THE ORACLE PROJECT



Student Workbook





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The Oracle Project

Context

The world is on the verge of a new pandemic following the identification of a new emerging virus. Several outbreaks are already spreading accross borders. Your team of scientists has been selected to quickly develop an effective vaccine to protect the population.

Overall objective

To develop up to three vaccines and to immunize the population against the circulating viral strains. You will have 4 rounds representing 8 turns in total to achieve these goals. The Project is divided into 3 Chapters that should be performed sequentially.



You will be using an online serious game called Immunization that simulates the vaccine development process. The game is available on the Tabletopia platform.

1. Download the **Tabletopia App** on your tablet and search for <u>The</u> Immunization Game.

Note: For labtops, go to https://tabletopia.com/games/immunization.

2. Create a free account if necessary and select Solo Mode (Cooperative Mode - 1 Player)

Note: if you use a private virtual game room, access it via the URL link provided by the Immunitarium team.

Set up of the gameplay

The gameplay is divided into 5 areas:

- **1** The Disease cards
- 2 The Player's biotech area where vaccines are developed and produced
- 3 The Research reagents and Tox/Clinical study cards
 - **4**) The Turn Counting board
 - The rule summary





For more details about the game rules, click <u>here</u> to watch a video tutorial.

Set up of the 1st Disease card (A)

- Enter 20 in the "Vaccine needs" field
- 2 Enter **435** as the Target antigen
- **3** Leave the "Recommended Vaccine Price" case empty or ignore it as you will not use the coins during this project
- **4** Enter **Ø** in the "Combo Incompatibility" field (this feature will be introduced in Chapter 1-Round 2)

This disease A represents the first circulating strain of the virus (wild type strain).

Set up of your Technologies & Expertise (T&E) cards

- 1. Reveal all the T&E cards displayed in the game area.
- 2. Select the following ones to represent the technologies and expertise available in your biotech:

Technologies [+] [-] [x]

These 3 technologies allow the development of vaccine formulas. Their combination helps improve the vaccine efficacy.



Note: You can use these technologies as often as you want to develop your vaccines.

Expertise "Clinical trial management"

This expertise allows a player to roll the clinical dice one more time in case of Ph1/2 or Ph3 study failure.



Note: This technology can be used every time a player performs a Ph1/2 or Ph3 study.

Set up of your Manufacturing Capacity

Before starting the game, set your production capacity at 5.







Chapter 1 – The never-ending chase

<u>Round 1 : Development of a monovalent vaccine</u>

Objective: Develop a vaccine (A) as fast as possible against the virus that just emerged. You have <u>2 turns and 3 actions per turn (6 actions in total</u>) to complete this task.

The Science behind

A monovalente vaccine is a vaccine that contains one antigen to protect against a single disease or a single pathogenic strain.



Click <u>here</u> to watch a short video to learn how to develop a vaccine formula and read explanations in **Annex 1**.

Notes:

- Describe each action taken during your turns in the Tables 1 & 2 available in Annex 2.
- The vaccine units are distributed to immunize the population at the end of each round.

B) Write below the antigenic formula you have developed and calculate the vaccine efficacy.

C) At the end of the 1st round, have you been able to launch your vaccine? If so, how many vaccine units have you distributed?

D) Update the vaccine needs on the Disease card (A) by substracting your number of vaccine units.

E) During this 1st round, your team has gained some knowledge and experience. You can select one new T&E card among the list displayed in Annex 3.
Which T&E card have you choosen? Explain why.

<u>Round 2: Development of a bivalent vaccine</u>

A new mutant strain has been detected.



Objective: Develop a combo vaccine (A/B) against the 2 circulating variants (a bivalent vaccine). You have <u>2 turns and 3 actions per</u> <u>turn (6 actions in total)</u> to complete this task.





The Science behind

A combination (or combo) vaccine is a vaccine that protects against multiple diseases or pathogenic strains.

The number of antigens included in a vaccine detemines the valency of the vaccine. Several vaccines have been developed based on monovalent (1 antigen), bivalent (2 antigens), trivalent (3 antigens) or quadrivalent formulations (4 antigens) and even more. Combo vaccines are also referred as multivalent vaccines.



Look for examples of combo vaccines on the Internet and name some of them.

Set up of the 2nd Disease card (B)

- **1** Enter **20** in the "Vaccine needs" field
- 2 Enter 403 as the Target antigen
- Enter [-] in the "Combo Incompatibility" field

Go to Annex 4 to learn how to develop a combo vaccine by taking into account the "combo incompatibility" limitations.



A) Evaluate the efficacy of your 1st vaccine (A) against the new strain. Comment on the impact of the virus mutations on the vaccine efficacy.

B) Write below the new antigenic formula of your 2nd vaccine (A/B) and calculate its efficacy.

C) At the end of the 2nd round, have you been able to launch your combo vaccine? If so, how many vaccine units have you distributed with this vaccine?

Have you also distributed vaccine units of your first monovalent vaccine? If so, how many? If not, why?

D) Update the vaccine needs on the two Disease cards (A & B) by substracting the respective numbers of vaccine units.

Note: Your combo vaccine units should be substracted from the vaccine needs of <u>both</u> Disease cards.

E) During this 2nd round, your team has gained some knowledge and experience. You can select one new T&E card among the list displayed in Annex 3.
Which T&E card have you choosen? Explain why.

Chapter 2 – The era of predictive vaccinology

Round 3: Develoment of a predictive vaccine

The virus is going to mutate again. The genetic evolution of the virus should be studied to predict the next variant and develop the new vaccine in advance.



Objective: Make a prediction of the target antigen for the next variant by studying the 2 circulating variants and develop a predictive vaccine. You have <u>2 turns and 3 actions per turn (6 actions in</u> <u>total)</u> to complete this task.



A) Use the graph below to plot the target antigen values of the first 2 variants and define the function that represents the genetic evolution of the virus.



B) Predict the target antigen value of the next variant by using the above function.



C) Use your 3rd Vaccine Board to develop the predictive vaccine (C), ideally up to the Ph1/2 study stage.

Write below the antigenic formula of your predictive vaccine and calculate its predicted efficacy.

Notes:

- Use 2 clinical dice for the validation of the predictive vaccine during the Ph1/2 study (+/- 1 dice depending on your Tox score).

- The Ph3 study will be initiated during the 4th round once the new strain is detected.

D) At the end of the 3rd round, have you been able to test your predictive vaccine in a Ph1/2 study?

Have you also distributed vaccine units of your monovalent and/or combo vaccines? If so, how many units?

E) Update the vaccine needs on the two Disease cards (A & B) by substracting the respective numbers of vaccine units.

F) Select a new T&E card among the list displayed in **Annex 3**. Which T&E card have you choosen? Explain why.

Chapter 3 – The resolution phase

<u>Round 4: Control & Eradication of the Pandemic</u>

As expected, a new viral strain has been detected among the population.



Objective: Finalize the development of your predictive vaccine and try to eradicate all the circulating variants.

You have <u>2 turns and 3 actions per turn (6 actions in</u> <u>total)</u> to achieve this objective.



The science behind

The concept of predicitve vaccinology is not new and is actually used to predict the Influenza strains that circulate every seasons.

Read this <u>CDC article¹</u> to learn more about the average efficacy of the seasonal Flu vaccines.

Set up of the 3rd Disease card (C)

- **1** Enter **20** in the "Vaccine needs" field
- 2 Enter **357** as the Target antigen
- **3** Enter **[x]** in the "Combo Incompatibility" field

A) Evaluate the "real" efficacy of your predictive vaccine against the new strain. Comment the accuracy of your prediction.



B) Perform the Ph3 study with your predictive vaccine.

Note: The number of clinical dice for the Ph3 study is determined based on the "real" vaccine efficacy (+/- 1 dice based on your Tox score).



Read this <u>article</u>² and comment on the approach used by these pharmaceutical companies to fight the Covid19 pandemic.

D) Based on this reading and assuming you were playing with other groups, what could you have done differently to stop this pandemic more efficiently?

How would you have allocated the T&E cards to each group to form an optimal consortium?



E) Find an article that illustrates the "Rapid response platform" T&E card that you may have used during your vaccine development simulation.In your opinion, which vaccine technology(ies) falls into this category?

F) Do you think that a virus mutates randomly or do you believe that the genetic evolution of a virus can be predicted? Explain your opinion.



Read this <u>research article</u>³ about applications of physical principles & laws to biological systems like DNA/RNA genomes (Section IV of the article). Discuss as a group the conclusions of this study and the similarities you see with this vaccine development simulation.



Find additional articles that support your arguments related to the existence of deterministic (predictable) patterns or stochastic (not predictable) patterns in the evolution process of viruses.



Read this <u>article</u>⁴ from CEPI about the development of a Global Vaccine Library based on AI-generated antigens.

G) Based on your litterature review and on what you have learned during this vaccine development simulation, describe in one concise paragraph the concept of predictive vaccinology as you were explaining it to a non-specialist audience.

Annex 1 - Vaccine development process summary and Action list



Note: When you develop your vaccines, you will need to use Technologies & Expertise () represented by T&E cards. The use of T&E cards does not count as an action. You can use your T&E cards as many time as you want during the gameplay.

Annex 2

Table 1. Action tracker related to Rounds 1 & 2

Round #	Turn #	Action #	Description (or Code)	Outcome or Score	Comments
Example A			3 Research Reagents ordered (or 3 REA)		10 ; 50 ; 80
Example B			Initiation of Tox study with in vitro model (or Tox IVM)	Tox score = 5	3 Clinical dice to be used based on Tox score
R1	T1	A1			
		A2			
		A3			
	T2	A4			
		A5			
		A6			
R2	тз	A7			
		A8			
		A9			
	Т4	A10			
		A11			
		A12			

Annex 2

Table 2. Action tracker related to Rounds 3 & 4

Chapt. #	Turn #	Action #	Description (or Code)	Outcome or Score	Comments
Example A			Initiation of PhI/II Clinical study (or Ph1/2)	Success	Monovalent vaccine against strain A with Efficacy = 98%
Example B			Launch of my vaccine (or VAC)		5 vaccine units distributed
R3	Т5	A13			
		A14			
		A15			
	T6	A16			
		A17			
		A18			
R4	Τ7	A19			
		A20			
		A21			
	Т8	A22			
		A23			
		A24			

Annex 3 – Technologies & Expertise Cards (see next page as well)

Technologies [+] [-] [x] [÷]

These technologies allow the development of antigenic formulas. Their combination can be useful to improve the vaccine efficacy.





Techno "High-throughput screening"

This technology allows a player to obtain two reagents (of any type) at no cost <u>each turn</u>. The procurement of these reagents does not count as an action.

Techno "Combo development"

This technology allows a player to develop <u>one</u> "combo" vaccine by bypassing the incompatibility constraints.

Techno "Digital Manufacturing"

This technology allows a player to purchase up to 3 Production units per action (instead of 2) to increase his/her manufacturing capacity.

Techno "Rapid Response Platform"

This technology allows a player to waive the Tox evaluation. The vaccine platform has been consistently demonstrated as safe and can be granted a Tox score of 4 by default. The player is <u>not obliged</u> to use this techno during the development of a vaccine.

Techno "Predictive Modeling"

This technology allows a player to roll the Tox dice twice and to select the highest score. This technology can be used every time a player performs a Tox study (in vitro or animal models).









Annex 3 – Technologies & Expertise Cards





Expertise "Clinical trial management"

This expertise allows a player to roll the clinical dice one more time in case of study failure. This technology can be used every time a player performs a Ph1/2 or Ph3 study.

Expertise "Quality by Design"

This expertise allows a player to increase the vaccine efficacy by 5% for <u>one</u> vaccine only.



Expertise "Structural Biology"

This expertise allows a player to use an exclusive reagent of a value equal to **3**. This reagent can be used indefinitely in the vaccine formulas without extra cost.



> Expertise "Regulatory"

This expertise means that your Company has mastered the regulatory procedures required to launch new vaccines. Any launch can be performed without counting as an action.



Expertise "Supply Chain Management"

This expertise allows a player to immediately gain 2 production units (only once) and to expand the production capacity of his/her manufacturing facility with 6 additional units (Maximum Capacity = 24 units). However, the player still needs to purchase the production units to reach this extra level of production capacity.

Annex 4 – How to develop a "combo" vaccine

A "Combo" vaccine is a vaccine protecting against several diseases at the same time, in comparison with a single vaccine that targets only one disease. The development of a "Combo" vaccine must respect the following rules :

- Only two diseases may be targeted at the same time.
- The Target Antigen to consider for the antigen design is choosen by the player.
- The **antigenic formula cannot contain any sign** displayed in the "**Incompatibility**" boxes of both targeted diseases.





Notes: some diseases may not have incompatibility signs (\emptyset) and may be combined without restriction in the development of the antigenic formula. The other rules still apply.

During the vaccine distribution, each vaccine unit of a "Combo" vaccine is counted twice. In other words, the vaccine needs of <u>each disease</u> should be updated by substracting the number of combo vaccine units.

Annex 5 – References

1. CDC article about seasonal Flu vaccine Efficacy

https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm

2. Article about partnership models during the Covid19 pandemic <u>https://www.biospace.com/article/sanofi-gsk-to-support-pfizer-and-biontech-vaccine-manufacturing/</u>

3. Research article about the second law of information dynamics <u>https://pubs.aip.org/aip/adv/article/12/7/075310/2819368/Second-law-of-information-dynamics</u>

4. CEPI article about Global Vaccine Library
<u>https://cepi.net/forecasting-viral-mutations-</u>
0#:~:text=A%20study%20published%20in%20Nature,of%20SARS%2DCoV%2D2.