Health Technology Assessment (HTA) Expert Advisory Group Meeting (NPHET COVID-19 Support)		
Meeting no. 10 : Monday 22nd February 2021 at 11.00am		
(Zoom/video conference)		
MINUTES		
Attendance:		
Chair	Dr Máirín Ryan	Director of Health Technology Assessment (HTA) & Deputy Chief Executive Officer, HIQA
	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 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 Lorraine Doherty	National Clinical Director Health Protection, HSE- Health Protection Surveillance Centre (HPSC)
	Ms Josephine Galway	National Director of Nursing Infection Prevention Control and Antimicrobial Resistance AMRIC Division of Health Protection and Surveillance Centre
	Dr Cillian de Gascun	Consultant Virologist & Director of the National Virus Reference Laboratory, University College Dublin
	Dr James Gilroy	Medical Officer, Health Products Regulatory Authority
	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	Deputy Director, HTA Directorate, HIQA
	Dr Muiris Houston	Specialist in Occupational Medicine, Clinical Strategist – Pandemic, Workplace Health & Wellbeing, HSE
	Prof Mary Keogan	Consultant Immunologist, Beaumont Hospital & Clinical Lead, National Clinical Programme for Pathology, 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
	Prof Paddy Mallon	Consultant in Infectious Diseases, St Vincent's University Hospital & HSE Clinical Programme for Infectious Diseases
	Dr Gerry McCarthy	Consultant in Emergency Medicine, Cork University Hospital & National Clinical Lead, HSE Clinical Programme for Emergency 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	Deputy Director, HTA Directorate, HIQA
	Dr Margaret B. O'Sullivan	Specialist in Public Health Medicine, Department of Public Health, HSE South & Chair, National Zoonoses Committee
	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, HTA Directorate, HIQA
	Dr Lelia Thornton	Specialist in Public Health Medicine, HSE- Health Protection Surveillance Centre (HPSC)
In attendance	Ms Susan Ahern	Health Services Researcher, HTA Directorate, HIQA
	Dr Paula Byrne	Health Services Researcher, HTA Directorate, HIQA
	Mr Paul Carty	Health Services Researcher, HTA Directorate, HIQA
	Dr Laura Comber	Senior HTA Research Analyst, HTA Directorate, HIQA
	Dr Eamon O Murchu	Senior HTA Research Analyst, HTA Directorate, HIQA
	Dr Susan Spillane	Senior HTA Research Analyst, HTA Directorate, HIQA
Apologies	Dr John Cuddihy	Specialist in Public Health Medicine & Interim Director, HSE-Health Protection Surveillance Centre (HPSC)
	Dr Derval Igoe	Specialist in Public Health Medicine, HSE- Health Protection Surveillance Centre (HPSC)
	Dr Siobhán Kennelly	Consultant Geriatrician & National Clinical & Advisory Group Lead, Older Persons, HSE
	Dr Michael Power	Consultant Intensivist, Beaumont Hospital & Clinical Lead, National Clinical Programme for Critical Care, HSE
	Dr Des Murphy	Consultant Respiratory Physician & Clinical Lead, National Clinical Programme for Respiratory Medicine, HSE

Proposed Matters for Discussion:

1. **Welcome**

   The Chair welcomed all members.

2. **Apologies & Introductions**

   Apologies recorded as per above. Noted that Dr James Gilroy has replaced Anne Tobin as the HPRA's nominated representative. The Chair thanked Anne for the support she had provided.

3. **Conflicts of Interest**

   No new conflicts raised in advance of or during this meeting.

4. **Minutes**

   The minutes of 25th January 2021 and 8th February 2021 were approved as an accurate reflection of the discussions involved once amendments to attendance were noted

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
1.	Duration of protective immunity (protection from reinfection) following SARS-CoV-2 infection	Drafted
2.	Review of international public policy response for weekly update	Ongoing
3.	Vaccination Priority Group 9 – are groups appropriate	Ongoing
4.	Preventative interventions pre-infection with SARS-CoV-2	Ongoing
5.	Vaccination of HCWs – consideration in the event of HCW not taking vaccination	Ongoing
	Database	Ongoing
	Public health guidance: - vulnerable groups - LTCFs	Ongoing

6. **Presentation of evidence summary on 'Duration of protective immunity (protection from reinfection) following SARS-CoV-2 infection' – key findings**

   The EAG were reminded that the most recent immunity evidence summary (November 2020) concluded that:

   - SARS-CoV-2 reinfection, as confirmed by whole genome sequencing, is possible
   - Antibody responses are present in most individuals 2-6 months post-symptom onset, however evidence of waning antibody titres in some studies.

The HIQA evaluation team undertook a rapid evidence summary to address the following review question:

"*How long does protective immunity (that is, prevention of reinfection) last in individuals who were previously infected with SARS-CoV-2 and subsequently recovered?"*

This request to HIQA from NPHET confirming the review question was agreed on 2 February 2021.

The Chair thanked the members for reviewing the draft rapid evidence summary. The Lead Analyst presented the key points arising from the rapid evidence summary.

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

A similar piece of work has been undertaken by the National Immunisation Advisory Committee (NIAC), their work arrived at the same findings and caveats as the HIQA evidence summary. While the NIAC work was undertaken to inform vaccine policy it will be important to ensure consistency of messaging across these reports. It was confirmed that the study by Dan et al. was also included in the HIQA review. The importance of caveating data with the uncertainties relating to emerging variants of concern was acknowledged. As the review included studies that investigated reinfection prior to December 2020, there is uncertainty regarding the presumptive immunity relating to variants that have emerged since then. Vaccination of individuals previously infected with SARS-COV-2 was discussed breifly, however it was emphasised that the HIQA review did not address questions surrounding vaccination policy. Discussion points included:

- International policies surrounding one-dose vaccination in cohorts of individuals who have documentation of a prior SARS-CoV-2 infection. It was noted that this review was undertaken at a time that vaccine scarcity and supply issues were of significant concern. However, the data in this review does not lend itself to determining if single-dose strategies, in an effort to reduce shortages, are effective.
- With regards to establishing if individuals were previously infected with SARS-CoV-2, a concern was raised that a small proportion of prior cases could have been false positives, in particular when indeterminate diagnoses were acted upon at the beginning of the pandemic. Such data need to be considered in the context of the overall index of suspicion. Additional evidence of prior infection, in the form of seropositive status, should be considered to increase our confidence that we are correctly identifying previously positive individuals. Study data suggest that a small proportion of individuals do not mount an antibody response; however, this may be due to inadequate follow-up or test performance. Failure to detect an immune response is more common in asymptomatic infections. Therefore, any decision regarding the vaccination of individuals with previously diagnosed SARS-CoV-2 infection should be placed in the context of whether or not they were symptomatic at the time of RT-PCR testing.

It was noted that early data from the SIREN study demonstrated that there was not an elevated incidence of reinfection in those with asymptomatic initial infection. It was clarified that in the HIQA evidence summary, it is not possible to determine if there is an increased risk of reinfection associated with asymptomatic initial infection in studies that enrolled antibody-positive participants at baseline.

It was noted that observed trends in the waning of SARS-CoV-2 antibodies but with persistence of immunity is in line with that of some other infectious diseases for example chicken pox. In particular, research on the orginal SARS-CoV found similar findings. Less is known about endemic seasonal coronaviruses due to a relative lack of research. In particular, cellular immunity and the production of neutralising antibodies have not been extensively examined in clinical settings.

It was noted that it should be made clear in the key points that only a subset of patients received whole-genome sequencing in the study by Abu-Raddad and not all patients (although this point is clarified in the 'results' section of the report).

It was highlighted that well-designed and executed cohort studies are likely to be the highest level of evidence that can be produced in this area, as experimental trials are unethical. Such cohorts can demonstrate strong longitudinal associations that come close to demonstrating a causal association. Therefore, the strength of this evidence should be articulated.

The Chair noted that clarifications will be made to the draft evidence summary report where necessary based on the above points. It was also noted a brief section in relation to Irish immunity studies would be added to the discussion for context. The draft was otherwise accepted by the EAG as a fair reflection of the evidence synthesis that was undertaken.

7. Advice: Duration of protective immunity (protection from reinfection) following SARS-CoV-2 infection *(for discussion)*

In the context of this evidence, the EAG was asked for their input in order to formulate the advice. Suggested issues to be considered included the:

- How long should derogation policies apply post-infection?
- Should there be a change to serial testing procedures in previously infected and vaccinated populations?
- If changes to current policy are proposed, are there subgroups to which the changes should not apply?
- How does our data apply to recent variants of concern?
- How does our data apply to vaccinated populations?
- How should transmissibility be assessed in reinfected individuals?

Feedback on advice from EAG:

- It was noted that current HSE guidance is that close contacts with a history of confirmed COVID-19 infection, within the previous 12 weeks, do not require restricted movement or active follow-up.

- Current approach of the HSE is that healthcare workers should not be considered for derogation unless absolutely necessary to provide essential care. However, it is clear that infection prevention and control measures are impeded when staff numbers fall in hospital settings. The impact of taking healthcare workers out of a hospital ward is not neutral in terms of quality of care. As with current policy, workers should not be considered for derogation if exposure relates to a high-risk exposure, including household contacts.

- The EAG expressed broad support that exemption from close contact status of healthcare workers could be extended to six months in light of the evidence findings. It was acknowledged that there is a level of uncertainty, particularly in light of emerging variants of concern (of which the production of immune-escape variants are inevitable) and whether immunity is the same in those with prior asymptomatic SARS-CoV-2 infections. Although the possibility of rare reinfection events is not eliminated, the evidence generally provides reassurance that the risk of reinfection is significantly reduced and the benefit to harm balance is in favour of of extending the current policy.

- Concerns were expressed in relation to the currently available data to adequately address potential transmissibility (particularly in the context of household contacts), noting a lack of B and T cell response in the absence of neutralising antibody response and that it is unclear whether those previously infected can carry the virus without developing symptoms. Asymptomatic individuals may be underrepresented in many studies.

- It was noted that currently, we are testing all admissions unless the patient had a laboratory-confirmed infection within the preceding three months. If this is extended to six months, there will be a significant positive impact on patient flow.

- It was noted that data in this review is mainly from healthcare workers, under the age of 65, along with two studies in the general population, that demonstrated a reduced risk of reinfection. It was noted that extrapolating data to other populations must be done with caution. The level of risk for HCWs in particular is typically different due to different levels of exposure.

- The primary caveat to these findings is the issue of emerging variants of concern and their potential for reinfection and transmissibility going forward. Any policy decisions should be monitored and reviewed in light of emerging variants.

- The large knowledge gaps with respect to SARS-CoV-2 were noted. The serial RT-PCR screening of staff in nursing homes and other settings, 50,000 nursing home staff screened in each cycle, was suggested as a potential data source that could be audited

to evaluate the risk of reinfection and infection in the context of a vaccinated population. These data could then potentially inform policy decisions related to this area.

- It was noted that it is very difficult to extrapolate from neutralising antibody in serum to potential for transmission. Neutralising antibodies, usually IgA in the respiratory tract, is required to prevent virus residing in the upper airways, until other arms of the immune system are clear.

  It was highlighted that it will be challenging to quickly determine if data are applicable to emerging variants. Contact tracing (particularly when history of travel or an association with travel history is present) and surveillance might inform an index of suspicion, however. The importance of surveillance and building WGS capacity was emphasised.

- It was noted that "variant of concern" may be confusing given that the variants of concern change over time. It is likely that these variants will become endemic, as per other seasonal coronaviruses, and the key will be protecting people from symptomatic infection. Importation of cases and vaccination in other countries will shape the virus's ability to adapt to new hosts and whether widespread emergence of variants occurs at population-level.The inevitability of emerging variants due intrinsic viral evolution and environments that result in selective pressure was discussed by the group. Varation was noted to be random, but selection would be shaped by acquired immunity.

- It was suggested that a lay summary of humoral versus cellular immunity is provided. This could be in the form of a glossary of key terms for clarity.

- Notwithstanding the multiple caveats expressed throughout the meeting, in particular issues regarding emerging variants, there was broad consensus that the presented data support presumptive immunity and protection from reinfection in most individuals for at least six months post-infection. However, it was acknowledged that uncertainty exists relating to reinfection potential with emerging variants. Any policy decision relating to this should be kept under review and informed by the international evidence and national surveillance data.

8. HIQA COVID-19 EAG Process Evaluation (for discussion)

Key findings of the EAG process evaluation (conducted in December) were presented. This evaluation process will be repeated in the future. There were no further comments on these findings.

9. Meeting Close

a) AOB

The Chair thanked the EAG members for their contribution to date and acknowledged the valuable feedback provided under short timelines.

b) Date of next meeting: 15th March 2021

a. Protocols with new questions will be circulated by email