Methods lead the way

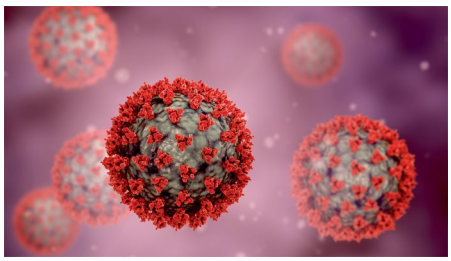
The COVID-19 pandemic has highlighted the importance of methodological advancements in basic biological research. We believe that method development will continue to propel both fundamental and applied studies on SARS-CoV-2 and other pathogens.

When cases of a mysterious respiratory virus circulating in China were reported in December 2019, little did we know that the world was on the brink of a catastrophic pandemic. Within a month of being detected in Wuhan, SARS-CoV-2 had spread globally, leading to complete chaos reinforced by political bungling and unprecedented spread of misinformation. Despite these challenges, the scientific response to COVID-19 has been nothing short of extraordinary. By January 2020, the viral genome was sequenced and available, and by 2021, there were several highly effective vaccines on the market.

This unparalleled speed of research and development has been paved by years of meticulous methods development stemming from the basic biological research community. In this special issue of *Nature Methods*, we reflect on some of the key recent methodological advances that have enabled a speedy and efficient response to the COVID-19 pandemic.

In their Comment, Serghei Mangul and colleagues discuss how genomics and metagenomics methods have become essential public health tools. Once the virus was detected, scientists immediately set about identifying and characterizing the pathogen, enabled by access to reliable and accurate sequencing methods. Similarly, computational tools allowed phylogenetic analyses of the genetic fingerprint of the virus that traced its origin and evolution; by these methods, SARS-CoV-2 was found to have close ancestral ties with bat coronavirus species. Genomic and bioinformatic methods continue to be used across the globe to monitor the emergence of new SARS-CoV-2 variants and track transmission routes.

By early 2020, the first structures of the viral spike protein were already available, including cryo-electron microscopy (cryo-EM)-based resolution of the interactions between the viral receptor-binding domain and the host ACE2 receptor. This remarkable pace of discovery has been facilitated by experimental and computational advances over the past decade in the field of structural biology, especially in cryo-EM and cryo-electron tomography (cryo-ET), and more recently



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in deep-learning-based protein structure prediction, write Jun Zhang and Bing Chen in their Comment. Understanding the intricacies of host–viral interactions at the atomic level has in turn powered studies into antibody-based therapeutics and rational vaccine design.

An important caveat in unraveling the molecular underpinnings of SARS-CoV-2 infection has been understanding the glycosylation patterns on the viral and host cell surface, explain Laura Kiessling and colleagues in their Comment. Recent developments in mass spectrometry have illuminated the mutational potential of spike protein glycosylation patterns, as well as guided approaches to develop broad therapeutic interventions. Lectin arrays and chemical-biology-based approaches have also been instrumental in understanding infection-induced altered glycosylation on host cells, which was shown to induce aberrant downstream cell signaling and help infected cells evade the immune system.

As the number of COVID-19 cases soared across the world, researchers raced to understand immune response elicited by SARS-CoV-2 infection and to leverage that to develop a protective vaccine. In their Comment, Ignacio Sanz and colleagues reflect on high-throughput immunological methods that have aided the effort to study B-cell and antibody-mediated immunity. For instance, the deep immune profiling of rare and sensitive populations of human B cells as well as analyses of the diversity of immune responses within the population have been made possible by recent advances in high-dimensional cytometry. Similarly, sensitive multiomics methods have pushed the limits of single-cell biology, enabling simultaneous analyses of the immune cell repertoire and the proteomic and transcriptomic trajectories of responding B and T lymphocytes.

To consolidate the global effort to understand the mechanisms of SARS-CoV-2 infection and pathophysiology, the World Health Organization launched a working group focused on animal models of COVID-19. As Kwok-Yung Yuen and colleagues discuss in their Comment, animal-based research on COVID-19 faced an impediment when it was established early on that commonly used experimental models such as rats and mice were not susceptible to infection by SARS-CoV-2. To circumvent this issue, the community, supported by decades of research on animal model development, quickly rallied and developed transgenic mice carrying the human ACE2 receptor and SARS-CoV-2 variants adapted to mouse ACE2.

Additionally, to study the biology of SARS-CoV-2 in natural hosts, researchers began to explore the disease in lesser-known animal models like Syrian hamsters, where the disease mimics the clinical and immunological features observed in humans. It was use of the Syrian hamster model that first suggested that surgical masks may protect against transmission of the virus. Primate models also proved indispensable for studies on immune correlates of protection and for first-in-line safety and efficacy testing of the vaccine candidates before they entered clinical trials. This is a reminder of the importance of animal models in biological research.

Of course, there are ethical considerations associated with animal-based research. Years of innovation and development of robust in vitro assays have culminated in organoid technology, which has proven to be an animal-free, physiologically relevant counterpart to model COVID-19 disease by complementary means, as reviewed by Shuibing Chen and colleagues in their Perspective. While lung and airway organoids were the first to be studied in the context of SARS-CoV-2 infection, models such as intestinal organoids, brain organoids and others have also been used to successfully explain seemingly unrelated symptoms experienced during infection. For instance, an inflammatory response

followed by loss of cellular function was observed in SARS-CoV-2-infected choroid plexus organoids, possibly explaining neurological deficits observed in a subset of patients.

However, questions about the biology of SARS-CoV-2 remain unanswered, leaving room for further methodological development. For instance, studies on the etiology of long COVID-19 may benefit from an appropriate in vivo or in vitro disease model. Similarly, we need more physiological organoid models that include vascular and immune compartments, while in structural biology, methods like cryo-ET have room for improved resolution, accessibility and ease of use.

The pandemic response by the scientific community has been an astounding success made possible by international collaboration, open science and the speed of biological research, all bolstered by decades of scientific achievements. In fact, one of the most positive outcomes of the pandemic has been the increased focus on open data and code sharing supported by both researchers and publishers. Although governments have left much to be desired when it comes to transparent information sharing, collaborative scientific discourse proved to be key in the rapid response against COVID-19.

Yet the staggering death toll left in the wake of the COVID-19 pandemic is a sobering thought and a reminder to do better next time. In our Technology Feature, journalist Vivien Marx presents personal perspectives from researchers across the Global South who have brought their experience with infectious diseases to the battle against COVID-19. The need for constant vigilance against emerging threats is further highlighted in a special Feature, where we asked 15 researchers around the globe what they thought was necessary, from a methods point of view, for tackling the next major pathogenic threat. The answers vary widely, ranging from the need for interpretable computational models to study gene enhancers to improved nanopore sequencing methods to biobanks of human organoids that reflect true human genetic diversity; they are a peek into the road that lies ahead.

The grim news is that there is far more work to be done to be ready for the next outbreak, but, as the COVID-19 pandemic has demonstrated, we have both the skill and the technology to do it. We hope that funding agencies also recognize that methods developed over the last decades have played a critical role in the response to COVID-19 and therefore continue to prioritize research funding for technology development.

Two years on, we at *Nature Methods* are more committed than ever to our mission to continue to publish and support new methodological developments and cutting-edge approaches that enable fundamental biological discovery. To us, always, the method comes first and forms the foundation for robust and reproducible scientific research. ❐

Published online: 8 April 2022
https://doi.org/10.1038/s41592-022-01474-7