Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol for evidence synthesis of serial testing using rapid antigen detection tests (RADTs) to detect SARS-CoV-2 in meat processing plant workers

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Purpose and aim

The purpose of this protocol is to outline the process by which the Health Information and Quality Authority's (HIQA's) Health Technology Assessment (HTA) directorate will synthesise evidence to inform advice from HIQA to the Health Service Executive (HSE). The advice will take account of expert interpretation of the evidence by HIQA's COVID-19 Expert Advisory Group. This evidence synthesis relates to the following policy question outlined by the HSE:

"What is the impact on transmission risk and resource requirements of different approaches to serial testing using rapid antigen detection tests (RADTs) in meat processing plants?"

The following research questions were formulated to inform this policy question:

1. To what extent do alternative scenarios to serial testing using RADTs impact the risk of transmission in meat processing plants?
2. How do these scenarios differ in terms of the following outcomes:
   - probability of undetected cases being present in the setting while potentially infectious
   - potential number of infections arising within the setting
   - number of tests (serial RADT and confirmatory RT-PCR) that must be carried out
   - number of false positives
   - resource requirements in terms of support staff to manage or supervise testing
   - total number of staff days in self-isolation or restriction of movement.

1. Process outline

Given the policy question under consideration, a model will be developed of the potential impact of serial testing with RADTs on the detection and transmission of SARS-CoV-2 in meat processing plants. Seven distinct steps in the process have been identified:

1. Outline the scenarios under consideration in the model and the outputs of interest.
2. Outline the necessary parameters for identification and inclusion in the model.
3. Develop and run the model for the different scenarios.

4. Consider additional factors not included in the model, but that may impact the overall outcomes.
5. Summarise the findings of the modelling exercise.
6. Present collective findings to COVID-19 Expert Advisory Group (EAG) for expert interpretation.
7. Provide advice to the HSE for consideration based on the findings of the evidence synthesis and informed by expert interpretation by the COVID-19 EAG.

1. Scenarios to be considered and outputs of interest

The modelling exercise will consider scenarios relating to the serial testing of individuals working in meat processing plants using RADTs. The intention of serial testing is to enable the early detection of cases to minimise the transmission of SARS-CoV-2. Serial testing is typically used in settings where adherence to public health guidance (for example social distancing) is challenging. Meat processing plants have been identified as a setting with an elevated risk of transmission and where there have been a large number of documented outbreaks.

The current national approach is for serial testing in meat processing plants using RT-PCR and based on combined oropharyngeal/nasopharyngeal samples collected by trained staff. As per current HPSC guidance, deep nasal/mid-turbinate swabs can be considered as an alternative to a nasopharyngeal sample or combined oropharyngeal/nasopharyngeal sample in adults. This can be implemented when the previous collection of a nasopharyngeal sample or combined oropharyngeal/nasopharyngeal sample has caused considerable distress, or in a person in whom there is reason to expect that it will cause distress, or in a person who declines consent for an oropharyngeal/nasopharyngeal sample.

Validation studies for a RADT compared with the gold standard of nasopharyngeal RT-PCR have been undertaken in meat processing plants; these studies have included comparisons of RT-PCR (based on combined oropharyngeal/nasopharyngeal samples) with:

- RADT using combined oropharyngeal/nasopharyngeal samples
- RADT based on deep nasal/mid-turbinate samples taken as supervised self-samples.

Irrespective of the sampling method or type, the RADTs were processed on site by medical scientists or by staff who successfully completed competency-based training. Following confirmation of satisfactory performance of a number of RADTs in the

validation studies, it is anticipated that RADTs may be deployed for serial testing or in outbreak scenarios in meat processing plants with testing based on deep nasal/mid-turbinate samples taken as supervised self-samples.

It is assumed that staff that are unwell or who have symptoms of COVID-19 or who have been identified as a close contact will not present at work, but rather will follow usual national guidance for accessing COVID-19 testing. Therefore, it is anticipated that the majority of individuals included in serial testing will be asymptomatic. Following a positive RADT, individuals are expected to immediately self-isolate, and will be referred for confirmatory RT-PCR testing at a local test centre.

A range of testing scenarios will be considered using the model. In all scenarios it is assumed that testing of close contacts of confirmed cases will be carried out using RT-PCR testing. Seven core scenarios will be considered:

- Scenario one: no serial testing with RADT.
- Scenario two: serial testing with RADT once a fortnight.
- Scenario three: serial testing with RADT once a week.
- Scenario four: serial testing with RADT twice a week.
- Scenario five: serial testing with RADT three times a week.
- Scenario six: serial testing with RADT four times a week.
- Scenario seven: serial testing with RADT five times a week.

It is assumed that testing follows a regular pattern (for example, that weekly testing will typically fall on the same day each week). Each scenario will be estimated as described with workers who are identified as close contacts referred for RT-PCR testing and asked to restrict movements in the event of identification of a colleague as a confirmed case of COVID-19. For each scenario an alternative approach will be modelled that includes a continuation of the existing monthly serial RT-PCR testing for all staff.

The outputs of interest from each modelled scenario to inform this policy question include the:

- probability of undetected cases being present in the setting while potentially infectious
- potential number of infections arising within the setting
- number of serial RADTs carried out
- number of RT-PCR tests carried out

- number of false positives
- resource requirements in terms of support staff to manage or supervise testing
- total number of staff days in self-isolation or restriction of movement.

The sensitivity of the RADTs tends to be lower than that for RT-PCR. RADTs are poorer at detecting people with high Ct values. A high Ct value indicates a low viral load at the time of testing and can imply that the individual is not infectious. The point in time nature of testing means that it is not possible to determine if an individual's peak Ct value was high enough to make them infectious. In the absence of suitable data, it is not appropriate to simulate viral load values. By not modelling Ct values, there will be a bias against RADTs as the low sensitivity may result in undetected cases that may lead to onward transmission. To account for this, the model will incorporate estimates for the proportion of undetected cases that may have viral loads too low to be considered infectious.

2. Necessary parameters for identification and inclusion in the model

Table 1 outlines the necessary parameters for inclusion within the model, alongside the sources used to estimate these parameters. Where available, Irish data will be used to populate the model. Where parameters are identified from the research literature, a non-systematic search will be conducted with the aim of including the best available evidence, preferably from high quality systematic reviews, including evidence summaries previously conducted by HIQA.

For a range of parameters, typically only limited data are available for asymptomatic cases (for example, period of infectiousness). For the simulation model, it is assumed that the course of disease is the same in symptomatic and asymptomatic cases with the exception of symptom onset. It is assumed that test sensitivity is related to whether the individual is symptomatic or asymptomatic. For simplicity, it assumed that the lag from appointment to testing and from test to result are constants for RT-PCR testing. It is also assumed that once an individual is informed of a positive RADT result, they will not attend work until the result of the RT-PCR test is known and, if confirmed positive, they will comply with the recommended period of self-isolation. It is also assumed that close contacts will restrict movements as advised.

Table 1. Parameter estimates for inclusion in model

Parameter	Description	Source(s)	Estimate
Disease factors			
Latent period	The time duration (in days) from exposure to becoming infectious.	HIQA evidence summary of incubation period combined with LSHTM modelling estimate of latent period[1, 2]	Mean: 3.8 95% CI (1.4 to 8.4)
Duration of infectiousness (pre-symptomatic)	The time duration (in days) from becoming infectious to symptom onset.	HIQA evidence summary of duration of infectiousness[3] combined with LSHTM modelling estimate of latent period[1]	Mean: 2.6 95% CI (0.3 to 9.8)
Duration of infectiousness (symptomatic)	The time duration (in days) from symptom onset to no longer being infectious. Adjusted for proportional reduction in infectious individuals over time.	HIQA evidence summary of duration of infectiousness[3] Singanayagam et al.[4]	Mean: 7.1 95% CI (2.8 to 11.5)
Proportion of asymptomatic infections	The proportion of all infected cases which remain asymptomatic (that is they do not show symptoms at any point).	Buitrago-Garcia et al.[5]	Mean: 0.31 95% CI (0.24 to 0.38)
Proportion of symptomatic individuals who identify as symptomatic	Proportion of people who are symptomatic and voluntarily seek testing (through their GP or a test centre).	To be confirmed	
Rate of infection of close contacts in setting	Attack rate in workplace setting.	To be confirmed through model validation	
Rate of infection of close contacts at home	Attack rate in home setting.	To be confirmed through model validation	
Proportion symptomatic cases that are infectious	Proportion of symptomatic cases that have a sufficiently high viral load to be infectious.	To be confirmed	
Proportion asymptomatic cases that are infectious	Proportion of asymptomatic cases that have a sufficiently high viral load to be infectious.	To be confirmed	
Outbreak factors			
Probability of an outbreak occurring	Likelihood of an outbreak occurring in a 28 day period.	CIDR database	To be confirmed
Number of close contacts at work	Number of people in the work setting that are considered close contacts.	Contact tracing data	0.7 (95% CI: 0 to 4)

Number of close contacts at home	Number of people at home that are considered close contacts.	Contact tracing data	2.5 (95% CI: 0 to 7)

Test characteristics			
Clinical sensitivity of RT-PCR testing for SARS-CoV-2 (symptomatic individuals)	Proportion of individuals with symptomatic COVID-19 correctly identified as infected with SARS-CoV-2 by RT-PCR testing, subject to pre-analytical factors.	HIQA Rapid HTA of diagnostic tests;[6] inferred as high sensitivity when appropriate pre-analytical time factors satisfied	Mean: 0.90 95% CI (0.83 to 0.95)
Clinical sensitivity of RT-PCR testing for SARS-CoV-2 (asymptomatic individuals)	Proportion of individuals with asymptomatic COVID-19 correctly identified as infected with SARS-CoV-2 by RT-PCR testing, subject to pre-analytical factors.	HIQA Rapid HTA of diagnostic tests;[6] inferred as high sensitivity when appropriate pre-analytical time factors satisfied	Mean: 0.90 95% CI (0.83 to 0.95)
Clinical specificity of RT-PCR testing for SARS-CoV-2	Proportion of individuals who do not have COVID-19 correctly identified as negative by RT-PCR testing for SARS-CoV-2.	HIQA Rapid HTA of diagnostic tests;[6] inferred as high	Mean: 0.99 95% CI (0.98 to 1.00)
Sensitivity of RADT for detection of SARS-CoV-2 (symptomatic individuals)	Percentage of individuals with symptomatic COVID-19 correctly identified as infected by RADT for SARS-CoV-2. Considered relative to RT-PCR as reference standard.	From serial testing validation data and published studies of diagnostic test accuracy	To be confirmed
Sensitivity of RADT for detection of SARS-CoV-2 (asymptomatic individuals)	Percentage of individuals with asymptomatic COVID-19 correctly identified as infected by RADT for SARS-CoV-2. Considered relative to RT-PCR as reference standard.	From serial testing validation data and published studies of diagnostic test accuracy	To be confirmed
Specificity of RADT for detection of SARS-CoV-2	Percentage of individuals who do not have COVID-19 correctly identified as negative by RADT for SARS-CoV-2. Considered relative to RT-PCR as reference standard.	Minimum acceptable performance criteria set out by the WHO[7, 8]	To be confirmed
Organisational factors			
Staff resources for test processing	Person-time of HCW or appropriately qualified staff required to process RADT tests on site.	From serial testing validation data.	To be confirmed
Cost of staff time	Cost per hour.		To be confirmed
Cost of RADT kits	Average cost of RADT kits.		To be confirmed
Cost of RT-PCR test	Cost of RT-PCR testing of a collected swab sample .		To be confirmed

3. Model development

The model will be based on an individual-level microsimulation to capture the variation in disease progression across individuals. Different testing strategies will be simulated to determine the numbers of individuals for whom a false-negative test may be returned (including due to pre-analytical issues such as timing of test), thereby potentially continuing to attend the workplace while infectious. In this context, a false positive occurs when the combination of RADT and confirmatory RT-PCR both return a positive test result in an individual who is not infected with SARS-CoV-2. In an RT-PCR-based serial testing programme, there is no confirmatory testing, and hence a false positive is defined as a positive RT-PCR test result in an individual who is not infected with SARS-CoV-2. A number of sensitivity analyses will be used to test the impact of the assumptions in both the model structure and the included parameters.

4. Additional factors for consideration

A number of additional factors that may affect overall outcomes, but are not feasible to include within the model, will be outlined in the final report. These factors are likely to include the extent to which individuals comply with testing and reporting positive test results, and how participation in a programme of serial testing impacts on how people interact with formal contact tracing processes in Ireland.

5. Summarise findings

A report will be produced summarising the findings of this analysis.

6. Quality assurance process

The analysis and modelling will be led by an experienced analyst. A small team of analysts will be assigned to assist. The model will be quality assured by a second analyst who will check that the model is running as intended, inputs to the model accurately reflect those in the report and that summary report accurately reflect the outputs of the analysis. The report will be reviewed by a senior member of the team, to ensure processes are followed and quality maintained.

7. Present collective findings to HIQA's COVID-19 Expert Advisory Group for input

The collective findings of the modelling exercise will be presented to HIQA's COVID-19 Expert Advisory Group for consideration, clinical interpretation and input to the subsequent advice to the HSE.

8. Provide findings to NPHET for consideration

A document outlining the advice informed by the key findings of the evidence synthesis and expert interpretation by the EAG will be provided to the HSE for consideration.

9. Timelines

This evidence synthesis will be conducted in line with the processes and timelines outlined for Phase 2 of HIQA's COVID-19 response. Work commenced on 8 March 2021 and it is anticipated that a final draft will be circulated to HIQA's COVID-19 EAG for review and input on the 26 April 2021, with a view to providing advice and recommendations to HSE Rapid Antigen Diagnostic Testing Working Group on 28 April 2021. However, this timeframe is contingent on agreement of the protocol. Should delays be encountered, then this timeline will be amended.

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