We declare no competing interests.

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COVID-19 spread in the UK: the end of the beginning?

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As the UK Government response to the COVID-19 pandemic reaches the end of its first phase, there are opportunities to be taken and challenges to be met. Specific opportunities include improving data collection and management, and putting in place as quickly as possible an effective test, trace, and isolate system for the UK. These are of immediate and high priority. The challenges include the development of high-level expertise within the newly established Joint Biosecurity Centre, a UK Government body.[1] The Joint Biosecurity Centre will take over some of the responsibilities of the UK Science Advisory Group for Emergencies (SAGE) in advising policy makers how best to control COVID-19. Ideally, the Joint Biosecurity Centre should be an informed body that distils knowledge for policy formulation, rather than a creator of that knowledge.

In the UK, lockdown measures were put in place some weeks too late to alleviate the rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For all epidemics, the earlier the measures are put in place to restrict transmission, the smaller the total size of the epidemic and the concomitant morbidity and mortality. By the end of April, 2020, the COVID-19 epidemic in the UK showed signs of suppression as daily reports of cases began to enter a slow decline. The UK Government's delay in implementing physical distancing measures centred on how long the population would tolerate strict lockdown measures and on an ill-defined and dangerous notion of the creation of herd immunity by natural infection. This delay resulted in the UK having one of the largest epidemics of any country at this stage of the pandemic, when judged both by cases per head of population and mortality per case of infection.[2]

The last few weeks have seen the relaxation of UK lockdown measures, but with guidance on sustaining many physical distancing precautions. There remained some uncertainty about the use of face masks in public spaces,[3] until their use was mandated on transport and in other settings in England.

As of July 30, 2020, many small outbreaks of COVID-19 remain throughout the UK. Government priorities have understandably been on managing a high burden of COVID-19 morbidity and mortality, but there is now an increasing focus on trying to revitalise the economy and create more social freedoms, given the devastating impacts of lockdown measures. However, this is a strategy fraught with danger. The apparent changes in people's behaviour triggered by a relaxation of the lockdown measures suggest there could be a resurgence in COVID-19 cases sooner than the expected rise later this year.[4] The next weeks will be crucial in judging if there will be a second wave in August and September, 2020. In many countries where lockdown measures were relaxed early, such as the USA, parts of Australia, and some countries in western mainland Europe, resurgence of cases has been recorded.[2]

Informative data on epidemics derive from longitudinal (over time) cohort-based (following the same individuals) studies of seroprevalence of past infections and the incidence of new infections, stratified by age, gender, ethnicity, occupation, pre-existing health conditions, spatial home and work or school locations, and clinical outcomes. The UK needs to expand collection of these data and to continue to review the sensitivity and specificity of the available COVID-19 diagnostic tests. The Office for National Statistics (ONS) has developed a COVID-19 infection survey that delivers population-weighted estimates of incidence by region and age. The survey data, together with the blood donor testing database, have provided important insights. Research-based studies such as the Real-time Assessment of Community Transmission (REACT) study are ongoing, but their scale is limited and aims somewhat narrow at present.[5,6] The creation of a large national cohort study should be a priority in the UK to provide information on many facets of the epidemic including immunity after recovery (both antibody and T-cell mediated) and duration of immunity.

See Online for appendix

There have been many problems in the UK on COVID-19-related data quality and access, not all of which have been resolved. Uneven quality and slow access to information on COVID-19 spread and impact, collected by different government organisations, such as the Department of Health and Social Care, Public Health England, and NHS Trusts, have been major impediments to epidemiological analysis of the state of the epidemic and predictions of future trends (Anderson RM, Vegvari C, Baggaley RF, Hollingsworth TD, Maddren R, unpublished). Good practice has been set by the ONS in reporting deaths, and progress is beginning on a single government web portal, which is in a trial format at present, for access to case numbers from various sources.[7] An authoritative body should acquire timely and relevant data at scale across government bodies and distribute it openly to researchers and the public through a well curated portal. Careful thought should be given to how a national database is effectively fed by local public health bodies, and how in return this national information portal feeds back to facilitate local action. Strengthening local public health capacity should be a priority in achieving this goal.

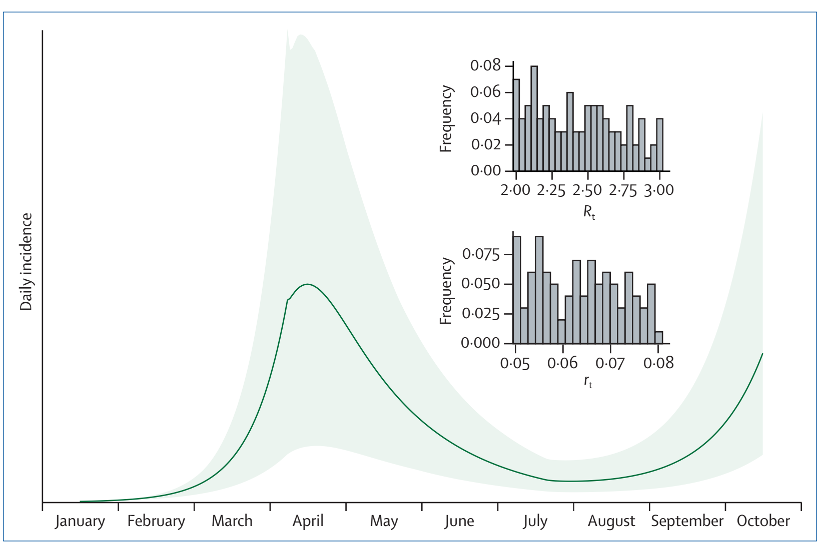

Figure: **Simulations of the possible patterns of COVID-19 spread in the UK in 2020, taking account of parameter uncertainty**

The simulations of COVID-19 spread in the UK shown in this figure are illustrative, not predictive. One way of examining epidemiological uncertainty is to simulate the epidemic by sampling from the full range of parameter estimates in the current literature. As an illustration, we assume that all values of the parameters are equally likely and use Latin Hypercube methods to sample the parameter space.[14] The graph shows a deterministic simulation of the epidemic in the UK, recording the incidence of infection over time in a population of 60 million people, based on the model described in the appendix. The solid line is the average prediction and the shaded area covers the 95% credible interval of the 100 showing (inset R_t and r_t in the week before lockdown). Uncertainty in key epidemiological parameters therefore generates much variability in estimates of R_t and to a lesser extent r_t. If we fix the parameter uncertainty, but instead take into account the negative binomial distribution of R_t, much variability in R_t and r_t is again generated across a series of model runs.[15] The message from both these examples suggests that the credible intervals around both parameters, R_t and r_t, are much wider than those reported at present.[16] These sources of variation must be combined with others that are also of great importance, such as spatial location and social factors.

What should be measured to give some advanced warning of a resurgence in COVID-19 case numbers in the UK, and how reliable are such measures given existing data sources? The UK Government's advisory group, SAGE, has broadened the information they release to include the effective reproduction number, R_t, which describes the average number of secondary cases generated by primary cases at time t, and the epidemic growth rate, r_t, which describes the rate of change in case numbers over a defined time.[8,9] The value of r_t is easier to estimate using simple statistical methods on changes in incidence over time. If negative in value, the epidemic is contracting. R_t is a more informative epidemiological measure (R_t <1 is the goal for stopping transmission over a long decay phase), although measurement requires assumptions to be made about other epidemiological parameters, such as the generation time of SARS-CoV-2 (average time from infection to passing the virus on to secondary cases) that can change over the course of the epidemic.

Sources of data for the estimation of R_t and r_t and how they change over time, include reported case numbers, serological surveys, data from contact tracing, and COVID-19 deaths. The specificity and sensitivity of the PCR tests for detecting active viral infection and the serological tests for detecting the presence of antibodies are key for interpreting data. Continued assessment of the accuracy for all tests in use in the UK is essential because of genetic heterogeneity in the SARS-CoV-2 genome at sites that might form the target of the PCR amplification process, and the period over which neutralising and other antibodies to viral antigens can be detected.[10–12] There would be greater clarity on these issues if it was made compulsory for commercial companies that manufacture these tests to make publicly available the precise location of the genome segment that is amplified in PCR tests and what antibodies are detected in serological tests. Many companies regard this information as commercially sensitive.

Much attention has focused on the magnitude of R_t at time t. But how precise is the measurement of R_t and what confidence should be placed on the ranges of values (region by region in the UK) reported by SAGE? Many sources of variability exist (figure).[13] There is uncertainty around some of the key epidemiological processes that determine the magnitude of R_t. These include the fraction of infections that are asymptomatic, how infectious asymptomatic infections typically are, and the duration of the infectious period before symptoms appear. Also of importance is the probability distribution of the generation of secondary cases,[17–19] which is overdispersed such that most infected individuals transmit none or a few infections, and a few individuals transmit many—the so-called superspreading events.[20] Contact tracing data provide crucial insights on this distribution, which has important consequences for COVID-19 control.[21]

A schematic representation of uncertainty in determining the magnitude of R_t and the course of the COVID-19 epidemic in the UK is shown in the figure with further information in the appendix. Estimates of R_t often rely on a model framework fitted to data on cases, deaths, or serology using Bayesian methods. What is assumed within the model therefore influences the numbers derived.

Uncertainty must therefore be factored into the advice given to policy makers. Relying on R_t estimates is not ideal, and greater emphasis should be placed on how the rate of decay in incidence (negative values in r_t) is changing and analysis of the second derivative (the rate of change of the rate of change), which suggests dangers ahead in terms of the start of a new exponential growth phase in case numbers and associated morbidity and mortality if it decreases rapidly. By the end of July, 2020, in the UK, daily reports of confirmed cases had stabilised at a fairly low level, but they are starting to exhibit the beginning of an increasing phase.[7] The concern at present is that the value of r_t (and concomitantly that of R_t) is expected to increase as physical distancing behaviours relax. All efforts must be made to increase the volume of testing, establish large-scale national serological studies, undertake more whole genome sequencing of the virus in isolates from people who test positive for infection to assess who infects whom, and to vigorously pursue enhancing trace, treat, and isolate activities with more reliance on, and support for, local authorities to gather data in the communities they understand.

The level of herd immunity required to eliminate SARS-CoV-2 transmission, when and if a COVID-19 vaccine becomes available that gives a defined duration of protection, is determined by the magnitude of R_0 (the basic reproduction number). Part way through the epidemic in the UK, when only herd immunity created by past infection is acting, the magnitude of R_t is the crucial determinant of what proportion of the population must be effectively immunised to halt transmission. Studies in the general population in the UK suggest the level of infection-induced herd immunity is low, with large variation in the percentage of the general population with antibodies to SARS-CoV-2, ranging from 0·5% to nearly 15% in different regions.[22] Progress on COVID-19 vaccine development has been encouraging and it might result in the availability of a vaccine earlier than expected in the UK, if phase 3 studies go well.[23,24] Then the challenges will include manufacturing a vaccine at scale and creating a high demand in the public such that more than 60% (if R_0 is around 2·5 in value) of the UK population are immunised.[25] Immunisation with a COVID-19 vaccine might have to be repeated annually if the duration of immunity is short, as suspected to be the case for other coronaviruses.[26]

When providing estimates of the key epidemiological parameters about COVID-19 to inform policy, as noted by George Bernard Shaw, the single biggest problem in communicating uncertainty is the illusion that it has taken place. Linked to this problem is that of selective hearing, with individuals typically hearing what they want to hear within the wide uncertainty bounds, whether they are policy makers, the media, or the public. A priority for the new Joint Biosecurity Centre will be to advise caution over the coming months in relaxing physical distancing measures when uncertainty in the current and future course of the epidemic is so high.

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