Notes on COVID-19

Part 1: 2020-02-24 to 2020-03-20

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2020-03-20

Sources

The NEJM has a coronavirus index page in which all articles concerning SARS-CoV-2 and Covid-19 are published with open access https://www.nejm.org/coronavirus .

The London School of Hygiene and Tropical Medicine has a page on Covid-19 https://www.lshtm.ac.uk/research/research-action/covid-19

As of course does The Lancet https://www.thelancet.com/coronavirus

And the Journal of the American Medical Association https://jamanetwork.com/journals/jama/pages/coronavirus-alert

And Imperial College London https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/news--wuhan-coronavirus/

The University of Oxford has a page about CoV research and involvement at Oxford http://www.ox.ac.uk/news-and-events/coronavirus-research

The Guardian newspaper https://www.theguardian.com/international , henceforth TheG. It has a daily coronavirus live blog, starting usually just after midnight UTC, as well as a daily UK coronavirus blog, which starts with the day in GB. This is why I am particularly interested in TheG: https://www.theguardian.com/world/2020/mar/20/coronavirus-the-guardians-promise-to-our-readers

And of course there is the Johns Hopkins Uni site for data https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6 which is put together by a team headed by Lauren Gardner

Notes

Since Monday 2020-02-24 until Tuesday 2020-03-03 there has been some fairly good news, as well as some bad. I am guessing that the spread in the Middle East won't be well contained. I think the spread in Italy is more likely to be contained. I have no guesses concerning S. Korea.

[2020-03-20 update. Boy was I wrong about Italy! In contrast, South Korea seems to have done a decent job of suppressing its outbreak.]

My state of North-Rhine Westfalia in Germany seems to have suffered a super-spreading event, a Carnival party in mid-February in Gangelt, in the Heinsberg district, on the Dutch border, west of the Rhine and just east of the Maas, roughly between Maasstricht and Roermond. Patient 1 presented in Düsseldorf with symptoms on February 16th. He was at the Carnival party on February 15th. Since then over 70 people, either present at the event or with contact to now-infected people who were then present, have Covid-19 in NRW. Bielefeld had 4 suspected cases last weekend

showing symptoms, all with such contact, but they all tested negative.

[2020-03-20 update Bielefeld has as of 2020-03-19 57 confirmed cases and 960 people in quarantine, including a music friend who has no symptoms and whose test was negative.]

The London School of Hygiene and Tropical Medicine predicted that the Wuhan outbreak would peak in mid- to late-February https://cmmid.github.io/topics/covid19/current-patterns-transmission/wuhan-early-dynamics.html . In fact, it seems to have peaked on February 17th, according to the "Active Cases" graph at Worldometer https://www.worldometers.info/coronavirus/coronavirus-cases/ So LSHTM got it right. Looking at the Worldometer histogram of daily new cases, it was rising superlinearly until February 4th, then decreased somewhat, with a spike on February 12th (and also 13th) which was caused by the reclassification of cases (previously only lab-confirmed cases were counted; at that date clinically-diagnosed cases without RT-PCR confirmation were also included for the first time). The decrease reached a low point between February 19th and 23rd, and then started increasing superlinearly again, presumably because of the outbreaks in South Korea, Italy and Iran.

[2020-03-20 update. It is still going up in what looks like the usual geometric progression, a month later.]

2020-03-03 The overall figures [2020-03-20: for the Chinese outbreak, not the world figures] are stabilising. Mild verses serious cases were around 80% to 20% for a while; now they are 82% to 18% (2020-03-03).

[2020-03-20 update. This is the good news. Worldwide it is now 95% mild to 5% serious.]

Preliminary guesses at death rate use the simple rule-of-thumb formula (deaths/(deaths+recovered)), which, besides being intuitively compelling, has some proper statistical reasoning behind it (Ghani et al., Am. J. Epidemiology, 2005 https://academic.oup.com/aje/article/162/5/479/82647 It is open-access). The thing it misses is unreported cases. It was hovering about 9% for some days up to 2020-02-25 and is down to 6% on 2020-03-03.

[2020-03-20 update. And this is the bad news. It is back up to 10%.]

The report by Guan et al. (see below) on 1,099 hospitalised patients up to 2020-01-29 (about 14% of the 7,700 or so hospitalised at that time in China) calculates the death rate at 1.4%. The analysis of the ICL MRC Centre Rapport 4 (also below) estimates approximately 1% overall, with 95% confidence in 0.5%-4%. For comparison, the death rate with SARS was thought to be at the time of the outbreak around 2%, but in fact turned out to be near 9%, as I understand it.

The Worldometer site has a variety of useful numbers and graphs https://www.worldometers.info/coronavirus/ . Some trends are immediately discernible if you look at the daily histograms. But I find the daily-rate charts misleading, because they amplify noise. For parameter-of-interest X they are calculated as (yesterday's value of X/the day before's value of X) and so any noise on one day affects the values for two days (that day, and the day after). For example, where X is daily deaths, there was a reclassification of cases of Feb 12, and a jump in deaths on Feb 23. Look at how those two outliers (one artificial, one presumably real) affect the "daily rate" graph. I find it better to "eyeball" the possible values of such basic parameters from the daily totals histograms. For example, if you want to know whether the daily death ratio is going below one, look at the daily-deaths histogram's average slope from what looks to be its peak and see if it looks to be steeper than a 45° decline.

[2020-03-20 update. These were observations on the Chinese figures. Of course, the world figures have overtaken China now. Indeed, there are now more deaths in Italy than there have been in China.]

The MRC Centre for Global Infectious Disease Analysis at Imperial College London is putting out a regular set of Rapports at https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/news--wuhan-coronavirus/ .

Rapport 3, shared with WHO and governments between 2020-02-22 and 2020-02-14 estimated the transmissibility rate: "*on average, each case infected 2.6 (uncertainty range: 1.5-3.5) other people up to 18th January 2020*."

Rapport 4 obtained "*estimates of the overall CFR in all infections (asymptomatic or symptomatic) of approximately 1% (95% confidence interval 0.5%-4%)*."

Rapport 6 "*estimated that about two thirds of COVID-19 cases exported from mainland China have remained undetected worldwide, potentially resulting in multiple chains of as yet undetected human-to-human transmission outside mainland China*"

I suggested in private correspondence on 2020-02-16 that you could probably get the test-results period down to a day. The Guardian (henceforth TheG) live blog said on 2020-02-24 that China is running 14,000 tests a day, with a 10-hour result delivery. So they are there already. Apparently it is still taking countries such as Germany, where I live, somewhat longer. Results from suspected Covid-19 cases in Bielefeld, where I live, on Friday 2020-02-28 took until Saturday afternoon 2020-02-29 to reach the city's emergency task force. (They were negative. But it is understood that there are false negatives.)

[2020-03-20 update. There is a lab near Bielefeld, in Bad Salzuflen, which tests. It still takes 24 hours for results.]

2020-02-25 There is now apparently a serological test as well as "the" nucleic-acid test (there are apparently seven nucleic-acid tests https://www.mdpi.com/1999-4915/12/2/244). There is a tweet from Global Times (a Chinese news agency) on 2020-02-25 at 03:36 GMT on TheG live blog which details preparedness, and it is pretty impressive: daily production of 330,000 sets of protective clothing, 844,000 medical masks, 1.7m nucleic-acid test kits and 350,000 antibody test kits (that is, serological). From what I understand about serology (which is not much), serological tests are generally regarded as being more sensitive.

2020-02-25 A vaccine has been announced in China, developed by Huang Jinhai of Tainjin Uni (tweet on TheG live blog on 2020-02-25 at 06:22). He has himself taken four doses of it and claims to have suffered no side effects, so there is hope. They are looking for partners for trials. Other research on vaccines was reported in TheG on February 1
https://www.theguardian.com/world/2020/feb/01/researchers-make-strides-in-race-to-create-coronavirus-vaccine
Jonathan Quick said in TheG on 2020-03-01 that the US company Moderna has a vaccine ready for human trial https://www.theguardian.com/world/2020/mar/01/the-worst-case-scenario-for-coronavirus-dr-jonathan-quick-q-and-a-laura-spinney

[2020-03-20 update: Moderna is already testing its product on a human. A vaccine produced in Oxford is ready now for animal trials for effectiveness and probably human safety trials in April.

2020-02-25 I recall noting, but now kicking myself that I did not record it, that one really sick 80+

year old in China was given HIV-antiretrovirals along with Tamiflu and recovered within 2 days. The HIV-antiretrovirals are being evaluated in trials in China https://www.theguardian.com/science/2020/feb/20/doctors-hiv-ebola-drugs-coronavirus-cure-covid-19

[2020-03-20 update. However, the HIV-antiretroviral mix didn't work in these trials. Reported 2020-03-18 in NEJM. Link below.]

There are two puzzling cases which have been noted.

One is reported in JAMA (open access) https://jamanetwork.com/journals/jama/fullarticle/2762028 . A cluster of 6 cases in Anyang, 5 with symptoms and 1 asymptomatic, related to each other. The asymptomatic family member had travelled from Wuhan. She took three nucleic-acid tests: negative, then positive, then negative. The reporters think she may have been the carrier (so, a mini-super-spreading event). But that is just a presumption, assuming the first test was a false negative. She could have got it from another family member, with the first test being under the detection threshold. But then the mini-outbreak would remain unexplained.

The other is (at the time supposed to be) an origin of the Italian outbreak, a 38-year-old man who is a researcher at Unilever. He is also a hobby runner, so presumably relatively fit. He was in intensive care last I read about it. [2020-03-20 He survived and was discharged from hospital some days ago, apparently.] People thought he might have caught it from an asymptomatic colleague who had recently been in China, but that colleague tested negative. So the Italians don't know how the runner became ill. Apparently he visited a GP, then the hospital twice, before he was finally admitted to hospital. It was apparently 7 days between his first visit and when he was tested for SARS-CoV-2. Hence the super-spreading event. No one yet knows how he was infected.

[2020-03-20. There are now thought to have been a number of such roughly concurrent events in Italy. “Matthia” is not the only one. The small town of Vò seems to have got through it by testing everyone, finding a few asymptomatic cases, and isolating those. See 2020-03-19.]

On the other hand, with 80,000 cases, having two unexplained is a very tiny proportion.

It has been known since at least early January that there are people who remain asymptomatic. But the WHO and the ECDC advice is - still – [in early March] that infectivity parallels severity of symptoms. These two unexplained cases seem to contradict that advice. But 2 exceptions in 80,000 is not much.

There could well be asymptomatic spreaders; indeed the first German spreader, a visitor from China, was asymptomatic and only started to show symptoms on the flight back (both her and her contacts only exhibited mild symptoms, apparently. The report in the NEJM is referenced below. There is some suggestion that she was not completely asymptomatic – see below from 2020-03-04 – but no further commentary has appeared in the NEJM). But you'll likely pick most of them up in a well-run intervention responding to the first symptomatic case (or the first few) in a population which is not otherwise infected.

[2020-03-20 Which is exactly what seems to have happened in Vò. However, very few places are in that enviable position.]

A few weeks ago [in early February], an epidemiologist in London said there could well be 100,000 infected people out there (at some point when the active cases lay around 20,000 - 40,000). I think the course of the disease, peaking on Feb 17 at just under 60K active cases, and decreasing steadily

since then, belies a suggestion that there are hoards of asymptomatic spreaders out there. On the other hand, the course of the virus seems to be (according to Worldometer): 5 days to symptoms, 6 days to hospitalisation, 7 days to ARDS, and recovery after 10 days in hospital (for those who recover).

[2020-03-20 But see reports suggesting that severe viral pneumonia is a 14-20-day hospital stay]

So recovery is 16 days after symptoms occur. If we extend those initial 5 days to the current advisory boundary of 14 days after exposure, we are left with a cycle of up to 30 days from exposure to recovery. That seems like a reasonable proxy for the course of the disease. Wuhan has been in lockdown for that long, and is still completely dominating the numbers. So it could simply be that the numbers are telling us that the epidemic has run its course in Wuhan and we can't from that alone draw any conclusions about the relative number of asymptomatic spreaders.

[2020-03-20 The epidemic certainly seems to have run its course in Wuhan. No reported new cases in two days. No one seems to be yet making good estimates of asymptomatic spreading, although Hong Kong and Singapore had some guesses at it from their experience of testing arrivals from China]

2020-02-28 Despite observations [at that time] that it is sort of like the 'flu, the virus can also be deadly to (formerly) relatively healthy people without comorbidity, such as Li Wenliang (codiscoverer, died 2020-02-07 at the age of 33) and Liu Zhiming (died 2020-02-18 at age 51). Most types of 'flu affect the upper respiratory tract, whereas CoVID-19 affects the lungs. A/H5N1 is a type of flu which also primarily affects lung function. It has a high mortality rate https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4933299/ The Hong Kong outbreak in 1997 had a morbidity rate of exactly 1/3 (6 deaths in 18 cases) and between November 2014 and April 2015 165 cases were reported to the WHO with 14 deaths, a rate of 8%. Such differences are intuitively plausible. The lungs are organs executing primary bodily functions, like the heart, liver and kidneys. The upper respiratory tract is how air gets to the lungs, but once it gets there then the oxygen-exchange behaves adequately in most cases of 'flu. The oxygen-extraction mechanism of the lung is a primary bodily function and this is where A/H5N1 and SARS-CoV and SARS-Cov-2 all take hold.

I suggested privately on 2020-02-07 that "*It would help, of course, if the Chinese cleaned up their animal markets. I imagine that will happen, but there is no telling how quickly.*" It is happening, and some reports suggest pretty fast: https://www.theguardian.com/environment/2020/feb/25/coronavirus-closures-reveal-vast-scale-of-chinas-secretive-wildlife-farm-industry The government had by that date already shut down nearly 20,000 wildlife farms and is working on a change in the law. But see the 2020-03-01 TheG interview with Jonathan Quick cited above for some scepticism on whether and how this might work.

On 2020-02-28 TheG spoke with Christl Donnelly of ICL http://www.imperial.ac.uk/people/c.donnelly . She conveyed the 1% mortality rate from the MRC Rapport 4. Note this is very different from the rule-of-thumb RoT = (deaths/(deaths+recovered)), which stands at 6% on 2020-03-03, and appears to be slowly decreasing at a rate of 1% every few days (according to Worldometer figures). It follows that Italy and Iran are significantly underreporting. RoT yielded Italy's rate at 37% and Iran's at 26% on 2020-03-01.

[2020-03-20 It is now back up to 10%]

TheG reported on 2020-02-29 that the Shanghai Public Health Clinical Centre had sequenced

SARS-CoV-2 on 5 January. It asked for permission to release the findings. No response. On 12 January, a week later, it released them globally anyway. The institution has now been closed for "rectification". Coupled with this, and the reports that Li Wenliang was arrested by the police and forced to keep quiet after having reported a cluster of patients with SARS-like symptoms in Wuhan at the beginning, the WHO's praise for China's "transparency" seems somewhat clouded. More information about the lack of transparency, and the pursuit of journalists, is at https://www.theguardian.com/world/2020/mar/01/li-zehuajournalist-wouldnt-stay-quiet-covid-19-coronavirus

[2020-03-20 Li Wenliang has been officially pardoned; his "offence" struck from the record and the authorities have apologised to his family https://www.theguardian.com/world/2020/mar/20/chinese-inquiry-exonerates-coronavirus-whistleblower-doctor-li-wenliang]

One more example of why reports of causes of death should not necessarily be taken at face value. From the Global Times, 2020-03-01 at 0347 (is at least GMT+1, since TheG reported it at 0259 GMT) *"Zhong Jinxing, 32, a doctor in South China's Guangxi Zhuang Autonomous Region, passed away on Friday after having worked consecutively for 33 days on the frontline against the #COVID19 epidemic. He died from overwork."* I understand that the transmissibility of overwork is globally very variable. In Silicon Valley, it seems to be in the tens to hundreds. Whereas in France it is nominally 0 (because overwork is illegal and therefore there is none).

As an example of what not to do, it is worthwhile to read Robert Reich's observations on 2020-03-01 on the Trump Administration's current attitudes and measures concerning public health https://www.theguardian.com/world/2020/mar/01/trump-coronavirus-cuts-robert-reich One imagines these might well change in the next few weeks.

[2020-03-20 Indeed so!]

2020-03-03 The New England Journal of Medicine (NEJM) published a study of 1,099 Covid-19 patients on Friday 2020-02-28 https://www.nejm.org/doi/full/10.1056/NEJMoa2002032 The data are from on or before 2020-01-29. I refer to it as Guan et al.

Guan et al. looked at 1,099 hospitalised Covid-19 patients from a total of 7,736 at that time (up to 2020-01-29), so 14.2%. Median age was 47. They defined the primary composite end-point (pcep) of the study to be admission to an ICU, use of mechanical ventilation, or death. 6.1% reached pcep with 5% ICU, 2.3% mech. vent. And 1.4% died. Median incubation period was 4 days, with interquartile range 2 to 7 days. On admission, 43.8% had fever, 67.8% cough, 83.2% lymphcytopenia and 56.4% "ground-glass opacity" on a CT scan. (Nausea/vomiting was rare at 5% and diarrhoea rarer at 3.8%). 23.7% had a coexisting illness (heart disease or CPOS). 877 patients had non-severe illness, and 173 severe. In 8.9%, SARS-CoV-2 was detected (RT-PCR assay) before development of viral pneumonia, or viral pneumonia did not develop.

Median stay in hospital was 12 days. 91.9% were diagnosed with pneumonia, but ARDS only 3.4% and shock 1.1%. Among all patients, the cumulative risk of pcep was 3.6%. Amongst the severe cases, it was 20.6%. Case fatality rate was 1.4%.

Guan et al. mention in discussion that SARS-CoV-2 was detected in the gastrointestinal tract, in saliva and in urine, so there are possible pathways to infection other than through expirated droplets and aerosols. As far as I know, as of 2020-03-03 nobody has as written about such pathways except to say that they must be looked at. The ubiquitous hand-washing and avoid-hand-contact advice obviously addresses such pathways.

Besides this article, the NEJM Coronavirus page has the report from Germany on the first known infection in Germany, originating from a Chinese business colleague who had visited a company for a few days' training https://www.nejm.org/doi/full/10.1056/NEJMc2001468 This case in Germany was reported to be asymptomatic transmission. Science (the weekly magazine/journal of the American Association for the Advancement of Science) reports that the Robert Koch Institute talked to the woman by telephone, and confirms she was not asymptomatic while she was in Germany. The article says that a correction has been submitted to the NEJM, but as of 2020-03-20 it does not seem to have appeared https://www.sciencemag.org/news/2020/02/paper-non-symptomatic-patient-transmitting-coronavirus-wrong

This information was obtained from the University of Oxford page about CoV research and involvement at Oxford http://www.ox.ac.uk/news-and-events/coronavirus-research

2020-03-06 Gabriel Leung, epidemiologist expert on SARS and Covid-19 at the Uni Hong Kong, says that he estimates the fatality rate of Covid-19 to be 1.4% https://www.chinadailyasia.com/article/123521 . Note you can be infected with SARS-CoV-2 without suffering from Covid-19, that is, you can be asymptomatic. During the incubation period, you are asymptomatic by definition (median 5 days, interquartile 2-7 days), but of course then you get the disease. It is not known if you can be infected and not develop Covid-19.

[2020-03-20 It is now. You can. Researchers in Germany studied 126 returnees from Wuhan brought into Frankfurt on a military flight. 115 were symptomless; 114 volunteered to be tested anyway, and there were two asymptomatic positives. One developed some mild signs of infection, the other not. More details below].

It is also – obviously – not known what the infectivity of asymptomatic carriers might be. It can be high for those in the incubation period, as is known from some super-spreading incidents.

2020-03-07 As an editorial in The Lancet said on 2020-03-07, "*This coronavirus is not benign. It kills.*" https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30522-5/fulltext The editorial references a study of 51 patients admitted to the ICU at Wuhan Jin Yintan hospital between late December 2019 and 2020-01-26, from 710 patients with confirmed SARS-CoV-2 pneumonia https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30079-5/fulltext . 32 patients (61.5%) had died at 28 days (primary end point). For non-survivors, time from admission to death was median 7 days, interquartile range 3-11 days. And, "*Most patients had organ function damage*." The editorial adds "*The political response to the epidemic should therefore reflect the national security threat that SARS-CoV-2 represents.*"

2020-03-07 The basic reproduction number R_0 seems to be somewhat larger than 2 (see an estimate from Anderson et alia below of 2.5, and one from Remuzzi & Remuzzi from the Italian outbreak of 276 to 3.25). The secondary attack rate (SAR) has been estimated for different types of social gatherings. For events where people come together in close proximity for some hours with at least one carrier, it has been estimated by authors at the LSHTM, Liu, Eggo and Kucharski, on 2020-02-27 to be 35%, with the 95% Confidence Interval to be 27%-44% https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30462-1/fulltext .

2020-03-07 Excellent article (in French) giving some grounds for optimism: https://theconversation.com/dix-informations-rassurantes-a-propos-du-coronavirus-132940

2020-03-09 Anderson, Heesterbeek, Klinkenberg and Hollinsworth write in the Lancet on country-based mitigation measures and how these might/will affect mitigation https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30567-5/fulltext . They talk of

an R_0 of 2.5, and suggest this leads to about 60% of the population being infected. The serial interval they take to be 4.4 to 7.5 days . Best current estimate for CFR is 0.3%-1% (for Influenza A it is 0.1%), but there are no large-scale serology studies yet that can say what proportion of infected people are asymptomatic, and this of course affects CFR.
They take the incubation period to be 5-6 days, and, with a similar serial interval, they say there could be considerable presymptomatic infectiousness. They cite a study of 17 Covid-19 patients in which peal viraemia was at the end of the incubation period, which suggests subjects might well be infectious for 1-2 days before symptoms appear. They cite ECDC data "*suggest[ing] that about 80% of people with COVID-19 have mild or asymptomatic disease, 14% have severe disease, and 6% are critically ill, implying that symptom-based control is unlikely to be sufficient unless these cases are only lightly infectious.*" They say that the duration of the infectious period appears long, perhaps up to 10 days after the incubation period. And they warn against overinterpreting super-spreading events, since these are "*a routine feature of all infectious diseases.*"

There follows an insightful discussion on the possible effectiveness of various mitigation measures and what social conditions will help or hinder the measures.

2020-03-10 A study on the incubation period from Johns Hopkins, U. Mass. Amherst, and LMU: https://annals.org/aim/fullarticle/2762808/incubation-period-coronavirus-disease-2019-covid-19-from-publicly-reported Median is 5.1 days; 14 days is 99% confidence. "*Results: There were 181 confirmed cases with identifiable exposure and symptom onset windows to estimate the incubation period of COVID-19. The median incubation period was estimated to be 5.1 days (95% CI, 4.5 to 5.8 days), and 97.5% of those who develop symptoms will do so within 11.5 days (CI, 8.2 to 15.6 days) of infection. These estimates imply that, under conservative assumptions, 101 out of every 10 000 cases (99th percentile, 482) will develop symptoms after 14 days of active monitoring or quarantine.*"

2020-03-10 Remdesivir is on trials in China, and has shown effectiveness against SARS and MERS in animal trials, "*particularly when it is given soon after symptoms appear. It has also shown promise when used against a wider variety of coronaviruses, including those that cause the common cold, and others that infect bats and pigs. The same replication process occurs in all coronaviruses, raising hope that if the drug works on one, it will work on all.*" TheG report: https://www.theguardian.com/world/2020/mar/10/hopes-rise-over-experimental-drugs-effectiveness-against-coronavirus

2020-03-11 Zhou et al. give the first cohort study of the clinical course and risk factors for mortality in inpatients in Wuhan https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30566-3/fulltext

Chinazzi et al consider how restrictions on travel affect the spread of disease, published 2020-03-06 in Science https://science.sciencemag.org/content/sci/early/2020/03/05/science.aba9757.full.pdf "*The travel quarantine of Wuhan delayed the overall epidemic progression by only 3 to 5 days in Mainland China, but has a more marked effect at the international scale, where case importations were reduced by nearly 80% until mid February. Modeling results also indicate that sustained 90% travel restrictions to and from Mainland China only modestly affect the epidemic trajectory unless combined with a 50% or higher reduction of transmission in the community.*"

Ganyani et al attempt to estimate the generation interval from data from Singapore, and Tianjin https://www.medrxiv.org/content/10.1101/2020.03.05.20031815v1 , posted on 2020-03-08. They conclude that the proportion of transmission from pre-symptomatic individuals was 48% in Singapore and 62% in Tianjin. This is bad news. The paper has not yet been peer-reviewed, but it has been noted in TheG: https://www.theguardian.com/science/2020/mar/12/coronavirus-most-

infections-spread-by-people-yet-to-show-symptoms-scientists

2020-03-12 Soap is very good at disassembling coronaviruses, explains a chemist. https://www.theguardian.com/commentisfree/2020/mar/12/science-soap-kills-coronavirus-alcohol-based-disinfectants (I say "disassembling" rather than "killing" because a virus is not really alive in any sense. The soap breaks up the bilipid layer in the virus.)

2020-03-12 Philip Ball interviews Roy Anderson, whose article in The Lancet on mitigation was published last week https://www.theguardian.com/commentisfree/2020/mar/12/britain-containing-covid-19-countries-hong-kong-singapore .

2020-03-12 Remuzzi and Remuzzi on Italy coping (or not coping) with Covid-91 https://www.thelancet.com/pb-assets/Lancet/pdfs/S0140673620306279.pdf They say Italy has 5200 beds in ICUs. Of those, 1028 were devoted to Covid-19 patients on 2020-03-11. Spahn has said that Germany has 28,000 such beds (no ref). R&R fit an exponential curve to the infections: "*The number of patients who are infected has been published daily since Feb 21, 2020. It is possible to fit the available data for the number of patients who are actively infected into an exponential model, as reported in figure 1A. The value of the exponent can be computed as r=0·225 (1 per day) and is consistent with the number of infected patients reported by the Italian Health Ministry. The consistency between the exponential prediction and the reported data is very close up until day 17.*" They then look at data available from the China outbreak (they suggest a social similarity between the Hubei provincial outbreak and Italy, but the appropriate data are not available from the province alone) and identify a similar r. This enables them to predict when the outbreak in Italy will peak, and what resources will be needed in ICUs. Answer: likely more than there are. They are calculating a different basic reproduction number from that in other studies: "*On the basis of the exponential curve prediction, and the assumption that the duration of infection ranges from 15 to 20 days, it is possible to calculate that the basic reproduction number ranges from 2·76 to 3·25. This number is similar to that reported for the initial phase of the infection outbreak in the city of Wuhan, China and slightly higher than 2·2, as reported by Li and colleagues in a more recent report.*"

2020-03-12 Baud et alia calculate mortality rates as 5·6% (95% CI 5·4–5·8) for China and 15·2% (12·5–17·9) outside of China, including deaths up to 2020-03-01 https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30195-X/fulltext

2020-03-14 On Feb 18, German doctors reported on a collection of 126 travellers, predominantly German, brought to Frankfurt on a German Air Force aircraft from Wuhan. All who were asymptomatic were offered testing for SARS-CoV-2, and all but one, namely 114 people, took the opportunity. Two tested positive, and were retested (also positive). A separate test determined their "potential infectivity". Then they went to hospital. "*After a thorough evaluation in the hospital ward, a faint rash and minimal pharyngitis were observed in one patient. Both patients remained well and afebrile 7 days after admission*." So there we have it. It is possible to carry the virus, be infective, and asymptomatic. Of course, that does not necessarily mean that there are many such people. But judging from this sample, 2 in 126 people can be that way: rounding, that is 2%. So even if everyone with contact to a symptomatic person, or showing symptoms, self-isolates, those measures are not enough to prevent infection spreading. I haven't done the math, but they might be enough to prevent infection spreading rapidly enough to overwhelm health-care systems. This does presume that persistently-asymptomatic people are infectious. But there were no results reported in this short note on infectivity or virus shedding https://www.nejm.org/doi/full/10.1056/NEJMc2001899 .

2020-03-14 French health ministry advises not to use anti-inflammatory ibuprofen against Covid-19

symptoms, because anti-inflammatories generally inhibit the immune system and you generally want to strengthen it https://www.theguardian.com/world/2020/mar/14/anti-inflammatory-drugs-may-aggravate-coronavirus-infection

[2020-03-20 On 2020-03-17 the WHO also warned against it, but on 2020-03-19 they took their warning back and said there was no evidence for negative consequences with Covid-19.]

2020-03-14 Talking about fake news, there was a WhatsApp chain voicemail (which was forwarded to me for an opinion) saying somebody at the Uni Vienna had discovered this, and this is why they are having problems in Italy at the moment. Half right that various organisations and people thought it might be a problem, but completely wrong that it has anything to do with Uni Vienna Medicine, and disgustingly misleading in its portrayal of why Italy has problems. Lombardy has problems because one of the most capable public health systems in the world, as adduced by previous international evaluations, is overwhelmed, as explained clearly by Remuzzi and Remuzzi (see above) in The Lancet on March 12. Anecdotes say health care workers are having to triage to see who gets the kit; this is consistent with Remuzzi & Remuzzi's estimates. [2020-03-20 These are no longer anecdotes. Published papers and opinions have cited it, in the sources here named.] The widely-read German newspaper die Welt has exposed this chain message for what it is, namely highly misleading: https://www.welt.de/wissenschaft/article206555049/Ibuprofen-und-Corona-Ist-das-Schmerzmittel-gefaehrlich-fuer-Infizierte.html

2020-03-15. A particularly good argument from Dr. Adam Visser, head of critical care at Toowoomba Hospital in regional Queensland, published in TheG live blog on this date at 0244 UTC https://www.theguardian.com/world/live/2020/mar/15/coronavirus-latest-updates-trump-tests-negative-as-spain-orders-nationwide-lockdown-uk-us-australia-italy-europe-global-economy

> *I'm an intensive care specialist in a small city.*
>
> *Coronavirus isn't just like the flu, but it's only really very dangerous to the elderly or the already unwell. Quite a lot of people in their 80s will die, but most of the rest of us will probably be OK.*
>
> *If you're in your 70s and you get Coronavirus, you've got a really good chance of survival. If I've got a bed for you.*
>
> *If you're in your 60s and you have a heart attack, you've got a really good chance of survival. If I've got a bed for you.*
>
> *If you're in your 50s and need bowel cancer surgery, you've got a really good chance of survival. If I've got a bed for you.*
>
> *If you're in your 40s and have a bad car accident, you've got a really good chance of survival. If I've got a bed for you.*
>
> *If you're in your 30s and have terrible pre-eclampsia as a complication of pregnancy, you've got a really good chance of survival. If I've got a bed for you.*
>
> *If you're in your 20s and have a bad reaction to a party drug, you've got a really good chance of survival. If I've got a bed for you.*
>
> *I have 7 beds equipped with life support machines. We have a plan to increase to about 25. Getting more isn't a matter or more equipment or more money, that bit is easy. There are not enough skilled staff, even if we all work double shifts every day for six months (and we*

probably will).

If 50% of my city gets infected, that's 75,000 people. If 5% of them need life support (which is the estimate), that's 3750 people. For 25 beds.

And then I might not have a bed for you.

So it's up to you to flatten the curve. Wash your hands. Stay home.

2020-03-15 Robert Reich's damning account of the USA's lack of attention to public goods such as public health https://www.theguardian.com/commentisfree/2020/mar/15/america-public-health-system-coronavirus-trump

2020-03-15 Yascha Mounk on social distancing: it is the right thing to do, and it demonstrably worked in the Spanish Flue pandemic of 1918: https://www.theatlantic.com/ideas/archive/2020/03/coronavirus-cancel-everything/607675/

2020-03-15 John Naughton, poignant as usual, on the damage that fake news about the virus and its associated illness can do: https://www.theguardian.com/commentisfree/2020/mar/14/fake-news-about-covid-19-can-be-as-dangerous-as-the-virus Naughton had the pointer to Mounk (above).

On 2020-03-06 Nature published a short news article on features of SARS-CoV-2, namely how it binds, or might bind, to cells. The spike protein on the virus might have a site that is activated by a host-cell enzyme called furin. Furin is not only found in lungs, but in liver and small intestine, which would enable the virus to invade multiple organs, and might account for the multiple organ failure seen in many severe cases of Covid-19. SARS-CoV and other related viruses don't have furin activation sites. There is another host-cell receptor, known as angiotensin-converting enzyme 2 (ACE2), to which SARS-CoV-2 binds "ten times more tightly" than SARS-CoV. https://www.nature.com/articles/d41586-020-00660-x Also a reference from Naughton.

2020-03-15 William Hanage of Harvard encapsulates many thinking people's thoughts about what we have heard [2020-03-10 up to that point. The UK strategy has now changed] of the UK strategy https://www.theguardian.com/commentisfree/2020/mar/15/epidemiologist-britain-herd-immunity-coronavirus-covid-19 It is very helpful to have this said by an eminent professional. My view is that we have a moral responsibility to keep death and severe discomfort as low as possible, and this moral responsibility is inherited by our governments. What the UK government has said in public sounds rather more like triage – but triage is something you do when you have to. It is surely not something on which a government can base policy. What's wrong with going the South-Korea/Singapore/Hong Kong/Taiwan route of testing, tracing and separating, which has manifestly worked out as intended?

2020-03-18 Favipiravir, manufactured by a subsidiary of Fujifilm, is in a trial in China, in Shenzen, and appears to be effective in treating those with Covid-19 https://www.theguardian.com/world/2020/mar/18/japanese-flu-drug-clearly-effective-in-treating-coronavirus-says-china People treated with it tested SARS-CoV-2-negative after 4 days, whereas 11 days was the median otherwise. Improvements in lung condition were detected by X-ray in 91% of the favipiravir-takers, whereas only in 62% of others.

2020-03-18 There is no better comment – there can be no better comment – on the UK's attitude to Covid-19 than this …… despairing cry? ….. from Richard Horton, editor of The Lancet, one of the top three venues for medical information https://www.theguardian.com/commentisfree/2020/mar/18/coronavirus-uk-expert-advice-wrong I

have been reading The Lancet's articles, along with those of JAMA and NEJM for many weeks now. I am not an epidemiologist but I can read and understand this kind of statistical science. I wonder only that Britain's government has been so slow on the uptake, given that LSHTM CCMID and IC MRC GIDA, amongst the world's most expert organisations in the subject, are British.

2020-03-18 An NEJM article reports the results of a controlled trial of lopinavir-ritonavir in a 4:1 mix on adult patients with severe Covid-19. Primary end point was time to clinical improvement. There was no benefit found over standard care. More's the pity.
https://www.nejm.org/doi/full/10.1056/NEJMoa2001282

2020-03-17 US NIAID and CDC and others have examined the stability of three coronaviruses, including SARS-CoV-2 and SARS-CoV-1, in aerosols and fomites. The two SARS-CoV viruses were comparable in stability. They remained viable in aerosols for 3 hours. Viable virus but much reduced was found after 72 hours on plastic and 48 hours on stainless steel. On copper, no viable SARS- CoV-2 was found after 4 hours (for SARS-CoV-1 after 8 hours) and on cardboard after 24 hours (for SARS-CoV-1 after 8 hours). https://www.nejm.org/doi/full/10.1056/NEJMc2004973

2020-03-18 Lisa Rosenbaum discusses the ethical dilemmas faced by doctors in Italy concerning who shall get mechanical ventilation and who not. Apparently it takes 15-20 days of ventilation until recovery (if recovery is effected). That is a big ask for old patients. Ethics committees have been convened and have reported (in the references). A key element is to separate the people performing triage from those performing primary care. Altogether a thoroughly disturbing article. A moral which emerges is to level with people and not to try to hide things.
https://www.nejm.org/doi/full/10.1056/NEJMp2005492

2020-03-17 A useful infographic showing the current horrifying progression of Covid-19 in Italy up to March 14th https://jamanetwork.com/journals/jama/fullarticle/2763401

2020-03-19 The small italian town of Vò in the Veneto, one of the original spots for Covid-19 outbreak, tested everyone, found 6 asymptomatic carries of SARS-CoV-2, performed isolation, and now claims to be free of the disease https://www.theguardian.com/world/2020/mar/18/scientists-say-mass-tests-in-italian-town-have-halted-covid-19

2020-03-20 Oxford university researchers have developed a vaccine which will start animal tests for effectiveness next week and maybe safety tests on people in April
https://www.theguardian.com/society/2020/mar/19/uk-drive-develop-coronavirus-vaccine-science

2020-03-19 On 2020-03-16 the Covid-19 response team at Imperial College published an extensive investigation into the effectiveness of “non-pharmaceutical interventions” in the Covid-19 epidemic, for example mitigation and suppression. They use a previously published micromodelling technique. This is said to be the study on which Public Health England and the HMG are relying.
https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf