

EDITORIAL

Science fiction has become reality: Best practice for future viral pandemics

Prior to December 2019, it may have been easy to feel complacent about the risk of a global viral pandemic. The world had not seen a truly global viral outbreak since the 1917 flu pandemic and the recent scares with Ebola, Middle East respiratory syndrome (MERS), and Severe Acute Respiratory Syndrome (SARS), while concerning, appeared to be contained or remained regional. To the lay public, a truly global pandemic might have seemed like something that belonged in the realm of science fiction.

Science fiction writers often explore dystopian themes and use their work as a vehicle for thought experiments about how society might cope with major global events. Perhaps unsurprisingly, uncontrolled viral pandemics are a recurring theme. The idea that a global response will be needed, uniting nations, private industry, and health organisations against a common (viral) foe, is both a familiar feature of our current human existence and is evident in several works of science fiction. Novels such as Dean Kootnz's 1981 work *The Eyes of Darkness* are claimed to have predicted the SARs-COV-2 outbreak, although this does not appear hold in the detail.¹ Other works (e.g., Vylar Kaftan's 2012 short story *Lion Dance*) feature now all too familiar pandemic practices such as the closure of schools, social distancing, the requirement for masks in public places, and self-isolation.² Even the 1960's television show *Star Trek* toyed with the theme of a global pandemic in an episode called "Miri" (aired October 1966). In this program, the entire population of a planet was a risk of extinction due to an invisible pathogen which required the rapid development and testing of a vaccine.

In the real world, science fiction became reality in late 2019 with the beginning of the current SARs-COV-2 outbreak in Wuhan, China. The declaration by the World Health Organisation in March 2020³ that the outbreak was a "pandemic" signalled that a coordinated global response was going to be needed to contain the disease. What followed was an unprecedented escalation of scientific efforts to rapidly develop vaccines against the SARs-COV-2 virus, identify potential drug treatments with expedited clinical trials, and repurpose existing drugs to treat COVID-19 disease.

Reflecting on the first 6 months of the pandemic, there was confidence, and perhaps too much comfort, that our available vaccines and approved medicines, developed through suitably rigorous and adaptable drug development and regulatory pathways, would be sufficient to navigate the world out of the SARs-COV-2 pandemic. What became apparent was that drug development and regulatory communities were caught "flat-footed" by COVID-19, mired in traditional slow-moving development programmes and regulatory

pathways with little room to pivot quickly in response to a global emergency. This was despite calls for adaptive licensing and other regulatory pathways for niche diseases to accelerate development to particularly vulnerable populations in the preceding decade.⁴

In this themed issue, we approached groups and researchers who have developed new best practice approaches for future pandemic planning. They have provided commentary, guidance, and exemplars developed from the experience gained during 2019–2021 that will hopefully put the global community in a position of preparedness for the next global pandemic. Contributions in this issue cover the development of vaccines, the repurposing of medicines for treatment and prophylaxis, the dosing of key patient populations, and running of clinical trials. These manuscripts should be utilised by researchers, drug and vaccine developers, clinicians, and policy makers to be the building blocks for guidance and policy documents that were absent at the start of the pandemic.

There are essentially three key themes that thread across much of the work presented: (1) the need to prepare for the next pandemic, (2) the importance of new and future *in silico* tools to expediate antiviral treatments, and (3) the critical place of global co-operation across sectors in future pandemics. Each of these is summarised in more detail below.

An important concern is that the lessons learned during the past 18 months will be quickly forgotten once the SARs-COV-2 pandemic has ended. This was arguably the case in the early 2000s when SARS-COV-1 disappeared and resources to combat the outbreak were redirected elsewhere. Preparedness for future pandemics therefore requires the development of policies and processes to identify, react to, and control future pandemics in a timely and efficient manner. This is introduced by Dodds et al.⁵ and further developed by Davda et al.⁶ who present a five-stage blueprint that will allow us to be prepared for, and react to, future viral outbreaks. Importantly, the blueprint is centred on pre-pandemic preparedness, including surveillance for new pathogens, high through-put screening for potential therapeutic options using human derived pulmonary cells, and the identification of key pharmacological indices such as IC50 values (or better EC90 values) using prior work on reference viruses.⁶ These processes can occur before a viral pandemic occurs so that realistic options for repurposing existing agents can be identified quickly in the event of new coronavirus outbreak.

Calvo Fernandez and Zhu⁷ present a comprehensive review of SARs-COV-2 vaccine development globally and highlight the importance of vaccine access and distribution. While vaccine developers

have shown that they are equipped to respond rapidly to a viral outbreak, what has not been resolved is how global vaccination can be achieved, and how equitable and timely vaccine access will be managed in future pandemics.

A commonly overlooked area early in the SARs-COV-2 outbreak was the profound impact the refocusing of resources towards the development of viral treatments and vaccines would have on existing drug development programmes and clinical trials. Vissers et al.⁸ point out that drug development and clinical trials are an essential part of the global health care system so any interruption should be carefully considered and managed. A decision-support framework based on ethical principles is presented by the authors that will provide invaluable guidance to regulators and trialists in future pandemics.⁸

The use of *in silico* tools, including pharmacokinetic-pharmacodynamic, systems pharmacology, and physiological-pharmacokinetic models, has become commonplace in drug development programmes. In the COVID-19 era, these tools were expanded to efficiently explore possible antiviral options. Patel et al.⁹ show how the incorporation of a viral kinetic model, to account for the viral life cycle, can be a valuable tool for understanding both the appropriate targets for drug action to combat the virus, but also the optimal timeframe post-infection for treatment. This concept was extended by Dodds et al.,¹⁰ who used a similar platform to show how targeting different aspects of the viral lifecycle with combinations of repurposed (or novel) agents will optimise treatment success. The use of *in silico* tools was also emphasised by Dodds et al.⁵ and Davda et al.⁶ as important platforms to allow for expedited drug repurposing efforts and drug development in future pandemics. In addition, *in silico* tools can be used to ensure that the basic principles of clinical pharmacology are not ignored in the haste to propose possible treatments, an important lesson from early in the COVID-19 crisis echoed in the contribution from Smith et al.¹¹ and the ASCEPT-BPS statement on drug repurposing.¹²


In terms of co-operation, the need for data sharing and transparency in clinical trials globally to combat mis-information, poorly conceived studies, and fraudulent therapeutic claims that occurred during the first 6–12 months of the pandemic is essential. Importantly, systems must now be put in place, as a defined act of preparedness, to ensure this is a reality before the next pandemic.⁷ This includes careful review of the role of traditional medicines in the supportive care of COVID-19 disease.¹³ In the current pandemic, the elderly, particularly those in residential aged care, were the population particularly vulnerable to COVID-19,¹⁴ while paediatrics were thought to be of low risk of infection and transmissibility. This further highlights the need for co-operation to improve the translation of available data to under-represented populations such as paediatrics and pregnant patients.¹⁵ These populations will need prophylaxis or treatment or indeed may be the next vulnerable target population due to an antigenic viral shift.

The current COVID-19 era will effectively end when the SARs-COV-2 virus is contained, the global population is vaccinated, and life returns to some semblance of the pre-COVID world. The lessons learned during the COVID-19 pandemic, as highlighted in

the papers presented here, can play an important role in how we prepare, implement, and coordinate effective responses for future pandemics. When future generations look back at this time in history, they should see more than fodder for new science fiction stories. Instead, we hope that this era will be recognised as the beginning of global scientific programmes and practices to prepare the world for future pandemics and enabled the necessary reset of how we develop and approve medicines and vaccines. The COVID-19 events were the catalyst needed to align *in vitro*, *in silico*, *in vivo*, and regulatory science in highly coordinated ways to answer urgent questions. These approaches must now be considered the new “best practice” for all medicines and vaccine development moving forward.

COMPETING INTERESTS

There are no competing interests to declare.

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