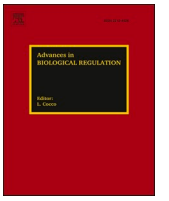
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Advances in Biological Regulation 86 (2022) 100922

Contents lists available at ScienceDirect

Advances in Biological Regulation

journal homepage: www.elsevier.com/locate/jbior



COVID-19 models and expectations – Learning from the pandemic

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The COVID-19 crisis has presented a major test for the scientific community and its research tools. With over 500,000 scientific papers already devoted to COVID-19 and over a million scientists likely involved in co-authoring them, no scientific field has been left untouched by the pandemic (Ioannidis et al., 2022). All types of research designs, tools and practices have been utilized in response to this unprecedented global healthcare challenge, with mixed results. The evolution of evidence has been rapid - full of surprises, upheavals, good and bad news, and plenty of debate. Perhaps regrettably, this has sometimes gone beyond the domain of strictly scientific argument. Bold questions have been asked, intriguing answers offered and challenged. Many issues, including some of the most hotly debated topics, remain unresolved – or perhaps not, as perspectives differ even on what has been answered and what not.

This special issue of Advances in Biological Regulation brings together a number of papers that address several critical issues concerning the pandemic and provide potential answers with different levels of certainty, ranging from the speculative to the definitive.

Some of the most intriguing questions surround the heterogeneity of disease impact and transmission. The overall impact on the population (e.g. on mortality, severe disease and hospitalizations) has varied, with some countries and locations clearly hit far more than others. The differences were extreme when single waves are considered. They tend to get attenuated when a long-term horizon over three years is taken into account, but still some geographies apparently did much better than others (Levitt et al., 2022; COVID-19 Cumulative Infection Collaborators, 2022). Extreme heterogeneity of impact has probably also been a feature of previous pandemics, with 25- to 70-fold differences across locations described for twentieth century pandemics (Murray et al., 2006; Simonsen et al., 2013; Viboud et al., 2016). While differences in health, demographic, and social./income indicators have been evoked as potential explanations, much of this diversity has remained unexplained or debated. Regardless, this heterogeneity is unlikely to simply reflect the impact of policy through non-pharmacological interventions. In fact, the large background heterogeneity makes concrete assessment of the effectiveness of any and all non-pharmacological measures based on observational data extremely difficult, if not impossible.

Bhattacharya and colleagues (Bhattacharya et al., 2022) try to dissect why Eastern Asian countries were spared (especially in 2020). They dismiss that age structure, non-pharmacological interventions (including more familiarity with and use of masking), genetics, seasonal/climatic differences, and lower rates of obesity could be the key determinants underlying this benevolent picture and conclude that some sort of pre-existing immunity may be responsible. This is a bold hypothesis that deserves further study, besides the pieces of corroborating evidence that is presented by the authors.

It is likely that a very large number of factors may each contribute modest differences in mortality impact and cumulatively they may create more substantive differences. For example, age structure can create major differences in total fatalities between countries: one evaluation (COVID-19 Forecasting Team, 2022) estimates that infection fatality rate may have varied by a factor of 30 across 190 countries and territories and age structure seemed to account for 74% of IFR variability. Differences in comorbidities such as obesity

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https://doi.org/10.1016/j.jbior.2022.100922
Received 6 October 2022; Accepted 6 October 2022
Available online 8 October 2022

may add another element with major differentiation in fatality rates. The proportion of obese people among adults is 2.1% in Vietnam, 4.3% in Japan, and 4.7% in South Korea (https://worldpopulationreview.com/country-rankings/obesity-rates-by-country and last accessed September 26, 2022), 10-20 times lower than in the USA. Obesity markedly increases mortality risk in COVID-19 (Tartof et al., 2020). Pre-existing immunity is also a tantalizing explanation, and it has been raised as a possibility not only for East Asian, but, perhaps more prominently, for Africa, where many studies that show high levels of anti-SARS-CoV-2 humoral immunity and where the low number of recorded COVID-19 deaths has also sparkled debate (Tso et al., 2021; Adams et al., 2021). This immunity may be related to cross-reactive exposure to malaria and dengue or perhaps some unknown coronavirus. Pre-existing T-cell immunity is even more puzzling (Le Bert et al., 2020). The clinical significance of such immunological observations should not be rushed, however. Nevertheless, such a perspective would put the COVID-19 pandemic more in the light of a continuum from the prior population history of infectious cycles rather than a complete disruption with the past. This perspective may be even more important for the future. If true, the future evolution of new variants and new waves may be heavily influenced by the immunity milieu that has already been developed in the global population from the many billions of SAS-CoV-2 infections plus, of course, vaccinations. This could be mostly excellent news, although unwelcome surprises are also possible.

Modeling (without empirical data, with limited empirical data, or with a lot of empirical data) acquired a dominant position in early COVID-19 scientific efforts, influencing initial decision-making and subsequently playing an ongoing important role in pandemic management (Saltelli et al., 2020). Heneghan and Jefferson (Heneghan and Jefferson (2022) offer a cautionary perspective on the interpretation of results and predictions from infectious disease models, especially regarding transmission. They focus on the early days of the pandemic when limited and potentially flawed data informed modeling efforts. Their review of studies that reported estimates of the basic reproduction number up to May 2020 shows extreme heterogeneity and almost all estimates were based on very problematic early Chinese datasets. Mathematical models were maximally used and potentially misused during the pandemic (Holmdahl and Buckee, 2020), with more model publications produced and circulated within the last 3 years than in the history of PubMed.

The uncertainty and large heterogeneity of modeling-derived estimates is not new. For example, past reported estimates of the basic reproductive number of measles have differed by more than 500-fold (1.43–770) across 18 studies and 58 reported estimates (Guerra et al., 2017). What is new is the overwhelming influence models have exerted during this pandemic on major public health decisions affecting billions of people in major ways. Heneghan and Jefferson (Heneghan and Jefferson (2022) express concern that this has been disproportionate to that which can be achieved through models, even with better data. Mathematical models have fallen outside the radar screen of traditional evidence-based hierarchies of study designs. Perhaps they do not even deserve to be seen as "studies", but more as semi-formal speculations. This does not mean, however, that models should be discarded or that there is no room for improvement in terms of their transparency and validation (Zavalis and Ioannidis, 2022). Medley (2022) presents an insider view of the difficulties and challenges that arose as models had to be produced, run, interpreted and applied in the UK in real time under critical circumstances. His experience is extremely insightful and allows putting expectations versus realities in a more proper context. His thoughtful view of the issues surrounding the function of the UK Scientific Advisory Group for Emergencies (SAGE: a key advisory group to government) and particularly the transmission dynamics sub-committee that he chaired, touch on the complex interrelationships between evidence, policy, action, science, and uncertainty. Nothing is straightforward and complexity should be acknowledged and respected.

Clinical impact is certainly determined directly by the extent of transmission that occurs in a population and by the type of people to whom the virus is transmitted, particularly their frailty and vulnerability for severe disease and outcomes. Zonta and Levitt (2022) offer an interesting, if speculative, approach to modeling the transmission dynamics in scale-free networks. Their work suggests that scale-free network spread can capture the Gompertz growth that seems to be seen consistently in COVID-19 outbreaks (Pelinovsky et al., 2022). In the Gompertz framework, the growth is ultrafast in the early phases (leading to justifiable alarm) but then it markedly slows down and gets dissipated. One can argue how much this slowing down and dissipation may be attributed to what the population does to protect itself, decreasing exposures (either by personal initiative or because on measures taken and imposed by public health authorities). However, Zonta and Levitt's model intriguingly does not require such decreases in exposures for the dissipation to happen eventually. They demonstrate that the universal properties of the network of social interactions can apply to very different topologies and connectivities. The key for the early viral spread is the nodes that have many connections. In this model it is possible to envision many forme fruste tiny epidemic waves dying in the early phases, unless they can reach such connection-rich nodes. This may take a while and it may explain why often it took a long time for the onset of discernible epidemic waves to become manifest in 2020, even though the virus was circulating in the globe for many months (Maxmen, 2022). Once the connection-rich nodes are reached, the process is extremely accelerated, but then it dies fast, as the connection-rich nodes are exhausted. Given this perspective, it is possible to test whether interventions that try to protect these connection-rich nodes may be far more effective and have fewer adverse consequences than blunt, horizontal interventions that target all society. Adding the dimension of differential clinical impact in different individuals may offer a principled approach on how to exercise precision public health (Ioannidis, 2021). The feasibility of precision-based approaches can certainly be debated, but it is a field that deserves further study.

Over time, rigorous evidence is needed to deal with a major crisis like COVID-19 and there is no excuse not to launch the best studies with the best designs to get the best evidence in a timely fashion. Traditionally, randomized trials have been considered the optimal way to get unbiased estimates of the effectiveness of interventions. COVID-19 led to many thousands of randomized trials being launched. The vast majority were small, uninformative and/or futile (Janiaud et al., 2021). However, well designed and executed randomized trials were probably one of the major successes of the COVID-19 scientific effort. Peto, Horby and Landray (Peto et al., 2022) present their experience from designing, leading, and bringing into fruition the Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial (Pessoa-Amorim et al., 2021). RECOVERY was launched in March 2020 and aimed to provide an

adaptive platform for testing rigorously the effectiveness of treatment for people hospitalised with COVID-19. Within two years, the cumulative enrollment approached 50,000. At least four interventions were found to confer statistically significant (and clinically meaningful) survival benefits, and for another 6 the results excluded clinically meaningful survival benefits. In contrast to prior beliefs that large randomized trials take for ever to run, RECOVERY provided definitive answers for these treatments within a matter of a few months. The concept can be extended to test also in large-scale non-pharmacological interventions, where randomized evidence has been very sparse (Hirt et al., 2022).

After three years of COVID-19, even the most central question "what will we do when/if a new pandemic hits", can lead to very different expectations and substantially different views from reasonable and well-informed scientists. Differences in opinion concerning some aspects of the pandemic may still be fundamental, but this should not be unexpected and it would be incorrect to conclude we have not learned any lessons at all. If and when a new pandemic arises, we may still not have easily transposable, generalizable answers on the best courses of action. However, hopefully we should be better positioned to ask the right questions earlier and in a better way.

Funding

None.

Declaration of competing interest

The authors are the guest editors of the Special Issue on COVID-19 models and expectations.
Stephen Powis is National Medical Director of NHS England and was a SAGE participant.

Data availability

No data was used for the research described in the article.

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