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(C190107)

Executive summary

I make two broader points and three smaller suggestions. For the former:

1. Avoid 'fighting the last war'. The scientific and technical developments which would have helped to tackle COVID-19 are not identical to those most effective in addressing future outbreaks. The latter, not the former, are the priority.
2. The UK, despite being world-leading in developing countermeasures to COVID-19, found itself facing the global challenge that there are no interventions which are both effective and fast: NPIs are very socially costly; a vaccine is still awaited months after the outbreak began. Current and horizon technologies can close this gap, and the UK SRT community is well placed to develop them.

The latter:

3. Disease forecasting is important for risk assessment and policy making. It may warrant a dedicated service akin to the UK Met Office.
4. A 'disease X' research agenda could give a broad knowledge base to inform initial responses before outbreak specific evidence is gathered (cf. masks).
5. Anticipatory ethical assessment for public health emergencies could allow better governance of unorthodox research (e.g. human challenge trials) in terms of speed and safety.

Introduction

0.1 I work at the Future of Humanity Institute at Oxford University, where I investigate the risk of extremely high consequence biological threats, and how these dangers are best addressed. (I write in a personal capacity.)

0.2 Surveying all ramifications of COVID-19 for UK Science, Research and Technology is beyond me. Instead, I suggest a couple of broader lessons broadly applicable to the inquiry, as well as some smaller points on particular topics.

Broader lessons

1. Avoid 'preparing for the previous pandemic'

1.1 Global health security has an infamous cycle of 'panic and neglect'. Major events spur a surge in interest and activity, which wanes over subsequent years as the major event fades from recent memory. This is compounded as severe pandemics, as rare major events, provide limited data which is easy to misinterpret, e.g.:

- Prevention paradox: It is hard to observe a 'successfully prevented pandemic', and still harder to attribute any such success to any particular attempt at risk mitigation. Thus effective efforts that reduce a real risk can look identical to pointless efforts addressed to an illusory one.
- 'False alarms' and crying wolf: Whether an outbreak of a new disease will develop into a global pandemic tends to be extremely hard to forecast. Optimal policy would err on the side of overreaction, as over-reacting to a 'false alarm' is much less costly than underreacting in the early stages of a pandemic. Yet these false alarms and 'precautionary overreactions' can erode public confidence.

1.2 One risk of panic in priority-setting is an S&T portfolio narrowly tailored to ensure 'this never happens again'. The next serious outbreak the world faces will not be a carbon copy of COVID-19: it may be a flu pandemic, but it may also be something which, like COVID-19, is to some degree unprecedented.

1.3 **Recommendation:** Do not 'fight the last war'. The scientific community should instead aim its response to best prevent, detect, and respond to the risks of the future, rather than those which have been realized in the past.

2 New technical capabilities need to be developed to meet 21st century threats.

2.1 The current portfolio of countermeasures to fight a pandemic can be divided into two categories. '*Pathogen blind'* countermeasures, which do not require knowledge specific to the pathogen (e.g. supportive hospital care; quarantine, contact tracing, and other NPIs); and *'pathogen specific'* counter-measures (e.g. vaccines and therapeutics), which do.

2.2 Pathogen blind countermeasures can be pre-positioned and deployed rapidly against an emerging pandemic. Yet they possess limited efficacy: across the world, they have only been effective at suppressing COVID-19 if implemented to a degree which causes substantial hardship to the population in their own right.

2.3 Pathogen specific countermeasures can be extremely effective, but these can only be developed after the pathogen and its disease are known. This takes too long: despite unprecedented efforts worldwide, a vaccine may not be available this calendar year; effective

therapies (i.e. Dexamethasone, Remdesivir), were only found several months after the pandemic began.

2.4 Although further incremental improvements to the UK's performance are welcome, the fact its performance in developing specific countermeasures is world-leading and yet was still much slower than the outbreak suggests a global challenge: the world does not have the technological capability to develop countermeasures to a disease outbreak which are both effective and fast.

- **Sequence-based detection:** Genetic sequencing has become roughly 100 000 times cheaper since 2001,[1] making it a viable tool in outbreak monitoring.[2, 3] It could also be a valuable tool for early detection: 'metagenomics' - sequencing all genetic material in a sample - could allow novel pathogens to be detected before they cause symptoms.[4, 5]
- **Platform vaccine technology:** Vaccines often need to be developed 'from scratch', both lengthening development and complicating rapid manufacture, as vaccine production capacity can neither be easily repurposed or quickly expanded.[6] Platforms, shared backbones which can be adapted for a given pathogen by 'plugging in' the relevant antigen, could greatly ease both challenges.[7,8]

2.5 **Recommendation:** The present pandemic demonstrates these future capabilities are already overdue. The UK is better placed than many countries to pioneer developing and deploying these due its advanced bioscience and biotech corpus, alongside initiatives to better utilize the same (e.g. UKARPA). It should.

Specific points

3 Develop excellence in disease forecasting to aid risk assessment and decision-making.

3.1 The UK national risk register assessed the danger of an emerging infectious disease as "several thousand people experiencing symptoms, potentially leading up to 100 fatalities."[9] There have been over 42 000 COVID-related deaths so far.[10] The risk assessment underestimated the potential danger by over 400-fold.

3.2 Although stark, an error of this magnitude is regrettably easy to explain. Many emerging infectious diseases are discovered each year, and even the most notorious recent examples (e.g. Zika, Ebola, SARS, MERS) have had relatively mild impacts on the UK. Anchored on recent memory, 'up to 100 fatalities' is a reasonable assessment for the typical event of this type.

3.3 The benefit of hindsight is not needed to see this was a very poor assessment of a reasonable worst case scenario. Emerging infectious diseases (which are not pandemic influenza) killing

more than 100 people in the UK is hardly unprecedented: HIV was also an emerging infectious disease, and kills more than 100 in the UK each year even now.

3.4 The impact of disease outbreaks have vary extremely widely: *atypically* bad outbreaks can be hundreds or thousands of times worse than what is usually observed. This means that most of the danger arises from extreme 'once in a generation' (or 'once in a century') events rather than typical ones.[11] Risk assessment based on what typically happens will greatly underestimate the real danger.

3.5 Bitter experience also teaches us that people tend to be inaccurate and overconfident when forecasting what could happen, especially with rare events. Subject matter expertise does not guarantee much greater forecasting skill:[12] prediction platforms have outperformed experts in forecasting various aspects of the COVID-19 pandemic.[13]

3.6 The modelling community has made impressive strides in developing infrastructure to enhance forecast performance: developing scoring systems, producing ensemble models, and trying to integrate expert judgement with mathematical modelling. [14-16] Given the importance of good forecasting, it seems worthwhile to develop a coordinated 'outbreak forecasting unit' from this structure, potentially housed inside government.

3.6 **Recommendation:** With risks that can vary greatly in severity, the UK should explicitly consider reasonable worst case events alongside typical events when weighting risk.

3.7 **Recommendation:** Consider a national 'disease forecasting unit', perhaps modelled after the UK Met office.

4. Mask use and the value of a 'disease X research agenda'

4.1 The UK, as well as many other countries had a large 'about face' on mask use in the community. In the early stages of the outbreak, public communication was that masks had little value, and may risk causing harm[17]; they are now widely recommended and sometimes mandated[18]. This had two costs: 1) forgoing the benefit of masks to reduce transmission in the early stages of the outbreak; 2) reversals tend to undermine public confidence in scientific advice.

4.2 Mistakes can almost always be avoided with the benefit of hindsight. The literature on mask use in general (and broad community administration in particular) was equivocal,[19] and the evidence arising from SARS-CoV-2 took time to appropriately synthesize.[20-21] What could have helped in navigating this uncertainty was a stronger 'pre-COVID' evidence base: if we

knew masks were typically beneficial in reducing community transmission of respiratory viruses (even if they were improvised, and even with 'imperfect use') we might, similar to hand-washing, have had a reasonable presumption of benefit rather than one of caution.

4.3 For global outbreaks of a novel pathogen, good 'prior' or 'interim' guidance can save lives before evidence from the novel pathogen itself can be gathered. Some of these needs can be anticipated (e.g. the typical base-rates of 'contact' and 'airborne' transmission for a respiratory virus, most effective means of improvised PPE and medical care, sterilization, cost-effective means of interdicting common modes of transmission). Developing this knowledge base will be occasionally useful for high-income countries facing a severe outbreak, as well as commonly useful in lower-income countries whose health systems are often resource limited.

4.4 **Recommendation:** Produce a 'pre-pandemic' or 'disease X' research agenda, and fund work directed to it.

5. Human challenge trials and 'anticipatory' regulatory and ethical infrastructure

5.1 Human challenge trials have been proposed as a tool to accelerate vaccine development. The ethical concerns are transparent, as it involves infection of volunteers with a virus which is potentially lethal, has possible long term sequelae, and no definitive treatment. Proponents nonetheless assert the risks to participants, when appropriately managed, are similar to those we consider acceptable in other contexts (e.g. altruistic kidney donation), are justified by the great humanitarian benefits of faster vaccine development.[22-23]

5.2 The WHO has worked to develop guideline criteria for HCTs.[24] Although opinion remains divided on the ethical merit of HCTs, both likely agree that developing these in the midst of a pandemic is not ideal: proponents do not welcome the extra potential delay this incurs; opponents may fear emergency situations may encourage lapses of judgement.

5.3 **Recommendation:** There seems a place for 'anticipatory' ethical review: to establish guidance for which experiments - especially those involving human subjects - should be considered in public health emergencies.

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