

Notes on COVID-19

Part 21: 2020-12-03 to 2020-12-31

Peter Bernard Ladkin
2020-12-31

2020-12-09 I was asked yesterday about the likelihood of masks causing unhealthy (re)inhalation of CO₂ trapped under the mask. Apparently it is a meme doing the rounds. I couldn't answer it right away, because I didn't have the numbers. But, once I did, simple arithmetic shows any effect is negligible. An adult breath is about 500 ml in volume. The air volume trapped under a mask is 5-10 ml, so 1%-2% of the breath volume. It follows that at least 98%-99% of each exhalation goes outside the mask, and the same proportion, 98%-99%, must be breathed in from outside air through the mask. The volume of airspace in the alveolar region of the lungs, in which the oxygen-CO₂ exchange takes place, is 150-200 ml. So at most 2/5 of each breath can contain CO₂ from the gas exchange in the alveoli, which makes 1-2 ml in the "mask space" which then can be rebreathed (as of course can any of the air surrounding the mouth-nose region in the next breath). That makes at most 0.4% of the air in the next breath consisting of CO₂ trapped in the mask since the last breath, a trivial amount. Numbers from <https://correctiv.org/faktencheck/hintergrund/2020/09/25/was-passiert-wirklich-wenn-der-co2-gehalt-unter-einer-stoffmaske-gemessen-wird-ein-experiment/> (in German), which also points out that the volume under the mask is a trivial physical extension of the mouse-nose-throat space where most breathed air briefly resides.

2020-12-09 A research letter from Amendola et al in Emerging Infectious Diseases 27(2) (Feb 2021) describes identification of SARS-CoV-2 in an oropharyngeal swab taken from a 4 year old child in Milan in early December 2019. https://wwwnc.cdc.gov/eid/article/27/2/20-4632_article In an article in Science of the Total Environment 750(1) dated January 1, 2021, La Rosa et al describe identification of SARS-CoV-2 in wastewater in Milan in mid-December 2019; also in Bologna end-January 2020. <https://www.sciencedirect.com/science/article/pii/S0048969720352402> So the virus was circulating in distinct geographical regions in Italy well before the first case of Covid-19 was identified.

2020-12-17 Voysey et al have published the interim analysis of the Phase 3 trials of the Oxford ChAdOx1 nCov-19 vaccine in The Lancet on 2020-12-08 [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32661-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext) The comment by Knoll and Wonodi emphasises the extent of the trials, the low cost of the vaccine, and its potential ease of logistics (transportation, distribution, storage) [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32623-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32623-4/fulltext)

2020-12-17 Flasche and Edmunds comment in The Lancet Infectious Diseases on 2020-12-08 on transmission of SARS-CoV-2 amongst schoolchildren. [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30927-0/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30927-0/fulltext) They make a number of important points. First, a study of school-age children which looked at Covid-19 illness found no great prevalence of Covid-19 amongst pupils attending school. Flasche and Edmunds note that, where symptom-agnostic testing was carried out, there was noticeably greater prevalence of SARS-CoV-2 amongst the children. They note *"Two large-scale, population-based swabbing studies have been set up in the UK in which households or individuals are randomly selected and offered a test for the presence of SARS-CoV-2. Both studies have shown that since September, when schools, universities, and colleges have been fully open, the highest rates of infection have been*

observed in young adults (about 18–25 years old). However, the next highest prevalence has been observed in secondary school children (11–18 years old), suggesting that they are likely to be an important source of infection to peers and others rather than a sink. Yet, primary school children (5–11 years old) have been found to have an infection prevalence comparable to that of working-aged adults.” They also note high attack rates noted during some early outbreaks amongst school-age children, and remark on UK ONS COVID-19 infection survey data: “preliminary modelling analyses based on data from the UK Office for National Statistics’s COVID-19 infection survey found that secondary school-aged children are about eight times more likely to introduce an infection to a household than adults. If restricted to only data up to September, when secondary schools were predominantly closed, that probability was only marginally higher than that of adults.” They note that the study by Ismail et al used largely passive data collection (only identifying symptomatic cases).

Flasche and Edmunds draw the obvious conclusion: “So how can we reconcile the growing evidence that children attending school seem to have an important role in transmission of SARS-CoV-2 with the evidence from Ismail and colleagues’ study? The answer is likely to lie in the low probability that children will experience disease that would have been picked up by the passive surveillance during the study period. This would imply that many outbreaks would have been missed and have been larger than identified. Furthermore, the partial reopening of schools in June and July with small bubbles and much fewer children attending, particularly in secondary education, might have led to considerably less within-school transmission than the reopening of schools to all children after the summer. In summary, Ismail and colleagues’ study supports the notion that opening of schools despite SARS-CoV-2 circulation in the community is largely safe for children, but secondary schools in particular might nevertheless play a considerable role in transmission between households.”

2020-12-17 Meyerowitz et al discuss in The Lancet Infectious Diseases on 2020-12-07 the characterisation of asymptomatic cases of SARS-CoV-2 infection [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30837-9/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30837-9/fulltext) They note that many studies reporting asymptomatic cases included a fair proportion of what turned out to be presymptomatic cases, namely people asymptomatic at time of testing who later developed symptoms. They suggest a 14-day follow up would distinguish the majority of presymptomatics from those truly asymptomatic. They also note various different classifications of symptoms, listing four, from WHO, ECDC, US CDC, and the Canadian government and indicate their preference for the Canadian definition. They note it took quite a while for some symptoms, such as anosmia and dysgeusia, as well as gastrointestinal involvement to be acknowledged. They propose, reasonably, that it is important to understand the characteristics of the truly-asymptomatic cohort and suggest that classification needs to be more thorough.

2020-12-17 Jacqui Wise points out in the BMJ on 2020-12-15 that the rapid lateral-flow tests used in the mass testing project in Liverpool missed about half the presymptomatic/asymptomatic cases <https://www.bmj.com/content/371/bmj.m4848> That is really not helpful, especially when/if those tests are used for university students, and for visitors to care homes.

2020-12-17 The BMJ and the Health Services Journal have published on 2020-12-15 a joint editorial by Alistair McLellan and Fiona Godlee warning, as iSAGE has done, that Christmas get-togethers could well result in the NHS being overwhelmed <https://www.bmj.com/content/371/bmj.m4847> As we now know, ministers did not decide on 2020-12-16 to restrict further the festivities allowed/recommended/encouraged/discouraged over Christmas.

2020-12-17 Martin McKee summarises in the BMJ on 2020-12-11 the observations of a very

critical NAO report into the (non- or not-very-well-)functioning Test & Trace organisation in the UK <https://blogs.bmj.com/bmj/2020/12/11/martin-mckee-nhs-test-and-trace-under-fire-a-system-flawed-by-design/> He highlights the failure to draw on international experience (all effective trace systems operating elsewhere are run by civil service) and a lack of engagement with public health professionals, who know better how to get such processes working than people seconded from other types of work.

2020-12-17 Polack et al report in the NEJM on 2020-12-10 preliminary results from about 45,000 participants in the Phase 3 trial of the Pfizer/BioNTech bnt162b2 vaccine for Covid-19 <https://www.nejm.org/doi/full/10.1056/NEJMoa2034577>

2020-12-17 Kalil et al report in the NEJM on 2020-12-11 on an RCT of baricitinib with remdesivir in the treatment of oxygen-supported or non-invasive-ventilated hospitalised Covid-19 patients. <https://www.nejm.org/doi/full/10.1056/NEJMoa2031994> The combination therapy reduced time to recovery (10 days versus 18 days in the control group), as well as the occurrence of adverse events.

2020-12-19 Eric Topol considers the ins and outs of AI-based diagnostic tools for various aspects of Covid-19, from forced coughing into a smart phone or internet microphone to interpretation of scan images. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32589-7/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32589-7/fulltext) Topol points out weaknesses of such studies as have been done, in particular generalisation and replication. Because it is hard for people to tell what deep-learning neural networks (DLNNs) are actually doing, their parameters of adaptability are obscure and the best that can be said is: these are the results for *this* cohort. Topol gives two examples of studies with initially promising results in which replication gave poor results. His conclusion: “*Until we have definitive evidence and replication and external validation, with all the caveats discussed here, that AI can be used to provide an accurate diagnosis of COVID-19 from a forced cough, we should resist the notion—no matter how alluring it seems.*”

2020-12-20 Peter Cobbold highlights in a letter to the BMJ on 2020-12-17 the possible importance of the antimicrobial peptide Cathelicidin LL37, found in saliva <https://www.bmj.com/content/371/bmj.m4838/rapid-responses> LL37 apparently binds in vitro as effectively to Spike as ACE2 does (new, from 2020-12-04) <https://www.biorxiv.org/content/10.1101/2020.12.02.408153v2> . It is already known that higher levels of LL37 are associated with periodontal health <https://link.springer.com/article/10.1007/s10989-020-10047-1> Cobbold suggests that bodily production of LL37 may be enhanced by sufficient levels of Vitamin D3. Jacqui Wise discusses the NICE-SACN-PHE view on Vitamin D and Covid-19 in the BMJ also on 2020-12-17 <https://www.bmj.com/content/371/bmj.m4912> NICE thinks the evidence is still out on Vitamin D and Covid-19 <https://www.nice.org.uk/guidance/ng187> A recent metastudy of RCTs testing whether Vitamin D helped prevent acute respiratory infections by Joliffe et al was published in preprint in MedRxiv on 2020-11-25 <https://www.medrxiv.org/content/10.1101/2020.07.14.20152728v3> A previous metastudy of 25 RCTs, with positive results, was published in 2017, and since then a further 20 RCTs have been completed, which the authors include. Their findings: “*Vitamin D supplementation was safe and reduced risk of ARI, despite evidence of significant heterogeneity across trials. Protection was associated with administration of daily doses of 400-1000 IU vitamin D for up to 12 months.*” The possible effects of Vitamin D levels on Covid-19 in particular are not yet known from such metastudies.

One “guru” of Vitamin D's effects on the immune system is Michael Holick of Boston Uni. He has performed two studies this year. One correlated seroprevalence of SARS-CoV-2 infection with levels of 25[OH]D (25-hydroxyvitamin D), a metabolite of Vitamin D3 in the blood, in around

190,000 cases in the US. There is a clear inverse relationship according to his graphs, and it is strong. PLOS One paper

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0239252> . He and his colleagues also found an inverse relationship between 15-hydroxyvitamin-D levels and severity of Covid-19 progress in hospitalised patients

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0239799>

Holick talks about this in a video (first 20+ minutes or so) at

<https://www.youtube.com/watch?v=8UzpvtrQleY&feature=youtu.be>

The health educator John Campbell has also vlogged regularly about Vitamin D and Covid-19, for example <https://www.youtube.com/watch?v=HxtddpoPMKo>

2020-12-22 Sayampanathan et al report in The Lancet on 2020-12-18 that, using data from the contact-tracing-and-quarantine practice in Singapore, "*the incidence of COVID-19 among close contacts of a symptomatic index case was 3.85 times higher than for close contacts of an asymptomatic index case (95% CI 2.06–7.19; $p < 0.0001$)*".

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32651-9/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32651-9/fulltext) This is the best estimate yet of comparative infectivity.

2020-12-29 Cresswell et al consider the impact of cloud-computing technology on health care during the pandemic, in The Lancet Digital Health dated January 2021

[https://www.thelancet.com/journals/landig/article/PIIS2589-7500\(20\)30291-0/fulltext](https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30291-0/fulltext) The article written in a style that I find barely readable. It makes some excellent points, but not with the clout that, as an informatician, I think they need.

2020-12-29 Pollock and Lancaster consider asymptomatic transmission of SARS-CoV-2 in the BMJ on 2020-12-21 <https://www.bmj.com/content/371/bmj.m4851> They indicate that the proportion of (truly) asymptomatics is 17%-20% (cited sources I used in my ScSS'21 paper). They also note that there is little, and variable, evidence for the prevalence of asymptomatic transmission. Transmission occurs of course with viable virus. PCR tests measure RNA, not viable virus; the only way to measure viable virus is with cell cultures, so it is not really known how much of the viral load of an asymptomatic SARS-CoV-s carrier is viable and thereby infectious. They note that no study successfully cultivated virus after the 9th day of illness from symptomatic Covid-19 sufferers, despite continued high viral loads. They also note that, although viral loads in symptomatic and asymptomatic carriers are similar, the duration in asymptomatics is shorter, which suggests they are less infectious. They also note that coughing, a prominent symptom, is likely to shed more virus than breathing or talking, which is how asymptomatics would be shedding, citing a preprint by Chen et al <https://www.medrxiv.org/content/10.1101/2020.10.13.20212233v3> . However, symptomatics are more likely to be isolating than asymptomatics.

2020-12-30 The Schools Infection Study, run by PHE, ONS and LSHTM tested 10,000 teachers and pupils in schools across England in November. They found infections amongst teachers and pupils mirrored community rates, and did not find any statistically significant difference between primary and secondary schools as measured by the 95% confidence intervals.

<https://www.lshtm.ac.uk/newsevents/news/2020/covid-19-infection-rates-schools-mirror-rates-community> These study results are a useful corrective to those who have been arguing that transmission and infection rates amongst young children are somehow much lower, and therefore that schools can remain open for presence teaching when other multiple-contact activities are inhibited.

2020-12-30 LSHTM has estimated the transmissibility of the new variant, known to them as Voc 202012/01, to TheG as B117 and to RKI as B.1.1.7, at (best guess) 56% with 95% Credible Interval 50%-74% across the three regions of England studied. Davies et al, 2020-12-23:
<https://cmmid.github.io/topics/covid19/uk-novel-variant.html>

2020-12-30 Imperial College MRC report 34 estimates IFR in a metastudy: *“We find that age-specific IFRs follow an approximately log-linear pattern, with the risk of death doubling approximately every eight years of age. Using these age-specific estimates, we estimate the overall IFR in a typical low-income country, with a population structure skewed towards younger individuals, to be 0.23% (0.14-0.42 95% prediction interval range). In contrast, in a typical high income country, with a greater concentration of elderly individuals, we estimate the overall IFR to be 1.15% (0.78-1.79 95% prediction interval range).”*
<https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-34-ifr/>

2020-12-30 Imperial College MRC report on infections in children, in a metastudy of “early” (first-wave?) studies on PubMed. Report 37 in the series. *“Our pooled estimate of the proportion of test positive children who were asymptomatic was 21.1% (95% CI: 14.0 - 28.1%), based on 13 included studies, and the proportion of children with severe or critical symptoms was 3.8% (95% CI: 1.5 - 6.0%), based on 14 included studies.”* The proportion of asymptomatics coheres with the figure used in my ScSS paper and the range reported by Pollock and Lancaster (see entry 2020-12-29).
<https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-37-children/>

2020-12-30 The Chinese CDC performed a seroprevalence survey in Wuhan, Hubei province, with some 34,000 participants, as well as other areas of China in April and estimated a seroprevalence almost 10 times the case rate. Reported in TheG
<https://www.theguardian.com/world/2020/dec/30/wuhan-nearly-490000-people-could-have-had-covid-study-finds> Wuhan reported some 50,000 cases (in the first and only wave). The study estimates a 4.43% rate of infection, which amounts to some 487,000 people in Wuhan.

2020-12-31 The Phase 3 study of the Moderna mRNA-1273 vaccine has been published in the NEJM on 2020-12-30 by Baden et al <https://www.nejm.org/doi/full/10.1056/NEJMoa2035389>

2020-12-31 The ACTIV-3/TICO LY-CoV555 study group reported in the NEJM on 2020-12-22 that the monoclonal antibody LY-CoV555 (bamlanivimab) did not improve the condition of hospitalised patients with Covid-19 receiving high standard of care (remdesivir and glucocorticoids as necessary), as measured by pulmonary function on Day 5.
<https://www.nejm.org/doi/full/10.1056/NEJMoa2033130> Bamlanivimab is, however, known to reduce viral load by Day 11 (Chen et al, 2020-10-28
<https://www.nejm.org/doi/full/10.1056/NEJMoa2029849>).

2020-12-31 Lumley et al report in the NEJM on 2020-12-23 that, in a study of some 12,000 UK health care workers in whom IgG was measured, those with igG antibodies had a “substantially reduced” risk of reinfection within 6 months
<https://www.nejm.org/doi/full/10.1056/NEJMoa2034545>

2020-12-31

The Bielefeld numbers have developed as follows.

Date	ni105r7d	new inf's	7dmi
------	----------	-----------	------

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
2020-12-02	190.9	111	93.0
2020-12-03	190.9	127	92.8
2020-12-04	181.9	116	90.6
2020-12-05	178.9	98	88.6
2020-12-06	188.5	95	94.0
2020-12-07	196.6	62	96.4
2020-12-08	204.7	78	99.6
2020-12-09	193.3	73	92.0
2020-12-10	180.7	89	86.6
2020-12-11	179.8	112	86.6
2020-12-12	184.3	114	89.4
2020-12-13	179.2	77	85.6
2020-12-14	176.5	53	85.8
2020-12-15	187.3	111	93.2
2020-12-16	194.8	100	97.8
2020-12-17	205.3	119	102.8
2020-12-18	202.0	101	100.6
2020-12-19	202.6	118	101.4
2020-12-20	201.4	74	100.8
2020-12-21	206.5	67	100.8
2020-12-22	195.4	73	93.2
2020-12-23	190.0	82	89.6
2020-12-24	193.9	130	89.6
2020-12-25	181.3	61	82.8
2020-12-26	159.2	43	71.4
2020-12-27	148.1	37	65.2
2020-12-28	143.6	52	62.2
2020-12-29	148.4	91	65.8
2020-12-30	143.3	65	62.4
2020-12-31	129.6	84	61.0

We shall have to wait to see if the reduction in new infections is an artifact of the different levels of recording over the Christmas break. There has been an general increase of about 25% in those hospitalised over this period, from around 110 to around 137, and a roughly 40% increase in those in ICU, from around 30 to around 42.

Admission to ICU tends to occur 4-7 days after hospitalisation; hospitalisation tends to occur a few days to a week after onset of symptoms, and onset of symptoms roughly 5 days after infection, so those numbers can lag positive test results by 2-3 weeks. Even if the reduction in transmission over the Christmas break is real, looking at the infection numbers we wouldn't expect to see a reduction in hospital admissions for some days yet, or a reduction in ICU patients for a little longer than that.