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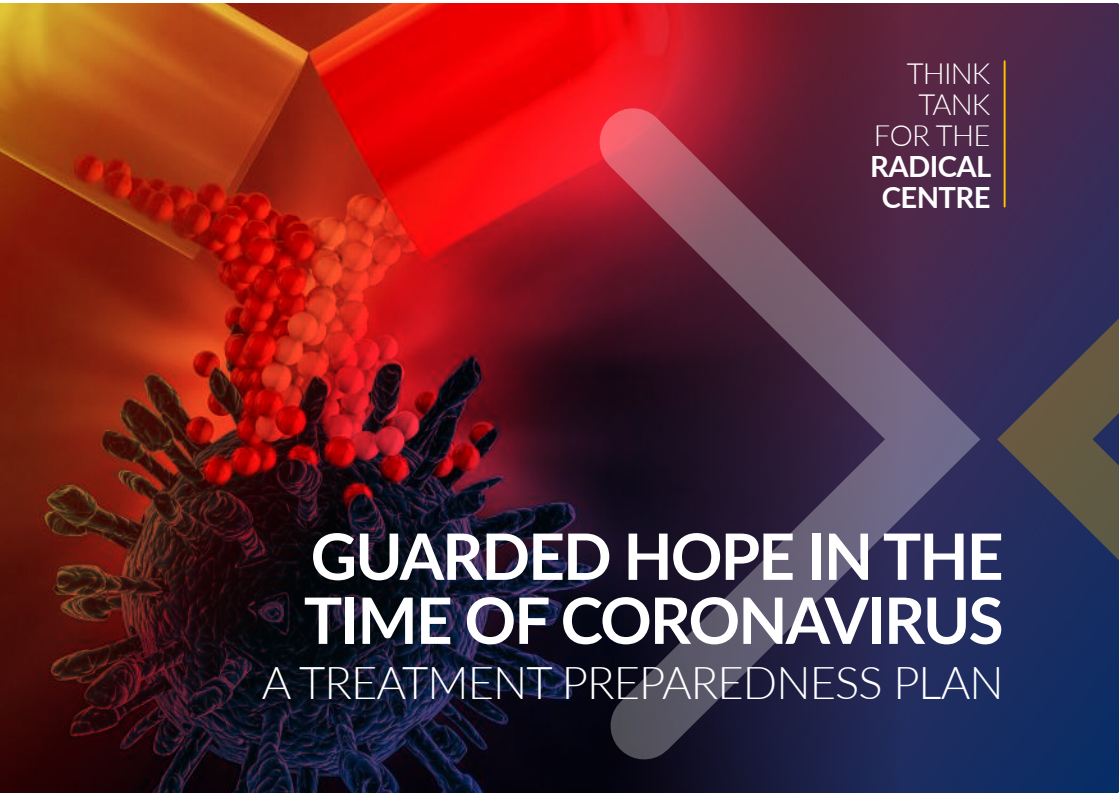
RADIX



THINK
TANK
FOR THE
RADICAL
CENTRE

GUARDED HOPE IN THE TIME OF CORONAVIRUS

A TREATMENT PREPAREDNESS PLAN


“GOOD FORTUNE
OFTEN HAPPENS WHEN
OPPORTUNITY MEETS WITH
PREPARATION.”
Thomas A. Edison

SUMMARY

This document considers the potential effective treatments for Covid-19 and their implications for government and clinical responses.

In particular, it focuses on treatments for patients in the early stages of the disease, as well as the use of drugs to help protect frontline healthcare workers.

It argues that there is a possibility that such treatments could be identified much sooner than a vaccine and maybe as soon as a matter of weeks, and that this would have very significant implications for the government's approach to the management of the crisis.

It goes on to argue that the government must start preparing now for the advent of such treatments, if it is to take full advantage of them and release the UK from lockdown earlier than might otherwise be the case.

From this, it goes on to recommend a specific treatment preparedness plan for the government and sets out a three-stage process to return to normality.

THE GOVERNMENT MUST START PREPARING NOW FOR TREATMENTS FOR COVID-19 POTENTIALLY BECOMING AVAILABLE

1. INTRODUCTION

NO GOVERNMENT WAS ADEQUATELY PREPARED FOR THIS EPIDEMIC

As no effective treatment for Covid-19 has yet been proven - as with the early years of the HIV outbreak - medical professionals have been forced to limit their interventions to supportive rather than curative care. This aims to manage the lung damage and organ failure caused during the second phase of Covid-19, assisting critically ill patients to survive while their own immune systems fight the infection. Tragically, as seen globally, this is not always successful and the mortality has been high in the older patients over 70,

By looking at a handful of existing drug options, section 2 of this report discusses some of the possible options . As it is a new virus, we are limited by a lack of data from properly controlled trials. Many studies have been initiated recently, most looking at the treatment of moderate to severely ill patients. Remdesivir and Lopinavir, one of the HIV protease inhibitors, are undergoing extensive trials at the current time.

Two of the other most interesting options are a drug called Hydroxychloroquine and an antiviral drug called Favipiravir, both of which will be discussed in more detail. The importance of these drugs is that they are particularly focused on treating patients at the earliest stages of

Covid-19 meaning they might also have potential as protection for medical staff on the frontline, as well as other critical workers.

It is too early to speculate as to what the results will be and to run victory laps. Even the possibility of such treatments, however, means that the government must start thinking now about the implications of the availability of efficacious and safe treatments on it's strategy for dealing with the epidemic and for gradually relaxing the lockdown rules.

ANTI/VIRAL DRUGS COULD TREAT PATIENTS AT THE EARLIEST STAGES OF COVID-19 AND PROTECT MEDICAL STAFF

No government was prepared for this epidemic, even when it was clear that the coronavirus was likely to spread fast from China through the rest of the world. The infectiousness and clinical severity of this virus in a non-immune world has been unprecedented.

The UK government cannot afford to be left behind at the next stage of the pandemic and so now needs detailed treatment preparedness plans for all eventualities, including the possibility of treatment of early cases, which might be available through the repurposing of existing drugs. The current anti-virals under review i.e. remdesivir and favipiravir, although developed against other indications, do possess some broader-spectrum antiviral activity and may hold promise, certainly when given early in the disease. Neither of these were developed as a specific anti-coronavirus agent, but it seems they have a measurable anti-coronavirus activity which needs full evaluation and then utilisation.

While we hope they may make a difference, this is unlikely to be a silver bullet but even limited responses from these treatments may change the profile of the pandemic.

A RELEASE OF THE LOCKDOWN IN THREE PHASES CONCLUDING HOPEFULLY IN THE SUMMER

Such a plan (set out in detail in section 3) needs to:

1. *Support and monitor clinical trials of all compounds for which there is proper scientific rationale and initial evidence of their effectiveness.*
2. *Continue to improve the understanding of the spread of the virus.*
3. *Be ready to fast-track regulatory approvals for any such treatment for which clinical trial outcomes are positive.*
4. *For each of the more promising drugs, start preparing a protocol and logistics for their dispensing.*
5. *Review the epidemiological models if there is a positive outcome for some of these trials.*
6. *Establish international collaboration and make sure that there is sufficient manufacturing capacity.*
7. *Review the government's overall epidemic management strategy.*

With a properly conceived treatment preparedness plan, the government would be working on all of these aspects in parallel, so that, as soon as new information becomes available, all of the above aspects of the epidemic strategy can be quickly adjusted and any proven treatment can be made immediately available.

This is turn will enable the government to move more rapidly towards a release of the lockdown in three phases, which are set out in section 4 of this document, starting, potentially, within the next few weeks and concluding hopefully in the summer.

2. REVIEW OF POTENTIAL TREATMENTS

THERE ARE 120 DIFFERENT DRUGS CURRENTLY UNDER INVESTIGATION FOR THEIR EFFECTIVENESS AGAINST COVID-19

The Milken Institute has identified 120 different drugs currently under investigation for their effectiveness against Covid-19, of which 40 are antiviral treatments. If any of them limit the severity of the illness, reduce the length of viral shedding, or provide protection to the Healthcare Professionals (HCP) working in close proximity – the benefit could be huge.

[Source: https://milkeninstitute.org/sites/default/files/2020-04/Covid19%20Tracker%20NEW4-9-20-2.pdf]

RECENT PUBLICATIONS BY PROFESSOR DIDIER RAOULT IN FRANCE STATE THE HYDROXYCHLOROQUINE, IN COMBINATION WITH AZITHROMYCIN, IS EFFECTIVE BUT THESE TRIALS ARE DISPUTED

Further research is needed urgently to test these agents in animal and human studies. Some have already been used for other diseases so are being repurposed for Covid-19.

Of the many possible treatments, the following have been targeted as priorities:

1. Chloroquine or Hydroxychloroquine.

The use of Chloroquine and Hydroxychloroquine is still under debate. Hydroxychloroquine has been used as an anti-inflammatory agent in auto-immune disease and is thought to act in Covid-19 partly by an immune modulatory effect. Despite both these two agents being known to have broad anti-viral properties, these are mostly in vitro and animal studies. The recent publications by Professor Didier Raoult in France say that this drug in combination with Azithromycin is effective, but many authorities are not yet convinced.

There is some dispute over the effectiveness of this drug, with several clinical trials currently underway and some completed with encouraging results. For example, in February 2020 experts in China recommended its use as it saw a decrease in hospitalisation of Covid patients and an improved outcome on those with the virus.

However, the Italian COVID19 Group recommended against the possibility of Chloroquine/Hydroxychloroquine as a treatment for Covid-19. Thus, there is yet to be a general consensus on the effective qualities of this drug. There are also concerns about some of the side effects in particular for patients with heart conditions, especially if high doses of Azithromycin are used.

2. Remdesivir.

Remdesivir (Gilead Science) is a relatively new agent used initially in the Ebola (2018) outbreak, and the initial studies have shown effectiveness in SARS and MERS – both corona viruses. On 10 April 2020, a report published in the New England Journal of Medicine demonstrated that two thirds of patients with severe Covid-19 improved significantly with use of this drug. This study is however not considered conclusive. A more recent widely reported study from China yielded disappointing results.

This drug is being researched widely but, as an intravenous drug, it has the drawback of needing a hospital setting. More data will be available soon as it is one of the drugs being tested in the WHO SOLIDARITY study and in the UK RECOVERY study. These results are awaited with interest.

FAVIPIRAVIR WAS TRIALLED IN WUHAN. EARLY DATA HAS SUGGESTED THAT IT IS BOTH EFFECTIVE AND SAFE

3. Favipiravir.

Favipiravir was produced years ago and has been kept by the Japanese Ministry of Health for pandemic flu since 2014. It has already been thoroughly tested and recently trialled for Ebola. It was also shown by several teams to elicit activity both in cell culture and animal models against a number of other viral infections.

Theoretically, Favipiravir would be most effective in recently infected Covid-19 patients. As an RNA polymerase inhibitor, it would slow down the virus's ability to reproduce itself and thus reduce the viral load in the body which would allow time for the patient's immune system to fight the infection.

This drug was trialled in Wuhan this year. Early data has suggested that this agent is both effective and safe apart from the teratogenicity. The clinical results from China indicate that, without the drug, the viral replication continues for an excess of ten days compared to three to four days with the drug. Additionally, it shows that after two days using Favipiravir, 72 per cent of the patients experience improvements in their clinical condition and, after six days, 78 per cent of patients demonstrate improvement in their lung imaging. The data from this study has been questioned and more studies are needed. However, the Japanese Prime Minister has recently stated that Favipiravir is now part of standard care for Covid-19 patients in Japan.

The drawback to this drug is that it may affect the foetus in pregnant women, and thus is contra-indicated for pregnant women. Even so, the presence of this drug washes out within a week and could thus be administered to women of child-bearing age as long as they are not pregnant and taking means of contraception during the treatment period.

China has been conducting further trials and producing this drug in large quantities and donating supplies to neighbouring countries and others. In Russia, they have been given permission to produce the drug and many other countries are preparing to do the same.

As mentioned in the Wall Street Journal on 16 April, Favipiravir is already at the centre of a diplomatic tug of war between China and Japan. (https://www.wsj.com/articles/japan-china-vie-to-be-global-supplier-of-unproven-coronavirus-drug-11587029402)

4. Lopinavir/Ritonavir.

Another treatment that was thought to be effective and was recommended in the treatment protocol for Covid-19 pneumonia in China was a combination Lopinavir/Ritonavir, a re-purposed antiviral used in HIV. This is known to have significant anti-coronavirus protease activity and was helpful in the SARS outbreak, especially when given early. Sadly, the most recent results published in New England Journal of Medicine in Covid-19 patients, were disappointing and did not show positive results (possibly because of the small number of patients involved).

LOPINAVIR/RITONAVIR, A RE-PURPOSED ANTIVIRAL USED IN HIV, WAS PART OF THE TREATMENT PROTOCOL FOR COVID-19 IN CHINA

5. Tocilizumab/Interferon.

The use of Tocilizumab is being evaluated in different studies either alone or in combination with an antiviral. The cytokine cascade which is triggered by Covid-19 contributes to the lung pathology that has often proved fatal. Preliminary results seem to indicate that this may be helpful in the severe lung disease phase. Other immune modulators such as the interferons are of great interest and are under trial as part of the WHO SOLIDARITY study.

6. Plasma based treatments.

Much has already been written about using plasma from recovered patients that would thus contain antibodies. By injecting this plasma into sick patients, it is hoped to help boost their defences. This kind of treatment is not new and has been used, sometimes successfully, for 100 years or so against other infections. It was used in the SARS outbreak. The UK has just approved a large trial to investigate this further and to collect plasma from convalescent patients who have recovered.

7. Vaccine development.

Vaccine development remains a top priority and is being aggressively pursued. It inevitably requires a lot more time and a lot more money than the re-purposing of existing drugs. Once effective vaccines have been developed it is possible that Covid-19 will eventually become another 'seasonal flu' that can be controlled by vaccination of the vulnerable. Most experts predict that this will take many months even though remarkable progress is being made with trials already underway. According to Professor Paul Stoffels, Chief Scientific Officer of J&J, one of the largest vaccine producers in the world, the soonest we can expect an effective vaccine is the late spring or summer next year. Pilot vaccine studies have been started in the UK and in the US.

THE SOONEST WE CAN EXPECT THE FIRST DOSES OF AN EFFECTIVE VACCINE IN SIGNIFICANT QUANTITIES IS THE LATE SPRING OR SUMMER NEXT YEAR

3. GOVERNMENT TREATMENT PREPAREDNESS PLAN - A PROPOSAL

WE MUST WORK ON ALL THE DIFFERENT ASPECTS OF PREPAREDNESS IN PARALLEL SO THAT, AS SOON AS NEW INFORMATION DEVELOPS, THE EPIDEMIC STRATEGY CAN BE QUICKLY ADJUSTED

Western governments were surprised by the rapidity and infectiousness of the epidemic, despite witnessing the effects in China. The possibility of effective treatment, which could soon be available through the re-purposing of effective drugs, however, could provide a partial solution so the UK needs to prepare for this.

For a properly conceived preparedness plan, the UK government must be working on all of the different aspects in conjunction with each other so that, as soon as new information develops, the epidemic strategy can be quickly adjusted and any proven treatment can be made immediately available.

FOR THE MOST PROMISING DRUGS, PREPARE A PROTOCOL AND THE LOGISTICS FOR DISPENSING THE DRUGS AS SOON AS THEY ARE PROVEN TO WORK

A potential Government Treatment Preparedness Plan for Covid-19 should include:

1. *Supporting and monitoring clinical trials of all compounds for which there is proper scientific rationale and initial evidence of their effectiveness, including all trials not only those which are government-sponsored. This should include studies that are aimed at intervening at the early stage of infection to reduce progression to more severe disease.*

There are many potential drugs that are being investigated through a proliferation of trials. The WHO and UK government are right to prioritise the trials and focus the efforts and the recruiting of patients on the most promising ones.

The WHO has launched the SOLIDARITY trial which will assess the clinical efficacy of Remdesivir, Lopinavir/ Ritonavir, Hydroxychlorquine and Interferon beta-1a. These are massive international trials involving thousands of patients. The first results are expected in the next few months.

Within the UK, the government has prioritised three collective trials. The first one is called PRINCIPLE and aims to test preventive drug strategies within the community for older risk groups. The second platform is ReMAP/CAP which is only suitable for the very sickest. The main one is the RECOVERY trial for which over 5,000 patients have been recruited. This trial will test standard of care, Lopinavir/Ritonavir, low dose Dexamethasone, Hydroxychloroquine and Azithromycin and Tocilizumab. (an anti-inflammatory treatment given by injection). This study focuses primarily on patients who are moderately to severely sick and who are already receiving oxygen treatment and potentially more intensive support, remaining in hospital for the duration of the study period. This has been designed so new arms to the study can be added as information evolves.

There are many other trials starting to look at other agents and, for the first time in the UK, a study is starting testing the efficacy of Favipiravir in a 3 arm trial involving also Hydroxychlorquine and focusing on early stage patients with mild to moderate symptoms. These drugs have been the focus of a great deal of international interest, but solid data is still lacking. This study, hopefully, will answer the question one way or the other, as to their effectiveness in a tightly controlled trial.

Results from quite a number of trials around the world will begin to be available in the next few weeks and months expanding our understanding of possible therapeutic options.

2. Continue to improve the understanding of the spread of the virus, especially through expanded testing.

Mass testing is crucial during a pandemic. Unfortunately, this was not part of the initial UK response, largely due to lack of capacity. Although recently recognising the need for increased testing, it is not just the amount of testing that matters. It is also the reliability of the testing because of the dangers created by false positives or false negatives.

The government has begun to organise random viral testing of representative samples of the population. This would enable a much more statistically valid estimate of the 'true' number of people infected with the virus, which is likely to be higher than the numbers officially confirmed. Antibody testing is also increasing as these tests are becoming increasingly available and reliable.

RESULTS COULD BE AVAILABLE AS SOON AS IN 6 TO 8 WEEKS TIME

Recently, according to the *Spectator* USA on April 10, the University of Bonn released results of a study conducted on a random sample in the City of Gangelt which indicated that - based on that sample - the percentage of infected people is about 15 per cent, substantially higher than the percentage of confirmed cases, and that the degree of lethality of the disease, estimated at 0.37 per cent is lower than often assumed. It is essential for the epidemiological models to be valid that better statistics of both the spread and the lethality of the virus are available. Data from more studies in Germany have indicated a seropositivity of 3 percent. There is much to learn.

THE UNIVERSITY OF BONN FOUND 15% PEOPLE IN THE CITY OF GANGELT TO BE INFECTED - HIGHER THAN EXPECTED - AND ESTIMATED LETHALITY AT 0.37%, LOWER THAN OFTEN ASSUMED

The UK government has not prioritised tracking people with mild Covid-19 symptoms 'at home'. While the NHS App provides the facility, it is not presented as a requirement. This renders the precise prediction of the number of people infected almost impossible, as the NHS has no accurate idea how many people have been infected.

THERE IS NO REASON WHY DRUGS THE SAFETY PROFILE OF WHICH HAS BEEN WELL ESTABLISHED AND THAT ARE DEMONSTRATED TO BE EFFICACIOUS COULD NOT BE APPROVED IN MAYBE DAYS - RATHER THAN WEEKS

Crucially, there is yet no definitive study on how long patients who have been infected by Covid-19 will remain immune. Expert opinion remains divided and the WHO advises caution in assuming immunity.

There has also been some debate over whether Covid-19 is affected by the weather, and therefore will be less harmful in the summer season, although, again, this is not yet clear. It is worth noting that the virus does not appear to have spread as quickly in many southern hemisphere countries.

With regard to level of infectious dose exposure, the initial view from experts was that it could well be a key factor in determining how sick the infected person could be. Further studies of the question however do not seem to support this theory and therefore more studies are required.

There are a few areas however where there is a general consensus including:

- ***Incubation period*** – *the length of the incubation period is now understood to be 1-14 days and the extent of the period in which individuals are contagious is estimated to be 1-2 days before symptoms appear, extending to 10-20 days after the beginning of the patient symptoms.*
- ***Transmission mechanism*** – *it has become clear that the virus is only transmitted through the mucous membranes of the eyes, nose and mouth. Therefore, straightforward precautions of physical distancing and good hygiene can vastly reduce the risk of exposure.*

3. Readiness to fast track regulatory approvals for any treatment in which clinical trial outcomes are positive.

If a credible trial has demonstrated the efficacy of drugs, such as Hydroxychloroquine or Favipiravir, both of which have previously approved for other purposes and to a lesser extent Remdesivir, the medicine approval authority (MHRA in the UK) will need to formally approve the use of these drugs for treating Covid-19, including posology and product labelling.

Normally, this would take months, however, in this crisis situation, it is the responsibility of the government and the regulatory authorities to fast-track the approval. There is no reason that drugs, the safety profile of which has already been well-established over years, if shown to be effective against Covid-19, could not be approved in a most compressed timeframe, maybe days rather than weeks.It is incumbent upon the relevant authorities to get ready now so that the approval can take place immediately if and when a positive outcome of the trials taking place. We hope that such planning is underway.

Within the UK, the MHRA (Medicines & Healthcare product Regulatory Agency) should be able to approve this based on their own review of the trials conducted. Many other countries, however, will be relying on the most recognised approval authorities such as the FDA in the US and the EMA in Europe to grant their own approval. Initial discussions with these are taking place.

TRIALS MUST INCLUDE THOSE AIMED AT INTERVENING AT THE EARLY STAGE OF INFECTION TO REDUCE PROGRESSION TO MORE SEVERE DISEASE

4. For the most promising drugs, prepare a protocol and the logistics for dispensing the drugs.

Depending on the type of drug and the type of patients who will be targeted, the government and the NHS should prepare a plan as to whom will be receiving these drugs and how they will be dispensed.

With regard to drugs such as Hydroxychloroquine and Favipiravir both of which are targeting early stage patients, what is important is that they are given in pill form which is thus easier to administer than through injections. They should also be relatively inexpensive as they are both off-patent and not too complicated to manufacture.

The Government, NICE and the NHS should start preparing for the possibility that any of the treatments being investigated could work. Depending on the drug treatment it should start defining the order of priorities among various categories of potential recipients, the likely numbers of patients in order to be able to estimate the number of doses that might be required, the possible costs of these, the distribution channels to be used and the overall logistical chain.

5. Review the epidemiological models used by the government to prepare for its response to take into account a potential positive outcome for some of these trials

The government has relied on the models developed by Imperial College to determine its response to the epidemic. The data presented were presumably done without the possibility that treatments could be available, in particular, treatments which could be administered early and potentially reduce the number of significantly ill patients requiring intense hospital treatment.

Much of the strategy of the government was driven by the need to 'flatten the curve' in order to make sure that the NHS had the ability to cope. Social distancing and hygiene advice has worked well but at a price. The availability of treatment, that would reduce the number of critically ill patients, would de facto, flatten the curve. Furthermore, if these drugs are indeed successful at reducing the viral load in infected patients and at shortening the time during which they are infectious, this will help reduce the so-called R factor further below 1.. This means that each infected person , instead of infecting two or three additional people, which was the case at the beginning of the epidemic, will infect, on average, less than one person. This could be achieved by the current lockdown measures but also by effective early or preventative therapy. A rerun of these models, taking these factors into account, could possibly lead to a different type of response from the suppression-through-confinement response used so far.

6. Establish international collaboration with the companies who have developed these drugs and make sure that there is sufficient manufacturing capacity so that the NHS, among others, will have immediate access to these drugs.

As important as identifying effective treatments for the coronavirus is making sure that the drugs will be immediately available and thus can be manufactured at the planetary scale that will be required to meet the massive demand that could materialise overnight. This is a gigantic but not insurmountable challenge. While it is primarily the responsibility and challenge of the worldwide pharmaceutical industry it is incumbent on governments to assist in any way they can.

One aspect where our government and Europe as a whole could play a leadership role is in diffusing the geo-political tensions which could arise if different governments start to outbid each other for access to the drugs, let alone impose embargoes on the export of drugs produced in their own country. This argues also for a potentially decentralised international manufacturing network.

GEO-POLITICAL TENSIONS WHICH COULD ARISE ARGUE FOR A POTENTIALLY DECENTRALISED INTERNATIONAL MANUFACTURING NETWORK

The two drugs Hydroxychloroquine and Favipiravir are relatively simple molecules and the manufacturing process is now established. Both of these are also off-patent so any pharma company can theoretically produce their own generic version and their basic ingredients are not particularly difficult to produce. Depending on whether these ingredients can indeed be sourced at the scale required, any major pharmaceutical company, generic manufacturer or CMO (contract manufacturing operation) should be able to retool existing production lines to be able to produce these drugs within weeks at the very large scale needed to treat hundreds of thousands if not millions of patients. Of course this would be an ambitious undertaking, however, in view of the urgency of the situation there will be immense pressure on the industry to act fast, in a responsible way, to pool their intellectual property and other resources, and agree to sell these critical drugs with small profit margins or ideally at cost. We can expect that a number of companies will be responsive but, if this is not the case, it will be incumbent upon governments to use their special powers to make it happen.

Sanofi, which already markets Hydroxychloroquine for other uses under the brand Plaquenil, has stated that once the clinical results are available they would be able to produce and deliver a "huge number of doses" (Interview of Olivier Bogillot, March 22, France 24). Other major pharmaceutical companies have made similar commitments,

In the case of Favipiravir, Fujifilm Toyama Chemical which sells this medicine under the name Avigan, albeit for other uses, has significant capacity, including through its CMO (Contract Manufacturing Organisation) subsidiary Diosynth but probably not enough to satisfy worldwide demand should Avigan prove to be an effective treatment. Therefore, they could either contract other CMOs to manufacture it or license generic or other pharmaceutical companies to produce and distribute Avigan outside of Japan and ideally in all major countries that would approve Avigan for treatment of Coronavirus. Alternatively, there are Chinese companies that have started producing a new generic version of Favipiravir in large quantities in a new factory built for that purpose and have already started shipping large volumes to a number of countries. Russia and other countries have also announced the start of production of a generic version. Whether the Chinese, Russian or other generic versions are bio-equivalent and can be approved for treatment in other countries as quickly as Avigan is unclear as it might require additional trials to assess the safety and efficacy of the alternative generic versions.

Fujifilm with the active support of the Japanese government should take the initiative to build a large scale international network of manufacturing partners to be ready in case and as soon as the trials yield positive results in order to be able to produce Avigan at the scale that might be required. Initial ideas along these lines are starting to take shape.

INDUSTRY MUST POOL THEIR IP AND OTHER RESOURCES AND, IF COMPANIES ARE NOT RESPONSIVE, GOVERMENTS MUST MAKE IT HAPPEN

The role of UK industry and of the UK government is to encourage and support such efforts. It would be tragic if a potential treatment were to be found and, for a lack of preparation and well-co-ordinated initiatives by governments and pharmaceutical companies around the world, it could not be made immediately available at the scale required to meet the huge demand that would materialise.

The Bill & Melinda Gates Foundation together with the Wellcome Trust and Master Card have created the COVID-19 Therapeutic Accelerator which aims to accelerate the introduction of new treatments. Also, the International Pharmaceutical Manufacturing Association of the 12 largest pharmaceutical manufacturers are already gearing up to produce at great scale any authorised drug for the treatment of Covid-19.

There is clearly an encouraging mobilisation of capabilities around the world to meet the challenges ahead. As long as all stakeholders, private or public, act responsibly and at speed, the manufacturing and distribution at planetary scale of any drug that would be proven to be effective and safe should not be an insurmountable obstacle to the immediate treatment of patients worldwide with such drug.

7. Review the government's overall epidemic management strategy to factor in the availability of drugs, enabling a move from away from a suppression-to-confinement strategy to an identify-and-treat strategy which would allow for a gradual, but hopefully rapid, relaxation of the lockdown.

Wholesale confinement of an entire population is a « primitive way » of dealing with an epidemic. Yet, due to many governments being ill-prepared in the face of a new lethal virus in a non-immune world, there was probably no other choice than to impose a total lockdown, despite the dramatic human and economic consequences.

There is a growing awareness of the human toll created by the strict confinement and questions are being raised as to "whether the cure will be worse than the disease".

There is increasing evidence of an increasing number of people with critical illness dying at home, for fear of going to hospitals. Mental health is also being affected, and incidents of domestic violence are sharply increasing as a direct result of the confinement. More broadly the increasing level of economic distress brought about by the lockdown will have a major detrimental impact on the resources which might be available to properly fund the NHS, thereby negatively impacting the health of the people for years to come.

This cruel trade-off between protecting people against Covid-19 versus deeply damaging the wealth and thus the health of the nation, implies that the government will need to be ready to make difficult decisions. So far, the choice has been clear: it has been all about fighting the virus and protecting lives, and rightly so.

The availability of a treatment, however, could radically change the picture. Any treatment that could reduce the lethality of the disease could in itself lead to a reassessment of the government's strategy which has been to focus exclusively on suppressing the epidemic in order ultimately to save lives. More significant would be the impact of drugs such as Hydroxychloroquine or Favipiravir that would be administered early.

If they are successful at slowing down the infection allowing the immune system to fight back, the availability of such treatments could fundamentally alter the nature of the epidemic because they would have multiple effects:

- *Slow down the progression of the infection within patients, reduce the number of patients whose condition could deteriorate and, thereby ultimately save lives.*
- *Reduce the number of patients who will require intensive care treatment, thereby reducing the pressure on the NHS.*
- *Ultimately reduce the spread of the disease by reducing the time during which the patients are contagious and have the ability to infect other people including healthcare personnel.*
- *A preventative treatment would allow key healthcare workers to remain on the frontline.*

Such options means that mass treatment could be available as soon as this summer. This would in itself significantly "flatten the curve" - one of the key reasons given by the government for the drastic confinement measures. It should be noted in that context that, with a few exceptions, most hospitals have seen a lesser case load than before the epidemic as all elective surgery and many clinics have been postponed, and people have refrained from going to hospitals.

The availability of proven treatments, in particular those that could be administered early, combined with large scale testing, would enable the UK to move from a "suppression through lockdown" strategy to a "test, isolate and, treat" strategy, which is the more normal way of dealing with any epidemic. The knowledge of an effective treatment would also help reverse the fear factor which otherwise will continue to weigh heavily on the speed of the economic recovery as is the case in Wuhan.

PROVEN TREATMENTS, ADMINISTERED EARLY, COMBINED WITH LARGE SCALE TESTING, WOULD ENABLE THE UK TO MOVE AWAY FROM AN ABSOLUTE "SUPPRESSION THROUGH LOCKDOWN" TO "TEST, ISOLATE AND, TREAT

4. PHASED RETURN TO NORMALITY

Phasing out the lockdown is a complex task that requires careful and detailed planning by the government based on the advice of health professionals and rigorous epidemiological models and without being influenced by political considerations.

We recognise that we are not epidemiologists and that we should thus be wary of appearing overly prescriptive with answers for all the detailed issues that will need to be addressed.

In the context of potential treatments coming on line, it is good, however, to have an aspirational approach. We recognise that social distancing and careful hygiene are going to be part of our daily lives for months or years to come, and that in the presence of later surges of disease, degrees of lockdown may need to be re-introduced. Relaxation of lockdown would in any case need to be combined with a comprehensive test, isolate and, treat strategy.

Looking at what other countries are planning and based on our first hand knowledge of the situation combined with our experience in dealing with epidemics and a degree of pragmatism , we think it could make sense to follow a three phased process.

WE SHOULD BE GETTING VERY CLOSE TO TRIGGERING THE FIRST PHASE OF RELEASE, AS THERE IS EVIDENCE, THAT THE RATES OF HOSPITAL ADMISSIONS HAVE DROPPED SIGNIFICANTLY

Phase One (possibly within 2 weeks):

Phase one could start as soon as it is clear that the number of people requiring hospital treatment is dropping. This could be viewed as a more accurate measure than the number of confirmed cases which is dependent on testing (with all the well known limitations) , or the number of deaths which is a lagging indicator. This would also correspond best to the main concern that the government used to justify the lockdown - without lockdown, the hospital system would not be able to cope. Extensive testing is still necessary to monitor the situation but possibly not to determine the timing of phase 1. Contact tracing is always important in managing an epidemic but at this stage it is unclear to us whether the rather extensive contact tracing infrastructure needs to be fully operational before initiating the first phase of lifting the lockdown.

We are getting very close to this point as there is evidence, that the rates of hospital admissions have dropped significantly (in a number of cases by more than half).

Another element that should give the government more confidence to take such steps is the degree of discipline and responsibility that people have demonstrated in the last few weeks.

The steps that could be taken would be:

- ***Individuals below 70 and without comorbidity,*** *could be allowed to exit strict confinement as long as they maintain reasonable social distancing.*
- ***Higher risk individuals should probably remain quarantined.***
- ***Pubs, nightclubs*** *and other indoor places where people are closely packed together are likely to have to* ***remain closed for the foreseeable future.***
- ***The schools could gradually reopen.*** *Children are not as vulnerable to the disease as the older patients. Care needs to be taken in multi-generational families.*
- ***Small (less than 5-10) gatherings*** *could be allowed for all categories as long as individuals have no symptoms and have not been in contact with anybody who has.*
- ***Smaller retailers and personal services businesses,*** *where you don't have major concentrations of people, could reopen - trusting that people will maintain social distancing and basic hygiene precautions.*
- ***Factories and construction sites*** *could also resume their activities with adequate precautions in terms of hygiene and distancing.*
- ***People should be made to feel free to go to hospital*** *when they either have symptoms of Covid-19 or for other conditions requiring immediate treatment.*
- ***Non-essential travel should remain restricted*** *and people arriving from abroad should be tested on arrival or commit to stay in self-quarantine for 14 days.*
- ***Hospitals should reconfigure their facilities*** *to allow for elective surgeries and other services to resume.*
- ***The wearing of masks should probably be mandatory*** *for all when in public places where social distancing is impossible, for example in shops or on public transport. It might also have the psychological and sociological benefit of showing the commitment of members of society to taking all steps possible to help protect themselves and others. Viral shedding can occur in a-symptomatic and pre-symptomatic persons and a mask may help in preventing aerosolisation and spread of droplets. We are not recommending the wearing of clinical masks, the limited supply of which should be reserved for medical staff, but the wearing of the simplest of face cover which could even be home-made.*

Phase 2 (aiming for June)

BY JUNE ALL INDIVIDUALS, EXCEPT THOSE IN HIGH RISK CATEGORIES, OR WITH SYMPTOMS, COULD POSSIBLY BE ALLOWED TO EXIT LOCKDOWN

If good news materialises and sufficient and credible evidence is available that treatments have been identified and to the extent that there has been no new unmanageable surge since the introduction of Phase 1, a second phase could be launched. The prospect of an effective treatment could de-risk and accelerate the launch of a second phase which we hope could happen in June although it depends on the progress of the trials taking place. Indeed, if there is a treatment, there is much less to fear about not being able to handle a second wave that could follow further lockdown relaxation.

If this happens, the next steps would be:

- *All individuals except those in high risk categories, or with symptoms, could be* ***allowed to exit lockdown.***
- ***Larger outside gatherings*** *could be allowed.*
- ***Gym and restaurants*** *could re-open although crowded venues such as pubs and nightclubs would remain closed.*
- ***Travel*** *should be allowed to resume within country including by airline, train and bus within country and to and from countries who have compatible policies with regard to the management of the epidemic and the exit from lockdown.*

THE LOCKDOWN COULD BE OFFICIALLY ENDED THIS SUMMER WITH THE RIGHT GLOBAL ACTION

THE CHALLENGE WITH REGARD TO ENDING THE LOCKDOWN ALL TOGETHER WILL BE THE AVAILABILITY OF THE DRUGS AT THE MASSIVE SCALE REQUIRED

Phase Three (aiming for mid-summer)

The last phase on the lockdown release process would start when treatments are approved and are available at large scale for administering to patients, baring of course a major surge following phase 2. The challenge with regard to timing will be the availability of the drugs at the massive scale required as discussed earlier.

At that point:

- ***Lockdown should be official over.***
- ***Individuals with symptoms*** *to be immediately treated and to remain quarantined.*
- ***Precautions*** *in terms of personal hygiene and physical distancing will still need to be taken.*
- ***The wearing of masks*** *in public places would no longer be required.*
- *And,* ***pubs and nightclubs could reopen!!***

There is no doubt that relaxing the lockdown implies calculated risks. It is possible that more people could get infected and possibly even die from Covid-19 than if the strictest lockdown was maintained. This risk, however, needs to be measured against the added human and economic damage that the lockdown will inflict if it is maintained longer than absolutely necessary. If potential treatments become available, these risks will be far reduced.

If, however our hopes are disappointed and no efficacious treatment appears to be a short-term possibility, the process for the removal of lockdown might still follow such phasing, though the risks of doing so would be higher and the timetable slower.

5. CONCLUSION

There is the possibility that effective treatments might soon emerge and this should give us a glimmer of hope. If clinical trial results from multiple studies are available by June and have positive results (which is by no means certain) and if the Government is properly prepared for such an outcome so that these treatments can be made quickly available, it is quite conceivable that the lockdown could be over in the summer. We recognise this may be optimistic, but we need urgency. This requires courageous and quick decisions by the authorities, but it is necessary to prevent economic paralysis.

SUCCESS IN MANAGING THE EPIDEMIC IN ONE COUNTRY WILL BE A SHALLOW VICTORY IF OTHER COUNTRIES DON'T SUCCEED THE SAME WAY

However, this must be a global response. Although it would be a great accomplishment if any country could achieve an exit from lockdown while minimising collateral damage, it is not enough. In an open world economy where people travel, supply chains are internationally integrated and international trade accounts for a significant share of the GDP – success in managing the epidemic in one country will be a shallow victory if other countries don't succeed the same way.

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The views expressed in this paper are the views of the authors and are not representative of the views of the organisations to whom they are affiliated

The authors are participating in a research project (PIONEER) based at Chelsea and Westminster Hospital and the University of Leuven which is looking into the use of drugs in the early phase of Covid-19.

GUARDED HOPE IN THE TIME OF CORONAVIRUS -

A Preparedness Plan

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'ALL GREAT NATIONS SPEND PEACETIME PREPARING FOR THE DAY WAR BREAKS OUT.'

Tim Marshall

Prisoners of Geography: Ten Maps That Tell You Everything You Need to Know About Global Politics

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