Notes on COVID-19

Part 6: 2020-05-01 to 2020-05-11

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2020-05-11

2020-05-02 Jones et al at the Charité Institute of Virology have released a study of viral loads in Covid-19 patients of various ages.
https://zoonosen.charite.de/fileadmin/user_upload/microsites/m_cc05/virologie-ccm/dateien_upload/Weitere_Dateien/analysis-of-SARS-CoV-2-viral-load-by-patient-age.pdf
"*Analysis of variance of viral loads in patients of different age categories found no significant difference between any pair of age categories including children. In particular, these data indicate that viral loads in the very young do not differ significantly from those of adults. ..... Children may be as infectious as adults.*" They advise caution concerning an unlimited reopening of schools and kindergartens.

This result contrasts with the case of the boy who caught Covid-19 at Les Contamines Montjoie and did not pass it on to any of his 170 close contacts, reported in Notes Part 3 on 2020-04-21.
https://www.thelancet.com/lancet/article/s0140-6736(20)31100-4
It also throws some doubt on the optimistic view in The Economist that schools could be opened up, since (they suggested) children are less prone to catching and passing on the disease https://www.economist.com/leaders/2020/04/30/when-easing-lockdowns-governments-should-open-schools-first Jones et al point out that, if infectivity correlates with viral load, it is not the case that children as less infectious; they can have the same (distribution) of viral load as anyone else.

2020-05-02 A pretty grim view from GB. A third of Covid-19 patients admitted to hospital die. https://www.bmj.com/content/369/bmj.m1794 , referring to preprint by Docherty et al at https://www.medrxiv.org/content/10.1101/2020.04.23.20076042v1 Patients were classified using the ISARIC WHO clinical characterisation protocol.

2020-05-03 Bill Gates in The Economist on 2020-04-23 on what happens next
https://www.economist.com/by-invitation/2020/04/23/bill-gates-on-how-to-fight-future-pandemics

2020-05-04 Some things don't get put on hold. There has been an increasing number of attempted cyberattacks against researchers and institutions working on vaccines for SARS-CoV-2. They are presumed to come from nation-states, and NCSC has been helped organisations protect themselves https://www.theguardian.com/world/2020/may/03/hostile-states-trying-to-steal-coronavirus-research-says-uk-agency . GCHQ now has "access ... to" and "oversight [of]" the HNS IT network. And there is a Five-Eyes document saying that China silenced doctors who "spoke out" about the early emergence of the disease, destroyed evidence of it in laboratories, and refused to provide live samples to "international scientists" working on a vaccine. But I think we have known much of that already for a couple of months. Li Wenliang was arrested and told not to spread his concerns about the new-pneumonia cases he had seen, and the laboratory which sequenced the genome was not allowed to distribute its findings, but did so anyway a week later. This was reported in TheG on 2020-02-29 and appeared in my Notes Part 1.

2020-05-04 Devi Sridhar proposes eight "lessons" we can learn from East Asian countries on how to deal with Covid-19 https://www.theguardian.com/commentisfree/2020/may/04/eight-lessons-controlling-coronavirus-east-asian-nations-pandemic-public-health First is "test, trace, isolate", which she points out is a complex social process. I have noted that Drosten and Fraser both think

eletronic aids are necessary. Second is protect health and social care workers. Third is constant surveillance to identify hotspots. Fourth is monitoring borders to detect imported cases. Fifth, clear and honest public communication about public policy. Sixth is recognising that an exit strategy will involve some persistent measures and permanent change of behaviour. Seventh is that lockdowns are not a solution; they can be used to buy time, but are "costly and crude" and should be instituted "sparingly". Eighth is that all of the above are short-term responses while science progresses. I buy the first four. Concerning the fifth, that lesson has surely not been practiced by all "East Asian nations". I am not sure that sixth, seventh and eighth are "lessons" – they are more or less obvious to all nations who have been talking about it.

2020-05-04 The paper of the studies of Hendrick Streeck and Gunther Hartmann in Gangelt in the district of Heinsberg, where the first German superspreading even occurred in mid-February, has been published as preprint
https://www.ukbonn.de/C12582D3002FD21D/vwLookupDownloads/Streeck_et_al_Infection_fatality_rate_of_SARS_CoV_2_infection2.pdf/%24FILE/Streeck_et_al_Infection_fatality_rate_of_SARS_CoV_2_infection2.pdf

2020-05-04 The entire collection of US National Academies' Rapid Expert Consultations on Covid-19 up to April 8 are now available without cost via https://www.nap.edu/catalog/25784/rapid-expert-consultations-on-the-covid-19-pandemic-march-14

2020-05-05 A man in a northern Paris suburb treated for pneumonia on 27 December had Covid-19. He had not travelled; his two children had the disease, but his wife not. The virus was circulating a lot earlier than previously thought. https://www.theguardian.com/world/2020/may/04/french-hospital-discovers-covid-19-case-december-retested

2020-05-05 A key figure from Streeck and Hartmann's Gangelt study is that one in five infected people were asymptomatic. They found that 15.5% of those they tested had been or were infected, and thereby calculated an IFR of 0.36% (95% CI 0.29% to 0.45%). Inferences about the general number of infected people in Germany are probably not apt from this singular superspreading event (even though TheG article referenced below attempts to do this), but comparisons between number of infected people and number of officially reported "cases" are. The officially reported "cases" were 3.1% of the population (Streeck et al). So they found 5 times the prevalence. Also, secondary infection rates within households increased to 43.6% for a two-person household, 35.5% in a three-person household, and 18.3% in a four-person household. Concerns about the serological test they used seem to have been misplaced. It is an ELISA test of over 99% specificity, and in a population with such a high percentage of positives that is good enough. Also, it is cross-reactive only with SARS-CoV-1 amongst the human coronaviruses. It was provided by Euroimmun of Lübeck, and has been validated by Charité Berlin and Erasmus Rotterdam.
https://www.theguardian.com/world/2020/may/04/german-covid-19-cases-may-be-10-times-higher-than-official-figures
Given that Germany is only testing people who are symptomatic and are either in a key profession (personal care of some sort) or have had contact with a known case, those one in five asymptomatics will ensure the virus continues to circulate in daily life. Physical distancing and public mask-wearing indoors will continue to be necessary.

2020-05-05 The Royal Society DELVE initiative has published a report supporting the use of face masks by the public in public areas. It seems to be a good summary of something which seems obvious to me (and to them): Asymptomatic and presymptomatic infected persons can be infectious; respiratory droplets from infected persons are a major transmission mode; and a face masks reduces droplet dispersal from the person wearing it. Those are their "key points" https://rs-delve.github.io/reports/2020/05/04/face-masks-for-the-general-public.html In other words, it doesn't

protect you, it protects everyone else from you. The full report is a lot longer. According to TheG its recommendations are controversial https://www.theguardian.com/world/2020/may/04/scientists-disagree-over-face-masks-effect-on-covid-19 I am tempted to say the controversy is contrived. I don't like wearing a mask – when I get off my bicycle and put one on to go into the store, my glasses steam up and I can't see what I am buying. So I have to take them off and then I really can't see what I am buying. Also, the lack of facial cues suppresses the banter with the store personnel. But I am really glad everyone (else) is wearing one and, if wearing one myself is the price of that, I am more than happy to do so.

2020-05-05 Devi Sridhar makes many of the points about models/simulations and their assurance and use which have been discussed amongst informatics and system-safety colleagues in private and in the SCSC WG. https://www.bmj.com/content/369/bmj.m1567

2020-05-05 David Smith and Lang Moore have a good introduction to the SIR model on the Mathematical Association of America WWW site. It is at the level of first-semester differential calculus. They also include computational examples which may be worked with Maple, Mathematica or Matlab, but the theoretical material doesn't use these https://www.maa.org/press/periodicals/loci/joma/the-sir-model-for-spread-of-disease-introduction

2020-05-06 A benchmark. Here are numbers from JHU Dashboard on May 1 sometime during the day. Countries are identified by ISO-3166-1 Alpha-2 code.

Country	Deaths	Confirmed cases	CFR
US	65,068	1,103,781	5.9%
ES	24,543	213,435	11.5%
IT	28,236	207,428	13.6%
GB	27,583	178,685	15.4%
FR	24,628	167,305	14.7%
DE	6,736	164,077	4.1%
BE	7,703	49,032	15.7%
NL	4,909	39,989	12.2%
CH	1,754	29,705	5.9%
PT	1,007	25,351	4,0%
SE	2,653	21,520	12,3%
IE	1,265	20,833	6,0%
AT	589	15,531	3.8%
PL	651	13,105	5.0%
DK	460	9,509	4.8%
NO	210	7,783	2.7%
FI	218	5,051	4.3%
LU	92	3,802	2.4%
IS	10	1,798	0.56%

The wide variety of outcomes amongst superficially similar societies with superficially similar understanding of public health and policy (except for US and possibly IS) is astonishing to me. Obviously, CFR is dependent on the definition of “case” and differences have been noted, most obviously whether care-home deaths are tested and/or counted. There is a plausible case to be made that IS shows most clearly the value of the WHO's recommendation to test, isolate and trace. There has been pervasive testing in IS, with government action supported by local biotechnology company deCODE Genetics.

2020-05-06 Figures for Bielefeld since 2020-04-26

Date	Total	Diff(=new)	Ill	Recovered	Died
2020-04-25	358	8	101	254	3
2020-04-26	360	2	103	254	3
2020-04-27	370	10	112	255	3
2020-04-28	373	3	69	301	3
2020-04-29	375	2	71	301	3
2020-04-30	375	0	60	312	3
2020-05-01	379	4	64	312	3
2020-05-02	379	0	63	313	3
2020-05-03	379	0	63	313	3
2020-05-04	379	0	61	315	3
2020-05-05	379	0	54	322	3

This is good news to those of us who live here. Why the big jump on 2020-04-27? That was Monday, and I suspect it is because of notifications being delayed over the weekend. This didn't happen on the next weekend because there were no new cases to notify. If the Heinsberg-study proportions hold for Bielefeld, we would expect the 379 cases to be the 4/5 who are symptomatic and there to be about 95 asymptomatic carriers still circulating, in a population of around 333,000. With only 9 new cases in 10 days, the distancing measures seem to be doing their job pretty well.

2020-05-06 Somehow I have omitted to reference the results of the Icelandic study, published in the NEJM on April 14th. https://www.nejm.org/doi/full/10.1056/NEJMoa2006100 Iceland is interesting, not only because of the government testing programs of symptomatic and high-risk individuals, similar to those of other countries such as Germany, but also because of the random population testing program being carried out by deCODE Genetics in concert with the health authorities. I noted about that Iceland is coming out with a very low CFR.

2020-05-06 Curtis et al (including Tedros Ghebreyesus, WHO DG) suggest considering BCG vaccination to mitigate Covid-19, in The Lancet on 2020-04-30 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31025-4/fulltext The reason is that "*In addition to its specific effect against tuberculosis, the BCG vaccine has beneficial nonspecific (off-target) effects on the immune system that protect against a wide range of other infections and are used routinely to treat bladder cancer.*" It must be done, however, in RCT. The authors cite possibly-comparable cases in which BCG helped.

2020-05-07 Lipsitch et al propose in The Lancet on 2020-05-06 that antiviral therapies which have shown little or no effect in treatment of severe Covid-19 might nevertheless help during early-stage mild disease to inhibit viral replication and thus progression to more severe disease when this occurs, for there is indication that maximal viral load occurs near to onset of symptoms. They cite analogies from treatment of influenza. They urge RCTs of treatments for mild Covid-19, say lopanivir-ritonavir, to see if this is so https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30372-8/fulltext

2020-05-07 Sweden's Johan Giesecke justifies that country's approach in The Lancet on 2020-05-05 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31035-7/fulltext He suggests that a “hard lockdown” neither protects people in care homes (whom it was designed to protect) nor decreases mortality from Covid-19. He cites the UK as evidence. But the German experience suggests distancing does protect people in care homes somewhat. It is also surely obvious that physical distancing measures and reducing contact hinders the disease spreading and if you have lower prevalence of disease you have lower mortality from it, all other things being equal, so it is hard to see how the second assertion might follow. It turns out he thinks everyone is going to be exposed to SARS-CoV-2 and most will become infected anyway, because Covid-19 is being spread largely by asymptomatic young people to each other. He thinks lockdown may dampen such spread but it is futile to try to avoid it. He says the “task” is to give optimal care to sufferers.

Well, if optimal care is the “task” then that is why the UK went into lockdown; amongst other things to avoid the Northern-Italian situation of massively overwhelmed health care services, so that is an argument for lockdown rather than against it, where it is needed. If Sweden's health services are not overwhelmed then they are fortunate (as well as prescient if it is because of good preparation for a pandemic). As for disease prevalence, he says that PCR testing and some “straightforward assumptions” indicate that half a million people in Stockholm county, representing 20%-25% of the population, have already been infected. He cites a personal communication from a colleague at the national health agency for this figure. It would be nice to see some solid evidence of this. If that turns out to be so, then Stockholm county is one-third of the way toward “herd immunity”. Still a long way to go.

But there is another reason besides avoiding overwhelming health services to slow down transmission of the disease as much as possible. People are learning how to treat the disease, and that is a matter of trying things (for which you need relatively relaxed rather than overwhelmed health services), writing up what works (and what doesn't work) and disseminating it, having others read it and try it, and so on. Like the write-up by Gross et al of a simple urine test to evaluate those Covid-19 patients with capillary leak syndrome and thereby at risk of later needing admission to ICU https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31041-2/fulltext
Like RCTs of this or that, such as the remdesivir trials, and the early-stage antiviral studies suggested by Lipsitch et al above. It takes time to build this experience and knowledge. Disease mortality does not stand still. It goes down, as people learn about the disease progression and what works at various stages, thereby saving people they would otherwise lose. Radical distancing, as in lockdown, gives health services worldwide that more time to build standards of care that will end up saving lives and improving outcomes.

2020-05-07 Paul Taylor has an article describing the history of the British modelling from LSHTM CMMID and Imperial MRC GIDA in the London Review of Books 42(9) 2020-05-07 https://www.lrb.co.uk/the-paper/v42/n09/paul-taylor/susceptible-infectious-recovered The PHSTM SIR model is described in some lay-technical detail, but the Imperial model not. He relates the UK change from a “mitigation” strategy to a “suppression” strategy, but I am not sure I understand the difference – there are infection-control strategies for a disease that cannot be cured, many of which come with have social disadvantages, and you can apply more of them or fewer of them. “More” and “fewer” does not yield a category distinction.

2020-05-08 To see how the disease is being controlled or not in various countries, I find it helpful to look at the histograms of daily new cases, in the JHU Dashboard lower-right graph with the toggle button “Daily Cases” (it doesn't automatically come up with the Dashboard; the graph of accumulated cases is shown). Each country has a very distinct histogram; it is easy to recognise a country from the shape of its histogram alone, without labelling.

2020-05-08 Cavalli et al report in The Lancet treatment of patients with Covid-19, ARDS and hyperinflammation, and non-invasive breathing support with anakinra, an interleukin (IL)-1 receptor antagonist that blocks activity of the proinflammatory cytokines IL-1α and IL-1β, used to treat autoinflammatory disorders https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30127-2/fulltext This was an observational study on 29 patients being treated also with hydrocholoroquine and lopinavir/ritonavir ("standard" treatment). Clinical progress was compared with that of 16 patients in similar condition with standard treatment only. Progress was assessed after 21 days. 72% (21) of the anakinra group showed reduced serum C-reactive protein, and respiratory function improvement, 5 were invasively ventilated and 3 had died. In the standard group, 50% showed respiratory improvement, 1 was invasively ventilated and 7 had died. Looks good, but the authors note that confirmation will require RCT.

2020-05-08 Treibel et al report in The Lancet regular testing of asymptomatic and pauci-symptomatic health care workers at a London hospital for Covid-19 https://www.thelancet.com/lancet/article/s0140-6736(20)31100-4 It is a 16-week study. The article presents data from the first 400 participants and first five weeks. The asymptomatic/pauci-symtpmatic infection level started at 7% in the first week of testing, went down to 5% in the second week and to around 2% in the subsequent three weeks (Figure 1 of the study). The authors write "*[t]aken together, these data suggest that the rate of asymptomatic infection among HCWs more likely reflects general community transmission than in-hospital exposure. Prospective patients should be reassured that as the overall epidemic wave recedes, asymptomatic infection among HCWs is low and unlikely to be a major source of transmission.*"

2020-05-08 The BMJ reports on Streeck and Hartmann's Heinsberg study https://www.bmj.com/content/369/bmj.m1862 Besides summarising the main results, BMJ includes some observations by interview with Hartmann.

2020-05-08 Roberts et al summarise in the BMJ blog the key aspects of medical phenomena involved in Covid-19, which is "*a complex multisystem clinical syndrome*", and "*not a straightforward viral pneumonia*" https://blogs.bmj.com/bmj/2020/05/01/covid-19-a-complex-multisystem-clinical-syndrome/

2020-05-08 Paul Garner, a Professor at Liverpool who specialises in infectious diseases, caught Covid-19, and was very ill at home for *seven weeks*, rather than the "two weeks" seemingly expected by a large proportion of the medical profession. Not at all fun, with "*constantly shifting bizarre symptoms.*" You really, really don't want to get this disease. https://blogs.bmj.com/bmj/2020/05/05/paul-garner-people-who-have-a-more-protracted-illness-need-help-to-understand-and-cope-with-the-constantly-shifting-bizarre-symptoms/

2020-05-08 I missed this. Abbott has a high-specificity-and-sensitivity serological test (greater than 99%), which has a CE mark. https://www.bmj.com/content/369/bmj.m1742 on 2020-04-29.

2020-05-10 Hung et al in Hong Kong performed an RCT of combination therapy on 127 hospitalised Covid-19 patients, with interferon beta-1b, lopinavir/ritonavir and ribivarin versus lopinavir/ritonavir alone https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31042-4/fulltext The protocols were started early, within 7 days of symptom onset (median 5). Primary endpoint was a negative nasal swab RT-PCR test. The combination group had significantly reduced time to negative test, 7 days (IRQ 5-11) compared with 12 days (IQR 8-15) for the control group. Encouraging results. Comment by Shalhoub https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31101-6/fulltext

2020-05-11 JHU Center for Health Security keeps a list of all serological tests available for SARS-

CoV-2 antibodies https://www.centerforhealthsecurity.org/resources/COVID-19/serology/Serology-based-tests-for-COVID-19.html
2020-05-11 Roche has launched the Elecsys Anti-SARS-CoV-2 immunoassay, which has extremely high specificity and sensitivity https://www.bioworld.com/articles/434881-roche-discusses-launch-of-newly-approved-serology-test-to-detect-covid-19 The JHU document above only includes the info from the April 17 announcement by Roche, which did not specify the specificity or sensitivity.

2020-05-11 The US FDA has a page listing the details of all Emergency Use Authorization (EUA) serological tests for SARS-CoV-2 antibodies. It includes Roche Elecsys, listed as having a specificity of 99.8%, and a sensitivity of 100%. The Euroimmun test used in the Heinsberg survey of Streeck and Hartmann has a specificity of 100%, but a sensitivity of 90% https://www.fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-test-performance

2020-05-11 One of the UK government's advisors, Neil Ferguson, on whose model and software the reportedly decisive Report 9 of MRC GIDA at Imperial College was based, has come under some criticism both for the quality of the code used, and for allegedly breaking lockdown rules. Some UK politicians have tried to use these phenomena to doubt the UK lockdown policy. The one doesn't have anything to do with the other. But apparently this is not obvious to everyone. So it has to be said publicly by many UK scientists in an open letter: https://docs.google.com/document/u/1/d/e/2PACX-1vSxP91cr4TOPVi9gwW4mGL9BL2wyQAVjFOw-pB2aRe3uXXXIfyDrJpef5Qp0B8_l9en6buM0LTjRSYq/pub

2020-05-11 Yesterday, on TheG live blog at 1056 BST, Angela Giuffrida gave some results of antibody testing of health care workers in Lodi, Italy, where the first case Matthia Mattei, “Patient 1”, was treated https://www.theguardian.com/world/live/2020/may/10/coronavirus-live-news-obama-trumps-covid-19--chaotic-as-global-cases-pass-4-million-mexico-russia-germany-south-korea-deaths-?page=with:block-5eb7ce748f08c0a2409bafb2 Apparently 20% of the total infected were asymptomatic. 2243 staff were tested, 296 had tested positive up until 8 May, and an additional 77 were discovered to be infected. That is, the level of asymptomatic infections amongst this cohort was 3.4%. I cannot yet find a more detailed reference to these results.

2020-05-11 Latest figures from Bielefeld:

Date	Total	New	Ill	Recovered	Died
2020-05-06	379	0	49	327	3
2020-05-07	386	7	48	335	3
2020-05-08	387	1	46	338	3
2020-05-09	387	0	44	340	3
2020-05-10	387	0	44	340	3

These figures are very encouraging for someone like me who lives here. First, a CFR of 0.78%. To put it another way, a mortality of 0.9 per 100,000 residents. Second, in the last 11 days, which is double the median incubation time, there have only been 12 new cases in this city of 333,000 people. That surely means we have a tiny number of carriers.