Notes on COVID-19

Part 28: 2021-08-01 to 2021-08-31

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2021-08-31

2021-08-07 The MIT Technology Review has an article on 2021-07-30 on how AI/ML is failing to help diagnose Covid in many attempts. The author interviews Laure Wynants of Maastricht University and David Driggs of Cambridge University as to why. Biases in training data sets are common. Some examples:
"*Frankenstein data sets ... are spliced together from multiple sources and can contain duplicates. This means that some tools end up being tested on the same data they were trained on, making them appear more accurate than they are.*
.....Many (researchers) unwittingly used a data set that contained chest scans of children who did not have covid as their examples of what non-covid cases looked like. But as a result, the AIs learned to identify kids, not covid.
... trained its ... model using a data set that contained a mix of scans taken when patients were lying down and standing up. Because patients scanned while lying down were more likely to be seriously ill, the AI learned wrongly to predict serious covid risk from a person's position."

Besides these almost amusing examples lies a serious and highly non-trival issue of how to get "clean" data sets from harried physicians and hospitals.

The Turing Institute has also held workshops with many participants on the use of AI/ML tools for many purposes during the pandemic.

William Douglas Heaven, Hundreds of AI tools have been built to catch covid. None of them helped. MIT Techology Review, 2021-07-30, https://www.technologyreview.com/2021/07/30/1030329/machine-learning-ai-failed-covid-hospital-diagnosis-pandemic/

Wynants L, Van Calster B, et al, Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal, BMJ 2020;369:m1328 2020-04-07 (1st version; 2020-04-07; latest version 2021-01-12), https://www.bmj.com/content/369/bmj.m1328

Roberts M, Driggs D, Common pitfalls and recommendations for using machine learning to detect and prognosticate for COVID-19 using chest radiographs and CT scans,Nature Machine Intelligence 3, 199-217 (2021), 2021-03-15, https://www.nature.com/articles/s42256-021-00307-0

The Alan Turing Institute, Data Science and AI in the age of COVID-19, 2021-06 (no date given in the document itself), https://www.turing.ac.uk/sites/default/files/2021-06/data-science-and-ai-in-the-age-of-covid_full-report_2.pdf The workshop reports themselves are also available through https://www.turing.ac.uk/research/publications/data-science-and-ai-age-covid-19-report

2021-08-07 The researchers who studied the prevalence in the US of cerebral venous thrombosis (CVT, aka cerebral venous sinus thrombosis, CVST) and portal venous thrombosis (PVT) shortly after vaccination have further studied the occurrence of these diseases in CoVID-19 patients. As before, they used the TriNetX Analytics network of electronic health records. They find that the occurrence of CVT up to two weeks after a diagnosis of CoVID-19 is 42.8 per million, and the occurrence of PVT up to two weeks after diagnosis of CoVID-19 is 392.3 per million. This is significantly higher than in a matched cohort of people receiving an mRNA vaccine (4.46 per million) or who have influenza (1.43 per million). These are also much higher than EMA estimates of VITT/TTS of around 5 per million vaccinations predominantly in women. Taquet M, Husain M, et al, Cerebral venous thrombosis and portal vein thrombosis: A retrospective cohort study of 537,913 COVID-19 cases, The Lancet EClinicalMedicine Vol. 39, 101061, 2021-07-31, doi 10.1016/j.eclinm.2021.101061 https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00341-2/fulltext

2021-08-13 The NEJM has published a prospective cohort study of the prevalence of VITT in vaccinated people in England up to 2021-06-01. At that point, the researchers had identified 220 definite or probable cases of VITT in around 24m first-dose-vaccinated people, exclusively with ChAdOx1-nCoV19. Patients presented 5-48 days after vaccination. There was no sex preponderance. There were no identifiable medical risk factors. Overall mortality was 22%, but 73% for those with intracranial hemorrhage and very low platelet count (under 30,000 per cubic millimetre). Pavord S, Scully M, et al, Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis, N. Eng. J. Med., 2021-08-11, DOI: 10.1056/NEJMoa2109908 https://www.nejm.org/doi/full/10.1056/NEJMoa2109908

The authors say: "*By the end of the study, approximately 16 million first doses of ChAdOx1 nCoV-19 had been administered to persons 50 years of age or older, and 8 million first doses had been administered to persons younger than 50 years of age. Thus, the approximate incidence of VITT was at least 1:100,000 among patients 50 years of age or older and at least 1:50,000 among patients in the younger group (<50 years of age).*" I make "*at least 1:100,000*" to be over 160 in this cohort, and "*at least 1:50,000*" to be over 160 in this second group, for a total of at least 320 patients. But they only had 220. I asked Dr. Pavord about the arithmetic. She said the authors are not party to precise information about vaccine numbers, and these incidences are those provided by the MHRA.

2021-08-20 The monoclonal antibody antiviral Ronapreve, developed by Regeneron and Roche, has been approved in the UK by the MHRA https://www.gov.uk/government/publications/regulatory-approval-of-ronapreve Ronapreve consists of a cocktail of casivirimab and imdevimab. From the Summary of Product Characteristics (available through the above), "*Casirivimab and imdevimab are intended to compensate/substitute for endogenous antibodies in those individuals who have yet to mount their own immune response.*" This is the first antiviral approved in the UK. Eli Lilly's antiviral has also shown positive results (see entry 2021-07-31 in Notes Part 27 on the NEJM article on its RCT). So maybe shortly there will be two?

2021-08-20 On Monday 2021-08-16, the NW reported on the first longitudinal study of hospitalised Covid-19 patients in Germany, performed under the auspices of the one of the country's health insurers ("Krankenkasse" – health insurance is mandatory for employees in Germany; your employer must sign you up to an insurer and contributions from salary plus employer include the other legally-required social insurance, such as disability, care, work-related accident, unemployment; these organisations provide services that, for example, in the UK are provided directly by DHSC). The Scientific Institute of the AOK (Wido) found that about 30% of hospitalised Covid-19 patients died within 6 months of admission, including those discharged.

The study followed 8,679 AOK-insured patients hospitalised between 2020-02-01 and 2020-04-30. Average age 69. The study is considered to be representative, since the AOK insures 1 in 3 Germans. 25% died in hospital, 27% of the survivors were readmitted within 6 months largely due to breathing or neurological problems. The majority were of course older, many with existing comorbidities.

2021-08-20 A second article has appeared in the Bulletin of the Atomic Scientists on the origins of Covid-19 by Nicholas Wade, How COVID-19's origins were obscured, by the East and the West, 2021-08-17, https://thebulletin.org/2021/08/how-covid-19s-origins-were-obscured-by-the-east-and-the-west/ Wade discusses again the negotiations and reasoning that led up to the Lancet and Nature Medicine letters about the natural origin and spread of SARS-CoV-2, a view which, Wade has argued and argues convincingly, was not scientifically well-supported at that time and is in doubt now.

2021-08-20 Wade's view is strongly supported by an article in The Economist, The world needs a proper investigation into how covid-19 started, 2021-08-21 (published on-line on 2021-08-19) https://www.economist.com/international/2021/08/21/the-world-needs-a-proper-investigation-into-how-covid-19-started It starts by relating the contents of a Danish documentary on the "joint report" on the origins, conducted by the WHO and Chinese authorities earlier in 2021. Peter Ben Embarek was a member of the committee, and criticises its conclusions significantly. "*In March the joint study reported that it was "extremely unlikely" that the virus had been released in a laboratory accident. Dr Ben Embarek revealed that this conclusion did not come from a balanced assessment of all the relevant evidence but from a steadfast refusal by the Chinese members of the joint study to support anything stronger. Indeed they only allowed even that minimal assessment on the condition that the report did not call for further investigation into the question. He also pointed out that the idea that the point of spillover was someone collecting bat samples for research purposes belongs in the "likely" basket, along with other human interactions with wild bats.*" There is also evidence for SARS-CoV-2 in other places, much earlier than December 2019. For example, 7 blood samples taken in November 2019 from some 9,000 people over 12 regions in France contained SARS-CoV-2 antibodies. The Economist mentions also positive samples in lung-cancer screening trials in Italy, in September 2019, as well as an antibody study in Lombardy at around the same time with positives. Most intriguing is a Lombardy study which looked for SARS-CoV-2 gene sequences. "*Examining 289 swabs and urine tests taken from people who had presented with a rash as far back as the second half of 2019, they found sars-cov-2 sequences in 13, the earliest of which was taken on September 12th.*" The Economist says it was published in The Lancet on 2021-08-06 but I have

been unable to find it there.

2021-08-21 The comments by Peter Ben Embarek have also been reported in the BMJ. Mahase E, Covid-19: China pressured WHO team to dismiss lab leak theory, claims chief investigator BMJ 2021;374:n2023 2021-08-13 doi:10.1136/bmj.n2023 https://www.bmj.com/content/374bmj.n2023 The article also notes that there were apparently some public comments by a "Swiss epidemiologist" by the supposed name of Wilson Edwards, who apparently claimed there was a US attempt to pressure the WHO into blaming China, and was widely cited in Chinese news media. Neither the Swiss not anybody else have been able to find out if such a person exists; the current supposition is that he doesn't (many news stories, e.g., Helen Davidson in TheG 2021-08-11 https://www.theguardian.com/world/2021/aug/11/chinese-media-fake-news-claims-swiss-scientist-wilson-edwards-critical-of-us).

2021-08-21 More good news on antivirals. Astrazeneca released on 2021-08-20 results of the PROVENT trial of its antiviral AZD7442, a cocktail of tixagevimab and cilgavimab. The MABs were developed by Vanderbilt University Medical Center and enhanced by AZ. AZD7442 is intended to prevent Covid-19 infection, rather than to treat existing infection.

There were just over 5,000 participants, 75% with comorbidities or other risk factors (such as compromised immune system), and all Covid-19-free at baseline. The randomisation was 2:1 AZD7442:saline placebo, via one intramuscular injection. Primary endpoint was positive RT-PCR determination of infection post-dose and prior to day 183. Risk of developing symptomatic Covid-19 was reduced 77% (95% CI 46-90). There were 25 cases in the trial. No cases of severe Covid-19 or death appeared in the AZD7442 arm; three severe cases with two deaths in the placebo arm. https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html

That makes three items of good news on antivirals in a month: First, Eli Lilly's good results reported in the NEJM (entry 2021-07-31 in Notes Part 27); second, the Regeneron-Roche approval by the UK MHRA; and now this.

2021-08-28 A study was performed on all Covid-19 patients in England between 2021-03-29 and 2021-05-23, exactly 8 weeks duration. Just over 43,000 presented with the δ variant and 34,000+ with the α variant. The proportion of people hospitalised within 14 days of the test with either variant was broadly similar – 2.3% with δ, 2.2% with α – but the proportion of those who were hospitalised or presented to emergency care with 14 days was significantly different between the two variants – 5.7% with δ whereas 4.2% with α. Infection with the δ variant resulted just over one-third more often in emergency care. However, after adjusting for differing risk factors and confounding variables, the authors concluded that the risk of hospitalisation with δ is around twice that of the risk with α. Twohig KA, Nyberg T, et al, Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study, The Lancet Infectious Diseases 2021-08-27, doi 10.1016/S1473-3099(21)00475-8, https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00475-8/fulltext

2021-08-28 Prone positioning helps adult patients who require respiratory support with high-flow nasal cannula for acute hypoxaemic respiratory failure due to COVID-19. Just over 1100 patients from hospitals in 6 countries were enrolled in the trial and randomly assigned to awake prone positioning or standard care. Primary composite endpoint (“treatment failure”) was intubation or dying within 28 days of commencing treatment. Treatment failure occurred in 40% of the prone-positioned patients and 46% of the controls (“standard care”). Prespecified adverse events were similar in both groups. Ehrmann S, Li J, et al, Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial, The Lancet Respiratory Medicine, 2021-08-20, doi: 10.1016/S2213-2600(21)00356-8 , https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00356-8/fulltext