Centre for Experimental Pathogen Host Research
University College Dublin
School of Medicine
Dublin 4
Ireland

16th June 2020.

Aileen Fallon
Clerk to the Committee
Special Committee on COVID-19 Response
Leinster House
Dublin 2.

Re: Invitation to make written submission
Your ref: SCC19R-I-0146

Dear Ms Fallon

Many thanks for your email and attached letter dated June 15th 2020. Please find attached a submission as requested. In preparing this submission I have attempted to follow the guidance notes provided in your original email. I wold be very happy to provide further detail and / or opinion as required by the Committee.

Please do not hesitate to contact me should further information be required.

Yours sincerely

Prof Patrick (Paddy) Mallon
MB BCh BAO PhD FRACP FRCPI

Professor of Microbial Diseases, University College Dublin
Director, UCD Centre for Experimental Pathogen Hot Research
Director, Wellcome-HRB Irish Clinical Academic Training programme
Consultant in Infectious Diseases, St Vincent's University Hospital, Dublin

Email: paddy.mallon@ucd.ie

15th June 2020. Dublin.

Introduction

1. The global health and economic consequences arising from the SARS-CoV-2 pandemic are unrivalled in modern society. Although a specific diagnostic test to detect the SARS-CoV-2 virus (polymerase chain reaction or PCR) was developed rapidly after the reports of the first cases, the high transmission rates meant that high throughput testing was required quickly after the infection was introduced into a new population.

2. SARS-CoV-2 is highly infectious. On 25th January 2020 a report by Imperial College London estimated the R0 of uncontrolled SARS-CoV-2 to be 2.6, a transmission rate that implied that control measures would need to block in excess of 60% of transmissions in order to be effective. The report suggested that control of SARS-CoV-2 would rely '*on the prompt detection and isolation of symptomatic cases*'[1].

3. SARS-CoV-2 has highly variable infectivity. Some affected individuals do not transmit the infection while others are capable of transmitting the virus to a large number of people (so called super-spreaders). It is increasingly agreed that individuals are capable of transmitting the infection in the period immediately prior to onset of symptoms (termed 'asymptomatic' or 'pre-symptomatic' transmission). In addition, although the incubation period (time from acquiring the infection to developing symptoms) for SARS-CoV-2 infection is estimated to be approximately 5 days[2], there are well described reports of individuals presenting with symptoms after much shorter incubation periods, in some cases as short as two days post exposure[3].

4. Physical distancing is highly effective at interrupting transmission of SARS-CoV-2 but its impact on societal functioning means that it has limited longevity as an effective public health measure. As a result, when considering alternatives to physical distancing, detection and isolation of cases becomes a core societal control strategy. The characteristics of the SARS-CoV-2 virus described above (paragraph 3) make it essential to identify those infected in the ***shortest possible time*** if the required interruption of 60% of transmissions is to be achieved.

5. Within a short period of time, countries have had to design and implement large-scale, national testing and contact tracing platforms, often on a background of inadequate pre-existing infrastructure. The rapid spread of this infection across the globe also resulted in rapid consumption of the available supply of equipment and consumables necessary to conduct testing at the scale required. In some cases, delays in increasing testing capacity appropriately may have contributed to the prolongation of the epidemic within countries, and the resulting negative health and economic impacts.

6. The challenge moving forward is maintaining maximally reduced transmission through effective testing and contact tracing. In times where the background rates of influenza-like illness (ILI) symptoms are low (such as currently), this is feasible. However, as we progress into the autumn and winter months, it is likely that ILI rates will increase due to the surge in common cold or seasonal influenza. At this stage, need for testing will likely increase dramatically with the risk that the testing capacity may quickly become saturated, resulting

1. Imai N et al. Imperial College London (25-01-2020), doi: https:/doi.org/10.25561/77148. Accessed June 15 2020. 2. Lauer SA et al. Ann Int Med. 2020 May 5;172(9):577-582. 3. Huang L et al. J infect. 2020 June; 80(6):e1-e13.

in delays in diagnosis of COVID-19 infection. This may result in increased hospitalisations and a requirement for return to societal restrictions as a method of control. It is vital that Ireland is prepared to address this challenge, when, not if, it arises.

7. I am the Full Professor of Microbial Diseases in University College Dublin. I am a Clinician Academic, having completed clinical training in Infectious Diseases in Sydney Australia alongside academic training in the Kirby Institute, aligned with the University of New South Wales in Australia from 2000 to 2007. The Kirby Institute is internationally renowned for epidemiological, clinical and basic science research into viral diseases such as HIV and hepatitis. My training included establishing a molecular laboratory programme researching drug safety in HIV. I returned to Ireland in 2007, where I established a molecular research laboratory at UCD, which became the HIV Molecular Research Group. This subsequently grew into the Centre for Experimental Pathogen Host Research (CEPHR), comprising research groups dealing with clinical, molecular and pathogen research into infectious diseases, spread across two UCD clinical sites as well as UCD Belfield. Alongside this, I have spent 10 years as a consultant in Infectious Diseases at the Mater Misericordiae University Hospital, which houses the National Isolation Unit. More recently I moved to a clinical position in Infectious Diseases at St Vincent's University Hospital with my appointment to Full Professor of Microbial Diseases at UCD, the only full clinical-academic professor of infectious diseases in Ireland. I am one of the founding directors of the Wellcome-HRB Irish Clinical Academic Training (ICAT) Programme, Head of Education for the European AIDS Clinical Society (EACS) and Chair of the EACS Guidelines Panel on Management of Comorbidities in HIV.

8. As requested by the Special Committee on COVID-19 Response, my submission will focus on aspects of testing and contact tracing as part of Ireland's response to the COVID-19 pandemic. I have divided my report into two sections, one dealing with testing and the other with contact tracing.

Testing

9. For the purposes of this report I will define 'testing' as the period from when an individual first experiences symptoms consistent with COVID-19 infection to the time that the result of the test is made available to the individual. Furthermore I will use turnaround time (TAT) as a term to describe this period.

10. Testing comprises eight steps;
    a. an affected individual requests a test
    b. the individual is assessed as meeting criteria for testing
    c. swab sample is collected
    d. swab sample is transported to the testing laboratory
    e. swab undergoes testing for SARS-CoV-2 in the laboratory
    f. laboratory result is verified and 'signed off' by a relevant laboratory official
    g. results is passed from the laboratory to an official responsible for reporting
    h. result is reported back to the affected individual

11. The most critical outcome of this process is the final step, where the affected individual is made aware of their infection status as this enables them to take the necessary precautions to avoid onward transmission as well as facilitating contact tracing. Ensuring the turnaround time for SARS-CoV-2 testing is as short as possible requires overall control and critical examination of each of these steps in order to identify inefficiencies that lead to delay in diagnosis (including the need to work under regulatory frameworks involving multiple official interactions). There are many examples internationally of innovative ways to reduce timelines across these steps, including use of IT solutions.

12. Other factors that add to the testing complexity as well as turnaround times include the different criteria for testing, or different testing 'pathways' that have emerged. Examples include testing in emergency departments (where rapid TAT is essential in order to provide acute medical care, ensure a safe hospital environment and maintain patient flow to avoid overcrowding), testing cases and contacts within outbreaks (e.g. in residential facilities, workplaces or homes, where short TAT is essential for outbreak control) and testing of asymptomatic individuals (e.g. hospital outpatients or quarantined travellers), where a longer TAT may be acceptable. Currently Ireland does not routinely report TAT broken down within specific clinical settings or according to specific laboratories (e.g. hospital versus community).

13. Many models for sampling have been developed, with the emphasis on safety for both the individual and staff as well as rapid throughput. In Ireland testing locations have variably been located within hospital complexes, within pre-existing community centres (e.g. sports grounds) or in community health settings, often staffed by healthcare workers who have been seconded from other full time roles. This model was able to rapidly upscale sampling capacity during the pandemic but is not feasible to maintain long term due to the need for the infrastructure and staff to return to original purposed functions and roles.

14. Most sampling occurs in 'hubs'. Sampling can involve four steps; 1) registration, 2) clinical assessment, 3) sampling and 4) post-sampling advice. Drive-through sampling procedures, with registration and clinical assessment conducted remotely, can reduce overall sampling time by up to 60%, with infrastructure costs reduced by use of tents as compared to solid infrastructure[4]. However the presence of solid infrastructure within a testing or assessment 'hub' and clinical oversight by a trained clinician provides additional flexibility as it enables full assessment of individuals who are either too unwell to drive or are considered too unwell to return home. Rapid onward referral, either to an emergency department or preferably direct admission to an isolation unit, can further improve efficiency of an assessment hub.

15. Detection of SARS-CoV-2, the virus that causes COVID-19 infection, is best achieved currently through use of nucleic acid amplification tests (NAAT). The polymerase chain reaction (PCR) test is one of the most commonly used NAAT, although several other NAAT platforms have been developed, including a cassette-based test available on the GeneXpert platform, which is currently used in some centres in Ireland. NAAT tests have the advantage of being both sensitive (low rates of false negative tests) and specific (low rates of false positives) for detection of SARS-CoV-2. PCR tests are commonly used in

4. Lee D et al. T.R.I.P. (2020). doi: https://dx.doi.org/10.1016/j.trip.2020.100111

clinical and research laboratories throughout Ireland and high levels of expertise are available, particularly in the academic (university) environment.

16. GeneXpert tests have the advantage of being quick to complete, less infrastructure requirement and less staff training but are currently limited by their availability, with one company manufacturing the tests. PCR-based tests are technically more difficult to perform, take longer to complete, require greater infrastructure investment and staff training but have the advantage of being able to use consumables (or 'kits') from a number of different suppliers, which potentially provides more security in terms of supply for large scale testing.

17. The equipment required to conduct testing for SARS-CoV-2 are not specific to this disease and can be used in routine diagnostic laboratories for other purposes when not conducting SARS-CoV-2 testing, including clinical and basic research.

18. Timelines for laboratory testing are generally longer for PCR over GeneXpert as, in most cases, PCR testing is run in batches and is more labour intensive, while GeneXpert is run on single samples, with less preparation time. Therefore, laboratories generally run PCR testing at intervals only after a pre-defined number of samples has accumulated.

19. Costs associated with testing include capital costs of procuring and maintaining equipment and laboratory infrastructure (including IT), including BCL3 laboratories, consumable or 'kit' costs, which in some cases include a limited shelf life, and staffing costs. Maintaining stand-alone laboratories to provide high levels of capacity during times of low needs will incur high cost per test. A model where mixed use of equipment and staff for other purposes (such as mixed clinical / academic purpose) with the ability to reconfigure quickly to scale up during times of high demand would reduce the overall cost per test.

20. Turnaround times (TAT) for testing have been shown to reduce significantly where laboratories are located on the same site as the swab testing (e.g. in-hospital laboratories)[5].

Contact Tracing

21. The principal goal of contact tracing should be to reduce the risk to public health by interrupting transmission of SARS-CoV-2 by identifying, testing, monitoring and if necessary, isolating contacts of a confirmed case of COVID-19 infection. Contact tracing facilitates:
    a. control of the epidemic (population level need)
    b. prevention of infections resulting in physical harm (individual need)

    In healthcare settings, such as hospitals or residential care facilities, the second consideration carries increased weight as the consequences for nosocomial transmission carry higher potential for resulting morbidity and mortality.

22. The HSE have provided guidance on management of contacts of a case of COVID-19 infection, which includes a definition of what constitutes a close contact and guidance on

5. Ward et al. J Allergy and Clinical Immunology (2020). doi: https://doi.org/10.1016/j.jaci.2020.05.012

follow-up through either passive or active monitoring. The responsibility for contact tracing is delegated to Occupational Medicine in the case of healthcare workers and to Infection Prevention and Control teams in hospital settings. The HSE has also provided interim guidance on the management of COVID-19 outbreaks (V1.1, dated 17 May 2020), which stipulates the importance of the Outbreak Control Team in managing COVID-19 outbreaks in healthcare settings, including acute hospitals.

23. A particular challenge in contact tracing involves reliance on the case to recall all close contacts within a period 48 hours prior to onset of symptoms. It is recommended that contact tracing be initiated at the point where a case is suspected (i.e. referral for testing in symptomatic cases). Should there be a significant additional time period between referral for testing and initiation of contact tracing (e.g. waiting for sampling and reporting of a positive result (example of three days) prior to contact tracing) this then involves reliance on the case to recall contacts dating back five days or more, which presents difficulties, especially when cases may be unwell at the time that they are being asked to recall.

24. Furthermore, in specific settings a case may be unable to provide reliable information on close contacts. Examples include where patients contract COVID-19 in clinical facilities where they are unfamiliar with their contacts or movements or where they may not have the ability or mental capacity to recall contacts.

25. As a result there is a real danger that close contacts may be missed. This will become more of an issue with easing of restrictions, as the average number of contacts for each case will increase. If contact tracing is not fully optimised, the overall result will be missed contacts, onward transmission and a reduction in the ability to interrupt 60% of transmissions, which is the minimal effect required from testing and contact tracing procedures if control of COVID-19 cases is to be maintained.

26. As with any complex intervention, no single measure it likely to be sufficiently effective in interrupting SARS-CoV-2 transmission and use of multiple interventions directed at the same outcome should be considered. For example, asking all individuals to record their movements and contacts on an ongoing basis is an intervention that in theory may help but in practice is unlikely to be taken up by sufficient numbers to be effective at the population level.

27. However a number of IT solutions have been implemented in other countries that involves geo mapping cases using information derived from mobile phones or personal electronic transactions to provide details on their movements both before and after symptom onset[4]. This information can then be used to notify other individuals, using their mobile phone data, that they may have been in contact with a potential case of COVID-19 infection. At a macro level, this information can also inform the population of areas where high rates of COVID-19 infection exist, to enable informed population movements away from 'hot spots' of COVID-19 transmission. Such innovative technologies have the ability to enhance current contact tracing activities, and enable all consenting individuals within a population to assist in contact tracing. However data protection and privacy legislation may limit their widespread application.

4. Lee D et al. T.R.I.P. (2020). doi: https://dx.doi.org/10.1016/j.trip.2020.100111

Recommendations

28. Laboratory testing should be conducted on the same geographical site as the sampling in order to maximally reduce turnaround times for testing, utilising the existing academic / health infrastructure.

29. Ireland should develop a detailed, National Testing Strategy for Pandemic Infections, within which specific testing pathways should be defined and target TAT that serve the needs of each specific pathway (e.g. screening versus outbreak control) established and reported as key performance indicators.

30. It is vital that Ireland maintains a national network of core clinical molecular laboratory capacity that can rapidly respond to future pandemic threats. This capacity should:
    a. be geographically linked to clinical centres
    b. include local and regional (level 4 hospital) laboratory capacity
    c. ensure larger, regional laboratories are integrated with academic research centres / programmes to ensure maximal return on investment and to maintain core expertise, training and test capacity between pandemics
    d. include widespread (if not compulsory) training of clinical laboratory staff in molecular techniques (NAAT) and integrate clinical and academic staffing so as to meet surge requirements when needed (including provision of 24 hour testing if required)
    e. Ensure availability of more than one testing platform within testing facilities to overcome supply / reagent issues

31. Any new testing platforms that are considered for introduction into service should have characteristics that at least match, if not exceed, current NAAT testing platforms in terms of sensitivity and specificity.

32. Ireland should develop a series of 'Assessment Hubs' geographically linked to testing laboratories that can facilitate safe assessment and sampling of a large number of individuals using both on site and drive through testing under the governance of a trained clinician and embedded within existing clinical services (e.g. Infectious Diseases clinical services). This will enable rapid reconfiguration of trained, specialist staff to address surge in need, clinical assessment (including admission avoidance) alongside onward referral or direct admission where appropriate.

33. To reduce cases of nosocomial COVID-19 infection, stringent adherence to published outbreak guidelines in healthcare facilities (including acute hospitals) should be enforced and closely monitored by relevant regulatory authorities.

34. Ireland should immediately pursue all available opportunities to enhance contact tracing for COVID-19 infection, including use of mobile technology to engage a consenting public in a national contact tracing effort.

35. Implementation of any recommendations should be rapid and be in place and operational in advance of the next expected increase in influenza-like illness, which may arrive by the latter period of the fourth quarter of 2020.