Science for Covid

This paper gives a high-level overview of science to meet the UK policy objectives, and which areas of science require most urgent research. It is not meant to be a comprehensive list of all science aspects and is focussed on some key priorities. It does not cover the operational activities required to achieve the objectives. Although this paper is focused on the UK, whatever we do must be part of the international effort, as this is a pandemic and will require a coordinated response to manage it globally.

Objective 1: Get numbers below the NHS ICU capacity and reduce *R* to below 1 as soon as possible

This is essential to keep control of the epidemic now and allow us to manage it longer term. It requires the very strong social distancing measures in place to have high compliance and for us to effectively shield the vulnerable. It also requires ICU capacity to be significantly increased as per NHS plan. ICUs should be used for those that need ICU care and not for those who can be managed differently (this will require clear guidance and triage). Most of the science advice for this objective is in place, but there are very key operational requirements such as the need for better protection of health care workers with testing and PPE. There is a need to better understand the individual and societal consequences of the social distancing measures taken.

Objective 2: Keep numbers down and *R* under control, and get a better handle on epidemiology in the medium term

Once the epidemic is slowed, this next phase will require a much better understanding of where new infections are occurring (geographical and social setting), fast isolation of cases, and a better understanding of immunity.

Key measures needed include:

- Testing active infection at population level to enable rapid (within 8h) detection of positives. This will require case testing, contact testing and well-planned sampling to get national coverage and accurate figures on spread.
- Establishing the essential data sources and systems that allow rates and locations to be tracked in real time. These data need to inform agile local planning and responses (e.g. in relation to ICU capacity) and to monitor effects of interventions and relaxing of measures.
- Implementing a system of contact tracing that does not rely only on manual tracing (e.g. phone/App based to detect close contacts quickly)
- Understanding the nature of the virus and its spread (i.e., where it is coming from), and how it changes in the community and within hospitals and other institutions (mass viral sequencing, phylogenetic trees, clinical information, epidemiology). Better understanding of nosocomial and spread in other healthcare settings should be a priority.
- Get serology set up at scale and have a clear proposal/protocols to use it to understand (i) proportion of population who have had disease (ii) how long immunity lasts and who gets it (iii) proportion of disease that is asymptomatic
- Model the effects of releasing measures. Model the overall health effects of continuing measures.

It will be necessary to have a clear testing strategy (owned by PHE), testing available at scale, and excellent informatics. The measures described will be particularly important to allow the restrictions imposed at a population level to be reduced and the effects of doing so monitored. There is an

urgent need to get these testing, data, and monitoring processes working well. Social science should address key questions around both maintaining and removing the various social measures in place.

Objective 3: Get as many people as possible back to work and school safely. This should start with NHS staff, but a plan should be to scale to the population at large with a clear approach to prioritisation (order and process for returning people to work). It will require rapid testing (positive/negative for virus) and ideally serology to determine who has had it and is immune. However, there are critical questions about immunity that need to be addressed in order to determine the feasibility of this approach.

Objective 4: Ensure we have treatments and preventative measures

These should be part of an international effort and linked with global trial objectives. It is important to note that most new medicines and vaccines will fail, and we should prepare to do a lot and accept that a failed trial is part of the process. We should avoid the situation of simply giving out experimental medicines or vaccines for use without collecting data as many will have the potential to do more harm than good and we must collect data for all medicines and interventions used.

Existing medicines and new medicines

Undertake clinical trials of existing medicines. These should include as many patients as possible. The trials can broadly be divided into three groups and should cover both preventative and treatment approaches; (i) antiviral approaches, (ii) interventions to reduce/prevent progression to severe disease, and (iii) treatment of severe disease. This will require coordination of large-scale simple protocols and should accommodate smaller scale trials to test quickly the viability of new options. Ideally every patient in hospital would be in a clinical trial (a single large adaptive protocol that allows addition of new arms could work). This requires the NHS to support and prioritise trials, a rapid regulatory and ethics approval system and operational support in hospitals. A full-time dedicated unit or clinical trials task force should be established to prioritise the trials, speed the route to trials and help with operational support/clear blockages and fast track funding. It is worth noting that everyone will be after the same medicines, so procurement is a key part of this. Trials of oxygen and supportive therapies should be undertaken.

A therapeutics taskforce is needed to pull all elements together.

Vaccines and preventatives

Key actions include:

- Support the international effort to discover new vaccines (through Coalition for Epidemic Preparedness Innovations). Prepare the UK to offer itself as an expert clinical testing site and possible manufacturing site.
- Accelerate the UK programmes in vaccines through UKRI and NIHR funding, regulatory support and fast tracking of clinical trials.
- Scope entire vaccines landscape and make connections with key companies (offering UK science support and facilities as required, including manufacturing)
- Explore and fund alternatives to vaccines and therapeutics that might be faster – including neutralising antibodies, passive immunity, siRNA approaches, live vaccine, convalescent serum
- Build manufacturing capability and capacity for new vaccines (especially mRNA and other newer technology vaccines that might rapidly provide a platform)

To optimise these measures a vaccines task force should be established that links funding, regulatory, trials, scanning, manufacturing and business links (this should build on existing resources).

Ensure that existing vaccines (particularly flu and pneumococcal) are used optimally for next winter to decrease other respiratory infections

Some key science questions that need to be addressed

Many of the requirements to achieve the 4 objectives are operational in nature and clear processes must be put in place to deliver these (e.g., the scale up of testing). There are also some key scientific unknowns that need to be addressed as a priority:

Epidemiology

What is the proportion of infections that are asymptomatic and how do they contribute to transmission (serology and epidemiology)?

What data flows and surveillance data are required to manage the epidemic longer term?

Immunology

Immunology: (i) what is the antibody response, how variable is it, who gets it and how long does it last for, (ii) why do some people progress to the more severe disease and what are the mechanisms (immunology, genomics and clinical science) and (iii) is there evidence of antibody-induced enhancement and, if so, what are the implications?

Why do some people progress to the severe stage and what is the nature of the immune response?

Is there cross protection from infection with other coronaviruses? (epidemiology, serology, immunology)?

Virology

Where else does the virus go in the body and what effects does that have? Is there any evidence of entry into the central nervous system (CNS) as was seen in 1918 flu epidemic? How important is gastrointestinal tract involvement? Is there important myocardial involvement?

Is mutation going to cause a problem with either enhanced pathogenicity or immune escape (genomics, clinical science, immunology)?

How important is viral load in determining the outcome in individuals?

What do we know about susceptibilities in the virus itself? What more do we need to know about survival of the virus in the environment?

Clinical/healthcare management

What can we learn from unusual presentations of severe disease (e.g., in younger patients or otherwise healthy people)? What is the role of comorbidities?

Can genomics help predict outcomes, progression to severe disease and treatment options?

What do we know about pregnancy and vertical transmission risks?

How important is nosocomial and other healthcare acquired infection and how can it best be managed?

What are the clinical markers of severe disease/at risk/ICU patients' need and how can these be used in practice (clinical science, genomics)?

Do healthcare spaces need to be reconfigured to stop spread? What is the role of robotics?

What are the overall health impacts (mental and physical) of the measures imposed to reduce the epidemic in the UK?

Treatments and preventative measures

What do we know about the virus and its susceptibilities? Can we identify targets for drug treatments?

Which existing drugs might have an effect and how should they be used in clinical trials?

Which vaccines can be fast tracked through to clinical testing and how can we make that happen (regulation, science funding, manufacturing, trial design)?

What other treatment options should be explored (e.g., neutralising antibodies, immune serum, siRNA, experimental approaches with live virus) and what funding calls and links to companies will be needed?

Data Science and Engineering

How can data science help inform all aspects of managing the epidemic? How can data flows be rapidly improved?

How can data science help rapid evaluation of clinical information and trial data in real time?

How can engineering help reconfigure clinical spaces to reduce nosocomial spread?

How can robotics help?

How can spatial mapping help contain outbreaks and manage the longer-term control of the epidemic?

Behavioural science

How can we promote high uptake of the flu vaccine among those over 70 and in at-risk groups for next flu season?

How can we best help people adhere to, and monitor adherence to, advice about shielding, household isolation and social distancing, considering regional and demographic variation?

How should we monitor and minimise any harm associated with these behaviours (psychological, physical, social, educational, economic)?

Do we understand the unique challenges that key workers and others involved in the response will experience, and how to mitigate the impact of these?

How can co-operative and altruistic behaviours among the public be harnessed to ensure that help is channelled to those who need it most in ways that interface with, compliment and do not compromise civil contingency responders?

Can we understand, predict, prevent and mitigate adverse public reactions to civil contingency messages, responses and measures, including stockpiling, social tension and conflict with the police?

What is the best way to communicate the Government's plan and all it entails to members of the public in order to build trust and promote behaviour change?

What will be the short-, medium- and long-term impact of the wider social changes required on, for example, crime, the legal system and education?

How can social distancing and social cohesion be maintained if the distancing measures need to be extended?

Operationalisation: meeting these research needs

The scaling and implementation of the requirements listed under objective 2 is particularly important and urgent and there needs to be clear ownership and metrics for each. It will be essential that these operational groups define which plans most require science input. The science needs to determine how best to use these resources to address the objectives. In addition, effective operationalisation of other objectives requires:

1. A vaccines task force
2. A clinical trials task force
3. A clear plan for funding critical science areas identified and ensuring that the outputs are timely and relevant to the current outbreak.
4. Funder forum to agree rapid funding of key areas that come from areas above.

Cross government operational group for testing and diagnostics is already established within DHSC.