What Can We Learn from COVID-19 Drug Development and Access for Non-Pandemic Diseases? A Chinese Perspective

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The target article by Lynch et al. (2021) offers approaches for improving trial availability and Expanded Access for non-pandemic diseases based on the analysis of the COVID-19 experience in the US. We argue, in this commentary, that similar approaches are applicable to other countries, citing China as an example.

To begin, we discuss China’s exceptional response to COVID-19, which included the development and access of diagnostics, therapeutics, and vaccines.

The Chinese government approved a sizeable allocation of funding for R&D support. It pooled resources from research institutes, universities, and enterprises to focus on five areas: clinical treatment, new medicines and vaccines, testing techniques and products, viral etiology and epidemiology, and animal model construction. It developed vaccinations in five categories: inactivated vaccines, recombinant protein vaccines, live attenuated influenza vaccines, adenovirus vaccines, and nucleic acid-based vaccines.

Meanwhile, the National Medical Products Administration (NMPA) immediately began reviewing applications for registration of emergency medical
products. A joint prevention and control mechanism of the State Council was established to manage and coordinate the collaboration of multiple sectors in order to maximize their performance. As a result of these concerted efforts, China preliminarily identified the novel coronavirus on January 9, 2020, shortly after it was first reported at the end of 2019, and notified the World Health Organization (WHO) of the progress. By January 26, 2020, the NMPA had approved four novel coronavirus test kits for market launch. As of May 31, 2020, the NMPA had authorized 19 applications for clinical trials of medicines and vaccines for coronavirus prevention and control. Further, as of June, 2021, China has granted conditional market authorization or emergency use to seven domestically developed COVID-19 vaccines; two of these are listed by the WHO for emergency use.

As the first country to be hit by the COVID-19 outbreak, China has sought effective marketed drugs and new therapies in the absence of a specific drug for the novel coronavirus and a protracted development cycle for new drugs. As the evidence grew, the National Health Commission (NHC) published seven editions of guidelines for the diagnosis and treatment of COVID-19 (hereinafter referred to as the Chinese guidelines) from January 15 to March 4, 2020, which included antiviral drugs, antibacterial drugs, immunotherapy, convalescent plasma therapy, Traditional Chinese Medicines (TCM) drugs, and other pharmacological treatment (The State Council Information Office of the People’s Republic of China 2020). As the Emergency Use Authorization (EUA) system is blank (save for vaccines) in China, these guidelines authorize off-label use of approved drugs, as well as the use of convalescent plasma therapy and TCM. Up to now, NMPA has approved the use of three existing TCM drugs for COVID-19 treatment and granted market approval of three new TCM drugs to treat COVID-19 (Chu et al. 2021; NMPA 2021).

We concur with the extensive and thoughtful analysis provided by Lynch et al. (2021) about the distinction between COVID-19 and non-pandemic diseases and believe that these exceptional responses are unlikely to be replicated in non-pandemic diseases in China.

Then, we discuss some of the shortcomings of China’s response to COVID-19 to draw lessons for non-pandemic diseases.

From a scientific standpoint, additional high-quality evidence is required to address critical questions concerning safety and effectiveness, as recommendations in Chinese guidelines were mainly based on the SARS experience, in vitro studies, case reports, and small sample clinical studies. Chinese scientists and physicians have conducted a series of clinical trials to test the efficacy of interventions against COVID-19. In a cross-sectional study of trials registered in the Chinese Clinical Trial Registry (ChiCTR) during the early COVID-19 pandemic (Xu et al. 2020), a total of 617 COVID-19 clinical trials were retrieved from January 23 to April 24, 2020. However, of the 265 interventional trials, 59.2% were randomized controlled trials, 45.7% had fewer than 100 participants, 85.3% were sponsored by universities/hospitals, and 66.4% were single-center studies. Some studies had limitations, such as failure to include control groups, insufficient sample sizes, duplication, and a lack of coordination. While an atmosphere of fear may induce patients to consent to participate in research (Zhang et al. 2020), these studies would put patients at potential risk, waste resources of research participants, and delay the discovery of what works.

From a regulatory perspective, the absence of EUA and Expanded Access approaches during the COVID-19 outbreak in China means that people will have less access to promising investigational products prior to their approval. For example, the compassionate use of remdesivir for the first positive case of COVID-19 in the US (Holshue et al. 2020) has garnered widespread public attention in China. However, only patients who met specific criteria had the opportunity to use remdesivir in randomized controlled clinical trials. Once the COVID-19 pandemic in China was brought under control, the trials for remdesivir were suspended due to a lack of sufficient cases (Xu et al. 2020); consequently, patients can no longer have access to this new drug. Thus, in both COVID-19 and non-pandemic scenarios, Expanded Access can provide a potential opportunity for patients with severe or immediately life-threatening diseases or conditions that lack comparable or satisfactory therapeutic alternatives to gain access to an investigational medical product outside of clinical trials.

We suggest that the above deficiencies should not be replicated for non-pandemic diseases and agree with Lynch et al. (2021) that efforts should be made to improve trial availability and Expanded Access.

Finally, in light of the relatively weak regulatory capacity compared with developed countries and the experience of Western countries, China has revised the “Provisions for Drug Registration” (effective July 1, 2020), which includes breakthrough therapy drug procedures, conditional approval procedures, priority evaluation and approval procedures, and special approval procedures, to expedite the development of
innovative drugs with clinical value for approval (Dai et al. 2021). Thus, we believe that the lessons learned from COVID-19 drug development and access in the US would also provide valuable ideas and references.

For trial availability, we can draw on the master protocols guidance for oncology and COVID-19 drug development (U.S. Food and Drug Administration 2018, 2021), the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), the WHO’s Solidarity Trial, and the UK’s Recovery Trial. We believe that conducting well-designed master protocols can reduce the overall sample size, improve data quality and efficiency, and accelerate drug development compared to traditional separate stand-alone trials in China. Several Chinese experts have advocated for adopting master protocols in TCM, oncology, and future pandemics. While coordination and cooperation may be challenging, given that the Chinese culture and social system are more conducive to concerted group efforts (Wang et al. 2021; Zhang et al. 2021), this type of innovative trial design is expected to play an essential role in addressing unmet treatment needs for non-pandemic diseases.

For Expanded Access, it is still in its nascent stage in China. On December 20, 2017, the “Administrative Measures for Compassionate Use of Investigational Drug (draft for comment)” was released; however, it had no legal impact because it was not officially announced. In 2019, the revised “Drug Administration Law of the People’s Republic of China” proposed the first legal framework for Expanded Access. Article 23 stated that “for drugs that are undergoing clinical trials which are to be used for the treatment of severe life-threatening diseases for which there is no effective treatment, where it is concluded from medical observation that such drugs are beneficial and comply with ethical principles, the drugs may, after review and obtaining informed consent, be used on other patients with the same condition within the clinical trial institutions that are conducting the trial” (National People’s Congress 2019); however, there are currently no specific regulations governing application conditions, application procedures, review, and approval procedures. As the authors noted, despite the fact that Expanded Access has a nearly four-decade history in the US, many companies resist it, and many physicians do not understand it (Lynch et al. 2021). Thus, in view of the enormous demand for Expanded Access and physicians’ busy schedules in China, we propose an incentive mechanism for companies and a simplified application procedure to promote the application of Expanded Access. We believe that by establishing this channel, the NMPA may engage to work with pharmaceutical companies and medical teams to provide ethical, regulated, and expedited access to unapproved medications in China.

As much of the exceptional response to COVID-19 could not be replicated for non-pandemic diseases, this commentary aims to verify the applicability of improving trial availability and Expanded Access outside the US by analyzing the necessity and feasibility of the aforementioned approaches in China. Additionally, we anticipate that learning from both scientific and regulatory perspectives will help shape future conversations concerning drug development and access to non-pandemic diseases.

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