

VIEWPOINT

Highlights from a year in a pandemic

Miriam Merad^{ID} and Nicolas Vabret

COVID-19 has emerged as one of the worst pandemics in recent history and has exposed the weaknesses of healthcare systems worldwide. Here, we reflect on the lessons learned from a year in a pandemic. We discuss the extraordinary scientific advances made in our understanding of a new disease, the failed and successful attempts to halt its progression, and the impact of the pandemic on the scientific discourse within the global community.

Introduction

COVID-19 has profoundly affected the daily lives of people across the globe and revealed striking healthcare inequalities between and within countries, including in the US. The initial hesitation of most governments to take radical preventive measures took a heavy toll in human casualties and triggered a worldwide economic recession. For scientists, 2020 severely disrupted research activity, with experiences halted, projects delayed, and conferences cancelled. With schools closing, the challenge to maintain a work-life balance often became overwhelming for young parents. Yet, 2020 also turned out to be a formidable year of scientific productivity, exchange, and collaboration. Within weeks after the first reports of a new form of lethal pneumonia in Wuhan, China, the causal agent SARS-CoV-2 was isolated, its genomic sequence published, and its cellular receptors identified. Within a year, COVID-19 has led to an unprecedented production of scientific knowledge, with more than 100,000 peer-reviewed articles published in scientific journals and many more manuscripts posted on preprint servers (Else, 2020). Medical teams have conducted thousands of clinical trials, including an astonishing number of 82 different vaccines evaluated to date on human volunteers. Never in the field of medical research have we witnessed such a worldwide mobilization of scientists, united by a fight against a common medical threat.

Mixed success obtained by repurposing antiviral drugs and hope for new therapeutics

A major effort of the medical community at the beginning of the pandemic has been to repurpose Food and Drug Administration-approved drugs to treat COVID-19 patients, with the hope to accelerate translation and clinical benefit, especially among the most severe patients. Unfortunately, large randomized clinical trials, such as the UK RECOVERY and the WHO SOLIDARITY, revealed that despite initial promise, several of these drugs, including the RNA polymerase inhibitor remdesivir, the cytokine IFN- β , the combination of anti-proteases lopinavir/ritonavir, and the highly publicized hydroxychloroquine, failed to significantly improve clinical outcome of hospitalized COVID-19 patients (WHO Solidarity Trial Consortium, 2021). One exception was the anti-inflammatory dexamethasone, which showed survival benefit in the most severe patients, emphasizing the importance of taming inflammation in COVID-19 patients. The efficacy of anti-inflammatory strategies was further strengthened by recent clinical benefits observed in severe COVID-19 patients treated with tocilizumab, an antibody blockade against IL-6 receptor (Horby et al., 2021 Preprint), and inhibitors of other pro-inflammatory cytokines are still under investigation. Importantly, countries with national health insurance

systems and widely used electronic health record platforms, such as the UK, were the ones able to provide definitive answers on drug efficacy through the swift development of large and informative clinical trials (Bugin and Woodcock, 2021).

Another major drug development effort, primarily driven by biotechnology companies, was the generation of therapeutic monoclonal antibodies targeting several SARS-CoV-2 proteins. A small clinical benefit was observed when they were administered in COVID-19 patients very early after infection, enabling therapeutic antibodies to receive an Emergency Use Authorization for the treatment of mild to moderate COVID-19 patients with high risk of disease progression (Chen et al., 2021; Weinreich et al., 2021). Several antiviral drug targets including SARS-CoV proteases PLpro or 3CLpro are currently in development (Dai et al., 2020), while the recent mapping of SARS-CoV-2 proteomic interactions during viral replication (Gordon et al., 2020) helped identify host proteins that may prove to be useful antiviral drug targets (White et al., 2021).

COVID-19 is primarily a disease of immune dysregulation

A striking observation made early during the pandemic was the large spectrum of clinical outcomes observed in infected individuals, with a majority of patients developing no or mild symptoms, while a

Precision Immunology Institute, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY.

Miriam Merad: miriam.merad@mssm.edu; Nicolas Vabret: nicolas.vabret@mssm.edu.

© 2021 Merad and Vabret. This article is distributed under the terms of an Attribution-Noncommercial-Share Alike-No Mirror Sites license for the first six months after the publication date (see <http://www.rupress.org/terms/>). After six months it is available under a Creative Commons License (Attribution-Noncommercial-Share Alike 4.0 International license, as described at <https://creativecommons.org/licenses/by-nc-sa/4.0/>).

subset progressed toward a severe or fatal disease. This difference in outcomes is unlikely to be determined by virus-mediated tissue damage or by a failure to mount an adaptive immune response against the virus, as most patients developed neutralized antibodies against SARS-CoV-2 by the time they were hospitalized, and the presence of neutralizing antibodies failed to prevent disease progression (unpublished data). Autopsies of infected lung tissues confirmed that, at the time of death, lungs of most patients were devoid of virus while heavily infiltrated by immune cells (Desai et al., 2020; Schaefer et al., 2020). The clinical heterogeneity of the disease course prompted a major scientific effort to identify biological and clinical predictors of disease severity. While comorbidities such as diabetes, hypertension, chronic kidney disease, and obesity significantly increased the risk of developing severe COVID-19, age appeared to be the most dominant determinant of disease severity. It is interesting that the clinical conditions associated with an increased risk for COVID-19 lead to a chronic inflammatory state and vascular damage, which may contribute to the heightened inflammation induced by viral infection. To identify biological predictors of disease outcome, several groups across the world built massive collections of biological samples, many of which have been profiled using high dimensional technology and with single-cell resolution. These studies revealed that dysregulated myeloid cell compartments, lymphopenia, and inflammatory cytokines such as elevated IL-6 and TNF- α correlate with disease severity (Del Valle et al., 2020; Lucas et al., 2020; Mathew et al., 2020; Silvin et al., 2020).

Important insights have been provided by clinical studies of patients treated with cytokine blockade for underlying conditions. These studies revealed that patients receiving anti-TNF- α antibody blockade at the time of the infection had significantly reduced hospitalization and death, while patients receiving steroids had a worse outcome (Brenner et al., 2020; Gianfrancesco et al., 2020). These results highlight that, similar to many other pathologies like autoimmunity and cancer, it is critical to parse the beneficial from pathogenic immune responses to improve the outcome of COVID-19 patients.

Several studies have also emphasized the role of type I IFN (IFN-I) pathway in COVID-19 pathology. For example, germline defects in genes of the IFN-I pathway (Zhang et al., 2020), the presence of auto-antibodies against IFN-I (Bastard et al., 2020), or the blunting of IFN-I responses after Fc receptor engagement by patients' own antibodies (Combes et al., 2021) have been associated with disease severity in COVID-19 patients.

Finally, a growing focus of research efforts aim to understand the post-COVID-19 clinical sequelae, also known as long COVID, that are significantly impacting patients' quality of life. Whether these yet ill-defined symptoms are due to defects in tissue repair, quite common in patients with comorbidities, triggered by autoantibodies elicited by SARS-CoV-2 infection, or due to a lasting reservoir of virus in convalescent patients are all hypotheses that are being examined.

The second coming of vaccination

The biggest scientific success story of 2020 is the record-breaking developmental pace of efficient vaccines. In a field known for its low success rate, its long and tedious validation processes, and where innovations are scarce, the fact that six different COVID-19 vaccines have already been approved in multiple countries is a technological breakthrough. Current vaccine platforms approved in the US and most European countries include adenovirus-based and mRNA-based platforms. Although it is difficult to compare vaccine efficacy side by side, as the vaccine trials were led at different times during the pandemic with different dominant viral strains in circulation and different endpoint analyses for each trial, clinical results suggest that all approved vaccines significantly protect against hospitalization and death (Carvalho et al., 2021). Among the different vaccine platforms developed against COVID-19, mRNA-based vaccines, with their flexible design, production, and impressive efficacy, represent a scientific revolution that will likely redefine the future landscape of vaccination and drug development.

As predicted early in 2020, mass vaccination is the only way out of the COVID-19 pandemic. However, vaccinating populations around the globe requires that manufacturers overcome the logistical challenge of scaling up production and adapting vaccine distribution to countries

with different storage capacities. Hopefully, this will be achieved through the mobilization of mass production and funding framework to ensure global affordability. The success of the vaccination campaigns will also depend on the ability of the vaccines to protect against emerging SARS-CoV-2 variants and the capacity of manufacturers to scale the production, and the distribution of updated vaccines against these variants in a timely fashion to avoid the emergence of additional variants. Several pharmaceutical industries with proven expertise in vaccine manufacturing have offered to help produce Food and Drug Administration-approved vaccines, and the hope is that many others will join this effort.

The new challenges of scientific communication

A major challenge that arose during the pandemic has been to reconcile the need to swiftly communicate new research findings with the slow process of traditional peer review, which led to a surge in the use of preprint servers where new studies could be immediately posted before peer review. In response, several community-driven review initiatives were developed with the objective to help curate and communicate the stream of new results (Vabret et al., 2020), and some of these initiative have now expanded beyond COVID-19 studies (Nature Reviews Immunology, 2021).

Another challenge has been the emergence of misinformation and conspiracy theories that have exploded across different media platforms. Because the scientific process is meant to be dynamic and to evolve according to new experimental evidence, discrepancies between studies or scientists are common especially when studying novel disease entities. However, in countries with strong anti-science stances, as was the case in the US in 2020, the scientific method was presented as uncertainty or ignorance and exploited by impostors. Scientific misinformation, especially when nurtured by high-authority officials, has dangerous consequences as we have seen during this pandemic, leading to the use of potentially dangerous medications without proper clinical testing, the refusal to follow healthcare policies, distrust in the vaccine campaign, and xenophobia against citizens of countries where the pandemic started.

Scientific misinformation fueled by a narrowing gap between academic and general audiences and the growing importance of social media is another epidemic that needs to be addressed and eradicated.

Conclusion

The past year has been a challenging time for communities around the world. The pandemic emphasized the critical role collectively played by scientists, researchers, and clinicians in the functioning of modern societies and in the fight against global health threats. While the COVID-19 pandemic is not over and the emergence of new variants may delay its ending, it is important to realize that viral epidemics will happen again. It is therefore a shared responsibility of governments, institutions, and scientists to improve future pandemic preparedness through more research funding for pathogen surveillance programs, a

sustained effort to decipher the complexity of the immune system and develop novel vaccines strategies, and the generation of science communication tools to enhance public trust and engagement.

References

- Bastard, P., et al. 2020. *Science*. <https://doi.org/10.1126/science.abd4585>
- Brenner, E.J., et al. 2020. *Gastroenterology*. <https://doi.org/10.1053/j.gastro.2020.05.032>
- Buglin, K., and J. Woodcock. 2021. *Nat. Rev. Drug Discov.* <https://doi.org/10.1038/d41573-021-00037-3>
- Carvalho, T., et al. 2021. *Nat. Rev. Immunol.* <https://doi.org/10.1038/s41577-021-00522-1>
- Chen, P., et al. 2021. *N. Engl. J. Med.* <https://doi.org/10.1056/nejmoa2029849>
- Combes, A.J., et al. 2021. *Nature*. <https://doi.org/10.1038/s41586-021-03234-7>
- Dai, W., et al. 2020. *Science*. <https://doi.org/10.1126/science.abb4489>
- Del Valle, D.M., et al. 2020. *Nat. Med.* <https://doi.org/10.1038/s41591-020-1051-9>
- Desai, N., et al. 2020. *Nat. Commun.* <https://doi.org/10.1038/s41467-020-20139-7>
- Nature Reviews Immunology. 2021. *Nat. Rev. Immunol.* <https://doi.org/10.1038/s41577-020-00489-5>
- Else, H. 2020. *Nature*. <https://doi.org/10.1038/d41586-020-03564-y>
- Gianfrancesco, M., et al. 2020. *Ann. Rheum. Dis.* <https://doi.org/10.1136/annrheumdis-2020-217871>
- Gordon, D.E., et al. 2020. *Nature*. <https://doi.org/10.1038/s41586-020-2286-9>
- Horby, P.W., et al. 2021. *medRxiv*. <https://doi.org/10.1101/2021.02.11.21249258> (Preprint posted February 11, 2021)
- Lucas, C., et al. 2020. *Nature*. <https://doi.org/10.1038/s41586-020-2588-y>
- Mathew, D., et al. 2020. *Science*. <https://doi.org/10.1126/science.abc8511>
- Schaefer, I.M., et al. 2020. *Mod. Pathol.* <https://doi.org/10.1038/s41379-020-0595-z>
- Silvin, A., et al. 2020. *Cell*. <https://doi.org/10.1016/j.cell.2020.08.002>
- Vabret, N., et al. 2020. *Nat. Rev. Immunol.* <https://doi.org/10.1038/s41577-020-0319-0>
- Weinreich, D.M., et al. 2021. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMoa2035002>
- White, K.M., et al. 2021. *Science*. <https://doi.org/10.1126/science.abf4058>
- WHO Solidarity Trial Consortium. 2021. *N. Engl. J. Med.* <https://doi.org/10.1056/nejmoa2023184>
- Zhang, Q., et al. 2020. *Science*. <https://doi.org/10.1126/science.abd4570>