Special Report

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Questions On The Coronavirus: An Expert Answers

BCA Research's strategists are not epidemiologists, and neither are most of our clients. Even after three months of the coronavirus epidemic, there are many unanswered questions about the science: What is the mortality rate of COVID-19? How much longer will the pandemic last? How do tests for the virus work, and why has testing varied so much from one country to another? These are some of the questions that come to mind, but there are many, many more.

To get some answers, we reached out to one of the world's leading medical researchers in the field of immunology, Professor Peter C. Doherty of the *Peter Doherty Institute for Infection and Immunity*, a joint venture between the University of Melbourne and The Royal Melbourne Hospital. Professor Doherty won the Nobel Prize for Medicine in 1996 for his work on how the body's immune cells protect against viruses.

Below is a lightly edited Q&A of Professor Doherty's replies to questions from *BCA Research* strategists Peter Berezin and Garry Evans (dated March 29).

BCA Research Questions *Re* COVID-19

Question 1: What is your perspective of how the pandemic will pan out? Views seem divided: The Imperial College paper[1] suggests there will be multiple waves over 18 months until there is herd immunity. A paper from Oxford University[2] modeled that 40%-60% of Italians and British may already have had COVID-19 and as such may be immune.

We can't answer that question yet, though it may be possible within the next several months. What we lack in all of this is a rapid antibody test for mass screening.

1 Neil M Ferguson, Daniel Laydon, Gemma Nedjati-Gilan, et al., "Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand," *Imperial College COVID-19 Response Team*, March 16, 2020.

2 Jose Lourenco, Robert Paton, Mahan Ghafari, Moritz Kraemer, Craig Thompson, Peter Simmonds, Paul Klenerman, and Sunetra Gupta, "Fundamental principles of epidemic spread highlight the immediate need for large-scale serological surveys to assess the stage of the SARS-CoV-2 epidemic," *medrxiv.org*, March 26, 2020.

That will tell us how many people have been infected and have recovered. Such assays are under development in lots of places and, as the technologies have been established for other pathogens, the tests should soon be fit for purpose. Producing massive numbers of antibody test kits really fast should be a top priority. Once people are antibody positive, they will be at (or near) zero risk of being transmitters, and they should be able to return to normal life.

Even in the absence of an antibody screening test — if, say, it is true that 40%-60% of Brits and Italians have already had the disease — we should see a massive drop in clinical case acquisition through the next month or so. An epidemiologist could model this and give better estimates. Of course, we don't know that 60% herd immunity will be enough. Maybe it will take 80% or 90%.

And, of course, even if there is a major fall in the new infection rate, those at high risk, like the elderly and/or people with severe comorbidities [existing illnesses], will still be at risk so long as there is any evidence of continuing transmission. Once the "recovered" numbers shoot up and the pressure on ICU units eases they should, at least, receive optimal care. What will end the risk for some is an effective vaccine. We could also protect those who don't have a functioning immune system by giving them serum from recovered people. That's done all the time with human immunoglobulin prophylaxis and we just need to add antibodies to COVID-19 to the mix.

Question 2: How do you rate countries' (and states') containment efforts? Too little, too late? Or excessive? How quickly can we ease rules – before we destroy the economy (as President Trump suggests)?

For "relaxing the rules" see ***Question 1*** above. The various US states may give us a range of "experiments." If we relax the rules before there is effective herd immunity, we'll just see a "kick-up" in clinical cases. As to the performance of different countries: Much of Europe and the USA are clearly in the "too late" basket, we're in somewhat better shape in Australia but (within the next month or so) we'll see how well we've done. Singapore did extremely well and (with massive testing) so, eventually, did South Korea. My understanding is that both are still seeing some new cases, but expect they have that under control. Both Israel and New Zealand closed the door early, so we'll see what happens there. With no herd immunity, they won't be back in business until there's an effective vaccine.

Question 3. How serious a disease is COVID-19? Two professors of medicine at Stanford[3] suggested it is no worse than the flu. Do you agree?

Again, that goes back to the discussion of disease prevalence and background infection rates addressed in ***Question 1***. Beyond that, the death rates for clinically affected individuals are at least 10 times higher than

[3] Eran Bendavid, and Jay Bhattacharya, "Is the Coronavirus as Deadly as They Say?" *The Wall Street Journal,* March 24, 2020.

for the flu, though the actual clinical disease for those who are severely afflicted (ICU cases) may be very similar. About 40,000 Americans die each year from the flu. If the current death rate of 1.4% from the Wuhan figures is right (as in ***Question 1***, they could still be massively underestimating background infection rates) then, if the US strategy is "let 'er rip," the death rate is 1%, and 60% of people are infected, at least two million Americans will die. We shall see.

Question 4: How good are the tests for COVID-19? How do the tests work? Why has it taken so long to manufacture test kits? Is there a significant percentage of false positives and false negatives, just as there is in most medical tests? Should countries be testing more people?

See ***Question 1*** above *re* antibody. Current testing is for the presence of the virus in infected (not recovered) individuals using a Polymerase Chain Reaction (PCR) strategy (PCR is best known for identifying rapists from semen samples) to detect the SARS-CoV-2 genome. The quality of these test varies from place to place and product to product, and our lab people have, for instance, spent a lot of time checking and validating the tests used here. Positives are retested and, if done properly, the super-sensitive PCR test is pretty much 100% valid. One strategy that's being rolled out is, for example, to pool 8 samples, test, then go back and test the individual samples from the positives.

The PCR test gives a result in a few hours, but the way it's generally done is that there's first a need to extract the RNA[4] prior to expansion in a thermocycler. Strategies (and technology) for bypassing the extraction stage (saving labor and reagents) are being evaluated and may soon be available. There's also the possibility of using faster and less accurate (say 85%) "first pass" screening assays. In addition, there's a lot of work going on to develop various "point of care" bedside tests.

When it comes to the reagents used in the current PCR testing regimes, production is maxed out and businesses are bringing more facilities online as rapidly as possible. R&D teams across the spectrum, from industry to government and academic laboratories, are doing their utmost to innovate in ways that expand, and extend the scope of, testing capacity.

Across the planet, there are a lot of very smart people working on "point of care" and screening antibody assays.

Question 5: There have been many estimates of the mortality rate. What is your view?

See ***Question 1*** above: The initial death rate estimate from Wuhan was 2.5%, with that being revised (from extensive PCR testing) down to 1.4%. That could drop dramatically if antibody screening shows that many more people were infected but showed few, if any, symptoms. I think most of us are betting on 1.0%-1.5%. The Italian and Spanish figures are much higher for fatal outcomes, perhaps because they've mainly been testing clinical cases.

[4] RNA (ribonucleic acid) is a singular strand (not double strand, like DNA) of nucleotides, containing genetic information.

Question 6: Is there evidence that viral load during initial infection affects disease outcomes? If so, does that mean you are better off being infected by a passing stranger than a sick family member who you are in a lot of contact with? What does that imply for proper quarantine strategies (China quarantined everyone immediately, while the west is sending people back home to self-quarantine there)?

I don't think we know a lot about this yet. One virus particle may be enough, so it's logical that you will be more readily infected by someone who is pushing out a lot of virus. In lab animal experiments with, say, the flu, the bigger the dose, the worse the disease for less virulent strains. For a "high path" strain, even a minimal dose can kill. Viruses multiply fast, and even a very small dose can quickly become a very big dose.

It is known that people can transmit for 24, and even 48, hours before they become ill, while others can (we think) transmit but show no symptoms. Some places that are currently dealing with a COVID-19 surge are accommodating health care workers in hotels close by, and not sending them home to their families. Australians are great travellers, and we're still repatriating large numbers of people. Returning citizens who arrive in Australia off international flights are now being taken straight to accommodation where they will be housed, fed, and restricted to a single room for two weeks, under police supervision. Our government is footing the bill for this. Too many people were breaking the requirement to self-quarantine at home.

Question 7: Is COVID-19 likely to be seasonal, like many influenzas?

We shall see. Too early to say. Once we're through this acute phase and have substantial herd immunity (enhanced by a vaccine) there is a possibility that it could "burn out" and disappear. A more likely possibility is that it will hang around as an annual, "flu-like" disease that (if it mutates significantly) may require (as for the flu) regular "tweaking" of the vaccine. Also, among those who have had the infection and survived, I'd expect there will be "background" CD8+ (killer) T cell memory that will give a measure of cross-protection. There won't be a repeat of what's happening now, at least not for SARS-CoV-2.

Question 8. What is the risk that the virus mutates? Could it become more virulent?

Most of the selected flu variants are escape (from antibody neutralization) mutants that, if they emerge as novel "seasonal" strains, require us to make a new vaccine. When flu strains mutate in ways that change the pathogenesis of the infection, they usually go to lower virulence. That happened from 1918 to 1919 with the "Spanish" flu. People who are infected and excreting the virus, but are otherwise reasonably well, are more likely to infect others than those who are out of circulation, at home, or in a hospital bed.

Coronaviruses have a "proofreading" capacity that the flu viruses lack, so should throw off many less mutants. We have, though, evidence of substantial gene deletions in coronaviruses, particularly after replication in tissue culture. As a general rule, the expectation would be that such variants would be "less fit" in the replication/transmission sense.

Question 9: Do people who have had COVID-19 have immunity permanently?

We'll only know the answer to "permanently" in the much longer term. My expectation is that people who have recovered from mild to severe infection will be protected from reinfection for, at least, a year or two, and likely much longer. Some suggestions of acute reinfection based on sequential PCR testing are, to my mind, more likely to reflect that, while the virus may have been persisting at low levels deep in the lung, a negative test may have been recorded from the upper respiratory tract. That could read as positive again if, for instance, the subject has coughed-up stuff from down below. People who had been infected with the 1918 H1N1 flu virus were still protected when a similar virus came back in the 1970's.

Question 10: How effective are masks for reducing the risk of catching the disease and passing it on to others if one is a carrier? Would universal mask wearing be effective at combating the virus?

Probably, as long as it's a good N95 mask (or better), if you can bear to wear one of these things, and if it doesn't get soaked with dribble/snot/mucus. Quality masks are certainly important for trained health care workers working at close quarters with patients but, otherwise, for general wear, the opinions of informed professionals are mixed.

My personal strategy is to have one round my neck if I have to go into a store or find myself in a situation where there are too many people, then pull it up when I need it. Think about it, if the mask is contaminated and wet, it's better not to have it over your nose when you're out in clean air. Nobody's absolutely certain but, in still air, we're probably reasonably safe at a distance of 2 (better 3) metres or so.

Most think that the virus is in sneezed mucus droplets in the air, not as minute, dispersed virus particles. That's why it's important to cough into a tissue (or your sleeve), and sneeze into a tissue. And there are strategies for reusing masks multiple times. Such information can be found online.

Question 11: Is there any work taking place trying to determine which genetic traits may predispose an individual for suffering the worst symptoms of the virus?

Given the current allocation of major resources to immediate needs, any detailed genomic analysis will likely be retrospective. From other diseases, we do know some of the markers that should be looked at. In addition, using the very sophisticated molecular technologies available to us, detailed analysis of blood (particularly white blood cells) and other samples from COVID-19 patient material should point to a number of possibilities. That could feed in immediately to recommendations, *re* therapy. This will be a fascinating and informative area of investigation.

Question 12: How quickly will a vaccine be ready? How long will it take to produce 7 billion doses?

The usual answer is 12-to-18 months, but we just don't know. An mRNA vaccine has already gone into people's arms in Seattle (*Phase I Safety Trial*) and the Australian "protein clamp" vaccine is in lab animals. In humans, the standard protocol is to go through a small phase I safety trial, a larger phase II safety/efficacy trial, then a large phase III. If all that goes smoothly, then the rate of production for vaccine doses obviously depends on the nature of what has to be made.

The problem with any vaccine is that, as it will be given to large numbers of regular individuals, it has to be both safe and efficacious. Earlier, experimental SARS and MERS vaccines gave some negative safety signals in lab animal tests, though at least one SARS product looked to work well and have no deleterious side effects when tried in rhesus macaques. In short, I'd be very surprised if we can't make a good COVID-19 vaccine, but we need to proceed with caution.

The other point is that, once we have a reliable antibody screening test, we won't need 7 billion doses of the vaccine straight off. If we've achieved 60%-70% "herd immunity," those who are already immune as a consequence of being infected can wait for a later "booster" vaccine shot. In this context, children, who aren't showing much disease could, unless there are identified risk factors, be left until later. In any case, many will probably be antibody positive after subclinical infection.

It's also likely that most frontline personnel will be antibody positive and will have been tested. Though the vaccine may still be a while off, we could test very widely for antibody positivity within six months. That is essential if we are to get people back to work and return to something like normality for, at least, the majority.

The primary target group for the vaccine will thus be those who have been isolating due to comorbidities or age, the over 60 age group. As with the flu, we may need a higher vaccine dose for these individuals, especially those over 70. Another priority population will be those in remote and indigenous communities, especially if we've been able to keep the virus out by in-country quarantine.

Question 13: There is talk that some existing drugs (for example, drugs used to treat malaria) may be efficacious on COVID-19. Is this likely to be true? How would these drugs work?

Yes, there are a number of pre-existing drugs under test, including hydrochloroquine that has long been used for malaria, and an experimental anti-ebola drug (*Remedisivir*). At this stage, product availability, even for robust, quick, clinical trials, is an issue. It's also a safe bet that there are already specific anti-SARS-CoV2 drugs being made in various laboratories, but these will need to go through safety testing. The antiviral drugs will likely be of most value if used early on in the infection. It's also possible that some of the interferons (especially β interferon) that are made normally by virus-infected cells could be useful if given at high dose for therapy.

A different therapeutic strategy is directed at diminishing the "cytokine storm" that can occur in those who require ICU-level care. As part of our "innate" host response that occurs immediately after infection, various cell types make a host of defence molecules that are broadly classified as cytokines and chemokines. These can help to "hold" the infection for a while before the specific (adaptive) immune response, that clears the virus and establishes antibody (*B* cell/plasma cell) and T cell memory, cuts in after 6-10 days or so.

Later, some of the cytokines and chemokines may also be involved in tissue repair, but they can be a major problem (early or late) if they are over-produced, causing vascular leakage (oedema) and excessive inflammatory damage. Blocking these effects by treatment with monoclonal antibodies (mAbs) directed at these molecules may help to reduce the inflammatory damage that limits gas exchange in the terminal bronchi, and pull very sick patients back from the brink.

Following early, promising results from Wuhan, a great deal of effort is being directed at the use of monoclonal antibodies (mAbs) to neutralize cytokines like interleukin 6 (IL-6). Other "pro-inflammatory" cytokines that are being looked at include IL-1 and TNF-α. People with various autoimmune diseases (eg., rheumatoid arthritis) are already being treated with these mAbs, so getting approval to use them in severe cases of COVID-19 should not be a major issue.

The point here is that, if you are in a "high risk" group due to age or comorbidities, isolate yourself as effectively as you can. The longer you can delay contracting this infection the more likely it is that life-saving treatments and/or a vaccine will be there for you. At the moment, most of the therapies discussed above are not available, with all the "product" that is at hand being used in various trials.

Question 14: What are the likely long-term health consequences from the disease in terms of lung damage and other considerations?

Likely severe and the possibility of permanently diminished lung function (with more stress on the heart) in those that are saved by ICU intervention, but the extent of that would also be related to age and general lung capacity. Elderly people who survive a bad dose of the flu are often tipped over into rapid decline.

Question 15: In the past few years, we have had SARS, H1N1, MERS, Ebola, etc. Should we assume that virus epidemics will become regular occurrences? Why have they increased in the past two decades? How high is the risk of a pandemic with a much higher mortality rate than COVID-19, that would kill a significant percentage of the population?

There's no way of answering that, though if we look at the "3 bat-origin CoV amigos" (SARS, MERS, COVID-19), the currently circulating SARS-CoV-2 virus is the most infectious and the least lethal. I discussed some of this for COVID-19 here.

Though it's a 2013 book, such issues are also considered in "Pandemics: what everyone needs to know." That's in an easy-to-read Q&A format, which also explains the basics of immunity.

Clearly, rapid air travel, forest clearance, factory farming, and ever increasing population size are all factors in the risk equation.

Question 16: What are the long-term lessons of the pandemic for health care services globally? How should pandemic planning improve? Do we need significantly more ICU facilities? Do we need to dramatically increase spending on health care?

See ***Question 15***. No medical system could ever build in sufficient capacity to deal with something like COVID-19. All countries might, though, think about restoring some of their own manufacturing capacity so they are not at the end of supply chains. Consideration might also be given to establishing an immediate response that, given any suggestion of an emerging pandemic, ensures that the available, "in country" medical supplies are not exported, for profit or some other motive. Either governments need to maintain stockpiles, or there needs to be legislation and immediate enforcement/surveillance to stop this.

Health care spending is already a massive cost for many governments. What might be seriously looked at is the way health care systems are organized and the dollars deployed. Canada and Australia are, I think, examples of good, effective taxpayer-funded systems, while the USA is, by any criterion that links cost and the deployment of services through the community, clearly a disaster.

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