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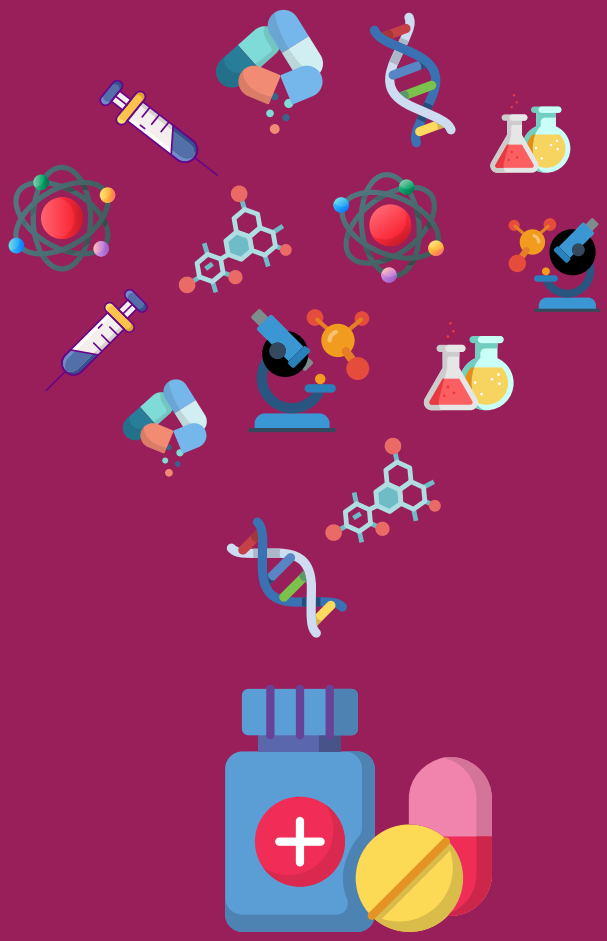

Driving the UK's leadership in vaccine research & innovation

SANOFI

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*Reformer Thought*s brings together the opinions of leading experts from academia, business and government; frontline practitioners and public service users, to provide readers with valuable insight into the challenges shaping the policy debate. The series aims to give a platform to innovative ideas and facilitate an open and informed conversation about how we can improve public services.

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Vaccination is our most powerful intervention in the fight against infectious diseases. But never has the contribution of vaccination to society been clearer than during this pandemic. As the UK leads global efforts to develop a safe and effective vaccine for the virus, opportunities must be seized to boost the uptake of current vaccines, build a strong portfolio of new vaccines, and strengthen the UK's leadership in research and innovation.

The UK has one of the most comprehensive immunisation programmes in the world. The value of vaccines is well understood and remains at the heart of the Government's approach to health promotion and disease prevention, with the 'prevention is better than cure' vision, the Prevention Green Paper, and the NHS Long-Term Plan laying out strong commitments to increase the uptake of current vaccines and supporting the development of new ones. The Government's forthcoming Vaccines Strategy also provides an opportunity to further crystallise the benefits that vaccines can create for health, reducing inequalities, and protecting the UK's economy. This adds to the ambitious agenda set by UK Life Sciences Industrial Strategy, which strives to position the country as a global hub for life sciences innovation, including vaccines research.

A strategic approach to vaccine development, regulation, manufacturing and supply has become even more important amidst the global COVID-19 pandemic. The UK has been at the forefront of international efforts to develop vaccinations and treatments to tackle the virus, with billions invested in vaccine R&D and in scaling up the country's manufacturing and distribution capacity.

The response to COVID-19 has also catalysed unprecedented levels of collaboration and partnership working between government departments, regulatory bodies, industry, academia, the charity sector, and the NHS. Temporary regulatory flexibilities have been introduced to expedite the review of clinical trials applications, streamline access to scientific advice, and maintain the continuity of supply of key medicines, diagnostics and medical devices. The scientific and research communities have moved at pace to research and develop new treatments against the virus, and deliver novel approaches for conducting clinical trials. A dialogue has begun about the need for new approaches to appraising the economic value of vaccines and rewarding innovation.

This *Reformer Thoughts* brings together experts from government, the scientific research community, and life sciences sector, to discuss the future of vaccination and how the UK can retain its leading position in vaccine research.

Claudia Martínez
Health Policy Fellow,
Reform

"A strategic approach to vaccine development, regulation, manufacturing and supply has become even more important amidst the global COVID-19 pandemic."

The value of vaccines: promoting access and uptake

Vaccinations are one of the most effective public health interventions for tackling the spread of contagious disease. To date, vaccines have saved tens of millions of lives and, in the case of smallpox, have eliminated whole diseases, with its eradication declared by the World Health Organization in 1980. Other diseases like polio, that were once rife globally, are now contained in just a few countries across the world.

We are however losing sight of this success story in many high-income countries including the UK. In 2018/19, uptake of all 13 routine childhood vaccinations declined in England, compared with the previous year. Statistics for 2019/20 indicate that uptake did show a small increase for most vaccinations in England, but this is little succour when you consider that still not one vaccination in England has reached the Government's 95 per cent coverage target at the correct time point. Across England, only 41 out of 148 local authority (LA) areas met the 95 per cent uptake target for the six-in-one vaccine by 12 months, and only 18 out of 148 LA areas met the 95 per cent target for the first dose of the MMR vaccine, which protects against measles, mumps, and rubella, by 24 months. These statistics also do not reflect the effect the COVID-19 pandemic has had on attendance at immunisation appointments or access to primary care services.

The reasons for this decline are complex and whilst in the era of 'fake news' there have been many reports of vaccine misinformation on social media and the internet, the British Society for Immunology has found that the reasons behind the decline are more nuanced. Instead, the World Health Organization's '3Cs' – confidence, complacency and convenience – are causing the current phenomenon.

Vaccination is a human success story but may also be viewed as a victim of this success. The absence of childhood diseases today diminishes the perceived risk of not having your child vaccinated. Of course, these diseases' absence has only come about thanks to vaccination efforts. Diphtheria, for example, killed an average of 3,500 people a year before a vaccine was introduced, but today there is an average of zero deaths per year, with the number of confirmed cases each year in the low double digits. This success can feed a sense of complacency, and public health campaigns must remind people that a dormant threat is still a threat.

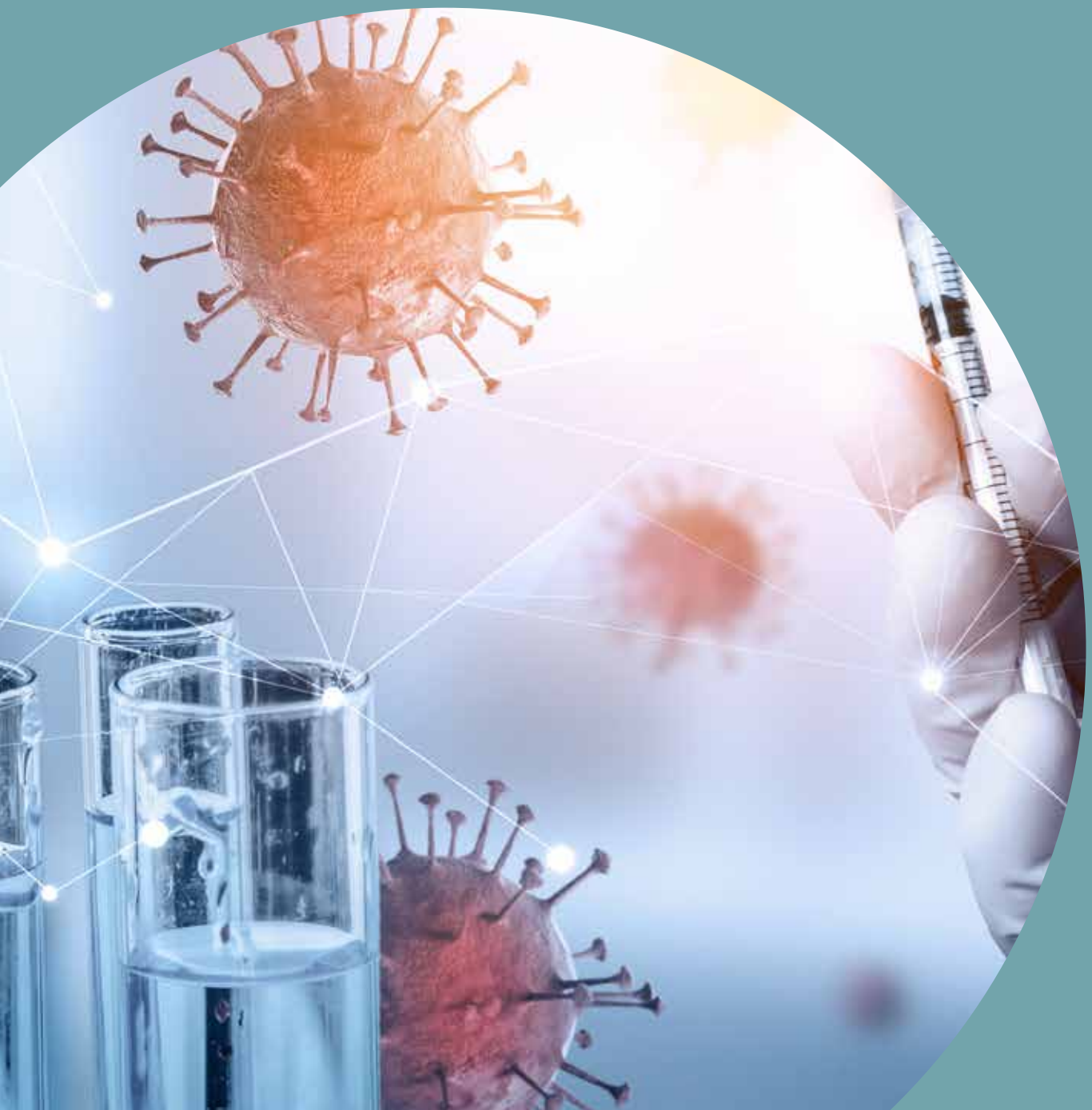
Convenience also plays an important role in whether people seek out vaccination. Vaccination should be delivered at a time and place that is convenient, comfortable and accessible. Widening provision of vaccination services through school visits by community nurses or mobile vaccination units could improve access, along with active outreach into under-vaccinated communities. The return of local immunisation coordinators would also be welcome; they mounted localised campaigns, trained immunisation staff and coordinated immunisation services, acting as a focal reference point for providers.

Dr Doug Brown
Chief Executive,
British Society for Immunology

"Vaccination is a human success story but may also be viewed as a victim of this success. The absence of childhood diseases today diminishes the perceived risk of not having your child vaccinated."

Health professionals must also be given the resources and training to give confidence to parents. As the most trusted source of vaccine information for parents, we should empower these medical professionals to engage with parents and actively welcome and answer their questions on vaccination.

As the media focuses on progress towards developing a COVID-19 vaccine and the benefit it will bring to our nation's health and economy, it is a chance to remind parents about the importance of all other available vaccines which have tempered diseases which have caused even greater cumulative misery and death than COVID-19. To tackle underperforming childhood vaccination uptake, we must focus on tackling the '3Cs' which comprise the primary barriers. It is paramount, too, that the Government publishes its vaccine strategy, as promised in the 2019 Conservative Party manifesto, so that the nation has a clear and comprehensive plan, and ensures that vaccination is a priority of the new National Institute for Health Protection.



Recognising the broader value of vaccines: worth a shot?

The COVID-19 pandemic has painfully revealed the broad and devastating health, economic and societal impact of a highly infectious and deadly disease for which there is, as yet no effective vaccine.

While initially the human suffering of COVID-19 patients made the headlines, this soon proved to be only the tip of the iceberg. Consider the heavy toll on patients' families, friends, colleagues, and other social networks. On all the healthcare staff working around the clock, wave after wave. And on the capacity of the NHS, buckling under the pandemic pressures with consequences that may last for years. Then add to that the disastrous economic impact, crippling economies in the UK and worldwide.

This clearly shows that an effective vaccine against this disease will have a broad value to society. Value that extends well beyond 'just' preserving the health of the vaccinated individuals and avoiding the costs of treating patients with COVID-19.

The ability to generate such broad value to society is by no means unique to a future COVID-19 vaccine. In fact, health economists have long recognised the broad value attributes of vaccines and called for the recognition of those in vaccines value assessment.

To date, however, these broader value implications are not typically recognised in the formal value assessments of vaccines, which are done by the Joint Committee on Vaccination and Immunisation (JCVI). This is an independent Departmental Expert Committee and a statutory body which advises UK health departments on "immunisations for the prevention of infections and/or disease following due consideration of the evidence on the burden of disease, on vaccine safety and efficacy and the impact and cost-effectiveness of immunisation strategies."

As a result, existing and future vaccines are likely undervalued and underused, leaving our health systems and societies more vulnerable than they need to be.

While we are experiencing the impact of COVID-19 on a daily basis, the time to rethink how we value vaccines in the UK is now. Vaccine research and development costs are to a large extent fixed and the herd immunity that results from vaccines against infectious disease is a public good. Markets have a problem to function properly under such conditions and a reduction in social welfare can be the consequence.

Formally recognising the broader value of future vaccines is therefore not trivial, nor is it straightforward to achieve. It requires transparent processes, advanced evaluation methodologies and reliable evidence.

Professor Lotte Steuten
Vice-President and Head of Consulting,
Office of Health Economics

"The time to rethink how we value vaccines in the UK is now."

But most of all it requires the willingness to challenge the status quo and consider novel ideas on how to appropriately reward for the value that is generated outside the health care system and which is therefore beyond the scope of the current value assessments done in the UK.

To pave the way towards the recognition of the broader value of future vaccines we need a three-pronged approach:

I. Proactively steer the generation of high-quality evidence to quantify the broader value of vaccines to society.

2. Develop and use the deep expertise available to agree on how to appropriately recognise the broad value of vaccines as generated within the health system and beyond.

3. Stimulate stakeholder engagement and buy in for more transparent and comprehensive value assessment processes for vaccines in the UK.

With the UK being on the forefront of developing a vaccine against COVID-19 it is therefore in our best interest to reconsider how to value vaccination programmes. To best protect our public health, our economy and societies, new thinking is required. Let's give it a shot.

Vaccine innovation in the era of genomics

The first SARS-CoV-2 genome sequence was made widely available by the 10th January 2020. This allowed the virus to be classified as a coronavirus that was highly related to SARS-CoV-1 (the cause of SARS) and provided fine-scale detail on gene content and organisation.

Access to SARS-CoV-2 sequence data has had a major influence on both diagnostic testing and vaccine development. The data informed the development of specific and sensitive molecular diagnostic tests that targeted several regions of the genome. It also identified genes that are present in other coronaviruses, which had already been studied in detail. This supported an early understanding of the likely structure and function of the SARS-CoV-2 virus despite its very recent emergence and provided a basis for selecting regions of the virus as vaccine targets. Decades of research combined with rapid access to sequence data led to the fastest progress in vaccine development in history.

As the pandemic continues over time and numerous vaccines edge closer to approval for human use, sequence data will once again come to the foreground. This is because mutations in the virus genome may lead to changes in the virus proteins – a very tiny fraction of which could change the way that the virus interacts with the human population, or responds to therapeutics and vaccines.

Mutations are a function of natural evolution and in the SARS-CoV-2 virus genome occur at a rate of around one or two mutations per month. Most mutations that we can detect have no effect on the biology of the virus and so persist in the descendants of that virus. As mutations accumulate, this leads to numerous differences in the virus population over time. This can be used during outbreak investigations to compare viruses isolated from different people to give extra granularity to outbreak investigations. A proportion of mutations will prove harmful to the virus and will not persist in the population.

Some mutations can change both the biological behaviour of the virus and persist if they confer an advantage to the virus. This may include mutations that result in an altered (increased or decreased) ability to cause disease or transmit from one person to another. One of the first major examples to date is the spike protein variant D614G, which was not present when the virus first emerged but is now almost ubiquitous. This mutation appears to increase the risk of transmission of SARS-CoV-2 and suggests that transmissibility can change over the course of the pandemic.

Spike protein mutations are of particular interest, since this is the target for most vaccines. To date, numerous mutations have arisen in this region and worryingly some may lead to lower vaccine efficacy.

Professor Sharon Peacock
Executive Director & Chair, Genomics UK (COG-UK) Consortium and Professor of Public Health and Microbiology, University of Cambridge

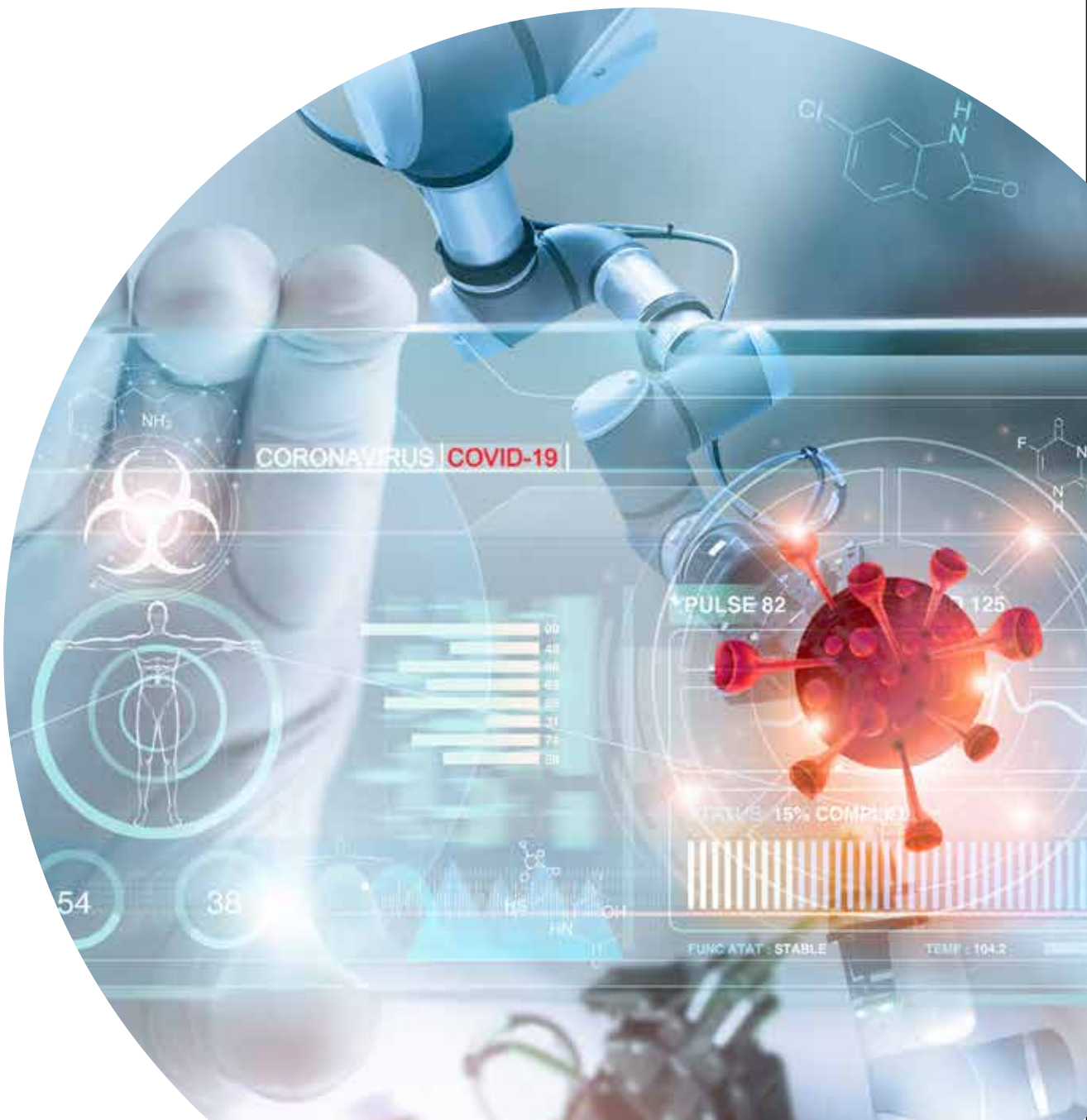
Dr Alessandro Carabelli
Post-Doctoral Research Associate, Genomics UK (COG-UK) Consortium

"Tracking mutations in the virus will become an essential surveillance partner to vaccine roll-out and is likely to be needed for as long as the vaccine is required."

Furthermore, once vaccines are approved and become widely used, viruses that can 'escape' the effect of a vaccine are likely to further evolve and spread.

Tracking mutations in the virus will become an essential surveillance partner to vaccine roll-out and is likely to be needed for as long as the vaccine is required. Systems are being developed that will detect the emergence of SARS-CoV-2 mutations over time, track the spread of such viruses, predict the likely effect on vaccine efficacy, and rapidly test such predictions in the laboratory. It is also important to endorse the tenet that virus genomes represent a global resource that should be shared openly, immediately, and without barriers.

It is important not to fan the flames of sensationalist reporting as mutations come to global attention, since most mutations will not prove to be significant for people who develop COVID-19, or to efforts to prevent infection. But allied to this is a need for rigorous planning and implementation of early warning systems for SARS-CoV-2 genome mutations that matter for vaccine efficacy.



Maintaining the UK's global leadership position

The UK is considered to be a global leader for its national immunisation programme; a challenging position to maintain in these uncertain times. Not only is there an innovative pipeline of vaccines to adopt, but there has been a decline in coverage rates for routine vaccinations and the UK has failed to meet key WHO targets in diseases such as measles and influenza. Coverage rates could also fall further with COVID-19 – many children have already missed out on routine vaccinations as the first national lockdown shut schools. The UK's hard-won status is at risk.

Now, more than ever, coordinated action is required from the Government, health service, academia and industry to ensure that the UK can continue to deliver a world-class immunisation system.

The Government's Vaccine Strategy is an opportunity to set the direction for the UK: it will be crucial for improving coverage and integrating innovative vaccines into the national immunisation programme. However, this opportunity needs substantial backing and without increasing the vaccines budget, this ambition will not be realised. Detailed analysis by Sanofi Pasteur suggests that the UK needs to almost double its annual vaccine budget over five years (from approximately £460 million per year to a minimum of £827 million) to support the vaccine pipeline and maintain current standards. This excludes provision for COVID-19 vaccines as well as the costs of implementing new vaccine programmes.

This increase in funding could allow people in the UK to benefit from new vaccines against diseases that they're not currently protected from, as well as innovation in existing areas. For example, new approaches in flu vaccines are being introduced to try and mitigate the effects of 'egg adaptation', which is when mutations occur within the manufacturing process of egg-based vaccines that can impact their efficacy. In recent years, vaccines utilising innovative methods of production – such as cell-based and recombinant – or adjuvant technology have been developed in an attempt to address these concerns and improve vaccine effectiveness. However, future innovation in vaccines will place extra burden on the Joint Committee on Vaccination and Immunisation (JCVI). To avoid bottlenecks in decision-making that could delay access, we believe the JCVI should be given additional resources. This should be considered alongside a broader review of the JCVI's processes to ensure it remains publicly accountable and its decisions on vaccination programmes are transparent, in line with the Committee's Code of Practice.

COVID-19 has shown the importance of working together to protect the UK population against infectious diseases. The UK's research ecosystem has been at the forefront of these efforts, supported by the Government's Vaccine Taskforce.

Hugo Fry
Managing Director,
Sanofi UK

"The value of vaccination is now front and centre of political thinking. However, we are at risk of losing our status as a global leader and significant investment is required to support the innovation pipeline and maintain standards."

References available upon request.

MAT-GB-2004977(v1.0)
November 2020

As part of our commitment to supporting patients, Sanofi – alongside our partner GSK – are cooperating with the UK Government and several other countries to develop a vaccine and make it available as quickly as possible.

The value of vaccination is now front and centre of political thinking. However, we are at risk of losing our status as a global leader and significant investment is required to support the innovation pipeline and maintain standards.

Once the Government's Vaccine Strategy is published, it will be our collective responsibility to deliver this ambition and ensure the UK has access to the best possible vaccines, both now and in the future.

References available upon request.

MAT-GB-2004977(v1.0)

November 2020

Driving the UK's leadership in research and innovation: what does it mean for immunology and vaccine research?

COVID-19 has served as reminder that while globalisation increases the threat of disease, it also enables scientific and international collaboration that is vital to tackling that threat. From the outset, the UK has been a key player in global health security. It has never wavered in its belief that health protection is a national security issue that can only be assured through global mechanisms, partners and collaboration.

Today we are the largest donors to multilateral bodies coordinating global health responses - like the World Health Organisation (WHO) – or vaccine development and deployment – like GAVI, the vaccine alliance which has helped vaccinate almost half of the world's children or Coalition for Epidemic Preparedness Innovations (CEPI).

With the good news from Pfizer and other vaccine trials, it would be easy to let our guard down, but that would be a terrible mistake. We must instead seek to strengthen and extend these cross-border collaborations. Because we will need them. While we can't predict exactly when or where the next epidemic or pandemic may emerge, we know it will.

The Centre for Disease Control and Prevention and Public Health England set out risk factors that contribute to pathogen emergence and spread, including:

- Increased risk of infectious pathogens "spilling over" from animals to humans
- Antimicrobial resistance
- Global travel and trade
- Climate change
- Acts of bioterrorism
- Weak public health infrastructures

These pathogens must be met with a new generation of vaccines that are effective, affordable and accessible to everyone who needs them. The evidence of efficacy and cost effectiveness of immunisation and global health security is unarguable. Vaccination has delivered huge public health benefits for a relatively small upfront investment. Preventing an estimated 2-3 million deaths every year and reducing pressure on health systems caused by infectious disease and preventable disability.

The Department of Health and Social Care spent approximately £397 million on vaccines in 2018/19 out of a total budget of £129 billion. The NHS has committed to an additional £30 million from 2020 to improve delivery of vaccination programmes through primary care to help achieve higher levels of uptake.

The Rt Hon Baroness Nicola Blackwood of North Oxford

"Our response to COVID-19 has proven we are able to deliver globally important clinical research at unprecedented pace and scale without compromising safety."

In 2007 the Chief Medical Officer calculated that the value to society of the first ten vaccines offered by the NHS between 1947 and 2007 was £6.6 billion per year. Health protection interventions which include immunisation average a return on investment of around £34 for every £1 spent.

Globally, the effect is even more stark. According to the WHO, GAVI has averted medical costs of $350 billion and brought $820 billion in economic and social benefits since 2000 across the 73 countries it has operated in.

The UK has a strong history of research and development in vaccines and immunology. Since Jenner developed the first vaccine against a contagious disease in 1796 for Ebola and now Covid-19, UK scientists have been at the forefront. UK expertise extends throughout the pipeline from fundamental research to vaccine development and disease surveillance.

In fact, the British Society for Immunology reports that "the UK top[s] the G7 for impact and influence... Despite being home to just 9% of the G7 population, the UK produces 14% of its immunity research publications."

So what can the UK do to drive forward its leadership in immunology and vaccine research and innovation?

Firstly, incentivise and invest in high-quality fundamental research. The Government are committed to increasing R&D investment to 2.4% GDP and although reports show grants for UK vaccine research lagging behind immunity research, it is important this trend is reversed. Secondly, we need to improve our clinical research ecosystem. In late 2019, the ABPI lamented that while the UK leads Europe in early phase trials, the advantage is lost as research moves to later stages.

Our response to COVID-19 has proven we are able to deliver globally important clinical research at unprecedented pace and scale without compromising safety. Professor Robin Shattock, of Imperial College London, who is building a vaccine development platform explains, "we were able to go from having the virus' genetic code to building a prototype vaccine and our first animal experiments within three weeks."

The RECOVERY-RS trial – focusing on respiratory support for Covid-19 – took only 10 days from requesting to design the trial through to enrolment of the first patient. The Clinical Trials' Unit at Warwick believes this is one of the most rapid trial set-ups in the UK and possibly ever.

Lessons from these exceptional achievements must be learnt and fed back into our clinical research system.

For a start, people should be able to give consent to participate in research in advance of illness and we should develop a national online "find, recruit and follow up" service so that clinicians and researchers, with appropriate safeguards in place, can contact citizens about upcoming trials and keep them updated as they progress.

The Health Research Authority and the Medicines and Healthcare products Regulatory Agency should stratify medical research applications according to risk. We should also aim to harmonise the ethics approval process to reduce friction through the creation of a single National Ethics Committee to centralise ethics approval. And, of course, we should invest in 21st century health data infrastructure and simplified information governance.

Finally, it takes many years and costs hundreds of millions of pounds to take a vaccine from bench to business to bedside. Pharma may appear to have the money and scale to take early-stage products through development, trial and manufacture vaccines, but in reality, vaccines only get to clinic – and certainly only become population health interventions – through multi-layered, multinational collaboration and coordination.

Global networks of scientists, regulators, manufacturers, funders and governments are vital not only for the success of vaccines but also for effective global health security. Before COVID-19, however, only the niche specialists within Whitehall and global health bodies really understood this. Now none of us have any excuse.

It is up to all of us to ensure the UK maintains and strengthens not only our national vaccine and immunology expertise but also our global leadership. This is the only way we can hope to be ready when the next global health crisis comes.

Conclusion

Leading the world beyond COVID-19

Vaccinations have proved perhaps the greatest success story of modern medical science. The eradication of major infections such as smallpox and polio attests to the ability of vaccination to deliver huge public health benefits for a relatively small upfront cost. Yet in high income countries including the UK, the success of vaccinology has encouraged a degree of complacency among both the public and health professionals. The absence of devastating communicable diseases, a product of widespread vaccine access, has diminished the perceived risks of going unvaccinated. The UK's position as a global research hub for vaccine science risks being undermined by inadequate funding and a lack of coordination between research institutions, government and the private sector.

The COVID-19 pandemic has provided a salutary reminder of the broad and devasting health, economic and societal impacts of infectious illnesses which lack effective vaccines. Importantly, it has forced policy makers, public health experts and the general public to take stock and ask important questions about the ways in which vaccines are researched, valued and deployed. This reckoning has provided a note of optimism: the UK remains a global leader in vaccines and immunology. COVID-19 has catalysed unprecedented levels of collaboration and partnership between research institutions, government departments and the pharmaceutical industry. Long-standing efforts to foster innovation in the life sciences has allowed the UK to deliver globally important clinical research at unprecedented pace and scale without compromising safety.

Yet harder lessons have also been learnt from the crisis. In the first instance, concern has emerged over rates of vaccine uptake in the community. As Doug Brown, the Chief Executive of the British Society for Immunology, notes, not one vaccination in England has reached the Government's 95 per cent uptake target at the correct time point, meaning that children in particular are missing out on necessary vaccines at the optimal age.

Many local government areas lag behind in delivering early childhood access to the especially vital Measles, Mumps and Rubella (MMR) vaccine. The Government's forthcoming Vaccine Strategy provides an opportunity to coordinate and strengthen uptake and ensure that vaccines are effective, affordable and accessible to everyone who needs them.

Sebastian Rees
Research and Events Assistant, *Reform*

"Though the UK has proved its ongoing centrality to global research initiatives in vaccinology and immunology, securing this position will involve consolidating gains made during the pandemic."

However, as Hugo Fry, Sanofi Pasteur's General Manager, argues, without increasing the vaccines budget, the ambitions of any government strategy will not be realised. The COVID-19 pandemic has encouraged a welcome rethink of the ways in which vaccines are valued. Professor Lotte Steuten of the Office of Health Economics points out that policy makers and the public realise more than ever that the value of vaccination extends well beyond preserving the health of vaccinated individuals and avoiding medical costs of treating infected patients. Yet it remains to be seen whether this recognition will translate into a wider funding pool for vaccine research and provision and the development of more encompassing metrics of vaccine evaluation.

Though the UK has proved its ongoing centrality to global research initiatives in vaccinology and immunology, securing this position will involve consolidating gains made during the pandemic. Baroness Nicola Blackwood emphasises that lessons from exceptional achievements in the field of vaccinology during the pandemic must be learnt and fed back into our clinical research system.

The first of these is that vaccine science and other public health interventions only progress through multi-layered, multinational collaboration and coordination. Maintaining the productive framework of cross-sector partnership vital in this time of crisis must remain a priority. The second is that funding and fostering innovative research in vaccine production and delivery will prove vital in developing new vaccines against diseases that we are currently not protected from. Just as importantly, innovative methodologies allow us to ensure the ongoing efficacy of existing vaccines. Professor Sharon Peacock and Dr Alessandro Carabelli of the Covid-19 Genomics UK Consortium (COG-UK) provide a useful case study in this regard. Long-standing support for innovative research in genomic sequencing allowed experts to gain an early understanding of the likely structure and function of the SARS-CoV-2 virus and provided a basis for selecting regions of the virus as vaccine targets. Genomic analysis will allow vaccine researchers to remain vigilant to mutations that matter for vaccine efficacy and better track and monitor future infectious threats.

News has emerged in recent weeks on the success of vaccine trials and excited public attention over the potential return to normality that these developments give rise to. Yet amongst the jubilation, experts in vaccinology remind us that supporting a research ecosystem and promoting vaccine uptake cannot be a priority only in times of crisis. As Baroness Blackwood reminds us, "while we can't predict exactly when or where the next epidemic or pandemic may emerge, we know it will." Investment and vigilance now will ready the UK to avoid or mitigate the damage of crises in the future.

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