Notes on COVID-19

Part 25: 2021-03-25 to 2021-04-15

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2021-04-15

2021-03-30 In the local newspaper NW today, two people in Euskirchen in NRW, both younger women (under 55) have suffered CSVT after being vaccinated with CovVacAZ. TheG reports that the government vaccination authority, the Paul Ehrlich Institute has said there have been 31 cases of CSVT after vaccination with CovVacAZ in Germany. Nine of these cases resulted in death. Nineteen had accompanying thrombocytopenia. 29 cases were in women aged 20-63. Two were men, 36 and 57 years old. https://www.theguardian.com/world/live/2021/mar/30/coronavirus-live-news-who-to-present-china-mission-findings-canada-pauses-astrazeneca-vaccine-for-under-55s , entry at 12.30 BST.

2020-04-01 There has been further trouble with CSVT in Germany. Last weekend, two women in the district of Euskirchen in NRW suffered from it, shortly after being vaccinated, and one has died. My music friend and colleague Inka has met a health professional whose young colleague was one of those who suffered and died. I understand that there have been 31 cases and 9 deaths from CSVT among 2.6m recently vaccinated in Germany with COVID-19 Vaccine AstraZeneca (hereafter CovVacAZ). TheG was reporting yesterday that there have been a total of 44 cases amongst 9.2m vaccinated with CovVacAZ in the EEA. So three-quarters of the cases have been in Germany, amongst 28% of those vaccinated in toto in the EEA. Apparently in GB there have only been 4 cases of CSVT in 13.7m vaccinated, but also 48 cases of thrombocytopenia. Here is an article (in German) written today about the results of Andreas Greinacher at the Uni Greifswald, who has established some immune-system reactive similarities with HIT https://www.mdr.de/wissen/astrazeneca-nebenwirkung-sinusvenenthrombose-wissenschaft-100.html Apparently he has looked at blood from 25 patients who were affected. His work has also convinced members of the German Society for Thrombosis and Hemostasis Research (Gesellschaft für Thrombose- und Hämostaseforschung, GTH). The chair of the GTH, Johannes Oldenburg of the University Hospital in Bonn, said in the article that, through the work of the Greifswald team, there was a quick diagnostic now available, and Professor Greinacher suggested again that the high-dose Ig tranfusion is an effective therapy, when the condition occurred (but not prophylactically).

2021-04-02 A readable and informative article on what is known about indoor-air quality and Covid-19: Lewis, D, Why indoor spaces are still prime COVID hotspots, Nature 592, 22-25 (2021) doi: https://doi.org/10.1038/d41586-021-00810-9 , 2021-03-30 https://www.nature.com/articles/d41586-021-00810-9

2021-04-02 Update on CSVT cases associated temporally with AZ vaccination in GB. The Guardian reports on MHRA figures today https://www.theguardian.com/society/2021/apr/02/covid-further-rare-blood-clot-cases-found-in-oxford-astrazeneca-recipients There have been 22 reports of

CSVT in recent AZ recipients along with 8 more reports of thrombocytopenia, in 18.1m recipients. TheG refers to the MHRAof 2021-04-01 at https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting This page is periodically revised; I don't know whether there is an archive available. Although closer to the German numbers than 4 in 13.7m AZ doses (a previous figure gleaned from TheG), 22 in 18.1m doses is still an order of magnitude different from 31 in 2.6m doses.

2021-04-03 The thrombocytopenia story has finally reached English publications. Science magazine has a long article about the Viennese cases of thrombocytopenia and CSVT, and how the hematologist Sabine Eichinger contacted Andreas Greinacher about it. Very informative. The first article I have seen in English to discuss this: Kupferschmidt K and Vogel G, A rare clotting disorder may cloud the world's hopes for AstraZeneca's COVID-19 vaccine, doi:10.1126/science.abi7283 , 2021-03-27, https://www.sciencemag.org/news/2021/03/rare-clotting-disorder-may-cloud-worlds-hopes-astrazenecas-covid-19-vaccine (Kupferschmidt and Vogel are Berlin-based contributors). The article refers to a preprint, Greinacher A, Thiele T, et al, A Prothrombotic Thrombocytopenic Disorder Resembling Heparin-Induced Thrombocytopenia Following Coronavirus-19 Vaccination, 2021-03-28, doi: 10.21203/rs.3.rs-362354/v1 https://www.researchsquare.com/article/rs-362354/v1 . There is also a blog post by Derek Lowe, Lowe D, Blood Clots and the AZ Vaccine, Revisited, 2021-03-30, https://blogs.sciencemag.org/pipeline/archives/2021/03/30/blood-clots-and-the-az-vaccine-revisited which includes some of the detail about the potential mechanism Greinacher and colleagues are looking at. (Lowe also refers to an earlier blog post of his, on 2021-03-16, at https://blogs.sciencemag.org/pipeline/archives/2021/03/16/what-is-going-on-with-the-astrazeneca-oxford-vaccine). I'm going for my AZ jab on Monday 2021-04-05. I am not worried about this.

2021-04-03 ChAadOx1-nCov19 (aka Covid-19 Vaccine AstraZeneca) is, according to an exploratory analysis just published in The Lancet, 70.4% efficacious against symptomatic Covid-19 infection with the British variant (Kent variant) B.1.1.7 (95% CI 43.6 to 84.5). Emary KRW, Golubchik T, et al, Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial, The Lancet, 2021-03-30, DOI:https://doi.org/10.1016/S0140-6736(21)00628-0 , https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00628-0/fulltext

2021-04-03 Østergaard and colleagues review the background level of various types of thrombotic events in Denmark and conclude that the occurrence of thrombosis temporally near to AZ vaccination in Danish cases is not above background. However, they did not consider CSVT+thrombocytopenia specifically. Østergaard SD, Schmidt M, et al, Thromboembolism and the Oxford–AstraZeneca COVID-19 vaccine: side-effect or coincidence?, The Lancet, 2021-03-30, DOI:https://doi.org/10.1016/S0140-6736(21)00762-5 , https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00762-5/fulltext

2021-04-04. Robin McKie, writing in The Observer today, calls hesitancy over the possible association of AstraZeneca jabs with occasional CSVT+thrombocytopenia a "*dangerous act of political folly*" https://www.theguardian.com/commentisfree/2021/apr/03/undermining-the-

astrazeneca-jab-is-a-dangerous-act-of-political-folly

What rot. My reply: https://abnormaldistribution.org/index.php/2021/04/04/1098/

2021-04-04 A metastudy of the effects of Vitamin D supplementation on acute respiratory infections (ARI) has confirmed an earlier meta-analysis, which showed a small but significant effect Jolliffe D, Carmago Jr CA, et al, Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials, The Lancet Diabetes and Endocrinology, 2021-03-30, DOI:https://doi.org/10.1016/S2213-8587(21)00051-6
https://www.thelancet.com/journals/landia/article/PIIS2213-8587(21)00051-6/fulltext

The comment by Paul Lips notes that the effect is small: 33 individuals would need to be treated (a daily dose of 400-1000 IU) for a year, in order to avoid 1 ARI. Lips also notes that studies of Vitamin D supplementation effects on Covid-19 are ongoing, with results not available yet.
Lips, P, Vitamin D to prevent acute respiratory infections, The Lancet Diabetes and Endocrinology, 2021-03-30 DOI:https://doi.org/10.1016/S2213-8587(21)00075-9
https://www.thelancet.com/journals/landia/article/PIIS2213-8587(21)00075-9/fulltext

2021-04-10 The EMA has conducted a safety review of Vaxzevria (formerly Covid-19 Vaccine Astrazeneca, formerly AZD1222/ChAdOx1-nCoV19), published on 2021-04-07, after the concern about the cases of thrombosis+thrombocytopenia which resulted in certain European states, amongst them Germany, Austria, Denmark, and the EEA states Norway and Iceland, temporarily restricting its use https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood

The review is based on "*62 cases of cerebral venous sinus thrombosis and 24 cases of splanchnic vein thrombosis reported in the EU drug safety database (EudraVigilance) as of 22 March 2021, 18 of which were fatal*." They also note "*As of 4 April 2021, a total of 169 cases of CVST and 53 cases of splanchnic vein thrombosis were reported to EudraVigilance. Around 34 million people had been vaccinated in the EEA and UK by this date. The more recent data do not change the PRAC's recommendations*." (PRAC is the Pharmacovigilance Risk Assessment Committee of the EMA.)

The splanchnic organs are stomach, liver, pancreas, spleen, and large and small intestines, which are of course connected by veins, nerves and so on. A nice picture can be found here:
https://doctorlib.info/physiology/medical/131.html

The PRAC's recommendation is that "*[t]he reported combination of blood clots and low blood platelets is very rare, and the overall benefits of the vaccine in preventing COVID-19 outweigh the risks of side effects*."

The statement includes information for health care professionals on symptoms and their temporal occurrence. It talks about a "*plausible explanation*" and cites the connection to HIT, but doesn't suggest there is anything more known about the mechanism, and thereby about causality. This is all in line with what I suggested was known (as distinguished from conjectured) beforehand (above

entry for 2021-04-03.

At least one worry (expressed to me privately) is that this odd illness might be somehow connected with the vector, the denatured chimpanzee adenovirus. The Janssen vaccine (Janssen is Johnson & Johnson's vaccine daughter company) is also based on an adenovirus, serotype 26. According to Reuters, there have been four reports from the US of thrombosis+thrombocytopenia with the Janssen vaccine, one in clinical trials, and one death https://www.theguardian.com/world/2021/apr/09/eu-agency-examines-reports-of-blood-clots-with-jj-covid-vaccine The EMA is of course monitoring the situation.

If the illness does turn out somehow to be causally connected with the ChAdOx vector, that would put a big dent in the Jenner Institute vaccine research, much of which I understand has been based on developing the vector as a universal component of vaccines.

2021-04-10 A preprint published on March 15th by Oxford researchers says the neutralisation effect of immune serum (either self-developed through infection with "early strains" of SARS-CoV 2, or induced by vaccination with AZD1222 or BNT162b2) is reduced against P.1 (the "*Brazilian variant*") similarly to against B.1.1.7 (the "*British variant*" or "*Kent variant*", depending upon whether you are outside or inside the UK). It is reduced further against B.1.351 (the "*South African variant*") (ll 131-136). https://www.biorxiv.org/content/10.1101/2021.03.12.435194v1.full.pdf Dejnirattisai W, Zhou D, et al, Antibody evasion by the Brazilian P.1 strain of SARS-CoV-2, 2021-03-15, BioRXiv preprint, doi: https://doi.org/10.1101/2021.03.12.435194

This suggests that Vaxzevria/Covid-19 Vaccine AstraZeneca/AZD1222/ChAdOx1-nCov19 is likely to be about 70% efficacious against P.1 (see Lancet article by Emary, Golubchik et al referenced above on 2021-04-03.

2021-03-10 There has been in the last few weeks considerable political developments responding to, amongst other things, the short supply of vaccines in many European countries compared with demand (in particular, in Germany it has just stopped short of a scandal); an illness possibly but rarely associated with Vaxzevria (which Germany was in the forefront of bringing to everyone's attention); various countries' reactions to that (let alone individual residents of those countries); and the per-country reaction to the EMA assessment of this illness and the continuing safety of Vaxzevria (as well as those of other agencies such as UK MHRA); and dealing with the third wave of Covid-19. A few points are worth remarking.

First, the third wave appears in many European countries to be predominantly driven by the British/Kentish variant of SARS-CoV-2 designated B.1.1.7. The hospitalised cohort, and those in ICU, is reported to be becoming younger.

Second, the per-country rates of incidence and the CFR appear to maintaining the wide disparities observed in the first and second waves, even in adjacent European countries.

Third, though no European countries (with the possible exception of the UK) are claiming at

government level that the third wave is over, or on the way to being over, some "loosening" of social restrictions on person-to-person contact is underway in many states. This is controversial, even highly controversial, where it is occurring.

Concerning the third point, it is highly controversial in Germany, for example. Some states, such as the Saarland, which is adjacent to Lorraine in France, have loosened restrictions on, for example, restaurant service. People were photographed by TheG sitting at restaurant tables in downtown Saarbrücken, without masks or significant distancing, as though everything were again OK (see entry at 11.39 BST = GMT+1 on TheG Liveblog for 2021-04-09 at https://www.theguardian.com/world/live/2021/apr/09/coronavirus-live-news-south-korea-to-close-bars-and-clubs-amid-fourth-wave-fears?page=with:block-60702d718f082c00a5ee1bf3)

Everything is of course very much not OK. Chancellor Merkel has been arguing for a lockdown, sharper than ever before, with evening curfew, for a number of weeks. Armin Laschet, the leader of Merkel's CDU party as well as the Minister-President of NRW, came out this week in favor of a "*bridge-lockdown*" to cut the rising numbers. Bavarian Minister-President Söder, a potential rival of Laschet to be the next Chancellor when Merkel steps down in September, has also explicitly supported imposing a lockdown. The head of the Robert Koch Institute, the government public health agency, Lothar Wieler, has said that a 2-4-week lockdown is necessary https://www.theguardian.com/world/2021/apr/09/merkel-sets-out-plan-to-take-control-of-germanys-covid-response The President of the German Interdisciplinary Association for Intensive and Emergency Medicine, Gernot Marx, has called for a 2-3-week lockdown (https://www.nw.de/nachrichten/politik/22989449_Intensivmediziner-fordern-sofortigen-harten-Lockdown.html , possible paywall, in German). There are about 4,500 patients in ICU, with 3,000 beds available; but 2,000 of those are normally reserved for acute cases, such as heart attacks or trauma from vehicle accidents. 4,500 current patients is double the figure of a month ago. The second-wave high was 6,000. Medical staff was way overloaded; and that was only three months ago.

Chancellor Merkel is preparing a set of federal laws which, if passed, will give power to the federal government to impose uniform measures, bypassing the states' current discretion on public health matters.

Vaccine hesitancy appears, though, to be very much on the wane. The appointments for the additional Easter jabs of the AZ vaccine for over-60's (450,000 doses in NRW) were all taken in 36 hours and, according to reports, all used (everyone turned up). An acquaintance who used to work in healthcare hesitated because she was not sure about the AZ product, regretted it a few hours after the bookings closed, found another way she was eligible, and got her AZ jab a couple days later. Another ex-healthcare acquaintance belongs to social chat groups which happen to include some vaccine sceptics, who have all recently gone silent about vaccines. It may be, though, that the Contrarian movement ("*Querdenker*", "lateral thinkers" – though manifestly not of the de Bono style) has polarised/cultified and those people are only sharing now with the "like-minded." Possible. Such inward focusing of "resistance" groups is a known phenomenon. But my impression is of much greater general willingness to be vaccinated, as well as general impatience that it is not

happening very quickly, and that there is still too much bureaucracy involved, with its mistakes, seemingly arbitrary restrictions, and inflexibility. But, at least in Bielefeld, our central Vaccination Centre is winning nothing but praise for its friendly and helpful personnel, its calm atmosphere, and its efficient organisation. I'd put in a picture but I can't find any with Creative Commons licence. Put "*Bielefelder Impfzentrum*" into your favorite search engine, and there are lots of (proprietary) images, of both the interesting exterior (it's a large half-pipe) and the current internal layout.

2021-04-12 The Principle trial has confirmed the efficacy of budesonide in treatment of non-hospitalised sufferers from Covid-19 https://www.principletrial.org/results

2021-04-13 The WHO noted in its briefing on Monday 2021-04-12 that the pandemic is still growing "exponentially" https://www.theguardian.com/world/2021/apr/12/covid-pandemic-still-growing-exponentially-who-says Not good. WHO doesn't think it's good either, 16 months in.

2021-04-13 The Janssen (J&J) vaccine has also been associated with CSVT+thrombocytopenia, in 6 cases, all women between the ages of 18 and 48, 6-13 days after vaccination. This in 6.8 million jabs, according to J&J. TheG live blog entry at 1444 (GMT+1) at https://www.theguardian.com/world/live/2021/apr/13/coronavirus-live-news-europe-death-toll-passes-one-million-india-approves-russias-sputnik-v-vaccine A concern is that this phenomenon might be related to the adenovirus component of the AZ and J&J vaccines. It hasn't occurred with the mRNA vaccines.

2021-04-13 The UK MHRA issued a press release on 2021-04-07 concerning the AZ jab and thrombosis+thrombocytopenia cases. By 2021-03-31 there had been 20.2m jabs, and 79 UK reports of thrombosis+thrbcytopenia. 44 were CSVT. 51 women and 28 men. MHRA calculates the risk as 4 in a million, less than the 1 in 100,000 cited by the EMA. https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots

2021-04-13 Prof. Marie Scully at UCL apparently experienced the same diagnostic progression on thrombosis+thrombocytopenia as the group of Prof. Andreas Greinacher at Greifswald https://www.theguardian.com/society/2021/apr/13/how-uk-doctor-marie-scully-blood-clotting-link-astrazeneca-covid-jab-university-college-london-hospital The good news is that the treatment is getting broadcast.

2021-04-15 People have been looking into the funding supporting the development of the ChAdOx vaccine vector technology, over the research lifetime. 97.1%-99% was public money. Why is funding identification research? Because, as the authors say, "*We ..... encountered a severe lack of transparency in research funding reporting mechanisms*." It has taken some two decades of research to develop the technology. Cross S, Rho Y, et al, Who funded the research behind the Oxford-AstraZeneca COVID-19 vaccine? Approximating the funding to the University of Oxford for the research and development of the ChAdOx vaccine technology, MedRXiv preprint, 2021-04-10, doi: https://doi.org/10.1101/2021.04.08.21255103 https://www.medrxiv.org/content/10.1101/2021.04.08.21255103v1

2021-04-15 Apparently, despite the recommendation from the EMA, Denmark has decided no longer to use the Vaxzevria vaccine, according to an article by Peter Beaumont in TheG 2021-04-14 https://www.theguardian.com/world/2021/apr/14/denmark-to-drop-astrazeneca-jab-from-covid-programme

2021-04-15 A cohort study in the UK found that the B.1.1.7 VOC does not lead to worse outcomes in hospitalised patients than other variants. Viral load, though, was higher . Frampton D, Rampling, T, et al, Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: a whole-genome sequencing and hospital-based cohort study, The Lancet Infectious Diseases 2021-04-12, DOI:https://doi.org/10.1016/S1473-3099(21)00170-5 , https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00170-5/fulltext

2021-04-15 An ecological study of B.1.1.7 VOC found "*no changes in reported symptoms or disease duration associated with B.1.1.7. [as well as] no evidence that the frequency of reinfections was higher for the B.1.1.7 variant than for pre-existing variants.*" Graham MS, Sudre CH, et al, Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study, The Lancet Public Health 2021-04-12, DOI:https://doi.org/10.1016/S2468-2667(21)00055-4 , https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(21)00055-4/fulltext

2021-04-15 Indeed, inhaled Budesonide in early Covid-19 helps to guard against progression to severe disease, as well as reducing time to recovery. Ramakrishnan S, Nicolau DV, et el, Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial, The Lancet Respiratory Medicine, 2021-04-09, DOI:https://doi.org/10.1016/S2213-2600(21)00160-0 , https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00160-0/fulltext Comment by Agusti A, Torres F, and Faner R, Early treatment with inhaled budesonide to prevent clinical deterioration in patients with COVID-19, The Lancet Respiratory Medicine, 2021-04-09, DOI:https://doi.org/10.1016/S2213-2600(21)00171-5 , https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00171-5/fulltext