Proposal for the testing of 'possible cases' of 2019-nCoV at Wales Specialist Virology Centre, Public Health Wales

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Situation

In the context of 2019-nCoV, the expansion of the *'possible case'* definition to include the wider geographical area of the whole of mainland China has resulted in an increase in the numbers of cases presenting for assessment. Meanwhile in preparation for the presentation of suspected 2019-nCoV cases in Wales the Specialist Virology Centre in Public Health Wales has developed testing capability for 2019-nCoV that has been used in the last few days to guide clinical assessment and decision making. A second sample has been collected from every case tested in Cardiff and sent to Colindale. Currently the Colindale test result is treated as the definitive result. However turnaround times for results from Colindale are now exceeding 36 hours.

This paper asks NERVTAG to endorse the test we are now using in Cardiff and to note that it would be our intention, if the Cardiff 2019-nCoV test result is negative, to stand down actions with respect to enhanced health protection and infection control procedures for this virus. Public Health Wales will continue to send a second sample to Colindale.

Background

The current guidance issued by Public Health England, *Investigation and initial clinical management of possible cases of novel coronavirus (2019-nCoV) infection*, dated 31 January 2020, requires clinicians to assess possible cases and undertake sampling for urgent diagnosis where the case definition is met.

At the time of writing all UK testing for novel coronavirus is carried out by the Respiratory Virus Unit in Public Health England at the Colindale Laboratory. Although PHE are planning a rollout of the test they are using they do not expect this to complete for another three weeks. Meanwhile results are taking between 36 and 48 hours to report. Until PHE test result is confirmed negative all 'possible' cases have to be cared for in strict isolation, if their clinical condition requires hospital stay, or in self isolation if the case meets stipulated criteria.

Public Health Wales' Specialist Virology Centre has validated a 2019-nCoV screening PCR assay that is now ready for use. This assay is based on one of the screening assays described in the WHO protocol and the Eurosurveillance paper(1) published on 23 January 2020. It should be noted that validation did not use live virus but this is also the case with the PHE test being used now.

The assay that we are using in Wales was developed by Christian Drosten's laboratory in Germany and is the test that has been validated and used across Europe including is the Republic of Ireland.

NERVTAG is requested to recognise the Cardiff 2019-nCoV test as a valid screening test for 2019-nCoV and that a negative result would lead Public Health Wales to stand down actions with respect to enhanced health protection and infection control procedures for this virus. Any positive results would be submitted to Colindale for confirmation.

Assessment

1. There is high level of confidence in the clinical and laboratory staff in Public Health Wales' Specialist Virology Centre that a negative result is a true negative.
2. Standing down actions with respect to enhanced health protection and infection control procedures, following a negative test result, allows for better patient management and use of NHS resources.

Scientific considerations

2019 nCoV Assay Selection and Validation.

On 13 January 2020 the WHO issued the protocols for the diagnostic detection of 2019-nCoV for use globally. At that time the virology cell of

the UK IMT had not issued any guidance on the use of diagnostic assays in the UK. This was not issued until the 28 January 2020.

The three assays described in the WHO document and the subsequent Eurosurveillance publication cover three targets of the 201- nCoV gene with a suggested testing pathway:

- First line screening assay = E gene assay
- Confirmation assay = RdRp gene assay
- Additional confirmatory assay = N gene

For the purposes of the response in Wales and in line with the rationale for the validation of assays for MERS CoV, the first line screening assay and control material (E gene transcript) were ordered from our normal supplier (Eurogentec) for primers and probe and the European Virus Archive for the target transcript.

The rollout plan from PHE requires primers and probes to be ordered from a specific supplier, the system for amplication and detection to be used under standard mode, and prescribes an enzyme for amplication that we do not routinely use in the Cardiff laboratory. In order to ensure quality within the Cardiff lab all new lab dev tests are designed to use the same parameters for our UKAS accredited methods wherever possible. This assay model was followed for the early development work for the E gene assay.

The systems used in Cardiff are identical to those used in PHE Colindale. The Cardiff laboratory extracts RNA using the BioMerieux Easymag and amplification and detection of the target is performed using the ABI 7500 FAST, used in *fast* mode. In other words, the system uses a rapid cycling and real-time detection for 45 cycles with a mean runtime of 50 minutes. Colindale use their system in *standard* mode, and as a result temperatures are reached at each step of the cycling process ('ramp rate') more slowly extending the time it takes for the assay to complete to around 2.5 hours. Furthermore the standard mode can lead to reduced specificity and background noise while the use of fast mode increases specificity and reduces background noise but with potential loss of sensitivity. The Cardiff laboratory test has been evaluated to confirm comparable sensitivity for detecting E-gene specific transcript and Frankfurt SARS CoV RNA, as well as the data published in both the WHO document and Eurosurveillance.

The technical limit of detection is 5 RNA copies per reaction for the E-gene transcript with 100% detection at 50 copies per reaction. The assay has proven to be more sensitive when using the Frankfurt SARS CoV RNA. To-date 70 clinical samples have been run through the assay (50% were negative by our routine respiratory screening and 50% were

positive for one or more respiratory viruses including seasonal coronavirus). There was no evidence of non-specific reactivity.

Clinical considerations to inform decisions

Criteria to be met before considering stand down actions with respect to enhanced health protection and infection control procedures:

1. While testing of samples is undertaken at the Wales Specialist Virology Centre all samples will still go to PHE's Respiratory Virus Unit Colindale for confirmation.
2. Possible cases will only be discharged if the treating clinicians are satisfied that it is clinically safe to do so.
3. Clear instructions are provided to possible cases that in the event their clinical condition deteriorates they are to contact healthcare facility and that the Health Boards are in a position to receive and manage them.

Recommendation

NERVTAG is requested to recognise the Cardiff 2019-nCoV test as a valid screening test for 2019-nCoV and that a negative result would lead Public Health Wales to stand down actions with respect to enhanced health protection and infection control procedures for this virus. Any positive results would be submitted to Colindale for confirmation.

Reference

1. Corman Victor M, Landt Olfert, Kaiser Marco, Molenkamp Richard, Meijer Adam, Chu Daniel KW, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3):pii=2000045. https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045