ALAN
Acute Leukaemia Advocates Network

CLLAN
CLL ADVOCATES NETWORK

Webinar

COVID-19 vaccination & immune challenges for leukemia

A webinar targeting patient advocates in the area of CLL & acute leukaemia

11 February 2021, 16:00-17:30 CET (+practice session 15:30-16:00 CET)

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Welcome, introduction to topic & panel, housekeeping notes

Zack Pemberton-Whiteley – host & moderator
(Chair - Acute Leukemia Advocates Network, ALAN)

Pierre Aumont – host & co-moderator
(Member of the Steering Committee - CLL Advocates Network, CLLAN)

Hosts & moderators

- Zack Pemberton-Whiteley (UK), Chair of the Acute Leukemia Advocates Network, ALAN
- Pierre Aumont (France), Member of the Steering Committee of the CLL Advocates Network, CLLAN

Speakers

- Professor Florence Cymbalista (France), Head Hematology Biology Department, Avicenne Hospital
- Dr Amit Patel (UK), Consultant in Cellular Therapies and Transplantation, The Christie NHS Foundation Trust, Haematology and Transplant Unit
- Dr Julio Delgado (The Netherlands / Spain), Seconded National Expert, Oncology Office, European Medicines Agency (EMA), Amsterdam / Department of Haematology, Hospital Clinic, Barcelona
- Professor Uwe Gerd Liebert (Germany), Institute of Virology, Leipzig University, Leipzig

Housekeeping Notes

- The audience will be muted.
- To ask a question, please use Q&A or chat. We will try to answer as many questions as possible.
- The webinar is being recorded. Recording and slides will be available for future viewing on our websites www.clladvocates.net and www.acuteleuk.org

Agenda (total time: 1,5 h)

Time	Topic	Presenter
10’	Welcome, introduction to topic & panel, operational & webinar housekeeping notes.	Zack Pemberton-Whiteley & Pierre Aumont
40’	Advice from the experts (4 speakers - 10 minutes each) • Safety and efficacy of the COVID-19 vaccines in patients with immune challenges • Roll-out of vaccines in the patient communities • Specific challenges of CLL and Acute Leukemia patients • And others…	Prof Florence Cymbalista (France) Dr Amit Patel (UK) Dr Julio Delgado (Spain/NL) Prof Liebert (Germany)
35’	Q&A - discussion session	Zack Pemberton-Whiteley & Pierre Aumont
5’	Conclusion, thank you & closing	Zack Pemberton-Whiteley

Advice from the experts

- Prof Florence Cymbalista (France)
- Dr Amit Patel (UK)
- Dr Julio Delgado (Spain/NL)
- Prof Liebert (Germany)

CLL, COVID 19, and vaccine

Pr Cymbalista

Hopital Avicenne, Paris 13 University

- COVID and CLL
  - Clinical studies
  - Recommendations

- mRNA vaccine
  - what do we know?
  - How does it work

- Vaccination against Sars Cov 2 and CLL
  - Indications
  - Contra indications
  - Recommendations

COVID 19 and CLL: European study

- ERIC study conducted mostly in Italy and Spain
  - Median age at COVID-19 diagnosis was 72 years
  - At the time of COVID-19, 76% of patients (145/190) carried one or more comorbidities,
    - hypertension 54% cardiovascular diseases 29%,
    - Diabetes mellitus 24%
    - Pulmonary disease 20%
  - Regarding CLL history, 38.4% patients were previously untreated, whereas 116 (61.1%) had previously received and/or were receiving treatment for CLL

Considering the median age of 72 years and the presence of at least one comorbidity in ~75% the high mortality rate (55/169, 32.5%) among the hospitalized patients was expected

Nonetheless, it is higher than reported in the general population (app 13,4%)

- 6 patients only are reported by the German group in a trial with Venetoclax, and 2 out of 6 were admitted in ICU and died

Scarfo L, Leukemia , sept 2020
Furstenau M, Leukemia, june 2020

American study

- 198 CLL patients diagnosed with symptomatic COVID-19 were included.
  - Median age at COVID-19 diagnosis was 70.5 years.
  - 39% were treatment naive while 61% had received at least one treatment
  - 45% were receiving active CLL therapy at COVID-19 diagnosis, most commonly BTKi
  - Among watch-and-wait and treated CLL patients
    - similar rates of admission (89%vs 90%),
    - intensive care unit admission (35% vs 36%),
    - intubation (33% vs 25%),
    - mortality (37% vs 32%)

Receiving a BTKi for CLL at COVID-19 diagnosis severe enough to require hospitalization did not influence case fatality rate in this study.

Mato AR, Blood sept 2020

COVID-19 in CLL patients

- These studies are mostly focused on hospitalized patients.
- Patients treated at home were scarcely reported
- In the French cohort (unpublished data) we observed
    - a similarly high mortality rate of hospitalized patients
    - But we also observed patients treated at home
    - And even asymptomatic patients, even among elderly

Risk factors (age, diabetes, hypertension, obesity) identified in the non CLL population have the same importance in CLL,

- COVID-19 treatment has been similar for CLL to treatment for patients without CLL

- Of note, Ibrutinib and Acalabrutinib have been proposed to non CLL patients to contain the cytokine storm. It seems that these trials are negative, but no detrimental effect.

CLL treatment and COVID

There is now a consensus among recommendations from various national groups

- No discontinuation of on going treatment
  - outside of on going severe COVID19 infection in ICU

- For patients in need of treatment for CLL , it is recommended to postpone initiation of therapy, if possible, until after vaccination.
- When treatment cannot be further deferred, preference of systemic therapy that requires fewer clinic visits and/or is less immune suppressive.
  - In France we have replaced Chemo immunotherapy by Ibrutinib during the epidemic waves
  - Limitation of anti CD20 infusions

- Limitation of routine lab samples
- For patients receiving Immunoglobulin supplementation, IV route to be replaced by SC
- Maintenance of vaccination program against influenza and pneumococcus

Results of vaccine trials

Pfizer vaccine

- Enrolled 43,448 participants who received two doses of the vaccine or placebo (1:1 randomisation), 21 days apart.
- Number of COVID-19 cases was 8 versus 162 in the vaccine or placebo arm, with 1 versus 9 severe cases.
- Mild adverse events were frequent (local reactions frequent systemic mild reactogenicity such as fatigue and headache
- Altogether, 6 participants died (2 in the vaccine arm and 4 in the placebo arm), all of them from unrelated causes.

Moderna vaccine

- Enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo . More than 96% of participants received both injections,
- Covid-19 illness was confirmed in 185 participants in the placebo group and in 11 participants in the mRNA-1273
- Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group.
- Serious adverse events were rare, and the incidence was similar in the two groups.

Overall mRNA-based vaccines have shown >90% protection from COVID-19 disease with good tolerance, whereas a non-replicating adenoviral vector-based vaccine has shown protection rates of 62%-90% conferred by different dosing regimens.

Polack FP, NEJM dec 2020

LR Baden, NEJM feb 2021

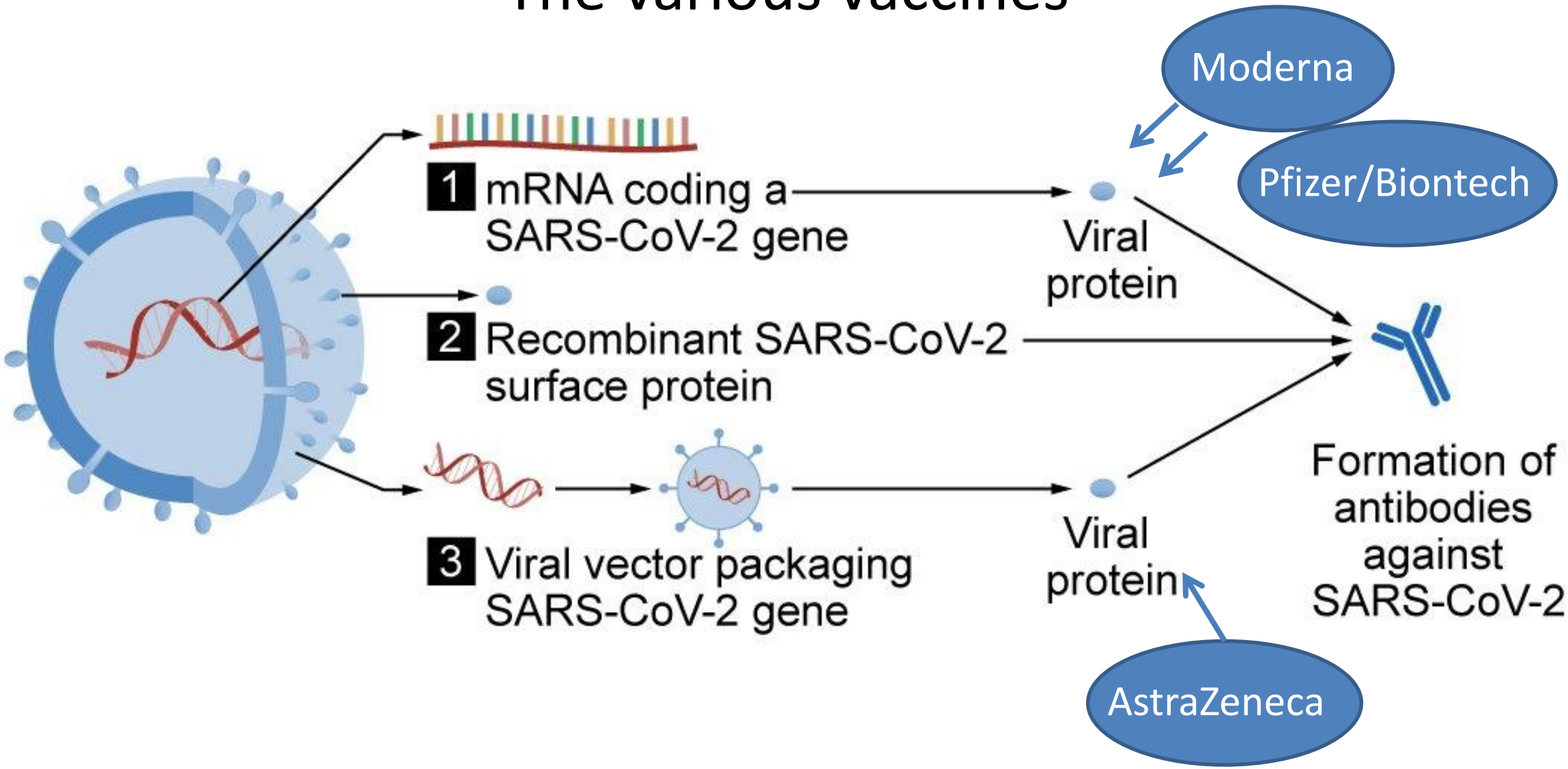
What do we know so far about response and efficacy of the COVID-19 vaccines in CLL patients?

NOTHING

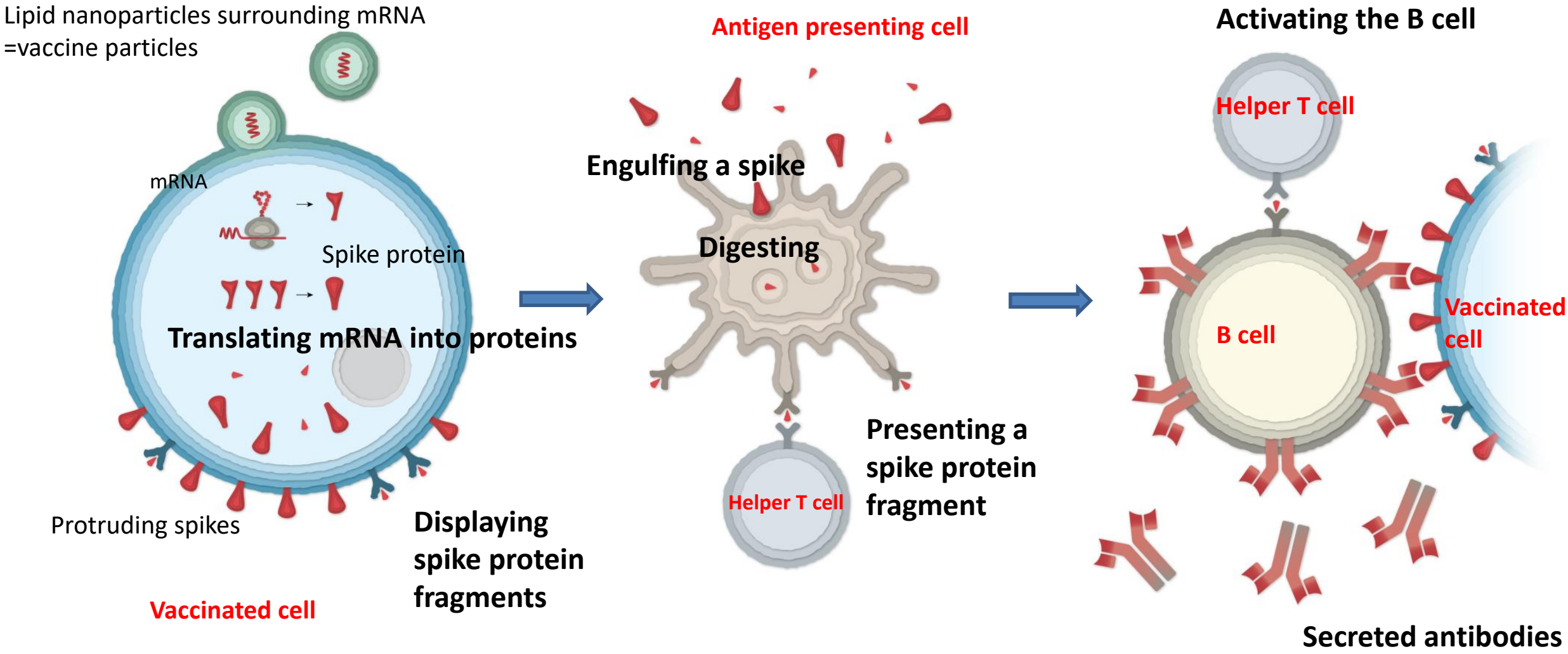
Can we extrapolate from some works done with other vaccines?

- There are few data on vaccine efficacy in patients with CLL
- But there is enough evidence to support anti-infective vaccination in patients with CLL undergoing therapy or not
  - even suboptimal responses to influenza vaccination can provide partial protection, reduce hospitalization rates, and/or prevent serious disease complications
- Which vaccine?
  - Considering the recent recommendations of several countries to use the Astra Zeneca vaccine for younger patients, it seems reasonable to prioritize mRNA vaccines

The various vaccines

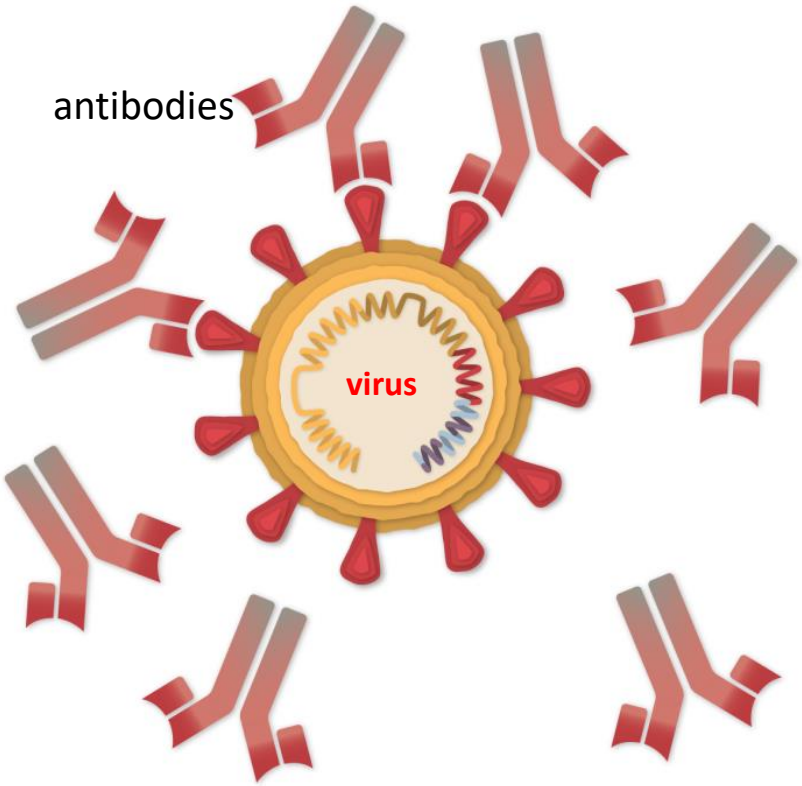


How the mRNA vaccine works

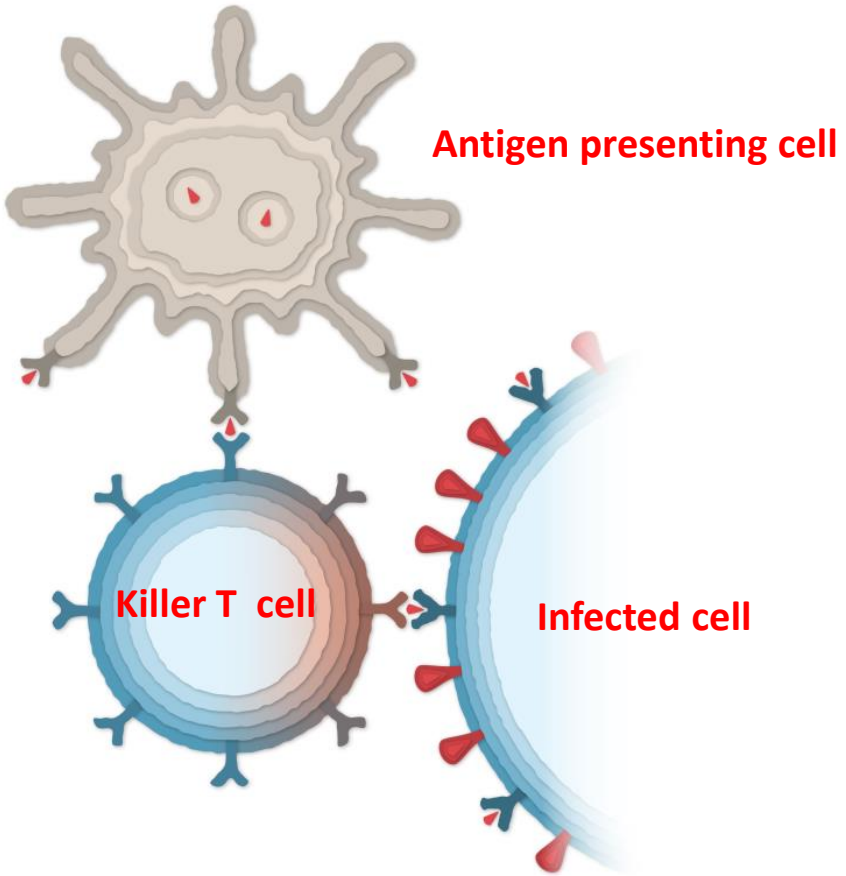


Stopping the spreading of virus

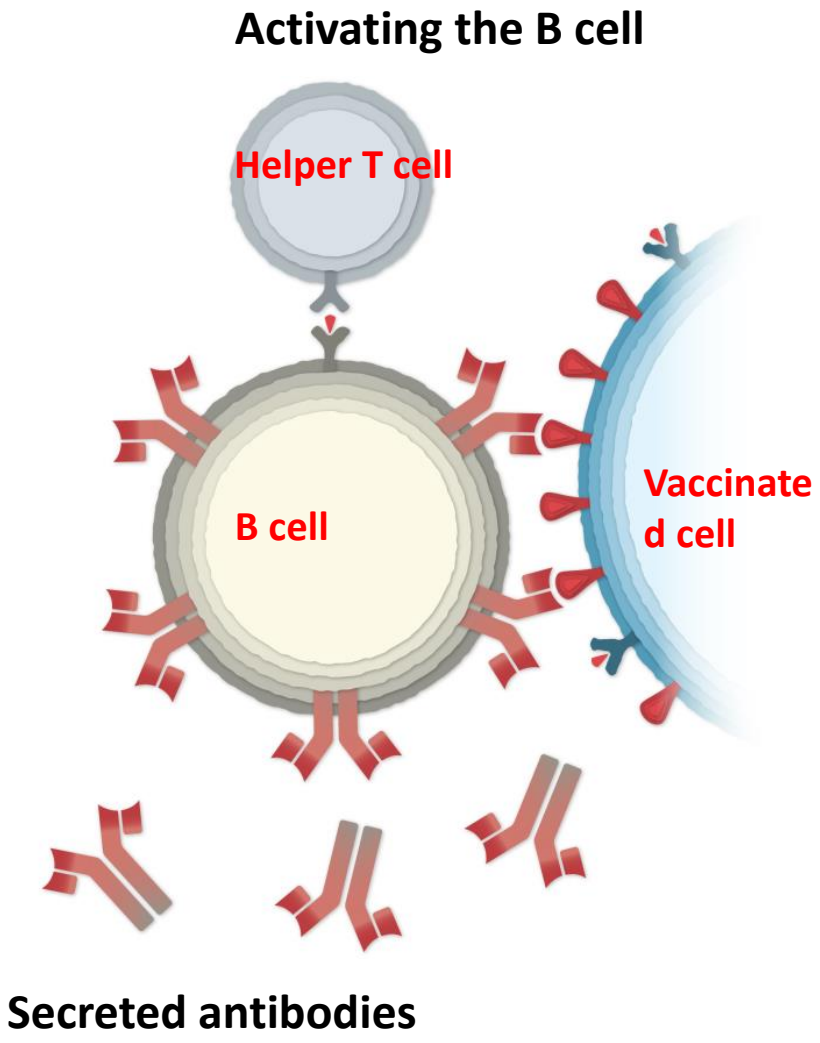
Stopping the Virus by antibodies



Killer T cell also seek out and destroy any coronavirus-infected cells



What are the typical immune challenges CLL patients are facing?



Reduced number of normal B cells

Bad B and T cell cooperation

If previous treatment, helper T cell numbers might be affected as well

Studies with other vaccine show that protective effects are reduced in CLL treated patients

- Three recent studies
  - Response to hepatitis B and VZV vaccine
    - CLL patients have decreased vaccine responses
    - The humoral immune response to novel antigens is impaired by BTKi's
    - But response to recall antigens (antigens already known in the body such as VZV) appears preserved.

  Another study on Influenza vaccine
    - Detection of meaningful vaccine responses
  - Another on VzV vaccine in Btki treated patients
    - Detection of B and T cell responses

Small numbers of patients, some discrepant results, and exploration of response limited to antibody production

Pleyer C et al, Blood. 2021 Jan 14; 137(2): 185–189
Whitaker JA, Vaccine 2021, 1122, 1130
Zent CS, Leukemia, 2020

Can we extrapolate results of mRNA SARS Cov2 vaccination from works done with other vaccines?

- YES
  - The mechanism of action of the COVID-19 vaccines (not live).
  - It is conceivable that the efficacy and safety may be estimated to be similar
  - We may expect a reduced efficacy in CLL, notably in patients on therapy
  - mRNA-based vaccines have been tested against some cancers(e.g. melanoma) for the past 10 years, without raising specific safety concerns

- NO but there is hope that mRNA vaccines work better
  - Promising preliminary data indicating the efficacy of messenger RNA–based vaccines in immunocompetent patients
  - Studies so far have focused on B cell responses
  - But T cell immunity is likely to play an important role in vaccine efficacy as well
  - There may be an advantage of mRNA vaccines as protein processing may allow better recognition by immune system

Roeker LE,. 2020;34(11):3047-3049

Zent CS, Leukemia. 2020;

Recommendations for vaccination

- Who should get the vaccination?
  - All CLL patients +++
  - High priority: patients with on going treatment
  - Patients who had previous COVID infection may be vaccinated but at least 3 months after infection

- Which vaccine?
  - There is a consensus currently to consider mRNA vaccine as most appropriate
  - Use of Astra Zeneca vaccine has been restricted in many countries to patients below 65.
  - This may change with the release of other vaccine

- When?
  - Prior to starting therapy if possible
  - In patients who have already initiated chemotherapy, the existing data do not support a specific timing of administration with respect to chemotherapy infusions
  - Treatment should not be discontinued.
  - Second dose should not be delayed: Max 4 weeks after first dose

Contra-indication to vaccination

- **The only contra indications are:(CDC recommendations)**
  - Severe allergic reaction (e.g., anaphylaxis) after an mRNA COVID-19 vaccine
  - Immediate allergic reaction of any severity to polysorbate or polyethylen glycol

- Allergy:
  - vaccination in allergy specialized centers if prior allergy to injectable therapies or iodine
  - No specific precautions for any other allergic reactions including
    - severe allergic reactions to food components or environmental allergies,
    - allergies to oral medications (including the oral equivalents of injectable medications)
  - Neither vaccine contain eggs, gelatin, latex, or preservatives

- Previous auto-immune episodes
  - No data are currently available on the safety and efficacy of mRNA COVID-19 vaccines in persons with autoimmune conditions but no signal from clinical trials

CDC ongoing safety recommendation for immune compromised patients post vaccination

- *Public health recommendations for vaccinated persons*
  - There is limited information on
    - how much the mRNA COVID-19 vaccines may reduce transmission in the general population
    - how long protection lasts
  - Vaccinated persons should continue to follow all current guidance to protect themselves and others.
  - This includes wearing a mask, staying at least 6 feet away from others, avoiding crowds, washing hands often

- Given the lack of data on the safety and efficacy of mRNA COVID-19 vaccines administered simultaneously with other vaccines, a minimum interval of 14 days before or after administration with any other vaccine is recommended

Dr Amit Patel (UK)

Consultant in Cellular Therapies and Transplantation The Christie NHS Foundation Trust, Haematology and Transplant Unit

EUROPEAN MEDICINES AGENCY
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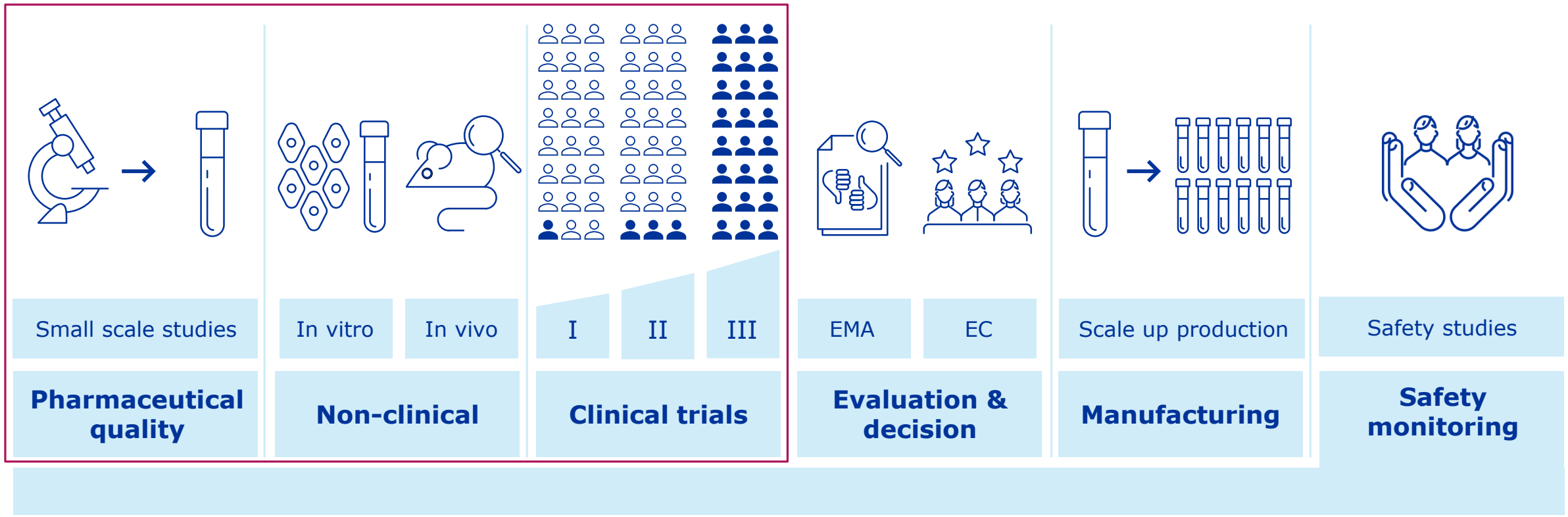
The development of COVID-19 vaccines

Dr. Julio Delgado
Seconded National Expert, Oncology Office, EMA

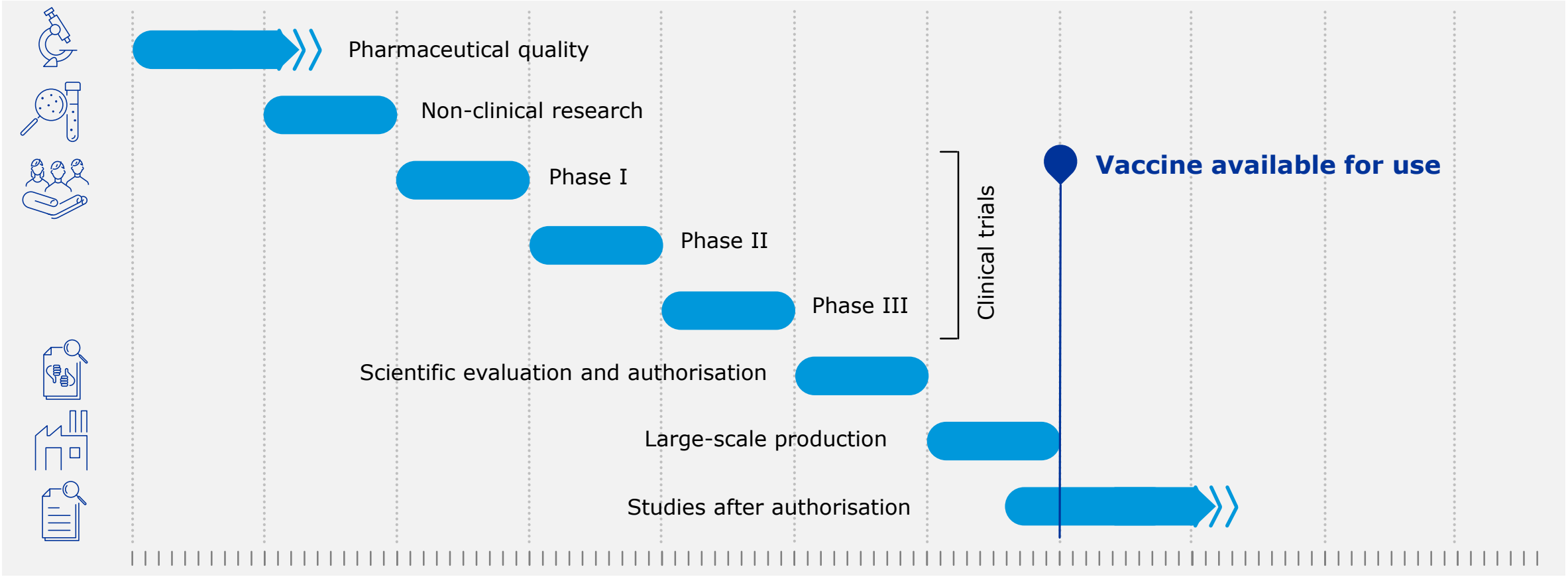
Overview

COVID-19 VACCINE DEVELOPMENT, EVALUATION, APPROVAL AND MONITORING



STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

Indicative timeline



STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

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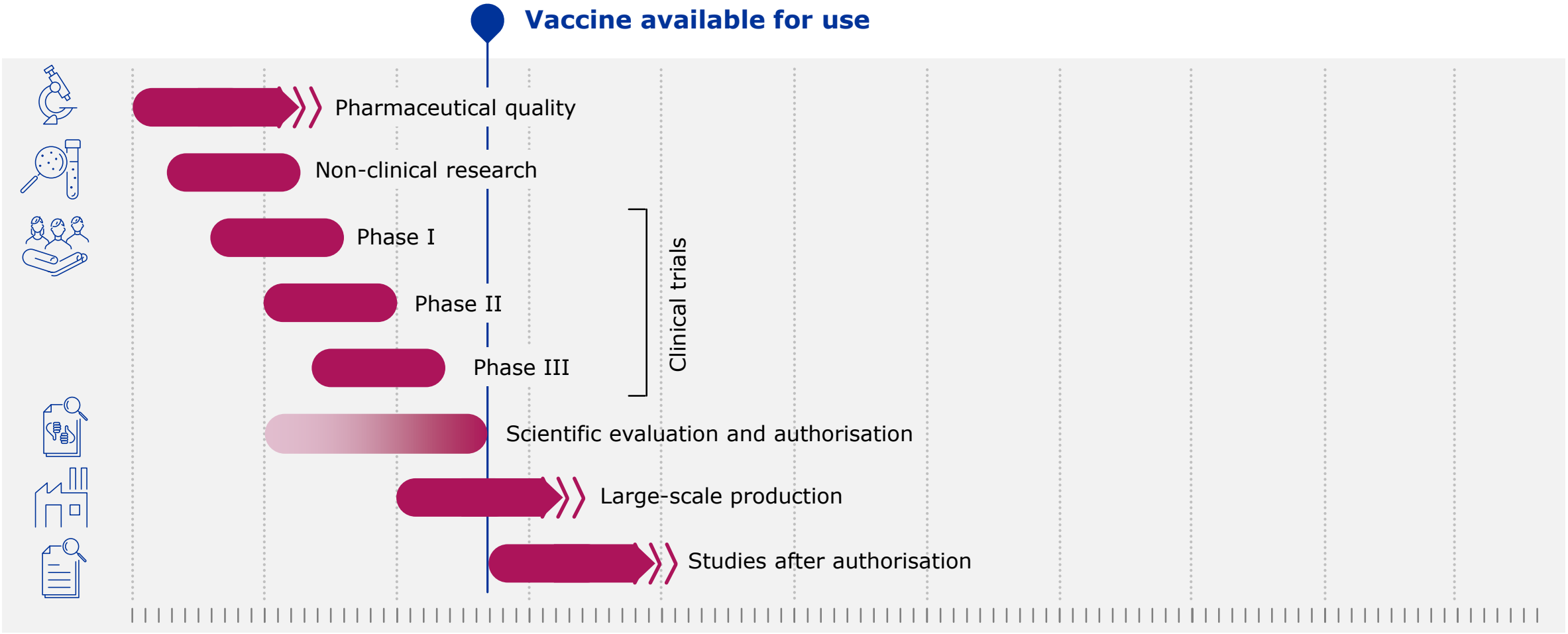


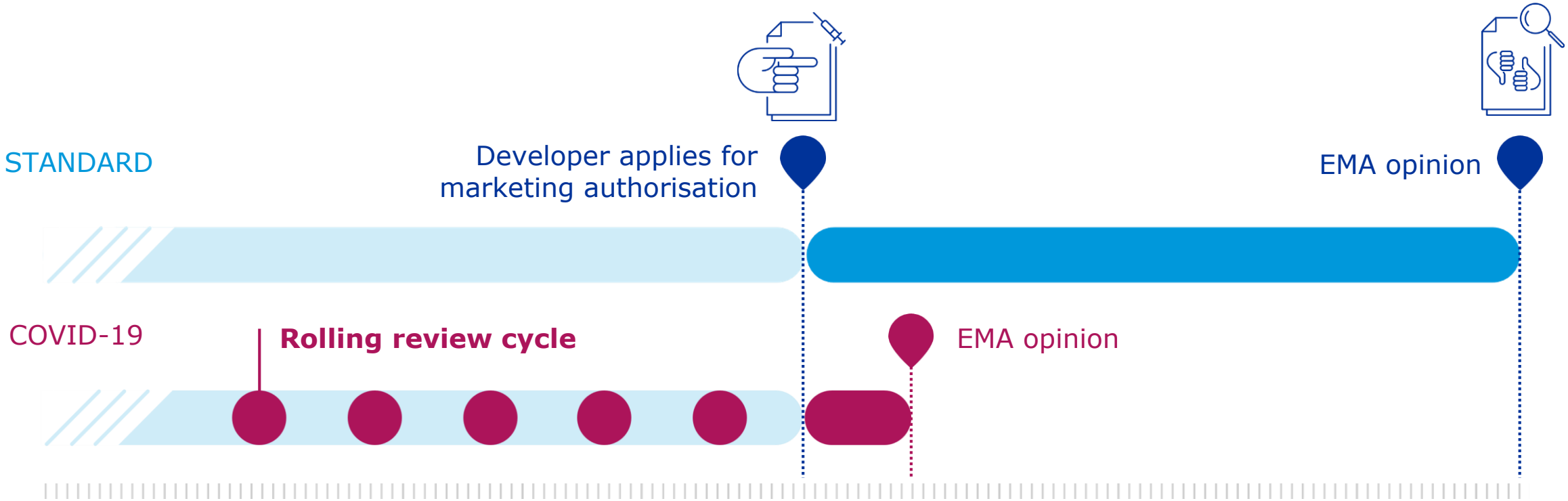
Rolling review

Research & development

Standard EMA evaluation

EMA evaluation with rolling review

- In public health emergency - EMA can **evaluate data** for a promising medicine **as soon as available**
- **Several** rolling review **cycles** can be done as data continue to emerge
- Once all **Quality, Safety and Efficacy** data are ready, the company can formally apply for marketing authorisation application to EMA



STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

Regulatory standards

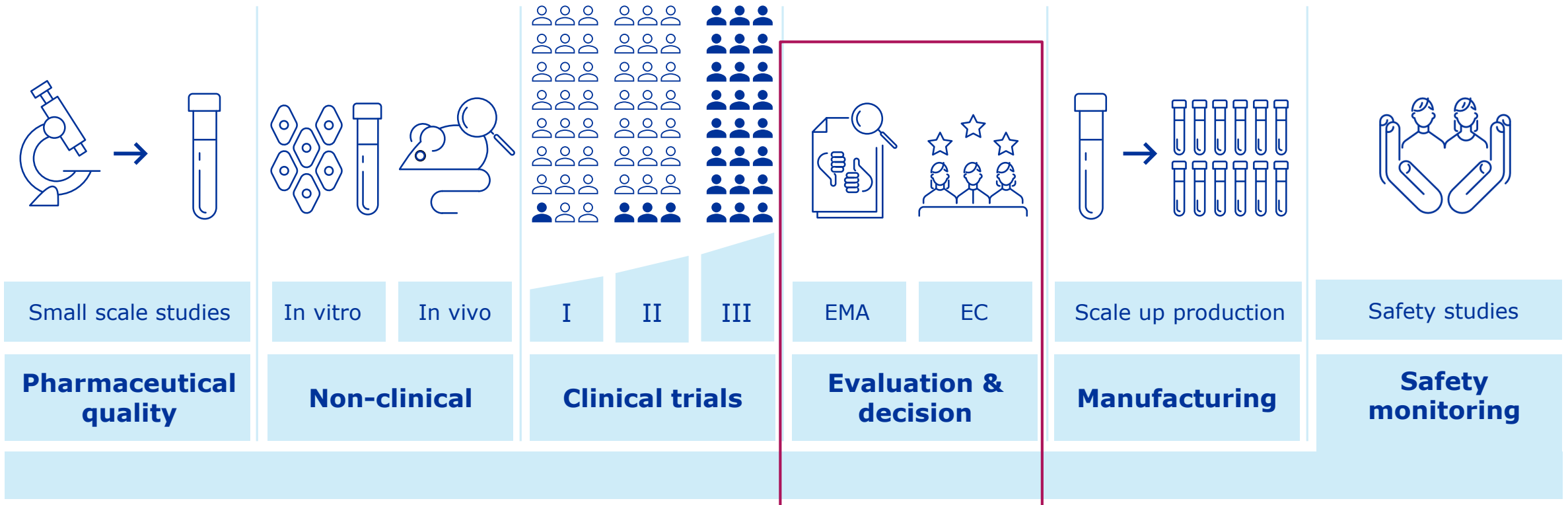
COVID-19 vaccines must be approved according to the **same standards** that apply to all medicines in the EU

STANDARD

COVID-19

Overview

COVID-19 VACCINE DEVELOPMENT, EVALUATION, APPROVAL AND MONITORING



Conditional Marketing Authorisation

- Medicines that address unmet medical needs
- The benefit of immediate availability of the medicine outweighs the risks
- Medicines intended for
  - treating, preventing or diagnosing seriously debilitating or life-threatening diseases
  - public health emergencies
- Other data must be provided by the company, after approval (e.g. long-term safety data)

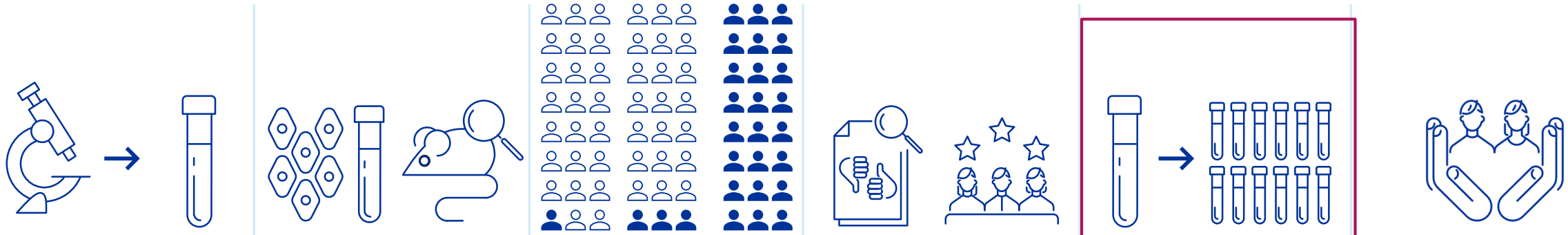
Conditional Marketing Authorisation

WHY CONDITIONAL APPROVAL IS THE MOST APPROPRIATE TOOL IN THE EU?

- **Formal approval** of a medicine across the EU: **all member states benefit** from the joint scientific assessment and approval
- It has **all safeguards and controls** in place to ensure high level of protection to citizens during a mass vaccination campaign:
  - A robust **monitoring plan** for managing **safety**
  - Clear **legal framework** for evaluation of **emerging efficacy data**
  - **Manufacturing** controls including **batch controls** for vaccines
  - Full **prescribing information** and **package leaflet** with defined conditions for storage and use of the vaccine
  - A **plan** for **use** of the vaccine **in children**
  - **Additional studies or other data** ('conditions') that the company is **legally obliged** to provide with defined **timelines**

Overview

COVID-19 VACCINE DEVELOPMENT, EVALUATION, APPROVAL AND MONITORING



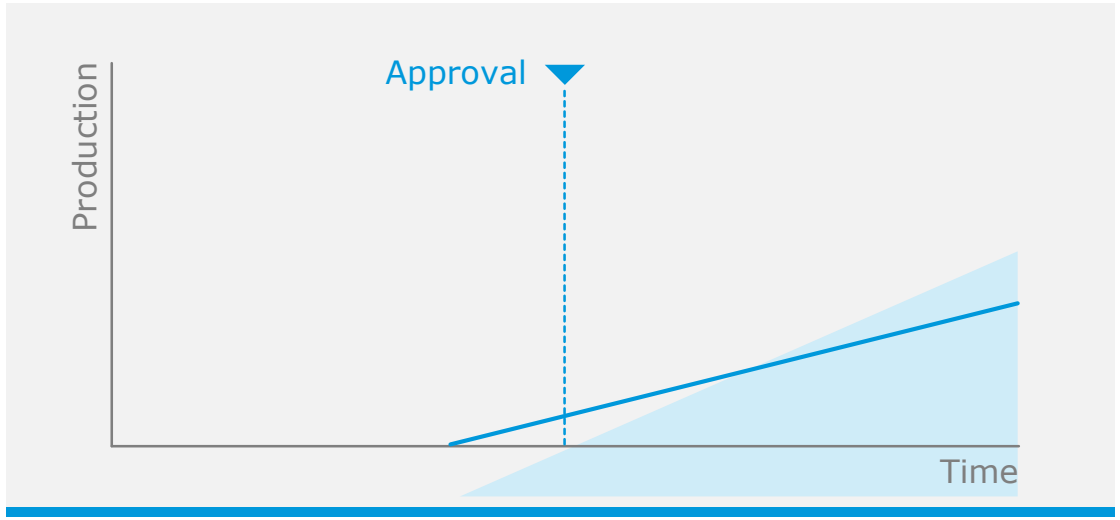
Small scale studies	In vitro	In vivo	I	II	III	EMA	EC	Scale up production	Safety studies
Pharmaceutical quality	**Non-clinical**		**Clinical trials**			**Evaluation & decision**		**Manufacturing**	**Safety monitoring**

STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

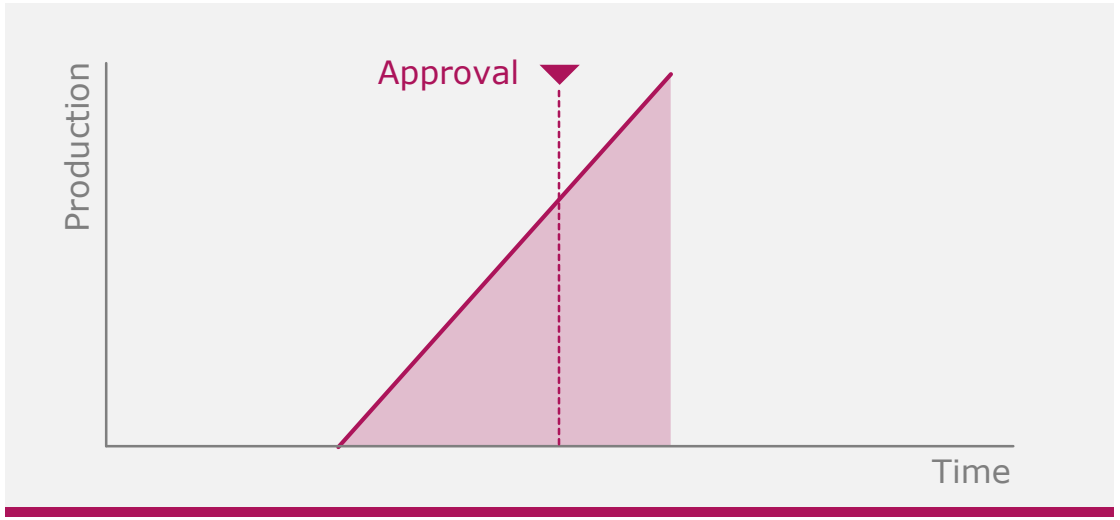
Manufacturing

Companies are **expanding** manufacturing and production **capacity** to ensure efficient vaccine deployment

STANDARD



COVID-19



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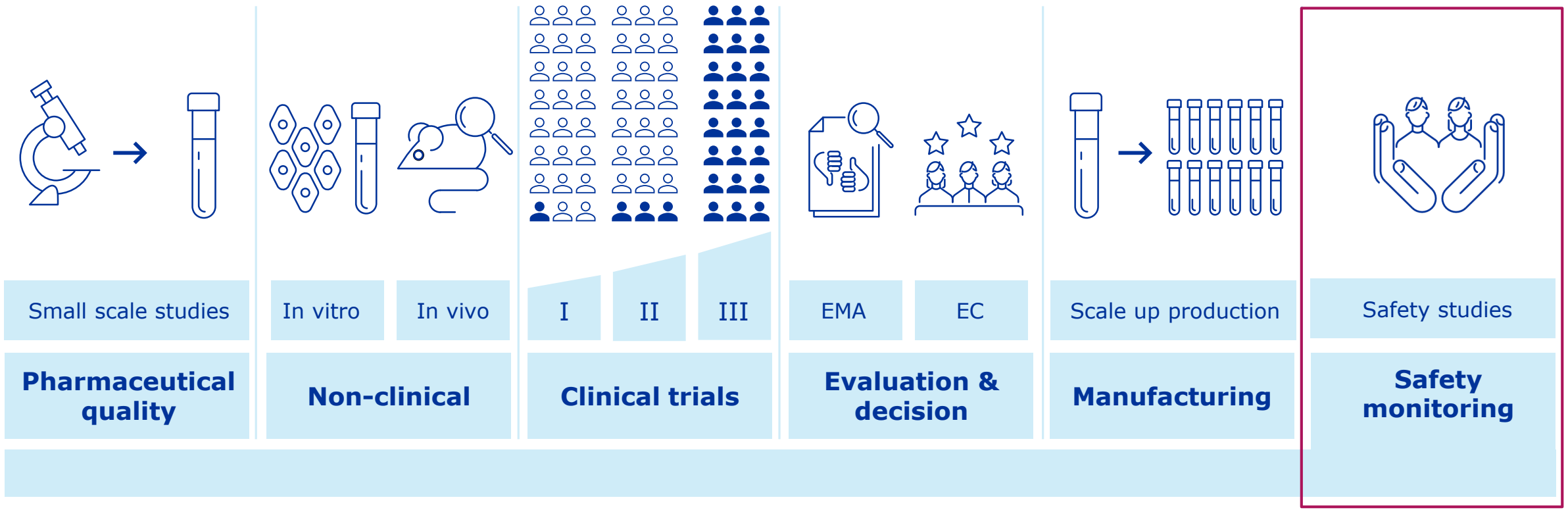
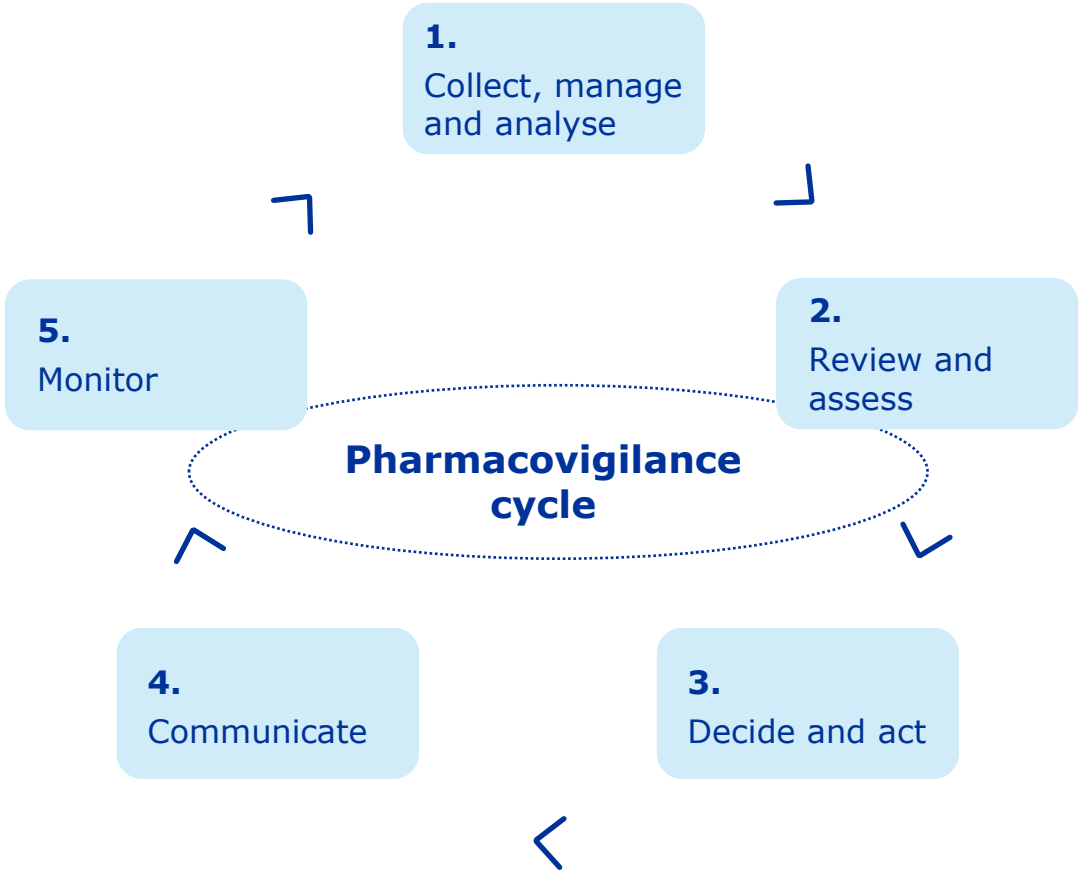
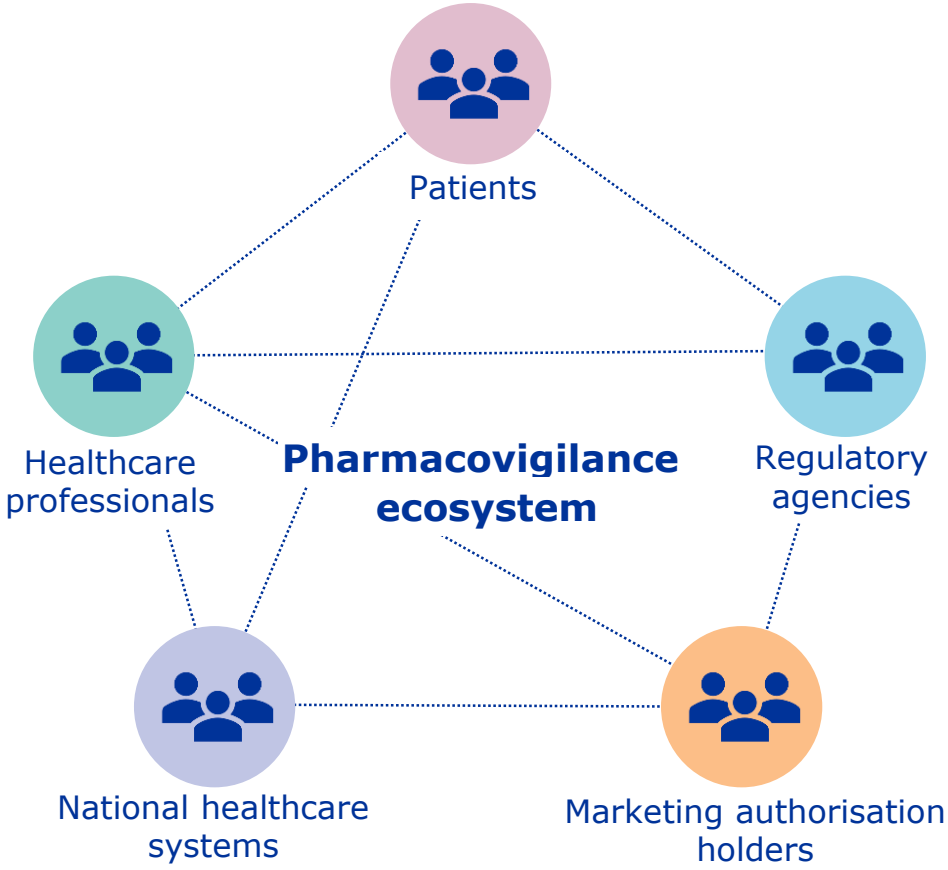


Who does the safety monitoring in the EU?

The EU has a comprehensive **safety monitoring** and **risk management** system known as the **EU pharmacovigilance system**





Transparency: exceptional measures for COVID-19 medicines

	Standard practice	COVID-19 medicines
Scientific advice	No information published	List of medicines that have received SA published
Start of rolling review	Not applicable	Announcement published within 1 day of application
Marketing authorisation application	Active substance listed in "Medicines under evaluation"	Announcement published within 1 day of application
Product information	Published with EPAR	Published within 1 day of positive CHMP opinion
European Public Assessment Report (EPAR)	Published at least 2 weeks after marketing authorisation	Published ASAP, ideally within 7 days of marketing authorisation
Monthly safety reports	No information published	Published monthly for approved COVID-19 vaccines

COVID-19 vaccination in patients with cancer

- Patients with cancer requiring active therapy and immunocompromised patients were excluded from pivotal trials
- Around 4% of patients included in the Pfizer pivotal trial had a prior history of malignancy (https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf)
- Although these people may not respond as well to the vaccine, no particular safety concerns are anticipated
- The benefit-risk ratio for patients with cancer is positive

Conclusions

- **Same assessment** as for other medicines – timelines shortened thanks to **rolling review**
- High regulatory standards for **quality**, **safety** and **efficacy** conferred by **conditional marketing authorisation**
- Exceptional measures taken to maximise **transparency**
- A strong EU pharmacovigilance system is in place; **safety will not be compromised**
- COVID-19 vaccine safety will be **stronger with your participation**

COVID-19 vaccination and immune challenges for leukaemia 11.02.2021

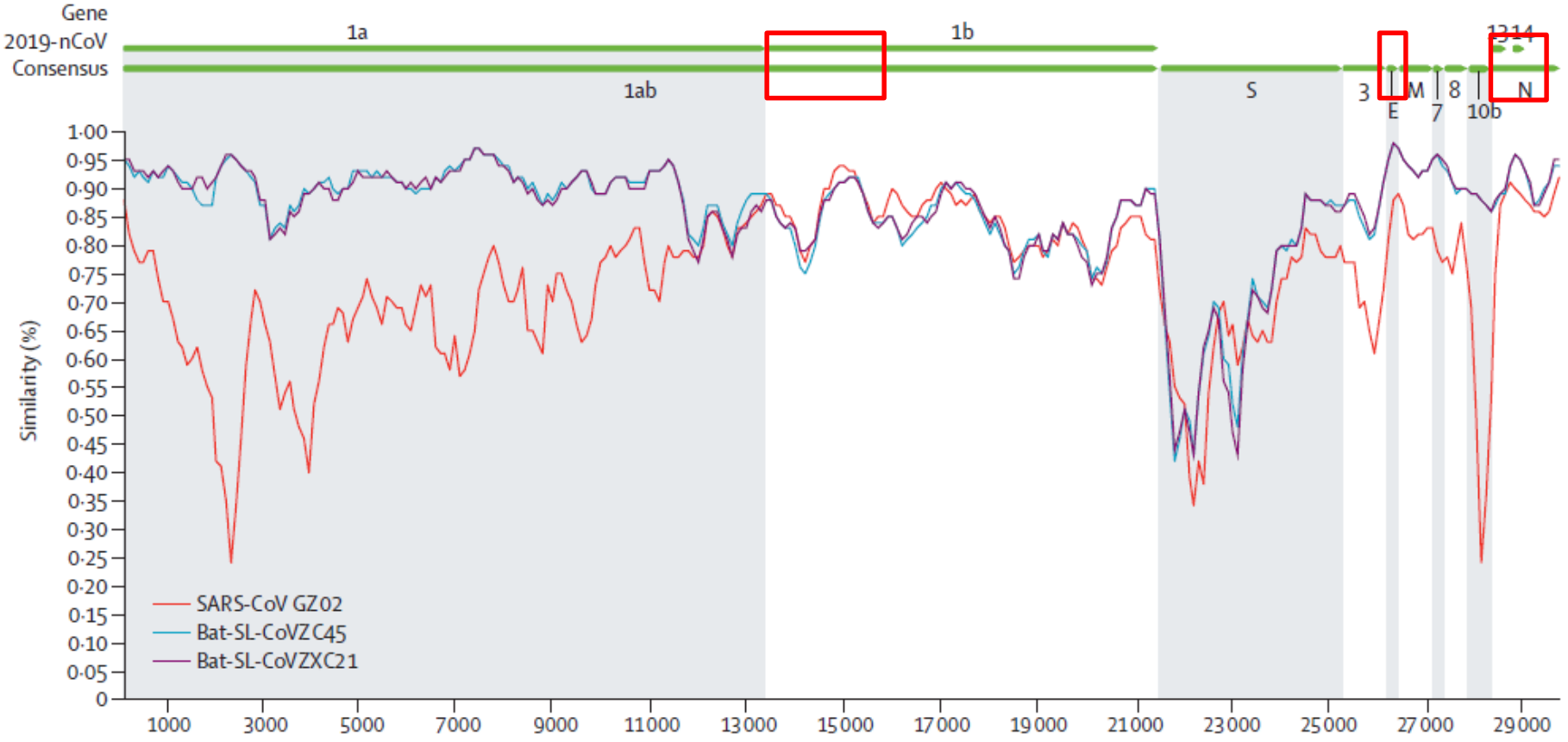
SARS-CoV-2 Variants

Uwe G. Liebert
Institut für Virologie
Universitätsklinikum und Universität Leipzig

Topics

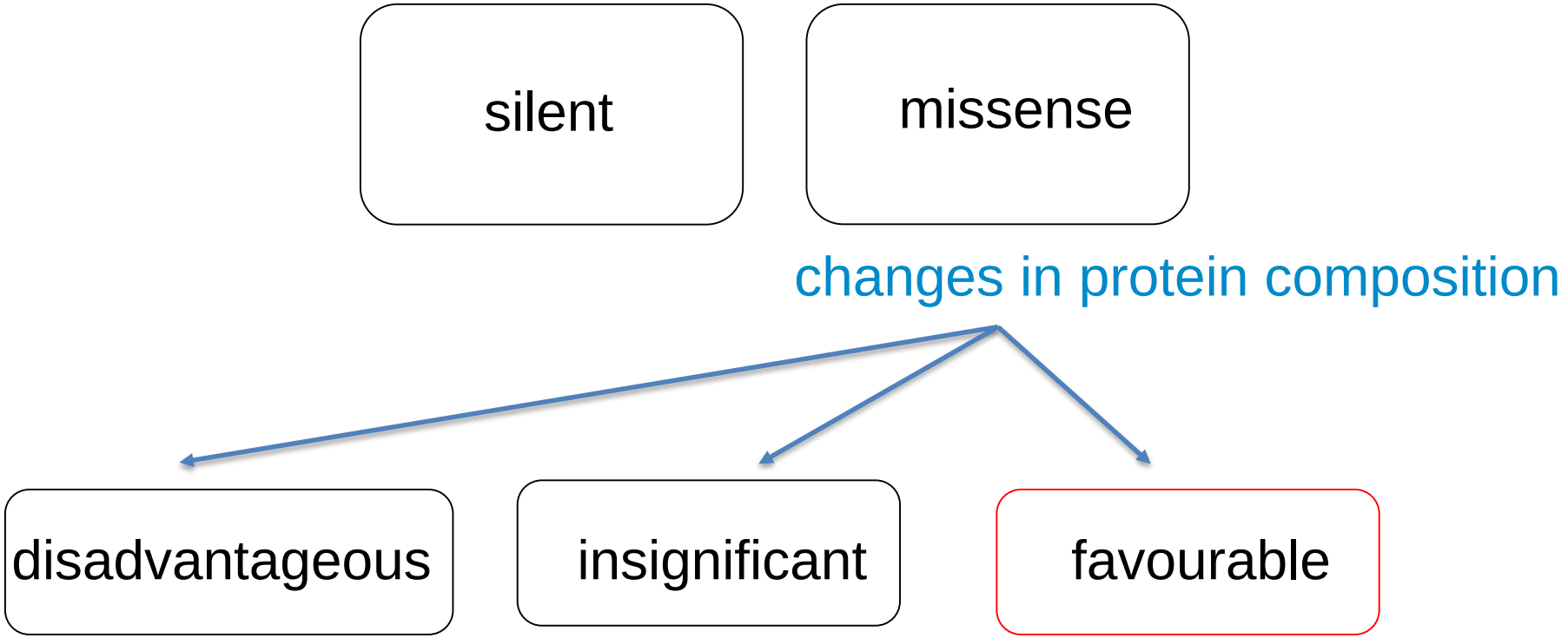
- How do the SARS-CoV-2 mutations occur?
- Some posts refer to an hypothetical favourable field for coronavirus mutations when contracted by immune-compromised patients. Is it true?
- If yes, shouldn’t those patients be ranked higher in the vaccination priority list, or get a preventive treatment?
- Is there a measurable specific incidence of COVID-19 on patients with depressed immunity?
- Does vaccination really help reach herd immunity?

Genomic Similarity of Human and Bat Coronavirus



Lu et al. 2020

Viral Mutations



Potential impact on

- transmissibility
- mortality/lethality
- vaccine efficacy

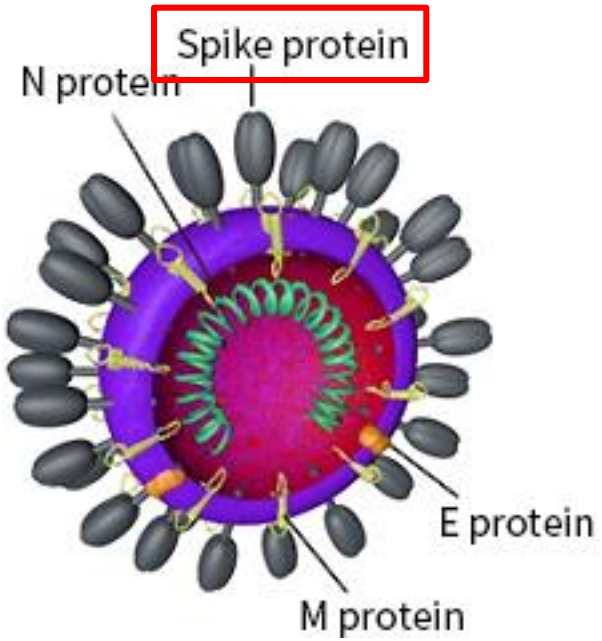
Evolution of Viral Variants

- SARS-CoV-2 is the result of mutated animal virus
- SARS-CoV-2 mutates continuously
- Which mutation develop is unpredictable
- Biological properties of viral variants are not foreseeable
- Close monitoring (viral sequencing) of newly developing variants is crucial for progression of the pandemic

Which are the critical mutations?

Spike Protein

- Virus entry into cells
- Recognition by the immune system
- Evolution of individual and herd immunity
- Vaccine development



Topics

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COVID-19 Vaccines

Moderna	mRNA	
BioNtech-Pfizer	mRNA	
Oxford (Astra-Zeneca)	vector, AdV5/AdV26	
Curevac	mRNA	up to 3 months at 4 °C
Sputnik	vector, AdV	
VJ&J (Janssen)	vector, AdV26	one shot, Ebola vaccine
Novavax	protein (S)	reduced effiency against B1.351
Sinovac	inactivated	50 to 90% efficacy
Sinopharm	inactivated	86% efficacy, Hungary

Questions & Answers

Conclusion, thank you and closing

Zack Pemberton-Whiteley & Pierre Aumont

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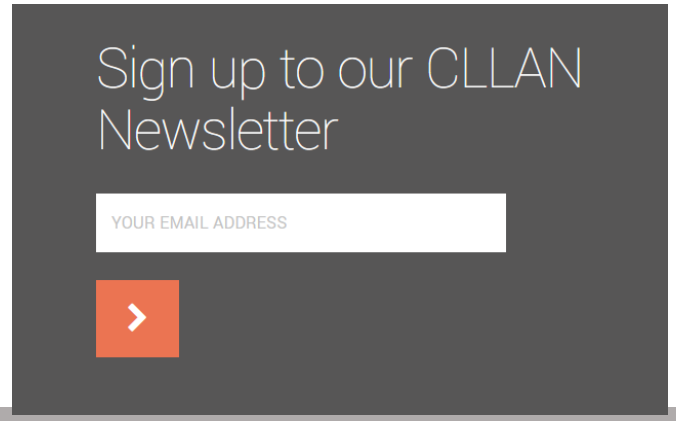
Please subscribe to *"CLL Matters"* on https://www.clladvocates.net



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Thank you for attending this first joint ALAN & CLLAN webinar!

Watch out for upcoming webinars at www.clladvocates.net and www.acuteleuk.org