Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

With the sharp rise in non-communicable diseases worldwide, the demand for surgical care is rapidly increasing. Surgical interventions are needed for 80% of injured patients and more than half of patients with cancer.[3] Given the high versatility and the clear value surgical teams and infrastructure have added to the pandemic response, it is surprising that surgical system strengthening has not received more attention as part of pandemic preparedness initiatives thus far. We suggest a paradigm shift where access to surgical care is mainstreamed into pandemic preparedness policies. A mainstreaming approach would entail that the pandemic treaty assures that every policy adopted or implemented from this treaty has been evaluated for its impact on national-level surgical care provision. Only policies that do not harm surgical care provision should be included in the final version of the treaty so as to avoid detrimental impact. While novel in global surgery discourse, this would entail a policy approach similar to WHO's Health in All Policies.

As defined by the UN General Assembly at the beginning of the pandemic, this approach involves considering the systemic impact of policy decisions on health and making those decisions across different sectors to achieve synergy, equity, and improved health outcomes.[4] By mainstreaming surgery into pandemic preparedness policy, we suggest that surgical care provision is taken into consideration for every policy recommendation or operative paragraph. This way, true health systems strengthening can take place to achieve a system where no-one is left behind before, during, or after a pandemic.

The 150th WHO Executive Board established a Standing Committee on Pandemic and Emergency Preparedness and Response to draft and negotiate the Pandemic Treaty under the sole auspices of the Member States.[5] We urge the committee to recognise the importance of surgery as an essential part of health systems by: (1) ensuring participation of civil society, including the surgical community, as key stakeholders in the treaty negotiation process; and (2) mainstreaming surgical care into the final draft of the Pandemic Preparedness Treaty.

The surgical and anaesthesia communities stand ready to be involved in this process.

We declare no competing interests. Signatories of this Correspondence are listed in the appendix.

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1 COVIDSurg Collaborative. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. *Br J Surg* 2020; **107:** 1440–49.
2 Simoes J, Bhangu A, COVIDSurg Collaborative. Should we be re-starting elective surgery? *Anaesthesia* 2020; **75:** 1563–65.
3 Pigeolet M, Marks I, Bentounsi Z, Wanjau W. Letter to Editor: can mainstreaming surgery advocacy into NCD advocacy help us overcome the NCD epidemic? *World J Surg* 2019; **43:** 2114–15.
4 UN General Assembly. Resolution adopted by the General Assembly on 11 December 2019. Global health and foreign policy A/RES/74/20. New York, NY: United Nations, 2020.
5 WHO. Executive Board 150th session EB150/17: Standing Committee on Pandemic and Emergency Preparedness and Response. Geneva: World Health Organization, 2021.

Host-targeting oral antiviral drugs to prevent pandemics

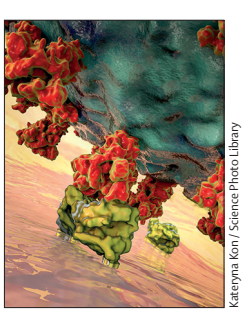
Unlike bacteria, viruses must use host cells to replicate. This has enabled us to identify the Achilles heel of many viruses. We want to exploit this knowledge for the therapeutic targeting of current major human pathogens, such as coronaviruses and influenza for which there is a great unmet need. The orally available small molecule broad-spectrum antiviral compounds we have developed over many years target the host[1] and are thus resistant to viral mutations. Host-targeting drugs can also be employed against newly emerging viruses even before detailed information about the virus becomes available.[2,3] This will be crucial in preventing the inevitable new epidemics from turning into pandemics.

Most enveloped viruses need to use a sugar-mediated pathway in the infected human host cell to form their correct three-dimensional structures, which involves adding and processing glycans on viral envelope glycoproteins.[2,3] The glycosylation process involves enzymes in the cell trimming the sugars of the viral glycoproteins for entry into this protein folding quality control pathway. Drugs that partially inhibit these enzymes prevent the virus from making proper use of this folding pathway and lead to inhibition of secretion of infectious virus.[4–8]

Over the past 25 years, we have developed a class of drugs called iminosugars—orally available sugar mimetics that are recognised by and inhibit these sugar processing enzymes that most enveloped viruses rely on.[1] The family of iminosugars derive from the parent compound initially isolated from the leaves of the mulberry tree.

Safety and efficacy data in animals accumulated over the past 20 years show that iminosugar derivatives reduce viral levels and increase survival in animal models of chronic hepatitis B infection,[6] hepatitis C, Japanese encephalitis, influenza,[9] and dengue.[7,8] When tested in vitro against over 31 clinical HIV isolates, including HIV-1, HIV-2, and multidrug resistant strains, iminosugars are active against a diverse panel of HIV-1 from different genetic subtypes and geographical regions, and against HIV-2 isolates and mutants resistant to antiretrovirals.[10] All HIV isolates tested were rendered non-infectious by iminosugar treatment. Similarly,

See Online for appendix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we have shown that iminosugars work against all hepatitis C genotypes tested and all four main dengue serotypes in vitro.[7]

When in-vitro testing against SARS-CoV-2 became possible, we showed that, as predicted, iminosugars are also antiviral against this virus.[11,12] As the drug target is not under the genetic control of the virus, the virus cannot mutate around it as readily, or at all. The iminosugars will also be antiviral against all variants of this coronavirus, including those for which vaccines are not yet available, and any mutants that might arise naturally or in response to direct acting antiviral drugs, such as protease inhibitors (eg, Paxlovid) and polymerase inhibitors (eg, molnupiravir).

We have data (NCT0269629; NCT02061358) that show that iminosugars could be administered at comparably low concentration three times daily for 7 days—ie, as long as required in an acute infection. This dosing regimen affects mainly ER glucosidase II and leads to antiviral effects. In a 2020 study, we made the discovery that a single higher dose of the iminosugar prevents death in mice infected with lethal doses of influenza or dengue virus even if administered days after infection, and that protection correlates with inhibition of ER glucosidase I.[8] This shifts attention to the latter enzyme as a broad-spectrum antiviral target for an oral drug that could be administered after infection in a single-dose manner. This would be particularly useful in pandemic settings, and in poorer countries.

Support for using ER glucosidase I as a broad-spectrum antiviral target comes from a study[13] that identified two siblings with a deficiency of ER glucosidase I, which is targeted by the single high-dose approach. Despite significant hypogammaglobulinaemia, the children had no history of viral disease and were not able to generate immune responses to live viral vaccines. The investigators concluded that there is a strong potential benefit of using inhibitors of glucosidase I as a means of controlling viral infections, especially those that pose a threat of rapid global spreading. But there is no need for complete inhibition of glucosidase I for therapeutic benefit.

We believe that the gravity of the pandemic urgently demands us to try so-called off the beaten track host-targeting antivirals rather than only the current direct acting antiviral approaches. The use of host-targeting antivirals is supported by encouraging animal and human toxicity data and could provide a broad-spectrum oral antiviral that is mutation-proof. We believe that the higher single-dose regimen (at most, two single doses) should be recommended for global ease of use. We want to initially clinically use the generically available potent iminosugar, MON-DNJ (NCT0269629), used in the above high-dose approach studies, for which some phase 1 data are available. The less potent, but generically approved, orally available iminosugar miglustat,[14] could be used at a single high dose to target coronaviruses and influenza as proof of principle. HIV patients have been given high doses of miglustat in a combination trial.[14] The safety of miglustat at lower concentrations is well documented in its routine use in Gaucher's disease for over 20 years.[15]

All currently available data make a clinical trial of this novel concept feasible and hence an imperative for promoting public health. This could be a transformational approach. Broad-spectrum, safe orally available antivirals are desperately needed worldwide, not only to help terminate this pandemic but to prevent the next one. This approach urgently needs support to further evaluate its promise to fill a major unmet need.

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1 Alonzi DS, Scott KA, Dwek RA, Zitzmann N. Iminosugar antivirals: the therapeutic sweet spot. *Biochem Soc Trans* 2017; **45:** 571–82.
2 Dwek RA, Butters TD, Platt FM, Zitzmann N. Targeting glycosylation as a therapeutic approach. *Nat Rev Drug Discov* 2002; **1:** 65–75.
3 Pieren M, Galli C, Denzel A, Molinari M. The use of calnexin and calreticulin by cellular and viral glycoproteins. *J Biol Chem* 2005; **280:** 28265–71.
4 Block TM, Lu X, Mehta AS, et al. Treatment of chronic hepadnavirus infection in a woodchuck animal model with an inhibitor of protein folding and trafficking. *Nat Med* 1998; **4:** 610–14.
5 Woodhouse SD, Smith C, Michelet M, et al. Iminosugars in combination with interferon and ribavirin permanently eradicate noncytopathic bovine viral diarrhea virus from persistently infected cells. *Antimicrob Agents Chemother* 2008; **52:** 1820–28.
6 Block TM, Lu X, Platt FM, et al. Secretion of human hepatitis B virus is inhibited by the imino sugar N-butyldeoxynojirimycin. *Proc Natl Acad Sci USA* 1994; **91:** 2235–39.
7 Warfield KL, Plummer EM, Sayce AC, et al. Inhibition of endoplasmic reticulum glucosidases is required for in vitro and in vivo dengue antiviral activity by the iminosugar UV-4. *Antiviral Res* 2016; **129:** 93–98.
8 Warfield KL, Alonzi DS, Hill JC, et al. Targeting endoplasmic reticulum α-glucosidase I with a single-dose iminosugar treatment protects against lethal influenza and dengue virus infections. *J Med Chem* 2020; **63:** 4205–14.
9 Warfield K, Barnard D, Enterlein S, et al. The iminosugar UV-4 is a broad inhibitor of influenza A and B viruses ex vivo and in mice. *Viruses* 2016; **8:** 71.
10 Pollock S, Dwek RA, Burton DR, Zitzmann N. N-Butyldeoxynojirimycin is a broadly effective anti-HIV therapy significantly enhanced by targeted liposome delivery. *AIDS* 2008; **22:** 1961–69.
11 Oxford Antiviral Drug Discovery Unit. SARS CoV-2 Cellular Tracker: Zitzmann lab. July 9, 2021. http://sarscov2.assaytracker.net/ (accessed March 3, 2022).
12 Franco EJ, Warfield KL, Brown AN. UV-4B potently inhibits replication of multiple SARS-CoV-2 strains in clinically relevant human cell lines. *Front Biosci (Landmark Ed)* 2022; **27:** 3.
13 Sadat MA, Moir S, Chun T-W, et al. Glycosylation, hypogammaglobulinemia, and resistance to viral infections. *N Engl J Med* 2014; **370:** 1615–25.
14 Fischl MA, Resnick L, Coombs R, et al. The safety and efficacy of combination N-butyl-deoxynojirimycin (SC-48334) and zidovudine in patients with HIV-1 infection and 200-500 CD4 cells/mm^3. *J Acquir Immune Defic Syndr* 1994; **7:** 139–47.
15 Cox T, Lachmann R, Hollak C, et al. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. *Lancet* 2000; **355:** 1481–85.