

PEI im Zentrum der Pandemiebekämpfung - Lessons learned from COVID-19 vaccine and biomedicine development -

Vaccine evaluation and batch release:

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Klaus Cichutek et al.

Stiftung Arzneimittelsicherheit

& House of Pharma

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Frankfurt/Main

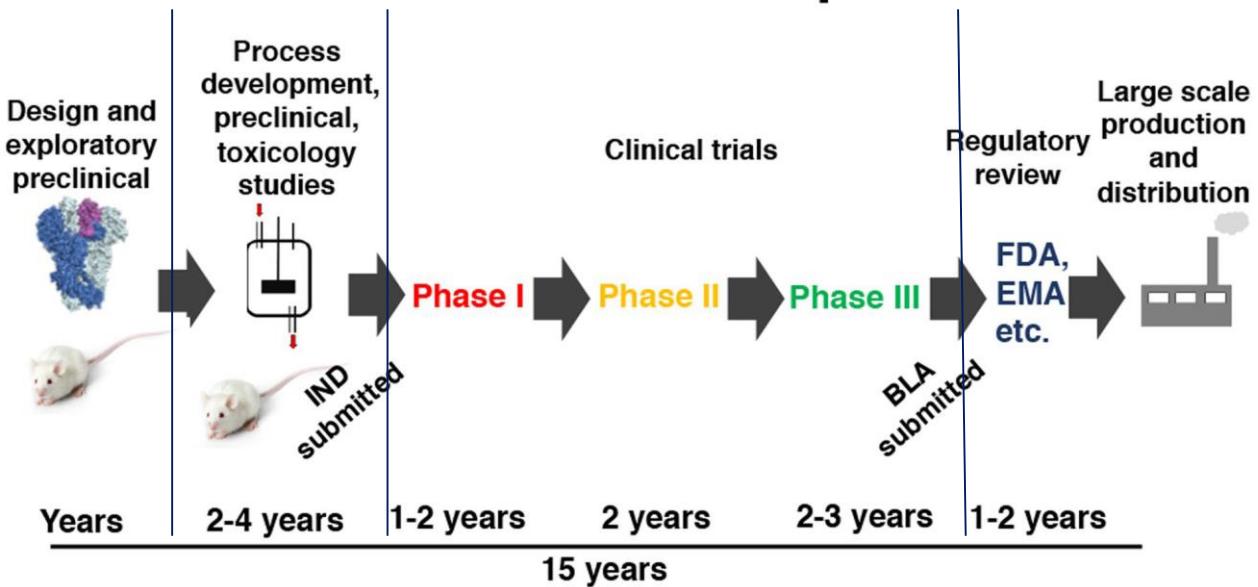
40 min-VC

Intro

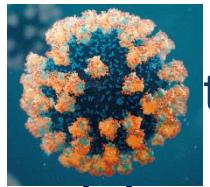
Compared to other novel vaccine products,
the time used for COVID vaccine development marked a new record

10-15 years usually taken for the development of a new vaccine product
- each individual vaccine product needs its own (long) development time -

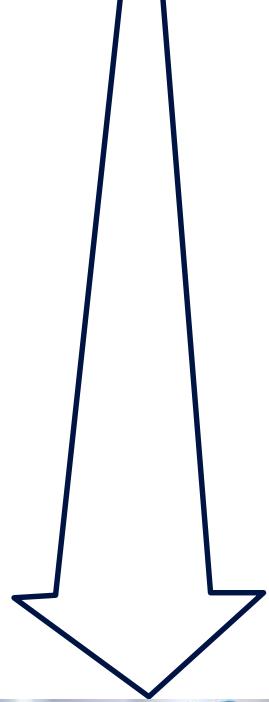
Traditional development



- Exploratory basic research needed to identify potentially protective antigen and suitable initial vaccine construct
- First-in-man clinical trials of phase 1 is carried out with a small number of healthy adult subjects
- Phase 3 clinical trials of vaccines benefit from being carried out in an epidemic/pandemic (challenge)
- Phase 3 clinical trials with 10,000 to 30,000 verum vaccinated subjects allow detection of rare adverse reactions (1 in 1,000)
- reg. review time for NCAs is only 6 months (180 days)



12 months from first isolation of SARS-CoV-2 to licensed COVID-19 vaccine products and batch release



- **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 in Germany
- **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 EC
- **24 Dec 2020** Batch release certificate (EU) of BioNTech/Pfizer vaccine product by PEI
- **06 Jan 2021** Conditional marketing authorization Moderna vaccine product by EC

How did we achieve this?

Key factors
of ultra-rapid pandemic vaccine development



Identification of the potentially protective antigen is key; MeV platform-based lab research at PEI allows better regulations



Nürnberger et al., J Virol 2019

Bodmer et al., Virol 2018

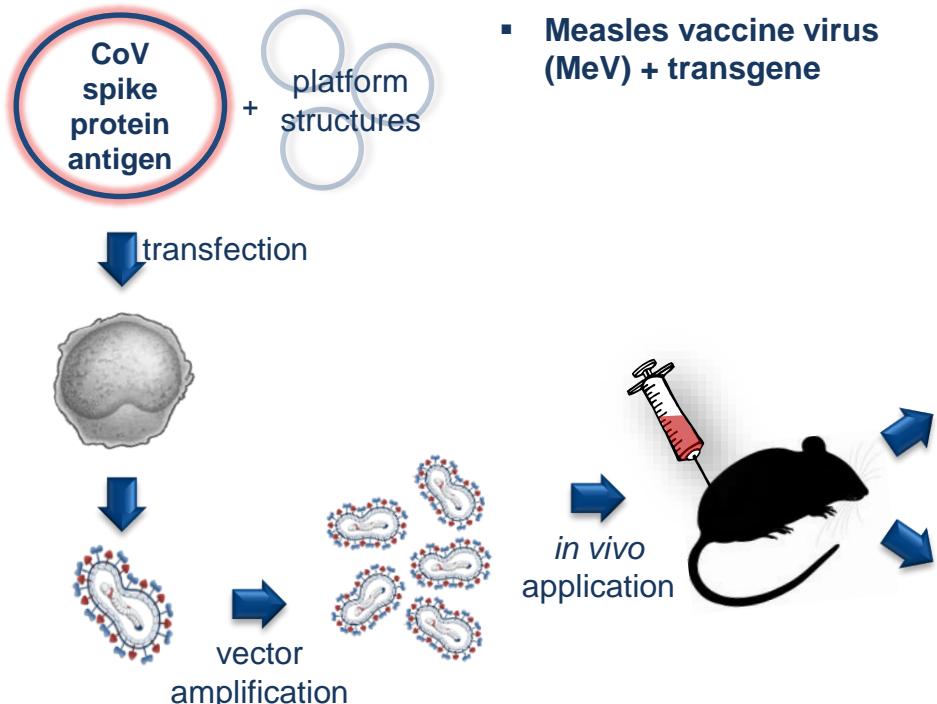
Gogesch et al., Mol Immunol 2018

Hutzler et al., Sci Rep 2017

Malczyk et al., J Virol 2015

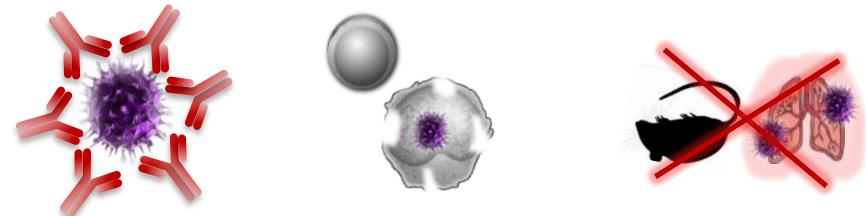
Uhlig et al., J Virol 2015

vector vaccine generation



protection in a suitable animal model

Ab responses T cell responses protection after challenge



safety



Protection from lower resp. tract infection demonstrated in NHPs with several vaccine types,
but with the identical antigen (CoV spike protein)

Company (reference)	Vaccine(type)	Dose range (route)	Neut titer after prime	Neut titer after boost	Neut titer after 2 nd boost	T-cell response	Challenge dose (route)	URT protection	LRT protection	Species
Sinovac ³⁴	PiCoVacc (Inactivated virion + aluminum hydroxide)	3-6ug (i.m.)	None ^a	1:10 range ^a	1:50 range ^a	Not assessed	10 ⁶ TCID ₅₀ (i.t.)	Partial ^c	High dose: yes; low dose: incomplete ^c	Rhesus macaques
Beijing Institute of Biological Products Ltd ³³ .	BBIBP-CorV (Inactivated virion + aluminum hydroxide)	4-8 ug (i.m.)	1:100 range ^a	1:200 range ^a	-	Not assessed	10 ⁶ TCID ₅₀ (i.t.)	Partial ^c	Complete ^c	Cynomolgus macaques
AstraZeneca ⁴⁹	ChAdOx1nCOV-19 (non-rep AdV)	2.4x10 ¹⁰ VP 1x or 2x (i.m.)	1:5-40 range ^a	1:10-160 range ^a	-	Yes	2.6x10 ⁶ TCID ₅₀ (i.t., oral, i.n., ocular)	None (1x) ^d None (2x) ^d	Partial (1x) ^d Complete (2x) ^d	Rhesus macaques
Janssen ⁴¹	Ad26COVS1 (non-rep AdV)	1x 10 ¹¹ VP (i.m.)	1:100 range ^b	-	-	Low	10 ⁵ TCID ₅₀ (i.n, i.t.)	Complete in S.P.P group ^d	Complete in S.P.P group ^d	Rhesus macaques
Moderna ⁵⁷	mRNA-1273 (mRNA via LNPs)	2x 10-100 ug (i.m.)	Not assessed using authentic SARS-CoV-2	1:501 - 1:3481 range ^b	-	Yes, CD4, T _{FH}	7.5x10 ⁵ TCID ₅₀ (i.n., i.t.)	None (10ug) ^d Partial (100ug) ^d	Partial (10ug) ^d Complete (10ug) ^d	Rhesus macaques
Novavax ⁶³	NVX CoV2373 (S protein + Matrix M)	2x 2.5ug-25ug	-	17,920 - 23,040 range ^a	-	Not reported	10 ⁴ (i.n., i.t.) ^e	Partial (low dose) ^d Complete (two higher doses) ^d	Complete ^d	Cynomolgus macaques

^abased on microneutralization assay with CRF as readout



C

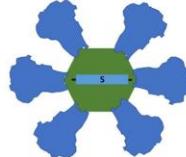
Inactivated vaccines are made of SARS-CoV-2 that is grown in cell culture and then chemically inactivated



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

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

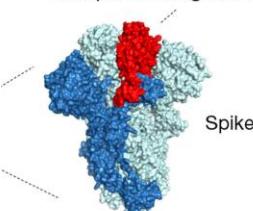


live attenuated virus vaccines

COVID-19

spike protein

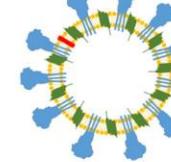
Receptor binding domain (RBD)



pre-fusion stabilized conformation

G

Virus-like particles (VLPs) carry genome but display the spike on surface



VLPs

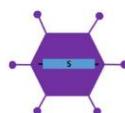
vaccine platforms

protective antigen identification

antigen design

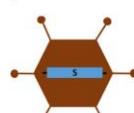
H

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



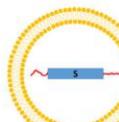
K

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

8



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



genetic vaccines

Guidelines on vector and mRNA vaccine development



World Health Organization

WHO Expert Committee on Biological Standardisation (ECBS)

Annex 2 WHO Technical Report Series, No. 1043, 2022

WHO manual for the preparation of reference materials for use as secondary standards in antibody testing

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

Annex 4 WHO Technical Report Series, No. 1043, 2022

Guidelines for the production and quality control of monoclonal antibodies and related products intended for medicinal use

Replacement of Annex 3 of WHO Technical Report Series, No. 822

Annex 3 WHO Technical Report Series, No. 1039, 2022

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

Prioritisation of pre-clinical studies with each vaccine candidate

- International Coalition of Medicines Regulatory Authorities -

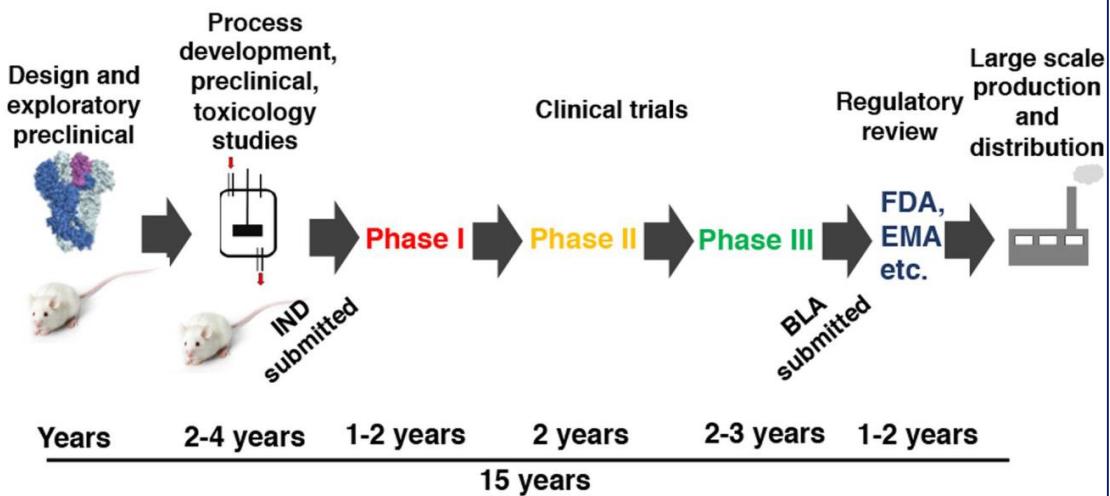


Study type	Guideline recommendations
Primary pharmacodynamics	Immunogenicity,
Safety pharmacology	CNS, CV, respiratory, temp. measures incorporated in tox. study.
Biodistribution	For live attenuated, DNA vaccines, new adjuvant, excipient, device.
Toxicity	Repeat-dose toxicity study, modelled on clinical 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



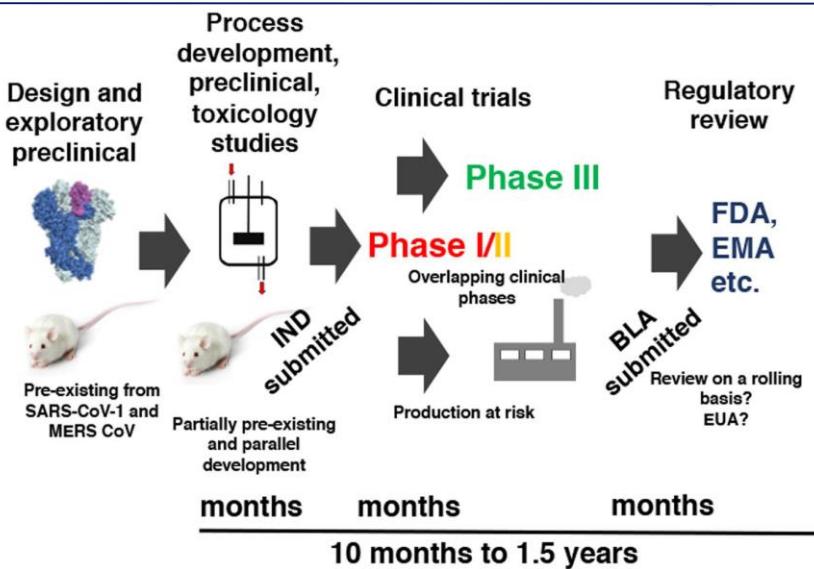
- Some non-clinical studies are mandatory before first-in-human studies of preventive vaccines.
- Some non-clinical studies may be carried out in parallel to clinical trials depending on the nature and target application of the vaccine and possible reference to platform experiences.

established/ traditional



- identification of the potentially protective antigen
- suitable vaccine platform
- ad hoc access to scientific advice and rapid 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

accelerated



Initial COVID vaccine efficacy

High COVID-19 vaccine efficacy (against COVID) in pre-licensing clinical trials, CHMP margins set in advance have been exceeded

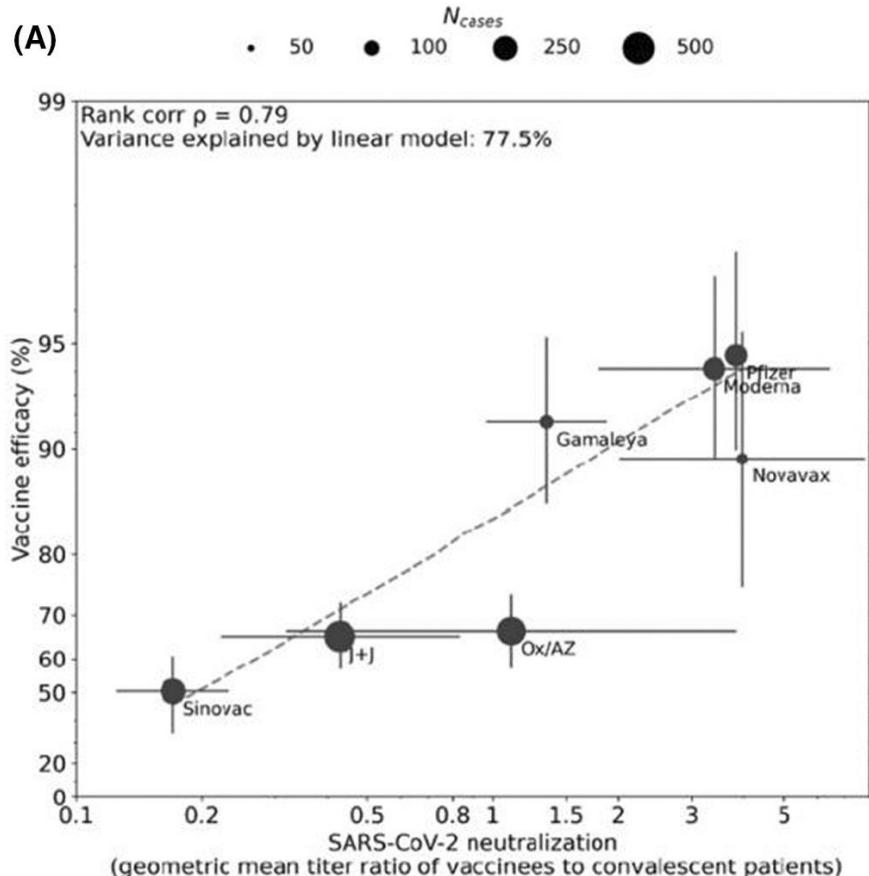
Table 1. Vaccine efficacy results from phase III trials

Vaccine manufacturer (name)	Vaccine type	Regime used	Number of trial participants	Efficacy	Eligibility	Endpoints	Data by disease severity
Pfizer-BioNTech (BNT162b2) [70]	mRNA	2 doses (21 days interval)	43,548	95%	>16 years (years) old	Symptomatic and RT-PCR positive	100% and 95.3% effective against CDC and FDA defined severe disease
Moderna (mRNA-1273) [71]	mRNA	2 doses (28 days interval)	30,420	94%	≥18 years old, if: 12–18 years enrolled to NCT04649151 6 months to 12 years, then NCT04796896	Symptomatic and RT-PCR positive	100% against severe disease
AstraZeneca-University of Oxford (AZD1222) [72]	Viral vector	2 doses, 6-week interval 2 doses, 12-week interval	17,178	55% for 6-week 81%, 12 weeks Pooled: 67%	≥18 years old Not pregnant	Symptomatic and RT-PCR positive	100% against severe disease
Johnson & Johnson (Ad26. COV2-S) [73]	Viral vector	1 dose	44,325	66%	≥18 years old	Symptomatic and RT-PCR positive	85.4%
Novavax (Novavaxovid)	Rec. Protein	2 doses (28 days interval)	30,000	94%	> 18 years old	Symptomatic and RT-PCR positive	90% ag. COVID-19 (alpha) 60% ag. severe disease
Valneva	Whole virus inactivated	2 doses (28 days interval)	30,000	immuno-bridging	18 - 50 years old	Symptomatic and RT-PCR positive	ag. severe disease (Ab titer > AZD1222)

Higher efficacy of COVID-19 vaccines

correlates with induction of higher serum titers of CoV-2 neutralising antibodies

(A)



- Good predictability of efficacy based on initial vaccine-induced neutralizing antibody titres.
- Exact titer predicting individual vaccinated or recovered person's COVID protection remains unknown.

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,

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

Definition of non-interventional studies of licensed vaccine products clarified by official deliberation of Ministry and NCA

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:

- a. Bei einer Studie mit einem Impfstoff der zur Vorbeugung einer bestehenden oder drohenden bedrohlichen übertragbaren Krankheit zugelassen ist, und
- b. 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.

Conclusion

- Initial efficacy of licensed vaccines against COVID-19 -



- Margins set by CHMP defined the necessary outcome of phase 2/3 and phase 3 vaccine clinical trials for marketing authorisation in the EU.
- Efficacy of mRNA COVID-19 vaccine products in phase 3 trials very high
 - protection against symptomatic CoV-2 infection (COVID-19) and
 - protection against any infection
 - in clinical trials including 30,000 study participants
- Immunobridging of immunogenicity (neutralising antibody titers) between candidate and any licensed COVID vaccine product
 - instead of demonstration of efficacy
 - enabled rapid licensing of additional COVID-19 vaccine products.



Manufacture of mRNA vaccines is a rather simple
biotechnological process,

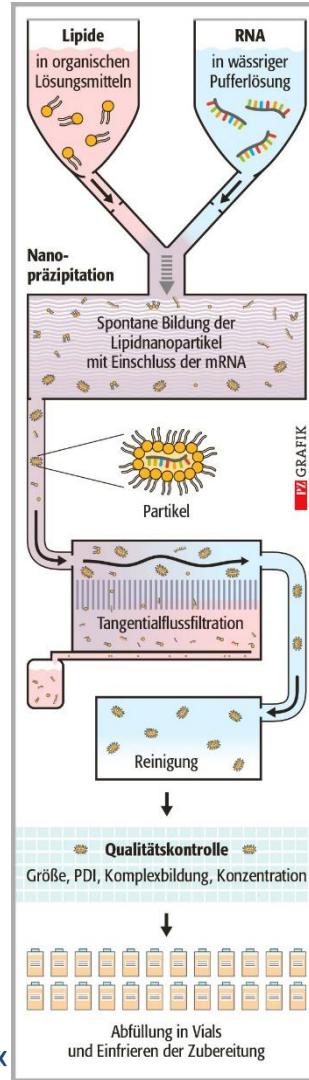
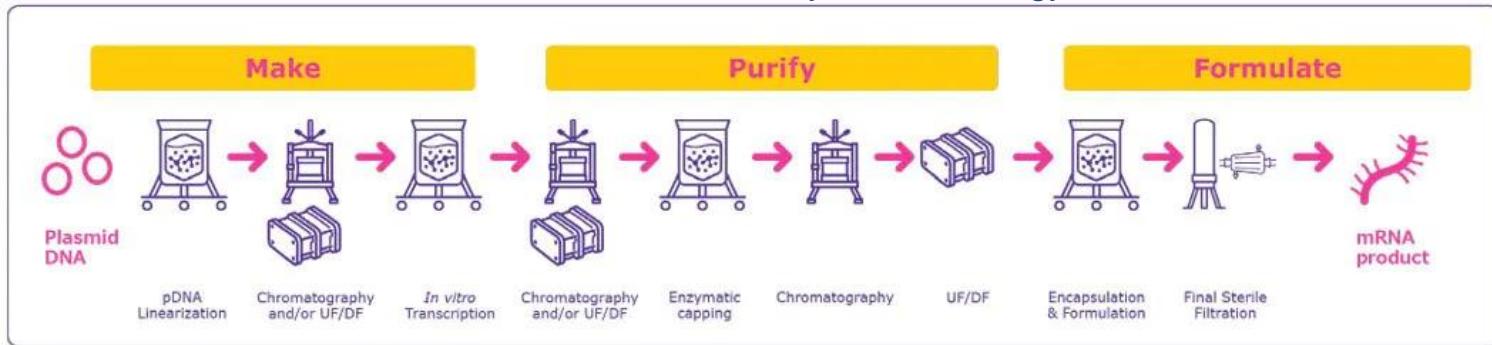
but vaccine construction/ mRNA design

as well as experimental batch control

are not simple

COVID19 vaccine mRNA structure, manufacture and lipid nanoparticle encapsidation

mRNA manufacture by biotechnology



mRNA structure



Moderna formulation:

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

Experimental COVID-19 mRNA vaccine batch testing by OMCL-PEI

Identity -> RT-PCR shows
presence of RNA and
identifies sequence.

Integrity -> Elektrophoresis and chromatography shows
mRNA length and level of degradation.

Potency -> Potency assay shows
concentration and amount of mRNA per dose,
level of mRNA encapsulated in nanoparticles.



WHO International Standard First WHO by NIBSC/UK International Standard for SARS-CoV-2 RNA NIBSC code: 20/146 Instructions for use (Version 3.0, Dated 11/02/2021)

World Health Organization
WHO Expert Committee on Biological Standardisation (ECBS)

WHO international reference materials established by the ECBS in October 2022

Standards for use in public health emergencies		
Anti-SARS-CoV-2 immunoglobulin	356 IU/ampoule	Second WHO International Standard
Antibodies to SARS-CoV-2 variants of concern	4250 IU/ampoule	First WHO International Standard
Antibodies to SARS-CoV-2 variants of concern	No unitage	First WHO International Reference Panel
SARS-CoV-2 antigen	5000 IU/ampoule	First WHO International Standard

Conclusion

- mRNA vaccine manufacture and batch testing/release -



- Having **competent, experienced OMCLs** with existing hands-on know-how in vaccine testing allowed rapid establishment of experimental assays for governmental batch control.
- **PEI has assessment and batch release as well as research under one roof**, which was extremely helpful for the rapid establishment of experimental batch testing.
- **Parallel testing** is employed widely in normal conditions but was critical to the rapid release of the COVID-19 vaccines.
- The central role of **EDQM in coordination of the network** activity allowed good points of contact for interaction with manufacturers and external partners (EMA) and between OMCLs.



COVID vaccine safety

spontaneous reports of suspected adverse reactions

vs.

recognized adverse reactions
of particular vaccine products or types

Vorübergehende erwartete Nebenwirkungen, mild bis moderat

(Klinik; Reaktogenität)



Die häufigsten Nebenwirkungen

alle vorübergehend (1-3 Tage), leicht erhöht in Altersgruppe bis 60 Jahre (Moderna) und nach 2. Dosis

Moderna

- Schmerzen an der Injektionsstelle (92%)
- Müdigkeit (70%)
- Kopfschmerzen (64,7%)
- Myalgie (Muskelschmerzen) (61,5%)
- Arthralgie (Gelenkschmerzen) (64,4%)
- Frösteln (54,4%)
- Übelkeit/Erbrechen (23%)
- Axilläre Schwellung/Empfindlichkeit (19,8%)
- Fieber (15,5%)
- Schwellungen / Rötungen an der Injektionsstelle (14,7% / 10%)

Biontech/Pfizer

- Schmerzen an der Injektionsstelle (>80%)
- Müdigkeit (>60%)
- Kopfschmerzen (>50%)
- Myalgie (Muskelschmerzen) und Schüttelfrost (> 30%)
- Arthralgie (Gelenkschmerzen) (>20%)
- Frösteln (54,4%)

- Fieber und Schwellungen an der Injektionsstelle (>10%)

Sicherheit:

sehr seltenes Auftreten von peripheren Fazialisparesen,
die sich bis auf einen Fall spontan zurückgebildet haben
(klinische Prüfungen; Häufigkeit <1:10.000)



Moderna (3 verum/ 1 placebo)

**Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the COVID-19 Vaccine Moderna group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2.

Biontech/Pfizer (4 verum/ 0 placebo)

†Während des bisherigen Verträglichkeitsnachbeobachtungszeitraums wurde von vier Teilnehmern in der COVID-19-mRNA-Impfstoffgruppe eine akute periphere Fazialisparese (oder Gesichtslähmung) berichtet. Der Beginn war am Tag 37 nach Dosis 1 (der Teilnehmer erhielt keine Dosis 2) und an den Tagen 3, 9 und 48 nach Dosis 2. In der Placebogruppe wurden keine Fälle von akuter peripherer Fazialisparese (oder Gesichtslähmung) berichtet.

Very rare serious adverse reactions caused by COVID-19 vaccines

< 10 reports per 100.000 doses, some age-dependent

- Ca. 1 billion single Covid vaccine doses until 30 March 2022 in EU/EEA
- <10 spontaneous reports of suspected serious adverse reactions per 100.000 vaccine product doses
- **Most adverse reactions in Summary of Product Characteristics (SmPCs) classified as „very rare“**
- ***Myocarditis/Perikarditis* after COVID-19 mRNA vaccines**
 - Increased risk in younger men <30 Jahre post second dose
 - Mostly benign outcomes (Peri-/Myocarditis patients) Risiko sehr selten, aber etwas höher bei Spikevax im Vergleich zu Comirnaty
- ***Anaphylaxis*** during or directly after administration of mRNA and adenovector COVID vaccines
 - <1 case per 100.000 doses
 - Probably not IgE-mediated, but via complement (CARPA; complement activation-related pseudoallergy)
- ***TTS* post adenovector vaccines**, consistent: single cases of death
- ***GBS* post adenovector vaccines** : 0.88 and 1.89 per 100.000 doses (Vaxzevria, Janssen, respectively)
- ***ITP (immune thrombocytopenia)***, single case reports post Janssen/Vaxzevria vaccination
- ***Thrombosis***: inconsistent study results – higher risk due to COVID-19

Vorsorgemaßnahmen bei anaphylaktoiden Reaktionen

(Moderna- und Biontech/Pfizer-Covid-Impfstoffprodukt)



Es besteht nach derzeitigem Kenntnisstand keine Kontraindikation für Allergikerinnen und Allergiker oder Menschen mit Anaphylaxien in der Vorgeschichte.

- **Fälle von Anaphylaxie wurden beobachtet**
 - **angemessene medizinische Versorgung sollte zur Verfügung stehen**
 - **eine engmaschige Beobachtung von mindestens 15 Minuten wird empfohlen**
 - **eine zweite Dosis sollte nicht an Personen verabreicht werden, bei denen eine Anaphylaxie nach der ersten Dosis aufgetreten ist**
- Impfungen sollten verschoben werden
 - bei Personen mit akuter, schwerer, fieberhafter Erkrankung oder
 - akuter Infektion.
 - Geringfügige Infektion und/oder leichtes Fieber sollten die Impfung nicht verzögern.
- **Gegenanzeigen:**
Überempfindlichkeitsreaktionen gegen den Wirkstoff oder einen der sonstigen Bestandteile.
- **www.pei.de -> Coronavirus und Covid-19 -> Coronaimpfung bei Allergikerinnen und Allergikern**

Mechanism underlying TTS (thrombosis with thrombocytopenia syndrome) associated with COVID-19 adenovector vaccines



- Within the first months of the Covid-19 vaccination campaign (e.g. by DE-PEI), previously healthy recipients were identified who
 - developed severe thrombosis (often cerebral and/or splanchnic vasculature) and
 - thrombocytopenia typically after adenovector-based vaccination.
- Similarities between this syndrome, vaccine-induced thrombocytopenia and thrombosis (VITT), and heparin-induced thrombocytopenia, prompted recognition of the
 - role of anti-platelet factor 4 (PF4) antibodies and
 - management strategies based on intravenous immunoglobulin and non-heparin anticoagulants, which improved outcome.
- The UK Haematology Expert Group developed consensus diagnostic criteria for VITT.

Mechanism underlying TTS (thrombosis with thrombocytopenia syndrome) associated with COVID-19 adenovector vaccines



THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Grainger, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D.,
Karin Waissar, Ph.D., Paul A. Kyrie, 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 clumping 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) plasmin-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 plasmin-activation assay in the presence of PF4 independent of heparin. Plasmin activation was inhibited by high levels of heparin, Fc receptor-blocking monoclonal antibody, and immune globulin (10 mg per milliliter). Additional studies with PF4 and PF4-heparin affinity-purified antibodies in 2 patients confirmed PF4-dependent platelet activation.

CONCLUSIONS

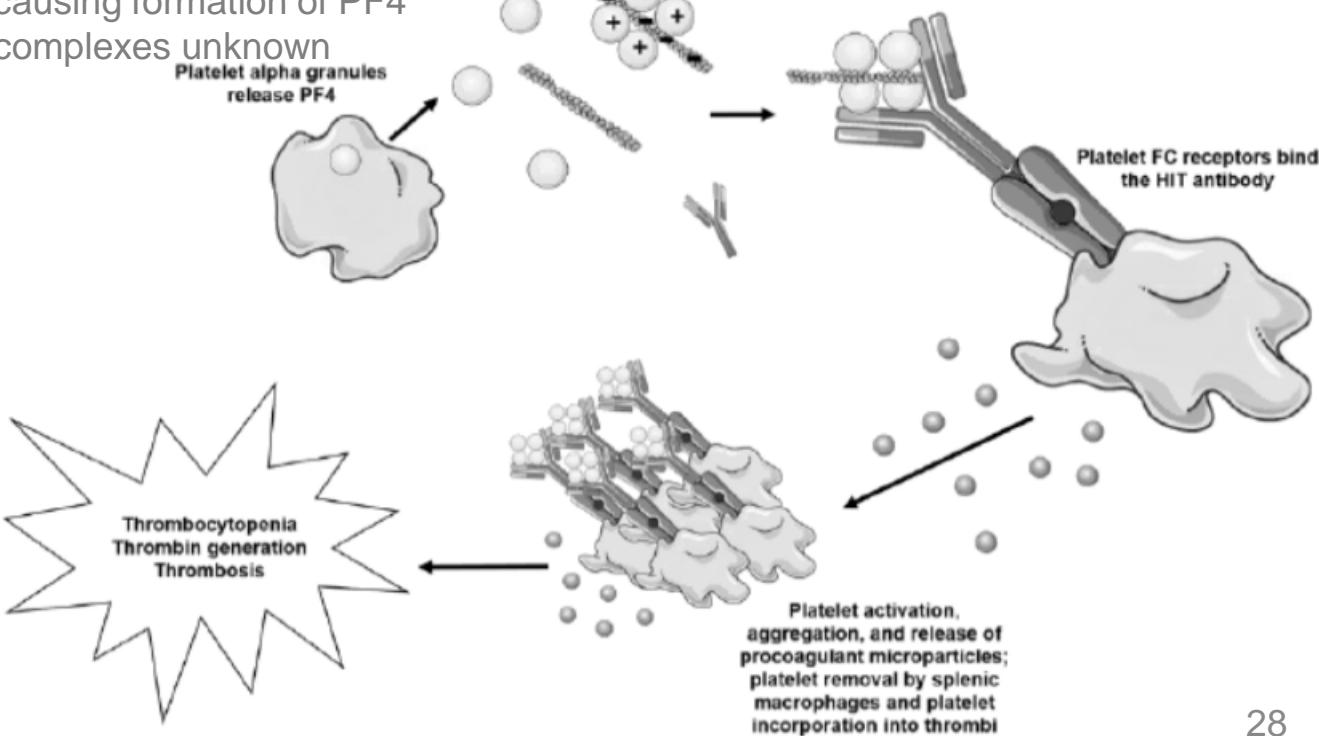
Vaccination with ChAdOx1 nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia. (Funded by the German Research Foundation.)

Substance in adenovector vaccines causing formation of PF4 complexes unknown

PF4 and heparin bind in stoichiometric ratios, forming a complex bound by IgG

Platelet alpha granules release PF4

28

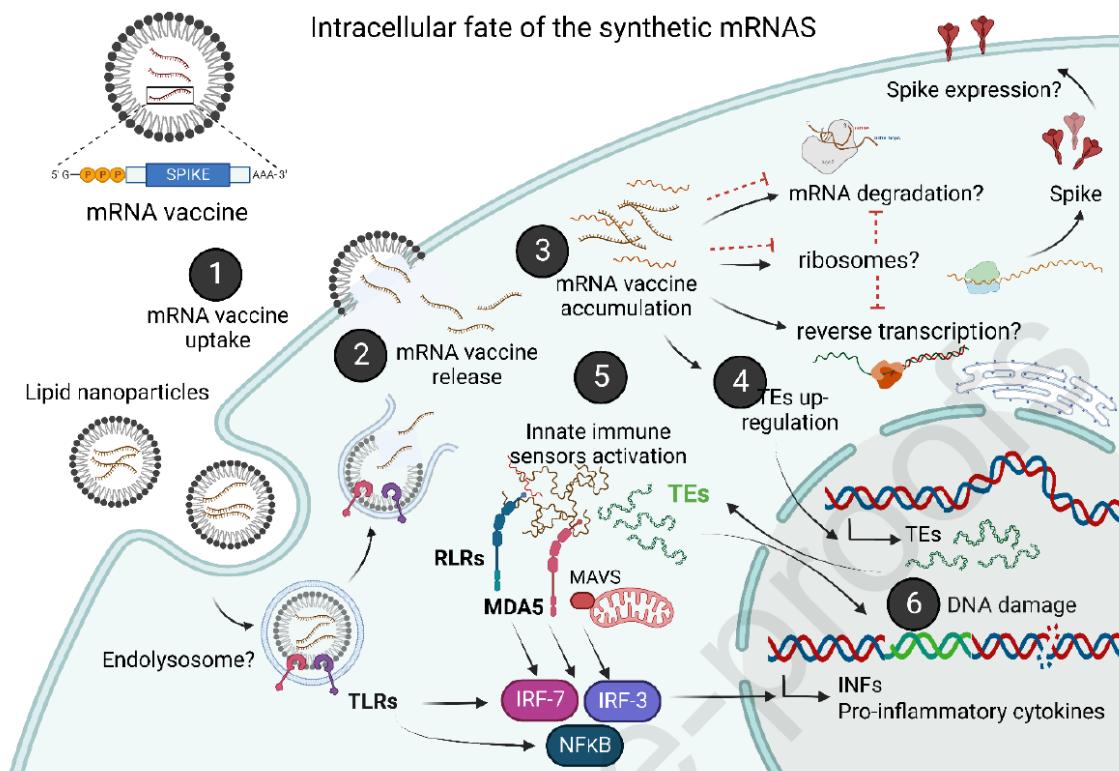




NiTAGs' COVID vaccination recommendations reduced TTS and myocarditis risks - STIKO in Germany -

Name (Hersteller)	Impfstofftyp	Altersgruppe	Dosierung für GI	GI	Empfohlen zur AI ³	Dosierung für AI	Besonderheiten
Vaxzevria (AstraZeneca)	vektorbasiert	≥ 60 Jahre; seit 01.12.2021 in Deutschland nicht mehr verfügbar	≥ 2,5 × 10 ⁸ IE	2 Impfstoffdosen	nein	–	Aufgrund seltener thromboembolischer Ereignisse Altersbeschränkung auf ≥ 60 Jahre
JCOVDEN, vormals COVID-19 Vaccine Janssen (Janssen Cilag International)	vektorbasiert	≥ 60 Jahre	≥ 8,92 log ₁₀ IE	zugelassen als Einzeldosis; Optimierung mit einer mRNA- oder Nuvaxovid-Impfstoffdosis empfohlen	nein	–	Aufgrund ungenügender Effektivität Optimierung der GI empfohlen; aufgrund seltener thromboembolischer Ereignisse Altersbeschränkung auf ≥ 60 Jahre
Spikevax bivalent Original/Omicron BA.1 (Moderna)	bivalent mRNA	Zugelassen für die Altersgruppe 6–11 Jahre	–	nein	ja, bei Kindern mit Vorerkrankungen und Immundefizienz	25 µg	präferenziell wird in dieser Altersgruppe Comirnaty empfohlen

No evidence for theoretical risk of insertional mutagenesis



Transposable elements in human somatic cells activated by synthetic mRNA

- may theoretically increase the risk of insertional mutagenesis of the retrotranscribed vaccine mRNA,
- although the necessary vRNA elements are missing.

Insertion of mRNA-derived DNA in chromosomal DNA of human somatic cells has not been detected (in vitro experiments)

expression of proinflammatory cytokines and type-I IFN (5). TE activity can lead to DNA damage via insertional mutagenesis and genomic instability, and enhancing the expression of pro-inflammatory cytokines and type-I IFN (6). Inflammasome activation may also have a regulatory role in preventing cGAS-STING mediated type-I IFN production, thus establishing a chronic regulatory circuit wherein

Transparency promotes vaccine confidence



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)
1 covid-19-vaccines-safety-update-12-may-2022.pdf (europa.eu)

- 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

EDITORIAL Ausgabe 1 | März 2022

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Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

Das BfArM überprüft die Wissenschaft, Sicherheit und Qualität von Arzneimitteln. Auch nach der Zulassung werden das BfArM neue Hinweise auf Gesundheitsschäden oder -verbesserungen sowie neue Maßnahmen zur Risikominimierung. Neben der kontinuierlichen Verbesserung der Arzneimittelsicherheit ist die Förderung der Pharmakovigilanz und Forschung und die Gestaltung wünschter Prüfungen, die Risikobewertung von Medikamenten und die Anwendung von Arzneimitteln ein weiterer Aufgaben des BfArM.

Paul-Ehrlich-Institut (PEI)

Das Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel überprüft die Qualität, Wirksamkeit und Unbedenklichkeit von Human- und Veterinärarzneimitteln sowie Diagnose- und Gewebeuntersuchungen, Antikörpern, Seren, Zell-/Gentherapeuten und Tissue Engineering-Produkten. Bei Verdacht auf eine unerwünschte Wirkung gehen die Gedenktagung, Untersuchung, Zulassung, gezielte Chargenprüfung und Sicherheitsbewertung von Arzneimitteln und deren Hersteller in-vitro-Diagnostica.

AUFLÄRUNGSMERKBLATT

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/DE/Content/Infekt/Impfen/Materialien/COVID-19-VektorimpfstoffTab.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



Janssen
PHARMACEUTICAL COMPANIES OF
Johnson & Johnson

19. Juli 2021

WICHTIGE ARZNEIMITTELINFORMATION

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



Dealing with real risks
(adverse reactions)

and

presumed risks
(often publicly discussed by vaccine critiques)

and

public perception

Spontanmeldesystem von Verdachtsfällen soll Risikosignale schnell entdecken

- Im Paul-Ehrlich-Institut werden VERDACHTSFÄLLE von Nebenwirkungen und von Impfkomplikationen erfasst. Verdachtsfälle sind keine Nebenwirkungen.
- Die meisten gemeldeten Verdachtsfälle von Nebenwirkungen beziehen sich auf die typischen Impfreaktionen, die innerhalb der ersten 7 Tage nach Impfung erwartungsgemäß auftreten und abklingen, ohne Schäden zu hinterlassen.
- Verdachtsfälle: körperliche Reaktionen im Zeitraum nach Impfung, bei denen ein kausaler Zusammenhang mit der erfolgten Impfung vermutet wird.
- Verdachtsfallmeldungen lassen keine direkten Rückschlüsse
 - auf die Kausalität zur Impfung zu oder
 - auf die Häufigkeit der unerwünschten Reaktionen zu.
- Es ist im Sinne der raschen Detektion von möglichen Risikosignalen jedoch ausdrücklich erwünscht, dass auch solche Reaktionen berichtet werden, deren Zusammenhang mit der Impfung fraglich ist.

Prüfung von Verdachtsfallmeldungen



- Ist das Ereignis durch eine bereits erkannte Nebenwirkung des Impfstoffs erklärbar?
- Gibt es Vorerkrankungen oder andere Umstände, welche das Ereignis erklären?
- Ist ein Zusammenhang mit der Impfung bzw. dem Impfstoff plausibel?
 - Ist der Zeitraum von Impfung bis Ereignis übereinstimmend mit bekannten Zeiträumen für das Auftreten des Ereignisses?
 - Ist ein Mechanismus, der die Reaktion auslösen könnte, bekannt oder auf Basis der wiss. Literatur erklärbar?
 - Liegen Verdachtsfallmeldungen zu diesem oder vergleichbaren Impfstoffen oder Impfstoffprodukten vor?
- Liegt eine statistische signifikante Häufung der Reaktion nach Impfung mit dem gleichen Impfstofftyp oder Impfstoffprodukt vor im Vergleich zum Vorkommen der Reaktion bei Ungeimpften (historische Vergleichsgruppe) -> Observed-vs-Expected-Analyse?
- Besteht ein Zusammenhang vergleichbarer Reaktionen mit einer bestimmten Charge eines Impfstoffprodukts?



- Rote-Hand-Briefe,
- Hinweise an Geimpfte, auf bestimmte Symptome zu achten und bei Auftreten sofort medizinische Behandlung zu suchen,
- Behandlungshinweise für Ärzte und Ärztinnen durch die Fachgesellschaften,
- Verhaltenshinweise in den Impfaufklärungen
- PEI-Hinwirken auf die Empfehlungen zur Impfung mit bestimmten COVID-19-Impfstoffprodukten in bestimmten Altersgruppen mit verringertem Risiko in den COVID-19-Impfempfehlungen der Ständigen Impfkommission (STIKO)
- Chargenrückruf
- Ruhen oder Widerruf der Zulassung/Genehmigung



- Die als Nebenwirkungen erkannten Reaktionen sind mit ihrer Häufigkeit den jeweiligen Fach- bzw. Produktinformationen zu entnehmen:
www.pei.de/DE/Arzneimittel/Impfstoffe/Covid-19/covid-19-node.html
- Impfschaden nach § 2 Nr. 11 Infektionsschutzgesetz (IfSG)
 - die gesundheitliche und wirtschaftliche Folge einer über das übliche Ausmaß einer Impfreaktion hinausgehenden gesundheitlichen Schädigung durch die Schutzimpfung verstanden.
 - Verfahren zur Anerkennung von Impfschäden nach §§ 60, 61 IfSG werden ausschließlich von den zuständigen Behörden der Bundesländer bearbeitet (z.B. Versorgungsämter).
 - Bei Verdacht auf einen Impfschaden
 - zuständigen Behörde ihres Bundeslandes kontaktieren
 - Für den Antrag auf Anerkennung eines Impfschadens ist das Melden eines Verdachtsfalls an das Paul-Ehrlich-Institut nicht erforderlich.

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

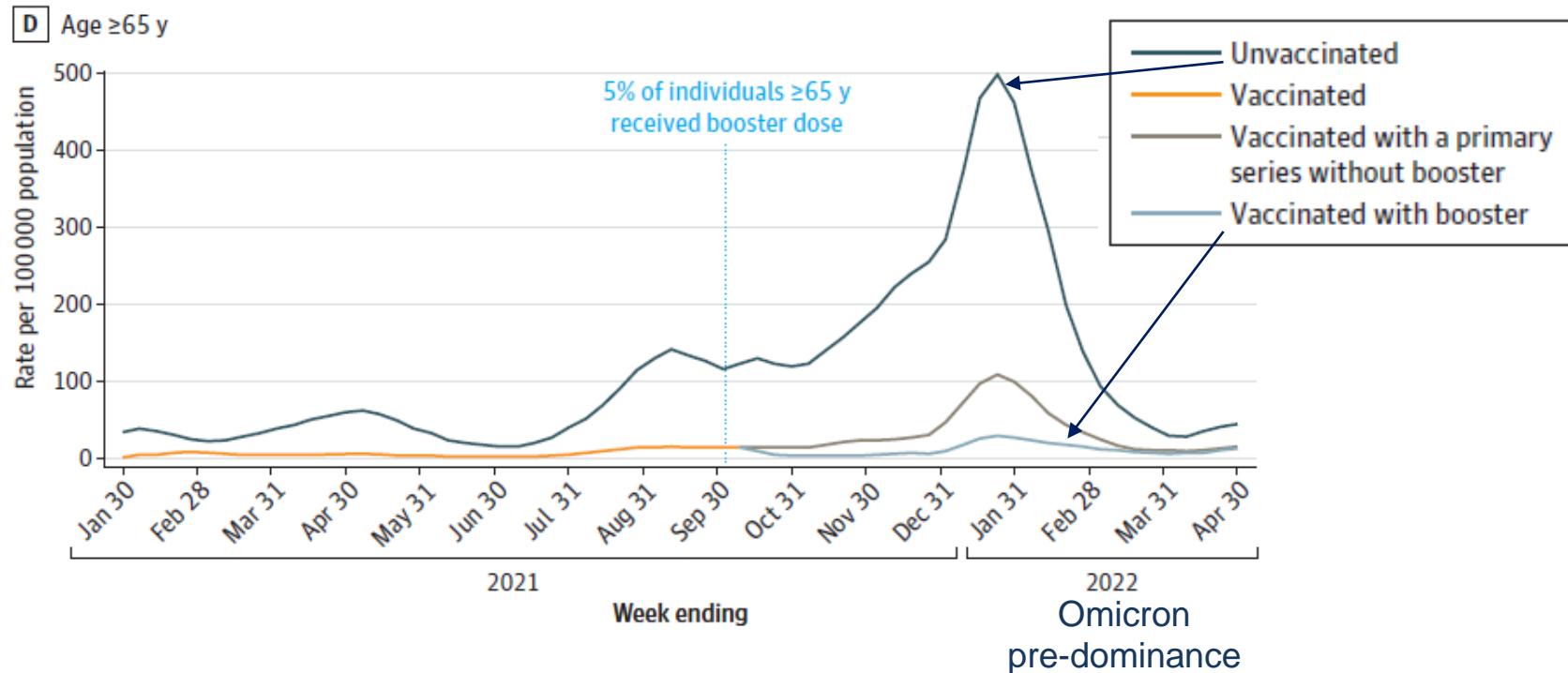


Figure 2. Three-Week Moving Average Population-Based Rates^a of COVID-19-Associated Hospitalizations Among Unvaccinated and Vaccinated (With and Without a Booster Dose)^b Adults 18 Years or Older Admitted January 30, 2021^c to April 30, 2022, by Week of Admission, COVID-19-Associated Hospitalization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

Conclusion

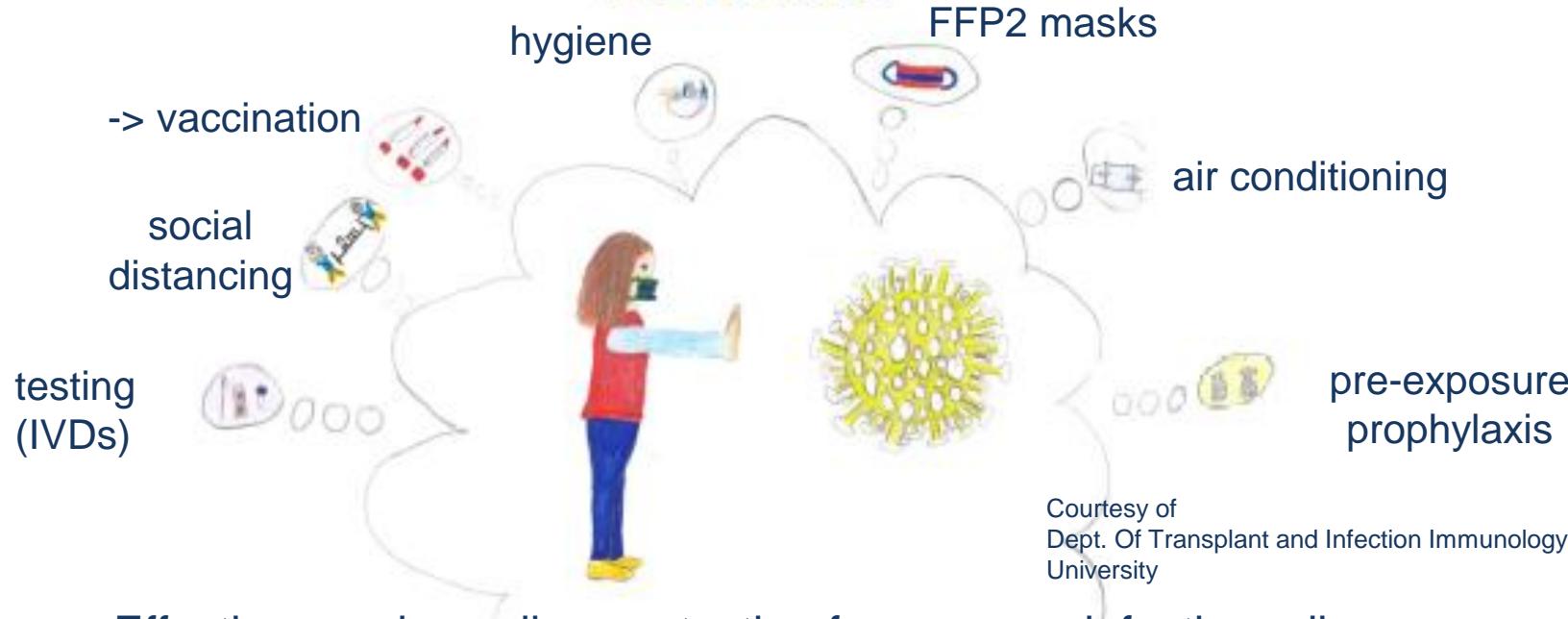
- Pharmacovigilance of licensed COVID-19 vaccine products



- Reactogenicity of the mRNA- and vector-based COVID-19 vaccine products is increased compared to current seasonal influenza vaccines.
- Serious adverse reactions of COVID-19 vaccines are very rare (<10 in 100.000 doses) and were not foreseeable.
- Rapid detection of severe adverse reactions and full transparency about reports of suspected adverse reactions and vaccination complications and their expert assessment by NCA and PRAC/EMA spur vaccine confidence.
- Rapidly initiated measures to reduce health risks due to adverse reactions were taken at the level of PRAC/EMA and nationally by NCAS in collaboration with NiTAGs
- Continuous discussions of presumed risks, especially in the social media, is correlated with vaccine hesitancy (data not shown).

Main Conclusions (1)

Prevention of virus spreading and outbreak control



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

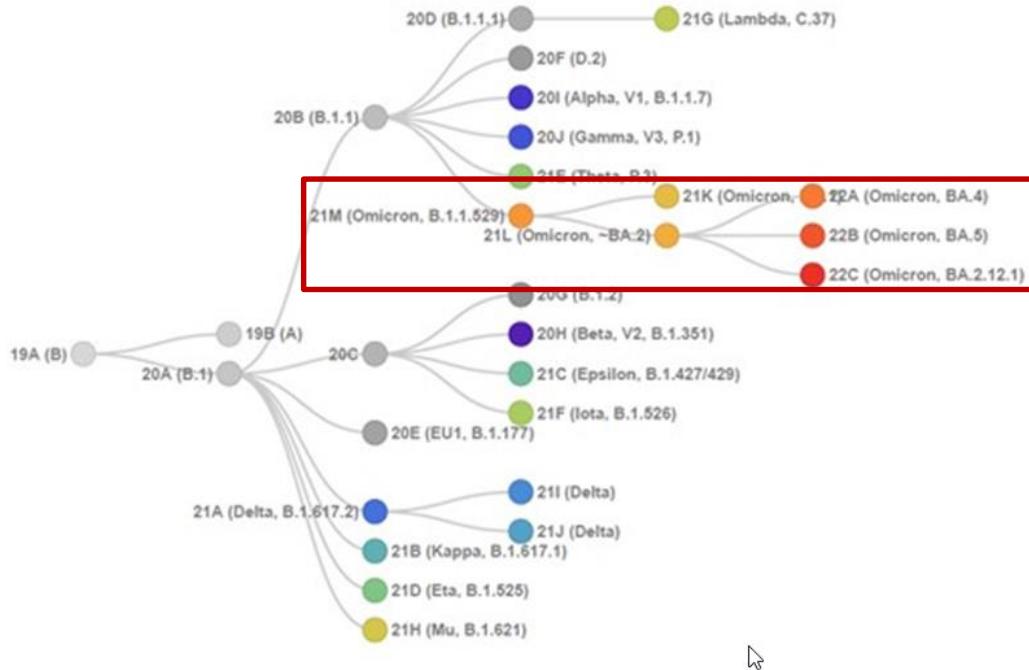
- > Effective vaccines allow protection from severe infectious disease courses, particularly if rapidly adapted to new escape variants.
- > Neutralising monoclonal antibodies allow a specific therapy.
- > Small molecule antivirals help to reduce the burden of hospitalisations, and would be needed early in a pandemic.



Initial COVID vaccine efficacy

wanes with time in absence of new variants and
is further undermined by new escape variants of CoV-2

BA.4/5 has started the continuous evolution of sublineages
and may be a prototype sublineage for fall 2023-sublineages to come



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



Vaccine	Platform	Strain	Use	Population
Comirnaty (BioNTech)	mRNA	Original strain	Primary vaccination	✓ 6 months to 4 years ✓ 5-11 years ✓ ≥12 years ✓ ≥18 years
			Booster	✓ 5-11 years ✓ ✓ ✓
		Original strain + Omicron BA.1 variant (adapted)	Booster	✓ ✓
		Original strain + Omicron BA.4-5 variants (adapted)	Booster	✓ ✓ ✓
Spikevax (Moderna)	mRNA	Original strain	Primary vaccination	✓ 6 months to 3 years ✓ 6-11 years ✓ ✓ ✓
			Booster	✓ 6-11 years ✓ ✓ ✓
		Original strain + Omicron BA.1 variant (adapted)	Booster	✓ ✓ ✓
		Original strain + Omicron BA.4-5 variants (adapted)	Booster	✓ ✓ ✓
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
and Wuhan/BA.1 booster mRNA vaccines
licensed in 2023

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

Conclusion

- Variant-adapted bivalent COVID-19 vaccine products -



- Waning immunity with time and escape from immunity of Omicron variants were counter-acted
 - initially by booster vaccinations (3rd and 4th vaccine doses) using the original Wuhan-based monovalent COCID-19 vaccine products,
 - later by Omicron-adaptation of the vaccines to bivalent vaccines containing the original Wuhan and one of the Omicron variant-derived antigens
- Evidence has been obtained that
 - an undefined level of neutralising antibody titers protect against infection and
 - cellular immunity protects against severe disease.



Periodic development of
new escape variants of SARS CoV-2
may require

- seasonal COVID-19 vaccinations and
- seasonal COVID-19 vaccine product updates

XBBs are recombinants between two BA.2 sublineages

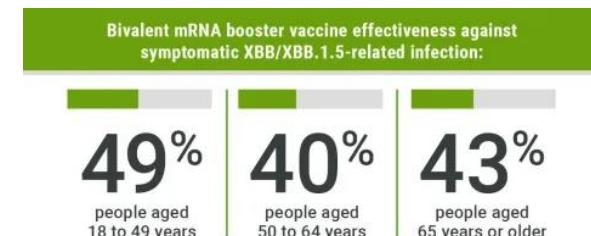
	N-terminal domain (NTD)				Receptor Binding Domain (RBD)			
BA.2	T19I L24S P25- P26- A27-	L24S P25- P26- A27-	P25- P26- A27-	P25- P26- A27-	G142D V213G G339D	G142D V213G G339D	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K Q954H N969K	Q949R Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K
BA.5	T19I L24S P25- P26- A27-	L24S P25- P26- A27-	P25- P26- A27-	P25- P26- A27-	G142D V213G G339D	G142D V213G G339D	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K Q954H N969K	Q949R Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K
BQ.1.1	T19I L24S P25- P26- A27-	T19I L24S P25- P26- A27-	V83A G142D Y145Q H146-	V83A G142D Y145Q H146-	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K Q954H N969K	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K Q954H N969K	Q949R Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	
BJ.1 (XBB parent, BA.2 plus additional mutations)	T19I L24S P25- P26- A27-	T19I L24S P25- P26- A27-	V83A G142D Y145Q H146-	V83A G142D Y145Q H146-	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K Q954H N969K	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K Q954H N969K	Q949R Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	
BA.2.75 sublineage (XBB parent, BA.2.75 plus additional mutations)	T19I L24S P25- P26- A27-	T19I L24S P25- P26- A27-	V83A G142D Y145Q H146-	V83A G142D Y145Q H146-	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K Q954H N969K	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K Q954H N969K	Q949R Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	
XBB.1 (XBB recombinant + G252V)	T19I L24S P25- P26- A27-	T19I L24S P25- P26- A27-	V83A G142D Y145Q H146-	V83A G142D Y145Q H146-	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K V445P G446S N460K S477N T478K E484A F486S F490S Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K V445P G446S N460K S477N T478K E484A F486S F490S Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	Q949R Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	
XBB.1.5 (XBB.1 + F486P)	T19I L24S P25- P26- A27-	T19I L24S P25- P26- A27-	V83A G142D Y145Q H146-	V83A G142D Y145Q H146-	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K V445P G446S N460K S477N T478K E484A F486S F490S Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	S371F S373P S375F T376A D405N D405N R408S R408S R417N N440K V445P G446S N460K S477N T478K E484A F486S F490S Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	Q949R Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	

XBB.1 includes the G252V mutation, and XBB.1.5 includes the G252V and F486P mutations

XBB is a recombinant (two BA.2 sublineages) with increased transmissibility, not increased immune escape



- XBB.1.5 substantially escapes NAb responses but not T cell responses after bivalent mRNA boosting.
- NAb titers to XBB.1 and XBB.1.5 were similar, suggesting that the F486P mutation confers greater transmissibility but not increased immune escape.
- By month 3, NAb titers to XBB.1 and XBB.1.5 declined essentially to baseline levels prior to boosting, while NAb titers to other variants declined less strikingly.
- Bivalent mRNA booster vaccines protect against XBB-induced COVID-19 (early after vaccine boost-data)



Lessons learned from COVID-19 vaccine development



- **Vaccine platforms:**
antigen design and usage of various technologies offer a better chance for successful development of efficacious vaccines
- **mRNA design is crucial and**
experimental batch testing assures identity, integrity of the drug substance and potency
- **Serious adverse reactions due to COVID-19 vaccines are very rare**
(**<1 in 10.000 doses**) and were not foreseeable
- **Bivalent BA.1-Wuhan and BA.4/5-Wuhan mRNA booster vaccine offer increased protection from former and current Omicron variant-induced COVID-19, less so from infection**
- **Improved future pandemic preparedness by more rapid availability of**
pandemic vaccines and therapeutics is now the job of ZEPAI at the PEI, HERA at EC and
the vaccine and pharmaceutical industry as well as academic research groups



Comparative experimental evaluation of the CoV-2 rapid antigen detection test sensitivities by PEI/RKI/Inst. Mikrobiol. Bundeswehr



- Comparative evaluation of sensitivity
- 245 tests evaluated (March 2022);
 - 80% passed
 - 199 passed (reimbursable; on PEI list)
 - 46 failed (non-refundable, removed from PEI list)
- Individual results first published on PEI homepage, then in EU RAT list
- Also the basis for the list of the European Commission "Common List of COVID-19 rapid antigen tests (RAT)"
 - In EU: for cross-border mutual recognition of test results
 - Listing only after prior independent review of the tests

Expert support by the Institute for Microbiology of the German Armed Forces

Not all evaluated rapid antigen detection tests (RDTs) were positive at virus levels indicative for a risk of transmission

	RDT number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Pool number	gc/mL	Cq	Omicron (B.1.1.529)																		
1	1.23×10^7	23.04	++	++	+++	+++	++	++	+	+	++	+	+	+	+	++	+	+	+	+	+
2	1.11×10^7	23.18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±	+	+	+	+
3	1.87×10^6	25.77	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±
4	1.25×10^6	26.36	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
5	6.16×10^5	27.39	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±
6	2.53×10^5	28.68	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7	1.17×10^5	29.80	+	±	+	+	+	±	±	±	±	±	±	±	±	±	±	±	±	±	±
8	4.16×10^4	31.31	+	+	+	+	+	±	+	±	+	±	+	+	+	+	+	+	+	+	±
9	1.67×10^4	32.63	±	±	+	+	+	−	±	−	−	±	−	−	−	−	−	−	−	−	±
10	3.33×10^3	34.98	±	±	+	+	±	+	+	−	−	−	−	−	−	±	±	−	−	−	±
11	3.16×10^3	35.06	−	−	−	−	−	−	±	−	−	−	−	−	−	−	−	−	−	−	−
Pool number	gc/mL	Cq	Delta (B.1.617.2)																		
1	4.84×10^6	24.39	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	±	±	+	±
2	2.12×10^6	25.59	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±	±	+	−
3	1.78×10^5	29.19	±	±	+	+	−	−	+	−	−	±	−	−	−	±	−	−	−	−	±
4	2.46×10^4	32.07	−	−	−	−	±	−	−	−	−	−	−	−	−	−	−	−	−	−	−



Paul-Ehrlich-Institut

Our focus is on health!

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Since 1896 our focus has been on health

