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Coronavirus Antiviral Research Database (CoV-RDB): An Online Database Designed to Facilitate Comparisons Between Candidate Anti-Coronavirus Compounds

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Abstract: Background: To prioritize the development of antiviral compounds, it is necessary to compare their relative preclinical activity and clinical efficacy. Methods: We reviewed *in vitro*, animal model, and clinical studies of candidate anti-coronavirus compounds and placed extracted data in an online relational database. Results: As of July 2020, the Coronavirus Antiviral Research Database (CoV-RDB; covdb.stanford.edu) contained >2,400 cell culture, entry assay and biochemical experiments, 240 animal model studies, and 56 clinical studies from >300 published papers. SARS-CoV-2, SARS-CoV, and MERS-CoV account for approximately 85% of the data. Approximately 75% of experiments involved compounds with a known or likely mechanism of action, including receptor binding inhibitors and monoclonal antibodies (20%); viral protease inhibitors (18%); polymerase inhibitors (9%); interferons (8%); fusion inhibitors (8%); host endosomal trafficking inhibitors (7%); and host protease inhibitors (5%). For 724 compounds with a known or likely mechanism, 95 (13%) are licensed in the US for other indications, 72 (10%) are licensed outside the US or are in human trials, and 557 (77%) are pre-clinical investigational compounds. Conclusion: CoV-RDB facilitates comparisons between different candidate antiviral compounds, thereby helping scientists, clinical investigators, public health officials, and funding agencies prioritize the most promising compounds and repurposed drugs for further development.

Keywords: Coronavirus; COVID-19; SARS-CoV-2; SARS-CoV; MERS-CoV; Antiviral therapy

1. Introduction

The Coronavirus Antiviral Research Database (CoV-RDB) is designed to promote uniform reporting of experimental results; to facilitate comparisons between different candidate antiviral compounds; and to help scientists, clinical investigators, public health officials, and funding agencies prioritize the most promising compounds and repurposed drugs for further development. By comprehensively reviewing published laboratory, animal model, and clinical data on potential coronavirus therapies, CoV-RDB makes it unlikely that promising treatment approaches will be overlooked. In addition, by making it possible to compare the underlying data associated with competing treatment strategies, stakeholders will be better able to prioritize the most promising anti-coronavirus compounds for further development.

2. Methods / Results

CoV-RDB contains four main types of antiviral experimental data, six main lookup/explanation tables, and a registry of ongoing or planned clinical trials. The four main types of antiviral experimental data include (i) cell culture and entry assay experiments; (ii) biochemical experiments; (iii) animal model studies; and (iv) clinical studies. The six main lookup/explanation tables provide information on viruses, virus strains/isolates, tested compounds, compound targets, cell types, and animal models.

CoV-RDB data are stored in a PostgreSQL relational database but there is not necessarily a one-to-one relationship for the tables displayed on the web and their underlying database structure. Indeed, several of the website tables contain information from more than one underlying database table. As of July 12, 2020, the CoV-RDB contains data from more than 1,500 virus cell culture experiments, 417 entry assay experiments, 431 biochemical experiments, 241 animal model studies, and 56 clinical studies from more than 260 peer-reviewed publications and 70 preprints. The following sections describe the purpose and contents of each of the CoV-RDB tables displayed on the web.

2.1. Experimental Data Tables

2.1.1. Cell culture and entry assay experiments

The cell culture experiments table contains 13 fields, including four fields present in each of the experiment tables: reference; compound; virus category; and virus isolate/strain. The nine fields unique to the cell culture experiments table include six that describe experimental conditions and three that contain experimental results. The six experimental conditions include the (i) cells used for antiviral testing; (ii) multiplicity of infection (MOI; the virus titer divided by the number of cells); (iii) time between addition of drug and addition of virus; (iv) drug concentration(s); (v) duration of virus infection; and (vi) indicator of virus replication.

The three experiment results are the half-maximal effective concentration (EC_{50}), percent inhibition, and the 50% cytotoxic concentration (CC_{50}). The EC_{50} can only be determined using a series of compound dilutions. While the EC_{50} is usually reported as μM, inhibitory activity for interferons is also often reported as international units (IU)/ml and inhibitory activity for monoclonal antibodies is often reported as ng/ml. The EC_{50} is available for the vast majority of *in vitro* cell culture experiments. However, for a few experiments, the experimental setup involved a single compound concentration (rather than a dilution series). For these experiments, the percent virus inhibition with the single compound concentration is reported.

There are two tables for entry assay experiments – one for pseudovirus entry assays and another for cell-cell fusion assays. The pseudovirus assay table contains the following six unique fields: (i) pseudovirus vector; (ii) pseudovirus number; (iii) target cell type; (iv) time to addition of drug; (v) indicator of virus replication; and (vi) EC_{50}. In the pseudovirus experiments, the virus strain is a virus construct composed of a virus that does not require a BSL-3 laboratory, such as vesicular stomatitis virus (VSV) or HIV-1, into which the coronavirus S gene has been cloned. This construct also has a reporter gene such as luciferase or GFP. The cell-cell fusion assay table contains the following seven unique fields: i) effector cell type; (ii) effector cell number; (iii) target cell type; (iv) target cell number; (v) time to addition of drug; (vi) indicator of virus replication; and (vii) EC_{50}.

2.1.2. Biochemical experiments

The biochemical experiments table contains two unique fields: the biochemical target and the half maximal inhibitory concentration (IC_{50}). The biochemical target is usually one of the virus enzymes including RNA-dependent RNA polymerase (RdRp), Main protease (also called 3Cl protease; 3CLpro), papain-like protease (PLpro), and helicase. However, cell-free assays that test inhibitors of the spike (S) protein binding to ACE2 are also included.

2.1.3. Animal model studies

The animal model experiments are characterized by comparisons between a group of animals receiving a treatment intervention either shortly before or after virus infection and a group of untreated virus-infected control animals. The animal model experiments table has two parts –experimental conditions and experimental results. The experimental conditions include the (i) animal model; (ii) size and route of virus challenge; (iii) treatment intervention; (iv) treatment dosage; (v) treatment timing in relation to the addition of virus; (vi) number of treated subjects; and (vii) number of control subjects. The experimental results, which are often depend on the study include endpoints such as mortality, weight loss, fever, respiratory rate, lung pathology, and virus load measurements. The reduction of endpoint severity is reported on an ordinal scale ranging from 0 to 3.

There are more than 50 references containing more than 240 animal model experiments, nearly all involving SARS-CoV-2, SARS-CoV, or MERS-CoV. Approximately 62% of studies involve mice, 21% involve non-human primates (rhesus macaques, marmosets, and cynomolgus macaques), and 16% involve hamsters, ferrets, or rabbits. The most commonly studied interventions have included monoclonal antibodies, fusion inhibitors, interferons, and the nucleoside analogs remdesivir and EIDD-2801.

2.1.4. Clinical studies

The clinical studies are represented using several enumerated and free text fields. The enumerated fields include the reference, virus category, and type of study (e.g., observational, randomized trial, randomized placebo-controlled trial). The free text fields include descriptions of the interventions and regimen details, the study population and methods, and the study findings. CoV-RDB does not provide an assessment of study quality such as validity and risk of bias as there are other research groups providing this type of assessment.

2.2. Lookup/Explanation Tables

2.2.1. Virus categories

Antiviral data on coronaviruses other than SARS-CoV-2 provide insight into the robustness of an antiviral compound in that compounds that are active against multiple viral species will be more likely to inhibit future pandemic coronaviruses and will be less vulnerable to the development of drug-resistance mutations. Indeed, for many drug targets, such as the virus RdRp and 3CLpro enzymes and for host processes upon which coronaviruses depend, inhibitory compounds may have broad-spectrum activity.

CoV-RDB contains antiviral data for six categories of coronaviruses: SARS-CoV-2, SARS-CoV, MERS-CoV, endemic human coronaviruses, bat coronaviruses, and non-bat mammalian coronaviruses. SARS-CoV (35%), SARS-CoV-2 (31%), and MERS-CoV (19%) accounted for 85% of the data. However, the proportion of data associated with SARS-CoV-2 is rapidly increasing. Figure 1 shows the distribution of study types for SARS-CoV, SARS-CoV-2, and MERS-CoV.

SARS-CoV and SARS-CoV-2 belong to the same betacoronavirus 2b (sarbecovirus) clade and their amino acids are approximately 97% identical in the RdRp and 3CLpro enzymes and 84% identical in the spike protein. In contrast, MERS, a clade 2c betacoronavirus, is approximately 75% identical to SARS-CoV and SARS-CoV-2 in the RdRp gene, 60% identical in the 3CLpro gene, and 40% identical in the spike gene. Within each of these three viruses, there is little diversity, with median pairwise distances ranging between 0 and 0.2%.

The four endemic human coronaviruses include two clade 2a betacoronaviruses and two alphacoronaviruses. Bat coronaviruses are distributed widely among different clades [1,2]. Indeed, 4 of the 9 betacoronavirus clades and 7 of 11 coronavirus clades are found only in bats. The mammalian coronaviruses include murine hepatitis virus (MHV), which is a longstanding experimental model for coronavirus infection, and several other coronaviruses that have been studied because they are important livestock diseases [3]. Although infectious bronchitis virus is an avian gammacoronavirus, we have included in the non-bat mammalian coronavirus category.

2.2.2. Virus isolates/strains

CoV-RDB uses the terms isolate and strains to describe the different viruses used in antiviral studies, although strains is usually reserved for describing isolates that have distinct phenotypic properties [4]. Where possible, isolates are named according to the recommendations from the International Committee on Taxonomy of Viruses [5], i.e. virus/host/location/isolate/date.

Most SARS-CoV-2 isolates are nearly identical to one another with the upper limit for the pairwise amino acid distance being about 0.1%, although this number varies depending upon the gene [6]. Therefore, the biological significance of the isolate used for a particular study is not known. However, for some treatments such as monoclonal antibodies, changes in the sequence encoding the relevant epitope, specifically in the S protein receptor binding domain may prove to have biological and clinical significance. Although SARS-CoV resulted from at least two zoonotic introductions from civet cats [3] and although MERS-CoV resulted from multiple zoonotic introductions from dromedary camels, these viruses also demonstrate little genetic variability.

Several of the most commonly used isolates have been cloned, either as intact viruses (e.g. by plaque purification or limiting dilution) or by constructing a cDNA copy representing a single sequence variant. Modification of these clones, such as selection of a resistant variant *in vitro* [7] or introduction of a reporter gene like GFP or luciferase, presumably retain the characteristics of the original parental virus isolate or strain [8]. Commonly used isolates that have been cloned and manipulated in the laboratory include MERS-CoV/human/Amsterdam/EMC/2012 [9], SARS-CoV/human/Hanoi/Urbani/2003 [10], SARS-CoV-2/human/USA/WA1/2020 [11] and SARS-CoV-2/human/Munich/929/2020 [12].

2.2.3. Target

The target table has two main fields: name and description. The target classification organizes drugs, treatments and compounds according to the virus or host process targeted by a compound. There are three virus enzyme inhibitor classes, including RdRp [13–16], protease (including 3CLpro, PLpro) [17–21], and helicase inhibitors [22]. There are three entry inhibitor classes including monoclonal antibodies [23–35], non-monoclonal antibody receptor binding inhibitors [36], and fusion inhibitors [37,38]. Monoclonal antibodies are treated differently because they are more potent than other drug classes and are often accompanied by additional forms of data including antibody sequences and structural data.

There are five compound classes targeting host processes, including host protease inhibitors [39–44], endosomal trafficking inhibitors [45–49], interferons [50–55], compounds reported to stimulate host immunity or induce interferon [56,57], and compounds that influence miscellaneous additional host processes [58,59]. Finally, there are two additional treatment categories – convalescent plasma [60,61] and compounds that have uncertain mechanisms of action. Table 1 describes each of the targets and lists a few of the most commonly studied compounds for each target. Figure 2 shows the distribution of experimental data types according to target.

2.2.4. Compounds

The database contains experiments involving approximately 1,200 compounds. More than 850 of these compounds appear in the online compounds tables which contains the following fields: (i) name; (ii) synonyms including abbreviations; (iii) closely related compounds; (iv) availability; (v) drug class; (vi) target; and (vii) description. The closely related compounds that are returned by a query even if that compound was not searched for. For example, queries for hydroxychloroquine also return results for chloroquine, queries for lopinavir also return results for ritonavir-boosted lopinavir (lopinavir/r), and queries for remdesivir also return results for its parent compound, GS-441524. The availability category indicates whether the compound has been licensed in the U.S. or another country or has been studied in humans.

For 724 compounds with a known or likely mechanism of action, 95 (13%) are U.S. FDA approved drugs (for indications other than COVID-19), 72 (10%) have been or are currently being evaluated in

human clinical trials or are approved outside the U.S., and 557 (77%) are preclinical investigational compounds.

Figure 3 displays EC_{50} values for many of the directly acting antiviral compounds currently in clinical trials for the treatment of COVID-19 including six polymerase inhibitors (remdesivir, EIDD-2801, favipiravir, ribavirin, galidesivir, and sofosbuvir), three HIV-1 protease inhibitors (lopinavir, atazanavir, and darunavir), and three entry inhibitors (receptor binding monoclonal antibodies, soluble recombinant human ACE2, and umifenovir). Figure 4 displays EC_{50} values for many of the repurposed compounds that target host processes required for virus replication including two host PIs that target the TMPRSS2 enzyme (camostat and nafamostat), three chloroquine analogs that interfere with endosomal acidification (chloroquine, hydroxychloroquine, and mefloquine), three other compounds believed to interfere with endosomal trafficking (niclosamide, imatinib, and chlorpromazine), and four compounds acting by a variety of different cellular mechanisms (ivermectin, nitazoxanide, ciclesonide, and cyclosporin).

Figures 3 and 4 shows that the potency of currently studied compounds extends over at six orders of magnitude with monoclonal antibodies having EC_{50}s in the high picomolar to low nanomolar range and some compounds displaying no activity at concentrations above 100 mM. However, there is also marked heterogeneity in the EC_{50} values for the same compound in different experiments. For several drugs the heterogeneity can likely be explained by the type of cells used, inoculum size, drug timing, and culture duration. For example, the host TMPRSS2 protease inhibitors camostat and nafamostat are inactive against SARS-CoV-2 in Vero cells but have EC_{50}s consistently below 1 mM in Caco-2 and Calu-3 cells possibly because these cells require TMPRSS2 to for virus replication whereas Vero cells may not [39,40,62,63].

2.2.5. Cell lines

The cell lines table provides descriptions for the cell lines used in cell culture and entry assay experiments. It contains four fields: (i) the cell line's commonly used name; (ii) the source of the cell line; (iii) closely related cell lines; and (iv) a description of the cell line and one or more of the closely related cell lines. The most commonly used cell lines for SARS-CoV and SARS-CoV-2 include a variety of different Vero cell clones [64–68] , Huh7 [64,69], Caco-2 [62], Calu-3 [70], and 293T/ACE2 cells [64–66]. While each of these cell lines express ACE2, only Calu-3 cells were originally derived from lung epithelial cells. 293T cells are typically used for cell-cell fusion and pseudovirus entry experiments. Several studies have also used human alveolar epithelial cells or a variety of different respiratory system or kidney organoids [71,72]. The cell lines used for MERS-CoV are similar, with the main exception that the 293T/DPP4 cells are used instead of 293T/ACE2 cells because DPP4 (aka CD26) is the MERS-CoV receptor [66].

2.2.6. Animal models

The over 10 different animal models used in experiments described in the CoV-RDB include three non-human primate models (rhesus macaques, cynomolgus macaque, and marmosets), multiple transgenic and non-transgenic mouse models, and several additional rodent models including hamsters and ferrets [73–90]. The transgenic mice have been modified in multiple ways, including to express hDPP4 so that they can be infected with MERS-CoV, to knock out the IFN-α/β receptor to compromise innate immunity [91], to knock out RAG1 to compromise adaptive immunity [92], to knock out carboxylesterase 1c which causes poor plasma stability of remdesivir, and to express human rather than mouse ACE2 [86–88]. Table 3 describes the utility of the most common non-human primate and mammalian models for studies of the pandemic coronaviruses.

2.3. Clinical Trials Registry

The Clinical Trials Registry table is a regularly updated, annotated list of ongoing, planned, or completed clinical trials obtained from the ClinicalTrials.gov, WHO ICTRP, and Chinese Clinical Trial websites. It contains those trials of compounds with potential antiviral activity but not studies of non-

antiviral interventions, such as those designed to optimize intensive-care management or reduce the inflammatory response and coagulopathy associated with many of the complications associated with severe disease. The Clinical Trials Registry classifies trials according to the compound target, the type of trial (e.g., observational or randomized controlled study), the status of the trial (pending, active, or completed), and the population studied. As of July 10, 2020, it contains nearly 600 trials of which about 80% are listed on ClinicalTrials.gov and 20% are listed only on the WHO International Clinical Trials Platform.

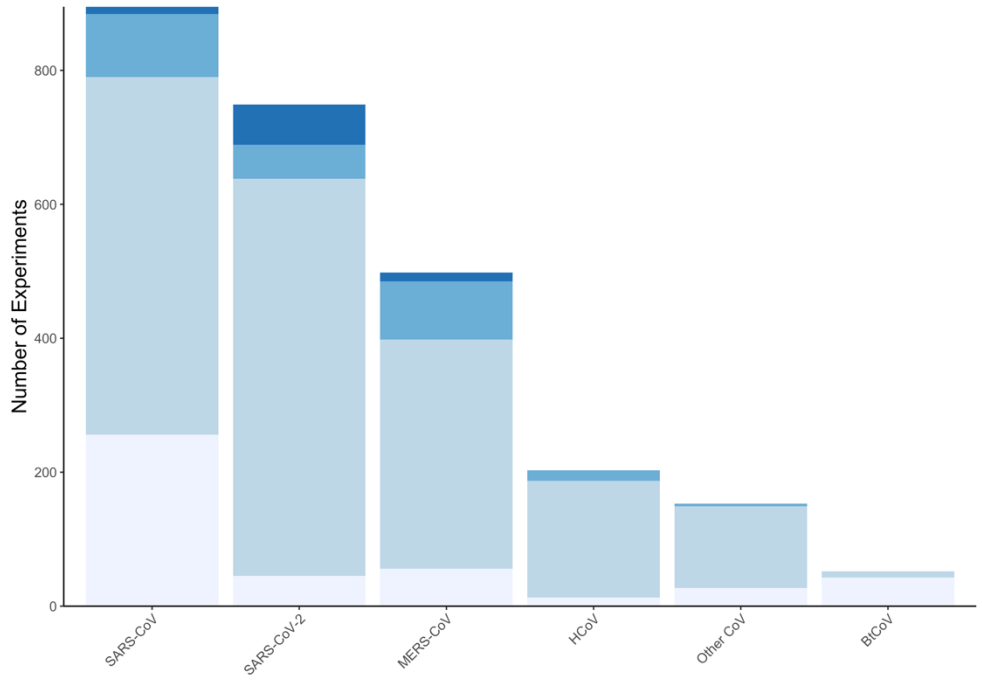
Figure 5A displays the distribution of planned, ongoing, and published studies according to the compound targets of the drugs being studied. Figure 5B displays the same distribution for those drugs in three or more studies. It is notable that many of the most commonly studied compounds have either little or no activity against SARS-CoV-2, including several drugs used for non-coronavirus infections such as the HIV protease inhibitor lopinavir and darunavir and the influenza inhibitors favipiravir, oseltamivir, and umifenovir. The chloroquine analogs, chloroquine and hydroxychloroquine, have weak *in vitro* activity but have failed to show clinical efficacy in several multiple studies [93–95].

2.4. Search Functions

The search function allows users to specify one or more of the following options from four drop-down lists: (1) compound target, (ii) compound, (iii) virus category, and (iv) study type. If the user selects "Any" for one of these and leaves the others in their default position, the search function returns the database's complete set of cell culture experiments, biochemical experiments, entry assay experiments, animal model studies, and published clinical studies. By selecting one or more of the above options, the search function restricts the data returned to those meeting the search criteria. The search function also provides a link to the trials in the Clinical Trials registry for selected compounds and compound targets.

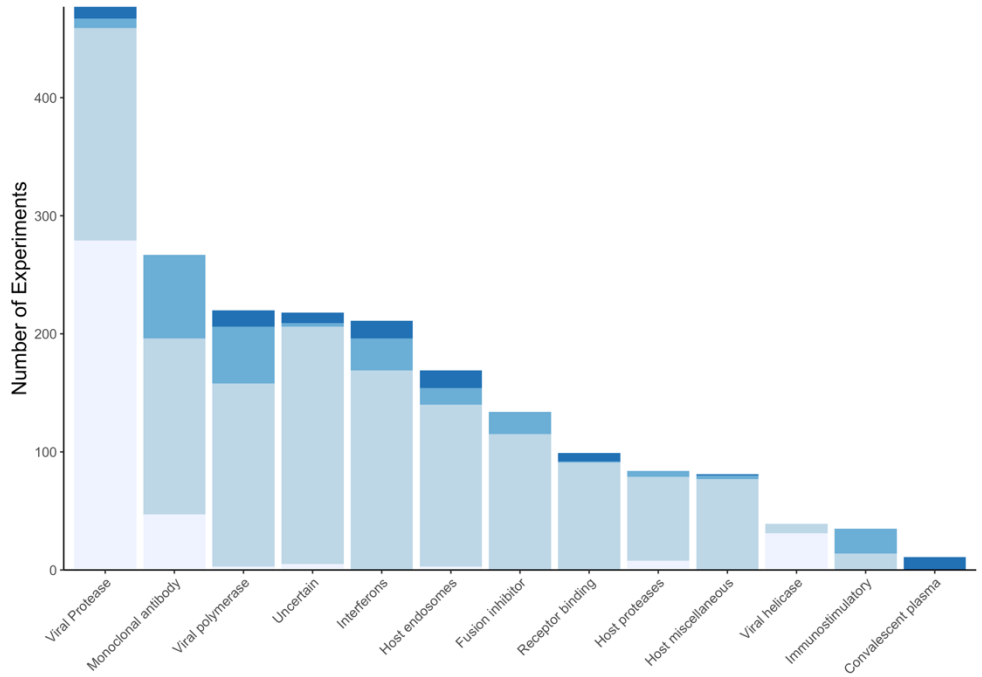
The compound drop-down list displays 60 of the most well recognized compounds. Selecting a compound returns the data for that compound as well as for an additional 194 closely related compounds (as described in the compound table section). If the user selects the compound target from the dropdown menu, then the compound menu will list all compounds designed to inhibit the selected target. The compounds entry on the compounds page also links to all the data on that compound in the database.

265 *2.5. Figures and Tables*



266

267 **Figure 1.** The distribution of biochemical experiments (lightest), cell culture experiments (light),
268 animal model studies (dark), and clinical studies (darkest) for the six categories of virus in the
269 Coronavirus Antiviral Research Database. The cell culture experiments also include entry assay
270 experiments.



271

272 **Figure 2.** The distribution of biochemical experiments (lightest), cell culture experiments (light),
273 animal model studies (dark), and clinical studies (darkest) for the different targets of antiviral therapy
274 in the Coronavirus Antiviral Research Database. The cell culture experiments also include entry assay
275 experiments. The results for approximately 600 experiments involving compounds with an unknown
276 or uncertain mechanism of action are not shown.

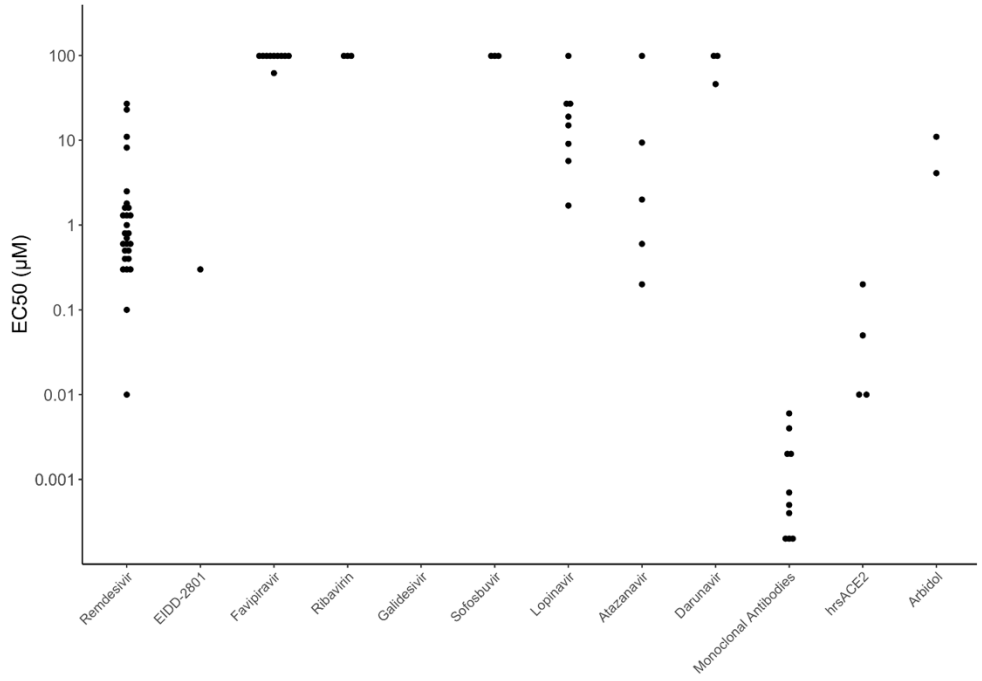


Figure 3. EC_{50} values for many of the directly acting antiviral compounds in clinical trials including six polymerase inhibitors (remdesivir, EIDD-2801, favipiravir, ribavirin, galidesivir, and sofosbuvir), three HIV-1 protease inhibitors (lopinavir, atazanavir, and darunavir), and three entry inhibitors (receptor binding monoclonal antibodies, soluble recombinant human ACE2, and arbidol). EC_{50} values above 100 mM and are plotted at 100 mM.

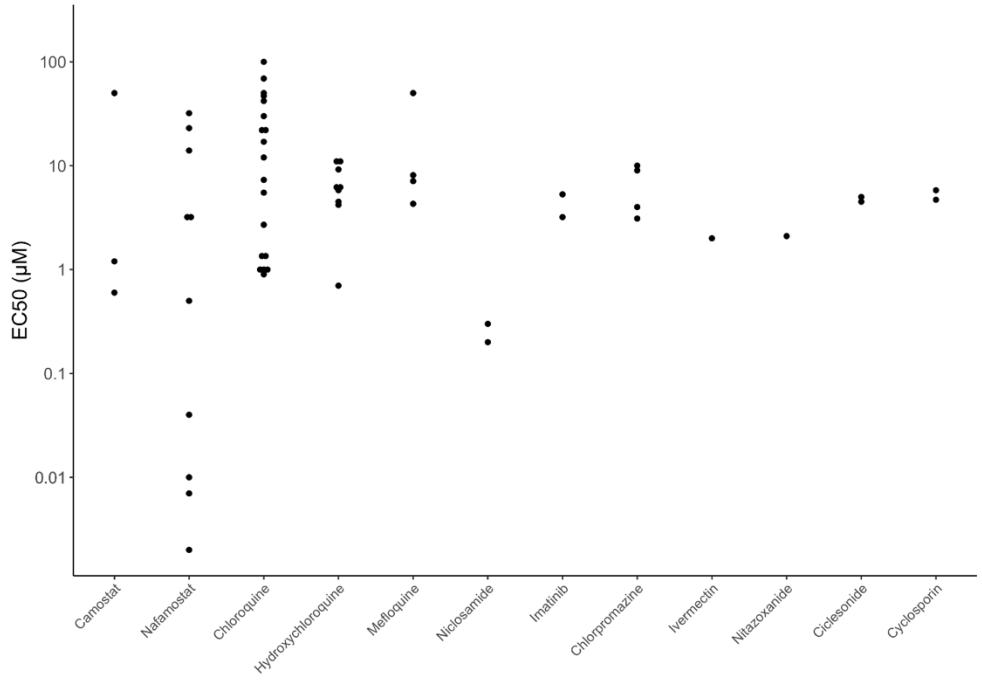


Figure 4. EC_{50} values for many of the repurposed host-acting compounds currently in clinical trials including the host protease inhibitors (camostat and nafamostat), five possible endosomal trafficking inhibitors (chloroquine, hydroxychloroquine, mefloquine, niclosamide imatinib, chlorpromazine) and four inhibitors acting by a variety of different mechanisms (ivermectin, nitazoxanide, ciclesonide, and cyclosporin).

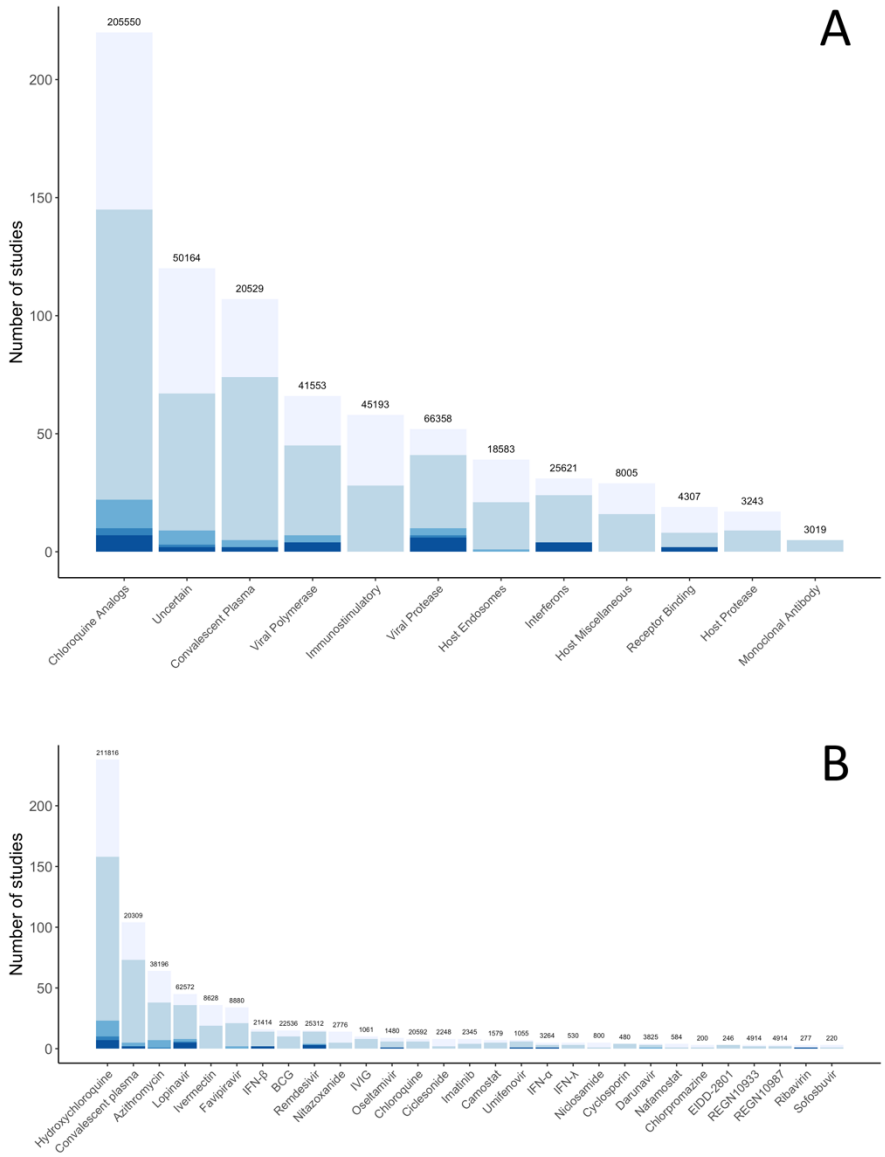


Figure 5. Distribution of targets (A) and the most commonly studied compounds (B) for published (bottom), ongoing (middle), and planned (top) antiviral clinical trials through June 25. Although chloroquine analogs are considered to act primarily through the inhibition of virus endosomal trafficking, they are separated out from other endosomal trafficking inhibitors in Figure 5A. Figure 5B shows those compounds included in three or more trials.

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Table 1. Antiviral Coronavirus Therapy Targets

Target	Description of the Viral or Cellular Target	Inhibitor Examples
Viral polymerase	Inhibitors of the coronavirus RNA-directed RNA polymerase (RdRp) enzymes are nucleoside analogs that cause immediate chain termination, delayed chain termination, or viral mutagenesis.	Four polymerase inhibitors are being studied in three or more clinical trials including remdesivir, EIDD-2801, favipiravir, and sofosbuvir [13–16]. Remdesivir has received emergency use authorization as a result of its effectiveness in a randomized clinical trial [13]. EIDD-2801 has entered phase I and II clinical trials.
Viral protease	Coronaviruses contain two protease enzymes: 3 chymotrypsin-like cysteine protease (3CLpro or Main [M]-pro) and papain-like (PLpro). There are many more candidate 3CLpro than PLpro inhibitors. Many of the viral protease inhibitors studied in vitro and all of the protease inhibitors being studied in clinical trials were developed to inhibit HIV-1 and HCV and have demonstrated weak or no coronavirus activity in vitro.	The HIV-1 protease inhibitor (lopinavir/r – lopinavir pharmacologically boosted by ritonavir) has been used in the largest number of clinical trials. Several additional repurposed protease inhibitors have been evaluated in vitro and multiple peptidomimetic investigational compounds have been identified in high-throughput biochemical screening assays [17–21].
Monoclonal antibodies	Many research groups have described the development of monoclonal antibodies targeting the SARS-CoV-1, MERS-CoV, and SARS-CoV-2 spike protein. The vast majority bind to the S1 receptor binding domain.	Monoclonal antibodies are the most potent coronavirus inhibitors often having activity in the high picomolar / low nanomolar range. Four SARS-CoV-2 monoclonal antibody preparations have entered clinical trials [96–99].
Receptor binding	SARS-CoV and SARS-CoV-2 spike S1 binds to the cellular angiotensin converting enzyme 2 (ACE2) receptor. MERS-CoV binds to dipeptidyl peptidase 4 (DPP4). Molecules that bind S1 are the most common receptor binding inhibitors.	Soluble recombinant ACE2 (rhACE2) and other molecular decoys have been shown to inhibit SARS-CoV-2 in vitro [36]. rhACE2 is also being studied in a clinical trial. Heparin and other heparan sulfate analogs may also interfere with coronavirus receptor binding.
Fusion inhibitors	Following receptor binding and spike S1/S2 cleavage and S2 priming, heptad region 1 (HR1), which is close to the fusion peptide sequence, and HR2, which is close to the virus membrane, collapse on to one another to bring virus and cell membranes together. Nearly all fusion inhibitors are HR2-mimicking peptides less than 70 kd that bind HR1, thus preventing HR1-HR2 binding.	Several HR2-mimicking peptides, including HR2P-EK1C4 [37] and IPB02 [38], have double-digit nanomolar activity in cell culture or pseudovirus assays. Both peptides are lipidated, which has been shown to improve viral inhibitory activity and pharmacokinetics. There are no clinical trials of fusion inhibitors.

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Viral helicase	Coronavirus helicases catalyze the unwinding of duplex RNA molecules into single strands.	Several high-throughput screens to identify SARS-CoV and MERS-CoV helicase inhibitors have been performed, but few have been studied in detail [22].
Host protease	Cleavage of coronavirus spike proteins is necessary for the virus to transition from receptor attachment to cell fusion. For SARS-CoV-2, there is a poly-basic furin cleavage site at the S1/S2 boundary and another cleavage site within S2 believed to be cleaved at the cell surface by host TMPRSS2 enzymes [44].	Camostat, nafamostat, and other TMPRSS2 inhibitors demonstrate variable coronavirus inhibitory activity in vitro [39–43] and have been approved for use for a variety of medical conditions. These drugs and several other host protease inhibitors are being evaluated in clinical trials.
Intracellular trafficking	Several intracellular processes prior to virus replication are vulnerable to pharmacologic inhibitors including endosomal acidification, trafficking, and membrane formation [100].	Chloroquine analogs and niclosamide are believed to act primarily by interfering with the endosomal acidification [46,48,49]. Tyrosine kinase inhibitors such as imatinib and apilimod are other drugs with in vitro activity that likely interfere with intracellular viral trafficking or membrane formation [45,47].
Interferons	Interferons (IFNs) have been extensively studied for their ability to inhibit each of the pandemic coronaviruses in cell culture, animal models, and/or clinical studies [54]. SARS-CoV-2 may be more susceptible to interferons than SARS-CoV [55]	IFN-α and IFN-β consistently demonstrate coronavirus inhibitory activity in cell culture and in animal models, although the timing of administration is likely to be critical as late administration may contribute to immunopathology [50,51]. IFN-λ has generated recent interest because it acts at epithelial barriers and has been reported to cause less inflammation than IFN-α and IFN-β [52,53]. All three IFN types are being studied in clinical trials.
Convalescent plasma	Convalescent plasma is one of the most widely used and widely studied treatments for COVID-19. Preliminary data suggest that it is safe and much more effective when administered shortly after the development of symptoms [60,61].	There are currently about 70 ongoing clinical trials of convalescent plasma of which about 10 are randomized controlled studies.
Immunostimulatory	There are several clinical trials using immunostimulatory cytokines and compounds reported to induce interferon.	Nitazoxanide is an anti-parasitic that has been reported to have broad-spectrum antiviral effects, possibly as a result of inducing interferons [56]. BCG has been hypothesized to stimulate innate immunity and is being evaluated in clinical trials to prevent severe COVID-19 [57].

Host miscellaneous	Several compounds have been shown to inhibit coronaviruses by interfering with miscellaneous cellular processes including cyclophilins, various signaling pathways, and autophagy.	Ivermectin, which inhibits SARS-CoV-2 in vitro, is being studied in many clinical trials [58].
Uncertain	Several compounds with uncertain mechanisms of action have been found to inhibit coronaviruses in vitro and have been studied in clinical trials.	Emetine is an FDA-approved drug for treating amebiasis that has been found to inhibit SARS-CoV-2 in vitro [59]. Ciclesonide is an inhaled corticosteroid that also inhibits SARS-CoV-2 in vitro and is being studied in several clinical trials [63].

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Table 2. Frequently Used Cells for Culturing Pandemic Coronavirus Antiviral Research

Cell Line	Source	Coronaviruses	Description
Vero cells (Vero E6, other clones; Vero E6/TMPRSS2)	African green monkey kidney epithelial cell line	MERS-CoV SARS-CoV SARS-CoV-2	Vero cells support the replication of many viruses often producing visual cytopathic effect [64–66]. They express ACE2 the receptor for SARS-CoV and SARS-CoV2 and DPP4, the receptor for MERS-CoV. Although Vero cells are IFN-deficient, they express the IFN-α/β receptor and thus retain the ability to respond to exogenous IFN [67]. Vero E6 cells engineered to express greater amounts of TMPRSS2 produce higher SARS-CoV-2 titers of SARS-CoV-2 [68]. Drugs that target TMPRSS2 are often inactive in Vero cells.
Calu-3 2B4	Human lung epithelial cell line	MERS-CoV SARS-CoV SARS-CoV-2	Calu-3 cells form differentiated pseudostratified columnar epithelia highly permissible to coronavirus infection. They are polarized with an apical domain facing the airway lumen and a basolateral domain facing internally. They produce visual cytopathic effect. The 2B4 clone has high ACE2 expression. They are often used for the preclinical development of respiratory drugs [70]
CaCo-2	Heterogeneous human epithelial colorectal adenocarcinoma	SARS-CoV SARS-CoV-2	CaCo-2 cells are considered to be more pharmacologically relevant than Vero cells for some studies because of their human origin [62].
Huh-7	Human hepatoma	MERS-CoV SARS-CoV SARS-CoV-2	Huh-7 cells express ACE2 and TMPRSS2 yet do not support levels of replication as high as Vero cells [64,69].
HEK-293T/ACE2 (HEK-293T/ DPP4)	Human embryonic kidney	MERS-CoV SARS-CoV SARS-CoV-2	293T cells are derived from the human embryonic kidney 293 cell line. 293T cells contain the SV40 large T-antigen, which facilitates replication of transfected plasmids containing the SV40 origin of replication. 293T/ACE2 cells are transfected to express ACE2 and have been used for many SARS-CoV cell-cell fusion and pseudovirus entry inhibitor studies [64–66].
HAE	Human Airway Epithelial cells	MERS-CoV SARS-CoV SARS-CoV-2	Differentiated human airway cells have occasionally been used to study antiviral agents, although they are more commonly used to study viral pathogenesis [71,72]

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Table 3. Animal Models for Pandemic Coronavirus Antiviral Research

Species	Coronaviruses Used	Comments
Mouse (C57BL/6, Balb/c)	MERS-CoV SARS-CoV SARS-CoV-2	Pathological changes observed in the aged mouse model infected with SARS-CoV more closely resemble those observed in humans [76]. RAG-/- mice lack T and B cells and lack adaptive immunity and experience prolonged coronavirus shedding [92]. IFNAR -/- mice are vulnerable to greater coronavirus disease severity [91].
Transgenic hACE2 mice	SARS-CoV SARS-CoV-2	There are many hACE2 transgenic mouse models. These mice are more likely to experience weight loss, detectable virus loads, and interstitial pneumonia following challenge with SARS-CoV-2 than those with the murine ACE2 receptor [86–88].
Rhesus Macaque	MERS-CoV SARS-CoV SARS-CoV-2	Infection causes a self-limiting disease associated with virus replication. Radiographic and pathologic examination of SARS-CoV-2 infected animals display evidence of pneumonia [73,77,79,89].
Cynomolgus Macaque	MERS-CoV SARS-CoV SARS-CoV-2	Infection results in a productive infection in respiratory epithelial cells Symptoms are minimal but virus shedding can last up to 2 weeks. Chest radiographs reveal unifocal or multifocal pneumonia. Autopsy reveals variable amounts of foci of diffuse alveolar damage [78,80].
Common Marmoset	SARS-CoV MERS-CoV	Infection causes severe acute disease that mimics severe human infection [27].
Ferret	SARS-CoV SARS-CoV-2	Upon infection, ferrets develop fevers and shed viruses in their upper airways, urine, and feces for up to 8 days. They can also transmit the infection to other ferrets [82–84].
Syrian hamster	SARS-CoV SARS-CoV-2	SARS-CoV and SARS-CoV-2, but not MERS-CoV, cause a self-limited respiratory tract infection in hamsters. Infection is associated with high-levels of virus and areas of lung pathology [75,81,85,90].

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3. Discussion

To prioritize licensed drugs and investigational compounds for the treatment of COVID-19, it is necessary to compare their relative antiviral activities. Compounds that are not active *in vitro* will almost certainly not be useful clinically. Therefore, pre-clinical data are necessary to prioritize animal model and clinical studies. Compounds that are active *in vitro*, however, may also not be clinically useful if their associated *in vitro* data do not reflect physiologic conditions or if standard dosing with these compounds does not result in sufficient inhibitory concentrations at sites of infection.

The creation of the CoV-RDB was motivated by the observation that many of the drugs being evaluated in CoVID-19 clinical trials demonstrate little or no *in vitro* anti-coronavirus activity. For example, as of July 12, 2020, four of the most commonly studied drugs – chloroquine analogs, azithromycin, lopinavir/r, favipiravir – demonstrated little if any *in vitro* activity. Chloroquine analogs, while having a median EC_{50} of about 5 μM median should not have been expected to be clinically beneficial because plasma drug concentrations obtained with standard dosing do not reach inhibitory concentrations *in vivo*. Not surprisingly, recent large clinical studies have failed to show that the chloroquine analogs are beneficial [93,94,102]. Lopinavir/r has a median EC_{50} of about 10 μM yet was being studied in 28 ongoing and 10 planned clinical trials. Favipiravir has an EC_{50} above 100 μM yet was being studied in 16 ongoing and 14 planned clinical trials.

The creation of the CoV-RDB was also motivated by the observation that results for the same compound often vary across different laboratories as a result of experimental design such as cell line, inoculum size, drug-addition timing, duration of culture, and method for measuring virus replication. Given sufficient data, it may eventually become possible to identify the experimental features that explain this variation, thus improving the ability to compare the antiviral activity of different compounds despite the frequent heterogeneity in published results. The presence of an online database allows researchers to place their findings in the context of previously published data, identifies divergent results, and encourages them to adopt uniform methods for reporting their data.

The CoV-RDB lookup tables ensure that there are explanations for all viruses, drugs, cell lines, and animal models used in reported experiments. These tables contain descriptions of viruses, virus isolate/strains, cell lines, animal models, and more than 280 licensed and investigational compounds. Work is underway to also include detailed annotated data on SARS-CoV-2 monoclonal antibodies and pharmacokinetic data for drugs with demonstrated *in vitro* inhibitory activity.

Of the compounds in clinical trials as of July 12, 2020, those with the greatest *in vitro* activity are monoclonal antibodies, two polymerase inhibitors (remdesivir and EIDD-2801), soluble human ACE2, the host protease inhibitor nafamostat, and the possible endosomal trafficking inhibitor niclosamide. Remdesivir has been shown to reduce the severity of illness in a phase III randomized placebo-controlled trial [13]. Four monoclonal antibody preparations entered clinical trials in June 2020 [96–99]. Despite their lower EC_{50}s compared with other host-acting repurposed compounds, it is uncertain whether standard doses of nafamostat and niclosamide attain inhibitory levels in patients.

Multiple additional web resources devoted to coronavirus drug development are likely to be developed. For example, the US NIH is developing a website devoted to high-throughput drug screening [103], another laboratory has a website devoted to the genetics of monoclonal antibodies [104] and several groups are prospectively performing meta-analyses of published clinical trials [105,106]. CoV-RDB, however, provides a uniquely integrated interdisciplinary synthesis of *in vitro*, animal model, and clinical studies of compounds with proven or possible anti-coronavirus activity. It helps researchers place their findings in the context of previously published data and it facilitates comparisons between different candidate antiviral compounds, thereby helping scientists, clinical investigators, public health officials, and funding agencies to prioritize the most promising compounds and repurposed drugs for further development.

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