When Vaccination Falters: Broad-Spectrum Antivirals are a Global Safety Net

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To the Editor,

The recent loss of measles elimination status in Canada-and by extension across the Americas[1]-underscores a sobering reality: vaccination alone no longer guarantees global protection against viral threats. Rising vaccine hesitancy and disrupted immunization programs threaten decades of progress in controlling respiratory pathogens. In this shifting landscape, antivirals offer an essential complementary approach. However, virus-specific drugs require enormous time and cost, as seen during COVID-19, often with limited success. Broad-spectrum antivirals represent a promising alternative, yet none are in routine clinical use.

In earlier correspondence to *The Lancet*[2], we highlighted host-targeting iminosugars as broad-spectrum antivirals in vitro and in animal models, though clinical development remains incomplete. These compounds inhibit ER-resident glucosidases, disrupting viral glycoprotein maturation essential for replication across diverse viruses.[3,4] Evidence includes activity in animal models of hepatitis B[5] and C, Japanese encephalitis, influenza[6] and, dengue,[7,8] as well as in vitro efficacy against HIV (including multidrug-resistant strains) and, all SARS-CoV-2 variants. Since our 2022 publication, the novel agent MON-DNJ has demonstrated efficacy against major SARS-CoV-2 strains, measles, and, RSV (Barbaglia et al., in preparation), highlighting its potential as a pan-respiratory antiviral targeting viruses most likely to cause pandemics.

Emerging evidence suggests a mechanistic explanation for sustained antiviral activity: activation of the unfolded protein response (UPR). By inhibiting glucosidases I and II, iminosugars such as MON-DNJ[7] may induce ER stress

through misfolded glycoprotein accumulation, triggering the UPR-a stress pathway enveloped viruses typically suppress to maintain access to the host glycosylation machinery.[9,10] Pharmacological activation of the UPR creates a prolonged intracellular environment hostile to viral replication, extending efficacy beyond the drug's pharmacokinetic window (Barbaglia et al., in preparation). This mechanism may explain observed success in animals infected with influenza or dengue after a single high-dose administration.[8] A one- or two-dose regimen offers a practical, scalable intervention during outbreaks, especially in resource-limited settings.

Safety remains paramount. Miglustat-a close relative of M*O*N-DNJ-has been approved since 2002 for Gaucher's disease, used daily by thousands without major side effects, providing a precedent for the therapeutic viability of host-targeting iminosugars. However, M*O*N-DNJ urgently requires completion of clinical development.

Unlike vaccines, which require time and widespread uptake, UPR-inducing antivirals could be deployed immediately, even in populations with high vaccine hesitancy. Investing in host-targeting antivirals such as M*O*N-DNJ - oral, cold-chain-free -could save countless lives and position the UK as a global leader in pandemic preparedness. There is not only a scientific and strategic imperative but also a moral one: to ensure effective, scalable antiviral solutions as vaccination programs face resistance and delays during new epidemics.

We urge renewed investment in host-targeting antivirals - not only for existing viruses like measles, RSV, and, dengue but also as strategic tools for future pandemics. M*O*N-DNJ opens a new frontier in antiviral pharmacology, offering a paradigm shift that could transform global responses and prevent the catastrophic losses seen during COVID-19.

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