100 Days Mission
Therapeutics Roadmap
January 2024
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Executive Summary

The 100 Days Mission Therapeutics Roadmap aims to provide a vision for an ideal state of preparedness for pandemic therapeutics, and a delivery plan for this vision for stakeholders to coalesce around.

At the March 2023 meeting of the 100 Days Mission Steering Group, members suggested that the International Pandemic Preparedness Secretariat (IPPS) - via its 100 Days Mission Science and Technology Expert Group (STEG) and working with international partners (see Acknowledgements section) - should support the development of a 100DM Therapeutics Roadmap. The original objective was to seek commitments from implementation partners to work together along the value chain to meet the 100 Days Mission goals for therapeutics.

A subgroup of the 100DM STEG was formed in Q2 2023, encompassing individual experts from a variety of fields, along with a diverse range of other partners. Together these stakeholders convened throughout 2023 to identify the key issues related to therapeutics development for pandemic preparedness, set out their own role in the therapeutics value chain, and establish ways of working collaboratively to deliver solutions. This work has formed the basis of the 100 Days Mission Therapeutics Roadmap.

The headline goal is the development of at least two ‘Phase 2 ready’ therapeutic candidates for each of the top 10 WHO priority pathogen families, while also advocating for pre-agreed routes for the conduct, coordination and oversight of clinical trials, accelerated regulatory pathways, at-scale manufacturing and procurement.

The roadmap has four high level objectives:

1. To raise awareness of the need for increased investment in the therapeutics pipeline and an end-to-end approach from discovery to development, with access embedded by design

2. To highlight ongoing scientific drug discovery and development activities being carried out by stakeholders aligned to 100DM therapeutics goals

3. To identify gaps in the current therapeutic discovery and development pipeline and setting milestones accordingly

4. To provide a framework for action, based on concrete milestones, as well as suggesting potential partners to implement the recommendations.

In the absence of a single end-to-end coordinator for therapeutics development, it is hoped that this roadmap will offer a step towards a more formalised ‘Therapeutics Coalition’, and, in time, the emergence of an appropriate coordinator.

Throughout 2024, IPPS and subgroup partners will convene a series of workshops to identify concrete next steps for the implementation of the roadmap. These workshops will cover early-stage R&D coordination, clinical trials and regulatory pathways, and access, market-shaping activities and manufacturing.

IPPS would like to give special thanks to Unitaid, the Medicines Patent Pool (MPP), Drugs for Neglected Diseases Initiative (DNDi), the INTREPID Alliance, READDI Inc for their contributions as part of the core working group, as well as wider subgroup members and partners, including CEPI, 100DM STEG members, World Health Organization (WHO) Science Division, PAD, The Cumming Global Centre for Pandemic Therapeutics, PAVM/Africa CDC, Pushpa Vijayaraghavan and GCTC, and looks forward to working with a growing number of partners to see the roadmap implemented.
The case for investing in therapeutics for pandemic preparedness and response

Safe and effective therapeutics are vital for reducing the burden of mortality and morbidity from pandemic diseases. They are essential for treating people who fall ill (in the community through to critical care settings), slowing or ameliorating symptom progression or preventing infection/disease, reducing the burden on health systems during emergencies. The deployment of effective therapeutics is particularly essential while a vaccine is being developed, tested and rolled out, for diseases for which vaccine development is difficult or impossible, or where vaccines do not block transmission to others.

Even if a vaccine becomes available for a given virus, breakthrough cases are likely and vaccine efficacy may wane over time or due to new variants. Crucially, for some patient groups a protective vaccine response is unlikely due to underlying co-morbidities, including immunocompromise; these may also be the people at highest risk of worse outcomes from infectious disease, making the availability of effective and durable therapeutics even more important, especially for sustained pandemics. Some sections of the population may be unwilling to accept vaccination, and while vaccine hesitancy must be structurally addressed rather than accepted, it is unlikely to ever be eradicated. These groups may be more accepting of therapeutics, particularly when unwell. Therapeutics can also be deployed as pre- and post-exposure prophylaxis (PrEP and PEP), especially for health workers and those in vulnerable groups. Additionally, therapeutics may make individuals less infectious, contributing to epidemiological control.

For these reasons, therapeutics should be a cornerstone of an effective rapid response to a new virus, in tandem with diagnostic and vaccine development and public health measures, but have often been neglected in successive epidemics and pandemics, receiving substantially less funding and political attention than vaccines. The Therapeutics Pillar of the Access to COVID-19 Tools (ACT) Accelerator received less than 10% of total donor funding, compared to nearly 70% allocated to the vaccines pillar, COVAX. The lack of funding for therapeutics was a key contributing factor in hampering efforts to develop and facilitate equitable and timely access to COVID-19 treatment. Despite a significant lead in development – thanks to prior efforts against SARS-CoV - nirmatrelvir/ritonavir became available long after the target of 100 days from the World Health Organization (WHO) COVID-19 Public Health of Emergency of International Concern (PHEIC) declaration, and at least a year later than the novel mRNA vaccine from the same manufacturer (see Figure 1), which benefitted from a long history of mRNA platform-based R&D. While in this case there may have been specific technical challenges related to the development of this particular antiviral therapeutic combination, it nevertheless emphasises the importance of sufficient preparedness development work to ensure timely availability. The development of remdesivir is a good illustration of the criticality of this approach; a well-characterised human safety and pharmacokinetics (PK) package from prior Ebola work enabled prompt review by the US Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) by May 2020, within the 100 day target. A key learning from the COVID-19 pandemic is the need for sustained investment across vaccines, diagnostics, and therapeutics, to develop medical countermeasures that can be rapidly deployed in a variety of settings, with equitable access a key principle of development and delivery.
It is also important to note that key interdependencies between different product types mean that development across products can bring dividends for future pandemic response. For instance, some types of therapeutics are best deployed rapidly following a positive diagnostic result, pointing towards the need to embed ‘test and treat’ approaches, with innovative access to treatment models. Ensuring co-ordination between vaccine and therapeutic developers can help target basic science and R&D towards pathogens where it’s harder to develop a vaccine; and given some of the similarities in manufacturing and regulatory processes for developing certain vaccines and biological therapeutics, there is a clear opportunity to converge development pathways and address constraints in manufacturing capacity.

Background, rationale and development

The 100 Days Mission (100DM) aims to prepare as much as possible during inter-pandemic periods, so that within the first 100 days of a PHEIC being declared by the WHO, safe, effective, and affordable diagnostic tests, therapeutics, and vaccines (DTVs) are ready to be produced at scale.

In 2021, G7 and G20 leaders welcomed the 100DM, agreeing that the first 100 days of a pandemic are crucial to changing its course and bringing it under control, and this is only possible with the right tools. While the 100 Days Mission has its origins in the G7, it is a global initiative that has been endorsed by a range of stakeholders across different regions, who subscribe to its core objective of achieving rapid and equitable access to pandemic countermeasures.

In the Second 100 Days Mission implementation report, it was highlighted that unlike vaccines and diagnostics - which have international R&D convenors and funders in the form of the Coalition for Epidemic Preparedness Initiative (CEPI) and the Foundation for Innovative New Diagnostics (FINN) - the therapeutics ecosystem lacked the same coordination and structure, and despite experiencing some of the same challenges with regards to clinical trials and regulatory issues, faced barriers that were distinct from other pandemic/outbreak response tools.

At the March 2023 meeting of the 100 Days Mission Steering Group, members asked the International Pandemic Preparedness Secretariat (IPPS) - via its 100 Days Mission Science and Technology Expert Group (STEG) and working with international partners - to support the development of a 100DM Therapeutics Roadmap. A subgroup of the 100 Days Mission STEG was formed in Q2 2023, encompassing experts in a variety of fields, along with a diverse range of other partners. Together these stakeholders convened throughout 2023 to identify the key issues related to therapeutics pandemic preparedness, consider their own role in the therapeutics value chain, and ways of working collaboratively to deliver solutions. This work has formed the basis of this roadmap, along with wider consultation with other partners.

The subgroup’s work is grounded in Recommendations 3, 5 and 6 of the original 100DM 2020 report, namely:

3. Develop prototype antiviral therapeutics, including antibody therapies, for pathogens of pandemic potential.

4. Invest in simplified cheaper routes for producing monoclonal antibodies and other new therapeutic modalities.

5. Strengthen the role of the international system in R&D capability and coordination for therapeutics.


7. The organisations in the subgroup are: Unitaid, DNDi, READDI Inc, the INTREPID Alliance, CEPI, MPP, GCTC, the Cumming Centre, PAD and Africa CDC, along with several individuals, including STEG members.
Building upon these principles and successive recommendations in 100DM reports, and in consultation with partners, this roadmap elaborates 3 new detailed vision statements upon which to set forward looking goals and milestones:

The new vision statements remove the 2026 target by which to develop the 25 ‘Phase-2 ready’ therapeutic candidates, recognising the the lack of products currently in the pipeline.

Work around the roadmap’s operationalisation in 2024, including detailed therapeutics pipeline attrition rate analysis, will lead to concrete timelines being attached to this objective in next year’s report. It is recognised that some viral families have greater pandemic potential, greater risk of transmission and animal to human spillover, and thus they will attract more research interest. WHO’s updated priority viral family list – due to be published in early 2024 - will provide helpful analysis to prioritise efforts, however it is important that medical countermeasures are developed against all priority viral families, given multiple uncertainties regarding the source of the next pandemic. For some pathogen families, it may be more challenging to identify targets to develop antivirals and it will take longer to reach this goal. While it is acknowledged that research groups and funders will prioritise different viral families, it is hoped that improved coordination and communication – linked to funding asks could lead to a diversity of investment across families, with improved resource allocation and a healthy degree of overlap. Furthermore, spreading efforts across viral families gives the world the best chance at being ready to tackle Disease X.

About this document

The purpose of the roadmap is to:

- Raise awareness of the need for increased investment in the therapeutics pipeline and an end-to-end approach to development, with equitable access embedded by design.
- Highlight ongoing scientific drug discovery and development activities being carried out by stakeholders, and facilitate collaboration and coordination aligned to 100DM therapeutics goals.
- Identify gaps in the current therapeutic discovery and development pipeline and set milestones accordingly.
- Provide a framework for concrete action, with suggested potential partners to implement the recommendations.

The roadmap aims to provide a springboard for action and further collaboration between partners, encompassing key strategic visions and milestones, as well as potential partners to implement the recommendations. At this stage, the 100DM Therapeutics subgroup represents a nascent coalition of stakeholders with a shared interest in the goals of the 100 Days Mission, convened by IPPS. The milestones that have been set this year prioritise building on the progress already made over the course of 2024, as well as identifying longer-term goals. The success of the roadmap’s implementation will depend on collective and individual accountability, continued collaboration and coordination to strengthen the relationships between partner organisations, the elaboration of workplans to deliver the milestones, and securing funding to enable the work.

See ‘Pre 100 Days (Preparedness)- Vision Statement’ section for more detail and rationale
Challenges

As we map out the steps needed to achieve the 100DM for Therapeutics, the single most challenging barrier identified by partners to its implementation is the lack of end-to-end funding, from early-stage R&D to market-shaping activities and downstream procurement. As exemplified by the 100DM Scorecard - drawing on data gathered by Policy Cures Research - funding for therapeutics for the current top 10 pathogens of pandemic potential (as per the WHO R&D Blueprint) is lacking depth and diversity, with the US Government providing the overwhelming majority of R&D funding in this space for the past decade.

As part of the development of this roadmap, the IPPS has worked with partners to produce preliminary estimates of the development cost of the 100DM goal of two ‘Phase-2 ready’ candidates per viral family. The Rapidly Emerging Antiviral Drug Development Initiative (READDI Inc) estimates a mean cost of $248M to advance 2 small molecule compounds from a single family to ‘Phase 2 readiness’ based on an average of 5 antiviral programmes and only including direct scientific R&D costs. Though considering the entire end-to-end development costs and hence not directly comparable, other published sources have estimated the development cost for a single infectious disease drug to get approval at $1.2bn9, similar to the recent US Government Accountability Office report of $800m-$2.5bn per pandemic drug10. At the moment, neither governments nor industry are investing sufficiently, and in fact, some pharmaceutical companies are retreating from the infectious diseases landscape altogether11. These factors are resulting in a pipeline that is very limited outside of COVID-19, influenza and Ebola Zaire (See ‘100 Days Mission therapeutic pandemic preparedness Goals and Progress Made’ section) or influenza.

The role of the private sector is crucial when it comes to developing new therapeutics for pandemic preparedness. However, market forces alone will not incentivise manufacturers to research and develop antiviral drugs for future pandemics, particularly given the market dynamics are less attractive than for other disease areas, such as chronic non-communicable diseases, including oncology or metabolism which attract significant industry investment. Traditional anti-infective development is hindered by issues such as stewardship, that while crucial from a public health perspective, limit end use and confound a traditional market paradigm. When it comes to therapeutics for Pandemic Preparedness and Response (PPR), there are uncertainties about how much product will be needed during a pandemic, particularly given unknowns surrounding the impact of Public Health and Social Measures, vaccination, and other factors. The intent is to invest in readiness, but many products will never be deployed or not in any significant volumes.

The roadmap also sets out the technical barriers to early-stage R&D, including the lack of investment in pre-clinical models, as well as issues surrounding regionally diversified manufacturing, regulatory challenges, and aspects of delivery and community engagement. For each of the challenges identified, a series of preparedness milestones are elaborated, which would take the world closer to realising the 100 Days Mission for Therapeutics.

ACCESS – A CORE PRINCIPLE

Equitable access should be a core objective of pandemic preparedness and response efforts. The ultimate long-term goal of this roadmap is to facilitate rapid, equitable access to pandemic therapeutics, enabled by a strong product pipeline, flexible supply capacity, optimized manufacturing, established regulatory pathways and market shaping activities. There is a global health security imperative to develop products that are genuinely accessible to all. Equitable access should not be an afterthought, and can be embedded in early-stage research through an ‘access by design’ approach to developing inclusive TPPs that meet the needs of diverse populations (especially those in low-resource settings), and by considering the role of voluntary licensing and generic manufacturers to ensure appropriately diversified manufacturing and affordable products.

One of the original 100DM recommendations was for there to be a standardised approach to access clauses within public R&D funding agreements, in order to enable predictability for all parties. Further discussion on the details and nuances of such potential agreements is needed, but for public funders, such clauses can be a route to ensuring a return on investment in terms of products that meet global needs. Such terms could include commitments to LMICs-relevant product design and development (i.e., usability within simplified models of care; diverse clinical trial settings) and access terms (e.g., cost-plus pricing for LMICs markets, or other mechanisms that balance sustainability and affordability; broad voluntary licensing and technology transfer)12.

However, these clauses have differing impacts, depending on at what stage of development the R&D funding is given and there is a need for further public-private discussion on the most impactful way of enabling access and equity to final products, without hampering innovation and industry engagement. As part of the commitment to pandemic access, the International Federation of Pharmaceutical Manufacturers & Association (IFPMA) proposed in 2022 to create a collaborative solution for more equitable rollout of vaccines, treatments and diagnostics for future pandemics via the Berlin Declaration, committing to reserve an allocation of real-time production of vaccines, treatments and diagnostics for priority populations in lower income countries and take measures to make them available and affordable.13

13. https://www.bloombergsviews.com/opinion/access-is-not-an-afterthought_00c7e6ae532aaf
The therapeutic landscape for a given viral infectious disease can encompass a variety of broad mechanisms of action (e.g., direct acting antivirals, host immunomodulation and others), as well as treatment modalities (e.g., small molecules, monoclonal antibodies (mAbs) etc) and indications (e.g., treatment of the acutely unwell, pre-exposure and secondary prophylaxis, Long COVID etc). Understanding the role treatment might play in the pandemic response is critical and needs to be conceptualised from the outset, to ensure appropriate TPPs are developed and to identify gaps or areas of weakness.

The COVID-19 pandemic provided important learnings about the role of therapeutics in pandemic scenarios. One important aspect of COVID-19 pathogenesis was the transition from predominantly viral mediated pathology in early disease, to host-driven inflammatory pathology in late and severe disease, which have had a significant influence on how treatments have been used. Here we set out the therapeutic paradigms for COVID-19, and learnings that can be taken forward.

**SMALL MOLECULE DIRECT ACTING ANTIVIRALS (DAAs)**

Several therapeutics were developed predominantly targeting the SARS-CoV-2 MPro (3-CL) protease, or as replication inhibitors acting through inhibition of RNA polymerase. Several had already completed early development steps from prior programmes including Ebola and SARS-CoV, with remdesivir the most advanced, having human PK and safety data, and crucially, a supply of readily available clinical trial material. The oral therapeutics were principally used in high and middle-income countries by patients with early COVID-19 disease and risk factors for disease progression, initiated within 5 or 7 days of symptom onset. There was more limited data studying direct-acting antivirals (DAA) use in severe disease, with the exception of intravenously-administered remdesivir.

Certain agents demonstrated resilience against loss of in-vitro potency against variants, unlike monoclonal antibodies (mAbs), which are susceptible to viral binding site changes. Some patients who may otherwise have benefitted from their use were unable to use these therapeutics due to contraindicated co-morbidities or drug-drug interactions (DDIs). A range of factors, including a lack of originator product, low demand at the time oral antivirals became more widely available and regulatory, delivery and access challenges resulted in access to COVID-19 antivirals in LMICs lagging significantly. In addition, even now, there remain limited paediatric treatment options.

- **Potential roles of DAAs in a future pandemic:** Oral DAAs with low toxicity and few DDIs are generally well suited for use as therapeutics to treat symptomatic cases in the community and outpatient setting, typically within a short window of infection or symptom onset, and potentially as PEP. Diagnostics developed in tandem would aid the test-and-treat paradigm, encourage uptake of testing and rapid access to novel treatments. In a pandemic with a new and mutable virus, DAAs may be less susceptible to loss of activity due to variants than mAbs or vaccines. However, unless long half-life formulations and combinations are developed, there remain potential challenges with their deployment as PrEP. Small molecule medicines may have relatively low manufacturing and distribution costs that facilitate broad access and use.

- **Opportunities for development:** Aiming for (once daily) oral administration with fewer toxicities and DDIs will broaden the eligible population. The development of broad-spectrum antivirals that are effective against multiple viruses or viral families is more likely than for mAbs. However, development times still need to be reduced across all stages of the process for both innovative and generic developers; indeed a number of DAAs still took far longer than 100 days to become available for use, including some that had already completed a degree of prior development (see Figure 1 for example). This emphasises the need to invest in more expansive and sufficient preparedness development work ahead of time to facilitate rapid availability within the goals of the mission. Therapeutics consisting of two or more active molecules with orthogonal mechanisms of action may provide a higher barrier to resistance development, which may be important for some viral pathogens.
ANTIVIRAL MONOCLONAL ANTIBODIES

Owing to higher costs, non-oral routes of administration and low adverse event profiles, monoclonal antibodies were largely used to treat patients with early mild-moderate COVID-19 within 5-7 days of symptom onset at risk of progressing to severe disease, who were otherwise unable to take oral treatment due to co-morbidities or DDIs. They were almost exclusively deployed in high-income countries (HICs) due to cost, transport and administration complexity. Half-life extending technologies were used in many approved mAbs, which meant that as single administration agents they were innately more suited than other therapeutics to a role in pre-exposure prophylaxis, particularly in the immunocompromised who are unable to mount effective vaccine responses. Despite this, they were not widely used for PreP, even in many HIC settings outside of the USA prior to the emergence of new variants due to cost. Some evidence of benefit in severe disease was demonstrated, despite their activity being predominantly antiviral.

The in-vitro neutralisation activity of all approved mAbs was impacted by the evolution of SARS-CoV-2 variants, albeit to a variable degree, limiting their utility in the later phase of the COVID-19 pandemic. The loss of in-vitro activity was not a unidirectional progression, and subvariants of resistant lineages have demonstrated reversion towards greater in-vitro susceptibility depending on the binding site for the mAb.

- **Potential roles of mAbs in a future pandemic**: mAbs are typically able to be isolated and tested rapidly as part of antiviral drug discovery efforts. In addition, human mAbs are usually able to rapidly move through preclinical and clinical development due to innate safety and typically predictable PK, and as such, could be available as some of the earliest therapeutics for a novel virus or Disease X. However, unless key challenges for access to mAbs, including high cost of manufacture, intravenous (IV) administration, health system, cold chain capacity, supply and manufacturing constraints can be overcome, they may have more utility as a low volume, high-impact part of the global therapeutic response, for example, in defined local/regional outbreak settings, for groups who are otherwise unable to use oral treatments (e.g., those with comorbidities, pregnant women), or in severe disease where IV administration may be less problematic. They are well suited as PreP agents for those in whom vaccines may be less protective and who require long-lasting protection (e.g., immunocompromised) or for front-line healthcare workers who require immediate protection that cannot be provided by vaccines, due to the lead time needed to develop a host immune response. Antibody dependent enhancement may be a theoretical risk for some viruses treated with partially neutralising mAbs, though it did not emerge as a major issue for SARS-CoV-2.

- **Opportunities for development**: Broadly neutralising (BiAbs) or mAbs directed against highly conserved molecular viral targets (e.g. those that are biologically fundamental to the virus and that are conserved between different members of the same viral family) may help reduce the risk of the development of resistance and potentially broaden their activity. Improvements to facilitate broader access include developing routes of administration to eliminate parenteral use, reducing cost and improving stability. Combination mAbs with non-overlapping, conserved binding sites may increase the barrier to resistance development but come at increased volume for injection and cost. Other antiviral biologics such as peptides, bispecific antibodies, and DARPin s, among many others, will likely expand the role of biological therapeutics in future.

IMMUNOMODULATORS

In the case of COVID-19 disease, the transition from virally mediated pathogenesis to host-mediated end organ disease meant that these agents were principally used for hospitalised patients with severe disease, complementing the utility of DAAs which were largely used to treat mild disease (small molecules and mAbs) or prevent infection (mAbs). Many were repurposed, existing drugs that were readily available in the early stages of the pandemic. During the COVID-19 pandemic, a variety of immunomodulatory mechanisms of actions demonstrated benefit including IL-6 and IL-1 inhibitors, JAK-2 inhibitors, and glucocorticoids, some of which were small molecules and some mAb drug products. Some products, such as dexamethasone, are cheap to produce and manufacture, and are globally available, while others are not.

- **Potential roles of immunomodulators in future pandemics**: as agents that principally act to reduce the inflammatory cascade in humans, these agents may demonstrate utility across any virus where inflammation features in the pathogenesis of the disease. Many already have well-characterised safety profiles and may be readily available for testing and use early in a pandemic as part of pragmatic platform trials, which may be less suited to new agents.

- **Opportunities for development**: Understanding which patients may benefit most from immunomodulation and at which point in disease, as well as better understand how different immunomodulatory therapies may best be used in combination will be important to study. Broader acting host-directed therapies with mechanisms of action beyond immunomodulation (e.g., in promoting proportionate and effective antiviral host defence responses) are an exciting new avenue of development and may have a role at earlier points in the therapeutic cascade, before severe disease stages, if they have antiviral activity.
The current state of progress for therapeutics against the current WHO R&D Blueprint pathogens is outlined in the table below. The data highlights the dearth of therapeutics candidates for some of the pathogens most likely to cause the next pandemic. Outside of COVID-19 and Ebola Zaire, there are no approved therapeutics for the WHO R&D blueprint pathogens and a concerning lack of late-phase candidates in development. The majority of candidates are still in early development, with a significant number in the pre-Phase 1 stage. It is important to note that the current analysis has not conducted a qualitative assessment of these candidates. This will be an important next step (see Milestone 2.3). While there has been a substantial increase in R&D funding in 2020-22 compared to 2017-2019, this is almost exclusively for COVID-19 therapeutics. Exempting COVID-19, the net spend on these pathogens has declined over 2020-2022, affected predominantly by a decrease in Ebola funding following the approval of a number of products. There are relative increases in funding of Nipah, Marburg and Lassa fever, though the overall spend remains low for these pathogens.

### Footnotes
- The data cut for the tabular pipeline data is correct as of August 2023 and represents small molecules and biologics. For COVID-19 it includes antivirals and immunomodulators. Data was extracted from the Policy Cures Research Infectious Disease Tracker (https://www.policycuresresearch.org/pipeline-database/) except COVID-19 data which was taken from BIO COVID-19 therapeutics development tracker (https://www.bio.org/policy/human-health/vaccines-biodefense/coronavirus/pipeline-tracker).
- # Approved products are products granted a marketing authorisation (product licence or registration certificate) by a designated medicines regulatory authority, defined as Stringent Regulatory Authorities (SRAs), National Regulatory Authorities (NRAs) of vaccine producing countries of maturity level 3 or above (as defined by WHO), listed Authorities (LA) or WHO Prequalification. Organisations included also need to have an accessible online database. For more details, please see pipeline curation methodology at https://www.policycuresresearch.org/pipeline-database/.
- Ω Counts include only unique candidates or combinations and active candidates defined as publicly available updates from the last 3 years. Candidates that have stalled more recently and whose information is not on the public domain may still be counted and so there may be an overestimation.
- ¥ EUAs granted to COVID-19 mAbs were all subsequently withdrawn due to SARS-CoV-2 variants, though approvals/authorisations remain in other regions e.g. EU. COVID-19 therapeutics include immunomodulators which treat the disease not the SARS-CoV-2 virus. Immunomodulators have been demonstrated to be efficacious and a number are approved for COVID-19. The denominator is hence not comparable with the other rows, but this reflects the more mature therapeutic and scientific landscape for COVID-19.
- Funding data source: https://gfinderdata.policycuresresearch.org/
- ** The WHO R&D Blueprint list is currently being revised, moving to a pathogen families approach. It is expected to be published in early 2024. Although influenza is a highly plausible cause of future pandemics, it is not included in the table as Policy Cures Research’s data source does not capture comprehensive information on this virus, and it is not currently a WHO R&D Blueprint priority pathogen. Disease X is not included in the table as no data was available.

### Table 1

| R&D Blueprint pathogen | Pre-clinical studies complete (ready for human use) | Clinical development | Approved | Funding
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<tbody>
<tr>
<td></td>
<td>Phase 1 trials (safety)</td>
<td>Phase 2/3 trials (efficacy)</td>
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<td>2020-22</td>
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<td>MERS</td>
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<td>Ebola Zaire</td>
<td>16 (8)</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>Ebola Sudan</td>
<td>13 (6)</td>
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<td>2</td>
<td>0</td>
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<tr>
<td>Marburg</td>
<td>5 (10)</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>Zika</td>
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<td>0</td>
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<tr>
<td>Nipah</td>
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<td>Crimean Congo Haemorrhagic Fever (CCHF)</td>
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<td>279 (64)</td>
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100 Days Mission therapeutic pandemic preparedness: progress made
As part of pandemic preparedness, development of at least two 'Phase 2 ready' therapeutic candidates for each of the top 10 WHO identified priority pathogen families (ideally at least two differentiated candidates; antiviral small molecules, biologics or other suitable modalities), based on inclusive TPPs, which address the needs of all patients and markets, and are conducive to rapid, equitable access. Therapeutics which are active against conserved viral targets and are therefore mostly likely to be active against multiple viruses within and beyond a viral family, and against new viruses originating from a given family (Disease X), should be prioritised. Where possible, consideration should be given to advancing beyond phase-2 readiness, particularly for diseases where the epidemiology could facilitate the conduct of clinical trials.

Develop scientifically rigorous and validated programmable platforms or technologies capable of speeding the delivery of new, or enhancing existing therapeutics in case of a pandemic, and able to be rapidly and safely applied to 'Disease X'.

Rationale

As set out in the introduction, the therapeutics landscape does not currently have a strong central co-ordinating framework or body with a global perspective to direct or fund research priorities. Individual organisations, companies and institutions in different countries are working on different viral families and aspects of the therapeutics value chain, but the absence of coordination and collaboration, with meaningful private sector engagement, has resulted in a fragmented landscape.

The aim of the Vision 1 is to enhance coordination of funding to avoid too much duplication of effort and help direct efforts towards gaps in the R&D landscape. The idea underpinning the formation of a potential 'Therapeutics Coalition' is to bring together partners under a shared framework to better coordinate efforts and create linkages where they currently do not exist. A new entity is currently not envisaged, but rather a genuine coalition with diverse, representative and global membership.

Vision 2 and 3 represent differentiated, but complementary approaches to achieve the same goal of facilitating a robust, adaptable pipeline of pandemic therapeutics. Strategic vision 2 focuses on advancing candidates that show promise against viral families that are the potential originators of a new pandemic virus to 'Phase 2 readiness'. In some cases, the pandemic virus may have overlap with existing viruses in the family (e.g. pandemic influenza or SARS-CoV-2 similarity to SARS-CoV), while in other cases, there may be significant evolutions, including mode of transmission, pathogenesis or reproduction rate, manifesting in a change in the viral genetic code. The premise is that essential similarities within a viral family, and in some cases between viral families, may mean a therapeutic developed against an existing viral family member could retain activity against others. The pandemic preparedness efforts set out in this roadmap would ensure that such products
are ready to be tested, with a range of ‘Phase 2 ready’ candidates available for definitive efficacy trials at the start of the new pandemic. An example of how this approach could work was demonstrated in COVID-19, where remdesivir was able to be tested as part of the pivotal ACTT-1 clinical trial for COVID-19 in Feb 2020, less than 30 days after the WHO PHEIC declaration. To enable this, pre-clinical evaluation against coronaviruses including MERS and SARS-CoV had been completed, in addition to Phase 1 clinical dose ascending studies and the generation of clinical safety and PK data from the Ebola treatment programme. The availability of sufficient existing drug product material was also a substantial factor in enabling the inclusion of remdesivir in the ACTT-1 trial and an important aspect of Phase-2 readiness. Advancing beyond Phase-2 readiness may be plausible and desirable, where the clinical and funding landscapes can support such efforts, and may provide more immediate benefits to communities affected by outbreaks or localised epidemics.

Strategic vision 3 focuses on the development of platform technologies that are able to rapidly and flexibly produce new therapeutic agents to treat pandemic infectious diseases. A focus on platforms that can develop or adapt broadly acting agents is a way to maximise breadth of pathogen cover. This an important complementary strategy to tackle a completely new pandemic virus, or those sufficiently differentiated from the progenitor family that the preparedness therapeutics advanced due to their activity against the former are ineffective. This vision will only be truly enabled with the development of novel approaches such as those that utilise Artificial Intelligence (AI) or Machine Learning (ML) to produce step-changes in speeding the end-to-end discovery and development of new therapeutics. At the same time, it is crucial that sufficient quality and safety assessments are built into the use of novel development processes, with appropriate regulatory oversight to ensure public trust is maintained in these new products.

Both of these approaches synergise with a third path to pandemic therapeutic development: the rapid and co-ordinated testing of repurposed therapeutics in sufficiently robust and statistically powered clinical trials. In this case, ‘repurposed’ may mean a medicine with an existing approved indication that has a well characterised safety, PK and efficacy profile for its given indication, as well as established formulation, manufacturing and distribution processes. Efficient implementation of this approach requires clinical trial and regulatory harmonisation as well as global co-ordination and leadership to prioritise repurposed candidates effectively. With these elements in place, repurposed medicines are likely to be able to be deployed as the first response therapeutics and best suited to meet the challenge of being available within 100 days of the PHEIC. These clinical trial and regulatory issues are to some extent also relevant to vaccines and diagnostics, and therefore are not elaborated as a separate vision statement in this roadmap, but rather are captured in the main body of work of the 100DM.

The intention of this chapter is to create SMART objectives where possible, providing a concrete framework for action by different stakeholders. Milestones are described as ‘2024’ or ‘longer-term goals’ if they are not envisaged to complete in 2024, or where they represent broader aspirations without defined stakeholders. There remain gaps in the path to achieving the strategic visions that cannot be fully elucidated at the moment of publication, particularly in the absence of a co-ordinating “Therapeutics Coalition”. The purpose is to provide a framework to establish consensus between international multisectoral stakeholders on what it would practically take to achieve these goals, rather than setting out a rigid structure. The intention is to leverage existing efforts and where necessary, shape these efforts towards the strategic goals of the 100 Days Mission.

The current framework is grounded in the reality of the situation at the beginning of 2024, with the intent of highlighting gaps to stimulate action, however this framework will need refinement and revision over time. Where there are cross-cutting themes that apply across the diagnostics, therapeutics and vaccines (DTV) development spectrum, only those issues that are specifically relevant to therapeutics are included in this roadmap. Broader themes are discussed in their own sections of the Third 100 Days Mission Annual Implementation report, including clinical trial harmonisation, regulatory process refinement, regional manufacturing and production capacity.
STRATEGIC VISION 1

Ensure sustained R&D funding throughout the discovery-development lifecycle and international co-ordination, ideally via a formal global Therapeutics Coalition, with capacity to bring together diverse existing and newly created stakeholders in pandemic therapeutics.

CONTEXT: CHALLENGES AND OPPORTUNITIES

Without leadership and co-ordination, there is a dual risk of duplication and wasted resources on the one hand, and neglect and a narrow pipeline of drugs, that do not cover the breadth of potential and pandemic risks on the other hand. This technical challenge is further compounded by the risk of a lack of global attention, from governments, funders and industry.

The therapeutics ecosystem does not benefit from the central coordinating entity that the vaccines R&D ecosystem has in the form of CEPI. Thanks to its clear mandate - to develop vaccines, and more recently biologics, against pathogens of pandemic and epidemic potential - CEPI has been able to make progress towards the 100 Days Mission for vaccines by leveraging a broad network of global partners to award grants for work on vaccine development for previously neglected pathogens. While no model is perfect, the combination of vision, partnership and funding has ensured strong political support (post-Ebola) and sustained donor commitments, enabling CEPI to set a clear direction for their research agenda and discovery activities.

An implicit challenge specific to therapeutics co-ordination is that expertise in small molecules and biologics (plus other modalities) are required, which may necessitate a broader consortium of experts and stakeholders to manage the distinct issues in each area. This effect may amplify when considering the need for specialist expertise in all the associated functions, such as regulatory and manufacturing.

A CEPI-like body would be challenging to recreate for therapeutics in the current resource-constrained context, with waning political attention on pandemics. However, lessons could be learned from the end-to-end approach and focus on partnerships inherent to CEPI’s model. If therapeutics funders, developers, and stakeholders from affected communities were to unite around a clear vision (as set out in this roadmap), formalise partnerships that create a win-win situation under a facilitating framework, and agree to direct their respective resources behind a shared strategy and investment case, there is an opportunity to make real progress. Ongoing discussions as part of the WHO-led Interim Medical Countermeasures Network (I-MCM-Net) process provide an avenue for progressing development of the concept of a more coordinated approach to therapeutics development.

A further challenge in the development of new therapeutics is the absence of a strong central procurer for global pandemic treatments, akin to Gavi in the vaccines space. During COVID-19, organisations such as UNICEF22 and The Global Fund23 played a role in procuring pandemic therapeutics for LMICs, learnings could be taken from this work to inform future decisions in this area. Recognising that many therapeutics for pathogens of pandemic potential will not be used in large enough quantities to provide a traditional market for industry - or at all in cases where a specific pathogen never materialises - additional push and pull incentives will be required to keep industry engaged in developing the drugs needed, in the face of considerable uncertainty. Examples of such incentives, such as accelerated approval and tradeable exclusivity vouchers have been employed to support antibiotic drug development. Advanced Market Commitments (AMCs) are another avenue for consideration in this area, and work on how this could apply to antivirals is under consideration by a number of 100DM partners, including SPRING24.

Preliminary development cost estimates of US$248m to develop oral antivirals for a single viral family have been produced in collaboration with READDI Inc. These do not include organisational costs and may not be representative of development costs for all families, however, they provide an idea of the scale of the challenge to develop the pandemic therapeutics pipeline. Publication of substantive cost modelling estimates would enable critical appraisal, broader stakeholder engagement and increase the credibility of the funding asks.

MILESTONES AND GOALS

1. IPPS to support nascent coalition of stakeholders involved in development of 100DM Therapeutics Roadmap to identify the role, expectations and needs of a therapeutics co-ordinating function or coalition, and support partners to outline a process for recommending its creation, with potential links to the WHO-led Interim Medical Countermeasures Network (I-MCM-Net) [noting that the governance of I-MCM-net is still under discussion]

2. Elaborate consolidated cost models for estimating funding requirements for delivery of the therapeutic pipeline as described in strategic vision 2, and agreed by potential coalition partners

3. Identify and agree on the most important push and pull incentives to deliver the pipeline of therapeutics as well as elaborating a strategy to facilitate their implementation through engagement of the key funders/stakeholders

4. Coalition partners to articulate a strategy towards securing the funding requested by the costed investment case for pandemic therapeutics, including the early-stage R&D required.

5. Funders (public, private and philanthropic) to coordinate funding calls to ensure complementarity and spread of investment across viral families. Potentially coordinated via proposed Therapeutics coalition
STRATEGIC VISION 2
As part of pandemic preparedness, development of at least two ‘Phase 2 ready’ therapeutic candidates for each of the top 10 WHO identified priority pathogen families (ideally differentiated candidates; antiviral small molecules, biologics or other suitable modalities), based on inclusive TPPs, which address the needs of all patients and markets, and are conducive to rapid, equitable access.

Therapeutics which are active against conserved viral targets and are therefore most likely to be active against multiple viruses within and beyond a viral family, and against new viruses originating from a given family (Disease X), should be prioritised. Where possible, consideration should be given to advancing beyond phase-2 readiness, particularly for diseases where the epidemiology could facilitate the conduct of clinical trials.

CONTEXT: CHALLENGES AND OPPORTUNITIES
TOWARDS THERAPEUTICS LIBRARIES
One of the overarching goals of the 100 Days Mission is to develop prototype libraries of medical countermeasures for pathogens of pandemic potential. In 2023, CEPI started a conversation with stakeholders on the concept of a ‘Global Vaccine Library’, with further discussions and elaboration set to take place in 2024. A therapeutics library, consolidating knowledge across the scientific landscape in a standardised way, could be a useful tool in achieving the goal of delivering new ‘Phase 2 ready’ therapeutics against pandemic viruses. Such a library could include a knowledge base of putative targets, including sequence and structure, a collection of assays and reagents that enable discovery, or known compounds that could be used for screening campaigns. Under pre-agreed access arrangements, this could enable contributory efforts from a wider range of credible stakeholders. There would be significant challenges to overcome in creating such a library, and engagement of the key contributory and end user groups is essential to move this forward. This could build on the work already started by some groups, such as the AI-driven Structure-enabled Antiviral Platform (ASAP) Antiviral Drug Discovery (AViDD) centre, which has already committed to public disclosure of pandemic related R&D efforts.25

25 https://asapdiscovery.org/outputs/
DEFINITION OF PHASE 2 READY

Sufficient pre-clinical and clinical safety and PK data to delineate a proposed dose range based on suitable validated in-vitro and in-vivo models to enable rapid Phase 2 and 3 trials in the event of a pandemic. It is important to consider where there is opportunity to push forwards at-risk beyond Phase 1 where there may be sufficient cases to enable clinical trials e.g. endemic diseases such as influenza or defined outbreaks. Consideration should also be given to parallel development routes, such as controlled human infection models (CHIM, see box) and animal rule approval pathways where this is not the case.

An example of Phase 2 readiness for a small molecule:

1. The drug has been shown to prevent infection and/or replication of the specific virus (or related virus family) in question or to prevent pathology or symptoms of disease resulting from the infection.
   - Robust evidence (repeated in different models and labs) available from in-vitro/vivo preclinical models or possibly even human studies.
   - Ideally, the mechanism of action of the drug should be known and relevant to the virus targeted.

2. The drug has been shown to be safe for human use in Good Laboratory Practice (GLP) regulatory preclinical safety and toxicology studies.

3. A Phase 1 development programme (e.g. single and multiple ascending dose, food effects and drug-drug interaction studies) has been completed in healthy human volunteers showing that the drug is safe for evaluation in patients and the human pharmacokinetics have been characterized enabling selection of a dose based on PK/PD modelling (e.g. significant time above antiviral IC90) likely to result in measurable reduction in viral load and/or clinical benefit in patients. (This package may be more applicable to small molecule development than single-dose non-oral mAbs for example, which may also undertake more streamlined development program.)

4. A suitable formulation has been developed and assessed in Phase 1 studies to allow (ideally oral) dosing to patients and the stability has been determined to allow (ideally oral) dosing to patients and the stability has been determined to allow (ideally oral) dosing to patients and the stability has been determined to allow (ideally oral) dosing to patients and the stability has been determined to allow (ideally oral) dosing to patients.

5. Sufficient clinical supplies (packaged, formulated drug product e.g. tablet or capsule) are available and in-date to conduct a Phase 2 Proof of Concept (PoC) clinical trial enrolling enough patients to produce statistically significant results, depending on the selected clinical and/or viral endpoint.

DISCOVERY: CHALLENGES AND OPPORTUNITIES

There is a need for alignment across stakeholders on the priority viral families to reduce duplication and focus efforts where they may bring the greatest gains. The publication of the updated WHO Priority Viral families list in early 2024 will provide a key reference point to direct efforts. Beyond this, optimal co-ordination of discovery organisations would ensure that this distinct and, where possible, complementary target identification, compound screening and candidate selection activities - ideally in a pre-competitive space - enable a diverse and robust pipeline to deliver the breadth of threats.

As outlined in the 100 Days Mission 2023 Annual Implementation report and scorecard, government and philanthropic stakeholders are investing across viral families to develop therapeutics. A large proportion of public investment in pandemic therapeutic discovery currently comes from the US government, including Project NextGen (focusing on SARS-CoV-2 vaccines and mAbs), the Antiviral Program for Pandemics (APP), the BARDA DRIVe initiative focussing on host-directed therapies, and Medical Countermeasures (MCM) programs (predominantly influenza and EBV/MCM for filoviruses and smallpox). Meanwhile NIH has funded nine antiviral pandemic preparedness AViDD centres to an estimated total of $577m, including for example, READY-AC (focused on paramyxoviruses, filoviruses, flaviviruses, coronaviruses and togaviruses). The AViDD funding is set to run to 2025 and there has been no public commitment to extend funding beyond this point to this critical discovery program, which would likely severely impact delivery of the pandemic therapeutics pipeline. In Europe, the European Health Emergency preparedness and Response Authority (HERA) includes promoting R&D for therapeutics in its pandemic preparedness remit, with an operating budget of approximately €1.7 billion earmarked for 2022-2027, and has made €100 million top-up to the HERA Invest initiative to support program costs for small and medium enterprises developing medical countermeasures including pandemic pathogens. The Pandemic Antiviral Discovery (PAD) and CEPI have prioritised henipah virus discovery work. Within the pandemic preparedness space, the biopharmaceutical industry has focused principally on SARS-CoV-2 and influenza, where a more traditional reimbursement market may exist. Funding comes from a diverse set of stakeholders across government, academia, philanthropy and industry, each investing according to their individual strategic priorities.

While the programmes do cover a significant number of pandemic potential viral families, they are not comprehensive or strategically co-ordinated, and there is at present no multinational-backed central funder of discovery research with sufficient resources to direct funding towards the discovery gaps, as there is for vaccines (CEPI) or diagnostics (FIND).

TPPs tend to reflect the specific perceived use case of the body responsible for producing them and can vary considerably, even for a given disease. TPP alignment between discovery and development leaders, and organisations responsible for procurement and delivery – including indication prioritisation, populations, and minimal versus optimal criteria - will ensure the generation of pandemic therapeutic candidates that are more likely to continue through development and are better suited for global deployment.

Identifying tractable targets for small molecules, which would ideally retain efficacy across variants and against different members of the same viral family or even across viral families, is a core activity needed to establish a pipeline. Ideally therapeutics with potential differentiated mechanisms of action would be taken forward to enable development of more robust combination therapies. Developing robust, standardised, reproducible in-vitro assays to characterise drug activity against the priority viral families is a precursor to moving candidates through development. These tools may be used throughout a candidate’s lifecycle, for enabling prioritisation of candidates, predicting dose, and even into the post-license phase, should new variants arise.

One major challenge is the paucity of pre-clinical models for pandemic potential viruses that are validated, recapitulate human disease, and predict human response. Better pre-clinical models to reduce attrition, improve dose selection and identify biomarkers could improve efficiency in
Pipeline development is a key starting point from which to assess the future therapeutic needs. The INTREPID pipeline is a key starting point from which to understand the current therapeutic landscape and identify the molecules that meet regulatory acceptability, lead-time issues related to manufacturing of viral challenge material, model validation (dose, timing and route of inoculum, variability in infection rates and quantitative infection, understanding of human disease and symptoms) create time challenges during a pandemic, where in any event, there may be a surplus of patients available for study in a standard clinical trial. These factors perhaps suggest that their principal role could be in preparedness activity, once robust models using appropriate inoculating strains are available (such as for influenza). Here they may provide useful information about biomarkers or virological course, PK in healthy subjects, as well as steering dose selection in early development. Finally, the translation of effect from healthy volunteers to the intended target population including the elderly or individuals with multiple co-morbidities remains an issue that limits their utility.

Many antiviral drugs that have been developed for one virus may have the potential for activity against other viral families (e.g., remdesivir). In general, comprehensive profiling of antivirals that have demonstrated clinical efficacy against one virus for repurposing against different viruses or viral families could represent an efficient way to populate an initial pipeline, especially if their mechanism of action, PK and safety is already well characterised.

At present a large proportion of discovery efforts identified in the wider pandemic preparedness therapeutic landscape are being conducted by SMEs or academic bodies. Programmatic costs amplify as a candidate moves through the development cycle, requiring larger clinical trials, increasing chemistry, manufacturing, and controls (CMC) needs, as well as larger pre-clinical supportive data packages. Industry engagement will be crucial to ensure promising candidates are pursued into later development. Forging better collaborative links between academic, multilateral and small biotech discovery organisations who are advancing target identification and candidate selection, and industry partners with experience in later phase development and regulatory filing will be beneficial. Agreeing on the essential drug properties and characteristics through shared TPPs in the early stages of development will ensure better traction and progress through late phases. A therapeutics coalition could foster these links and establish ways of working together. Understanding the current pandemics therapeutic pipeline is a key starting point from which to assess the future therapeutic needs. The INTREPID Alliance, representing seven large companies and IFPMA, is now assessing this with industry experts, to identify the molecules that meet criteria commonly used for progression through pharmaceutical development, starting with those in clinical phases and working backwards into earlier phases of discovery for 12 viral families of interest, which it intends to publish in early 2024. READDI Inc has recently completed a similar pipeline mapping exercise. Together with the Policy Cures Research source data that underlies Table 1 of this roadmap, these three databases could be triangulated to inform the validity of the findings and provide better insights to a potential ‘Therapeutics Coalition’ about pipeline depth, diversity, advancement and robustness. Beyond INTREPID, other biopharmaceutical companies have maintained a broad base of interest in the 100DM, including therapeutics pandemic preparedness, and continue to engage with the mission through facilitated meetings and updates.

While global clinical trials co-ordination and design, and regulatory reform and international harmonization are both critical aspects of meeting this strategic vision, advancements in this area will affect vaccines and diagnostic development to a large degree, and as such are reflected in cross-cutting themes (see Section 6), and actioned more broadly as a core part of the objectives of the main 100DM [see 31 100DM Annual Implementation Report]. As such specific milestones are not included for these domains in the therapeutics roadmap.

With increasingly robust and validated pre-clinical models comes the opportunity for conditional drug approvals through pathways such as the US FDA Animal Rule, though such approvals may have limited global applicability. In addition, controlled human infection models (CHIM) have been developed for influenza, SARS-CoV-2 and dengue, and while these are typically utilised for vaccine development, can also be useful for therapeutics to aid understanding of pathogenesis and identify biomarkers, in addition to testing the effect of a given therapeutic on symptom development/resolution or viral load.

For a CHIM to be applicable, the inoculating agent cannot cause severe disease in a healthy volunteer and treatments ideally need to be available, meaning that this model will not be suitable for studying many of the viruses from high-risk pandemic families. In addition to ethical considerations and barriers to regulatory acceptability, lead-time issues related to CDRP manufacture of viral challenge material, model validation (dose, timing and route of inoculum, variability in infection rates and quantitative infection, understanding of human disease and symptoms) create time challenges during a pandemic, where in any event, there may be a surplus of patients available for study in a standard clinical trial. These factors perhaps suggest that their principal role could be in preparedness activity, once robust models using appropriate inoculating strains are available (such as for influenza). Here they may provide useful information about biomarkers or virological course, PK in healthy subjects, as well as steering dose selection in early development. Finally, the translation of effect from healthy volunteers to the intended target population including the elderly or individuals with multiple co-morbidities remains an issue that limits their utility.

MILESTONES AND GOALS

NB: The publication of the WHO Priority Viral Families list in 2024 will facilitate many of the milestones listed below.

**2024 milestones**

1. Consolidate mapping exercises that summarise the knowledge of potential viral targets across the priority viral families, linked to known development programs and funding as data sharing permits to establish a shareable baseline.

2. Complete a mapping exercise of the gaps and priorities in in-vitro assays and pre-clinical models for the target viral families that recapitulate human disease. (Preliminary scoping work of pre-clinical models has been completed by READDI Inc, as presented in Table A1, Appendix).

3. Establish and regularly update a central database across the discovery and development area, to track progress of the most promising candidates towards Phase 2-readiness and beyond. Include a qualitative assessment of candidates to assess diversity and pipeline robustness, identify gaps and assess progress. The INTREPID Alliance will publish their analysis for clinical phase programmes in early 2024, followed by pre-clinical programmes in the second half. Insight into industry led activities through INTREPID and engagement with non-INTREPID organisations, who are active in the pandemic infectious disease area should complement this work.

4. As part of the therapeutics coalition, foster links between early-stage public and privately funded R&D discovery partners with industry development stakeholders and aim to set objectives and agreed workplan to collaborate on antiviral development towards the target of at least 2 phase-2 ready therapeutic candidates per viral family.

5. Explore with key stakeholders across the pandemic preparedness drug discovery and development ecosystem the scope and feasibility of creating a therapeutics library.

6. Assess the use of novel pre-clinical and clinical development methodologies for non-traditional regulatory approaches for therapeutics pandemic preparedness.

7. Early-stage researchers collaborate to implement workplan and where possible, avoid excess duplication of efforts, while incorporating a variety of approaches and healthy competition.

8. Scientific stakeholder groups should aim to develop human dose prediction models based on standardised and robust methodologies that enable fair assessment and prioritisation of the pipeline.

9. Scientific stakeholder groups should aim to profile existing antivirals for activity against a broader spectrum of viruses to assess the potential for repurposing. Consider profiling the pathogenesis of known diseases caused by pandemic potential viruses to assess the potential for benefit with immunomodulators that could be tested in clinical trials.

**TARGET PRODUCT PROFILES:**

Agreeing on a TPP for a pandemic therapeutic is a critical first step in aligning strategic priorities and ensuring traction through the development process across the various stakeholders that will be involved in ultimately delivering the medicine. Target product profiles (TPPs) outline the key safety, PK and efficacy characteristics of a medicine, together with its intended population, use cases, indication, dose and administration, and durability and stability properties. As these characteristics may be different depending on indication, elaborating a number of TPPs (e.g. for PrEP, PEP and treatment) as well as by modality (e.g. small molecule vs biologic) will provide better clarity. For pandemic therapeutics, including details on spectrum of activity and desirable pre-clinical attributes including definitions of in-vitro and/or animal model activity and PK/PD drivers are useful additions. Cost is an important consideration for access, with inclusive TPPs ideally featuring low-cost APIs that do not make therapeutics unaffordable when scaled up. Resistance profiles, though considered desirable, tend to be difficult to parameterise in a meaningful clinical sense. ‘Minimal’ and ‘optimal’ profiles are defined by the needs of their intended population and scope of use. NIH have produced TPPs for a number of pandemic priority viral families, which INTREPID alliance have recently provided feedback on. These are detailed pandemic profiles, developed for the US context, which include the ‘global population’ in the ‘optimal’ attributes, along with other characteristics that may be considered essential for equitable global access and use. WHO TPPs, which are intended for development in 2024 following the new priority viral families list, will consider the global perspective, similar to the existing DNDi TPP for COVID-19.
Develop scientifically rigorous and validated programmable platforms or technologies capable of speeding the delivery of new, or enhancing existing therapeutics in case of a pandemic, and to be able to rapidly and safely applied to‘Disease X’. 

Alongside the concept of preparedness outlined in Strategic Vision 2, developing new platforms that can facilitate more rapid, responsive and efficient therapeutics development or refinement will be essential to enhance preparedness in the medium to long term. The goal here is exemplified by the utility of mRNA vaccines in the COVID-19 response, a platform technology with a decades long development history mostly in oncology, that was able to be deployed in the pandemic situation to more rapidly develop vaccines than traditional means. Finding such similar platforms for therapeutics and advancing their progress in the pre-pandemic period will benefit pandemic responses as well as medicine as a whole. This aim is unlikely to be achieved without use of novel technologies such as AI and machine learning that can help discover, develop and deploy the application of rich new omics data sources. Ensuring that public trust is maintained for such platforms through continuous rigorous safety and quality assessment as well as regulatory oversight will be vital.

The implementation of AI and computer-aided design in the drug discovery and development process is a long sought-after goal to improve pipeline efficiency. A recent Wellcome report on the application of AI in drug discovery identified five major AI use cases, four pertinent to therapeutics, and resources should be focused, though it’s important to note that such programmes may yet take years to develop and validate. While AI augurs great promise for drug discovery and development, there are also key remaining barriers and adoption challenges for its use, including varying levels of trust and understanding on its value, as well as a lack of widespread access to mature datasets, tools and computational capabilities. Novel platforms that can rapidly generate tailored therapeutics for Disease X require functioning, well-resourced global surveillance networks by which to detect new viruses, genetically characterise them and share accurate data globally with stakeholders. During COVID-19, the genetic sequences of the newly identified virus were shared rapidly internationally, which enabled, for example, the first trial for remdesivir to start in February 2020 building on prior development work completed for Ebola. This example, and others, highlight the importance of such surveillance networks and real-time open channels of communication in support of the development of new pandemic therapeutics. 

**Biological therapeutics for pandemics**

A biologic is a therapeutic substance that is produced through a biological process, typically from purified large-scale cell cultures of animals, bacteria, yeast or plant cells, rather than chemical synthesis. The range of potential biological therapies has increased significantly over time (including antisense oligonucleotides, aptamers and siRNAs), gene and gene-editing therapies, and cell therapies. Together with these new therapeutic modalities, the rapid expansion in the size and quality of pathogen-related omics-based datasets linked to computational biology could lead to rapid progress for biologic drug discovery. While not all of these modalities may yet prove to yield valuable therapeutics for a global pandemic response, and will need to overcome some of the challenges associated with mAbs such as cost, complexity of distribution and use, the breadth of new and novel options available to explore is promising.

A number of biologicals (mAbs) were approved as both therapeutics and prophylactic agents for use against SARS-CoV-2, while some of these other biological modalities were explored as potential therapeutics including DARPin, and aptamers. In addition, nucleic acid therapeutics such as siRNAs are currently under development for other viruses. There are a number of organisations actively exploring the utility of novel biological agents for pandemic preparedness. The Cumming Global Centre for Pandemic Therapeutics, for example, aims to use gene editing and silencing technologies (e.g., therapeutic oligonucleotides and gene editing tools), to recruit the innate immune system as part of host directed therapy, and develop broadly neutralising antibodies that might work across multiple pathogens and may be more resilient to resistance development. Meanwhile SPRiNt in Germany has funded four research teams – shortlisted from nine original teams – developing a variety of antiviral platform technologies from CRISPR-CAS9 to DNA ‘viral traps’. In the US, the BARDA DRIVe initiative is seeking to develop host directed therapies, including biologics, to as part of a threat agnostic approach for a variety of health security threats, including pandemics. They may offer a significant advantage for pandemic preparedness by eliminating the need for pathogen identification and pathogen specific treatment.

**Manufacturing and Supply Chains: Optimisation for mAbs**

Compared to small molecules, mAbs are expensive to make due to complex biomanufacturing processes and resource-intensive regulatory requirements. There are opportunities to decrease development and manufacturing costs through novel, higher-yield technologies and more disruptive innovations that are in the pipeline to further simplify antibody-based therapies and their manufacturing. Product optimisation could also improve processes for biologics, for example, by increasing potencies and therefore reducing dose requirements. Prioritising mAbs that have non-parenteral routes of administration will facilitate global use. Wellcome, Unitaid and Medicines Patent Pool (MPP) are collaborating to understand the barriers and define the incentives and enablers that would facilitate accessible access to mAbs for infectious disease indications. Possible accessible business model solutions include investment portfolio linkage across epidemic/endemic indications and in combination with non-ID indications.
MILESTONES AND GOALS

2024 milestones

3.1. As part of the longer-term goal to implement AI in pandemic preparedness therapeutic development, therapeutics coalition partners should track the success of known groups such as ASAP to find examples of best practice and conduct horizon scanning of known AI drug discovery tools that may contribute.

3.2. Coalition partners should track the progress of organisations developing novel antiviral platforms, including host defence, such as Cummings and SPRIN-D, to assess their potential to increment the pandemic therapeutic pipeline, and incorporate findings into 2024’s 100 Days Mission Scorecard.

3.3. Early-stage researchers and industry should assess the use of AI and computer-aided design in the pandemic preparedness drug discovery process to realise pipeline efficiencies.

3.4. All stakeholders - funders and industry in particular - should pursue the development of platform technologies that can generate broad-acting antiviral therapeutics or are rapidly adaptable.

3.5. Enhance the global surveillance of pathogens for early detection together with the ability to rapidly characterise viruses and share information globally.

3.6. Explore novel technologies and business model strategies with appropriate incentive mechanisms to reduce mAbs manufacturing and deployment costs.

Longer-term goals
Many of the challenges faced in developing new therapeutics will be common to vaccines and diagnostics and are addressed in the Third 100 Days Mission Annual Implementation report. Preparedness activities to develop pandemic clinical trial platforms to a point of readiness in advance, or agree regulatory pathways to product licensure, will enable standardised and efficient implementation at the point of a PHEIC declaration. This section provides a high-level overview of these cross-cutting challenges, which are more fully elaborated in the 100DM report, before highlighting issues within these areas that are particular to therapeutics.

Clinical trials

Challenges persist in advancing clinical trials and streamlining regulatory processes during inter-pandemic periods to ensure readiness for future pandemics. Addressing these challenges requires a commitment to the establishment of a sustainably funded, regionally dispersed network of clinical trial sites that can pivot for emergency response. Such a network needs to be complemented by pre-agreed trial protocols within prototype libraries for vaccines, therapeutics and diagnostics, and reinforced regulatory capacity globally with regional regulatory harmonisation to ease the burden on innovators.

WHO has begun the process to develop a joint vision on strengthening clinical research capabilities, aligned with the World Health Assembly resolution (WHA75.8). A key goal is to improve coordination and streamlining of regulatory and ethics review and approval processes, as well as ensure that trials infrastructure is fully functional and ‘always on’ in inter-pandemic times, via testing MCMs that treat endemic diseases closer to affected communities.

The overarching end goal of a clinical trial system that would enable a 100-day response is built on the following components:

- Sufficient sustained, functional and used clinical trial capacity and capability, especially in areas where outbreaks are most prevalent
- Moving away from the stop start of project-by-project clinical trials
- Coordinated clinical pipelines for this global network of trials
- Best practices on trial design embedded across global efforts

44 Available at https://ippsecretariat.org/publications/
46 https://apps.who.int/gb/ebwha/pdf_files/WHA75/A75_R8-en.pdf
There is a need to develop an agreed master protocol for testing the efficacy of meaningfully repurposed drugs – under stringent criteria - while final approvals are sought for novel products, building on learnings from the COVID-19 RECOVERY, ACTIV-NIH, ANTI-COV and SOLIDARITY trials. The vast majority of clinical evaluation efforts with repurposed products during COVID-19 were too small, inefficient and undertaken in an uncoordinated way, severely limiting their usefulness. National, regional and global co-ordination of platform trials to undertake the fewest, suitably statistically powered studies to provide actionable results would enable a greater number of products to be tested in a shorter period of time, avoiding bottlenecks in trial capacity and participant numbers, and ultimately faster approval of appropriate medicines.

Given that funding for clinical trial infrastructure and training is generally limited, more effort is needed for therapeutics and vaccines actors to work together to identify areas of complementarity and overlap, particularly as they are often engaging with the same in-country stakeholders. It is important to consider the need for contemporaneous clinical trials in key LMIC countries, especially where such trials are a precondition for regulatory review. Example of clinical trial platforms focussing on pandemic preparedness in LMICs are ISABIC® and PANTHER®, while a global adaptive platform trial that has continued to evolve towards pandemic preparedness is the REMAP-CAP Trial. Bringing together networks to understand synergies and complementarities is a key enabler of better clinical trials for future pandemics.

Manufacturing

The inequitable access to medical countermeasures seen during COVID-19 highlighted a potential need for diversified manufacturing ecosystems. Regional entities and coalitions joining forces to collaborate and bolster manufacturing capacity may alleviate some of the challenges experienced in ensuring access to products at a global scale, particularly during times of high demand.

There is a need to further strengthen regional manufacturers with the capacity to manufacture and supply pandemic products regionally to prevent bottlenecks in global supply that were seen during COVID-19. While there remain challenges in establishing and sustaining new manufacturing capacity such as funding, workforce and infrastructure maintenance, situating this within centres that are able to produce in-demand routine therapeutics in inter-pandemic periods will engender resilience and independence. An example may be exploring surge capacity in regionally important generics manufacturers, who could fulfill capacity needs for both antivirals and anti-infectives, an important link in the current lack of regional generic antibiotic manufacture. Another important lesson from COVID-19 was the need for more resilient chains that supply the basic materials and reagents needed to synthesise drugs including deeper reserve and improved surge capacity.

There are challenges with the manufacture of monoclonal antibodies, where high costs and the specialist manufacturing techniques needed mean there is unlikely to be enough distributed capacity to meet global needs during a pandemic. Incentivising existing manufacturers to invest in capacity to produce new antivirals and biologics is a key opportunity in this space, particularly given the lack of predictable, sustained demand signals, but in the limited funding environment, should be appraised and prioritised according to impact assessments. One challenge is that biosimilars are significantly more expensive to manufacture and qualify than generic small molecules. Nevertheless, there should be due consideration given to preparedness activities that identify strategic manufacturing sites for biologics in LMICs that have existing and sustainable biosimilar manufacturing capacity. It is plausible that in a future pandemic scenario that mAbs might be the first available therapeutics due to speed/ease of identifying. Formulating strategies in pre-pandemic times that address supply and CoGs constraints for mAbs would be important to ensure standing capability when needed in pandemics, such as that proposed by IAVI®. Access models for mAbs have so far had limited success in other disease areas, and there is a need to explore ways in which these could be put in place for pandemics, including LMIC-based biosimilars, where appropriate.

In cases in which licensing agreements between innovator and generic manufacturers will be a mechanism to facilitate access to new therapeutics in LMICs, it will be important that licensing and tech transfer take place as early as possible in product development, to reduce to a minimum the lag between the availability of the innovator product and that of the generic versions for supply in the licensed territory. Access to key starting materials, intermediates and reference products by licensees will be critical to enable the rapid development and registration of licensed generics in parallel with innovator products and ultimately expedite access. Consideration should also be given to the implementation of mechanisms to reduce the risk taken by manufacturers developing generic versions of products before efficacy data is fully available.

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46 https://www.iavi.org/
47 www.pantherhealth.org
Regulatory

Challenges persist in streamlining regulatory processes during inter-pandemic periods to ensure readiness for future pandemics. A key tenet of this is flexible regulatory procedures, including pre-agreed emergency regulatory procedures during a PHEIC. Other considerations include the potential adoption of preparatory regulatory approaches, such as pathway master files, cloud-based data platforms and shared risk-benefit frameworks, as well as strengthened regulatory capacity in all regions to expedite national approvals.

Despite exceptional regulatory processes and collaboration during the COVID-19 pandemic, there were still significant time lags for quality assurance of generic products, which in turn meant that the products could not be procured by international agencies, even when they were approved in the country of manufacture and the country of sale.

Regulatory innovation is needed for pandemic products in order to preserve stringent requirements for safety and efficacy, and to look for ways to arrive at required information more efficiently. Industry and research-based institutions should prioritize sharing data with WHO and regulatory authorities alike, and can engage in early discussions to establish data requirements or a common simplified submission to accelerate the process, both for first product authorization and follow-on generic versions. New models could also be applied to regulatory approval for clinical trials to avoid unnecessary delays in emergencies. It should be acknowledged that for some pathogens, it will not be ethical to undertake classic placebo-controlled studies in phase 2/3 trials (e.g. filoviruses) and regulatory pathways must be developed that take this into consideration and utilise alternative data generation methods within appropriate risk-benefit frameworks, such as the animal rule pathway.

Part of a strategy for expedited regulatory approval of pandemic therapeutics could be to prioritize products already registered by stringent regulatory authorities (SiRAs)/WHO Maturity Level 4 or prequalified by WHO, using mechanisms such as Collaborative Registration Procedure (CRP) or mutual recognition that can facilitate and accelerate registration. This can also prioritize registration in countries with a high burden of specific diseases, which are more likely to produce an outbreak, focusing on medicines with access gaps in LMICs.

Licensing and technology transfer

Voluntary licensing is one of the tools that can be used to help facilitate access to medicines. Voluntary licensing agreements can contribute to increasing supply and supporting affordable access in the countries covered. They can be established through bilateral negotiations between companies – as seen in the case of Gilead’s remdesivir during COVID-19 or facilitated by organisations such as the MPP, as per agreements concluded with MSD and Pfizer respectively during COVID-19. The voluntary nature of these partnerships makes this approach much more attractive to both innovators and generics manufacturers, creating the environment for successful cooperation, especially in areas of tech transfer. Indeed, G20 health ministers have recognized the need to leverage existing networks of generic manufacturers built during the COVID-19 pandemic for equitable access to future pandemic countermeasures.

For licensing to deliver on access to new treatments, it is important to reduce to a minimum the lag between availability of the innovator product and availability of generic versions for supply in the licensed territory. Making progress requires a multi-faceted approach. Early licensing (while the innovator product is still under development), prior identification of qualified manufacturers, sharing of technical-how, streamlined mechanisms for sharing of reference product, mechanisms to de-risk manufacturers (where appropriate) and accredited regulatory pathways for quality assurance and in-country regulatory approval are some of the enablers for licensing to deliver rapid access to new therapeutics during a pandemic. These options should be coupled with a broader set of considerations, including a base of experienced partners, open trade, strong and diversified supply chains, healthcare delivery systems including trained medical professionals, delivery and logistics systems as well as WHO and regulatory lists of medicines that are approved.

Voluntary licenses delivered bilaterally and through the MPP during COVID-19 enabled the use of preexisting generic production capacity to manufacture at-scale oral antivirals in different LMICs. However, eventually demand for the licensed products declined with the changes in epidemiology, with some generic manufacturers disengaging as a result. Suitable market interventions that can de-risk demand fluctuations and uncertainty - also for more predictable demand for health tools between pandemics - can also increase generic manufacturers’ capacity to address future outbreaks. The sustainability of generic manufacturers between pandemics is reliant on the ability to produce non-pandemic health tools with the ability and willingness to rapidly pivot to a new pandemic threat when needed.

Partnerships between originators and generics manufacturers will play an important role in ensuring equitable supply of new medicines across LMICs during a pandemic, creating sufficient regional manufacturing capacity, especially in Africa, to enable resilience in a pandemic. In 2024, building on the efforts of several actors in the area of voluntary licensing such as MPP and new regional initiatives, partners could look to develop an operational framework for the pre-selection of a regionally diverse network of generic manufacturers with the required capacity and commitment to rapidly develop and supply LMICs across different types of therapeutics that can be engaged as possible licensees, as appropriate, for innovative pandemic therapeutics. In the long-term, the aim could be to develop a network of pre-selected regionally diverse manufacturers of potential pandemic therapeutics and put in place standard operating procedures that would enable rapid implementation of possible licensing and technology transfer agreements to accelerate development and registration (including streamlined mechanisms for access to the reference products by prospective licensees).
How to make this vision a reality – 2024 milestones

This table only focuses on the delivery aspects of the 2024 milestones, not on the longer term

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Lead organisations /sctors</th>
<th>Description</th>
<th>Progress and notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Identify coalition responsibilities</td>
<td>IP:R, WHO: United, NIH, CEPI, INTREPID Alliance, READDI Inc</td>
<td>It is uncertain if a single existing body has the expertise and capacity to fulfil the needs of taking the co-ordinating role at this time. Establishing a new body would be time consuming and inefficient, and a coalition of existing trusted actors with expertise in pandemic therapeutics development might instead be an option. IP:R will lead on a series of convenings in early 2024 to discuss practical next steps for implementation of the roadmap.</td>
<td>WHO is currently consulting on the development of an interim medical countermeasures network (i-MCM-net) which could play a key role in inclusive coordination (noting that no governance decisions have yet been made).</td>
</tr>
<tr>
<td>1.2 Generate cost estimates for the therapeutic pipeline</td>
<td>Stakeholders involved in pipeline delivery activities, e.g., READDI Inc, INTREPID</td>
<td>Preliminary funding estimates based on modelled costs that are available from individual stakeholders for single programs could be shared with other stakeholders for review. A holistic cost estimate to deliver the therapeutic pipeline would be a useful tool in negotiating future funding agreements. Costs for wider goals such as a therapeutic library could be next steps.</td>
<td>Seek to publish a final cost model in a peer-reviewed publication to provide transparency and legitimise the ask.</td>
</tr>
<tr>
<td>1.3 Identify push and pull incentive instruments to deliver the pipeline</td>
<td>Avi and partners INTREPID and other Industry representative SPRIND</td>
<td>Once a costed estimate for delivery of the pipeline is available, understanding how such funding may become available will be important. In addition to direct funding of discovery programs such as the AViDD centres (which may be considered a ‘push’), pull incentives may facilitate pipeline delivery through typically more indirect funding. Some of these have been used for antibiotic development such as accelerated approval or fungible priority review vouchers, while yet others have been proposed. Advanced market commitments are under consideration by the SPRIND.</td>
<td>Examples of initiatives that have been used, or are under consideration to facilitate antimicrobial development, which are impeded by market failure issues include the UK subscription model61; US Pasteur Act62.</td>
</tr>
<tr>
<td>2.1 Summarise knowledge of small molecule viral targets for the pandemic potential viruses</td>
<td>R&amp;D discovery organisations including INTREPID and other R&amp;D discovery organisations including AViDD centres, Cummings Centre, INTREPID, NINDS / NIAID, NIH, CDC, NCI, IMET</td>
<td>Identify a lead coalition actor to synthesise a definitive report linking knowledge of small molecule viral targets to known R&amp;D activities and their funding streams. This would create a valuable strategic resource to identify areas of strength and weakness in the early-stage pipeline and potentially be used towards costing R&amp;D funding deficits.</td>
<td>Aim to make the data public by publishing summary outcomes.</td>
</tr>
<tr>
<td>2.2 Describe gaps in in-vitro assays and pre-clinical models to support the therapeutics pipeline</td>
<td>READDI Inc have completed preliminary scoping work for animal models</td>
<td>The next steps will be to identify the viral families with the greatest need for further in-vitro assay and pre-clinical model development taking a holistic view aligned to the 100DM objectives and estimating costs for such programs that could be used to support funding requests to donors.</td>
<td>See Table 1, Appendix, for preliminary animal model scoping.</td>
</tr>
<tr>
<td>2.3 Establish a central database of pandemic pathogen discovery and development programs</td>
<td>INTREPID, PCC</td>
<td>Consolidating the discovery and development therapeutics mapping exercises to create a dataset that can be prospectively updated over time. Aim to scrutinise qualitative aspects and remove programs that have ceased active development. Numerous sources of publicly available pandemic therapeutic development funding data exist including Pandemic DACT - Global research collaboration for infectious disease preparedness (GCRDP).</td>
<td>Include a qualitative assessment of the pre-clinical candidates identified in Table 1.</td>
</tr>
<tr>
<td>2.4 Set objectives and agree workplan to collaborate on antiviral development for subset of viral families</td>
<td>Coalition of early stage funded R&amp;D researchers and later phase developers</td>
<td>With an emphasis on global equitable access, a consortium of currently funded antiviral R&amp;D groups will establish foundational principles and guidelines for collaboration coordination to advance promising assets and fill gaps in existing R&amp;D efforts. Communication and collaboration strategies and workplans will be developed to maximize expertise and resources across groups to accelerate antiviral drug discovery and development.</td>
<td>Arrange first in-person meeting in early 2024 to agree (1) pre-discussed objectives and mission of the coalition, (2) establish preferred ways of working amongst coalition members, (3) identify initial demonstration projects to illustrate the added value of collaborative efforts towards therapeutics R&amp;D for pandemic preparedness. Prepare to engage with other stakeholders by contributing to an integrated R&amp;D ecosystem for PID (noting that no governance decisions have yet been made).</td>
</tr>
<tr>
<td>2.5 Explore creation of a pandemic therapeutics library</td>
<td>Academia Industry End users Community</td>
<td>The creation of a library is a cross-cutting recommendation from the original 100DM applicable to DTV. In 2024, work will build on the conversation started by CEPI regarding a vaccines library concept. Groups identified as contributing to scientific progress in Objectives 2.1-2.4 which are founding pillars of any library would be in scope. Subject matter experts across a range of disciplines, including basic science, clinical, data management, IP, regulatory and legal among others would be needed. The group should aim to identify how the sharing of knowledge might accelerate progress towards the ultimate goal of generating new clinical candidates as well as discuss issues related to library intent (repository vs standardised platform), scope, curation, data management, governance, access and oversight.</td>
<td>CEPI have begun work towards a vaccine library which will be informative to the therapeutics process. Other examples of virtual drug development collaborations or similar exercises should be sought for learning (e.g. European Lead Factory, EBBATB).</td>
</tr>
</tbody>
</table>
## How to make this vision a reality – 2024 milestones

This table only focusses on the delivery aspects of the 2024 milestones, not on the longer term

<table>
<thead>
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<th>Objective</th>
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<tr>
<td>2.6 Assess the use of novel pre-clinical and clinical development methodologies for non-traditional regulatory approaches</td>
<td>Academia, Regulatory bodies, Drug development organisations</td>
<td>Assess the potential use of CHIMs and animal rule pathways towards non-traditional regulatory approvals for pandemic preparedness therapeutics. Development of better animal models.</td>
<td>10Day Sooner, an advocacy group for CHIMs, has initiated dialogue with key stringent regulators on the applicability of such approaches, building on the experiences from COVID-19.</td>
</tr>
<tr>
<td>3.1 Track the progress of AI implementation in pandemic drug design</td>
<td>Stakeholders with expertise in AI driven pandemic drug development aligned to the 10DM goals - AGAP, Cummings Centre</td>
<td>AI may be used across the development process, for example in target identification or screening or clinical trial implementation. Some aspects of AI based development have a greater degree of validation or contribute disproportionately to efficiency gains. Many AI processes based on large language models or adaptive learning are iterative, with the number of iterations crucial to the quality of the output. These technologies will continue to increment in time becoming more and more reliable and useful. At this point, understanding which AI modalities may make the greatest contribution through tracking key delivery partner progress is a valuable step towards wider AI implementation in pandemic preparedness. Horizon scanning for where other validated AI technologies might meaningfully contribute to pandemic therapeutic development would be an important second step. Engage AI drug development experts to facilitate horizon scanning and identify potential stakeholders. Alphafold protein folding structure prediction would be an invaluable tool if used to fill gaps in target structures for pandemic viral families.</td>
<td></td>
</tr>
<tr>
<td>3.2 Novel programmable platforms that enable rapid development</td>
<td>Cummings Centre, SPRIND, Industry, Academia, AViDD centres</td>
<td>Novel platforms to develop nucleic acid based therapeutics could be rapidly implementable and scalable in the case of a pandemic. However novel nucleic acid based medicines are in the early stages of regulatory acceptability as medicines and may instead be part of future solutions rather than immediate ones. An increasing number of therapeutic oligonucleotides are being approved including for infectious disease, and while they have attractive properties as medicines (low off target toxicity rates, long duration of action), they also have unique challenges in target site delivery and PK and may be better suited to chronic infections. Broad-acting, safe antivirals that could work across a number of viruses within and outside of a viral family while maintaining efficacy would represent a major efficiency. They would need to have a high barrier to resistance development as their utility might also promote widespread use, but this may be consistent with their activity against conserved viral targets. Recruiting the innate immune system might be able to achieve similar aims but would need to avoid complications related to autoimmunity, immune hyperstimulation or inadvertent downregulation. Despite challenges, the promise of novel platforms is too great to ignore and tracking the progress of these ambitious programs and other similar ones in the early stages will help prioritise future research.</td>
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</tbody>
</table>
DAY ZER0 ONEWARDS (RESPONSE)

The vision of success for the response from Day Zero onwards (i.e. the moment a PHEIC is declared), is that the preparedness activities outlined in the previous sections of this roadmap facilitate a rapid, agile and equitable response. Agreeing frameworks for co-operation in advance of the next pandemic across the domains of clinical trials, manufacturing including supply of basic materials and reagents and distribution networks, as well as international scientific and regulatory collaboration is paramount.

Crucial elements of this ‘Day Zero onwards’ vision include:

FINANCING

- The rapid release of at-risk funding for push-pull mechanisms for priority pandemic products

REGULATORY

- Expedited review of clinical trials by SRAs
- Channels for emergency use authorisations
- Coordinated review of product dossiers by champion regulatory authorities (across regions) and WHO
- Post-marketing authorisation data sharing and pharmacovigilance

PRODUCTION

- Pivot production capacity for priority pandemic products; at-risk manufacturing starts, with financing to support this.
- Generic licensing discussions begin, with pre-approved network of licensees in place
- Support expanded production of priority products in Phase 2 and 3, including tech transfer as relevant
- Co-ordinate and prioritise supply chains of basic reagents and materials necessary to synthesise the most impactful therapeutics in the most efficient and equitable manner

CLINICAL TRIALS AND PIPELINE DEVELOPMENT

- Launch of strategic globally-coordinated Phase 2 clinical trials for priority therapeutics, meeting TPPs in pre-established platform trial sites, with protocols agreed
- Support product optimisation of pre-developed priority candidates for better adoption in LMICs
- Reactive pipeline that is continually refreshed
- Coordinate and optimise pipeline, and consider coherences with other tools

Second 100 days

Once therapeutics for a given pathogen have been developed and manufacturing activities have commenced, ensuring all populations can access them is critically important. While not the main focus of this roadmap, delivery considerations are vital when starting early-stage discovery research, to ensure that products are developed to meet the needs of all populations. During COVID-19, many lessons were learned with regards to procurement, delivery, population confidence in medical countermeasures and reaching those in remote or low-resource settings. A mix of health systems capacity issues, implementation barriers, and uneven country prioritization all contributed to a lack of equitable patient access.

In 2023, the G7 under Japan’s Presidency - together with UNICEF and other partners - launched the MCM Delivery Partnership for equitable access (MCDP), which aims to bring together partners to prepare for the delivery of MCMs for future pandemics, drawing in particular on lessons from the COVID-19 Vaccine Delivery Partnership (COVDP).

Drawing on key learnings from COVID-19, there are several prerequisites that need to be in place to enable a well-planned, efficient roll-out of therapeutics:

- Coordinated strategies across all medical countermeasures, and consider key interdependencies in use cases i.e. the need for access to diagnostics in order to link to certain treatments
- Scenario planning and demand data projections, to help governments and international organisations with planning
- Firm procurement agreements for global LMIC supply, factoring in potential volumes required and access considerations for key populations e.g., migrants, pregnant women, immunocompromised patients etc.
- Coordinated equitable allocation models for scarce supply scenarios, along the lines of the WHO-hosted COVAX Allocation Mechanism
- Better understanding of Costs of Goods and Supply (COGS) and source information for products
- Support for community outreach, health literacy and community health workers to engage with populations and clinicians and increase uptake of new products
- Work to increase antiviral prioritization by countries and their health care infrastructures to support rapid delivery, including test-and-treat programs
- Obtain country feedback on what it will take to facilitate rapid uptake of antivirals and to strengthen health systems
- Streamline contracting process. Streamline governments’ contracting systems that could be activated during a pandemic, working end-to-end across the value chain including manufacturing and final product procurement
- Secure logistics and delivery, including distribution chains all the way down to the last mile to ensure access, involving communities, and strengthened health systems.
MAINTAINING THE PIPELINE

Constant review of product efficacy and tool optimisation is essential, even once the first products become available. Robust processes need to be in place, including via geographically dispersed clinical trials, to review how well tools are working and later via real-world evidence, particularly in LMIC contexts.

As seen during COVID-19, there will be a constant need to repeat the R&D cycle to optimise treatments and develop new ones, to keep pace with viral evolution. Given the wide variety of therapeutic uses cases and the risk of certain classes of drug driving viral mutations, there is a constant need to expand and update the treatments available, even when several products are approved and available.

Next steps

This document has been produced to provide a framework for stakeholders working in a variety of different sectors and to kickstart a series of conversations about what it will take to achieve the 100 Days Mission for Therapeutics.

It is anticipated that this roadmap will be updated on an annual basis, and develop over time to incorporate additional aspects including detailed attrition rates analysis for the therapeutics pipeline, a validated cost estimate for investing in new pandemic therapeutics, and eventually a full investment case for what it would take to fund the 100 Days Mission for therapeutics.

In the short term, IPPS and the 100DM Therapeutics Working Group, together with other stakeholders such as WHO, will be convening a series of implementation workshops in 2024, dedicated to different parts of the value chain, from early-stage discovery research, through to market shaping and manufacturing. The aim is to bring partners together to discuss tangible areas of progress that could be made, and build support for a potential coalition of pandemic therapeutics partners, to enhance the world's preparedness for the next pandemic.

Acknowledgements/contributors

A subgroup of the 100 Days Mission STEG was formed in Q2 2023, encompassing experts in a variety of fields, along with a diverse range of other partners. Together these stakeholders convened throughout 2023 to identify the key issues related to therapeutics pandemic preparedness, consider their own role in the therapeutics value chain, and ways of working collaboratively to deliver solutions. This work has formed the basis of this roadmap, along with wider consultation with other partners.

IPPS is very grateful to the following contributors for their inputs and advice on the development of this roadmap:

100DM STEG members: Ruxandra Draghia-Akli (Johnson & Johnson, INTREPID Alliance), Ranna Eardley-Patel (CEPI), Jean-Francois Toussaint (Sanofi), Ken Ishii (University of Tokyo)

1DaySooner

Africa Center for Disease Control (CDC)

Coalition for Epidemic Preparedness Innovations (CEPI)

Cumming Global Centre for Pandemic Therapeutics

Drugs for Neglected Diseases Initiative (DNDi)

European Medicines Agency (EMA)

Gilead

Good Clinical Trials Collaborative (GCTC)

GSK

International AIDS Vaccine Initiative (IAVI)

International Federation of Pharmaceutical Manufacturers and Traders (IFPMA)

Johnson & Johnson Global Public Health R&D

INTREPID Alliance

Medicines Patent Pool (MPP)

Merck

Pandemic Antiviral Discovery (PAD)

Policy Cures Research (PCR)

Pushpa Vijayaraghavan - Sathguru Management Consultants & MPP Board Member

Rapidly Emerging Antiviral Drug Development Initiative (READDI Inc)

SPRIND

Unitaid

United Nations Children’s Fund (UNICEF)

Wellcome

World Health Organization (WHO)

IPPS Therapeutics Roadmap Authors:

Dr Andrew Skingsley, Chief technical author, Senior Director, Drug Development R&D, GSK (seconded to IPPS)

Charlotte Baker, Deputy Head, International Pandemic Preparedness Secretariat (IPPS)

The organisations in the subgroup are: Unitaid, DNDi, READDI Inc, the INTREPID Alliance, GCTC, MPP, GCTC, the Cumming Centre, RAD and Africa CDC, along with several individuals, including STEG members.
## TABLE A1: Summary of Select Preclinical Animal Models by Viral Family

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>TYPE(S)</th>
<th>READOUTS</th>
<th>RECAPITULATE HUMAN DISEASE?</th>
<th>LEVEL OF STANDARDISATION, VALIDATION AND REGULATORY CONSENSUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CORONAVIRIDAE</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>SARS-CoV-2</strong></td>
<td>Syrian Golden Hamster</td>
<td>viral load, target organ histopathology, transmission</td>
<td>Yes, mild to moderate disease</td>
<td>overall reasonable standardisation. Variability in challenge dose and timing</td>
</tr>
<tr>
<td></td>
<td>Mice (mouse adapted virus)</td>
<td>viral load; target organ pathology; long term disease sequelae</td>
<td>Yes, severe and chronic disease</td>
<td>good standardisation, good regulatory consensus</td>
</tr>
<tr>
<td></td>
<td>NHP (Cynomolgous)</td>
<td>viral load</td>
<td>Yes, mild to moderate disease</td>
<td>reasonable standardisation; useful for demonstrating efficacy for regulatory review</td>
</tr>
<tr>
<td></td>
<td>Ferret</td>
<td>viral load, transmission, disease pathology</td>
<td>Yes, mild disease and transmission</td>
<td>reasonable standardisation; useful for efficacy testing for transmission inhibitors</td>
</tr>
<tr>
<td><strong>MERS</strong></td>
<td>NHP (Rhesus and marmoset)</td>
<td>viral load, target organ histopathology, disease progression and severity</td>
<td>Yes</td>
<td>reasonable standardisation; useful for testing therapeutics; likely useful for regulatory review</td>
</tr>
<tr>
<td></td>
<td>Mice (hDPP4 transgenic)</td>
<td>viral load, target organ histopathology, disease progression and severity</td>
<td>Yes</td>
<td>good standardisation, though limited use; useful for testing therapeutics</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>viral load, though replication and pathology are limited</td>
<td>No</td>
<td>reasonable standardisation; likely of limited use in regulatory review</td>
</tr>
<tr>
<td><strong>SARS-CoV</strong></td>
<td>Mice (mouse-adapted)</td>
<td>viral load; target organ pathology; severe and mild disease; chronic disease pathology</td>
<td>Yes</td>
<td>good standardisation, though limited use; useful for testing therapeutics</td>
</tr>
<tr>
<td></td>
<td>NHP</td>
<td>low viral load; minimal target organ pathology</td>
<td>No</td>
<td>good standardisation, good regulatory consensus</td>
</tr>
<tr>
<td></td>
<td>Hamster</td>
<td>viral load; target organ pathology; mild disease</td>
<td>Yes</td>
<td>reasonable standardisation, widespread acceptance as efficacy model for clinical endpoints</td>
</tr>
<tr>
<td><strong>FILOVIRIDAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ebola (all strains)</strong></td>
<td>NHP</td>
<td>viral load, target organ dysfunction, gross pathophysiology</td>
<td>Yes</td>
<td>reasonable standardisation, widespread acceptance as efficacy model for clinical endpoints</td>
</tr>
<tr>
<td></td>
<td>Mice (mouse-adapted)</td>
<td>viral load, lethality, overall animal health &amp; welfare</td>
<td>Partial</td>
<td>variety of models, useful for initial efficacy; unclear usefulness for regulatory review in isolation</td>
</tr>
<tr>
<td></td>
<td>Guinea pig</td>
<td>viral load; limited disease or pathology</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Marburg</strong></td>
<td>NHP</td>
<td>viral load, target organ dysfunction, gross pathophysiology</td>
<td>Yes</td>
<td>reasonable standardisation, widespread acceptance as efficacy model for clinical endpoints</td>
</tr>
<tr>
<td></td>
<td>Guinea pig</td>
<td>viral load; limited disease or pathology</td>
<td>No</td>
<td>some standardisation; requires virus adapted to host; limited regulatory usefulness</td>
</tr>
<tr>
<td></td>
<td>Mice (mouse-adapted)</td>
<td>viral load, disease severity and progression; lack severe coagulation disorder</td>
<td>Partial</td>
<td>some standardisation; requires virus adapted to host; limited regulatory usefulness</td>
</tr>
<tr>
<td><strong>TOGAVIRIDAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHIKV</strong></td>
<td>NHP</td>
<td>viral load, target organ pathology</td>
<td>Yes</td>
<td>reasonable standardisation within a species; well accepted models and reasonable regulatory consensus</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>viral load, target organ pathology; disease burden</td>
<td>Yes</td>
<td>standardized and validated model of disease; less regulatory consensus than NHP models</td>
</tr>
<tr>
<td><strong>VEEV</strong></td>
<td>Mice</td>
<td>viral organ; target organ dysfunction and pathology</td>
<td>Yes</td>
<td>limited standardisation; useful for reduction in viral load and pathology; unclear use in regulatory filing</td>
</tr>
<tr>
<td></td>
<td>NHP (cynomolgus)</td>
<td>viral organ; target organ dysfunction and pathology; disease progression</td>
<td>Yes</td>
<td>limited standardisation; disease dependent on dose, route and virus strain; unclear use in regulatory review</td>
</tr>
<tr>
<td>PATHOGEN</td>
<td>TYPE(S)</td>
<td>READING(S)</td>
<td>RECAPITULATE HUMAN DISEASE?</td>
<td>LEVEL OF STANDARDISATION, VALIDATION AND REGULATORY CONSENSUS</td>
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<tr>
<td><strong>FLAVIVIRIDAE</strong></td>
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</tr>
<tr>
<td>Dengue</td>
<td>NHP (rhesus)</td>
<td>viral load, disease course and disease similar to humans; develops ADE</td>
<td>Partial</td>
<td>reasonable standardisation; unclear regulatory consensus for therapeutics</td>
</tr>
<tr>
<td></td>
<td>Mice (immunocompromised)</td>
<td>viral load, low disease similarity to humans</td>
<td>No</td>
<td>unclear role in regulatory review due to limited similarity to human disease</td>
</tr>
<tr>
<td></td>
<td>Humanized mice</td>
<td>viral load, target organ pathology, disease burden</td>
<td>Yes</td>
<td>unclear role in regulatory review; good similarity to human disease; limited standardisation due to intrinsic differences between test animals</td>
</tr>
<tr>
<td>West Nile</td>
<td>NHP</td>
<td>viral load, some degree of pathology</td>
<td>Partial</td>
<td>limited disease compared to humans; useful for measuring reduction in viral load, though unclear role in defining reduction in disease</td>
</tr>
<tr>
<td></td>
<td>Mice (B16)</td>
<td>viral load, pathology and lethality during acute infection</td>
<td>Yes</td>
<td>good standardisation; useful for efficacy testing for therapeutics</td>
</tr>
<tr>
<td></td>
<td>Mice (collaborative cross)</td>
<td>different mouse lines better reflect different aspects of disease (e.g., neurological involvement, persistence, etc.)</td>
<td>Variable based on target indication</td>
<td>minimal standardisation; different lines may be more appropriate for different disease indications</td>
</tr>
<tr>
<td>Zika</td>
<td>NHP (rhesus)</td>
<td>viral load, disease pathology and clearance, fetal transmission model</td>
<td>Yes</td>
<td>some standardisation; useful model for therapeutic efficacy and disease reduction, as well as maternal transmission</td>
</tr>
<tr>
<td></td>
<td>Mice (immune compromised)</td>
<td>viral load and lethality</td>
<td>No</td>
<td>some standardisation, however different virus strains have variable outcomes; useful for measuring reduction in viral load, but not disease severity/progression</td>
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<tr>
<td>Powassan</td>
<td>NHP</td>
<td>limited information</td>
<td>Yes</td>
<td>unclear utility for regulatory review due to limited study/usage of the model</td>
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<tr>
<td></td>
<td>Mice</td>
<td>viral load (acute and persistent); inflammation and neurological symptoms</td>
<td>Yes</td>
<td>some standardisation; useful model for therapeutic efficacy for regulatory review</td>
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<td><strong>PARAMYXOVIRIDAE</strong></td>
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<tr>
<td>Nipah</td>
<td>NHP (african green monkey)</td>
<td>viral load, disease progression and pathophysiology</td>
<td>Yes</td>
<td>reasonable standardisation; useful in regulatory review</td>
</tr>
<tr>
<td></td>
<td>Hamster</td>
<td>viral load, disease severity and progression</td>
<td>Yes</td>
<td>limited standardisation; may be useful as one component of regulatory filings</td>
</tr>
<tr>
<td></td>
<td>Ferret</td>
<td>viral load, disease severity and progression</td>
<td>Yes</td>
<td>reasonable standardisation; may be useful as one component of regulatory review</td>
</tr>
<tr>
<td>Hendra</td>
<td>NHP (african green monkey)</td>
<td>viral load, disease severity and progression</td>
<td>Yes</td>
<td>reasonable standardisation; useful in regulatory review</td>
</tr>
<tr>
<td></td>
<td>Hamster</td>
<td>viral load, disease severity and progression</td>
<td>Yes</td>
<td>reasonable standardisation; useful in regulatory review</td>
</tr>
<tr>
<td></td>
<td>Ferret</td>
<td>viral load, disease severity and progression</td>
<td>Yes</td>
<td>reasonable standardisation; may be useful as one component of regulatory review</td>
</tr>
<tr>
<td><strong>ARENAVIRIDAE</strong></td>
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<tr>
<td>Lassa</td>
<td>NHP (cynomolgus)</td>
<td>viral load, target organ dysfunction; acute and chronic disease manifestation</td>
<td>Yes</td>
<td>reasonable standardisation; accepted in regulatory review</td>
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<tr>
<td></td>
<td>Outbred Hartley guinea pig (mouse-adapted virus)</td>
<td>viral load, pathology, requires adapted virus</td>
<td>Yes</td>
<td>reasonable standardisation; closely mirrors human disease; unclear usefulness in regulatory filings</td>
</tr>
<tr>
<td></td>
<td>Mice (immune compromised)</td>
<td>viral load, lethality due to unclear pathological outcomes</td>
<td>No/unclear</td>
<td>limited standardisation; useful for reduction in viral load; unclear use in regulatory filing</td>
</tr>
<tr>
<td>Guanarito</td>
<td>NHP</td>
<td>viral load, minimal pathology and non-lethal</td>
<td>No</td>
<td>unclear usefulness in regulatory review</td>
</tr>
<tr>
<td></td>
<td>Guinea pig (S13 and Hartley)</td>
<td>viral load and pathophysiology; lacks hemorrhage</td>
<td>Partial</td>
<td>reasonable standardisation; useful as one aspect of regulatory review</td>
</tr>
<tr>
<td>Machupo</td>
<td>NHP (african green monkey)</td>
<td>viral load and pathology; lethality</td>
<td>Yes</td>
<td>reasonable standardisation; useful for demonstrating efficacy for regulatory review</td>
</tr>
<tr>
<td></td>
<td>Mice (immune compromised)</td>
<td>viral load and pathology; disease progression and severity</td>
<td>Yes</td>
<td>reasonable standardisation; previously used to measure ribavirin efficacy; likely relevant for regulatory review</td>
</tr>
<tr>
<td>PATHOGEN</td>
<td>TYPE[S]</td>
<td>READOUTS</td>
<td>RECAPITULATE HUMAN DISEASE?</td>
<td>LEVEL OF STANDARDISATION, VALIDATION AND REGULATORY CONSENSUS</td>
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<tr>
<td>Rift Valley Fever</td>
<td>NHP (marmoset)</td>
<td>viral load and pathology; disease progression and severity</td>
<td>Yes</td>
<td>reasonable standardisation; clear recapitulation of human disease; useful in therapeutic efficacy testing for regulatory review</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>viral load and pathology; disease progression and severity</td>
<td>Yes</td>
<td>reasonable standardisation with variation between mouse strains; useful for testing therapeutic efficacy for regulatory review</td>
</tr>
<tr>
<td></td>
<td>NHP</td>
<td>limited information</td>
<td>No</td>
<td>limited disease limits utility in testing and regulatory filings</td>
</tr>
<tr>
<td></td>
<td>Mice (immune-compromised)</td>
<td>viral load, disease pathology and progression; lethality</td>
<td>Yes</td>
<td>reasonable standardisation; useful for efficacy testing for therapeutics in support of regulatory filings</td>
</tr>
<tr>
<td></td>
<td>NHP (macaque)</td>
<td>viral load and pathology; disease progression and severity</td>
<td>Yes</td>
<td>limited standardisation due to limited use (requires use of virus passaged in deer mice); useful for therapeutic efficacy testing for regulatory review</td>
</tr>
<tr>
<td></td>
<td>Mice (Peromyscus)</td>
<td>viral load</td>
<td>No</td>
<td>limited use leaves critical disease parameters undefined; may be useful for demonstrating viral load reduction by therapeutics</td>
</tr>
<tr>
<td></td>
<td>Hamsters (Andes virus infection)</td>
<td>Hamsters infected with related Andes provide only model of lethal disease; useful for measuring viral load, pathology and disease severity</td>
<td>Yes, with model virus</td>
<td>some standardisation, though limited use; useful for therapeutic efficacy testing; likely useful for regulatory review in absence of other models</td>
</tr>
<tr>
<td></td>
<td>Hamster (immune-compromised)</td>
<td>viral load and persistence; pulmonary inflammation and edema; lethality</td>
<td>Yes</td>
<td>limited use; useful for therapeutic efficacy testing for regulatory review in absence of other models</td>
</tr>
</tbody>
</table>

| SOURCE: provided for use in this Therapeutics Roadmap by READDI Inc |

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<thead>
<tr>
<th>APPENDIX</th>
<th>100 DAYS MISSION</th>
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100 Days Mission

Therapeutics Roadmap
23 January 2024