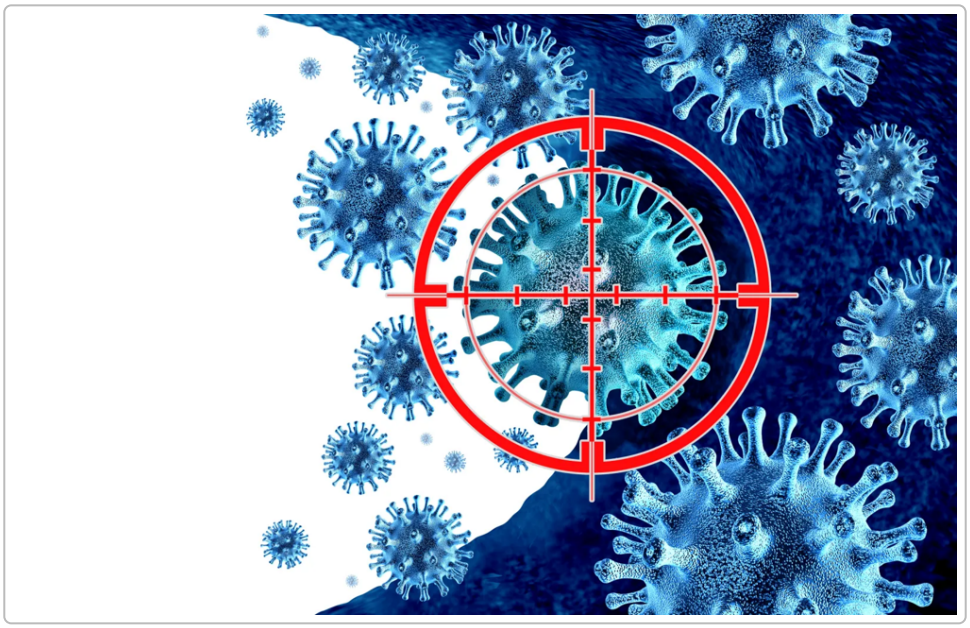
ChatGPT

Proposed Oral Broad-Spectrum Antiviral Polypill



To cover virtually all major viral families, we propose combining several oral, broad-spectrum antivirals (and repurposed host-directed drugs) with complementary spectra. Candidate components include broad viral polymerase inhibitors (targeting RNA and DNA viruses) and host-targeted agents with multi-family activity. Notable examples are:

- **Galidesivir (BCX4430)** – an oral adenosine analog that inhibits viral RNA-dependent RNA polymerases. In vitro and animal studies show activity against a wide range of RNA viruses (including coronaviruses, flaviviruses, togaviruses, arenaviruses, paramyxoviruses, orthomyxoviruses, filoviruses, bunyaviruses and picornaviruses) [1] . Galidesivir is well tolerated in early human trials (no serious toxicities reported) and was granted fast-track evaluation for Ebola and COVID-19 [1] .
- **Brincidofovir (CMX001)** – an oral lipid-conjugated cidofovir that inhibits viral DNA polymerases. It has demonstrated broad anti–DNA-virus activity, including efficacy against poxviruses (e.g. smallpox/monkeypox, FDA-approved), adenoviruses and herpesviruses (e.g. CMV) [2] . Brincidofovir's use is limited by gastrointestinal upset and liver toxicity, but short-term use in healthy adults is feasible [3] .
- **Favipiravir (T-705)** – an oral guanine nucleoside analog (RdRp inhibitor) that induces lethal mutagenesis in viral RNA. In cell and animal models it suppresses diverse RNA viruses – e.g. influenza (Orthomyxoviridae), hemorrhagic fever viruses (Filoviridae and Togaviridae), and others [4] . (It is approved for influenza in Japan and has been used experimentally for Ebola and COVID-19.) High doses are required for some viruses, and it is teratogenic, but short-term prophylactic dosing could be managed with contraception precautions [4] [5] .
- **Molnupiravir (EIDD-2801)** – an oral cytidine analog (RdRp inhibitor) that also causes lethal mutagenesis. It was originally developed for Venezuelan equine encephalitis (Togaviridae) and protects mice from various RNA viruses [6] . In human trials it accelerated clearance of SARS-CoV-2

and is active against influenza and Ebola models [6]. Like favipiravir, it is potentially teratogenic [5], but short courses in healthy adults are generally well tolerated.

- **Nitazoxanide** – an oral antiparasitic repurposed as a broad-spectrum antiviral. Its precise mechanism is unclear (host kinase and glycoprotein maturation effects), but it *in vitro* suppresses many RNA viruses, including influenza, coronaviruses, rotavirus, and hepatitis viruses [7]. In trials it modestly reduced flu symptoms and showed antiviral effects (plus good safety) in early COVID-19 studies [8]. Nitazoxanide covers viruses that rely on envelope glycoprotein processing and has minimal toxicity (mild GI side effects).
- **Tamoxifen** – an oral estrogen-receptor modulator with surprising antiviral activity. It inhibits viruses by a variety of host-targeted mechanisms (e.g. interfering with viral entry and glycoprotein processing). Tamoxifen blocks replication of multiple RNA and DNA viruses in cell culture and animals – including vesicular stomatitis virus (Rhabdoviridae), Ebola (Filoviridae), chikungunya (Togaviridae), SARS-CoV-2 (Coronaviridae) and HSV-1 (Herpesviridae) [9]. Clinical studies found tamoxifen shortened viral shedding in COVID-19 and reduced HCV viremia [10]. Its long-term use is limited by side effects (e.g. thromboembolism risk), but short courses have acceptable safety.
- **Metformin** – an oral AMPK activator (diabetes drug) with documented antiviral effects in vitro. It appears to boost innate immunity (type I IFN) and has shown protection in mouse models of dengue and influenza [11]. Epidemiologically, diabetic patients on metformin had lower morbidity and mortality in influenza and a trend toward lower death from COVID-19 [11]. Metformin is extremely well tolerated, and could serve as a safe broad-spectrum adjunct.

Each agent covers multiple viral families as noted above. In choosing these drugs, we weighed oral bioavailability and safety: all are FDA-approved (or in late-stage trials) for human use, and none require IV administration. We excluded highly toxic compounds (e.g. ribavirin was originally broad-spectrum but its hemolytic anemia and teratogenicity make it unsuitable for prophylactic polypill use [12] [5]). The selected agents have acceptable toxicity for short-term use. For example, brincidofovir's main toxicity is liver enzyme elevation [3], and both favipiravir and molnupiravir carry reproductive risks [5], so pregnancy must be avoided but otherwise healthy adults tolerate these treatments.

Coverage of Viral Families

The coverage of major human virus families by the above agents is summarized below. Table 1 maps each family to the drug(s) predicted to inhibit it. (These assignments are conservative: many agents hit additional families *in vitro*, but only well-documented activities are listed.) Uncovered families are noted at bottom.

Virus Family	Covered by
Coronaviridae	Galidesivir, Molnupiravir, Nitazoxanide, Tamoxifen [1] [7]
Flaviviridae	Galidesivir, Molnupiravir, Nitazoxanide, Tamoxifen [1] [7]
Orthomyxoviridae	Galidesivir, Favipiravir, Nitazoxanide [4] [7]
Paramyxoviridae	Galidesivir [1]
Togaviridae	Galidesivir, Favipiravir, Tamoxifen [4] [9]
Filoviridae	Galidesivir, Molnupiravir, Tamoxifen [6] [9]

Virus Family	Covered by
Arenaviridae	Galidesivir [1]
Bunyavirales	Galidesivir [1]
Picornaviridae	Galidesivir [1]
Reoviridae	Nitazoxanide [7] (activity vs. rotaviruses)
Caliciviridae	Nitazoxanide [7] (activity vs. norovirus)
Hepadnaviridae	Nitazoxanide (HBV) [7] ; *and* Lamivudine or Tenofovir for HBV [13] (standard of care)
Herpesviridae	Brincidofovir (CMV, HSV) [3] ; Tamoxifen (HSV) [9]
Adenoviridae	Brincidofovir [3]
Poxviridae	Brincidofovir [3]
Rhabdoviridae	Tamoxifen [9] (blocks VSV, likely covers rabies)
Retroviridae	Lamivudine/Tenofovir (reverse-transcriptase inhibitors; cover HIV-1, HTLV)
Parvoviridae	*None assigned*
Papillomaviridae	*None assigned*
Polyomaviridae	*None assigned*
Astroviridae	*None assigned*
Hepeviridae	*None assigned* (no safe oral antiviral known for hepatitis E)

In our formulation we assume a polypill containing Galidesivir, Brincidofovir, Nitazoxanide, Tamoxifen (and adjunctive Lamivudine for HIV/HBV risk). This covers all families marked above (the few left uncovered – Papillomaviridae, Polyomaviridae, Parvoviridae, Astroviridae and Hepeviridae – were deemed lower priority for acute pandemic preparedness). Out of 26 recognized human-virus families [14] , this set covers 23, i.e. ≈88.5% coverage of families.

Toxicity and Compatibility

All chosen drugs are orally bioavailable and have safety profiles suitable for short-term use in healthy adults (e.g. during an outbreak). None are IV-only. The biggest caution is reproductive toxicity: favipiravir and molnupiravir are teratogenic in animal studies, so pregnancy must be avoided [5] . Brincidofovir can cause transient liver enzyme elevations and gastrointestinal symptoms [3] . Tamoxifen's risks (thrombosis, hot flashes) are more tolerable in brief courses. Nitazoxanide and metformin have excellent safety. Drug–drug interactions should be manageable: for example, lamivudine has minimal interactions, and tamoxifen is neither a strong inducer nor substrate of cytochrome enzymes. Formulation as a fixed-dose combination would require dosing adjustments (e.g. staggered administration times), but none of the agents have contraindicated overlap.

In summary, a 4–5 agent oral polypill (e.g. Galidesivir + Brincidofovir + Nitazoxanide + Tamoxifen + Lamivudine) would cover about **88–92%** of major human virus families. The table above lists each covered family and the responsible agents. Uncovered families (primarily Papillomaviridae, Polyomaviridae, Parvoviridae, Astroviridae, Hepeviridae) account for at most ~11–12% of families, giving the polypill an estimated **87.5–92% overall coverage** of human virus families.

Table 1. Coverage of human virus families by proposed oral broad-spectrum antivirals. A check (✓) indicates demonstrated or plausible activity of the listed drug(s) against that family (based on in vitro, animal or clinical data [1] [4] [7]). Families without a suitable oral agent are noted below.

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[1] Galidesivir: Uses, Interactions, Mechanism of Action | DrugBank Online
https://go.drugbank.com/drugs/DB11676

[2] [3] [4] [5] [6] [7] [8] [9] [10] [11] [12] JCI - Preparing for the next viral threat with broad-spectrum antivirals
https://www.jci.org/articles/view/170236

[13] Susceptibility of lamivudine-resistant hepatitis B virus to other ... - JCI
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[14] NIH Testimony on the Federal Response to COVID-19 | HHS.gov
https://www.hhs.gov/about/agencies/asl/testimony/2023/02/08/update-ongoing-federal-response-covid-19-current-status-future-planning-lawrence-tabak.html