Minutes of the NERVTAG COVID-19 Ninth Meeting: 13 March 2020

Date & Location:	11:00 – 12:30, 13 March 2020 Via telecon only
In attendance:	Peter Horby (Chair), Camille Tsang (Secretariat), Emma Petty (Temporary Secretariat) NERVTAG Members: Peter Openshaw (PO), Ben Killingley (BK) Calum Semple (CSm), Wei Shen Lim (WSL), Robert Dingwall (RD), John Edmunds (JE), Jim McMenamin (JMM), Wendy Barclay (WB) PHE Observers: Gavin Dabrera (GD), Maria Zambon (MZ), DHSC Observers: Jonathan Van-Tam (JVT), Ursula Wells (UW), Sadia Dorsani (SD), Bethan Loveless (BL) SAGE: Catherine Yule (CY) NHSE: Chloe Sellwood (CSw) APHA: Ian Brown (IB) HPS: Lisa Ritchie (LR) DFID: Cathy Roth(CR)
Apologies:	Neil Ferguson, Andrew Hayward, Cariad Evans, James Rubin Cheryl Cavanagh, Mary Ramsay, Martyn Underdown, David Connell, Kevin Rooney,

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NERVTAG COVID-19 EIGHTH MEETING: SUMMARY

NERVTAG RECOMMENDED THE FOLLOWING:

ADAPTION OF THE PANDEMIC FLU IPC GUIDANCE INTO COVID-19 VERSION

DHSC has provided NHSE with an adapted pandemic influenza IPC guidance document as this was urgently required. The document will be reviewed by DHSC and then circulated to NERVTAG for review. Time frame to be clarified by DHSC.

THE POTENTIAL FOR REINFECTION WITH SARS-COV-2

NERVTAG discussed the evidence around reinfection/short term sterilising immunity. Concerns were raised that the length of immunity is unclear. Evidence from endemic coronaviruses is that after a mild infection antibody response may wane and individuals can become re-infected and shed further virus. Three months may be a reasonable point after which susceptibility due to waning immunity may occur in those who suffered a mild initial infection.

Members agreed that the novel nature of SARS-CoV-2 means that immune response may be more robust than for seasonal coronaviruses.

Members agreed that although there is considerable uncertainty, reinfection is a possibility that should be considered in modelling and longitudinal studies to identify reinfections are recommended.

High Consequence Infectious Disease (HCID)
Advisory Committee for Dangerous Pathogens (ACDP) and SAGE have declassified COVID-19 and it is no longer a HCID.

CASE DEFINITIONS

Concerns were raised regarding the case definition for self-isolation. Fever or cough may not cover those with other common symptoms such as myalgia. Information from the FF100 system and CO-CIN study may help inform this more.

FULL MINUTES

1 Introductions

1.1 The Chair welcomed everyone to the meeting and thanked them for joining the meeting at short notice. Apologies were received from those listed above.

2 Adaption of the pandemic flu IPC guidance into COVID-19 version

2.1 The Chair introduced the topic with some background information. The draft pandemic flu infection, prevention and control (IPC) guidance was signed off by NERVTAG towards the end of last year and was in the process of finalisation and publication.

2.2 The Chair proposed there were three areas for consideration with the IPC document:

- Whether the statements in the document are accurate and evidence based
- Whether the document is internally consistent
- Whether the document is externally consistent with advice already given regarding COVID-19.

2.3 JVT commented that he has sent a revised version to the NHS yesterday as a matter of urgency. LR noted that there is another version that may need to be included. LR agreed to review JVT's version and make any required changes to consolidate the documents.

2.4 It was proposed that the version sent to the NHS would remain active for the time being, while LR reviewed a consolidated version. If there were no major differences, the document would not need to come to NERVTAG however, if the consolidated document was quite different, this could be reviewed by NERVTAG via correspondence. The NERVTAG agreed version would then replace the original NHS version as the approved guidance.

2.5 JVT noted that the guidance was needed to help relieve pressure points on the NHS in England such as decontamination of ambulances. Under the HCID specification, it takes 3 hours and guidance is required for a simpler and faster method.

Action: JVT & LR to update IPC guidance document
Action: NERVTAG to review and approve IPC guidance via correspondence if required

2.6 Members discussed the recommendations for certain aerosol-generating procedures, including non-invasive ventilation (NIV) and high-flow nasal oxygen (HFNO).

2.7 JVT clarified that NIV and HFNO are still AGPs in the guidance and noted that the guidance would define what precautions to take to ensure that the procedures were undertaken safely. It is not a clinical management guidance to specify which procedures should be used.

2.8 JVT explained that given current reasonable worst case scenario planning, there may be no other option but to use NIV, the issue is how to use this safely. There are also concerns regarding oxygen supplies and there would not be any clinical superiority for HFNO over other NIVs. [This was previously advised by the NERVTAG NIV and nosocomial transmission subcommittee]

2.9 Members noted that the guidance is recommending the use of fluid resistant surgical masks (FRSM) outside of AGP hotspots as per pandemic flu as opposed to the HCID recommendations of FFP3 respirators.

2.10 DHSC noted that they are moving towards FRSM over FFP3 and members discussed the argument for the reclassification of COVID-19 from a high consequence infectious disease (HCID) by the Advisory Committee on Dangerous Pathogens (ACDP). JVT agreed to discuss this issue with Professor Tom Evans (ACDP Chair) with the recommendation from NERVTAG that classification as an HCID needs to be urgently reconsidered by ACDP.

2.11 JMM provided an update where JVT had spoken with Professor Tom Evans, Chair of ACDP who advised that the HCID status was discussed at the ACDP meeting and the committee were unanimous in supporting the declassification of COVID-19 as a HCID.

3 The potential for reinfection with SARS-CoV-2

3.1 The Chair introduced the paper kindly put together by Paul Kellam and Wendy Barclay on the potential for reinfection, for consideration with the susceptible, infected, recovered (SIR) models for SARS-CoV-2 epidemiological modelling. It is accepted that infection may not result in lifelong immunity based on extrapolation from other respiratory infections. The Chair noted that SPI-M are meeting on Monday and would like a view from NERVTAG on the issue of reinfection.

3.2 JE (who is also a member of SPI-M) noted the urgent question for this epidemic was whether there is evidence of any short-term sterilising immunity -can a person can be re-infected within a matter of months. A second question of longer term immunity could be addressed in due course. Members discussed whether there was going to be a second wave due to reinfection and how long the sterile immunity window was.

3.3 WB stated that the paper highlighted two studies. The first[1] concerned a challenge model with human coronavirus 229E. Adults were inoculated with 229E and then again with the same strain after one year. It was found that antibody levels were raised after the first infection but then waned over the year and led to 66% (6/9) reinfection after one year when the adults were inoculated again. It was noted that those who were re-infected a year later had very mild or no symptoms.

3.4 The second[2] paper was a longitudinal community based study in Kilifi, Kenya of human coronavirus epidemiology, the most relevant in the study is human coronavirus NL63. Individuals (mainly children and some adults) were found to be positive for virus shedding in March, then negative for a short period of at least 14 days and then positive again in May. The reinfection rate was 28% (43/163) and these were split into two groups; those with symptoms and those without symptoms. The majority had low viral load and no symptoms but some did become unwell with low ct values and high levels of viral shedding that were comparable to their earlier infection.

[1] Callow, K.A., Parry, H.F., Sergeant, M. and Tyrrell, D.A. 1990. The time course of the immune response to experimental coronavirus infection of man. *Epidemiology and Infection* 105(2), pp. 435–446.

[2] Kiyuka, P.K., Agoti, C.N., Munywoki, P.K., Njeru, R., Bett, A., Otieno, J.R., Otieno, G.P., Kamau, E., Clark, T.G., van der Hoek, L., Kellam, P., Nokes, D.J. and Cotten, M. 2018. Human coronavirus NL63 molecular epidemiology and evolutionary patterns in rural coastal kenya. *The Journal of Infectious Diseases* 217(11), pp. 1728–1739

3.5 WB explained that the other evidence covered in the paper for seasonal coronavirus showed some evidence of people having mild symptoms and not seroconverting at all or had made antibody that waned quite rapidly within three months after infection. In summary, there is evidence that in people with mild illness, the antibody response can wane quite rapidly and there is evidence that people can get re-infected and can shed quite robust titres of virus within 2-3 months.

3.6 It was noted that most children become seropositive for seasonal coronavirus by about 6 years of age and yet adults get infected by seasonal coronaviruses, which account for 20-25% of common cold illnesses. It is presumed that these adults would have been infected by seasonal coronaviruses as children. However, this point is related to more long-term duration of immunity.

3.7 PO noted that the immunology is similar to Respiratory Syncytial Virus (RSV) where you can get re-infected by the same strain.

3.8 Members discussed the possibility of antibody-dependent enhancement (ADE) for SARS-CoV-2. PO noted that ADE has been demonstrated in feline coronavirus when vaccines were attempted for feline peritonitis, however the mechanisms for this is unclear.

3.9 MZ noted that with regards to modelling, the immunological responses may be different for a virus that is well adapted to humans compared with a new virus. This needs to be considered when looking at reinfection.

3.10 Members are only aware of one report from Japan of a possible reinfection with COVID-19. JE agreed to check on the details of the case. Members discussed whether waxing and waning of the viral load could be mistaken for reinfection.CR noted that data presented to WHO also suggested that viral loads could fluctuate. It was noted that fluctuations are not uncommon with other pathogens and caution should be taken due to the number of uncertainties when considering potential reinfection.

Action: JE to check on details of the reported reinfection case

3.11 PH suggested that it may be useful to do a sensitivity analysis of models to assess the impact of assuming a subset of patients with mild disease could be reinfected after a certain period. Members discussed whether 80 days (the second paper mentioned above) was appropriate to use as a meaningful threshold for reinfection in the model. WB noted that 80 days' threshold was when there was evidence for robust viral shedding that correlated with getting full genome sequences versus not. There was evidence of apparent reinfection at 20, 30, and 40 days after initial infection but it is difficult to separate this from the waxing and waning effects that members have described or whether this was a result of continuous shedding. However, WB noted that at 80 days was a meaningful threshold as this is when robust shedding has been observed and therefore may lead to onward transmission.

3.12 Members discussed whether it might be plausible for the virus to, for example, peak in the UK in June 2020 and then have a resurgence in November 2020 through reinfection. This scenario would need to be answered by the modellers taking into careful consideration the different parameters needed. There should be consideration of the fraction of individuals who lose immunity, the rate of immunity loss and the infectiousness of the second infection. It was discussed whether data from China could be useful however the data quality from China has been varied and members thought that the data now being produced outside of China could be better, provided there are good studies following people who have had a known infection and whether they subsequently get re-infected.

3.13 WB noted that it would be very useful if there was a longitudinal study that could be undertaken to measure antibody levels. This could provide evidence of whether antibody levels wax and wane or are maintained over 60-80 days.

3.14 The Chair summarised two recommendations; one to ask JE to review Wendy's paper to determine the parameters to be used with modelling; and secondly to recommend that appropriate studies are in place, such as a case cohort study with serial serological sampling (for antibody levels) and swabbing if they become unwell (to identify reinfection). It was noted that different scenarios could be considered as this was a novel virus and that reasonable worst-case scenario modelling needs to be undertaken.

Action: JE to determine modelling parameters and check on studies

3.15 NERVTAG agreed that the fact this is a novel virus may be important for modelling, but that it cannot confirm or exclude the possibility of reinfection based on the limited data available. However the data are sufficient for the committee to recommend modelling of the scenario of reinfection.

3.16 Members discussed protocols already underway for the follow up of cases and other potential vehicles for obtaining data. It was noted that mild cases should be followed as well as hospitalised cases. It was suggested that the First Few 100 (FF100) cohort could be followed or an extension to the Clinical Characterisation Protocol (CCP) as well as planned household and serological studies being undertaken by PHE. The FF100 was noted as being potentially in a particularly good position to follow up as these are the first few hundred that were infected in the UK. PH noted that the milder, community cases will probably be the most informative as these would represent the experience of the majority of cases.

3.17 JVT and PH agreed to take the minutes and points raised at today's meeting to SPI-M and then through to SAGE.

3.18 Members discussed the recent paper regarding the possibility of two variant strains. It was noted that the data set was limited and there were substantial overclaims within the paper. It needs to be understood whether viral sequence changes affect the antibody recognition of the virus. Very little antigenic mapping data is available for seasonal coronaviruses.

3.19 NERVTAG agreed to review antibody-dependent enhancement. WB, PO & MZ were tasked with drawing together a paper on this topic for consideration at the next NERVTAG meeting.

4 AOB and Next Meeting

4.1 The Chair noted the large number of recent meetings. It was proposed that the next meeting would focus on major scientific questions, such as antibody-dependent enhancement.

4.2 JE raised an issue with the new case definition for the current self-isolation guidelines. There was concern that the phraseology might mean that a number of individuals with the virus may not meet the definition. JE was working off a recent paper[3] that could mean that 1 in 4 cases could be missed if the criteria of only a cough and/or fever are used and this is if there was 100% compliance to the current definition, which is unlikely.

4.3 Members discussed the other major symptoms associated with infection, such as myalgia. It was noted that with the FF100 cases the main symptoms were cough, fatigue, fever and muscle ache. Similar symptoms were recorded in the CO-CIN study. The Chair asked for details to be provided from both studies to determine if the case definition is fit for purpose.

4.4 The next meeting would take place on Friday 20th March to cover major scientific questions.

[3] Bi,Q et al. 2020 *Epidemiology and Transmission of COVID-19 in Shenzhen China: Analysis of 391 cases and 1,286 of their close contacts,*
medRxiv 2020.03.03.20028423; doi: https://doi.org/10.1101/2020.03.03.20028423