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Paul-Ehrlich-Institut

Fighting the Pandemic: contributions of the Paul-Ehrlich-Institut

Ralf Wagner, Eberhardt Hildt, Heidi Meyer, Isabell Bekeredjian-Ding, Dirk Mentzer, Brigitte Keller-Stanislawski, Jan Müller-Berghaus, Klaus Cichutek

Klaus Cichutek *et al*.
Paul-Ehrlich-Institut
DGRA Annual Congress
13th September 2021
Bonn

Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit.

The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health.

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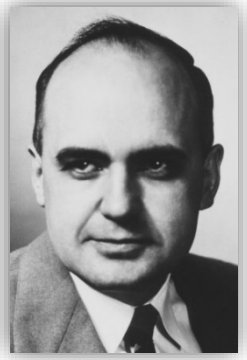
Heroes of vaccine research and development



Maurice Hilleman
1919-2005

Live virus vaccines

- mumps
- measles
- influenza
- Japanese encephalitis

Katalin Kariko

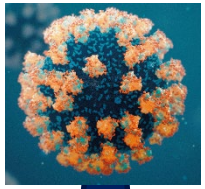
Pioneer in RNA technology

- 1989 in vivo transfer of RNA in mice mediates encoded protein expression
- 1993 RNA methylation reduces acute innate immune response

Ugur Sahin

Cancer immunotherapy pioneer

- Actively personalized cancer immunotherapy
- COVID-19 mRNA vaccine



Timeline from first isolation of SARS-CoV-2 to licensed Covid-19 vaccine products

- **31 Dec 2019** China informs WHO about cluster of cases of 'viral pneumonia of unknown cause' in Wuhan
- **12 Jan 2020** Publication of the gene sequence of SARS-CoV-2
- **16 March 2020** First clinical trial in humans initiated
- **20 April 2020** PEI authorizes first human clinical trial for COVID-19 vaccine
- **01 Oct 2020** Rolling Review of first vaccine by CHMP/EMA
- **20 Nov 2020** Emergency Use Authorization submission to US FDA
- **30 Nov 2020** Over 240 Covid-19 vaccines under development globally (ref WHO)
  - 250 are in preclinical stage
  - 65 are in clinical trials
- **11 Dec 2020** Marketing/Emergency Use authorization of Covid vaccine products (USA, Canada, UK)
- **23 Dec 2020** Conditional marketing authorization BioNTech/Pfizer vaccine product by EU
- **06 Jan 2021** Conditional marketing authorization Moderna vaccine product by EU

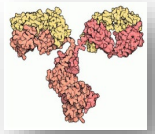
Paul-Ehrlich-Institut
Federal Institute for Vaccines and Biomedicines

Vaccines

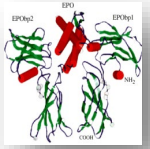
vaccines
(human & vet).

vector-
& DNA/RNA vaccines

Antibodies, Proteins, Allergens



monocloncal antibodies,
(hyper) immunoglobulins,

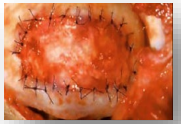


coagulation-
factors

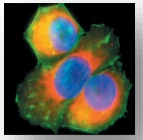
allergens

Stem Cell Preparations, Gene and Cell Therapy

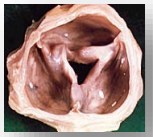
blood products,
haem. stem
cell transfer



tissue engineering-
products



cell &
gene therapy medicinal
products



tissue
preparations

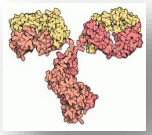
Paul-Ehrlich-Institut
Federal Institute for Vaccines and Biomedicines

Vaccines

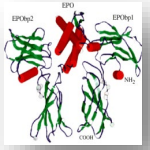
vaccines
(human & vet).

vector-
& DNA/RNA vaccines

Antibodies, Proteins, Allergens



monoclonal antibodies
(hyper) immunoglobulins,



coagulation-
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Stem Cell Preparations, Gene and Cell Therapy

blood products,
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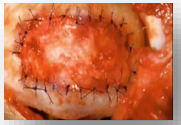
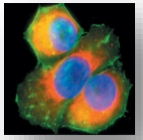


tissue engineering-
products



cell &
gene therapy medicinal
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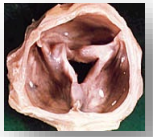

tissue
preparations

Fighting the pandemic: contributions of the Paul-Ehrlich-Institut

- Heroes of vaccine research and development
- Experimental evaluation of CoV-2 rapid antigen tests and blood safety
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- National framework of Emergency Use authorization

SARS-CoV-2 asymptomatic and symptomatic patients and risk for transfusion transmission

Corman VM, … Ciesek S.; Virological Institutes, Berlin, Frankfurt, Düsseldorf & Paul-Ehrlich-Institut, Transfusion 2020 June; 60:1119-22.

https://onlinelibrary.wiley.com/doi/full/10.1111/trf.15841

Patients	Age 18 - 65 y	No symptoms	Symptoms	Oral swab/ Sputum qRT-PCR Ct	Blood, plasma, serum qRT-PCR Ct
3	X	+	-	24.1 – 30.2	15 x negative
7	X	-	Flu -like	17.4 – 31.7	25 x negative
5	X	-	Fever	15.3 – 39.1	19 x negative
2	X	-	Pneumonia	34.8 – 35.1	10 x negative
1	X	-	ARDS	22.6	7 x negative 1 x positive
18	**X**			**positive**	**76 x negative 1 x positive**

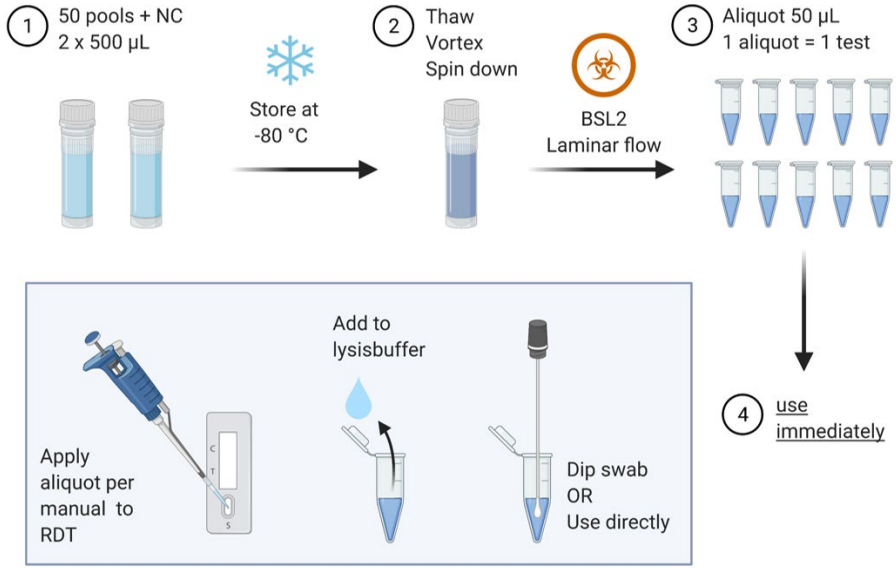
- Molecular detection of SARS-CoV-2 in 18 patients with asymptomatic or symptomatic infection
- CoV2-specific PCR detection attempts on nasopharyngeal swabs, sputum, serum and blood plasma

Safe blood recommendations of PEI on the basis of ad hoc experimental research by PEI and RKI

Absence of PCR detectable CoV-2 genomes of SARS-CoV-2 infected patients

https://www.pei.de/DE/newsroom/pm/pressemitteilungen-node.html

Experimental evaluation of CoV-2 rapid antigen tests (point-of-care tests (POCTs))



	CT <25 (n=18)	CT 25-30 (n=23)	CT >30 (n=9)
Infectivity cell culture	**possible**	**unprobable**	**not possible**

Comparative Evaluation

- **Evaluation Panel** (n=50; RKI)
  - pools of pharyngeal swabs
  - viral load (PCR: CT 17 – 36 CT, 25 ≈ 1 mio RNA copies / ml))
    - cell culture: infectious virus
- **Criteria** (www.pei.de)
  - sensitivity: >80% of at least 100 unselected PCR-positive samples, positive in SARS-CoV-2-rapid antigen test
  - specificity: >97%

Experimental evaluation of CoV-2 rapid antigen tests (point-of-care tests (POCTs))

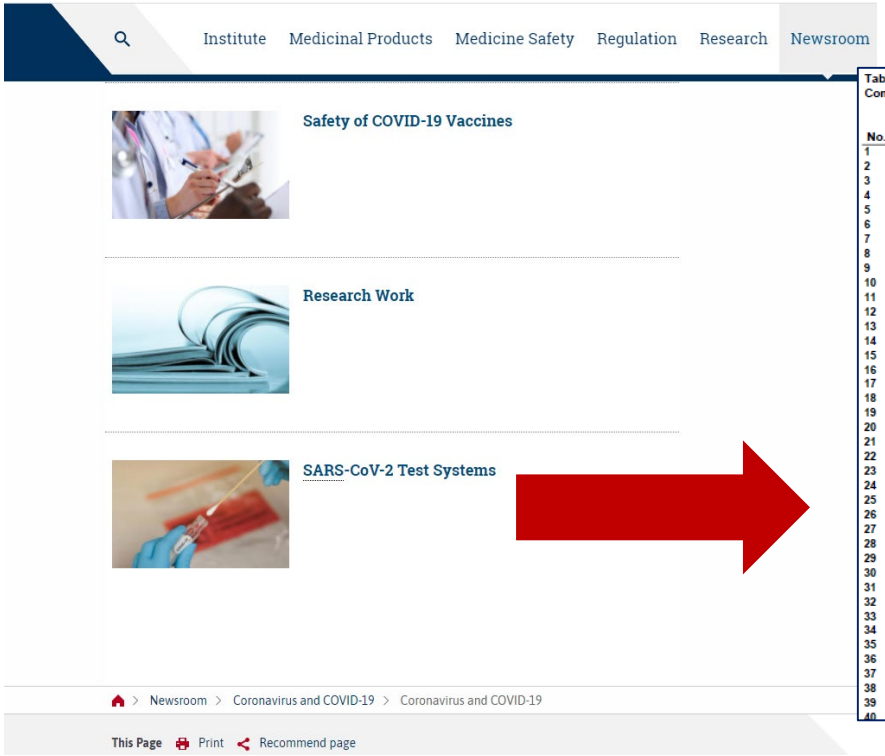


Table 1
Comparative evaluation results of SARS-CoV-2 antigen RDT passing the sensitivity criteria

No.	Manufacturer	Test name	Sensitivity CT <25	Sensitivity CT 25-30	Sensitivity CT >30	Sensitivity CT 17-36
1	Abbott Rapid Diagnostics Jena GmbH	Panbio™ COVID-19 Ag Rapid Test Device (NASOPHARYNGEAL)	100,0%	60,9%	0,0%	64,0%
2	ACON Biotech (Hangzhou) Co., Ltd	Flowflex SARS-CoV-2-Antigenschnelltest (Nasopharynxtupfer)	94,1%	4,3%	0,0%	34,0%
3	Aesku Diagnostics GmbH	Aesku Rapid SARS-CoV-2 Rapid Test	82,4%	17,4%	0,0%	36,0%
4	Affimedix	TestNOW® - COVID-19 Antigen	94,4%	47,8%	0,0%	56,0%
5	Amazing Biotech (Shanghai) Co., Ltd	CoroVisio Covid-19 Ag Versiegelungsröhrchen Teststreifen (Kolloidales Gold)	76,5%	8,7%	0,0%	30,0%
6	Ameda Labordiagnostik GmbH	AMP Rapid Test SARS-CoV-2 Ag	100,0%	78,3%	0,0%	70,0%
7	AmonMed (Xiamen) Biotechnology Co., Ltd.	COVID-19 Antigen Rapid Test Kit (Colloidal Gold)	100,0%	82,6%	30,0%	78,0%
8	Anbio (Xiamen) Biotechnology Co., Ltd	Rapid Covid-19 Antigen Test (Colloidal Gold)	100,0%	52,2%	0,0%	58,0%
9	Anhui Deepblue Medical Technology Co. , Ltd.	COVID-19 (SARS CoV-2) Antigen Test Kit (Colloidal Gold)	100,0%	52,2%	0,0%	58,0%
10	ASAN PHARM.CO.,LTD.	Asan Easy Test COVID-19 Ag	100,0%	69,6%	0,0%	66,0%
11	Atlas Link Technology Co.,Ltd.	Nova Test SARS-CoV-2 Antigen Rapid Test Kit	100,0%	60,9%	0,0%	62,0%
12	Avalun	Ksmart® SARS-COV2 Antigen Rapid Test	94,1%	13,0%	0,0%	38,0%
13	AXIOM Gesellschaft für Diagnostica und Biochemica mbH	Axiom Diagnostics COVID-19 Ag Schnelltest	100,0%	52,2%	0,0%	58,0%
14	Azure Biotech Inc.	Dia Su				
15	Becton Dickinson	BD Ver				
16	Beijing Beier Bioengineering Co., Ltd.	Covid-				
17	Beijing Hotgen Biotech Co., Ltd.	Novel C				
18	Beijing Lepu Medical Technology Co., Ltd	SARS-				
19	Beijing Tigsun Diagnostics Co.;Ltd.	Tigsun				
20	BIOMERICA Inc.	COVID				
21	BIONOTE	NowCh				
22	BioRepair GmbH	Covid				
23	BIOSYNEX SWISS SA	BIOSY				
24	BTNX, Inc. (Biotrend Chemikalien Gmbh)	Rapid				
25	Chi Tibbi Mal. San. Tic. Ltd. Şti	COVID				
26	Core Technology Co., Ltd.	Canea				
27	DNA Diagnostic A/S.	Covid-				
28	Edinburgh Genetics Limited	Edinbu				
29	Eurobio Scientific	EBS S				
30	Fujirebio Inc. (Mast Diagnostics GmbH)	ESPLIN				
31	Genrui Biotech Inc.	Genrui				
32	GenSure Biotech Inc.	DIA-CO				
33	Getein Biotech, Inc.	One St				
34	Green Cross Medical Science Corp. (Weko Pharma GmbH)	Genedi				
35	Guangdong Hecin Scientific,Inc.	2019-n				
36	Guangdong Wesail Biotech Co., Ltd.	COVID				
37	Guangzhou Wondfo Biotech Co. Ltd	Wondfo				
38	Hangzhou Clongene Biotech Co., Ltd.	Clunge				
39	Hangzhou Immuno Biotech Co.,Ltd.	IMMUN				
40	Hangzhou Laihe Biotech Co., Ltd. (Lizhiger Gl GmbH)	Laihe				

Comparative sensitivity evaluation for 122 CE-marked SARS-CoV-2 antigen rapid tests

Heinrich Scheiblauer[1], Angela Filomena[1], Andreas Nitsche[2], Andreas Puyskens[2], Victor M Corman[3], Christian Drosten[3], Katrin Zwirglmaier[4], Constanze Lange[5], Petra Emmerich[6], Michael Müller[7], Olivia Knauer[1], C Micha Nübling[1]*

[1] *Paul-Ehrlich-Institute, Paul-Ehrlich-Str. 51-59, D-63225 Langen*

[2] *Robert Koch-Institute, Seestrasse 10, D-13353 Berlin*

[3] *Institute of Virology, Charite, Chariteplatz 1, D-10117 Berlin*

[4] *Bundeswehr Institute of Microbiology, Neuherbergstr 11, D-80937 Munich*

[5] *LADR GmbH, Lauenburger Str. 67, D-21502 Geesthacht*

[6] *Bernhard-Nocht Institute, Dep.Virology, Bernhard-Nocht Str. 74, D-20359 Hamburg*

[7] *MVZ Labor 28 GmbH, Mecklenburgische Str. 2, D-14197 Berlin*

www.pei.de

Fighting the pandemic: Contributions of the Paul-Ehrlich-Institut

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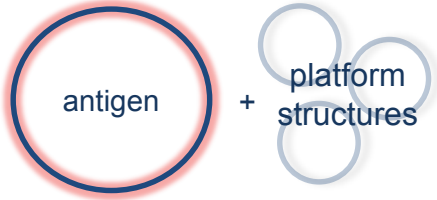
- PEI periodic safety reports on COVID-19 vaccines
- National framework of Emergency Use authorization

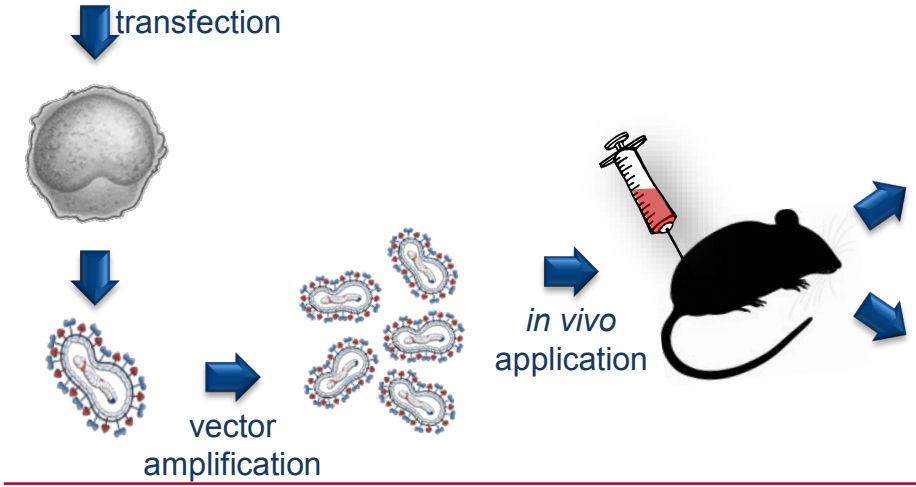
Analysing efficacy and safety in mice of an MeV platform-based research vaccine allows better regulations

Nürnberger *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 generation

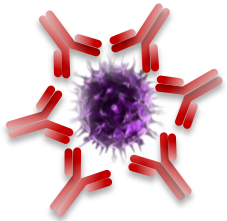


- Measles vaccine (MeV)
- LV protein-transfer vectors
- MLV-VLP
- HBV TLM-VLP

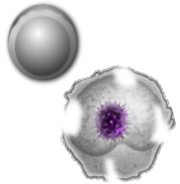


efficacy

Ab responses



T cell responses



protection after challenge

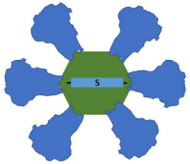
safety

Vaccine platforms and techno-logies

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

whole virus vaccines inactivated

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



F
Recombinant RBD protein based vaccines

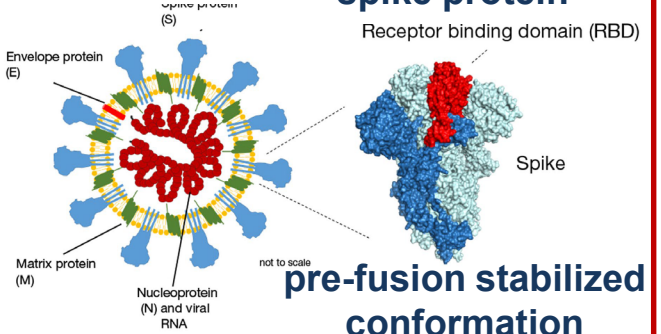
E
Recombinant spike protein based vaccines

protein subunit vaccines

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

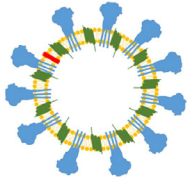
live attenuated virus vaccines

A
SARS-CoV-2



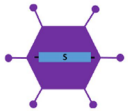
pre-fusion stabilized conformation

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

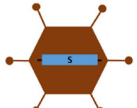


VLPs

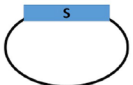
H
Replication competent vector vaccines can propagate to some extend in the vaccinee's cells and express the spike protein there.



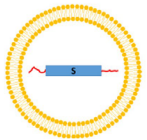
I
Non-replication competent vector vaccines cannot propagate in the vaccinee's cells but express the spike protein there



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



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

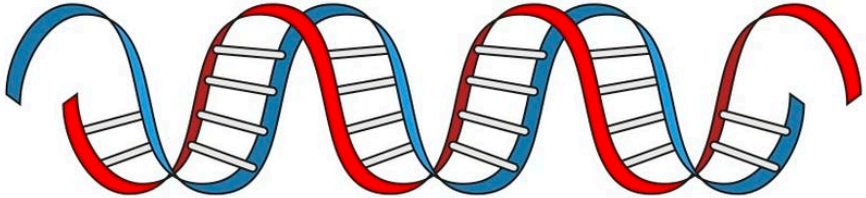


genetic vaccines

genetic vaccines
vector
DNA
RNA

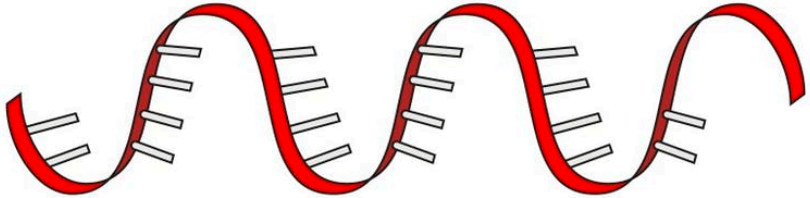
Vektor

DNA



Transcription

mRNA

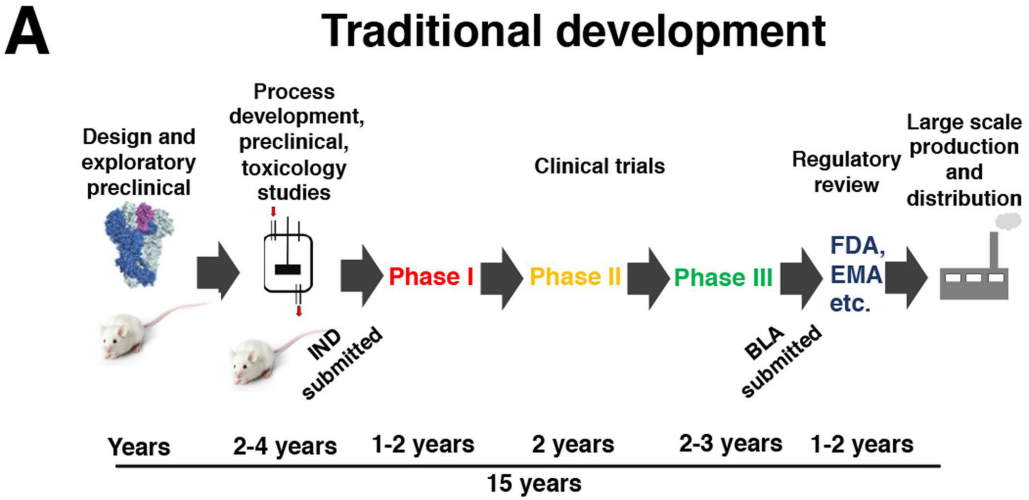


Translation

protein vaccines/
inactivated vaccines
whole virus
VLP
rec. protein

Protein

established



Joined action towards accelerated vaccine development

→ Global regulators (ICMRA)-Meeting on 18th March 2020

SARS-CoV-2 Global Regulators T-Con

March 18, 2020

AGENDA (CET timing)

Introduction and Meeting Objectives

Meeting Co-chairs:
Dr. Marco Cavaleri, Head of Office, Anti-Infectives & Vaccines, EMA
Dr. Marion Gruber, Director, Office of Vaccines Research & Review, USFDA

Regulatory Considerations – Preclinical Data and Studies

Speaker: Prof. Klaus Cichutek, President, Paul Ehrlich Institute

This session will introduce preclinical vaccine development considerations, including:

- Preclinical safety package needed to support First in Human clinical trials
- CMC and Product characterization data
- Repeat dose toxicity studies
- Proof of Concept studies in animal models
- Assays

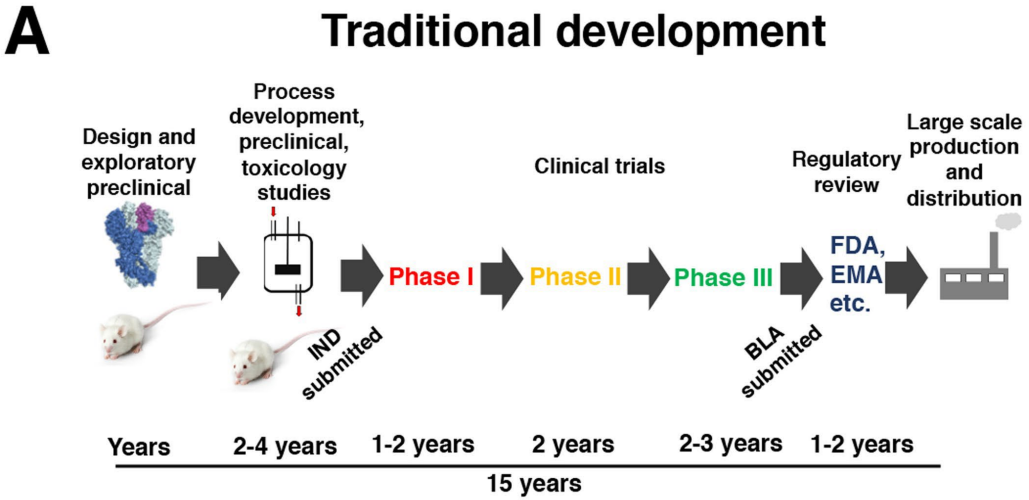
Main conclusions:

- No Covid-19 vaccine specific **„GLP repeat dose toxicity“** study required before entering into clinical evaluation (first-in-man FIM, Phase I/IIa) – but prior to larger Phase IIb Studies (need for GLP rep-dose tox before Ph IIb currently under discussion amongst regulators could be cases-by-case decision, vaccine product specific)
- No Covid-19 specific **Data for Evaluation of ADE / ERD Risks** required before entering into clinical first-in-man FIM and Phase I/IIa – but required prior to larger Phase IIb Studies

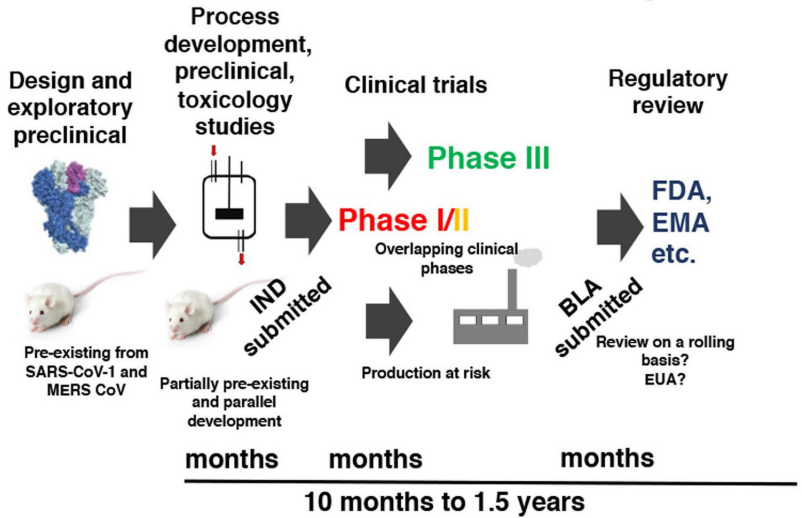
  Relevant qualified animal models for investigation/evaluation of ADE/ERD risk for COVID-19 vaccines are currently under development (WHO working group) **ADE / ERD Data to be generated as soon as models are available – prior to Ph Iib**
- Relevant **Immunogenicity data for particlar Covid-19 vaccine** in animal model required before entering into FIM

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH
Paul-Ehrlich-Institut
U.S. FOOD & DRUG ADMINISTRATION

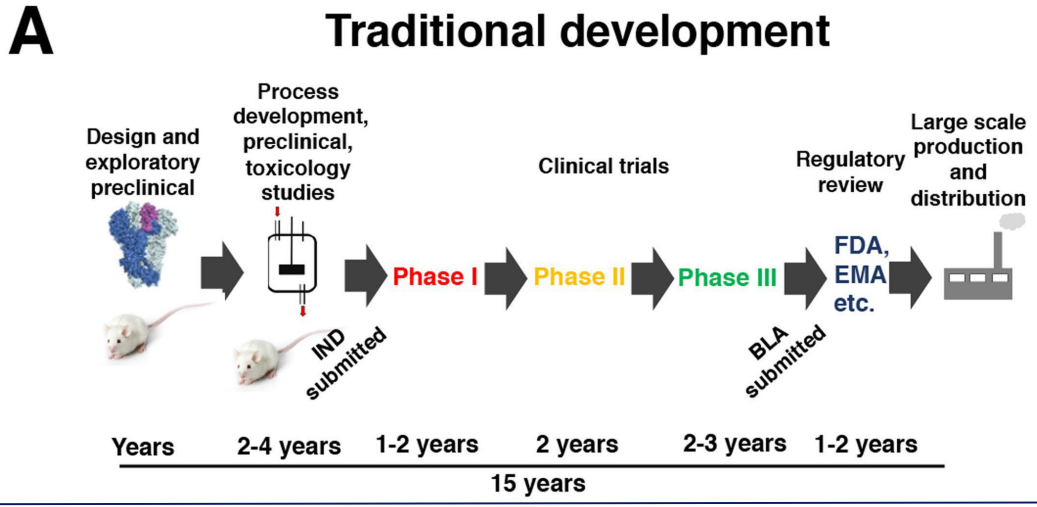
established



accelerated

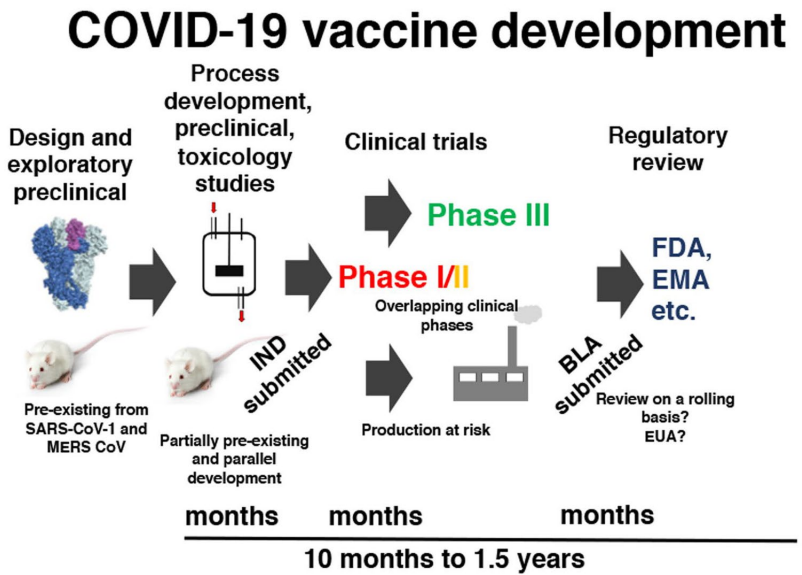


established



- early and frequent interaction with medicines agencies
- prioritizing pre-clinical studies
- adaptive clinical trial desings
- conditional marketing authorization
- active pharmacovigilance
- vaccine effectiveness studies

accelerated



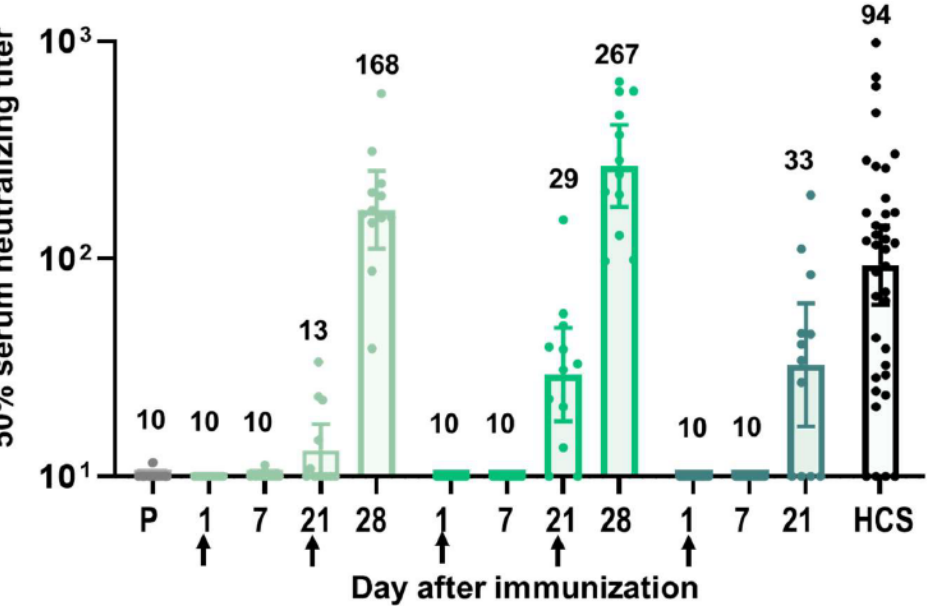
- rapid large-scale production
- platform-based development
- novel administration methods
- identification of putative protective antigen

- provision of manufacturing plants and source material

- international network and convergence
  - vaccine developer
  - vaccine manufacturer
  - medicines agencies

- financial investment by industry and government

Phase 1/2 immunogenicity and dosing

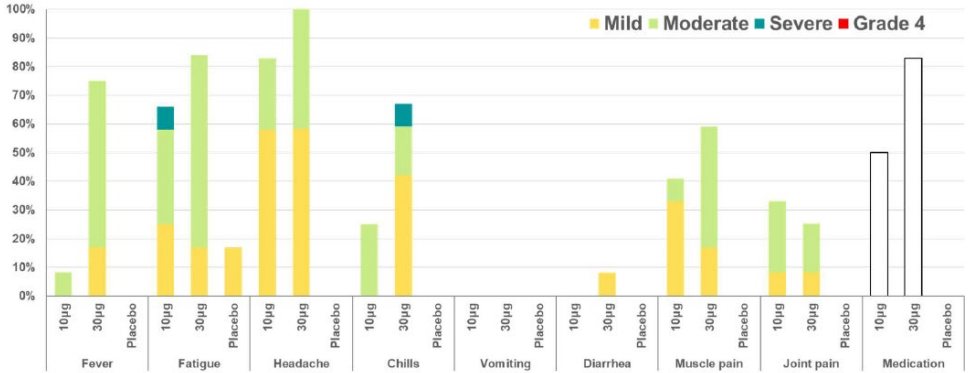


50% serum neutralizing titers
(replicating reporter gene CoV-2)

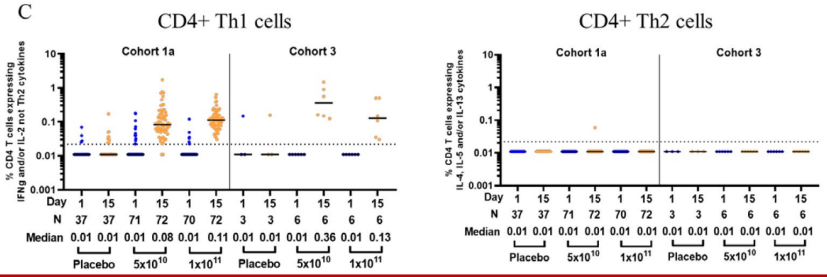
- Placebo
- 10 μg dose level
- 30 μg dose level
- 100 μg dose level
- HCS

Phase 1/2 general safety, tolerability, reactogenicity, systemic effects

(within 7 days p.v.)



Addressing known and theoretical candidate vaccine risks early and taking pre-active counter-measures



vaccines

MDPI

Perspective

Accelerated Development of COVID-19 Vaccines: Technology Platforms, Benefits, and Associated Risks

Ralf Wagner, Eberhard Hildt, Elena Grabski, Yuansheng Sun, Heidi Meyer, Annette Lommel, Brigitte Keller-Stanislawski, Jan Müller-Berghaus and Klaus Cichutek *

Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines, 63225 Langen, Germany; ralf.wagner@pei.de (R.W.); Eberhard.Hildt@pei.de (E.H.); elena.grabski@pei.de (E.G.); Yuansheng.sun@pei.de (Y.S.); Heidi.Meyer@pei.de (H.M.); Annette.Lommel@pei.de (A.L.); brigitte.keller-stanislawski@pei.de (B.K.-S.); Jan.Mueller-Berghaus@pei.de (J.M.-B.)
* Correspondence: klaus.cichutek@pei.de

July 2021,
9,747

September 2020,
117/39 Dtsch Arztebl

Communicating regulatory means of vaccine development acceleration

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Pre-pandemic communication between industry, PEI and politics

- Annual Stakeholder consultations at PEI vfa
  - BPI
  - BAH
  - BfT
- Jour fixe with vaccine companies

- Pharma dialogue of Federal Ministries of Health, Education & Research, and Economics with pharma associations and companies under participation of BfArM and PEI
  - Topic-focused dialogue sessions to be continued

- SARS-CoV-2 pandemic
  - Regulatory advice to the government
  - No participation in consultations on „advance purchase agreements“

International networks provide assurance of a certain level of regulatory convergence

ICMRA (International Coalition of Medicines Regulatory Authorities)

- biweekly TCs

WHO committees & WGs

- vaccine
- animal studies
- clinical trial design
- reference material for assays

HMA – Heads of Medicines Agencies

- business continuity
- availability

EMA – European Medicines Agency

- accelerated licensing -rolling review
- ETFs
- EMRN meetings

Global vaccine development

>184 vaccine projects

>112 clinical trials with COVID-19 vaccines

>31 phase III clinical trials

WHO 08/2021

PEI contributions to WHO
ECBS - Expert Committee on Biological Standardization

World Health Organization

since Dec 2020

First WHO International Standard for SARS-CoV-2 RNA (NIBSC code: 20/146)

Material: Inactivated virus, WHO IS

Intended use: Primary calibrant for molecular assays based on nucleic acid amplification techniques

Description: Acid-heat inactivated SARS-CoV-2 virus, formulated in a TRIS buffer with human serum albumin, trehalose and human genomic DNA. Non-Infectious. Requires extraction prior to downstream application.

Enquiries: standards@nibsc.org

First WHO International Standard for anti-SARS-CoV-2 immunoglobulin, human (NIBSC code: 20/136)

Material: Antibody, human, convalescent plasma, WHO IS

Intended use: Primary calibrant for serological assays

Description: Pool of convalescent plasma from recovered COVID-19 patients, containing high titre antibodies against SARS-CoV-2. Plasma has been solvent detergent treated to minimise the risk of presence of enveloped viruses.

Enquiries: standards@nibsc.org

First WHO International Reference Panel for anti-SARS-CoV-2 immunoglobulin, human (NIBSC code: 20/268)

Material: Antibody, human, convalescent plasma, WHO reference panel

Intended use: Serological assay development and evaluation, Vaccine evaluation, Research,

Anticipated delivery date: comprises of 5 panel members; four pools of convalescent plasma from recovered COVID-19 patients, containing high, medium, low anti-S but relatively high anti-N, low antibodies against SARS-CoV-2, and a negative control, pool of plasma from healthy donors collected before 2019.

Enquiries: standards@nibsc.org

PEI contributions to WHO
ECBS - Expert Committee on Biological Standardization

World Health Organization

World Health Organization

WHO/BS/2021.2402
ENGLISH ONLY

Call for comments

Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations

Guidelines on the quality, safety and efficacy of plasmid DNA vaccines

March 2021

Replacement of Annex 1 of WHO Technical Report Series, No. 941

Guidelines on the quality, safety and efficacy of Ebola vaccines

July 2018

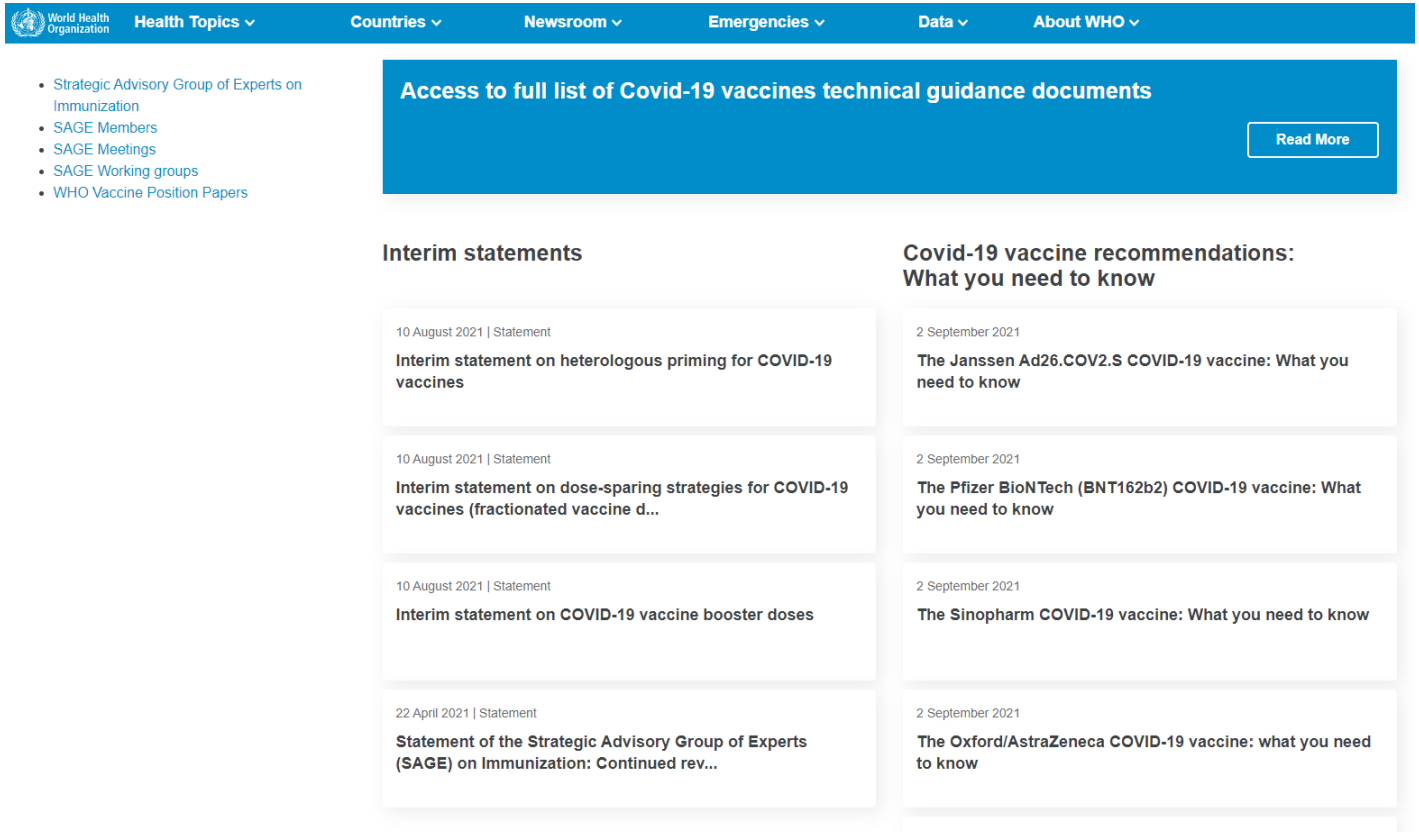
PEI contributions to WHO

SAGE- Strategic Advisory Group of Experts on Immunization

Working Group on COVID-19 vaccines

Subgroup evidence gathering

World Health Organization



PEI Support COVID-19 Vaccine Development
(September 2021)

Scientific Advices (SA) PEI and PEI/EMA

- 60x PEI SA COVID-19 vaccines
- 40x PEI SA COVID-19 therapeutics incl. binational advices (SNSA)
- 11x Emergency Task Force EMA/PEI meetings vaccines
- 29x Emergency Task Force EMA/PEI meetings therapeutics

Clinical trial authorisations by PEI

- 22x specific COVID-19 vaccines
- 4x unspecific, immunomodulting vaccines
- 7x convalescent plasma therapy
- 17x mAb
- 2x ATMP

Batch testing (298 national releases)

Pharmacovigilance (PRAC)

Inspections (13 national, 5 EMA)

Assessment of MA applications (13 (co-)rapporteurships))

Diagnostics-Performance

Research

ICMRA (regulatory convergence)

- 65x global TCs with US-FDA/WHO/ICMRA

Covid-19 vaccines WG of the
WHO Strategic Advisory Groupe of Experts (SAGE) on Immunization

WHO Expert Committee for Biological Standardisation (ECBS)

WHO Blueprint Committees

Daily and weekly reports on COVID-19 vaccine development to BMG

STAKOB

Vaccination policy / Vaccine availability
BMG, Federal States of Germany, RKI, PEI

BMBF-Reviewer

advance purchase agreements
(not involved)

Optional offers of booster vaccinations (6 months after first series) with one of the licensed COVID-19 RNA vaccines in Germany

Resolutions (excerpts) of the Conference of Health Ministers of the Federal States of Germany (GMK) in agreement with the Federal Minister of Health (on 2nd and 9th August 2021 and on 6th September 2021)

- persons who have a rapidly waning immune response after a full first series of COVID-19 vaccination and
  persons suffering from immunodeficiency or immunosuppression
  (oncology patients, organ transplant recipients, patients treated for rheumatoid arthritis)
- persons (and employees) in nursing and retirement homes or in need of care in their own homes
- persons in regular professional contact with people potentially infected with CoV2
  (e.g. outpatient and inpatient medical staff, emergency services personnel, mobile vaccination teams)
- persons living in facilities for integration assistance and other facilities for vulnerable groups
- elderly (from 60 years old on)
- persons having completed the first series of vaccination (s) with AstraZeneca or Johnson & Johnson COVID-19 vaccine,
- persons who have received one of these vector vaccines after recovering from COVID-19

- The Paul Ehrlich Institute expects no significant differences in immunogenicity in persons co-administered with inactivated influenza and COVID-19 mRNA vaccine (vaccinations on the same day on different extremities).

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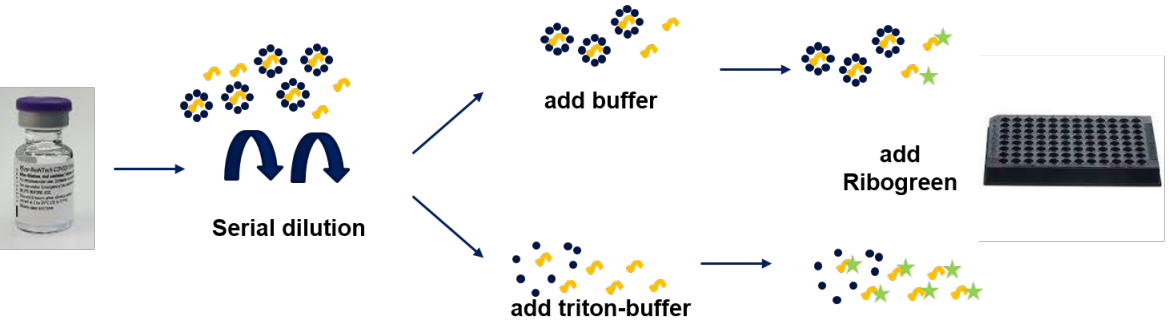
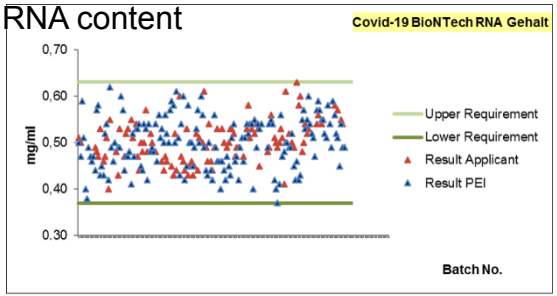
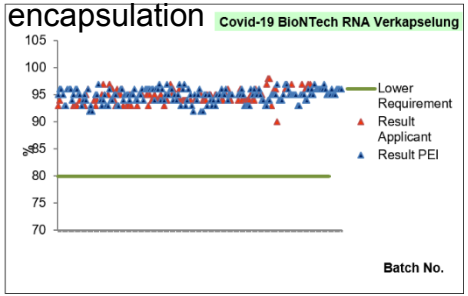
Experimental COVID-19 vaccine testing by OMCL-PEI (markers)

Potency assay RNA vaccine







- Identity
  - RT PCR
- Integrity
  - capillary gel electrophoresis
  - Ion Pair-Reversed-Phase chromatograpy

Experimental COVID-19 vaccine testing by OMCL-PEI (time lines)

October

November

December

22 Dec 2020
1st Comirnaty batch release (EU) by PEI

delivery of devices & start of operation

sample material for establishment

establishment methods

validation

sample receipt

21 Dec 2020
MA

Batch testing

35
30
25
20
15
10
5
0

Dezember
Januar
Februar
März
April
Mai
Juni

Comirnaty
Janssen

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Langen, den 19.08.2021

SAFETY REPORT

Suspected cases of side effects and vaccination complications after COVID-19 vaccination

All vaccines
- Anaphylactic reactions

Adenovector vaccines
- Thrombotic thrombocytopenia syndrome (TTS/VITT)
- Guillain-Barré syndrome
- Idiopathic thrombocytopenic purpura (ITP)

mRNA vaccines
- Myocarditis/pericarditis

Reactions of special interest to the public and press
- Menstrual cycle disorders
- Chromosomal integration of vaccine mRNA
- Infertility of women
- Cases of death shortly after vaccinations

Providing updated safety information on COVID-19 vaccines gives assurance to the public,

especially persons willing to get vaccinated,

and counter-acts fake news about vaccines

Periodical Covid vaccine safety reports
https://www.pei.de/DE/newsroom/dossier/coronavirus/coronavirus-inhalt.html?nn=169730&cms_pos=6

FAQs corona virus
https://www.pei.de/EN/newsroom/dossier/coronavirus/coronavirus-content.html;jsessionid=B2C8A2EEAE947AF3219B8D2F92B8426D.intranet232?nn=164146&cms_pos=4

Cohort Study via Mobile Phone SafeVac 2.0 App

- Objectives
  - Real-time monitoring of AEs
  - Frequencies, severity, duration and outcome of AEs
  - Vaccine effectiveness
- Study participants
  - Adult vaccinees
  - Voluntary (electronic consent)
  - Smartphones (IOS ≥12, Android ≥5.0)
  - Consent available
- Monitoring
  - Intensified monitoring for up to 28 days post dose 2
  - 6 + 12 months
- Sample size not limited
- No identification of participants possible

Human Medicines Committees at EMA
(28 EU MSs + 2 (Iceland, Norway))

5 „double members“

BWP

SAWP

PhVWP

PCWP

SWP

QWP

BPWP

BMWP

VWP

GMDP
IWP

BWP

CTFG

Paul-Ehrlich-Institut

Way forward: Was bleibt?

Project management	Vaccine development	Vaccine safety	Manufacture	Distribution

Fighting the pandemic: contributions of the Paul-Ehrlich-Institut

- Necessary pre-requisites for early pharmaceutical interventions in a pandemic
  - Identification of potentially protective viral antigens and
  - development of vaccine platforms
- Blood and blood products are safe in times of a pandemic caused by a respiratory viral disease
- SARS-Coronavirus-2 antigen tests are highly specific and most have acceptable sensitivity
- Fast lane to licensed COVID-19 vaccines was possible by educated methods of regulatory support
- International networks and political support towards COVID-19 vaccines and therapeutics are essential
- Experimental COVID-19 vaccine testing required new technical methods
  (and experimental regulatory research allowed PEI to react rapidly)
- PEI periodic safety reports on COVID-19 vaccines
- National frameworks of Emergency Use authorization allow rapid availability of emergency therapies

Paul-Ehrlich-Institut

Our focus in on health!

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YouTube www.youtube.com/PaulEhrlichInstitutGermany

PEI als Zentrum der Pandemiebekämpfung durch Impfstoffe und Biomedizin

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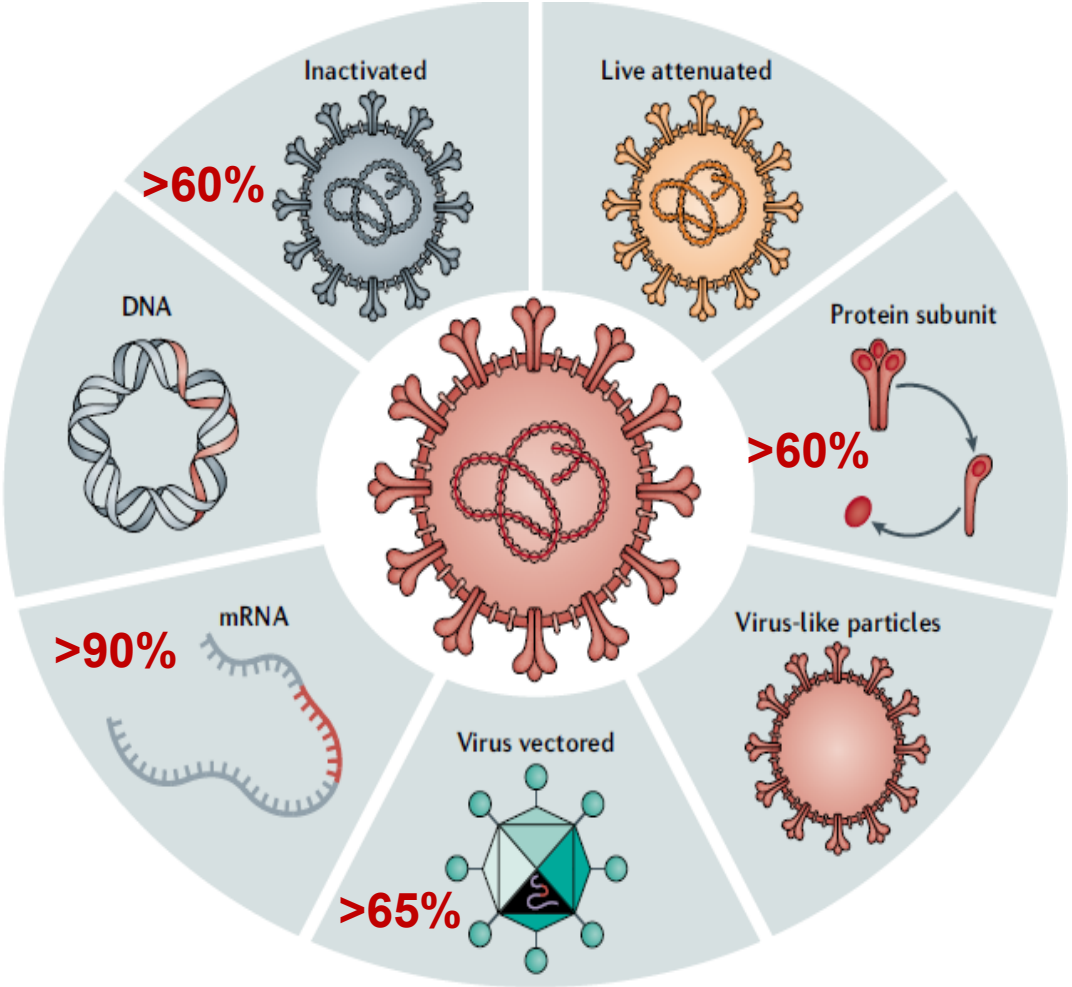


The figure shows the seven strategies being explored as vaccines for coronavirus disease 2019 (COVID-19).

Source: Nature Rev. Immunol., Vol. 21, Feb. 2021

Covid-19 vaccine types

highly effective
safe
available in 100s of million doses

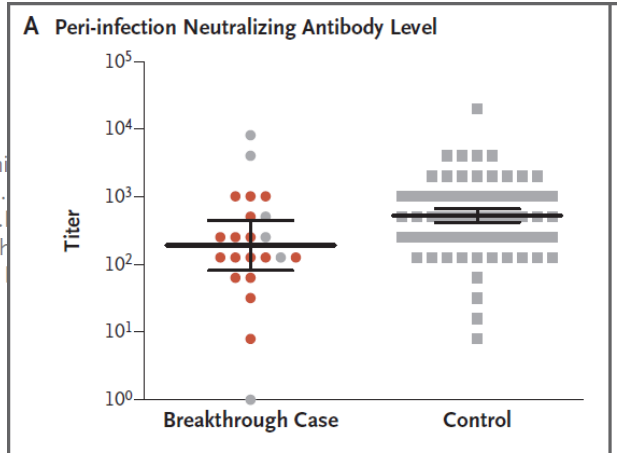
Covid-19 Breakthrough Infections in Vaccinated Health Care Workers

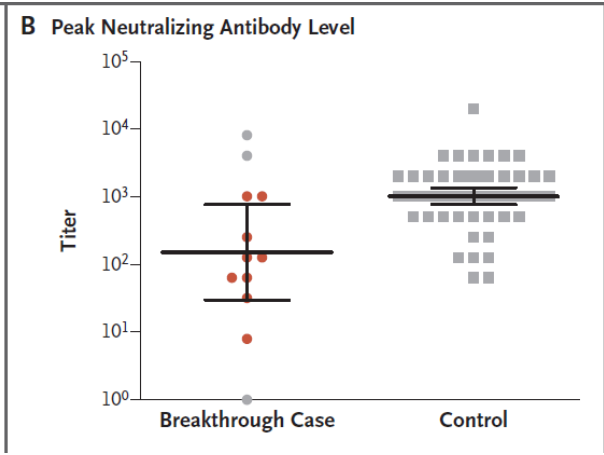
Moriah Bergwerk, M.B., B.S., Tal Gonen, B.A., Yaniv Lustig, Ph.D., Sharon Ami
Marc Lipsitch, Ph.D., Carmit Cohen, Ph.D., Michal Mandelboim, Ph.
Einav Gal Levin, M.D., Carmit Rubin, N.D., Victoria Indenbaum, Ph.
Ilana Tal, R.N., Ph.D., Malka Zavitan, R.N., M.A., Neta Zuckerman, Ph
Adina Bar-Chaim, Ph.D., Yitshak Kreiss, M.D., and Gili Regev-Yochay,

This article was published on July 28, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2109072

From the Infection Prevention and Control Unit (M.B., T.G., C.C., E.G.L., C.R., I.T., M.Z., G.R.-Y.), the Department of





- Percentage of breakthrough cases following COVID-19 mRNA vaccinations is low (<10%)
- Neutralising antibody titers, before (and after) breakthrough infection, may be predictors of the level of protection
- Virus load (and infectivity) of persons with breakthrough infections may inversely correlate with neutralising antibody titers just prior to infection

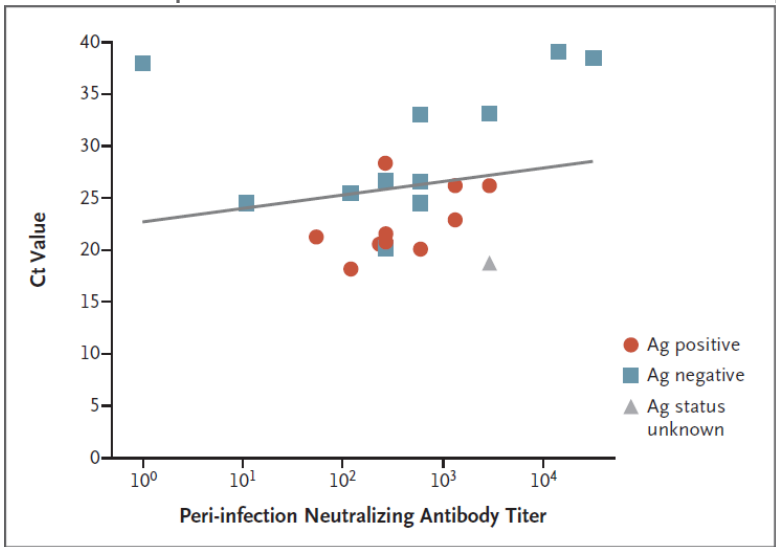
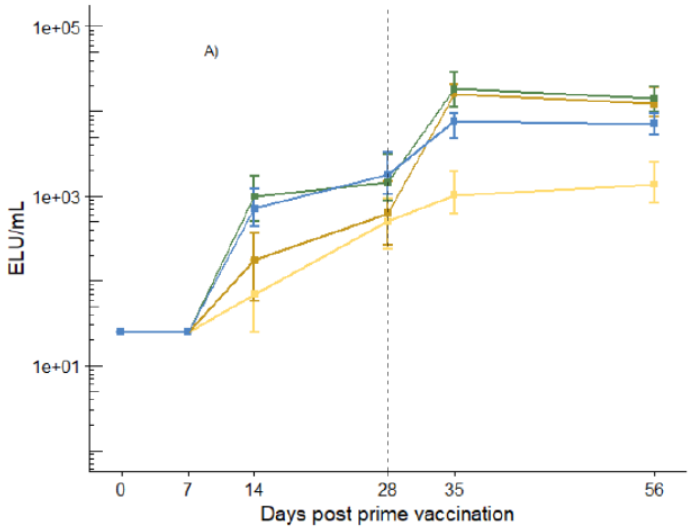
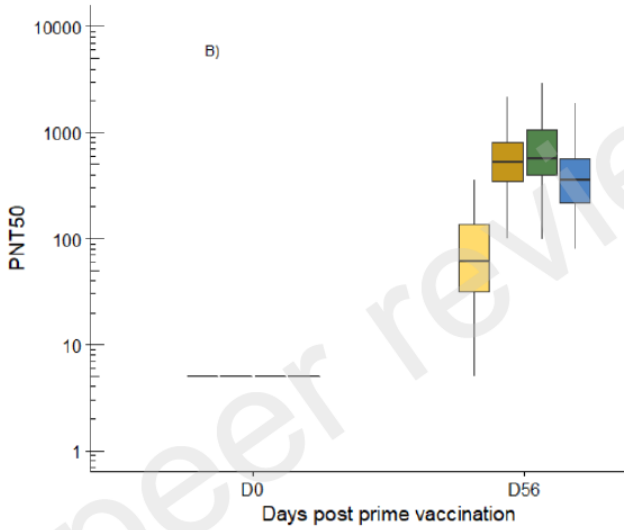
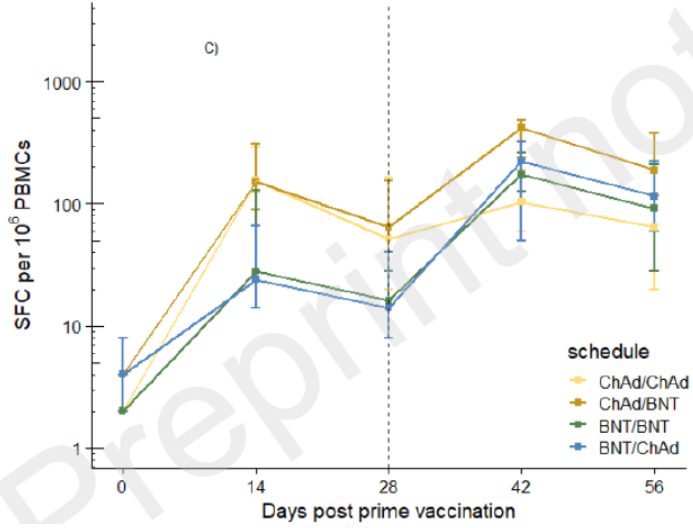


Figure 3. Correlation between Neutralizing Antibody Titer and N Gene Cycle Threshold as Indication of Infectivity.







Heterologous vector/RNA vaccinations increase immunogenicity

ComCoV-Studie in UK (2021/06)

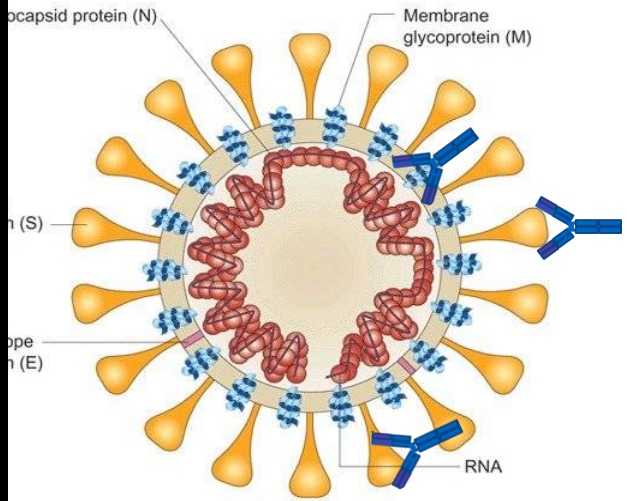
Safety and immunogenicity report from the Com-COV study – A single-blind randomised non-inferiority trial comparing heterologous and homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine.

Xinxue Liu*[1], PhD; Robert H Shaw*[1,2], MRCP; Arabella SV Stuart*[1,2], MSc; Melanie Greenland[1], MSc;

1. Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford OX3 9DU, UK
2. Oxford University Hospitals NHS Foundation Trust, Oxford, UK
3. Public Health England

Conclusions

- The COVID-19 vaccine products licensed in EU/EEA for COVID-19 preventione are
  - highly efficacious and effective (>70%),
  - safe


ocapsid protein (N)
Membrane
glycoprotein (M)
n (S)
ope
n (E)
RNA

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- (Co)-rapportages CHMP/PRAC/ETF
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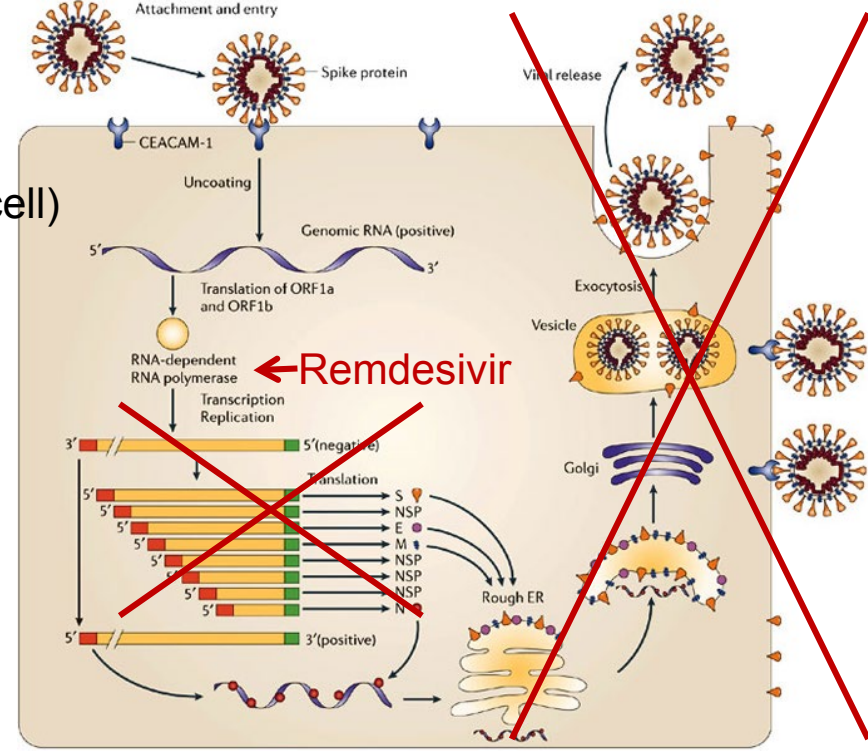
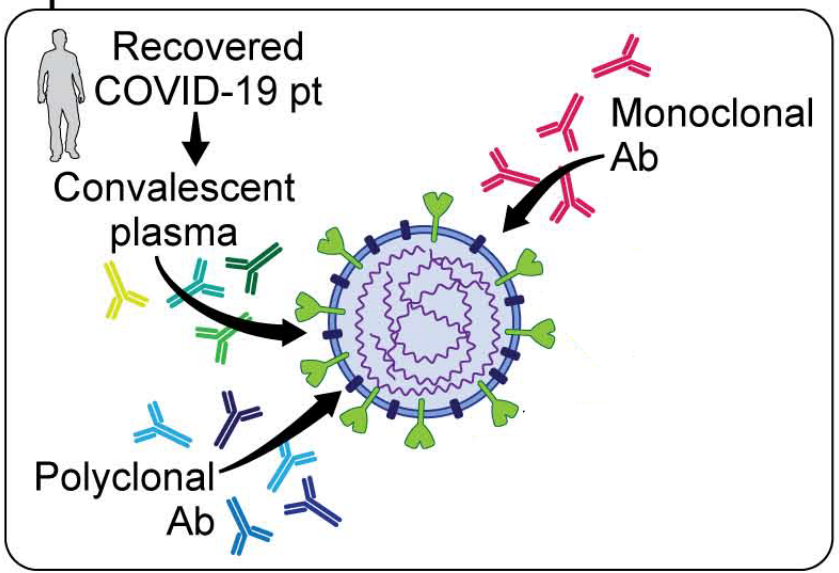
Medicines for Covid-19 therapy

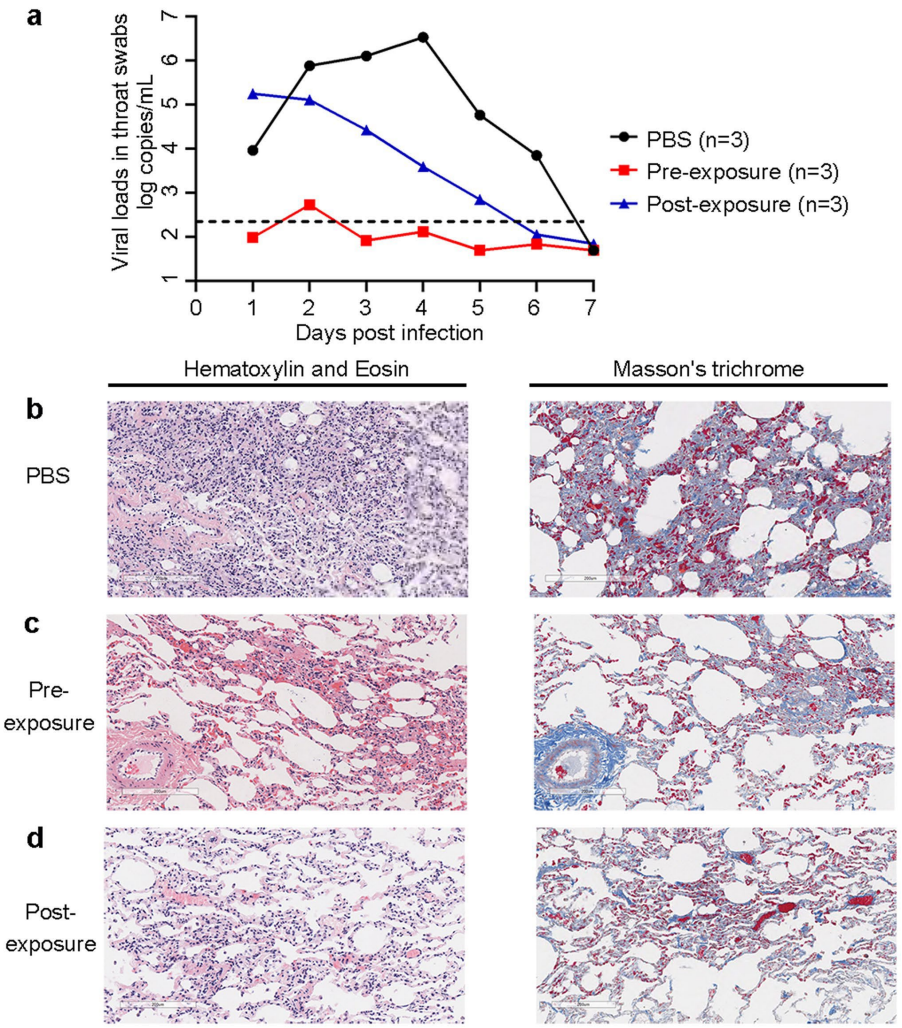
- Viral replication inhibitors (small molecules, inside cell)
  - Reduce the multiplication of viral genomes and new virus particle formation within each infected cell
- Neutralising antibody-containing medicines reducing spread of virus within the body
  - Neutralising monolconal antibodies and antibody cocktails
  - Specific immunoglobulin preparations
  - Convalescent plasma (directional administration)
- Immunomodulation
  - Monoclonal antibodies reducing cytokine storm targeting e.g. the IL-6 receptor

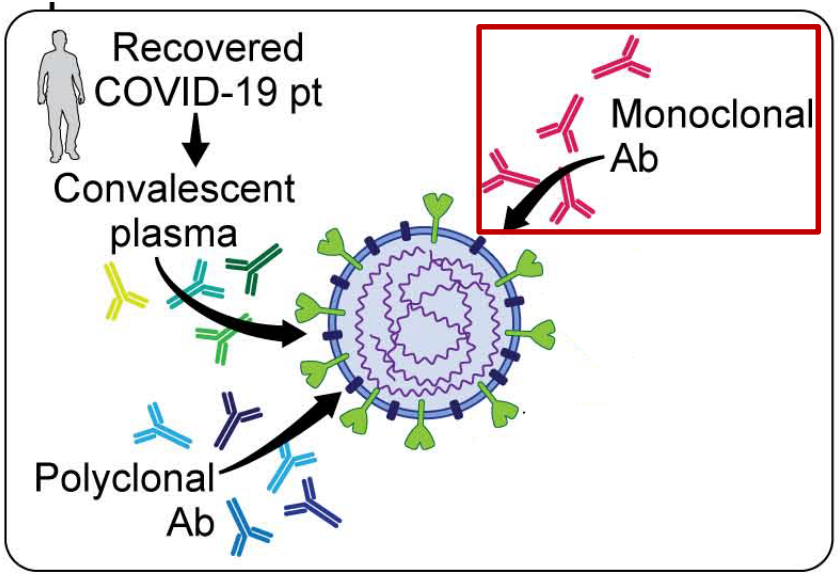


Biomedicines for Covid-19 therapy

- Viral replication inhibitors (small molecules)
  - Reduce the multiplication of viral genomes and new virus particle formation within each infected cell
- Neutralising antibody-containing medicines reducing spread of virus within the body
  - Neutralising monoclonal antibodies and antibody cocktails
  - Specific immunoglobulin preparations
  - Convalescent plasma (directional administration)
- Immunomodulation
  - Dexamethasone
  - Monoclonal antibodies reducing cytokine storm targeting e.g. the IL-6 receptor





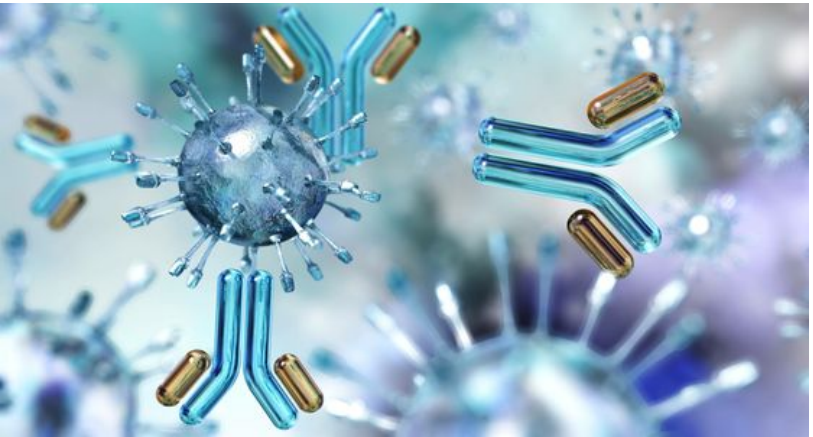


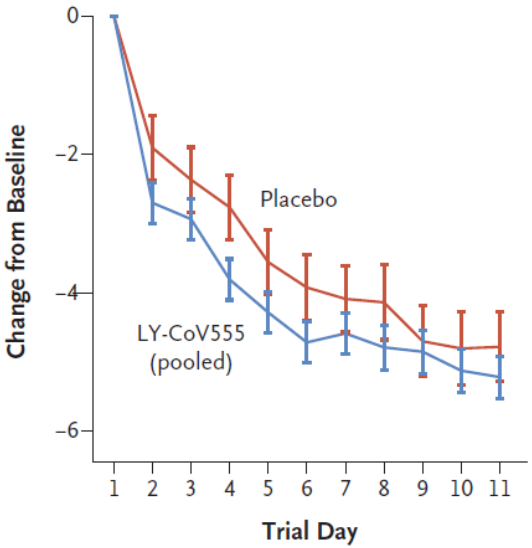
Neutralising antibodies can reduce viral load *in vivo*

Fig. 3 | CB6 MAb can effectively reduce viral load and alleviated infection-related lung damage in rhesus macaques. a, Nine male rhesus macaques were divided into pre-challenge (prophylactic), post-challenge (treatment) and control groups with 3 animals in each group. Before infection, the animals of pre-challenge group were infused with 50 mg/kg CB6-LALA intravenously. One day later, all macaques were inoculated with 1×105 TCID50 SARS-CoV-2 via intratracheal intubation. While the post-challenge group were also infused with 50 mg/kg antibody CB6-LALA on days 1 and 3 post challenge and three monkeys in the control group were given PBS as a control. Viral RNA loads in throat swabs determined by qRT-PCR were monitored for 7 days. Data were average values from three monkeys (n=3) for the first 5 days, from two monkeys (n=2) for the 6 dpi, and from one monkey (n=1) for the 7 dpi. To

Neutralising monoclonal antibodies for Covid-19 therapy (Feb. 2021)

In this interim analysis of a phase 2 trial, one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11. (Funded by Eli Lilly; BLAZE-1 ClinicalTrials.gov number, NCT04427501.)





	Delta Value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)
Day 3	−0.57 (−1.12 to −0.01)
Day 4	−1.04 (−1.60 to −0.49)
Day 5	−0.73 (−1.28 to −0.17)
Day 6	−0.79 (−1.35 to −0.23)
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

Figure 3. Symptom Scores from Day 2 to Day 11.

Shown is the difference in the change from baseline (delta value) in symptom scores between the LY-CoV555 group and the placebo group from day 2 to day 11. The symptom scores ranged from 0 to 24 and included eight domains, each of which was graded on a scale of 0 (no symptoms) to 3 (severe symptoms). The I bars represent 95% confidence intervals. Details about the symptom-scoring methods are provided in the Supplementary Appendix.

Ordinance assuring the supply of products for medical needs for the population in the context of the epidemic caused by the coronavirus SARS-CoV-2[*])
(Supply Assurance for Medical Needs Ordinance - MedBVSV)

Section 1 **Purpose of the Ordinance and definitions**

- This Ordinance serves to **ensure that the population is provided with products for medical needs during the epidemic** situation of national scope that the German Bundestag recognised on 28 March 2020.
- Products for medical needs within the meaning of this Ordinance are
  - **medicinal products, their active ingredients, source materials and excipients,** ….
  - medical devices,
  - laboratory diagnostics, ….

Section 2 **Procurement and delivery by federal authorities**

- For the purpose specified in Section 1(1), the **Federal Ministry can also procure, store, manufacture and market products** for medical needs centrally for positions outside the Federal Administration itself or through commissioned bodies.

Section 3 **Exceptions to the Medicinal Products Act and the Medicinal Products Ordinance on procurement and supply in accordance with Section 2**

- If a medicinal product intended for procurement or procured in accordance with Section 2(1) is not permitted within the scope of the Medicinal Products Act,
  - the **manufacturer shall provide the federal higher authority** responsible in accordance with Section 77 of the Medicinal Products Act with all documents relating to the **information on quality, efficacy and safety** required for approval in accordance with Section 22 of the Medicinal Products Act.
  - The competent **higher federal authority checks and evaluates the documents as a matter of priority** and immediately informs the procuring body of the result of the evaluation.
  - The **Federal Ministry must include the assessment in the decision on the procurement and placing on the market** of the medicinal product.

SARS CoV-2 neutralising antibody combinations available in Germany based on an Emergency Use Authorisation (MedBVSV)

Combination of two neutralizing monoclonal antibodies reduces 28 day-mortality in seronegative COVID-19 patients by 6%

(June 2021, Recovery study Regeneron on Casirivimab und Imdevimab)

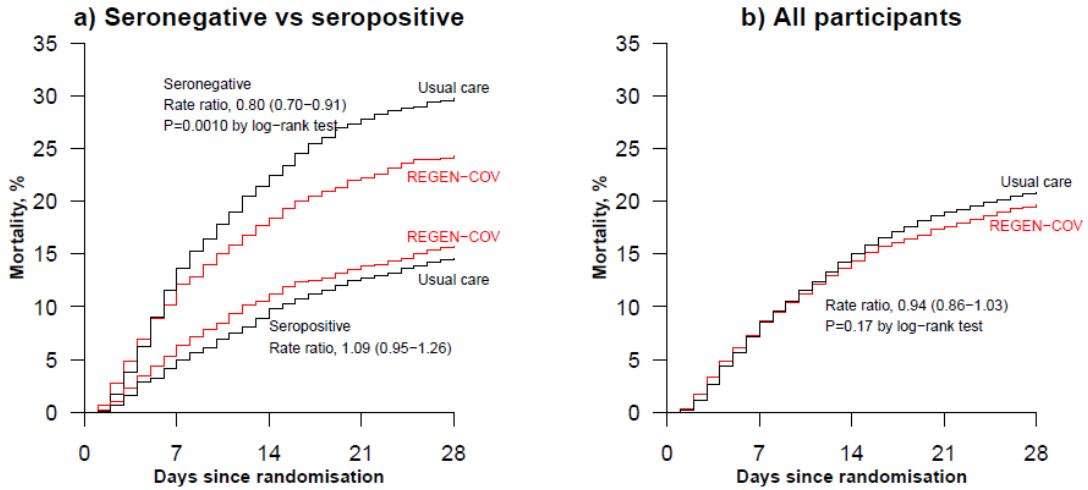
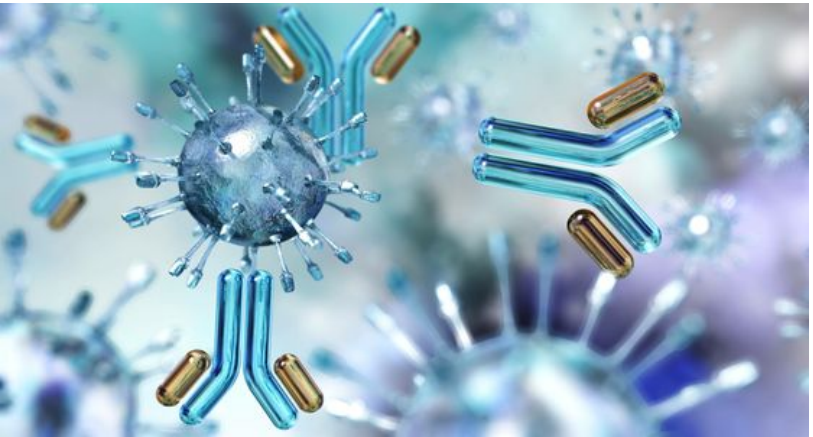


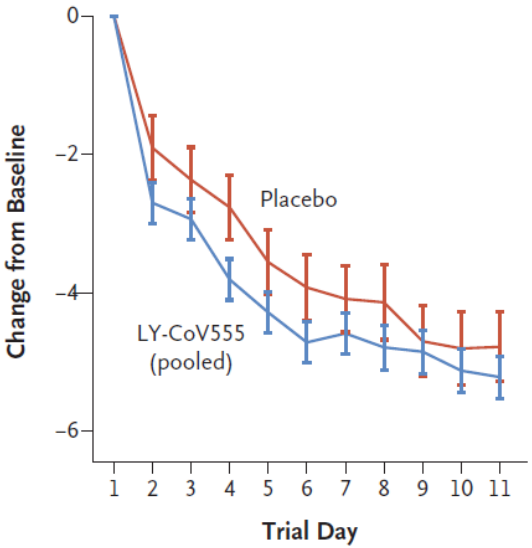
Table 2: Effect of allocation to REGEN-COV on key study outcomes among seronegative participants

	REGEN-COV (n=1633)	Usual Care (n=1520)	RR (95% CI)
Primary outcome			
Mortality at 28 days	396 (24%)	451 (30%)	0.80 (0.70-0.91)

Neutralising monoclonal antibodies for Covid-19 therapy (Feb. 2021)

In this interim analysis of a phase 2 trial, one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11. (Funded by Eli Lilly; BLAZE-1 ClinicalTrials.gov number, NCT04427501.)





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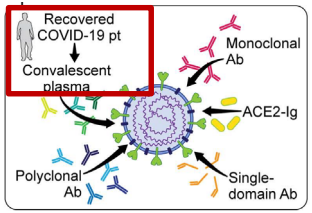
CONVALESCENT PLASMA for COVID-19

Plasma from recovered COVID-19 patients contains antibodies that fight the virus.

Dating back over 100 years C.P. has been used for polio spanish flu, SARS. Very minor adverse events!

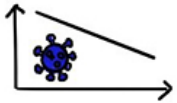


Early evidence from SARS on *

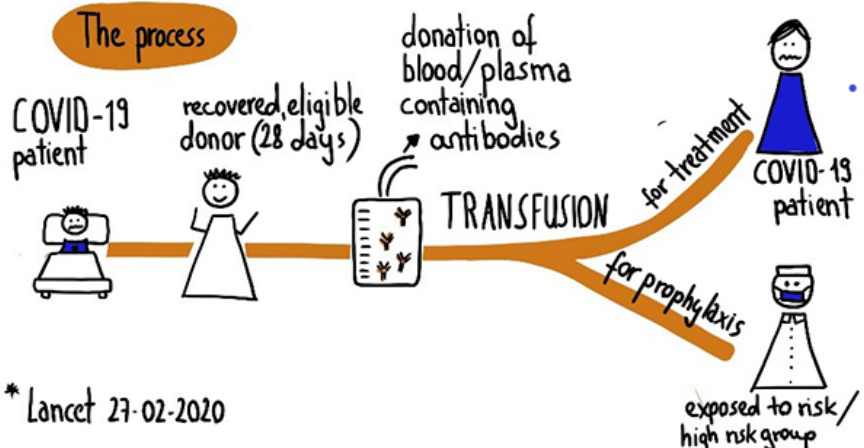
- shorter hospital stay
- reduced mortality
- lower viral load

to release pressure on hospitals

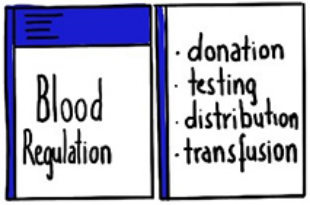
odds ratio: 0.20
95% CI 0.06-0.63
p = 0.01

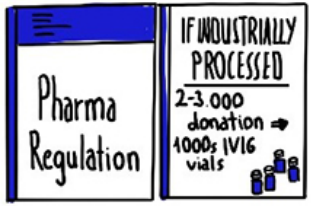


The process



* Lancet 27-02-2020





- Convalescent plasma is used directionally, not knowing the neutralising antibody titer necessary for efficacy
- Clinical trial use is highly recommended to determine
  - efficacy,
  - neutralising antibody titer and volume as well as
  - optimal time point for treatment in the disease course.
- ADE not observed.

Biomedicines for Covid-19 therapy

- Viral replication inhibitors (small molecules)
  - Reduce the multiplication of viral genomes and new virus particle formation within each infected cell
- Neutralising antibody-containing medicines reducing spread of virus within the body
  - Neutralising monoclonal antibodies and antibody cocktails
  - Specific immunoglobulin preparations
  - Convalescent plasma (directional administration)
- Immunomodulation
  - Dexamethasone
  - Monoclonal antibodies reducing cytokine storm targeting e.g. the IL-6 receptor