Title

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Preparing for the Big One

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Early in the COVID-19 pandemic, it was suggested that drugs to meaningfully impact the pandemic would come from either our current antiviral armamentarium or from drug repurposing (1). Genuinely new therapeutics, while likely to be the most effective, were too risky and would take too long. As it happened, drug repurposing paid few lasting dividends (2,3) and the effective drugs that did emerge were from our pre-existing armamentarium. Remdesivir had been developed for Ebola and targeted a mechanism broadly applicable to RNA viruses. Nirmatrelvir, the active ingredient in Paxlovid, while not previously advanced into clinical trials drew on related compounds that had been developed against the major protease (Mpro) of the highly related SARS-CoV-1, almost two decades earlier. On page ??? of this issue, Boby et al describe an effort to discover drugs from scratch to treat Covid-19 (4). This and other efforts, now underway, could help repay our debt to drug discovery by developing new candidate drugs to treat SARS-CoV-2, its emerging drug resistant variants (5) and other coronaviruses to emerge in the future.

The effort began early in the pandemic and alloyed innovations in the techniques and in the organization of drug discovery. Here, scientific innovations included high-throughput crystallographic fragment screening (the structures of over 70 “fragments”—about 1/3 to ½ the size of a more drug-like inhibitor— bound to the SARS-2 enzyme Mpro were determined [PMID: 33028810], as were the structures of over 500 more advanced compounds), computational free-energy calculations, and machine learning for compound design that helped guide subsequent medicinal chemistry. Organizationally, it integrated the expertise of 212 scientists in 47 organizations across 15 countries, mostly in academia but including several pharmaceutical companies. All donated their time in an open access model, capturing some of the strengths of a vertically integrated pharmaceutical company in a federated, academic environment. The results to date are several leads with cellular antiviral potencies competitive with those of nirmatrelvir, and with encouraging *in vivo* pharmacokinetics that may support advancement toward clinical trials (4).

By focusing on Mpro, the authors drew on a legacy of successful drug discovery against viral proteases. Since the introduction of the first HIV protease inhibitor drugs in the early 1990s, proteases have been well-accepted targets for antiviral intervention. They control a key step in the life cycle of many viruses, cutting the nascent chain of strung-together viral proteins into their component, activated parts. Without this protease activity viruses

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cannot propagate, and HIV protease inhibitors, for instance, continue to be part of anti-AIDS cocktails to this day.

In the 1980s and ‘90s, attacking a viral protease was a new approach, replacing the nucleoside analogs for viral polymerases that had dominated until then. Subsequently, the success of the HIV protease inhibitors inspired the community to target the proteases of hepatitis C virus (HCV), the dengue protease, SARS CoV-2 MPro and PLPro. Each has its own unique story, for example the intensive combined efforts of academic and pharmaceutical scientists to identify a treatment for AIDS targeted HIV PR by using its three-dimensional structure to computationally screen chemical compounds to rapidly identify an inhibitor (6), one of the first uses of a technique that is now widespread in pharmaceutical research. Intriguingly, and as with Paxlovid, the initial protease inhibitors capitalized on the nearly 20 years of previous research on renin inhibitors, a human homolog of the viral aspartyl protease. There are now nine FDA approved drugs against HIV protease with one of them, ritonavir, being used to boost the pharmacokinetic properties of anti-HIV drugs and, in another borrowing from the past, also Paxlovid.

The lead therapeutics described in Boby *et al*. are unlikely to affect the current pandemic. Nevertheless, they, and the techniques which they used, will likely impact human health. The leads themselves represent new departures for Mpro inhibitors, and the methodology used to find them, not to mention the organization of the project, will inspire others. More broadly, the Pandemic inspired investigation of several other SARS-CoV-2 enzymes that, like HIV-1 protease in the mid-1980s, have few precedents as antiviral targets, but are known to drug discovery more broadly. These enzymes, including those that combat the cellular innate immune system, that fool the cell into treating viral RNA as human RNA, and that unwind viral RNA to support viral replication, have been shown to be crucial for the life cycle of SARS-CoV-2, and are likely good targets for many other viruses as well. Against each of these, new inhibitors have been discovered that, if not as far along as those for Mpro described by Boby et al, show promise (7–10) These are being developed in both pharmaceutical companies and in universities, including in nine antiviral research centers supported by the US Government that are focused on preventing current and potential pandemics of the future. Through these efforts we may restock our antiviral armamentarium, in preparation for the next pandemic wave. Such waves have swept through the human population not only in the last century (influenza, polio, AIDS, Covid-19), but regularly throughout recorded history. From the plague of Athens (430 BC), to that of the Antoinines (160 to 189 AD), to that of Justinian (beginning in 541 AD), to the Black Death (14th through 16th centuries), to modern era Smallpox and the Cholera epidemics of the 17th through 19th centuries, viral and bacterial plagues have devastated human populations (Figure 1); there is every reason to expect these plague cycles to continue (. Until the 1930s, we had no good drugs to treat microbial pandemics, and even in recent years, when new threats emerged it was on previously discovered drugs and drug leads that we initially relied. The drugs in whose development we invest in today will pay dividends in upcoming pandemics. The big ones are still out there.

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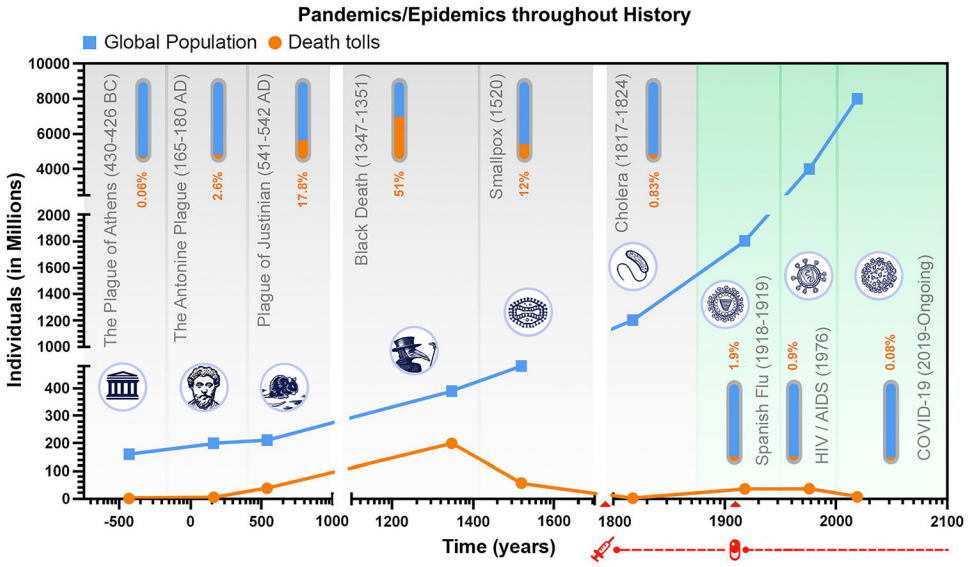

Figure 1.

Historical depiction of numerous pandemic events spanning from 500 B.C. to the present day. The featured line charts illustrate the world's population (blue) and pandemic-related death tolls (orange) over time, revealing the quantitative impact of each pandemic on global populations throughout history. To further highlight this relationship, each panel also displays a thermometer shown in blue and orange, which represents the % of the world's population affected by each pandemic event over the years. Red arrows denote two pivotal milestones in the history of infectious disease control: The advent of the first smallpox vaccine in 1796 and the introduction of the first antibiotic, Salvarsan in 1910. These breakthroughs mark the transition of human society from the 18th century into the modern era of therapeutics against infectious diseases, with enduring implications to the present day.