Possible pathways to the end of the COVID-19 epidemic: health and scientific considerations.

COVID 19 is a completely new disease with high transmissibility, a low but significant morbidity and mortality and there is no pre-existing immunity in the population. It is a global pandemic and knows no borders and there is much that we do not know about it from a scientific and medical perspective, although information is rapidly accumulating. This paper concentrates on the medical and scientific aspects of the next stages; wider aspects relevant to policy decisions including economic issues are covered by others. It is focussed specifically on the UK domestic response.

1) As a recap, the **medical aim is to minimise mortality** over the course of the epidemic. Excess mortality will come from a number of causes:

a) *Direct mortality* from people dying of the virus despite best medical care.

b) *Indirect mortality* from NHS emergency services being overwhelmed and degrading care both for those with coronavirus and for those with other medical emergencies.

c) Increased ill-health due to *postponement of important but nonurgent* medical care whilst the NHS is diverting resources to manage the epidemic.

d) In the long-term any prolonged *increase in poverty* due to our countermeasures will feed through to poor physical and mental health outcomes.

We should recognise that there is potentially tension between these aims. For example the flatter the coronavirus epidemic curve is made, the lower the mortality from coronavirus directly and indirectly (a, b) but the longer the epidemic, so there may be higher mortality and morbidity due to postponements and a bigger impact on increasing deprivation (c and d). Currently the key measure is coronavirus specific mortality, but in the long run all-cause mortality will be an important metric.

2) The immediate tactical priority is to ensure that deaths due to the NHS critical care and other capacity being overwhelmed does not occur. The approach taken is a combination of reducing the peak numbers through social distancing (which also reduces direct coronavirus deaths) and by expanding NHS capacity. Although the aim is not yet achieved, this paper starts from the point it is achieved, and looks to the next stages out to the end of the epidemic.

3) Central to future planning is that if R, the force of transmission, creeps back above 1 for any prolonged period of time, exponential growth in cases will resume with the inevitable impact on the NHS. There are a number of options to maintain R at 1 or below. None is easy and all are painful socially and economically.

4) Two critical pieces of information remain unknown. These are the proportion of people with infection who get it *asymptomatically* (likely to be available in crude approximation in the next few weeks) and the *nature and duration of immunity* that might occur after natural infection.

5) There is no reason to believe that this global pandemic can eradicated, (only one human disease, smallpox, has been eradicated). The epidemic will therefore have to be managed by some combination of three possible routes, which are not mutually exclusive. These are: (i) a *vaccine*; (ii) *drug treatments/prevention*; (iii) *managing the natural shape of the epidemic curve* through public health measures.

Vaccines.

6) A vaccine can be used in a several ways to help manage down the epidemic. Broadly in public health terms these can be divided into an *epidemic modifying* vaccine strategy and a *disease modifying* vaccine strategy.

7) An *epidemic modifying mass vaccine* strategy aims to induce immunity to the infection at the population level and therefore stop the epidemic. Individuals who are vaccinated are protected and they also protect those around them through their immunity (the more people who are resistant to becoming infected the more effective R falls). To be epidemic modifying the vaccine has to be very safe (because it is used in the entire population) and highly effective. Because of this need for efficacy, safety and scale, it may take longer to produce a potentially epidemic modifying vaccine than a disease modifying vaccine.

8) A *disease modifying vaccine strategy* aims to protect all or selected vulnerable parts of the population from the worst effects of the disease, even if the vaccine is not capable of complete protection against infection. It might for example ensure that those vaccinated are much less likely to die from the disease. A partially effective vaccine may be sufficient for this purpose. The epidemic may continue its natural course but with significantly reduced mortality and long-term health effects. An example of this kind of vaccine strategy are vaccines against shingles in elderly citizens; it does not have a significant impact on the epidemiology of chickenpox but does reduce the effects of the disease. In practice seasonal influenza vaccine is used in this way to protect the most vulnerable.

9) One variant of using vaccines for affecting epidemics is *ring vaccination* where the contacts of those who are infected all rapidly given vaccination. This was used in Ebola and eradication of smallpox but is unlikely to be relevant to this epidemic.

10) Whilst an epidemic modifying vaccine would theoretically be ideal, the probability of having one that can be used at scale globally in the next calendar year is not high. There are multiple vaccine candidates, some already in early clinical trials, but the large scale safety and efficacy studies and manufacturing scale up the would be needed will take many months. It is also possible that a safe and effective vaccine for COVID-19 will not be developed for a very long time (or even ever) and therefore a strategy which relies solely on there being one available is highly risky.

11) Preventative alternatives to vaccines are also in development (for example neutralising antibodies, small interfering RNA inhibition of virus replication etc). These might provide shorter term protection for a few months and could be of value in protecting those at highest exposure (eg health care workers), or the particularly vulnerable during outbreaks. None are yet in clinical trials.

Drug treatments.

12) There are many major infections for which we do not have an effective vaccine but where drug treatment reduces mortality to low levels. The same epidemic curve in terms of infections will therefore produce a much lower impact on direct mortality and the health service. Major potentially epidemic diseases such as HIV, TB, typhoid and malaria largely depend on drug treatments rather than vaccination, and the same could be true for COVID-19.

13) Drugs can be used to *treat* the infection itself and prevent disease progression, or be used in severe cases to prevent death and shorten time in intensive care. The epidemic continues it natural course but without significant mortality.

14) Drugs can also be used as *prophylaxis*. This could be long-term prophylaxis of vulnerable patients providing a form of chemical shielding, occupational prophylaxis for those at high risk of infection for example in healthcare workers, or prophylaxis of contacts of cases as part of a contact tracing system.

15) Currently the priority in clinical trials is to test existing drugs for which we have licensed products, known side effects, drug supply and manufacturing capacity. There is a reasonable chance that this repurposing of older drugs may discover combinations which take the mortality from COVID-19 lower (below 1%) and could suppress transmissibility. We may have initial answers within weeks.

16) It is likely however that drugs that very substantially reduce mortality or are protective enough to change the course of the epidemic will have to be designed and developed specifically for coronavirus. If so this will take at least a year and probably a lot longer, and success cannot be guaranteed.

17) Research to develop new vaccines and drugs must therefore be seen as an essential medium to long-term investment, but is unlikely to change the path of the global pandemic over the next 12 months, and may take much longer. It is an area that the UK is very strong at and we should do everything we can to develop new options and create new infrastructure and industry.

Modifying the epidemic curve through public health interventions.

18) Once the initial peak is under control and new cases are falling, if all social distancing interventions were to stop R would rise rapidly back to close to its initial R_0 value of around 3 and the epidemic would resume exponential growth with a doubling time of a few days. We would rapidly return to a second wave with a risk of ICU capacity being exceeded. The newly increased capacity in the NHS would delay but not prevent reaching the point where it was overwhelmed. Any relaxation of social distancing measures which leads to R>1 as a long-term trend will also lead to exponential growth of the epidemic, albeit at a slower rate at lower values of R.

19) Once the morbidity and mortality rate has dropped from its initial peak and the NHS urgent and critical care capacity has not been exceeded, there are broadly three possible aims.

a) *Suppress the virus to the lowest achievable level*, accepting eradication is not possible. This would imply a more aggressive social distancing policy to get R well below one and more intrusive public health measures. These measures would probably need to be maintained until a sufficiently effective vaccine or drug is available as population immunity would take a very long time to accrue. It would minimise direct coronavirus deaths but is likely to lead to higher rates of other indirect causes of mortality and morbidity.

As a subset of this approach it is possible to consider an approach in which infection is supressed to a very low level through social distancing, and then maintained through rapid case identification and automated efficient contact tracing. Individuals would need to be isolated very actively but the population as a whole would have reduced social distancing measures (see track and trace below), although it is unlikely they could be abandoned. This approach may be very difficult to achieve if the rates of minimally symptomatic or pre-symptomatic transmission are high.

b) *Maintain sufficient social distancing measures, combined with enhanced shielding, and keep R at or just below 1*. With this approach population immunity should gradually accrue (assuming that immunity does occur in everyone infected and that it lasts) whilst the most vulnerable are shielded. There would need to be work to identify more accurately the vulnerable in all age groups. The NHS

would continue to be able to provide urgent care but other care would be reduced unless NHS capacity could be scaled quickly. Significant social and economic restrictions would need to be in place probably for about two years based on current data unless asymptomatic infection is at much higher rates than currently estimated (we may have an answer to this within weeks). This could also be combined with a track and trace approach that would again allow reduced but not abandoned social distancing measures.

c) To *cycle* between periods of greater social distancing to push the R significantly below one leading to drops in case numbers, followed by periods of relaxation during which numbers grow again. This is conceptually attractive but is operationally likely to be hard. Theoretically this could also be done regionally or when outbreaks occur locally but again this is operationally difficult. It could be combined with very active track and trace approaches to rapidly isolate cases and contacts.

Current modelling is relatively crude and achieving a package which keeps R just below one will be difficult to do with precision. All measures will require accurate, fast data collection and analysis. We do not have data on how durable public acceptance of social distancing measures will be, or the effects on adherence and public acceptance of imposing, lifting and then re-imposing them is.

Testing.

All of the approaches require testing to be substantially increased in scale, speed and accessibility.

20). *Direct virus testing* (acute testing/swab based testing/antigen testing/PCR) is an important tool for clinical management, and for allowing workers who are self isolating to return to work. On its own it has little impact on the epidemic curve.

21) *Track and trace*. This has been put forward as an alternative to social distancing (and is used as part of the package in South Korea, China, Singapore, Hong Kong, although in all cases is ***combined*** with social distancing as well). It is a variant of conventional case finding, contact tracing and isolation, but can be automated to allow it to happen at scale and quickly (eg through phone-based tracing). To be effective it would require initial rates of transmission to be low, and would need to be alongside rather than instead of social distancing measures. To be efficient it would have to be accompanied by widespread rapid viral (PCR/antigen) testing so that people and contacts of non-cases were released from isolation early, and positive cases and their contacts identified quickly. It should be seen as an enhanced and targeted version of the 7 day Stay at Home and 14 day Household Stay at Home that has been used from early in the epidemic. It is unlikely to be sufficiently effective on its own but could mean that fewer social distancing measures were required for the population as a whole, combined with much greater targeting of individuals and groups in response to test results.

22) Using *antibody testing* to release NHS/critical workers/volunteers for shielding/general workers into the general workforce ("immunity passports"). There are two limitations of this at present. The first, and most important scientifically, is that we do not yet have clear evidence that presence of antibodies correlates with substantially reduced infectiousness to others, nor do we know that it confers protection for the individual or for how long. It almost certainly does mean that people will not get severe disease, but will not necessarily translate into not getting infected, or becoming infectious (although it is likely at least for a time). The other practical reason is that early in the epidemic the proportion of people infected is likely to be low and therefore the proportion immune will also be low. As a tool it will therefore become more useful for returning workers to the workplace as the epidemic progresses. On its own it will have only a marginal impact on the

epidemiology, but as immunity develops across the population it may be possible to relax social distancing measures for some and still keep R<1.

23) For the next six months period variations on social distancing, possibly enhanced by track and trace, alongside shielding the most vulnerable provide the most realistic routes to controlling the effects of this epidemic. In the longer run (assume >12 months) vaccines or drugs may provide a technological exit strategy, but they will take time and should not be relied on as the easy way out. It is a policy choice whether to run R as low as it can be achieved, implying very long-term suppression of the epidemic or running R as near to 1 as it can be managed within the boundaries the NHS can cope with. The latter would imply an ongoing significant direct COVID-19 mortality but potentially with less social damage and indirect mortality, and quicker although still lengthy exit from the epidemic as population immunity accumulates (assuming it does).

24) If the proportion of asymptomatic infections is much higher than anticipated, the degree of immunity in the community is higher than expected, or the drugs in current clinical trials show reasonable effects then other options could be considered.

25) Five key technologies are likely to provide help with exit – quick accurate testing at scale, data systems to monitor epidemic with regional granularity, automated contact tracing, drugs and vaccines. Of these the two technologies which are sufficiently mature it is currently mainly about operational deployment are tests and data. Drugs, vaccines and automated contact tracing all have discovery and development risks. The UK needs to have a clear approach to all 5.