IMI2 Project ID 101005077

CARE – Corona Accelerated R&D in Europe

WP3- hits to leads

D3.7 Small Molecule (SM) system impact model - SM consortium system maps

Lead contributor	KU Leuven (Access to medicines Research Centre)
Other contributors	KU Leuven Various other consortium partners contributed as stakeholders/participants/validators

Document History

Version	Date	Description
V1.0	15 March 2025	View on how the consortium was structured and what behavior it has exposed. This report includes (1) key highlights of the five years of the project and (2) take aways for future consortia like CARE. These has been discussed at the last consortium in Paris, March 5& 6, 2025.

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Abstract

This deliverable, small molecule consortium system map, presents a summary view on the general findings of our modelling experiences with respect to a comprehensive system dynamics model of antiviral drug development in the context of a public-private consortium responding to a pandemic. The model itself has been written down in deliverable 3.6. and spans from early drug discovery through to patient treatment, incorporating key subsystems including drug discovery, clinical development, marketing authorization, marketing access, and patient dynamics. Also, learnings from the literature and discussions both within and outside the consortium revealed that modeling adds value to this kind of research endeavors. The specific nature of the emergence situation in the pandemic and after project research sustainability are key elements leading to the conclusions. Basically, the systems thinking and system dynamics modelling approach leverages the efforts of consortia like CARE, making it transferable to other medical products such as antibodies and repurposing (which were on the plate of CARE but was not the scope of Task 3.6: 'CARE Small molecules impact system modelling'), vaccines, diagnostics and more general medical and non-medical countermeasures. This is of interest to various direct and indirect consortia stakeholders.

Methods

Data collection

For matter of completeness, we repeat that the data used for this research was collected from literature, qualitative interviews and model building sessions with stakeholders from the specified subsystems in the drug development process. Semi structured interviews and model building sessions were conducted with either one or two participants at a time. The interviews were approved by the Ethics Committee of UZ/KU Leuven (S66267) and by the Social and Societal Ethics Committee of the KU Leuven University (G-2021-3911). For matter of completeness, we only summarize the data collection sources. More details can be found in the other reports 3.5 and 3.6.

Regulatory/marketing access
Based on 17 interviews, we were able to map the special regulatory and market access practices deployed during COVID and whether or not these processes would also work in non-COVID times. These interviews (with Zilke Claessens, Liese Barbier and Isabelle Huys acting in WP8 and pharmaceutical and pharmacological sciences, KU Leuven). These findings eventually turned into a system dynamic model in Stella Architect[1], complemented elements from the academic and grey literature.

Drug development
Here 11 experts were engaged in semi-structured interviews and model building sessions, including validation sessions to confirm the model correctness. Key goal was to understand the drug development process both in pandemic and non-pandemic times, embedded in a consortium structure like CARE. Here also, both academic and grey literature was used to complement the own findings.

Patients
For this part the basic input relied on literature and the format of the semi-structured interviews was tested. Further patient interviews have not yet been conducted for reason of almost no availability of patients anymore. Additionally, as no small molecule antivirals were available to treat early COVID-19 patients, it was not possible to analyse initial uptake. This is already one of our key learnings from the project.

[1] Stella Architect, Version 3.7.2, Isee Systems Inc., Lebanon, NH, USA, 2023

System dynamics

Systems thinking is based on the idea that a problem cannot be considered in isolation, but in the full context of everything it could potentially influence. System dynamics, a quantitative implementation of systems thinking, offers a simulation methodology to understand the dynamic behavior of the small molecule development system. The Access-To-Medicines Research Centre team has experience in using systems dynamics in other health systems: immunization (Decouttere et al., 2021), HIV drug resistance, pandemic preparedness, among others. However, CARE was the first-time systems dynamics was applied in a consortium structure responding to an emergency. Our work in Task 3.6 confirmed that system dynamics was deemed to be the most appropriate methodology for the scope of this research, to be able to capture such additional complexities within the system (see report 3.6).

Concluded, all inputs described above led to the construction of a system dynamics model, through the in between steps of stock and flow diagrams (see report 3.6 for technical details).

Synopsis

The goal of this deliverable 3.7 was to list the various learnings by using systems thinking and system dynamics modelling within CARE. In order to derive conclusions on the small molecules system as structured within CARE, we performed the modelling steps as described in the other reports. Based on these results, alongside the project duration, we listed and took note of many observations, reactions, comments and insights while executing the core research actions. These have led to the conclusions in this report, which are basically based on:

- At each consortium meeting, next to the delivery of the scientific results, we solicited for formal and informal reactions from various actors within CARE; especially the last consortium meeting on March 5 &6 was instructive, as it was the closing compilation of all the learnings.
- In the semi-structured interviews, statements and opinions related to consortium structure and modus operandi were noted on the side.
- Similarly, in workshops when similar things popped up, we also took note of these.
- In research seminars, doctoral seminars, conference participations and internal team meetings, we kept track of the similar elements.

So all that is taken together to formulate the learnings reported.

Results and Discussion

In this section we review the basics of the methodological outcomes for convenience to frame and support our findings. The details can be found in the other reports.

From the **literature** we learned the following key messages, which were in general agreement, based on the reactions on several consortium meetings:

- There has been more funding and resources made available in R&D for incremental research compared to radical research paths.
- The attention has traditionally been higher for chronic diseases than for acute diseases.
- COVID surged an enormous spike in funding and research efforts, which has levelled out rather fast (meaning faster than the duration of CARE).
- Uptake usually fades, with one exception being HIV. However, recently with the halting of international support, HIV treatment with antivirals may also become under severe pressure.

Overall conclusion: **sustainability of R&D 'investments' in research resources is hard to materialise**, both at universities, research centra and companies. This is illustrated by the CARE consortium that,

despite nice fundamental results, lacks a clear framework to continue and to be embedded in a preparedness structure to be more responsive in a future outbreak situation.
When we turn to the **conceptual model**, the model itself revealed four lines of intervention which turned out to determine the behaviour and this the outcome of the consortium activities.

Schematically, the overarching system is visualized in Figure 1. It shows the four subsystems delineated during the project: (1) Preclinical Development; (2) Clinical Development; (3) Regulatory/Market access; (4) Patient. All four subsystems have been modelled conceptually as well as qualitatively.

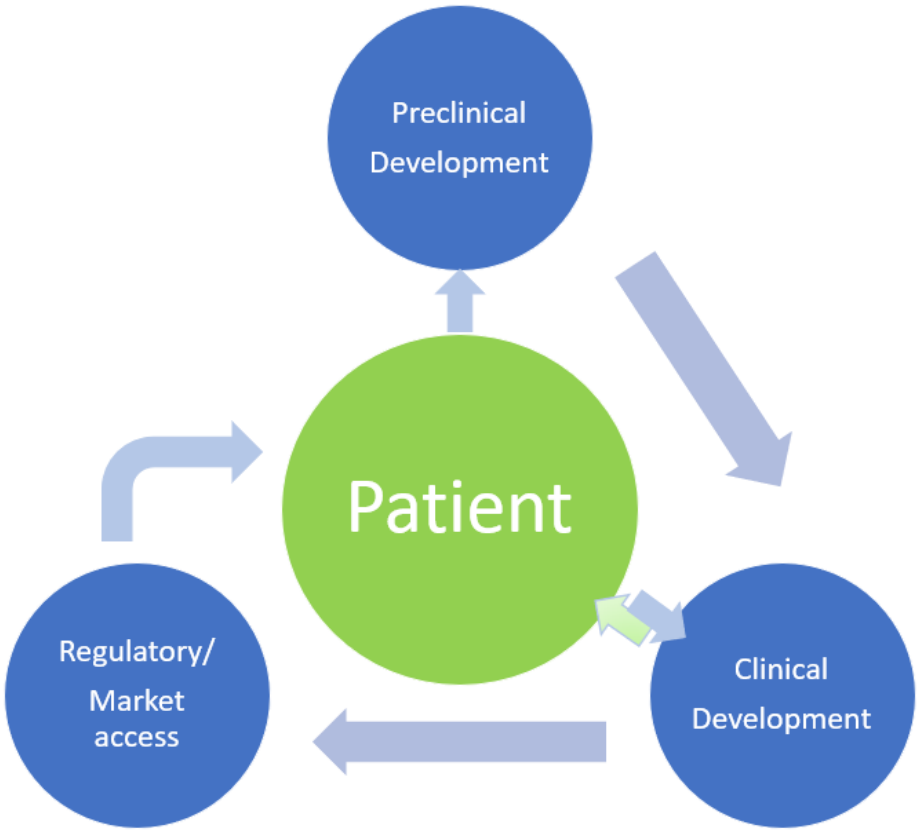

Figure 1: Four composing sub-systems of small molecule system model.

Based on the interviews, workshops and validation sessions, the focus concentrated on the speed and efficiency of the consortium. The major conclusions can be summarized as follows:

- impact of the budget, which is based on the deployed resources any kind;
- governance and organization of the consortium;
- decision making time and structure;
- flexibility of the consortium;

Turning the results into learnings, it became clear that:

- **Flexibility is key**.
    - It is a real challenge for a consortium to scale-up in emergency times. Resources have to be added, people have to be trained, funding has to be provided, all taking precious time while being in a response mode.

    - The same accounts for the later scale-down, which is often neglected or forgotten. What do we do when the high tide is over? Where will these resources reside or go to? Alternative usage should be considered while preparing, otherwise researchers will need to be dismissed, which is an uncomfortable action to be taken with great care.
    - Tech-transfer of resources deployed in emergency modes to other applications and settings after the emergency.
- **Keeping resources warm in preparedness time is even more key.**
    - Resource maintenance: installations and equipment need to kept in optimal condition, samples stored properly, etc. Based on our findings, this is mainly a funding issue.
    - More importantly: how do we keep brains warm, as these are the core resources in R&D in this type of consortia. Next to fund the intelligence captured in the on-board human resources, the biggest challenge lies in the motivational area: how do you keep research challenges needed for pandemic response if there is no pandemic at that moment.
- **The state of obesity versus anorexia.**
    - This is a key balancing decision for some key variables modelled, namely the impact of the budget, organizational structure and time to make decisions. It is a way in between two extreme states of the system: either the system is obese, i.e., having too much resources for the performance it needs to bring up, with inefficiency as a consequence. Or conversely, being in an anorexic state, where the resources are insufficient to perform properly with the risk of collapse. So, in the context of consortia like CARE, the obese state can be too much budget, too complicated organisational structure, too complex governance and too slow decision processes (e.g., frequency of decision making meetings, too many partners, …). On the other hand, the anorectic state can be represented by too tight budgets (or too high ambitions given the budget), sloppy decision making processes and poor consortium organization. Somewhere in the middle these two to-be-avoided states are balanced, which could be considered as a preferable CMI, a kind of Consortium Mass Index, comparable to the BMI, the Body Mass Index, known in human health. A 'healthy Consortium Mass Index' promotes the best good quality outcomes and innovation potential.

The **quantitative system dynamics model,** which is a quantification of the high level conceptual model in Figure 1, is visualized in Figure 2, where for each subsystem the next level subsystems are shown as there are: drug discovery, repurposing, hits to leads, clinical development, marketing authorisation, market access, patient antiviral market, budget allocation, virus learning and consortium dynamics. Please take note that these lower level subsystems are fully detailed in report 3.6, which will not be repeated here.

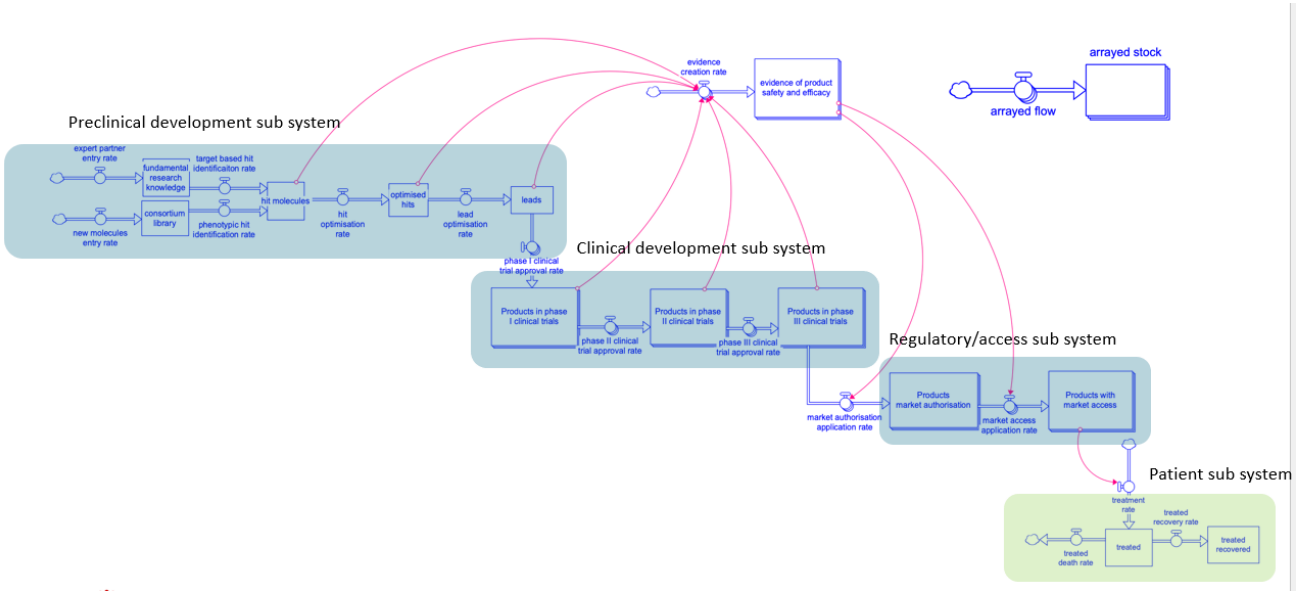

Figure 2: Four composing sub-systems of small molecule system model.

Following the conceptual modelling outcomes, the quantification was oriented towards allocation of resources, collaboration, governance and risk; as in indicated in Figure 3.

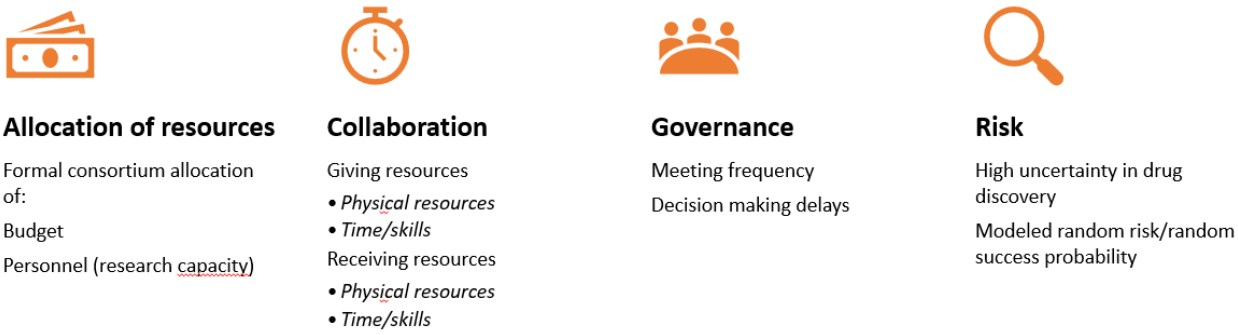

Figure 3: Main focus point of analysis for the simulation models.

When turning the qualitative models in to a quantitative model, we followed a five-step system modelling approach (Decouttere et al., 2016), which visualized in Figure 4.

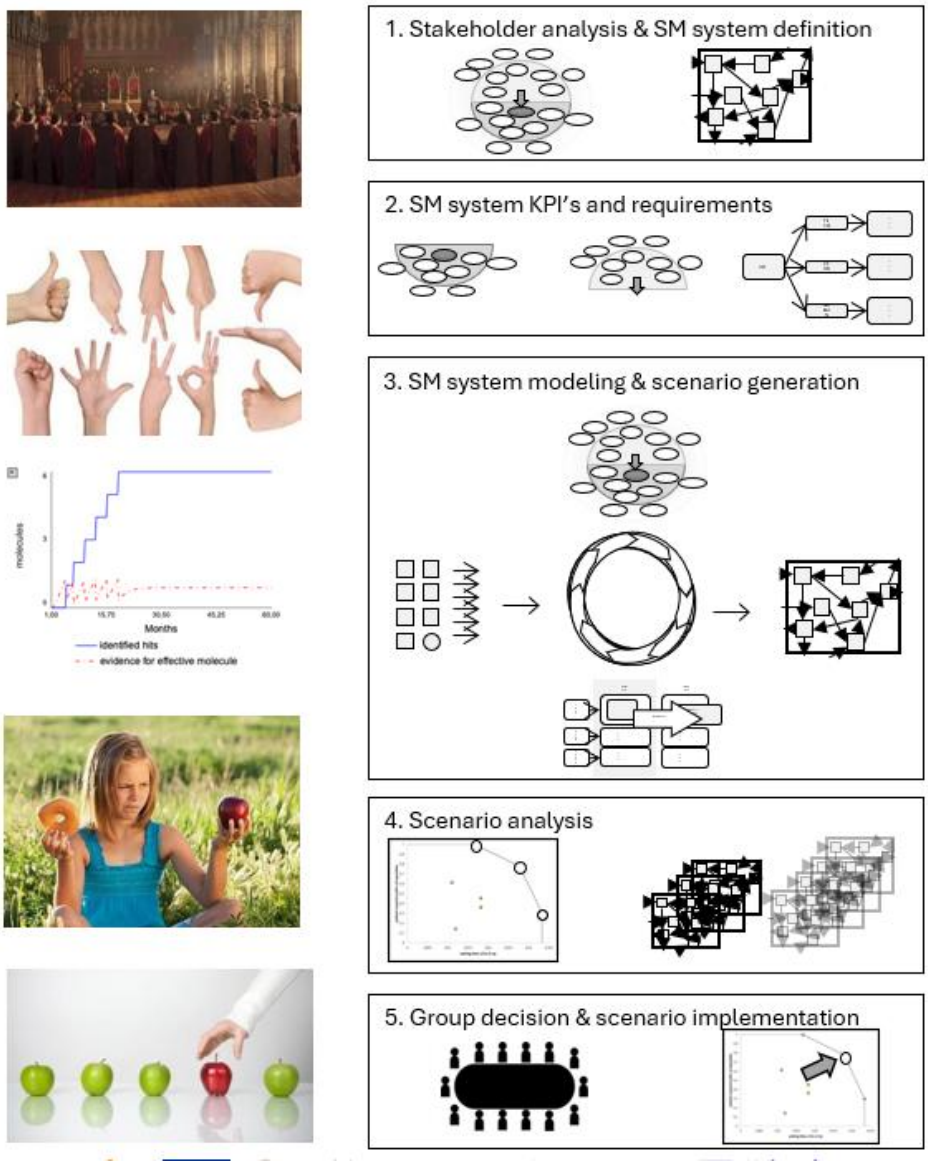

Figure 4: Five step system modelling approach.

Without detailing al the steps, it basically boils down to:

1. Stakeholder analysis and Small molecule system definition
   This has been primarily executed in the first actions' of the project through the interviews, literature consultation and group workshops.
2. Small molecule system Key Performance indicators and system requirements
   Here the expert consultations and key stakeholder interviews were used to nail down the KPI's the model should obtain. Examples of KPIs are
   - number of molecules screened, consortium library
   - hits optimized
   - leads optimized
   - candidates for preclinical identified.
3. Small molecule modelling and scenario generation
   This step turns the qualitative models into simulation models, with the stock and flow diagrams used as in between structuring steps (see figure 2 and report 3.6). The exemplary

KPIs listed in the previous step, are shown in Figure 5:

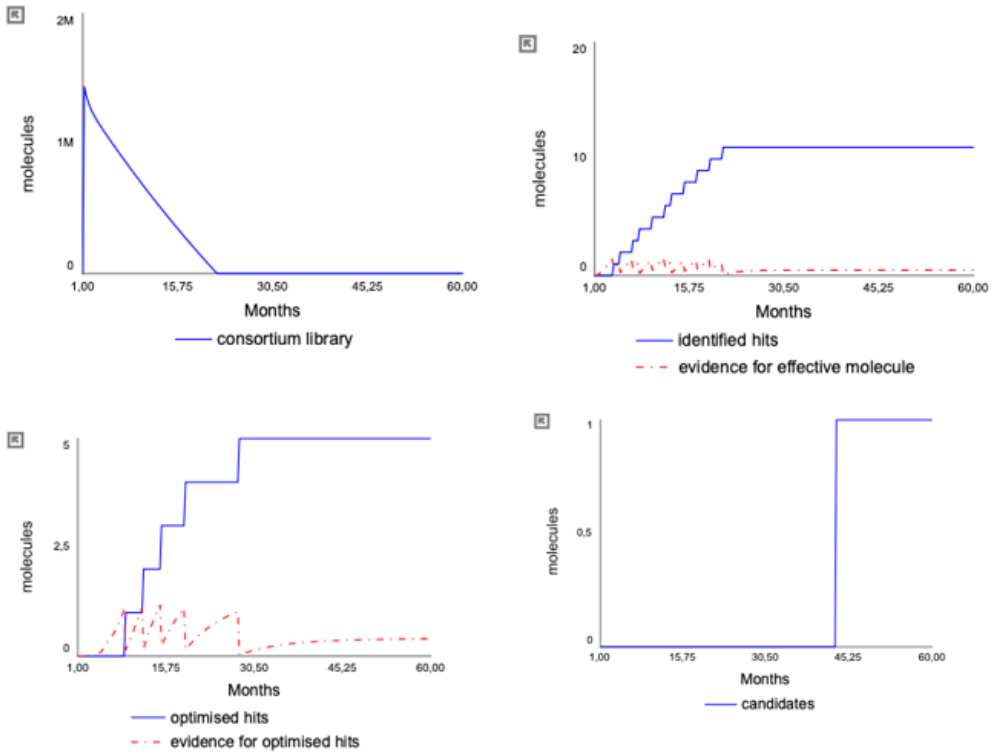

Figure 5: Four KPIs from the preclinical subsystem

Continuing the example, in summary, this scenario produces:

- 1.5 million molecules screened within 24 months
- 10 hits identified within 30 months
- 5 leads identified within 60 months
- 1 candidate for clinical trials after 45 months

4. Scenario analysis

   Several scenarios are co-created and evaluated with key-stakeholders. They have dealt with different budgets, different collaboration structures, differ decision speed and different risk levels. Examples of such scenarios are listed in Table 1.

	Total molecules screeend	Time to screen	Hits identified	Time for hits identified	Optimised hits	Time to leads identified	Preclinical candidates identified	Time to candidates identified
Baseline	1.5M	24 months	6	30 months	4	33 months	0	-
Scenario 1 budget	1.5M	24 months	6	30 months	4	33 months	1	24 months
Scenario 2 collaboration	1.5M	22 months	6	27 months	4	30 months	0	-
Scenario 3 decision speed	1.5M	23 months	6	29 months	4	31 months	0	-
Scenario 4 risk	1.5M	24 months	10	30 months	6	33 months	1	45 months

Table 1: Set of four scenarios simulated against a baseline.

5. Group decision making and scenario implementation

   This is the step where the most interesting and stakeholder supported intervention from the scenarios step will be implemented. As this was not intended in the CARE task 3.6, we use this

opportunity to reflect on the applicability of the approach and the learnings on the approach aspects from the CARE work.

Discussion

In this part key learnings from the CARE project are summarized. First the learnings for the CARE consortium itself are listed after which learnings beyond CARE are covered.

Learnings within the scope of CARE

1. A key learning is the fundamental **tension** exists **between consortium size and efficiency** - larger consortia benefit from increased innovation potential and collaborative quality improvements but suffer from greater administrative overhead and more complex governance structures. This became clear when difficult and/or impacting decisions have to be taken within the consortium.

2. Three critical trade-offs were observed:
    a. the trade-off between collaborative benefits and coordination complexity, as larger consortia typically involve more and diverse partners. CARE was by definition diverse with respect to the stakeholder base as it was composed of academic, private and public organizations;
    b. the resource allocation trade-off between prioritizing promising candidates versus maintaining backup options. This of course is part of a mitigating strategy, and needs to find a balance between risk seeking and risk avoidance, which was observed as being dynamic based on the result in the different development steps of the project;
    c. target product profile trade-off between broader patient benefit and development complexity. Broader TPPs increase the likelihood of finding effective compounds but may result in lower overall product impact, through having a lower target patient population;

In general, the small molecule system model serves as a valuable tool for multiple applications: it is possible to include patient perspectives earlier in drug development, it enables optimization of consortium structure to be better prepared for future pandemics. It also helps to decide on investment under uncertainty. Being interactive, it allows stakeholders to conduct scenario simulation to obtain system-wide impacts of local decisions and/or events. In this way it is valuable for both policy making as well as for consortium designers and project program (funding) setup.

Taking a step back and evaluating the application of a systems thinking and systems modelling approach to CARE, the following lines came up:

- Modelling small molecule development as a system: it is valuable to analyse the interplay of individuals, teams, partners and their activities within a large consortium. Through co-creation and validation with the internal stakeholders, it can be concluded that CARE was:

    - Much more complex than initially thought. Several stakeholders confirmed that, by joining the stakeholder consultation actions, they had a clearer picture of their own position and role, and obtained a better sight what the impact is of their actions to the consortium and the impact of the consortium as a whole on pandemic preparedness and response;

- Many relationships and causalities within CARE are definitely (highly) non-linear. As an example, it was very enlightening to see that starting from millions of molecules, you finally end-up with 1 candidate for clinical trials after 45 months (see Figure 5);

- The consortium contains feedback loops for which the impact on the overall outcomes is hard to predict without a model. For instance, when a promising pathway for a prioritized candidate was slowed down and a backup option was revisited;

- The entire methodology is based on the active involvement of stakeholders, experts and actors within CARE. In the case of CARE, being a pandemic response consortium acting in an emergency mode, much of the dynamic behaviour of the consortium became apparent while the project was executed, so the models had to be continuously adapted and final validation could only be done closer to the end. This posed a constraint on finishing all the modelling and validation actions within the consortium time lines. This is clearly a learning for future modelling actions in consortia like CARE: additional time/resources after project closure should be foreseen or reserved. A related timeline factor is that patients (intended to be treated with the antivirals) are not there anymore. Starting these actions earlier in the consortium process is also difficult as there are no details of the antiviral small molecules TPP available at the beginning.

- Scenarios are a rewarding way to get grip on the inherent uncertainties of an R&D project consortium deployed in an emergency setting. In order to get an idea of the overall outcomes and impact of particular interventions and events in the consortium system (e.g., budget changes/reallocation, decisions made, stochastic process outcomes, et.) the scenario approach turned out be very insightful. Additionally, due to the factors of complexity, non-linearity and feedback loops listed above, the overall impact is very hard to grasp.

- The impact of the small molecules system modelling is also valuable for stakeholders in the close and remote consortium environment. Obviously interested stakeholders are the consortium funding and supporting bodies, as there are IMI, BMGF, private company funding, among others. In more remote positions in the consortium environment, stakeholders as national and international agencies working on pandemic preparedness and response can benefit from the models. Examples of these are for instance HERA, ZEPAI, WHO, WLPF, CEPI, among others.

Learnings beyond the scope of CARE

Consolidating insights of CARE project enhance preparedness and outbreak response for the next pandemic, also beyond the scope of CARE. Therefore, we want to elaborate on the broader ecosystem where the small molecule R&D system (as defined in CARE) itself is a subsystem of a larger eco-system. A mind-expanding example is shown in Figure 6, which is taken from our vaccine modeling research projects. As can be imagined, the R&D vaccine subsystem is behind the 'Vaccine supply'. It can be observed in the causal loop diagram, that vaccine supply serves 'Vaccine distribution' which leads to 'Vaccination' and subsequently to health outcomes 'Population health status'. On the left side, several feed-backs are in place which impact the 'Vaccine supply', and thus the R&D subsystem, indirectly. Also observe that the entire right hand part related to the disease development in outbreak/pandemic situations, has its own dynamics and impacts the left hand side dynamics. The details of this vaccine eco-system model are beyond the scope of the report but can be found in the literature (Decouttere et al., 2021). The key message is here that a similar antiviral eco-system model can be conceptualized and built for antivirals, embedding the small molecule R&D subsystem model in a broader antiviral model. Of course, this will entail a much more extended and larger modelling effort. As a first step, particular key subsystems next to R&D can be prioritized for detailed development. And finally, this is of course applicable to diagnostics, medical materials in general and also for non-medical items (masks, protective clothing, …), which also become critical in pandemic times.

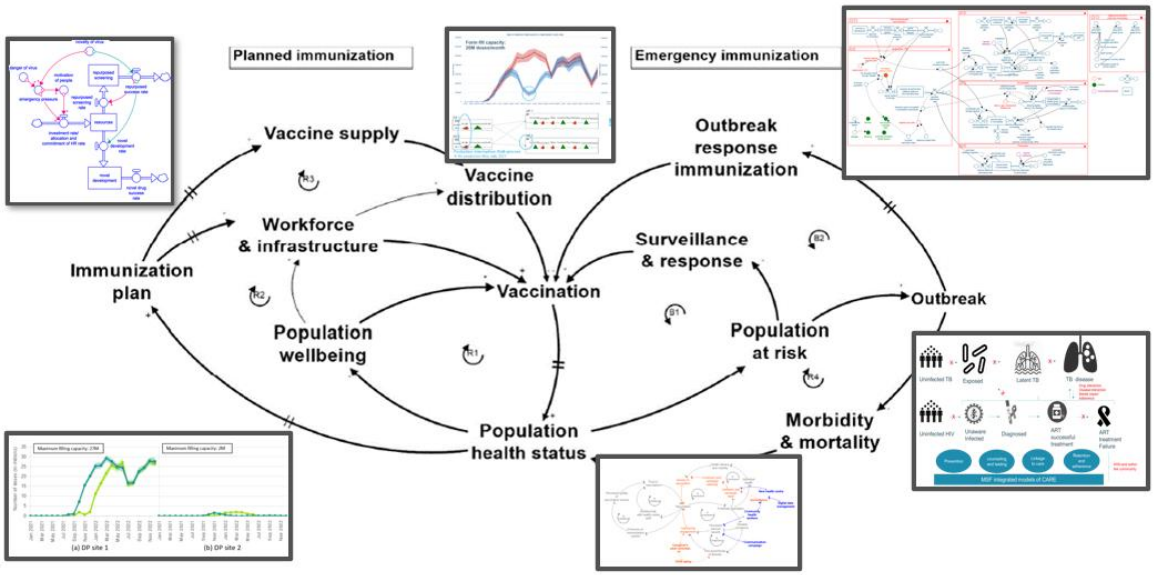

Figure 6: The Immunization eco-system as inspiration for a antiviral eco-system (causal loop diagram)

Conclusion

This small molecule system model contributes to understanding and optimizing antiviral drug development, particularly in the context of public-private partnerships and pandemic preparedness and response. The model's comprehensive scope and interconnected structure make it valuable for multiple stakeholder groups and applications.

Taken all reports and models together, we can finally conclude that

- Patient-centric drug development is possible by connecting the early drug discovery with the impact on patients, where the end-to-end visibility enables stakeholders to consider patient preferences and needs much earlier in the development process. In general, the modelling approach allows researchers to optimize early-stage decisions with a clearer visibility of their impact on the final patient outcomes.
- This kind of a decision support tool for R&D consortium design and management is to our knowledge not yet available. This first attempt with CARE encourages us to continue the construction and use of this kind of models. It not only helped to analyse the impact of resources, budget, consortium structure and operation. It also helped to demonstrate roles, functions and impact.
- As it also contains risk and dynamic features, combined with a scenario approach, it is suitable to use for investment and/or funding decisions, even under the pressure conditions of an pandemic emergency.
- The model can also be used for policy making and help funders and external stakeholders to understand the complexity, challenges and opportunities of these kind of consortia setups for R&D

As final project conclusions we like to state that for modelling the R&D small molecule system within CARE:

- A qualitative analysis is a necessity before jumping in to quantitative modelling
- Stakeholder engagement is key at various steps in the modelling process
- In complex projects, many data are qualitative, emphasizing expert engagement
- Modelling a system in emergence setting is pushing the results towards the end and beyond the project

- Modelling serves as a basis for sustainability as it captures the mental models of a consortium, of which the partners will most likely disperse again after the project. It may constitute one of the remedies for keeping the brains warm up to the next emergency

The ATM team wants to conclude by thanking al the researchers and stakeholders who collaborated with the modelling actions at various stages and roles. Without this open-minded collaborative mindset, a modelling trajectory would not have been possible.

References

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