INTREPID ALLIANCE

INTERNATIONAL READINESS FOR PREVENTING INFECTIOUS VIRAL DISEASE

OCTOBER 9, 2024

Antiviral Clinical and Preclinical Development Landscape – 3rd Edition

JIM DEMAREST

RICHARD MACKMAN

LEE RUGGIERO

JOHN C. POTTAGE, JR.

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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.

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About the INTREPID Alliance Antiviral Landscape

INTREPID Alliance Antiviral Landscape: Our Approach

- **INTREPID Alliance Landscaping Activities**
  - Highlight strengths and weaknesses of the antiviral drug development pipeline for potential pandemic viral pathogens
  - Support the 100 Days Mission (100DM) which seeks to identify two 'Phase 2 ready' therapeutic candidates against each of the identified viral pathogen families of greatest pandemic potential
- **Landscape Analysis**
  - A living analysis of the antiviral landscape that will be updated based on emerging data
  - Derived from Airfinity database information on diverse compounds against 13 viral families (See Slide 6)
  - Focused on direct-acting small molecule antivirals
- **Timing and Publication on Website**
  - **1st Edition:** Initial triage and selection of clinical compounds with favorable properties and antiviral mechanism of action – January 2024
  - **2nd Edition:** Detailed review and identification of most Promising Clinical and Approved-Indication Expansion Compounds – April 2024
  - **3rd Edition**: Inclusive of the quarterly update for Clinical Development Landscape; initial Antiviral Preclinical Development Landscape release; Mpox Clinical and Preclinical Landscape - October 2024
  - Quarterly Updates – Ongoing

Landscape Analysis Components*

Airfinity monitors 13 viral families that pose the greatest risk of pandemic potential.
With thanks to Airfinity for its contributions to the presentation.

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)

Figures & Tables:

- 13 Viral Families of Interest for Pandemic Preparedness
- Total Pipeline by Viral Family
- Promising Clinical and Indication-Expansion Compounds
- Compounds by Viral Family and Phase of Development
- Compounds by MOA/Target and Viral Family
- Phase of development vs viral disease for each MOA
- Developer or Sponsor
- Preclinical compounds

- Emerging information is reviewed on a monthly basis.
- Antiviral Landscape updated on the INTREPID Alliance website on a quarterly basis.

*Now 13 viral families to align with updated World Health Organization (WHO) Pathogens Prioritization report from June 2024.

INTREPID Alliance Antiviral Landscape: Overview of 13 Priority Viral Families*

As of July 12, 2024, for the 13 viral families with greatest risk of pandemic potential, clinical phase & approved antiviral compounds fall into 9 of 13 and preclinical into 10 of 13.

Primarily Respiratory Transmission:

	Disease Indication (n)**	
Viral Family	**Preclinical**	**Clinical**
Adenoviridae	HuAdeno A-G (3)	HuAdeno A-G (0)
Coronaviridae	COVID-19 (73) MERS-CoV (5) SARS-CoV-1 (5)	COVID-19 (29)
Orthomyxoviridae	Influenza (12)	Influenza (9)
Paramyxoviridae	Hendra virus (3) Measles (1) Nipah virus (3) Parainfluenza (0)	X
Picornaviridae	X	Polio (2) Rhinovirus (1)

X = absence of preclinical or clinical phase antivirals

Primarily Contact/Vector-Mediated Transmission:

	Disease Indication (n)**	
Viral Family	**Preclinical**	**Clinical**
Arenaviridae	Lassa fever (1) Argentine hem. fever (0) Lujo hem. fever (0)	Lassa fever (1) Chapare hem. fever (1)
Filoviridae	Ebola (1) Marburg (3)	Ebola (2)
Flaviviridae	Dengue (4) West Nile (1) Yellow fever (3) Zika (2)	Dengue (3) Japanese encephalitis (0)
Hantaviridae	Hantavirus (1)	X
Nairoviridae	X	Crimean Congo hem. fever (2)
Peribunyaviridae	X	X
Poxviridae	Mpox (2) Smallpox/Other poxviruses (1)	Mpox (1)
Togaviridae	Chikungunya (3)	X

*As of July 12, 2024; **Number of compounds in ongoing development; those with (0) only have “Archived” compounds.

Clinical Antiviral Development Landscape as of July 2024

INTREPID Alliance Clinical Antiviral Landscape: 1st Edition of the Clinical Antiviral Compounds Analysis (January 2024)*

- 1st Edition of the clinical antiviral landscape data as of November 16, 2023 was posted on the INTREPID website on **January 24, 2024**.
  - Two rounds of rigorous scientific triage on 300 clinical phase entries reduced the number to 61 distinct compounds associated with 80 compound/indication pairings.

Initial Analysis

Exclusion Criteria:

- Antibodies
- Antibiotics & Anti-infectives
- Cell-based Therapy
- HIV or HCV-specific
- Host Targets (incl. Imm. Mod.)
- Natural Products/ Nutraceuticals/Herbals
- Vaccines

Inclusion Criteria:

- Known Antiviral MOA
- *In Vitro/In Vivo* Activity
- Small Molecules
- Peptides
- RNA-based
- SAD/MAD Data
- FIH Completed
- No Major Safety Signals

*As of November 16, 2023

INTREPID Alliance Clinical Antiviral Landscape: Clinical Antiviral Compounds Analysis Update (July 2024)*

- 2nd edition of the clinical landscape analysis of data through March 2024 was reported on the INTREPID website in April 2024.
- Data were organized based on stage of clinical development and regulatory approval:
  - Novel Unapproved Clinical Phase Antiviral Compounds (e.g., not yet approved for a virus disease indication)
  - Approved-Indication Expansion Antiviral Compounds (e.g., initial approval for one viral indication and under evaluation for other viral indication(s))
- Additional scientific analysis** of only the novel compounds categorized them as follows:
  - **Promising**
  - **Watch & Wait**
  - **Archived**
- This 3rd edition analysis of the data through July 2024 shows that there are 64 distinct antiviral compounds in the antiviral clinical development landscape.
  - **22** are approved and **42** are novel unapproved
  - **7** new unapproved and **3** new approved compounds were added

*As of July 12, 2024; **See criteria and references on slides 11-12.

Criteria* for Promising Clinical Antiviral Compounds Analysis (July 2024)**

- FIH trial completed and data at adequate doses and dosing duration available.
- POC study ongoing *or* completed and data available
  - POC demonstration via viral endpoint, symptom alleviation, etc.
  - POC in animal model may be applicable for certain viral diseases where clinical POC is not feasible.
- Adequate PK/PD to support Phase 2/3 dose selection and route of administration.
- Safety and tolerability consistent with the target dose/exposure and no difficult-to-manage clinical safety signals.
- Other criteria such as chemical structure, synthesis, scalability, etc. are taken into account where data are available.

*In addition to the collective antiviral drug development experience of INTREPID member companies, guidance documents from Regulatory Authorities such as the U.S. FDA routinely used by drug developers, and publicly available Target Product Profiles such as the NIH/NIAID Target Product Profiles for Antivirals, were used to inform the clinical phase triage.

**As of July 12, 2024; FIH: first-in-human; POC: proof-of-concept; PK/PD: pharmacokinetic/pharmacodynamic; CMC: chemistry, manufacturing, and controls

Categories for Clinical Antiviral Compound Analysis (July 2024)*

- **Promising** (e.g., meets “Promising Criteria”)
  - 100DM Ready
  - Registration & Approval for established viral diseases
- **Watch & Wait**
  - FIH or POC Study just starting/ongoing or data are unavailable for a completed study
  - Unable to make a data-driven evaluation
- **Archived**
  - Development paused, no recent information >5 years
- **Exclude**
  - Known disqualifying data related to safety and tolerability, efficacy, developability, chemical structure, etc.

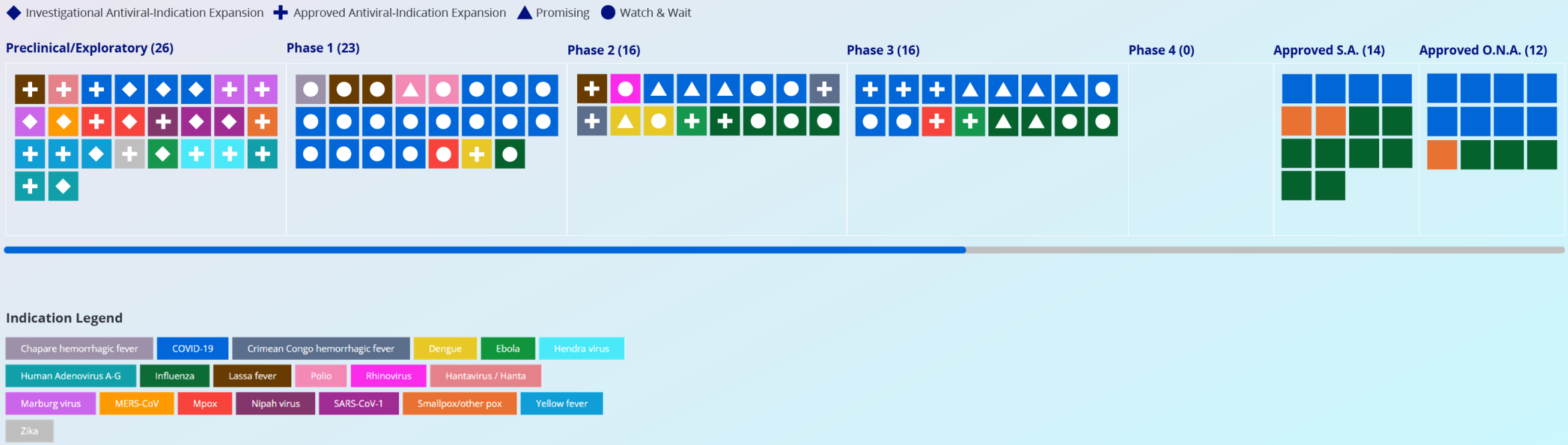
*As of July 12, 2024; FIH: first-in-human; POC: proof-of-concept

Summary of Updated Antiviral Clinical Development Landscape with Promising Clinical Compounds (July 2024)*

- Identified **64** distinct antiviral compounds with ongoing clinical phase activity
  - **22** Approved Compounds: **19** Approved for COVID-19 and/or Influenza; **3** for Smallpox/Other Poxviruses
    - 13 by Stringent Authority (S.A.)
    - 8 by Other National Authority (O.N.A.)
    - 1 by S.A. and O.N.A.
  - **42** Unapproved Compounds
- There are **79** indications associated with the 64 distinct antiviral compounds**
  - **26** Approvals for COVID-19 and/or Influenza
    - 8 Approved for COVID-19 only
    - 7 Approved for Influenza only
    - 4 Approved for both COVID-19 and Influenza (n=8 total)
    - 3 Approved for Smallpox/Other Poxviruses
  - **9** other viral indications under evaluation for **6** of the **22** distinct Approved antiviral compounds
  - **44** indications for Unapproved compounds; **1** compound being evaluated for two indications
- Unapproved Promising and Watch & Wait clinical compounds target entry (**11**), protease (**18**), replication (**12**), and assembly-release (**3**).

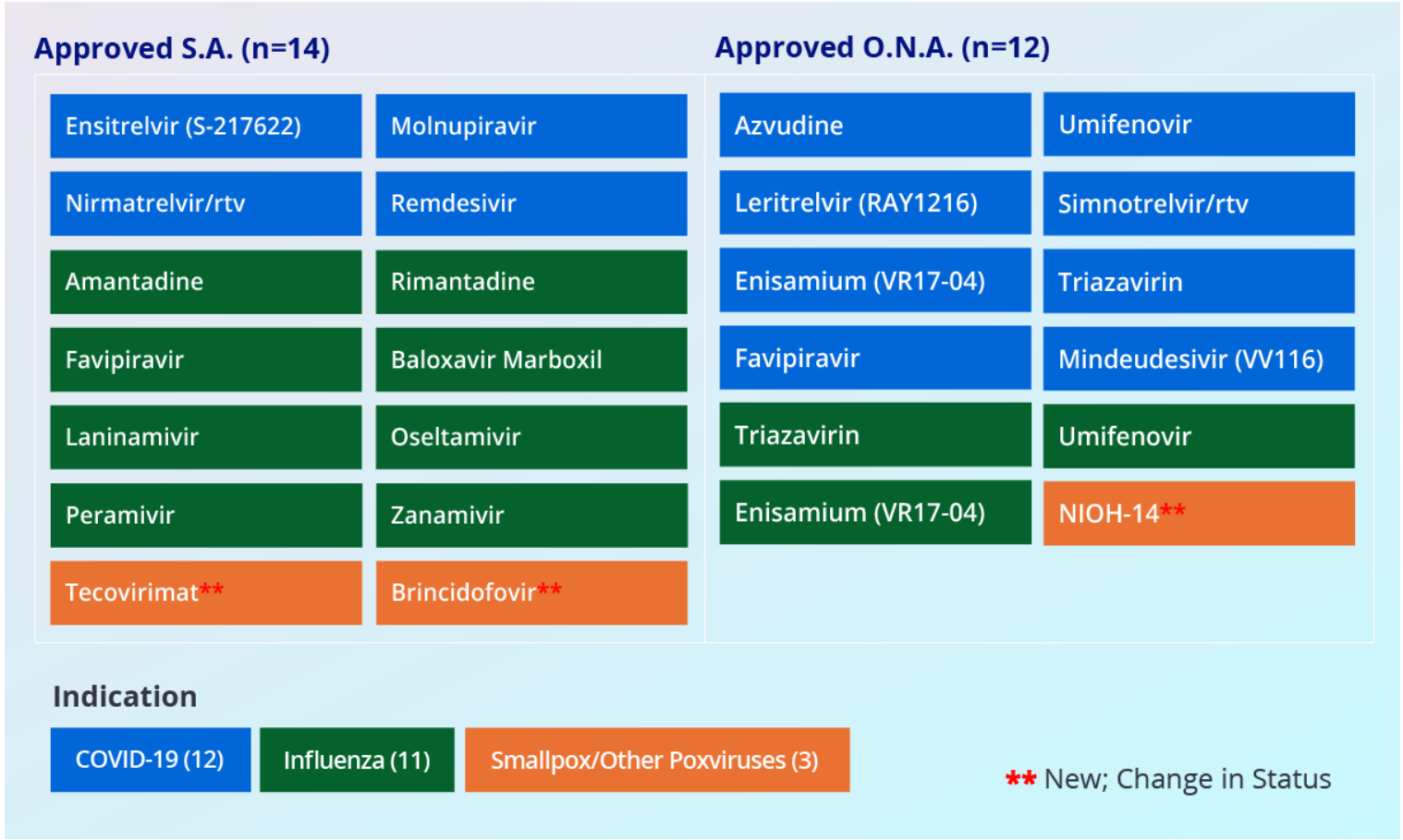
*As of July 12, 2024; **Some compounds are being evaluated for more than 1 viral indication.

Static View of Interactive Antiviral Clinical Development Pipeline: INTREPID Alliance Analysis (July 2024)*



*As of July 12, 2024; WHO-defined Other National Authority (https://www.who.int/publications/m/item/list-of-transitional-wlas)

Approved Antivirals: COVID-19, Influenza, Smallpox/Other Poxviruses*



- 22 distinct antiviral compounds have received regulatory approval for COVID-19, Influenza, or Smallpox/Other Poxviruses
- 4 compounds are approved for COVID-19 and Influenza (favipiravir, triazavirin, umifenovir, and enisamium)
- 3 compounds have regulatory authorization by Animal Rule Development or similar mechanism
  - Tecoviramat is approved for Smallpox in U.S. & EU, and Cowpox and Mpox in EU only
  - Brincidofovir for Smallpox in U.S.
  - NIOH-14 for Smallpox in Russia

*As of July 12, 2024; WHO defined Other National Authority (https://www.who.int/publications/m/item/list-of-transitional-wlas)

Antiviral-Indication Expansions: Preclinical & Clinical Compound/Indications

Investigational: Antiviral compounds in clinical phase development for a different virus disease indication.
Approved: Antiviral compounds approved for treatment of a different virus disease indication.

- 6 of these antivirals (favipiravir, remdesivir, molnupiravir, amantadine, oseltamivir, & zanamivir) are approved for treatment of COVID-19 and/or Influenza.
  - Valganciclovir and cidofovir are approved for treating CMV disease.
- **Favipiravir** has the most indication expansions under evaluation (9) followed by **remdesivir** (6).

*As of July 12, 2024

All Clinical Phase & Approved Antivirals (N=103)

INTREPID Alliance Analysis (July 2024)*

*July 12, 2024 data with “Promising” Analysis defined in March 2024; **Clinical phase and Approved antivirals being explored for expanded indications.

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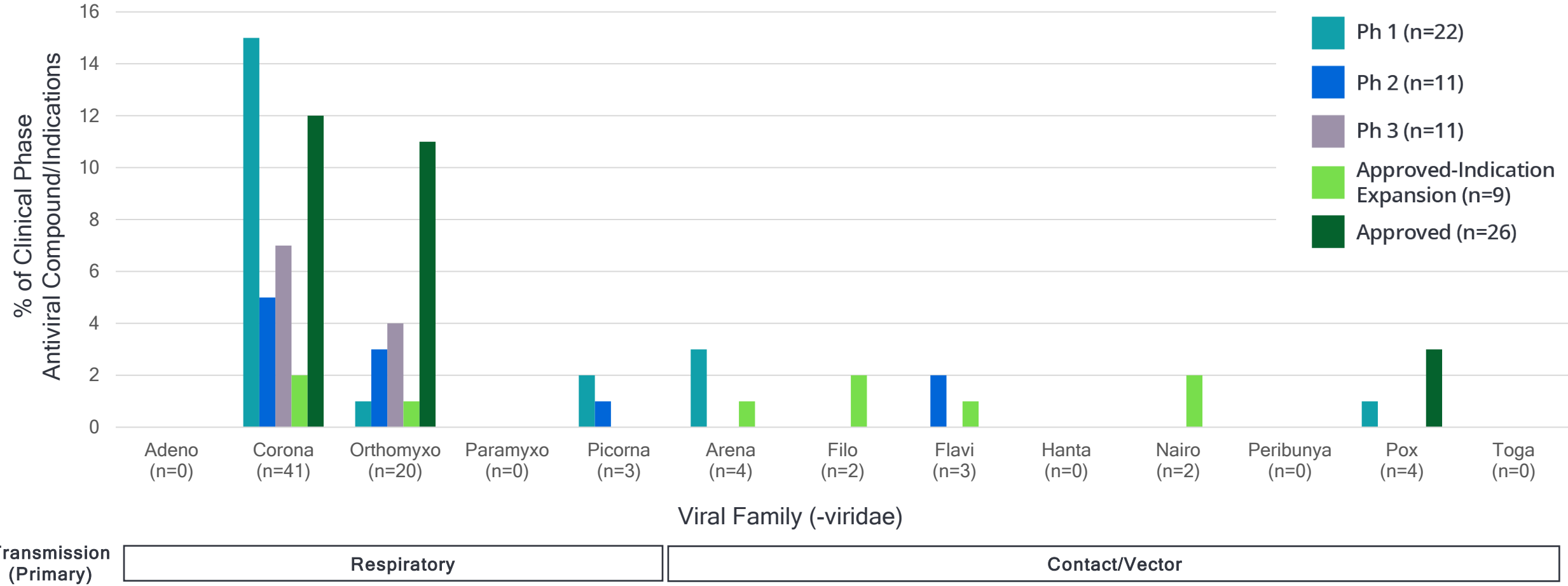
The Majority of Clinical Phase Antiviral Compound/Indications Are Targeting Coronaviruses and Orthomyxoviruses*

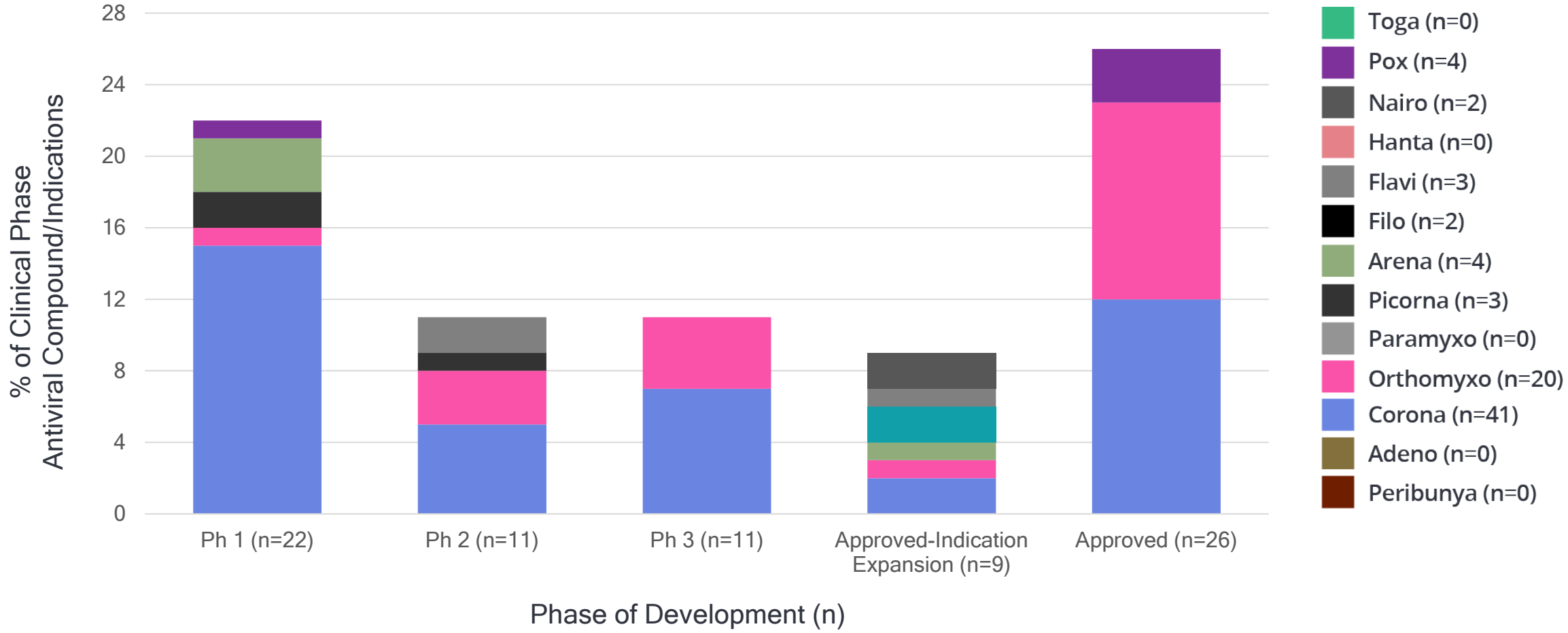
% Clinical Phase Antiviral Compound/Indications by Virus Family (July 2024, N=79)



*As of July 12, 2024. Adenoviridae has 1 clinical phase program listed in Archived.

The Majority of Clinical Phase Antiviral Compound/Indications Are Targeting Coronaviruses and Orthomyxoviruses*

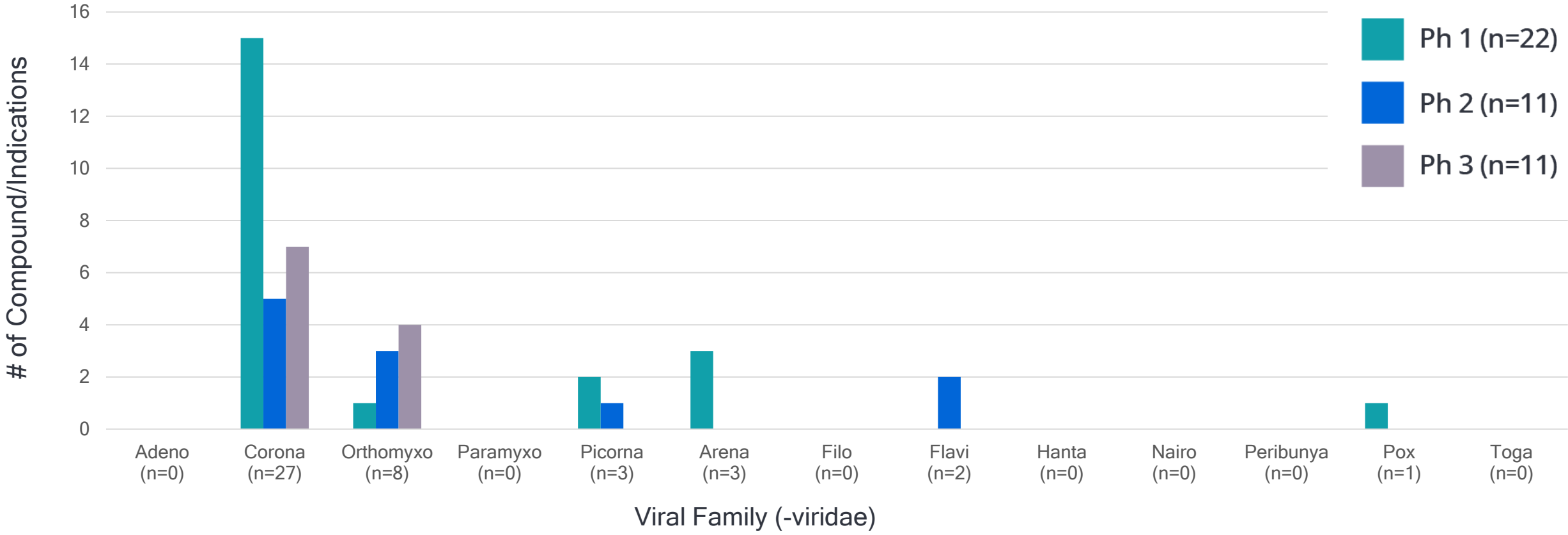
% Clinical Phase Antiviral Compound/Indications by Virus Family (July 2024, N=79)



*As of July 12, 2024

“Promising” Clinical Compounds Analysis (July 2024)*

Unapproved Compounds (Promising and Watch & Wait) by Virus Family (N=44)



Transmission (Primary)	Respiratory	Contact/Vector

*As of July 12, 2024

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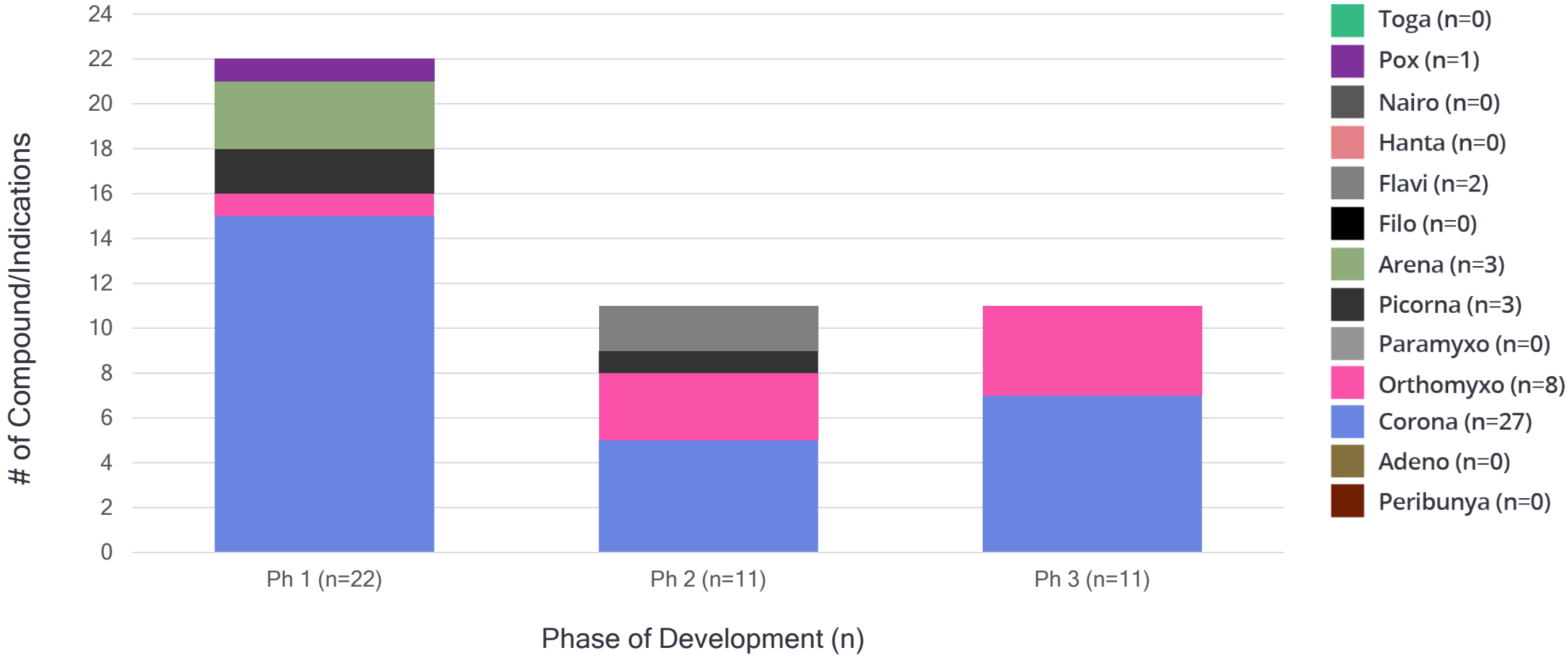
“Promising” Compounds Analysis (July 2024)*

Novel Compound/Indications (Promising and Watch & Wait) by Phase of Development (N=44)



*As of July 12, 2024

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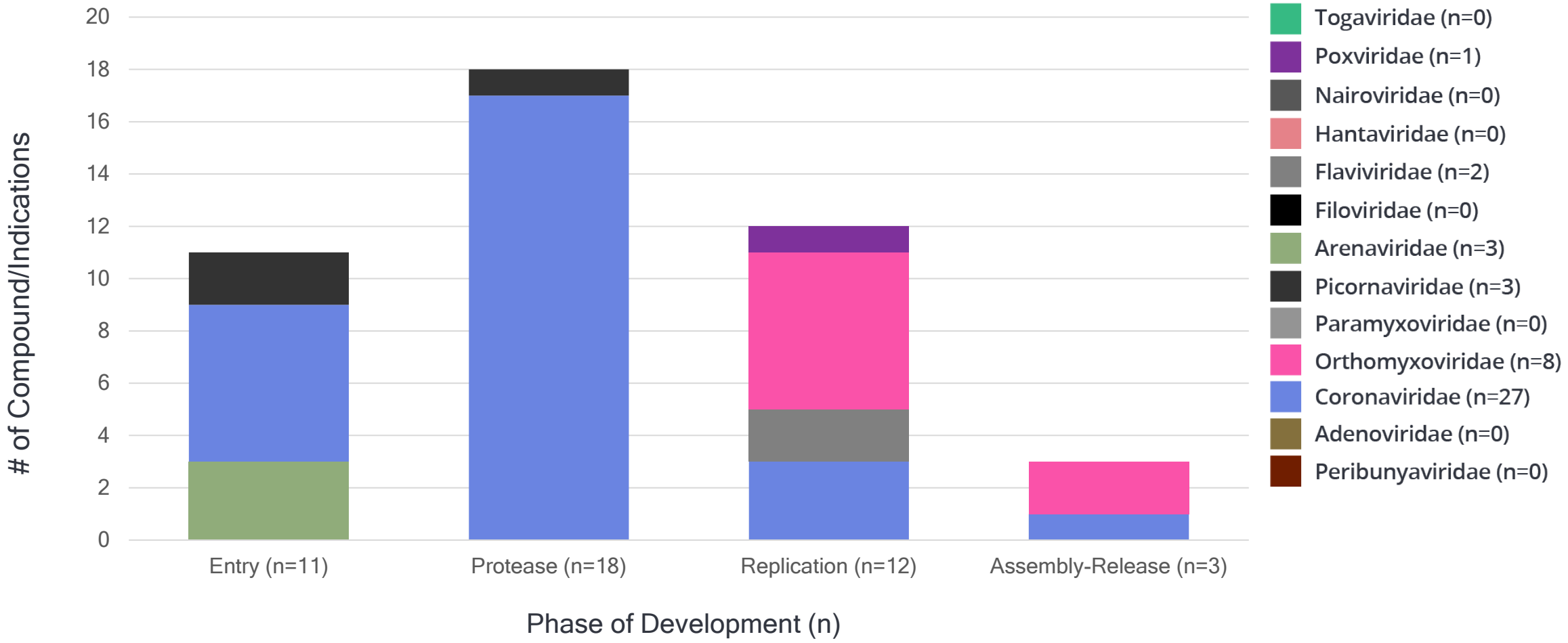
“Promising” Compounds Analysis (July 2024)*

Novel Compound/Indications (Promising and Watch & Wait) by MOA and Viral Family (N=44)



*As of July 12, 2024

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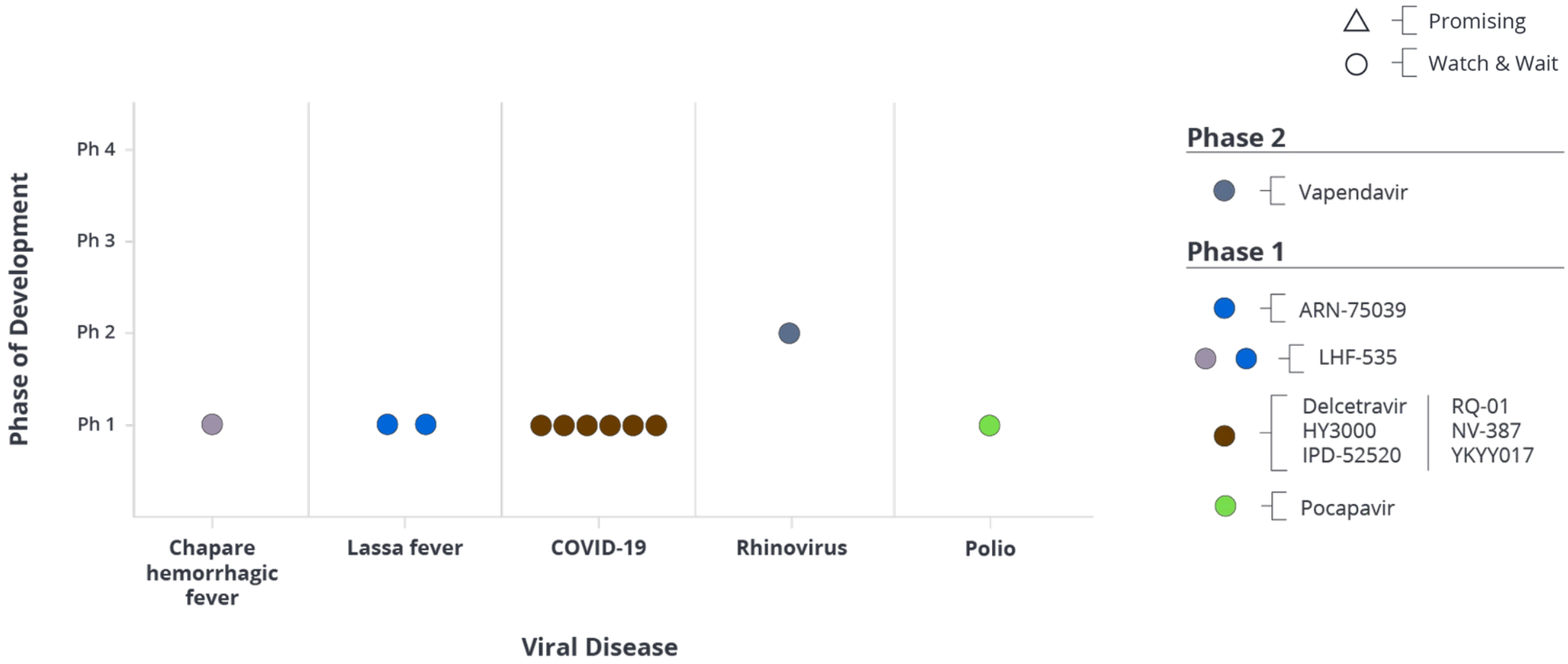
Novel Clinical Antiviral Entry Inhibitors*

Novel Compound/Indications (Promising, Watch & Wait (N=12))



*As of July 12, 2024; Attachment, Capsid (Rhinovirus), Fusion

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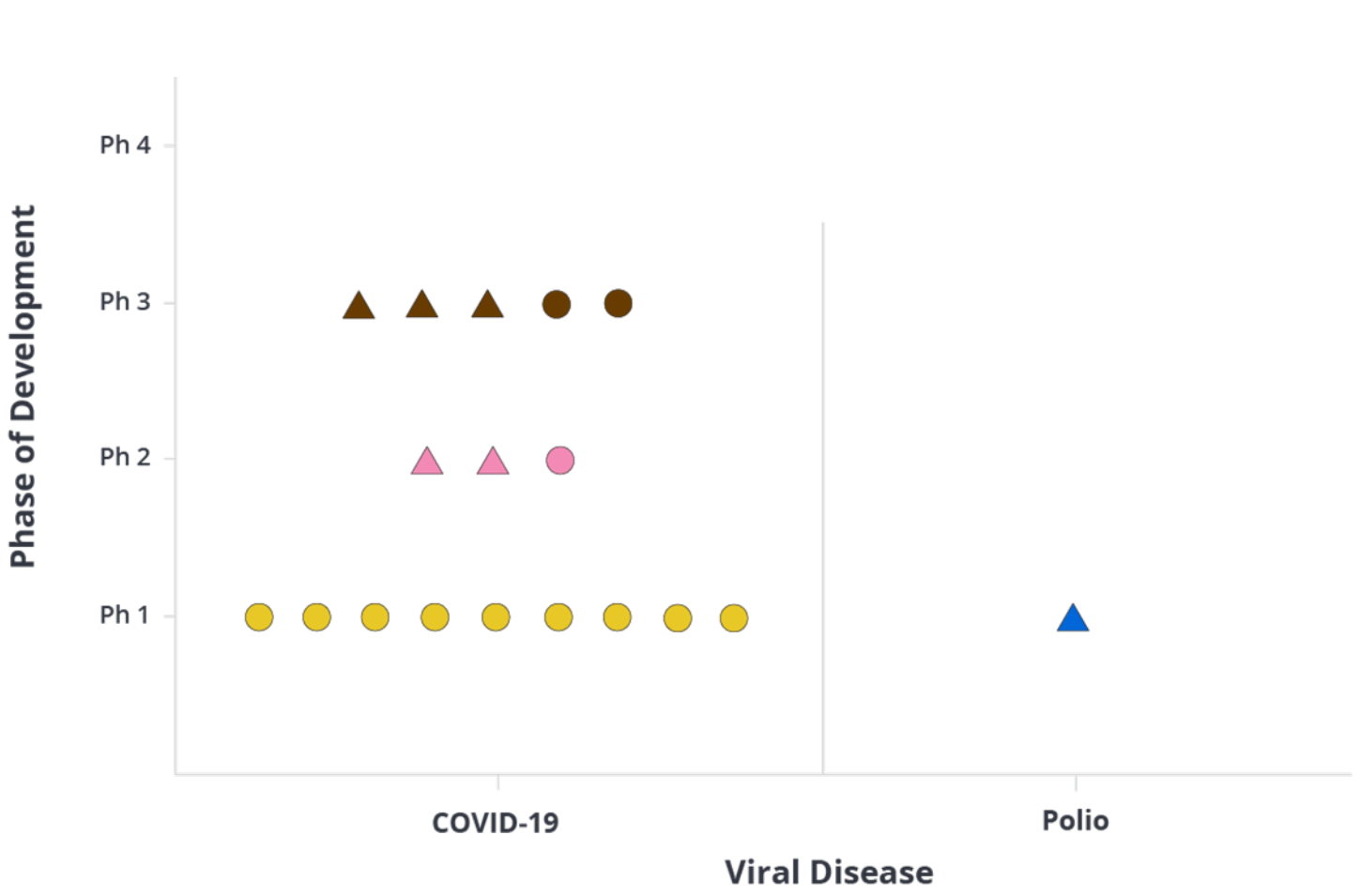
Novel Clinical Antiviral Protease Inhibitors*

Novel Compound/Indications (Promising, Watch & Wait, Archived (N=18))



△ Promising

○ Watch & Wait

** New; Change in Status

Phase 3

▲ GST-HG171, QLS1128, STI-1558

● FB2001, WPV01**

Phase 2

▲ EDP-235, PF-07817883

● HS 10517/rtv

Phase 1

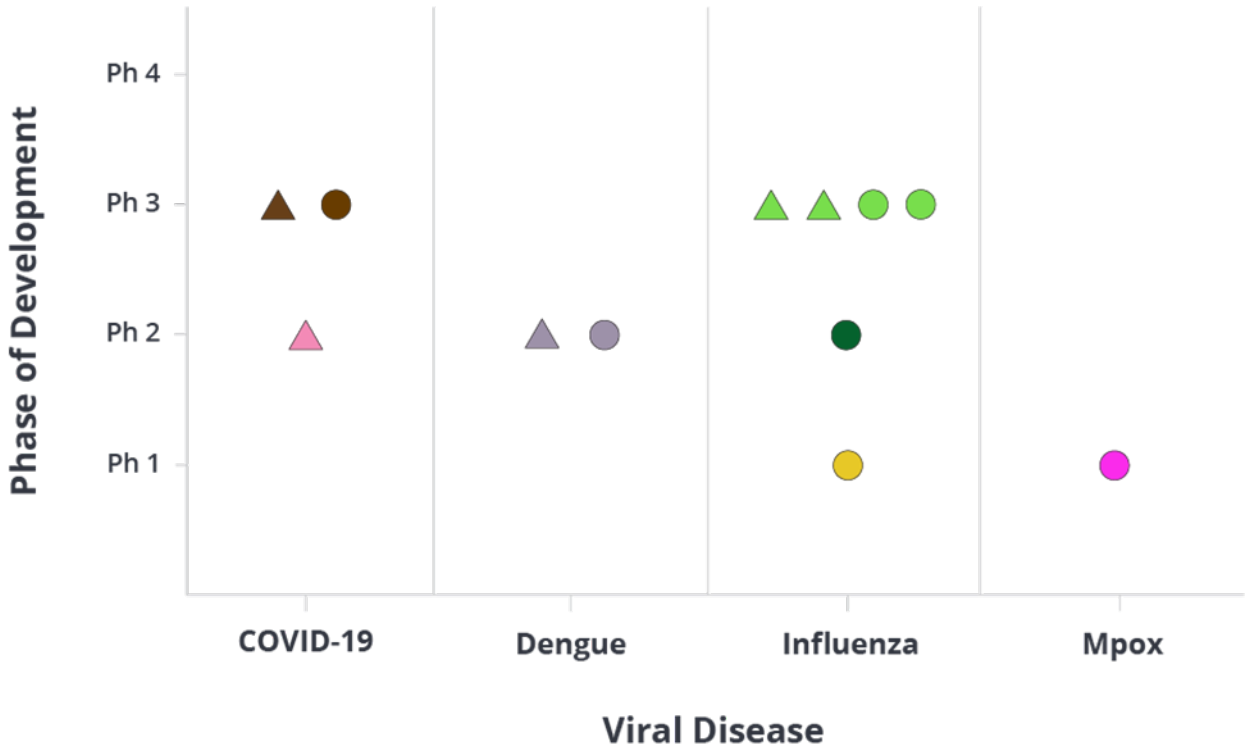
▲ V-7404

● ABBV 903, ALG-097558, ASC11/rtv, CDI-988, ISM3312, S-892216, WPV01/rtv, GS-00202**, ISM036-076 PCC**

*As of July 12, 2024; Mpro (Coronavirus and Enterovirus)

Novel Clinical Antiviral Replication Inhibitors*

Novel Compound/Indications (Promising, Watch & Wait (N=12))



△ Promising

○ Watch & Wait

** New; Change in Status

Phase 3

- ▲ Obeldesivir
- ● Bemnifosbuvir
- ▲ Onradivir GP681
- ● ZX-7101A TG-1000**

Phase 2

- ▲ SHEN26
- ▲ Mosnodenvir
- ● EYU688
- ● CC-42344**

Phase 1

- ● TRX100 (AV5124)**
- ● ASC10**

*As of July 12, 2024; Polymerase, Endonuclease, Replicase, DENV NS4B

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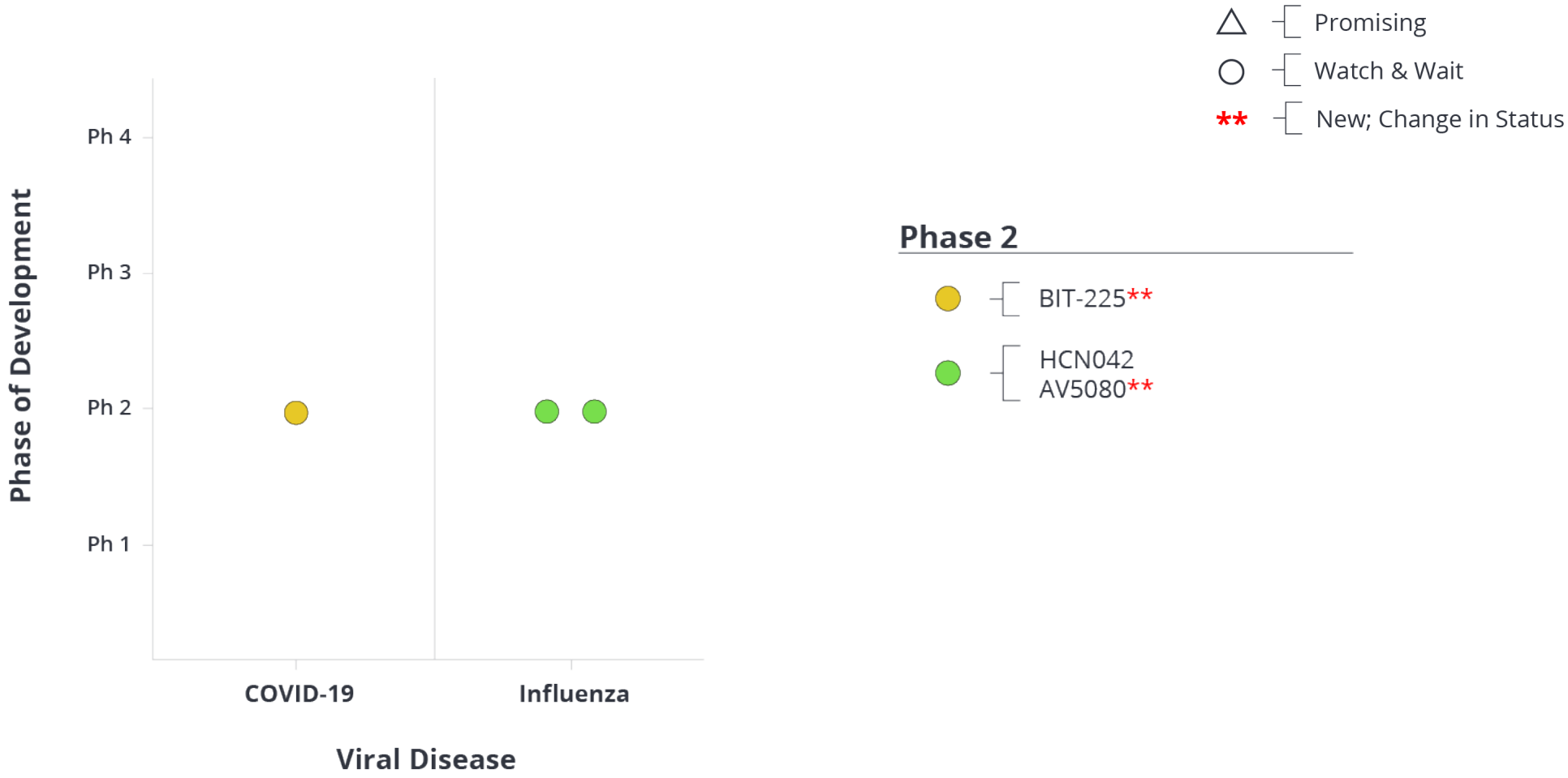
Novel Clinical Antiviral Assembly-Release Inhibitors*

Novel Compound/Indications (Promising, Watch & Wait, Archived (N=3))



*As of July 12, 2024; Neuraminidase

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Summary of Updated Antiviral Clinical Development Landscape with Promising Clinical Compounds (July 2024)*

- Identified **64** distinct antiviral compounds with ongoing clinical phase activity
  - **22** Approved Compounds: **19** Approved for COVID-19 and/or Influenza; **3** for Smallpox/Other Poxviruses
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  - **42** Unapproved Compounds
- There are **79** indications associated with the 64 distinct antiviral compounds**
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  - **44** indications for Unapproved compounds; **1** compound being evaluated for two indications
- Unapproved Promising and Watch & Wait clinical compounds target entry (**11**), protease (**18**), replication (**12**), and assembly-release (**3**).

*As of July 12, 2024; **Some compounds are being evaluated for more than 1 viral indication.

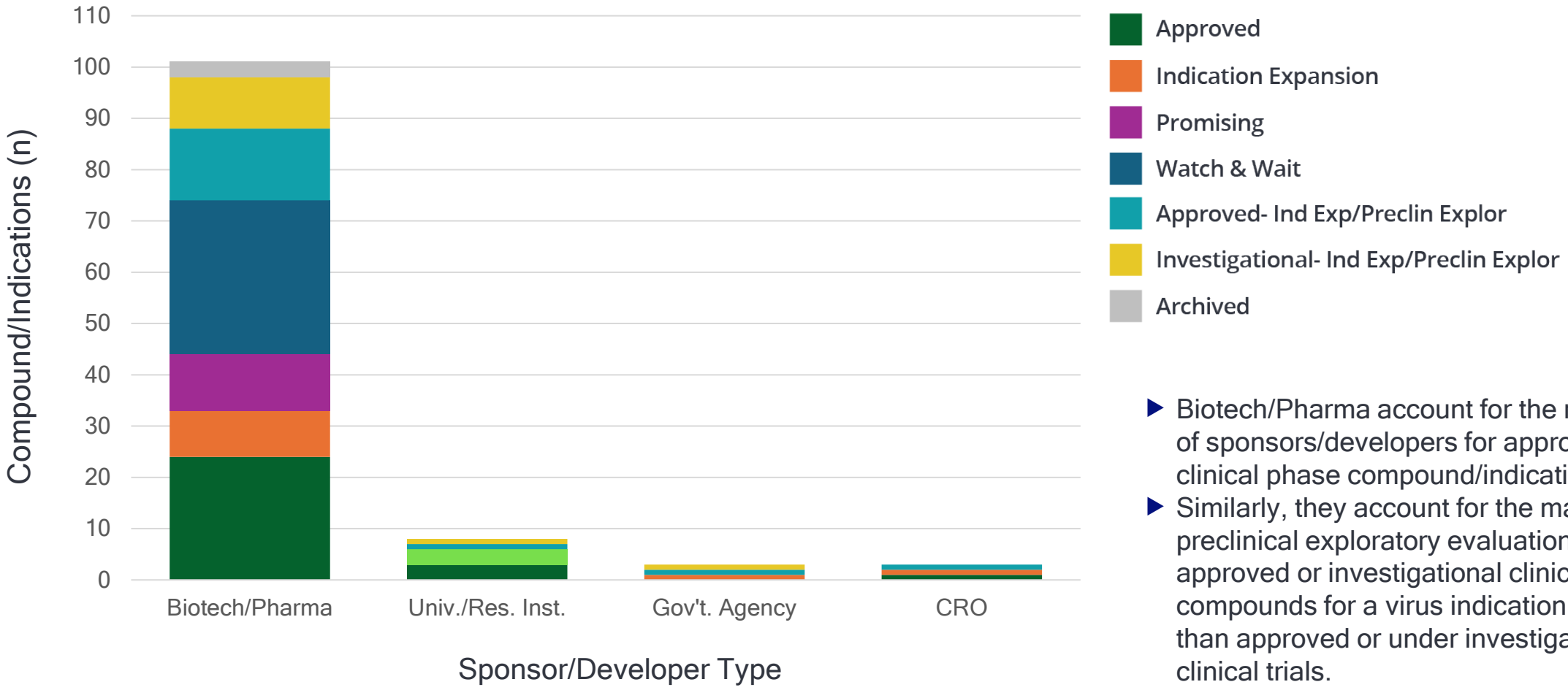
Clinical Antiviral Sponsors and Developers

Clinical Antiviral Landscape: Sponsors & Developers*

- The biopharmaceutical industry (both large and small companies) represents ~**92%** of the global antiviral clinical developers.
  - Academia ~5%
  - Government groups <2%
  - Contract Research Organizations (CRO) <1%
- For the **44** Promising and Watch & Wait clinical compound/indications:
  - The countries most represented by developers/sponsors are the United States (**45%**) and China (**35%**). Others include:
    - Australia 4.5%
    - Remainder of 16% with 2.3% each in Belgium, Hong Kong, Japan, Russia, Switzerland, Taiwan, and United Arab Emirates.
  - The majority (65%) of developers/sponsors are located in countries with high-income economies.
    - The remainder are located in China which has an upper-middle income economy class.

*As of July 12, 2024

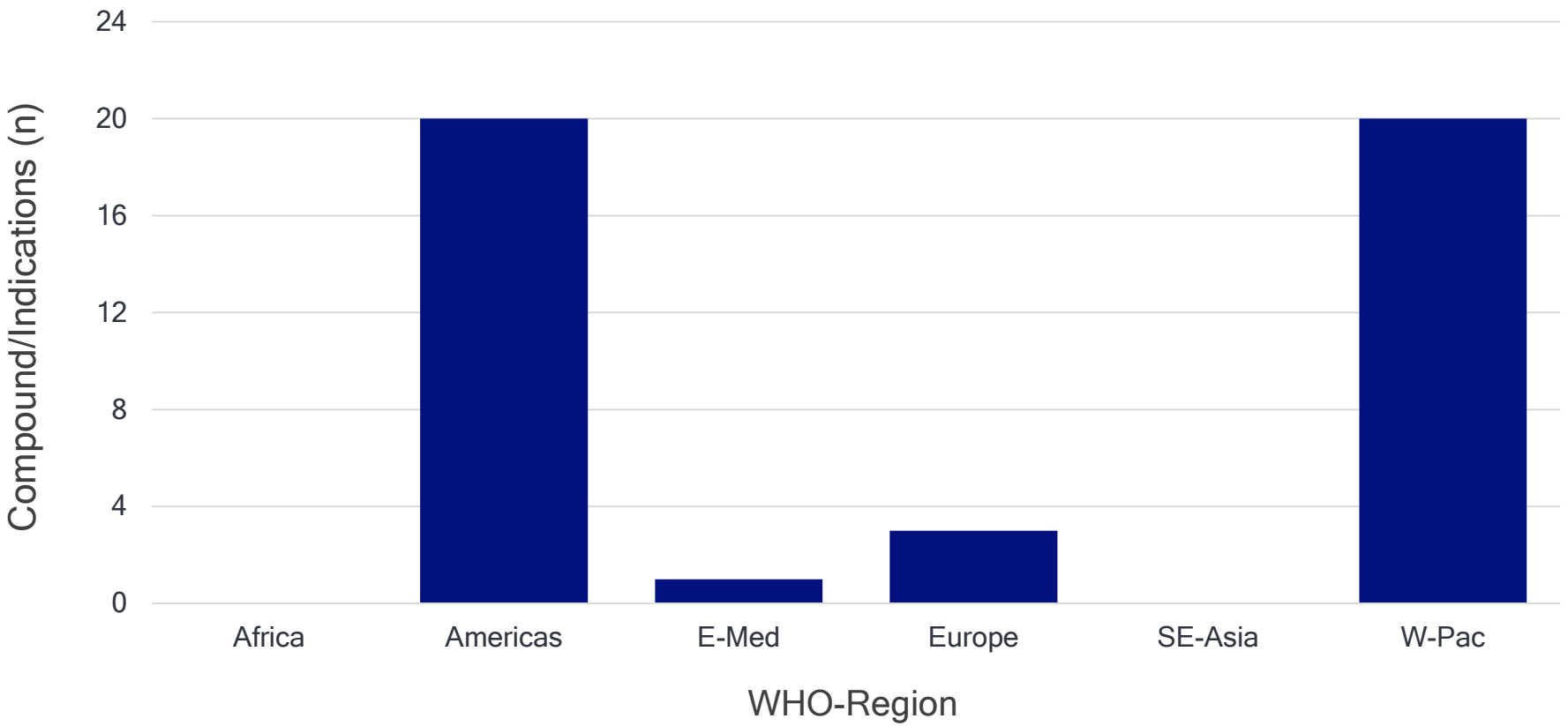
Clinical Antiviral Compound/Indications by Sponsor/Developer Type*



- Biotech/Pharma account for the majority of sponsors/developers for approved and clinical phase compound/indications.
- Similarly, they account for the majority of preclinical exploratory evaluations with approved or investigational clinical compounds for a virus indication other than approved or under investigation in clinical trials.

*As of July 12, 2024

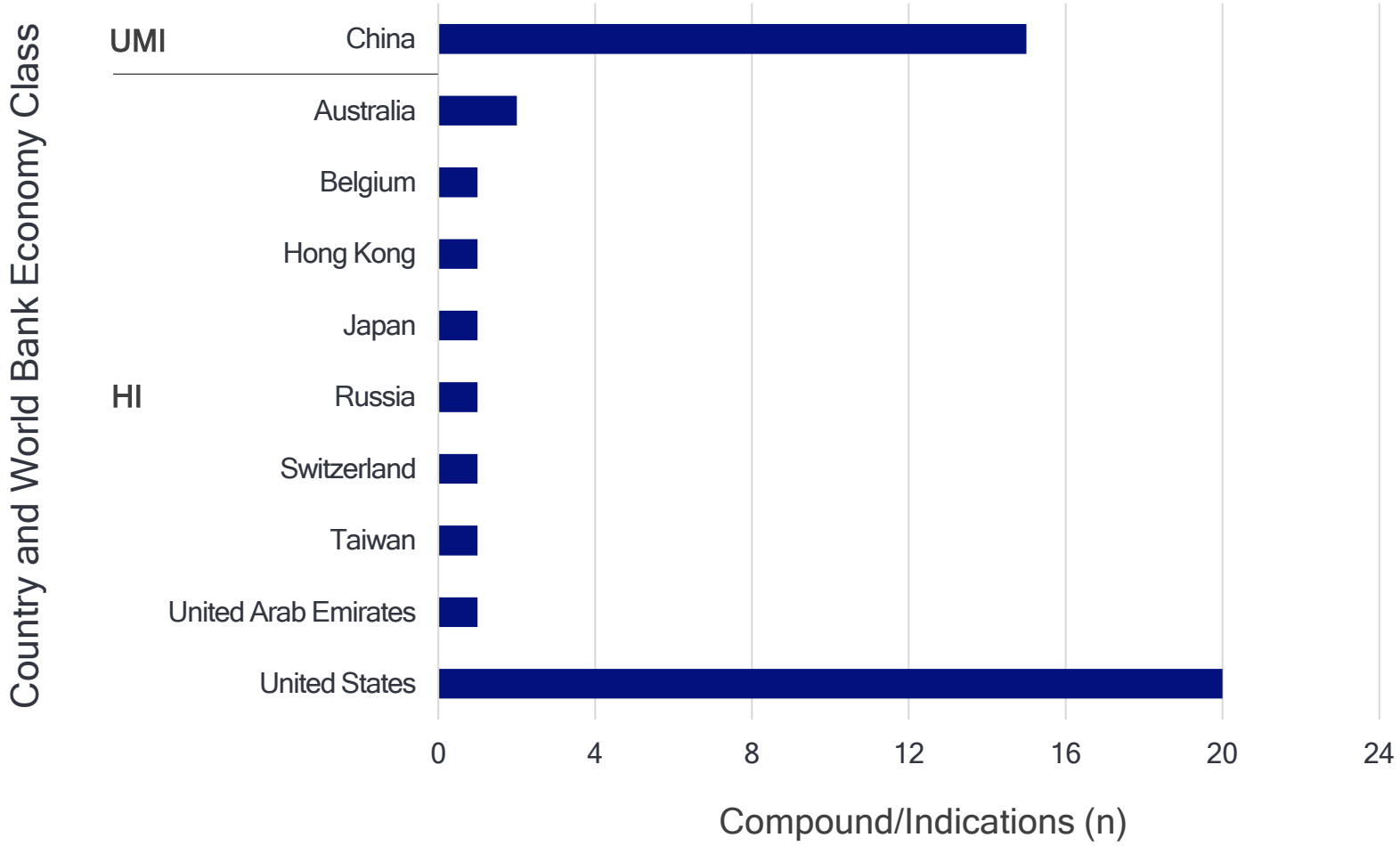
Clinical Antiviral Compound/Indications by Sponsor/Developer WHO-Region* (N=44)



- The Americas and Western Pacific regions are primarily driven by the United States and China.

*As of July 12, 2024

Promising and Watch & Wait Clinical Antiviral Compound/Indications* by Country and World Bank Economy Class**



- The majority (65%) of sponsors/developers of Promising and Watch & Wait clinical antiviral compound/indications are located in countries with high-income economies.
  - The remainder are those with upper-middle income economies.
- The United States (HI) and China (UMI) have the most representation.

*As of July 12, 2024; **World Bank country classifications by income level for 2024-2025; UMI: upper-middle income; HI: high-income

Supplemental Information

12 Compounds Approved by a Stringent Regulatory Authority (S.A.)*

COVID-19 (n=4), Influenza (n=8), Smallpox/Other Poxviruses (n=2)

Compound	Developer/Sponsor	Mechanism/Target
COVID-19		
Ensitrelvir (S-217622)	Shionogi	Protease – 3CL pro
Molnupiravir (MK-4482)	Merck & Co./Merck Sharp & Dohme (MSD), Ridgeback Biotherapeutics	Replication – RdRp
Nirmatrelvir/Ritonavir	Pfizer	Protease – 3CL pro
Remdesivir	Gilead Sciences	Replication – RdRp
INFLUENZA		
Amantadine	Novartis	Entry – Proton Channel M2
Baloxavir Marboxil	Shionogi, Roche	Replication – Endonuclease
Favipiravir**	FUJIFILM Toyama Chemical	Replication – RdRp
Laninamivir	Daiichi Sankyo, Biota Pharmaceuticals	Assembly/Release – NA
Oseltamivir	Roche	Assembly/Release – NA
Peramivir	BioCryst Pharmaceuticals	Assembly/Release – NA
Rimantadine	Allergan	Entry – Proton Channel M2
Zanamivir***	GlaxoSmithKline (GSK)	Assembly/Release – NA
SMALLPOX/OTHER POX VIRUSES		
Tecovirimat	Siga Technologies	Assembly/Release
Brincidofovir	Chimerix	Replication – DNA Polymerase

*As of July 12, 2024; WHO defined Stringent Authority (https://www.who.int/publications/m/item/list-of-transitional-wlas);
**Favipiravir also has O.N.A. approval; ***Zanamivir also has Dengue study via Investigator Sponsored Study.

9 Compounds Approved by Other National Authority (O.N.A.)*

COVID-19 (n=5), Influenza (n=0), COVID-19 & Influenza (n=3), Smallpox/Other Poxviruses (n=1)

Compound	Developer/Sponsor	Mechanism/Target
COVID-19		
Azvudine	HeNan Sincere Biotech, Zhengzhou Granlen PharmaTech, Genuine Biotech, Fosun Pharma	Replication – RdRp
Favipiravir**	Promomed, R-Pharm	Replication – RdRp
Leritrelvir (RAY1216)	Guangdong Zhongsheng Pharmaceutical	Protease – 3CL pro
Simnotrelvir/Ritonavir	Simcere Pharmaceutical, Shanghai Institute of Materia Medica (SIMM), Jiangsu Simcere Pharmaceutical	Protease – 3CL pro
Mindeudesivir (VV116)	Shanghai Junshi Biosciences	Replication – RdRp
INFLUENZA		
–	–	–
COVID-19 & INFLUENZA		
Enisamium (VR17-04)	Farmak	Replication – RdRp
Triazavirin	Medsintez Pharmaceutical	Replication – RdRp
Umifenovir	Pharmstandard	Entry – Fusion
SMALLPOX/OTHER POX VIRUSES		
NIOH-14	Vector Center	Assembly/Release

*As of July 12, 2024; WHO defined Other National Authority (https://www.who.int/publications/m/item/list-of-transitional-wlas);
**Favipiravir also has S.A. approval.

11 “Promising” Novel Clinical Antiviral Compounds*

COVID-19 (n=7), Influenza (n=2), Dengue (n=1), Polio (n=1)

Compound	Developer/Sponsor	Country	Mechanism/Target	Phase of Development	Viral Disease
EDP-235	Enanta Pharmaceuticals	U.S.	Protease – 3CL pro	2	COVID-19
GST-HG171	Fujian Cosunter Pharmaceutical	China	Protease – 3CL pro	3	COVID-19
Obeldesivir (GS-5245)	Gilead Sciences	U.S.	Replication – RdRp	3	COVID-19
Ibuzatrelvir (PF-07817883)	Pfizer	U.S.	Protease – 3CL pro	2	COVID-19
QLS1128	Qilu Pharmaceutical	China	Protease – 3CL pro	3	COVID-19
SHEN26	Kexing Biopharm	China	Replication – RdRp	2	COVID-19
STI-1558	Sorrento Therapeutics	U.S.	Protease – 3CL pro	3	COVID-19
Mosnodenvir (JNJ-1802)	Janssen Pharmaceuticals	Belgium	Replication – DENV NS4B	2	Dengue
GP681	Jiangxi Qingfeng Pharmaceutical	China	Replication – Endonuclease	3	Influenza
Onradivir (ZSP1273)	Raynovent	China	Replication – Polymerase Complex	2	Influenza
V-7404	ViroDefense, Pfizer	U.S.	Protease – EV 3C pro	1	Polio

*As of July 12, 2024

“Watch & Wait” Novel Clinical Antiviral Compounds (N=16 of 33)*

COVID-19 (n=9), Influenza (n=1), Dengue (n=1), Rhinovirus (n=1), Polio (n=1)

Compound	Developer/Sponsor	Country	Mechanism/Target	Phase of Development	Viral Disease
ALG-097558	Aligos Therapeutics	U.S.	Protease – 3CL pro	1	COVID-19
Bemnifosbuvir	Atea Pharmaceuticals	U.S.	Replication – RdRp	3	COVID-19
BIT-225**	Biotron	Australia	Assembly/Release	2	COVID-19
CDI-988	CoCrystal Pharma	U.S.	Protease – 3CL pro	1	COVID-19
GS002-02**	Gusen Pharma	China	Protease – 3CL pro	1	COVID-19
HS 10517/Ritonavir	Abbott Laboratories, AbbVie, Gilead Sciences, Jiangsu Hansoh Pharmaceutical	U.S., U.S., China	Protease – 3CL pro	2	COVID-19
IPD-52520	IAVI	U.S.	Entry	1	COVID-19
ISM036-076 PCC**	Insilico Medicine	United Arab Emirates	Protease – 3CL pro	1	COVID-19
ISM3312	Insilico Medicine	Hong Kong	Protease – 3CL pro	1	COVID-19
RQ-01	Red Queen Therapeutics	U.S.	Entry	1	COVID-19
S-892216	Shionogi	Japan	Protease – 3CL pro	1	COVID-19
WPV01/rtv	Westlake University	China	Protease – 3CL pro	1	COVID-19
EYU688	Novartis	Switzerland	Replication – NS4B	2	Dengue
CC-42344	CoCrystal Pharma	U.S.	Replication – Flu A Pol	1	Influenza
Vapendavir	Vaxart, Altesa Biosciences	U.S., U.S.	Entry – Capsid	2	Rhinovirus
Pocapavir	ViroDefense	U.S.	Entry – Capsid	1	Polio

*As of July 12, 2024; **New Addition

“Watch & Wait” Novel Clinical Antiviral Compounds (N=17 of 33)*

COVID-19 (n=8), Influenza (n=5), Lassa fever (n=2), Chapare hemorrhagic fever (n=1), Mpox (n=1)

Compound	Developer/Sponsor	Country	Mechanism/Target	Phase of Development	Viral Disease
LHF 535**	Kineta	U.S.	Entry – Fusion	1, 1	Chapare hemorrhagic fever; Lassa fever
ABBV 903	AbbVie	U.S.	Protease – 3CL pro	1	COVID-19
ASC11/Ritonavir	Ascletis Pharma	China	Protease – 3CL pro	1	COVID-19
Delcetravir	Esfam Biotech	Australia	Entry – Attachment	1	COVID-19
FB2001	Frontier Biotechnologies	China	Protease – 3CL pro	3	COVID-19
HY3000	Hybio Pharmaceutical	China	Entry – Fusion	1	COVID-19
NV-387	NanoViricides	U.S	Entry – Attachment	1	COVID-19
WPV01	Westlake University	China	Protease – 3CL pro	3	COVID-19
YKYY017	Yuekang Pharmaceutical	China	Entry – Fusion	1	COVID-19
AV5080***	Viriom	Russia	Assembly/Release – NA	2	Influenza
HNC042	Guangzhou Henovcom Bioscience Co. Ltd.	China	Assembly/Release – NA	2	Influenza
TG-1000**	TaiGen Biotechnology	Taiwan	Replication – DdRp	3	Influenza
TRX100 (AV5124)***	Traws Pharma	U.S.	Replication – Endonuclease	1	Influenza
ZX-7101A	Nanjing Zenshine Pharmaceuticals	China	Replication – Endonuclease	3	Influenza
ARN-75039	Arisan Therapeutics	U.S.	Entry – Fusion	1	Lassa fever
ASC10***	Ascletis Pharma	China	Replication – RNA Polymerase	1	Mpox

*As of July 12, 2024; **LHF535 under evaluation for two viral diseases; ***New Addition

Ribavirin has several ongoing activities in both the Clinical and Preclinical space

Clinical Studies (n=5); Preclinical Exploratory (n=10)

Viral Disease	Developer/Sponsor	Country	Mechanism/ Target	Phase of Development
COVID-19	Bausch Health	Canada, Switzerland, Japan	IMPDH1**	Phase 3
Crimean Congo hemorrhagic fever***	Bausch Health, Roche, Chugai Pharmaceutical	Canada, Switzerland, Japan	IMPDH1	Phase 2
Influenza	Bausch Health, Roche, Chugai Pharmaceutical	Canada, Switzerland	IMPDH1	Phase 2
Japanese encephalitis	Bausch Health, Roche, Chugai Pharmaceutical	Canada, Switzerland, Japan	IMPDH1	Phase 2
Lassa fever	Bausch Health, Roche, Chugai Pharmaceutical	Canada	IMPDH1	Phase 2
Argentine hemorrhagic fever	Bausch Health, Roche, Chugai Pharmaceutical	Canada, Switzerland, Japan	IMPDH1	Preclinical
Dengue	Bausch Health, Roche, Chugai Pharmaceutical	Canada, Switzerland, Japan	IMPDH1	Preclinical
Hendra virus	Bausch Health	Canada	IMPDH1	Preclinical
Human Adenovirus A-G	Bausch Health	Canada	IMPDH1	Preclinical
Lujo hemorrhagic fever	Bausch Health, Roche, Chugai Pharmaceutical	Canada, Switzerland, Japan	IMPDH1	Preclinical
Measles	Bausch Health, Roche, Chugai Pharmaceutical	Canada, Switzerland, Japan	IMPDH1	Preclinical
Nipah virus	Bausch Health, Roche, Chugai Pharmaceutical	Canada, Switzerland, Japan	IMPDH1	Preclinical
Parainfluenza	Bausch Health, Roche, Chugai Pharmaceutical	Canada, Switzerland, Japan	IMPDH1	Preclinical
Zika	Bausch Health, Roche, Chugai Pharmaceutical	Canada, Switzerland, Japan	IMPDH1	Preclinical
Mpox	Bausch Health, Roche	Canada, Switzerland	IMPDH1	Preclinical

*As of July 12, 2024; **IMPDH1: Inosine-5'-Monophosphate Dehydrogenase 1;
***A second Phase 2 study is also ongoing for ribavirin in combination with favipiravir.

Archived Antiviral Compounds* (N=18 of 28)

COVID-19 (n=18)

Viral Disease	Compound	Developer/Sponsor	Country	Mechanism/Target	Phase of Development
COVID-19	1KJ0-7	Shahid Chamran University	Iran	Protease – 3CL pro	Preclinical**
COVID-19	2ERW-9	Shahid Chamran University	Iran	Protease – 3CL pro	Preclinical**
COVID-19	Ab001	Agastiya Biotech	U.S.	Replication – Endonuclease	Preclinical**
COVID-19	AB-343	Arbutus Biopharma	U.S.	Protease – 3CL pro	Preclinical
COVID-19	Antisense Oligonucleotides	Sarepta Therapeutics	U.S.	Replication – RNA	Preclinical
COVID-19	ATV006	Guangdong Provincial Center for Disease Control and Prevention	China	Replication – RdRp	Preclinical
COVID-19	Bananin	Medsintez Pharmaceutical	Russia	Replication – Helicase	Preclinical**
COVID-19	chromone-4c	Pritzker School of Molecular Engineering	U.S.	Replication – Helicase	Preclinical**
COVID-19	Coumarin-EM04	Sambalpur University	India	Protease – 3CL pro	Preclinical**
COVID-19	GDI-4405	Jiangsu Hansoh Pharmaceutical	China	Protease – 3CL pro	Preclinical
COVID-19	GS-621763	Gilead Sciences	U.S.	Replication – RdRp	Preclinical
COVID-19	GS-6620	Gilead Sciences	U.S.	Replication – RdRp	Preclinical
COVID-19	H89	Beijing Institute of Biotechnology	China	Replication – Helicase	Preclinical
COVID-19	LMed-052	State Univ. of Londrina, Fed. Univ. of Rio de Janeiro	Brazil	Replication – RdRp	Preclinical**
COVID-19	LMed-087	State Univ. of Londrina, Fed. Univ. of Rio de Janeiro	Brazil	Replication – RdRp	Preclinical**
COVID-19	Monomethylated Triazolopyrimidine	Univ. of Hyderabad, National Inst. of Animal Biotech.	India	Replication – RdRp	Preclinical**
COVID-19	Oral nsp12 inhibitor	Arbutus Biopharma	U.S.	Replication – RdRp	Preclinical
COVID-19	PF-00835231	Pfizer	U.S.	Protease – 3CL pro	Preclinical

*As of July 12, 2024; **These compounds only have *in silico* modeling data.

Archived Antiviral Compounds* (N=10 of 28)

Influenza (n=6), and 1 each for Human Adenovirus A-G, Mpox, Parainfluenza, and SARS-CoV-1

Viral Disease	Compound	Developer/Sponsor	Country	Mechanism/Target	Phase of Development
Human Adenovirus A-G	Brincidofovir	Chimerix	U.S.	Replication – DdDp	Phase 3
Influenza	Flufirvitide-3	Autoimmune Technologies	U.S.	Entry – Flu HA	Phase 2
Influenza	Radavirsen	Sarepta Therapeutics	U.S.	Replication – Translation	Phase 1
Influenza	CD-SA cyclodextrin	University of Geneva	Switzerland	Entry	Preclinical
Influenza	Oral FluCide	NanoViricides	U.S.	Entry – Attachment	Preclinical
Influenza	STP-702	SirnaOmics	U.S.	Replication – RNA	Preclinical
Influenza	Tamiphosphor	TaiMed Biologics	Taiwan	Assembly/Release – NA	Preclinical
Mpox	Simeprevir	Johnson & Johnson Innovative Medicine	U.S.	Assembly/Release	Preclinical**
Parainfluenza	GS-441524	Gilead Sciences	U.S.	Replication – RdRp	Preclinical
SARS-CoV-1	Bananin	Medsintez Pharmaceutical	Russia	Replication – Helicase	Preclinical**

*As of July 12, 2024; **These compounds only have *in silico* modeling data.

Select References for "Promising" Novel Clinical Antiviral Compounds*

These were cited in addition to information provided by Airfinity.

Compound	Selected References
EDP-235	• Encanta Pharmaceuticals. Enanta Pharmaceuticals Announces Positive Data from a Phase 1 Clinical Study of EDP-235, its Oral 3CL Protease Inhibitor Designed for the Treatment of COVID-19. Accessed: July 29, 2022. • Encanta Pharmaceuticals. Molecular Basis for the Antiviral Action of EDP-235: A Potent and Selective SARS-CoV-2 3CLpro Inhibitor. Accessed: April 4, 2022. • Encanta Pharmaceuticals. Enanta Pharmaceuticals Reports Positive Topline Results from Phase 2 SPRINT Trial Evaluating EDP-235 in Standard Risk Patients with COVID-19. Accessed: May 8, 2023.
GST-HG171	• Zhang H, et al. Phase I study, and dosing regimen selection for a pivotal COVID-19 trial of GST-HG171. Antimicrob Agents Chemother68:e01115-23. https://doi.org/10.1128/aac.01115-23. Accessed: April 10, 2024. • ClinicalTrials.gov. Study of GST-HG171/Ritonavir Compared With Placebo in Patients With Mild to Moderate COVID-19. Accessed: April 10, 2024. • Chinese Clinical Trial Registry. A randomized, controlled clinical study to evaluate the efficacy and safety of GST-HG171 tablets in combination with ritonavir in adult subjects with mild/moderate COVID-19. Accessed: April 10, 2024.
(GS-5245)	• Anoshchenko O., et al. 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); Copenhagen, Denmark. Poster 2620. https://shorturl.at/bHJMP. Accessed: April 13-18, 2023. • Pitts J., et al. IDWeek; Boston, MA, USA. Poster 539. Efficacy in Multiple SARS-CoV-2 Animal Models Supports Phase 3 Dose Selection for Obeldesivir. https://doi.org/10.1093/ofid/ofad500.608. Accessed: November 23, 2023. • Mackman R, et al. J Med Chem. Discovery of GS-5245 (Obeldesivir), an Oral Prodrug of Nucleoside GS-441524 That Exhibits Antiviral Efficacy in SARS-CoV-2-Infected African Green Monkeys. https://doi.org/10.1021/acs.jmedchem.3c00750. Accessed: August 19, 2023. • Martinez D., et al. BioRxiv. Efficacy of the oral nucleoside prodrug GS-5245 (Obeldesivir) against SARS-CoV-2 and coronaviruses with pandemic potential. https://doi.org/10.1101/2023.06.27.546784. Accessed: June 28, 2023. • Martinez D., et al. Sci. Transl. Med. The oral nucleoside prodrug GS-5245 is efficacious against SARS-CoV-2 and other endemic, epidemic, and enzootic coronaviruses. https://doi.org/10.1126/scitranslmed.adj4504. Accessed: August 30, 2024.
Ibuzatrelvir (PF-07817883)	• Tuttle J, et al. Discovery of PF-07817883: A Next Generation Oral Protease Inhibitor for the Treatment of COVID-19. ACS First Time Disclosures (#3933296). Presented August 16, 2023. (Available to American Chemical Society members). • ClinicalTrials.gov. A Study to Understand the Effect and Safety of the Study Medicine PF-07817883 in Adults Who Have Symptoms of COVID-19 But Are Not Hospitalized. Accessed: April 10, 2024.
QLS1128	• ClinicalTrials.gov. A Phase 2 Study to Evaluate the Efficacy and Safety of QLS1128 Orally in Symptomatic Participants With Mild to Moderate COVID-19. Accessed: April 10, 2024.
SHEN26	• Chen Q., et al., Org Process Res Dev. Optimized Kilogram-Scale Synthesis and Impurity Identification of SHEN26 (ATV014) for Treating COVID-19. https://doi.org/10.1021/acs.oprd.3c00248. Accessed: November 20, 2023. • Zhou Q., et al., Signal Transduction and Targeted Therapy. Preclinical characterization and anti-SARS-CoV-2 efficacy of ATV014: an oral cyclohexanecarboxylate prodrug of 1'-CN-4-aza-7,9-dideazaadenosine C-nucleoside. https://doi.org/10.1038/s41392-023-01310-0. Accessed: January 12, 2023. • ClinicalTrials.gov. A Phase 1 Study of SHEN26 Capsule in Healthy Participants. Accessed: April 10, 2024. • ClinicalTrials.gov. Study of SHEN26 Capsule in Patients With Mild to Moderate COVID-19. Accessed: April 10, 2024.

*As of July 12, 2024

Select References for "Promising" Novel Clinical Antiviral Compounds* (cont'd)

These were cited in addition to information provided by Airfinity.

Compound	Selected References
STI-1558	• Sorrento Therapeutics. OVYDSO STI-1558. Accessed: April 10, 2024. • NIH National Library of Medicine. Olgotrelvir (sodium) | C22H29N4NaO7S | CID 166157330. Accessed: April 10, 2024. • Sorrento Therapeutics. Sorrento Releases Positive Results from a Phase 1b Study in China in COVID-19 Patients and is Ready for Pivotal Phase 3 trials with OVYDSO™ (STI-1558), an Oral Mpro Inhibitor as a Standalone Treatment for COVID-19 without the Need for Ritonavir Boosting. Accessed: January 9, 2023. • Sorrento Therapeutics. Sorrento Announces the Full Enrollment of the Pivotal Phase 3 Trial with Olgotrelvir (OVYDSOTM) (STI-1558), a Second Generation Oral Mpro Inhibitor, as a Standalone Treatment for COVID-19. Accessed: June 26, 2023. • Sorrento Therapeutics. Sorrento Announces Phase 3 Trial Met Primary Endpoint and Key Secondary Endpoint in Mild or Moderate COVID-19 Adult Patients Treated with Ovydso (Olgotrelvir), an Oral Mpro Inhibitor as a Standalone Treatment for COVID-19. Accessed: September 12, 2023.
Mosnodenvir (JNJ-1802)	• Goethals O., et al. Nature. Blocking NS3-NS4B interaction inhibits dengue virus in non-human primates. https://doi.org/10.1038/s41586-023-05790-6. Accessed: April 10, 2024. • Ackaert O., et al. Clin Infect Dis. Safety, Tolerability, and Pharmacokinetics of JNJ-1802, a Pan-serotype Dengue Direct Antiviral Small Molecule, in a Phase 1, Double-Blind, Randomized, Dose-Escalation Study in Healthy Volunteers. https://doi.org/10.1093/cid/ciad284. Accessed: April 10, 2024. • Janssen. Janssen Announces Promising Antiviral Activity Against Dengue in a Phase 2a Human Challenge Model. Accessed: October 20, 2023.
GP681	• ClinicalTrials.gov. Evaluation the Safety and Tolerance of GP681 Tablets in Healthy Subjects. Accessed: April 10, 2024. • ClinicalTrials.gov. To Assess the Efficacy of GP681 Tablet Versus Placebo in Patients With Acute Uncomplicated Influenza Virus Infection. Accessed: April 10, 2024.
Onradivir (ZSP1273)	• Chen X., et al. Pharmaceuticals (Basel). Preclinical Study of ZSP1273, a Potent Antiviral Inhibitor of Cap Binding to the PB2 Subunit of Influenza A Polymerase. https://doi.org/10.3390/ph16030365. Accessed: April 10, 2024. • Hu Y., et al. Expert Opinion on Investigational Drugs. Single and multiple dose pharmacokinetics and safety of ZSP1273, an RNA polymerase PB2 protein inhibitor of the influenza A virus: a phase 1 double-blind study in healthy subjects. https://doi.org/10.1080/13543784.2021.1994944. Accessed: April 10, 2024. • Yang Z., et al. Lancet. Safety and efficacy of onradivir in adults with acute uncomplicated influenza A infection: a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial. https://doi.org/10.1016/s1473-3099(23)00743-0. Accessed: April 10, 2024. • ClinicalTrials.gov. A Study of ZSP1273 Tablets in Patients With Acute Uncomplicated Influenza A. Accessed: April 10, 2024.
V-7404	• Kankam M., et al. American Society for Microbiology. A Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Oral Doses of V-7404 in Healthy Adult Volunteers. Accessed: April 10, 2024. • NIH GSRS. V-7404 (nih.gov). Accessed: April 10, 2024.

*As of July 12, 2024

Preclinical Antiviral Development Landscape as of July 2024

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.

INTREPID Alliance Preclinical Triage: Initial Context and Classification

- Preclinical compounds in Airfinity database:
  - Triage based on publicly available data into general therapeutic categories/mechanism
  - Airfinity provided the key references/citations associated with the preclinical compounds
- Challenges in classifying preclinical compounds:
  - Amount/Type of data available varies substantially
  - Not every "published" preclinical compound is or will be a clinical candidate
    - Tool compound, lead series, etc. in publications
- Proposed classification on type of data available consistent with industry stages of discovery R&D:
  - Preclinical compounds designated as "hit", "early lead", "late lead", "potential candidate"
  - Archived preclinical compounds lack of published data suggesting no further development; only computational-based antiviral data reported.
  - Compounds with prior clinical data designated as Approved Antiviral-Indication Expansion, Investigational Antiviral-Indication Expansion, or Repurposed (non-antiviral)

Examples of publicly available data for INTREPID review of preclinical compound/indications:

in vitro	Structure/Sequence	*in vivo* Exposure (animal)	*in vivo* Efficacy (animal)	Prior Clinical Data Available
Biochemical Cell-based (e.g., replicon, pseudovirus) Cell-based antiviral (wild-type, variants) ADME Resistance profile	Chemical structure Amino acid sequence RNA sequence	PK Safety/Toxicology	Treatment Prevention	Yes No

ADME: absorption, distribution, metabolism, and excretion; PK: pharmacokinetic

INTREPID Alliance Preclinical Triage: Stages of Preclinical Development

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.
  - **Archived** – progress on the compound has been stopped (timeframe stopped, >5 years); antiviral evidence is only computational; previously optimized drug from another antiviral/other indication that only has weak activity.
- Preclinical Exploratory are Investigational (“unapproved”) and Approved antivirals exploring antiviral activity against a different virus from the Investigational/Approved antiviral indication, including:
  - **Approved Antiviral-Indication Expansion** – antiviral approved for one or more viral disease indications
  - **Investigational Antiviral-Indication Expansion** – antiviral in clinical development, not yet approved

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

Triage of Preclinical Data Through July 2024*

- Initial triage of preclinical antiviral landscape data as of July 12, 2024, show 362 preclinical compound/indications.
- Preclinical antiviral compounds of interest are those that are directed at specific viral targets.

General Category	N	%
Antiviral	157	43
Ribavirin	10	3
Other/Excluded	195	54
TOTAL	362	100

Initial Triage

Airfinity Data by Compound/Indications

106 with confirmed antiviral mechanism of action

- 72 (68%) for COVID-19
- 34 (32%) for Non-COVID-19

2nd Triage

INTREPID Triage by Antiviral Mechanism

Preclinical Compound/Indication Category:

- Hit
- Early Lead
- Late Lead
- Approved Antiviral-Indication Expansion
- Investigational Antiviral-Indication Expansion
- Ribavirin- Indication Expansion
- Archived

Exclusion Criteria:

- Antibodies
- Antibiotics & Anti-infectives
- HIV or HCV-specific
- Host Targets (incl. Imm. Mod.)
- Natural Products/Nutraceuticals/Herbals
- Vaccines

Inclusion Criteria:

- Known Antiviral MOA
- *In Vitro/In Vivo* Activity
- Small Molecules
- Peptides
- RNA-based
- Preclinical Exposure & Efficacy
- Prior Clinical Data Available

*As of July 12, 2024

Summary of Preclinical Antiviral Landscape (July 2024)*

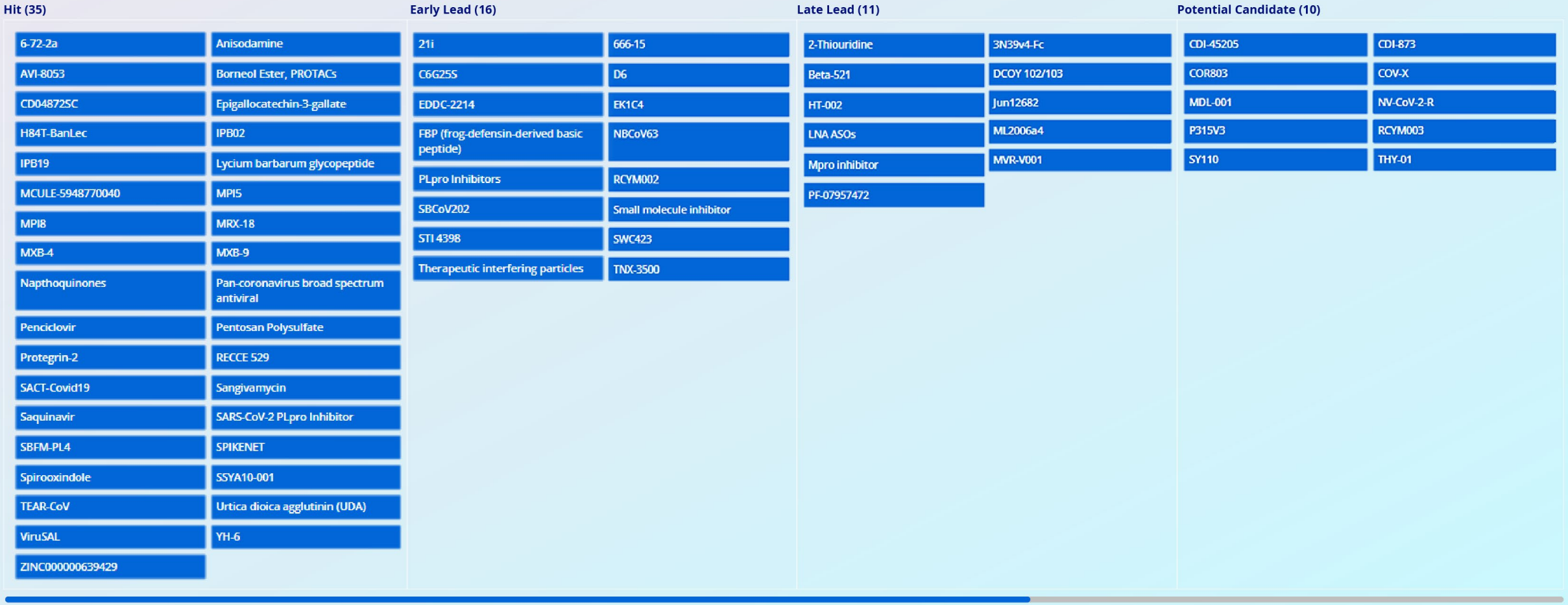
- **362** preclinical compounds/indications were evaluated from the July 2024 dataset:
  - **157** compound/indications are associated with an antiviral mechanism of action
    - **106** are ongoing with an antiviral mechanism of action and only have preclinical data or no clinical data available
      - **72** (68%) for COVID-19
      - **34** (32%) for Non-COVID-19; 12 (35.3%) of these are under evaluation for Influenza
    - **25** are Archived due to having only computational antiviral evidence and/or the compound is no longer progressing
    - **26** are Preclinical Exploratory analyses with Investigational (unapproved) or Approved antivirals
  - **10** Preclinical exploratory analyses are ongoing with ribavirin
  - The remaining **195** were primarily host-targeting (77%) or other non-antiviral mechanisms (23%)
- **Mechanism of Action** for Preclinical (106) and Preclinical Exploratory (26) Compounds:
  - In total, compounds target entry (38), protease (43), replication (48), assembly/release (2), and unspecified (1)
    - **COVID-19:** entry (25), protease (36), replication (14), assembly/release (0), and unspecified (1)
    - **Non-COVID-19**: entry (13), protease (7), replication (34), and assembly/release (2)

*As of July 12, 2024; **Some compounds are being evaluated for more than 1 viral indication.

Preclinical Compounds by Stage of Preclinical Development: COVID-19 Indications

The majority of preclinical compounds are under evaluation for SARS-CoV-2/COVID-19 (72/106, 68%).

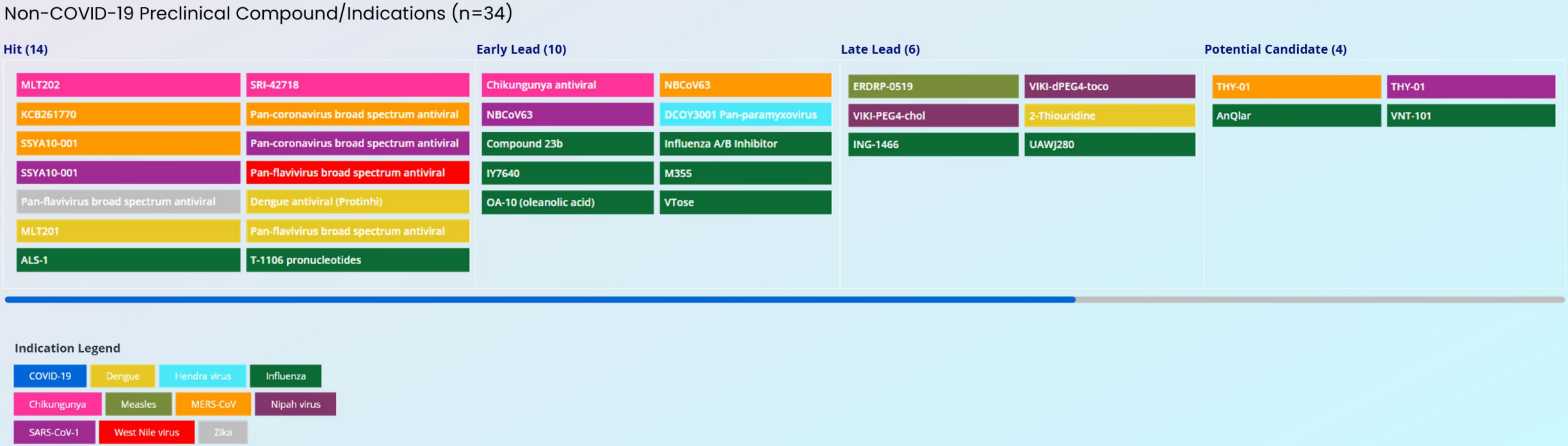
COVID-19 Preclinical Compound/Indications (n=72)



*As of July 12, 2024; Archived compounds are not included in this summary.

Preclinical Compounds by Stage of Preclinical Development: Non-COVID-19 Indications

For Non-COVID-19 preclinical compounds, Influenza has the highest number under evaluation (12/34, 35%).



*As of July 12, 2024; Archived compounds are not included in this summary.

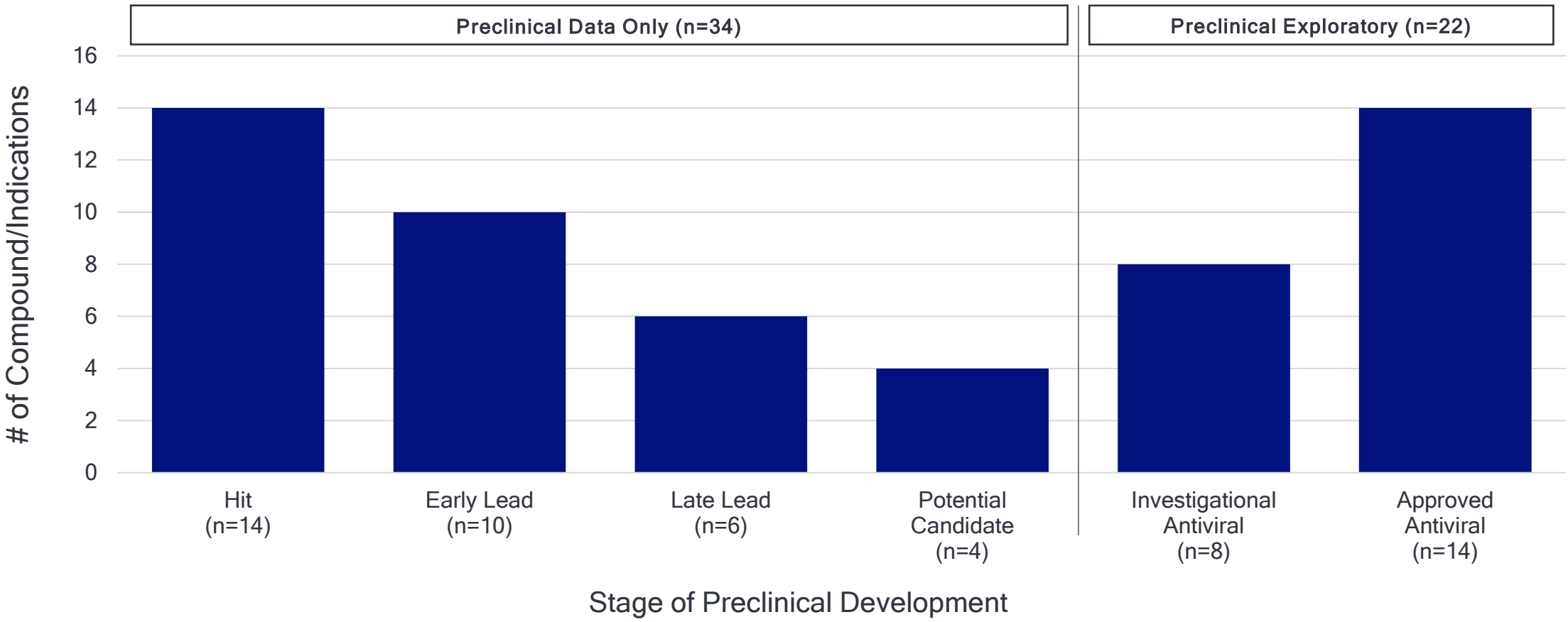
INTREPID Alliance Preclinical Antiviral Landscape: Key Takeaways

- A total of **106 preclinical antiviral compounds** under evaluation for the **13 viral families** of pandemic potential; the majority of preclinical compounds are targeting COVID-19.
  - Non-COVID-19 preclinical compounds are mostly targeting Influenza.
  - Ribavirin is being evaluated for 10 potential expanded virus indications.
- No preclinical development activity was found for 3 of the 13 viral families (*Nairoviridae, Peribunyaviridae, & Picornaviridae*).
- In view of the 100 Days Mission for Non-COVID-19 indications, there are 10 compounds (preclinical data only) at the Late Lead or Potential Candidate stage of preclinical development.
  - Influenza (n=2 potential candidates, n=2 late leads)
  - Nipah (n=2 late leads)
  - Measles & Dengue (each with 1 late lead)
  - SARS-CoV-1 & MERS-CoV (each with 1 potential candidate)

*As of July 12, 2024

Preclinical Non-COVID-19 Indications

Preclinical Compound/Indications by Stage of Preclinical Development (Non-COVID-19; N=56)*



- Compound/Indications span the various stages of preclinical development.

*As of July 12, 2024

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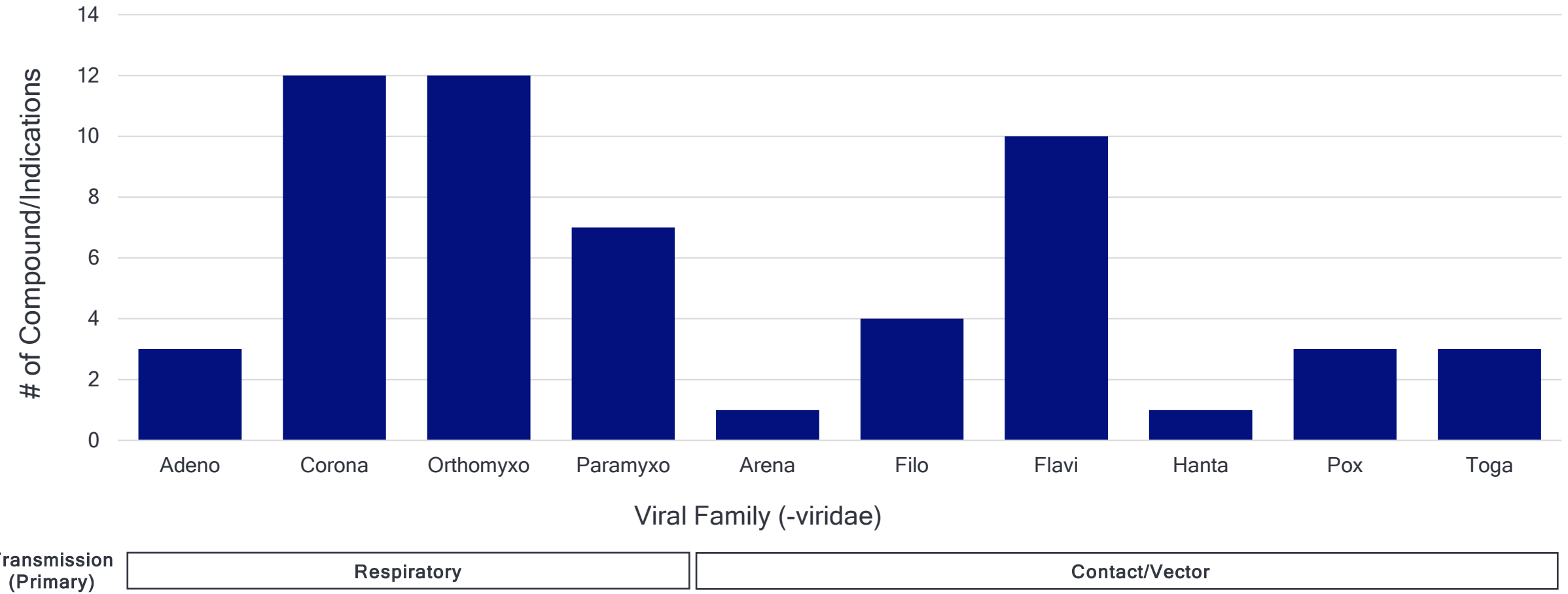
Preclinical Compound/Indications by Viral Family (Non-COVID-19; N=56)*



- Ten of the 13 viral families with pandemic potential have preclinical compound/indications.
  - *Orthomyxoviridae* has the most compounds and is focused on Influenza.

*As of July 12, 2024

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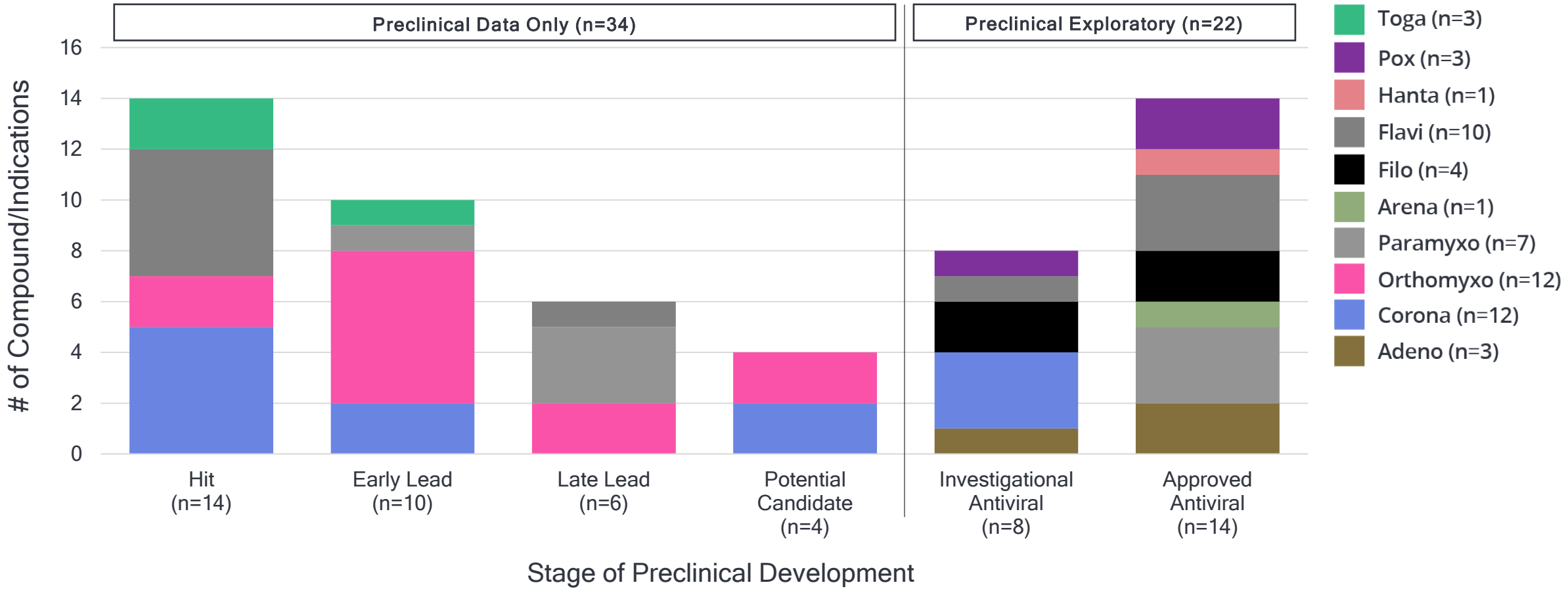
Preclinical Compound/Indications by Stage of Preclinical Development and Viral Family (Non-COVID-19; N=56)*



- Compound/Indications span the various stages of preclinical development.
- *Orthomyxoviridae* (Influenza) has the most compound/indications.

*As of July 12, 2024

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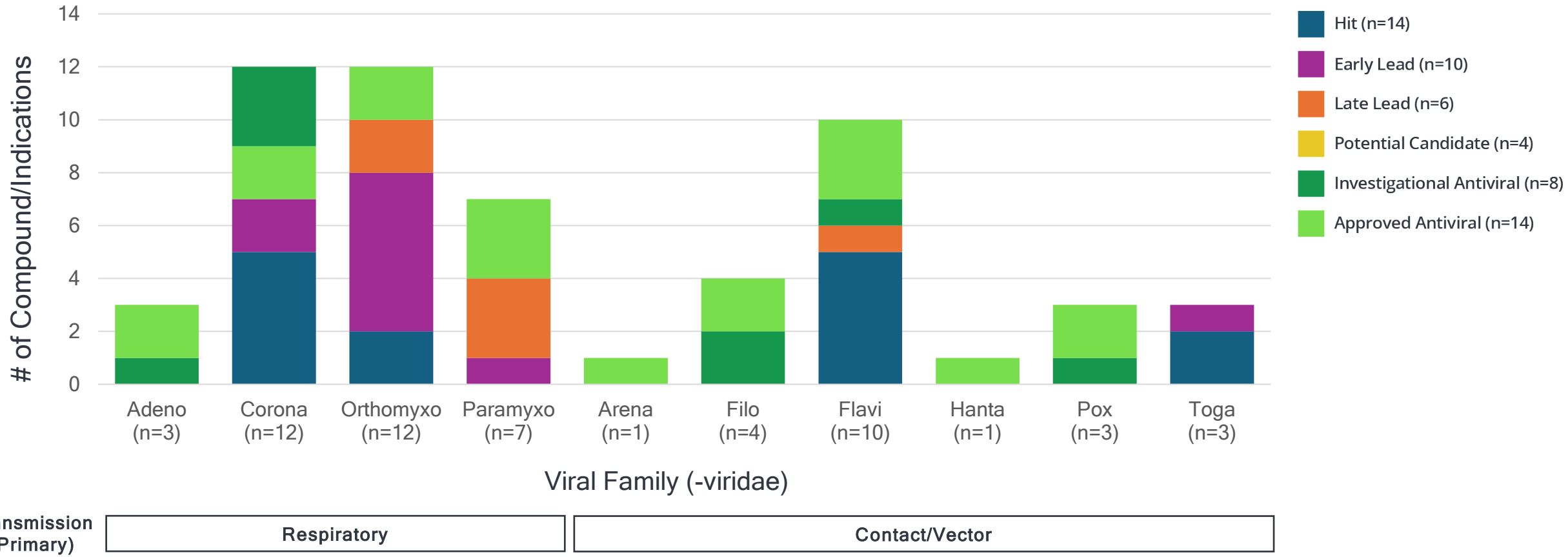
Preclinical Compound/Indications by Viral Family and Stage of Preclinical Development (Non-COVID-19; N=56)*

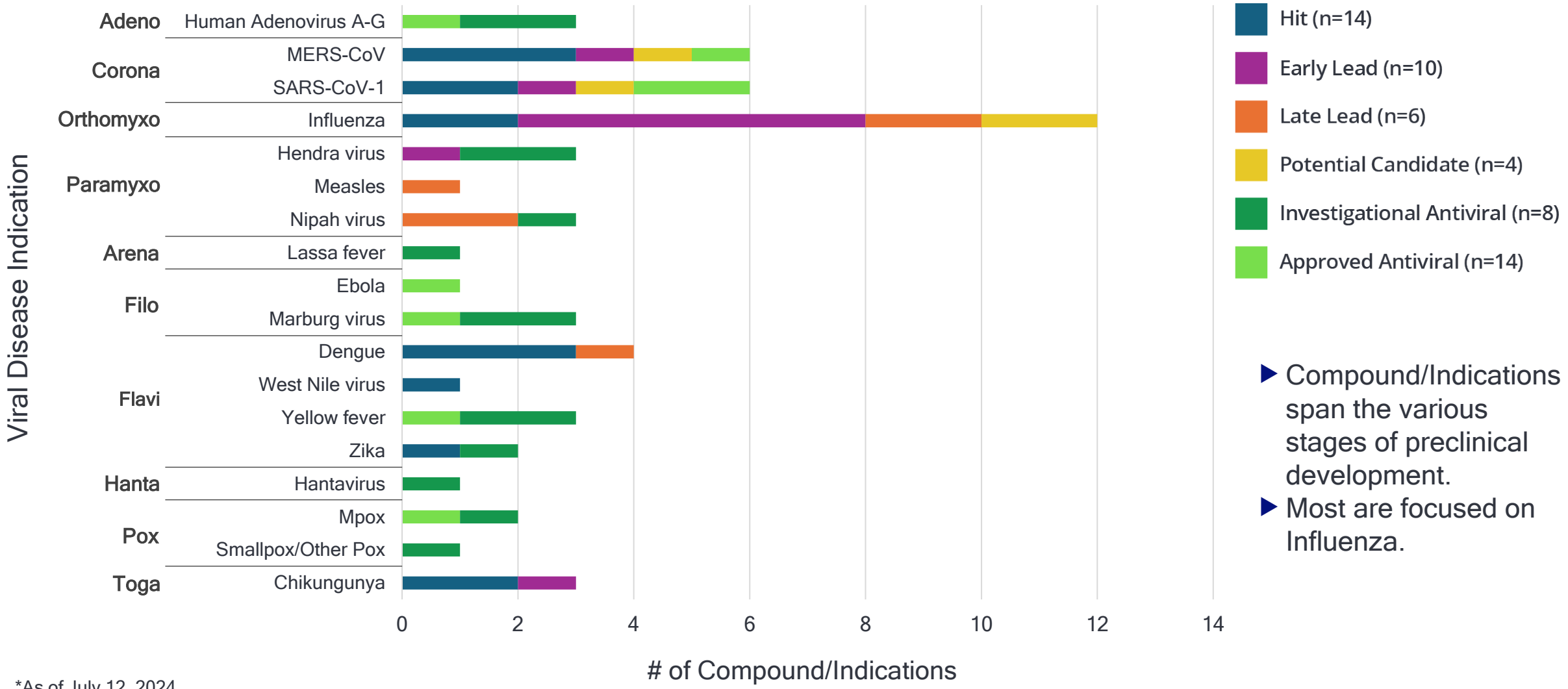


- Compound/Indications span the various stages of preclinical development.
- The majority (12/46, 27%) are focused on *Orthomyxoviridae* (Influenza).

*As of July 12, 2024

INTREPID ALLIANCE

Preclinical Compound/Indications by Viral Disease and Stage of Preclinical Development (Non-COVID-19; N=56)*

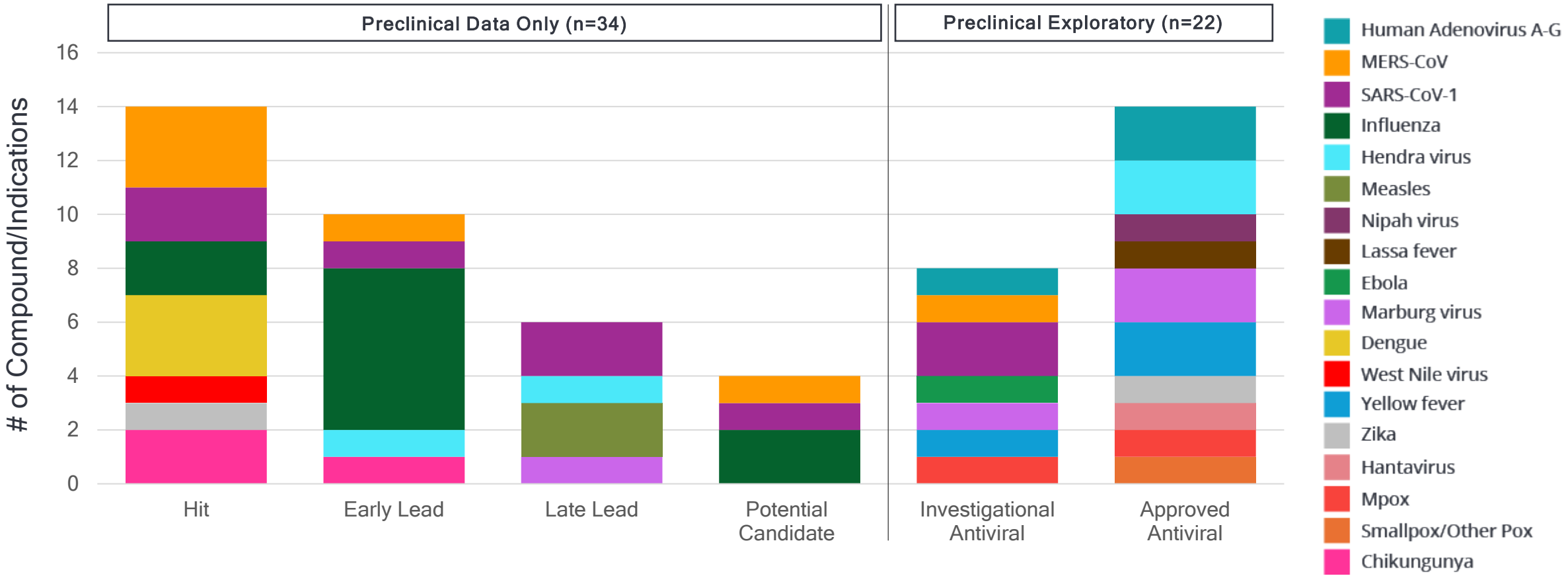


- Compound/Indications span the various stages of preclinical development.
- Most are focused on Influenza.

*As of July 12, 2024

INTREPID ALLIANCE

Preclinical Compound/Indications by Stage of Preclinical Development and Viral Disease (Non-COVID-19; N=56)*

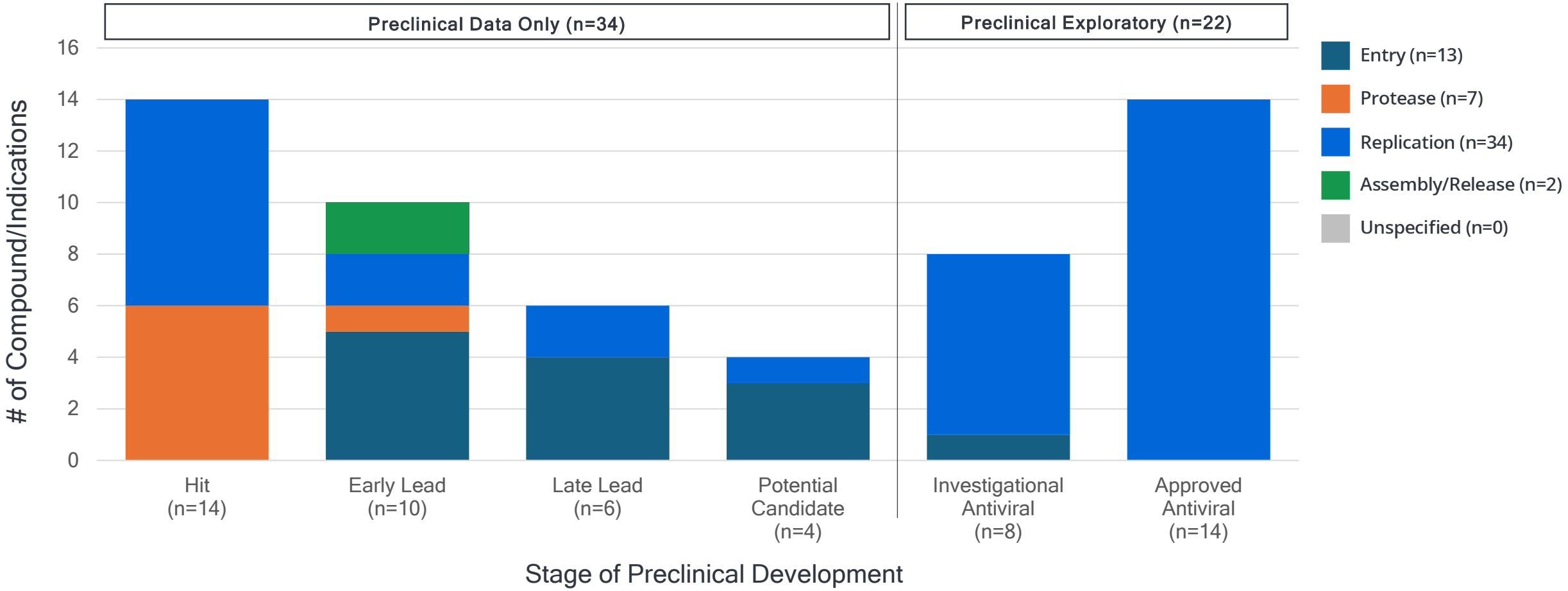


- Compound/Indications span the various stages of preclinical development.
- Most are focused on Influenza.

*As of July 12, 2024

INTREPID ALLIANCE

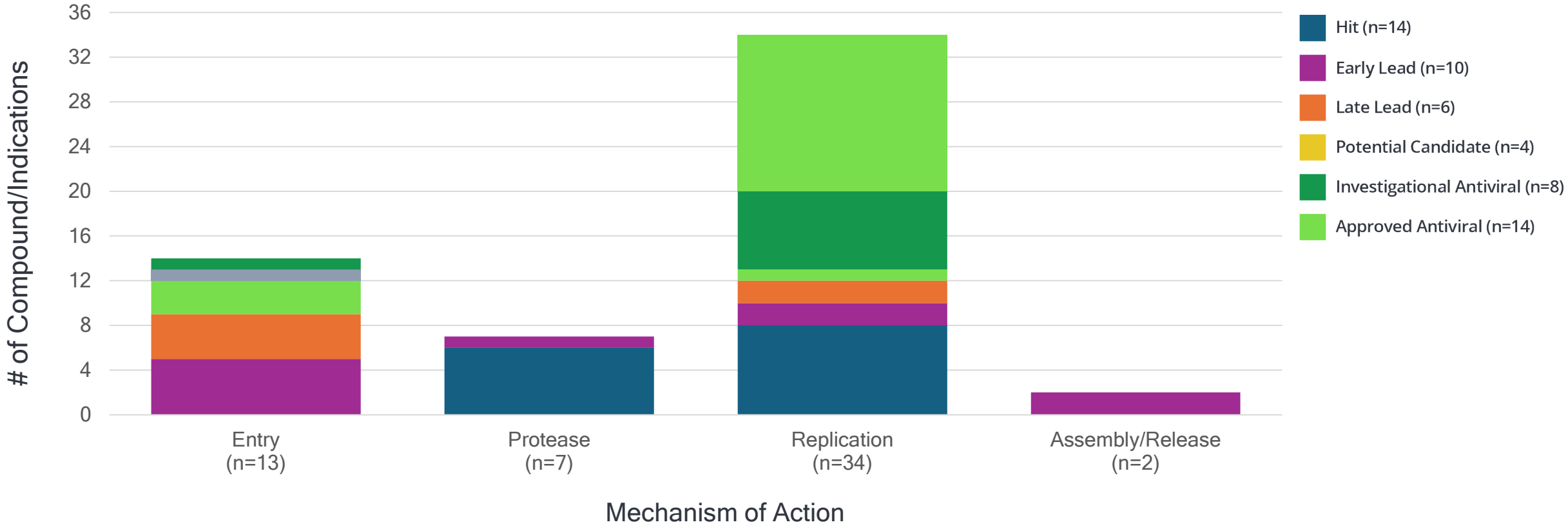
Preclinical Compound/Indication Category by Stage of Preclinical Development and Mechanism of Action (Non-COVID-19; N=56)*



- MOAs for Compound/Indications span the various stages of preclinical development.
- The majority of Approved or Investigational Antivirals for indication expansion are replication inhibitors.

*As of July 12, 2024

Preclinical Compound/Indication Category by Mechanism of Action and Stage of Preclinical Development (Non-COVID-19; N=56)*

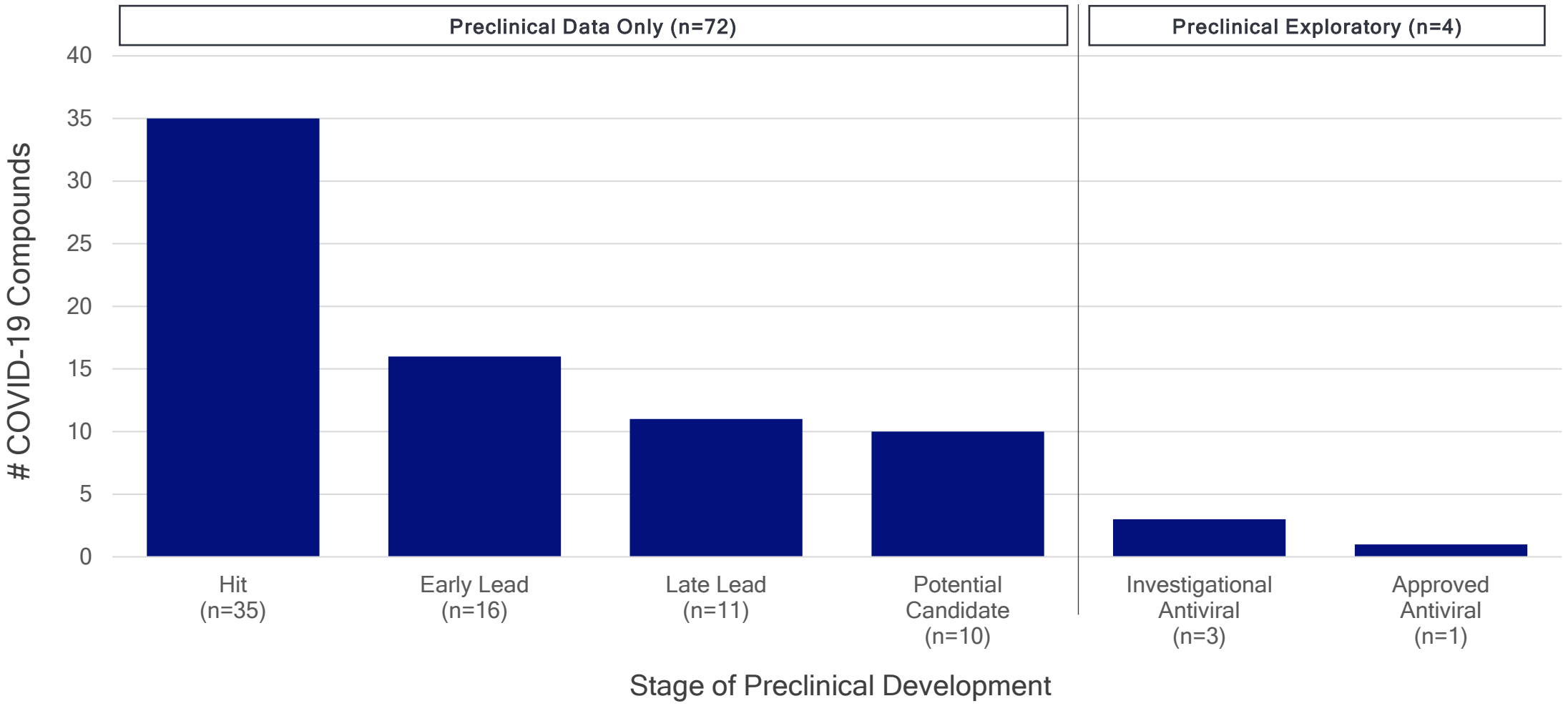


- Compound/Indications span the various stages of preclinical development and MOAs.
- The MOA rank order is Replication, Entry, Protease, Assembly/Release.

*As of July 12, 2024

Preclinical COVID-19 Indications

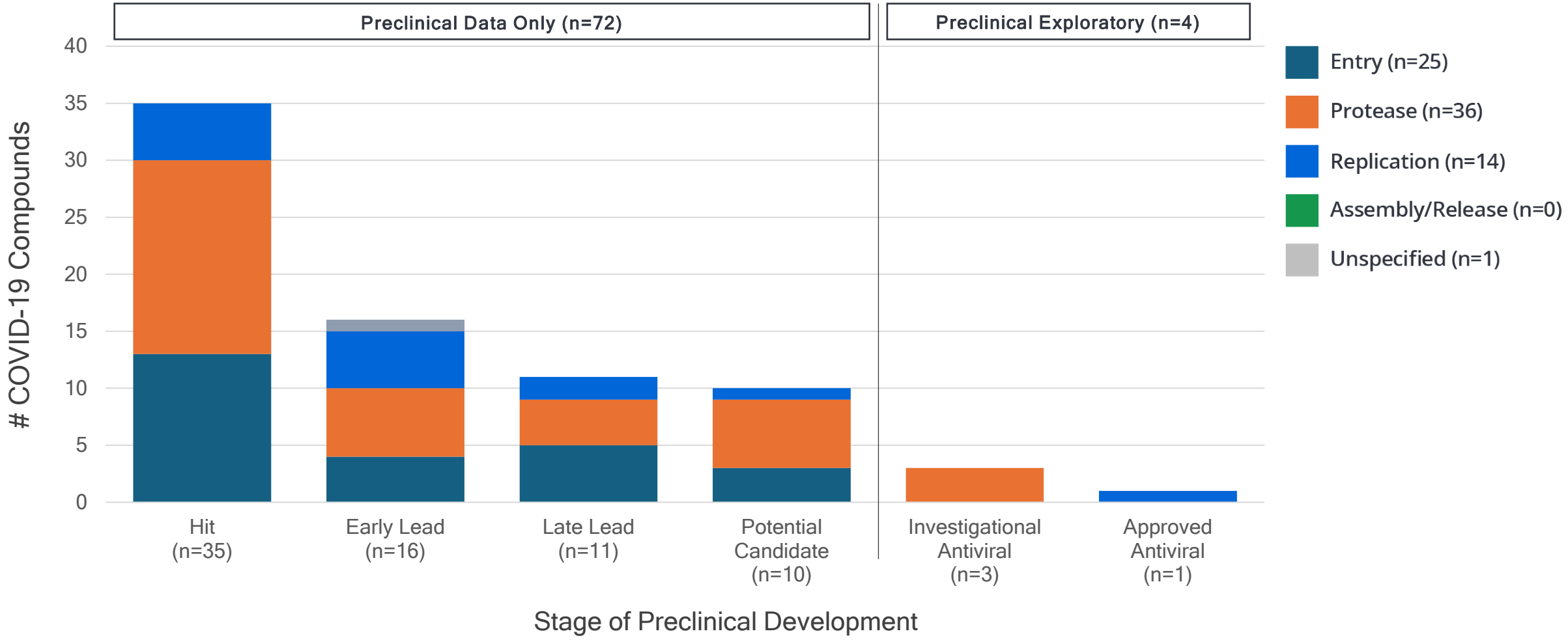
COVID-19 Compounds by Stage of Preclinical Development (N=76)*



*As of July 12, 2024

INTREPID ALLIANCE

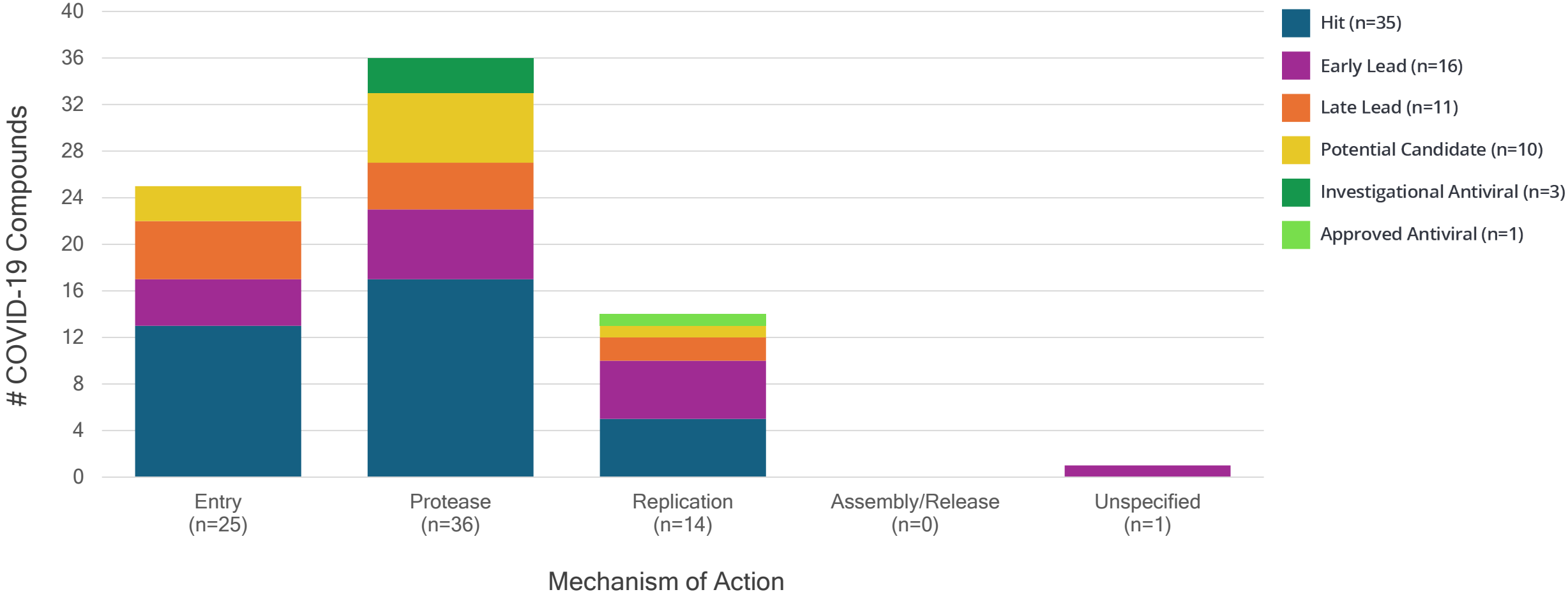
COVID-19 Compounds by Stage of Preclinical Development and Mechanism of Action (N=76)*



*As of July 12, 2024

INTREPID ALLIANCE

COVID-19 Compounds by Mechanism of Action and Stage of Preclinical Development (N=76)*



*As of July 12, 2024

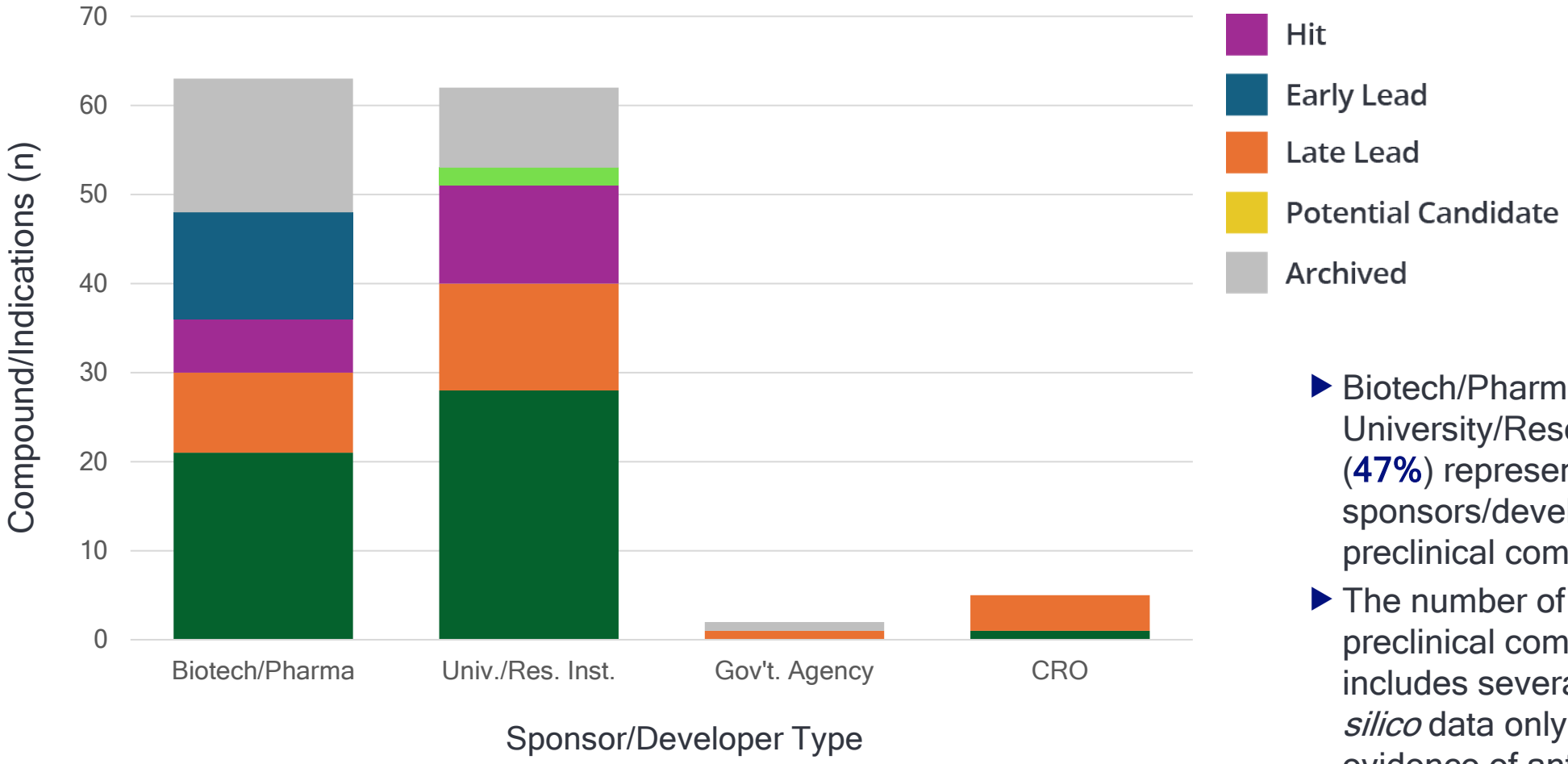
Preclinical Antiviral Sponsors and Developers

Preclinical Antiviral Landscape: Sponsors & Developers*

- Biotech/Pharma and University/Research Institutes represent the majority of sponsors/developers for preclinical compound/indications.
  - As programs move towards Potential Candidate, the relative contribution of sponsors/developers shifts more towards Biotech/Pharma. This is consistent with the increased resources needed to prepare for regulatory submissions and entry into clinical development.
- Sponsors/Developers of preclinical antiviral compound/indications are located in **27** countries across **5** of the 6 WHO-Regions.
  - The majority (**80.5%**) are located in countries with high-income economies.
  - The remainder have upper-middle income (**18.7%**) or lower-middle income (**0.8%**) economies.
- The United States (WHO Americas; High income) and China (WHO Western Pacific; Upper-middle income) have the most representation.

*As of July 12, 2024

Preclinical Antiviral Compound/Indications by Sponsor/Developer Type (N=131)*

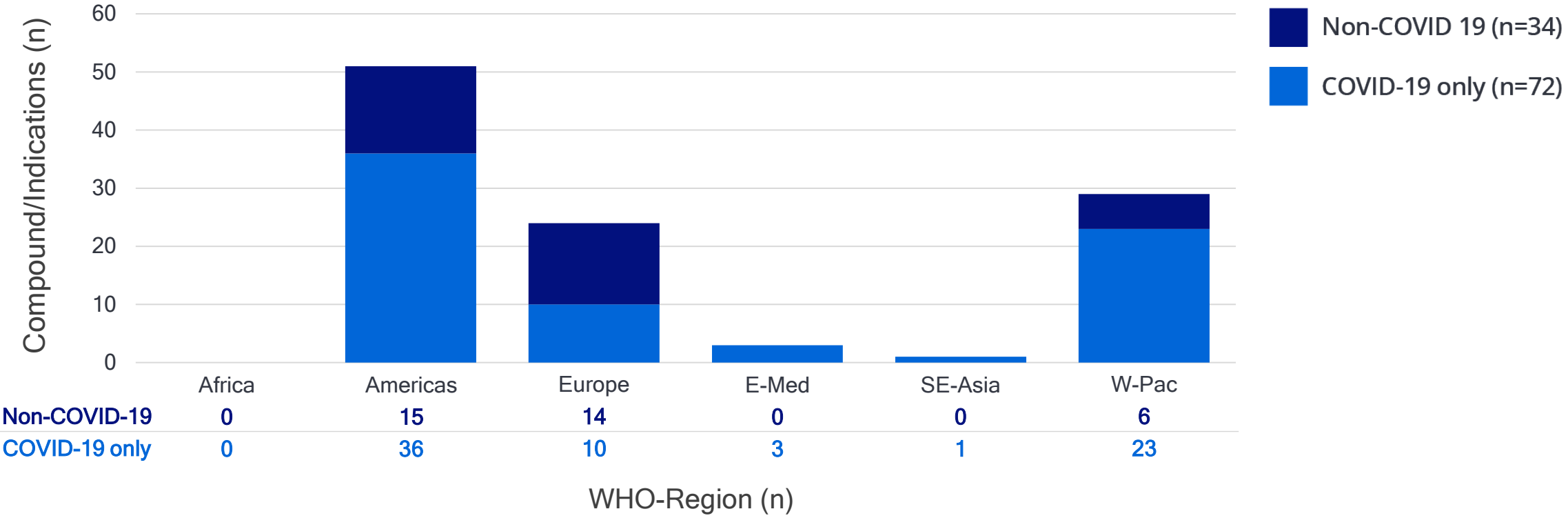


- Biotech/Pharma (**48%**) and University/Research Institutes (**47%**) represent the majority of sponsors/developers for preclinical compound/indications.
- The number of Archived preclinical compound/indications includes several that have *in silico* data only; no direct evidence of antiviral activity.

*As of July 12, 2024

Preclinical Antiviral Compound/Indications by Sponsor/Developer WHO-Region*

(COVID-19 only and Non-COVID-19; N=106)

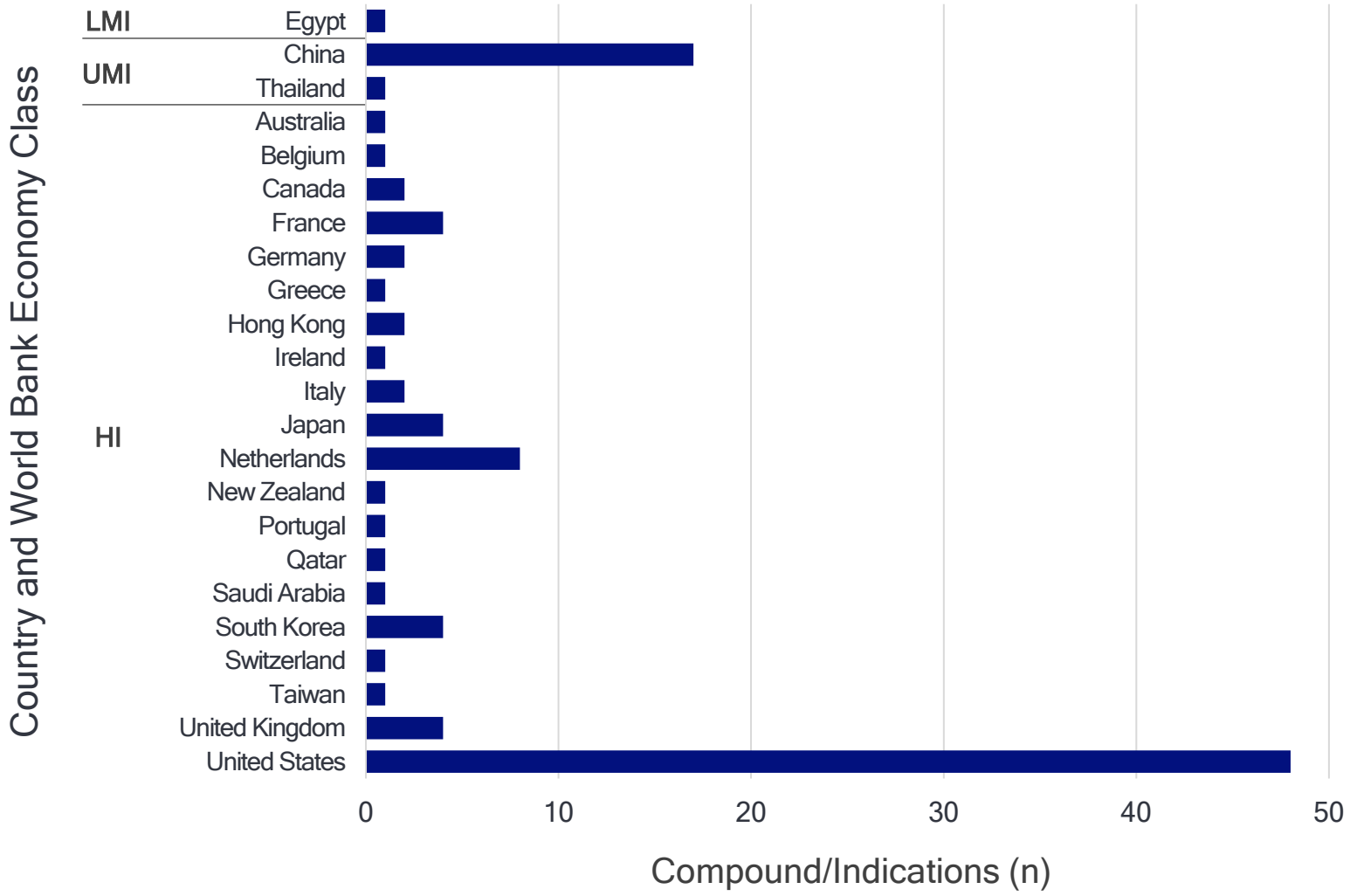


	Africa	Americas	Europe	E-Med	SE-Asia	W-Pac
Non-COVID-19	0	15	14	0	0	6
COVID-19 only	0	36	10	3	1	23

- There are twice as many COVID-19-specific versus Non-COVID-19 preclinical compound/indications.
  - COVID-19-specific: 90 are located in 5 of the 6 WHO-Regions.
  - Non-COVID-19-specific: 41 are located in 3 of 6 WHO-Regions.
- The Americas and Western Pacific regions are primarily driven by the United States and China.

*As of July 12, 2024; excludes Archived

Promising and Watch & Wait Clinical Antiviral Compound/Indications* by Country and World Bank Economy Class**



- The majority (**82.5%**) of sponsors/developers of are located in countries with high-income economies.
  - The remainder are those with upper-middle income (**16.5%**) or lower-middle income (**0.9%**) economies.
- The United States (HI) and China (UMI) have the most representation.

*As of July 12, 2024; ** **World Bank country classifications by income level for 2024-2025; LMI: lower-middle income; UMI: upper-middle income; HI: high-income

Preclinical & Clinical Development Landscape for Mpox & Poxviruses

Preclinical and Clinical Development Landscape for Mpox and Poxviruses

- 2 antivirals approved by Stringent Regulatory Authority (U.S., EU) and 1 by Other National Authority (Russia) for the treatment of human smallpox disease.
- For the treatment of Mpox disease, 1 antiviral is approved by a Stringent Regulatory Authority (EU) and permitted for emergency use to treat Mpox in the U.S.

Assembly/Release

Tecovirimat (oral; IV)

- Adults and pediatric
- Oral tablet, twice daily for 14 days
- Approved for Smallpox (U.S., EU)
- Approved for Mpox (EU)
- Expanded Access-Investigational New Drug (EA-IND) protocol for Mpox (U.S.)

NIOCH-14 (oral; Russia only)

Replication

Brincidofovir

- Adults and pediatric
- Oral tablet, oral suspension, once weekly for two doses
- Approved for Smallpox (U.S., Canada)
- FDA-authorized single-patient emergency use IND (e-IND) for Mpox (U.S.)

- Relatively small number of established oral [antiviral] treatment options for Mpox disease
- Potential need for additional classes of oral drugs with complementary MOA
- Vaccination is only available option for prophylaxis; pre- and post-exposure prophylaxis (PrEP & PEP)
- Preparedness must consider manufacturing time and stability; stockpiling is common and may vary between countries

Compound/Indications for Poxviridae* by Stage of Development

Compound	Developer/Sponsor	Developer Country	Poxviridae Indication(s)	Mechanism of Action	Category
Approved Antiviral					
NIOH-14	Vector Center	Russia	Smallpox/Other Poxviruses	Assembly/Release	Approved – O.N.A.
Tecovirimat (oral)	Siga Technologies	United States	Smallpox/Other Poxviruses	Assembly/Release	Approved – S.A.
Tecovirimat (oral; IV)	Siga Technologies	United States	Mpox	Assembly/Release	Approved – S.A.
Brincidofovir	Chimerix	United States	Smallpox/Other Poxviruses	Replication	Approved – S.A.
Phase 1					
ASC10	Ascletis Pharma	China	Mpox	Replication	Watch & Wait
Preclinical					
Cidofovir	Chimerix, Emergen BioSolutions	United States	Mpox	Replication	Approved Antiviral-Indication Expansion
Cidofovir	Chimerix, Emergen BioSolutions	United States	Smallpox/Other Poxviruses	Replication	Approved Antiviral-Indication Expansion
Simeprevir	Johnson & Johnson Innovative Medicine	United States	Mpox	Assembly/Release	Archived – in silico data only
NV-387-T	NanoViricides	United States	Mpox	Entry	Investigational Antiviral-Indication Expansion
Ribavirin	Bausch Health, Roche	Canada, Switzerland	Mpox	IMPDH	Ribavirin-Indication Expansion
CP-COV03 (Niclosamide)	University of California Berkeley, Hyundai Bioscience	United States, South Korea	Mpox	Anthelmintic	Anthelmintic
Nitroxoline	Goethe University Frankfurt	Germany	Mpox	Antibiotic	Antibiotic
Brilacidin	Innovation Pharmaceuticals	United States	Mpox	Antibiotic	Antibiotic
Sabizabulin	Veru	United States	Smallpox/Other Poxviruses	Host Target	Host Target
Naldemedine	Shionogi	Japan	Mpox	Host Target	Host Target
Lixivaptan	Centessa Pharmaceuticals	United Kingdom	Mpox	Host Target	Host Target
Fosdagrocorat	Pfizer	United States	Mpox	Host Target	Host Target

*As of July 12, 2024

Glossary of Terms

- **ADME:** absorption, distribution, metabolism, and excretion
- **Approved Antiviral-Indication Expansion**: antiviral approved for one or more viral disease indications (e.g., cidofovir, favipiravir, molnupiravir, remdesivir, valganciclovir)
- **'Archived' Compound**: clinical compound where development has paused or no recent information available from the past 5 years
- **CMC:** chemistry, manufacturing, and controls
- **'Exclude' Compound**: clinical compound with known disqualifying data related to safety and tolerability, efficacy, developability, chemical structure, etc.
- **FIH**: first-in-human
- **Investigational Antiviral-Indication Expansion**: antiviral in clinical development, not yet approved (e.g., AT-752, filociclovir, galidesivir, GC736, GRL0167, NV-387-T, obeldesivir, & rupintrivir)
- **PD:** pharmacodynamic
- **PK:** pharmacokinetic
- **POC**: proof-of-concept

Glossary of Terms (cont'd)

- **Preclinical Compounds with only preclinical data and no clinical data:**
  - **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.
  - **Archived** – progress on the compound has been stopped (timeframe stopped, 5 years); antiviral evidence is only computational; previously optimized drug from another antiviral/other indication that only has weak activity.
- **Preclinical Exploratory**: Investigational ("unapproved") and Approved antivirals exploring antiviral activity against a different virus from the Investigational/Approved antiviral indication
- **'Promising' Compound**: clinical compound that aligns with 100 Days Mission goals and/or has been registered and approved for established viral diseases
- **'Watch & Wait' Compound**: clinical compound that has FIH or POC studies just starting/ongoing or data are available for a completed study or unable to make a data-driven evaluation at the time of the analysis

INTREPID ALLIANCE

INTERNATIONAL READINESS FOR PREVENTING INFECTIOUS VIRAL DISEASE

Interested in engaging with us?

We welcome all feedback through our online portal. As with previous listings, developers are invited to submit non-confidential information on their compound candidates. All reports are updated quarterly.

For more information, contact nina@intrepidalliance.org.

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