A PRIMARY SPOTLIGHT ON POLITICAL RISK

Vaccine rollout and beyond
Justin Stebbing Interview

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Professor Justin Stebbing is an oncologist specialising in a range of malignancies and their treatment with immunotherapy. He has published over 600 peer-reviewed papers in journals such as the Lancet, NEJM, Blood, JCO and the Annals of Internal Medicine. His laboratory focus is on new druggable target discovery and gene regulation in cancer.

He is a Fellow of the Royal College of Physicians and the Royal College of Pathologists, and sits on the advisory Boards of a number of international cancer committees. He has chaired the World Vaccine Congress and the Irish Cancer Society oversight committee and has sat on editorial boards of a number of world leading general medical and cancer journals such as the Journal of Clinical Oncology. Professor Stebbing was awarded the Silvia Lawler prize in 2015 and appointed as Editor-in-Chief of Oncogene in 2016. He was also elected to the American Society for Clinical Investigation.

Like many physicians, Justin turned his attentions to the unfolding coronavirus pandemic early last year and has become renowned as a commentator on the rapidly emerging scientific research and epidemiology of this pathogen. Justin has led broad international collaborations to advance COVID-19 research in a number of areas, including an AI based project that identified the already available medicine baricitinib as a potential treatment for the disease which led to phase 3 trials and an FDA EUA approval.

(Professor Stebbing did not receive any form of compensation for this interview)

Amid all of the contradictory claims and counter- claims, is it not the case the EU's reliance upon the precautionary approach to novel medicine and medical techniques is the real villain in the piece in explaining why the vaccine rollout was so delayed? How does this inform us about the future of the European pharmaceutical industry? For example

I am not best placed to comment on the politics of all of this but your premise I think is very right and timely. I would however separate politics from the future of the European pharmaceutical industry. These are truly global companies that perform basic science research, clinical translational development and sell worldwide, in the US, Asia and rest of the world, not just Europe. Thinking of it as one unit, the challenges from understanding biology and true innovation to patent risks and funding required to develop drugs are not unique to any geographic location.

For COVID-19, much of my own work has been on the therapeutics side and it was very evident early on that barriers between academia, industry, individuals and institutions were falling for the common good, and speed of collaboration along with willingness to work together was

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remarkable. For example, my early Lancet publications using artificial intelligence to find a drug that would be useful not just as an anti-cytokine but also as an antiviral occurred with the wonderful scientists and team from a London, UK company BenevolentAI.

We found baricitinib, a simple tablet used in rheumatoid arthritis might be useful. Next, we collaborated with Eli Lilly who manufacture the medicine to understand the mechanisms via which this occurred in the laboratory, then leading to global studies co-ordinated by all stakeholders and the National Institutes of Allergy and Infectious Diseases.

Within 10 months of our first publications, baricitinib received an Emergency Use Authorisation from the US Food and Drug Administration and my last paper has over 50 authors on it from over 30 institutions in a dozen countries. This included research using mini-livers in dishes, so-called organoids with academics at the Karolinska Institute and stunning images of the baricitinib preventing SARS-CoV-2 getting into cells using super-resolution microscopy in collaboration with the team at Oxford Nanoimager, ONI.

Having said all this, therapeutics have been something of a disappointment though the joined up nature of the NHS hospitals and again team work at a national level, led to large randomised studies of the steroid dexamethasone showing benefits in the sickest patients, and equally important was the evidence that many postulated anti-virals did not demonstrate positive benefits.

When all is said and done though, I think the speed of vaccine development, from the first Wuhan sequence in January 2020 to results of massive phase 3 studies and then with its flaws, twists and turns of approvals, subsequent roll out, has been one of the greatest scientific achievements ever. The speed is simply breath-taking. We also have a new class of drug based on messenger RNA (mRNA), which I think of as the software inbetween the DNA (hard-drive) and proteins (hardware), which I think is set to revolutionise large aspects of bio-pharmaceutical development. This isn't a European or single site phenomenon.

Long before the AstraZeneca vaccine brouhaha, several European countries (France most notably so) had a significant anti-vaxx lobby, widely supported among the population. How can such negative viewpoints be reversed, especially now we too have decided to withhold the AZN vaccine from the under 30s. Isn't this further support for the anti vaxx community everywhere?

The need to control outbreaks and pandemics has long created tensions between liberty and interdependence, similar to those playing out worldwide today. There are historical precedents and odd alliances: anti-vaccine, anti-mask, anti-5G are getting in the way of public health right now and vaccination has always been a lightning rod for storms brewing over other problems.

The people who protested against mandatory smallpox vaccination in 19th century England had previously led opposition to the 1834 Poor Law Amendment Act, which proposed that unemployed people must labour in workhouses for food, often under conditions of exploitation,

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child labour and family separation. The protesters saw mandatory vaccination as a similar assault on poor people's autonomy.

Figures vary but clearly the anti-vaxx community varies in size between different countries and within those countries within different age, social, demographic and even voting groups. The first thing I'd say it's important to distinguish between vaccine hesitancy and anti-vaxxing, the latter replete with its horrid conspiracy theories. There will always be anti-vaxxers and it's been no surprise that in large trials of vaccines, some side effects have emerged but these are rare.

For a vaccine given to millions, some side effects won't be seen in trials, and will only be picked up subsequently. For AstraZeneca, the incidence of the rarer more dangerous cerebral type blood clots has been 4.6 per million. This is very rare, so no wonder the WHO have said its benefits outweigh its risks. But as you say much comes down to trust and the twists and turns of the saga. I can't comment on the Chinese vaccines though as my recent opinion piece in Foreign Affairs on the matter states where we still haven't seen their phase 3 data and need to.

For those with intent to be vaccinated, interventions such as default appointments and onsite vaccination effectively increase uptake. Less is known about how to increase uptake by modifying beliefs of the hesitant. Again, one tries to be guided by data. In one randomised trial targeting parents with children eligible for the measles–mumps–rubella (MMR) vaccine, researchers tested various messaging strategies that either corrected misinformation or had emotional appeal.

One strategy refuted the claim that vaccines cause autism, while others featured pictures of children with the diseases the MMR vaccine prevents or a dramatic narrative about an infant who nearly died of measles. These strategies not only failed to increase intent to vaccinate, but among vaccine sceptics, they actually did the opposite. Graphic pictures of a child with measles increased fears of vaccine-related side effects rather than fear of the disease itself. And though accurate information reduced the misperception that vaccines cause autism, intent to vaccinate still decreased among the most hesitant parents.

Extrapolating these sorts of findings to a global pandemic comes with numerous caveats but we do know that the confidence of physicians and public health officials can be instrumental in allaying fears. One good thing has been that since health care workers are among the first groups to be vaccinated, they have been able to speak to their patients with authority and confidence but not a day goes by when I am not asked by a patient whether it's ok to have a vaccine and which one I'd recommend (the answer has been any that are approved).

Though the pandemic has put dangers of misinformation into our everyday lives, it was always there and it seems that giving accurate and correct data doesn't reverse this. Various strategies from involvement of religious leaders/vaccinations in church car parks to knowing someone who has been sick with COVID-19, and someone who 'did fine' with the vaccine, seem to work to some extent, and it's a gradual process.

Clearly anti-vaxxing with its various web groups has been very well organised. It's easy for me to say that the root causes of vaccine rejection must be appreciated and addressed. Although the

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history of vaccination recounts advances in modern science, it is also part of the wider story of society wrestling with the promises and perils of technology. It is a story of parents coming to terms with the death or disability of a child (almost always unrelated to vaccinations), of the pressure to parent this way or that, and of belonging to society, a community, or not. And it's a story of activist groups that don't so much deny science as carefully select straws of information and misinformation to build their nests of belief. We should distinguish between those who reject vaccination, and those who lack access to health care. There should be more emphasis on the have-nots, in my view.

This is a common blind spot in explanations of low take-up. Poverty, and lack of access to social resources and primary care, greatly affect uptake, as do housing insecurity, gender inequity and racism. The largest measles outbreaks in 2019 were in countries without sufficient primary care, such as Madagascar, or where conflict had displaced people and disrupted their access to vaccines, such as Yemen. Some of the most effective interventions include ensuring that supply chains are reliable, making services highly convenient and simply reminding people that they need to be vaccinated.

The current pandemic reminds us that governments cannot ignore poverty and social exclusion if they are to prevent and manage this virus, others unvanquished and those yet to come. To me, vaccines almost always stop diseases safely, so we should ask why all the suspicion. Measures such as Facebook and Youtube removing anti-vaxxing promotion can only help, but it's a global phenomenon from Pakistan to San Francisco, not a Western one.

Although the scientific community's obligation will always begin with championing truth, the pandemic has shown that society's health also depends on understanding why so many people reject it and this is why it's so important for science and scientists to be able to explain things to the public. And conversely also, for the public to explain things to scientists.

There has been much talk about how the pandemic has and continues to change clinical practice. As a leading physician and as someone involved in research collaborations on the pandemic itself, what are your personal experiences of these changes, good or bad, and what do you think will be most enduring when COVID is finally a distant memory.

My personal experiences have only been good here. Walls have fallen. People have wanted to come together, to work together for the common good. The speed of work and depth of collaboration has been unprecedented but to me, what will be most enduring will be that science has led us out of the pandemic.

Importantly however, things like the hydroxychloroquine debacle have also showed us the right way to do science, via randomised studies for example with groups closely matched at baseline. This removes so much of the bias we see from single arm observational cohorts. Sometimes randomised studies aren't possible but these studies can help us understand safety signals and possible toxicities. For example, even though SARS-CoV-2 infection can be associated with blood clots and some studies in rheumatoid arthritis suggested baricitinib can be associated with clots,

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its use in the pandemic in both the single arm observational studies and larger randomised studies didn't show this worrying occurrence.

We actually showed using RNA sequencing in liver organoids that the virus activates pro-clotting (so called platelet activation) genes, and that baritinib can block this. Of course, as mentioned even randomised phase 3 studies of more than 30,000 people might not show very rare side effects of vaccines, which is especially important if you're going to give this to many millions of people including the very frail and children, which is why ongoing surveillance is so important.

The other aspect of the pandemic that will endure for me is that the scientific advances have intersected with very real human stories. This isn't about me or any one person but of course it's affected all of us. For me, the worst thing was seeing the raw distress of my family members simply not being able to visit my uncle who died alone after being ventilated for a month in York (he was headmaster of a large school) due to Covid pneumonia. A year ago, at that time we knew so much less than we do now and it was a scarier less familiar virus then compared to now, but the very human stories I think have served to inspire so many. He set up the local Selby food bank and understood this was about communities. And, right now, Brazil which is 3% of the world's population has nearly one third of Covid deaths. It's a massive global issue and I was pleased that baricitinib is a once/daily tablet and cheap when used for a short time, which means it can be used in low and middle income countries too, not just the developed world, showing the benefits of the computer-laboratory-clinic-regulatory process wherever you are.

Few fully appreciate how good our testing network and data have become. This is now evident in two areas. Our use of genomic analysis to understand and control variants is world-leading - 47% of all genomic sequencing is completed in the UK. Secondly, and much less widely acknowledged, the volume of testing we are doing is now unparalleled (and means comparison of cases numbers across geographies will skew against the UK) - 6 million tests conducted week ending March 13th. Does this make you more optimistic about the outlook for UK Healthcare, or was a lot of this going on already and simply not visible to the public?

The UK has undoubtedly led the world in both of these aspects here thanks in part to government initiatives early on. It's incredible to have thought that some have erroneously said that we only diagnose the disease more as we test more, and of course if we look for variants like B.1.17 we find them. We now realise that variants with their differing levels of vaccine resistance (this is not an all or nothing phenomenon) are and will be incredibly important. Whilst vaccine durability might determine how often we need booster shots, the variants might determine what the booster will look like.

We are learning all the time and every day there is another study on this. We know differing variants have different transmission rates, different mortality rates and importantly differences in their biology. And we have joined up thinking from the laboratory, studying neutralisation of pseudoviruses with different mutations, with studies of different vaccines such as Oxford-AstraZeneca's, Novavax's or Johnson & Johnson's data in South Africa and Brazil. And, whilst we are on this subject, the mRNA vaccines made by Pfizer/BioNtech and Moderna giving us 95% efficacy rates, have only been possible due to advances in next generation sequencing technologies.

In the UK, Oxford Nanopore has not only enabled rapid sequencing of the viral spike gene, but also has provided us with its test which is highly scalable, allowing deployment in both high-throughput, traditional laboratory settings as well as smaller, local environments — addressing the need for rapid, routine testing of large numbers of people. LamPORE for example and specifically, combines loop-mediated isothermal amplification (LAMP) and nanopore sequencing to provide a highly scalable, multi-gene assay for the detection of SARS-CoV-2. LAMP is a single-tube technique for the amplification of DNA and as a standalone method it can even be considered as a low-cost, rapid alternative to RT-PCR – the standard test. Reverse transcription loop-mediated isothermal amplification (RT-LAMP) combines LAMP with a reverse transcription step to allow the detection of SARS-CoV-2 RNA. Target sequence is amplified at a constant temperature. Its sensitive and specific which we need but also can be used on nasopharyngeal swabs and saliva, in asymptomatic, presymptomatic or symptomatic individuals.

There is a lot of talk about 'long COVID', but to the layperson it remains a rather nebulous constellation of symptoms and not yet defined globally. How big of a problem do you think this is and how do we get to a point of defining and then identifying who actually has it, is at risk of it etc. and can we treat these patients to alleviate their symptoms and allow them a full recovery?

Long Covid is a massive problem and its going to be huge, not least because of our inability to define it or even have biomarkers to show people have it or are getting better. This week alone we've learned from a Lancet study that one in three people who have suffered from Covid-19 was diagnosed with a neurological or psychiatric condition within 6 months of infection, according to Oxford scientists who have carried out the largest study of the mental health effects of coronavirus.

They found that Covid-19 was 44% more likely to cause neurological and mental problems than a case of influenza of comparable severity, and this included anxiety, depression and even strokes. Anxiety and mood disorders were the most common diagnosis among those with Covid, and these were more likely to be down to the stress of the experience of being very ill or taken to hospital, the researchers explained.

Conditions like stroke and dementia were more likely to be down to the biological impacts of the virus itself, or of the body's reaction to infection in general. Covid-19 was not associated with an increased risk of Parkinson's or Guillain-Barré syndrome (a risk from flu). Mood, anxiety or psychotic disorders affected 24% of all patients but this rose to 25% in those admitted to hospital, 28% in people who were in intensive care and 36% in people who experienced delirium while ill. Strokes affected 2% of all Covid patients, rising to 7% of those admitted to ICU and 9% of those who had delirium. And dementia was diagnosed in 0.7% of all Covid patients, but 5% of those who'd experienced delirium as a symptom.

In a BMJ study, 3 major findings were found examining post-covid syndrome in 47,780 patients admitted to hospital with covid-19 in England, matched to controls. Firstly, admission to hospital for covid-19 was associated with an increased risk of readmission and death after discharge: 29%

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were readmitted and 12% died within a mean follow-up of 140 days. Secondly, rates of multiorgan dysfunction after discharge were raised in individuals with covid-19 compared with those in the matched control group, suggesting extrapulmonary issues ie. many problems outside of the lungs. Diabetes and major adverse cardiovascular event were particularly common in fact. Thirdly, the absolute risk of death, readmission, and multiorgan dysfunction after discharge was greater for individuals aged 70 or more than for those aged less than 70, and for individuals of white ethnic background than non-white individuals, interestingly.

This is potentially huge but can impact all of our lives, and deserves long term study. There are a few interesting drugs in development looking at this such as the LYT-100 tablet too and am especially keen to see results of the randomised studies looking at this.

The policy response to the pandemic has clearly had a negative effect on mental health, cancer detection and presumably many other areas of 'routine' public health. What other areas would you expect to see gain prominence as we emerge blinking into the daylight? Will solving this be a relatively simple matter of managing a backlog or are there any other likely implications?

It's been so hard for so many people to balance everything, right from those who mandated immediate cordon sanitaires to those who said forget the lockdown, both sides insistent they were absolutely correct and theirs was the only way, let's call it Sweden versus China type approaches. But, in one study I published, the mortality in cancer patients who contracted COVID-19 in a meta-analysis approached one third, driven across cancer types but especially blood cancers and lung tumours.

Hospitals became scary places, epicentres themselves of infection and visitors haven't been allowed. Of course, virtual consultations and telemedicine have become the norm, in concert with zoom meetings in the rest of our lives. There's been a bidirectional impact on mental health with those with mental illness more likely to contract COVID-19, and those with COVID-19 as per the long COVID study above, developing more mental illness. Hopefully we will be better planned for SARS-CoV-3 or the next pandemic.

One encouraging finding has been that most studies do not show an increase in suicides as a result of the pandemic, and many studies show that in the overall population, depression and anxiety have returned to pre-pandemic levels. Hopefully now vaccines are our way out. In another collaboration I was lucky enough to be involved in, we published last week that using an mRNA vaccine in very frail or disabled elderly people in nursing homes, they induced a robust immune response. These weren't the sort of volunteers that could be recruited into trials, again adding to the evidence that vaccines are truly our way out.

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