Notes on COVID-19

Part 16: 2020-08-28 to 2020-09-09

Peter Bernard Ladkin
2020-09-09

2020-08-28 Public Health England is publishing its evaluations of serological assays https://www.gov.uk/government/publications/covid-19-laboratory-evaluations-of-serological-assays There are nine reports so far.

2020-08-28 The why's, wherefore's and how-much's of personal distancing have come under considerable scrutiny recently, as indeed have almost all key measures to dampen the transmission of Covid-19, for obviously good reason, namely there is probably nothing more important to do at present (apart from eating, sleeping and staying healthy oneself). Jones et al review physical distancing rules in the BMJ on 2020-08-25. https://www.bmj.com/content/370/bmj.m3223 They suggest much is based on old science, and refer to newer work.

2020-08-28 The first demonstrated case of reinfection has occurred in a 33-year-old man in Hong Kong, reported by Parry in the BMJ on 2020-08-26 https://www.bmj.com/content/370/bmj.m3340 He had Covid-19 in March, and has been infected again by a different strain in August. He is currently paucisymptomatic. UHK's Hung notes that the current leading vaccine candidates would all cope with the minor mutation exhibited here, but also notes it means that vaccination would be indicated also for those who have had the disease. LSHTM's Wren notes that, with 24 million cases worldwide, one case of reinfection "*needs to be taken into context*". In other words, don't worry so much. University of Birmingham's Zania Stamataki argues why this event is more good news than bad, namely that the reinfection is paucisymptomatic, in both The Conversation and TheG https://theconversation.com/coronavirus-reinfection-what-it-actually-means-and-why-you-shouldnt-panic-144965
https://www.theguardian.com/commentisfree/2020/aug/27/coronavirus-reinfection-what-it-actually-means-and-why-you-shouldnt-panic

2020-08-28 In The Lancet Respiratory Medicine on 2020-08-27, Ware comments on two studies of ARDS in Covid-19 patients, published on the same day https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30369-6/fulltext Ware says that the studies show, in general, that Covid-19-related ARDS is clinically not that much different from "classical" (non-Covid-19-related) ARDS, indicating that standards of care developed for classical ARDS are appropriate also for Covid-19-related ARDS. The studies are by Grasselli et al https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30370-2/fulltext in Italian hospitals, and Sinha et al https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30366-0/fulltext in two UK ICUs.

2020-08-27 Nisreen Alwan comments on the weaknesses of current surveillance systems for Covid-19 and argues that surveillance case definitions for infection and recovery are urgently needed. Not

only are not all people with Covid-19 symptoms tested and identified, but there is no definition of recovery, often leaving so-called “long haulers” out of the picture. The author self-identifies as a “long hauler” (my term).

2020-08-28 And the band plays on. The NW newspaper reports today on a press conference with NRW Families Minister Joachim Stamp and the NRW Health Minister Karl-Josef Laumann, who have issued a statement in response to a request from the NW newspaper. Minister Stamp said “*The threat of [taking children into] protective custody concerning [adherence to] quarantine [regulations] leads to mistrust [of the government] and should be avoided*.” Minister Laumann agreed, and added “*I cannot imagine a situation in which the non-adherence to quarantine regulations alone could justify removal [of a child] from a family.*” That's what I said yesterday, and that is what my lawyer colleague said. Laumann said further that it needs to be made clear to the district health authorities that “*such [inappropriate] measures, that are disconcerting and lead only to insecurity, are no longer to be threatened*”. It is the responsibility of the health authorities to find a “*practical solution that guarantees the protects the health [of the child] and that means, for me, solutions in which children and parents remain together.*” The catch here is that the health authorities are the agencies of last resort – the Ministers cannot order them to refrain from such threats. The article also reports in depth on the opinion of the children's protection researcher Michael Böwer, who is Dean of the Catholic Higher Education Institute (Hochschul) of NRW. His observations on the legal situation are consonant with what I have observed in previous Notes: enacting such a measure as threatened is likely unconstitutional.

2020-08-28 Those who think Germany has its act together on Covid-19 might like to dampen their enthusiasm a little. Chancellor Merkel had yet another five-plus-hour meeting with the heads of the Federal states about Covid-19 measures and there is a lot of divergence. Saxony-Anhalt won't implement fines for those not wearing masks in public. Bavaria doesn't agree that its pervasive border testing of those returning from vacation didn't help much. Lower Saxony is allowing private gatherings of up to 50 people, whereas NRW allows them up to 150, which may mean that a lot of NRW cities bordering Lower Saxony are going to host an increased number of largish private parties (weddings, large birthday parties and so on). No decisions were taken as to what to do about Carnival (starts on November 11 at 11:00) or what to do about Christmas Markets. Bielefeld has had to give up on a replacement event for its wine festival, which usually attracts tens of thousands of closely packed visitors, in early September, all spending fair amounts of money on wine and food. There are a lot of small businesses making and selling things such as decorations, wooden toys, small pottery buildings illuminated by candles, who earn almost all their income from Christmas markets. It is going to be really bad for many of them if they have no income in 2020. Those problems may financially be minor compared with those of Lufthansa, but culturally they are important parts of the landscape almost everywhere.

2020-08-29 Saliva tests for Covid-19 now look to be better than swabs. Wyllie et al at Yale report in the NEJM on 2020-08-28 on results of comparative saliva-sample versus swab testing for Covid-19 https://www.nejm.org/doi/full/10.1056/NEJMc2016359 Of 70 inpatients, the saliva samples were somewhat more reliable indicators than swabs. They also tested 495 asymptomatic health care workers. 13 tested positive with saliva samples; of those, 9 had swab tests, 7 of them negative. All

13 persons later confirmed positive for Covid-19.

2020-08-29 Geberhiwot et al at University Hospital, Birmingham, report in JAMA on follow-up after hospital discharge for Covid-19 https://jamanetwork.com/channels/health-forum/fullarticle/2770074 They established a multidisciplinary in-house clinic and put in a system for telephone follow-up, using defined criteria for prioritising follow-up. They had 3566 Covid-19 inpatients total up to July 27. 625 of those, just over one in six, met the criteria for follow-up, and 56 were subsequently seen in the clinic.

2020-08-30 PHE published a general study of the "first wave" of Covid-19 infection in England, in the BMJ Archives of Disease in Childhood, on 2020-08-12
https://adc.bmj.com/content/early/2020/07/28/archdischild-2020-320042
There was no "excess mortality", as there noticeably has been with adults. Children tested positive for Covid-19 at a far lower rate than adults. The highest proportion of children testing positive at a time period was around 15% in the under-3-months and 10-15 years age groups, at the end of March – beginning of April (Figure 1).

Matthew Snape argued in TheG on 2020-08-18 that this data, and other, argue for a not-very-high risk in reopening schools. https://www.theguardian.com/commentisfree/2020/aug/18/children-covid-19-english-schools-virus-safe-reopening The headline on his essay says "*[t]here is now clear data on Covid-19 and children*...." but I am not sure I agree with that. Neither do the PHE authors: "*It is still unclear why the epidemiology, clinical features and outcomes of COVID-19 are so different in children compared with adults.*" They also say "*[a] key unanswered question remains whether asymptomatic children might be contributing to community transmission of SARS-CoV-2.*" Nothing has yet contradicted the Charité study, which found viral shedding in children to occur at similar rates to those in adults. If you equate quantity of virus shedding with infectiousness, then the children seen by the Charité study are just as infectious as any adult. The PHE study says, though, that there were noticeably fewer of them. It gives a possible reason in just one sentence, namely that children have less ACE2 enzyme expressed in their nasal epithelium than adults, and it is this to which SARS-CoV-2 binds to gain entry to a cell, but doesn't explore this further.

It is probably fair to say that everybody's holding their breath – actually all over Europe – and hoping it will turn out alright. And to observe that, if they continue to hold their breath, then it will. It's only when someone breathes out that there can be transmission problems…..

2020-09-02 Gudbjartsson et al have published a major study on immune response to SARS-CoV-2 in Iceland, with over 30,000 participants, in the NEJM on 2020-09-01
https://www.nejm.org/doi/full/10.1056/NEJMoa2026116 A key result is that immune response, measured by antiviral antibodies, did not decline within 4 months after diagnosis. Also that 44% of people infected with SARS-CoV-2 in Iceland were not detected by qPCR assay. The total population of Iceland is just over 364,000, so the study involved a substantial fraction of the population. In an accompanying editorial, Alter and Seder note that this is a more definitive result than others which have shown variance in immune response over short time periods; that it is nevertheless over quite a homogeneous population, and that the study incidentally showed that

serological testing is more accurate that the RT-PCR testing for presence of viral RNA
https://www.nejm.org/doi/full/10.1056/NEJMe2028079

2020-09-02 The MRC Biostatistics Unit at the University of Cambridge is producing regular nowcasting and forecasting reports for the spread of Covid-19 in England https://www.mrc-bsu.cam.ac.uk/tackling-covid-19/nowcasting-and-forecasting-of-covid-19/ The latest is dated 2020-08-06; they report that their model is under further development and more predictions will be available "soon".

2020-09-02 I was asked by Mike Parsons last Thursday, 2020-08-27, what the situation was with regard to Covid-19 in Germany. I have a Gestalt, or, rather, a number of them, but I found it oddly hard to answer. It may be because the Gestalt does not necessarily cohere with what I take to be key parameters. First, the Robert Koch Institut (without "e"), the German Federal public health body, has a Dashboard based on the JHU software, as far as I can tell
https://experience.arcgis.com/experience/478220a4c454480e823b17327b2bf1d4

The Dashboard brings up a map of the districts of Germany. The district is an administrative area. There are 294 districts, and 107 districtless cities or city-districts, so 401 administrative entities in total. The pure average would be about 200,000 residents per district, but of course this varies with geography. My "district-free" city of Bielefeld has about 330,000 residents; the Herford district to the immediate north about 250,000; some of the big rural districts in East Germany about 100,000, and Hamburg (also "district-free") about 2m.

On the RKI Dashboard, the districts are colour-coded to the number of new infections per 100,000 residents in the last 7 days. There are six categories, colored white; cream; yellowish-cream; ochre, red, and deep red. Numerically, these represent 0; 1-5; 6-25; 26-50; 51-100; 101-500.

Eyeballing, I can see 20 white; 12 orange; no red or deep-red; and about even numbers of cream and yellowish-cream. So
*) about half the country has had 0-5 new infections;
*) and the other half 6-25;
*) with only 12 districts (3%) with more than 26 new per 100,000 in the last 7 days.

That doesn't seem too bad a picture.

There is a histogram of new infections. There is a period from about mid-May to mid-July when these were under 1,000 per day. But then they started going up again, until in the two and a half weeks from 2020-08-10 to 2020-08-28 they were well up over 1,000 per day. It is a wave, of which the peak seems to be about 2020-08-19.

Since last Friday, the wave seems to be going down considerably, but this may be a consequence of late capture of data. There are a couple of different kinds of data being captured. One is date of illness, one is date of notification. Symptomatic people usually can say on which day they got ill. Asymptomatics or paucisymptomatics may only find out as the result of a test, so the test date

would be the date of notification. And the point at which RKI gets the notification date would a day or two afterwards or even longer, because the data gathering is hierarchically organised through the district public health administrations and there are going to be delays in there. So in the last few days up to the present, the histogram always shows a sudden drop due to these delays.

We are being told deaths are down. They seem to be around 10-15 per day at present. There have been almost a quarter of a million infections, and 9,313 deaths to date. That yields a CFR of about 3.8%, with the usual caveats.

There is a regular report from RKI. The latest is https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/2020-08-27-de.pdf They say that there are outbreaks which have two sources. First, celebratory events amongst family or friends. Second, those returning from travel (summer holiday trips). Amongst those returning from travel, a high proportion of infected are younger people. Figure 3 ("Abbildung 3") shows the histogram of the newly infected (divided into the two groups, above).

Looking at the total figures of daily newly infected (Abbildung 3, or on the RKI Dashboard) I suggest there are five periods.
* March 2nd to about March 18th. The exponential increase typical of infectious diseases with R well above 1, over two weeks, peaking at roughly 5,500 cases on March 18;
* March 19th to about May 26th. Gradual concave decrease from the peak to around 500-600 new infections per day;
* May 27th to about July 14th. Stable lowish rate of infection, 500-ish per day (with one blip);
* July 15th to about August 19th. Steady concave increase with R above 1 but not much, to a peak of about 1500 new infections per day;
* August 20th to date. A decrease from the August 19th peak. Some of the decrease is real, the rest is because of data processing delays, so the shape is not a good guide to what is happening.

There were concerns that many people were holidaying in defined areas of risk. All those who returned from such areas should have been tested on return, because that is the law. Test centres were established at airports, and major rail stations. I have seen no estimate of how successful that was. Bavaria set up tests on roads into the state from out-of-country and was aiming on testing everybody who came in, but that turned into a debacle after they lost thousands of tests. It is clear, though, that lots more people are being tested for various reasons, and that tests are more readily available – for example, in NRW, teachers and child-care workers can be tested at state expense every two weeks, and there is the test capacity to do so, which there was not in March-May. More and easier testing will inevitably turn up more infections, because of asymptomatic cases. However, pervasive seriological testing in various cities and districts around Europe yield different figures for seroprevalence, from 5-11% in Geneva in four weeks from April into May, to 14% in Gangelt, site of the first German superspreading event in February, to under 1% in population screening in Iceland in April-May. So it is not really possible to guess effectively how many asymptomatic carriers there are at present.

In Bielefeld, the numbers of newly infected have generally followed the national trend, although

there is considerable variation because the numbers are so low. On 12th March there were suddenly 13 new cases (up from 4 total, all in the preceding week). The city government met urgently and decided on the first restrictions (e.g., all public gatherings cancelled). Then 4 days of lowish figures and then back up – each day until 12th April there were average between 10 and 20 new cases (allowing for reporting delays, which were also present at the city level) but mostly hovering around 10. Then from 12th April – about 30th April an average of under 10 new infections per day.

In the 6 weeks from 2nd May – 16th June there were mostly 0 new cases/day, with 5 days with 1 new case, 4 days with 2 new cases, and 1 day with 3. This was an extraordinary period. People were following the hygiene regulations and recommendations closely and it was having a superb effect. Of course, shops were closed, nobody was meeting anyone else, we were encouraged to stay at home as much as possible, but it worked. It gave people a sense of power: we can really control this; we know how to behave so that it doesn't take us over. On the other hand, it has been a business disaster for many businesses, especially in travel, retail, hospitality. Those business owners won't have felt much of a sense of power; more like staring into a bottomless pit, I should think.

17th June – 13th July there were mostly 0-10 new cases/day, with 9 days with no new cases. Then 14th July – 13th August mostly between 0 and 10 new cases/day, peaking on 13th and 15th August at 16 and 19, but back on 22nd August to 0-5 new cases/day. That peak will have been travellers returning from vacation. All in all, for a city of 333,000 people not very high numbers at all.

Speaking of the bottomless pit, the travel business in Düsseldorf which I have used for over a decade for non-regular trips, went insolvent in May. That did not feel at all right. It was a century-old enterprise which had the Bielefeld University account and got the Causalis one too, which seamlessly rebooked me out of Limerick during the February-March storm in 2018, got me an excellent price in 1st class on the ICE and TGV down to Lyon and on to Grenoble in November 2018, and which arranged the rail trip to York for me for SSS20 in superquick time after the storm in early February 2020 wrecked my original plans, people who gave me superb and rapid service when I needed it. The restaurant chef-owner across the road in the village square, who runs what is consistently Bielefeld's highest-rated restaurant, quickly went in March to a restricted menu and pick-up/take-away service on weekends. He did what looked like plenty of business, judging by the cars parking for 10 minutes and people walking back with paper bags, but it can't have been anything like filling the restaurant and having people spend three times that amount on multiple courses with wine. I haven't talked to him yet about how he's making it, but he has outdoor service on the square in summer and there is lots of space for distancing, unlike most locations in Bielefeld, and demand does appear to have come back to something approximating normal.

2020-09-03 Rosadas et al take a close look at one of the two antibody tests that form the "cornerstone" of the UK's response to the Covid-19 pandemic. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31830-4/fulltext They find it very much wanting. Their conclusions: "*The UK Government's decision to facilitate use of Abbott' assay was intemperate. Anti-NP is insensitive in the field: why was this insensitivity not recognised by those who validated its use in the UK? Moreover, Abbott's assay does not indicate accurately the presence of neutralising and potentially protective antibodies in the convalescent individual. Those*

who might still deign to use this assay as the sole marker of past infection would be wise to consider confirmatory algorithms to better inform individuals investigated for anti-NP."

2020-09-03 Four studies of corticosteroids in the treatment of critically-ill Covid-19 patients were published on 2020-09-02 in the Journal of the AMA. Three of them were individual studies. The fourth is a meta-analysis by the WHO REACT Working Group of seven studies, including these three.

The WHO REACT Working Group performed a meta-analysis of 7 RCT studies of the use of systemic corticosteroids in critically-ill Covid-19 patients, including the three above, and found they clearly reduce the incident of mortality (primary outcome was defined as 28-day all-cause mortality; secondary outcome physician-defined adverse events).
https://jamanetwork.com/journals/jama/fullarticle/2770279 The three substances investigated were dexamethasone, hydrocortisone and methylprednisolone.

In their editorial, Prescott and Rice summarise the encouraging results. At time of writing, only the first two paragraphs are shown. A summary appeared in TheG on 2020-09-02
https://www.theguardian.com/science/2020/sep/02/two-types-of-steroid-found-to-save-lives-of-some-covid-19-patients Basically, sophisticated use of corticosteroids reduces the risk of death by about 20%. Lead author on the study is said to be Jonathan Sterne of the University of Bristol.

The three indivisual studies are as follows.

Dequin et al report on the use of hydrocortisone in French treatment.
https://jamanetwork.com/journals/jama/fullarticle/2770276 They found that low-dose hydrocortison was likely ineffective, but the study was stopped early.

Tomazini et al report on the CoDEX RCT of dexamethasone in critically-ill patients in Brasil.
https://jamanetwork.com/journals/jama/fullarticle/2770277 *"In this randomized clinical trial that included 299 patients, the number of days alive and free from mechanical ventilation during the first 28 days was significantly higher among patients treated with dexamethasone plus standard care when compared with standard care alone (6.6 days vs 4.0 days).*"

The REMAP-CAP investigators report on an RCT of the use of intravenous hydrocortisone and its effects on organ-support in critically-ill Covid-19 patients
https://jamanetwork.com/journals/jama/fullarticle/2770278
"*In this bayesian randomized clinical trial that included 403 patients and was stopped early after results from another trial were released, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority, respectively, with regard to the odds of improvement in organ support–free days within 21 days.*"

2020-09-03 Swann et all have published a major study of the clinical charateristics of children and young people hospitalised with Covid-19, covering 260 hospitals in England, Wales and Scotland

from January to June 2020. https://www.bmj.com/content/370/bmj.m3249 651 young people under 19 years of age were admitted to 138 hospitals and enrolled in the ISARIC WHO Clinical Characterisation Protocol UK study. The main outcome was admission to high-dependency or intensive care, death, or meeting the criteria for MIS-C. 18% were admitted to critical care, associated with those under 1 month, 10-14 years old, and black ethnicity. 6 died, all with "*profound comorbity*". 11% met the WHO MIS-C criteria. There were no deaths in the MIS-C group. Main conclusions: "*Children and young people have less severe acute covid-19 than adults. A systemic mucocutaneous-enteric symptom cluster was also identified in acute cases that shares features with MIS-C.*"

2020-09-03 The BMJ publishes a running comparison of drug treatments, a "living systematic review and network metaanalysis" at https://www.bmj.com/content/370/bmj.m2980 It was already evident on the last update, on 21 July, that glucocorticoids were moderately helpful.

2020-09-06 Philip Oltermann and Lois Hoyal write in The Observer today about Ischgl in early March, and the consequences of the apparently not very well thought-out evacuation https://www.theguardian.com/world/2020/sep/05/everyone-was-drenched-in-the-virus-was-this-austrian-ski-resort-a-covid-19-ground-zero

Oltermann and Hoyal recount events in Ischgl from 3rd-13th March. They write "*an Austrian lawyer compiling a class action lawsuit against the Tirol region, alleging it failed in its public health duties, has gathered the signatures of more than 6,000 tourists from 47 countries who believe they caught the virus in Ischgl, including people from Canada, Cambodia and Zimbabwe. Around 180 of them are British citizens, who took the virus back to London, Manchester, Birmingham, Norwich and Brighton.*" 6,000 people. Wow.

Wikipedia has a somewhat lower figure of 600 infections in Austria and 1,200 in "*Germany and the Nordic countries*" https://en.wikipedia.org/wiki/Ischgl An interesting question is what proportion of visitors and locals this might represent. Ischgl has a population of about 1,600 and there are 12,000 beds available in local hotels and hostels for visitors https://de.wikipedia.org/wiki/Ischgl (in German). According to the German Wikipedia page, some newsmedia investigations found up to 11,000 infections could be traced back to Ischgl. Those various estimates form a very broad band.

If we take the time between the Icelandic notification of an outbreak via EWRS (4th March) and the closure of the resort (13th March), and we think of an average skiing holiday to be 3 days, that would allow for three cohorts of overnight visitors, plus residents. But some people (such as the Icelandic group) stay for a week. The Icelandic people who first knew were there for a week, 22nd - 29th February, say Oltermann and Hoyal. That would make a total of 3 weeks until closure. If we imagine 6,000 of the 12,000 are 3-day visitors and the other 6,000 for a week, that gives us a weekly turnover of about 18,000 visitors, which is 54,000 people in the three weeks from the Icelandic arrival to resort closure, which adding the residents is 55,600. Even taking the high figure of 11,000 infected, that is just under 20% of those there. The 6,000 figure is just under 11%, and the 1,800 figure only just over 3%. The Gangelt seroprevalence was 14+%. The Geneva seroprevalence study was up to 10% in some weeks in April. The Diamond Princess outbreak involved 634 of

3,711 on board, 17%. So even the higher figures for Covid-19 transmission in Ischgl seem to me to be plausible (and the 3% figure seems to me to be a low guess). Of course, my estimate of the numbers potentially exposed could be way off.

In talking about public health administrative liability, the narrow time band is between the official notification of a problem, and closure, which is the 9 days 2020-03-04 to 2020-03-13. The Icelandic people who became ill arrived on 2020-02-22. So let us define the "total period" to be 2020-02-22 to 2020-03-13; the "earlier period" to be 2020-02-22 to 2020-03-03 and the "later period" to be 2020-03-04 to 2020-03-13. The question is then what proportion of transmission could have taken place during the later period? Most visitors to Ischgl are said to be Germans. So the RKI Dashboard might give us some idea of the run of the disease. On 2020-03-02 and 2020-03-03, the RKI Dashboard records under 300 new infections. From 2020-03-04 to 2020-03-13, the later period, it records 17,080 new infections. If we extrapolate those 300 new per day at the end of the earlier period back through the entire earlier period (which is surely an overestimate), we get an estimate of about 3,000 new infections for the earlier period, and with 17,080 for the later period a total of around 20,000 for the total period. That means the proportion of new infections in the earlier period is almost exactly 15% of those in the total period; 85% occurred in the later period. So, whatever the real number of infections occurring in Ischgl, it seems justified to estimate that at least 85% of them will have occurred during the later period, which encompasses the time between formal notification of a specific problem in Ischgl via EWRS and closure. That is exponential growth for you. No wonder the lawyers are looking at the delayed response.

The period recounted in the article is almost entirely the later period. Just to understand what people were ignoring, it is worth recalling what had already happened in Europe before that. It is three weeks after I had already decided no longer to travel, after I returned home from a trip on 13th February. The last time I was on a Bielefeld city bus was 14th February. Since then, I have only been out shopping, and only on my bicycle (except for a couple of 1km trips in my housemate's car). Superspreading events had already happened in Europe and had been recounted in the news by 22nd February: the Gangelt Carnival festival event in the Heinsberg district, the moderate spreading event in Contamines-Montjoie, and the emerging superspreading in Lombardy (links below). That is a week and a half before the beginning of the later period recounted by Oltermann and Hoyal, and two and a half weeks before bars closed in Ischgl on Tuesday 10th March (but not all did, according to Oltermann and Hoyal) followed by the evacuation/quarantine order from the Austrian government on Friday 13th March.

The history (seen from here) is as follows. The first cases in Bavaria had already been registered at the end of January and had been in the newspapers. Details were known of a British mini-superspreading event (from Singapore to Contamines-Montjoie and then to Sussex) on Monday 10th February https://www.theguardian.com/world/2020/feb/10/super-spreader-brought-coronavirus-from-singapore-to-sussex-via-france On 10th February, the Convenors of the IEC MT 61508 1-2-3 meetings in Japan in early March asked members of the MT about their travel plans. I am a member. I expressed the following view in an email response:

> Folks,
>
> A question on what everyone thinks risks omitting the moral dimension. Thousands and potentially millions of people's lives are at stake here.
>
> Here is what I think, which addresses the moral dimension.
>
> Nobody should be travelling non-essentially between East Asia and the other continents and subcontinents at the moment until:
>
> 1. the epidemiology of 2019-nCoV is better understood, in particular who is carrying it (and how many people), how virulent the virus is, and what the risk factors are;
>
> 2. The daily death growth factor is well below 1 and staying there;
>
> 3. There is a vaccine.
>
> People have guesses about the answers to 1, but there is hope, not medical consensus. It may be better understood in a month. Concerning 2, things do appear to be going in this direction and it may well be so in a month. Concerning 3, it is going to be at least May. And assuming trials go well then there are the logistics of producing such a vaccine (likely there will be more than one) and distributing.

(I guess it was not true that "it is going to be at least May" 2020 before there is a vaccine. There were already some. But they had not entered human trials. Even my imagining that a vaccine would be available in May 2020 may seem unreasonably optimistic. The timetable, though, was and is highly influenced by recruitment into Phase I-II-III human trials. Europe largely contained Covid-19 after about mid-March, and this led it to be hard to recruit Europeans into the Phase III trial of ChAdOx1. The Phase I-II trials were completed in April, even though the disease had been contained. I don't think it was such a hugely implausible guess to make on 10th February.)

This view was manifestly not shared by all MT members. Many responded that they would be attending. Two weeks later, on 2020-02-25, the face-to-face meeting in Japan was cancelled, and replaced by a Zoom meeting. By that date, many of the large companies whose engineers would have been attending had stopped all employee international travel.

On 12th February, I had discussed the emerging pandemic in an after-dinner talk at SSS'20, including my view expressed in the email two days before to the prospective IEC MT 61508 1-2-3 meeting participants. On my trip to York by rail, on the same day on which I talked, there had already been cases amongst travellers in London, through which I passed on the way to York, but I wasn't in any crowded situations, nor on the way back the next day. The first British moderate-spreading event had happened, and had been reported in TheG on 2020-02-10 https://www.theguardian.com/world/2020/feb/10/super-spreader-brought-coronavirus-from-singapore-to-sussex-via-france It occurred via a traveller who had been in Singapore and went from there in late January to a ski chalet in the French Alps at Contamines-Montjoie with friends, and then back to Sussex (a report by Hodcroft with excellent graphics in the Swiss Medical Weekly of 2020-02-27 at https://smw.ch/article/doi/smw.2020.20212).

When I returned home to Bielefeld from York on 13th February (the next day), I decided I wasn't going to travel anywhere any more until this epidemic (as it was then) had played its course. I did travel by bike into the centre of Bielefeld for my usual Saturday shopping on 15th February, but stopped even such trips when the news came of the superspreading event in the Heinsberg district (on 15th February). The Heinsberg event was in the news in the week of 17th February, but there were still face-to-face standardisation meetings, including international travellers, occurring in Frankfurt on 19th and 21st February, which I did not attend in person. I believe the last time I went into Bielefeld city centre shopping was Saturday 22nd February.

The Lombardy outbreak had become known on Friday 21st February and the first deaths, and many more infections, had been confirmed on 22nd February (according to Wikipedia https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Italy) There was a report on the outbreak in The Observer on Sunday 23rd February https://www.theguardian.com/world/2020/feb/23/coronavirus-northern-italian-towns-close-schools-and-businesses

So that was what we knew by the beginning of the total period. Companies may have stopped international travel by employees by then, or soon after, but private people could still do what they liked. One may wonder why, given the news, so many moderately wealthy people would still take skiing holidays in early March. One answer, of course, is that there are lots of people who neither understand epidemics nor their risks. Also, many visitors would have paid substantial sums for their trip up front and would not have recovered the money had they cancelled. Finally, most of those who did go through with their skiing holidays until general European lockdown in fact did not get Covid-19 from it. Even in Ischgl.

The reasoning of such visitors in early March may not have been appropriate from a whole-society point of view. If that reasoning was “if I go and ski and party, will I get Covid-19? Probably not” then that reasoning was, however, right much more often than not. That is the individual-versus-social dilemma which is facing governments and public health administrations during and after the summer holiday season, with continuing violations of distancing guidelines in many countries. Six months after the Ischgl events, the dilemma seems to me to be no better addressed than it was then. But is has become more sophisticated. It is now ““if I go and <have fun while violating distancing and protection guidelines>, will I get Covid-19? Probably not. And even if I do, will I suffer? Probably not life-threateningly.” That is a young person's argument, noting David Spiegelhalter's observation that the risk of death doubles with every six years of age. But it is out there. And it is right if you are young and otherwise healthy.

2020-09-08 The report on the Phase I/II trials of Russian vaccines by Logunov et al appeared in Tghe Lancet on 2020-09-04 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31866-3/fulltext They involved a total of 76 participants. Not by any means as large as the Phase I/II studies for, say, ChAdOx1. There were no adverse events, and they achieved an immune response in all the 40 participants of the first trial, and in Phase II, 85% of participants had detectable antibodies 14 days after the prime dose, and all at 21 days. A booster dose was given. In

their Comment, Bar Zaev and Ingelsby discuss not only the encouraging results, including a very strict neutralisation assay, but also the potential difficulties in vaccine introduction and the consequences of getting it wrong. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31867-5/fulltext

2020-09-08 Furtado et al report on a trial of azithromycin, a broad-spectrum antibiotic with some anti-inflammatory properties, in the trial of hospitalised patients with severe Covid-19 in Brasil (The COALITION II trial). https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31862-6/fulltext There was difference to those patients receiving standard of care (which included hydroxychloroquine at the time in Brasil). There were no adverse effects. Oldenburg and Doan note in their Comment https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31863-8/fulltext that azithromycin has been shown to be effective in vitro against viruses including SARS-CoV-2, and suggest that it is important to know whether administering it earlier could affect progression of the disease, since it is often prescribed for out-patient treatment.

2020-09-08 Paul Garner's latest blog in the BMJ on his long-haul Covid-19 experience https://blogs.bmj.com/bmj/2020/09/04/paul-garner-on-long-haul-covid-19-dont-try-and-dominate-this-virus-accommodate-it/ It's now been six months for him, with symptoms well-known to those with ME/CFS.

2020-09-09 Ashfield and Folegatti of the Jenner Institute explain the trials of ChAdOx1 and how they are being conducted. https://theconversation.com/oxford-scientists-these-are-final-steps-were-taking-to-get-our-coronavirus-vaccine-approved-144623 In Phase III, they have already vaccinated 17,000 participants in the UK, Brazil and South Africa, and more are to be enrolled in the US and India. However, the trials are being paused because of one adverse event, which needs to be analysed before trials resume https://www.theguardian.com/world/2020/sep/09/oxford-university-astrazeneca-covid-vaccine-trial-put-on-hold-due-to-adverse-reaction-in-participant Such events are not unexpected – in such a large trial, someone is likely to get ill over the period, but safety requires that it must be shown and known that this is not associated with the vaccine. An estimate in the article says it will take about a month to do this and restart (presuming that the adverse event is not related with vaccination).

2020-09-09 Britain is seeing a rise in infections. There have apparently been 8,500 new positive tests in the last three days, after having been in the low hundreds earlier in the summer. There are apparently difficulties with all parts of TTI. The opposition leader Sir Keir Starmer has said that the test-and-trace system "*is on the verge of collapse*" (see TheG article linked below). It is apparently not unusual for people to be advised to travel up to hundreds of miles for a test, and results are not promptly available. Track and trace was apparently reaching only 50% of contacts at the beginning of August https://www.theguardian.com/world/2020/aug/03/boost-test-and-trace-this-month-or-risk-second-uk-covid-19-wave-ministers-warned , inducing some councils with high infection rates to devise their own systems https://www.theguardian.com/society/2020/aug/04/english-councils-with-highest-covid-rates-launch-own-test-and-trace-systems . Isolation is being flouted by house parties and other gatherings, especially amongst young people, who are now said to be the main spreaders. It is so blatant that the seven north-eastern councils have issued a joint statement about following

protection guidelines https://www.durham.gov.uk/article/24137/North-East-council-leaders-urge-people-to-protect-themselves-and-others-to-prevent-coronavirus-spreading They say that "*[a] significant minority believe it is OK to have house parties, hold events with unregulated crowds, ignore the rules – well it isn't. Household transmission remains the biggest danger.*" There are six areas of the country in some version of lockdown https://www.theguardian.com/world/2020/sep/08/coronavirus-gatherings-of-more-than-six-to-be-banned-in-england (see graphic "UK covid-19 hotspots"). Thus there will be a law prohibiting gatherings of more than six people, with certain exceptions – "*[t]he only exemptions are when households or support bubbles are larger than six people; where gatherings are for work or education purposes; or for weddings, funerals, and organised team sports conducted in a safe way*", taking effect from Monday 2020-09-14. Up to now, this limit was guidance, with the legal limit set at 30, but now it is to become law and can thus be enforced.

The UK situation is not currently as bad as that of France, which recorded over 6,500 new infections in the last 24 hours https://www.theguardian.com/world/live/2020/sep/09/coronavirus-live-news-oxford-covid-19-vaccine-trial-put-on-hold-england-bans-gatherings-over-six (Last page, first entry).

This all seems to be very different from the situation in Germany, which has registered just over 250,000 infections and just over 9,000 deaths in total. Germany is also experiencing a rise in infections, from 250-300 per day at the ebb during the most stringent distancing measures in May, to just over 1,000 per day at the moment – RKI is registering 7,810 in the last 7 days on its case-figures page https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Fallzahlen.html (in German).

Testing has always been available locally in Bielefeld, at first with a 1-2 day wait, and a significant wait for results (3-5 days). This was even so of those self-isolating – testers would visit. Now, tests are available same-day (but are paid for, unless you are a teacher, child-care, health-care, or emergency-services worker or in some other professions) and notification is invariably next-day, electronically. In June, during the outbreak at the slaughterhouse Tönnies in Rheda-Wiedenbrück, the civil service recruited testing help from the civil disaster relief organisation and the military, tested and traced almost every Tönnies worker (ultimately missing 30-40, I understand) from over 7,000, and offered free tests to any residents of the two involved districts who were about to go on holiday, some 640,000 residents in all. Eventually, there were between 2,119 and 2,186 cases by Tönnies employees, but almost no spreading into the local community beyond household members https://www.landundforst.de/landwirtschaft/betrieb/coronavirus-ausbruch-toennies-folgen-ticker-562326 (In German, figures from entry on 2020-07-23).

There is no comment in newspapers about the tracing system; everybody seems to be assuming it is working. Flouting quarantine or isolation also appears to be very much the exception. People seem to be conforming (it helps, of course, that this is the law). However, there are concerns, as in GB, of the infection rates rising amongst young people, and this being because of flouting distancing guidelines, which were announced by Health Minister Spahn as well as noted by RKI in August

(e.g., https://www.swr.de/swraktuell/ursachenforschung-anstieg-neuinfektionen-coronavirus-100.html , in German; no date but graphics show figures from late August). This is apparently so across much of Europe https://www.theguardian.com/world/2020/sep/08/how-europe-is-tackling-spread-of-covid-19-with-appeal-to-young-people

In the last 7 days, Bielefeld has registered 22 new infections, a rate of 6.7 per 100,000 residents, and in the week before that 29 new, a rate of 8.8 per 100,000. In Germany overall, the 7-day new infection rate is over 9 per 100,000. RKI produces a daily situation report on Covid-19 in Germany, available in German and English from https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/Gesamt.html (the page is written in German, but you can scan down without reading; the daily report link is evident in German and English, as are the archives, gathered by month).

2020-09-09 Ahmed et al published on 2020-09-04 in EClinicalMedicine a systematic review of MIS-C https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30271-6/fulltext

2020-09-09 Stephen Reicher, a member of SAGE, writes in TheG on 2020-09-09 about social aspects of current Covid-19 containment measures (which of course are mainly social) https://www.theguardian.com/commentisfree/2020/sep/09/scapegoating-young-people-britain-coronavirus-rates He refers to refers to Smith et al https://www.medrxiv.org/content/10.1101/2020.06.01.20119040v1 who conducted a survey on conformance to isolation requirements in the UK, amongst 2240 participants. (Isolation is called quarantine in Germany.) They found conformance at a shockingly low 25% in May 2020. If that is still the case, it surely indicates why there is still significant transmission in the UK. In Germany, conformance with quarantine requirements is supported (by city-administration-organised home delivery teams for essentials), and is also checked. It might help that it has the status of a regulation (a by-law).