Notes on COVID-19

Part 20: 2020-10-30 to 2020-12-02

Peter Bernard Ladkin
2020-12-02

2020-10-30 The October interim results from the React-1 Covid-19 prevalance survey were made available on 2020-10-29 https://www.gov.uk/government/publications/react-1-study-of-coronavirus-transmission-october-2020-interim-results/react-1-real-time-assessment-of-community-transmission-of-coronavirus-covid-19-in-october-2020 The survey was taken 2020-10-16 to 2020-10-25 inclusive. It found the weighted national prevalence of infection to have risen to 1.28% (1.15-1.41) from half that in September, and R_t to be 1.56 (1.27, 1.88) in comparison with 1.16 in September.

2020-10-30 Julian Tang, one of the signatories of the July Morawska-Milton letter (Notes Part 12, 2020-07-08), considers aerosol transmission in a short piece for TheG https://www.theguardian.com/commentisfree/2020/oct/28/understanding-aerosol-transmission-key-controlling-coronavirus-wash-hands

2020-10-30 The Tang article above points to the Hamner et al account of the now-infamous superspreading choir practice in Skagit County, Washington on March 10th 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6919e6.htm , published in CDC MMWR 69(19):606-610 of 2020-05-15. There is a more detailed account in Indoor Air on 2020-09-26 by Miller et al https://onlinelibrary.wiley.com/doi/full/10.1111/ina.12751 The authors attempt to quantify the emission rate of viable virion in terms of quanta (used here because the actual infectious-dose size is unknown), as well as infection-risk reduction achievable by changing parameters such as aerosol loss rate and shortening exposure time. It is based upon the Wells-Riley model of distribution of quanta in an enclosed space. When points (here: quanta) are distributed randomly according to a uniform distribution in space, then quanta in a given fixed volume are Poisson distributed. (This is an old and venerable observation – I found it on p157 and p159, with an example using data from flying-bomb hits on London from WWII on p161, of Feller's An Introduction to Probability Theory and Its Applications, Volume 1, Academic Press, 1950. I have the Third Edition from 1967.) It follows that the chance of encountering a quantum in a given volume is exponentially distributed, which is quite convenient, since the process of aerosol virions becoming unviable, as well as the deposition of fomites, and the air exchange with ventilation, are all inversely-exponentially distributed also, so you can pack all these rates into the \lambda parameter of the exponential distribution (which is really an inverse-exponential distribution).

So this model is mathematically very convenient. However, it is not necessarily realistic, because simulations show that quanta emanating from one source are by no means uniformly distributed in space. See for example the diagrams from Wolf GmbH: Covid-19: Studie zur Partikelverbreitung https://www.wolf.eu/ueber-wolf/presse/pressemitteilungen/covid-19-studie/ (in German, but go to the bottom of the page where it says “Download Bild” – “Bild” means picture in German –

download the zip file, and look at the picture with name *Grafik_Aerosole_Klassenraum.jpg* for a study of how aerosols from a point source in the SE corner of the room, assuming top is N, distribute under conditions of window ventilation (the top row), in which windows are left ajar ("gekippt"), then fully opened ("geöffnet"), then returned to ajar, over a period of 45 minutes. The distribution is anything but uniform. The Skagit Valley Chorale practice had two 45-minute rehearsals in different configurations, a 10-minute break, and a further 50-minute rehearsal, so time periods are similar.

Miller et al derive an estimate of emanation: "*The mean (± SD) inferred emission rate was E = 970 (±390) quanta/h.*" Obviously, the emission rate depends highly on the physiology of the index case. There are some people who spread an order of magnitude more droplets and aerosols than others when they sing or speak. And it obviously depends on the virion density in the emanations. So it is not as if there is going to be one number associated with quantum emanation - it is is going to be parametrised at least by those two characteristica.

2020-10-30 Lednicky et al report in the International Journal of Infectious Disease 100, November 2020, pp 476-482 on their collection of viable Covid-19 virions from the air in a hospital room containing two Covid-19 patients (one ready for discharge). They found viable virions at concentrations of 6 to 74 $TCID_{50}$/L at distances 2m to 4.8m from the patients, with genome identical to that of the newly-admitted patient.

That should settle the question whether aerosol transmission of Covid-19 is possible. There was an issue that no one had yet managed to culture virus from aerosol-sampled virions. Apparently that may have been caused through harsh air sampling techniques. This study used gentler sampling.

2020-10-31Laxminarayan et al published seroprevalence surveys of two Indian states, Tamil Nadu and Andhra Pradesh, which they describe as a "high-incidence setting", in Science on 2020-09-29 https://science.sciencemag.org/content/early/2020/09/29/science.abd7672

2020-10-31 Shaman and Galanti consider in Science 370(6516):527-529 on 2020-10-30 whether Covid-19 will become endemic https://science.sciencemag.org/content/370/6516/527 Summary: a definite maybe.

2020-10-31 Enserink, Kupfrschmidt and Desai have put a helpful graphic article together in Science on 2020-10-20 explaining the science of Covid-19 superspreading and tracing https://vis.sciencemag.org/covid-clusters/

2020-10-31 Chen et al report in the NEJM an interim analysis to September 5 of the Phase 2 study of Eli Lilly's antiviral monoclonal antibody therapy LY-CoV555, aka bamlanivimab https://www.nejm.org/doi/full/10.1056/NEJMoa2029849 The primary outcome was the change from baseline in the viral load at Day 11. Participants received one of three doses or placebo. The middling dose achieved significant reduction; the lower and higher not as much.

2020-10-31 People are making public their best guess as to an infectious dose of SARS-CoV-2. Correspondence in the NEJM on 2020-10-23 concerning an article by Gandhi and Rutherford have Brosseau, Roy and Osterholm estimating such a dose https://www.nejm.org/doi/full/10.1056/NEJMc2030886 They suggest that, similar to SARS-CoV, 300 virions is infectious, and refer to Watanabe et al, Risk Analysis 30(7):1129-1138, 2010 https://onlinelibrary.wiley.com/doi/full/10.1111/j.1539-6924.2010.01427.x (open access). They say further that "*Normal talking can generate up to 3000 1-micron particles per minute in exhaled breath, and each particle could contain more than 250 virions, which means that a single minute of speaking potentially generates more than 750,000 virions.*" The reference for the first conjunct, concerning the number of particles per minute in exhaled breath while talking, is Asadi et al, Nature Scientific Reports 9, Article 2348 (2019-02-20) https://www.nature.com/articles/s41598-019-38808-z).

Brosseau et al are claiming talking for a minute releases up to 2,500 infectious doses. Whereas in the modelling performed for El Pais, Jímenez suggested a talking infected person released 1,500 infectious doses per hour (Notes Part 19, entry of 2020-10-29). The difference is exactly two orders of magnitude (a factor of 100). Who is right (if either)?

2020-11-01 There are now a number of therapies and potential therapies for Covid-19 which are based on monoclonal antibody (mab) technology. At least two of them, REGN-COV2 (which is a "cocktail" of two monoclonal antibodies, REGN10933 and REGN10987 https://en.wikipedia.org/wiki/REGN-COV2) and LY-CoV555 (see above, 2020-10-31) have been specifically designed as Covid-19 therapies. One mab therapy which was designed to treat cytokine storm syndrome (a hyperinflammatory reaction, a variant of which can occur following SARS-CoV-2 infection), tocilizumab, has been enrolled in the RECOVERY trial. Recent cohort trials incorporating tocilizumab, though, have exhibited disappointing results for it (Notes Part 19, the COQUIMA trial, entry of 2020-10-19, and Stone et al, entry of 2020-10-24).

A Nature article by Klaus Rajewsky on 2019-11-04 succintly describes the history of monoclonal antibody technology https://www.nature.com/articles/d41586-019-02840-w Mab therapies have often been targeted towards treatment of cancer, because it is a series of diseases in which the immune system is unable to kill the rapidly-duplicating mutant (cancerous) cells and it is hoped that characteristics of these cells can be specifically targeted by engineered antibodies, mabs, which, when they attach to a mutant cell, either stimulate the immune system to kill the cell or carry a "payload" which does the job. That, of course, is exactly what you want to happen with SARS-CoV-2-infected cells in the case of Covid-19, because those cells are where the virus is replicating. The American Cancer Society explains the naming conventions: "*Monoclonal antibodies are man-made proteins that act like human antibodies in the immune system. There are 4 different ways they can be made and are named based on what they are made of.*

> *Murine: These are made from mouse proteins and the names of the treatments end in -omab.*
>
> *Chimeric: These proteins are a combination of part mouse and part human and the names of the treatments end in -ximab.*

Humanized: These are made from small parts of mouse proteins attached to human proteins and the names of the treatments end in -zumab

Human: These are fully human proteins and the names of the treatments end in -umab."

https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/monoclonal-antibodies.html

2020-11-04 In an appearance before the UK House of Commons Science and Technology Committee, Chief Scientic Advisor Patrick Vallance said that SAGE had identifed "fatal flaws in the argument" of the Great Barrington Declaration.
https://www.theguardian.com/world/2020/nov/03/chris-whitty-decries-great-barrington-plan-to-let-covid-run-wild
Chief Medical Officer Chris Whitty said that with the great majority of infectious diseases, herd immunity was never achieved naturally, and it was "*simply impractical*" to effectively shield the vulnerable. He said the strategy assumed that "*very large numbers of people would inevitably die*" unless vulnerable people could be identified and perfectly isolated for some years.

2020-11-05 Wu et al have published research linking higher Covid-19 death rates to air pollution, on 2020-11-04 in AAAS Science Advances https://advances.sciencemag.org/content/6/45/eabd4049 "*….we found that higher historical $PM_{2.5}$ exposures are positively associated with higher county-level COVID-19 mortality rates after accounting for many area-level confounders.*" A summary and commentary is available in TheG on 2020-11-05
https://www.theguardian.com/environment/2020/nov/04/tiny-air-pollution-rise-linked-to-11-more-covid-19-deaths-study Preliminary results were reported by TheG's environment editor Damian Carrington on 2020-04-07 (linked from the article above). I remember it well and thought I had included it in previous Notes, but apparently not. I did report in April a study which showed that 78% of the Covid-19 deaths across 66 regions in Italy, France, Germany and Spain were in just 5 regions, and these were the most polluted with NO_2 (Notes Part 4, entry 2020-04-21).

2020-11-07 Hydroxycholoroquine has been shown not to be effective in preventing progression of Covid-19 to severe disease (a hyperinflammatory reaction). The question remained whether pre-infection use of hydroxychloroquine could inhibit or otherwise affect infection and progression of disease. Rentsch et al used records from the UK OpenSAFELY database, which includes the medical records of about 40% of the UK population, to identify hydroxchloroquine users (predominantly patients with rheumatic illness) before the emergence of SARS-CoV-2 and Covid-19. No association between such use and subsequent Covid-19 mortality was found. The paper appeared in The Lancet Rheumatology on 2020-11-05
https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30378-7/fulltext The Comment by Jorge notes the usual caveats with cohort studies, namely the necessity of retroactive rather than proactive control for possible confounding factors but such a large cohort, carefully studied, is as about as definitive as you can get
https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30390-8/fulltext Jorge mentions two other studies of prophylactic use of hydroxychloroquine in health-care workers, with the primary outcome of SARS-CoV-2 infection, which also showed no difference. It seems pretty

clear now that the stuff doesn't work for Covid-19, either prophylactically or post-infection.

2020-11-07 Ed Holt reported in detail in The Lancet on 2020-10-31 about the Slovakian government's mass-testing decision and programme, along with all its pros and cons https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32261-3/fulltext

2020-11-07 The BMJ's Godlee and Looi interviewed the UK's Chief Medical Officer, Chris Whitty, on 2020-11-04 on pretty much everything https://www.bmj.com/content/371/bmj.m4235 He is very critical of the approach suggested by the Great Barrington Declaration for (I would judge) decisive reasons. It is interesting that he self-identifies primarily as a doctor, and is still practicing clinically. He doesn't think the virus will disappear. Developing medical countermeasures will make it much less of a risk than it now is, so it will become managed.

2020-11-07 The BMJ's Gareth Iacobucci reports that Simon Stevens, the chief executive of NHS England, has said that NHS England is to ask GPs to prepare for vaccinations starting in December 2020. He doesn't expect a vaccine to be available then – rather in early 2021. There is considerable logistics involved – some of the vaccines need to be maintained at -70°C up to point of delivery https://www.bmj.com/content/371/bmj.m4291

2020-11-07 The NEJM has published the final report of the RCT of remdesivir by Beigel et al and the ACTT-1 Study Group on 2020-11-05 https://www.nejm.org/doi/full/10.1056/NEJMoa2007764 Remdesivir was superior to placebo in time to recovery in adults hospitalised with Covid-19 and evidence of lower respiratory tract infection. Time to recovery was mean 10 (95%: 9-11) days; with placebo mean 15 (95%: 13-18) days. Mortality was also lower at days 15 and 29. However, Goldman et al found no difference between a 5-day course and a 10-day course of remdesivir in a cohort of patients with severe Covid-19 who were not mechanically ventilated (but not an RCT) https://www.nejm.org/doi/full/10.1056/NEJMoa2015301

2020-11-07 Rita Rubin reports in JAMA on 2020-11-06 about increasing refusals (in the US, but also with a comment concerning the UK) to be tested for SARS-CoV-2 infection, and the ethicolegal implications https://jamanetwork.com/journals/jama/fullarticle/2772860

2020-11-09 Miller has published a Viewpoint in JAMA on 2020-11-02 on the phenomenon of "science denial" and conspiracy theories surrounding Covid-19 and SARS-CoV-2, linked it with brain physiology, and suggested enhancing science education in order to mitigate it. https://jamanetwork.com/journals/jama/fullarticle/2772693 I treat this as a contribution to infodemiology. But I don't think that identifies, or will be sufficient to mitigate, the variety of problems arising from variant interpretation and valuation of information surrounding SARS-CoV-2 and Covid-19. I explain why, in detail, in my paper "Confounding Covid: Part 1 – Some Considerations of Infodemiology".

2020-11-09 A (good-)news release from Pfizer and BioNTech in TheG on 2020-11-09 https://www.theguardian.com/world/2020/nov/09/covid-19-vaccine-candidate-effective-pfizer-biontech Preliminary Phase 3 trial results of BNT162b2 show the vaccine is 90% effective and has

no unsafe side-effects.

2020-11-10 TheG live blog is reporting that Eli Lilly's bamlanivimab antibody treatment, aka LY-CoV555 for non-hospitalised Covid-19 sufferers has received US FDA EUA. https://www.theguardian.com/world/live/2020/nov/10/coronavirus-live-news-who-warns-covid-not-tired-of-us-as-top-uk-scientist-says-vaccine-feels-like-watershed-moment , entry at 00:51 UTC It is an antibody treatment (as per its name) and AFAIK is the first successful treatment for mild-to-moderate Covid-19. According to the report, it has shown no beneficial effects on patients with severe enough Covid-19 to be hospitalised. I noted above (see 2020-10-31) Chen et al's article on their RCT.

2020-11-13 The UK government is mass-testing people in Liverpool, using a lateral-flow test developed by California company Innova which yields results in 15 minutes using an accompanying small evaluation device. The overriding impression I get from this TheG report is that the major concern is how to use this test effectively en masse https://www.theguardian.com/world/2020/nov/13/covid-test-for-mass-uk-screening-could-miss-up-to-half-of-cases-say-scientists Apparently it is very accurate, but the sensitivity seems to vary depending on who you ask in which context. The company itself suggests two tests, two days apart, and then possibly waiting two more days (presumably to see if you develop symptoms). It is not clear from the article if that is what is being done in Liverpool or other settings.

2020-11-13 Monk et al report in The Lancet Respiratory Medicine on an in-hospital phase 2 RCT of Synairgen's inhaled nebulised interferon beta-1a (SNG001). https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30511-7/fulltext About 100 patients were enrolled; primary outcome was clinical improvement on the WHO Ordinal Scale of Clinical Improvement during the dosing period in those who received at least one dose, assessed at Day 15/16 and at Day 28. The results were greater odds of improvement and more rapid recovery from SARS-CoV-2 infection amongst recipients than those receiving placebo. In their comment, Peifer-Smadja and Yazdanpanah note that this result differs from the results of the SOLIDARITY/DisCoVeRy trial of interferon-beta-1, and suggest that could lie in the different condition of participants (in the SNG001 trial they were generally less severely ill) as well as in the mode of delivery of the drug (directly inhaled into the lungs, versus subcutaneous), and propose what should be prioritised in larger trials, which presumably will follow. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30523-3/fulltext

2020-11-13 In The Lancet Global Health on 2020-11-11, Ginsburg and Klugman point out that much of the mortality of the 1918-9 influenza pandemic came down to superinfection with bacterial pneumonia. https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30444-7/fulltext They point out that it can be hard to determine a bacterial superinfection in severely ill Covid-19 patients. A biomarker is needed, and they suggest elevated procalcitonin concentrations might be one. They discuss the use of antibiotics, awarethat some bacteria can be resistant, and that increased antibiotic use leads to more prevalent resistance.

2020-11-14 Some truly astonishing news from MIT, which came to me via the ACM Risks Forum

Digest Volume 32 Number 37, curated by Peter Neumann
https://catless.ncl.ac.uk/Risks/32/37#subj11 . Jordi Laguata, Ferran Hueto and Brian Subirana of MIT have adapted a tool they were building to identify early-Alsheimer's patients from audio analysis of their (artificial, deliebrate) coughs to be able to identify asymptomatic Covid-19 cases. The MIT press release is at https://news.mit.edu/2020/covid-19-cough-cellphone-detection-1029 The method seems to be quite accurate. The full paper is published in IEEE Open Journal of Engineering in Medicine and Biology at https://ieeexplore.ieee.org/document/9208795 A universally-available accurate on-the-spot test for asymptomatic Covid-19 would be a significant advance in countering transmission of the disease.

2020-11-19 The results of the Phase 2/3 trial of the Oxford ChAdOx1 nCoV-19 vaccine (aka AZR1222) have been published by Ramasamy et al today 2020-11-19 in The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32466-1/fulltext 560 participants were enrolled between May 23 and August 8 in the single-blind RCT, and they obtained 552 analysable results. Participants were stratified into age cohorts. As we know from the preliminary results, the vaccine showed similar (good) immunogenicity across all age cohorts, and was better tolerated by older participants that by younger. There were no adverse events related to the vaccination (there were some relating to other causes). Andrew & McElhaney note in their Comment that "*[t]he strengths of the study include a large sample with a wide age range, and a robust trial design. The inclusion of measures of cell-mediated immunity is important given the limitations of relying solely on antibody titres in older adults.*"
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32481-8/fulltext

2020-11-20 An informative news article in Nature on 2020-11-18 by Bianca Nogrady on asymptomatic Covid-19 infection https://www.nature.com/articles/d41586-020-03141-3 First, we distinguish asymptomatic from presymptomatic – presymptomatic infected people do on to develop symptoms, whereas asymptomatic infected people are those who do not display symptoms at any time during infection (although it may be hard to distinguish asymptomatic from paucisymptomatic infection).

It turns out about one in five infections is asymptomatic. A meta-analysis referenced in the article, published on 2020-10-09 by Byambasuren et al in the Journal of the Association of Medical Microbiology and Infectious Disease Canada " ..... *included 13 studies involving 21,708 people, [and] calculated the rate of asymptomatic presentation to be 17%.*"
https://jammi.utpjournals.press/doi/10.3138/jammi-2020-0030
The analysis also found that "*asymptomatic individuals were 42% less likely to transmit the virus than symptomatic people.*"

A recent large population study in Geneva has apparently determined that, in households, "*the risk of an asymptomatic person passing the virus to others in their home is about one-quarter of the risk of transmission from a symptomatic person.*" The study is by Bi et al, in preprint on medRxiv https://www.medrxiv.org/content/10.1101/2020.11.04.20225573v1 posted 2020-11-04. It seems that there are various opinions as to the degree to which asymptomatic infection might be contributing to community transmission.

That gives us some good numbers to calculate back-of-envelope risk. In order to do so, though, I need an estimate of how long, and to what proportion, it takes to exhibit symptoms in a symptomatic case of Covid-19; the incubation period. Such was estimated by Lauer et al from Wuhan data in the Annals of Internal Medicine on 2020-05-05 https://www.acpjournals.org/doi/10.7326/M20-0504 They concluded that 97.5% of sufferers will exhibit symptoms within 11.5 days.

I exhibit a decision method for, for example, young-child day carers in a paper Risk of Covid-19 Infection in Day Care Settings, 2020-11-20.

2020-11-22 Regeneron's REGN-COV2 antibody cocktail has gained EUA in the US on 2020-11-21 https://www.fda.gov/media/143891/download The names of the two components are casirivimab and imdevimab. To my knowledge, this is the first drug for use in non-hospitalised mild to moderate cases which are are risk of proceeding to severe Covid-19 and/or hospitalisation (as per the authorisation).

2020-11-23 The news today says that the AdChOx1-nCoV19/AZD1222 team has conducted an interim analysis of its Phase 3 trial, with data "locked" on 4 November (called "Interim Phase 3 data"). In one dosage the vaccine is 90% effective https://www.ox.ac.uk/news/2020-11-23-oxford-university-breakthrough-global-covid-19-vaccine#
There is also a suggestion in the data that it can reduce asymptomatic infection. The final results of the Phase 1/Phase 2 trials was published in The Lancet just a few days ago (see entry here for 2020-11-19).

2020-11-24 The German virological assessment of Covid-19 patients as a consequence of the January Bavarian outbreak was published in Nature on 2020-04-01, as Nature 581:465-469(2020) https://www.nature.com/articles/s41586-020-2196-x

2020-11-26 A well-written article by Megan Scudellari in Nature 587, 536-539 (2020) on Iceland's experience with comprehensive testing https://www.nature.com/articles/d41586-020-03284-3

2020-11-28 Laura Spinney opines in TheG on 2020-11-28 about how human behaviour can modify the virulence of a virus https://www.theguardian.com/commentisfree/2020/nov/19/coronavirus-evolving-deadlier-evidence-social-distancing-covid-19 The idea is there are many strains of the virus circulating. Quarantine and isolation measures for those who are sick and those who had contact with symptomatic sufferers tend to hinder the spread of virulent strains, as well as aid the spread of strains which generally cause mild or no symptoms, because if you are paucisymptomatic you don't necessarily quarantine or isolate. Paul Ewald of the Uni Louisville in Kentucky pointed out that the transport conditions for soldiers sick with the Spanish flu in the Western Front aided the spread, since they were kept together rather than being isolated, and may have contributed to the persistence of the virulent strain. Spinney says it circulated in less virulent form until 1957, when it was suppressed by the "Asian flu" outbreak.

2020-11-28 Reports in TheG today 2020-11-28 that NHS hospitals have been told to prepare to receive and use bnt162b2 in ten days' time (2020-12-07). Because of the storage and transport conditions of the vaccine, it is aimed to use it first on front-line NHS health personnel in and around hospitals, since that will require only two journeys (from manufacture in Belgium to distribution centre, and from distribution centre to hospital). This all supposes that MHRA authorises the vaccine next week. JCVI had prioritised care homes and residents, with health-care personnel and older people not in care homes as second, but the logistics of bnt162b2 delivery required a rethink.

2020-11-28 James Brophy points out in the BMJ blogs on 2020-11-24 that the data in the DANMASK-19 trial, performed in Denmark in April and May, could be interpreted differently from what the reporters said https://blogs.bmj.com/bmj/2020/11/24/covid-19-controversial-trial-may-actually-show-that-masks-protect-the-wearer/ The trial was an RCT of surgical-mask wearing in public. "*The study was designed to find a 50% reduction in infection rates among mask wearers. Among the 4862 participants who completed the trial, infection with SARS-CoV-2 occurred in 42 of 2392 (1.8%) in the intervention arm and 53 of 2470 (2.1%) in the control group."* This primary outcome was not shown. Brophy points out that the convention of establishing a null hypothesis and testing for significance against that, which the authors used, obscures some significant positive results here.

> "*The results of DANMASK-19 do not argue against the benefit of masks to those wearing them but actually support their protective effect. ..... it can be shown that these data best support an 18% reduction in infections among mask wearers and find as much evidence for a 33% reduction as for no effect. [8]*
>
> *Bayesian analysis of the DANMASK-19 trial alone shows an 81% probability of fewer infections among those encouraged to wear a mask and a 35% probability that mask wearers will avoid more than five infections/1000 individuals. Similar results are achieved with a Bayesian analysis that combines the DANMASK-19 results with prior knowledge about masks, expressed as the relative risk observed in the Cochrane review of older randomised trials of masks (RR 0.91 95%CI [0.66, 1.26]).*"

The study by Bundgaard et al was published in the Annals of Internal Medicine on 2020-11-18 https://www.acpjournals.org/doi/10.7326/M20-6817

Note that the study was not designed to determine the protection of others by the use of masks, just a level of protection to the wearer. So the most obvious claim to be made for mask-wearing of any sort, that it inhibits the cloud of droplets and aerosols emanating from a human, was not tested. I would also suggest not only that it is hard to test in an RCT, but that the physical effects of mask-wearing on the emission of droplets and aerosols is evident from various lab videos and thereby doesn't need to be statistically tested.

Carl Heneghan, Professor of Evidence-Based Medicine at the Uni Oxford, and colleague Tom Jefferson commented in The Spectator the next day 2020-11-19 that mask-wearing appears to have no significant effect upon wearers. https://www.spectator.co.uk/article/do-masks-stop-the-spread-of-covid-19- Brophy's observations above say that this is not what the data showed.

The US CDC agrees with Brophy and others that mask-wearing can protect the wearer – see the article by Joan Stephenson in JAMA on 2020-11-17 on the new guidelines from 2020-11-16 https://jamanetwork.com/channels/health-forum/fullarticle/2773247

2020-11-28 Peter Doshi argues coherently and convincingly in BMJ blogs on 2020-11-26 for a release of the full data on the Moderna mRNA-1273 and BioNTech bnt162b2 Phase 3 vaccine trials https://blogs.bmj.com/bmj/2020/11/26/peter-doshi-pfizer-and-modernas-95-effective-vaccines-lets-be-cautious-and-first-see-the-full-data/

2020-11-28 An Indian RCT reported by Astogi et al in BMJ Postgraduate Medical Journal of 40 Indian Covid-19 patients with a Vitamin D deficiency, given Vitamin D showed statistically significant improvement https://pmj.bmj.com/content/early/2020/11/12/postgradmedj-2020-139065 . The primary outcome was being free of the virus by Day 21 and change in inflammatory markers. It reminded me to take my Vitamin D supplement. (Oddly, no date is given for publication.)

2020-11-28 Bajema et al have estimated SARS-CoV-2 seroprevalence in the US in September 2020 https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2773576 , published in JAMA on 2020-11-24. They looked at residual sera from two commercial laboratories, including samples from all 50 states, D.C., and Puerto Rico; 52 jurisdictions, analysed by jurisdiction. They looked at 177 919 residual clinical specimens. "*[T]he estimated percentage of persons in a jurisdiction with detectable SARS-CoV-2 antibodies ranged from fewer than 1% to 23%. Over 4 sampling periods in 42 of 49 jurisdictions with calculated estimates, fewer than 10% of people had detectable SARS-CoV-2 antibodies.*"

The Commentary by Spielberg, Nielsen and Casadevall emphasises the importance of such data https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2773575 "*For all but a few states, seroprevalence remained below 10% throughout the study period; New York was the only state where seroprevalence increased above 20%. In several states, seroprevalence stayed below 1%.*"

2020-11-28 Simonovish et al conducted an RCT of convalescent plasma in cases of severe Covid-19 and concluded it didn't appear to help. NEJM, 2020-11-24 https://www.nejm.org/doi/full/10.1056/NEJMoa2031304

2020-12-02 I have not reported on the local situation in Bielefeld for some time. Going back some three weeks, people were seriously worried about the October rise in infections. A week after the November "lockdown light" was implemented, the local newspaper NW summarised the previous few weeks in a short article on 2020-11-10.

Three weeks prior to that, mid-September, there had been 15 hospitalised Covid-19 patients. On 2020-11-08 there were 6 times that many, 90. Most of them were in one specific hospital, whose head doctor remarked on Friday 2020-11-06 that there were 43, and this number was two and a half times the number the week before that (that would have been Friday 2020-10-30). On 2020-11-30 there were 110 hospitalised Covid-19 patients, so the number has not increased greatly over the three weeks previous. The situation is similar in ICU. We had on the weekend 2020-11-07/08 30 people in ICU; on 2020-11-30 it was 38, so that number has not gone up so starkly either. Similarly we have 23 being mechanically ventilated on 2020-11-30 and on 2020-11-09 it was 19. Having had a total of 11 deaths from Covid-19 from March through October, though, there were 21 deaths in November 2020.

In early October, Bielefeld was worried about reaching the trigger-number of 35 new infections per 100,000 residents in the previous 7 days (ni10^{5}r7d). The day after we reached that figure, which triggered legal restrictions, we reached the second trigger-number of 50 ni10^{5}r7d, which triggered even more restrictions. Then it just "blew up". The figures are below. It is not an encouraging sight. The one positive point to note is that the hospitalisation figures are not tracking the new-infection figures. From general experience, one would expect them to be about one week behind, but in fact they have stayed relatively constrained in November, even as the number of infections has climbed.

In the new-infection figures, I have also included the 7-day-modified-incidence: *7dmi*, calculated as follows. For each day, I take the new infections over the previous 7 days, remove the highest value and the lowest value, average the five remaining, giving the number to one decimal place. This is a trivial technique to smooth outliers in the daily numbers, which we experience when accounting adjustments are made, or when reporting is delayed or when it catches up. I think the smoothing effect is clear in the figures. I start the 7dmi calculation on 20th October.

Note that this table is being updated until the date of publication of these Notes.

Date	ni10^{5}r7d	new inf's	7dmi
2020-10-14	34.1	23	
2020-10-15	43.7	49	
2020-10-16	51,5	43	
2020-10-17	50.0	17	
2020-10-18	56.6	35	
2020-10-19	58.3	6	
2020-10-20	61.6	33	30.2
2020-10-21	65.5	40	33.6
2020-10-22	63.7	46	33.6
2020-10-23	73.9	71	34.2
2020-10-24	90.1	71	45.0
2020-10-25	99.0	68	51.6
2020-10-26	103.8	36	52.2
2020-10-27	109.5	35	52.2

2020-10-28	114.3	56	55.4
2020-10-29	120.3	66	59.4
2020-10-30	129.6	100	59.4
2020-10-31	131.1	77	60.6
2020-11-01	130.2	65	60.0
2020-11-02	131.1	39	60.6
2020-11-03	141.2	69	66.6
2020-11-04	163.1	129	75.4
2020-11-05	164.3	68	75.8
2020-11-06	163.7	100	75.8
2020-11-07	166.1	85	77.4
2020-11-08	167.0	68	78.0
2020-11-09	175.1	66	78.0
2020-11-10	178.6	81	80.4
2020-11-11	163.4	77	75.8
2020-11-12	170.3	91	80.4
2020-11-13	172.7	108	80.4
2020-11-14	176.5	99	83.2
2020-11-15	177.7	72	84.0
2020-11-16	175.3	58	84.0
2020-11-17	162.5	38	79.4
2020-11-18	166.4	91	82.2
2020-11-19	164.6	83	80.6
2020-11-20	162.8	103	80.6
2020-11-21	175.6	140	81.4
2020-11-22	172.1	61	79.2
2020-11-23	173.0	61	79.8
2020-11-24	199.0	125	92.6
2020-11-25	195.4	80	90.4
2020-11-26	209.2	128	99.4
2020-11-27	221.4	143	106.8
2020-11-28	211.6	108	100.4
2020-11-29	211.6	68	101.8
2020-11-30	204,1	35	101.8
2020-12-01	181.6	50	86.8

People have been crediting the “lockdown light” measures of November with dampening the growth of new infections. That might be seen in the period from 2020-11-12 to 2020-11-23 in the 7dmi figures. But then they shoot up again from ~ 80 to a new plateau 25% higher at ~ 100 three days later on 2020-11-26. The figures are reducing from 2020-11-27, but I think it is too soon to guess whether this will continue.

At the beginning of October, the city was concerned about damping down potential superspreader events. One, a party on September 15th, led to over 70 secondary infections, 11 school partial or full

closures and a blip in the daily “infected” figures which manifested itself over a few days, starting 12 days after the event. Seeing specific events in the figures has not been possible for some weeks now. The city crisis management team has said there seems now to be pervasive “community transmission”, which means the health authority doesn't know any more where the infections are coming from.

The new infections per day since March, when infections began in Bielefeld, may be seen in the graph at https://www.bielefeld.de/de/covi/ as well as in the daily reports underneath. The current wave started most obviously in the fourth September week (after 2020-09-22). An explanation for the large figure on 2020-11-04 could be that a week previously was when the Chancellor and state governments announced the stringent “lockdown-light” measures for November. People may have “made use” of the last few days of comparative laxity, leading to higher new-infection figures after the incubation period. Since it is “community transmission” rather than secondary infections stemming from a superspreader event, the blip manifests itself corresponding to the average incubation time, rather than over a longer chain of infections. (The sudden reduction in ni10^{5}r7d on 2020-11-11 of course results from the very high figure of new infections on 2020-11-04 dropping out of the average.)

Going to the RKI daily reports (which are also available in English), the reports have been saying since 2020-11-09 that R_t is “*fluctuating .... around 1*” (p2, Section *General current assessment*). https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/Nov_2020/2020-11-09-en.pdf The entire collection of RKI daily reports in English may be found at https://www.rki.de/EN/Content/infections/epidemiology/outbreaks/COVID-19/Situationsberichte_Tab.html

2020-12-02 A fitting end to this Part of the Notes. The UK regulator MHRA has approved the BioNTech vaccine bnt162b2 for emergency use https://www.theguardian.com/society/2020/dec/02/pfizer-biontech-covid-vaccine-wins-licence-for-use-in-the-uk Rumors are that first vaccinations under this approval will occur early next week.