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6th ForTra Workshop for Translational Research
“Financing and manufacturing - important things to consider to
propel your project from lab to clinic”, Frankfurt/Main, 09/10
September 2024,
30 min

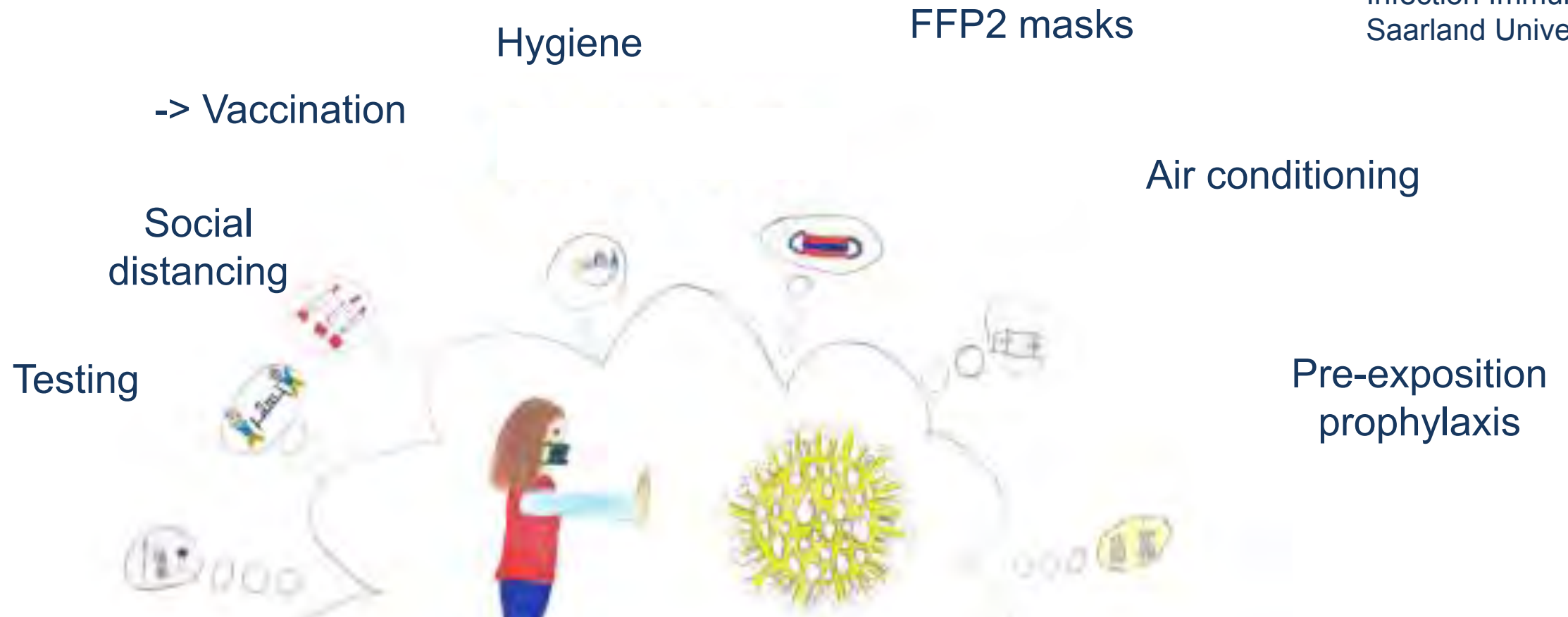
Lessons learned from Paul-Ehrlich-Institut’s support of pandemic vaccine and biomedicine development

Klaus Cichutek

Former President, Paul-Ehrlich-Institut, Langen
apl. Prof. of Biochemistry,
Goethe University Frankfurt/Main, Germany

Prevention of virus spreading and outbreak control

Courtesy of
Dept. Of Transplant and
Infection Immunology,
Saarland University



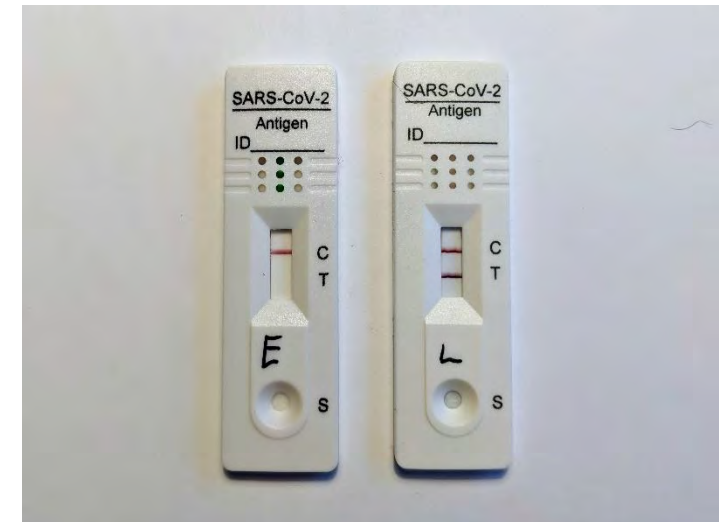
- > Public health measures decelerate pathogen spread
- > Rapid tests need to have sufficient sensitivity
- > Effective vaccines allow control of pandemics (to a certain extent)
- > Therapeutics are needed, if vaccines have low effectiveness or cannot be taken

Result of the comparative experimental evaluation of the detection sensitivity of CoV-2 antigen tests by PEI/RKI/Bundeswehr

Comparative evaluation of CoV-2 rapid antigen test sensitivity

- 245 tests evaluated (March 2022);
- 199 (80%) passed (reimbursable; on PEI list)
- 46 failed (not reimbursable, removed from PEI list)
- Individual results were initially published on the PEI homepage, later in the EU-RAT list.
- Also the basis for the European Commission's list "Common List of COVID-19 rapid antigen tests (RAT)"
- In the EU: for the cross-border mutual recognition of test results
- Listing only after prior independent review of the tests (PEI)

PEI's work as EU Reference Laboratory for defined IVDs will improve the sensitivity of marketed test kits.

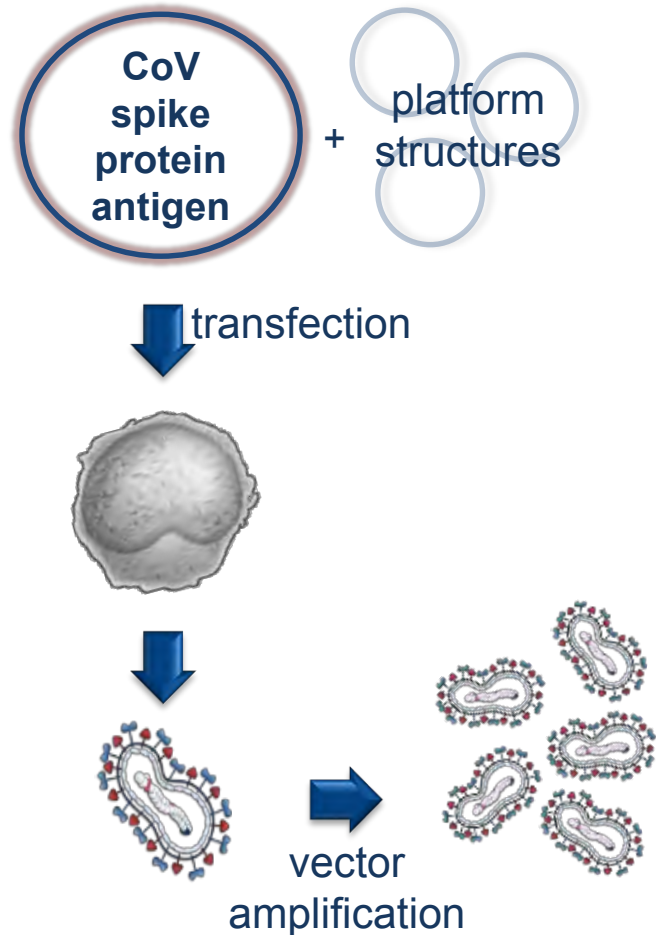


Identification of the potentially protective antigen prior to the pandemic

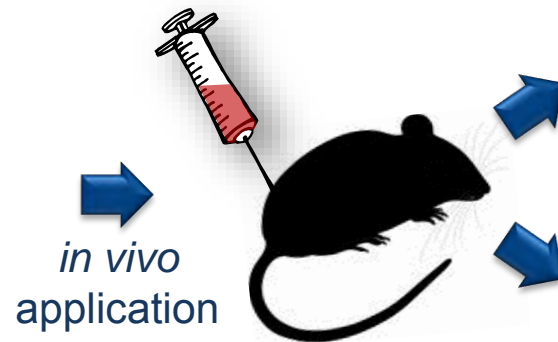
Measles vector vaccine research in CoV infections at PEI contributed and allowed better regulations

Nürnbergger *et al.*, J Virol 2019
Bodmer *et al.*, Virol 2018
Gogesch *et al.*, Mol Immunol 2018
Hutzler *et al.*, Sci Rep 2017
Malczyk *et al.*, J Virol 2015
Uhlig *et al.*, J Virol 2015

vector vaccine generation

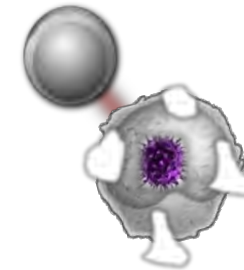
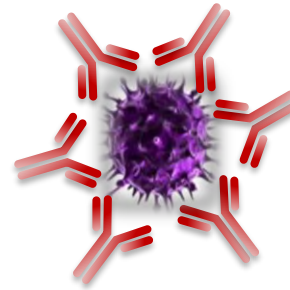


- Measles vaccine virus vector (MeV) + antigen gene



protection in a suitable animal model

Ab responses T cell responses protection after challenge



safety

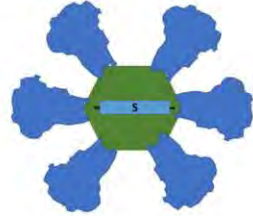


C Inactivated vaccines are made of SARS-CoV-2 that is grown in cell culture and then chemically inactivated



whole virus inactivated vaccines

J Inactivated vector vaccines carry copies of the spike on their surface but have been chemically inactivated



F Recombinant RBD protein based vaccines



E Recombinant spike protein based vaccines



protein subunit vaccines

vaccine platforms

D Live attenuated vaccines are made of genetically weakened versions of SARS-CoV-2 that is grown in cell culture

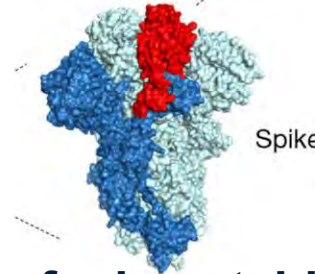


live attenuated virus vaccines

COVID-19

spike protein

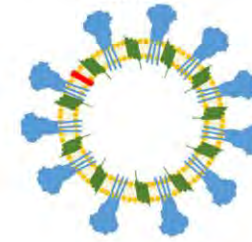
Receptor binding domain (RBD)



Spike

pre-fusion stabilized conformation

G Virus-like particles (VLPs) carry no genome but display the spike on the surface

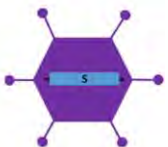


VLPs

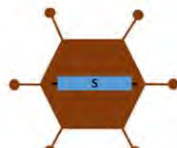
protective antigen identification

antigen design

H Replication competent vector vaccines can propagate to some extent in the vaccinee's cells and express the spike protein there.



I Non-replication competent vector vaccines cannot propagate in the vaccinee's cells but express the spike protein there

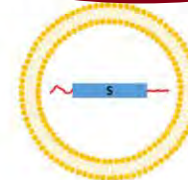


K DNA vaccines consist of plasmid DNA coding for the spike gene under a mammalian promoter

4



L RNA vaccines consist of RNA encoding for the spike protein and are typically packaged in lipid nanoparticles (LNPs)



genetic vaccines

Lessons 1

- Previous experience with a variety of vaccine platforms (and respective licensed vaccine products) allowed ultra-fast development of new pandemic vaccine products.
- Clinical trial experience with mRNA immunotherapy product candidates and patient follow-up for years ensured trust in the safety and immunogenicity of mRNA inoculated i.m.
- Protective antigen identification for SARS-CoV in suitable animal models years before the pandemic saved a lot of time at the beginning of the pandemic.
- Intelligent antigen design (pre-fusion stabilized S protein conformation) learned from bad experience with a Respiratory Syncytial Virus candidate vaccine supported vaccine safety and immunogenicity



Lessons 1 adapted for new therapeutic medicines

- Already licensed therapeutics based on a comparable or identical platform may provide important supportive evidence which can be used in clinical trial and licensing applications
- Compassionate use (German „Heilversuch“, not „Härtefallanwendung“) in a very small number of patients do not provide compelling evidence on the safety or pharmacodynamics of a therapeutic, but give some assurance that the candidate medicine does not induce immediate toxicity
- Evidence that the intended mechanism of action is achieved in vivo (in the body) can be obtained in a suitable animal model
- Taking new developments ad hoc into account keeps the product development at state-of-the-art



Global consensus on prioritisation of particular pre-clinical studies

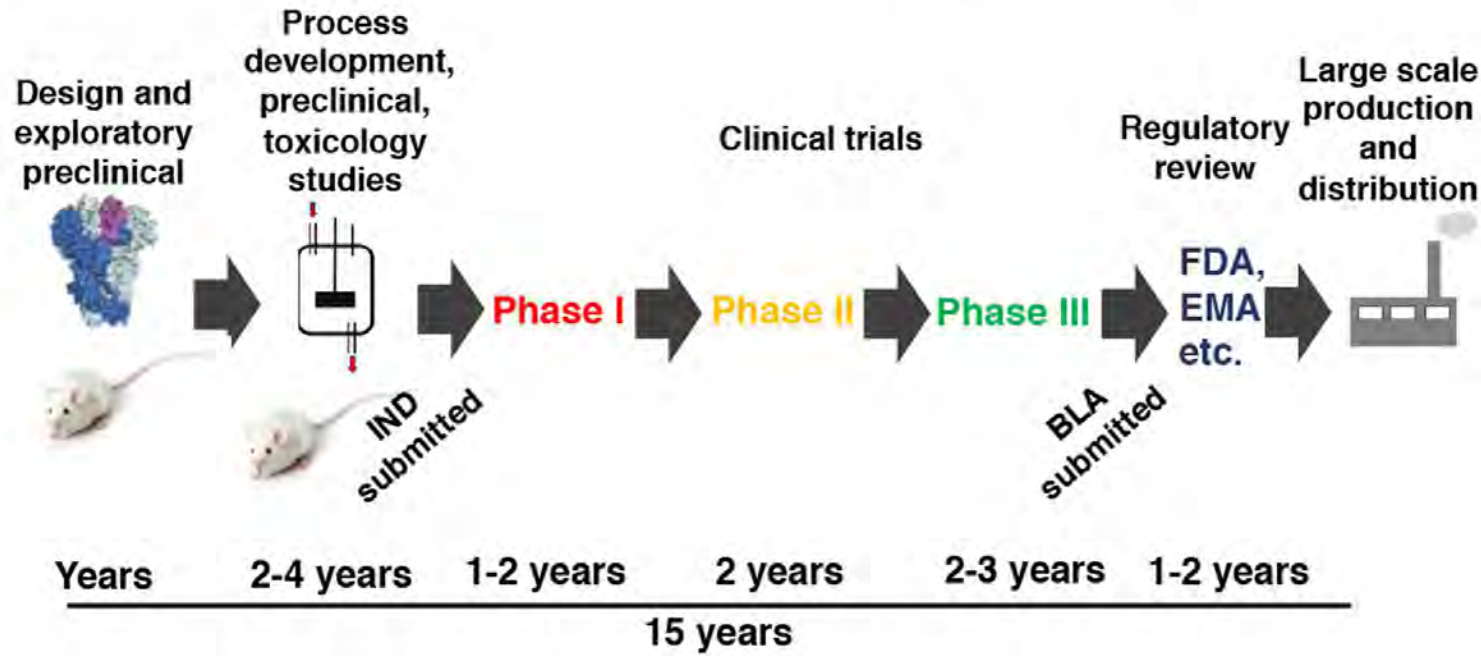
PEI is member of the International Coalition of Medicines Regulatory Authorities

Study type	Guideline recommendations
● Primary pharmacodynamics	Immunogenicity,
● Safety pharmacology	CNS, CV, respiratory, temp. measures incorporated in tox. study.
● Biodistribution	For live attenuated, DNA vaccines, new adjuvant, excipient, device.
● Toxicity	Repeat-dose toxicity study, modelled on clinical regimen.
● Local tolerance	Assessed in repeat-dose toxicity study, or independently.
● Reproductive toxicity	Need depends on target population.
● Protection	Protection from infection or disease in a suitable animal model

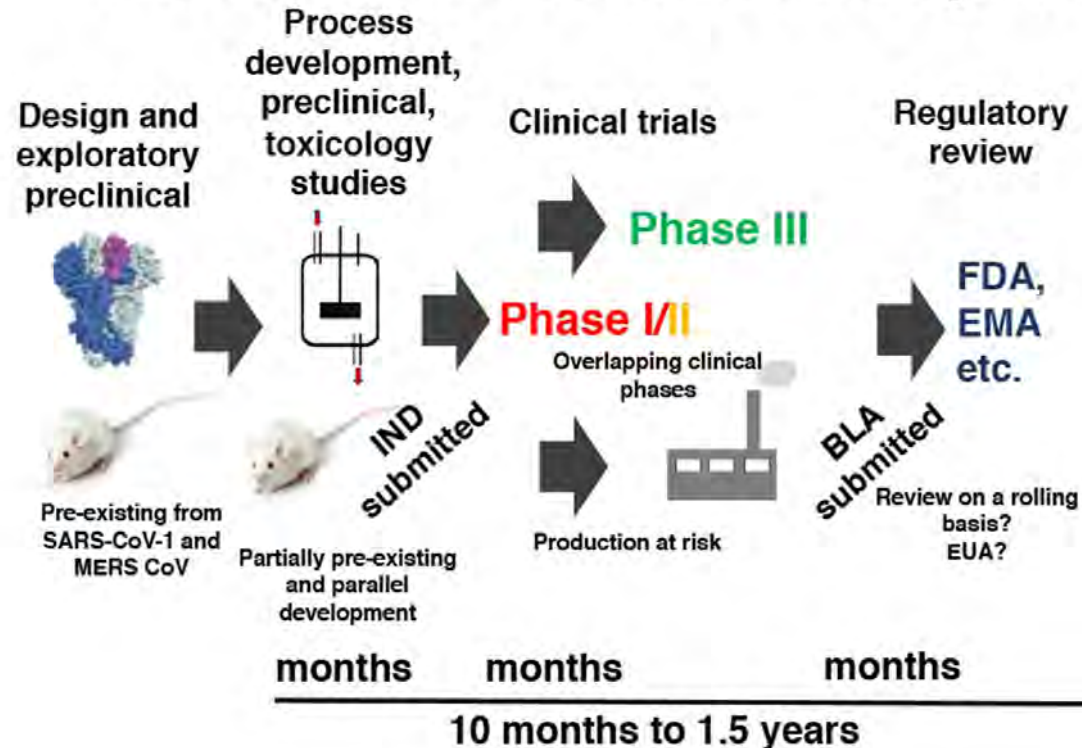


- Some non-clinical studies are mandatory before first-in-human studies of preventive vaccines.
- Some non-clinical studies may be carried out in parallel to clinical trials depending on the nature and target application of the vaccine and possible reference to platform experiences.

established/
traditional



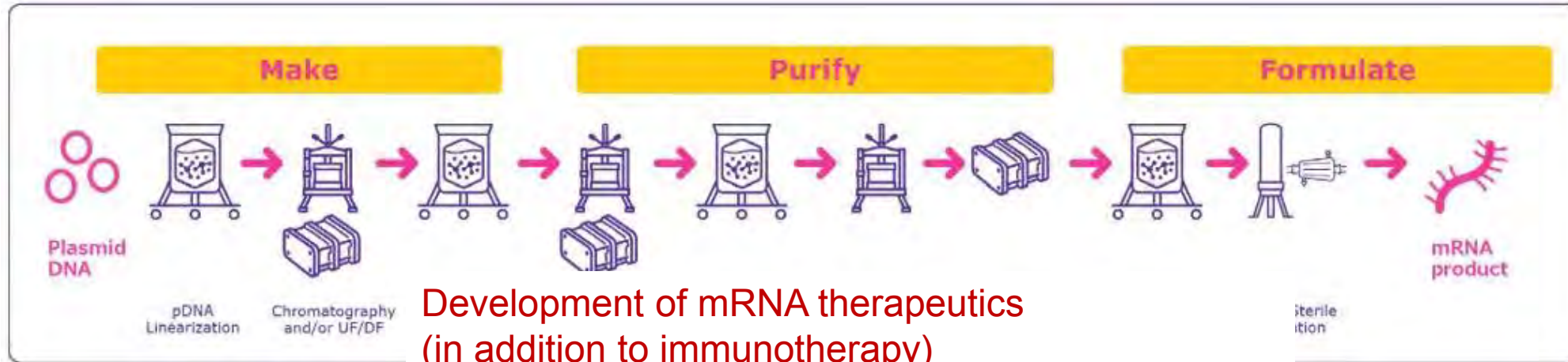
accelerated



- identification of the potentially protective antigen
- suitable vaccine platform
- ad hoc access of developers to PEI's scientific advice and expedited authorisations
- prioritization of non-clinical investigations
- adaptive clinical trial designs
- conditional marketing authorisations (Mas with conditions)
- fast production methods, high number of doses
- platform development
- start of large-scale manufacture before MA
- financial commitment from industry and government

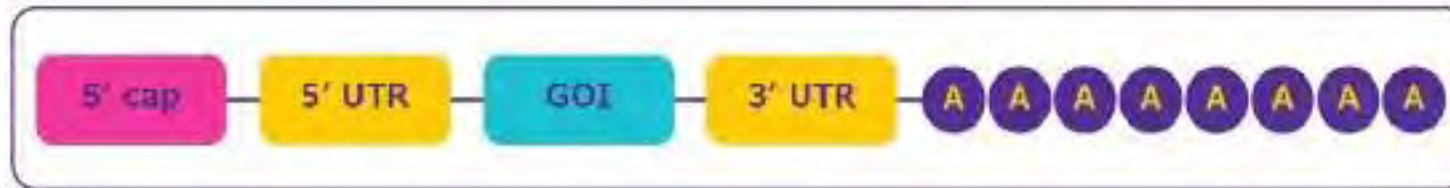
mRNA vaccine platform allows constructing vaccines and large-scale vaccine manufacture of millions of doses within weeks

mRNA manufacture by biotechnology

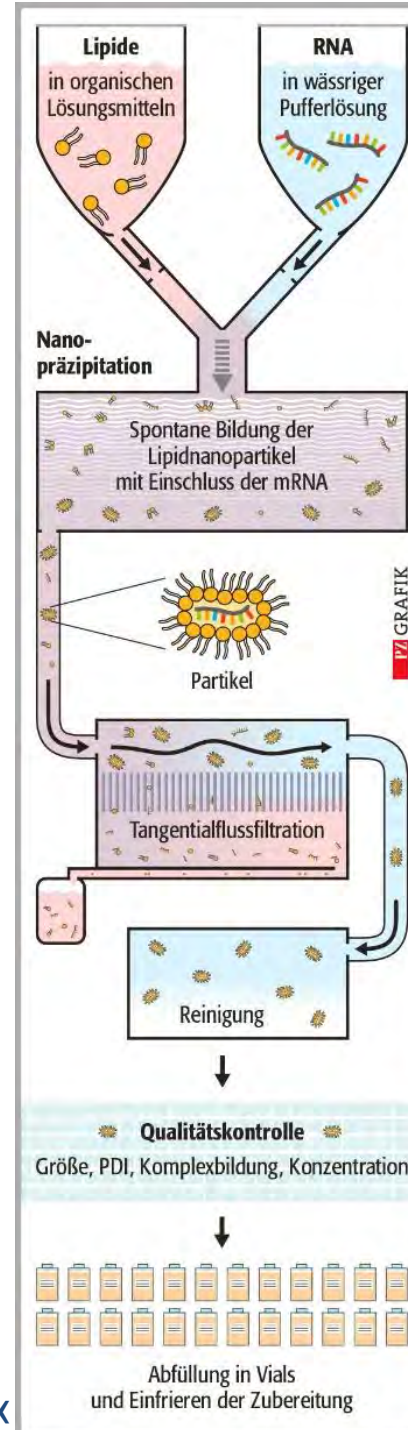


Development of mRNA therapeutics (in addition to immunotherapy) may be the next big medicinal products group and spur a number of developments

mRNA structure



Moderna formulation:
100 µg mRNA encapsidated in »SM-102 lipid nanoparticles«

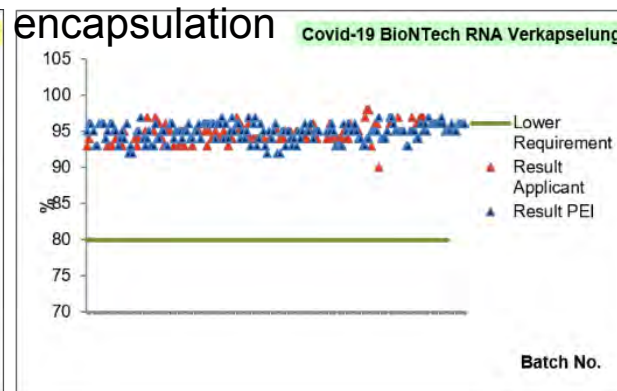
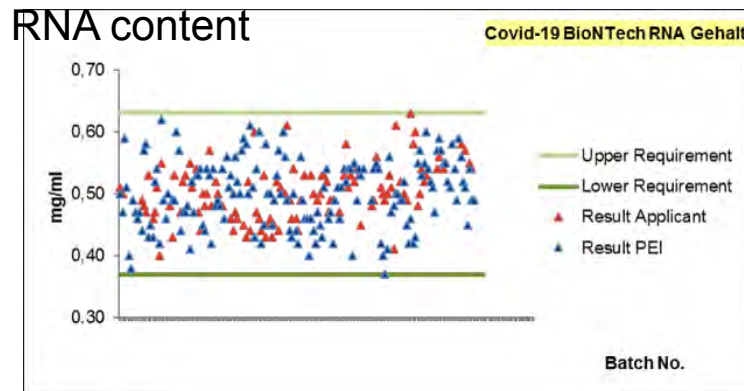


Experimental COVID-19 RNA vaccine batch testing by OMCL-PEI requires validated assays and standard materials from the manufacturer

Experimental experience of the regulatory higher competent authority with the product group allows for better support of pharmaceutical developments.

Manufacturers of mRNA therapeutics may benefit from mRNA vaccine batch release tests.

add triton-buffer



- Identity
 - RT PCR
- Integrity
 - capillary gel electrophoresis
 - ion pair-reversed-phase chromatography
- Potency

Regulatory flexibility increased by rapid adaptation of the legal medicines regulatory framework nationally and in the EU

COMMISSION DELEGATED REGULATION (EU) 2021/756

of 24 March 2021

amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

In order to ensure the continued effectiveness of authorised COVID-19 vaccines, it may be necessary to modify them in ways that involve changing their composition so as to protect against new or multiple variant strains in the context of the pandemic or otherwise. Such changes, which include the replacement or addition of a serotype, strain or antigen or a combination of serotypes, strains or antigens, should be considered as variations to the

8 June 2022
EMA/175959/2021 Rev.2
Human Medicines Division

Procedural guidance for variant strain(s) update to vaccines intended for protection against Human coronavirus

Regulatory and procedural requirements



Variation of a marketing authorisation instead of a new initial marketing authorisation

Neutralising antibody titer comparison instead of clinical efficacy

Non-interventional studies of licensed vaccine products simplified science accompanying the vaccination campaign

BEKANNTMACHUNG DES BUNDESMINISTERIUMS FÜR GESUNDHEIT UND DES PAUL-EHRLICH-INSTITUTS

vom 29. Juli 2022

Nichtinterventionelle Studien mit zugelassenen Impfstoffen

Blutentnahmen und nichtinvasive Untersuchungen, die jeweils ein minimales Risiko und eine minimale Belastung für die betroffene Person darstellen, gehören bei folgenden Studien zur normalen klinischen Praxis:

- Bei einer Studie mit einem Impfstoff der zur Vorbeugung einer bestehenden oder drohenden bedrohlichen übertragbaren Krankheit zugelassen ist, und
- wenn Impfstoff zur Sicherstellung der Versorgung der Bevölkerung mit Impfstoffen gegen eine bestehende oder drohende bedrohliche übertragbare Krankheit benötigt wird.

Diese Studien können damit als nichtinterventionelle Studien im Sinne des § 4 Absatz 23 Satz 2 des Arzneimittelgesetzes durchgeführt werden. Ein Genehmigungsverfahren für die Durchführung einer klinischen Prüfung ist in diesen Fällen nicht erforderlich.

Lessons 2 (not previously discussed)

- Regulatory flexibility experienced regulators and sometimes changes in the legal framework, which needs to be done by the government (in the EU: national or European Commission)
- Continuous exchange of information between regulators in the EU is assured by their work
 - in EMA committees and working parties,
 - in committees and working groups of the EDQM (Europe, Russia),
 - In the group of the Heads of Medicines Authorities HMA (in Europe (EU and EEG)
- Continuous exchange of information between regulators globally is assured by their work
 - in the International Coalition of Medicines Regulatory Authorities ICMRA,
 - In WHO committees,
 - in the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)



Overview of authorised COVID-19 vaccines

Vaccine	Platform	Strain	Use	Population			
				≥6 months	≥5 years	≥12 years	≥18 years
Comirnaty (BioNTech)	mRNA	Original strain	Primary vaccination	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
			Booster		✓ 5-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted)	Booster			✓	✓
		Original strain + Omicron BA.4-5 variants (adapted)	Booster		✓ 5-11 years	✓	✓
Spikevax (Moderna)	mRNA	Original strain	Primary vaccination	✓ 6 months to 5 years	✓ 6-11 years	✓	✓
			Original strain + Omicron BA.1 variant (adapted)				
		Original strain + Omicron BA.4-5 variants (adapted)					
Vaxzevria (AstraZeneca)	Adenoviral vector	Original strain	Primary vaccination				✓
			Booster				✓
Jcovden (Janssen)	Adenoviral vector	Original strain	Primary vaccination				✓
			Booster				✓
Nuvaxovid (Novavax)	Protein	Original strain	Primary vaccination			✓	✓
			Booster				✓

COVID-19 vaccines licensed in the EU (as of December 2022)

Bivalent Wuhan/BA.4/5 Omicron booster mRNA vaccines first licensed in 2023

Lesson 3:

Information on heterologous vaccination schemes and timing of booster vaccinations came from UK and Israel

Existing or newly initiated registries or clinical studies during the introduction of a new medicines may provide important safety and application scheme information

Vaccine	Platform	Strain	Use	Population
COVID-19 Vaccine Valneva (Valneva)	Inactivated	Original strain	Primary vaccination	✓ 18-50 years
VidPrevtyn Beta (Sanofi Pasteur)	Protein	Beta variant	Booster	✓

COVID-19 vaccination reduced COVID-19-related hospitalisation rates, before and during the Omicron wave

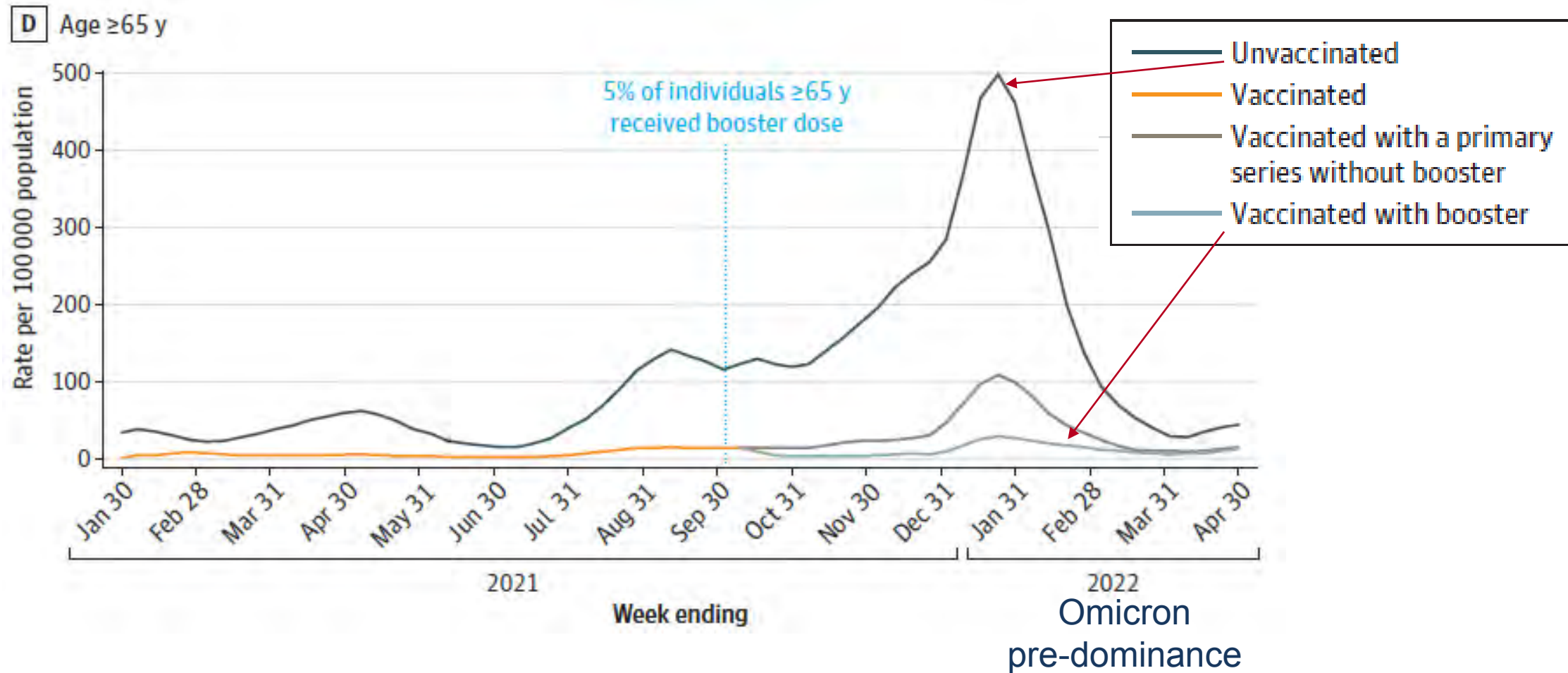
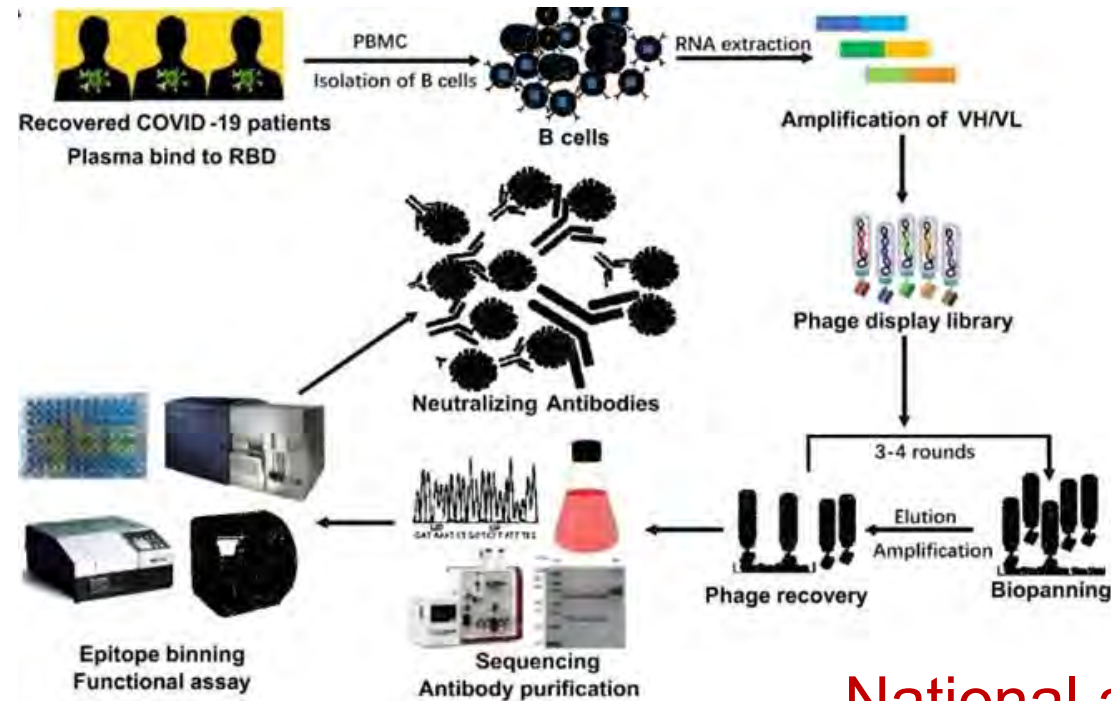


Figure 2. Three-Week Moving Average Population-Based Rates^a of COVID-19-Associated Hospitalizations Among Unvaccinated and Vaccinated (With and Without a Booster Dose)^b Adults 18 Years or Older Admitted January 30, 2021^c to April 30, 2022, by Week of Admission, COVID-19-Associated Hospitalization Surveillance Network (COVID-NET), 13 States^d

JAMA Internal Medicine | [Original Investigation](#)
 COVID-19-Associated Hospitalizations
 Among Vaccinated and Unvaccinated Adults 18 Years or Older
 in 13 US States, January 2021 to April 2022

First available therapy and prevention for persons not amenable to vaccination: Generating mAb binding to SARS-CoV.2 spike proteins from B cells of human COVID-19 patients



Verordnung zur Sicherstellung der Versorgung der Bevölkerung mit Produkten des medizinischen Bedarfs bei der durch das Coronavirus SARS-CoV-2 verursachten Epidemie* (Medizinischer Bedarf Versorgungssicherstellungsverordnung - MedBVSV)

MedBVSV

- National antibody authorisation in Germany for rapid access (in absence of EU license by EC)
- by Federal Ministry of Health taking PEI's evaluation of expected benefit-riks into account,
 - based on German Ordinance for a pandemic situation

National authorisation and rapid access schemes such as possible through §4b German Medicinal Product Act may provide regulatory flexibility, but in very few instances only

COVID-19 vaccine safety and regulation made fully transparent

Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut 

Langen, 7 September 2022

SAFETY REPORT

In the current safety report, the Paul-Ehrlich-Institut summarises the reports about suspected cases of adverse events and vaccination complications that it has received from the start of the vaccination campaign in Germany on 27 December 2020 through 30 June 2022.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 May 2022

COVID-19 vaccines safety update

Comirnaty (BioNTech Manufacturing GmbH)

- Vaccinees' information leaflets
- „Dear Health Care Professionals“-letters by marketing authorisation holders
- Recommendations by professional medical societies to physicians on diagnostic and therapy options



BULLETIN ZUR ARZNEIMITTELSICHERHEIT
Informationen aus BfArM und PEI

IMMUNITÄT Ausgabe 1 | März 2022

EDITORIAL	Die SARS-CoV-2-Pandemie: Entwicklung von Impfstoffen und Therapeutika	03
ARZNEIMITTEL IM BLICK	Dabigatran und Rivaroxaban: Behandlung und Reizidrophobie von venösen Thromboembolien bei Kindern und Jugendlichen	04
PHARMAKOVIGILANZ TRANSPARENT	Verdachtsfälle von Nebenwirkungen und Impfkomplikationen nach Impfung mit Comirnaty® bei Kindern im Alter von 5–11 Jahren aus Deutschland	15
PRAC-MELDUNGEN	Nebenwirkungsreaktionen in Deutschland: Aktuelles und Hintergründe	27
PRAC-MELDUNGEN	PRAC-Empfehlungen im Rahmen von EU-Referal-Verfahren – Issuar bis März 2022	29
PRAC-MELDUNGEN	Neufassung des Wortlauts der Produktinformationen – Auszüge aus den Empfehlungen des PRAC zu Signalen	35
AKTUELLE RISIKOINFORMATIONEN	Hinweise auf Rote-Hand-Briefe und Sicherheitsinformationen	46

Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
Das BfArM überprüft die Wirkstoffe, Sicherheit

AUFKLÄRUNGSMERKBLATT

Zur Schutzimpfung gegen COVID-19 (Corona Virus Disease 2019)

– mit Vektor-Impfstoffen –

(Vaxzevria[®], ehemals COVID-19 Vaccine AstraZeneca von AstraZeneca und COVID-19 Vaccine Janssen[®] von Janssen Cilag International/ Johnson & Johnson)

Diese Informationen liegen in leichter Sprache und Fremdsprachen vor:
www.rki.de/BfE/Content/Infektion/Impfen/Materialien/COVID-19-Vektorimpfstoff_Tab.html

Vektor

Stand: 19. Oktober 2021

(dieses Aufklärungsmerkblatt wird laufend aktualisiert)

CASIRIVIMAB/IMDEVIMAB (RONAPREVE) 120 MG/ML INJEKTIONS-/INFUSIONSLÖSUNG

Stark verminderte Neutralisierungseigenschaften des Volllängen-Spike-Proteins der Omikron-Variante durch die Antikörperkombination Casivimab/Imdevimab

Das Bundesministerium für Gesundheit (BMG) und das Paul-Ehrlich-Institut (PEI) informieren über folgende Sachverhalte im Zusammenhang mit der Anwendung von Casirivimab und Imdevimab (Ronapreve) 120 mg/ml Injektions-/ Infusionslösung.

Rapid publication of safety and efficacy evidence allows for transparency and trust in new therapies.

deutlich verringerte Neutralisierungsaktivität gegenüber der Omikron-Variante
19. Juli 2021

WICHTIGE ARZNEIMITTELINFORMATION

COVID-19 Vaccine Janssen: Kontraindikation bei Personen mit vorherigem Kapillarlecksyndrom (Capillary Leak Syndrome, CLS) und

Mechanism underlying TTS (thrombosis with thrombocytopenia syndrome) associated with COVID-19 adenovector vaccines revealed by Greinacher lab supported by PEI

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodora E. Warkentin, M.D., Karin Wassan, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

ABSTRACT

Background

Several cases of unusual thrombotic events and thrombocytopenia have developed after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ChAdOx1 nCov-19, AstraZeneca). More data were needed on the pathogenesis of this unusual clotting disorder.

Methods

We assessed the clinical and laboratory features of 11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19. We used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)-heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions. Included in this testing were samples from patients who had blood samples referred for investigation of vaccine-associated thrombotic events with 28 testing positive on a screening PF4-heparin immunoassay.

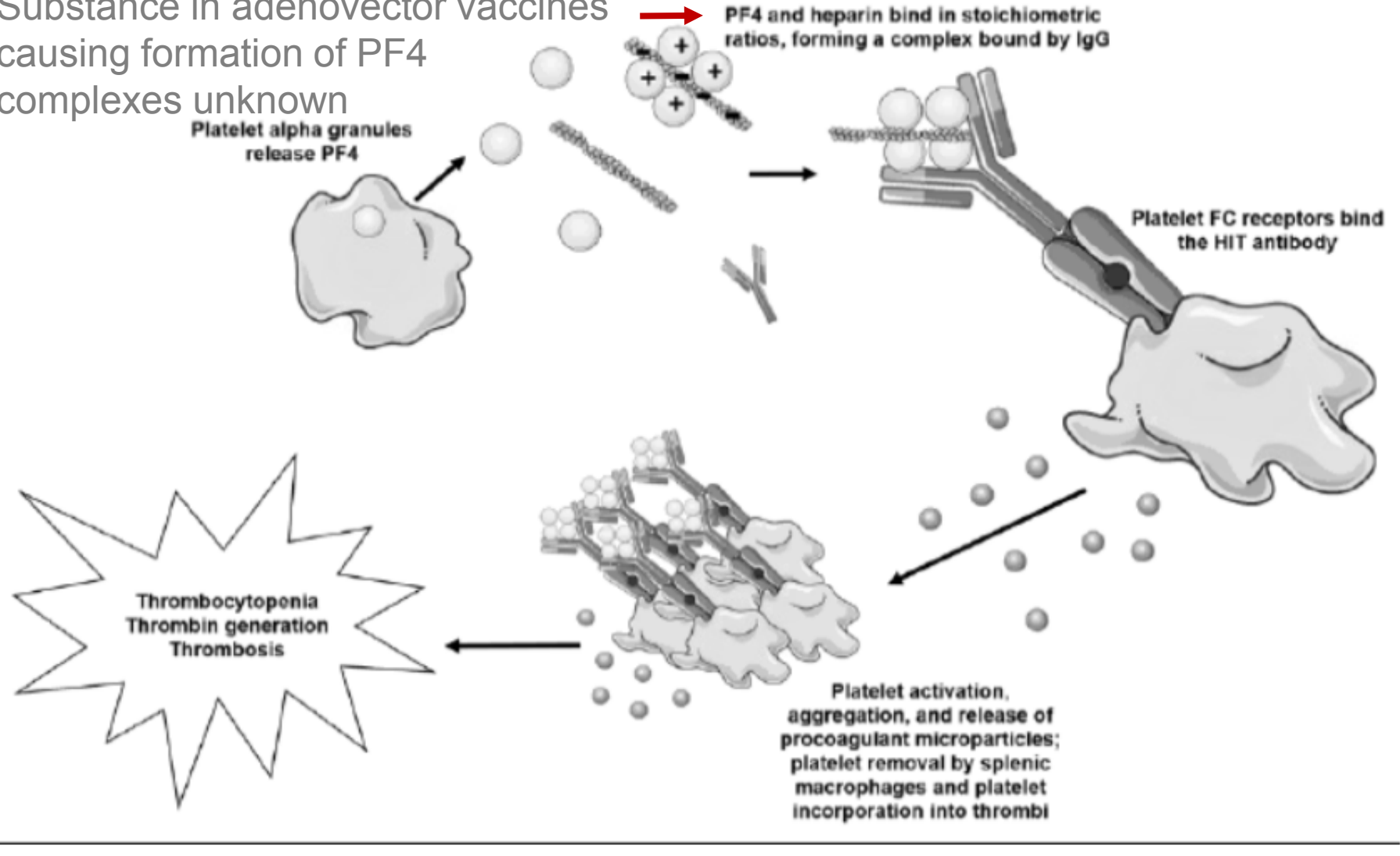
Results

Of the 11 original patients, 9 were women, with a median age of 36 years (range, 22 to 49). Beginning 5 to 16 days after vaccination, the patients presented with one or more thrombotic events, with the exception of 1 patient, who presented with fatal intracranial hemorrhage. Of the patients with one or more thrombotic events, 9 had cerebral venous thrombosis, 3 had splanchnic-vein thrombosis, 3 had pulmonary embolism, and 4 had other thromboses; of these patients, 6 died. Five patients had disseminated intravascular coagulation. None of the patients had received heparin before symptom onset. All 28 patients who tested positive for antibodies against PF4-heparin tested positive on the platelet-activation assay in the presence of PF4 independent of heparin. Platelet activation was inhibited by high levels of heparin, Fc receptor-blocking monoclonal antibody, and immune globulin (30 mg per milliliter). Additional studies with PF4 or PF4-heparin affinity-purified antibodies in 2 patients confirmed PF4-dependent platelet activation.

Conclusions

Vaccination with ChAdOx1 nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia. (Funded by the German Research Foundation.)

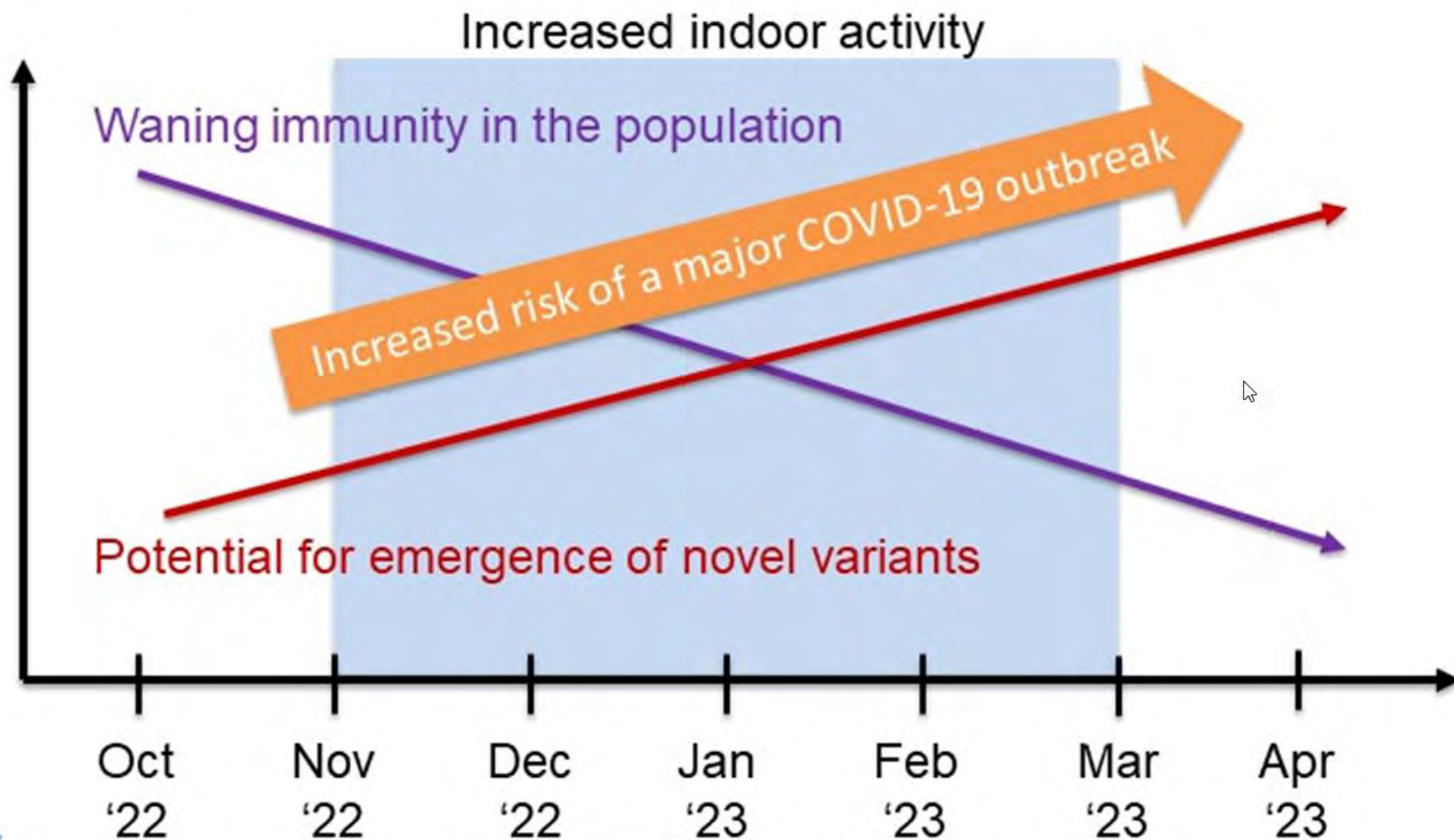
Substance in adenovector vaccines causing formation of PF4 complexes unknown



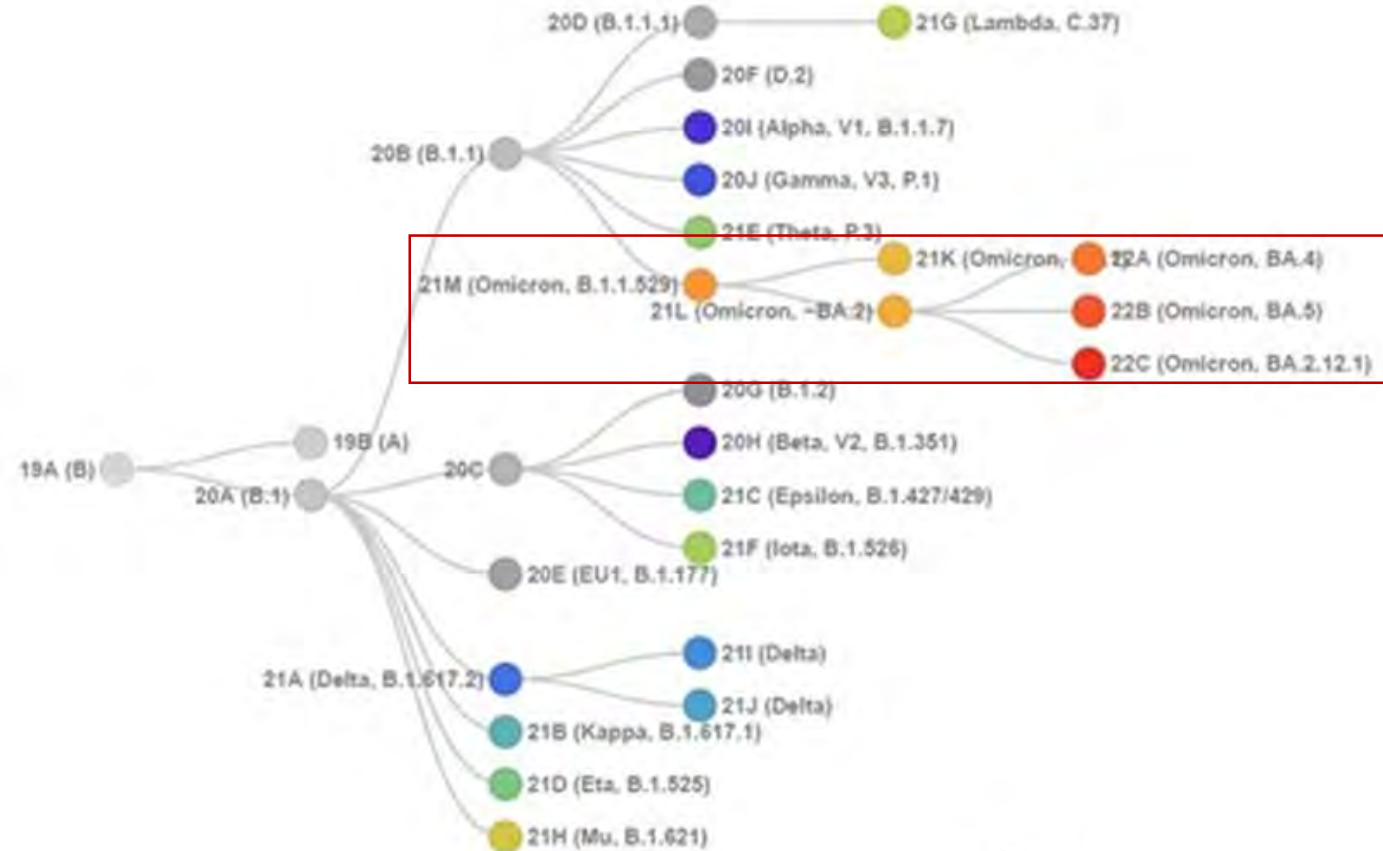
Hogan M, Berger JS 2020

Schönborn L et al., DOI: 10.1056/NEJMc2112760

Potential Evolution of COVID-19

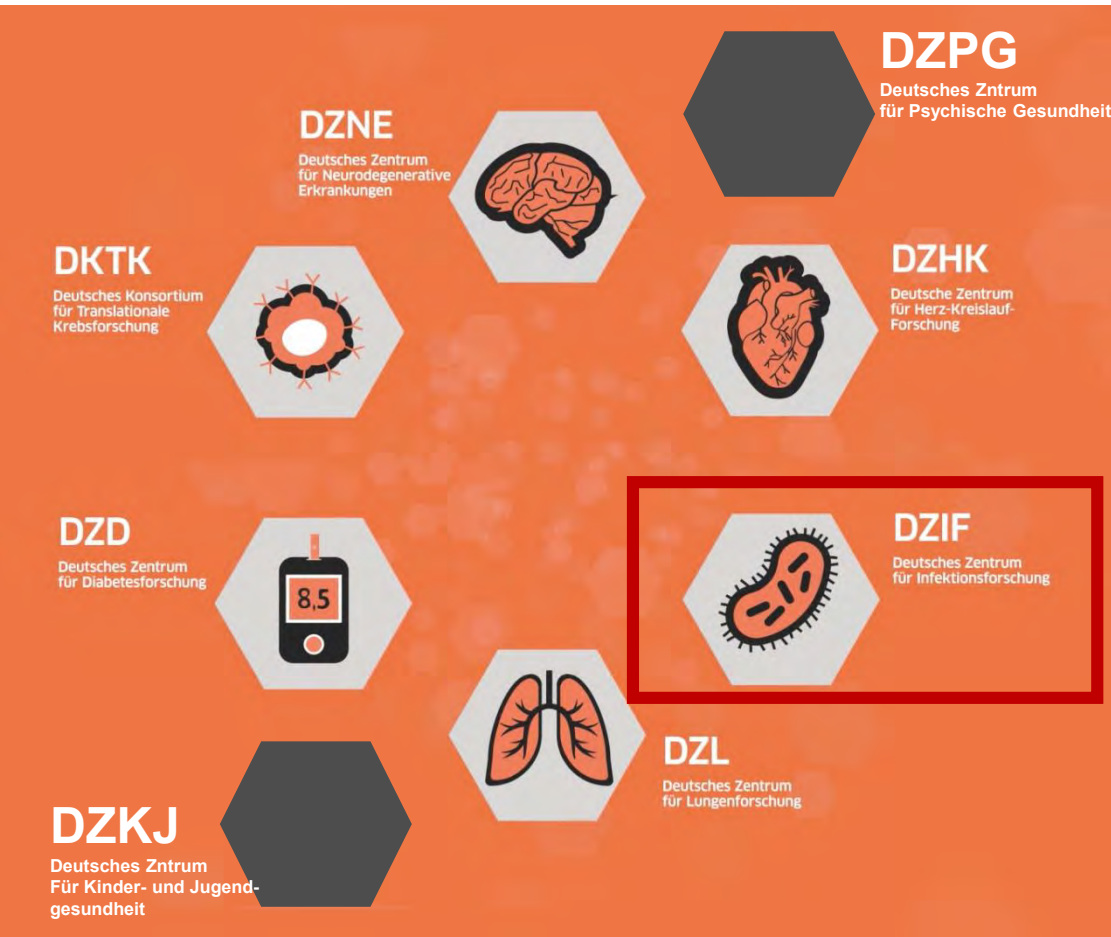


BA.4/5 has started the continuous evolution of sublineages from the Omicron strain



Phylogenetic relationships SARS-CoV-2 clades – from <https://covariants.org/> using Nextstrain data (<https://nextstrain.org/>)

Classified as restricted by the European Medicines Agency



The German Centers for Health Research (DZG)

Their common goal: to combat major widespread diseases by new medicines more effectively.

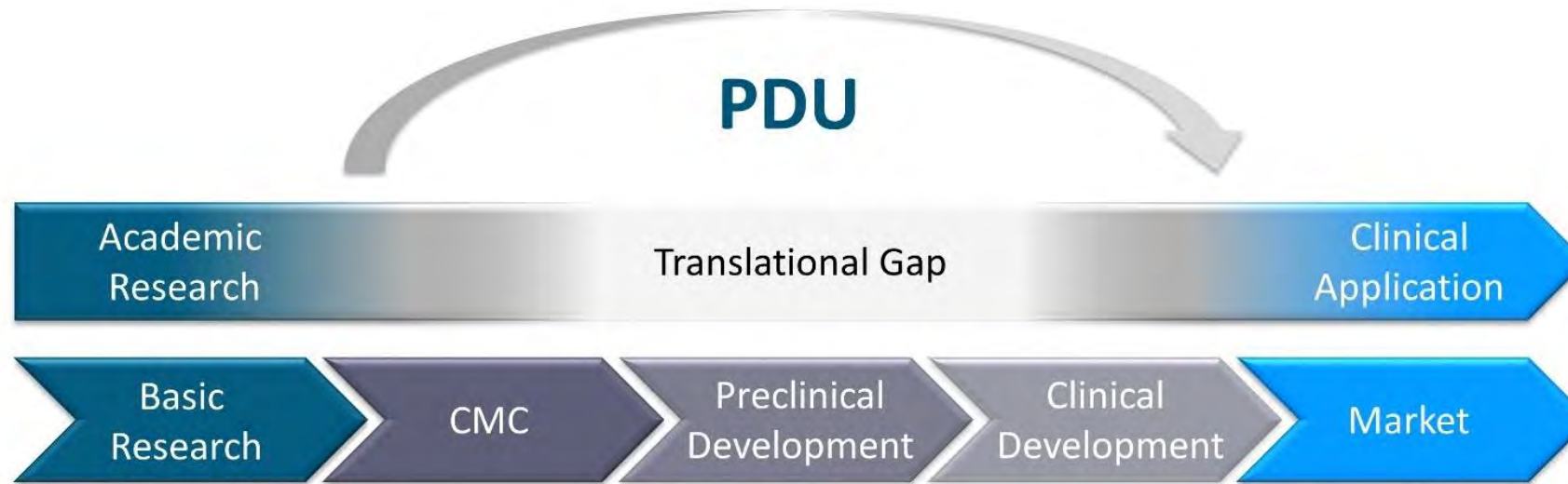
Their financing: The Federal Ministry of Education and Research (BMBF; 90%) and the respective states of partner sites (10%).

Further DZG Centers at the start, on

- Mental Health (launched in 2023)
- Child and Adolescent Health (coming in 2024)

Berlin Center for Gene and Cell Therapies established by Charité and Bayer

Product Development Unit (DZIF)



PDU is a service unit that supports academic scientists in DZIF in achieving important project steps in product development (vaccines, therapeutics and in-vitro diagnostics).

Goal: adequate support and acceleration of early developments.

PDU: *Product Development Unit*
CMC: *Chemistry, Manufacturing and Controls*

DZIF PDU concept



Project planning and management



Regulatory and scientific advice (PEI or BfArM)



Technology transfer and enabling of industry partnering



Education and coaching

Development support by OSRA (Office for scientific and regulatory advice; DZIF)

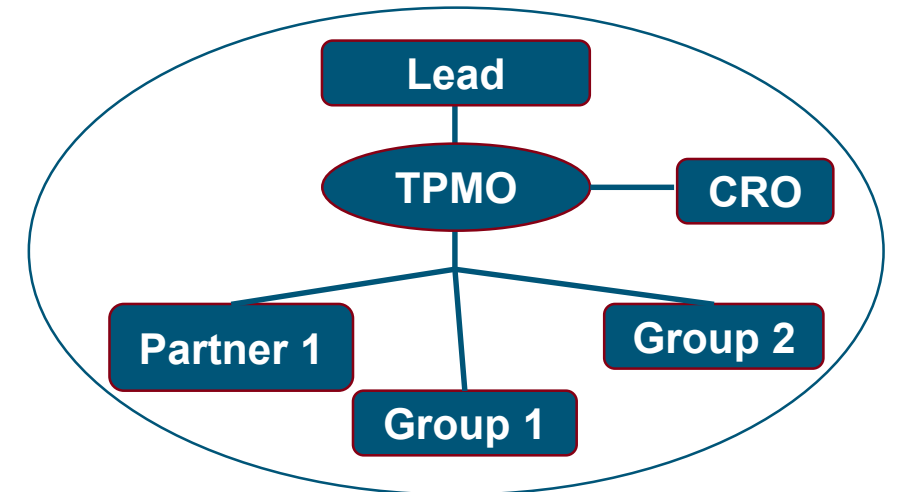
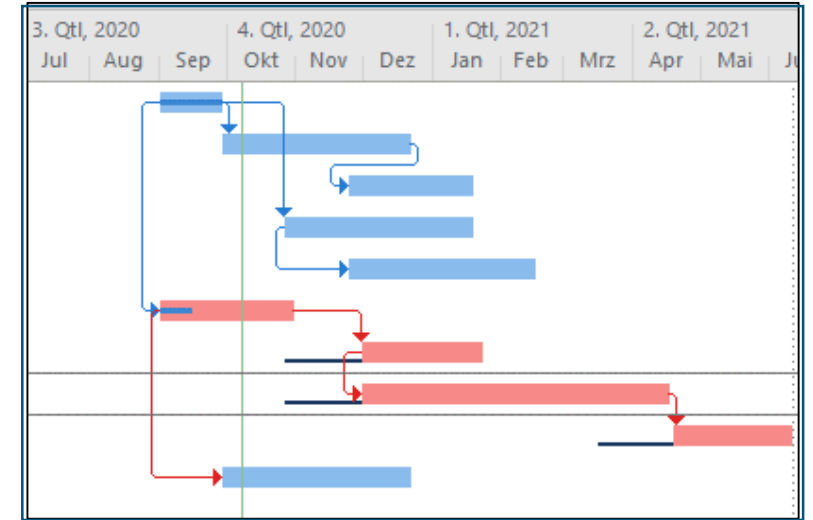
- Scientific and regulatory consultations, e.g. regarding product specifications, preclinical development or clinical study design
- Clarification of regulatory issues
- Organization and planning of regulatory training
- Point of contact with national, European and international expert groups
- Evaluation of DZIF funding applications with regard to regulatory requirements



TPMO

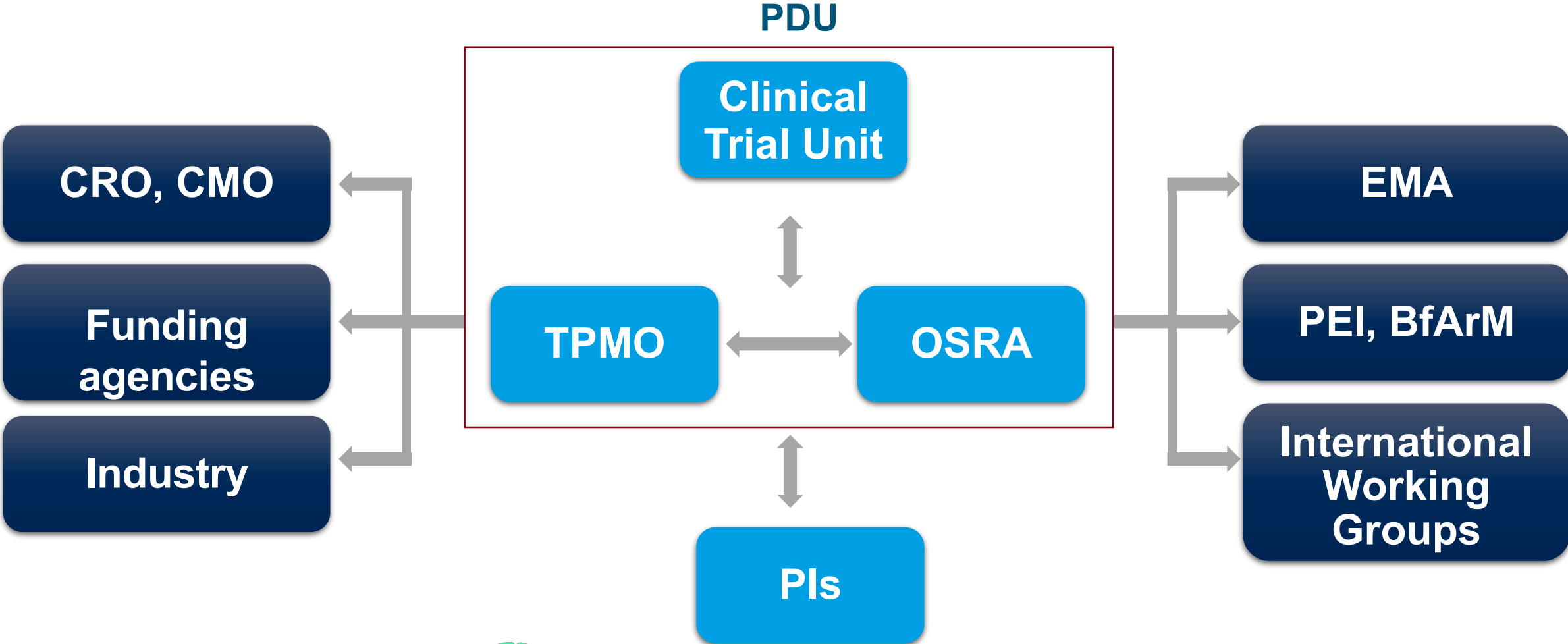
PDU's Translational Product Management Office

- Project planning and management
- Market analyses
- Regulatory assistance, e.g. preparation of documents for National Scientific Consultations
- Support in applying for funding
- Organization of partnerships and consortia
- Technology transfer
- Evaluation of DZIF funding applications
- Organization of Project Advisory Group Meetings



CRO: *Contract Research Organization*

Interaction between various stakeholders



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