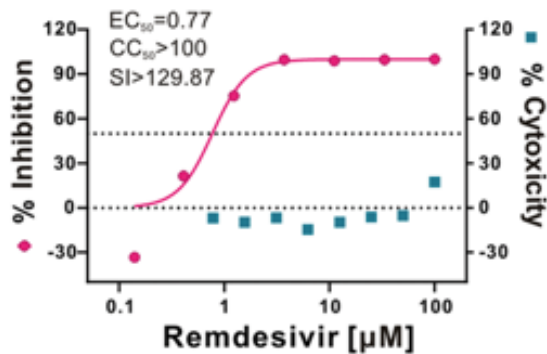
## SARS-CoV-1 query vs SARS-CoV-2

RNA-dependent RNA polymerase [Severe acute respiratory syndrome coronavirus 2]  
Sequence ID: [YP\\_009725307.1](https://www.ncbi.nlm.nih.gov/nuclorf/YP_009725307.1) Length: 932 Number of Matches: 7

Range 1: 1 to 932 [GenPept](#) [Graphics](#) [Next Match](#) [Previous Match](#)

Score	Expect	Method	Identities	Positives	Gaps
1914 bits(4957)	0.0	Compositional matrix adjust.	898/932(96%)	916/932(98%)	0/932(0%)
Query 4370	SADASTPLNRVCGVSAARLTPCGTGTSTDDVVYRAFDIYNKVFAGFAKFLTKCCRFQEKD				4429
Sbjct 1	SADA +PLNRVCGVSAARLTPCGTGTSTDDVVYRAFDIYN+KVAGFAKFLTKCCRFQEKD				60
Query 4430	EEGNLLDSYFVVRHTMSYQHEETIYNLVKDCPAVAVHDFKFRVDDGMVPHISRQRLT				4489
Sbjct 61	E+ NL+DSYFVVRHT MSYQHEETIYNL+KDCPAVA HDFFKER+DGMVPHISRQRLT				120
Query 4490	KYTMADLVYALRHFDGNCIDLKEILVTYNCDDDDYFNKKDWDYFVFNPDILRVYANLGE				4549
Sbjct 121	KYTMADLVYALRHFDGNCIDLKEILVTYNCDDDDYFNKKDWDYFVFNPDILRVYANLGE				180
Query 4550	RVRQSLKTVQFCDAMRDAGIVGVLTLDNQDLGNWYDFGDFVQVAGCGGVIVDSYSSL				4609
Sbjct 181	RVRQSLKTVQFCDAMR+AGIVGVLTLDNQDLGNWYDFGDF+Q PG GVP+VDSYSSL				240
Query 4610	LMPILTLTRALAESHMADLAKPLIKDWLLKYDFTEERLCLFRVYFYWDQVTHPNCIN				4669
Sbjct 241	LMPILTLTRAL AESH+D DL KP IKDWLLKYDFTEERL LFRVYFYWDQVTHPNC+N				300
Query 4670	CLDDRCILHCANFNFLSFTVFPFSTPGPLVRRKIFVDGVPFVVSQYHFRGLVHNVQDN				4729
Sbjct 301	CLDDRCILHCANFNFLSFTVFPFSTPGPLVRRKIFVDGVPFVVSQYHFRGLVHNVQDN				360
Query 4730	LHSSRLSFKELLYAADPAMHAASGNLLDKRRTCFSAALTNNAFQTVKPGNFNDFY				4789
Sbjct 361	LHSSRLSFKELLYAADPAMHAASGNLLDKRRTCFSAALTNNAFQTVKPGNFNDFY				420
Query 4790	DFAVSKGFFKEGSSVELKHFFFAQDGNAAISDYDYRYNLP+MCDIRQLLFVVEVDKYF				4849
Sbjct 421	DFAVSKGFFKEGSSVELKHFFFAQDGNAAISDYDYRYNLP+MCDIRQLLFVVEVDKYF				480
Query 4850	DCYDGGCINANQVIVNMLDKSAGFPFNKWKARLYYDSMSYEDQDALFAYTKRNVIPFIT				4909
Sbjct 481	DCYDGGCINANQVIVNMLDKSAGFPFNKWKARLYYDSMSYEDQDALFAYTKRNVIPFIT				540
Query 4910	QMNLKYAISAKNRARTVAGVSICTMTNRQFHOKLLKSIATRGATVVIQTSKPYGGWHN				4969
Sbjct 541	QMNLKYAISAKNRARTVAGVSICTMTNRQFHOKLLKSIATRGATVVIQTSKPYGGWHN				600
Query 4970	MLKTVSDVEPHLMGWDPKCDRAMPNMLRIMASLVLARKHTCCSLSHRFYRLANECA				5029
Sbjct 601	MLKTVSDVEPHLMGWDPKCDRAMPNMLRIMASLVLARKHTCCSLSHRFYRLANECA				660
Query 5030	QVLSMVMCGGSLYKPGGTSAGDATTAYANSVFNICQAVTANVALLS+TDGNKIADKYV				5089
Sbjct 661	QVLSMVMCGGSLYKPGGTSAGDATTAYANSVFNICQAVTANVALLS+TDGNKIADKYV				720
Query 5090	RNLQHRLYECLYRNRRVD+EV+EFYAYLKRHFMSMILSDDAVVCFNSYASQGLVASIK				5149
Sbjct 721	RNLQHRLYECLYRNRRVD+EV+EFYAYLKRHFMSMILSDDAVVCFNSYASQGLVASIK				780
Query 5150	NFRVLYYQNNVFMSEAKCWTETDLTKGPHFCSQHTMLVKQGGDDVYVLPYDPSRILGA				5209
Sbjct 781	NFRVLYYQNNVFMSEAKCWTETDLTKGPHFCSQHTMLVKQGGDDVYVLPYDPSRILGA				840
Query 5210	GCFVDDIVKTDGTLMIERFVSLAIDAYPLTKHPNQEYADVHLYLQYIRKLDHDLTGHML				5269
Sbjct 841	GCFVDDIVKTDGTLMIERFVSLAIDAYPLTKHPNQEYADVHLYLQYIRKLDHDLTGHML				900
Query 5270	DMYSVMLTNDNTRSYWEPEFYEAMYPHTVQLQ 5301				
Sbjct 901	DMYSVMLTNDNTRSYWEPEFYEAMYPHTVQLQ 932				

## SARS-CoV-2 in human cells



## SARS-CoV-1 in mice

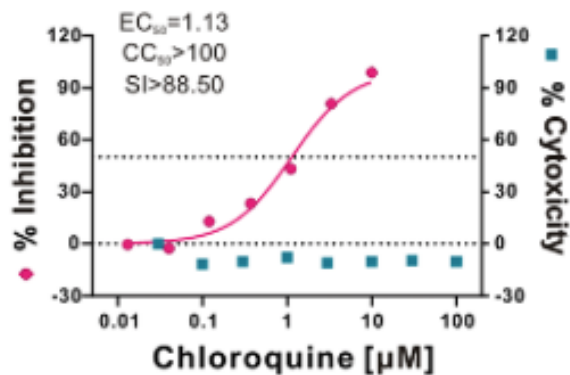
- Vehicle
- 50 mg/kg GS-5734 QD
- 25 mg/kg GS-5734 BID

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

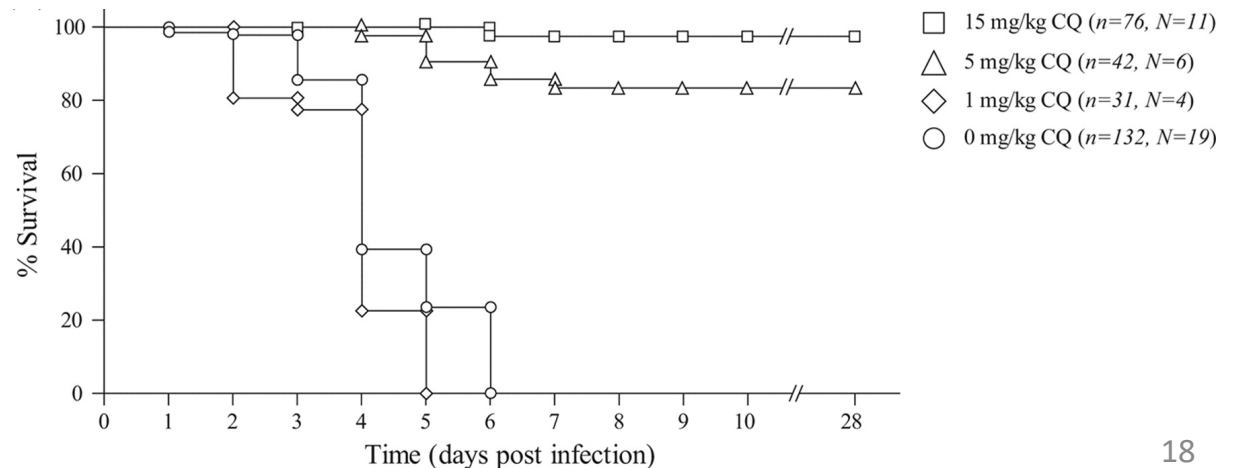
## Chloroquine

- Works against SARS-CoV-2 in human cells, EC<sub>50</sub> = 1130nM (below-left, Pubmed [32020029](#)).
- Works against CoV OC43 in mice (below-right, Pubmed [19506054](#)).
- Reported by Chinese health ministry in early February news briefing to work in patients: “results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus- negative conversion, and shortening the disease course according to the news briefing” but no data shown (Pubmed [32074550](#)).
- Side-effects can be serious, but it has been safely used for malaria prevention: <https://www.drugs.com/mtm/chloroquine.html>
- In prophylactic trials in China and US (<http://www.startribune.com/university-of-minnesota-to-test-three-drugs-for-covid-patients/568766632/>)

SARS-CoV-2 in human cells



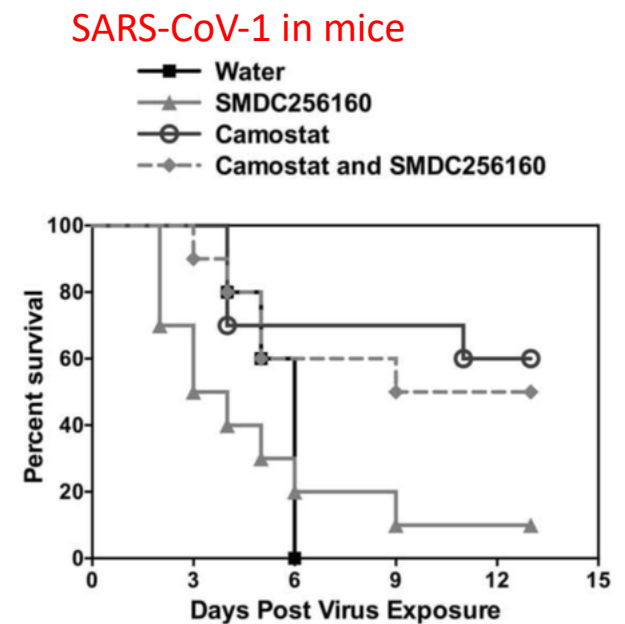
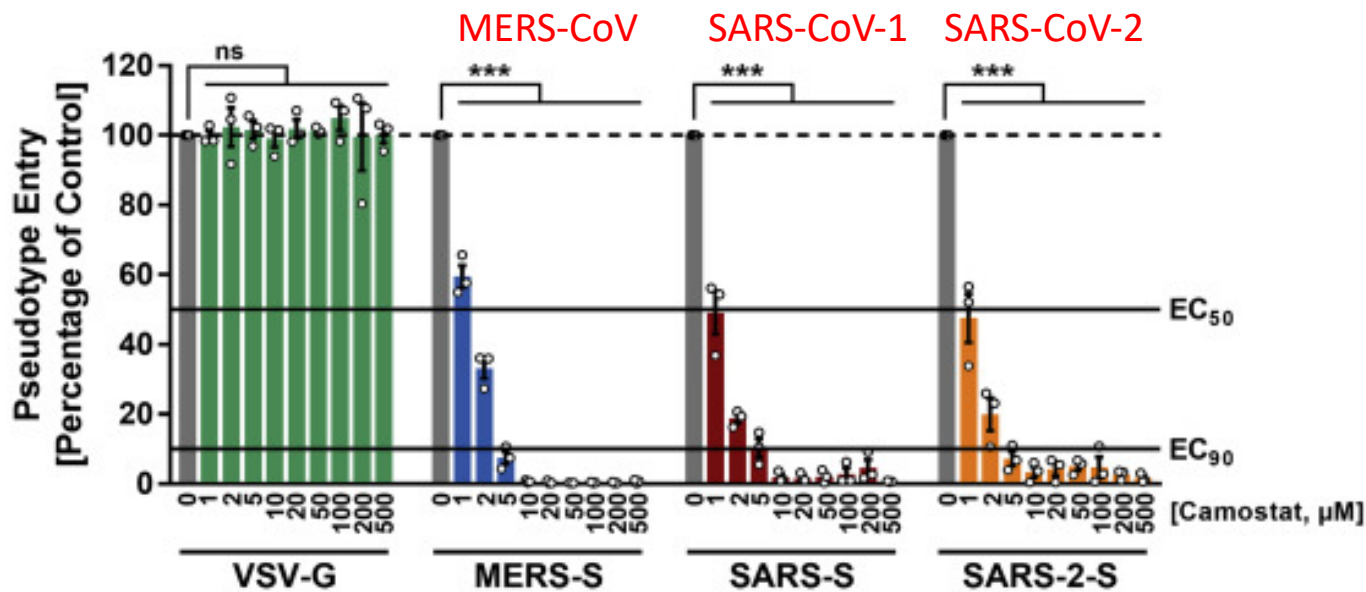
CoV OC43 in mice



# 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 EC<sub>50</sub> = 1000 nM (left, from [doi.org/10.1016/j.cell.2020.02.052](https://doi.org/10.1016/j.cell.2020.02.052))
- Also helps prevent death in mice with SARS-CoV-1 (right, Pubmed [25666761](https://pubmed.ncbi.nlm.nih.gov/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

- Kaletra (HIV protease inhibitor) 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](http://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.
- Death is often from cytokine release syndrome (cytokine storm) treatment: once virus replicates to high levels in the lungs, the large release of cytokines cause multi-organ failure: [www.vox.com/2020/3/12/21176783/coronavirus-covid-19-deaths-china-treatment-cytokine-storm-syndrome](http://www.vox.com/2020/3/12/21176783/coronavirus-covid-19-deaths-china-treatment-cytokine-storm-syndrome)
  - Anti-IL-6 mAb was approved for CRS in COVID-19 by China: [www.reuters.com/article/us-health-coronavirus-china-roche-hldg/china-approves-use-of-roche-drug-in-battle-against-coronavirus-complications-idUSKBN20R0LF](http://www.reuters.com/article/us-health-coronavirus-china-roche-hldg/china-approves-use-of-roche-drug-in-battle-against-coronavirus-complications-idUSKBN20R0LF)
  - 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 SARS and COVID-19 (Pubmed 32129518) ([www.startribune.com/university-of-minnesota-to-test-three-drugs-for-covid-patients/568766632/](http://www.startribune.com/university-of-minnesota-to-test-three-drugs-for-covid-patients/568766632/))
  - This only deals with lung injury secondary to viral replication, not the virus itself.
  - This comes from an old hypothesis (2005) that SARS lethality was due to downregulation of ACE2 ([www.nature.com/articles/nrd1830](http://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 are pretty different 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; this probably doesn't matter either because a virus particle isn't going to care if the cell it's sitting on has 100 or 300 receptor molecules when it's stuck on the surface and has time to swim around ([www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30116-8/fulltext](http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30116-8/fulltext)).
  - I think it's better to concentrate on specific antiviral medications and not worry about the complex ACE2/AT1R pathway.



# 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 (demonstrating again the immense value of that technique), so the SARS-CoV-2 structure can then be easily predicted (<https://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](http://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](http://www.chemistryworld.com/news/rna-vaccines-are-coronavirus-frontrunners/4011326.article)
- Some more summary and speculation here: <https://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 mice. The mice got lung inflammation on challenge, but this could be because they get a ton of virus directly in the lungs, which would not happen in natural exposure. Also, an inactivated MERS-CoV-1 vaccine with a different adjuvant was protective and safe in mice (Pubmed [30658390](https://pubmed.ncbi.nlm.nih.gov/30658390/)).
  - This has been proposed for SARS-CoV-2 (<https://www.nature.com/articles/s41541-020-0170-0>); I hope someone is doing 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. need travel or exposure history)
- CDC created a test requiring a slow RT-PCR reaction on a specific model of machine to be run overnight, not designing the right primers, and not realizing this for a month. This was both strategically (using 30-year-old technology) and tactically (designing wrong primers) incompetent. I would expect most graduate students to do better.
- FDA had stringent rules on testing: 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](http://www.cnn.com/2020/03/12/asia/coronavirus-south-korea-testing-intl-hnk/index.html)), and 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](http://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 (<https://www.aamc.org/news-insights/coronavirus-testing-how-academic-medical-labs-are-stepping-fill-void>)
  - Finally on 3/13 approved rapid Roche test (<https://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.
  - Maybe the surgeon general (Jerome Adams) should say something – where has he been during this crisis?

# 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](http://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 fail

- 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.

## 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 – that's an easy one.
- 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?
- I'll provide some details. I treat hands and objects similarly, and I am pretty strict:
  - To protect yourself, sanitize your hands immediately before eating and immediately after touching things touched by others to avoid getting viruses.
  - To protect others, use clean hands to touch others' things or when handling things to others.
  - Sanitize objects given to you and only pass objects that have passed your own cleanliness test to others. For example, I have my hand sanitizer bottle open and ready to clean my credit card immediately after I get them back from cashiers, before I put it back in my wallet.
  - Sanitize smooth surfaces you are going to touch directly with your hands (e.g. tables and chair edges, places where you set down 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 encountered 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.
  - Sanitization can be done by soap and water (hands) or hand sanitizer (hands or objects) or windex (objects)
  - Finally, if your hands are clean, you can touch your face! But remember to sanitize your hands before you touch other people's stuff.

# Recommendations - activities

- If you are young, the worry is more about transmitting virus to older people than about yourself.
- It is fine to go out, buy essentials, get takeout, if you are responsible about taking precautions against transmission (the strict hygiene steps above). It is also fine to go to your workplace, if you work primarily alone and can avoid large gatherings and can carry out the same hygiene procedures.
- I think it is fine to see select friends and family if you know who is in the room with you, if you are comfortable discussing their hygiene habits, and if you can clean your hands and your belongings before you see them. I have heard some public health professionals with similar views, and others with zero tolerance for human interactions, but I think contact with a small number of people you know who are not sick is acceptable at the current infection rates if you are able to practice strict hygiene.
- I'd suggest not eating prepared salads or sandwiches. There may be no evidence that these are risky, but I prefer my foods cooked anyway.
- 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 breathe 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
- My opinion is it's okay to carry out essential flight plans already made, e.g. for an important family/friend event. Students also need to go home! But due to the many points when exposure from strangers can occur, travel requires high vigilance. 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 airplane trays, seat belts, armrests. Keeping your hands clean before 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). I would make sure the ventilation nozzle is on full blast (it puts out HEPA-filtered air).
- Rules can be adjusted for each person's personal situation, e.g. someone may want to be extremely careful if they live with older people.
- But we all should be more careful than we were before, and big untraceable gatherings that are just for fun and are not promoting healthy habits would be irresponsible.

# No need to worry about supplies

- 50% of people with virus have no symptoms but will become immune just like most infected 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. Home recipes suggest aloe vera gel, but that may be hard to find. You can use glycerol instead; it is a common ingredient in moisturizers and makeup.
- Lin Lab recipe: Mix two parts 95% non-denatured ethanol with 1 part 90-100% glycerol.
  - Use non-denatured ethanol, which lacks toxic additives (that is, avoid bottles with the health hazard logo).
  - Do not use dehydrated/absolute/anhydrous/100%/200-proof ethanol as that has benzene from the purification process.

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