

# The Pandemic Response Box—Accelerating Drug Discovery Efforts after Disease Outbreaks

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**ABSTRACT:** The current Covid-19 pandemic has underlined the need for a more coordinated and forward-looking investment in the search for new medicines targeting emerging health care threats. Repositioning currently approved drugs is a popular approach to any new emerging disease, but it represents a first wave of response. Behind this would be a second wave of more specifically designed therapies based on activities against specific molecular targets or in phenotypic assays. Following the successful deployment and uptake of previous open access compound collections, we assembled the Pandemic Response Box, a collection of 400 compounds to facilitate drug discovery in emerging infectious disease. These are based on public domain information on chemotypes currently in discovery and early development which have been shown to have useful activities and were prioritized by medicinal chemistry experts. They are freely available to the community as a pharmacological test set with the understanding that data will be shared rapidly in the public domain.

**KEYWORDS:** *Pandemics, screening, drug discovery, antivirals, antibacterials, antifungals*



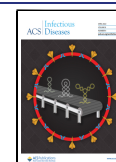
Finding new agents to combat emerging pandemic diseases requires preparation and foresight. The initial response to a new pathogen is to reposition existing anti-infective agents or other supportive therapies. The primary drivers for this approach are clinical safety—ensuring that the drug causes no additional harm and efficacy; the arena for testing is the clinic. It is estimated that around 40% of medicines approved for treatment of tropical diseases have been identified through repurposing. The best known are albendazole for echinococcosis and neurocysticercosis, and azithromycin for trachoma.<sup>1</sup> The key driver here is often the off-label use of well-known anti-infective drugs in compassionate use programs clinically. The FDA has set up the Collaborative Use Repurposing Engine (CURE) to capture and centralize the global experience of new uses of approved medical products to treat emerging threats, NTDs (neglected tropical diseases), and infections with multidrug-resistant organisms, with a Web site [cure.ncats.io](http://cure.ncats.io) that allows health care providers to report their experiences of both successful and unsuccessful treatments. The other approach is to use cellular anti-infective assays to screen compound collections for potential new treatments. An initial submicromolar response triggers initial interest. On the basis of known or modeled tissue concentrations in humans, an analysis can be made as to whether such concentrations can be achieved safely in the clinic. As has been seen from the recent flood of molecules for

treating Covid-19 patients, although many candidates are suggested, few make it past the first hurdle of being predicted to be able to safely achieve an effective tissue exposure in humans.

An alternative approach would be to test molecules that have potential as anti-infectives but are not yet completely optimized. This is a slower approach, since these molecules would still need preclinical optimization and human testing, and so this is often seen as less attractive given the pressing need for short-term solutions. However, if such an approach had been taken when the Ebola virus was first discovered in 1975, new agents could well have been available for the epidemic in Liberia in 2014/2015. If there had been a more coordinated search for new agents against SARS-CoV (1) after the outbreak in Hong Kong in 2003, then the global armamentarium of drugs to fight SARS-CoV2 would have been stronger.

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The difficulty with such an approach is maintaining long-term funding in the absence of a specific threat. Analysis of the U.S. NIH (National Institutes of Health) spending according to the Research, Disease, and Condition Categorization (RCDC) shows little investment in diseases with less than 0.5 million DALYs (Disability Adjusted Life Years<sup>2</sup>). On the face of it, this is logical, even though this means that fewer than ten of the classical neglected diseases would be funded based on global public health impact (malaria, schistosomiasis, dengue, hookworm, visceral leishmaniasis, onchocerciasis, ascariasis, and rabies<sup>3</sup>).

The challenge is therefore how to efficiently catalyze drug discovery in areas of emerging disease, where the associated DALYs have not (yet) exceeded the threshold needed for large-scale investment. Clearly this also has to involve more efficient use of existing resources and thus the open sharing of information and reagents. Following the release of the Malaria Box in 2011,<sup>4</sup> MMV (Medicines for Malaria Venture, Geneva, Switzerland) analyzed the use of these open-source compounds,<sup>5</sup> since a large proportion of them were used by groups who were not actively working on malaria. Several trends emerged: First, that for emerging pathogens there are very few starting points for drug discovery, and so access to compound sets enriched with scaffolds likely to cross membranes and hit molecular targets was in high demand. Second, that there was a clear scientific drive in the biology community to find new molecules against emerging infectious diseases, with the establishment of relevant assays indicative of disease pathology, where screening of compound libraries is carried out under very stringent biosafety conditions. There was a need to not only supply compounds but also to offer additional services. With the MMV open platform,<sup>6</sup> MMV has been able to supply standardized information on metabolism and pharmacokinetics as well as early safety read-outs—essential for rapidly prioritizing any scaffolds that are positive. In addition, an initial hit can be rapidly expanded to a series by compound purchase and synthesis, but many of the project teams needed early medicinal chemistry support. In short, it is possible to progress drug discovery using the existing networks, but there was a need for catalytic investment in chemistry, drug metabolism, and in managing the logistics of making compounds available. With this it would be possible to form a community of the willing. Additionally, the availability of a standard testing set means that results can be compared between laboratories, and trends around the impact of assay conditions and different pathogens can be identified.<sup>5</sup> Finally, these open-source compound collections have been extremely useful in providing testing sets of interesting molecules for those working in Low- and Middle-Income Countries, and against rarely studied primary isolates of disease (references for each Box are cited below).

There are several commercial libraries of FDA-approved drugs available, ranging from less than 1000 to almost 3000 compounds, at a cost of around \$5 per compound. If the drug being repositioned is an existing anti-infective agent there is a fast route to clinical testing.<sup>7</sup> This approach has been applied to emerging viral pathogens, with tilorone and pyronaridine shown to be active against the Ebola virus in infection assays.<sup>8,9</sup> However, if the initial cell biology hit is from a different therapeutic area, the road from that hit to confirmation of activity in animals and thence human patients can be a long one.<sup>10,11</sup>

One issue with registered drugs is that they have been optimized for a specific pathogen; so, in the ideal case they represent a “home-run”. However, if an optimal drug candidate cannot be directly identified, it may be better to start with compounds from earlier in development which have not been completely optimized against a specific target. The ReFRAME collection was created by Calibr in 2018 as a collection of 14 000 compounds based primarily on all compounds currently in clinical development, stalled, or registered.<sup>12</sup> This is an extremely powerful resource for facilities with access to high-throughput screening technologies. Facing the inherent threat of a new epidemic caused by a viral, bacterial, or fungal agent, it was clear that a standard set of compounds would be valuable as a resource for supporting work on emerging pathogens. To meet this perceived need, MMV and DNDi (Drugs for Neglected Diseases *initiative*, Geneva, Switzerland) have collaborated to generate a set of 400 compounds that span these three therapeutic areas, focusing on a chemically and pharmacologically diverse mixture of early stage, emerging anti-infective scaffolds, and more mature compounds currently undergoing clinical development. The decision to select a box of 400 compounds was framed by feedback from the biological partners. With emerging infections, the number of new compounds that can be tested is limited, given the need to use clinical isolates of pathogens and, typically, nonrobotic procedures. The idea is not primarily to identify new drugs to target today’s emerging pathogen(s) but to prepare a solid grounding and network of collaborators who can work to develop therapeutic approaches to tomorrow’s pathogen before it emerges as a global threat.

The methodology for the choice of compounds followed the previous MMVopen projects: the Malaria Box<sup>4,5,13</sup> and the Pathogen Box.<sup>14,15</sup> The key criterion for selecting molecules for the Pandemic Response Box was that they have demonstrated potent, preferably sub-micromolar efficacy, against viral, bacterial or fungal microorganisms in *in vitro* assays. A few FDA-approved drugs, such as saquinavir, itraconazole, levofloxacin, and tobramycin were inserted as positive controls. However, for the rest of the set, there was a desire to have a balance between compounds that were taken from discovery and those with some development exposure. The discovery-sourced chemotypes could be expected to be pleiotropic but have more risk in terms of unknown side effects. However, this may increase the opportunities for identifying a novel hit, as such discovery compounds may not be fully optimized against a particular biological target or pathogen. Chemotypes that have already been taken into development are somewhat derisked but carry the counterbalance that this optimization may reduce the possibility of having activity against other pathogens. “Launched” compounds may have been registered locally or for specific indications and formulations, which may or may not fit uses for other diseases. Some molecules’ clinical development may also have been stopped for commercial or disease-specific reasons which would not *a priori* prevent their use in pandemics. Although some molecules may be covered by current intellectual property claims, it was considered that by the time any new treatments have been clinically validated, many of these claims will have expired. In any case, the assumption is that the community will take a responsible view of intellectual property.<sup>16</sup> As such, some of the compounds were purchased in bulk from suppliers, but many were made within the project using in-house synthetic experience.

## METHODS

**Selection of the Pandemic Response Box Compounds.** A list of antibacterial and antiviral compounds that either had been in clinical development or else represent promising scaffolds from drug discovery was compiled from public domain databases. Promising compounds from the discovery list were reviewed by a panel of medicinal chemistry experts and were then combined with compounds selected from chemotypes in clinical development. The details of the workflows are outlined below. In general, compounds were not triaged using physicochemical properties or structural alerts unless specified. From a compound collection perspective, this would risk prematurely eliminating certain drug classes or mechanisms of action. Such risks could be addressed during future lead optimization campaigns.

**1. Antibacterial and Antiviral Development Compounds.** All antiviral and antibacterial development compounds were abstracted from the Cortellis (Clarivate Analytics) database with molecules included since 1990 (see S1 for details). Via this process, 233 antibacterial development candidates were identified, and therefore, no further triage of this list was performed. Abstraction of antiviral development candidates from the Clarivate Analytics Cortellis database identified 1336 compounds, so further triage was required. These antiviral compounds were clustered and analyzed for molecular properties such as molecular weight, published potency in cellular assays, and pan-assay interference compounds (PAINS<sup>17</sup>). Viral selectivity and molecular target information were captured for each compound, and one compound was picked per viral family. In addition, one compound was picked per molecular target for those targets not covered by the preceding organism-based selection. Compound selection was guided by a Harrington multiparameter optimization to bias toward potency and lower molecular weight:<sup>18</sup>

Weighted compounds in the 300–400 MW range favorably (+1 score), monotonically dropping off to zero at 200 or below and 500 or above

Weighted compounds with  $pIC_{50} > 6$  favorably (+1 score), monotonically dropping off to zero at  $pIC_{50} = 5$  or below

Negatively weighted compounds (−2 score) with any reactive functional groups or PAINS alerts

Generated a combined score for each molecule by summing up the three weighting values

Within each cluster the compound with the highest MPO (multi parameter optimization) score<sup>18</sup> was selected as the representative. A list of 235 antiviral development compounds was selected using this method, which when combined with the 233 compounds from antibacterial selection, resulting in a set of 468 compounds representing development scaffolds.

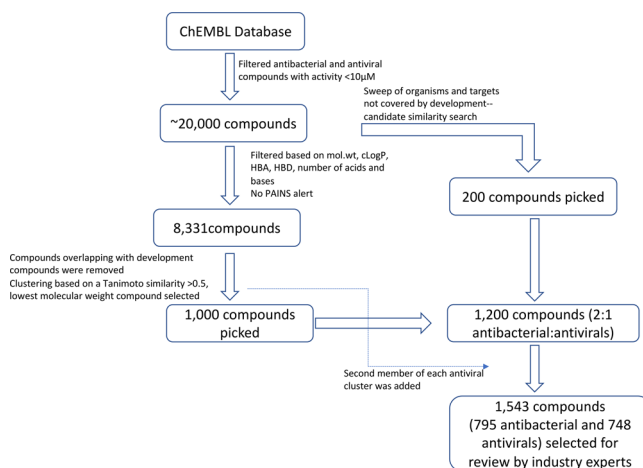
**2. Antibacterial and Antiviral Discovery Scaffolds.** From the ChEMBL database, compounds with defined antiviral or antibacterial activity ( $<10 \mu\text{M}$ ) were abstracted. This produced a list of more than 20 000 compounds that was initially filtered by application of the following physicochemical properties (these were chosen to eliminate compounds with extreme properties but remain relaxed enough to be inclusive at this stage):

MW 200–700;  $\text{clogP}$  0–7; HBA (hydrogen bond acceptors)  $<20$ ; HBD (hydrogen bond donors)  $<10$

Number of: acids  $<3$ ; bases  $<4$ ; rings  $<11$ ; rotatable bonds  $<25$ ;  $\text{sp}^2$  atoms  $<25$

## No PAINS alert

The revised set of 8331 compounds was then subjected to the following triage (Figure 1). Compounds that were

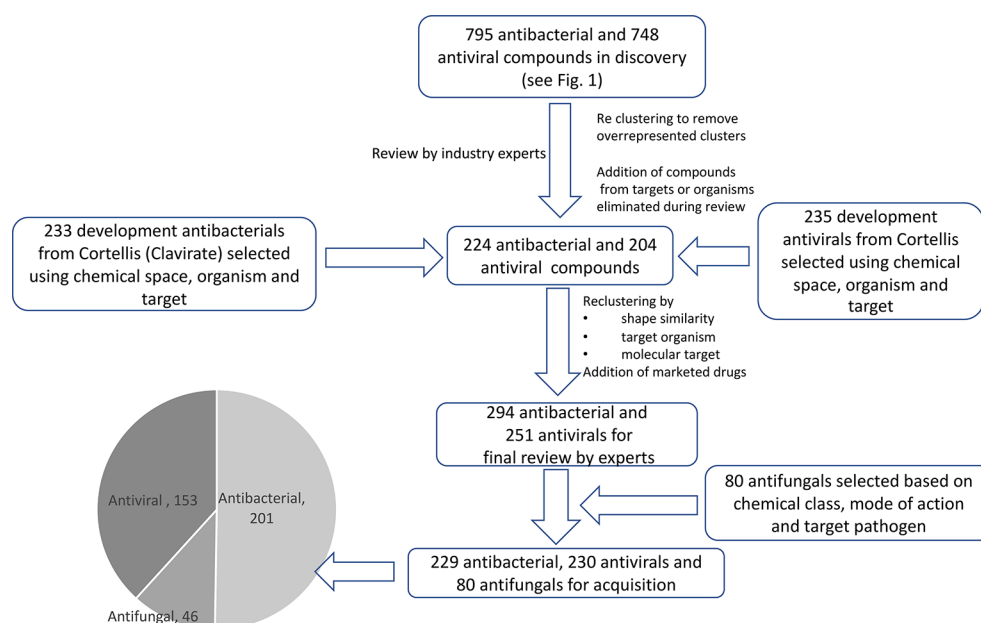


**Figure 1.** Workflow for triage of ChEMBL compounds.

overlapping with the previous Clarivate Analytics list of development compounds were removed. Compounds were then clustered based on a Tanimoto similarity of  $>0.5$ , and the compound with the lowest molecular weight selected to represent each cluster. Clustering was performed with an in-house algorithm that employs single linkage clustering and Morgan fingerprints. All pairwise similarity values were calculated and compounds placed in the same cluster if their Tanimoto similarity was above a threshold value. Multiple similarity threshold values were used to enable interrogation of cluster data at different levels of granularity. For example, compounds could be viewed trellised by cluster calculated using a low similarity value (e.g., 0.5), and colored by cluster calculated using a higher similarity threshold (e.g., 0.7) to give a more informed view of the space being analyzed. Some clusters were eliminated from the analysis due to the presence of reactive functionalities such as aldehydes, thiols, and oximes. This method selected 1000 compounds.

The molecular targets and target pathogens for the original 20 000 ChEMBL hits were reviewed. Compounds with a pathogen target or a molecular target not already covered by the first 1000 compounds were prioritized per target or organism on the basis of their MPO scores as described above. This selected an additional 200 compounds. Finally, since this overall initial list of 1200 promising discovery compounds was biased 2:1 in favor of antibacterials, a second member of each antiviral cluster was added, resulting in a total of 748 antiviral compounds, 1543 discovery compounds in total.

These 1543 compounds were then reviewed by an industry-experienced medicinal chemistry panel. Two reviewers were randomly assigned per compound, and each reviewer was asked to score a compound simply as selected or nonselected. Compounds selected by both reviewers were reclustered to 70% similarity<sup>19</sup> to reduce the number of compounds representing each cluster to no more than two. The coverage of targets and organisms was then reanalyzed to identify any mechanisms that were no longer covered, and in that case, compounds previously rejected by the reviewers were proposed for reintroduction to cover these gaps. The resulting compounds were reduced to a collection of 224 antibacterial



**Figure 2.** Selection of the final compound set (HBA: hydrogen bond acceptors, HBD: hydrogen bond donors, PAINS: pan assay interference compounds).

and 204 antiviral discovery compounds, selected with a preference for high potency, low clogP, and avoidance of complex chemical structures.

**3. Antifungal Compounds.** A list of 300 antifungal compounds from discovery and development phases including fungicides was extracted from the Clarivate Analytics Cortellis database. There is limited structural diversity among antifungals as compared with antibacterial and antiviral compounds, and the set also contained multiple formulations of the same compound. Formulation duplicates and complex natural products were removed from the list to bring it to a collection of 80 compounds. Since these compounds are representative of antifungal targets reported in the literature, and given our earlier experience of observing attrition at the acquisition (procurement or synthesis) stage, all these compounds were included in the final list of compounds for procurement and synthesis.

**Selection of the Final List.** Feedback from some of the original testing groups working on the Malaria or Pathogen Boxes had underlined that 400 seemed to be the optimal number for a Box. This is especially important for groups working in neglected disease areas with limited resources and with pandemic pathogen assays, which have to be performed in biosafety level (BSL) 3 or 4 facilities. The selection process still left us with a set of 457 antibacterial and 439 antiviral compounds that was triaged further to reduce the list to a reasonable number for acquisition and provide a slot for inclusion of a substantial number of antifungal compounds (Figure 2).

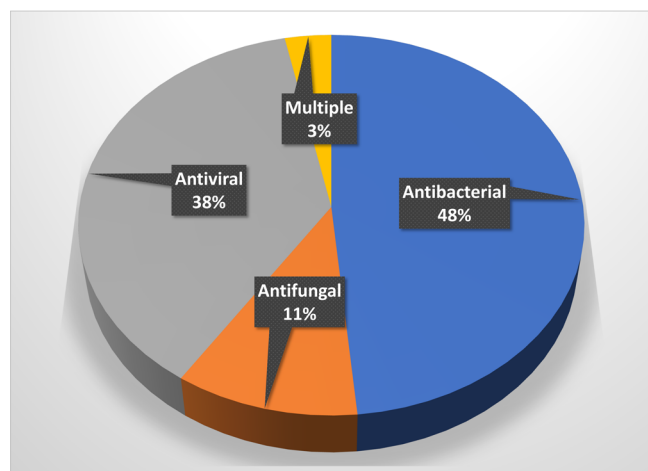
Antibacterial compounds were reclustered by Tanimoto structural similarity of  $>0.7$  and also separately clustered by target mechanism. One commercially available compound was taken from each structural cluster, and one was taken from each target cluster. For clusters where compounds were not commercially available, one compound was selected for synthesis based on structure, launch phase (higher launch phase prioritized), and simplicity of synthesis. Representative compounds from the clusters with no listed molecular targets

were also selected. This list was then supplemented with launched antibacterial compounds, providing 294 compounds in total. This set was then reviewed a final time by anti-infective experts to select 229 compounds for acquisition (procurement or synthesis).

Similarly, for antivirals, compounds were clustered by structure, target virus, and molecular target, if known. Using this combination, 245 clusters were identified, and a representative from each cluster was selected on the basis of commercial availability or synthetic simplicity. From clusters that lacked either a defined molecular target or a known target organism, one compound was selected. This list was further supplemented with launched compounds and shared with experts for final selection. After a final visual check, 230 compounds were selected to ensure minimum chemical overlap and representation of clusters.

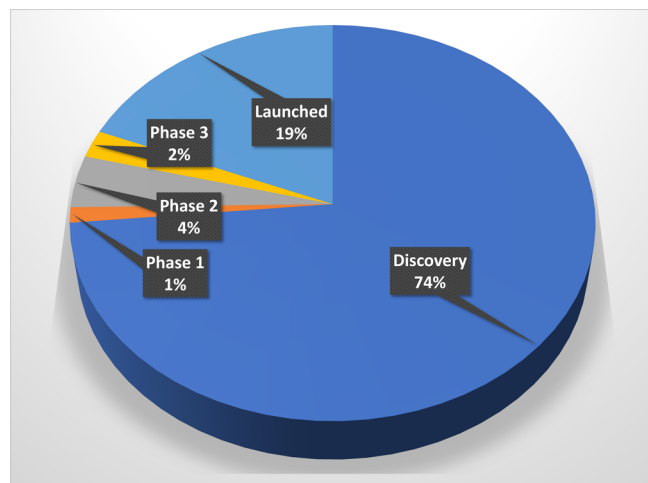
A final list of 539 compounds, including 80 antifungals, was assimilated for procurement or synthesis. Compounds with high cost of synthesis ( $> \$1000$  for  $\sim 25$  mg) were eliminated at this stage, leaving around 40% of the compounds planned for synthesis. As experienced earlier with the Malaria and Pathogen Boxes, a 20% attrition was observed due to unexpected synthetic difficulties, high cost, or extended lead time of starting materials or reagents. Furthermore, some of the synthesized compounds were not included in the box because less than 30 mg could be made. Of the 400 compounds that made it to the box, 164 were synthesized *de novo*.

**4. Composition of Pandemic Response Box.** The final set of Pandemic Response Box compounds comprises 201 antibacterial, 153 antiviral, and 46 antifungal compounds, with some of them reported as active in multiple disease areas (Figure 3). The initial aim was an approximate equal split between discovery and development/launched compounds. However, the extreme synthetic complexity and lack of an affordable commercial source for many of the development/launched compounds resulted in a larger proportion of discovery compounds in the final box (Figure 4). These



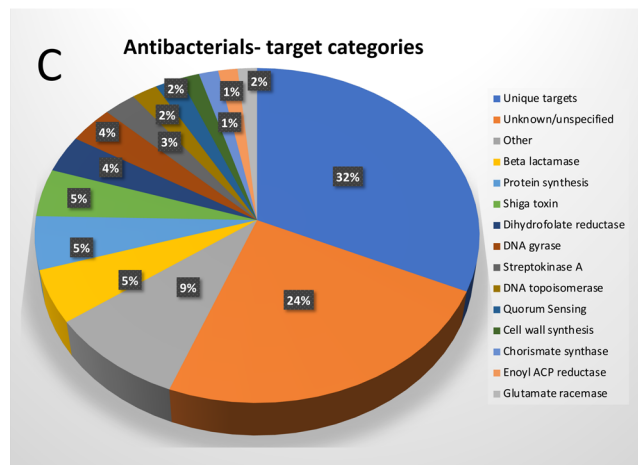
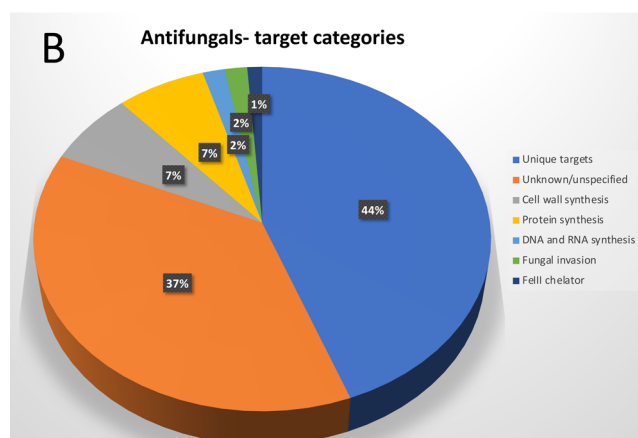
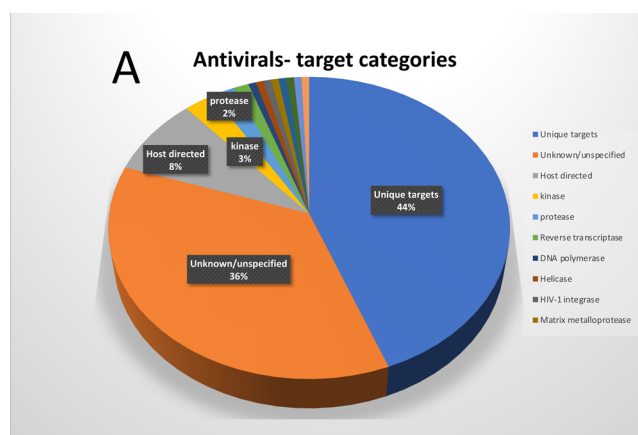
**Figure 3.** Composition of the Pandemic Response Box, by disease area.

molecules act on a wide variety of targets, as summarized in Figure 5.



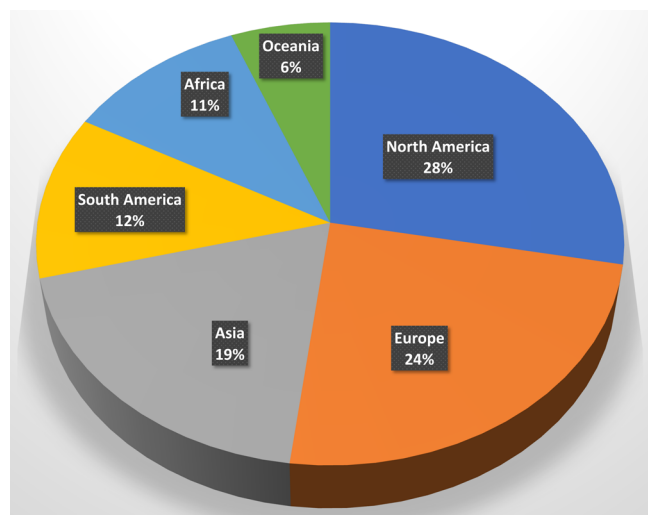
**Figure 4.** Composition of the Pandemic Response Box, by stage of development.

Each 96-well plate has 16 wells left empty to allow for the addition of the appropriate positive and negative controls for the biological assay. The plate layout of the Pandemic Response Box has been designed to be flexible and to accommodate different screening setups. The wells contain 10  $\mu\text{L}$  of a 10 mM solution in DMSO, supplied in V-shaped 96-well plates and are shipped frozen. The antifungal compounds are plated on Plate A, antibacterials on plate A–C and antivirals on plate D and E. Nine compounds that could not be solubilized to produce 10 mM DMSO solutions are provided as 2 mM stocks. The Pandemic Box is available free of charge from MMV upon request ([www.mmv.org/mmv-open/pandemic-response-box](http://www.mmv.org/mmv-open/pandemic-response-box)). The details of the compound set are in Supplement S2, which lists structures, SMILES, molecular mass, calculated polar surface area, target class, chemical name, and MMV code. Importantly, there are considerable additional public domain data available for these molecules within databases such as ChEMBL.<sup>20</sup> A literature or patent reference has been included for any compound not listed in ChEMBL.



**Figure 5.** Mode of action for compounds included in the Pathogen Response Box by (A) antivirals, (B) antifungals, and (C) antibacterials. For (A), the categories not labeled in the pie are all 1%.

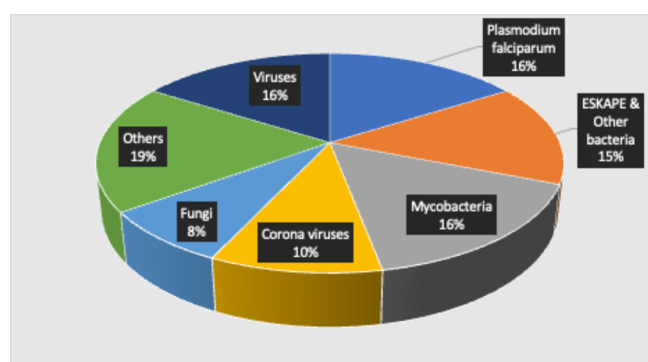
**5. Roll Out of the Pandemic Response Box Compound Set.** Since the launch of the box in 2019 over 140 requests for the compound set have been received, indicating the great interest among researchers to screen high-quality compound collections. The wide geographic distribution of the recipients (Figure 6) is a testament to the demand for this type of discovery tool, with 42% coming from Africa, Asia, and Latin America. Many of the recipient laboratories are located in regions where epidemic outbreaks or pandemic origins are frequent. The distribution pattern of this box is similar to what



**Figure 6.** Distribution of the Pandemic Response Box compound set, by region.

was observed with the Pathogen Box, where 36% of the boxes went to these regions.

To date, more than 50% of the Pandemic Response Boxes have been sent for screening against various viruses, including corona viruses and bacterial pathogens (Figure 7). A sudden

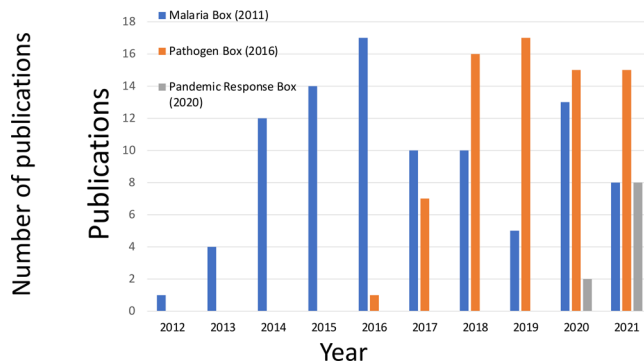


**Figure 7.** Pathogen diversity for screening of Pandemic Response Box.

spike in requests for the Box for antiviral screening was observed in 2020, and by March 2020, MMV had already shipped a few copies for screening in SARS-CoV2 assays. The set has been screened in multiple assays developed to identify potential drugs for treatment of SARS-CoV2. This has led to the identification of active compounds *in vitro*<sup>21</sup> that are being further characterized. The box has also been screened against other different high-priority pathogens, many of which have been listed as such by the U.S. CDC (Centers for Disease Control) and WHO (World Health Organization).

This is in stark contrast with screening campaigns run with the Pathogen Box, where only 5% of requests were for antiviral screening. On the other hand, fewer screens have been performed against kinetoplastids and Apicomplexa.

Screening of the Pandemic Response Box has resulted in 11 publications so far.<sup>21–31</sup> Such a lag is similar to what was observed for earlier boxes with the peak 2–3 years after launch, as seen in Figure 8. Throughout 2020 and early 2021, the pandemic has shifted research, with a focus on SARS-CoV2, impacting the number and delaying publications.



**Figure 8.** Number of PubMed-listed publications, by year, that cite one of the three Boxes.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscinfecdis.1c00527>.

S1 Search strategy (pathogen list) used for the Cortellis search (PDF)

S2 List of Pandemic Response Box compounds with compound details (XLSX)

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### Author Contributions

T.N.C.W. conceived of the original idea. K.D.S., P.G., J.M., G.W., R.H., A.M., C.M., B.P. and P.A.W. designed and implemented the research plan described in the manuscript. A.D. and B.D.P. supervised the synthesis of compounds. K.D.S., D.B., A.D., A.S., and P.A.W. managed the launch and distribution of the Pandemic Response Box. K.D.S., B.P., R.H., and P.A.W. wrote the manuscript with input from all authors.

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### Notes

The authors declare no competing financial interest.

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