Minutes of the NERVTAG Wuhan Novel Coronavirus Fourth Meeting: 30 January 2020

Date & Location:	14.00 – 15:00, 30 January 2020 Via telecon only
In attendance:	Peter Horby (Chair), Camille Tsang (Secretariat). NERVTAG Members: Wendy Barclay (WB), Peter Openshaw (PO), Calum Semple (CSm), Jim McMenamin (JMM), Cariad Evans (CE), Neil Ferguson (NF), Ian Brown (IB), Wei Shen Lim (WSL), Robert Dingwall (RD), Ben Killingley (BK) PHE Observers: Gavin Dabrera (GD), Meera Chand (MC), Maria Zambon (MZ), Ruth Parry (RP) DHSC Observers: Chris Witty (CW), Jonathan Van-Tam (JVT), Jennie Harries (JH) NHS-E: Chloe Sellwood (CSw) HPS: Lisa Ritchie (LR) Co-opted clinician: Kevin Rooney (KR), David Connell (DC)
Apologies:	Keith Willet (KW)

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NERVTAG Wuhan Novel Coronavirus Fourth Meeting

1 Introductions

1.1 The Chair welcomed everyone to the fourth extraordinary meeting. It was noted that the draft minutes of the third meeting had not yet been shared and members were asked to make their comments as soon as they received them as they were an important record of the discussions of the group and the recommendations given.

1.2 The Chair reminded all participants that discussions and papers are 'official sensitive'. As one of the subjects for discussion was therapeutic options, participants were asked to declare potential conflicts of interest online during the meeting or to the Secretariat.

2 Potential Conflicts of Interest

2.1 The Chair declared that he was involved in China with a trial of lopinavir/ritonavir and also the development of a protocol for a remdesivir trial in patients with 2019-nCoV. These trials are not industry sponsored but sponsored by the Chinese Government.

2.2 CSm declared that he worked with Chiesi Farmaceutici on surfactant for use in babies with bronchiolitis, for which the plausible mechanism of action is at the type II pneumocyte and he noted that this is also the proposed receptor for the novel coronavirus, so surfactants could possibly be a therapeutic.

2.3 WSL declared that he had a long-standing agreement with Pfizer for a study on which he is chief investigator, but he is not aware of any specific antivirals for 2019-nCoV developed by Pfizer.

2.4 The Chair considered that the declarations of CSm and WSL did not constitute significant conflicts of interest for this meeting and CW and JVT agreed that the Chair's own declaration did not constitute a conflict of interest.

2.5 PO declared that he was on the scientific board for J&J for antivirals for influenza and RSV but was not aware of any direct conflict of interest relevant for this meeting.

3 Revising the Case Definition

3.1 The CMO, CW asked NERVTAG to discuss the case definition and a PPE query from the last meeting before the other agenda items to ensure that DHSC were clear on the recommendations from NERVTAG for other upcoming cross government meetings.

3.2 CW explained that following the last meeting where the committee agreed to expand the geographical case definition to provinces with a higher risk, the feedback and evolving nature of the incidence meant that it would be better to extend the definition to include the whole of mainland China.

3.3 The DCMO, JVT explained that the aim of case detection at this stage of the epidemic was to do everything possible strategically and operationally to prevent the establishment of community transmission in the UK – detection and isolation being the critical things.

3.4 Following a short discussion, NERVTAG agreed with DHSC on **expansion of the geographical element of the case definition to include the whole of mainland China**. NERVTAG is aware of the operational complications this will have on the health system (especially the diagnostic and detection aspects) but feel that it is a necessary change at this time.

3.5 CW explained to NERVTAG that there has been feedback from front-line commissioners and PHE to suggest changes are made to the clinical aspect of the case definition such as removing “sore throat” and adding “fever”. Therefore, the clinical aspect of the case definition would include cough, fever and shortness of breath although it was noted that not all would need to be present i.e. cough OR fever OR shortness of breath.

3.6 CW noted that if this was agreed by NERVTAG, DHSC would hope to operationalise the new case definition as soon as possible and via PHE ensure all guidance is revised in quick succession.

3.7 **Members largely agreed with the proposed revision to the clinical component of the case definition**, and agreed to deemphasise coryzal symptoms.

3.8 CSm suggested a revision to the “shortness of breath” part to ensure it is applicable to any paediatric cases by placing a comma after “shortness of breath” and adding “or increased work of breathing in children”.

3.9 Members noted that the case definition being used in China may not be diagnosing milder cases and that DHSC should be aware that the UK might not see the same clinical spectrum as is being reported from China.

3.10 WSL requested clarification on whether the symptom was ‘fever’ or ‘history of fever’. CW suggested ‘fever or history of fever’.

3.11 The Chair summarised the recommended changes to the clinical aspect of the case definition as follows: **fever or history of fever; <u>or</u> cough <u>or</u> shortness of breath, or increased work of breathing in children.**

3.12 CSw noted that this would need to be factored into the NHS111 algorithm and agreed to give the service advance notice of the change; CW advised cross governmental agencies are primed to expect changes to the case definition but not to activate any changes until all relevant parties have agreed.

Action 1: Members to send drafting changes to DHSC for the case definition straight after the meeting should they have any further comments to raise.

3.13 JVT asked NERVTAG to clarify whether the PPE recommendations from the last meeting indicated that Border Force and customs officials would not need to wear PPE.

3.14 The Chair indicated that at the last meeting NERVTAG recommended that professional staff who were exposed to healthy individuals from at risk areas did not require PPE and emphasis should be made on hand hygiene.

4 Clinical management of severe cases and novel therapeutics

4.1 JVT noted that the management of severe cases and novel therapeutics are linked agenda items and are put to NERVTAG in the context of this outbreak escalating to the reasonable worst-case scenario. DHSC are seeking advice from NERVTAG that confirms that it is not aware of any licenced or existing, proven options for the treatment of coronavirus infection. If that is the case it is assumed that severe cases will be treated with supportive care.

4.2 The Chair outlined the main experimental treatment options of which he was aware -

- Direct acting antivirals such as Lopinavir/ritonavir and remdesivir, but neither of these are licenced or proven to be effective in coronavirus infections.
- Indirect acting antivirals such as the interferons; not licenced for that indication or proven to be effective in coronavirus infections
- Biologicals such as convalescent plasma, polyclonal or monoclonal antibodies. These are currently not available, licenced or proven to be effective in coronavirus infections.
- Host directed therapies such as Clarithromycin or Naproxen. These are currently available, but not licenced for this indication, or proven to be effective in coronavirus infections.

4.3 Steroids or surfactants were also mentioned by members. WSL commented that the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) programme have asked if the Adjuvant Steroids in Adults with Pandemic influenza (ASAP) Trial can be amended to respond to a novel coronavirus outbreak; and he was in the process of modifying the ASAP trial to include novel coronavirus.

4.4 Other therapies suggested –MZ noted Nitazoxanide and a paper in BioRxv that detailed screening of a large number of other drugs against 2019-nCoV.

4.5 PH suggested that NERVTAG rely on the WHO process to prioritise experimental therapeutics for consideration, using the WHO Blueprint list of priority drugs as a starting point for review. The committee agreed with this proposal.

4.6 Kaletra® (lopinavir/ritonavir) - this has shown activity in MERS in vitro and in animal models and is being assessed in a clinical trial in MERS-CoV patients in KSA, with interferon. WB stated that it is a protease inhibitor and therefore the mechanism of action should be theoretically viable in 2019-nCoV. BK agreed that the drug is readily available and was unlikely to have significant side-effects. MZ agreed with both comments. It was agreed that it would not be recommended unless there was evidence of efficacy from a clinical trial.

4.7 Interferons – PO would not recommend unless there was evidence of efficacy from clinical trials and pointed out the possibility of enhancement of disease and increases in viral load under certain conditions. WB agreed that there should be hesitancy about using it for treatment however, it may be better used as a prophylactic but this is not for consideration at this time.

4.8 Remdesivir – this is an experimental drug (a nucleoside analogue), not licenced for use (i.e. not market available) but was used in clinical trials for the treatment of Ebola and will be tested in clinical trials in China. It was noted that this was one of the more promising drugs. WB commented that the current preparation was IV. It was noted that there was some data in the literature indicating that Remdesivir had activity against a number of coronaviruses but it would not be possible to predict activity against 2019-nCoV.

Post meeting note: A manuscript has been published reporting activity of remdesivir against 2019-nCoV in vitro. PMID: 32020029

4.9 Biologicals – CSm noted that it had been possible to operationalise use of convalescent plasma in West Africa. A key factor is the development of assays to identify individuals with high titres of antibody. JVT noted a reduction in mortality in trials of convalescent plasma for treatment of severe influenza. MZ noted that there was some successful use of convalescent plasma in SARS.

4.10 The Chair noted that work was being done in many places to develop antibody products for 2019-nCoV.

4.11 MZ noted that a single monoclonal antibody was unlikely to be sufficient and a cocktail was likely to be needed. The limitations of method for screening for high affinity antibodies was raised. The 'bovine chromosome' approach was also suggested as being a possibility, but that also has some limitations.

4.12 WB noted that there were published papers about antibody dependent SARS enhancement in animal models.

4.13 Host directed therapies – The most obvious of these is steroids. WSL noted there is a 'sleeping trial' on the use of steroids in the event of a pandemic influenza. It had been suggested that this could be extended to other viruses. KR suggested that as an intensivist, outside of a clinical trial, he would only recommend the use of steroids in patients with novel coronavirus if there was another indication, such as septic shock or an exacerbation of COPD. WS agreed that it was not wise to use steroids in a viral infection if there was nothing in place to combat the virus itself. PO would not recommend as routine but that steroids should be evaluated in the context of a clinical trial.

4.14 JVT raised the possibility of advice from NERVTAG in the future on which of the 'sleeping contracts' to activate.

4.15 At this point, NERVTAG is not able to recommend routine use of any experimental therapeutics in patients with confirmed 2019-nCoV.

5 AOB

What is NERVTAG's view of the IPC risk associated with non-invasive ventilation (NIV)?

5.1 JVT explained the background to this question which was asked because there was an anticipation of increased numbers of cases. NERVTAG was asked for advice on whether there was a risk if NIV was used for patients with coronavirus. PH suggested that this may be extrapolated from influenza. WSL highlighted a number of reports of the use of nebulisers and NIV in which it was thought that transmission may have been associated with the techniques.

Post meeting note: WSL provided the following papers on nosocomial transmission as an important risk. These papers are from the early days of SARS and suggested that nebulisers were an important risk for nosocomial transmission. The opinions of the

Hong Kong and Canadian teams were that droplet spread was still the most likely and important mode of spread, but aerosolisation was not measured.

PL Ho, XP Tang, WH Seto. SARS: Hospital Infection Control and Admission Strategies SARS: hospital infection control and admission strategies. Respirology 2003; 8: S41–S45 https://doi.org/10.1046/j.1440-1843.2003.00523.x

M. Varia, S. Wilson, S. Sarwal, et al. Investigation of a nosocomial outbreak of severe acute respiratory syndrome (SARS) in Toronto, Canada. CMAJ Aug 2003, 169 (4) 285-292;

PH added the following paper that highlighted the importance of nosocomial transmission in patient with 2019-nCoV:

Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. Published online February 07, 2020. doi:10.1001/jama.2020.1585

5.2 Would different precautions than those used in influenza be needed? WSL suggested that for the time being NIV should not be used in patients with coronavirus. CSm noted that it would be difficult to tell the critical care community not to use NIV.

5.3 There was not consensus within the committee as to whether high flow nasal oxygen should be considered an AGP. It is not currently listed as an AGP.

5.4 NERVTAG agreed to form a subgroup to consider infection control for high flow oxygen as an aerosol generating procedure. LR agreed to lead the subgroup.

Action 2: LR to lead a subgroup to consider whether high flow oxygen is an aerosol generating procedure and what IPC is needed when it is being carried out on a patient with 2019-nCoV and report back to NERVTAG

Post meeting note: LR identified some prior recommendations from the Health Protection Scotland National Infection Prevention and Control Manual regarding the Aerosol Generating Procedures and pressurised humidified O2: *http://www.nipcm.hps.scot.nhs.uk/resources/literature-reviews/transmission-based-precautions-literature-reviews/*

> *Page 7 of 12 of the Aerosol Generating Procedures (V1.0, Nov 2019)*
> *'…there is now published evidence that nebulisation and oxygen therapy (pressurised humidified O2) do not result in an increased risk of aerosols.[4, 10]'*
> *4. Tran K, Cimon K, Severn M, et al. Aerosol generating procedures (AGP) and risk of transmission of acute respiratory diseases (ARD): A systematic review. PloS One 2012; 7. Conference Abstract.*
>
> *10. Simonds A, Hanak A, Chatwin M, et al. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. Health Technology Assessment 2010; 14: 131-172. DOI: 10.3310/hta14460-02.*

There are a few studies that look at aerosol escape but much like nebulisers these aerosols aren't patient derived and the studies are focussed on the effect of aerosol escape on treatment rather than infection control.

WSL noted that there is an important nuance in the interpretation of the findings above. WSL noted that the review by Tran et al, to be about the "risk of transmission" as measured by infection in HCWs. By that measure, NIV appears to be associated, though studies are uncontrolled, whilst nebuliser use was not. (The studies did not necessarily measure aerosolisation). The statement that nebulisation does not result in aerosolisation is probably more directly answered by Anita's work, and indirectly supported by the Review by Tran et al. Overall, I agree that the main mode of transmission is droplet spread, rather than aerosolisation.

Action 2: Following discussions after the meeting, DHSC has requested that NERVTAG convene a subgroup to review and advise on 2019-nCoV transmission risk of non-invasive ventilation.

If someone was symptomatic but now resolved, are they no longer an infectious risk?

5.5 This question was posed from PHE. WB noted that there are not enough longitudinal data to be able to make a prediction on viral shedding. Caution was advised about assuming that virus shedding was zero once symptoms had ceased. PO also noted that it was important to differentiate between PCR-detected virus and infectious virus. CSm noted that it was difficult to say in children and to be cautious. It would only be possible at this stage to say that virus shedding was likely to be less in the absence of symptoms than in the presence of symptoms.

PPE questions from the Department of Transport via DHSC, to go outside of Government to operational staff working with people arriving from China

5.6 NERVTAG indicated that the advice given at the previous meeting on PPE when dealing with healthy individuals who have been in at risk areas also applies to other staff groups dealing with asymptomatic individuals.

6 Summary of Actions

Action 1: Members to send drafting changes to DHSC for the case definition straight after the meeting should they have any further comments to raise.

Action 2: Following discussions after the meeting, DHSC has requested that NERVTAG convene a subgroup to review and advise on 2019-nCoV transmission risk of non-invasive ventilation.