COVID: The whole truth or most of it. Tom Boyde, 25th May 2020

Introduction - from a London base.

Matthew Syed in the 'Sunday Times' of 17th May takes a justified view, even a fair view, of the science around COVID and two other stories in the same issue similarly merit attention - a diary of early events in Wuhan, from Fang Fang (highly critical of the authorities though it is unclear how far justified), and scathing attacks on a study from Manchester University which dared to suggest that many more people in Britain have been infected by the virus than is officially supposed. Here follow, first, a survey of the nature of the problems, then analyses of what is publicly known, as illuminated by personal experience, and what action can or should be taken. It may appear that journalists have not done very well (they're supposed to know about words if nothing else): then again the pundits identified as doctors or scientists have not done much better or not until the last few days, with honourable exceptions in the 'Spectator' of 2nd May and 'Private Eye'. Petty instances of ignorance: 'molecular' is not a synonym for nucleic acid: *fomites* is the plural of Latin *fomes* not fomite (the latter being a back-formation roundly condemned by the Oxford English Dictionary).

In thinking (not necessarily when talking) about the epidemic we should distinguish between virus, infection, illness, disease and epidemiology ('disease' includes disease mechanisms - 'pathology' as properly understood). These are different things: studies of each one should inform studies of the others but each has its own sphere both conceptually and in practice: for example, a virus is not an epidemic, viruses are not alive, people don't die of the virus …. .

The structure of the epidemic.

We can accept presumably that the first definite cases and first deaths occurred in Wuhan; doctors there saw one or two, then more and more, patients with a severe respiratory illness and came to realise that there were common features sufficient to define a new disease or syndrome. It takes a while to reach that understanding and your bosses don't like being asked to do something themselves and spend money budgeted for other purposes; problems not confined to authoritarian regimes or even governments. A lot is said about transparency and treatment of individuals, but by any objective yardstick the public-health actions taken by the Chinese authorities were prompt, vigorous and rational, and the nucleic acid sequence of the new virus was disclosed to the world within about two months of the first cases; probably a record. Just possibly, we might all be better off now if other governments had been more alert and receptive to the Chinese experience. And 'rational' here does not mean correct or best possible, just 'based on reason'.

The source of the virus? Conspiracy theories sell newspapers. It is indeed conceivable that the new virus is a deliberate or accidental laboratory release; but did that occur in China, or in the USA for use against China? - twin hypotheses about equally likely and for both the probability is very close to zero. In short, it is an animal virus until proved otherwise.

Means of spread and incubation period: these must be discussed again in connection with disease mechanisms, but it was obvious early that there was a rather long incubation period (anyway for a coronavirus-based disease); obvious too that this would make it much more difficult to predict spread and plan for containment. If people are infected and don't know it, what can be done? Well, one thing is testing contacts, another is lockdown, but neither is much good unless done thoroughly; and a muddled or partial lockdown guarantees a second

wave. We assume that spread is by droplets, contact and *fomites*, because we are dealing with a coronavirus, so it does seem rational (again not *necessarily* correct) to use face masks, disinfect surfaces, maintain social distancing and so on. There is scant evidence that any of these things work for *this* epidemic, however, because all the analyses are confused by huge numbers of symptomless spreaders .

As it happens, an instructive, early, 'Experiment of Nature' is on public record. The ship 'Diamond Princess' had 3700 people on board of whom about half were passengers, mostly elderly people, and since a cruise ship is not an isolation hospital it is a fair assumption that all 3700 had contact with the virus. One 80-year-old who boarded in Yokohama on 20th January, left the ship in Hong Kong on 25th January, fell ill and was admitted to hospital on 1st February and tested positive. The ship was quarantined in Yokohama on 4th February until the end of the month, all on board were tested, some 700 were positive for virus nucleic acid though half of those 700 did not develop any symptoms at all, total 14 died.
What can be concluded? i] If that first case got infected on board, virus was already present, and incubation no longer than 12 days: but it seems much more likely that he was the one who brought the virus to the ship, suggesting an interval between exposure and serious illness more like 20-30 days though he was infective long before he became seriously ill. ii] Either the nucleic acid test gave a lot of false negatives or only 20% of those exposed were infected, or both: perhaps only 20% could be infected; and if so, susceptibility varies a lot. iii] Only half of those testing positive had symptoms; that is 10% of the total exposed. iv] A few became terribly ill; of those with symptoms 4% died - that is 0.4 % of the total exposed and we should recall that this total included a high proportion of older, vulnerable people..

What is the incubation period? First, what does the question mean - from exposure to first symptom, or to becoming infective, or to becoming seriously ill? Next, for how long does a person remain infective; after exposure, after first symptom, or after becoming very ill? The truth is, there is nearly no hard evidence in answer to any of these questions and yet guesses of some kind must be made to start using any of the epidemiological models, and they must be good guesses to calculate a correct R value (number of new infections per case). Can direct clinical observation provide clues?

Personal experience as a clinician.

My own clinical practice (in addition to pathology) is such that we rarely saw coughs and colds, "upper respiratory tract infections" (URTI), until this year, when they began to appear in numbers already in January. Two young male relatives had severe chest infections in February/March, one shortly after returning home to Sydney after a business trip to China, the other in London after a business trip to New York. Right now, patients are coming to my clinic with long-standing, slowly-progressive, slow-resolving throat and chest symptoms of kinds never seen before, notably a special kind of throat discomfort, possibly due to swelling of the tongue (a lymphoid organ), and a sense of oppression or tightness of the chest; many also have symptoms of immune-system over-activity such as evening rigors, sleeplessness, limb pains; beginning 3 to 4 weeks after they were first taken ill in a more ordinary way; nearly all have no detectable signs or measurable fever; rather few have loss of smell or taste: the most common sign is accumulation of exudate in the middle ear though only mild inflammation. I am obliged to propose, from personal observation and without reference to the COVID story, that a new respiratory virus disease appeared early this year, was already widespread in February all over the world, and has a prolonged clinical course though few patients become dangerously or even seriously ill. If (though only if) my cases are in fact due

to COVID infection, I can tell the government and whoever else is willing to listen that COVID deaths in this country in March and April were due to infections in January and February; the same is true of the USA; most people who can be infected already are (that means most of those susceptible; in Britain some 10-20 million just like that Manchester study said); a second wave is inevitable but the death rate will be much less than in the first wave - especially as we shall be counting as cases those who are symptomless but test positive whereas first time around the testing system wasn't up to snuff.

Disease mechanisms ('pathology').

Viruses don't grow by themselves; they induce the infected cell to both replicate the viral nucleic acid genome and synthesise viral proteins; which act in spreading infection by several different tricks. So it is not obvious from first principles that there must be illness following a viral infection. The body's reacts to recognise the 'foreign' molecules and stimulates the immune system by an outpouring of hormones best-known under the name 'cytokines'. They are made by immune-system cells and induce other relevant immune-system cells to replicate furiously and make antibodies, T-cells with appropriate receptors, etc., in rapidly increasing numbers and improving precision. Cytokines have other effects such as fever and allowing more fluid to leave blood vessels (for example, the swelling from inflammation of any kind). In CT scans from the very earliest days in Wuhan, available publicly, we can see massive fluid outpouring into the lungs: some people even thought that was how to diagnose the infection but really it is one manifestation of immune over-reaction; 'cytokine storm' or 'toxic shock', like in meningococcal infections; and is one of the ways that patients die and why artificial respiration is often necessary. Deaths of young people have often been like this or by other auto-immune reactions (the immune system triggered to harm one's own body) including, commonly, thrombosis affecting the smallest arteries. In older people and those with other illnesses, there are additional ways. Longer-term illness includes fibrosis of the lungs and other organs (also a kind of auto-immune reaction). Key to understanding is that the virus itself is not lethal; failure to react, over-reaction, bizarre reaction, failure to deal with secondary bacterial infection - these are the mechanisms of severe illness and death. So there is not just one kind of illness, but many, varying with the response of the infected person; not one disease but many even though there is just the one root cause.

Testing and Immunity.

In principle we can test for the virus itself or antibodies against it, in the first case either the virus genome (nucleic acid sequence) or a virus antigen. 'Antigen' here means a virus protein, but there are several and to produce such a test means choosing either one of them or a crude mixture and then proving that detecting it can be done with 100% accuracy and is reliable as a test in the real world: both are difficult, and anyway the virus might then change on us, mutate, and render our test useless.

When people talk about 'molecular' methods they generally mean nucleic acid sequence detection - which might be by simple hybridisation or the more sensitive and reliable PCR. With reasonable skill and luck, the latter methods may be 100% correct at laboratory level though there is always the chance of mutations affecting nucleic acid sequences and throwing everything out of gear. Greater difficulty lies in collection and transmission of samples. Laboratory work is maybe 10% of the total effort and expense, and can be readily expanded; not so the training and deployment of sample takers and those who then ensure that results are correctly transmitted, received and acted upon. Just the act of taking of samples from

throat and nose is difficult enough and many examples including those already given suggest that misleading negative results have been and continue to be very common. Sir Paul Nurse was talking sense about these matters, on BBC radio, 22nd May.

In 'The Times' of 23rd May, information is given about approval of a new bedside nucleic acid test giving virus detection in 75 minutes and very few false negatives. But what is the evidence for this and many similar claims? How do you know that a negative is false? It will be great if tests really are that good but scepticism remains justified for now and indeed we know that there are dozens of highly-dubious bedside tests on the market.

Antibody testing uses isolated, perhaps laboratory-synthesised, viral antigens to find out whether a patient already has antibodies to them circulating in the blood stream. Here too it means choosing your antigens or else using a crude natural mixture. We expect the first antibodies to appear will be IgM, perhaps after ten days or so though that varies from one disease to another, followed by IgG and the other less-often-talked-about kinds IgA, IgD and IgE. It makes sense to test for both IgM and IgG, the latter being usually more persistent and more specific. In an ideal world the presence of antibodies is proof of previous exposure (not necessarily illness) and will provide immunity: the world is not ideal so both of those are problems for study rather than established fact. By the bye, antibodies are not 'Y-shaped molecules' (only the elementary diagram is truly Y-shaped) and there is no rule either to say there are two antigen-binding sites per antibody molecule: in human IgG it is two, in IgM, ten - for good reasons.

Immunity to coronaviruses generally is said to be neither strong nor long-lasting - which may be because of mutation of the viruses, yielding strains with antigens sufficiently different from the last lot that neither testing nor immunity can be relied on. In the case of influenza, a new set of vaccines is made every year: COVID may turn out similar, but actually we don't yet know that and the world might just get lucky. There is talk of already many mutated strains of the COVID virus but it is also possible that immunity to one coronavirus provides some resistance to a new one (part of that variable susceptibility?).

Isolation: Test and trace: Source of infection.

Public Health is very different from ordinary curative medicine both in principles and in practice: inhumane decisions may be required; to be blunt it may be sometimes better to allow sick people to die alone if that prevents a vicious infectious disease spreading to the whole population. Eliminating the source of infection is obviously much better, if it can be done, and the first definite success was in a cholera epidemic in London in 1848 - Dr John Snow and the Broad Street pump; brilliant, but rarely possible to replicate. An alternative, if circumstances permit, is to trace the contacts of each infected person and treat or isolate them: required are methods to identify those infected, a skilled workforce, sufficient resources and a bit of luck, because the circumstances must indeed be appropriate. South Korea appears to have done very well using this approach; they must have thrown all possible resource at it, and quickly, but perhaps also they had that bit of luck in that there was just one major source of their outbreak. Can this possibly work in Britain? I suggest that it cannot and will not succeed because i] the testing methods available are not good enough (taking all aspects in to consideration), ii] the new workforce lacks skill and experience, iii] there are already far too many infectious and/or convalescent people out there - not just a few hundred who attended one church service, as in Korea.

Epidemiology: the 'Science'.

Epidemiological models are mathematical equations. However good an equation or a computer program may be, the answer obtained depends on the unknowns and parameters we put in, such as that magic R figure. Suppose i] that the R deduced from observation depends upon assumptions about the incubation period, ii] those assumptions are wrong because iii] the incubation and infectivity periods are much longer and iv] the number of infected people is much greater than has been estimated, because v] the testing system is not good enough - then all predictions will be wrong. In short, the 'science' upon which the UK government relies in trying to deal with this epidemic is unsoundly based, little better than guesswork. It does not follow that the politicians have made wrong decisions; it does seem worthwhile thinking how this could happen in a country and a subject area where, 172 years ago, we led the world; and one possible answer is that a Public Health system complete with Medical Officers of Health, laboratories and isolation hospitals was deliberately dismantled forty years ago as part of the drive to commercialise the NHS; making it supposedly more efficient - whereas of course it merely became more profitable for some people and has had to be revamped to deal with this epidemic.

Susceptibility: Ethnicity and Social Class.

The figures suggest that in Britain 'BAME' people have experienced higher rates of severe illness and an understandable suspicion is that this must be because of social and financial deprivation. Of course and indeed, there could be such a contribution; no contest; but genetic differences between people perhaps also affect outcomes. Examples: it may be that East Asian people are more resistant on average, helping to account for the remarkably quick control achieved there; British BAME deaths have included prominent and well-off members of society, including senior doctors (who bravely exposed themselves); certain African countries have had, so far, unexpectedly low case numbers; and even in supposedly homogeneous populations there is great variation in susceptibility, which also is more likely to be immunology- or gene-based than of social origin.

Treatment and Vaccination.

Viruses are not alive so we can't kill them with antibiotics. Antiviral drugs work differently and in different ways for each of the very few examples where there is something effective. Hydroxychloroquine is not an important antimalarial (that's chloroquine): even if it did work in COVID there is no reason to expect benefit from other antimalarial or anti-parasitic drugs; but oddly enough it works well in some autoimmune diseases, notably Lupus, so might be helpful in COVID for that reason - a question worth asking, and a number of hasty trials have been done with so far little or no evidence of benefit, and it is the same with most other drugs, including antivirals. Known helpful treatments are antibacterials (for secondary infections) or supportive, to do with life-maintenance. Various kinds of immune suppression (including corticosteroids such as dexamethasone) may soon appear as valuable.

Vaccines: Much of the background has been covered already. To develop a vaccine that is both effective and safe must take time; let's encourage that work. But even when we have a good one it is impossible to know how long immunity will last until it has been tried out in the real world - and other known coronaviruses are notorious immune evaders. Vaccines based on three very different principles are under development by the numerous and varied teams involved: i] virus antigens; ii] virus nucleic acid (modified for safety) delivered within

a completely different and non-dangerous virus; iii] virus-derived mRNA alone, packaged so as to gain access to the host cells, and which will then directly instruct the production, on site, of virus-antigen proteins. *Only the first kind has ever been widely used before (in other diseases) and though early tests are encouraging nothing can yet be guaranteed*.

How bad is the situation, overall, really?

The great majority of those exposed to the virus do not become infected or if so never even know it or don't become seriously ill: a fair proportion will have troublesome symptoms for many weeks: a small proportion become terribly ill with many of them dying in a distressing manner, something that neither can nor should be under-rated. It remains true that up to now and looking at it from a dispassionate, 'Public Health', kind of viewpoint; as an epidemic this is a pussycat, no way comparable with the huge influenza and other epidemics of the past. It seems likely that when it is all over and some serious counting is done we shall find that there were many more deaths from the panic than the pandemic.

Did the UK government have any alternatives; and what can be done about the economic impact? It seems certain that lockdown was too little too late, if needed at all. In the light of Chinese experience that was already becoming known, action about 1st February, might have delayed spread in Britain; but delayed only, the true infection rate is so high that prevention of spread was already impossible. Even if test and trace had been introduced with the same vigour as was shown in East Asia, it is very unlikely that infection could have been contained in the very different socio-political and genetic situation of Western Europe and North America. But then if politicians had been told truth instead of being fed those half-baked constructs, if in turn they had told the people truth, would we have accepted lockdown? Would it have mattered if we didn't?

What, then, shall we do?

Ministers thought they had to be seen to do something, anything; so if what they did has not been successful, is that a surprise? If narrow-minded, party-political, personal-advantage thinking had not influenced their actions we might have ignored the whole thing. Would that have been better? Well, probably yes!

Much bigger problems lie in the future and the economic disaster that we face. Again the position of a national government is unenviable, because an economy is not just us alone; it is influenced, even dominated, by the rest of the world and what other countries do. The proposition now formally advanced, nevertheless, is that there is no point in continuing with lockdown and quarantine. Neither has helped; neither is going to help anyone. Whatever other countries do, open the borders, re-open business in Britain; people will continue to get ill and some of them will die, but no worse than what was going to happen anyway. A severe depression will continue for many months because financial markets are like that - they have momentum and are heavily influenced by panic - but if the causes are removed now recovery will come sooner, the wave will not run so far up the beach, the undertow will be less, a fascist revolution less likely.