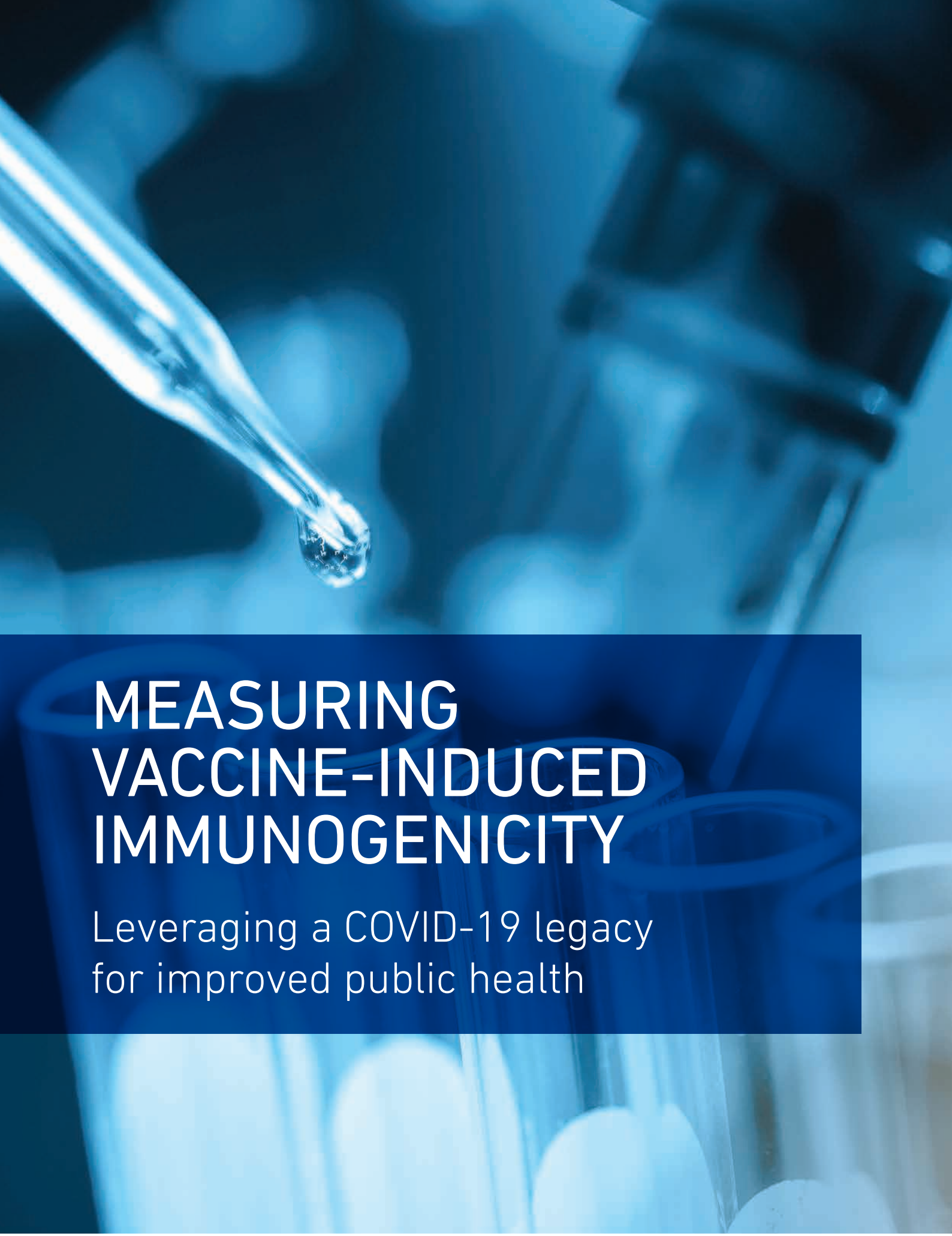

MEASURING VACCINE-INDUCED IMMUNOGENICITY

Leveraging a COVID-19 legacy for improved public health

MSD

MSD fully funded and attended the roundtable meeting. This report was fully funded by MSD and was fact checked for accuracy and balance only.

British Society for immunology

CONTENTS

ABOUT THE BRITISH SOCIETY FOR IMMUNOLOGY

The British Society for Immunology is the leading UK charity organisation representing scientists and clinicians who study the immune system in humans or animals. As a membership organisation, we act as a focus hub for the immunology community, supporting and empowering immunologists working in academia, industry and clinical settings to drive forward scientific discovery and application together. We also aim to harness the knowledge generated by our membership and reach out to the wider world – policymakers, public, the media – to ensure that society is aware of and can benefit from the health benefits that immunology research can deliver.

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EXECUTIVE SUMMARY

The rapid development and deployment of vaccines during the COVID-19 pandemic has enabled unprecedented scrutiny of the immune response following vaccination, across the breadth and diversity of the global population. This has begun to permit us a better understanding of the components of immunity that confer short- and longer-term protection from infection and severe disease outcomes. There have also been parallel advances in the development of novel research and routine clinical diagnostic devices to measure elements of this immune response.

Emerging from the COVID-19 pandemic presents an exceptional opportunity to drive forward our general understanding of the immune system and how vaccines work. Immunogenicity is the ability for a foreign substance, in this case a vaccine, to provoke an immune response. Discovering exactly how vaccines provoke protective immune responses can lead to a clear understanding of how they protect against different stages of infection and disease; this may lead to the development of surrogate markers of vaccine effectiveness that will be helpful in future vaccine development. Demonstrating immunogenicity is also important for regulatory approval and progression through trial phases.

To utilise immunogenicity as a measure of vaccine effectiveness, it is essential to agree on and be able to accurately and reliably measure the relevant components of the immune response. To enable a rapid response to future pandemics, a clear process for the development of standardised, high-quality assays for the relevant components of the immune response is essential.

To facilitate vaccine development, regulators should work with industry to clarify the additional laboratory evidence needed to bring a vaccine to market. We propose the creation of an agreed 'toolbox' of companion diagnostics to support comparative studies of vaccine effectiveness. This should be approved by regulators, working with academia and industry, to identify which of these other diagnostics would be most useful for future vaccine licensing and ensure standardised performance of the agreed diagnostics.

Regulators also have the opportunity to consider positive additional benefits of vaccines in licensing, such as prevention of transmission. This could help unlock vaccines that exploit mucosal immunity or other vaccine technologies and encourage investment in this field. Companion diagnostics tailored to the mucosal space will require developing and standardising.

As the COVID-19 pandemic illustrated, the risks to people who are immunocompromised can be much greater than for the general population. Additional research is urgently needed into how vulnerable populations can be protected, recognising that such studies are difficult to perform in the face of low case numbers and disease heterogeneity. Again, reliable immunological surrogates are essential.

The pandemic has seen the creation of innovative models of working, including research consortia such as the UK Coronavirus Immunology Consortium (UK-CIC) and the Government's Vaccine Taskforce. A UK vaccinology network based on pandemic models of working, with continued funding and strong leadership, should be established to address key questions and challenges in immunogenicity. Such a network would improve coordination within the UK's immunological community. Key deliverables for the network would include mapping of the UK's academic innovation and capacity, identifying gaps and developing a log of biobanked samples stored in UK laboratories.

We are at an exceptional juncture to learn lessons from the COVID-19 pandemic, to reform regulatory decision-making and clinical trial design. We should now work to make vaccine development cheaper and easier to conduct. Point of care and home testing for immunogenicity should be continued as a legacy of COVID-19 and should be used in post-marketing authorisation studies to bridge the divide between immunogenicity studies and real-world data.

We must build on the legacy from COVID-19 in terms of science, research infrastructure and innovative working, which will confer long-term benefits to patients and public health. The key to securing this legacy will be the adoption of the recommendations that we make to support future vaccine development and implementation by breaking down barriers between academia, industry, clinical medicine, regulators, and government.

The scientific progress made as a result of the COVID-19 pandemic can be harnessed to benefit future generations in the form of longer lasting and even more effective vaccines. To do this, we must cement the legacy from COVID-19 for immunology and science. By working together, the UK can continue to be world leading in this area of clinical science.

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RECOMMENDATIONS

LESSONS FROM MEASURING VACCINE-INDUCED IMMUNOGENICITY IN COVID-19

- Immunogenicity research should be recognised as a central part of the UK's pandemic preparedness plans.

VACCINES REGULATION AND MONITORING

- Regulators should clarify the laboratory evidence needed to bring a vaccine to market and what industry can do to collect these data.
- Decision-makers should clarify what post-marketing surveillance immunogenicity studies are required to inform the need for booster vaccines and prioritisation of at risk groups.
- An agreed toolbox of companion diagnostics should be defined to support vaccine development, licensing and adoption.

VALIDATION AND STANDARDISATION OF ASSAYS

- There should be a clear process for the development and monitoring of standardised, high-quality assays for immunogenicity that can be used as surrogates of vaccine protection.
- Guidance should be provided to the scientific community on standardisation requirements for assays and the steps required for developing international reference standard reagents.

MUCOSAL IMMUNITY

- We must prioritise research into the understanding and accurate measurement of mucosal immunity.
- We need to develop methods for predicting how well a vaccine will confer sterilising mucosal immunity and prevent onward transmission of infection.
- Regulators must clarify the regulatory requirements for vaccines designed to reduce transmission to stimulate research by industry into this area.

PEOPLE WITH WEAKENED IMMUNE SYSTEMS

- We are urgently calling for more research on which assays correlate with protection for people who are immunocompromised.
- People who are immunocompromised should be included in licensing and post-marketing surveillance programmes for vaccines.
- Vaccine development should consider achieving successful immunogenicity in people who are immunocompromised.

POINT OF CARE AND AT HOME TESTING

- A legacy of COVID-19 should be ensured through continued point of care and at home testing for immunogenicity and recognise how this can be of use to post-marketing authorisation studies mandated by the MHRA to bridge the divide between immunogenicity studies and real-world data.
- We must ensure that there is proper government and industry support for the UK diagnostics sector through boosting capacity, inward investment and skills.

LEADERSHIP AND CO-ORDINATION

- A UK vaccinology network based on pandemic models of working, with continued funding and strong leadership, should be established to devise and address key questions and challenges in immunogenicity.
- We must ensure that routes for knowledge transfer in a pandemic situation are clearly delineated with a focus on knowledge generation.
- Coordination within the UK's antibody and vaccine development research community should be improved, and this should include mapping the UK's academic innovation and capacity, as well as developing a virtual biobank of samples stored in UK laboratories.
- There should be template agreements drawn up in advance between academic research institutions, government and industry on compensation for components used in assay development and for intellectual property arrangements.
- There should be clear and transparent advice ahead of time from the Health and Safety Executive that allows UK researchers to provide their expertise in the event of another pandemic. This should be combined with establishment of a standardised and centralised portal for material transfer agreements.

INTRODUCTION

Immunogenicity is the ability of a foreign substance (in the context of this report, a vaccine) to provoke a response from the immune system. The importance of measuring immunogenicity lies in its application to vaccine development and licensure, as well as post-marketing immune surveillance; this was never more acutely apparent than during the COVID-19 pandemic. Immunogenicity is key in understanding the immune response of different sections of the population, how vaccines behave in terms of sterilising and protective immunity, and in determining the longevity of the immune response.

This report examines the value of further study of immunogenicity to support decision-making around vaccine development, adoption and implementation. The objective is to support policy makers, researchers, industry, regulators and clinicians on how immunogenicity can be better measured to improve the evaluation of the effectiveness and value of vaccines to the ultimate benefit of the NHS and the public.

The report was informed by roundtable discussions with experts from academia, industry, government, regulators, and clinical medicine (see appendix 1). They brought a range of experiences of working in different areas before and during the COVID-19 pandemic, and recommended actions and interventions that could unlock measuring immunogenicity as a key tool to improving the vaccine development pipeline.

Immunogenicity is key in understanding the immune response of different sections of the population, how vaccines behave in terms of sterilising and protective immunity, and in determining the longevity of the immune response.

The issues discussed included:

- New insights and tools to measure components of the immune system.
- How such tools can assist the industrial development of assays by identifying the most promising leads with respect to measuring meaningful immunogenicity following vaccination.
- The practicalities of measuring immunogenicity in a clinical setting, and how clinical trial leads can build an evidence base that can support policy choices and empower regulatory decisions on vaccines.
- How the information needs of regulatory bodies can inform the design of clinical trials, and the inclusion of innovative measurements of immunogenicity throughout the vaccine development pipeline can be encouraged.

The learning points that were identified can be applied to a range of pathogens and vaccine platforms to cement a legacy from COVID-19 in vaccine development.

BACKGROUND ON MEASURING VACCINE-INDUCED IMMUNOGENICITY IN COVID-19

The UK is the world leader in immunology research, topping the G7 for our level of impact and influence. Despite being home to just 9% of the G7 population, the UK produces 14% of its immunity research publications, has the second most cited research by the World Health Organization and in clinical trials and patent applications, and the most cited research by the UK Government. Our immunologists already make an outsized contribution to their field of study, not least demonstrated during the pandemic, but with the right support they can exceed their current achievements and meet their real potential.

Building on this foundation of excellence, the UK's pandemic response was necessarily rapid. We drew on our knowledge of other respiratory pathogens such as respiratory syncytial virus (RSV), and Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) outbreaks, to research the immune response to SARS-CoV-2 and further the development of assays in a short period of time. As a legacy to this work, we have an enormous opportunity to enhance the UK's future pandemic preparedness by using advances gained through COVID-19 research to bolster our knowledge of other respiratory viruses with pandemic potential.

Different pathways and approaches to measuring immunogenicity were explored, using assays that included:

- Antibody detection and quantification
- Live virus antibody neutralisation
- Pseudovirus antibody neutralisation
- T cell ELISpot

At the beginning of the pandemic, it was not clear which of these assays could be used to accurately reflect immunogenicity and correlates of protection against SARS-CoV-2. Hence all these assays have been utilized to present evidence for licensing in various combinations.

While antibody binding assays were used to quantify antibody levels, there was a recognition that live virus assays would be needed in order to establish functionality. However, these assays were difficult to perform at scale, and so pseudovirus assays were also carried out as an alternative. All three of these approaches were developed in parallel but it took longer to scale up the live neutralisation assay and also to validate this assay to a level of good practice. The timeframe taken for scaling and validation should be addressed for any future instances of emerging novel viruses. It is recognised that there are complexities with immunogenicity and its measurement, and its nature is not constant or static for every pathogen.

Throughout the course of the COVID-19 pandemic, the importance, accuracy, and usefulness of the different assays has been clarified. For COVID-19, in the majority of people, there is a strong correlation between the amount of antibody that a person has – the antibody magnitude – and the neutralisation activity of the antibody (although exceptions exist in some people who are immunosuppressed). Furthermore, in most of the systems that have been examined, the relative antibody binding against the original Wuhan variant correlates well with neutralisation of Omicron SARS-CoV-2 (though it should be noted that antibody binding to the Omicron spike in ELISA does not correlate to the Omicron neutralisation).

Therefore, due to the advent of multiple SARS-CoV-2 variants, regulators will now place a greater reliance on neutralisation data rather than ELISA data; a functional antibody readout is required, rather than a total antibody readout. Since infection studies are now much more difficult to design and recruit to as there are no longer naïve populations, neutralisation function is increasingly serving as a surrogate for the full immune response to the vaccine. Another effect of there no longer being naïve populations is that there are no new approvals happening for primary indications, only booster vaccines. Acceptance of agreed immunogenicity assays facilitates the licensing of vaccines designed using the same technology using non inferiority of the immune response as the primary endpoint e.g., a new mRNA vaccine might be tested in comparison to the Pfizer-BioNTech vaccine.

RECOMMENDATION

- Immunogenicity research should be recognised as a central part of the UK's pandemic preparedness plans.

VACCINES REGULATION AND MONITORING

Most commonly, measures of a vaccine's efficacy (the endpoints) are determined through randomised controlled trials (RCTs). For policy makers and regulators, blinded, randomised, placebo-controlled trials will likely remain the gold standard and will continue to be requested by regulators unless they are not feasible.

Short term clinical studies, however, do not always provide all the information required by decision makers when examining whether to adopt a vaccine into a national screening programme and data is often inferred. During the COVID-19 pandemic, the approved vaccines were shown to provide short term, high efficacy against symptomatic infection.

Neutralisation assays provide data on the ability of antibodies to bind to the surface of a virus to prevent viral entry. The options are to perform live virus neutralisation or use pseudo particles. Live virus neutralisation assays have to be performed in high bio-security environments, which limits the number of samples that can be processed and the laboratories where this can be undertaken. In addition, during the pandemic, there was no inter-laboratory standardisation and historically, functional assays do exhibit some variation. Pseudo particles offer a safer alternative but first have to be standardised to assess performance against live virus neutralisation assays before being adopted. The advantage of a functional test is that it provides, albeit *in vitro*, some idea of antibody function and so is often preferred by regulators.

Immunogenicity studies can be used to inform post-marketing surveillance studies and allow continued monitoring of different demographics.

An alternative assay approach is to assess antibody binding, which measures the amount of antibody present against the pathogen but not its function. There were significant attempts worldwide to standardise and compare the performance of these assays as they were used to determine both sero-prevalence and vaccine immunogenicity. During the COVID-19 pandemic, the Office for National Statistics (ONS) undertook antibody binding studies on a sample of the population and extrapolated the results to inform prioritisation for vaccination and the frequency/intervals between booster doses. Antibody binding assays are easier to perform and can be adapted for high throughput processing or point of care testing and are widely used to assess immunogenicity to many pathogens. For SARS-CoV-2, antibody binding assays correlated closely with live virus neutralisation assays with the original Wuhan strain. However, divergence occurred with the evolution of variants of concern.

There is precedent from other vaccines for regulators and policy makers to use immunoassay data as correlates or surrogates of protection. For the pneumococcal vaccine, which is used in adults and infant populations, a functional assay is used for licensing in adults, and a binding IgG assay for children. The meningococcal vaccines were moved forward based on immunogenicity alone. There are examples of vaccines where it is known that T cells are necessary to protect against disease, such as with shingles vaccines (e.g. Shingrix), yet the assays that are used to help with regulatory submissions are antibody and serology assays.

For COVID-19, regulators made an assumption that neutralisation is a surrogate for the immune response for vaccines using the same platform and, if a close link between neutralisation and antibody binding can be established, then immunoassays can be used to establish non-inferiority in immunogenicity. An example of this approach of licensure based on comparative immunogenicity was the licensing of the Valneva COVID-19 vaccine.

T cell antigen stimulation assays were also performed in many studies and, whilst they provided useful information on the immune response, it is still not clear how these should be used for licensing of vaccines. A number of correlates of protection have been proposed using different assays, but none have been widely adopted.

LOOKING FORWARD

Initial licensing studies should ensure that a range of immunogenicity assays are included alongside clinical outcome measures. Establishing surrogate markers of protection will help to facilitate future vaccine licensing trials with support from regulators to establish whether a surrogate would be accepted. This enables smaller, cheaper, more rapid trials to bring new vaccines to market.

Initial licensing studies should ensure that a range of immunogenicity assays are included alongside clinical outcome measures.

Immunogenicity studies can be used to inform post-marketing surveillance studies and allow continued monitoring of different demographics. Pre-determining which immunogenicity diagnostics should be deployed in which population groups, would facilitate regulators and government in determining which cohorts would most benefit from primary vaccination and additional vaccine doses by providing an insight into longevity of the immune response and ability to respond to vaccination.

RECOMMENDATIONS

- Regulators should clarify the laboratory evidence needed to bring a vaccine to market and what industry can do to collect these data.
- Decision makers should clarify what post-marketing surveillance immunogenicity studies are required to inform the need for booster vaccines and prioritisation of at risk groups.
- An agreed toolbox of companion diagnostics should be defined to support vaccine development, licensing, and adoption.

VALIDATION AND STANDARDISATION OF ASSAYS

When developing an approach to the validation of an assay, there needs to be clarity on whether the assay is for clinical use or for supporting clinical trials and vaccine development in the research setting. There are differences between ISO and Good Clinical Practice (GCP) requirements and, in addition to ICH guidelines, there are specific requirements from different regulators, i.e., the MHRA, EMA and FDA, for the validation of an assay. Furthermore, in addition to the assay itself, the equipment or platform that it uses needs to be validated and technology needs to be accessible to pathology services if it is to be used for clinical diagnostics.

Reference standards are essential for assay validation. Firstly, these reagents have to be developed and then there are many steps until these can be classified as international reference standards. This is a key step in enabling test results to be reproducible and accurate across laboratories, an essential requirement for producing regulatory data. During the COVID-19 pandemic, the NIBSC produced a portfolio of reference and research reagents to support areas of diagnostics, vaccine development and research on COVID-19 and SARS-CoV-2 to standardise antibody binding assays.

The approach by the NIBSC was informed by previous experience with other virus outbreaks including Zika, Ebola and MERS. They began by issuing an early, interim set of research reagent materials in March 2020. End-user feedback provided data on how the materials are being used and how effective they were, allowing refinement and calibration. By December 2020, these became WHO international standards for antibodies and nucleic acid assays. In between, the NIBSC also produced sets of samples for verification and validation panels, which enabled further analysis of assays' limits of detection, specificity and other metrics of performance.

These standards, however, took longer to develop than the time it took to develop the first COVID-19 vaccine (Pfizer-BioNTech), including approval. While access to live virus samples was straightforward, convalescent sera (which is required for antibody binding assays) was more difficult to obtain, particularly early in the pandemic. The quality of the spike protein is also important; at the beginning of the pandemic, multiple companies produced spike protein, but using different technologies. This meant that stabilities were not necessarily the same and this led to different qualities, which affected the performance of assays. The timing of assay development, and supportive validation processes and material, is essential to run in parallel with the vaccine development process to support clinical trials and research.

The rapid evolution of SARS-CoV-2 resulted in new variants of concern, which the original assays were not optimised for. As new variants emerged, ongoing evolution of assays was required to detect differences in immunogenicity. The original NIBSC standard was not suitable to standardise these assays, highlighting the need for ongoing adaption of reference material.

LOOKING FORWARD

In the beginning stages of an assay's development, there may be a risk in standardising too early, and in doing so reducing opportunities for experimentation and learning. Once the decision is made to move forward, however, there needs to be a clear process for developing standardised, high-quality assays for immunogenicity that can be used as surrogates of vaccine protection.

The transition of an assay from a research laboratory to a clinical laboratory setting can be challenging: the requirements for assay development differ from those for accreditation, where it would be used by multiple laboratories. The clinical quality requirements are slightly different, and the verification and validation depend on the purpose. UKAS produced a set of standards for the assays to meet, while HSE, UKHSA and others produced verification and validation criteria and guidance. However, some smaller laboratories or clusters of laboratories can find it difficult to use these criteria.

The further development of an assay can lead to three different but overlapping activities that require different workstreams and efforts:

There needs to be a clear process for developing standardised, high-quality assays for immunogenicity that can be used as surrogates of vaccine protection.

1. **Clinical accreditation** – this requires a specific approach and, as an assay moves along in its clinical development, at each step it requires a more robust package of validation.
2. **Use for regulatory purposes.**
3. **Developing reference standards** so that different assays around the world can produce the same results with the same materials.

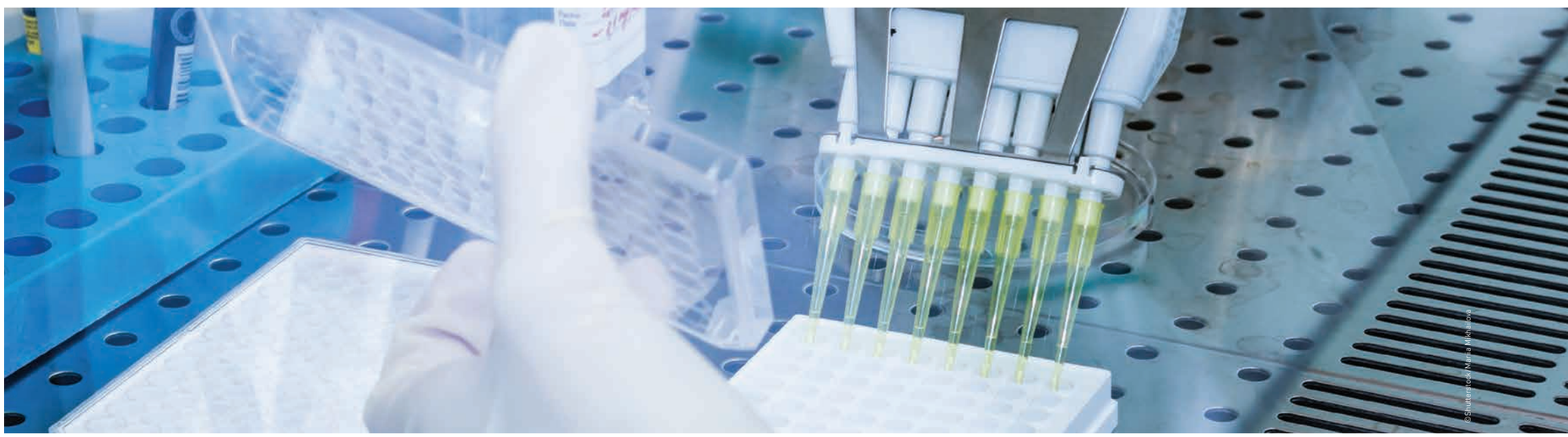
Because these activities overlap, work in one area can support development in another. So, if an assay is being developed for diagnostic use, it may have potential uses in industry and for regulatory requirements.

RECOMMENDATIONS

- There should be a clear process for the development and monitoring of standardised, high quality assays for immunogenicity that can be used as surrogates of vaccine protection.
- Guidance should be provided to the scientific community on standardisation requirements for assays and the steps required for developing international reference standard reagents.

ACRONYM SUMMARY

EMA	European Medicines Agency, EU
FDA	Food and Drug Administration, USA
GCP	Good Clinical Practice
HSE	Health and Safety Executive
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISO	International Organization for Standardization
MHRA	Medicines and Healthcare products Regulatory Agency, UK
NIBSC	National Institute for Biological Standards and Control, UK
UKAS	United Kingdom Accreditation Service
UKHSA	UK Health Security Agency
WHO	World Health Organization



MUCOSAL IMMUNITY

Vaccines can impact the transmission of an infection in different ways. Inducing sterilising immunity, such as occurs with the measles vaccine, means that an individual is unable to get the infection if they subsequently encounter the virus and cannot pass it on to others.

COVID-19 vaccines have greatly enhanced protective immunity, i.e. protection against severe illness if you catch the virus. However, it has had less of an impact on sterilising immunity, and infection rates themselves remain high. The reasons why sterilising immunity has not been achieved for COVID-19 vaccines have not been fully explained. One prominent theory is that intra-muscularly delivered vaccines provide limited mucosal immunity at the site of viral entry for SARS-CoV-2 (the moist mucosal linings of the nose and respiratory track).

Protective immunity	Immunity conferred by an immune response which gives protection against an infectious disease. It will not prevent person to person transmission
Sterilising immunity	Immunity in which the immune system is able to prevent the replication of a pathogen within the body. It will prevent person to person transmission

Vaccines delivered directly to the mucosal space are a future alternative that may enhance local mucosal immunity. Nasal flu vaccines that take this latter approach have advantages in how they can be deployed and administered.

There are significant gaps in our knowledge of mucosal immunity. The assays required to study mucosal immunity are not easy to develop and are not in routine use. An additional challenge is that mucosal samples need rapid processing. Functional antibodies are difficult to measure in mucosal samples; instead, binding antibodies are likely to be the optimum approach, in particular to study whether the secretion of IgA is predictive of the ability of a vaccine to make a person less infective to other people. During the COVID-19 pandemic, neutralisation assays were prioritised to determine antibody functionality. This meant that some assays, including mucosal assays and other antibody functional assays such as complement, were relatively neglected and research into this mucosal space delayed.

The development of vaccines to reduce transmission, rather than prevent infection in an individual, is less straightforward, as regulators use a drug model for vaccine licensure looking for direct effects. They are interested in the individual who received the vaccine – whether they had a safety signal, and whether they were protected or had immune responses. Indirect effects, such as reduction in virus transmission at a population level, are not usually taken into account and are not needed for licensure; vaccine manufacturers therefore often do not study these effects during vaccine development, and they are left to be investigated following licensure. This can mean that a vaccine that cuts transmission might be extremely cost beneficial but may never be licensed if its direct benefits are less compelling. There are precedents, however. The rollout of the meningitis ACWY vaccine is based on indirect effects – it is being given to teenagers in the UK, who are significant carriers and transmitters of the disease, even though much of the more severe disease is seen in infants.

CDC/Douglas Jordan MA

LOOKING FORWARD

Understanding mucosal immunity is particularly important for the development of other vaccines against respiratory illnesses, including influenza, respiratory syncytial virus (RSV), and pneumococcus.

This area, therefore, presents significant opportunities for immunologists, not only to understand the mucosal immune space, but also to develop assays that can predict how well a vaccine can reduce transmission. A research focus is required to unpick the ways in which the systemic and nasal immune environments are separate, and where they are a continuum. A suite of assays can then be developed that can be used to select the vaccines that are most likely to be successful in clinical development, whether through direct or indirect effects, and to show how impactful a vaccine will be.

Vaccines delivered directly to the mucosal space are a future alternative that may enhance local mucosal immunity.

To encourage investment in this area, the regulatory requirements need to be clarified and updated. Industry recognises the benefits of and opportunities for a vaccine's population level effects, and wish to develop vaccines that exploit this, and to generate the evidence that will assist their implementation and widespread use. But taking such vaccines forward is difficult without top-line indications for the prevention of transmission from the regulators. If the regulators elaborate such indicators, companies may then pursue more vaccines that prevent transmission, as it will provide a new avenue for investment and development.

RECOMMENDATIONS

- We must prioritise research into the understanding and accurate measurement of mucosal immunity.
- We need to develop methods for predicting how well a vaccine will confer sterilising mucosal immunity and prevent onward transmission of infection.
- Regulators must clarify the regulatory requirements for vaccines designed to reduce transmission to stimulate research by industry into this area.

PEOPLE WITH WEAKENED IMMUNE SYSTEMS

Studies of clinical protection in people who are immunosuppressed/immunocompromised can be complex as the numbers of patients with each individual condition can be small. Although there are approximately half a million people with weakened immune systems in the UK, they are a heterogeneous group. The causes of their immune deficiencies can vary markedly, and so there can be relatively few patients in each individual group. Similarly, these patients are rarely included in vaccine licensing studies.

Studies of the effectiveness of vaccines in patients who are immunosuppressed and immunocompromised are critical as they are a high-risk population.

THE OCTAVE TRIAL

The OCTAVE trial has studied post-SARS-CoV-2 vaccination in patients who are immunocompromised. By August 2021, 2,577 participants had been enrolled in the study across 20 UK sites.

Initial data from the trial found that a significant proportion of clinically at-risk patients with specific immunocompromised or immunosuppressed conditions mounted a low (40%) or undetectable (11%) immune response after two doses of the same SARS-CoV-2 vaccine, the standard vaccine dose schedule at the time.

The proportion of patients with lower levels of antibody reactivity was dependant on the disease cohort. Lower response levels were seen from:

- 87% of those with Rituximab-treated ANCA-associated vasculitis
- 51% of those with inflammatory arthritis
- 29% of those on haemodialysis
- 42% of those on haemodialysis receiving immunosuppressive therapy
- 36% of those with hepatic disease
- 10% of those with solid cancer
- 33% of those with haematological malignancies
- 17% of patients who had undergone haemopoietic stem cell transplant

Source: NIHR, OCTAVE trial: Initial data on vaccine responses in patients with impaired immune systems, 24 August 2021

At present, it is not clear what the correlates of protection are for such patients, i.e. how much antibody is required or how many T cells are needed to protect an individual against contracting and falling very sick with SARS-CoV-2. Generally, where people have lower antibody responses, they will have a more limited neutralisation function, i.e. they will not be able to mount a protective immune response against the virus. It may be more complex in patients with T cell abnormalities and common variable immunodeficiency (CVID), as the quality of the antibodies may be impaired. In such cases, the correlation between antibody binding and neutralisation may be lost.

Large-scale studies that bring together multiple centres – such as the OCTAVE trial for COVID-19 vaccines (see box) – are required to generate study participant numbers to a point where such studies are helpful in determining vaccine immunogenicity in groups where responses may be impaired. It is not certain whether simply administering further doses of vaccine can overcome this reduced immunogenicity.

LOOKING FORWARD

Studies of the effectiveness of vaccines in patients who are immunosuppressed and immunocompromised are critical as they are a high-risk population. It is essential for clinicians to have, for their most vulnerable patients, the additional information needed for clinical decision-making, i.e. dose-regimen data.

RECOMMENDATIONS

- We are urgently calling for more research on which assays correlate with protection for people who are immunocompromised.
- People who are immunocompromised should be included in licensing and post-marketing surveillance programmes for vaccines.
- Vaccine development should consider achieving successful immunogenicity in people who are immunocompromised.

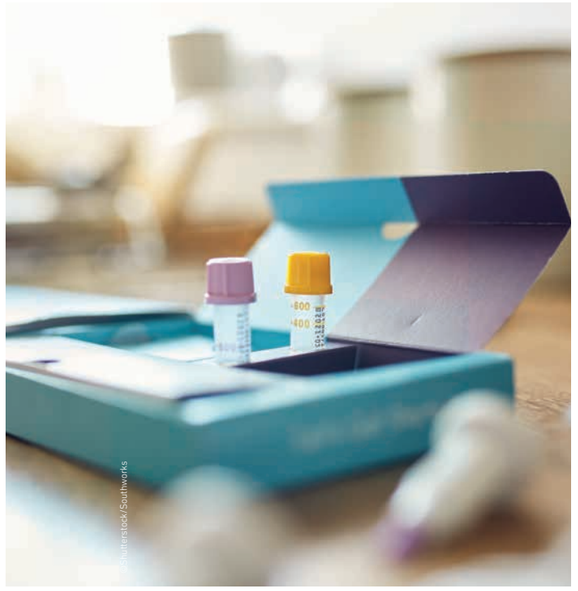
POINT OF CARE AND AT HOME TESTING

The COVID-19 pandemic has seen a transformation in the use of point of care and at home testing, and in its acceptance by the UK population. Remote sampling, dried blood spots, lateral flow tests and point of care T cell assays, amongst others, have all contributed to the UK's pandemic response. They have advantages not only in scale and reach, but also in cost and patient safety; home testing has been used to help monitor immunosuppressed leukaemia patients, for example.

There is a question as to whether, in the post-COVID world, people will continue to use home-based testing or sampling as much as might be expected. It is, probably, an inexorable change, although the pace may be difficult to predict. The possibility of at home testing also opens up a wealth for opportunity for the research community.

LOOKING FORWARD

For immunogenicity studies, the potential for people to take a test at home, and for this test to then be analysed centrally, is transformational. As phlebotomists are not required, such assays make trials much easier and cheaper. For example, after each annual flu vaccine rollout, one could run a large monitoring study to send out hundreds or thousands of finger prick tests to better understand the immune response.



For immunogenicity studies, the potential for people to take a test at home, and for this test to then be analysed centrally, is transformational.

There also are opportunities for post-marketing authorisation studies that are mandated by the MHRA to use point of care or at home data, which would help bridge the gap between immunogenicity studies and real-world efficacy. Additionally, if the Joint Committee on Vaccination and Immunisation (JCVI) needs to re-examine vaccine schedules, point of care or at home studies could provide data on whether the schedules are working or should be changed.

The UK's diagnostics capability is already strong; each year, the NHS performs over a billion diagnostic tests and the UK exports well over £1 billion in *in vitro* diagnostics. But the COVID-19 pandemic has underlined the need for us to stop treating diagnostics as simply a service industry for healthcare. Instead, we need to recognise that diagnostics has the potential to improve public health far beyond a clinical setting and is actually integral to making research into topics such as immunogenicity much cheaper and more accessible through opening up remote testing. The Government and industry need to exploit this opportunity highlighted by the pandemic to boost capacity, skills, and inward investment into the diagnostics sector, especially in supporting SMEs. This move has the potential not only to bring significant benefits for patient care and public health, but also to cement the UK's place at the forefront of this expanding and innovative sector.

RECOMMENDATIONS

- A legacy of COVID-19 should be ensured through continued point of care and at home testing for immunogenicity and recognise how this can be of use to post-marketing authorisation studies mandated by the MHRA to bridge the divide between immunogenicity studies and real-world data.
- We must ensure that there is proper government and industry support for the UK diagnostics sector through boosting capacity, inward investment and skills.

LEADERSHIP AND CO-ORDINATION

The UK has been at the cutting edge of science throughout modern history, and research into immunology and vaccination is no exception. From understanding the immune system to tracking infections, developing new vaccines to life-saving clinical trials, our researchers have made, and continue to make, a major contribution to progress in public health at home and abroad. We have enjoyed a flourishing research ecosystem that has seen strong links built between partners in academia, industry, and government. This excellence is particularly acute within immunology, where the UK ranks first amongst the G7 nations for the quality of our research.

CO-ORDINATION AND COLLABORATION

This collaboration between academia, industry, and government was key during the early stages of pandemic and was one of the reasons the UK was able to enact such an agile but robust response from our research community. For example, when the trials of the AstraZeneca COVID-19 vaccine started, the team set up an in-house validated ELISA assay. To increase scale, they worked closely with MSD to set up their platform; this was facilitated through PPD, a provider of clinical research services, which ran the assays. They also worked with the UKHSA team, based at Porton Down, to set up live virus neutralisation assays, and with the US company Monogram for pseudo neutralisation assays.

To respond rapidly to future pandemics, there is a need to map the UK's academic innovation and capacity – who is working on what assays with which engineers or computer scientists. An understanding of what each stakeholder is doing and where the expertise lies will mean that, for example, if an assay is developed in academic laboratory A, it can then go to laboratory B to be fully validated, and then to laboratory C to be fully validated with standards accordant to good clinical practice (GCP). There should be laboratories in place with expertise along the whole diagnostic pathway from assay development all the way along to regulatory approval.

This will also require agreements in principle, in advance, between academic research institutions, government, and industry on compensation for development of different components used in these assays and for intellectual property (IP) arrangements; ; this was a hinderance that slowed down this aspect of the UK's COVID-19 pandemic response.

Alongside this, research and development would be greatly assisted by a catalogue of which UK laboratories have what samples stored. For example, a number of laboratories have paediatric and/or adult saliva samples, linked to clinical data, stored and available for research studies. These samples do not need to be centralised; instead, a 'virtual biobank' would be effective, with all the samples catalogued and clarity over how they could be accessed and shared.

The COVID-19 pandemic highlighted a weakness in the community, however. The activities of the various laboratories and organisations are not always as coordinated as they could be. Some laboratories are expert in developing assays, but do not necessarily have means to do routine testing with fully regulatory compliance. Others have the capacity to do large-scale testing in one area but not in another. A network hub to help co-ordinate the roles of these laboratories and organisations or be a repository of information on different expertise and capacities could play an important part in correcting this weakness.

This collaboration between academia, industry, and government was key during the early stages of pandemic and was one of the reasons the UK was able to enact such an agile but robust response from our research community.

Along the same theme of COVID-19 learning, there should be work in advance to ensure that appropriate health and safety protocols are in place for academic organisations. There should be clear and transparent advice ahead of time from the Health and Safety Executive that allows UK researchers to be able to provide their expertise in the event of another pandemic. Health and safety permissions were too slow to be approved during COVID-19, and this, combined with the lack of a standard and centralised portal for material transfer agreements, significantly slowed down research efforts.

LEADERSHIP

To be successful, managed science depends on good leadership, and trust in that leadership. For a vaccinology initiative, leadership could come from industry, academia, the NHS or the Department of

Health and Social Care, and it would aim to bring together other stakeholders, such as UKRI, UKHSA and the professional bodies.

During the COVID-19 pandemic, a number of organisations brought researchers and other experts together to collaborate; the UKRI/NIHR-funded UK Coronavirus Immunology Consortium (UK-CIC) was a national effort to understand the immunology of SARS-CoV-2 and COVID-19. This work has subsequently been built on by National Core Studies Immunity, a consortium funded by UKRI. The Vaccine Task Force (VTF) had the responsibility of procuring the correct vaccine for the UK. The National Immunisation Schedule Evaluation Consortium (NISEC) is a collaboration between a network of Academic Clinical Research groups and UKHSA, conducting clinical research relevant to UK immunisation policy. These COVID-19 vaccine studies directly fed into decision making by the Joint Committee on Vaccination and Immunisation (JCVI).

For example, the COV-Boost study examined the safety and immunogenicity of different COVID-19 vaccines, comparing them head-to-head following a primary course. This research provided the evidence base for the autumn 2021 COVID-19 booster campaign. This study is an excellent example of where the UK has excelled at the rapid translation and adoption of independent clinical research.

We have learned from research consortia like UK-CIC that the UK immunology sector, when faced with a substantial challenge, can set the pace, and get results, not least through strong, competent leadership and colossal buy in from the wider immunological research community.

The UK-CIC was funded in a way almost unique to COVID-19 research, encouraging collaborative, team science. Rather than research groups compete with each other for funding and then not co-ordinate what they are studying, UK-CIC has seen over 20 of the UK's leading immunology research institutes funded as a consortium, focused around five themes: primary immunity, protective immunity, immunopathology, cross-reactive coronavirus immunity and immune evasion. It proved highly effective, providing some of the key findings which informed UK COVID-19 vaccine policy. This should be strongly considered as a model for future funding of research both for vaccine and wider immunology research. A number of strengths were identified including:

- Researchers found that the ability to share ideas and findings, almost always pre-publication, between teams was implicit in the success of its outcomes. This 'team science' approach helped to generate more innovation and co-operation to take the science forward more quickly and robustly.
- Standardisation of protocols between groups to allow science to move forward more quickly.
- Ability to carry out larger studies due to using patient samples from multiple sites. This led to more robust findings and more diverse patient cohorts.
- The consortium facilitated increased sharing of reagents and samples.
- Regular engagement with other groups in the consortium helped to engender ambition and fostered a sense of scientific community.
- Duplication of research was avoided, but complementarity was built into the design.
- Patient and public involvement was built into the consortium's structure, facilitating early and sustained engagement with these important stakeholders, leading to more optimally designed research and more targeted communication of findings.

We have learned from research consortia like UK-CIC that the UK immunology sector, when faced with a substantial challenge, can set the pace, and get results, not least through strong, competent leadership and colossal buy in from the wider immunological research community. The research infrastructure that was built up throughout the COVID-19 pandemic including deep links between industry, academia, the NHS, and clinicians should be maintained and replicated to meet other public health challenges. This would, at a stroke, enormously improve the level of future pandemic preparedness in the UK.

Going forward, similar topic-led collaborations could be set up to address ongoing challenges in understanding immunogenicity, such as mucosal immunity, importance of T cell immunogenicity and responsiveness of vaccines in the immune vulnerable. It should be noted that such managed research is not always successful, and not every collaborator in such projects will be able to deliver, so this can be more expensive in the long run. It is also important that the right questions are being asked, but this ties in with ensuring that the project has strong, scientific leadership from the outset.

Leadership in this space goes beyond the science, however. There must be political leadership and co-ordination from government so that routes for knowledge transfer are known before a pandemic event occurs. A weakness of the COVID-19 response was that government was forced to seek knowledge in the first instance from who they knew, rather than who knew best. In order to rectify this, there must be a formal way to feed in expertise and transparency about how all the taskforces and advisory groups interact with each other and to whom they report.

RECOMMENDATIONS

- A UK vaccinology network based on pandemic models of working, with continued funding and strong leadership, should be established to devise and address key questions and challenges in immunogenicity.
- We must ensure that routes for knowledge transfer in a pandemic situation are clearly delineated with a focus on knowledge generation.
- Coordination within the UK's antibody and vaccine development research community should be improved, and this should include mapping the UK's academic innovation and capacity, as well as developing a virtual biobank of samples stored in UK laboratories.
- There should be template agreements drawn up in advance between academic research institutions, government, and industry on compensation for components used in assay development and for IP arrangements.
- There should be clear and transparent advice ahead of time from the Health and Safety Executive that allows UK researchers to be able to provide their expertise in the event of another pandemic. This should be combined with the establishment of a standardised and centralised portal for material transfer agreements.

APPENDIX 1 – LIST OF CONTRIBUTORS

The British Society for Immunology would like to thank the following people for their expertise, advice, and input in constructing this report:

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With thanks to **Professor Peter Openshaw CBE**, Imperial College London, for his time to review the report text before publication.

More information on this report and an online version can be found on the British Society for Immunology's website. Visit **www.immunology.org/publications/bsi-reports** for more information. For further information, please email the BSI policy team at **bsi@immunology.org**.

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