Janet Bonner

From:	Paul Nurse
Sent:	10 March 2020 09:47
To:	gcsa@go-science.gov.uk
Cc:	Chris.whitty@dhsc.gov.uk
Subject:	Francis Crick Institute : Support
Attachments:	Crick work to support COVID-19 research.doc
Follow Up Flag:	Follow up
Flag Status:	Completed

Dear Patrick

In view of the current situation with COVID-19 I thought you might like to be aware of what work the Crick is currently undertaking to support the research endeavour. I have attached a short summary. If there is anything in this summary you would like us to prioritise please let me know.

The Crick obviously only has certain expertise but I would like to offer any support we have that might be useful to you. For example, we could use volunteer laboratory staff if needed for diagnostics, or offer use of our high-quality containment or our general lab facilities.

Please do let me know if there is anything else you feel the Crick can do to support the overall effort against COVID-19.

Best wishes

Paul

Paul Nurse FRS
Director
The Francis Crick Institute
1 Midland Road
London NW1 1AT

Irrelevant & Sensitive
E: paul.nurse@crick.ac.uk
W: www.crick.ac.uk

[redacted]

Crick work to support COVID-19 research

Crick hosts one of the international World Influenza Centres (WIC). The WIC has world-leading expertise in the handling, growing and characterisation of Influenza virus and, as such, are world leaders in the protocols and facilities required for high level containment (levels 3 & 4) work on viruses. They are therefore expert in the quality assurance methodologies involved with maintaining the sterility required for diagnosis and characterisation of viruses to avoid contamination giving rise to false positive results. As part of the Crick's response to the Coronavirus outbreak, WIC stands ready to provide advice and training in relevant protocols particularly with respect to appropriate training and practice in the safe use of high-level containment facilities. The WIC has already provided a member of staff on secondment to PHE to assist with the initiation of full genome sequence analysis for COVID-19 and will provide any other such assistance as requested.

One of our scientists' research on Coronavirus will aim to look at how the receptor binding domain of the larger surface spike protein interacts with its cell surface receptor ACE. More specifically, to characterise differences in the sequence of the viral protein from bat, pangolin (a potential intermediate species) & human, differences in the sequence of the ACE receptors from the same 3 species, and how they relate to empirical changes in affinity between virus and receptor. These studies are probing the same paradigm we have examined for flu viruses in Coronavirus; namely what are the cause & effect in receptor binding specificity associated with transfer between host species. With flu, bird to man, with Coronavirus from (probably) bat to human.

[redacted]

One of our clinical scientists is researching genetic screens for host factors involved in replication of 2019-nCoV. They will perform CRISPR/Cas9 screens for host factors involved in replication of 2019-nCoV. Either A549 cells expressing both Cas9 and the ACE2 gene (the viral receptor), or alternatively Cas9 expressing HuH7 cells (that express ACE2) will be used. In order to detect viral replication in these cells we will need to develop and validate antibodies to the structural and accessory proteins of 2019-nCoV. Once suitable antibodies have been identified (either generated de novo or using existing antibodies to related SARS proteins), we will then perform pilot studies to identify which antibodies perform best in flow cytometry. Once these initial studies are completed, we will use existing CRISPR libraries to identify host cell factors that are essential for replication of 2019-nCoV. The cells will be infected at a MOI of 3-5 and killed by addition of 1% paraformaldehyde at an appropriate time point to be experimentally determined in the preliminary experiments. They will then be sorted into high and low expressing populations, and next generation sequencing will be performed to identify genes disproportionately targeted in the two populations.

Finally, in association with Google DeepMind, the below text has been released to the general scientific community.

"The recent COVID-19 outbreak has galvanised the scientific community, building on decades of basic research characterising this virus family. Labs at the forefront of the outbreak shared genomes of the virus in open access databases, which enabled researchers to rapidly develop tests for this novel pathogen. Other labs have shared experimentally-determined and computationally-predicted structures of some of the viral proteins, and still others have shared epidemiological data.

[redacted]

We've decided to contribute to the scientific effort using the latest version of our AlphaFold system by releasing structure predictions of several under-studied proteins associated with SARS-CoV-2, the virus that causes COVID-19. We hope these structures may stimulate the scientific community's interrogation of how the virus functions, and serve as a hypothesis generation platform for future experimental work in developing therapeutics.

Knowing a protein's structure provides an important resource for understanding how it functions, but experiments to determine the structure can take months or longer, and some prove intractable. For this reason, researchers have been developing computational methods to predict protein structure from the amino acid sequence. In cases where the structure of a similar protein has already been experimentally determined, algorithms based on "template modelling" are able to provide accurate predictions of the protein structure. AlphaFold, our recently published deep learning system, focuses on predicting protein structure accurately when no structures of similar proteins are available, called "free modelling". Since we have continued to improve these methods since that publication and want to provide the most useful predictions, we are sharing predicted structures for some of the proteins in SARS-CoV-2 generated using our newly-developed methods.

It's important to note that our structure prediction system is still in development and we cannot be certain of the accuracy of the structures we are providing, although we are confident that the system is more accurate than our earlier CASP13 system. We confirmed that our system provided an accurate prediction for the experimentally determined SARS-CoV-2 spike protein structure recently shared in the Protein Data Bank, and this gave us confidence that our model predictions on other proteins may be useful. We recently shared our results with several colleagues at the Francis Crick Institute in the UK, including structural biologists and virologists, who encouraged us to release our structures to the general scientific community now. Our models include per-residue confidence scores to help indicate which parts of the structure are more likely to be correct. We have only provided predictions for proteins which lack suitable templates or are otherwise difficult for template modelling. While these understudied proteins are not the main focus of

[redacted]

current therapeutic efforts, they may add to researchers' understanding of SARS-CoV-2.
Normally we'd wait to publish this work until it had been peer-reviewed for an academic journal. However, given the potential seriousness and time-sensitivity of the situation, we are releasing the predicted structures as we have them now under an open license.
Interested researchers can download the structures here [LINK], and can read more technical details about these predictions in a document included with the data. To emphasise, these are predicted structures which have not been experimentally verified. Work on the system continues for us, and we hope to share more about our methods in due course"

Janet Bonner

From:	Paul Nurse
Sent:	19 March 2020 15:50
To:	WWarr@no10.gov.uk
Cc:	minister.zahawi@beis.gov.uk; gregclarkmp@parliament.uk; minister.solloway@beis.gov.uk; John Browne (L1 Energy)
Subject:	COVID-19

Dear Will

You may know that early last week I contacted Sir Patrick Vallance to offer the institute's support in the work to tackle the COVID-19 pandemic. The Crick can offer research experts with relevant skills as well as scientific technology such as high throughput screening, mass spectrometry and containment facilities.

Since then, we have been considering in more detail what practical help we can offer.

We have facilities and expertise to offer to support the scale-up in diagnostic testing that is now required to combat the virus.

PCR appears to be a significant diagnostic bottleneck. We have a large number of qualified volunteers ready to help; nearly 300 of our staff who are experts in PCR methods have offered their services in the last 24 hours.

The Crick also has significant capacity that could be turned over to testing, including 20 class B fume hoods in Containment Level 3 labs, and a very large number of lab spaces that are ready to be turned into a Containment Level 2 space. We are one of the very few places in the country with CL4 facilities, should those be needed, and we also have science technology facilities ready to support the research into the virus.

We are prepared to quickly turn significant resources over to diagnostic testing, should that be useful. Our Clinical Research Director Peter Ratcliffe is a lead in this initiative.

Crick researchers are also contributing to the international scientific drive to understand the virus, with a number of labs already carrying out research into COVID-19.

This email is to keep you informed of how we are contributing. If there is anything else that you think we could do to help, just let me know.

Best wishes

Paul

Paul Nurse FRS
Director
The Francis Crick Institute
1 Midland Road
London NW1 1AT

Irrelevant & Sensitive
E: paul.nurse@crick.ac.uk
W: www.crick.ac.uk

Janet Bonner

From: Peter Ratcliffe
Sent: 19 March 2020 00:19
To: WHITTY, Christopher (UNIVERSITY COLLEGE LONDON HOSPITALS NHS FOUNDATION TRUST)
Cc: Paul Nurse; Sam Barrell
Subject: RE: Assistance with Covid 19 from the Francis Crick Institute

Dear Chris,

Thank you – we are getting quite a few things together that should hopefully be of use in scale-up of diagnosis as well as biological understanding. We now have good contacts in labs at several of the London Hospital and PHE for resource transfer and support.

Please let us know if/when we can be of use in any other way.

All good wishes. Peter.

From: WHITTY, Christopher (UNIVERSITY COLLEGE LONDON HOSPITALS NHS FOUNDATION TRUST) <c.whitty@nhs.net>
Sent: 18 March 2020 23:49
To: Peter Ratcliffe <peter.ratcliffe@crick.ac.uk>; chris.whitty@dhsc.gov.uk
Cc: Paul Nurse <paul.nurse@crick.ac.uk>
Subject: Re: Assistance with Covid 19 from the Francis Crick Institute

Dear Peter

Many thanks, that is very kind indeed. I am ccing my government address (apologies for the delay, I only check this one frequently when on the wards) and will discuss with the team there.

Best wishes and thanks again

Chris

From: Peter Ratcliffe <peter.ratcliffe@crick.ac.uk>
Sent: 17 March 2020 00:35
To: WHITTY, Christopher (UNIVERSITY COLLEGE LONDON HOSPITALS NHS FOUNDATION TRUST)
Cc: Paul Nurse
Subject: Assistance with Covid 19 from the Francis Crick Institute

Dear Chris,

As you may know I am the Clinical Research Director at the Francis Crick Institute

My purpose in this mail is to determine what immediate practical help the Crick may contribute to control of Covid19 – particularly in assistance with the rapid scale up of testing capacity.

At present I am contacting heads of NHS labs in London and Oxford to determine if they can deploy extra personnel – as the easiest first step.

You might indicate if there is any other immediate step that would be helpful.

We will also scope out methods, reagents, equipment etc.

Should it be helpful I can be reached on 07747468042

All good wishes. Peter (Ratcliffe).

(I am also making contact with PHE)

The Francis Crick Institute Laboratory 1 Midland Road London NW1 1AT
I&S info@crick.ac.uk www.crick.ac.uk

By email: permanent.secretary@dhsc.gov.uk

Sir Chris Wormald KCB
Permanent Secretary
Department of Health
Richmond House
79 Whitehall
LONDON SW1A 2NS

1 April 2020
Our ref: PN/JB

Dear Sir Chris

I am writing to update you on progress being made by the Francis Crick Institute on supporting national testing for COVID-19. On March 19, we informed 10 Downing Street, through the Prime Minister's advisor William Warr that the Crick had decided to turn significant institute resources over to PCR testing, to help support the national COVID-19 testing effort. Our email is attached.

We have made significant progress in this work, in collaboration with UCLH hospital and Health Service Laboratories, and this week we received and successfully processed our initial test samples.

This effort has been pioneered by scientists and clinicians at the Crick who also work in UCLH and other London hospitals.

Over the past few days the Crick testing methods have been verified against national standards.

We are now in a position to scale up, starting with around 100 tests a day later this week, moving to 500 a day by next week. Subsequently, we are aiming for at least 2000 a day. Our objective is to have results within 24 hours, as this will help return healthcare staff rapidly to the front line, which is our initial priority.

In addition to the testing in the building, we also have many expert volunteers on standby to support Public Health England to scale up their testing laboratories.

The Crick is also undertaking research to develop understanding of the biology of the virus and how it affects people.

We will keep you informed of future developments.

Yours sincerely

Personal Data

Paul Nurse FRS
Director

paul.nurse@crick.ac.uk
I&S

Cc: William Warr

Janet Bonner

From: Sam Barrell
Sent: 19 May 2020 17:47
To: Paul Nurse
Subject: Document produced for the call with DHSC yesterday
Attachments: DHSC 18 May 20SR.docx

Dear Paul,

This is the finalised version of the document we produced for the call with DHSC yesterday - I have just sent it to Sam Roberts.

Best wishes

Sam

Sam Barrell
Chief Operating Officer
The Francis Crick Institute
1 Midland Road
London
NW1 1AT

Irrelevant & Sensitive

E: sam.barrell@crick.ac.uk

[redacted]

Opportunities to increase throughput in the testing pipeline:

The experience of the Francis Crick Institute:

PROGRESS SO FAR

- The Crick set-up its testing pipeline, in collaboration with UCLH and HSL, within 3 weeks. Testing began on 1st April.
- It now has capacity to do 2,000 tests a day, increasing to 4,000. Approximately 14,000 tests have now been undertaken so far.
- Testing is fully concordant with HSL and has been inspected for quality assurance.
- It was set up in response to local need.
- We are now testing at multiple hospital sites, including community trusts, mental health trusts and GP testing.
- We have made our SOPs publicly available and have provided information, support and advice to over 40 other sites.
- We have also developed a very exciting bioassay that confirms, in a highly sensitive manner, the presence of antibodies and their protective immune response (neutralising effects).
- A coordinated programme of Covid-19 research projects, involving a number of Crick researchers, has also begun.
- The collaboration with UCLH and the wider sector has been exceptional, largely due to the superb leadership and 'can-do' attitude from key leads in the NCL system.

This experience of contributing to this national effort, when we had no previous diagnostic capability, has allowed us some insights on the problems and issues facing hospitals and other settings when trying to access testing capability; these remarks are, however, given only from our personal experience and perspective.

These issues can be categorised into:

A. Strategic
B. Operational
C. Specific testing issues

A. STRATEGIC ISSUES

Strategic issues/problems acting as limiting factors:

There are a number of strategic problems/issues that are limiting the throughput of the testing pipeline. This can have an impact on:

i. sampling a sufficient number of people;
ii. sampling the correct people;
iii. sampling people at the optimum frequency

There are 3 main logistical stages that can be affected:

1. How we get the samples
2. Testing the samples in the lab
3. Relaying the result

Main issues

Ambition appears to have been limited by early capacity issues - early, and well publicised, issues of lack of testing capacity may have had the result of limiting the ambition of those involved, such as senior managers, medical directors, nursing directors and CEOs, to increase sampling.

There appears to be a nervousness in all parts of the health-care system about both patient and health-care worker (HCW) testing. There are concerns expressed about the national capacity and this appears to result in a corresponding reluctance to encourage too much sampling. There is a concern that lack of overall testing capability will continue to be a problem and so setting up more optimal testing may not be sustainable. This is not helped by supply issues in specific regions.

Equitability - alongside this, some have expressed the importance of 'equitability' - a sense that, whilst capacity might be available in one's own area, it might not be in another and so "it would not be fair" to move to the next level of testing, especially if there could be a need to help neighboring sites with basic capacity. This may result in all moving at the pace of the slowest and underutilisation of overall testing capacity. It would be very useful if exemplar sites are able to move at a faster pace if they can. This would give advance warning of issues, and allow those sites to develop solutions to these issues, before they become a problem for others.

Supply chains - there are also concerns about the specific supply chains that support the testing capacity, e.g. the supply of swabs. Even if there were clearer guidelines about who can be tested, and an ambition to enable this, this can be a limiting factor. Sites are currently having allocations of swabs which are not always large enough to meet optimal testing need. They are also sometimes supplied with swabs which are incompatible with the labs themselves.

Relaying the result - with a diversity of sites, there is a divergence of IT systems in use. Streamlined and rapid relaying of results depends critically on the ability of the local IT requesting platform/reporting platform to converge with the IT system of the testing platform. Establishing the interface so that it works effectively takes time for each new site.

Turnaround times - the results have to be returned in an acceptable timeframe: 24-48 hours. Confidence is lost in local health-care systems regarding the usefulness of testing if there are protracted turnaround times. **[Appendix A]**

National Guidelines

- It would be helpful if the current guidelines could be urgently updated as they are not yet clear enough - this can result in a lack of clarity regarding the right testing approach and it results in brakes being applied to the amount of testing undertaken, rather than acting to optimise it. For example, on the guidelines for HCWs, and for those (permitted) members of the public seeking a test, the advice is that you can only do so if you are on days 1-3 of showing symptoms. We have confirmation from sector leads **[Appendix B]** that this is current NHS guidance and it is also confirmed in the leaflet for NHS staff on accessing testing **[Appendix C]**

- There appear to be no national PHE Guidelines regarding the testing of asymptomatic HCWs. Sam Barrell spoke to Duncan Selbie (CEO PHE) on 20th April with Charlie Swanton and Peter Ratcliffe, and discussed the importance of testing asymptomatic HCWs as there is evidence to indicate that they are almost certainly a source of cross infection. **[Appendices: D,E,F,G,H]**

- Shortly after this, Sam Barrell and Peter Ratcliffe spoke to Sharon Peacock (Director of National Infection Service), who agreed. Sharon Peacock said that guidelines would be produced that weekend and that they would send them to us - we did not receive them and have not seen them released. There has been a subsequent letter about patient testing from Ruth May and Stephen Powiss. **[Appendix I]**

- There is some guidance but we feel it would benefit from further clarity. Simon Stevens issued a letter referring to infection prevention and control guidance **[Appendices J,K]** and there is varying Royal College or specialty guidance **[Appendix L]**. For example, the Royal College of Surgeons has been issued with a set of "principles, recommendations and key considerations" for "the recovery of surgical services during and after Covid-19". On the subject of testing, these say only "Hospitals should know their diagnostic testing availability and develop clear policies for addressing testing requirements and frequency for staff and patients".

- National guidelines would be useful for each unit of health care provision, such as hospitals, community providers, primary care, care homes and other social care settings, so they are better informed. As far as we are aware, for example, there are no specific guidelines for care homes or prisons on accessing testing.

Messaging - in addition to this, it would be useful to have a change in the tone of messaging. To overcome the nervousness described above, there needs to be a much more positive message that we are now in a different situation and can conduct more tests. If possible, these messages need to be conveyed through CEOs, medical and nursing directors and regional coordinators, instilling confidence that testing is available and should be accessed.

B. OPERATIONAL ISSUES

1. Hospitals

Because the Covid landscape is so new and unfamiliar, when a new hospital site wishes to access testing, they encounter many operational issues that they do not know how to navigate, and they therefore require a great deal of support.

We know from the case of West Suffolk Hospital **[Appendix M]**, that sites in this position require a significant amount of 'hand-holding'. We have been able to provide this directly to them but other sites may experience confusion if they don't have excellent local coordinators for advice and support, together with a lab that can provide this level of support. Ideally, there needs to be a single coordinator who can help these new sites and liaise with other key individuals to enable the site to rapidly implement their testing.

A solution for this might be to have a project team working beneath a local coordinator. Our experience is that this team would need to be comprised of highly competent, relatively senior individuals and, ideally, experienced project managers. Such a structure would then provide a single point of contact to the hospital site, greatly facilitating the process.

Each site could be provided with a comprehensive induction pack that explains the process and includes a list of FAQs (we know from our experience that the same questions arise repeatedly).

Possible ways that the Crick might be able to contribute locally:

- If additional project resource were given to the Crick, we would be able to take onboard more sites more rapidly and effectively. Alternatively, this resource could be allocated to the NCL NHS team.
- The Crick could help support the preparation of an induction pack, including FAQs, for new local sites,

2. Care homes

2 options:

- Train community providers, if they are known to be competent, and use these to cascade down to care homes.
- If a care home is not under that umbrella (i.e. they are independent or under GP or council control), then they will require the support of a dedicated coordinator and an induction pack, as described above.
- We understand that care homes are now predominately being managed via the national offer, but think a local solution may be needed depending on turnaround time and access during an outbreak. The amount of support required by care homes to set up testing should not be underestimated.

3. Primary Care/Community hubs

Current problems:

Testing - there needs to be regular testing of patients and HCWs. This is happening now in two pilot sites but has been slow to set up across the sector. There are a number of reasons for this that relate to many of the points already mentioned. It would be helpful if this could be urgently resolved to create safer practice and increased confidence as the NHS re-opens. **[Appendices N,O,P]**

Contractual - Primary care workers need a clear understanding of the contractual arrangements and, in particular, invoicing arrangements, for the tests as concerns that these costs could impact their practice budgets might inhibit access to testing. In NCL, UCLH has underwritten the costs of the tests to move this forward but this is a short-term fix for an issue that needs a longer-term solution.

IT - Primary care workers are working between blue and green zones, thus seeing patients and staff who are not from their own practices in the blue zone. The IT needs to track patients to their originating practices. This could become an increasing issue as primary care begins to open up more of its normal services.

Solution - These IT issues are best solved at local level by those most impacted by them. A pilot project has already been set up, with a project team, to look at this. This should be used to feed back learnings for implementation at national level. It may or may not be that this is eased as GP practices go back to utilising practices as before, without COVID hubs.

C. SPECIFIC TESTING ISSUES

Confidence in capacity- it would be helpful if labs assessed and estimated their testing capacity based on actual capability (including staffing, availability of supplies etc.) and not just machine capacity.

A way to address this is through personal relationships - putting in place a liaison/ relationship manager who regularly speaks in person to a contact in the lab to establish realistic limiting factors, such as problems with reagents. These factors could then be collated to inform future improvements. Our experience is that local conversations within and across sectors are more transparent and realistic and help to address 'equitability' concerns across a sector.

Issues with swabs

Supply Issues - there have been issues with swab supply and professional testers. The Crick has addressed these as follows:

- We are moving as far as possible to self-swabbing (we have good data on the reliability of this).
- We have designed a PCR test system that doesn't have a dependency on a single type of swab but rather allows us to test any type - many labs don't have this capability and that limits their capacity.
- We are moving to dry swabs - this has benefit as there is an unlimited supply of these, at the moment at least.
- We are also using universal containers as they are readily available.

Does it help, or hinder, the national supply issues for all labs to adopt a more diversified approach?

Swab test life - a swab lasts 48 hours from the time the sample is taken. This creates barcode issues for self-swabbing samples, i.e. at what point should the barcode be issued and how does this relate to the time the sample is taken and returned to the lab?

Barcodes - there are issues more generally with barcodes in ensuring the sample is tracked from end to end and the result delivered correctly and to an agreed timeline. It would be helpful to have a senior key point of contact for IT issues in labs with sufficient capacity to take on this role.

Diagnostic test

Several labs, including our own institute, have considered other testing systems, e.g. RT LAMP, that are less complex, needing fewer reagents, fewer process steps and having fewer chain supply chain issues. We have developed contingency testing that includes such alternative approaches. Once in place, however, the demands on these emerging diagnostic test systems is unclear; for example, will the need be to provide different types of test/workflow for different cohorts of HCWs (symptomatic/asymptomatic) or patients (elective/pre-op/symptomatic)? The

rational design of laboratory diagnostic testing with specific workflows and TATs requires a strategy that addresses the purpose/outcome for testing each group.

SUMMARY

The Crick's experience of setting up a testing pipeline, and helping other organisations to do the same, has made us aware of a number of issues which we have outlined above. Recognising, of course, that some of these are more easily tractable than others, we believe that, if these can be addressed, it would greatly facilitate increasing throughput in the testing pipeline.

Dr Sam Barrell
Dr Sonia Gandhi
Professor Charles Swanton

18 May 2020

We would like to thank Charmaine Griffiths, CEO of the British Heart Foundation, for the information provide in Appendices N and O.

We would also like to express our sincere thanks to Laura Churchward, whose invaluable help, advice and support throughout this endeavour has made it possible for the Crick to contribute to the national testing effort.