# Significant Gaps in the Antiviral Landscape for Vector/Contact-Transmitted Viral Infections of Pandemic Potential: A Call-to-Action

James F. Demarest[1], Richard L. Mackman[1], Lee Ruggiero[1], Randall Lanier[1], and John C. Pottage, Jr.[1] on behalf of the INTREPID Alliance Scientific Working Group

[1] INTREPID Alliance, Cambridge, MA, USA

LB-9257

## ABSTRACT

The INTREPID Alliance is a non-profit consortium of eight pharmaceutical companies and affiliates dedicated to accelerating antiviral research and development for current and future pandemic viral threats. Using Airfinity database and other information sources, INTREPID monitors publicly available data on antiviral R&D for the selected WHO-listed viruses with the greatest pandemic potential. These include 9 viral families primarily transmitted via vectors or direct contact that continue expanding globally. Our analysis focused on direct-acting antivirals includes small molecules, peptides, and RNA-based therapies, but excludes antibodies, vaccines, and host-targeted therapies, across these 9 viral families. As of June 23, 2025, deep gaps exist in the number of both preclinical and clinical stage antiviral compounds for all 9 viral families; there are only 10 clinical and 25 preclinical phase compounds. In the clinical space, the majority are existing approved or investigational compounds (6/10) currently explored for potential indication expansions; these mostly target viral replication (5/6). Novel compounds (4/10) in early clinical development are limited to only 3 of 9 viral families (*Filo-, Flavi-, Poxviridae*); these target viral entry (3) or protease (1). Among the 25 preclinical compounds, 6 are approved or investigational antivirals under exploratory evaluation for potential indication expansions and all are replication inhibitors. Of the 19 novel antivirals having only preclinical data, most are replication inhibitors (14/19). *Flavi-* and *Poxviridae* have the most preclinical compounds (6 and 7, respectively), while 4 of 9 viral families have none (*Filo-, Hanta-, Nairo-, Peribunyaviridae*). In view of the lengthy time needed for antiviral drug development (~10 years) and expected attrition, the number of compounds found in our analyses are clearly inadequate. Urgent attention must be given to research, policy, and funding priorities to mitigate the risk of emerging and future pandemic viral threats impacting the global population.

## INTREPID Alliance Antiviral Landscape*

Overview of ongoing preclinical and clinical phase antivirals across 14 viral families.
This poster presentation will focus on those with primarily vector/contact-mediated transmission.

**Primarily Respiratory Transmission**

| Pillar | Disease Indication (n)** Preclinical (103) | Clinical (39) |
|---|---|---|
| Adenoviridae | X | • HuAdeno A-G (1) |
| Coronaviridae | • COVID-19 (74)<br>• MERS-CoV (5)<br>• SARS-CoV-1 (5)<br>• Seasonal CoV (1) | • COVID-19 (25) |
| Orthomyxoviridae | • Influenza (12) | • Influenza (10) |
| Paramyxoviridae | • Hendra virus (1)<br>• Measles (1)<br>• Nipah virus (3)<br>• Parainfluenza (1) | X |
| Picornaviridae | X | • Polio (2)<br>• Rhinovirus (1) |

X = absence of preclinical or clinical phase antivirals

**Primarily Vector/Contact-Mediated Transmission**

| Pillar | Disease Indication (n)** Preclinical (24) | Clinical (16) |
|---|---|---|
| Arenaviridae | • Junin virus (1)<br>• Lassa fever (1) | • Lassa fever (3)<br>• Chapare hem. fever (1) |
| Filoviridae | X | • Ebola (2)<br>• Marburg (1) |
| Flaviviridae | • Dengue (5)<br>• West Nile (1)<br>• Yellow fever (1)<br>• Zika (2) | • Dengue (3) |
| Hantaviridae | X | X |
| Nairoviridae | X | • Crimean Congo hem. fever (1) |
| Peribunyaviridae | X | X |
| Phenuiviridae | • Rift Valley fever virus (1) | • SFTSV (1) |
| Poxviridae | • Mpox (8) | • Mpox (2)<br>• Smallpox/Other (2) |
| Togaviridae | • Chikungunya (4) | X |

*As of June 2025;
**Number of compounds in ongoing development; excludes indication expansions;
SFTSV: Severe fever with thrombocytopenia syndrome virus.

## INTRODUCTION

**Founded in March 2022, the INTREPID Alliance is a non-profit consortium of eight pharmaceutical companies and affiliate organizations dedicated to accelerating the development of new antiviral treatments for emerging/future pandemic threats.**

intrepidalliance.org  linkedin.com/company/intrepid-alliance

Antiviral Pipeline https://www.intrepidalliance.org/antiviral-pipeline/

**The INTREPID Alliance augments the antiviral R&D ecosystem by:**

- Providing a landscape and listing of preclinical and clinical phase antivirals based on rigorous review of public information on antiviral compounds as described on our website.
- Generating publications on topics such as target compound profiles, animal/assay models, and "Deep Dives" on viral families
- Piloting an advisory program for biotechs and academia
- Advocating for the importance of antivirals as part of pandemic preparedness and will help catalyze funding for antiviral R&D

## METHODS (I)

**Derived from the Airfinity* database, the INTREPID Alliance Antiviral Landscape includes compounds selected based on publicly available sources using objective, scientific criteria. The review is conducted at arm's length from commercial influence of our member companies.**

**Baseline Information Identified:**
- Diverse Compound/Indications by Viral Family and Disease
- Phase of Development (e.g., Preclinical through Phase 4, Approved)
- MOA/Target
- Route of Administration
- Developer or Sponsor (Type, Location)
- Clinical Trials (Links, Status, Trial Site Locations)

**Inclusion Criteria:**
- Preclinical & Clinical
  - Known antiviral MOA
  - *In vitro/In vivo* activity
  - Small molecules
  - Peptides
  - RNA-based approaches
- Clinical
  - SAD/MAD data ongoing or completed
  - FIH ongoing or completed
  - No major safety signals

Antiviral Landscape
https://www.intrepidalliance.org/antiviral-pipeline/

Emerging information is reviewed, and the Antiviral Landscape is updated on the INTREPID Alliance website on a semi-annual basis.

*Airfinity https://www.airfinity.com/. Now 14 viral families to align with updated World Health Organization (WHO) Pathogens Prioritization report from June 2024.
MOA: mechanism of action; SAD/MAD: Single Ascending Dose/Multiple Ascending Dose; FIH: first-in-human.

## METHODS (II): Preclinical Compounds

**Categories generally align with movement of a compound across the stages of drug discovery.**

- **Preclinical Compounds** with only preclinical data and no clinical data designated as:
  - **Hit** – high-throughput or compound library screening hit, initial antiviral activity requiring significant optimization. Limited or no *in vitro* data available supporting antiviral mechanism of action (MOA).
  - **Early Lead** – limited Structure-Activity Relationship (SAR), antiviral activity associated with MOA, may have limited *in vitro/in vivo* pharmacokinetic data reported.
  - **Late Lead** – potency consistent with candidate quality for the specific MOA, more extensive *in vitro* characterization (e.g., ADME profile, activity against clinically relevant virus strains/isolates), *in vivo* PK and/or animal efficacy model data reported.
  - **Potential Candidate** – *in vivo* efficacy and safety dataset consistent with preparation for FDA IND (or similar) submission; compound has been reported by developer as a pipeline clinical candidate and/or in IND (or similar) enabling studies.
- **Preclinical Exploratory** are Investigational ("not yet approved") and Approved antivirals exploring antiviral activity against a different virus from the Investigational/Approved antiviral indication, including:
  - **Approved Antiviral-Indication Expansion** (**AppAV-IE**) – antiviral approved for one or more viral disease indications.
  - **Investigational Antiviral-Indication Expansion** (**InvAV-IE**) – antiviral in clinical development, not yet approved.

ADME: absorption, distribution, metabolism, and excretion; PK: pharmacokinetic; IND: Investigational New Drug.

## Vector/Contact-Mediated Transmission: Clinical Phase and Approved

**The majority of clinical antiviral R&D activity targets viral replication (10 of 16 viral disease indications) ***

| Viral Family | Viral Indication | Investigational Antiviral (n=6) Phase 1 | Phase 2 | Phase 3 | Indication Expansion (Clinical Phase) (n=7) InvAV-IE | AppAV-IE | Approved (n=3) |
|---|---|---|---|---|---|---|---|
| Arenaviridae | Chapare HF | LHF535 | x | x | x | x | x |
| | Lassa fever | LHF535<br>ARN-75039 | x | x | x | Favipiravir (Ph 2) | x |
| Filoviridae | Ebola | x | x | x | x | Remdesivir (Ph 3)<br>Favipiravir (Ph 2) | x |
| | Marburg | x | x | x | Obeldesivir (Ph 2) | x | x |
| Flaviviridae | Dengue | x | EYU688 | x | x | Molnupiravir (Ph 2)<br>Zanamivir (Ph 2) | x |
| Hantaviridae | - | x | x | x | x | x | x |
| Nairoviridae | CCHF | x | x | x | x | Favipiravir (Ph 2) | x |
| Peribunyaviridae | - | x | x | x | x | x | x |
| Phenuiviridae | SFTSV | x | x | x | x | x | Favipiravir |
| Poxviridae | Mpox | ASC10 | NV-387-T | x | x | x | x |
| | Smallpox/other pox | x | x | x | x | x | Brincidofovir<br>NIOCH-14 |
| Togaviridae | - | x | x | x | x | x | x |

Distinct Compounds (n=12) by Mechanism of Action

Phase 1-3 Investigational (n=5)
- Entry (n=3)
- Protease (n=0)
- Replication (n=2)
- Assembly-Release (n=0)

Approved (n=3) or Indication Expansions (n=5)**
- Entry (n=0)
- Protease (n=0)
- Replication (n=5)
- Assembly-Release (n=2)

**Favipiravir is counted for both approved and indication expansions.

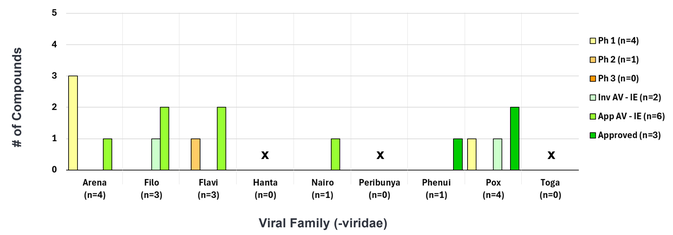
* Based on publicly available information with Airfinity and INTREPID Alliance as of June 2025; InvAV-IE: investigational antiviral-indication expansion; AppAV-IE: approved antiviral-indication expansion; Chapare HF: Chapare hemorrhagic fever; CCHF: Crimean Congo hemorrhagic fever; SFTSV: Severe fever with thrombocytopenia syndrome virus.

- Three compounds have regulatory approval for viral families with primarily vector/contact mediated transmission.
- Clinical phase replication and assembly-release inhibitors are all approved or investigational antivirals with ongoing evaluation for a viral disease indication expansion.
- Clinical phase entry inhibitors consist of only investigational (unapproved) compounds

## Vector/Contact-Mediated Transmission: Clinical Stage of Development

**Clinical antiviral R&D activity span the stages of clinical development and regulatory approval status (N=16)***

11 of 16 clinical phase activities are with either approved compounds (n=3) or potential indication expansions (n=8);
The remaining 5 ongoing activity is primarily Phase 1 studies and only within 3 of 9 viral families.

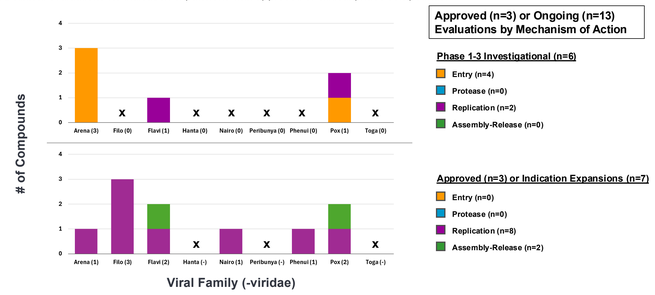



*As of June 2025; Number of compounds in ongoing development;
Inv AV – IE: ongoing evaluation with an unapproved antiviral for different indication from advanced clinical trial;
App AV – IE: ongoing evaluation with an antiviral already approved for a different virus disease indication.

## Vector/Contact Mediated-Transmission: Clinical Phase Mechanisms of Action

**The MOA for the majority of clinical phase and approved compound target viral replication (N=10 of 16)***

6 of 9 viral families have no ongoing clinical activity;
Limited clinical evaluations for indication expansions with approved or clinical phase compounds.




*As of June 2025; Number of compounds in ongoing clinical development or approved for a viral disease indication.

## Vector/Contact-Mediated Transmission: Preclinical

**The majority of preclinical antiviral R&D activity targets viral replication (31 of 39 ongoing evaluations)***

| Viral Family | Antiviral Type (# evaluations) | Viral Indication* (# evaluations) | Hit (n=9) | Early Lead** (n=8) | Late Lead (n=3) | Potential Candidate (n=4) | Preclinical Exploratory Indication Expansion: Investigational (n=2) | Approved (n=13) |
|---|---|---|---|---|---|---|---|---|
| Arenaviridae | | Junin virus (1) | x | x | x | 4'-Fluorouridine | x | x |
| | | Lassa fever (2) | x | x | x | 4'-Fluorouridine | x | Remdesivir |
| Filoviridae | | Ebola virus (1) | x | x | x | x | Obeldesivir | x |
| | | Marburg virus (2) | x | x | x | x | x | Favipiravir<br>Remdesivir |
| Flaviviridae | | Dengue (5) | MLT201<br>Pratirivir Dengue<br>Protirivir pan-flavivirus | x | 2-Thiouridine<br>JNJ-A07 | x | x | x |
| | | West Nile (1) | Protirivir pan-flavivirus | x | x | x | x | x |
| | | Yellow Fever (4) | x | x | BSBI-YF | x | AT-752 | Favipiravir<br>Remdesivir |
| | | Zika (4) | MLT201<br>Protirivir pan-flavivirus | x | x | x | x | Favipiravir<br>Sofosbuvir |
| Hantaviridae | | Hanta virus PS (1) | x | x | x | x | x | Favipiravir |
| Nairoviridae | | CCHF (1) | x | x | x | x | x | Remdesivir |
| Peribunyaviridae | | | x | x | x | x | x | x |
| Phenuiviridae | | Heartland virus (1) | x | x | x | x | x | Favipiravir |
| | | Rift Valley Fever (2) | G2G2-0362 | x | x | x | x | Favipiravir |
| Poxviridae | | Mpox (9) | x | S-lodo-2-deoxyuridine<br>SAH analogs<br>CHLDBUK1230/PDPHs<br>Diaminopurines | ST357 (TTP-6171)<br>TTP-8171<br>UMP-766 | x | NV-387-T | Cidofovir |
| | | Smallpox/Other (1) | x | x | x | x | x | Cidofovir |
| Togaviridae | | Chikungunya (4) | MLT201<br>SRI-42718 | Protirivir Chikungunya | x | 4'-Fluorouridine | X | x |

Distinct Compounds (n=25) by Mechanism of Action

Preclinical (n=19) (no clinical or human exposure data)
- Entry (n=1)
- Protease (n=3)
- Replication (n=14)
- Assembly-Release (n=1)

Preclinical Exploratory (n=6) (Approved/ Indication Expansion)
- Entry (n=0)
- Protease (n=0)
- Replication (n=6)
- Assembly-Release (n=0)

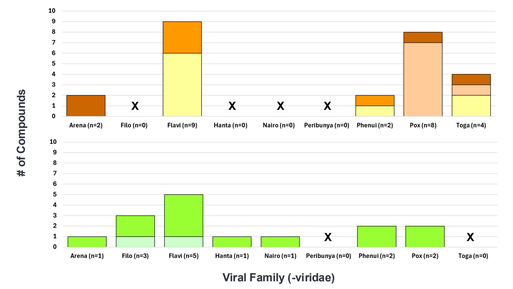
*Based on publicly available information with Airfinity and INTREPID Alliance as of June 2025; Hanta virus PS: Hanta virus pulmonary syndrome; CCHF: Crimean Congo hemorrhagic fever; **SAM analogs: 7-deaza analogs of S-adenosyl methionine; PDPM's: pyridopyrimidinones

- 19 distinct preclinical antiviral compounds are under evaluation
  - The majority (14/19) are replication inhibitors
- 6 distinct replication inhibitors, investigational or approved, are in preclinical exploratory studies

## Vector/Contact-Mediated Transmission: Preclinical Stage of Development

Significant gaps in Preclinical Antiviral R&D

4 of 9 viral families have no preclinical activity; Limited preclinical activity is ongoing with approved or clinical phase compounds.
**The number of compounds, including potential candidates, is insufficient to address the unmet need and account for attrition.**

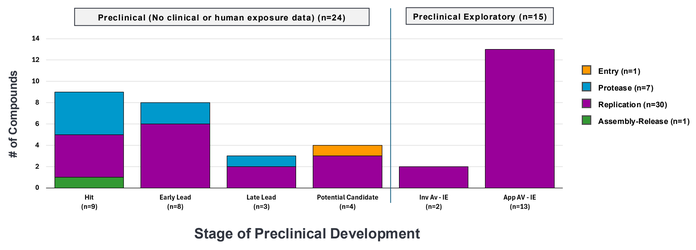



* As of June, 2025; Number of compounds in ongoing development;
Inv AV – IE: ongoing evaluation with an unapproved antiviral for different indication from advanced clinical trial;
App AV – IE: ongoing evaluation with an antiviral already approved for a different virus disease indication.

## Vector/Contact-Mediated Transmission: Preclinical Mechanisms of Action

**The mechanisms of action for the majority of preclinical phase compounds target viral replication (N=30 of 39)***

15 of 24 preclinical compound evaluations are with replication inhibitors;
All 15 preclinical exploratory evaluations for indication expansions with approved or clinical phase compounds are replication inhibitors.




* As of June 2025; Number of compounds in ongoing development;
Inv AV – IE: ongoing evaluation with an unapproved antiviral for different indication from advanced clinical trial;
App AV – IE: ongoing evaluation with an antiviral already approved for a different virus disease indication.

## Disclaimer

The INTREPID Alliance is a not-for-profit consortium of innovative biopharmaceutical companies committed to accelerating antiviral research, aiming to ensure that we have a stronger pipeline and are better prepared for future pandemics.

As part of our efforts, the INTREPID Alliance maintains and publishes a centralized list of promising investigational candidate compounds, with the purpose of knowledge-sharing and to support better pandemic preparedness. These compounds have been selected based on objective, scientific criteria, using publicly available sources, and at arm's length from commercial influence of our member companies. See criteria listed in the report "Antiviral Clinical Development Landscape and Promising Clinical Compounds." The designation of certain compounds as promising is based upon currently available information, and exclusively upon an assessment against these criteria. "Promising" is not a promotional claim. Candidate compounds have not been assessed by regulatory authorities to be safe and efficacious for the treatment of disease in humans. Our content is designed to be factual, informative, and non-commercial. It is not designed or intended to advertise or promote any pharmaceutical product or therapy or to advance the commercial interests of any company.

## References

- G7 and International Pandemic Preparedness Secretariat (IPPS) 100 Days Mission https://ippsecretariat.org/
- INTREPID Alliance http://www.intrepidalliance.org/
- World Health Organization (WHO) Pathogens Prioritization report, June 2024.

## Summary of Antiviral Landscape for Viral Infections with Vector/Contact-Mediated Transmission

- **Significant gaps exist in the preclinical and clinical phase R&D efforts across 9 viral families with primarily vector/contact mediated transmission**
- **Clinical Phase Activity**
  - 6 of 9 viral families have no ongoing clinical activity and most ongoing clinical evaluations are for potential indication expansions
  - Unapproved investigational compounds are primarily Phase 1 and only include 3 of 8 viral families
- **Preclinical Phase Activity**
  - 4 of 9 viral families have no preclinical activity
  - Limited preclinical activity is ongoing with approved or unapproved clinical phase compounds
- **Replication inhibitors predominate** the MOA for antivirals in the preclinical and clinical spaces
- **Urgent attention must be given to research, policy, and funding priorities to mitigate the risk of emerging and future pandemic viral threats impacting the global population.**

INTREPID ALLIANCE
INTERNATIONAL READINESS FOR PREVENTING INFECTIOUS VIRAL DISEASE