INVESTMENT RESEARCH UPDATE

Beyond *the* Pandemic

IS COVID STILL A THREAT TO GROWTH?

August 2022

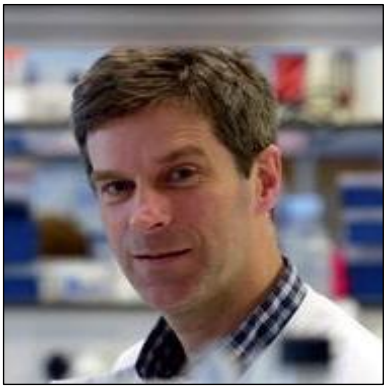
Professor Gerry Graham

in conversation with

Sandy Nairn

Executive Director of the Global Opportunities Trust plc

Professor Gerry Graham



Professor Gerry Graham is holder of the Gardiner Chair of Immunology at the University of Glasgow and a world expert in immunology, with a particular focus on the study of chemokines and their receptors. He has over 30 years of experience working in this area and publishes widely in the top international journals. He is currently chair of the Wellcome Trust Expert Review Group in the Immune System in Health and Disease and has been involved with numerous national and international funding agencies. He is a Fellow of the Royal Society of Edinburgh, a Fellow of the Academy of Medical Sciences and recipient of a Wolfson Royal Society Research Merit Award. His work is funded by an MRC Programme Grant and a Wellcome Investigator Award.

Introduction

In late December 2019, the World Health Organization (WHO) was notified of a cluster of pneumonia cases in Wuhan City, China. Although it took some months for the significance to be recognized this was the emergence of Covid 19 a virus which caused an economic convulsion. Entire economies were forced into lock-down, unemployment soared, GDP slumped, and emergency fiscal and monetary measures were the order of the day.

The root cause was a virus which was not only highly contagious but carried a significant mortality rate. The human toll was immense not just for those infected but also through those impacted by the financial and social impacts of the isolation policy response.

For financial markets, understanding the medical response was a precondition to understanding how the virus and the economic impact would unfold. We were fortunate to have access to Professor Gerry Graham as an expert advisor in the area of biological sciences. Professor Graham's insights proved extremely prescient, most importantly in how the vaccination programme would be likely to evolve and the timescale within which an effective vaccine could be deployed.

Uncertainty is the enemy of financial markets and this knowledge helped us to understand and place boundaries round the potential consequences and hence reduce this uncertainty. Although the pandemic has now ended, the virus continues to circulate.

It is a good moment therefore to revisit our original discussions with Professor Graham and consider those areas where the out-turn differed from the original expectations. This then allows us to consider what, if any, influence the virus may continue to have on economic activity.

For comparative purposes the original questions and answers are retained with updates in italics.

DR SANDY NAIRN, CFA, FRSE
Director, Global Opportunities Trust plc
September 2022

A Dialogue with Professor Gerry Graham FRSE

Q. The press loves a story about reinfection but it is hard to know what the rates are and how meaningful this is.

A. Reinfection rates remain low. However, neither previous infection nor vaccination is an absolute guarantee of protection from subsequent infection. It is likely however that, in the majority of cases, reinfection following either natural infection or vaccination will be associated with less severe symptoms and reduced likelihood of hospitalisation or severe illness.

The emergence of much more transmissible variants of Covid has turned the assumption that reinfection is rare on its head. Curiously, full vaccination (three doses in the UK), even alongside natural infection, is not a barrier to reinfection. Indeed, reinfection is now much more common even within a relatively short period of time.

This is probably driven by a combination of waning immunity following vaccination and the emergence of covid variants that are able, at least in part, to evade the vaccine-driven immune response. Certainly, residual immunity is likely, in most cases, to mean that reinfections are less severe, but these reinfections will still lead to significant illness and time off work with implications for the economy and productivity.

Q. Can you explain viral load, reduction in transmission and amplification of virus particles?

A. Following an initial infection, the virus enters our cells which it then uses to help make more virus particles. Essentially our cells become factories for making new viruses. These viruses are then released by our cells and can then be passed on to other cells in the body for further expansion. Eventually virus released by cells can be transmitted to other people through a variety of routes, most commonly through the airway in essence a positive PCR test indicates.

If the virus remains unchallenged in the infected individual, then cumulative infection of numerous cells can lead to very high viral loads. The higher the viral load that is produced in the body of the infected individual the higher the likelihood of the virus to be transmitted and the higher the viral load that is likely to be transmitted. Interestingly, this does not necessarily relate to the extent of disease that the infected individual displays. Note that many people, particularly younger people, remain asymptomatic

and yet the virus is still present in their body and amplifying itself to a level that allows it to be transmitted to others.

In people who successfully raise an immune response to the virus their immune system (B and T cells in particular) start to fight the virus and limit its ability to spread to other cells within the body and therefore to amplify itself. The more the virus is destroyed by the immune system the less it is able to amplify and therefore the lower the viral load in the infected individual. This therefore would correlate with reduced chance of transmission.

The same is essentially true in vaccinated individuals. Vaccination does not stop you becoming infected but it should reduce the ability of the virus to infect cells and make new viral particles compared to the extent that it would in an unvaccinated individual. This will therefore lead to reduced viral loads in the vaccinated individual which will be associated with reduced disease and a strong reduction in the ability of this individual to transmit the virus particularly at high loads.

It is now clear that the major impact of vaccination is on preventing illness and death, and not on suppressing viral transmission. Indeed, a number of studies suggests that even vaccinated individuals can present with viral loads that are not dissimilar to those of unvaccinated individuals. That being said, on a population basis, if vaccines can reduce the total number of people infected then this should lead to an overall reduction in transmissible virus within the population. Overall, therefore, vaccines appear to have had less of an impact on transmission than might initially have been anticipated.

Q. There is a great deal of discussion about the PCR test. Could you explain how it works please?

A. The PCR test is not an 'all or nothing' test. It is an extremely sensitive test that is able to detect and quantify minute quantities of nucleic acids. The genome of the virus is composed of RNA and the PCR test can indirectly measure the levels of viral RNA in body fluids. This viral RNA is present usually in intact viruses that have been released into body fluids following infection of cells as mentioned above. This viral RNA is below the limits of detection and PCR works by amplifying its target to a level at which it can then be detected. It does this by making copies of the target in a cyclical fashion.

Essentially every PCR cycle doubles the amount of the target. You can therefore go from one copy of the target to 1 billion copies in 30 cycles of PCR and in this way amplify something that is undetectable to a level at which it can then be detected. If you run fewer cycles you can detect viral RNA that is present at relatively high levels and if you run more you can then start to detect viral RNA that is present at very low levels.

Therefore, the ability of PCR to detect the virus depends on how many cycles it is put through. Essentially if you push it far enough you can use PCR to detect almost anything, even something present at vanishingly small quantities. That is why the PCR test has a graded aspect to it. A high viral load would require fewer cycles of PCR to bring it to level at which it can be detected. In contrast a low viral load might require in excess of 30 cycles to be detected and there does come a point at which so many cycles of PCR are required to bring the viral RNA up to levels of detection that it is safe to assume that it is present in only vanishingly small quantities.

Overall, therefore, a positive PCR test indicates the presence of virus in the individual who is therefore designated as 'infected' and likely to transmit the virus to others. The quantitative aspect of the PCR test gives an indication as to how prevalent the virus is and this may relate to pathology (although may not as some individuals are infected but asymptomatic) and is quite likely to relate to the ability of the individual to transmit the virus.

As part of the strategy of 'living with Covid' the UK network of Lighthouse labs, set up to use PCR to routinely test samples for Covid, is being wound down. There will remain a basal level of activity using PCR to screen samples of the population to follow the prevalence of the virus in the community and the emergence of novel variants. However, individuals who now believe themselves to be infected with Covid will not be required to submit samples for PCR tests as they will not now be routinely available.

Lateral flow tests will also cease to be made available, free of charge, through the NHS and individuals suffering from Covid-like symptoms will simply be encouraged to isolate until symptoms resolve. Given the large number of asymptomatic individuals, this will inevitably mean an increase in the number of Covid-infected people in the general population. However, this is something that will have to be tolerated to ensure that we really do start to 'live with Covid'. This is likely to be a common position worldwide, not least because of the cost of publicly funded testing.

Q. How effective is vaccination in targeting spike protein?

A. The spike protein that is targeted by the vaccination programmes is the Achilles' heel of the virus. It is a molecule that allows the virus to enter our cells. To be able to function properly the spike protein has to be in a very precise configuration or shape, and this is defined by its 'sequence'. Therefore, it can't be radically mutated, as mutations affect the sequence and therefore the overall shape of the spike protein. If there are too many mutations it may simply not work.

A reasonable analogy would be a Yale key which can probably tolerate a small amount of change in shape and still function but it certainly cannot tolerate radical change. In addition, the vaccine induces what is called a polyclonal response to the spike protein, that is it induces antibody responses to multiple parts of the spike protein. Therefore, if

a mutation occurs in one part of the spike protein there is still good reason to believe that the vaccines will still successfully target the other parts.

Overall it is unlikely that the virus spike protein will mutate to the point that it can completely avoid recognition by the vaccines. What this means is that with high vaccination rates, the likelihood of vaccines being able to work despite mutations in the virus will evolve. it is unlikely (although not impossible) that we will encounter a variant that will lead to disruption similar to what we have seen over the past 18 months.

Waning immunity, to some extent, makes sense as a possible explanation for reinfection, although we should still retain a robust immunological memory that probably helps reduce the severity of the reinfections. One major surprise however is the apparent ease with which emerging Covid variants (particularly the omicron variants) are able to evade vaccine-induced immune responses.

As discussed previously, vaccination is against the spike protein of the virus. There is a limit to how much this protein can be mutated and still function and, as it is essential for the propagation of the virus, it might therefore be expected to be less prone to mutations. However, the omicron variants have numerous mutations in the spike protein.

Vaccination induces what is called a polyclonal response to the spike protein i.e. it protects against multiple parts of the spike protein. What is not clear yet is why the omicron variants are able to evade the immune system. One option is that the vaccination induces preferential protection against a relatively small number of parts of the spike protein which can be mutated without adversely affecting viral transmission.

Q. There has been a rising level of comment about the duration of protection from vaccinations. Is there any evidence of the need for boosters?

A. The jury is out on this one. The key question is how long vaccine-mediated immunity lasts for and we simply don't know the answer to this yet. If it wanes quickly then boosters will certainly be needed. However, there is a reasonable probability that vaccine-mediated immunity will be long lived as it is for many other viral infections, such as chickenpox. Essentially we will have to wait for more long-term data on longevity of the immune response in vaccinated people. We are basically in the middle of an extremely large clinical trial!

As mentioned above, we now have much more information on this and the emergence of highly transmissible Covid variants has highlighted the issue of reinfection, which is probably a result of a combination of reduced protection from vaccine, and viral evasion of the immune response. It is probable that boosters will indeed be needed, particularly for vulnerable individuals. Whether these will be best delivered every six months, or annually, is not yet clear.

There is then the question of whether it is worth generating vaccines specifically for each of the newly emerging variants. This may be useful but would depend very much on the speed of

emergence of subsequent variants and an understanding of how likely they are still to respond to the new vaccine. It may be that we will have to live with the vaccines we have which, alongside natural infections and presumably a limited number of mutations that can be tolerated in the spike protein, may mean that eventually our immune system will be able to comprehensively deal with this virus. This, however, is perhaps wishful thinking and time will tell.

Q. Hospital capacity seems to be a binding constraint in designing anti-Covid restrictions, but what other factors apart from infection rates ares important in the capacity calculation?

A. Hospitals are suffering from numerous difficulties. Firstly, there is the rise in hospitalisations and ICU admissions as a result of increasing Covid infections. It is important to note that whilst the majority of these are currently unvaccinated individuals, the vaccine is not 100% protective and therefore it is expected that some vaccinated individuals will still require hospital care. Secondly there is the problem of the enormous backlog of work that was put on hold to help with the initial waves of the Covid pandemic. Thirdly there is the issue of staff isolating as a result of having contact with infected individuals. In hospitals this can have a major impact on workload as a result of staff absence and resulting pressure on remaining staff.

Absence from work has now emerged as a general Covid-related problem, with obvious implications for productivity and competitiveness. Importantly, this is not just relevant to individual infections. If children or childminders are affected, or if schools and nurseries have infections, this then often necessitates at least one adult taking time off from work to care for nursery or school-age children.

There is also the broader issue of a lasting legacy of Covid in terms of its impact on how we work and whether home, or hybrid, working, on the whole, is as efficient as office working. This clearly depends on the individual. One consequence of home and hybrid working has been a significant reduction in socialising between colleagues. This is important, not only for engendering a sense of identity, but also for ensuring that problems are widely discussed and solutions sought from as many different sources as possible. In many cases, therefore, home or hybrid working may lead to significant inefficiencies. The impact will depend very much on the nature of the individual worker and the type of work being undertaken.

Q. Covid and the flu are discussed in the press in an almost interchangeable manner, not least in terms of annual flu mutations. This tends to influence discussion on the permanence of the Covid vaccine.

A. Covid and influenza are quite different types of viruses. The flu virus can change/mutate quite markedly and therefore vaccines against one strain do not necessarily work against other strains. This coupled with evidence for short lived immunity means that annual

boosters are needed. These boosters cope with the potential short-lived immunity and with seasonal variation in viral strain. In contrast Covid changes to a lesser extent and therefore there is the hope that the vaccines will have an effect on most mutant variants. We do not yet know how long-lived the immune response to Covid is and have to await further analysis.

Whilst Covid and flu are quite different, the scientific community has been surprised by the reinfection rates. At the current time it appears that regular boosters may be required. It is not clear the extent to which the vaccine will require to be altered over time to remain effective.

Q. In public discourse about Covid it sometimes seems that many 'experts' are commenting on areas which lie beyond their area of expertise?

A. This is a very interesting phenomenon. One of the issues is that there is no single area of expertise that will provide comprehensive and accurate scientific advice about all aspects of the pandemic. Understanding the virus and the population response requires insights from molecular and cellular scientists, virologist, immunologists, behavioural scientists, philosophers, psychologists etc. The challenge is to take advice from these quite disparate academic specialities and distil it into a meaningful government and public response. It goes against the grain for a scientist to offer definitive advice on the basis of conflicting views and research findings. This is the unenviable job of politicians.

The broad range of expertise required to understand the pandemic and its ramifications also means that some academic commentators in the media find themselves being asked to comment on aspects of the virus and the societal response which are not within their immediate area of expertise. This can be tricky.

This answer still stands.

Q There appears to be a continuing mismatch in how Covid and non-Covid-related illnesses are treated. There also seem to be flaws in statistics derived from reported Covid cases where other existing illness may also have contributed?

A. It is quite clear that people with underlying health issues are particularly vulnerable to serious illness and death following Covid infection. The statistics on deaths relate to people who have died after a positive Covid test. This does not necessarily mean that the cause of death was the infection. In the majority of cases, however, it is likely that Covid either was a cause of death or accelerated death as a result of other underlying health conditions. This is particularly the case in older vulnerable adults where in many cases death was accelerated, but not caused solely by Covid infection. In younger people currently admitted to hospital and intensive care units with Covid infection, there are frequently underlying health issues, perhaps most notably obesity.

There is no doubt that the impact of isolation is now emerging in the general population both in terms of mental health and the absence of diagnosis and treatment of serious illnesses. There is a strong argument that the approach to dealing with Covid subordinated other priorities for a period longer than was necessary. It is likely that lessons will be learned from the retrospective analysis of the response to the epidemic.

Q. Currently under-18s are largely excluded from vaccine programmes. This seems odd given they may well be the most likely to congregate and spread the virus?

A. Deaths and severe illness in under 18s is extremely rare (only 25 cases in the UK throughout the pandemic and 50% of these had serious underlying health issues) and so the direct benefits of vaccination to people in this age group is limited. Nevertheless, extending the vaccination programme to under 18s would be likely to increase herd immunity and therefore help in the overall strategy to reduce Covid transmission within the population. Clearly some young people suffer from immune disorders and are therefore vulnerable and should be vaccinated. In addition, young people living with vulnerable adults should also be vaccinated to reduce the chance of transmission but not necessarily to protect the under 18s.

Despite the clear evidence that Covid-related severe disease and death are rare in under-18s, there has been a progressive move to vaccinate young people. In large part this is due to our emerging understanding of their role as reservoirs for virus transmission. That being said, and as mentioned above, the impact of vaccination on viral transmissibility on an individual level may be weak and so the overall value of this approach will only become apparent in future years. Certainly, vaccination will protect vulnerable children from Covid-induced severe disease and death.

Q. There has been considerable debate, albeit possibly somewhat politically tinged, on the specific origin of the virus with the nearby research facility coming under suspicion. Do you have a view on this?

A. *Whilst the origins of Covid are not yet clear, most analysis strongly suggests that it 'jumped species' from wild animals to humans although the transmitting animal species has not yet been identified. It remains unlikely that Covid is a man-made virus which escaped from a research laboratory.*

Q. Reacting to cathartic events such as war or a pandemic often produces cause rapid advances and breakthroughs in science. Can you see anything emerging in your field as a consequence of the focus and resources that have been devoted to Covid?

A. This is an interesting and complicated question. Probably the most important change has been the speed at which vaccines have been approved. This is a result of a number of changes, most notably more rapid ethical and licensing approval by appropriate authorities. There should therefore now be a template for rapid approval of new medications and clinical trialling for future pandemics.

A further important development has related to the speed of production and supply of vaccines and the use of alternative (although not new) technologies for vaccine development. Much of what has led us to where we are today has therefore been the rapid development of existing science and technology, rather than the emergence of completely new breakthroughs.

I think that there is no question that 'post-pandemic preparedness' will now be a major focus for research funding throughout the world. That being said, it is also important to point out that the key scientific breakthroughs and technologies underpinning the development of the vaccines, and other medical interventions for treating Covid, have arisen as a result of very basic discovery science (sometimes decades old) which is ultimately the engine that drives clinical innovation and therapy development. It is therefore highly unlikely that funding for investment in discovery science.

Investment Implications

Our discussions with Professor Graham have been immensely helpful in clarifying the impact of Covid, given the confused and increasingly politicised nature of public and media discourse about the virus. The following conclusions from our earlier discussions remain valid.

- The healthcare profession has reacted with unprecedented speed to produce effective vaccines, improved remedial care and preventative measures
- To the extent that these are incorporated into daily life, the economic impact of the virus is minimised
- Political motives have produced some differences in spread rates, but the general conclusion for most developed economies is one of reasonable confidence that the worst is over and the economic threat of the virus has diminished
- The main caveat to that is evidence of resistance to preventative measures and the ability of lower income nations to access and pay for mass vaccination
- There may be a booster vaccination programme, but whether or not there is one does not alter the conclusion that the worst of the effects of Covid are now over

If this is an accurate view, then where we have price weakness related to scares about a pandemic re-occurrence this should be treated as an opportunity, so long as valuations permit.

Postscript on the investment implications

The main area where scientific opinion has shifted is on reinfection risk. From a position where this was deemed highly unlikely, the view now seems to be that protection is limited regarding reinfection, but meaningful in terms of mitigating the worst health outcomes. This is the new reality of living with Covid.

In practice this may well mean annual booster programmes become part of the world we will live in. A booster programme carries a direct cost in terms of provision and funding will be an issue depending upon the national healthcare structure.

It is not at all clear that for some countries universal coverage will be the result, with low income groups typically the worst affected. Even with a universal vaccination programme there will remain an indirect cost in terms of periods of incapacity. On top of this we have seen attitudinal shifts regarding workplace vs home working as well as shifts in work/life balance.

The jury is out on whether this adds to productivity or not and whether these shifts are temporary or permanent. The test will likely emerge when economic conditions worsen, employment becomes scarce rather than abundant, and governments face serious funding issues. The positive elements are that the advances in genomics and medical science allowed discovery and deployment of an effective vaccination in record time. It is likely that we will continue to see these advances with health benefits across the spectrum of disease treatment.

September 2022

DR SANDY NAIRN, CFA, FRSE
Director, Global Opportunities Trust plc

About the Author

Sandy Nairn is the manager of the Global Opportunities Trust plc, a self-managed global equity investment trust, and an experienced professional investor and author of three original books about investment. He has won multiple performance awards for the management of global equity portfolios.

Sandy was a founder and CEO of the independent investment boutique Edinburgh Partners in 2003. It was subsequently acquired by Franklin Templeton Investments in [2017], since when he has been Chairman of the Templeton Global Equity Group. Before founding Edinburgh Partners, he was Chief Investment Officer of Scottish Widows Investment Partnership, from 2000 to 2003, and Executive Vice President and Director of Global Equity Research at Templeton Investment Management, from 1990 to 2000.

In 2001 he published a book entitled *Engines that Move Markets: Technology Investing from Railroads to the Internet and Beyond*. In 2012 he co-authored, with Jonathan Davis, *Templeton's Way With Money* and in 2021 published *The End of the Everything Bubble: Why $75 trillion of investor wealth is in mortal jeopardy*, warning investors about an imminent severe decline in both stock and bond markets.

Sandy Nairn graduated from the University of Strathclyde in 1982 and in 1985 was awarded a PhD in Economics from the University of Strathclyde/Scottish Business School. He is an Associate of the UK Society of Investment Professionals in the UK and is a CFA charterholder

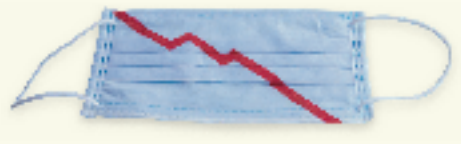
with the CFA Institute in the United States. In 2020 he was elected a Fellow of the Royal Society of Edinburgh.

Important

This material should not be considered as advice or an investment recommendation. The views expressed within are those of the author and no reliance should be placed on the fairness, accuracy, completeness or correctness of the information or opinions contained herein.

About the Author

DR SANDY NAIRN has more than 30 years of experience in fund management and investment research. He is Executive Director of the Global Opportunities Trust plc (www.globalopportunitiestrust.com) and the author of three critically acclaimed books about the stock market, most recently *The End of The Everything Bubble* (Harriman House 2021).



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