IMI2 Project ID 101005077

CARE – Corona Accelerated R&D in Europe

WP3 – Hits to Leads

D3.5 1-CARE Small Molecule (SM) System Impact Model

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Document History

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Abstract

Our research applies a systems approach to record and evaluate the research and development processes and decisions taken in the development of antiviral drugs for Covid-19 as part of the CARE consortium. The aim is to model their impact on the entirety of the antiviral drug development system, to create the end-to-end insights into potential effectiveness and efficiency gains. By creating a system dynamics model of the drug development process from end to end, similar to previous systems dynamics research applied to health (Homer and Hirsch, 2009), we will evaluate the downstream impact of these research and development decisions on the health system, on the patient and health outcomes in general.

This model can be used to develop a preparedness strategy to safely speed up the treatment of novel coronavirus outbreaks with antivirals. Spill-over results with respect to other diseases will be part of the results.

Methods

This model is based on a series of in-depth interviews with stakeholders with extensive expertise in the relevant parts of the development stage.

Based on their expertise and literature knowledge, we are building a systems model that captures the end-to-end drug development system. The purpose of building this kind of system wide model is to give a full picture of the value added to the entire health system of a particular intervention. To show how effective the antiviral drug candidates produced by CARE are, their impact needs to be evaluated in the context of the entire system, to identify and quantify all impacts and possible negative externalities, if any, and give the full picture of potential improvements that could make drug development even faster and better applied to the patients' needs in the next pandemic.

We use the human-centred health system framework of WHO that was designed to explore a health system and assess the effect of and intervention on the system. The framework describes the health system as six intertwined building blocks or subsystems, namely 1) governance, 2) information, 3) financing, 4) service delivery, 5) human resources, 6) medicines and technologies (De Savigny and Adam, 2009). These building blocks are tightly interconnected, and people are put at the centre as mediators, beneficiaries, decision makers and actors of the system.

A first round of interviews was conducted to create an initial conceptual model of the system. Participants explained in detail how they see the drug development process and/or drug delivery process. The participants were asked about their understanding of the overarching system wide process as well as their specific area of expertise, for example, target based or phenotypic drug discovery, lead optimisation, clinical development, regulatory approval etc. These interviews not only focused on the description of the process, but also on the decision points within the system and practical or structural barriers in the development stage. Based on these initial interviews as well as a broad literature review, we developed a draft high-level conceptual model representing the end-to-end system-wide process.

Further model validation interviews were conducted with the initial participants to iteratively refine the draft version and to confirm that the draft model accurately

represents the system as they understand it and captures all the relevant components. These model validation interviews are a further opportunity to gain more detailed insights and information updates from stakeholders and build on the information gathered in the initial interviews, including a way to lay our hand on the dynamics of the development process.

Following further interviews, we will begin to quantify the model and conduct a systems dynamic evaluation. Some of the more important data we need relates to the number of candidates in each stage of the drug development and how and when they progress between stages i.e. library molecules and entry of new library molecules to the consortium, the successful candidates at each stage gate, the number of labs working on each candidate and the number of people working in each lab.

Results

A summary of the high-level model is shown in Figure 1. This shows the drug development and delivery journey from the patient perspective (demand side) and the supply side, as well as how these two journeys interconnect. This high-level conceptual summary map contains numerous complicated subsystems, that detail insights about the consortium.

Figure 1 gives a high-level overview of the drug demand side or patient journey and how it is interrelated to the supply side or drug development process. The patient journey provides an information input to the supply journey through the R&D sub system. The emergence of new strains and their impact on population health has direct implications for the R&D process, the success of drug candidates is, in part, measured in terms of its potency in treating new strains. Furthermore, the impact of the virus on global population health motivates the entire R&D process. The supply journey feeds back into the patient side, when the approved antiviral is distributed to hospitals or pharmacies where patients can have access.

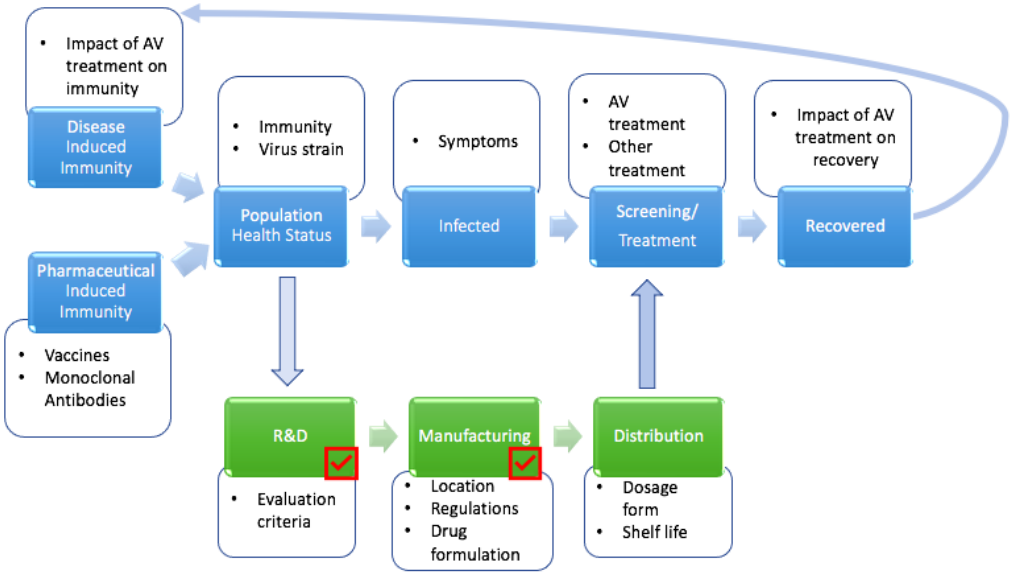

Figure 1: high-level conceptual model (AV = anti-viral)

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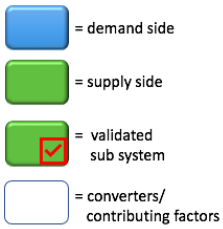

Figure 2 is a stock-flow diagram that represents the first section of the fully detailed drug development sub system, showing only the progression of molecules in the consortium from the initial library to the identification of hit molecules. This demonstrates how a variety of factors are interrelated and impact the identification of hit molecules. Through the development and validation of this system map, we were able to identify a range of topics of interest that will be explored further to create insight about the performance of the system, such as the number of partners, the decision-making process and governance of the consortium and funding.

In figure 2, in particular, there are two stocks represented, the 'consortium library' and the 'hit molecules'. The model represents how molecule candidates enter the consortium, populating the 'consortium library' stock. Successful molecules then move to the 'hit molecule' stock by means of high throughput screening. This screening is impacted by several other factors, including the target product profile, assay results, a selection decision, etc. The stock of hit molecules is further optimised by hit triage. Further, either of these stocks can be depleted by members leaving the consortium, taking their intellectual property with them.

The R&D drug development subsystem has been fully validated via stakeholder interviews. The WHO building blocks will be further explored for each subsystem defined in Figure 1. The connections between all these subsystems will allow us to assess the impact of early R&D decisions on the health outcomes of the patient.

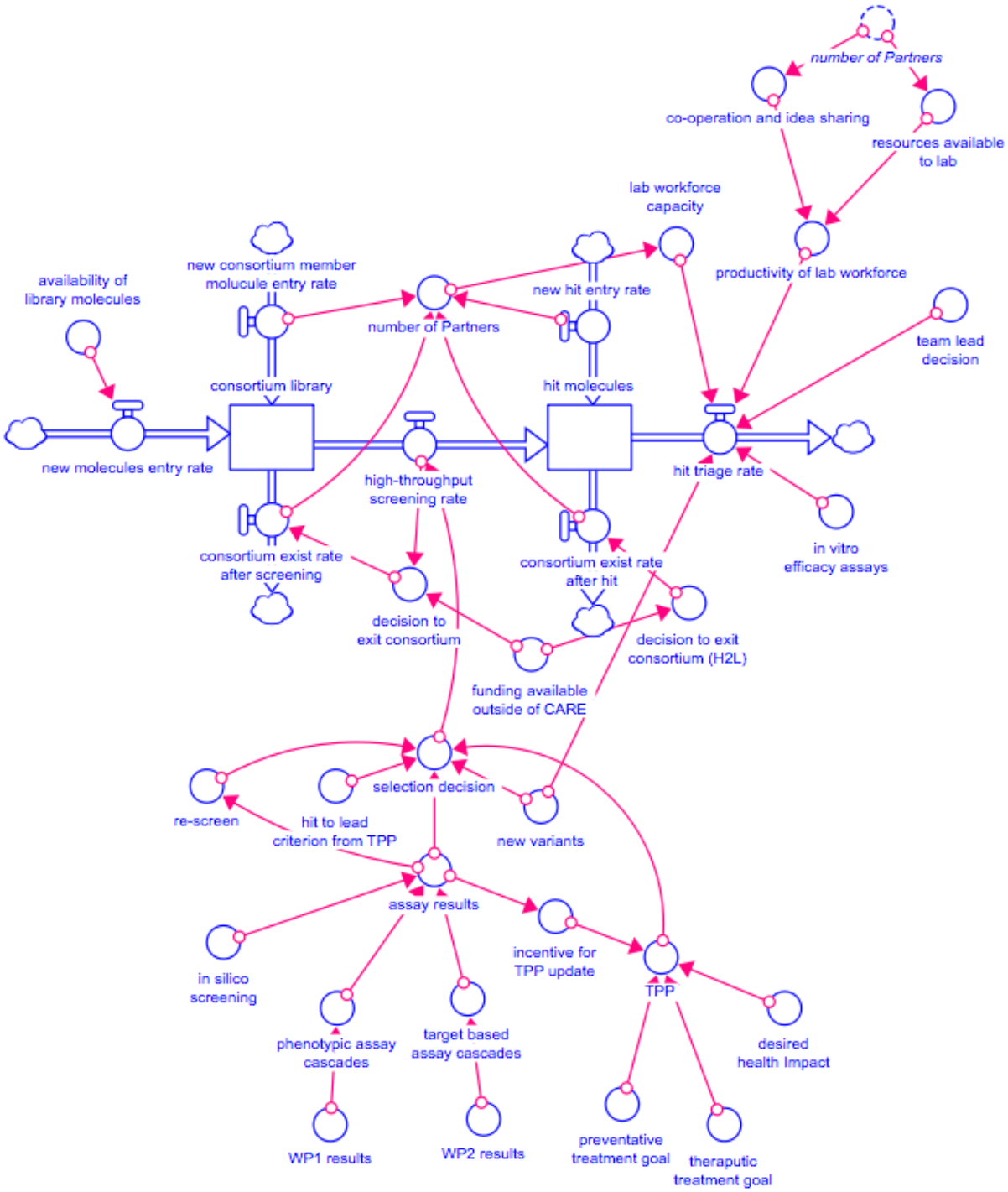

Figure 2: Extract from Drug Development Sub System (stock and flow model)

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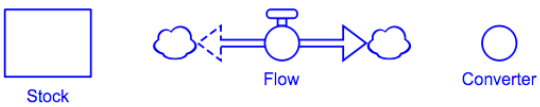

Discussion

Through conducting interviews and building these models we were able to identify important aspects of the R&D subsystem that will require further attention to improve the drug development process.

- **The size and composition of the consortium:** It is of value to consider who is in the consortium, what the members are doing independently, what they are doing together, and what they would have been doing, had they not been a member of the consortium. There are many potential benefits of such a large consortium, such as the ability to collaborate, share ideas and learn from each other. We want to explore what, if anything, can be further done to promote and facilitate this cooperation and what factors that could potentially be limiting the collaboration across the consortium. Some identified potential limiting factors include:
    - Potential competition for resources between consortium members,
    - Complicated approval and decision making since there are many parties involved,
    - Potential hesitancy in collaboration and cooperation (e.g. due to fear of loss of intellectual property)

  It is also important to consider the impact of members exiting the consortium, and the reasons why members may leave the consortium.
  Because of such factors, understanding the value of the size of the consortium is highly relevant to understanding the success of the consortium.

- **Governance and approval:** Governance is of particular importance for a consortium as large as CARE. There are many parties involved in any decision made as part of the consortium and transparency of decision making is vital. The transparency of the governance structure likely has the benefit of leading to more careful decision making and to optimizing the use of money/resources. However, it might as well be that reporting rules or other elements in the governance/approval structure of CARE, could reduce the speed of the decision-making process. To this end, our model will be used to further investigate how well the current governance structure of CARE achieves this balance between transparency and efficiency of decisions and investigates if there are any potential ways in which this structure could further be improved on.

- **The role of funding:** It is valuable to understand to what extent the funding of the project, or the funding for each individual team will drive the development process. Some important questions to consider are:
    - Do funding opportunities external to the consortium impact a member's decision to leave or cooperate less?
    - Which part of the process is most dependent on funding and why?
    - What is the value of spreading funding across a large consortium as opposed to concentrating more funding into one of few labs?

- **Pandemic context:** The consortium was founded and build in the early days of the pandemic in a 'crisis mode' context. This had a significant impact on the speed at which it was formed, the willingness of partners to come together, the speed at which decisions were made and willingness to come to an agreement. What are the implications of this for the setting up of similar consortia in normal time, and in another pandemic situation.
    - Can the efficiency gains achieved in the crisis context be brought into normal times? Is there anything to be learned from the improved decision making and cooperation that came with the urgency of the pandemic, that could become part of a standardised process for setting up consortia or collaboration across partners?
    - Can anything be learned that could streamline the process of setting up a large consortium in another pandemic or crisis situation?

- **Decision making processes of the consortium:** The decisions that are made, and the processes for decisions to be made is of clear importance for the actions of the members of the consortium.
    - What are the most relevant factors influences perspectives and mental models of the individuals' making decisions along the drug development process, are the decisions that are being made within the consortium timely and optimal (in terms of the downstream health effects)?
    - Do the decisions of the consortium effectively represent the values of the project, as was originally intended. Further, to what extend does the TPP reflect the goals and values of the consortium members and how does it evolve as new information is generated?

All these factors are represented in Figure 2, and further quantitative analysis will help to identify which of these factors have the strongest impact on the system. Next, other sub systems will be mapped and the connections with the already shown subsystems will be modelled. This will allow us to assess impact of actions in the consortium on the broader health system.

Conclusion

Early model building interviews and model validation interviews have helped to identify some of the relevant variables in the drug development system. With further investigation of these important aspects, we see useful research questions starting to emerge, such as consortium dynamics and behavioural factors, that span beyond the technical development aspects of drug discovery. The conceptual models shown in the previous section will be quantified and further quantitative analysis needs to be conducted.

Further research and analysis should investigate how we can ensure equity in terms of antiviral drugs reaching patients. Patient preferences could also be considered in the drug development system, and we are looking into conducting patient preference studies as part of CARE.

References

De Savigny, D. and Adam, T. eds., 2009. *Systems thinking for health systems strengthening*. Alliance for Health Policy and Systems Research, World Health Organization.

Homer, J.B. and Hirsch, G.B., 2006. System dynamics modeling for public health: background and opportunities. *American journal of public health*, *96*(3), pp.452-458.