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Commentary

Emergency drug use in a pandemic: Harsh lessons from COVID-19

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The scientific and clinical communities have both experienced several harsh lessons on clinical care management and drug development during the COVID-19 pandemic. Here, we discuss several key lessons learned and describe a framework within which our two communities can work together and invest in to improve future pandemic responses.

Over a year has passed since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified. Since then, coronavirus disease 2019 (COVID-19) has claimed more than 4 million lives worldwide and affected billions more through reduced economic opportunity, healthcare access, educational progress, and community interactions. The pandemic spurred an unprecedented effort among scientific and medical communities to develop interventions to improve patient outcomes and alter the trajectory of the outbreak. However, vaccines and dexamethasone aside, other therapeutic interventions have had minimal impact on overall mortality from COVID-19. Further, in the chaotic early days of the pandemic, the principles of evidence-based medicine were often brushed aside—circumstantial evidence formed the basis of clinical management strategies, and anecdotes and hunches were the rationale for scientifically weak hypotheses in research. There was widespread duplication of research effort due to poor coordination, leading to wasted funding and time.

Here, we contextualize the shared experience of scientific and clinical communities during the COVID-19 pandemic, and examine some mis-steps and the lessons we have (re)learned. We frame these as a future-ready battleplan for the ongoing threat of emerging viral diseases; a plan that makes the best use of available resources and minimizes risk to patients.

Pattern recognition is a cornerstone of clinical care, even for a new disease

Outbreaks in China and Italy defined the COVID-19 clinical syndrome early; patients presented with respiratory symptoms (cough and shortness of breath) and systemic symptoms (fever, malaise, and myalgias), with some setting off on a trajectory to acute respiratory distress syndrome (ARDS), severe pulmonary fibrotic changes, refractory hypoxemia, multiorgan failure, refractory shock, and ultimately, death. These features suggested a pathophysiology analogous to that of other severe respiratory infections and especially similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).

Despite this, much of the research activity in the early months of the pandemic involved attempts to differentiate COVID-19 from other respiratory viral illnesses through nuances in clinical and laboratory parameters. While some of this knowledge ultimately showed some prognostic value and identified potential therapeutic targets (as discussed later), this effort overshadowed the fact that severe COVID-19 was an inflammatory acute respiratory distress syndrome (ARDS). There was extensive argument about whether COVID-associated respiratory failure should be managed as ARDS (Gattinoni et al., 2020). Eventually, decades-old evidence that low-stretch tidal volume ventilation is the primary method of ARDS treatment (Brower et al., 2000; Thompson et al., 2017) prevailed, with improved ICU mortality, but only after many died from ARDS: a well-recognized disease process. Furthermore, it was clear early in the pandemic that patients died primarily because of immune dysfunction. Imbalanced immune activation was responsible for morbidity and mortality from SARS-CoV and MERS-CoV (Tay et al., 2020). Parallels could have been drawn about SARS-CoV-2 after early retrospective reports indicated that the progression from mild to moderate to severe COVID-19 is associated with features of hyper-inflammatory response and sepsis (Zhou et al., 2020). These data were later reinforced by multiple studies showing that patients who died of COVID-19 ARDS evinced a pattern of distinct immune activation related to viral response and inflammation in the alveolus (Grant et al., 2021). A clear and coordinated clinical focus on immune dysfunction in COVID-19 could have helped design better trials with greater emphases on immunomodulatory strategies. In line with this, the World Health Organization International COVID-19 trial is set to restart with a focus on three immunomodulatory drugs.

A key lesson from this experience is that pattern recognition based on similarity to known clinical syndromes is critical as a foundation upon which additional

therapeutic modalities can be evaluated—even in times of uncertainty.

Principles of evidence-based clinical care must not be abandoned in the midst of a pandemic

Both antiviral and immunomodulatory drugs were considered and utilized early in the pandemic. However, much of this was administered off label, outside of observational studies and certainly outside of clinical trials. The most prominent example of this was hydroxychloroquine, used widely and repeatedly, based on highly politicized and poorly scrutinized research findings, eventually doing more harm than good (Axfors et al., 2021). More recently, we have seen this play out with the antiparasitic drug, Ivermectin—which was considered a bona fide therapeutic option in many settings based on *in vitro* data, despite high quality meta-analyses showing little or no effect. The use of investigational drugs as immediate therapeutic or prophylactic options has, in fact, limited their ability to be tested through robust clinical trials (Reardon, 2021).

It is understandable that, in the face of substantial mortality and overwhelmed health systems with little access to clinical trials, some clinicians resorted to therapies without strong clinical evidence. Yet herein lies a key lesson from the COVID-19 pandemic—the need to default to core principles of evidence-based medicine. Especially amidst uncertainty, evidence-based practice allows the definition and testing of therapeutic interventions most likely to work, while we prove or disprove alternative hypotheses. In the face of an emerging deadly viral pathogen, sticking to these principles is more critical than ever. Pandemics give rise to a huge number of people at risk, providing a unique opportunity to conduct robust clinical drug trials. Conversely, the *ad hoc* use of experimental therapies results not only in an opportunity cost, but puts a vast number at risk of receiving unproven therapies that are either ineffective, harmful, or both. However, key to maintaining public "trust" in the evidence-based approach is to design therapeutic trials that have the highest likelihood of success, through the best use of solid scientific knowledge available at the time.

Systematic failures during therapeutic development against COVID-19

This pandemic witnessed an unprecedented number of drugs clinically tested in less than 2 years, but few have borne out to be effective. Here, we discuss possible reasons for these inefficiencies in clinical drug development and highlight areas for possible improvement.

Antiviral drug development

Antiviral drugs target key processes during the viral life cycle, such as entry, replication, translation, or egress, and are typically selective for viral proteins/processes with few off-target effects, theoretically making them ideal viral pandemic therapeutics. Despite a large number of antiviral drugs being tested clinically, only one thus far, Remdesivir, has shown significant clinical benefit (Beigel et al., 2020), and its utility in reducing death remains uncertain (Rochwerg et al., 2020). One of the reasons why many antiviral candidates failed is that in the panicked push for effective "emergency response" drugs, there was reduced scrutiny of preclinical experimental designs. Unlike Remdesivir, which had a known mechanism of action (MOA) and activity against related coronaviruses, many other candidate drugs were identified through unbiased screening assays. While such assays have their use, they have several caveats; for one, drug potencies can vary greatly based on the assay used. A large proportion of early testing involved the *in vitro* use of a single cell line (e.g., Vero-E6). Such cell lines often have altered immune responses to infection and do not fully recapitulate viral growth *in vivo*. Second, the MOA and *in vivo* bioavailability for drugs identified in unbiased screens were often unknown, making it difficult to ascertain off-target effects, and ultimately leading to many being false positives. Both limitations could be overcome through the focusing on repurposed drugs with known MOA and pharmacokinetics/pharmacodynamics (PK/PD) focusing on molecules that can be administered orally and tested in multiple cell lines and, where available, animal models.

Another contributing factor was the failure to consider viral dynamics during COVID-19 disease. Several experimental drugs were used by pre-treating or treating experimental animals very early during infection (e.g., less than a day post-infection). This is unrealistic in clinical practice: most people are unaware of when they become infected, SARS-CoV-2 has a long incubation period during which a person is asymptomatic, and viral burden peaks very early in the symptomatic phase. Drugs that show efficacy in pre-treated animals would only be useful in humans if given in the pre-symptomatic phase of illness or prophylactically, which is improbable even when health systems are functioning optimally. Prophylactic antiviral therapy for COVID-19 seems implausible, as this requires administration to be regular or immediately prior to a known exposure, whereas exposure to COVID-19 is typically unpredictable. Regular drug administration requires a huge volume of drug to be manufactured, and even if such a prophylactic antiviral was readily available, the challenge of dispensing sufficient drug in a short time while balancing the risk of adverse events from a mass administration is daunting.

For future pandemics, it would be reasonable to clinically evaluate only anti-viral agents that have shown efficacy against similar infectious pathogens *in vivo*, as was done for Remdesivir. Testing molecules discovered through *in vitro* assays alone without considering the natural history of the disease, PK/PD and viral replication kinetics is risky and unlikely to succeed. Attention must be paid to these variables, even if doing so may require time and patience. This is likely to be a thorough, more efficacious, and ultimately safer approach for patients. These principles, however, are different for immunomodulatory drugs.

Repurposing immunomodulatory therapies

Early retrospective analyses showed that COVID-19 patients who had higher expression of inflammatory cytokines had poorer survival prognoses. This led to hypotheses that inhibiting specific cytokine-mediated pathways would be beneficial, and consequently, immunomodulatory therapies such as Anakinra (anti-IL1b) and Tocilizumab (anti-IL6) were repurposed for COVID-19. While monotherapy with these agents has thus far proved unsuccessful, broad-spectrum immunomodulators such as Dexamethasone, Baricitinib (anti-Janus kinase), or

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combinations of immunomodulatory drugs have shown efficacy in those with severe COVID-19 (Group 2021; Kalil et al., 2021).

In hindsight, it may have been possible to predict which drugs were likely to be efficacious and in which target patient population. Since the inflammatory response to SARS-CoV-2 involved multiple inflammatory pathways and regulators driving large, complex, often non-overlapping transcriptional networks (Ho et al., 2021a), it was more likely that broad-based rather than specific immunomodulatory targeting would be needed (Rialdi et al., 2016). Similarly, an immunomodulatory strategy would only be necessary or helpful for those with immune dysregulation (severe COVID-19) and could be harmful when the immune system is working effectively to control viral replication and disease (mild to moderate COVID-19). Some may argue that until specific drug were clinically evaluated in specific patient strata, we could not have known this to be true. However, we propose that knowledge of disease pathogenesis could have filtered earlier into prioritization of key drugs repurposing in specific patient populations.

Finally, perhaps the hardest lesson we had to learn is that our arsenal of (usable) antivirals and immunomodulatory drugs is relatively empty and poorly equipped to deal with emerging pathogens. It is clearly time to re-think how antivirals and anti-inflammatory drugs are prioritized, designed, and identified. A novel method of making vaccines (RNA-based vaccine) revolutionized our world during this pandemic. Novel drug design strategies, possibly embracing new technologies, are needed more than ever (Ho et al., 2021b).

Strategies for better drug repurposing and improving pandemic responses

Definitive criteria and framework for short-listing drugs used in clinical trials

So how should we choose appropriate repurposed anti-inflammatory/anti-viral agents for clinical development during a pandemic, especially one with immunological features such as COVID-19? Immunological effects are difficult to evaluate without *in vivo* studies. Given the unavoidable and lengthy delay in establishing the best humanized animal model, starting directly with human studies using repurposed drugs may be acceptable if done with close interaction between clinicians and scientists.

As randomized controlled trials (RCTs) cost time and money, choosing the wrong drugs or wrong approach for an RCT has a large opportunity cost. Starting RCTs with agents that are well established in clinical practice (e.g., Dexamethasone) is acceptable and has succeeded. However, in this pandemic, the initial choice for clinical evaluation of less understood anti-inflammatory drugs was largely driven by expert clinical opinion (not necessarily with pre-clinical rationale) and through observational reports (which suffer from selection bias). The case of Hydroxychloroquine, with hundreds of wasted randomized trials attempting to prove/disprove its effects, attests to the need for a stringent framework for the clinical development of repurposed agents in a global pandemic. We propose that the following key considerations be addressed through pre-clinical studies and early single-arm clinical studies, to "short-list" agents that are most likely to work prior to running large, randomized trials:

- Biological and pre-clinical rationale and/or evidence in other analogous clinical situations
- Established safety profile; expected toxicities
- PK for modified dosing
- Evidence of PD activity on target (analogous to phase 0 studies in oncology)

The traditional clinical development model is an observational study followed by a single-arm trial assessing safety, and then by randomized studies in the select patient population (phase 2 followed by phase 3). In oncology, a phase 1b followed by a phase 2 expansion in a specific patient cohort is a commonly used approach, even in the setting of drug repurposing. An important component of these single-arm studies in the setting of cancer, however, is the inclusion of translational readouts to define the disease and response to treatment. Similarly, even within the exigencies of a viral pandemic, early single-arm studies testing efficacy and safety of repurposed drugs with known MOA and safety profiles should include as many biological assays of activity as possible, developed through close collaboration between clinicians and scientists. Clinical investigators must obtain input from virologists, immunologists, and pharmacologists to choose agents that will work during key viral kinetic time-points or that blunt specific (or broad) immune phenomena, and select drug doses and pharmacodynamic end-points to best assess on-target activity. These initial studies may need to focus on PK/PD, or surrogate biochemical or virological end-points, prior to looking at hard clinical end-points such as incidence of intubation, time in intensive care, or 30-day mortality, which typically need a much larger sample size and well defined control arms.

Simultaneous animal studies can be used to refine these early trial protocols prior to agents being evaluated in phase 3 trials. When agents are ready for assessment in phase 3 trials, adaptive trial designs, which permit the testing of multiple agents simultaneously or in rapid sequence, is an efficient, cost-effective approach for otherwise time- and resource-intensive RCTs. Such a strategy will allow a shift from "logic-based medicine" to a sound evidence-based application, maximizing input from ongoing fundamental research and reducing the number of futile phase 3 trials testing drugs that were never likely to work.

Investing in research and development

Unfortunately, logistic and economic decisions have severely hampered drug discovery in the last few decades. Until very recently, antiviral drug development has been considered slow compared to other diseases (~5% drugs approved between 1972 to 2017, many against one virus [HIV], compared to 17% cancer). Drugs are also available to only ~9 or 10 viruses out of the >200 known to cause human disease. Orphan viral diseases often have no coverage, setting us up for the next pandemic. To counter this, there needs to be a global effort to dedicate resources to (1) cataloging/sequencing new and emerging viruses/variants, (2) developing experimental models *in vivo* and *in vitro* for infectious diseases, (3) drug discovery for orphan viruses, (4) multiply

medicinal chemistry efforts on known molecules with the potential of pan-viral activities (chain terminator or protease inhibitors), and (5) focus on molecules that are easy to administer (e.g., orally bioavailable).

Managing ethical issues and regulatory hurdles even before pandemics hit

An important lesson from COVID-19 is the need to have, at the ready, rapidly implementable clinical trial protocols testing repurposed drug "X," whose safety profiles are known and acceptable, whose MOA has biological plausibility, or at a minimum, has early *in vivo*/ *ex vivo* data in two independent systems supporting its use. Such trial protocols should have interim ethics and regulatory approval prior to a pandemic, which would then require final rapid review from regulators when the next pandemic hits. Forward planning would allow the testing of multiple candidate drugs simultaneously during the exponential growth in numbers seen during the initial stages of a pandemic. Most importantly, having such trials immediately implementable would limit the use of experimental therapies in poorly designed observational studies, or worse, *ad hoc* use that puts patients at risk and is destined at best for uninformative retrospective analyses.

This requires the establishment of scientific/clinical cooperatives across state, national, and global borders to coordinate clinical trials and needs to be an international effort. It divides the work, divides the cost, builds capacity, and makes the impact instantaneously global. In addition, any candidate drug that gets tested simultaneously worldwide would put to rest concerns about its efficacy in specific social or racial groups—aspects that invariably come up in discussions whether founded in science or not. The establishment of such global cooperatives would also expedite the process for drug approval globally. Currently, drug approval is meted out by national government agencies even though safety and efficacy are evaluated similarly throughout the world. Nation-specific drug approvals have resulted in delays in drug distribution to communities that need them the most. If trials are conducted globally and subject to review by an international regulator, this could help expedite drug review processes within local jurisdictions. Such an international regulator is not unimaginable; as has been done for other global threats such as nuclear arms regulation and climate change. Once suitable broad-acting drugs are identified, manufacturers could be regulated against holding market exclusivity or have this limited through government "buyouts." The rapid production of generic drugs would reduce cost and ensure equitable global distribution. Ensuring equitable access to a drug of utility in a viral pandemic setting is one of the foremost lessons learned from the COVID-19 pandemic.

By instituting a global cooperative scientific effort to find drugs that work, the scientific community could influence the distribution of any treatment more equitably. Inequitable distribution is perilous both to those with and without access to the treatment. As long as a pandemic virus rages and mutates "elsewhere," the entire world remains at risk. Thus, a cooperative effort from the medical and scientific community, based on the principles outlined above, is essential to both identify suitable therapeutic interventions and to facilitate their distribution in the setting of a pandemic. Solidarity in the scientific community will also facilitate public education and legal reforms on misinformation, which are essential for the ultimate translation of research activity into lives saved.

REFERENCES

Axfors, C., Schmitt, A.M., Janiaud, P., Van't Hooft, J., Abd-Elsalam, S., Abdo, E.F., Abella, B.S., Akram, J., Amaravadi, R.K., Angus, D.C., et al. (2021). Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. Nat. Commun. *12*, 2349.

Beigel, J.H., Tomashek, K.M., Dodd, L.E., Mehta, A.K., Zingman, B.S., Kalil, A.C., Hohmann, E., Chu, H.Y., Luetkemeyer, A., Kline, S., et al.; ACTT-1 Study Group Members (2020). Remdesivir for the Treatment of Covid-19 - Final Report. N. Engl. J. Med. *383*, 1813–1826.

Brower, R.G., Matthay, M.A., Morris, A., Schoenfeld, D., Thompson, B.T., and Wheeler, A.; Acute Respiratory Distress Syndrome Network (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N. Engl. J. Med. *342*, 1301–1308.

Gattinoni, L., Chiumello, D., Caironi, P., Busana, M., Romitti, F., Brazzi, L., and Camporota, L. (2020). COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. *46*, 1099–1102.

Grant, R.A., Morales-Nebreda, L., Markov, N.S., Swaminathan, S., Querrey, M., Guzman, E.R., Abbott, D.A., Donnelly, H.K., Donayre, A., Goldberg, I.A., et al.; NU SCRIPT Study Investigators (2021). Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. Nature *590*, 635–641.

Group, R.C.; RECOVERY Collaborative Group (2021). Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet *397*, 1637–1645.

Ho, J.S.Y., Mok, B.W., Campisi, L., Jordan, T., Yildiz, S., Parameswaran, S., Wayman, J.A., Gaudreault, N.N., Meekins, D.A., Indran, S.V., et al. (2021a). TOP1 inhibition therapy protects against SARS-CoV-2-induced lethal inflammation. Cell *184*, 2618–2632.e7.

Ho, J.S.Y., Zhu, Z., and Marazzi, I. (2021b). Unconventional viral gene expression mechanisms as therapeutic targets. Nature *593*, 362–371.

Kalil, A.C., Patterson, T.F., Mehta, A.K., Tomashek, K.M., Wolfe, C.R., Ghazaryan, V., Marconi, V.C., Ruiz-Palacios, G.M., Hsieh, L., Kline, S., et al.; ACTT-2 Study Group Members (2021). Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N. Engl. J. Med. *384*, 795–807.

Reardon, S. (2021). Flawed ivermectin preprint highlights challenges of COVID drug studies. Nature *596*, 173–174.

Rialdi, A., Campisi, L., Zhao, N., Cesar Lagda, A., Pietzsch, C., Sook Yuin Ho, J., Martinez-Gil, L., Fenouil, R., Chen, X., Edwards, M., et al. (2016). Topoisomerase 1 inhibition suppresses inflammatory genes and protects from death by inflammation. Science *352*. https://doi.org/10.1126/science.aad7993.

Rochwerg, B., Agarwal, A., Siemieniuk, R.A., Agoritsas, T., Lamontagne, F., Askie, L., Lytvyn, L., Leo, Y.S., Macdonald, H., Zeng, L., et al. (2020). A living WHO guideline on drugs for covid-19. BMJ *370*, m3379.

Tay, M.Z., Poh, C.M., Rénia, L., MacAry, P.A., and Ng, L.F.P. (2020). The trinity of COVID-19: immunity, inflammation and intervention. Nat. Rev. Immunol. *20*, 363–374.

Thompson, B.T., Chambers, R.C., and Liu, K.D. (2017). Acute Respiratory Distress Syndrome. N. Engl. J. Med. *377*, 562–572.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., et al. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet *395*, 1054–1062.