

## Notes on COVID-19

### Part 9: 2020-06-01 to 2020-06-07

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**2020-06-07**

2020-06-01 The Accord trial is to trial five drugs to see if they ameliorate the ravages of Covid-19  
<https://www.theguardian.com/world/2020/jun/01/uk-hospitals-trial-five-new-drugs-search-coronavirus-treatment>

- Heparin is a common blood-thinner. It is a polysaccharide produced in the liver. If it is nebulised rather than injected, it can have a “dramatic effect in the lung”, said the project academic lead, Tom Wilkinson.
- Bemcentinib is used to treat blood disorders, but has been discovered to have an antiviral effect.
- Medi3506 is an anti-inflammatory intended for skin disorders and COPD, and has been trialled for asthma. It is a potential dampener of cytokine storm. It is manufactured by AstraZeneca
- Acalabrutinib is also manufactured by AstraZeneca (which calls it Calquence), used to treat mantle cell lymphoma. Some observational evidence has indicated it might ameliorate lung inflammation associated with Covid-19.
- Zilucoplan is a small synthetic molecule designed to inhibit portions of the immune system called the complement system. It is a macrocyclic peptide inhibitor of the complement protein C5.

The trial is aiming to recruit 60 patients per drug.

2020-06-01 Jama has a page explaining ECMO, by Haday and Benharash  
<https://jamanetwork.com/journals/jama/fullarticle/2766774>, dated 2020-05-28.

2020-06-01 Tolles and Luong have a useful survey in JAMA 2020-05-27 of the ins and outs of various epidemic modelling techniques, concentrating on SIR  
<https://jamanetwork.com/journals/jama/fullarticle/2766672>. Jewell et al had discussed the ins and outs of predictive modelling, and suggested useful caveats on how results are presented, in a JAMA Viewpoint article on 2020-04-16 <https://jamanetwork.com/journals/jama/fullarticle/2764824>

2020-06-01 There was an outbreak in Göttingen over the weekend with 36 infected and 150 in quarantine. They had to do with a number of private parties and an “illegally opened” shisha bar  
<https://www.theguardian.com/world/live/2020/jun/01/coronavirus-live-news-brazil-passes-500000-covid-19-cases-as-india-extends-lockdown-in-high-risk-zones> at 13:30 BST (Philip Oltermann). This looks very much as if it will be the “new normal” everyone has been talking about.

2020-06-02 AP (aka Associated Press) has reconstructed the initial timeline of the Covid-19 spread and scientific reaction to the disease within China, from a number of source documents and interviews <https://apnews.com/3c061794970661042b18d5aeaed9fae> Shi Zhengli at the Wuhan Institute of Virology returned in haste from a conference on December 30, and had decoded the

entire genome by January 2. The WHO learned about the outbreak on December 31 from an open-source information “platform”, and requested more information from the Chinese government. The government responded on January 2 that there were 44 cases and no deaths. Consider the history of the sequencing efforts alone:

*“By Jan. 2, Shi had decoded the entire genome of the virus, according to a notice later posted on her institute's website.....*

*On Jan. 3, the [Chinese] National Health Commission issued a confidential notice ordering labs with the virus to either destroy their samples or send them to designated institutes for safekeeping. The notice, first reported by Caixin and seen by the AP, forbade labs from publishing about the virus without government authorization. The order barred Shi's lab from publishing the genetic sequence or warning of the potential danger.*

*Chinese law states that research institutes cannot conduct experiments on potentially dangerous new viruses without approval from top health authorities. Although the law is intended to keep experiments safe, it gives top health officials wide-ranging powers over what lower-level labs can or cannot do.*

*By Jan. 3, the Chinese CDC had independently sequenced the virus, according to internal data seen by the Associated Press. And by just after midnight on Jan. 5, a third designated government lab, the Chinese Academy of Medical Sciences, had decoded the sequence and submitted a report ... Yet even with full sequences decoded by three state labs independently, Chinese health officials remained silent.....*

*On Jan. 5, the Shanghai Public Clinical Health Center, led by famed virologist Zhang Yongzhen, was the latest to sequence the virus. He submitted it to the GenBank database, where it sat awaiting review, and notified the National Health Commission.....*

*By Jan. 7, another team at Wuhan University had sequenced the pathogen and found it matched Shi's, making Shi certain they had identified a novel coronavirus.....*

*On Jan. 11, a team led by Zhang, from the Shanghai Public Health Clinical Center, finally published a sequence on virological.org, used by researchers to swap tips on pathogens. The move angered Chinese CDC officials, three people familiar with the matter said, and the next day, his laboratory was temporarily shuttered by health authorities.”*

For 9 days, the WHO and others were thus kept entirely in the dark about essential information concerning a deadly new infectious pathogen. Nine days is a huge amount of time concerning the progress of an infectious disease with these characteristics (recall the blog post by James Annan reported in Notes Part 7 on 2020-05-20, using retrospective values  $Re_{\text{before lockdown}}$  and  $Re_{\text{after lockdown}}$ , showing that the death rate in GB would have been reduced by a factor of 4 had lockdown been imposed 7 days earlier). The response of Chinese scientists was extraordinary and exemplary. Would that the rest of the world had had Ms. Shi's information on January 2!

The Chinese government response has been considered in a paper by Gu and Li in the Journal of Chinese Governance on 2020-03-24, which comments on this delay <https://www.tandfonline.com/doi/full/10.1080/23812346.2020.1740468> From the abstract: “we identify the lack of autonomy of scientific/professional communities—in this case, virologists, physicians, and epidemiologists—as one of the major contributing factors to the malfunction of the early warning system.”

Note added on 2020-06-03 The Chinese government has responded to the AP report by reportedly rejecting its claims as untrue. However, Gu and Li's observations stand. Their point: the bureaucrats trump the scientific/medical community governance. It is hard to see how the Chinese government could vitiate that observation, because it is a conclusion from agreed facts.

2020-06-03 Hufyys et al (55 authors in total!) have uploaded a survey of Computational Strategies

to Combat Covid-19 (as the paper is titled) to Researchgate (open access, preprint):

[https://www.researchgate.net/publication/341593156\\_Computational\\_Strategies\\_to\\_Combat\\_COVID-19\\_Useful\\_Tools\\_to\\_Accelerate\\_SARS-CoV-2\\_and\\_Coronavirus\\_Research](https://www.researchgate.net/publication/341593156_Computational_Strategies_to_Combat_COVID-19_Useful_Tools_to_Accelerate_SARS-CoV-2_and_Coronavirus_Research) At a first glance, it seems to be a useful compendium. It was recommended by a bioinformatics colleague in Bielefeld.

2020-06-03 The company Surgisphere appears to own a large patient database which has been used to study the effects of chloroquine and hydroxychloroquine on the progress of hospitalised Covid-19 patients. Papers have been published in NEJM and The Lancet reporting analyses of these data. Some anomalies arose with data purportedly from Australia; The Lancet issued a correction. TheG started an inquiry into the company and its personnel, which has raised further concerns about the integrity of the data and its analysis <https://www.theguardian.com/world/2020/jun/03/covid-19-surgisphere-who-world-health-organization-hydroxychloroquine> The Lancet has published an Expression of Concern <https://www.thelancet.com/lancet/article/S0140673620312903>

2020-06-03 The LSHTM CMMID projections of the effect of non-pharmaceutical interventions in the progress of Covid-19 in the UK has been published in The Lancet [https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667\(20\)30133-X/fulltext](https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30133-X/fulltext) The findings: “*We projected a median unmitigated burden of 23 million (95% prediction interval 13–30) clinical cases and 350 000 deaths (170 000–480 000) due to COVID-19 in the UK by December, 2021. We found that the four base interventions were each likely to decrease  $R_0$ , but not sufficiently to prevent ICU demand from exceeding health service capacity. The combined intervention was more effective at reducing  $R_0$ , but only lockdown periods were sufficient to bring  $R_0$  near or below 1; the most stringent lockdown scenario resulted in a projected 120 000 cases (46 000–700 000) and 50 000 deaths (9300–160 000). Intensive interventions with lockdown periods would need to be in place for a large proportion of the coming year to prevent health-care demand exceeding availability.*” The UK is currently on 281,000 cases and almost 40,000 deaths, according to the JHU Dashboard, but not under “*most stringent lockdown conditions*”. We are nowhere near December 2021. My mathematical instinct says it is OK to extrapolate to whenever you like while considering the “do nothing” scenario but if you are considering modifying social behaviour then it only makes sense to consider a few months at a time, since, as politicians and social scientists have been saying, such modification might well not last for much longer than that. I am sure the authors are well aware of this. They must know that the extrapolation of any scenario except “do nothing” is artificial. The larger question is still why they phrase the results this way. Surely there must be a reality-friendlier way of saying it? BTW, for all the fuss attached to Imperial MRC GIDA Report 9 by observers of UK politics, it is worth observing – loudly – that other modellers such as LSHTM CMMID, also contributing to the SAGE, were getting similar results.

2020-06-03 Chu et al have published a meta-analysis of the effects of physical distancing, face masks, and eye protection on the transmission of SARS-CoV-2 virus

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31142-9/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31142-9/fulltext)

Looks thorough, but there doesn't seem to be anything definitive one can pick out. They all help, more or less. We knew that, but it is good to have it sort-of confirmed. Somehow, I think that detailed droplet/mini-droplet/dispersion studies will derive more satisfying answers. Compare:– we can presumably confirm that a door handle used without protection by an infected person and not disinfected will spread disease somewhat. But I think we are more interested in such details as how much infective material is deposited, how long it takes to degrade (e.g., half-life), and how much a subsequent user needs to pick up to stand what chance of becoming infected his/herself.

Comment by MacIntyre and Wang at [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31183-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31183-1/fulltext)

2020-06-04 TheG “is investigating how the UK government prepared for – and is responding to – the coronavirus pandemic. We want to learn more about recent decisions taken at the heart of government” <https://www.theguardian.com/world/2020/jun/03/we-were-packed-like-sardines-evidence-grows-of-mass-event-dangers-early-in-pandemic> The article by David Conn contains some key observations, e.g.,

Having examined his evidence, Prof Tim Spector, of the Covid-19 Symptom Study, told the BBC last week that “sporting events should have been shut down at least a week earlier, because they’ll have caused increased suffering and death that wouldn’t otherwise have occurred”.

On 11 February, the Sage sub-group SPI-M [noted](#) that “in most larger events, such as sports matches, attendees will come into close contact with at most a handful of people, so the risk to attendees is low.”

Minutes of Sage meetings published for the first time last week [reveal that](#) as late as 3 March, the scientists advised: “There is currently no evidence that cancelling large events would be effective.”

Although the government still insists that attaining “herd immunity” was not part of its plan, its chief scientific adviser and the chair of Sage, Sir Patrick Vallance, explained on 13 March that allowing 60% of the population to become infected, then recover and attain herd immunity, was one of “the key things we need to do”.

Prof Neil Ferguson, of Imperial College and a leading Sage scientist [until 5 May], told the Guardian he had informed the government well before March that under the “mitigation” policy they were planning, about 250,000 people would die.

Prof John Edmunds, of the London School of Hygiene and Tropical Medicine, and a leading Sage member, explained to the Guardian his basis for advising that “mass gatherings” had little impact on the spread of a virus.

“Very few people actually go to these events” as a proportion of the population. The events are outside, and “you don’t actually come into contact with that many people. So the total number of contacts made in these situations compared with every day in a pub for instance, is really negligible.”

However, says TheG, “there is evidence [from postcode data] suggesting mass gatherings did have a significant impact on the spread of the disease.”

There are, clearly, dissenting views apart from those of Prof. Ferguson.

Dr William Hanage, [a British epidemiologist who is] associate professor of epidemiology at Harvard, says that many contacts are made at a packed modern event, and that the large crowds increase the chance of superspreading.

“Cancelling large events at the early stage of a pandemic is an essential part of reducing opportunities for transmission.

We recall Prof. Hanage's article in TheG, reported in Notes Part 1 with date 2020-03-15, expressing incredulity at Sir Patrick Vallance's public suggestion that achieving herd immunity was “one of the key things we need to do.”

Sir David King, the chief scientific adviser from 2000-07, argues that major events are “ideal” spreading episodes. Told by the Guardian that Sage scientists had advised that large gatherings have minimal impact on the spread of the virus, King said: “I find it very difficult to believe scientists said that; I am absolutely astounded.”

The assertions about what happened when and the decisions are all sourced, with the exception of Prof. Ferguson's comment to TheG. SAGE minutes have been released, and some statements were already in the public domain. Conn also reports interviews with Covid-19 survivors who attended these mass events, or who were associated with them in some way.

Neither Prof. Hanage nor Sir David King participated in 2020 SAGE meetings, as far as we know. We recall also the view of Prof. Allyson Pollock and coauthors in the BMJ, reported in Notes Part 3 on 2020-04-05, that “*The scientific evidence has been dominated by behavioural science and mathematical modelling, with communicable disease control and public health sidelined. This leads to a lack of scientific challenge, as in the 2009 flu epidemic.*” We may assume she was referring to SAGE and its subcommittees. Pollock et al did not express a view as to mass gatherings.

When some governmental intervention in UK is seen to go wrong, there is usually a public inquiry, a nominally-independent fact-finding process. Many would agree that the current UK experience with Covid-19 is an example of something which likely could have been handled with far less distress than has been apparent this last couple of months. Prominent people have said an inquiry is inevitable. It will surely be part of that inquiry to ask how HMG derived policy as if mass gatherings were no big deal, and claiming this policy is based on “science”, when there were apparently plenty of prominent UK scientists around with a contrary view, and when other countries with capable scientists, such as Germany, had taken a different line, based equally “on science”.

2020-06-04 The Lancet has retracted a paper on the (lack of) effectiveness of chloroquine and hydroxychloroquine in treating Covid-19, on request of three of the authors, who said they could not satisfactorily complete an independent peer-review of the data which the article had used, which derived from the US company Surgisphere

<https://www.thelancet.com/lancet/article/S0140673620313246>

The now-retracted paper was reported in my Notes Part 7 as the first of three entries on 2020-05-23. This is thought to be a big deal, as the WHO stopped its RCTs of these drugs based in part on the work reported in the paper <https://www.theguardian.com/world/2020/jun/04/covid-19-lancet-retracts-paper-that-halted-hydroxychloroquine-trials>

2020-06-05 The Recovery project in the UK does, however, have reliable negative results on

hydroxychloroquine. The UK Medicines and Healthcare Products Regulatory Agency asked the project's independent monitoring board to review the project's data on hydroxychloroquine. They found it doesn't work – not statistically any better than a placebo – and recommended to the researchers that that part of the trial be stopped

<https://www.theguardian.com/world/2020/jun/05/hydroxychloroquine-does-not-cure-covid-19-say-drug-trial-chiefs>

2020-06-06 People are apparently wondering how The Lancet could come to publish a peer-reviewed paper based on unreliable data. Those of us with long experience of scientific publishing are not surprised. There is a good explanation by James Heathers

<https://www.theguardian.com/commentisfree/2020/jun/05/lancet-had-to-do-one-of-the-biggest-retractions-in-modern-history-how-could-this-happen> to which I can add a couple of comments.

First, peer review is an inspection, it is not an assurance. Kicking the tires – seeing if it has tires to kick – not performing a TÜV or MoT. A reviewer will comment on the originality and importance of the work and the coherence of the written paper, and, in many cases, recommend improvements in one or all of these three aspects. If the paper is recommended for publication, there will then follow a negotiation between publisher, authors and reviewers until all agree the paper is ripe for publication.

This process is extremely variable, both amongst journals and amongst subjects. My most-cited paper took between 6 and 7 years in this process, in a prestigious journal (that meanwhile considers such protracted processes to be inappropriate). Other journals ask authors for a fee, provide cursory inexpert review and then publish (so-called “vanity journals”, or “predatory journals”; such journals are not taken seriously by scientists of any repute). In mathematics, the peer-review is traditionally quite rigorous. The most important results are often checked – indeed in some cases reproduced – in detail over weeks or indeed months by reviewers who do end up being known to the community. Indeed, new and important mathematics ends up being done in reviews. Reviewers find counterexamples to claims whose proofs are not thoroughly given; authors fix them, sometimes by pursuing quite different lines of argument. It doesn't happen with all or even most papers by any means, but it does happen with some. In contrast, as with the Lancet paper, biological and social scientists often derive results from data for whose provenance they cannot necessarily personally vouch – for example, all metastudies necessarily use third-party data, namely those from the research they are meta-studying. Someone who can vouch for the data will normally become a coauthor. But then, as in the Lancet case, this network of trust can all fall apart if someone shows the data not to be trustworthy.

Trusting the data has long been an issue in science, and it is not simply a matter of ethics. For example, the philosopher and historian of science Gerard Holton suggested that, in Millikan's famous oil-drop experiments that allowed him to calculate the charge on an electron and which ultimately won him the Nobel Prize, Millikan removed from his datasets those data from experiments which he felt “hadn't gone right”, so there was a subjective-selective component to his dataset (Gerard Holton, *Subelectrons, Presuppositions, and the Millikan-Ehrenhaft Dispute*, *Historical Studies in the Physical Sciences* 9:161-224, 1978. Available at



<https://www.jstor.org/stable/27757378> ). Nowadays, scientists are fired from universities and research institutions for picking and choosing their data in such a manner.

One significant social constraint on the review process is rightly highlighted by Heathers. Authors and publishers get something out of publication; the reviewers generally get nothing at all, despite the amount of time it has taken. (Except with momentous results in mathematics, as noted above, in which the mathematics performed in review often resounds to the benefit of the reviewer.) Sometimes it is a real privilege to review significant results in one's area of expertise. But there are far more papers submitted for review that are not worthy of publication, and reviewing these is just a chore as well as ultimately taking work time which does not subjectively feel as if it has been used well.

A final observation is that the whole business of scientific publishing has become a topic of scientific research in itself. Not just questions of quality, and identification of fraud, but of its role in science in times in which it is impossible to read all relevant publications in one's discipline, as well as the economics of large scientific publishing houses (which are often for-profit companies) and the transfer of intellectual property from the scientists who did the work and wrote the paper and the organisations, often government, who paid for it to the publishing house who publishes it, and the moral justification (if any :- ) for such transfer.

2020-06-06 More wise words from Rupert Beale

<https://www.theguardian.com/commentisfree/2020/jun/05/britons-immune-coronavirus-mistakes-covid-19-spread> The main messages: testing is now ramped up and this is a good thing; test, trace, isolate now needs to be followed assiduously, including with the help of a (dependable) app. And he has a couple of choice words for Karl Friston's suggestion of German “immunological dark matter.” As a German ex-health-care friend said about this suggestion from one of Britain's most-cited scientists (Bev Littlewood points out he has an h-index of over 280), “those Brits – they're nuts”.

2020-06-07 AstraZeneca is “close to a breakthrough” on antibody treatment. This is different from a vaccine, which stimulates a body's own antibody production. It is a combination of two virus antibodies which could be given to those in early stages of infection to neutralise viral reproduction. In particular, it would help those whose immune systems are not as capable, such as older people and those who are immunocompromised in some way

<https://www.theguardian.com/world/2020/jun/07/breakthrough-close-on-coronavirus-antibody-therapy-reports> AstraZeneca has already signed an agreement on 2020-06-04 with CEPI to help manufacture 300m doses of the Oxford Uni Jenner Institute vaccine candidate, now going by the name of AZD1222 <https://www.theguardian.com/business/2020/jun/04/astrazeneca-doubles-capacity-for-potential-covid-19-vaccine-to-2bn-doses> This is encouraging news. We are five months into the pandemic and Oxford+AstraZeneca seem to be holding to the unprecedentedly rapid development plan they proposed in January. Let us hope they can continue to make good on it.

2020-06-07 Robin McKie of TheG has interviewed some British epidemiological scientists to see “where we stand”. I found the observations instructive and offer the following summary. First, Martin Hibberd (LSHTM) said Covid-19 was the worst scenario: a highly transmissible disease

with a 1% death rate. David Nabarro (Imperial) points out it is not just a respiratory disease but has manifold complications. One can list blood clots, cytokine storms, kidney damage, heart attacks, Kawasaki syndrome. Second, Martin Woolhouse (Edinburgh) notes it is a disease of old age, and that we will have to develop, permanently, biosecurity measures for all older people, not just those in care homes. Third, testing technology is improving rapidly. Anne Johnson (UCL) points out that modelling is only as good as the data, and good data from testing technology is key for implementing biosecurity measures (think the first two T's in TTI). Note that data is dependent on testing technology because of the prevalence of asymptomatic infectious carriers. Fourth, Hibberd notes that establishing immunity properties and antibody research is key to controlling the disease. Fifth, Tom Wingfield (Liverpool School of Tropical Medicine) notes the importance of developing high standards of care. For example, the discovery that CPAP is very effective help, avoiding invasive ventilation. Other key points are not yet known, such as who should be on blood thinners to avoid clotting and when. Sixth, Woolhouse and Nabarro think it unlikely that a vaccine will become widely available this year. When there is one (or two, or three), the logistics problems of delivering it should not be underestimated (cf. polio, measles). Seventh and finally, Hibberd hopes that all in all it might be possible to reduce the death rate by an order of magnitude, to 0.1%, which would put us in a “different, much better position” that we are now.

<https://www.theguardian.com/world/2020/jun/07/after-six-months-of-coronavirus-how-close-are-we-to-defeating-it>

2020-06-07 Laura Spinney in The Observer gets to grips with the fact that numbers concerning Covid-19 are very different in different parts of the planet, indeed in European countries. Why would this be? <https://www.theguardian.com/world/2020/jun/07/immunological-dark-matter-does-it-exist-coronavirus-population-immunity> There has been some amusement about Karl Friston's reference to “immunological dark matter” in Germany, but it seems clear to some that factors are in play about which we know little to nothing. Spinney refers to research recently published in Cell on T-cells drawn from people between 2015 and 2018 which reacted to fragments of SARS-CoV-2, which did not yet exist. So there is likely some cross-reactivity with other coronaviruses which did exist then. The 2020-05-14 paper by Grifoni et al is at [https://www.cell.com/cell/fulltext/S0092-8674\(20\)30610-3](https://www.cell.com/cell/fulltext/S0092-8674(20)30610-3) Braun et al posted a preprint on 2020-04-22 which specified reactivity in 83% of Covid-19 patients but also in 34% of healthy seronegatives <https://www.medrxiv.org/content/10.1101/2020.04.17.20061440v1.full.pdf>, also suggesting some cross-reactivity with other coronaviruses.

Spinney wrote the book Pale Rider in 2017, about the Spanish flu epidemic of 1918-19, positively reviewed not only by my colleague Harold Thimbleby recently but in print by Miranda Seymour in The Observer on 2017-06-04 <https://www.theguardian.com/books/2017/jun/04/pale-rider-laura-spinney-spanish-flu-review-absorbing-study>, by Colin Grant in TheG on 2017-07-22 <https://www.theguardian.com/books/2017/jul/22/pale-rider-laura-spinney-review>, by Suzanne Shablovsky in Science on 2017-09-18 <https://blogs.sciencemag.org/books/2017/09/18/pale-rider/> and by Tommy Bengtsson in the journal Population and Development Review on 2018-11-28 <https://onlinelibrary.wiley.com/doi/full/10.1111/padr.12215>