A TALE OF TWO SCIENTIFIC PARADIGMS: CONFLICTING SCIENTIFIC OPINIONS ON WHAT "FOLLOWING THE SCIENCE" MEANS FOR SARS-COV-2 AND THE COVID-19 PANDEMIC

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ABSTRACT

During the COVID-19 pandemic, many governments have adopted responses revolving around the open-ended use of non-pharmaceutical interventions (NPIs), including "lockdowns", "stay-at-home" orders, travel restrictions, mask-wearing, and regulated social distancing. Initially these were introduced with the stated goals of "flattening the curve" of hospital demand and/or the eradication of the virus from the country (i.e., "zero covid" policies). Over time, these goals have shifted to maintaining sufficient NPIs in place until such time as population-wide vaccination programmes have achieved an appropriate level of herd immunity to allow lifting of these measures without excessive hospital demand. Supporters of this approach have claimed to be "following the science", insisting that criticism of any aspects of these measures is non-scientific or even "scientific misinformation". This idea that only one set of scientifically valid opinions on COVID-19 exists has encouraged the media, social media and even scientific journals to suppress and/or dismiss any differing scientific opinions as "erroneous", "discredited" or "debunked", resulting in discouragement of open-minded scientific inquiry or discussion. Accordingly, in the current article we identify two distinct scientific paradigms to analysing COVID-19 adopted within the medical and scientific community. Paradigm 1 is primarily model-driven, while Paradigm 2 is primarily empirically-driven. Using these two paradigms we have analysed the epidemiological data for 30 northern hemisphere countries (with a total population of 882 million). Remarkably, we find using each paradigm leads to diametrically opposite conclusions on many policy-relevant issues. We discuss how these conflicting results might be reconciled and provide recommendations for scientists and policymakers.

SUMMARY BOX

- We describe two different scientific paradigms that have been used for analysing the ongoing COVID-19 pandemic. We show that analysing the epidemiological data from 30 northern hemisphere countries (total population of 882 million) with each paradigm leads to diametrically opposite conclusions on how governments and societies should respond to this pandemic.
- Paradigm 1, mostly model-driven, implies that non-pharmaceutical interventions (NPIs) are effective and essential until a population-wide vaccination programme has been completed. By corollary, Paradigm 1 implies that a public perception that therapeutics might reduce the severity of COVID-19 would be dangerous if it led to the premature lifting of NPIs.
- Paradigm 2, mostly empirically driven, is unable to find compelling evidence that the NPIs are particularly effective, but plenty of evidence that "the cure is worse than the disease". Meanwhile, Paradigm 2 finds no need for a population-wide vaccination programme, although smaller-scale voluntary vaccination programmes may potentially be helpful in shielding the vulnerable and health-care workers. Paradigm 2 also implies that research into identifying effective therapeutics to reduce the severity of COVID-19 should be actively encouraged.
- We discuss how these two paradigms can be reconciled and provide recommendations for scientists and policymakers on how governments should be responding to the pandemic.

INTRODUCTION

There is a popular perception that science represents a linear, incremental process leading inexorably towards a single, incontrovertible scientific "truth" on all matters of science. This leads to the mistaken belief that all scientists must necessarily converge towards the same scientific opinion, thus implying a false dichotomy whereby we can either agree with "the science" or be "anti-science". Therefore, it is unsurprising that many politicians and policymakers claim to be "following the science" [1,2] in response to the ongoing COVID-19 pandemic. Simultaneously, many media outlets have adopted a policy of only reporting one set of scientific opinions, assuming that anything else is non-scientific "misinformation". [3] Even some in the scientific community have actively suppressed or dismissed views they consider "misinformation".[4–7] This has been mirrored by social media platforms and internet search engines making "an aggressive effort" to prevent the dissemination of "misinformation about the coronavirus".[3]

Conversely, free speech advocates argue that the active suppression of "misinformation" is frequently counter-productive [8]. Further, the suppression of opposing perspectives can lead to cynicism and support for conspiracy theories that might have gained less traction with open dialogue.[9]

Accordingly, in the current article, we have adopted the Kuhnian view of the progress of science through scientific paradigms [10]. Kuhn (1962) argued that historically "normal science" pragmatically required that prevailing paradigms within a given scientific field were not questioned. Those who question the paradigms were actively criticised and even ostracised from the community. However, as anomalies that cannot be explained by the prevailing paradigm accumulate over time, paradigm shifts can occur. Kuhn noted that the paradigms of one field may contradict those of other field, but this is rarely noticed as interdisciplinary communication is relatively infrequent.

We suggest that the multi-disciplinary nature of COVID-19 research has brought this conflict between competing paradigms to the fore. Specifically, we identify two distinct scientific paradigms that have been adopted by rival scientific groups:

- Paradigm 1 takes a largely model-driven approach, emphasising the results from standard mathematical models for epidemiology.
- Paradigm 2 takes a largely empirically-driven approach, assessing the emerging clinical and epidemiological data within the context of previous similar events and new scientific insights.

Both approaches have their pros and cons, e.g., Paradigm 1 might be more useful in the first few months of a pandemic from a novel virus when the available data for Paradigm 2 is still limited. Yet, we might expect that both approaches should be compatible with each other and yield complementary results. Indeed, the importance of integrating both approaches is often emphasised, [11] including during the COVID-19 pandemic [12–14]. However, remarkably we find that each paradigm leads to diametrically opposed conclusions on the validity of many of the policies which have been implemented in response to the COVID-19 pandemic.

PARADIGM 1: THE MODEL-DRIVEN APPROACH

The SIR/SEIR model framework (and related models)

Kermack and McKendrick (1927) introduced a simple mathematical model for epidemics known as the "SIR model", where the epidemic population is divided into three compartments: Susceptible (S), Infectious (I) and Recovered or Removed (R). [15] A common variant of this model is the SEIR model which adds an intermediate Exposed (E) compartment for those not yet infectious. The SIR/SEIR models have been the primary approach used by a significant proportion of modelling groups for evaluating the COVID-19 pandemic. [16–18] Others have used more sophisticated "agent-based models" [19] developed from the framework of the SIR/SEIR model. Hence, to understand Paradigm 1, it is important to have a basic understanding of this SIR/SEIR model framework.

In the classical SIR model, it is assumed that 100% of the population begins as susceptible, i.e., with no pre-existing immunity. However, when susceptible individuals are exposed to an infected individual, they become infected and move into the "I" compartment. After an assumed recovery time, they recover (or die), moving into the "R" compartment. So, in the model, everybody begins in the S compartment, but once exposed to the virus, they follow a path through the compartments (S→ I→R for SIR; S→E→I→R for SEIR) until they have either recovered or died. Recovered individuals are explicitly assumed to be immune for the rest of the epidemic. Other variants of this compartmentalised modelling approach are sometimes used, however a significant majority of COVID-19 modelling in the literature has tended to employ the SIR/SEIR approach. [16–18]

Application of the classical SEIR model to the COVID-19 pandemic

When the classical SEIR model framework is applied to the COVID-19 pandemic, it may result in some concerning predictions. Figure 1 illustrates how Paradigm 1 predicts that the COVID-19 pandemic would unfold in the absence of any non-pharmaceutical interventions (NPIs) or population-wide vaccination programme.[20]

Figure 1 implies that, if left unchecked, the final size of the epidemic (FSE) for a given country is determined by the "basic reproduction number" (R_0) of the virus. R_0 can be approximated as the average number of people infected by each infected person prior to recovery. Assuming $R_0>1$, the total number of infections initially increases exponentially. However, according to the model, as the epidemic unfolds and more people enter the "Recovered" compartment, the *effective* reproduction number at a given moment in time, R_e (sometimes reported as R_{eff} or R_t), should decrease as shown in Figure 1(b). Once R_e falls below 1, i.e., the "herd immunity threshold" (HIT), the number of active infections should peak and start decreasing. However, since this simply marks the expected peak in infection numbers, the expected FSE is higher still – a prediction known as the "overshoot effect".

The exact value of R_0 for SARS-CoV-2 is still unknown and likely varies between and within populations, with most estimates ranging between 2 and 6 [20,21]. For comparison, median estimates for the last four influenza pandemics occur in the range R_0=1.46–1.8, and for seasonal influenza, R_0=1.28 [22].

Assessing the effectiveness of NPIs using the SEIR model

From Paradigm 1's perspective, the predictions described above are *projections* of what would be expected to unfold *in the absence of any NPIs* and/or a mass vaccination programme. However,

governments across the globe adopted NPIs on the back of recommendations from Paradigm 1, specifically to avert these *projections*, although there were some exceptions, e.g., Sweden [23–25]. Initially, these NPIs were seen as temporary measures, but at the time of writing (17 months later), many remain. Moreover, many countries did not begin mass vaccination programmes until early 2021, so Paradigm 1 assumes that the predictions from Figure 1 have not yet been tested and therefore still represent valid predictions of what could unfold if governments decided to completely lift all NPIs before herd immunity was achieved through mass vaccination.

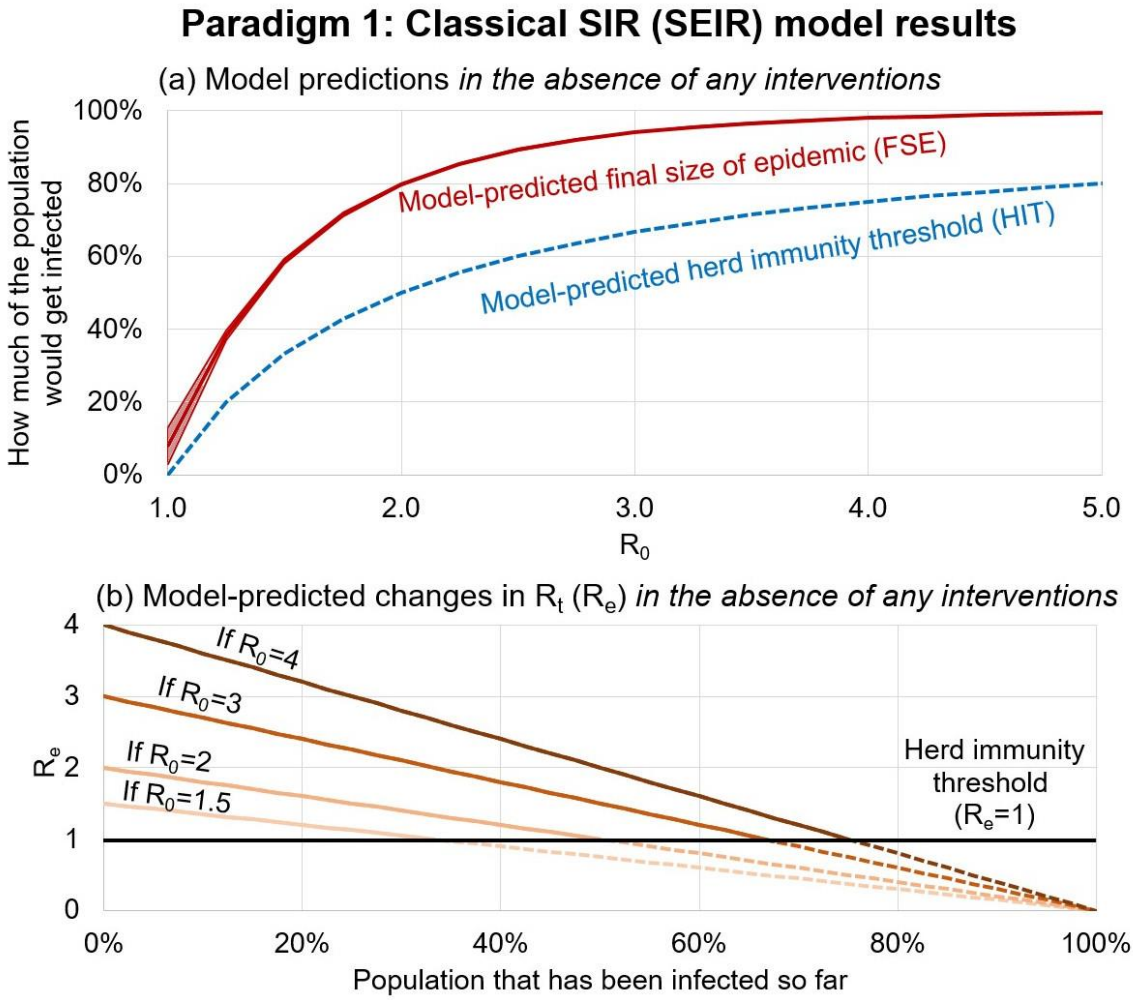

Figure 1 The predictions of how the COVID-19 pandemic would unfold for a given country *in the absence of* any non-pharmaceutical interventions (NPIs) or pharmaceutical interventions, according to the classical SIR (SEIR) model, i.e., the main modelling approach used by Paradigm 1. Note that the results plotted here do not include a timeframe, but rather describe the expected pandemic in terms of the percentages of the population infected. The SEIR model we used for estimating the FSE values for (a) was the model developed for the Irish Epidemiological Modelling Advisory Group (IEMAG) by Gleeson et al. (downloaded from https://github.com/obrienjoey/ireland_covid_modelling; accessed 09/02/2021). [18]

If the model predictions of Figure 1 have not yet been tested, how can we know that the NPIs are working? Paradigm 1's answer is encapsulated by Figure 2.

The calculated population-weighted average daily R_e values for the EU, UK, USA and Canada (30 Northern Hemisphere countries, total population = 882 million) are presented in Figure 2(a), alongside calculated model-expected values of R_e in the absence of NPIs for each day (Figure 2d) due to the build-up of population-wide immunity through natural infection (Figure 2b) and vaccination (Figure 2c).

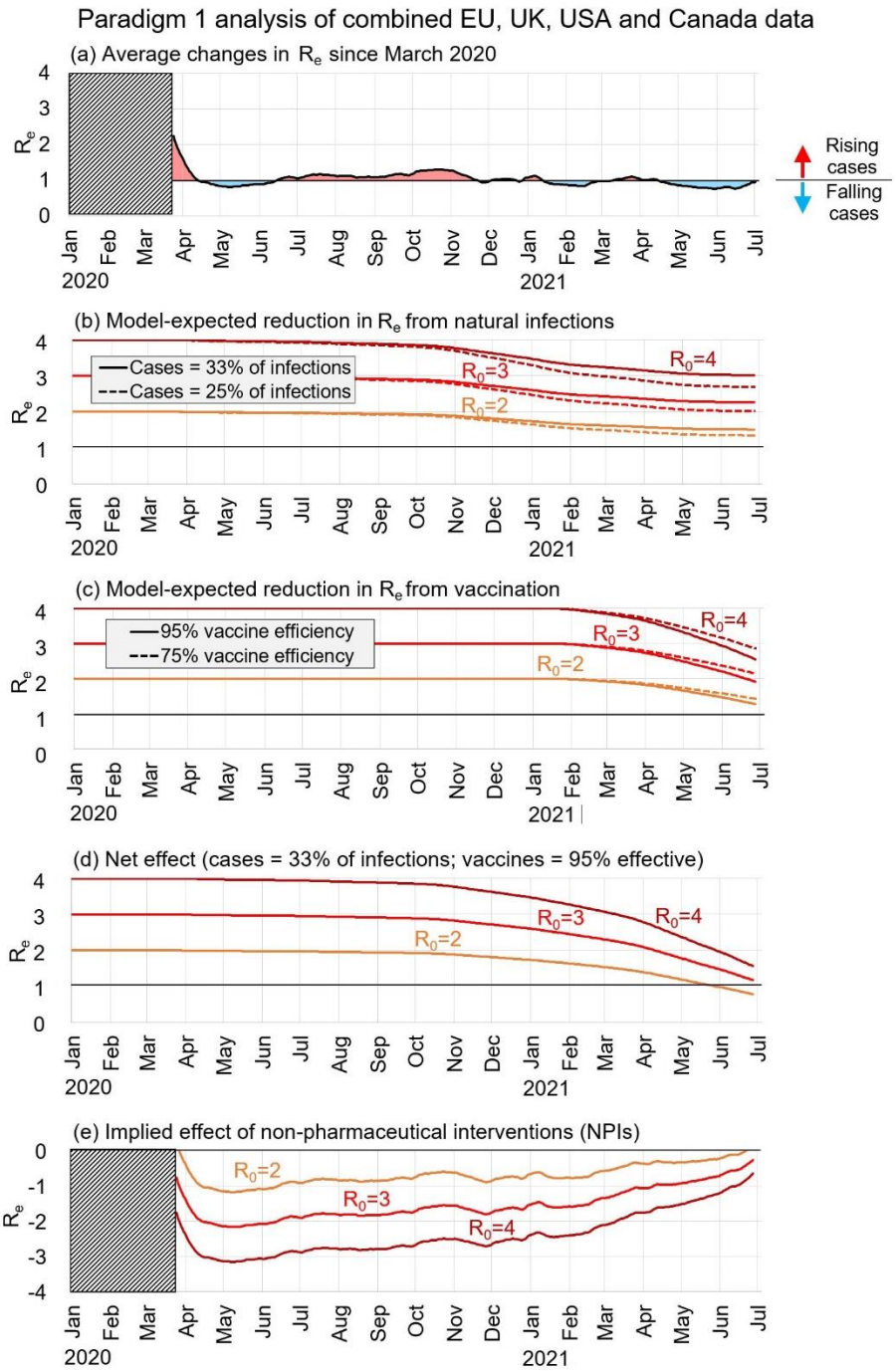

Figure 2 An example of how Paradigm 1 might interpret the combined statistics for the EU, UK, USA and Canada up to July 2021. (a) The average R_e values calculated from all available country estimates for that date, weighted according to the population of each country. (b) The implied changes in R_e due to natural infections according to Figure 1(b) based on the fraction of the total population that had been infected, assuming that identified cases represented either 33% (solid lines) or 25% (dashed lines) of all infections. (c) The equivalent analysis for vaccination based on the fraction of the total population that had been fully vaccinated, assuming that vaccination is either 95% (solid lines) or 75% (dashed lines) effective. (d) The combined effect of (b) and (c). (e) The difference between panels (a) and (d). The data for this figure and Figure 4 are taken from Ritchie et al.'s "Our World In Data" dataset (https://ourworldindata.org/coronavirus; accessed 04/07/2021). [26]

Figures 2(a) and (d) are significantly different, as evidenced in Figure 2(e). A foundational assumption of Paradigm 1 is that SIR/SEIR model projections are reasonably accurate – they are, after all, based on the standard epidemiological model [11] which has been used for nearly a century [15]. Therefore, viewed through Paradigm 1, Figure 2 offers strong evidence for the following:

- Although the exact efficiencies of individual NPIs remains uncertain, they have collectively, successfully kept the projections from Figure 1 at bay.
- In order to prevent the likely consequences of Figure 1, it is essential that NPIs remain in place until herd immunity is achieved through mass vaccination.[27]
- Researchers suggesting that NPIs could be lifted earlier, without vaccination, are promoting dangerous misinformation, [27–30] whether the proposal involves a targeted "focused protection" strategy (https://gbdeclaration.org/), the use of therapeutics, [31–34] or a general "rethinking" in light of emerging evidence. [35]

PARADIGM 2: THE EMPIRICALLY-DRIVEN APPROACH

The original SIR model by Kermack and McKendrick (1927) [15] comprised multiple simplifying assumptions and approximations — understandably, as this occurred well before the "computing era". Broadly speaking, proponents of Paradigm 2 are researchers who have revisited one or more of these assumptions in light of empirical data and/or scientific advances since 1927. In this section, we will summarise some of these issues that have been highlighted in the scientific literature on COVID-19:

1. The possibility of pre-existing immunity to COVID-19.
2. The role of "population heterogeneity"
3. Substantial differences between the modelled estimates of the effectiveness of NPIs and empirically-derived estimates.
4. Inconsistencies in the definitions of "COVID-19 cases" over the course of the pandemic
5. The role of "seasonality" in the COVID-19 pandemic

Pre-existing immunity

The default SEIR model assumes that 100% of the population are initially characterised as "susceptible" to infection. However, numerous recent studies report that many people do not get infected with SARS-CoV-2 even after significant exposure. For example, a large meta-analysis of the "secondary attack rate" (i.e., number of new infections among contacts ÷ number of contacts) among households where a household member was infected, estimated it to be 17%. [36] Among pre-symptomatic and asymptomatic infections, the secondary attack rate would appear to be significantly lower, at 0.7%. [36]

One possible explanation is that the "100% susceptible" assumption is inherently flawed.[37] Indeed, although antibody-based immunity is a learned process, antibodies are just one line of immune defence [38]. Studies find that 20–50% of people without previous exposure to the virus demonstrated T-cell reactivity against SARS-CoV-2 [37,39,40]. Moreover, it has been shown that the immune system's response to a human rhinovirus infection seems to temporarily prevent SARS-CoV-2 infection (although not vice versa). [41]

Lourenço et al. (2020) [39] demonstrate that allowing for prior immunity dramatically reduces Paradigm 1 projections. If R_0 =3, Paradigm 1 modelling predicts a HIT of 67% of the population and an FSE of 94% of the population (in the absence of intervention). However, as can be seen from Figure 3(a), if the population is characterised by an initial 20% partial immunity to COVID-19, the predicted HIT is reduced to 46% and the equivalent FSE to 69% for the same R_0 =3. If prior immunity was 50%, then the expected HIT would be reduced to 16.7% and the FSE to 29%.

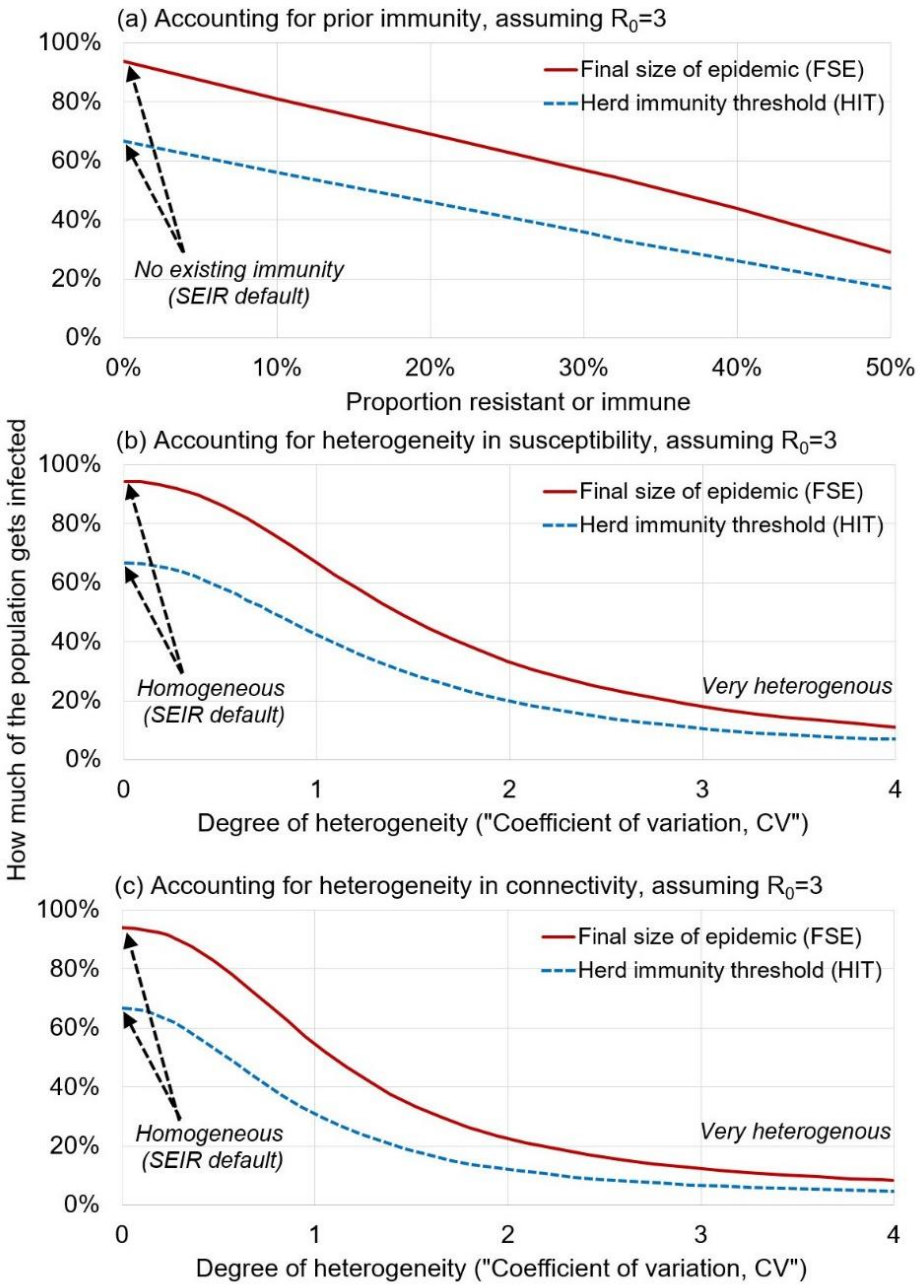

Figure 3 (a) The effect of incorporating the possibility of prior immunity on the final size of epidemic (FSE, red solid lines) and the herd immunity threshold (HIT, blue dashed line) without intervention, assuming R_0 =3. The standard SIR assumption of a 100% susceptible population means that 0% are resistant. The data is digitised from Figure 1 of Lourenço et al. (2020). [39] (b) and (c) The equivalent effects of incorporating the heterogeneity of either (b) susceptibility to infection or (c) connectivity (dashed lines) into the SEIR model. The data is digitised from Figure 3 of Gomes et al. (2020). [42,43]

"Population heterogeneity"

A central simplifying approximation of the original SIR model is an assumption of population "homogeneity", i.e., that everybody is equally likely to become infected. However, several studies have demonstrated that this assumption dramatically overestimates the expected HIT and FSE. [42–46] Conversely, Paradigm 2 allows for "population heterogeneity" in terms of the possibility of infection

and/or transmission, i.e., that some individuals are more likely than others to become infected and/or to spread the virus. Two aspects of "population heterogeneity" are particularly important: variability in "susceptibility" (the chances of becoming infected) and variability in "connectivity" (the average number of people they interact with).

In terms of susceptibility, it is well-established that immunity varies between people and over time, due to multiple factors, e.g., stress; [38,47] obesity; [48] fitness; [49]age; [50] diet; [51] and alcohol consumption. [52] Moreover, some factors linked to the immune system are seasonal, e.g., the role of vitamin D [53,54] and the effects of cold exposure on the immune system. [55]

Figure 3(b) shows that accounting for varying susceptibilities to infection substantially reduces the HIT and FSE for a given R_0 value. [42,43] Depending on how much heterogeneity in susceptibility is incorporated, the expected HIT for R_0=3 could be reduced from 67% to 5–10%, and the corresponding FSE could be reduced from 94% to 10–20%. Likewise, Figure 3(c) indicates that accounting for varying levels of physical interaction leads to a similar but separate reduction.

It is still unclear exactly how much population heterogeneity should be incorporated. [42–46] Nonetheless, the general result leads to the conclusion that the standard homogeneous SIR model substantially overestimates both the HIT and FSE of the pandemic.

Empirical assessment of NPI efficacy

As discussed, proponents of the Paradigm 1 approach may argue that the NPIs *must* be working because model predictions of what should have occurred in the absence of NPIs, have not occurred. [16,17] Conversely, proponents of Paradigm 2 argue that the NPIs should be tested *empirically*, i.e., using experimental and/or observational data. However, most of these empirical studies suggest the NPIs are far less effective than the models imply [46,56–61].

Indeed, in general, if NPIs were consistently effective, measures should be anti-correlated with case numbers, i.e., the more stringent the NPIs, the greater the ensuing fall in cases. However, as can be seen from Figure 4(a), the stringency of NPIs is partially correlated to case numbers. One possible explanation for a positive correlation is that governments have tended to increase NPIs during periods characterised by rising case numbers.

Meanwhile, others wonder why the course of the pandemic in Sweden has been so similar to that in other European countries [23,24], given that Sweden only implemented modest and voluntary NPIs.[25] This is surprising, as we might intuitively expect that NPIs *should* help to reduce the spread of the virus. Therefore, it is worth considering why our intuitive expectation might be wrong.

Let us consider the wearing of masks, a particularly common NPI since about mid-2020 On mechanistic grounds, it seems plausible that, *in theory*, masks *should* help reduce the spread of the virus [62,63]. However, *in practice*, few have identified a *statistically significant* effect [64,65], while some have identified a *non-statistically significant* effect.[65,66] For example, Bundgaard et al. (2020), a randomized control trial (RCT) of the effects of wearing masks on reducing the spread of COVID-19, [65] could be interpreted differently by adherents of either Paradigm. This study found that 2.1% (53/2994) of the control group and 1.8% (42/3030) in the mask-wearing group caught COVID-19, a statistically insignificant difference. Most proponents of Paradigm 2 would probably concede that this does not rule out the possibility of a small effect size for mask wearing NPIs, but the absence of a statistically significant effect size indicates that it is probably modest at best.

In contrast, several studies have reported that NPIs may inadvertently bestow negative effects on immunity:

- NPIs have significantly increased psychological stress.[67,68] In this context, Cohen et al. found that volunteers given nasal drops containing a common cold virus were 4–5 times more likely to develop symptoms if highly stressed [47].
- Lockdowns, stay-at-home measures and travel restrictions can negatively influence multiple factors which influence immunity, e.g., nutrition, [51] obesity,[48] alcohol consumption,[52] exposure to sunlight, [53,54] and physical fitness. [49] In terms of the latter, Chastin et al. (2021) found a 31% risk reduction in community-acquired infectious disease for those who had more than 150 minutes/week of regular physical activity compared to those who exercised less than 150 minutes/week. [49]
- NPIs may be leading to a net loss of microbial diversity [69] that can affect immunity[69–71].

Underestimating the first waves through under-testing

In the initial stages of the pandemic, testing was largely confined to those with severe symptoms and/or front-line workers. This made sense from a healthcare perspective to ensure an accurate diagnosis for patients with severe symptoms, and to reduce hospital-acquired (nosocomial) infections. However, it created unintended challenges in tracking the spread of the virus and estimating virulence [72]:

- Early "cases" were identified from a subset of infections that included those with the worst symptoms. Therefore, the initial case fatality rate/risks (CFR) estimates of ~2.3%[73] were higher than the infection fatality rate/risk (IFR), [74] with similar overestimates of hospitalisation rate.
- Significant underestimates of the total number of people infected in the early stages of the pandemic. [74]

Accordingly, studies report that the true number of infections during this early stage could have been underestimated by a factor ranging from ×4–7[75–78] to ×13–18[74]. Hence, Ioannidis (2021) recently estimated the IFR at ~0.15%.[74] Moreover, this estimate assumes that all "deaths *with* COVID-19" were "deaths *from* COVID-19". Yet, for many countries, the average age of death with COVID-19 is similar to national life expectancy, with most of these cases having co-morbidities.[23] That is, it is likely that only a fraction of the deaths *with* COVID-19 were deaths *from* COVID-19. For example, in Sweden, the number of "COVID-19 deaths" up to mid-November 2020 was 6410, while the excess mortality over the same period was only 1479. [23] While these two metrics are not directly comparable for various reasons, [23] it is striking that the latter is only 23% of the former.

Overestimating recent waves through over-testing

By mid-2020, with increased testing capacity (and reduced demand), many countries redefined the "case definition" for COVID-19 to no longer require any clinical criteria.

Currently, a new "case" is typically defined as a person who tests positive in an RT-PCR test for COVID-19. This test amplifies a part of the SARS-CoV-2 viral RNA sequence that might be present in a swab sample. However, several studies have noted that this test only detects a specific stretch of viral RNA and does not indicate whether this fragment is part of an infectious virus. Therefore, attempts have been made to estimate the infectiousness of cases by trying to culture the virus from the sample in a laboratory. [79–82] The probability of infectiousness decreases dramatically as the "cycle threshold" (Ct) for the RT-PCR test is increased. The exact values of Ct associated with infectiousness depend on various factors including the test itself [83], yet it appears that a Ct of greater than 30–35 is probably not infectious [79–82].

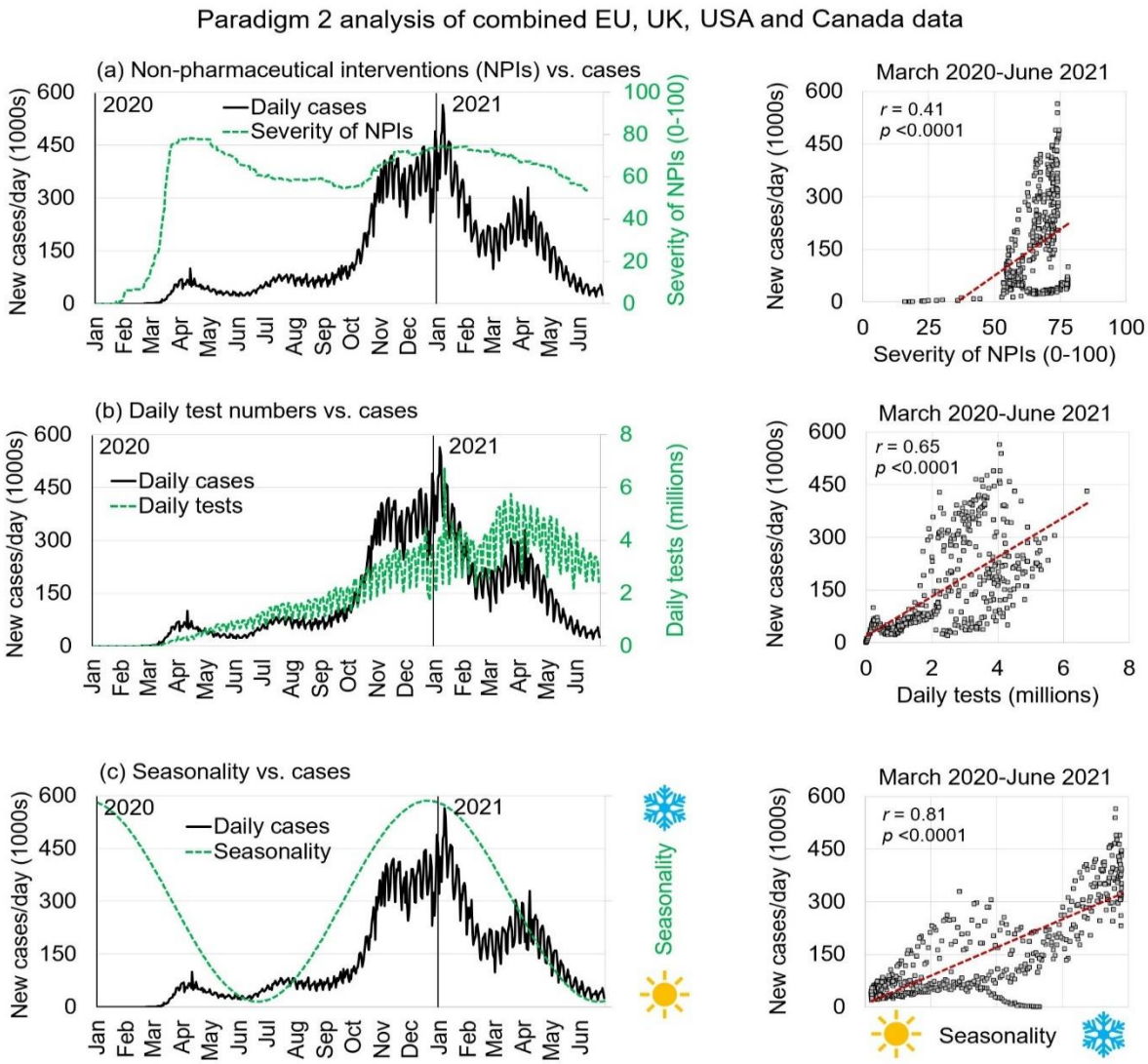

Figure 4 An illustrative example of how Paradigm 2 might interpret the combined statistics for the EU, UK, USA and Canada up to July 2021. The panels on the left compare the daily new cases (solid black line) to different factors (green dashed lines) over time. The corresponding right-hand panels evaluate the correlation (or anti-correlation) between that factor and the daily cases. The three factors are: (a) the average of the Oxford Covid-19 Government Response Tracker's "Stringency Index" of the 30 countries (population-weighted average), which we use as a proxy for the relative severity of non-pharmaceutical interventions (NPIs); (b) the total daily tests for the 30 countries; (c) a crude generic approximation of "seasonality", which was defined as the cosine of the fraction of the year since the Northern Hemisphere winter solstice (21st December). This periodic function reaches a maximum at winter solstice and a minimum at summer solstice.

Despite this, assays for COVID-19 RT-PCR tests are sometimes run up to 40 cycles or more. [80,82] Therefore, a person could be asymptomatic, non-infectious and even immune, yet still be defined as a "new case" equivalent to a severely ill and infectious case. Indeed, as herd immunity builds up in the population (whether through natural infection or vaccination), it is plausible that an increasing fraction of the "new cases" are immune and non-infectious.

Therefore, according to proponents of Paradigm 2, the changes in case definitions, testing capacity and testing priorities over the course of the pandemic represent a major challenge for analysing the pandemic. Indeed, Figure 4(b) shows a strong correlation between the number of new cases and the number of tests carried out, although proponents of Paradigm 1 might counter that *some* increases in testing coincide with an increase in demand.

The role of seasonality in the COVID-19 pandemic

Proponents of Paradigm 1 often argue that COVID-19 is "not seasonal" because seasonality cannot explain all of the observed COVID-19 epidemic behaviour, e.g., outbreaks across several regions during summer periods. [84,85] Proponents of Paradigm 2 counter that this does not rule out seasonality *as a contributing factor*. Figure 4(c) suggests that seasonality is indeed a significant factor. This is not surprising since the four endemic human coronaviruses are seasonal, overlapping closely with seasonal influenza. [86]

Hope-Simpson suggested that an over-familiarity with the annual occurrence of "cold and flu season" has led to a remarkable lack of curiosity about the exact reasons for this seasonality. [87,88]. Nonetheless, many potential mechanisms have been identified, which can be divided into two types:

1. Seasonality affecting the virus. Temperature, humidity and sunlight have been shown to significantly influence the length of time SARS-CoV-2 virus remains viable in aerosols [89] and on surfaces [90,91].
2. Seasonality affecting the host. Several aspects of the immune system are influenced by seasonality,[55] with Vitamin D as one plausible candidate.[53,54]

CONFLICTING SCIENTIFIC CONCLUSIONS IN "FOLLOWING THE SCIENCE" WITH EACH PARADIGM

How effective have the various NPIs been?

Both paradigms lead to diametrically opposed conclusions on this question. On the basis of the differences between the modelled expectation of how R_e should unfold in the absence of NPIs and the observed values (e.g., Figure 2), proponents of Paradigm 1 conclude that the NPIs are collectively not just effective, but essential until such time as herd immunity has been achieved by mass vaccination. Conversely, researchers deploying Paradigm 2 have struggled to empirically identify significant effects of NPIs, whether individually or collectively. Moreover, the NPIs may in fact be negatively impacting immunity.

Is the cure worse than the disease?

Proponents of Paradigm 2 are highly concerned about the negative effects that NPIs have on health and society, [92–94] e.g., morbidity and mortality implications of delayed cancer care; [95,96] mental health burden; [67,68] elderly care [98–100]; domestic violence [101] and education; [97] Therefore, while proponents of Paradigm 1 are convinced that these adverse impacts are a necessary evil, many in Paradigm 2 believe that the cure is worse than the disease.

What are the relative roles of therapeutics and vaccines in managing COVID-19?

There is a striking contrast between the two paradigms on the relative importance of therapeutics and vaccines. The safety and effectiveness standards that appear to be held for both types of pharmaceutical intervention seem almost equal yet opposite for each paradigm.

Proponents of Paradigm 1 believe that NPIs cannot be lifted until >70–80% of the population has been vaccinated. They are of course concerned about the safety and effectiveness of the vaccines in question, but vaccination is of the utmost urgency. In contrast, they fear that any suggestion that therapeutics might exist to reduce the severity of COVID-19 would be disastrous if it reduced public support for the NPIs. Therefore, proponents of Paradigm 1 have actively criticised studies claiming to have identified promising therapeutics, e.g., hydroxychloroquine [7,28,30] or ivermectin. [29]

Meanwhile, many in Paradigm 2 argue that research into promising therapeutics that might potentially reduce the severity of COVID-19 should be encouraged. [31–34] By contrast, they do not see the necessity for a population-wide vaccination programme, for multiple reasons:

- The IFR is much lower than originally assumed [72,74]
- The NPIs are less effective than assumed [46,56–61]
- Herd immunity is much closer than assumed, due to pre-existing immunity; [39] population heterogeneity; [42–46] or underestimation of total infections during the first waves [72,74–78].
- Natural herd immunity through heterogeneity requires a much lower threshold than a random vaccination programme [43,45]

However, opposition to these population-wide COVID-19 vaccination programmes might mistakenly be perceived as merely part of a non-scientific general "anti-vaccination" movement. Therefore, it is important to clarify and unpack several distinct objections to the ongoing vaccination programmes among different researchers in Paradigm 2:

1. There is concern over the unprecedented speed with which the vaccines have been rolled out on a population-wide basis, since adverse reactions to vaccines sometimes take months or years to become apparent. [102,103] In particular, the safety thresholds for a population-wide vaccination programme should be even higher than for a treatment programme, since the vaccine is to be administered to a healthy population. [102,104,105]
2. Some argue that a population-wide vaccination programme is neither necessary nor desirable. [39,43,45] Instead, vaccines should be directed to those most at risk of developing serious COVID-19 illness, or to front-line workers. [105] Vaccination should remain voluntary, and societal pressure to become vaccinated minimised. [106]
3. There has been little effort to identify and exclude people with naturally acquired immunity from vaccination, despite the fact that naturally acquired immunity is at least as effective as vaccine-acquired immunity.[107]
4. During the clinical trials, very few volunteers in either the vaccinated *or* the control group tested positive for SARS-CoV-2—typically a total of 1–2% of all volunteers. Yet the public is largely unaware of this, since the vaccines have been promoted by reference to "relative risk reduction" (RRR) results without also emphasizing the very low "absolute risk reduction" (ARR) results of the clinical trials [103,108].
5. Others emphasize that the main vaccines being rolled out would be better described as "gene therapy-based" technology rather than conventional vaccines. The idea of "mRNA vaccines" (e.g., Pfizer, Moderna) and "DNA vaccines" (e.g., AstraZeneca, Johnson & Johnson, Sputnik) has been in development for more than a decade[109,110], but this is the first time it has been attempted on the public. Therefore, there is concern that they have been subjected to less stringent clinical trials than usual.[102,103] That said, some of the WHO-approved vaccines have taken a standard vaccine approach, such as using an inactivated version of the virus (e.g., the Chinese "Sinopharm" and "Sinovac"). [111] However, at the time of writing, many countries have not yet approved or recognised any of these conventional vaccines, even if WHO-approved[112].
6. There is some concern that the protein which the mRNA and DNA vaccines prompt cells in the body to synthesise is the "spike protein", since it has been suggested that this protein itself might "in some cases, result in the pathogenesis of certain diseases". [105]

CONCLUSIONS

We identified two distinct scientific paradigms deployed by the medical and scientific community to study COVID-19. Paradigm 1 is mostly model-driven, while Paradigm 2 is mostly empirically-driven.

Although it might be expected that both paradigms should yield compatible conclusions, we found that each paradigm leads to remarkably different conclusions. See Table 1 for a summary of the main differences between the two paradigms.

Table 1 Comparison of the key differences between the two paradigms

	Paradigm 1	**Paradigm 2**
Most important tool for assessing the ongoing pandemic	Model projections of future scenarios	Analysis of clinical and epidemiological data
How effective are NPIs in controlling the spread of the virus?	✓ Very effective	✗ Largely ineffective; possibly counter-productive
Was there pre-existing immunity to COVID-19 before 2019?	✗No	✓Yes
Can strengthening immunity reduce our chances of developing severe COVID-19?	✗No	✓Yes
Is seasonality an important factor?	✗No	✓Yes
Is accounting for changes in testing capacity, testing priorities and case definitions important?	✗No	✓Yes
Is accounting for "population heterogeneity" important?	✗No	✓Yes
How does COVID-19 compare to other influenza-like illnesses (ILIs)?	Worse than any we have experienced in at least a century	Worse than average for older generations; milder than average for younger generations
Use of vaccines	A population-wide vaccination programme is essential before NPIs can be lifted completely	Voluntary vaccination of those most at risk of developing severe COVID-19 and/or front-line workers could help, provided the vaccine has been well-tested *and* proven to be both safe and effective
Use of therapeutics	The promotion of any therapeutics could be catastrophic as they might reduce public support for NPIs, unless a therapeutic were identified that is well-tested *and* proven to be both safe and effective	The identification of any promising therapeutics that might reduce the severity of COVID-19 is welcomed.
Which is worse: "the cure" (NPIs until 80-90% of the population is vaccinated) or "the disease" (i.e., COVID-19)?	The disease	The cure

We recommend that policymakers who want to "follow the science" should begin considering the science from both paradigms, rather than relying on just one paradigm. Governments that have been

using scientific advisory boards to identify suitable policies should ensure that these boards contain advisers from both paradigms.

Media outlets, social media platforms and internet search engines that have been suppressing scientific opinions that disagree with one of the paradigms under the mistaken assumption that this has been reducing the spread of "misinformation about the coronavirus" [3] should instead encourage open scientific discussion. [8]

We encourage researchers from both paradigms to be respectful of the scientific insights from the opposing paradigm. Moreover, we also recommend researchers from each paradigm to start framing their research to be compatible with both paradigms. For instance, Paradigm 1 researchers who are basing their analysis on model projections should begin offering methods by which the reliability of their model projections can be evaluated. Meanwhile, Paradigm 2 researchers should recognise that many governments currently prefer to make decisions which have considered model projections of plausible scenarios. Therefore, if a Paradigm 2 researcher disputes the reliability of a Paradigm 1 model, they could consider presenting alternative model projections.

Acknowledgments We thank Jeff Connell of the Irish National Virus Reference Laboratory (NVRL) for constructive feedback and clarifications on some of the issues covered by this manuscript.

Competing interests GQ and RC both signed the Great Barrington Declaration (which is consistent with Paradigm 2) in November 2020. GQ is also a member of Health Advisory & Recovery Team (HART) which broadly has followed Paradigm 2. This might initially be perceived as indicating a bias towards one of the two paradigms. Indeed, RC and GQ concede that they initially were biased towards this paradigm. However, their contributions to the manuscript were motivated in part by their efforts to better understand both paradigms.

Funding PH's contribution was in part funded through a Science Foundation Ireland (SFI) research grant (COVID-19 Rapid Response Funding Call). RC's contribution was part funded by the Center for Environmental Research and Earth Sciences (CERES). The aim of CERES is to promote open-minded and independent scientific inquiry. For this reason, donors to CERES are strictly required not to attempt to influence either the research directions or the findings of CERES. Readers interested in supporting CERES can find details at https://ceres-science.com/.

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