Notes on COVID-19

Part 23: 2021-02-01 to 2021-02-28

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2021-02-28

2021-02-01 Stringhini and colleagues conducted a second seroprevalence survey in Geneva in Nov.-Dec. 2020. Stringhini S et al, Seroprevalence of anti-SARS-CoV-2 antibodies after the second pandemic peak, The Lancet Infectious Diseases 2021-02-01, DOI:https://doi.org/10.1016/S1473-3099(21)00054-2 https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00054-2/fulltext They found that seroprevalence had roughly doubled over the results during the "first wave", to 21·1% (95% credible interval 19·2–23·1). "*Compared with adults aged 25–34 years, children aged 6 years and older and adolescents had similar seroprevalence, whereas children aged 0–5 years were 43% less likely to be seropositive, and adults aged 65–74 years and those aged 75 years and older were 42% and 64% less likely to be seropositive, respectively*." Their data thus indicates that young childen (under 5) have about half the infection risk of older children and adults.

2020-02-04 Hunter and Brainard at the University of East Anglia have analysed data from Israel on one shot of bnt162b2 and found that it gives above 90% protection after 21 days. News report https://www.theguardian.com/world/2021/feb/03/one-pfizerbiontech-jab-gives-90-immunity-from-covid-after-21-days In Israel, there was an increase in infection in the 8 days immediately following the vaccination, which researchers suspect might well be involved with a change in behaviour. The preprint is: Hunter PR and Brainard JS, Estimating the effectiveness of the Pfizer COVID-19 BNT162b2 vaccine after a single dose. A reanalysis of a study of 'real-world' vaccination outcomes from Israel, MedRXiv https://www.medrxiv.org/content/10.1101/2021.02.01.21250957v1 , 2020-02-03 doi: https://doi.org/10.1101/2021.02.01.21250957

2020-02-04 Interim results from a Phase 3 trial of the Russian rAd26/rAd5 combination vaccine, aka Gam-COVID-Vac, show it is over 90% efficacious. It involved almost 22,000 participants over 25 clinics and hospitals in Moscow. Logunov DY et al, Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia, The Lancet, 2020-02-02, DOI: https://doi.org/10.1016/S0140-6736(21)00234-8 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00234-8/fulltext Comment by
Jones I and Roy P, Sputnik V COVID-19 vaccine candidate appears safe and effective, The Lancet, 2020-02-02, DOI: https://doi.org/10.1016/S0140-6736(21)00191-4
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00191-4/fulltext

2020-02-05 An inexpensive drug used to treat gout has been found beneficial to hospitalised Covid-19 patients. The RCT was small, enrolling 75 patients and having 72 complete. The trial took place from April to August 2020 in Brasil. The results: "*Median (and IQR) time of need for supplemental*

oxygen was 4.0 (2.0–6.0) days for the colchicine group and 6.5 (4.0–9.0) days for the placebo group (p<0.001). Median (IQR) time of hospitalisation was 7.0 (5.0–9.0) days for the colchicine group and 9.0 (7.0–12.0) days for the placebo group (p=0.003). At day 2, 67% versus 86% of patients maintained the need for supplemental oxygen, while at day 7, the values were 9% versus 42%, in the colchicine and the placebo groups, respectively (log rank; p=0.001). Two patients died, both in placebo group. Diarrhoea was more frequent in the colchicine group (p=0.26)."
Lopez MI, Bonjorno LP, Giannini MC et al, Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial, RMD Open 2021;7:e001455. doi: 10.1136/rmdopen-2020-001455
https://rmdopen.bmj.com/content/7/1/e001455
Colchicine is also being evaluated in the RECOVERY trial https://www.recoverytrial.net

2021-02-10 An important further study of the ChAdOx1-nCoV19/AZD1222 vaccine data is available in Lancet preprint form. There are two key points. First, a single dose provided protection against symptomatic Covid-19 with an efficacy of 76% for 90 days, and showed no evidence of waning in this period. Second, a single dose reduced PCR positivity by 67%, which suggests it is reducing infectivity by two-thirds. That will surely help to get and keep R_0 below 1, since it was thought to be between 2 and 3. But new variants might well have a higher R_0. Two quotes:
p14: "*Protection against primary symptomatic COVID-19 with a single SD vaccine was modelled against time since the first dose and showed no evidence of waning of protection in the first 3 months after vaccination (Figure 2A). A single standard dose of vaccine provided protection against primary symptomatic COVID-19 in the first 90 days of 76%, (95%CI, 59%, 86%), but did not provide protection against asymptomatic infection in the same period (VE 16%, 95% CI - 88%, 62%). (Table 2)*
However, overall cases of any PCR+ were reduced by 67% (95%CI 49%, 78%) after a single SD vaccine suggesting the potential for a substantial reduction in transmission."

p18: "*A further important question is whether vaccines can provide impact against transmission, and therefore combined with physical distancing measures contribute to reductions in human to human transmission of the virus. While transmission studies per se were not included in the analysis, swabs were obtained from volunteers every week in the UK study, regardless of symptoms, to allow assessment of the overall impact of the vaccine on risk of infection and thus a surrogate for potential onward transmission. If there was no impact of a vaccine on asymptomatic infection, it would be expected that an efficacious vaccine would simply convert severe cases to mild cases and mild cases to asymptomatic, with overall PCR positivity unchanged. A measure of overall PCR positivity is appropriate to assess whether there is a reduction in the burden of infection. Analyses presented here show that a single standard dose of the vaccine reduced PCR positivity by 67%, and that, after the second dose, the SD/SD schedule reduced PCR positivity by 49.5% overall. These data indicate that ChAdOx1 nCoV-19, used in the authorised schedules, may have a substantial impact on transmission by reducing the number of infected individuals in the population.*"

Voysey M, Costa Clemens SA et al, Single Dose Administration, And The Influence Of The Timing Of The Booster Dose On Immunogenicity and Efficacy Of ChAdOx1 nCoV-19 (AZD1222) Vaccine, 2021-02-01 https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268

2021-02-11 Inhaled budesonide appears to mitigate Covid-19 if taken during the early symptomatic phase of the illness. A small randomised open-label trial in Oxford gave inhaled budesonide or "usual care" to about 140 early-symptomatic people. 10 of the usual care group ended up visiting hospital or in hospital, whereas only 1 of the budesonide group did. The budesonide group also had fewer and milder symptoms one Days 14 and 28 compared with the usual care group.
Sanjay Ramakrishnan S, Nicolau Jr. DV et al, Inhaled budesonide in the treatment of early COVID-19 illness: a randomised controlled trial, 2021-02-08,
doi: https://doi.org/10.1101/2021.02.04.21251134
https://www.medrxiv.org/content/10.1101/2021.02.04.21251134v1.full.pdf
The study is directed by Prof. Mona Bafadhel, the corresponding author.

Very promising. I have used the stuff for nearly 25 years (in its form as Pulmicort) for a couple of days in the spring when certain plants are pollinating (I don't know which) and my airways itch, but in the last few years I haven't needed it. Time to renew the prescription…..

2021-02-11 On 2021-02-10, the WHO recommended ChAdOx1-nCoV19/AZD1222 for use in all adults, without restriction https://www.theguardian.com/world/2021/feb/10/who-backs-use-of-oxfordastrazeneca-covid-vaccine-for-adults-of-all-ages I cannot access the relevant WHO download pages at the moment for the original documents. This recommendation enables use of the vaccine in all countries (much of the world) which do not have their own medical regulator capable of analysing the data.

2021-02-12 The RECOVERY trial has published results of its study of tocilizumab, with about 4000 hospital patients enrolled, on breathing support (55%) or supplementary oxygen (45%). About half received tocilizumab and half the standard of care, with 82% receiving corticosteroids. 29% of the patients receiving tocilizumab and 33% of the patients receiving usual care died within 28 days. "*Patients allocated to tocilizumab were more likely to be discharged from hospital alive within 28 days (54% vs. 47% ….). Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (33% vs. 38% …..). Interpretation: In hospitalised COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes regardless of the level of respiratory support received and in addition to the use of systemic corticosteroids*."
Horby PW, Campbell M et al, Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial, preprint, MedRXiv, 2020-02-11 https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

The Remap-CAP trial had also shown a benefit of tocilizumab (Notes Part 22, entry of 2021-01-08). RECOVERY has apparently shown benefit in a wider range of patients. Looking at 33% versus 38% may not seem that impressive, but the exact difference is some 14%, which is the takeaway, i.e., use of tocilizumab reduces the risk of death by about 14%. And this is in addition to use of corticosteroids. TheG quotes joint chief investigator Peter Horby: "*We think about half the patients admitted would benefit from this drug based on our calculations……. We think that can be*

happening almost immediately." TheG also quotes joint chief investigator Martin Landray: "*Now we can reduce the risk of death by anything between about a third and up to half [compared with spring last year], depending on exactly which patients are treated.*" Tocilizumab is, however, not cheap, costing about £500 per dose. https://www.theguardian.com/world/2021/feb/11/arthritis-drug-tocilizumab-found-to-help-covid-icu-patients-has-wider-benefits-trial-finds

This is significant, not only because it is a another concrete result of RECOVERY https://www.recoverytrial.net but because it, along with the Remap-cap results clearly demonstrate benefit to tocilizumab, whereas other trials had exhibited mixed results.

2021-02-13 A study of seroprevalence amongst very young children in day care, the carers, and a comparator group was performed in France in mid-2020. Almost 330 children were enrolled, almost 200 day care staff, and just over 160 adults in the comparator group. 14 children (4.3%) were seropositive, as well as 14 staff (7.7%). After adjustment for sensitivity and specificity of the assay, these percentages were revised to 3.7% and 6.8%. The comparator group had raw 5.5%, adjusted 5.0% seropositivity. It appeared that seropositive children were more likely than seronegative children to have been exposed to an adult household member with lab-confirmed COVID-19.

This is to my knowledge the first clear evidence that (a) COVID-19 is less prevalent amongst very young children in day care than amongst adults, and that (b) COVID-19 is only slightly more prevalent amongst day care workers that in the general adult population, as well as that (c) day care does not appear to be the most significant transmission environment for young kids. The summary is worth quoting in full.

"*Findings*
Between June 4 and July 3, 2020, we enrolled 327 children (mean age 1·9 [SD 0·9] years; range 5 months to 4·4 years), 197 daycare centre staff (mean age 40 [12] years), and 164 adults in the comparator group (42 [12] years). Positive serological tests were observed for 14 children (raw seroprevalence 4·3%; 95% CI 2·6–7·1) and 14 daycare centre staff (7·7%; 4·2–11·6). After accounting for imperfect sensitivity and specificity of the assay, we estimated that 3·7% (95% credible interval [95% CrI] 1·3–6·8) of the children and 6·8% (3·2–11·5) of daycare centre staff had SARS-CoV-2 infection. The comparator group fared similarly to the daycare centre staff; nine participants had a positive serological test (raw seroprevalence 5·5%; 95% CI 2·9–10·1), leading to a seroprevalence of 5·0% (95% CrI 1·6–9·8) after accounting for assay characteristics. An exploratory analysis suggested that seropositive children were more likely than seronegative children to have been exposed to an adult household member with laboratory-confirmed COVID-19 (six [43%] of 14 vs 19 [6%] of 307; relative risk 7·1 [95% CI 2·2–22·4]).
Interpretation
According to serological test results, the proportion of young children in our sample with SARS-CoV-2 infection was low. Intrafamily transmission seemed more plausible than transmission within daycare centres. ....."

Lachassine E, de Pontual L et al, SARS-CoV-2 transmission among children and staff in daycare centres during a nationwide lockdown in France: a cross-sectional, multicentre, seroprevalence

study, The Lancet Child & Adolescent Health, 2021-02-08, DOI:https://doi.org/10.1016/S23524642(21)00024-9 , https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00024-9/fulltext

2020-02-13 The Lancet COVID Commission has published three main recommendations for 2021. First, areas of high prevalence (including Europe and the US) should intensify containment measures and rapidly deploy vaccines. Second, governments should urgently and fully fund the WHO and the ACT, including COVAX. Third, the G20 should empower the IMF and multilateral development banks to increase financing and debt relief.
Commissioners of The Lancet COVID Commission et al, Priorities for the COVID-19 pandemic at the start of 2021: statement of the Lancet COVID-19 Commission, The Lancet, 2021-02-12, DOI:https://doi.org/10.1016/S0140-6736(21)00388-3 , https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00388-3/fulltext

2021-02-18 Masks have been shown to help in terms of dampening infection rates in the US. Early-adopting US states fared better than late-adopting states, and both better than not-adopting states in new-infection rates. Rebeiro PF, Aronoff DM and Smith MK, The Impact of State Mask-Wearing Requirements on the Growth of COVID-19 Cases in the United States, Clin. Inf. Dis. 2021 Feb 7;ciab101. doi: 10.1093/cid/ciab101

2021-02-24 Two French universities, in Lille and Marseille, have developed a fast almost-real-time Covid-19 electrochemical test, which is said to be comparably accurate to PCR. Only a news report and a press release so far https://www.theguardian.com/world/2021/feb/23/new-covid-test-delivers-results-three-times-faster-than-lateral-flow

2021-02-24 A report on the EU's approach to vaccination approval and distribution by Rob Hyde in The Lancet. Hyde R, von der Leyen admits to COVID-19 vaccine failures, 2020-02-20 DOI:https://doi.org/10.1016/S0140-6736(21)00428-1 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00428-1/fulltext

2021-02-24 The efficacy of AZD1222 was investigated after one dose, from the available trials data. From the findings: "*Exploratory analyses showed that vaccine efficacy after a single standard dose of vaccine from day 22 to day 90 after vaccination was 76·0% (59·3–85·9).*"
Voysey M, Costa Clemens SA et al, Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials, The Lancet, 2021-02-19, DOI:https://doi.org/10.1016/S0140-6736(21)00432-3 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00432-3/fulltext

2021-02-24 TheG is also reporting PHE and PHS studies into the efficacy of one dose of either AZD1222 or BNT162b2. The results appear to be at least as good as the analysis of Voysey, Costa Clemens et al (see last item) demonstrates.
https://www.theguardian.com/world/2021/feb/22/one-vaccine-protection-severe-covid-evidence

2021-02-26 About a quarter of the Scottish population has already received one dose of a vaccine. A university/Public Health Scotland study has shown that hospital admissions have considerably reduced.
News story: Torjesen, I, Covid-19: First doses of vaccines in Scotland led to a substantial fall in hospital admissions, BMJ 2021; 372 doi: https://doi.org/10.1136/bmj.n523 2021-02-22 (Cite this as: *BMJ* 2021;372:n523) https://www.bmj.com/content/372/bmj.n523
Preprint of study paper: Vasileiou E, Simpson CR, Robertson C, et al. Effectiveness of first dose of covid-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people. [Preprint.] 2021,
https://www.ed.ac.uk/files/atoms/files/scotland_firstvaccinedata_preprint.pdf

2021-02-26 A study of just under 1.2m people, half vaccinated with BNR162b2 and half not, in Israel has shown similar effectiveness of the vaccine as in the trials. "*Each study group included 596,618 persons. Estimated vaccine effectiveness for the study outcomes at days 14 through 20 after the first dose and at 7 or more days after the second dose was as follows: for documented infection, 46% (95% confidence interval [CI], 40 to 51) and 92% (95% CI, 88 to 95); for symptomatic Covid-19, 57% (95% CI, 50 to 63) and 94% (95% CI, 87 to 98); for hospitalization, 74% (95% CI, 56 to 86) and 87% (95% CI, 55 to 100); and for severe disease, 62% (95% CI, 39 to 80) and 92% (95% CI, 75 to 100), respectively. Estimated effectiveness in preventing death from Covid-19 was 72% (95% CI, 19 to 100) for days 14 through 20 after the first dose. Estimated effectiveness in specific subpopulations assessed for documented infection and symptomatic Covid-19 was consistent across age groups, with potentially slightly lower effectiveness in persons with multiple coexisting conditions.*" Dagan N, Barda N, et al, BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting, N. Eng. J. Med. 2021-02-24 DOI: 10.1056/NEJMoa2101765
https://www.nejm.org/doi/full/10.1056/NEJMoa2101765

2021-02-28 It seems the German standing commission on vaccination, StIKo, is about to change its mind on not recommending AZD1222 for the over-65's, Philip Oltermann and Robin McKie report in TheG on 2021-02-27 https://www.theguardian.com/world/2021/feb/27/germany-signals-astrazeneca-vaccine-may-be-approved-for-over-65s There are two very good reasons for this that I see. First, StIKo said "not recommended" and this has largely been interpreted as "recommended not"; they had declined to issue a recommendation, they had not recommended against (StIKo had said that there was not enough data on over-65's for them to draw a conclusion). Second, Daniel Boffey reported in TheG on 2021-02-25 that almost 1.5m doses of AZD1222 have been delivered to Germany and less than 200,000 used. The 1.3m doses are just sitting there, waiting for takers. To put it bluntly, this is silly. How can the government be saying, on the one hand, that "*we don't have enough vaccine and people must be patient*", and, on the other, sitting on 1.3m unused doses?
https://www.theguardian.com/world/2021/feb/25/acceptance-problem-as-most-oxford-covid-jabs-delivered-to-eu-not-yet-used

2021-02-28 The US FDA has issued an EUA for the Janssen (Johnson & Johnson) Ad26.COV2.S vaccine. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-third-covid-19-vaccine The vaccine is one-shot, based on a human adenovirus

(number 26), modified so that it does not replicate (if replicative, it can cause mild illness) with DNA for the SARS-CoV-2 spike protein attached. So it makes S and the immune system reacts to S. The FDA briefing document is available at https://www.fda.gov/media/146217/download

2021-02-28 Coroneo and Collignon argue in The Lancet Microbe that eye protection may be more important than we appear to be treating it.
Coroneo MT and Collignon PJ, SARS-CoV-2: eye protection might be the missing key, The Lancet Microbe 2021-02-23 DOI: 10.1016/S2666-5247(21)00040-9
https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00040-9/fulltext

2021-02-28 The US National Academies of Sciences, Engineering and Medicine held a workshop on airborne transmission of SARS-CoV-2, with a number of luminaries, in October 2020. I have just read the (short) proceedings (18pp). I wish I had read them back in Autumn 2020 but better late than never. It is available free from https://www.nap.edu/catalog/25958/airborne-transmission-of-sars-cov-2-proceedings-of-a-workshop but the National Academies Press WWW site requires you to register with them to download. The workshop anticipates much of what is now consensual understanding on droplet and aerosol transmission, but one aspect in particular is worth noting. There is considerable divergence between "infectious disease practitioners" (this apparently means medics involved in infectious disease medicine, not people who go around spreading diseases) and aerosol scientists on the size of particle which can constitute an aerosol. The arbitrary medical size difference is less than 5 microns (μm, a millionth of a metre) for aerosols and greater than 5 μm for droplets. Table 1 calls this "*Traditional Thinking (based on longstanding misconceptions, not informed by aerosol science*". The physical distinction is between what remains or can remain suspended in the air for a period of time, and what falls to the ground in a short while under gravity. Aerosols can contain particles up to about 100 μm; anything larger is more or less a droplet which falls to the ground inside about 2m, depending on the aerial environment and how it was discharged. (This observation is credited to the talk by Linsey Marr of Virginia Tech U., reported in the paragraph Overview of Aerosols and Transmission of Respiratory Viruses, pp4-5.) There is also a distinction between transmission modes: "*Droplets are sprayed on to the body and its mucus membranes, a form of contact transmission, while aerosols are inhaled into the respiratory system.*" Lidia Morawska (Queensland U. Tech.) noted that "*The smallest aerosols are probably ..... associated with speaking and singing. Larger aerosol particles and droplets are associated with specific ... speech articulation movement, as well as coughing and sneezing.*" Further, "*[t]he vast majority of aerosols observed in human breath are <10 μm. Breathing, talking, and singing produce ~100– 1,000× more aerosol particles (<100 μm) than droplets (>100 μm).*" Enough quotation for now – the full report is replete with useful information.