Health Technology Assessment (HTA) Expert Advisory Group Meeting
(NPHET COVID-19 Support)

Meeting no.3: Tuesday 20th October 2020 at 12:00

(Zoom/video conference)

(DRAFT) MINUTES

Attendance:		
Chair	Dr Máirín Ryan	Director of Health Technology Assessment & Deputy Chief Executive Officer, HIQA
Members via video conference	Prof Karina Butler	Consultant Paediatrician and Infectious Diseases Specialist, Children's Health Ireland & Chair of the National Immunisation Advisory Committee
	Dr Jeff Connell	Assistant Director, UCD National Virus Reference Laboratory, University College Dublin
	Dr Eibhlín Connolly	Deputy Chief Medical Officer, Department of Health
	Prof Máire Connolly	Specialist Public Health Adviser, Department of Health and Adjunct Professor of Global Health and Development, National University of Ireland, Galway
	Prof Martin Cormican	Consultant Microbiologist & National Clinical Lead, HSE Antimicrobial Resistance and Infection Control Team
	Ms Sinead Creagh	Laboratory Manager at Cork University Hospital & Academy of Clinical Science and Laboratory Medicine
	Dr John Cuddihy	Specialist in Public Health Medicine & Interim Director, HSE- Health Protection Surveillance Centre (HPSC)
	Dr Cillian de Gascun	Consultant Virologist & Director of the National Virus Reference Laboratory, University College Dublin
	Dr Lorraine Doherty	National Clinical Director Health Protection, HSE- Health Protection Surveillance Centre (HPSC)
	Prof Jim Duggan	Professor of Computer Science, NUI Galway
	Dr Vida Hamilton	Consultant Anaesthetist & National Clinical Advisor and Group Lead, Acute Hospital Operations Division, HSE
	Dr David Hanlon	General Practitioner & National Clinical Advisor and Group Lead, Primary Care/Clinical Strategy and Programmes, HSE
	Dr Patricia Harrington	Head of Assessment, Health Technology Assessment, HIQA
	Dr Derval Igoe	Specialist in Public Health Medicine, HSE- Health Protection Surveillance Centre (HPSC)
	Prof Mary Keogan	Consultant Immunologist, Beaumont Hospital & Clinical Lead, National Clinical Programme for Pathology, HSE
	Dr Siobhán Kennelly	Consultant Geriatrician & National Clinical & Advisory Group Lead, Older Persons, HSE
	Ms Sarah Lennon	Executive Director, SAGE Advocacy
	Mr Andrew Lynch	Business Manager, Office of the National Clinical Advisor and Group Lead - Mental Health, HSE
	Dr Gerry McCarthy	Consultant in Emergency Medicine, Cork University Hospital & National Clinical Lead, HSE Clinical Programme for Emergency Medicine
	Prof Paddy Mallon	Consultant in Infectious Diseases, St Vincent's University Hospital & HSE Clinical Programme for Infectious Diseases
	Dr Desmond Murphy	Consultant Respiratory Physician & National Clinical Lead, HSE Clinical Programme for Respiratory Medicine
	Dr John Murphy	Consultant Paediatrician & Co-National Clinical Lead, HSE Paediatric/Neonatology Clinical Programme
	Dr Sarah M. O'Brien	Specialist in Public Health Medicine, Office of National Clinical Advisor & Group Lead (NCAGL) for Chronic Disease
	Dr Gerard O'Connor	Consultant in Emergency Medicine, Mater Misericordiae University Hospital HSE Clinical Programme for Emergency Medicine
	Ms Michelle O'Neill	HRB-CICER Programme Manager, HTA Directorate, HIQA
	Dr Margaret B. O'Sullivan	Specialist in Public Health Medicine, Department of Public Health, HSE South & Chair, National Zoonoses Committee

	Dr Michael Power	Consultant Intensivist, Beaumount Hospital & National Clinical Lead, HSE Clinical Programme for Critical Care
	Dr Lynda Sisson	Consultant in Occupational Medicine, Dean of Faculty of Occupational Medicine, RCPI & HSE National Clinical Lead for Workplace Health and Well Being
	Prof Susan Smith	Professor of Primary Care Medicine, Royal College of Surgeons in Ireland
	Dr Patrick Stapleton	Consultant Microbiologist, UL Hospitals Group, Limerick & Irish Society of Clinical Microbiologists
	Dr Conor Teljeur	Chief Scientist, Health Technology Assessment, HIQA
	Ms Anne Tobin	Assessment and Surveillance Manager, Medical Devices, Health Products Regulatory Authority
In attendance	Dr Christopher Fawsitt	Senior Health Economist, HIQA
	Dr Eamon O'Murchu	Senior HTA Analyst, Health Technology Assessment, HIQA
	Dr Sinead O'Neill	Epidemiologist/Health Services Researcher, Health Technology Assessment, HIQA
	Dr Karen Cardwell	Postdoctoral Researcher, Health Technology Assessment, HIQA
	Dr Laura Comber	HTA Research Analyst, Health Technology Assessment, HIQA
	Dr Kieran Walsh	HTA Research Analyst, Health Technology Assessment, HIQA
	Dr Paula Byrne	Health Services Researcher, Health Technology Assessment, HIQA
Secretariat	Ms Debra Spillane	PA to Dr Máirín Ryan, HIQA
Apologies	Dr Niamh Bambury	Specialist Registrar in Public Health Medicine, HSE- Health Protection Surveillance Centre (HPSC)
	Dr Ellen Crushell	Consultant Paediatrician, Dean, Faculty of Paediatrics, Royal College of Physicians of Ireland & Co-National Clinical Lead, HSE Paediatric/Neonatology Clinical Programme
	Ms Josephine Galway	National Director of Nursing Infection Prevention Control and Antimicrobial Resistance AMRIC Division of Health Protection and Surveillance Centre
	Dr Muiris Houston	Specialist in Occupational Medicine, Clinical Strategist – Pandemic, Workplace Health & Wellbeing, HSE
	Prof Simon More	Professor of Veterinary Epidemiology and Risk Analysis within the UCD School of Veterinary Medicine, UCD
	Dr Eavan Muldoon	Consultant in Infectious Diseases, Mater Misericordiae University Hospital, National Clinical Lead for CIT and OPAT programmes & HSE Clinical Programme for Infectious Diseases
	Dr Mary O'Riordan	Specialist in Public Health Medicine, HSE- Health Protection Surveillance Centre (HPSC)

1. **Welcome**
   The Chair welcomed all members to the meeting with the addition of two new members, Professor Jim Duggan from NUI Galway and Simon More from UCD.

2. **Apologies**
   Noted above.

3. **Conflicts of Interest**
   No conflicts of interest raised.

4. **Minutes of Meeting 6.10.2020**
   There was one correction to the minutes to reflect the point "Most labs have accreditation, but not all; it is not a legislative requirement". Otherwise the minutes were accepted as a fair and accurate representation of the discussion.

5. **Work Programme**
   The group was provided with an overview of the current status of the work programme including:

No.	Review Questions	Status of work	NPHET date
1.	RQ 22 Testing at day 7 and 10 to reduce duration of restriction of movement	Drafted	22/10/2020
2.	RQ 9 – Long term immune response and reinfection post SARS-CoV-2 infection	Drafted	22/10/2020
3.	RQ 20 – Conditions that are at very high risk (extremely medically vulnerable) from COVID-19	Ongoing	5/11/2020
4.	RQ 21 – High risk activities and settings for the transmission of SARS-CoV-2	Ongoing	5/11/2020
	Database	Ongoing	
	Public health guidance: - vulnerable groups - LTCFs	Ongoing	

6. Presentation of testing at day 7 and 10 to reduce duration of restriction of movement

Arising from the HIQA advice to NPHET (meeting date 01/10/2020) in relation to the duration of restriction of movements, it was noted that the HIQA evaluation team had been requested by NPHET to undertake a modelling exercise to inform a new policy question concerning testing of close contacts with the goal of reducing the duration of restriction of movements. As per the agreed deliverables document, two key research questions were addressed in the report:

RQ1) What is the potential impact of different testing scenarios to reduce the duration of restriction of movement for close contacts of a confirmed COVID-19 case?

RQ2) What is the International Public Health guidance for restriction of movement? (updated review)

Presentations were provided on key points for both the modelling exercise and the update to the international review.

The following points were raised as matters for clarification or discussion by the EAG:

- A suggestion to use a health economics approach to present the balance between the benefits and the harms where the benefits are a reduction in the total person time and quarantine or unrestricted movement and the harm is the increase in the number of person days for infectious people are out in the community. It was noted this is included in report as an appendix.
- Possibility of considering data on the difference in testing time between those who can travel, compared to those for whom transport to testing hubs must be arranged. These data could potentially highlight issues different socio economic groups are experiencing in accessing timely testing.
- To aid clarification, it was requested that a flow diagram highlighting how people can move between different states and progress through the disease, along with more detail around how the model was constructed and put together be added to the report.

- Based on HSE antigen test validation exercises, concerns was expressed around the manufacturers' claims for sensitivity of over 95%. The team agreed to rerun the model using a value of 75% sensitivity. Noted WHO recommendation that antigen tests should have a minimum of 80% sensitivity.
- An estimate of onwards infections based on an R of 1.1 is used in the report. It was, requested that an appendix to show estimates if R is lower or higher be added.

7. Advice from Testing at day 7 and 10 to reduce duration of restriction of movement

The EAG were reminded that the analysis had modelled current practice and eight alternatives

1st test - Day 0 (PCR or RADT)

2nd test - Day 7 or Day 10 (PCR or RADT)

The estimates suggested that the use of a day 10 RT-PCR test with end of restricted movements on receipt of a "not detected" result present the largest benefit and lowest risk relative to the current standard of practice in Ireland.

On the basis of these findings, the EAG were asked to consider the balance of benefits and risks estimated by the model (benefits were estimated in terms of person-days of restrictive movements and the risks were estimated as the number of additional infectious person-days in the community) as well as broader issues including; adherence, the ability to comply with testing, and the impact on the test and trace process currently in place. The EAG were also asked to consider if there may be circumstances where the acceptability of the risk-benefit differs for example, health care workers or nursing home settings or if there may also be considerations around further guidance required post ending restriction of movements, e.g. wearing masks, physical distancing, which is recommended internationally.

The following points were raised as matters for clarification or discussion by the EAG:

- It was highlighted that the advice will need to be appropriate to the context within which the testing is conducted, flexible in terms of derogations and influenced by local public health and occupational health opinion in terms of what those risks are, with necessary caveats outlined.
- The risk from people who will broadly follow guidance being allowed to go back to their lives earlier was noted as probably a very small element of the global risks that we are dealing with. For those who are really struggling to adhere to the guidance, they may not adhere to any level of restricted movements, regardless of the (change in) guidance.
- It was acknowledged there are large knowledge gaps around compliance with better information required. Anecdotally it was highlighted that compliance levels were questionable among the general public.
- The fact that many frontline workers are becoming close contacts was noted, with an almost consistent exposure to COVID-19 during busy periods. Any effort to enable

them to return to work a little earlier, would be very welcome in terms of the healthcare workforce.

- Communication strategy required to ensure people are aware that a negative test means not detected at this point, with an emphasis to people that they may have a latent period before they become detectable. Also clear communication on the purpose of the two tests, with the first test for source control and the second for contact tracing
- Noted that there currently is capacity in the system to perform two PCR tests on close contacts. Lab-based antigen testing, is currently unavailable, however there are ongoing developments in this area.
- It was remarked that the nasopharyngeal swab was felt to be a barrier for people; alternative samples likely to have improved acceptability should be considered to improve compliance with the second test. Consideration could be given to extending the use of nasal swabs (which has already been agreed for children) or mid-turbinate swabs.
- Any policy decision will have to be based around the risk appetite and the considerations outlined, noting that the modelled estimates point towards the day 10 PCR based scenario having the highest benefits for lowest risk relative to current practice.

8. Presentation: Long-term duration of the immune response and reinfection following SARS-CoV-2 infection

It was noted that this is the fourth iteration of the report, updating versions published on 13 May, 9 June and 6 August 2020. The evaluation team noted that in the course of the updates, the research questions and methodology used have been refined, with the fourth update limited to studies investigating 'true' reinfection with SARS-CoV-2 based on comparative genomic analysis, and the long term (≥60 days) duration of antibody responses (IgG and neutralising antibodies) to SARS-CoV-2. The research question was identified as:

What is the rate of reinfection/duration of immunity in individuals who recover from a laboratory-confirmed coronavirus infection?

A presentation was provided summarising the key findings of the evidence summary.

The following points were raised as matters for clarification or discussion by the EAG:

- It was noted that while patients tend to develop an IgG response, there is a subset of people who do not develop a response (as in, fail to ever mount a response). Looking at studies with long follow-up, often only patients who mounted a baseline response are followed with attrition of the non-responders, leading to an underestimation of the proportion who remain seronegative.
- Unpublished Irish data will soon be available on a cohort of patients followed beyond day 60, looking at IgG and IgM responses.
- The context for the focus on antibody detection should be clearly explained in the report, noting that the presence of antibodies alone does not equate to immunity as

the relative contribution of antibody-mediated immunity versus memory cells is not yet known.

- For those previously infected with SARS-CoV-2, there is a distinction between potential immunity from disease (that is, risk of clinical sequelae from disease if re-infected) and lifetime immunity from infection (risk of re-infection). These have long term policy implications.

9. Advice: Long-term duration of the immune response and reinfection following SARS-CoV-2 infection

In developing the advice, the group was reminded of the conclusions of the evidence review, specifically that:

- recent evidence demonstrates that reinfection is possible following recovery from SARS-CoV-2 infection. To date, these events have only been very rarely documented and, of the cases identified, there is a lack of evidence regarding infectiousness of these reinfected patients.
- antibody responses, including IgG and neutralising antibodies, are maintained in most patients 2-6 months post-symptom onset. However, neutralising antibody titres and neutralising capacity declines substantially from 60 days onwards, with rapid decline after 100 days.

The following points were raised:

- Serology (antibody) testing has a role in the diagnosis and management of patients who present to the hospital with negative SARS-CoV-2 RT-PCR, but a high clinical suspicion of COVID-19 infection. A positive antibody test aides in the differential diagnosis and can guide clinical management.
- Current practice is that pre-admission testing is not required for patients with a history of laboratory-confirmed COVID-19 in the previous three months (i.e., as part of pre-screening for scheduled admissions, or for non-COVID-19 unscheduled admissions).
- Guidance around serial testing and testing prior to scheduled and unscheduled care will need to be consider the findings of the review.
- It is not possible to draw conclusions regarding the potential clinical picture for those experiencing reinfection given the mixed evidence of severity.
- A very clear message is required around communication of risk, particularly for the public regarding the ongoing requirement to adhere to public health measures including for individuals that have previously had COVID-19.
- The performance of whole genome sequencing on all healthcare workers with suspicion of reinfection would require additional resources and the availability of wide-scale sequencing technology.
- It was highlighted that a C_t (cycle threshold test) is not an absolute measure of viral load; C_t values vary hugely it between different PCR platforms, so it is not possible to compare levels of infectivity between first and subsequent infections.

- Group agreement on the importance of communicating the risk of true reinfection, despite how rare the event is. It is important that public health measures remain in place for patients who have recovered from a SARS-CoV-2 infection, due to the risk of reinfection. Based on the evidence to date, it is not known how common reinfection is, and how infectious these cases are

10. Conditions that are at very high risk (extremely medically vulnerable) from COVID-19

The policy question outlined by NPHET was, based on the available international evidence, is the current definition of what constitutes extremely medically vulnerable, that is, among those who were previously asked to cocoon, in relation to COVID-19 appropriate. The agreed research question formulated to inform this policy question is, *"what is the evidence underpinning the categorization of extremely medically vulnerable groups who may be at risk of severe illness from COVID-19".*

The protocol was presented along with an update on the progress of the review.

- Group members agreed to share any relevant information or research they are aware of, including a body of work that was done by the Society of Occupational Medicine in relation to calculating a COVID age and work on immunosuppressed patients.

11. High risk activities and settings for the transmission of SARS-CoV-2

It was noted that NPHET has requested an evidence review on what constitutes higher risk areas activities or workplaces, in regards to transmission of COVID-19. As per the agreed deliverables document, the following research question formulated by the evaluation team in response to the policy issue will be addressed "*What activities or setting are at a higher risk of SAR-CoV-V2 transmission?"*

It was noted that given the timeframe, the focus will be on a high level review of evidence summaries, as well as primary observational research studies of population-based data with the review structured into three main sections:

1) Where have clusters been observed?

2) What is the risk of transmission associated with different settings and activities?

3) What is the Secondary Attack Rate (SAR) associated with different settings and activities?

An update on the progress of the review was provided, which will be discussed in full at the EAG meeting on the 3rd November 2020.

12. Meeting Close

a) AOB

- Policy and our process around publication of the advice: the advice and the underlying evidence would be published ordinarily within three weeks, but allowing for any periods of deliberation by NPHET or by the government before the advice would be made public. The EAG will be informed of publication of the reports.

- Group members can share the policy questions that we are being asked with members of the group they represent. Once the relevant research question and protocol are agreed we will make this publicly available on the website.
- An evaluation on the EAG processes will be undertaken shortly and we would appreciate feedback on our approach to date.

b) Date of next meeting: Tuesday 3rd Nov 12pm by Video Conference.