Minutes of the NERVTAG Novel Coronavirus Seventh Meeting: 21 February 2020

Date & Location:	11:00 – 13:00, 21 February 2020 Via telecon only
In attendance:	Peter Horby (Chair), Camille Tsang (Secretariat). NERVTAG Members: Peter Openshaw (PO), Ben Killingley (BK) Calum Semple (CSm), Wei Shen Lim (WSL), Andrew Hayward (AH), Neil Ferguson (NF), Robert Dingwall (RD), Wendy Barclay (WB), John Edmunds (JE). PHE Observers: Gavin Dabrera (GD), Meera Chand (MC), Maria Zambon (MZ), Mary Ramsay (MR) DHSC Observers: Jonathan Van-Tam (JVT), Cheryl Cavanagh (CC), Luke Collet-Fenson (LCF), Tom Irving (TI) SAGE: Olivia Tolania (OT), Marie Louise Taylor. NHS-E: Chloe Sellwood (CSw) HPS: Lisa Ritchie (LR) APHA: Ian Brown (IB) Co-opted: Kevin Rooney (KR)
Apologies:	Cariad Evans (CE), James Rubin (JR), Jim McMenamin (JMM), David Connell (DC), Martyn Underdown (MU),

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NERVTAG COVID-19
SEVENTH MEETING: SUMMARY

NERVTAG RECOMMENDED THE FOLLOWING:

Review of the PHE risk assessment

NERVTAG does not recommend a change to the PHE risk assessment at this time.

Clinical assumptions to inform SPI-M modelling

NERVTAG agreed the following for the COVID-19 reasonable worse case scenario(RWC) for modelling purposes:

Parameter	**Denominator**	**COVID-19 RWC upper estimate**
Infection attack rates	Whole population	85%
Illness rates	Whole population	50%
Complications that require hospitalisation	Of those ill	4% seems low
Duration of hospitalisation	NA	10 days average
Requirement for ventilatory support- Non-invasive ventilation (NIV)	Hospitalised population	25% seems high, NIV would be higher than IMV
Requirement for ventilatory support- Invasive mechanical ventilation (IMV)	Hospitalised population	
Duration of ICU care	NA	10 days average
CFR	Of those ill	0.25-4%- SPI-M to comment

Advice on principles for trialling COVID-19 treatments in the UK

NERVTAG view was since treatments are speculative and unproven they strongly recommend that experimental therapeutics for the treatment of COVID-19 should be evaluated for efficacy and safety within the context of clinical trials.

NERVTAG recommended central oversight of clinical trials to ensure therapeutic evaluation, including patient enrolment, is co-ordinated. NERVTAG recommended that a sub-group of NERVTAG, co-ordinated by DHSC is formed to do this.

What do we know about how the virus affects vulnerable groups (e.g. children, older adults)?

NERVTAG view is that severe disease is possible in children but is rare. Severe disease is most frequent in older adults (over 50) and those with co-morbidities. There is currently no signal of worse disease or outcomes in pregnant women but this is based on very limited data.

What do we know about effective clinical treatments and patient recovery?

NERVTAG view is that there are currently no robust data on treatment effectiveness.

Members recommended rapid throughput of screening, utilising universities to generate that data. A number of universities in the UK are licensed to handle live virus under high containment facilities.

FULL MINUTES

1 Introductions

1.1 The Chair welcomed everyone to the meeting and apologies were received from those listed above.

1.2 Out of the fourth NERVTAG COVID-19 meeting, DHSC has requested NERVTAG to convene a sub-group to review and advise on 2019-nCoV transmission risk of non-invasive ventilation specifically including high flow nasal oxygen use. This is now being led by WSL and this is a topic of great interest globally.

1.3 During the fifth NERVTAG COVID-19 meeting, AH was actioned to find out what PPE was being used in London to help the committee understand what PPE was being used in home visits. This was part of previous discussion around harmonising PPE across the country. This is in progress and CSw will also query what is being done at a pilot in North London.

1.4 Minutes of the meetings 3-5 have been finalised.

2 Epi-update and review of the PHE risk assessment

2.1 GD gave an update of the current epidemiology as of 21 February 2020:

- In China, there are now reported 75,465 cases, this is an increase of 889 overnight.
- Members of the committee will be aware that China had previously reported clinically diagnosed case but the above figures are only for the laboratory confirmed cases.
- Of the cases in Mainland China, 83% were reported from Hubei province and of the Hubei province cases, 72% were attributed to Wuhan.
- In total, in Mainland China, there have been 2,236 fatalities, an increase of 118 overnight.
- Outside of Mainland China, the total now stands at 1,259, an increase of 106 cases overnight. There are 625 cases distributed across 29 countries and areas and 634 cases on the Diamond Princess cruise ship.
- Overall outside of Mainland China, there have been 11 fatalities including 2 on the Diamond Princess; 2 in Hong Kong; 2 in Iran; 1 in Japan; 1 in Taiwan; 1 in France; 1 in the Philippines; and 1 in the Republic of Korea.

2.2 Current PHE risk assessment of the disease is moderate. The PHE risk assessment to the UK population is also moderate. This is a composite of what is known about transmission and the impact on public health globally and in the UK.

2.3 Some members commented that there may be sustained transmission outside of Mainland China. Others commented that there is plenty of scope for escalation in the UK and this would be an argument to keep the assessment as moderate rather than high at this time.

2.4 PH asked the committee if anyone thought that the PHE risk assessment should change. No objections were raised however after the meeting, JE emailed to say that he was online but for some technical reason could not be heard. JE believes that the risk to the UK population (in the PHE risk assessment) should be high, as there is evidence of ongoing transmission in Korea, Japan and Singapore, as well as in China.

2.5 NERVTAG does not recommend a change to the PHE risk assessment at this time.

3 Clinical assumptions to inform SPI-M modelling

3.1 There are four specific questions that DHSC would like NERVTAG to consider as well as the SPI-M considerations for modelling and the Reasonable Worst Case (RWC)

- ***What proportion of the population could be infected with SARS-CoV2?***
- ***What proportion of these could be symptomatic?***
- ***Within this who will require hospital care?***
- ***And of those, what proportion will require respiratory support?***

3.2 NF introduced the assumptions that SPI-M are working with:

- SPI-M are informed by the Reproduction number (R0) that they have estimated for the virus which makes a large assumption that children are contributing to transmission and are susceptible even if they are have mild or no symptoms. This has led to the assumption that the attack rate would be ***80% in the first year of transmission in the absence of any intervention.***
- The modellers (including NF) at Imperial College London and those at the LSHTM (including JE) have been undertaking various assessments on the severity of infection and in particular the different case fatality rates which are dependent on the case population.

- In Mainland China, the Case Fatality Rates (CFRs) are in the region of 15% but can be up to 20% particularly in Wuhan where they are appearing to only be detecting the more severe cases.
- Outside of Mainland China, the deaths have increased slightly this week but we are getting estimated CFRs of 2-4% where the case population are mainly symptomatic not including the population on the cruise ships.

3.3 NF noted the public health impact can be measured by working out the infection fatality rate but requires estimates of the proportion of cases that might be subclinical. There are a few modelling groups looking at this and his modelling group at Imperial are publishing a report[1] today about the sensitivity of detection of COVID-19 outside of Mainland China.

3.4 NF noted that there were a few modelling groups estimating a higher infection rate when comparing case populations in Singapore, South Korea and Japan, this suggests that at least a third have been missed. JE commented on this after the meeting taking into account the issue of asymptomatic cases, where the evidence suggests that 40% of virologically confirmed cases are asymptomatic.

3.5 NF commented that the Wuhan repatriation flights at the end of January suggested that there was about a 1% infection prevalence in the population of Wuhan. At that time, that can be compared with official case numbers and suggests that the cases numbers represented around 5% of all cases.

3.6 SPI-M would like NERVTAG to comment on the likely asymptomatic infection rate for coronaviruses and how that might differ from flu; likely hospitalisation rate of severe cases (these are currently based on pandemic influenza assumptions); length of hospital stay and potential impact of hospital bed dependency; and any age dependant patterns or patterns of co-morbidity.

3.7 Members noted the data from the cruise ships can give an indication of asymptomatic cases, however population mixing patterns on cruise ships will be different to the general public and there is no complete follow up data yet on various case populations.

3.8 Members noted that we do not know the proportion of infected people who seroconvert and the proportion of infected people who shed virus.

[1] https://www.imperial.ac.uk/news/195564/two-thirds-covid-19-cases-exported-from-mainland/

3.9 JVT commented that the hospitalisation data is quite important for DHSC's planning for surge events and would like NERVTAG to comment on what proportion of hospitalised patients would require ventilatory support.

3.10 RD asked members what they thought about the high prevalence of smoking in males in China and whether this had any effect on potential hot spots for severe outcomes due to prior lung damage from smoking.

3.11 Members noted that information out of China is very varied, some reporting high prevalence and others low prevalence of smoking in hospitalised patients. It is too early to say whether smoking has an effect on severe outcomes.

3.12 JVT clarified that the SPI-M modelling will be broken down over time and they are sensitised to areas where there may be hotspots due to underlying co-morbidities such as chronic lung disease and age as well.

3.13 MZ asked NF a question about the proportions of asymptomatic and symptomatic populations and how this might change based on different age profiles as some may think that this is not consistent by age.

3.14 NF responded to say that they can quite accurately calculate CFR by age in China. The comparison of age distribution in Wuhan with the rest of China is useful for severity filtering. The testing capability in Wuhan is more limited and so the more severe cases are being tested where in the rest of China where testing capability is larger, a wider range of cases are being tested.

3.15 NF commented that they are seeing a rapid deterioration among older age groups (50+) but the data on asymptomatic and symptomatic proportions in China are not well documented. Data from Japan and Singapore suggest that children are getting infected and the infection rates are similar to adults but showing relatively mild symptoms.

3.16 MZ provided a link to NERVTAG relating to a field briefing on the Diamond Princess cruise ship dated 19/02/2020 by the National Institute of Infectious Disease in Japan[2].

[2] https://www.niid.go.jp/niid/en/2019-ncov-e/9407-covid-dp-fe-01.html

3.17 MR asked whether having upper estimates for all the parameters was the best option, for example if the virus is highly transmissible, is this compatible with a high fatality rate i.e. does the model take into account interdependencies between the different variable?

3.18 NF commented that a high CFR would not necessarily match transmissibility e.g. the 1918 flu pandemic where it was very transmissible and those who were infected and symptomatic was 40-45% of the population over two waves, the CFR was around 2.5%. However, calculating the upper estimates for these parameters does match up to what we are seeing in the data but will be different and change as the case definition and management of the disease changes.

3.19 Members discussed the different parameters in Table 1 and made the following suggestions in relation to the upper estimates for pandemic reasonable worst case scenario (RWC):

Table 1. Pandemic influenza RWC planning assumptions (red = amendments from the discussion)

Parameter	Denominator	COVID-19 RWC upper estimate
Infection attack rates	Whole population	85%
Illness rates	Whole population	50%
~~Complication rate~~	~~Of those ill~~	~~25%~~
~~Case hospitalisation rate~~	~~Of those ill~~	~~4%~~
Complications that require hospitalisation	Of those ill	4% seems low
Duration of hospitalisation	NA	~~6~~ 10 days average
~~ICU rate~~	~~Hospitalised population~~	~~25%~~
Requirement for ventilatory support- Non-invasive ventilation (NIV)	Hospitalised population	25% seems high, NIV would be higher than IMV
Requirement for ventilatory support- Invasive mechanical ventilation (IMV)	Hospitalised population	
Duration of ICU care	NA	10 days average
CFR	Of those ill	2.5%-4% SPI-M to comment

Infection attack rate and illness rate

3.20 NERVTAG's view on the infection attack rate and illness rate estimates is that there is no reason to change these at this time.

Complication rate and hospitalisation rate

3.21 The meaning of the 'Complication rate' parameter is not clear.

3.22 NERVTAG's view is that it would be more useful to have a single parameter called 'complications that require hospitalisation' combining the complication rate and hospitalisation rate.

3.23 Members commented that 4% for those who require hospitalisation seems too low from the data at the moment, the hospitalisation rate amongst symptomatic cases may well be substantially higher than that. More work is required to get a figure for this.

3.24 TI and JVT will be contacting Keith Willet's teams in NHS-E to find a better parameter for the complication rate and will bring the outcome from those discussions to NERVTAG for review.

Duration of hospitalisation

3.25 JVT raised a word of caution regarding the interpretation of length of stay in hospital suggesting that the hospital discharges in Wuhan is likely to be earlier than other places as a matter of necessity rather than in places such as Singapore where hospital discharges are around 14 days. During a surge event, it may be that patients can be discharged from hospital moderately safely at some point less than 14 days.

3.26 Duration of hospitalisation of 6 days seems low and current data is suggesting 10-12 days average duration for all hospitalisations including ICU.

3.27 The Wang et al. publication in JAMA supports the idea of an average of 10 days although the average duration was for those who had gone home and some of the patients were still hospitalised at the time of publication. From member's personal communications, duration of stay in Singapore was 12 days and in Hong Kong, this was 18 days, and longer in the Republic of Korea.

3.28 Members commented that many cases outside of mainland China have been hospitalised on an isolation basis and not necessarily for clinical reasons and this is difficult to disentangle. Members also commented that there was also a tendency towards hospital focused care in Asia, rather than community focused care.

3.29 Members commented that it may be better to split hospitalisation into ICU hospitalisation and non-ICU hospitalisation. SPI-M are waiting for NHS-E to comment on this too.

3.30 WSL commented that average hospitalisation stay for community acquired pneumonia for adults was 5-7 days, all cases hospitalised (ICU and non-ICU). Members commented that COVID-19 patients may require a slightly longer hospital stay than influenza patients.

3.31 NERVTAG agreed it would be safer to assume 10 days for average duration of hospitalisation including ICU.

ICU rate

3.32 Members commented that the 25% was based on historical data but the technology and the availability of side rooms especially for non-invasive ventilation may reduce the 25%. JVT also commented that information from Singapore suggests around 21% of hospitalisation patients required supplementary oxygen.

3.33 NERVTAG view was that it would be better to have a parameter called ‘requirement for ventilatory support’ and that this should be split into two parts mechanical ventilation and non-invasive ventilation rather than ICU for those hospitalised:

3.34 JVT confirmed that discussions within NHS-E around how to segment patients during a surge and one of the primary reasons is desaturation and the requirement for supplemented oxygen.

3.35 NERVTAG’s view on this was that 25% is highly precautionary and the likely requirement is probably lower for ventilatory support.

Duration of ICU care

3.36 NERVTAG's view on the duration of ICU care is that there is no reason to change this at this time.

CFR

3.37 NERVTAG view is they are not better qualified than SPI-M to comment on the CFR.

4 Advice on principles for trialling COVID-19 treatments in the UK

4.1 PH introduced the paper and indicated that there were a lot of organisations setting up protocols to look at clinical trials including WHO and NIH.

4.2 NERVTAG endorsed the underlying scientific principles of the paper drafted by PH and strongly recommend the principle that any *unproven therapeutics for the treatment of COVID-19 should be evaluated for efficacy and safety within the context of clinical trials.*

4.3 The planning assumptions outlined in the paper drafted by PH:

1. *Unproven therapeutics for the treatment of COVID-19 should be evaluated for efficacy and safety within the context of clinical trials.*

2. *The UK should be prepared to initiate clinical trials for unproven therapeutics for COVID-19.*

3. *UK activities should align with international efforts, either through alignment of methods or direct participation in multi-country trials.*

4. *Some level of central coordination of clinical trials in COVID-19 is desirable to make sure: they happen, avoid competition for patients, avoid implementation of low value or poor-quality trials, align with international efforts, inform DHSC considerations.*

5. *If an unproven therapeutic (experimental or repurposed) is used outside of a clinical trial framework e.g. for compassionate use, then*

data should be collected systematically on safety and efficacy to inform future use.

4.4 NERVTAG view was since treatments are speculative and unproven they strongly recommend that experimental therapeutics for the treatment of COVID-19 should be evaluated for efficacy and safety within the context of clinical trials.

4.5 NERVTAG suggested it would be useful to have behavioural science input into information provided to patients receiving unproven therapeutics use to ensure that patients and family members hear the that the key messages e.g. a specific script to help clinicians and healthcare workers have this discussion.

4.6 NERVTAG recommended central oversight of clinical trials to ensure therapeutic evaluation, including patient enrolment, is co-ordinated. NERVTAG recommended that a sub-group of NERVTAG, co-ordinated by DHSC is formed to do this.

Action 1: NERVTAG to set up a subgroup co-ordinated by DHSC is formed to have central oversight of clinical trials to ensure therapeutic evaluation, including patient enrolment, is co-ordinated.

5 What do we know about how the virus affects vulnerable groups (e.g. children, pregnant women, older adults)?

5.1 NERVTAG view is that severe disease is possible in children but is rare. Severe disease is most frequent in older adults (over 50) and those with co-morbidities. There is currently no signal of worse disease or outcomes in pregnant women but this is based on very limited data.

6 What do we know about effective clinical treatments and patient recovery?

6.1 NERVTAG view is that there are currently no robust data on treatment effectiveness.

6.2 Members recommended rapid throughput screening of potential therapeutics, utilising universities to generate that data. A number of universities in the UK are licensed to handle live virus under high containment facilities.

Action 2: Members to send to the secretariat to collate a list of individuals and universities who may be interested in the work of rapid throughput screening of drugs; and/or are licensed in handling live virus; have high containment facilities. Then for this list to be shared with DHSC.