

Experience with software platforms qualification for mechanistic models for agent-based modelling approaches: UISS case

Francesco Pappalardo, University of Catania, Department of Drug and Health
Science – francesco.Pappalardo@unict.it

- Agent based modelling (ABM) and UISS Platform: Capabilities & Applications
- Regulatory & Technical Readiness
- Challenges in Regulatory Acceptance of ABMs: what I learned and what we need to discuss
- Opportunities & Future Directions
- Key Takeaways and Open points



What is Agent-Based Modelling (ABM)?

- **Definition:** A computational approach that simulates the actions and interactions of autonomous **agents** to assess their effects on the system as a whole.
- **Key Ingredients**
 - **Agents:** Discrete entities with their own goals, behaviours, and attributes.
 - **Rules:** Govern how agents interact with each other and the environment.
 - **Environment:** The overall system where agents live and act.
- **Why It Matters**
 - Captures **bottom-up emergence** of complex phenomena.
 - Allows exploration of “**what-if**” **scenarios** and surprises.
 - Complements equation-based or statistical modelling.



Cells



Biological
Interactions



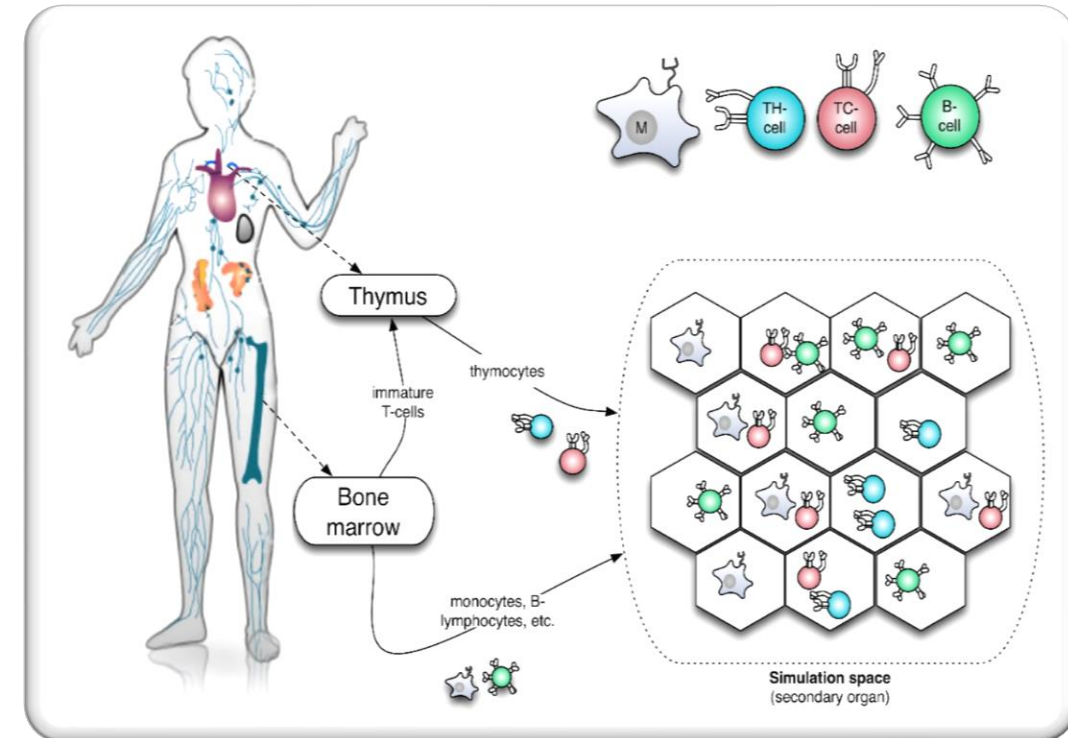
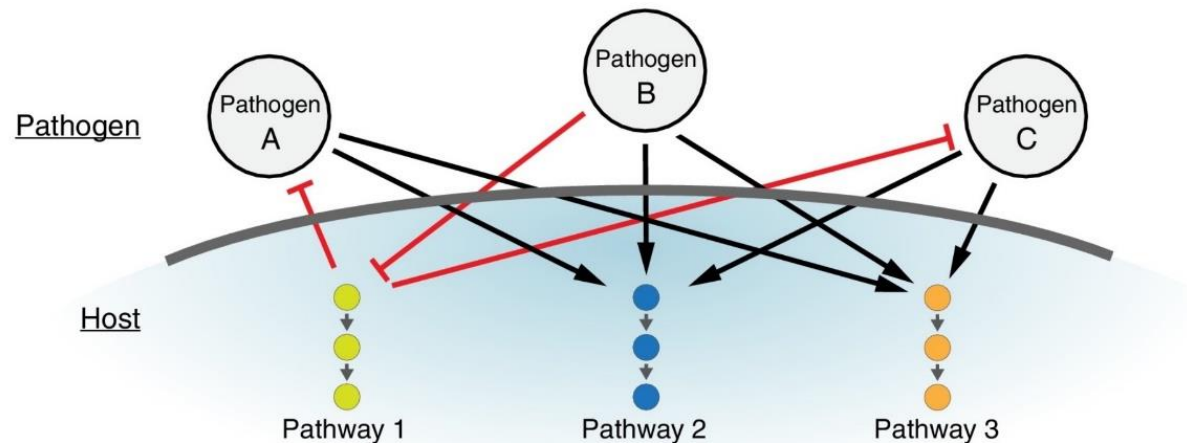
Organs

Why Use ABM?

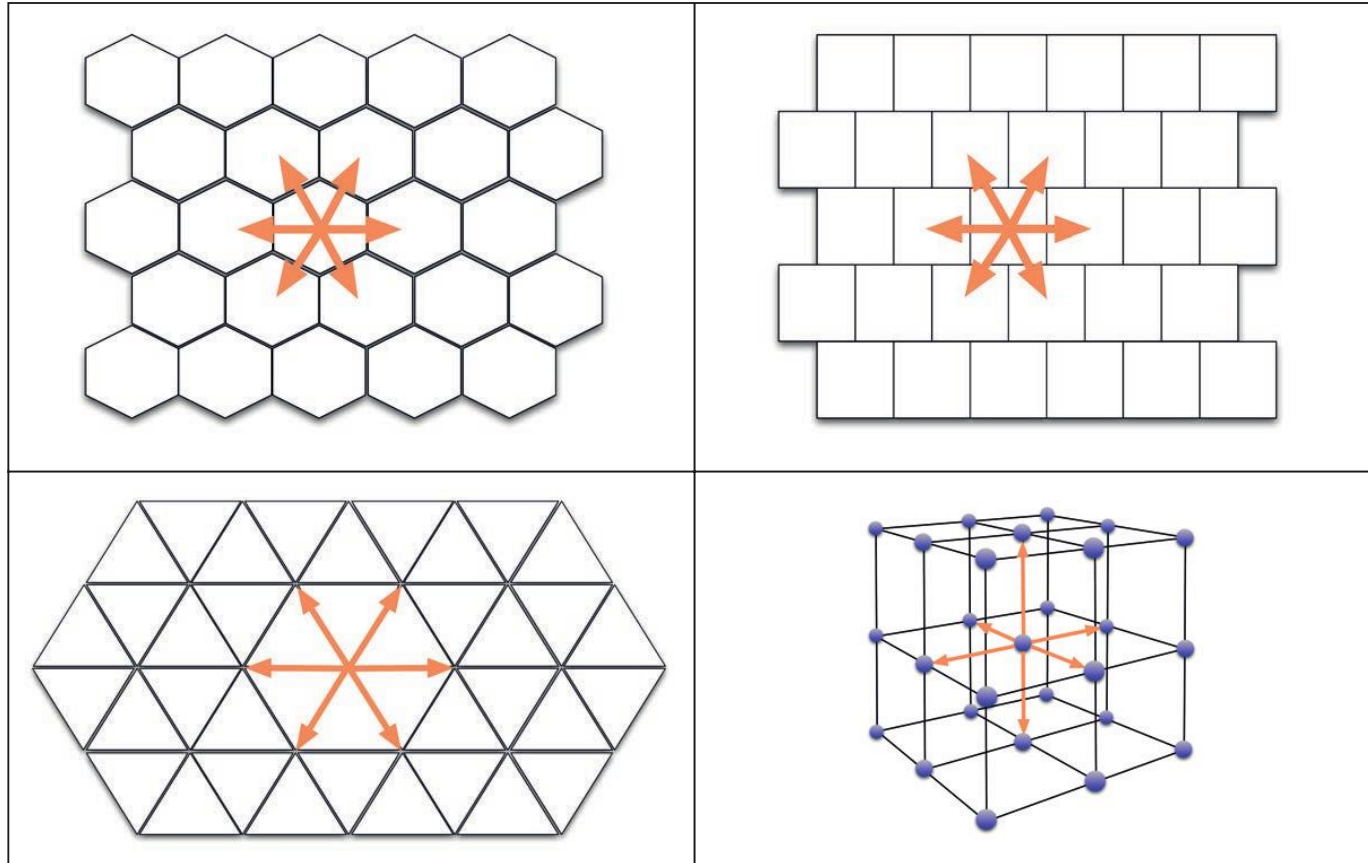
- **Complex Systems Need Micro-Level Insight**
 - Social systems, biological systems, infrastructures, economic markets.
 - Decentralized decision-making, heterogeneous actors, local interactions.
- **Key Features**
 - Models diversity of agents (cells, people, robots...).
 - No central controller; system behaviour emerges naturally.
 - Supports spatial and network dynamics, movement, and adaptive behaviours.
- **Key Advantages**
 - **Your model, your rules:** start from agents, define interactions, watch the system evolve.
 - ABM offers a **powerful lens for understanding and simulating complex systems.**

UISS – an ABM example

The **U**niversal **I**mmune **S**ystem **S**imulator Framework (**UISS**) is a **multi-scale** (at cellular and molecular level), **multi-compartment**, **polyclonal**, **agent based simulator** of the immune system dynamics.



UISS - environment

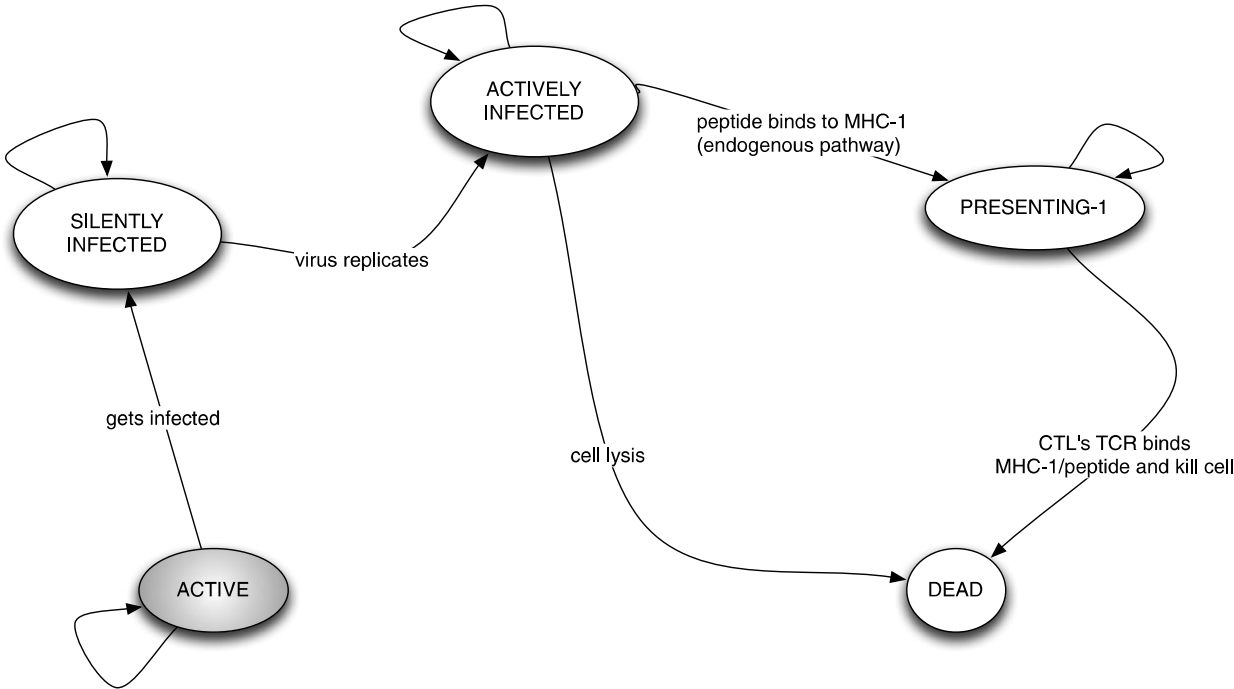


The space is discrete. UISS grid is a hexagonal lattice (top, left) or square-shifted (top, right). This is equivalent to the triangular lattice if you look at the edges instead of the nodes (bottom-left). For specific purposes, three-dimensional version could be implemented. In this case, the space is a Cartesian lattice (bottom-right).

Agents...

	Cells	Small molecules	Large molecules
Who	Cytotoxic T cells Helper T cells (TH1, TH2, TH17) Regulatory T cells NK M DC	IL-2 IL-4 IL-6 IL-10 IL-12 IL-17 IL-23 IFN-γ TNF TGF-β Type 1-IFN D-signal Vit. D Chemokines	Antibody (Ab) Ig (M, D, G1, G2, E) Antigen (Ag) IC
Represented by	Discrete variables (agents)	Continuous variables	Discrete variables (no internal states)
Interaction based on	Binary strings (n bits)	Only concentration on the lattice site is needed	Binary strings (n bits)
How they move	Chemotaxis and random diffusion	Diffusion equation (parabolic PDE) $\frac{\partial C}{\partial t} = D \nabla^2 C - \lambda C$	Random diffusion

... and Interactions!



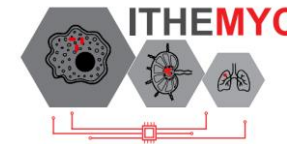
How a generic epithelial cell change its status during a virus infection

UISS: a bundle of applications...

... and a bundle of EU funded projects



ERAMET: ataxia-telangiectasia



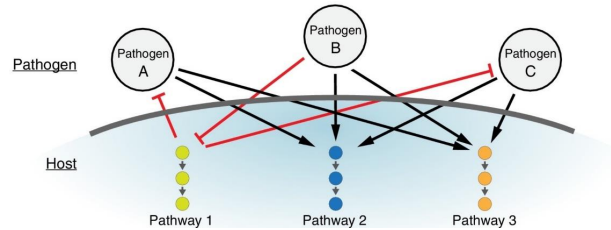
ITHEMYC and STRITUVAD: MTB



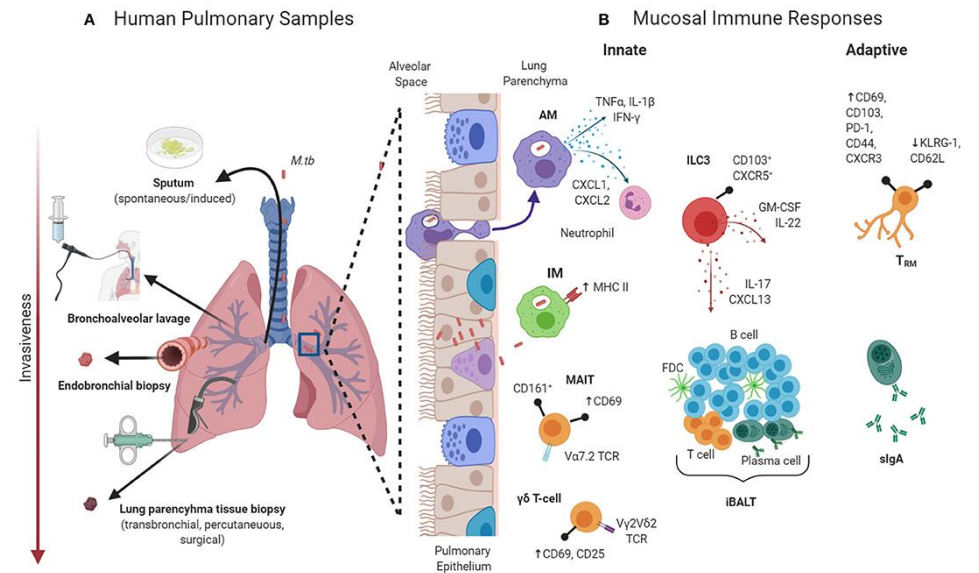
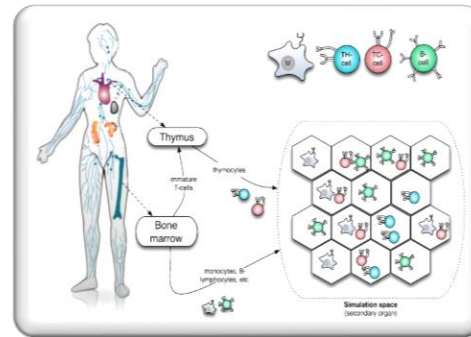
Multiple Sclerosis, COVID19 and Influenza

UISS-TB-DR in a picture

The Universal Immune System Simulator Framework (UISS) is a **multi-scale** (at cellular and molecular level), **multi-compartment, polyclonal, agent-based simulator** of the immune system dynamics.



UISS



→ UISS-TB

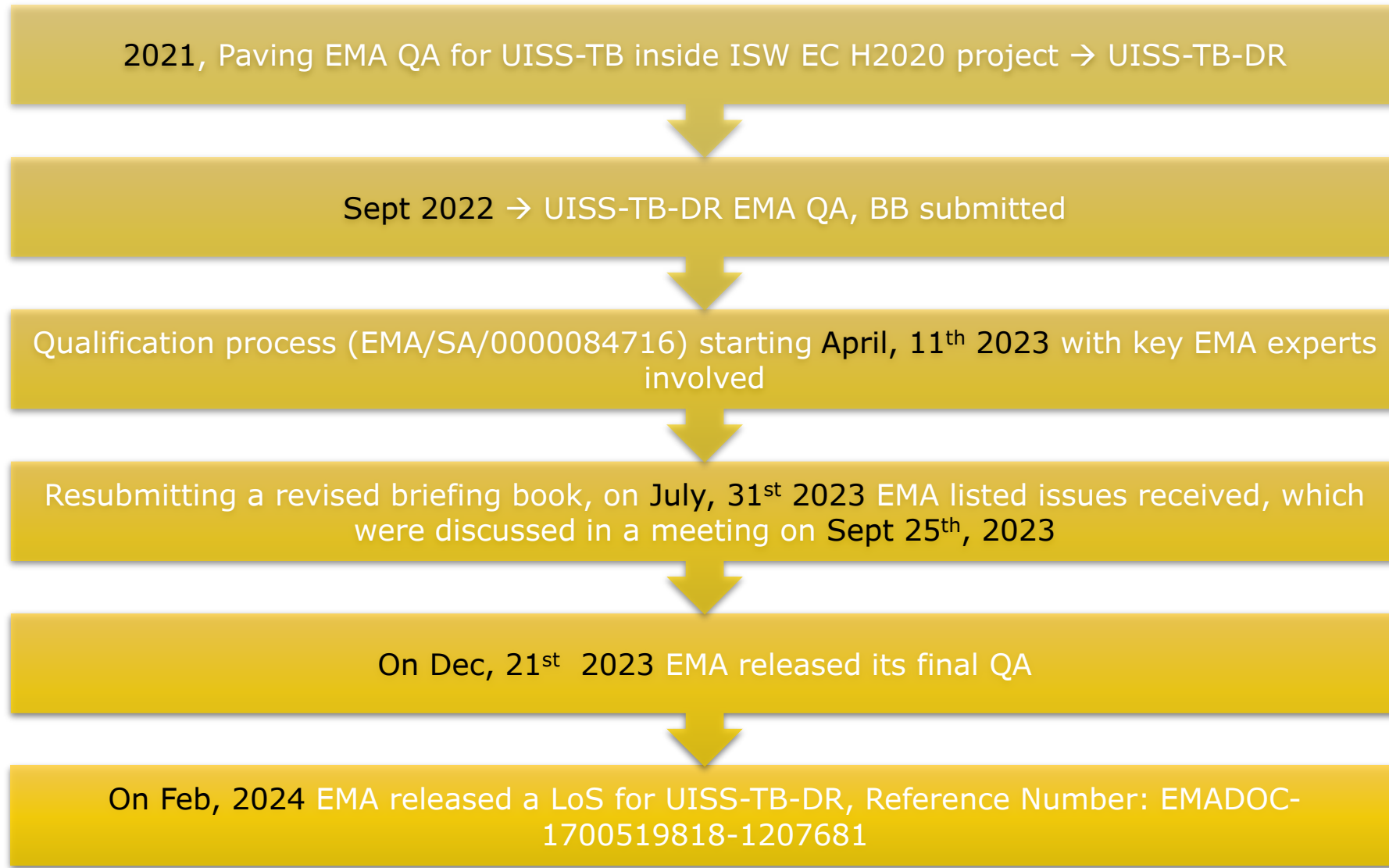
Digital model predicting how a certain TB strain multiplies in the lungs, considering immune responses and treatment effects.

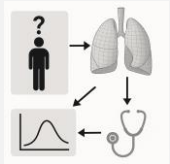


UISS-TB-DR

(EMA QA submission)

A summary of EMA QA procedure





Q1: CoU definition



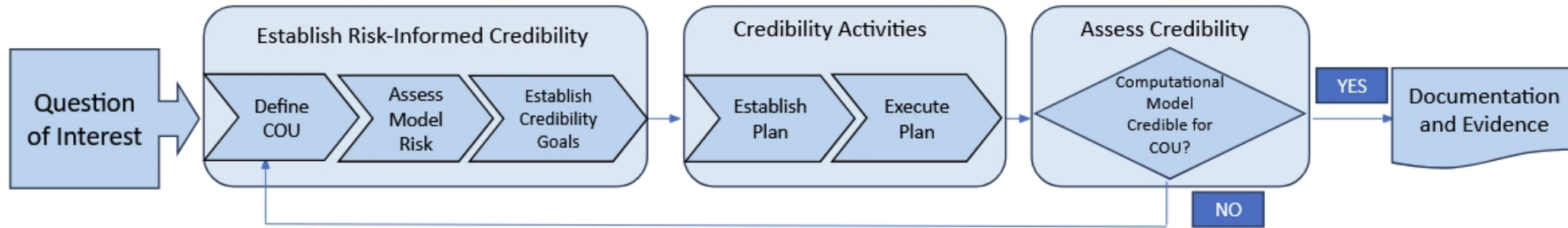
Q2: Risk assessment



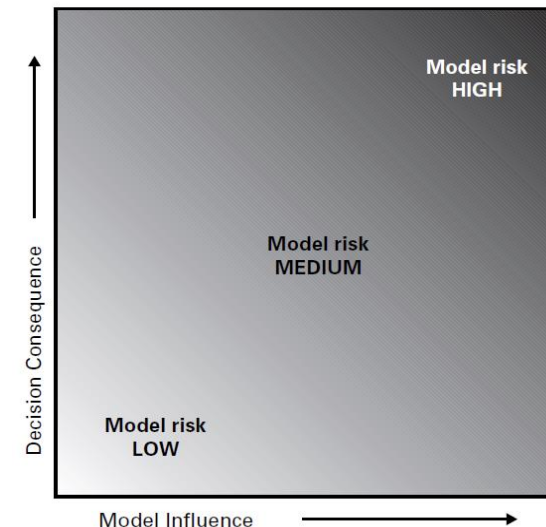
Q3: Credibility assessment plan

- **CoU:** Use the UISS-TB-DR model to predict how the circulating interferon gamma (IFN- γ) changes over time as a function of the treatment dose being tested in a cohort of virtual patients to select the doses to be tested in an escalating dose phase IIa trials of new therapeutic vaccines designed for pulmonary TB.
- Does EMA agree with the overall strategy in general, and the **risk assessment** in particular, that we propose to evaluate the validity of the UISS-TB-DR as an in silico methodology for the optimisation of dose-response phase IIa clinical trials?
- Does the EMA agree that the proposed **credibility assessment** plan is adequate to support the request for qualification of the UISS-TB-DR in silico methodology for the proposed context of use?

ASME V&V-40 as a Risk and Credibility Assessment?



- *Model influence* is the contribution of the computational model relative to other contributing evidence in making a decision.
- *Decision consequence* is the significance of an adverse outcome resulting from an incorrect decision.



CoU

Aspect

General principle of the CoU (using UISS-TB-DR for phase IIa dose selection)

Reliance on IFN- γ as the key quantity of interest

Scope restricted to whole-cell/fragmented vaccines and RUTI dataset

Co-medication (antibiotics) effects

Dose-range vs middle-dose selection

EMA's Position

Agree in principle. They explicitly say the CoU statement “could be agreed” and they recognise the simulator can optimise dose regimens.

Not yet accepted. They highlight IFN- γ is not an established surrogate and want evidence of prognostic/predictive value.

Insufficient. They call for validation with other vaccines (M. vaccae, MIP, additional RUTI data).

Missing. They advise you to address this; they consider it key to dose optimisation.

Prefer dose-range optimisation. They want you to use the simulator to select an optimal/informative range, not just a middle dose.

Question 1 = **PARTLY AGREED (conditional).**

Risk Assessment

Aspect

EMA's Position

Risk assessment if used only for middle dose selection

Agree. They explicitly say model influence and decision consequence would be low/medium and acceptable.

Risk assessment if used for broader dose-range optimisation

Caution / conditional. They warn that model influence and decision consequence rise to medium-high and that patient safety/tolerability margins must be respected.

Overall strategy (population-level prediction, Phase III dose ultimately from trial data)

Agree. They find the approach "understood and considered acceptable."

Virtual patient population / trial simulation effort

Positive. They praise the considerable effort and accept population-level focus.

Dependence on final CoU & quality of preclinical data

Conditional. They link their agreement to conditions already highlighted in Q1.

Question 2 = AGREED (but conditional on scope / CoU).

Credibility Assessment

Aspect

EMA's Position

General structure of the credibility plan (verification, UQ, validation)

Supported in principle. They explicitly say it is “most appreciated and supported in principle.”

Choice of IFN- γ as quantity of interest

Problematic. They reiterate IFN- γ is not a validated biomarker; predictive value still to be established.

Uncertainty quantification

Acknowledged but incomplete. Monte Carlo on 22 inputs is noted, but they want you to quantify **epistemic uncertainty** and check transposability of host-directed therapy distributions to therapeutic vaccination.

Validation dataset (only RUTI PhIIa)

Bottleneck. They explicitly call for additional datasets (other RUTI data, M. vaccae, MIP).

Question 3 = PARTLY AGREED /
CONDITIONAL

Food for thought (and possibly chaos)



It has been provided evidence that for RUTI, the applicant could predict more than 3 dose levels, but validation data are missing. But if we already provided evidence for three doses why EMA requires evidence for 100 doses? **It is very hard to do a clinical trial that validates these predictions.**



The link between time course of IFN- γ and prevention of active TB disease still needs to be substantiated. But we proposed the usage of IFN- γ to select the best dosage not for predicting the efficacy. **Immunogenicity vs efficacy issue? Maybe we have to be more clear on this.**



In the first stage EMA requested to narrow our initial CoU but now: “The Applicant is narrowing the context of use to whole cell/fragmented based vaccines that are designed for latent pulmonary TB in adult subjects...” Why? **Maybe the initial narrowing request helped us to get a precise evaluation of model credibility and now they would like the model to be used for a wide range of vaccines against TB.**



The other issues are simple to address.

Credibility matrix for METHODOLOGY

Item	Definition	Instruction	METHODOLOGY
Question of Interest ¹	The question that is intended to be answered by modelling and simulation to inform a decision.	State the question of interest.	
Context of Use	A description of the model(s) and its specific role and scope to address the question of interest. The context should be outlined as a short and concise description of what the outputs of the model(s) will be used for and what data type is used for building the model(s), as well as what other data or evidence support the decision.	Describe the context of use. It should be outlined as a short and concise description of what the outputs of the model(s) will be used for and what data type is used for building the model(s), as well as what other data or evidence support the decision.	
Model Influence	The intended weight of the model outcomes in decision-making considering the contribution other relevant information.	Describe the model influence and rate it as low, medium, or high considering other relevant information (e.g., nonclinical and clinical) for regulatory decision-making.	
Consequence of Wrong Decision	The consequences (e.g., with respect to patient safety and/or efficacy) if a wrong decision is made, based on all available information.	Describe the consequence of a wrong decision and rate it as low, medium, or high based on the severity of the consequences a wrong decision may have on patient safety and efficacy.	
Model Risk	The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.	Describe and derive the risk (low, medium, or high) based on the model influence rate and the consequence of a wrong decision rate.	
Regulatory Impact	The contribution of the model outcomes for answering the question of interest in relation to current regulatory expectations or standards, where applicable.	Describe the impact and rate it as low, medium, or high considering current regulatory expectations or standards, where applicable	
Appropriateness/ of Proposed modelling and simulation Approach	Rationale for the modelling and simulation approach, including related key assumptions and required data to answer the question of interest.	Include a description and justification sufficient to facilitate regulatory determination of the appropriateness of the proposed modelling and simulation approach to answer the question of interest.	
Technical Criteria	A summary and rationale of the key criteria for model evaluation and model outcomes to establish the acceptability of the model application (e.g., using an acceptance standard such as bioequivalence acceptance limits).	Include a description of the technical evaluation, adequacy of the data to be collected, and related decision criteria, as required.	
Model Evaluation	A summary of the key results of the technical evaluation of the model relevant for the context of use.	Include a summary of the output of model evaluation. Technical details should be provided in the regulatory assessment/review or associated MARS.	
Modelling and simulation decision/ modelling and simulation Outcome/ Answer to the Question of Interest	The multidisciplinary decision made regarding the overall assessment of modelling and simulation evidence.	State the multidisciplinary decision made regarding the overall assessment of modelling and simulation evidence.	

Opportunities & Future Directions

1. Prototype an EMA “ABM Qualification Sandbox”

- Co-design **fit-for-purpose credibility metrics** with regulators, not after the fact.
- Test version control, uncertainty protocols and cross-disease portability inside a regulatory pilot.
- Cross-disease portability as a qualification criterion.

2. Move from Case Study to Platform

- Turn UISS-TB into a **template** for ABM qualification?
- Qualification bridging: borrow PBPK’s concept of “cross-version” or “inter-version” qualification: once the core is qualified, new versions only need delta-verification.

Opportunities & Future Directions

3. Expanding the Definition of Mechanistic Modelling

- **PBPK / PBBM / QSP** models are essential but represent **only one layer** of mechanistic modelling.
- **As VPH Institute, we proposed feedback (May 2025) to “Development of a Guideline on assessment and reporting of mechanistic models used in the context of model informed drug development EMA/5875/2025”**
 - Proposed **explicit inclusion** of:
 - *Agent-Based Models (ABM)*
 - *Multi-scale & Multi-physics models*
 - *Digital twins and virtual populations*
 - These approaches offer mechanistic rigor beyond pharmacokinetics—capturing **disease dynamics, immune responses, and treatment interactions.**
- Many emerging regulatory use cases (e.g., disease progression, vaccine response, individualized therapy) require **bottom-up, system-level modelling.**



Key Takeaways

- **EMA is Listening:** The Scientific Advice process shows **ABMs can enter the same regulatory conversations** as PBPK and QSP.
- **Proof-of-Concept Delivered:** UISS-TB demonstrates a **risk-based, transparent pathway** to qualification of agent-based models.
- **Collaboration Is Non-Negotiable:** Regulators, industry and academia must **co-design standards, sandboxes and credibility criteria** together.

Thank you

francesco.pappalardo@unict.it

