[redacted]

From: Smith G (Gregor)
Sent: 10 September 2020 12:04
To: First Minister; Cabinet Secretary for Health and Sport
Cc: Hutchison D (David); Lloyd E (Elizabeth)
Subject: COVID 19 - duration of lasting immunity
Attachments: 2020-09-07 1_3_ Immunity_Spotlight_OS FINAL (1).docx

Follow Up Flag: Follow up
Flag Status: Completed

First Minister

We've informally touched on the apparent anomaly that, despite rising cases elsewhere, previous hot spots of infection, such as London and Inverclyde, have not shown the same rising infection rates. The question arose as to whether this was a phenomenon of chance, or a signal that something relating to this previous exposure was having a protective effect.

The JBC has published three reports, the production of which have been supported by Professor Sir Roy Anderson, an eminent infectious diseases epidemiologist from Imperial, that examine the evidence in relation to immunity and SARS-CoV-2.

There is much of interest in them, including views on the nature of immunity and its endurance, and what this may mean for future vaccination programmes. Much here will be dependent on the degree of mutation we see in the virus and it is plausible and perhaps likely, as we've discussed before with [redacted] that vaccination will become necessary on a regular basis as we do with flu.

One passage sticks out in relation to the experience of hot spots:

Seroprevalence estimates. *Given the available evidence that circulating antibody levels can decline rapidly, especially in those recovering from asymptomatic or mild disease, it is highly likely that estimates reliant on blood antibody sampling to determine how many people have had the disease are underestimates. If the antibody levels observed by Long et al. in asymptomatic patients is a true representation of the rest of the population [14], then 40% of asymptomatic patients who have had the virus would be unaccounted for 8 weeks post-infection.*

Coupled with a lack of large-scale testing during the beginning of the pandemic, it is highly likely that estimates for the numbers of those infected during the early stages of the pandemic are low. It is also likely that areas that experienced a high attack in March and April are also significantly closer to a level of protective herd immunity than appreciated.

Though insufficient in itself to change any of our current approaches, it perhaps emphasises that any judgements on current or future levels of sero-prevalence inherently underestimate the population level of immunity that will exist. This is a conversation and line of enquiry I'll continue to develop.

Dr Gregor Smith
Interim Chief Medical Officer for Scotland
Scottish Government
Room 1E:02A St Andrews House Regent Road Edinburgh EH1 3DG
Telephone: [redacted] **Twitter: @DrGregorSmith**

EXTRACT FROM ATTACHMENT: Coupled with a lack of large-scale testing during the beginning of the pandemic, it is highly likely that estimates for the numbers of those infected during the early stages of the pandemic are low. It is also likely that areas that experienced a high attack in March and April are also significantly closer to a level of protective herd immunity than appreciated.

[redacted]

From: Smith G (Gregor)
Sent: 26 February 2020 12:10
To: First Minister; Cabinet Secretary for Health and Sport
Cc: Chief Medical Officer; Calderwood C (Catherine); SGoRR Major Events; SGoRR Information; SG CoronaVirus; [redacted] DG Health & Social Care; Director of Population Health; [redacted] Scottish Government Health Resilience Unit; [redacted] [redacted] Russell GE (Gillian); [redacted]; Hutchison D (David); McQueen F (Fiona); Leitch J (Jason); Connaghan J (John) (Health)
Subject: Email - Briefing: SAGE 10 - Surveillance and Non-Pharmaceutical Countermeasures - 26.02.20

First Minister / Cabinet Secretary,

[Redacted - Not in Scope]

The range of NPI available rely on quarantine and social distancing and are likely to be cumulative when deployed together. However, the primary impact of such measures is to delay transmission and reduce peak incidence; when they are lifted, transmission can be expected to resume given the measures only protect the population while in operation (unlike vaccination). The overall impact on overall attack rate is therefore limited – though if measures are fine-tuned to allow sufficient transmission to allow population immunity (acquired through infection) to reach the herd-immunity threshold, significant reductions in overall attack are also possible. In this context, measures which are too effective merely push all transmission to the period after they are lifted, giving a delay but no substantial reduction in either peak incidence or overall attack rate. SAGE will examine further imminent evidence on the experience of using NPI elsewhere over the next week before making a recommendation here.

[Redacted - Not in Scope]

[Redacted - Not in Scope]

G

Dr Gregor Smith
Deputy Chief Medical Officer for Scotland
Scottish Government
Honorary Clinical Associate Professor, University of Glasgow
Room 1E:02A St Andrews House
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Telephone: [redacted]

Twitter: @DrGregorSmith

[redacted]

From: Foggo R (Richard)
Sent: 16 March 2020 10:30
To: [redacted] Grisewood A (Aidan); [redacted] Bell D (Donna); Cowan WJ (Willie); Sheppard L (Lesley) (Covid-19); Mitchell E (Elinor); Johnston ATF (Alan); Calderwood C (Catherine); Smith G (Gregor); Leitch J (Jason); DG Health & Social Care; Head of HSCA; [redacted] Thomson KAL (Ken) (Director-General); [redacted]
Subject: FM briefing - testing, key workers etc

My notes from FM briefing:

[Redacted - Out of Scope]

Questions:

- [Redacted - Out of Scope]

- [Redacted - Out of Scope]
- Herd immunity - best protection? What if no vaccine. Not chicken pox party approach. Not our policy. Vaccine coming, small clinical trials already. Might become seasonal.
- [Redacted - Out of Scope]

Richard Foggo|Director of Population Health|Director, COVID-19 Policy and Coordination|The Scottish Government

From: scotpages@gmail.com <scotpages@gmail.com>
Sent: 28 April 2020 15:43
To: First Minister <firstminister@gov.scot>
Subject: Facebook issue.

Dear Nicola or advisor

Please remove this recent Facebook post:

https://m.facebook.com/story.php?story_fbid=3014211308633694&id=200786289976224&anchor_composer=false

The post shows Jason Leitch displaying a "flattening the curve" diagram which is utterly flawed in relation to our approach to Covid-19.
The curve, whether Leitch knows it or not, describes herd immunity.
The original usage of that curve was by Drew Harris, who specified that it delays but does not reduces cases. Nor, indeed, deaths.
His graph represents Scottish deaths in the tens of thousands, and UK deaths in the hundreds of thousands.
It was abandoned even as Westminster strategy on March 16th, so to have this pop up on my timeline on 28th April, having been posted on 22nd April shows a distinct lack of knowledge somewhere.

Of course, even when Leitch was using this graph, a clinical advisor with any nous would know that, with any death-causing virus, you want to flatten the curve within the timescale of the original peak - and absolutely not accept the same number of cases and deaths but just over a more manageable timescale.

Please remove the terrible post, since it is clear that the SG have understood that the path that WM sought was flawed. To repeat this graph and it's discredited approach is ill-considered.

[redacted]

[redacted]

[Email redacted - Out of Scope]

From: [redacted]
Sent: 02 September 2020 22:34:33 (UTC+00:00) Dublin, Edinburgh, Lisbon, London
To: Smith G (Gregor)
Cc: Steedman N (Nicola) (DCMO); Bain MB (Marion); [redacted]
Subject: Flu epidemiology in Australia 2020

Dear Gregor

[Redacted - Out of Scope] there are very little flu in Australia this year compared to previous years and similar picture is also seen in New Zealand and South Africa. Possible explanations put forward for this unusually mild flu season are as follows:

- [Redacted - Out of Scope]
- Uptake of flu vaccine this year in Australia was very high compared to previous years and hence preventing transmission with good herd immunity
- [Redacted - Out of Scope]

[Redacted - Out of Scope]

Hope this is helpful

Regards

[redacted]
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Tel: [redacted]
Mob [redacted]
PA: [redacted]

[Redacted - Not in Scope]

From: NCRC.SPOC <NCRC.SPOC@dhsc.gov.uk>
Sent: 28 September 2020 08:02
Subject: OFFICIAL: PHE COVID-19 INTERNATIONAL EPI DAILY SUMMARY 20200928

[Redacted - Not in Scope]

Additional Information:

[Redacted - Not in Scope]

Brazil

- New surge of cases are being reported in the city of Manaus, prompting health officials to close bars and river beaches, implement a 30-day ban on parties and other gatherings, and restrict restaurant and shopping hours
- These trends indicate that herd immunity may not have been reached in Manaus after all, despite University of Sao Paulo researchers recently suggesting that a drastic fall in COVID-19 deaths in Manaus pointed to herd immunity having been attained

[redacted]

From: [redacted]
Sent: 04 April 2020 16:08
To: [redacted] First Minister; Scottish Ministers; [redacted] wendy.chamberlain.mp@parliament.uk; Calderwood C (Catherine); McQueen F (Fiona)
Cc: [redacted]
Subject: Fwd: Covid - 19 PPE

[Redacted - Out of Scope]

It seems to me that we are still going down the unacceptable route of 'herd immunity' with health professionals being used as cannon fodder at the moment. I have worked for the NHS since 1985 and it saddens me greatly that I may be forced into the position of having to resign due to the inadequate response to protect front line workers, and, the vulnerable patients that we are potentially going to infect.

[Redacted - Out of Scope]

I look forward to your reply
Kind Regards

[redacted]

I hope this email

Sent from my iPad

Begin forwarded message:

[Email redacted - Not in Scope]

The dynamics of the humoral immune response following SARS-CoV-2 infection and the potential for reinfection.

Paul Kellam and Wendy Barclay
Department of Infectious Disease, Faculty of Medicine, Imperial College London.

Purpose and recommendations

This document summarises knowledge about the antibody response to human coronavirus infections, and catalogues recent insights into SARS-CoV-2 serology, including non-peer reviewed studies, in humans and non-human primates. Its purpose is to provide a framework for the interpretation of serological testing during the current COVID19 pandemic, and to consider the potential for reinfection of individuals by SARS-CoV-2.

Top line messages:

1. **Most patients infected with SARS CoV2 mount an antibody response at 10-14 days after clinical infection, but a small proportion (30% in one recent study, often after mild disease) show a later response (first detected at 28 days) or no antibody response at all.**
2. **Low or absent immune response might be partly explained by poor sensitivity (70%) of the tests being employed, but nonetheless there is considerable variation in the amount of antibody produced by different individuals after infection.**
3. **There is no data in the public domain about how long antibody responses last after SARS CoV-2 infection, beyond about 2 weeks after recovery.**
4. **A single animal study (NHP) shows that antibody protected from reinfection with SARS CoV-2 at 28 days after infection and this supports antibody as a correlate of immunity.**
5. **Based on literature for other coronaviruses, mild infections can result in low antibody responses that wane over the months after infection.**
6. **People who have experienced mild infection with SARS-CoV2 may mount weak antibody responses, making it difficult to detect them using serological assays and such low responses may wane over months allowing them to be reinfected in a second wave.**

Recommendations:

1. **Longitudinal serology studies are urgently required to understand whether antibody to SARS CoV-2 will wane and over what time scale, especially from mild cases.**
2. **If immunity passports were issued to allow key workers to return to work, frequent (monthly) retesting would be important to ascertain antibody levels were maintained over time.**
3. **Seroepidemiology should take into account low sensitivity and slow time course of the antibody response when serological tests are used to detect mild cases.**

Supporting assessment of current knowledge about humoral responses to coronavirus infection.

Serological decline after MERS CoV and SARS CoV infection

A few studies have assessed antibody titres to MERS CoV and SARS CoV in the months and years following primary infection. Robust immune responses with long lived (> 1 year) functional antibodies were seen following severe MERS CoV infections or those with prolonged virus shedding (Choe et al. 2017; Alshukairi et al. 2016). This was also observed in a small study of MERS CoV, where neutralizing antibodies, were detectable in 6 (86%) of 7 persons who had previously had severe MERS (including 5 with pneumonia) for at least 34 months after infection. However, in this small group there was evidence of antibody waning; 4/7 showed 4 to 16-fold reduction in nucleocapsid binding titres and 4/7 show a 2 fold reduction in neutralising titres over 34 months, with 4/7 assessed as having a low neutralising tires throughout (Payne et al. 2016). After mild or asymptomatic MERS CoV infections, antibody responses were either limited or rapidly declined (Choe et al. 2017; Okba et al. 2019). Although numbers are small, no neutralizing antibody response was seen in 4/6 and 2/3 mild MERS CoV longitudinal samples either within three months and in some cases, not even immediately after infection (Choe et al. 2017; Alshukairi et al. 2016). In a separate study of 280 contacts of 26 confirmed MERS CoV index cases, 12 contacts likely to have been infected were identified. 7/12 contacts sampled within 4-14 days of index contact were virus genome positive by RT-PCR but serologically negative (actively infected), whereas 5/7 were virus genome negative, but had detectable binding and neutralising antibody titres (infected and recovered) (Drosten et al. 2014).

Similarly, although SARS CoV was largely associated with symptomatic disease, antibodies decline over time. In a 3-year follow-up of hospitalised SARS CoV patients, SARS CoV IgG binding titres were undetectable in 19.4% of people by 30 months post infection and neutralizing tires were undetectable in 11.1% of people at this time (Cao et al. 2007). Consistent with this observation, a study of 98 SARS patients over 2 years showed all had detectable antibody binding titres over 2 years but that, in a subset, titres declined over this period. 18 individuals with neutralizing antibodies had titres that peaked on day 30, then decayed gradually so that by 2 years 1/18 had no detectable neutralizing antibodies, and the remaining patients had a low antibody titres close to background levels (Mo et al. 2006). Similarly, in a study following 176 previously SARS CoV infected people, the ELISA optical densities (ODs) that indicate antibody titre reduced by 33% within one year, 46% by 2 years and ~75% by 3 years (Wu et al. 2007).

In summary, studies of MERS and SARS CoV indicate total binding antibodies and neutralising antibodies decrease to a level where by 2-3 years everyone previously infected will have minimal detectable antibody response, but with those suffering more severe disease having the highest titre responses for longer. Although the time dependent decay of neutralizing antibody titers implies a lack of protection from reinfection, this cannot be concluded unequivocally, due to the possibility of other protective mechanisms, perhaps from disease rather than infection, through other arms of the immune response (memory and cytotoxic T cells). It is, however, suggestive of a population level reduced protection from reinfection by epidemic CoVs over a short period of time.

Seroconversion rates to seasonal human coronaviruses

One indication of the strength of immune protection from coronavirus infection is to consider what is known for the endemic seasonal CoVs, namely the genetically related alphacoronaviruses NL63 and 229E, and the genetically related betacoronaviruses HKU1 and OC43. There is some evidence for antigenic cross protection between the Human CoVs in the same genetic group (see below). A cross sectional seroprevalence study for seasonal human alphacoronaviruses NL63 or 229E, showed 75% and 65% of children in the age group 2.5-3.5 years are seropositive for NL63 and 229E

respectively, and most children are seropositive by 6 years (Dijkman et al. 2008). In adults, respiratory infection by human seasonal CoVs accounted for 22% (43/195) (Gorse et al. 2020) and 25% (Ambrosioni et al. 2014) acute respiratory illness. The ability of human seasonal coronaviruses to infect adults who have likely been infected as children can be accounted for either by:

a) virus escape from neutralization (drift),
b) reinfection with a heterologous CoV of a different genotype (alpha followed by betacoronavirus infections, or vice versa) due to lack of cross protective antibodies,
c) reinfection with homologous coronavirus due to sub-protective/waning antibody responses.

The lack of extensive time resolved virus genetic data and a lack of extensive serology studies against extant and historic strains of the 4 seasonal coronaviruses makes the contribution of virus genetic drift to escape from pre-existing protective immune response difficult to judge. One paper describes genetic drift mapping to sugar binding domains in S protein of CoV OC43 suggesting drift may account for persistence of this genotype in the human population (Ren et al. 2015). Similar studies on other genotypes are lacking.

In the absence of drift, bearing in mind we only identify 4 genotypes of CoV endemic in humans and estimate they account for 20% clinical colds and likely many more asymptomatic infections each year, we can infer that each person gets infected at least once every 5 years by a coronavirus, and so homologous reinfection must take place, otherwise we would not get reinfected after the age of 20 or so.

Reinfection by seasonal human coronaviruses in the community

A small number of studies have attempted to detect reinfections in the community. In a cohort study of community acquired and childhood pneumonia admissions to hospital in Kenya, reinfections by human coronavirus NL63 were detected over a 6 month period (Dec-May 2010) in 46 of 163 patients (28%) (Kiyuka et al. 2018). Most reinfections resulted in low virus titres and decreased disease. However, for a small number (11%), reinfection resulted in higher virus shedding compared to the previous infection, with the caveat that peak of virus in first infection could have been missed. When reinfections occurred up to 80 days after first infection, the virus load was usually low. However, reinfection after 80 days sometimes resulted in high viral genome load, compatible with such viruses being capable of onwards transmission. Sequence analysis of paired viral samples from the same individual reinfected after 80 days suggested reinfection was by a homologous CoV (Kiyuka et al. 2018). No antibody levels were measured in this study.
In a recent population study from the FLUWATCH project, over 5 seasons 2006-7 to 2010-11, the seasonal CoVs NL63, 229E and OC43, were detected at a rate of 390 infections (95% CI 338-448) per 100,000 person-weeks. The rates of infection stratified by age showed a bimodal distribution with peaks at ages 0–4 and ages 16–44 consistent with previous serology studies. Importantly, 8 subjects had more than one consecutive coronavirus infection. Of these, no participants had the same coronaviruses strain twice; modelling suggests this provides some evidence for lasting immunity. Nonetheless, analysis of the CoV infection pairs per person shows these small numbers partition into 4/8 having a reinfection within 7-15 weeks whereas 4/8 have a reinfection between 23-56 weeks. The former group all comprise infection-reinfection with heterologous alpha (NL63 or 229E) and beta (OC43) CoVs consistent with lack of serological cross protection, whereas 3/8 of the latter group had homologous reinfection of alphacoronaviruses (Aldridge et al. 2020). Although too small in numbers to be definitive, this suggests that serological protection from reinfection does exist but that it declines over a year, when infection with a virus of the same genotype becomes possible.

Evidence to support seroprotection against homologous virus genotypes exists in children, using serology assays specific for carboxyl-terminal region of the nucleocapsid protein of each of the four viruses. Seroconversion to NL63 (alphacoronavirus) and OC43 (betacoronavirus) occurs more frequently in children in both households and in hospitals. When examining small numbers of reinfections, seroconversion to NL63 was correlated with protection from infection by 229E, both alphacoronaviruses. Seroconversion to OC43 can protect from reinfection by HKU1, both betacoronaviruses. However, the reciprocal protection (229E protects against NL63 and HKU1 against OC43) did not occur (Dijkman et al. 2012), suggesting that even homologous protection by genetically related CoV is not immunological simple.

Reinfection by seasonal human coronaviruses in controlled human infection models (CHIM).
One way to distinguish between infection due to virus escape from neutralization, including heterologous challenge or infection in the presence of sub-protective antibody responses, is to attempt to experimentally infect adult volunteers with seasonal human coronavirus either in the presence of their preexisting immunity or by re-challenge with a homologous virus. Inoculation of healthy adult volunteers with human coronavirus 229E led to infection in 10/15 people and clinical symptoms in 8 of those 10 infected people, even though most must have already experienced 229E infection previously. All those infected had increased antibody titres within 3 weeks of infection, which rapidly declined by 12 weeks and returned to baseline by 52 weeks. When re-challenged at 1 year, 66% (6/9) became re-infected but none developed clinical symptoms (Callow et al. 1990). There are no data about the levels of virus shedding after the first or second challenge. These data were different to earlier studies where reinfection by a homologous coronavirus after 1 year did not occur, but reinfection with heterologous virus produced symptoms of infection. However, in the absence of sequence information about these heterologous '229E-like' CoVs and the possibility that Reed's volunteers were more robustly infected initially, so their antibody titre took longer to decay these data are not easy to interpret (Reed 1984).

Serological responses to SARS-CoV-2.

Antibody responses to SARS-CoV-2 infection in humans and animal models have been reported in very recently published papers and non-peer reviewed preprints. These early studies suggest the immune response to SARS-CoV-2 is similar to that for SARS-CoV and MERS-CoV. Most infected individuals (RT-PCR positive) seroconvert 10-14 days after symptoms, but antibody levels in some mild cases take longer to appear and are low or undetectable. There is no data at all on how long the antibodies remain and what level of antibody is associated with immune protection. In comparing studies, caution should be exercised because many of the studies use different assays to measure the serological response and these are not yet calibrated against each other.

Different tests to measure SARS CoV2 antibodies:
The gold standard test for antiviral antibody is the **virus neutralization** test. This demonstrates that antibodies in a serum sample can prevent susceptible cells from being infected when mixed with a standard challenge dose of virus. However, using this test for SARS CoV-2 requires work inside a high containment (Containment Level 3) laboratories with infectious virus. A surrogate neutralization test uses **pseudotyped virus** particles (PV) that bear the Spike protein of the SARS CoV-2 virus. This test can be performed at containment level 2 and is read out with a suitable reporter such as luciferase. However, it is still not suitable for high throughput or point of care testing.
Immunofluorescent test (IF) also use virus-infected cells, detecting antibody present in the patient blood sample through its reaction with a viral antigens expressed in the fixed cells.
Enzyme-linked immunosorbent assays (ELISA) tests and point **of care lateral flow assays** are suitable for high throughput butdo not measure the function of the antibody, only that antibody can bind to a given antigen. The antigen is usually a recombinant protein such as whole Spike protein or a fragment thereof. Some tests are using just the spike subdomain (S1), and others even only use the receptor binding domain (RBD) a small piece of S. It is possible that the smaller the spike fragment used, the less likely it is that antibodies in the sera raised against other human coronaviruses will cross react, however, this may come at the price of sensitivity. Some tests use the virus nucleoprotein N as the antigen. This is rather more conserved amongst human coronaviruses and SARS CoV2 and so these tests may lack specificity.

A recent study compared 3 CE-marked commercial ELISA assays and 6 POC tests that were available in Denmark (Lassaunière et al., 2020). Thirty serum samples from severe COVID patients were assessed, along with 10 negative sera and another 71 sera from people with other viral infections to test for specificity. The Wantai SARS CoV2 total antibody ELISA that has Spike RBD as the antigen was the most sensitive test, 100% day 10 samples were positive. The Euroimmun IgG test was less sensitive and only detected 78% of the same samples. In addition, the Euroimmun IgG ELISA showed poor specificity because it detected antibodies in 3 sera from patients not infected by SARS CoV2.

Antibody responses reported in SARS CoV2 patients.
A study of 173 people admitted into hospital in China with acute respiratory infection syndromes and/or abnormalities in chest CT images (Zhao et al 2020) used three different assays to measure seroconversion. Similar to the Wantai commercial test above, one measured total antibody to the Spike receptor binding domain (RBD), the second measured IgM to the same Spike RBD antigen and the third assay measured IgG against nucleoprotein (N). The first assay detected positive sera in 93.1% (161/173) with a median response time of 11 days, the second measured a seroconversion rate of 82.7% (143/173), median response time 12 days, and the response rate for IgG to the nucleoprotein was lower at 64.7% (112/173) and took longer to appear, with median response time of 14 days. In later samples collected between 15-39 days from disease onset, the assay that measured Spike RBD antibodies detected seronconversion in 100% patients, whereas the other assays were less sensitive: RBD IgM in 94.3% and N IgG in 79.8%. This study showed that SARS-CoV-2

seroconversion occurs on a time course that is consistent with other epidemic CoVs and antibodies to Spike RBD were the most reliable for case counting. At 2 weeks post symptom onset, antibody titres were statistically higher in critical compared to non-critical patients, possibly due to different rates to a maximal antibody response or reflecting similar disease severity observations from MERS-CoV and SARS-CoV patients as described above (Zhao et al. 2020).

In a separate European collaborative study, in-house and commercial ELISAs together with a virus neutralization assay were used to measure antibodies in a total of 19 severe and mild cases. A temporal study of seroconversion in three patients showed the patient with severe disease became antibody positive earlier than the other two who had mild disease, indeed, one mild patient only gave a positive serum sample using the nucleocapsid ELISA or the neutralization test at 28 days after symptoms (Okba et al., 2020). In 9 mild cases from early in the German outbreak, antibody responses were measured by neutralization assay and by immunofluorescence detecting IgG and IgM binding antibodies. There was incomplete correlation between the titres in the different tests. Seroconversion occurred by day 7 in 50% patients and in all patients by 14 days after symptom onset. The onset of the antibody response did not result in a rapid decline in virus shedding (Wölfel et al. 2020). In contrast, the timing and functionality of the immune response to SARS CoV-2 infection was considered in a detailed study of a single female patient with moderate disease in Australia. The appearance of antibody secreting cells, T follicular helper cells and CD8 positive T cells in the blood of this patient at day 7-9 was coincident with a fall in virus titre and recovery (Thevarajan et al., 2020). The antibody response was also investigated in 23 patients in Hong Kong (To et al. 2020). In this study, the correlation between virus neutralisation activity and IgG titres to nucleoprotein and the S1 RBD were excellent. Antibody trajectories over 20 days from this small number of severe and mild cases again demonstrate variability in individual early antibody responses, that did not correlate with disease severity. A further study from a recovered cohort of 175 patients in Shanghai, measured neutralizing antibody (Nab) titres by the ability of sera to block pseudotyped virus entry (Wu et al., 2020). The average time for seroconversion was 10-15 days. The typical pattern was observed: patients with more severe illness showed higher NAb. Importantly, in this study around 30% patients showed very low Nab titre, and 10 patients (6%) who were confirmed to have been infected from having an RT-PCR positive respiratory sample did not show any antibody response at all even at a later time point 2 weeks after hospital discharge. In the positive samples taken 2 weeks after hospital discharge there was no evidence of antibody waning. The authors comment that the individuals with no antibody measured clearly recovered from COVID without any antibody help, but whether they are at risk of reinfection is not known. Wu et al also emphasize the importance of screening convalescent plasma if it is to be used from prevention or treatment. Indeed, the same PV neutralization assay was used to measure potent antibodies raised in rats immunized with a potential SARS CoV-2 vaccine based on the spike protein RBD fragment. The antibodies were as potent at inhibiting PV entry as ACE2- Ig, a potent SARS CoV-2 entry inhibitor (Quinlan et al., 2020).

Studies on SARS-CoV2 antibodies in experimental animal infections.

Animal studies have found several species to be susceptible to SARS CoV-2 infection including non-human primates, ferrets and cats (Chen 2020; Munster et al. 2020; Kim 2020). Infected ferrets had serum neutralizing antibodies at 12 days post infection, but so far, no re-challenge experiments were reported (Chen 2020). Rhesus macaques are susceptible to SARS-CoV-2, where infection causes a respiratory disease lasting 8-16 days, with detectable high viral loads in the nose, throat and bronchoalveolar lavages. All animals seroconverted to the Spike protein and showed neutralising antibodies by 10 days post infection (Munster et al. 2020). Rhesus macaques were productively infected by SARS-CoV-2, by clinical, virology and serological assessment. At 28 days from the primary infection, when anti-spike antibodies were detectable, two animals were rechallenged with virus

and neither became infected (Bao et al. 2020). This is unsurprising as the animals were most likely at or near the peak of their seroconversion but suggests that immediate reinfection in the face of robust neutralising antibodies to SARS-CoV-2 is not possible.

Concluding remarks:

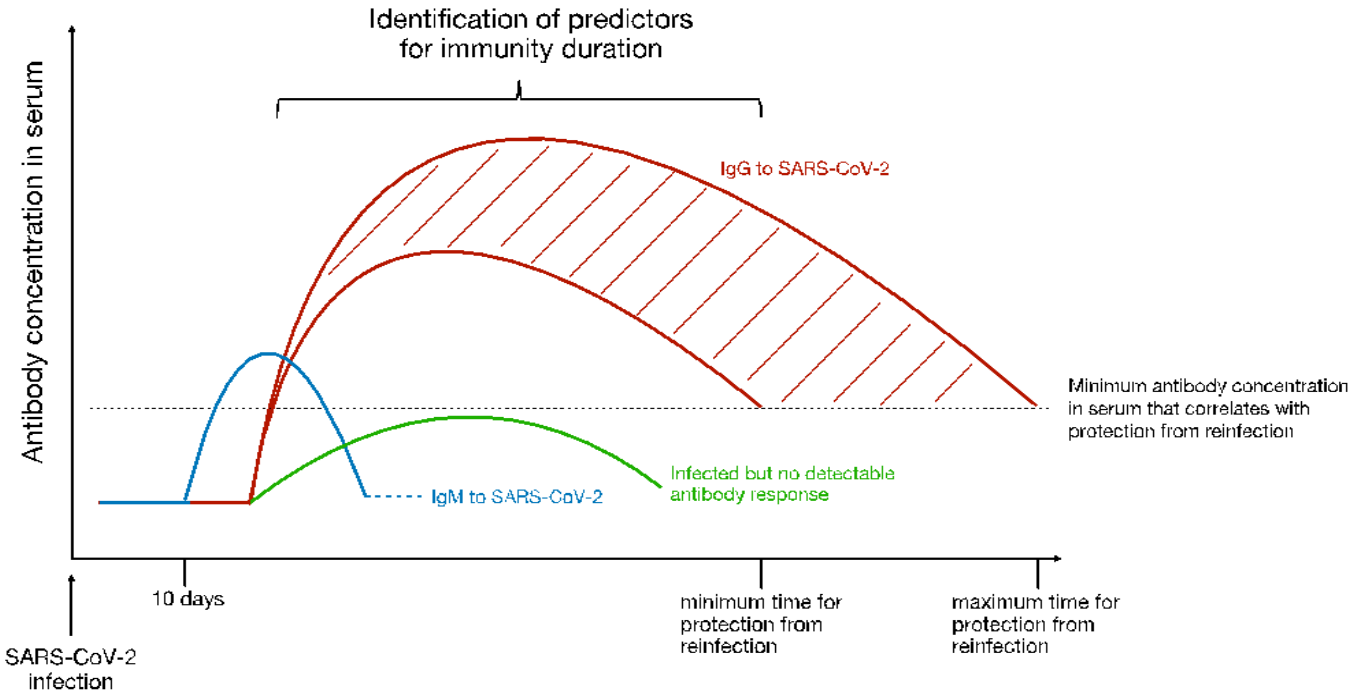
It is clear most people infected with SARS-CoV-2 display an antibody response between 10 and 14 days after infection. In some mild cases, detection of antibodies requires a longer time after symptoms, and in a small number of cases, antibodies are not detected at all, at least during the time scale of the reported studies. There is a paucity of information about the longevity of the antibody response to SARS-CoV-2, but it is known that antibodies to other human coronaviruses wane over time, and there are some reports of reinfection with homologous coronaviruses after as little as 80 days. Thus, the possibility of reinfection of previously mild SARS-CoV-2 cases is a realistic possibility, and should be considered. Such reinfection may be less likely to result in clinical disease, unless antibody dependent disease enhancement by sub-neutralising antibody titres occurs. It is unclear if such reinfections will result in onward transmission, but that cannot be excluded. The potential effect of this should be explored in epidemiological models. Obtaining longitudinal serological data where both binding titres and functional neutralisation titres stratified by age groups and previous disease severity status should be undertaken as a matter of urgency.

We recommend that:

1) The possibility for an individual to be reinfected by SARS-CoV2 is introduced into the epidemiological models, acknowledging that a proportion of those reinfected may go on to develop disease.
2) The reinfection parameter could be applied taking into account the following: the time when reinfection becomes possible is likely correlated with viral load or symptoms in the initial infection. This is because people with symptomatic disease are likely to mount a high antibody titre that decays over time until it crosses a threshold which is no longer protective against infection, whereas people known or predicted to have had mild (non-hospitalised) infections mount lower or even non-existent antibody response that decays at the same rate but will cross the protection threshold sooner.
3) The delay from primary infection recovery to being susceptible for reinfection should range from 30-720 days, with parameters to explore different starting antibody titres related to disease severity proportions but with a constant rate of serological decline.
4) Scenarios of the proportion of people susceptible to reinfection should range from 0 – 66% (the upper boundary here based on small numbers from a MERS study; the seasonal NL63 study would suggest 28% as a reasonable number) and in some scenarios anchored on disease severity proportions.
5) It should be borne in mind for future modelling, based on wide scale serology, that a proportion of people with mild or asymptomatic first infections may not seroconvert at all and therefore serology may not reveal the total number of infections that have occurred.

What studies should be established to assess the risk or reinfection?

- The effect of waning antibody titers and the possibility of reinfection and recurrent disease should be modelled.
- People with low antibody titres after mild disease should be followed up for evidence of reinfection and recurrent disease by regular clinical monitoring and by Q-RT-PCR. If a case of reinfection is detected, serial viral load by Q-RT-PCR should be performed and measures of antibody status at the time of reinfection established.
- Studies should be initiated to determine the relationship between serological antigen binding titres and functional virus neutralisation titres to interpret the likely level and length of seroprotection in the UK population, and to inform correlates for vaccine seroprotection to be used in Phase 1 clinical studies for vaccines in the UK.


Identification of predictors
for immunity duration
Antibody concentration in serum
IgG to SARS-CoV-2
Minimum antibody concentration
in serum that correlates with
protection from reinfection
Infected but no detectable
antibody response
IgM to SARS-CoV-2
10 days
minimum time for
protection from
reinfection
maximum time for
protection from
reinfection
SARS-CoV-2
infection

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[redacted]

From: [redacted]
Sent: 20 April 2020 11:52
To: [redacted]
Cc: [redacted] Covid-19 Director; [redacted] Head of HSCA; [redacted] Halliday R (Roger) [redacted]; Chief Medical Officer; Chief Scientific Adviser for Scotland; DCMO Health COVID19; [redacted]; Brown GJ (Gareth); [redacted] mith G (Gregor); Kleinberg D (Daniel); [redacted]
Subject: Re: briefing on immunity and herd immunity

Dear All

This review in PNAS presents a balanced view on whether immune enhancement likely:

https://www.pnas.org/content/117/15/8218

Bottom line - no one really knows but the negative experience of the dengue vaccine Dengvaxia has increased concern - the vaccine protected those who had been previously exposed to dengue but in naive individuals it made disease worse. However, immune enhancement is well known in natural dengue infections - scant evidence that it is of any importance in infections with coronavirus.

Best wishes

[redacted]

[redacted]
University of Glasgow
Level 4, Glasgow Biomedical Research Centre,
120 University Place,
Glasgow G12 8TA
UK
[redacted]
Phone: [redacted]

On 19 Apr 2020, at 22:14, [redacted] wrote:

[redacted] a great guy but he's not an immunologist (and nor am I).
I expect you saw the reference to enhancement in the Kellam & Barclay.
You might look at this paper too:
Quinlan, B.D., Mou, H., Zhang, L., Gao, Y., He, W., Ojha, A., Parcells, M.S., Luo, G., Li, W., Zhong, G., et al. (2020). The SARS-CoV-2 receptor-binding domain elicits a potent neutralizing response without antibody-dependent enhancement. BioRxiv.
Evidence can change of course, but we have to start with what we have I think.
Kind regards,
[redacted]

From: [redacted]
Sent: 19 April 2020 22:01
To: [redacted]
Cc: [redacted] covid-19.director@gov.scot <covid-19.director@gov.scot>; [redacted]; HeadofHSCA@gov.scot <HeadofHSCA@gov.scot>; [redacted] roger.halliday [redacted] <roger.halliday [redacted]>; [redacted]; CMO@gov.scot <CMO@gov.scot>; ChiefScientificAdviser@gov.scot <ChiefScientificAdviser@gov.scot>; DCMOHealth.COVID19@gov.scot <DCMOHealth.COVID19@gov.scot>; [redacted] Gareth.Brow [redacted] <Gareth.Brown [redacted]; [redacted] Gregor.Smith [redacted] <Gregor.Smith [redacted]; [redacted] Daniel.Kleinber [redacted] <Daniel.Kleinberg [redacted]
Subject: Re: briefing on immunity and herd immunity

hi [redacted]

Thanks for this. Reading through the 'optimistic' long-term scenario below, I think there are major unknowns as highlighted by Prof Marc Lipsitch (Harvard) who notes that it might actually be the opposite in terms of severity of disease when re-infection occurs. Pasting below the relevant bit of his article on immunity. Sounds like we need to keep all scenarios still on the table from best-case to worst-case. Worst-case (immune enhancement and no vaccine) means national elimination with border control becomes more and more attractive to the governments which have the ability to actually do that in the medium term.

With kind regards, [redacted]

https://www.nytimes.com/2020/04/13/opinion/coronavirus-immunity.html

"And yet getting a handle on this fast is extremely important: not only to estimate the extent of herd immunity, but also to figure out whether some people can re-enter society safely, without becoming infected again or serving as a vector, and spreading the virus to others. Central to this effort will be figuring out how long protection lasts. With time, other aspects of immunity will become clearer as well. Experimental and statistical evidence suggests that infection with one coronavirus can offer some degree of immunity against distinct but related coronaviruses. Whether some people are at greater or lesser risk of infection with SARS-CoV-2 because of a prior history of exposure to coronaviruses is an open question.
And then there is the question of immune enhancement: Through a variety of mechanisms, immunity to a coronavirus can in some instances exacerbate an infection rather than prevent or mitigate it. This troublesome phenomenon is best known in another group of viruses, the flaviviruses, and may explain why administering a vaccine against dengue fever, a flavivirus infection, can sometimes make the disease worse.
Such mechanisms are still being studied for coronaviruses, but concern that they might be at play is one of the obstacles that have slowed the development of experimental vaccines against SARS and MERS. Guarding against enhancement will also be one of the biggest challenges facing scientists trying to develop vaccines for Covid-19.

> On 19. Apr 2020, at 21:29, [redacted] wrote:
>
> Dear AG colleagues,
>
> As promised, here is a briefing on immunity and herd immunity SARS-CoV-2 ahead of our meeting on Monday.
>
> The attached document by Wendy Barclay and Paul Kellam at Imperial College is an excellent guide to the current state of knowledge.

A key point to make is that there is very little information on human immunity to SARS-CoV-2, and therefore a lot of reliance on studies of other human coronaviruses as a guide.

The most likely scenario is that there is antibody-induced immunity but it is partial and relatively short-lived. The Kissler et al. paper circulated previously assumes a mean duration of 44 weeks. However, this is far from certain and could well be revised as further data become available.

It is worth stating the short, medium and long term implications of this scenario.

Short term (weeks). At the current stage of the epidemic immunity and herd immunity are unimportant; too small a fraction of the population have been exposed.

Medium term (months/years). As is widely accepted, the very limited amount of herd immunity that will build up during the first wave may leave us vulnerable to a second wave in the coming months. Modelling work by Rowland Kao and Gianluigi Rossi at the University of Edinburgh suggests that if immunity is much less than life-long then subsequent waves are also likely, though these could diminish in size. Kissler et al. suggest that the waves could become seasonal.

Long term (years/decades). The Kao and Rossi model predicts that SARS-CoV-2 will become an endemic infection with many people experiencing multiple infections over their lifetime. The great majority of those over 70 years old will have experienced multiple prior infections (unlike now when any infection is a first infection). This will be extremely important if, as Barclay and Kellam propose, immunity acquired from prior infections reduces the severity of disease even when it doesn't protect against re-infection. In other words, it is possible that 'living with SARS-CoV-2' will be a far less serious public health concern in the long term.

I hope this is useful.

Kind regards,

[redacted]

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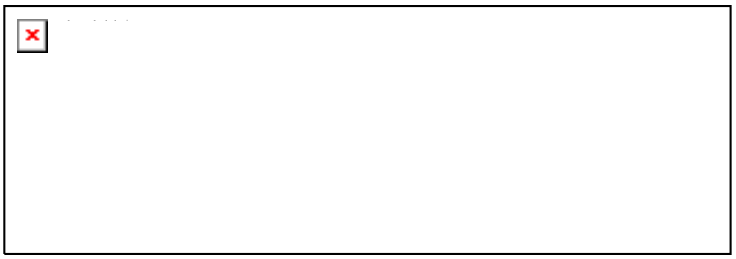

<immuneresponsetosarscov215thapril.pdf>

[redacted]

From: [redacted]
Sent: 01 May 2020 00:12
To: [redacted]; Smith G (Gregor) [redacted] Covid-19 Director; Halliday R (Roger); [redacted]
Cc: Chief Medical Officer; Brown GJ (Gareth); [redacted]
Subject: Re: Draft slide pack for FM deep dive

Can I make a small – but I think important – point of language. One of the reasons why the term 'herd immunity' evokes such distaste is that – irrespective of whether it is meant as a strategy or simply describes a parameter – it suggests a disdain towards the public. To refer to people as a herd suggests contempt (they are like sheep) and dispensability (slaughtering animals is more acceptable than slaughtering people). It is irreducibly elitist ('the common herd') so divides the speaker from the public… the last thing one wants!

I would suggest we always employ a more neutral term such as 'population immunity' or something similar.

[redacted]

[Emails redacted - Out of Scope]

[redacted]

From: Smith G (Gregor)
Sent: 14 March 2020 18:21
To: MEDICALDIRECTOR2, England (NHS ENGLAND & NHS IMPROVEMENT - X24); [redacted]
Cc: SPI-M@dhsc.gov.uk; SAGE@go-science.gov.uk; Jonathan Van Tam
Subject: RE: FOR INFO: NHS Scotland Surge Capacity

Thanks Steve.

This next phase of work from SPI-M is critical as it walks that fine line between closing the gap between achieving herd immunity and NHS capacity. Very grateful to everyone working on it and look forward to hearing more next week.

Sent with BlackBerry Work
(www.blackberry.com)

[Emails redacted - Out of Scope]

[redacted]

From: [redacted]
Sent: 23 October 2020 11:04
To: [redacted]
Cc: [redacted] ICJU Expert Advisory Group Mailbox; [redacted]; C-19 Secretariat - Analysis and Information Team (Sensitive); [redacted]; Chief Medical Officer; [redacted]
Subject: RE: IBPAG Forum (14 October - 21 October)

I agree with the idea that Vaccine is not the 'fairy tale' ending we are looking for, however the main use of vaccine, in a pandemic situation, with limited time/supplies, will be to protect the most vulnerable either from personal circumstance (age, chronic disease etc.), or exposure (frontline workers). Further down the line will be mass vaccination which moves us to 'herd immunity'. I do not see the language of mitigation/suppression as being clear enough since both are nebulous concepts, which are aspirational but difficult to measure

Best wishes

[redacted]

[redacted]

From: [redacted]
Sent: 21 April 2020 17:51
To: Kleinberg D (Daniel) [redacted]

[redacted] Director for Covid 19 Testing [redacted]; Head of HSCA; Halliday R (Roger); Chief Medical Officer; Chief Scientific Adviser for Scotland; [redacted] DCMO Health COVID19; [redacted] Smith G (Gregor); Covid-19 Director; [redacted]; Brown GJ (Gareth); [redacted]

Subject: Re: IN STRICT CONFIDENCE - ADVICE REQUEST FROM FM AND CMO - [redacted] on contact tracing

I think there are two different types of trade-off which have become confounded and which make this debate so difficult.

One is the trade off between human harm and some other criterion (such as wealth maximisation) for determining strategy. This was implied in early discussions of 'herd immunity' and is not only morally repugnant but also utterly corrosive of public trust and compliance.

[Redacted - Out of Scope]

[redacted]

From: [redacted]
Sent: 21 April 2020 16:34
To: [redacted]
Cc: [redacted] Director for Covid 19 Testing <directorcovid19testing@gov.scot>; sdr@st-andrews.ac.uk; [redacted] Head of HSCA <HeadofHSCA@gov.scot>; Kleinberg D (Daniel) [redacted]; Halliday R (Roger) [redacted]; Chief Medical Officer <CMO@gov.scot>; Chief Scientific Adviser for Scotland <ChiefScientificAdviser@gov.scot>; [redacted] DCMO Health COVID19 <DCMOHealth.COVID19@gov.scot>; dcc7@st-andrews.ac.uk; [redacted] Smith G (Gregor) [redacted] Covid-19 Director <covid-19.director@gov.scot>; [redacted] Brown GJ (Gareth) [redacted]
Subject: Re: IN STRICT CONFIDENCE - ADVICE REQUEST FROM FM AND CMO - [redacted] on contact tracing

I think we need a form of words that doesn't change policy. As I understand policy (SG colleagues please correct me) it is (and always has been) to save lives, protect NHS staff, and not overwhelm NHS capacity. It is NOT (and never has been) about herd immunity, minimizing transmission rates, or driving levels of infection to the lowest possible levels.
We need to be clear that the policy objectives can be met in various ways, some of which do not involve any of the above.
The immediate issue is not to paint ourselves into a corner unnecessarily.
[redacted]

[redacted],

[redacted]

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[Emails redacted - Not in Scope]

[redacted]

From: [redacted]
Sent: 14 April 2020 20:15
To: [redacted] Director for Covid 19 Testing; Brown GJ (Gareth); Chief Medical Officer; Chief Scientific Adviser for Scotland; [redacted]; Covid-19 Director; [redacted] dcc7@st-andrews.ac.uk; DCMO Health COVID19; Halliday R (Roger); Head of HSCA; [redacted]; [redacted] sdr@st-andrews.ac.uk; [redacted] Smith G (Gregor); [redacted]
Subject: Re: Input on Welsh Public Health Recovery Plan

Importance: High

Thanks [redacted] I think this is a helpful note but wanted to flag this sentence

'

1. A short-term interim recovery plan (12 month) is required until population level immunity is either conferred from a mass vaccination programme or from herd immunity through continued infection.

This assumes that either a vaccine would be both approved, manufactured, and delivered to populations within 12 months, or that herd immunity can somehow build which seems to be 80-90% of the population if we go off other vaccine-preventable diseases. Given uncertainty in this area, it seems risky to depend on herd immunity building especially if immunity lasts a year or less, and even ambitious timescales think a vaccine is 18 months away. Therefore we need to be planning for a scenario in which immunity is short, and a vaccine is not yet ready, and so a 'short-term recovery plan' might end up being in place for 1.5-2 years. It seems like the most promising scientific developments will be in rapid antigen testing (ideally within minutes) and repurposing existing medications for treating COVID symptoms, all while pursuing as much containment as possible to limit any further spread of the virus and keep the load on the NHS as manageable as possible.

With kind regards, [redacted]

On 14. Apr 2020, at 19:26, [redacted] wrote:

Dear all,

Gregor has been asked by the First Minister to get a view from the CMO Advisory Group on the merits of the approach that Wales sets out in the attached paper.
This is a paper from the Welsh CMO that focuses on the public health response which would be needed to accompany any lifting of the lockdown.

It would be greatly appreciated if you could reply to me with your views on this by **2pm tomorrow.**

Kind regards,

[redacted]

From: Smith G (Gregor)
Sent: 21 March 2020 08:47
To: Connaghan J (John) (Health); Covid-19 Director; McCallum R (Richard); McQueen F (Fiona); [redacted] Mitchell E (Elinor); Grisewood A (Aidan); Calderwood C (Catherine); Leitch J (Jason); Russell GE (Gillian); Chalmers MJ (Michael)
Cc: [redacted] Covid-19 Deputy Directors; Head of HSCA; Halliday R (Roger); [redacted] DG Health & Social Care; covid-19 Policy
Subject: RE: Modelling

I agree Richard - from the beginning, I've tried to stress the need for an exit strategy from any countermeasures and the move to suppression rather than mitigation narrows this further. Various papers through SPI-M and SAGE have suggested the need for these measures for 12-18m (until vaccine implanted at scale provides this strategy). It's less likely we'll achieve herd immunity with this strategy and at the moment there's still no good evidence of pharmaceutical countermeasure.

[Redacted - Out of Scope]

Sent with BlackBerry Work
(www.blackberry.com)

Emails redacted - Out of Scope]

[redacted]

From: [redacted]
Sent: 14 April 2020 08:53
To: Chief Scientific Adviser for Scotland
Cc: [redacted]; Head of HSCA; Kleinberg D (Daniel); Halliday R (Roger); [redacted] Chief Medical Officer; DCMO Health COVID19; [redacted] Smith G (Gregor); Covid-19 Director; [redacted] Brown GJ (Gareth)
Subject: Re: Official Sensitive -Lockdown Review Advice

Follow Up Flag: Follow up
Flag Status: Completed

hi Sheila,

[Redacted - Out of Scope] the short-term options are cycles of lockdown/release while keeping under NHS capacity (and working towards 60-80% herd immunity, of which we are estimated 5% there), [Redacted - Out of Scope] So we need to present alternative options to just letting the virus circulate unchecked and hoping some immunity builds over many many months.

With kind regards, [redacted]

Emails redacted - Out of Scope

From: Smith G (Gregor) [redacted]
Sent: 04 March 2020 00:32
To: First Minister <firstminister@gov.scot>; Cabinet Secretary for Health and Sport <CabSecHS@gov.scot>; Calderwood C (Catherine) [redacted]
Cc: Minister for Public Health, Sport and Wellbeing <MinisterPHSW@gov.scot>; Minister for Mental Health <MinisterMH@gov.scot>; Chief Medical Officer <CMO@gov.scot>; Lloyd E (Elizabeth) [redacted]; Hutchison D (David) [redacted]; DG Health & Social Care <DGHSC@gov.scot>; Connaghan J (John) (Health) [redacted]; Grieve DA (Derek) [redacted] Foggo R (Richard) [redacted] McQueen F (Fiona) [redacted]; Leitch J (Jason) [redacted]; SGoRR Major Events <sgorrmajorevents@gov.scot>; SG CoronaVirus <SGCoronavirus@gov.scot>; [redacted]
Subject: Sensitive: SAGE 12 - COVID-19 planning assumptions and non-pharmaceutical interventions.

Non Pharmaceutical Interventions (NPI)

[Redacted - Out of Scope]

The second tension lies between reducing transmission enough to reduce the peak without compromising the development of herd immunity so that withdrawal of the intervention simply leads to a later peak of the same magnitude.

In summary (over 13weeks):

- **Mass Gatherings**: no evidence to support effectiveness in containing outbreak, very little evidence to support delaying outbreak, reducing peak or mortality on its own
- **Closure of schools**: unlikely to contain an outbreak on its own, 2-3w delay to peak, 10-20% reduction in peak if children have same role in transmission as flu, modest impact cases/deaths <5%
- **Home isolation symptomatic cases**: unlikely to contain outbreak on its own, 2-3w delay to peak, reduction in peak by circa 20%, modest impact number of cases/ deaths <5%
- **Whole household isolation**: unlikely to contain an outbreak on its own; 2-3w delay to peak, reduction in peak by circa 25%, modest impact number of cases / deaths <10%
- **Social distancing**: unlikely to contain an outbreak on its own, 3-5w delay to peak, substantial reduction to peak, up to 50-60%, reduction 20-25% deaths
- **Social distancing for >65s**: will not contain an outbreak, negligible impact on delaying peak; 25-35% reduction in deaths and demand for hospital beds; reduction <5% cases but 20-35% of deaths

[Redacted - Out of Scope]

G

Dr Gregor Smith
Deputy Chief Medical Officer for Scotland
Scottish Government

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Room 1E:02A St Andrews House
Regent Road Edinburgh EH1 3DG

Twitter: @DrGregorSmith

[redacted]

From: [redacted]
Sent: 14 May 2020 17:45
To: [redacted] Smith G (Gregor); Steedman N (Nicola) (DCMO); [redacted]
Subject: RE: Sweden v UK/Scotland RE: Agenda item for the HPT Led National Incident COVID-19 Response Coordination Group

I suspect that Sweden is allowing the EDR to roll along at around 1 on the basis that the health system can cope with that level of infection and that it gives them the balance they want between individual freedom, economic pain and disease impact. By doing this they may be building up "herd immunity" that in the end we will all need if a vaccine does not transpire or is not that much more effective than a flu vaccine. So far, efforts to produce a coronavirus vaccine (SARS, MERS and feline infectious peritonitis) have not been hugely successful though I hope it is different this time. The MERS work may help.

In the end, we are all (well mostly) going to have to get this virus unless they get an effective vaccine quickly and I wonder if that has been Sweden's thinking.

Ireland is an interesting comparison with Scotland (by that I mean the Republic not the island of Ireland) and have been more successful in getting the disease under control though with around the same death rate as reported in Sweden (3.25 per 10,000 in Sweden, 3.07 in Ireland to date). Of course, Ireland has a quite different age demographic than the UK and Sweden (which are similar) which helps in terms of deaths but they have also tested at a higher rate than the UK and Sweden which are similar in that regard.

New Zealand have done a fantastic job in seemingly pretty much eradicating the infection. But what next? Tourism is a large part of their GDP and will be tricky to restart at the same scale (although a fair bit is from Aus so a reason why they are looking at a common travel zone).

In the end, Sweden may be doing the smart thing, deliberately or not, though I think they have also got lucky but then again, luck is often a key part of disease control in my experience, though you can give it a helping hand.

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