Notes on COVID-19

Part 29: 2021-09-01 to 2021-10-31

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2021-10-31

2021-09-18 The UK NHS is to use Ronapreve, the Regeneron-Roche antibody cocktail, to treat those with Covid-19 who do not mount a significant immune response https://www.theguardian.com/world/2021/sep/18/covid-antibody-drug-ronapreve-to-be-given-to-vulnerable-nhs-patients Ronapreve was approved by the MHRA on 2021-08-20 (see my Notes Part 28, entry 2021-08-20).

2021-09-18 Young and colleagues looked at transmission of SARS-CoV-2 in schools during presence schooling in 201 English schools from April 2001 to near the end of June 2001. Schools were assigned to either the intervention protocol or the control protocol, in which neighbours of infected children in school were assigned either to daily LFT testing without quarantine for 7 days ("intervention"), or 10-day quarantine ("control"). No significant difference in transmissibility occurred between intervention and control. The authors also observed that "[i]nfection rates in school-based contacts were low, with very few school contacts testing positive." Young, BC, Eyre DW, et al, Daily testing for contacts of individuals with SARS-CoV-2 infection and attendance and SARS-CoV-2 transmission in English secondary schools and colleges: an open-label, cluster-randomised trial, The Lancet 2021-09-14, DOI: 10.1016/S0140-6736(21)01908-5 , https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01908-5/fulltext There is comment by Viner and Koirala: Viner RM and Koirala A, Daily antigen testing to reduce disruption when schools return, The Lancet 2021-09-14, DOI: 10.1016/S0140-6736(21)02092-4 , https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02092-4/fulltext

This is hugely good news. The PH department in my home city of Bielefeld has recently complained at length in the local newspaper about how tracing of neighbours of infected pupils in school is overreaching their resources, and the city has switched to LFTs and non-quarantining for such neighbours, in the absence of significant evidence that school transmission is high and such quarantining is effective. This is positive evidence that school transmission is generally low and quarantining is no more effective than daily LFTs.

2021-09-18 It appears from the results of the DosCoVeRy trial that remdesivir is no better than standard of care at helping hospitalised Covid-19 patients requiring oxygen support. The trial took place with 857 participants between 2020-03-22 and 2021-01-21 in 48 sites in 5 European countries. Ader F, Bouscambert-Duchamp M, et al, Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial, The Lancet Infectious Diseases 2021-09-14, DOI: 10.1016/S1473-3099(21)00485-0 , https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00485-0/fulltext The

commentators Gyselinck and Janssens note that this is the fifth large trial of remdesivir; they mention the ACTT-1 and WHO Solidarity trials. ACTT-1 showed some benefit to early onset of treatment, and there was some indication of that in the DisCoVeRy results also, but they also point out that in DisCoVeRy and Solidarity, which failed to show significant effects, that there was greater use of steroids (almost half of participants). Gyselinck I and Janssens W, Remdesivir, on the road to DisCoVeRy, The Lancet Infectious Diseases 2021-09-14, DOI: 10.1016/S1473-3099(21)00559-4 , https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00559-4/fulltext

2021-09-18 Mayo Clinic researchers conducted a RCT of Regeneron-Roche's casivirimab-indevimab cocktail on 696 Covid-19 patients at high risk of progression to severe disease, with 696 controls. The outcome was hospitalisation at 14, 21 and 28 days after infusion. The intervention group had significantly lower rates of hospitalisation at all three dates (1.3% vs. 3.3%; 1.3% vs. 4.2%; 1.6% vs. 4.8%). Razonable RR, Pawlowski C, et al, Casirivimab–Imdevimab treatment is associated with reduced rates of hospitalization among high-risk patients with mild to moderate coronavirus disease-19, EClinicalMedicine 2021-08-30, DOI: 10.1016/j.eclinm.2021.101102 , https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00382-5/fulltext

2021-09-18 Baricitinib is a Janus kinase 1 / 2 inhibitor with anti-inflammatory properties. An RCT was performed on hospitalised Covid-19 patients between 2020-06-11 and 2021-01-15 in 101 centres across 12 countries on four continents, enrolling 1525 patients with 764 in the intervention group and 761 in the placebo group. The composite primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28. A secondary endpoint was all-cause mortality by day 28; all-cause mortality by day 60 was an exploratory endpoint. 27.8% of intervention and 30.5% of control participants reached the primary endpoint. All-cause mortality by Day 28 was 8% of baricitinib receivers versus 13% of placebo receivers; by Day 60 it was 10% versus 15% respectively. Adverse events were similar in the two groups. Marconi VC, Ramanan AV, et al, Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial, The Lancet Respiratory Medicine 2021-09-01, DOI: 10.1016/S2213-2600(21)00331-3 , https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00331-3/fulltext . So it looks as if baricitinib does help to prevent Covid-19 patients dying. The commentators Kalil and Stebbing explore why this may be. They compare with the onset of sepsis in bacterial infections, which they suggest may be due to a disregulated immune response that is the result of human evolution in some way, and suggest that baricitinib might well be helping regulate an immune response in the case of Covid-19. Kalil AC and Stebbing J, Baricitinib: the first immunomodulatory treatment to reduce COVID-19 mortality in a placebo-controlled trial, The Lancet Respiratory Medicine 2021-09-01, DOI: 10.1016/S2213-2600(21)00358-1 , https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00358-1/fulltext

2021-09-25 An article in Nature Medicine concerns the poor quality of most studies of the effect of ivermectin on Covid-19 patients. One large study with data problems noted by others has been retracted from the preprint server; another study has so far declined to provide others the data on which it was based. In consequence, a meta-study has been retracted and will be reperformed: “*The*

authors of one recently published meta-analysis of ivermectin for COVID-19 [cited] have publicly stated that they will now reanalyze and republish their now-retracted meta-analysis and will no longer include either of the two papers just mentioned. As these two papers [cited] were the only studies included in that meta-analysis to demonstrate an independently significant reduction in mortality, the revision will probably show no mortality benefit for ivermectin." The authors suggest a change to current practice in that clinical studies should make individual patient data (IPD) available for third-party review and analysis. They acknowledge there need to be basic protection measures in place: "*Hurdles to the release of IPD from clinical trials are well described, and generally addressable with careful anonymization and integration of data sharing plans at the ethical approval stage of trial planning.*" Lawrence JM, Meyerowitz-Katz G, et al, The lesson of ivermectin: meta-analyses based on summary data alone are inherently unreliable, Nature Medicine 2021-09-22, DOI: 10.1038/s41591-021-01535-y , https://www.nature.com/articles/s41591-021-01535-y

2021-10-02 More good news on antivirals. On 2021-10-01 Merck announced an interim analysis of its Phase III trial MOVe-OUT of its oral antiviral molnupiravir developed with Ridgeback Biotherapeutics. The interim analysis suggests the drug, administered to patients with mild or moderate Covid-19 and at high risk of progression to severe disease, reduced the chance of hospitalisation or death "by approximately 50%" https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/

2021-10-06 The "smoking anomaly" has been settled. It was originally thought that smokers were at lower risk of contracting Covid-19 and lower risk of hospitalisation, which was considered to be anomalous, since smokers are people who engage in an activity which causes respiratory inhibition and damage and therefore are more likely to be susceptible to poor outcomes during a bout of respiratory disease. This supposition seems now to be true. A study of over 400,000 records in the UK has shown that smokers are in fact more at risk for hospitalisation and death than never-smokers. Clift AK, von Ende A, et al, Smoking and COVID-19 outcomes: an observational and Mendelian randomisation study using the UK Biobank cohort, BMJ Thorax, 2021-09-27, DOI: 10.1136/thoraxjnl-2021-217080 https://thorax.bmj.com/content/early/2021/09/12/thoraxjnl-2021-217080

2021-10-06 A view in the NEJM on US public health law as it is playing out during Covid-19. Some of it is frightening. "*Taken together, these cases pose new challenges to officials' ability to protect public health.*" ….. "*Emergencies can lead to abuses of authority and the disregard of individual rights. Courts are rightly charged with rectifying such abuses. But in their zeal to protect religious liberty and constrain executive action, courts may be leaving officials with fewer tools to fight Covid-19 and the next pandemic.*" Mello MM and Parmet WE, Public Health Law after Covid-19, N. Eng. J. Med. 2021; 385:1153-1155, 2021-09-23, DOI: 10.1056/NEJMp2112193 https://www.nejm.org/doi/full/10.1056/NEJMp2112193

2021-10-07 A number of reports on vaccine trials (and the Regeneron-Roche antiviral) appeared

during September in the New England Journal of Medicine. I list them here without further comment.

Falsey AR, Sobieszczyk ME, et al, Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine, N. Engl J. Medicine , 2021-09-29, DOI 10.1056/NEJMoa2105290, https://www.nejm.org/doi/full/10.1056/NEJMoa2105290

Weinreich DM, Sivapalasingam S, et al, REGEN_COV Antibody Combination and Outcomes in Outpatients with Covid-19, N. Engl J. Medicine , 2021-09-29, DOI 10.1056/NEJMoa2108163, https://www.nejm.org/doi/full/10.1056/NEJMoa2108163

El Sahly HM, Baden LR, et alEfficacy of the mRNS-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase, N. Engl J. Medicine , 2021-09-22, DOI 10.1056/NEJMoa2113017, https://www.nejm.org/doi/full/10.1056/NEJMoa2113017

Thomas SJ, Moreira ED, et al, Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 months, N. Engl J. Medicine , 2021-09-15, DOI 10.1056/NEJMoa2110345, https://www.nejm.org/doi/full/10.1056/NEJMoa2110345

2021-10-08 The UK government conducted a health planning exercise in February 2016 called Exercise Alice, for a coronavirus epidemic, specifically MERS-CoV. The report on Exercise Alice was obtained by a physician, Dr. Moosa Qureshi, using FOIA. The results were, apparently (I have not read it yet), identification of the need to stockpile PPE, to have effective contact tracing (a WWW-based app was apparently suggested), and entry controls from abroad. All three of these were notoriously problematic during the first two waves of the Covid-19 pandemic.
Dr. Qureshi has published the 23pp report at
https://s3.documentcloud.org/documents/21080373/report-exercise-alice-middle-east-respiratory-syndrome-15-feb-2016.pdf
This all from a TheG article by Robert Booth:
https://www.theguardian.com/politics/2021/oct/07/coronavirus-report-warned-of-impact-on-uk-four-years-before-pandemic

2021-10-10 David Spiegelhalter and Anthony Masters have published a book, Covid by Numbers, based on their weekly stats columns for The Observer. I ordered a copy within a few minutes of finding out about it in their column on 2021-10-10.
https://www.theguardian.com/world/2021/oct/10/covid-by-numbers-10-key-lessons-separating-fact-from-fiction
Some takeaways from the column.
* There were over 1,000 introductions into the UK in and before March 2020, not just one or a few. Known from sequencing the genomes of early cases.
* Reported deaths depend on the day of the week. This is obvious to those who have been watching the numbers. I noticed it with the reported-infection data coming from Bielefeld way back when. Number crunching runs differently at weekends from the way it runs during weekdays.
* In the first year of Covid, the over-90's had 35,000 times the risk of dying from it as young

childred did. Wow!
* The two years in which annual deaths in England and Wales have exceed 600,000 are 1918, the year of the flu pandemic, and 2020, the first year of Covid-19.
* The UK has led the world in testing Covid-19 treatments. Namely, the RECOVERY trial, possible in Britain because of the NHS.
* People who have died with Covid-19 have lost on average some 10 years of life. Very sad indeed.
* Most people died "of" Covid-19 rather than "with" it, although most also had other medical conditions.
* Average alcohol consumption stayed the same during lockdown. Some people drank more, others obviously drank less.
* Most people with SARS-CoV-2 don't infect anyone. It was estimated early on by LSHTM that overdispersion was around 0.1 (first published April 2020, latest version July 2020), meaning around 80% of the cases came from around 10% of the carriers.
* Apparently in the age groups 15-29, there were 300 fewer deaths than the five-year average for England and Wales.

2021-10-30 A cheap, widely available SSRI, fluvoxamine, has achieved very good prophylactic results in an RCT involving 1,497 patients in Brasil. It cuts the death rate by 90% and the chance of severe illness by 65%. The study was coauthored by Angela Reiersen at Washington University in St. Louis, USA, and Edward Mills at McMaster University in Hamilton, Ontario. A ten-day course of fluvoxamine costs about US$4 and it is no longer under patent.
https://www.nature.com/articles/d41586-021-02988-4 The study itself: Reis G, dos Santos Moreira-Silva EA, et al, Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial , The Lancet Global Health, 2021-10-27, DOI: 10.1016/S2214-109X(21)00448-4
https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00448-4/fulltext Comment by Berwanger O, Fluvoxamine for outpatients with COVID-19: where do we stand?, The Lancet Global Health, 2021-10-29, DOI 10.1016/S2214-109X(21)00501-5
https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00501-5/fulltext

2021-10-30 The EAVE-II project in Scotland has collected and analysed essentially all the data on breakthrough infections in Scotland. The database contains 5.4m people, about 99% of the entire population of Scotland. Result: few breakthrough infections after the first dose. "*Between Dec 8, 2020, and April 18, 2021, 2 572 008 individuals received their first dose of vaccine—841 090 (32·7%) received BNT162b2 and 1 730 918 (67·3%) received ChAdOx1. 1196 (<0·1%) individuals were admitted to hospital or died due to COVID-19 illness (883 hospitalised, of whom 228 died, and 313 who died due to COVID-19 without hospitalisation) 14 days or more after their first vaccine dose.*" Agrawal U, Katikireddi SV, et al, COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2·57 million people in Scotland (EAVE II): a prospective cohort study, The Lancet Respiratory Medicine, 2021-09-29, DOI: 10.1016/S2213-2600(21)00380-5
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00380-5/fulltext
Comment by Leshem E, Nelson K and Lopman BA, Severe breakthrough COVID-19 infections in Scotland—implications for immunisation programmes, The Lancet Respiratory Medicine, 2021-09-

29, DOI: 10.1016/S2213-2600(21)00413-6
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00413-6/fulltext

2021-10-30 ECMO is not hugely helpful. An analysis of the International Extracorporeal Life Support Registry showed 4812 patients receiving ECMO in 2020. In the early-adopting group, in-hospital mortality was 36.9%,and after May 1 51.9%. In later-adopting centres, 58.9%. As the commentator points out, ECMO is not a prophylaxis, it is an aid to allow compromised lungs to maybe heal when it is judged they are unlikely to survive the rigours of mechanical ventilation. Barbaro RP, MacLaren G, et al, Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry, The Lancet 2021-09-29, DOI: 10.1016/S0140-6736(21)01960-7
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01960-7/fulltext
Comment by Vuylsteke A, ECMO in COVID-19: do not blame the tool, 2021-09-29, DOI: 10-1016/S0140-6736(21)02137-1
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02137-1/fulltext

2021-10-30 The RECOVERY trial has shown that colchicine does not help hospitalised patients. Colchicine is a drug with anti-inflammatory properties used to treat gout and pericarditis. The RECOVERY Collaborative Group, Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial, The Lancet Respiratory Medicine, 2021-10-18, DOI: 10-1016/S2213-2600(21)00435-5
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00435-5/fulltext

2021-10-30 The Lancet Respiratory Medicine has a lengthy article discussing immunity and immune responses after vaccination against SARS-CoV-2. Milne G, Hames T, et al, Does infection with or vaccination against SARS-CoV-2 lead to lasting immunity? The Lancet Respiratory Medicine, 2021-10-21, DOI: 10.1016/S2213-2600(21)00407-0
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00407-0/fulltext

2021-10-30 The mathematical modelling group at Imperial College has modelled the lifting of non-pharmaceutical interventions against Covid-19 in light of vaccination as well as emergence of the Delta variant. “Our findings show that the risk of a large wave of COVID-19 hospital admissions resulting from lifting NPIs can be substantially mitigated if the timing of NPI relaxation is carefully balanced against vaccination coverage. However, with the delta variant, it might not be possible to fully lift NPIs without a third wave of hospital admissions and deaths, even if vaccination coverage is high. Variants of concern, their transmissibility, vaccine uptake, and vaccine effectiveness must be carefully monitored as countries relax pandemic control measures.”
Sonabend R, Whittler, LK, et al, Non-pharmaceutical interventions, vaccination, and the SARS-CoV-2 delta variant in England: a mathematical modelling study, The Lancet, 2021-10-27, DOI: 10.1016/S0140-6736(21)02276-5
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02276-5/fulltext The Comment by Gabriel Leung considers generally the use of modelling for nowcasting. Leung G, Nowcasting towards sustainable SARS-CoV-2 endemicity, The Lancet, 2021-10-27, DOI: 10.1016/S0140-6736(21)02386-2

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02386-2/fulltext

2021-10-31 There has been a flurry of articles on vaccine and antiviral RCTs published in the New England Journal of Medicine in mid-late September 2021, as well as some further investigations into VITT and pre-VITT syndrome. The DOIs may be read off from the URLs, so I don't give them separately.

The AstraZeneca AZD1222 Clinical Study Group reports on a Phase 3 RCT study in the US, Chile and Peru in Falsey AR, Sobieszczyk ME, et al, for the AstraZeneca AZD1222 Clinical Study Group, Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine, N. Eng. J. Med. 2021-09-29 https://www.nejm.org/doi/full/10.1056/NEJMoa2105290

The Trial Investigators report a relative risk reduction of 71.3% for hospitalisation or death in a Phase 3 trial of the REGEN-COV antibody cocktail of casivirimab and imdevimab in Weinrich DM, Sivapalasingam S, et al, REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19, N. Eng. J. Med. 2021.09-29 , https://www.nejm.org/doi/full/10.1056/NEJMoa2108163

The Vaccine Effectiveness Among Healthcare Personnel Study Team reports an effectiveness of 77.6% after one dose and 88.8% with full vaccination for BNT162B2 (Pfizer-BioNTech) and 88.9% after one dose and 96.3% with full vaccination for mRNA-1273 (Moderna). Pilishvili T, Gierke R et al, Effectiveness of mRNA Covid-19 Vaccine among U.S. Health Care Personnel, N. Eng. J. Med. 2021-09-22, https://www.nejm.org/doi/full/10.1056/NEJMoa2106599

The COVE Study Group reports an efficacy of 94.1% at the completion of the blinded phase of an RCT for mRNA-1273 (Moderna), after which the trial went to open-label. El Sahly HM, Baden LR, et al, Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase, N. Eng. J. Med. 2021-09-22, https://www.nejm.org/doi/full/10.1056/NEJMoa2113017

The C4591001 Clinical Trial Group reports an efficacy of 91.3% for BNT162b2 (Pfizer-BoiNTech) through 6 months. Thomas SJ, Moreira Jr ED, et al, Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months, N. Eng. J. Med. 2021-09-15, https://www.nejm.org/doi/full/10.1056/NEJMoa2110345

Bar-On et al report the effectiveness of a booster dose of BNT162B2 (Pfizer-BioNTech) after 5 months in over-60s. "*At least 12 days after the booster dose, the rate of confirmed infection was lower in the booster group than in the nonbooster group by a factor of 11.3 (95% confidence interval [CI], 10.4 to 12.3); the rate of severe illness was lower by a factor of 19.5 (95% CI, 12.9 to 29.5). In a secondary analysis, the rate of confirmed infection at least 12 days after vaccination was lower than the rate after 4 to 6 days by a factor of 5.4 (95% CI, 4.8 to 6.1).*" Bar-On YM, Goldberg Y, et al, Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel, N. Eng. J. Med. 2021-10-07, https://www.nejm.org/doi/full/10.1056/NEJMoa2114255

Thompson et al looked at the effectiveness of vaccines in the situations of ambulatory and inpatient care in the US. "*The effectiveness of full messenger RNA (mRNA) vaccination ... was 89% ...*

against laboratory-confirmed SARS-CoV-2 infection leading to hospitalization, 90% ... against infection leading to an ICU admission, and 91% .....against infection leading to an emergency department or urgent care clinic visit." Thompson MG, Stenehjem E, et al, Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings, N. Eng. J. Med. 2021-10-07 https://www.nejm.org/doi/full/10.1056/NEJMoa2110362

Barda et al investigated the safety of BNT162B2 nationwide in Israel. "[T]*he BNT162b2 vaccine was not associated with an elevated risk of most of the adverse events examined. The vaccine was associated with an excess risk of myocarditis (1 to 5 events per 100,000 persons). The risk of this potentially serious adverse event and of many other serious adverse events was substantially increased after SARS-CoV-2 infection.*" Barda N, Dagan N, et al, Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting, N. Eng. J. Med. 2021-09-16, https://www.nejm.org/doi/full/10.1056/NEJMoa2110475

The team around Andreas Greinacher in Greifswald has looked at the decline of anti-PF4 IgG antibodies over time in VITT (VITT is caused by these antibodies) in 35 patients with VITT (27 women, 8 men). The median follow-up was 11 weeks. "*Our study indicates that anti-PF4 antibodies are transient in most patients with VITT. In a subgroup of these patients, pathogenic platelet-activating anti-PF4 antibodies may persist for more than 12 weeks. Further studies are needed to clarify whether these patients should receive prolonged anticoagulation or additional treatment.*" Schönborn L, Thiele T, et al, Decline in Pathogenic Antibodies over Time in VITT, N. Eng. J. Med. 2021-09-08, https://www.nejm.org/doi/full/10.1056/NEJMc2112760

Salih et al present evidence that "*vaccine-induced thrombocytopenia (VIT) without associated cerebral venous sinus thrombosis (CVST) or other thromboses and with severe headache as the heraldic symptom may precede VITT ("pre-VITT syndrome").*" Salih F, Schönborn L, et al, Vaccine-Induced Thrombocytopenia with Severe Headache, N. Eng. J. Med. 2021-09-15, https://www.nejm.org/doi/full/10.1056/NEJMc2112974