mRNA-Technologie – Zulassungsverfahren, Inhaltsstoffe, Wirksamkeit

Corona - modRNA-Technik – Kontrolle / Versagen

Pharmaindustrie

Kontrolle?

Behörden (PEI, RKI etc.)

=> Versagen

COVID-19: Eine neue Seuche?

- Neues Virus aus Wuhan?
- Erster Fall in Deutschland Ende Januar 2020 (Webasto)
- Symptomlose Übertragung?
- Maskenpflicht
- Lock-Down (März/April 2020)
- Schulschließungen
- etc.

Symptomlose Übertragung?

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

February 2, 2020
DOI: 10.1126/science.abb1524

› Nat Commun. 2020 Nov 20;11(1):5917. doi: 10.1038/s41467-020-19802-w.

Post-lockdown SARS-CoV-2 nucleic acid screening in nearly ten million residents of Wuhan, China

Shiyi Cao [1], Yong Gan [1], Chao Wang [1], Max Bachmann [2], Shanbo Wei [3], Jie Gong [4], Yuchai Huang [1], Tiantian Wang [1], Liqing Li [5], Kai Lu [6], Heng Jiang [7 8], Yanhong Gong [1], Hongbin Xu [1], Xin Shen [1], Qingfeng Tian [9], Chuanzhu Lv [10], Fujian Song [11], Xiaoxv Yin [12], Zuxun Lu [13]

Abstract

Stringent COVID-19 control measures were imposed in Wuhan between January 23 and April 8, 2020. Estimates of the prevalence of infection following the release of restrictions could inform post-lockdown pandemic management. Here, we describe a city-wide SARS-CoV-2 nucleic acid screening programme between May 14 and June 1, 2020 in Wuhan. All city residents aged six years or older were eligible and 9,899,828 (92.9%) participated. No new symptomatic cases and 300 asymptomatic cases (detection rate 0.303/10,000, 95% CI 0.270-0.339/10,000) were identified. There were no positive tests amongst 1,174 close contacts of asymptomatic cases. 107 of 34,424 previously recovered COVID-19 patients tested positive again (re-positive rate 0.31%, 95% CI 0.423-0.574%). The prevalence of SARS-CoV-2 infection in Wuhan was therefore very low five to eight weeks after the end of lockdown.

=> Symptomlose Übertragung spielt keine Rolle!

Gefährlichkeit?

Infection fatality rate

Global perspective of COVID-19 epidemiology for a full-cycle pandemic

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Funding information
Laura and John Arnold Foundation

Abstract

As of October 2020, there are >1 million documented deaths with COVID-19. Excess deaths can be caused by both COVID-19 and the measures taken. COVID-19 shows extremely strong risk stratification across age, socioeconomic factors, and clinical factors. Calculation of years-of-life-lost from COVID-19 is methodologically challenging and can yield misleading over-estimates. Many early deaths may have been due to suboptimal management, malfunctional health systems, hydroxychloroquine, sending COVID-19 patients to nursing homes, and nosocomial infections; such deaths are partially avoidable moving forward. About 10% of the global population may be infected by October 2020. Global infection fatality rate is 0.15-0.20% (0.03-0.04% in those <70 years), with large variability across locations with different age-structure, institutionalization rates, socioeconomic inequalities, population-level clinical risk profile, public health measures, and health care. There is debate on whether at least 60% of the global population must be infected for herd immunity, or, conversely, mixing heterogeneity and pre-existing cross-immunity may allow substantially lower thresholds. Simulations are presented with a total of 1.58-8.76 million COVID-19 deaths over 5-years (1/2020-12/2024) globally (0.5-2.9% of total global deaths). The most favorable figures in that range would be feasible if high risk groups can be preferentially protected with lower infection rates than the remaining population. Death toll may also be further affected by potential availability of effective vaccines and treatments, optimal management and measures taken, COVID-19 interplay with influenza and other health problems, reinfection potential, and any chronic COVID-19 consequences. Targeted, precise management of the pandemic and avoiding past mistakes would help minimize mortality.

KEYWORDS

COVID-19, epidemiology, infection fatality rate, mortality, risk factors

Eur J Clin Invest. 2020;50:e13423.
https://doi.org/10.1111/eci.13423

Infection fatality rate

Eur J Clin Invest. 2021;51:e13554.
https://doi.org/10.1111/eci.13554

Maßnahmen mussten sein,
die Wissenschaft(ler) hat
(haben) dies so gesagt.

Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations

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Funding information
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Abstract

Background: Estimates of community spread and infection fatality rate (IFR) of COVID-19 have varied across studies. Efforts to synthesize the evidence reach seemingly discrepant conclusions.

Methods: Systematic evaluations of seroprevalence studies that had no restrictions based on country and which estimated either total number of people infected and/or aggregate IFRs were identified. Information was extracted and compared on eligibility criteria, searches, amount of evidence included, corrections/adjustments of seroprevalence and death counts, quantitative syntheses and handling of heterogeneity, main estimates and global representativeness.

Results: Six systematic evaluations were eligible. Each combined data from 10 to 338 studies (9-50 countries), because of different eligibility criteria. Two evaluations had some overt flaws in data, violations of stated eligibility criteria and biased eligibility criteria (eg excluding studies with few deaths) that consistently inflated IFR estimates. Perusal of quantitative synthesis methods also exhibited several challenges and biases. Global representativeness was low with 78%-100% of the evidence coming from Europe or the Americas; the two most problematic evaluations considered only one study from other continents. Allowing for these caveats, four evaluations largely agreed in their main final estimates for global spread of the pandemic and the other two evaluations would also agree after correcting overt flaws and biases.

Conclusions: All systematic evaluations of seroprevalence data converge that SARS-CoV-2 infection is widely spread globally. Acknowledging residual uncertainties, the available evidence suggests average global IFR of ~0.15% and ~1.5-2.0 billion infections by February 2021 with substantial differences in IFR and in infection spread across continents, countries and locations.

KEYWORDS
bias, COVID-19, global health, infection fatality rate, meta-analysis, seroprevalence

The Great Barrington Declaration

The Great Barrington Declaration – As infectious disease epidemiologists and public health scientists we have grave concerns about the damaging physical and mental health impacts of the prevailing COVID-19 policies, and recommend an approach we call Focused Protection.

Coming from both the left and right, and around the world, we have devoted our careers to protecting people. Current lockdown policies are producing devastating effects on short and long-term public health. The results (to name a few) include lower childhood vaccination rates, worsening cardiovascular disease outcomes, fewer cancer screenings and deteriorating mental health – leading to greater excess mortality in years to come, with the working class and younger members of society carrying the heaviest burden. Keeping students out of school is a grave injustice.

Keeping these measures in place until a vaccine is available will cause irreparable damage, with the underprivileged disproportionately harmed.

Fortunately, our understanding of the virus is growing. We know that vulnerability to death from COVID-19 is more than a thousand-fold higher in the old and infirm than the young. Indeed, for children, COVID-19 is less dangerous than many other harms, including influenza.

As immunity builds in the population, the risk of infection to all – including the vulnerable – falls. We know that all populations will eventually reach herd immunity – i.e. the point at which the rate of new infections is stable – and that this can be assisted by (but is not dependent upon) a vaccine. Our goal should therefore be to minimize mortality and social harm until we reach herd immunity.

The most compassionate approach that balances the risks and benefits of reaching herd immunity, is to allow those who are at minimal risk of death to live their lives normally to build up immunity to the virus through natural infection, while better protecting those who are at highest risk. We call this Focused Protection.

Adopting measures to protect the vulnerable should be the central aim of public health responses to COVID-19. By way of example, nursing homes should use staff with acquired immunity and perform frequent testing of other staff and all visitors. Staff rotation should be minimized. Retired people living at home should have groceries and other essentials delivered to their home. When possible, they should meet family members outside rather than inside. A comprehensive and detailed list of measures, including approaches to multi-generational households, can be implemented, and is well within the scope and capability of public health professionals.

Those who are not vulnerable should immediately be allowed to resume life as normal. Simple hygiene measures, such as hand washing and staying home when sick should be practiced by everyone to reduce the herd immunity threshold. Schools and universities should be open for in-person teaching. Extracurricular activities, such as sports, should be resumed. Young low-risk adults should work normally, rather than from home. Restaurants and other businesses should open. Arts, music, sport and other cultural activities should resume. People who are more at risk may participate if they wish, while society as a whole enjoys the protection conferred upon the vulnerable by those who have built up herd immunity.

On October 4, 2020, this declaration was authored and signed in Great Barrington, United States, by:

Dr. Martin Kulldorff, professor of medicine at Harvard University, a biostatistician, and epidemiologist with expertise in detecting and monitoring infectious disease outbreaks and vaccine safety evaluations.

Dr. Sunetra Gupta, professor at Oxford University, an epidemiologist with expertise in immunology, vaccine development, and mathematical modeling of infectious diseases.

Dr. Jay Bhattacharya, professor at Stanford University Medical School, a physician, epidemiologist, health economist, and public health policy expert focusing on infectious diseases and vulnerable populations.

Der neue „Impfstoff“

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 31, 2020 VOL. 383 NO. 27

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

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ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

Peter Doshi: Pfizer and Moderna's "95% effective" vaccines—let's be cautious and first see the full data

November 26, 2020

Only full transparency and rigorous scrutiny of the data will allow for informed decision making, argues Peter Doshi

In the United States, all eyes are on Pfizer and Moderna. The topline efficacy results from their experimental covid-19 vaccine trials are astounding at first glance. Pfizer says it recorded 170 covid-19 cases (in 44,000 volunteers), with a remarkable split: 162 in the placebo group versus 8 in the vaccine group. Meanwhile Moderna says 95 of 30,000 volunteers in its ongoing trial got covid-19: 90 on placebo versus 5 receiving the vaccine, leading both companies to claim around 95% efficacy.

Let's put this in perspective. First, a relative risk reduction is being reported, not absolute risk reduction, which appears to be less than 1%. Second, these results refer to the trials' primary endpoint of covid-19 of essentially any severity, and importantly not the vaccine's ability to save lives, nor the ability to prevent infection, nor the efficacy in important subgroups (e.g. frail elderly). Those still remain unknown. Third, these results reflect a time point relatively soon after vaccination, and we know nothing about vaccine performance at 3, 6, or 12 months, so cannot compare these efficacy numbers against other vaccines like influenza vaccines (which are judged over a season). Fourth, children, adolescents, and immunocompromised individuals were largely excluded from the trials, so we still lack any data on these important populations.

=> Absolute Risikoreduktion < 1%

Spezifikationen Biontech

▪ ***Table P.5-1. BNT162b2 drug product specifications.***

Quality Attribute	Analytical Procedure[a]	Acceptance Criteria
Composition and Strength		
Appearance	Appearance (Visual)	White to off-white suspension
Appearance (Visible Particulates)	Appearance (Particles)[b]	Essentially free from visible particulates
Subvisible Particles	Subvisible Particulate Matter[b, c]	Particles ≥10 µm: ≤6000 per container[b,c] Particles ≥ 25 µm: ≤600 per container[b,c]
pH	Potentiometry[b]	6.9 – 7.9
Osmolality	Osmometry[b, d, e]	425 - 625 mOsmol/kg
LNP Size	Dynamic Light Scattering (DLS)	40 to 180 nm
LNP Polydispersity	Dynamic Light Scattering (DLS)	≤ 0.3
RNA Encapsulation	Fluorescence assay	≥ 80%
RNA content	Fluorescence assay	0.50 ± 0.13 mg/mL
ALC-0315 content	HPLC-CAD	4.50 to 9.25 mg/mL
ALC-0159 content	HPLC-CAD	0.55 to 1.20 mg/mL
DSPC content	HPLC-CAD	0.90 to 2.05 mg/mL
Cholesterol content	HPLC-CAD	1.80 to 3.90 mg/mL
Container content for injections	Volume of injections in containers[e, f]	Not less than the sum of the nominal
Identity		
Lipid identities		sistent with references 0159, Cholesterol, DSPC)
Identity of encoded RNA sequence	RT-PCR[e]	Identity confirmed
Potency		
In Vitro Expression	Cell-based flow cytometry	≥ 30% Cells Positive
Purity		
RNA Integrity	Capillary Gel Electrophoresis	≥ 50% intact RNA
Adventitious Agents		
Bacterial Endotoxin	Endotoxin (LAL)[b]	≤ 12.5 EU/mL
Sterility	Sterility[b]	No Growth Detected
Container Closure Integrity	Dye incursion[g]	Pass

Zusammensetzung?

a. All assays performed on stability unless otherwise noted.
b. Compendial
c. USP<787> (obscuration method), and aligned with upcoming (Jan 2021) revision of Ph. Eur. 2.9.19
d. USP<785>; also in accordance with Ph Eur. 2.2.35, with minor difference in instrument calibration
e. Assay not performed on stability.
f. Procedure is aligned with Test for Extractable Volume of Parenteral Preparations.
g.Tested at release and on stability for stability batches only
Abbreviations: LNP = Lipid nanoparticles; CAD = charged aerosol detector; RT-PCR = reverse transcription polymerase chain reaction; FACS = fluorescence activated cell sorter; ddPCR = droplet digital PCR; qPCR = quantitative PCR; dsRNA = double stranded RNA; LAL = Limulus amebocyte lysate; EU = endotoxin unit

Phantastische Toleranzen!

=> 0.37 bis 0.63 mg / mL

Tab. P.5-1. des 'Rapporteur's Rolling Review assessment report'

Dosierung?

- modRNA Inhalt : 0.5 ± 0.13 mg/mL
- Intakte modRNA im Bereich 50 – 100%

=> Variationsbreite des Gehalts von aktiver modRNA in Comirnaty

modRNA Gesamtgehalt: 0.5 +/- 0.13 mg / mL => 0.37 bis 0.63 mg / mL

Von der modRNA sind 50% bis 100% intakt

=> es sind mindestens 0.185 mg / mL und maximal 0.63 mg / mL aktive mRNA vorhanden.

=> der Gehalt von aktiver modRNA in den Impfstoffen darf um einen Faktor von 0.63/0.185 ≈ 3.4 variieren.

Dosierung?

- Weitere unbekannte Faktoren:

- Wie viel Spikeprotein wird pro modRNA produziert?
- Wie viel modRNA wird aufgenommen
- Wie ist die Verteilung der modRNA im Körper
- Welchen Einfluss hat die Partikelgröße
- etc.

$\Rightarrow$ Dosis vollkommen unklar; Wirkungsweise vielfach auch

$\Rightarrow$ Russisch Roulette

Menge an Nanopartikeln und modRNA ?

Table P.1-1. Composition of BNT162b2 Tris/Sucrose Finished Product, 30 µg RNA dose in 0.3 mL Injection Volume, 6 Dose Multi-dose Vial

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per 2.25 mL vial[a]	Amount per dose
BNT162b2 drug substance	In-house specification	Active ingredient	0.1	225 µg	30 µg
ALC-0315	In-house specification	Functional lipid	1.43	3.22 mg	0.43 mg
ALC-0159	In-house specification	Functional lipid	0.18	0.41 mg	0.05 mg
DSPC	In-house specification	Structural lipid	0.31	0.70 mg	0.09 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	1.40 mg	0.19 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	231.8 mg	31 mg
Tromethamine (Tris base)[b]	USP-NF, Ph. Eur.	Buffer component	0.20	0.45 mg	0.06 mg
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[c]	In-house specification	Buffer component	1.32	2.97 mg	0.4 mg
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[d]					
Ethanol	Ph. Eur.	Processing aid	N/A		
Citric acid monohydrate	Ph. Eur.	Processing aid			
Sodium citrate	Ph. Eur.	Processing aid			
Sodium hydroxide	Ph. Eur.	Processing aid			
HEPES	In-house specification	Drug substance buffer component			
EDTA	Ph. Eur., USP-NF	Drug substance buffer component			

a. Values are rounded to maintain the same level of precision as the label claim, with trailing decimals not shown, where applicable.
b. Also known as Trometamol
c. Also known as Tromethamine HCl and Trometamol HCl
d. The processing aids and drug substance formulation buffer
not considered ingredients (excipients).
Abbreviations:
ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)b
ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecyla
DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine
q.s. = quantum satis (as much as may suffice)
HEPES = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
EDTA = edetate disodium dihydrate

=> Stoffmenge aller Substanzen in den Lipid Nanopartikeln = 1.43+0.18+0.31+0.62 = 2.54 mg/ml = 2.54 g/l.

Unter der Annahme dass die Dichte 1g/cm³ beträgt (Dichte von organischem festem Material liegt zwischen 0.9 und 1.4 g/cm³

=> Gesamtvolumen der Partikel in einem Liter = 2,54 cm³.

Anzahl der Nanopartikel

⇒ Bei einem Partikeldurchmesser von 50 nm => Volumen = 65445 nm^3 = $6.54 \cdot 10^4$ nm^3 = $6.54 \cdot 10^{-17}$ cm^3.

⇒ Gesamtvolumen der Partikel = 2,54 cm^3

⇒ Anzahl der Partikel = 2.54 cm^3 / $6.54 \cdot 10^{-17}$ cm^3/Partikel = $3.88 \cdot 10^{16}$ Partikel pro Liter

⇒ Anzahl pro Dosis (0.3 ml): $3.88 \cdot 10^{16}$ Partikel pro Liter mal 0.0003 l = $1.17 \cdot 10^{13}$ Partikel.

⇒ Pro Dosis circa 11.6 Billionen Partikel.

Anzahl der modRNA Moleküle

Table P.1-1. Composition of BNT162b2 Tris/Sucrose Finished Product, 30 µg RNA dose in 0.3 mL Injection Volume, 6 Dose Multi-dose Vial

⇒ 30 µg Substanz pro Dosis := $3 \cdot 10^{-5}$ g pro Dosis.

⇒ Molmasse der modRNA circa 1377 kD := $1.377 \cdot 10^{6}$ g/mol

⇒ Anzahl der modRNA Moleküle: Masse / Molmasse • $6.022 \cdot 10^{23}$ Teilchen / mol

$$3 \cdot 10^{-5}\ \text{g} / 1.377 \cdot 10^{6}\ \text{g/mol} \cdot 6.022 \cdot 10^{23} \cdot \text{Teilchen/mol} = 1.32\ 10^{13}\ \text{Teilchen.}$$

⇒ Pro Dosis werden circa 13 Billionen modRNA Moleküle verabreicht.

Größe der modRNA Moleküle

⇒ **modRNA circa 4284 Nukleotide**

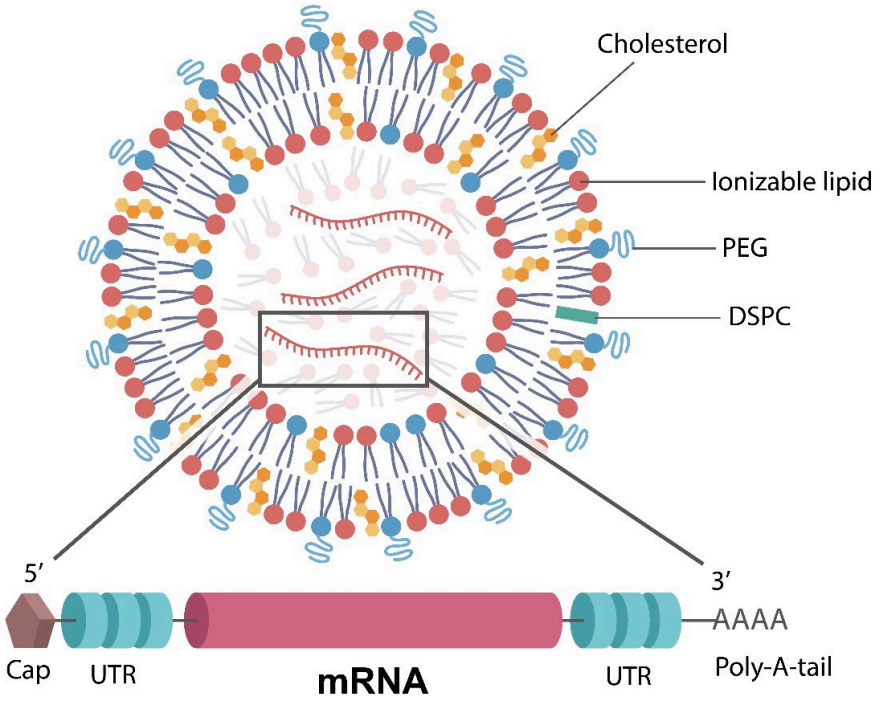
⇒ **Mittleres Volumen pro Nukleotid = 0.3 nm^3**

⇒ **Gesamtvolumen circa 1285 nm^3**

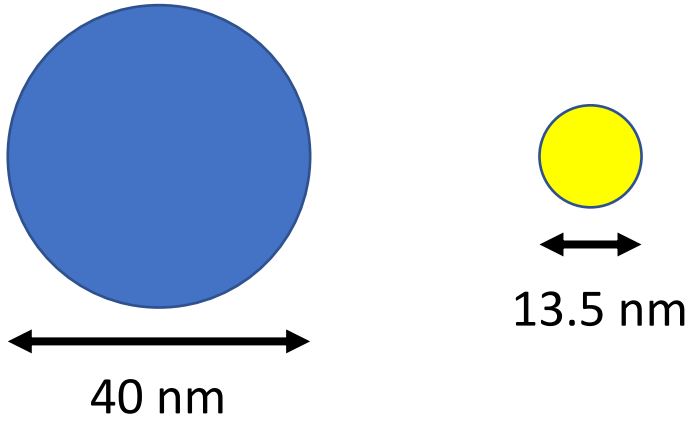
⇒ **Volumen einer Kugel mit Radius 6.74 nm**

⇒ **Durchmesser der modRNA circa 13.5 nm**

Modell des Aufbaus der modRNA beladenen Nanopartikel

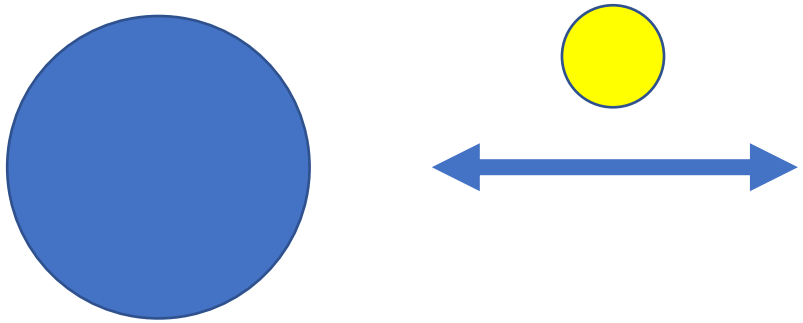


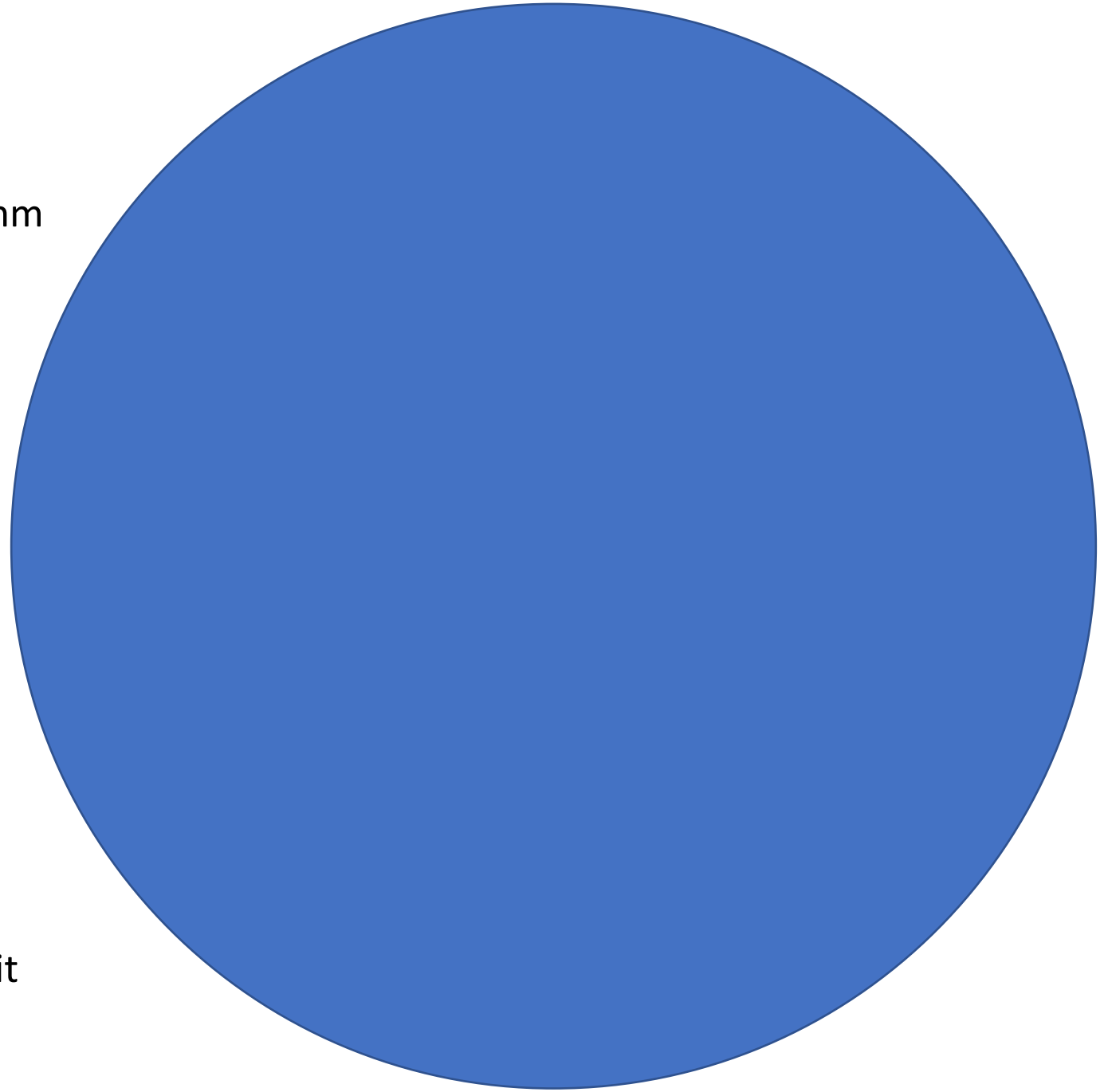
- Teilchengröße der Nanopartikel: 40 - 180 nm



=> Bei den kleinen Nanopartikeln circa 1 modRNA Molekül pro Partikel

- Teilchengröße der Nanopartikel: 40 - 180 nm

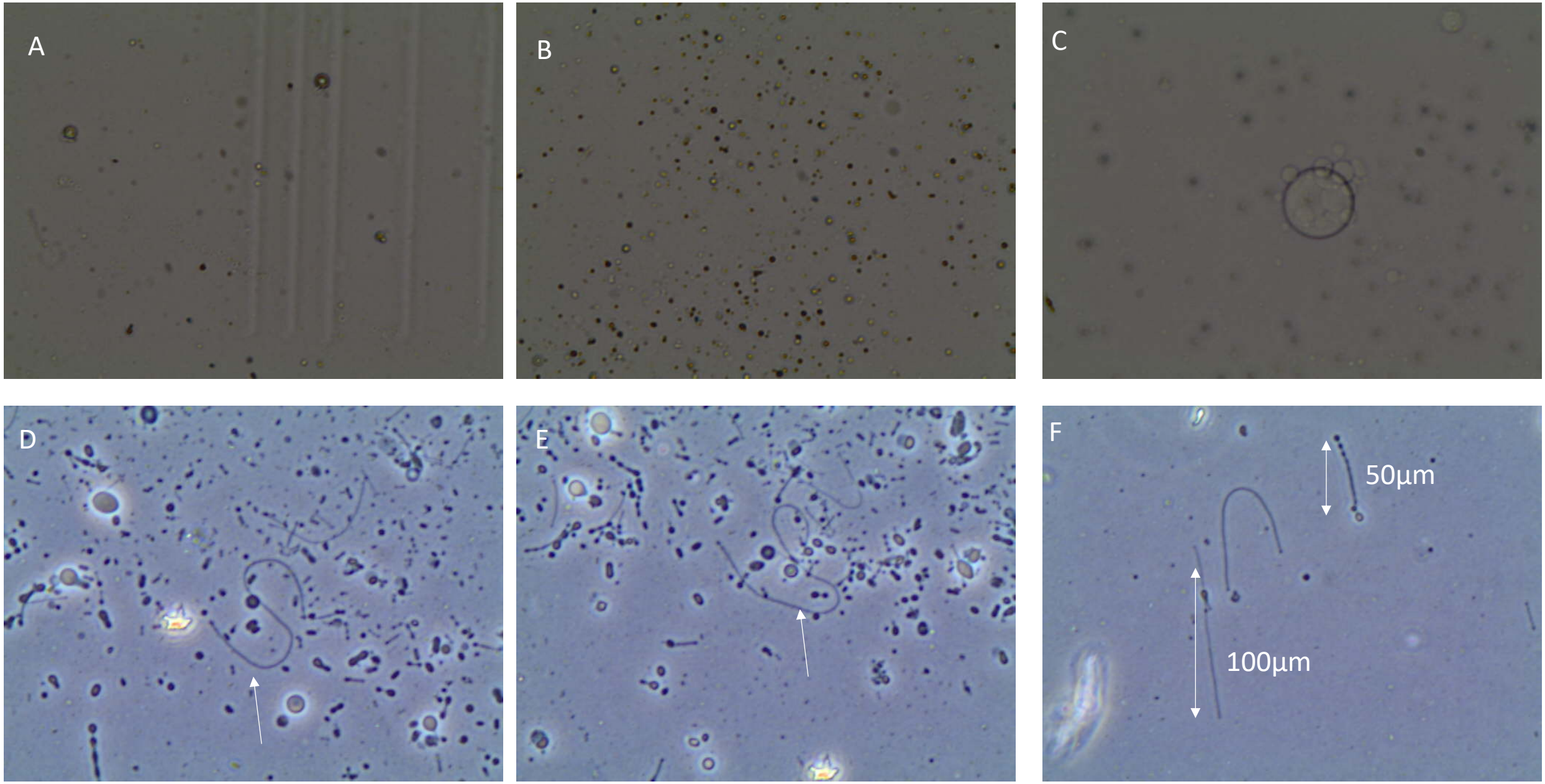




=> Volumenvariation: 33.510 - 3.053.628 nm^3

=> Massive Unterschiede in Beweglichkeit
und lokaler Konzentration

Biontech seen in a Neubauer improved chamber slide at day light (A-C) and phase contrast (D-F), note in D+E same structure with 5 min time lapse
Phase contrast pictures taken after incubation at room temperature under the microscope for 20 min, light microscope immediately after filling the chamber



Vermessung einer Biontech Probe mittels

Dynamischer Lichtstreuung (DLS) bei

Raumtemperatur direkt nach Entnahme

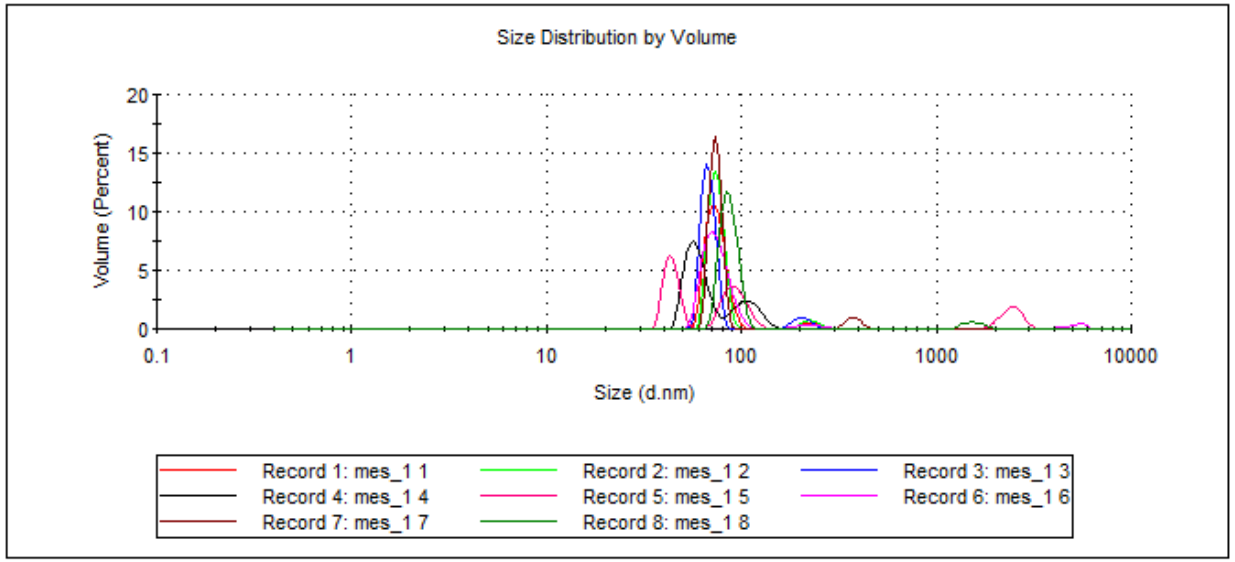
aus dem gekühlten Vial:

Sample Name:	mes_1 8		
SOP Name:	mansettings.nano		
File Name:	AS1.dts	**Dispersant Name:**	Water
Record Number:	8	**Dispersant RI:**	1.330
Material RI:	1.45	**Viscosity (cP):**	0.8872
Material Absorbtion:	0.001	**Measurement Date and Time:**	Donnerstag, 12. Januar 2023 15:5...

Temperature (°C):	25.0	**Duration Used (s):**	60
Count Rate (kcps):	347.6	**Measurement Position (mm):**	4.65
Cell Description:	Glass cuvette with round aperture	**Attenuator:**	6

			Size (d.nm):	**% Volume:**	**St Dev (d.nm):**
Z-Average (d.nm):	88.06	**Peak 1:**	86.18	95.0	8.843
PdI:	0.173	**Peak 2:**	1542	5.0	162.3
Intercept:	0.955	**Peak 3:**	0.000	0.0	0.000

Result quality : Good



Qualitätskontrolle?

Sicherheitskontrolle durch PEI ?

Chargenlaufzettel Comirnaty

- Formblatt –

Antragsteller: BioNTech / Pfizer
Produkt: **Comirnaty (0,45 ml / 6 Dose)**

Erlaubter Liefertemperaturbereich
☐ Temperatur-Indikator
☐ Temperatur-Logger in °C
☐ Temperaturmessung Materiallager in °C

[redacted]

Erlaubter Lagertemperaturbereich

Prüfmusterdaten		Antragsdaten		geprüft von der Laborleitung
Charge	[redacted]	Eingang Antrag	03.02.2022	
Probeneingang	15.12.21	Bearb.-Nummer	[redacted]	OMCL-Liste ☐
Anzahl / Art der Behältnisse	[redacted]	Kosten		
Prüfmuster für Testung akzeptiert ☒ **ja** ☐ **nein** Abweichung wenn ja: Begründung notieren nein: weiteres Vorgehen bei Bemerkungen notieren				
Datum / Kürzel	15.12.21 [redacted]	Datum / Kürzel	03.02.22 [redacted]	

Prüfungen

1. Visuelle Kontrolle:

Suspension	[redacted]	[redacted]

2. Identität RNA Sequence:

Test Nr. / Kürzel	[redacted]	überprüft:	[redacted]

3. [redacted] **(RNA): Gehalt / Verkapselung**

RNA	Spezifikation	PEI		überprüft	Hersteller
		Ergebnisse	Test Nr. / Kürzel		Ergebnisse
RNA Gehalt	[redacted]	[redacted]	[redacted] 16.12.21	15.12.2021	[redacted]
RNA Verkapselung	[redacted]	[redacted]	[redacted] 16.12.21	[redacted]	

Chargenlaufzettel Comirnaty

- Formblatt –

4. RNA Integrität: **Spezifikation:** [redacted]

[redacted]

Bemerkungen:

Ergebnisbericht von FG 3/1

Zugehörige Anweisung: 3/1-V-030

ID [redacted]

FG:	2/1	**B-Nr:**	
Präparat:	COMIRNATY 30 µg	**Ch.-Bez.:**	[redacted]
PU:	BioNTech Manufacturing GmbH	**Haltbar bis:**	
Eingang Laborbuch:	15.12.2021	**Ausgang:**	20.12.2021

Test/Methode	Einheit	Spezifikation	Hersteller	PEI
RNA / Integrität	[redacted]			

Wiederholungsmessungen

Kommentare/Auffälligkeiten:

Bewertung: [redacted]

Seite **1** von **1**

20. Dez. 2021
Datum, Unterschrift: [redacted]

Druckdatum: 20.12.2021

Sicherheitskontrolle durch PEI ?

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany
phone: +49-6131-9084-0
fax: +49-6131-9084-390

BIONTECH

Lot Results Report

COMIRNATY

Lot/Batch No.: [redacted]

Product Code: BNT162b2 DP (Drug Product) **Manufacturing Date:** [redacted]
Batch size: [redacted] **Expiration Date:** [redacted]

Registered Test	Acceptance Criteria	Result	Analysis Date
[redacted]			
Fluorescence assay			
RNA content	[redacted]	[redacted]	16-Dec-2021
RNA Encapsulation	[redacted]	[redacted]	16-Dec-2021
[redacted]			

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany
phone: +49-6131-9084-0
fax: +49-6131-9084-390

BIONTECH

Lot Results Report

COMIRNATY

Lot/Batch No.: [redacted]

Product Code: BNT162b2 DP (Drug Product) **Manufacturing Date:** [redacted]
Batch size: [redacted] **Expiration Date:** [redacted]

Registered Test	Acceptance Criteria	Result	Analysis Date
[redacted]			

The results comply with the acceptance criteria.
I hereby certify that all tests were performed according to GMP requirements. All of the above information is authentic and accurate.

Electronic signature

Issued By: [redacted]
Associate Director Quality Control East Wing

Issued Date: 03-Feb-2022
Disposition Date: 03-Feb-2022

Transparenz?

Testung von Identität und Integrität der modRNA vor Freigabe

Anlage Ausgangsbescheid vom 27.07.2022 (Testmethoden-Chargenprüfung-Comirnaty)

Testprinzip zur Überprüfung der Integrität der mRNA

Die Integrität der mRNA ist ein qualitätsbestimmender Parameter dieses Impfstoffes, da nur die intakte mRNA von den Körperzellen exprimiert werden kann. Zur Bestimmung der Integrität muss das die mRNA umhüllende Lipid-Vesikel zerstört werden. Hierfür wird der Impfstoff mit einer Lösung aus einem Detergenz und einem Alkohol gemischt und inkubiert. Anschließend wird die Probe mit einem Marker versetzt, bei 70°C denaturiert und danach mithilfe von Kapillargelelektrophorese am Fragment-Analyzer analysiert.

Nein, auch verkürzte modRNA kann exprimiert werden, wobei dann andere Proteine entstehen mit unbekannter Wirkungsweise.

Nach der Trennung erfolgt die Quantifizierung mithilfe einer Software. Dabei wird die Integrität der mRNA als %-Anteil des Hauptpeaks (intakte mRNA) zur gesamten detektierten Fläche im Chromatogramm bestimmt.

Hier sind phantastische Toleranzen erlaubt, d.h. es müssen nur 50% die richtige Größe haben und die anderen 50% eben nicht!

Testprinzip zur Überprüfung der Identität der mRNA

Zur Überprüfung der Identität der mRNA wird eine „Single Step Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR)“ durchgeführt. Bei der RT-PCR wird in Echtzeit die Fluoreszenz einer fluorophormarkierten, sequenzspezifischen Sonde gemessen. Für dieses Verfahren werden Primer und Sonden verwendet, die für die Spike-Glykoproteinsequenz spezifisch sind.

Es werden also nur kleine Bereiche der circa 4300 Basen langen modRNA geprüft. Was dazwischen ist, ist unklar.

Mit der RT-PCR-Technologie werden nur die modRNA-Stränge vervielfältigt, die auf dem „Primer“ „kleben“ bleiben. Wenn RNA mit anderer Codierung vorhanden ist, wird diese nicht gefunden, kann aber durchaus aktiv sein.

Erlkönig Johann Wolfgang von Goethe (1782): 226 Worte; 1062 Zeichen; 1305 Zeichen (mit Leerzeichen)

Wer reitet so spät durch Nacht und Wind? …… Mein Vater, mein Vater, und hörest du nicht,

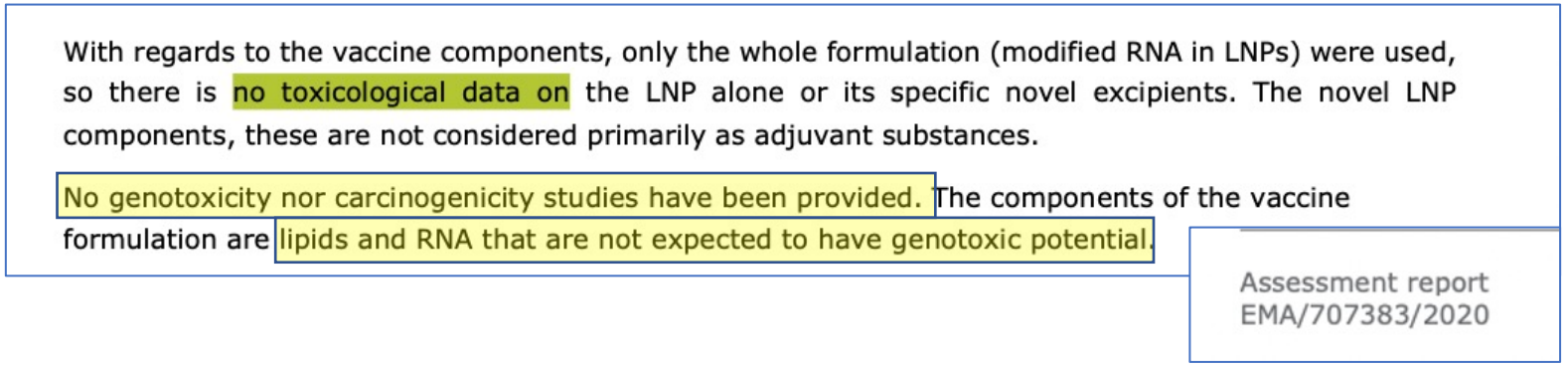
=> Erlkönig …….. In seinen Armen das Kind war tot. (33 Zeichen)

oder Der Knabe lebt das Pferd ist tot. (33 Zeichen)

⇒ Identität ???

König Erl (Heinz Erhardt)

Toxizität?



With regards to the vaccine components, only the whole formulation (modified RNA in LNPs) were used, so there is no toxicological data on the LNP alone or its specific novel excipients. The novel LNP components, these are not considered primarily as adjuvant substances.

No genotoxicity nor carcinogenicity studies have been provided. The components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

Assessment report
EMA/707383/2020

Genotoxizität nicht zu erwarten? Bei einem Lipid, das zum Binden ans Phosphatgerüst optimiert wurde?

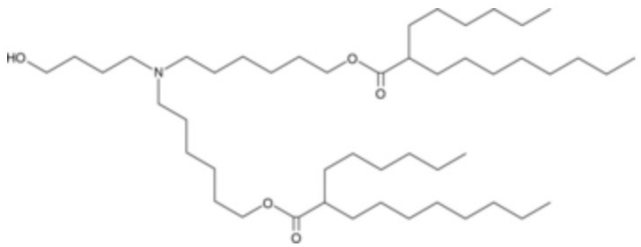
Toxizität Lipid ALC-0315

Achtung

Nur für Forschungszwecke und Laboruntersuchungen: Nicht für die Anwendung im oder am Menschen!

ALC-0315

Item No. 34337



0.4 mg dieser Substanz subkutan: welche „may cause cancer“

“Causes skin irritation“

“Causes serious eye irritation“

Page 1/11

Safety Data Sheet
acc. to OSHA HCS

Printing date 09/22/2021 Revision date 09/22/2021

1 Identification

· **Product identifier**

· **Trade name: ALC-0315**

· **Article number:** 34337
· **Application of the substance / the mixture**
This product is for research use - Not for human or veterinary diagnostic or therapeutic use. It is the responsibility of the purchaser to determine suitability for other applications.

· **Details of the supplier of the safety data sheet**
· **Manufacturer/Supplier:**
Cayman Chemical Co.
1180 E. Ellsworth Rd.
Ann Arbor, MI 48108
USA

· **Information department:** Product safety department
· **Emergency telephone number:**
During normal opening times: +1 (734) 971-3335
US/CANADA: 800-424-9300
Outside US/CANADA: 703-741-5970

*

2 Hazard(s) identification

· **Classification of the substance or mixture**

GHS02 Flame

Flam. Liq. 2 H225 Highly flammable liquid and vapor.

GHS08 Health hazard

Carc. 1A H350 May cause cancer.

GHS07

Skin Irrit. 2 H315 Causes skin irritation.
Eye Irrit. 2A H319 Causes serious eye irritation.
STOT SE 3 H335 May cause respiratory irritation.

(Contd. on page 2)

Product Description

ALC-0315 is an ionizable amino lipid that has been used in combination with other lipids in the formation of lipid nanoparticles.[1] Administration of severe acute respiratory coronavirus 2 (SARS-CoV-2) mRNA in ALC-0315-containing lipid nanoparticles induces the production of IgG that binds to the SARS-CoV-2 receptor-binding domain (RBD) in rhesus macaques, with a boost in antigen-specific IgG geometric mean titers (GMT) seven and 14 days after a second dose. Formulations containing ALC-0315 have been used in the development of lipid nanoparticles for the delivery of mRNA-based vaccines.

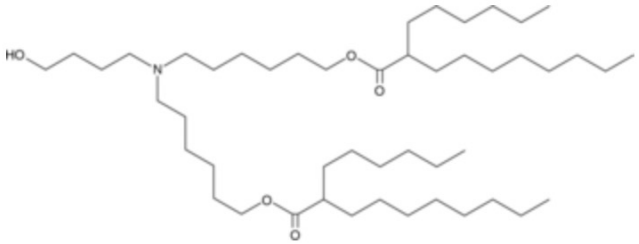
WARNING This product is **not** for human or veterinary use.

https://cdn.caymanchem.com/cdn/msds/34337m.pdf

https://www.caymanchem.com/product/34337/alc-0315

ALC-0315

Item No. 34337



Safety Data Sheet
acc. to OSHA HCS

Printing date 02/14/2022 Revision date 02/14/2022

1 Identification

· **Product identifier**

· **Trade name: ALC-0315**

· **Article number:** 34337
· **Application of the substance / the mixture**
This product is for research use - Not for human or veterinary diagnostic or therapeutic use.

· **Details of the supplier of the safety data sheet**
· **Manufacturer/Supplier:**
Cayman Chemical Co.
1180 E. Ellsworth Rd.
Ann Arbor, MI 48108
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During normal opening times: +1 (734) 971-3335
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2 Hazard(s) identification

· **Classification of the substance or mixture**

GHS02 Flame

Flam. Liq. 2 H225 Highly flammable liquid and vapor.

GHS07

Skin Irrit. 2 H315 Causes skin irritation.
Eye Irrit. 2A H319 Causes serious eye irritation.
STOT SE 3 H335 May cause respiratory irritation.

· **Label elements**
· **GHS label elements**
The product is classified and labeled according to the Globally Harmonized System (GHS).

(Contd. on page 2)

Heute ist der Hinweis verschwunden

Nebenwirkungen?

Nebenwirkungen im Vergleich:

- 2002 – 2020: alle Impfstoffe: 750 Mio. Dosen
  => 54.888 Verdachtsfälle auf Nebenwirkungen
  => 0.07 pro 1000

- „Corona Impfstoffe“: 90 Mio. Impfdosen
  => 130.000 Verdachtsfälle auf Nebenwirkungen
  => 1.4 pro 1000

- 108 Mio Impfdosen
  => 172.188 Verdachtsfälle auf Nebenwirkungen
  => 1.6 pro 1000

  1.6/0.07 = 22.9 => „Corona Impfstoffe“ haben 23 mal mehr Nebenwirkungen

Nebenwirkungen?

Table 1
Number of symptoms reported in VAERS, restricted to the US population, for the year 2021, for various adverse effects that could be caused by inflammation in associated major nerves, showing total counts for COVID-19 vaccines and for all vaccines.

Symptom	Inflamed Nerve(s)	Covid-19 Vaccines	All Vaccines	Percent COVID-19
Anosmia	olfactory nerve	3,657	3,677	99.5
Tinnitus	vestibulo-cochlear nerve	13,275	13,522	98.2
Deafness	cochlea	2,895	3,033	95.5
Bell's Palsy/ facial palsy	facial nerve	5,881	6,129	96.0
Vertigo	vestibular nerve	7,638	7,819	97.7
Migraine headache	trigeminal nerve	8,872	9,059	97.9
Dysphonia	glossopharyngeal nerve	1,692	1,751	96.6
Dysphagia	several lower cranial nerves	4,711	4,835	97.4
Nausea	vagus nerve	69,121	71,275	97.0
Vomiting	vagus nerve	27,885	28,955	96.3
Dyspnea	vagus nerve	39,551	40,387	97.9
Syncope	vagus nerve	14,701	15,268	96.3
Bradycardia	vagus nerve	673	699	96.3
TOTAL	–	**200,552**	**206,409**	97.2

Table 2
Number of symptoms reported in VAERS, restricted to the US population, fo
year 2021, for various disorders of the heart, showing total counts for COVID-19 vaccines and for all vaccines.

Symptom	Covid-19 Vaccines	All Vaccines	Percent COVID-19
Myocarditis	2,322	2,361	98.3
Arrest	1,319	1,371	96.2
Arrhythmia	1,069	1,087	98.3
Myocardial infarction	2,224	2,272	97.9
Cardiac failure	1,156	1,190	97.1
TOTAL	8,090	8,281	97.7

Kommt dies überraschend?

Food and Chemical Toxicology 164 (2022) 113008

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs

Stephanie Seneff [a,*], Greg Nigh [b], Anthony M. Kyriakopoulos [c], Peter A. McCullough [d]

[a] Computer Science and Artificial Intelligence Laboratory, MIT, Cambridge, MA, USA, 02139
[b] Immersion Health, Portland, OR, 97214, USA
[c] Research and Development, Nasco AD Biotechnology Laboratory, Department of Research and Development, Sachtouri 11, 18536, Piraeus, Greece
[d] Truth for Health Foundation, Tucson, AZ, USA

Table 4
Number of symptoms reported in VAERS, restricted to the US population, for the year 2021, for various specific types of thrombosis, showing total counts for COVID-19 vaccines and for all vaccines. Pulmonary embolism, a highly related symptom, is also shown.

Symptom	Covid-19 Vaccines	All Vaccines	Percent COVID-19
	3,899	3,951	98.7
sis	2,275	2,297	99.0
osis	631	646	97.7
Cerebral thrombosis	211	215	98.1
Portal vein thrombosis	89	90	98.9
Superficial vein thrombosis	81	81	100
Peripheral artery thrombosis	74	74	100
Mesenteric vein thrombosis	55	56	98.2
Venous thrombosis	41	41	100
TOTAL	**7,356**	**7,451**	98.7
Pulmonary embolism	**3,100**	**3,137**	98.8

Studie von Peter Doshi in Vaccine: Re-Analyse der klinischen Studien von Moderna und Pfizer

=> Gegenüberstellung von Impfschäden mit gewünschter Impfwirkung (Reduktion der Hospitalisierungszahlen)

Vaccine 40 (2022) 5798–5805

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults

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[c] Institute of Evidence-Based Healthcare, Bond University, Gold Coast, QLD, Australia
[d] Fielding School of Public Health and College of Letters and Science, University of California, Los Angeles, CA, USA
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[f] Clinical Excellence Research Center, School of Medicine, Stanford University, CA, USA
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mRNA vaccines
Pfizer-BioNTech COVID-19 vaccine
BNT162b2
Moderna COVID-19 vaccine mRNA-1273
NCT04368728
NCT04470427
Serious adverse events
Adverse events of special interest
Brighton Collaboration
Coalition for Epidemic Preparedness Innovations
Safety Platform for Emergency vACcines

ABSTRACT

Introduction: In 2020, prior to COVID-19 vaccine rollout, the Brighton Collaboration created a priority list, endorsed by the World Health Organization, of potential adverse events relevant to COVID-19 vaccines. We adapted the Brighton Collaboration list to evaluate serious adverse events of special interest observed in mRNA COVID-19 vaccine trials.

Methods: Secondary analysis of serious adverse events reported in the placebo-controlled, phase III randomized clinical trials of Pfizer and Moderna mRNA COVID-19 vaccines in adults (NCT04368728 and NCT04470427), focusing analysis on Brighton Collaboration adverse events of special interest.

Results: Pfizer and Moderna mRNA COVID-19 vaccines were associated with an excess risk of serious adverse events of special interest of 10.1 and 15.1 per 10,000 vaccinated over placebo baselines of 17.6 and 42.2 (95 % CI −0.4 to 20.6 and −3.6 to 33.8), respectively. Combined, the mRNA vaccines were associated with an excess risk of serious adverse events of special interest of 12.5 per 10,000 vaccinated (95 % CI 2.1 to 22.9); risk ratio 1.43 (95 % CI 1.07 to 1.92). The Pfizer trial exhibited a 36 % higher risk of serious adverse events in the vaccine group; risk difference 18.0 per 10,000 vaccinated (95 % CI 1.2 to 34.9); risk ratio 1.36 (95 % CI 1.02 to 1.83). The Moderna trial exhibited a 6 % higher risk of serious adverse events in the vaccine group: risk difference 7.1 per 10,000 (95 % CI –23.2 to 37.4); risk ratio 1.06 (95 % CI 0.84 to 1.33). Combined, there was a 16 % higher risk of serious adverse events in mRNA vaccine recipients: risk difference 13.2 (95 % CI −3.2 to 29.6); risk ratio 1.16 (95 % CI 0.97 to 1.39).

Discussion: The excess risk of serious adverse events found in our study points to the need for formal harm-benefit analyses, particularly those that are stratified according to risk of serious COVID-19 outcomes. These analyses will require public release of participant level datasets.

3.4. Harm-benefit considerations

In the Moderna trial, the excess risk of serious AESIs (15.1 per 10,000 participants) was higher than the risk reduction for COVID-19 hospitalization relative to the placebo group (6.4 per 10,000 participants). [3] In the Pfizer trial, the excess risk of serious AESIs (10.1 per 10,000) was higher than the risk reduction for COVID-19 hospitalization relative to the placebo group (2.3 per 10,000 participants).

Schaden ist größer als Nutzen!

Das ist die Basis für die bedingte Zulassung; wie kann eine solche Entscheidung passieren?

Publikation von Peter Doshi am 31. August publiziert und am 16. September schlägt die EMA die Vollzulassung vor.

Dabei wird argumentiert, aufgrund der verfügbaren Effizienz- und Sicherheitsdaten der breiten Anwendung braucht es keine spezielle Auflagen mehr. (Sie geben aber nicht an welche Daten sie meinen)

Außerdem wären alle zusätzlichen Daten zur Qualität übermittelt worden?

Außerdem soll die Zulassung auch für die angepassten „Impfstoffe“ gelten.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA recommends standard marketing authorisations for Comirnaty and Spikevax COVID-19 vaccines

News 16/09/2022

EMA's human medicines committee (CHMP) has recommended converting the conditional marketing authorisations of the COVID-19 vaccines Comirnaty (BioNTech/Pfizer's vaccine) and Spikevax (Moderna's vaccine) into standard marketing authorisations. These no longer need to be renewed annually. All other obligations for the companies remain in place.

Both vaccines were granted a conditional marketing authorisation at the time of their authorisation[1]. This imposed obligations on the companies to submit results from the ongoing clinical trials and to provide additional data on the pharmaceutical quality of the vaccine in light of the planned manufacturing scale-up.

These trials and additional studies, including observational studies, have provided reassuring data on key aspects such as how well the vaccines prevent severe COVID-19. In addition, the companies have provided all requested additional data on the pharmaceutical quality of the vaccines.

Taking into account the totality of the available efficacy and safety data resulting from the large utilisation of these vaccines, the specific obligations are no longer considered key to the benefit-risk (of the products), which has cleared the way to move from a conditional to a standard marketing authorisation.

Conditional marketing authorisations are reviewed annually. The CHMP recommended their conversion to standard marketing authorisations as an outcome of the second annual renewal procedure. This recommendation covers all existing and upcoming adapted Comirnaty and Spikevax vaccines, including the recently-approved adapted Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4/5 and Spikevax bivalent Original/Omicron BA.1.

As for any medicine, Comirnaty and Spikevax continue to be closely monitored. EMA will continue to assess any new data promptly and take action to protect patients as needed.

Übersterblichkeit?

Medicine & Clinical Science

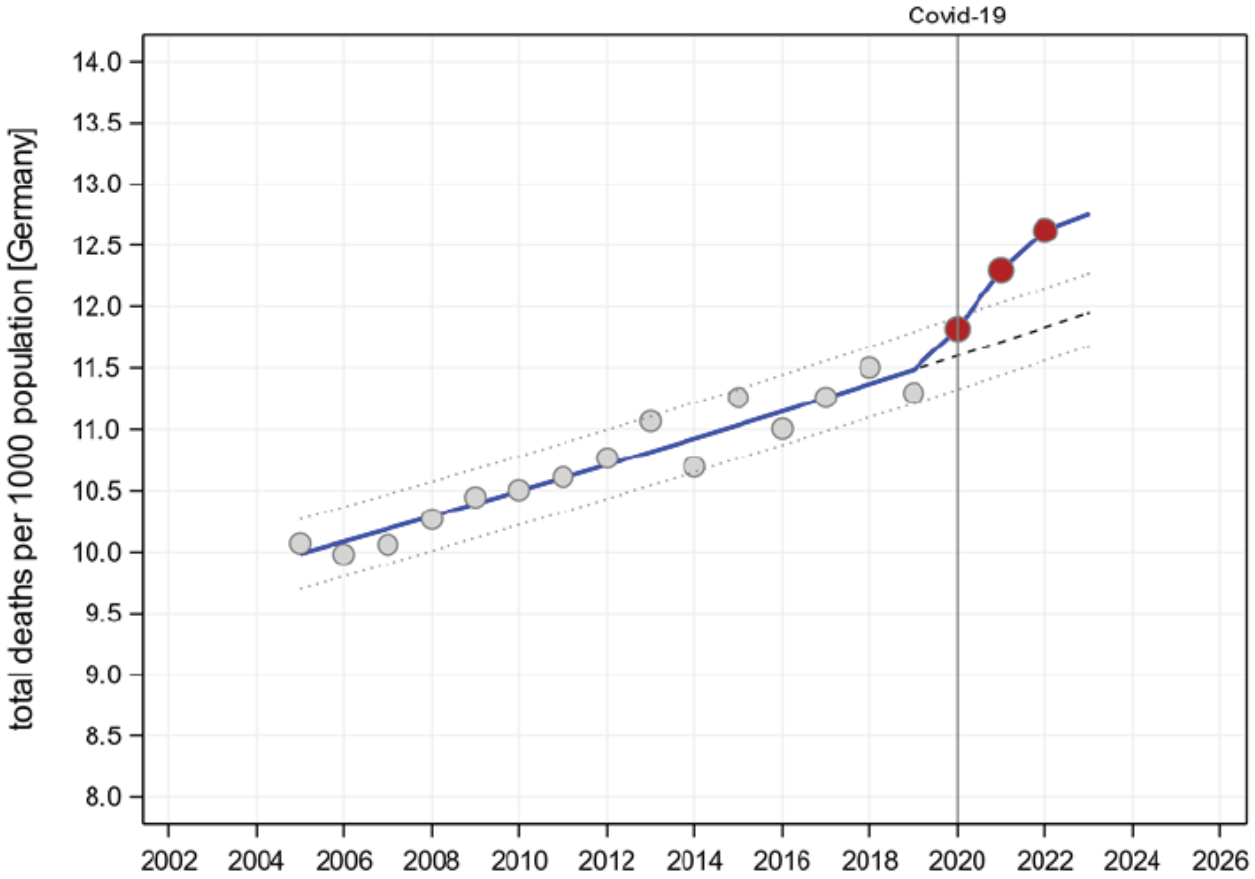
Research Letter

Annual All-Cause Mortality Rate in Germany and Japan (2005 to 2022) With Focus on The Covid-19 Pandemic: Hypotheses And Trend Analyses

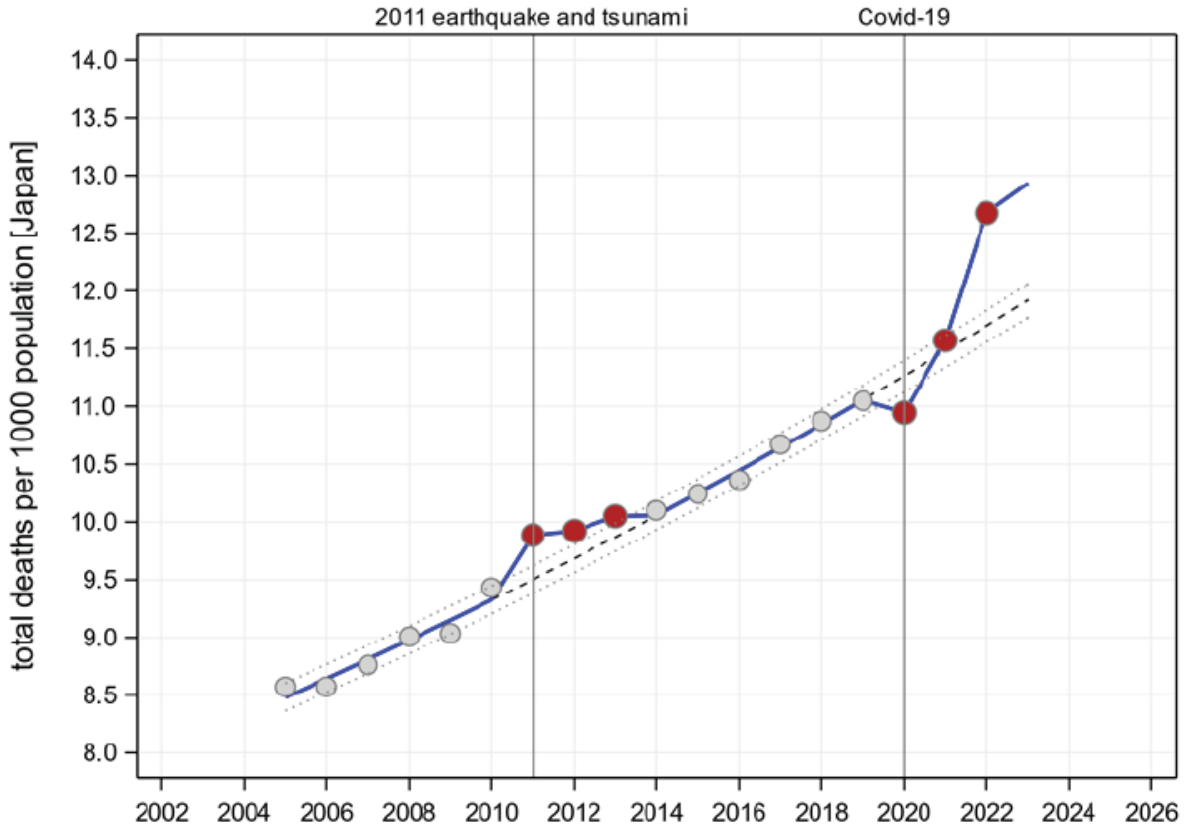
Hagen Scherb[1], Keiji Hayashi[2]

[1]Dipl.-Math. Dr. rer. nat.; Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Computational Biology, Ingolstädter Landstr. 1, D-85764 Neuherberg, Germany.
[2]Medical Doctor (MD), Hayashi Children's Clinic, 4-6-11-1F Nagata, Joto-ku Osaka-Shi 536-0022 Osaka, Japan

Correspondence
Hagen Scherb



Gesamtzahl Todesfälle in Deutschland pro 1000 Einwohner (gepunktete Linien: 95%-Vorhersageband)



Gesamtzahl Todesfälle in Japan pro 1000 Einwohner (gepunktete Linien: 95%-Vorhersageband)

Warum keine Alarmmeldungen vom PEI?

Analyse Kuhbandner bezüglich PEI Modell zur Risikobewertung (Observed-versus-Expected Sicherheitsanalyse)

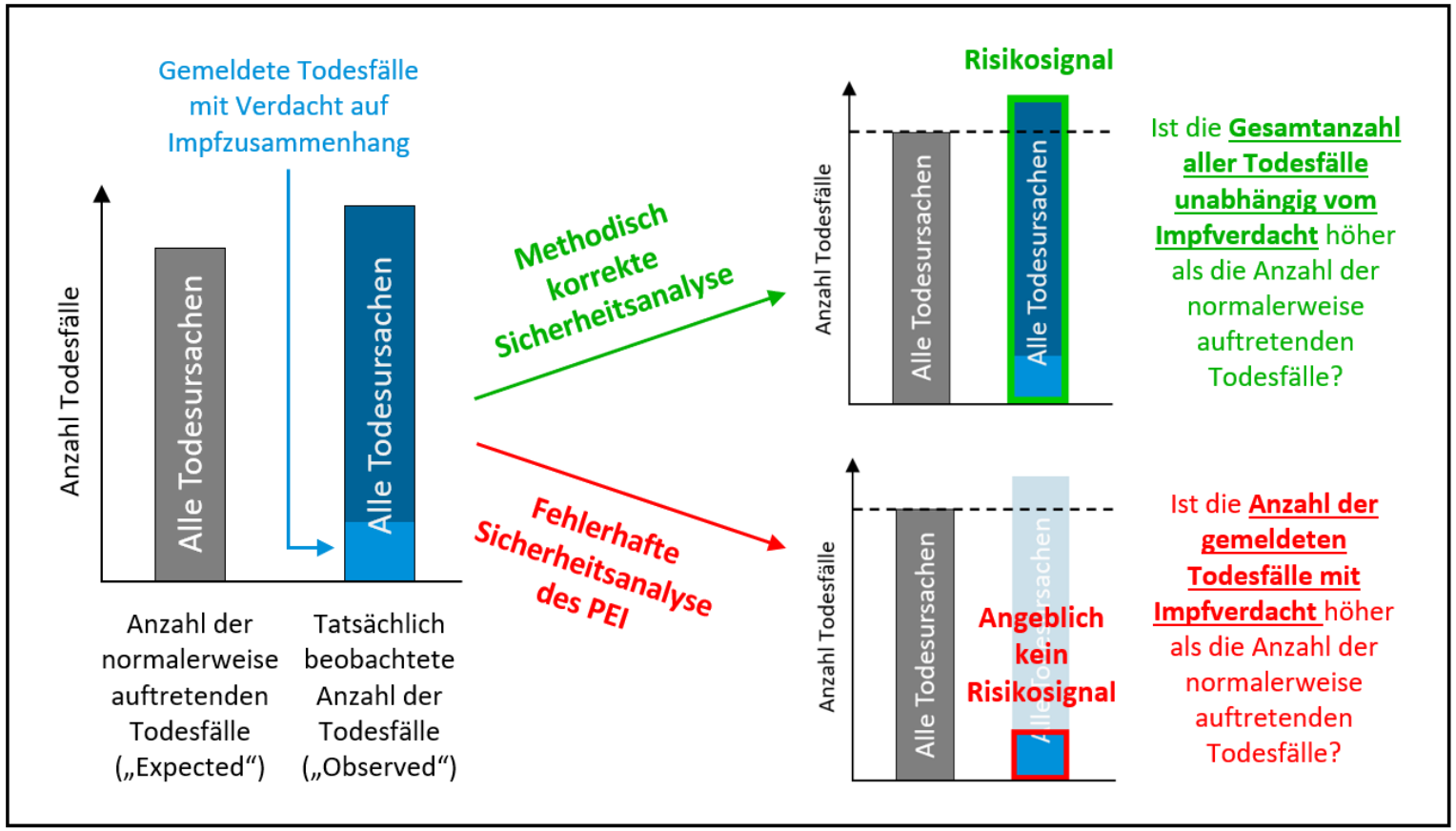


Illustration der methodisch korrekten Anwendung der Observed-versus-Expected Sicherheitsanalyse und der fehlerhaften Anwendung durch das Paul-Ehrlich-Institut.

=> Die Anforderungen an ein „Signal“ werden vom PEI aufgrund der verwendeten OvE-Analyse so hoch angesetzt, dass selbst bei gemeldeten impfbedingten Verdachtstodesfällen in sechsstelliger Höhe noch kein Signal ausgelöst werden würde.

Dies wurde auch im Zuge der Verhandlung vor dem Bundesverwaltungsgericht explizit bestätigt. Auf die Frage *„Ist es korrekt, dass das PEI selbst bei 75.000 gemeldeten Todesfällen mit Verdacht auf einen Impfzusammenhang [diese Zahl bezog sich auf den Sicherheitsbericht vom 19.8.2021] behaupten würde, dass der Impfstoff sicher sei?“* antwortete die geladene Sachverständige Dr. O. vom PEI: *"Das ist korrekt."*

Auf Nachfrage der Richterin, ob inzwischen die für ein Warnsignal zu übertreffende Schwelle im sechsstelligen Bereich liegen würde, wurde auch das von Dr. O. bestätigt.

Mit welcher Begründung wird diese Praxis nicht umgehend geändert?

Zusammenfassung

- Versagen wissenschaftlicher Mechanismen.
  - Keine Diskussion
  - Stattdessen: Diffamierung und Ausgrenzung
- Versagen standardisierter Kriterien der Zulassung

  => Sofortiger Zugang zu den vollständigen Daten der klinischen Studien
- Versagen bzw. falsch angewendete Sicherheitskriterien
- Versagen der Qualitätskontrolle

Konsequenzen?

Ärztlicher Berufsverband Hippokratischer Eid

https://impfen-wer-will.de/

Der ÄBVHE fordert daher aus ethischen wie medizinischen Gründen

- ➔ den sofortigen Impfstopp weltweit
- ➔ eine Aufarbeitung der Versäumnisse und Fehlentscheidungen der Verantwortlichen für dieses Zulassungs- und Impf-Desaster, welches der Bevölkerung weit mehr geschadet hat, als es die Krankheit selbst jemals vermocht hätte
- ➔ ein Verbot der Gain-of-Function-Forschung weltweit, welche uns dieses Problem per Unfall oder Absicht erzeugt hat
- ➔ Gesundheitsminister ohne Lobbyismuseinfluß, d.h. auch ohne „Pharmabiographie“ oder familiäre Pharmanähe
- ➔ unabhängige wissenschaftliche Kontrollen aller Arznei- und Impfstoffzulassungsstudien VOR deren Zulassung

Bitte folgen Sie uns auf: https://www.aerzte-hippokratischer-eid.de/de/mitmach-aktionen/newsletter-bestellen/

Zusatzfolien

Received: 22 January 2023 | Accepted: 26 March 2023
DOI: 10.1111/eci.13998

RESEARCH LETTER

WILEY

Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine

Max Schmeling[1] | **Vibeke Manniche**[2] | **Peter Riis Hansen**[3]

[1]Innometric, Skørping, Denmark
[2]LIVA, Copenhagen, Denmark
[3]Department of Cardiology, Kobenhavns Universitet, Copenhagen, Denmark

Correspondence
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Email: prha@sund.ku.dk

Einheitliche Qualität?

Woher kommt die Variation im Schadpotential je nach Charge?

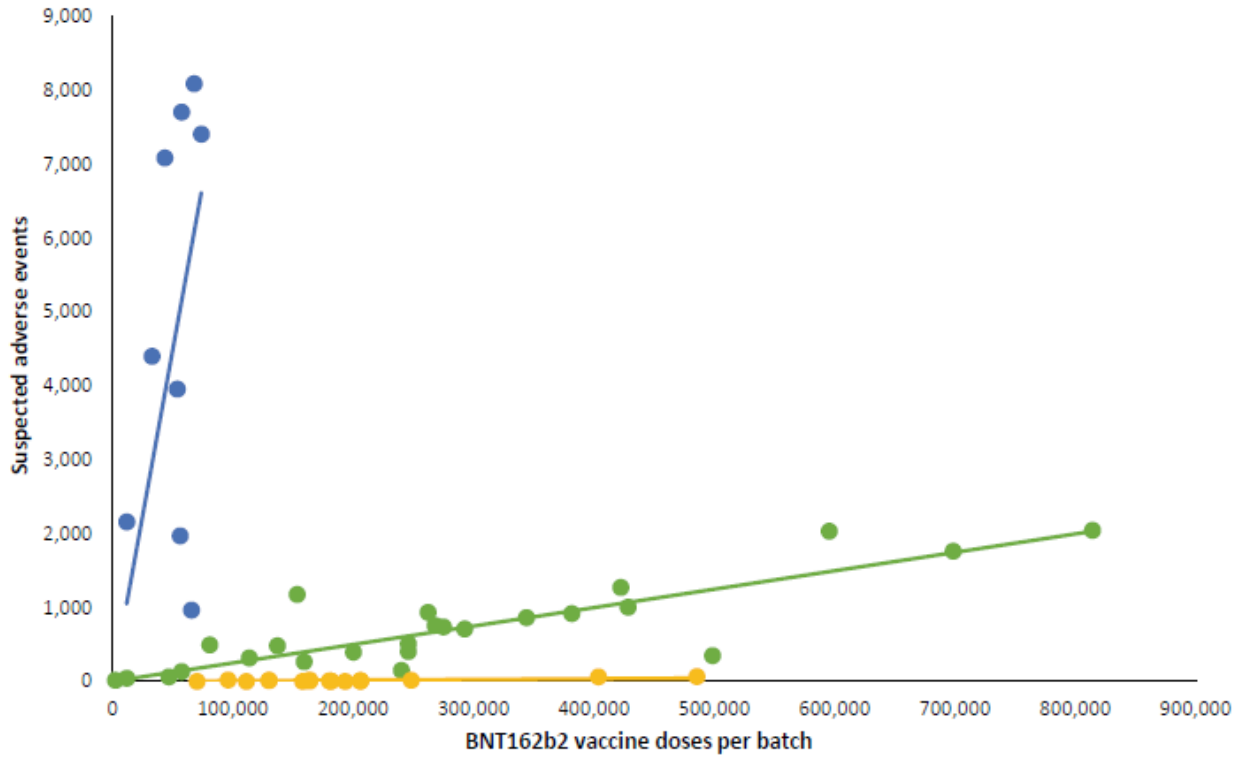


FIGURE 1 Numbers of suspected adverse events (SAEs) after BNT612b2 mRNA vaccination in Denmark (27 December 2020–11 January 2022) according to the number of doses per vaccine batch. Each dot represents a single vaccine batch. Trendlines are linear regression lines. Blue: $R^2 = 0.78$, $\beta = 0.0898$ (95% confidence interval [CI] 0.0514–0.1281), green: $R^2 = 0.89$, $\beta = 0.0025$ (95% CI 0.0021–0.0029), yellow: $R^2 = 0.68$, $\beta = 0.000087$ (95% CI 0.000056–0.000118). Vaccine batches representing the blue, green and yellow trendlines comprised 4.22%, 63.69% and 32.09% of all vaccine doses, respectively, with 70.78%, 27.49% and 47.15% (blue trendline), 28.84%, 71.50% and 51.99% (green trendline), and 0.38%, 1.01%, and 0.86% (yellow trendline) of all SAEs, serious SAEs, and SAE-related deaths, respectively.

180 Grad Wende von einem Absatz zum anderen!

Pfizer Responds to Research Claims

Friday, January 27, 2023 - 08:00pm

Pfizer macht keine gain of function oder gezielte Evolutionsforschung

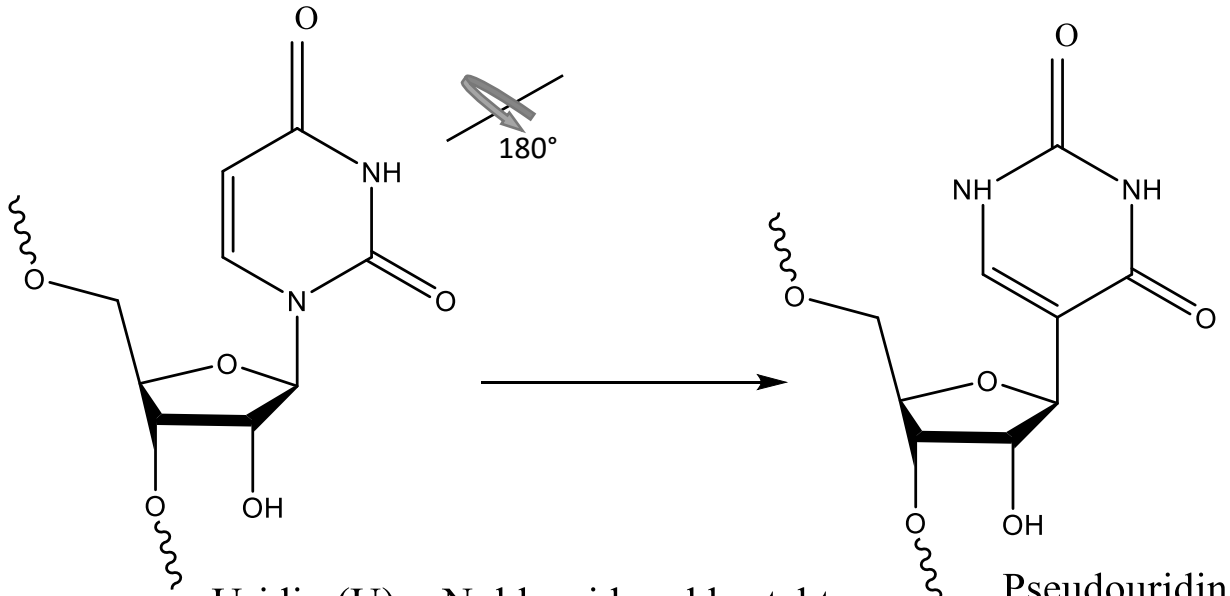
New York, N.Y., January 27, 2023 – Allegations have recently been made related to gain of function and directed evolution research at Pfizer and the company would like to set the record straight.

In the ongoing development of the Pfizer-BioNTech COVID-19 vaccine, Pfizer has not conducted gain of function or directed evolution research. Working with collaborators, we have conducted research where the original SARS-CoV-2 virus has been used to express the spike protein from new variants of concern. This work is undertaken once a new variant of concern has been identified by public health authorities. This research provides a way for us to rapidly assess the ability of an existing vaccine to induce antibodies that neutralize a newly identified variant of concern. We then make this data available through peer reviewed scientific journals and use it as one of the steps to determine whether a vaccine update is required.

.. außer in einigen Fällen, d.h. sie machen es doch.

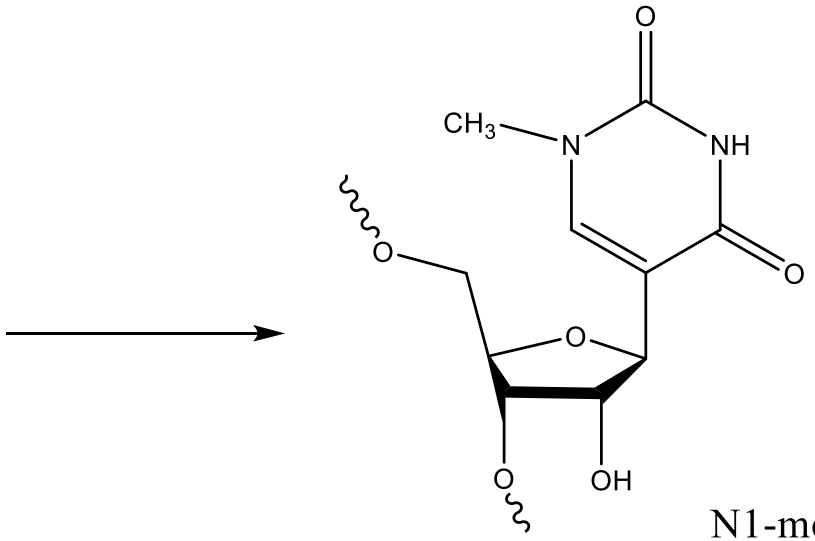
In addition, to meet U.S. and global regulatory requirements for our oral treatment, PAXLOVID™, Pfizer undertakes in vitro work (e.g., in a laboratory culture dish) to identify potential resistance mutations to nirmatrelvir, one of PAXLOVID's two components. With a naturally evolving virus, it is important to routinely assess the activity of an antiviral. Most of this work is conducted using computer simulations or mutations of the main protease–a non-infectious part of the virus. In a limited number of cases when a full virus does not contain any known gain of function mutations, such virus may be engineered to enable the assessment of antiviral activity in cells. In addition, in vitro resistance selection experiments are undertaken in cells incubated with SARS-CoV-2 and nirmatrelvir in our secure Biosafety level 3 (BSL3) laboratory to assess whether the main protease can mutate to yield resistant strains of the virus. It is important to note that these studies are required by U.S. and global regulators for all antiviral products and are carried out by many companies and academic institutions in the U.S. and around the world.

Fact-based information rooted in sound science is vitally important to overcoming the COVID-19 pandemic and Pfizer remains committed to transparency and helping alleviate the devastating burden of this disease.



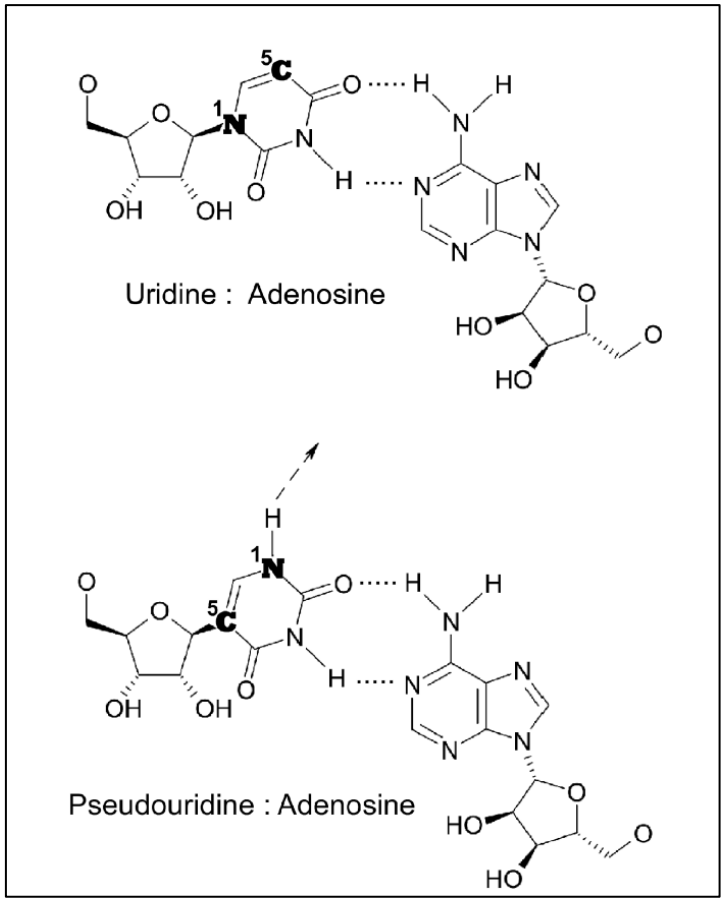
Uridin (U) = Nukleosid und besteht
aus der Nukleinbase Uracil
und dem Zucker ß-D-Ribose

Pseudouridin
(Ψ)



N1-methyl-Pseudouridin
(N1-methyl-Ψ)

Variation Uridin → N1-methyl Pseudouridin



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doi:10.1093/nar/gkr586

Nucleoside modifications in RNA limit activation of 2′-5′-oligoadenylate synthetase and increase resistance to cleavage by RNase L

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Examining translation in RNase L [illegible] cells and mice confirmed that RNase L activity reduces translation of unmodified mRNA, which is not observed with modified mRNA. Additionally, mRNA containing the nucleoside modification pseudouridine is translated longer and has an extended half-life. The observation that modified nucleosides in RNA reduce 2-5A pathway activation joins OAS and RNase L to the list

Published online 23 February 2017

Nucleic Acids Research, 2017, Vol. 45, No. 10 6023–6036
doi: 10.1093/nar/gkx135

N1-methyl-pseudouridine in mRNA enhances translation through eIF2α-dependent and independent mechanisms by increasing ribosome density

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ABSTRACT

Certain chemical modifications confer increased stability and low immunogenicity to *in vitro* transcribed mRNAs, thereby facilitating expression of therapeutically important proteins. Here, we demonstrate that N1-methyl-pseudouridine (N1mΨ) outperforms several other nucleoside modifications and their combinations in terms of translation capacity. Through extensive analysis of various modified transcripts in cell-free translation systems, we deconvolute the different components of the effect on protein expression independent of mRNA stability mechanisms. We

Spike-Proteine: Swissmedic ahnungslos

Die Zulassungsbehörde kann nicht sagen, welche Dosis an Spike-Proteinen durch mRNA-Impfstoffe im Körper entsteht.

Philipp Gut

Die Antwort von Swissmedic darauf ist, dass Swissmedic darauf keine Antwort hat. «Die Produktion von Spike-Protein ist von verschiedenen Faktoren abhängig, so zum Beispiel Immunschwäche, Krankheiten, welche die Person hat, individuellen Faktoren etc. So können wir nicht sagen, wie viel Protein bei Ihnen gebildet wird», schrieb Swissmedic am 6. Januar 2023.

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journal homepage: www.elsevier.com/locate/jconrel

Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes

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ABSTRACT

In recent years, in vitro transcribed messenger RNA (mRNA) has emerged as a potential therapeutic platform. To fulfill its promise, effective delivery of mRNA to specific cell types and tissues needs to be achieved. Lipid nanoparticles (LNPs) are efficient carriers for short-interfering RNAs and have entered clinical trials. However, little is known about the potential of LNPs to deliver mRNA. Here, we generated mRNA-LNPs by incorporating HPLC purified, 1-methylpseudouridine-containing mRNA comprising codon-optimized firefly luciferase into stable LNPs. Mice were injected with 0.005–0.250 mg/kg doses of mRNA-LNPs by 6 different routes and high levels of protein translation could be measured using in vivo imaging. Subcutaneous, intramuscular and intradermal injection of the LNP-encapsulated mRNA translated locally at the site of injection for up to 10 days. For several days, high levels of protein production could be achieved in the lung from the intratracheal administration of mRNA. Intravenous and intraperitoneal and to a lesser extent intramuscular and intratracheal deliveries led to trafficking of mRNA-LNPs systemically resulting in active translation of the mRNA in the liver for 1–4 days. Our results demonstrate that LNPs are appropriate carriers for mRNA in vivo and have the potential to become valuable tools for delivering mRNA encoding therapeutic proteins.

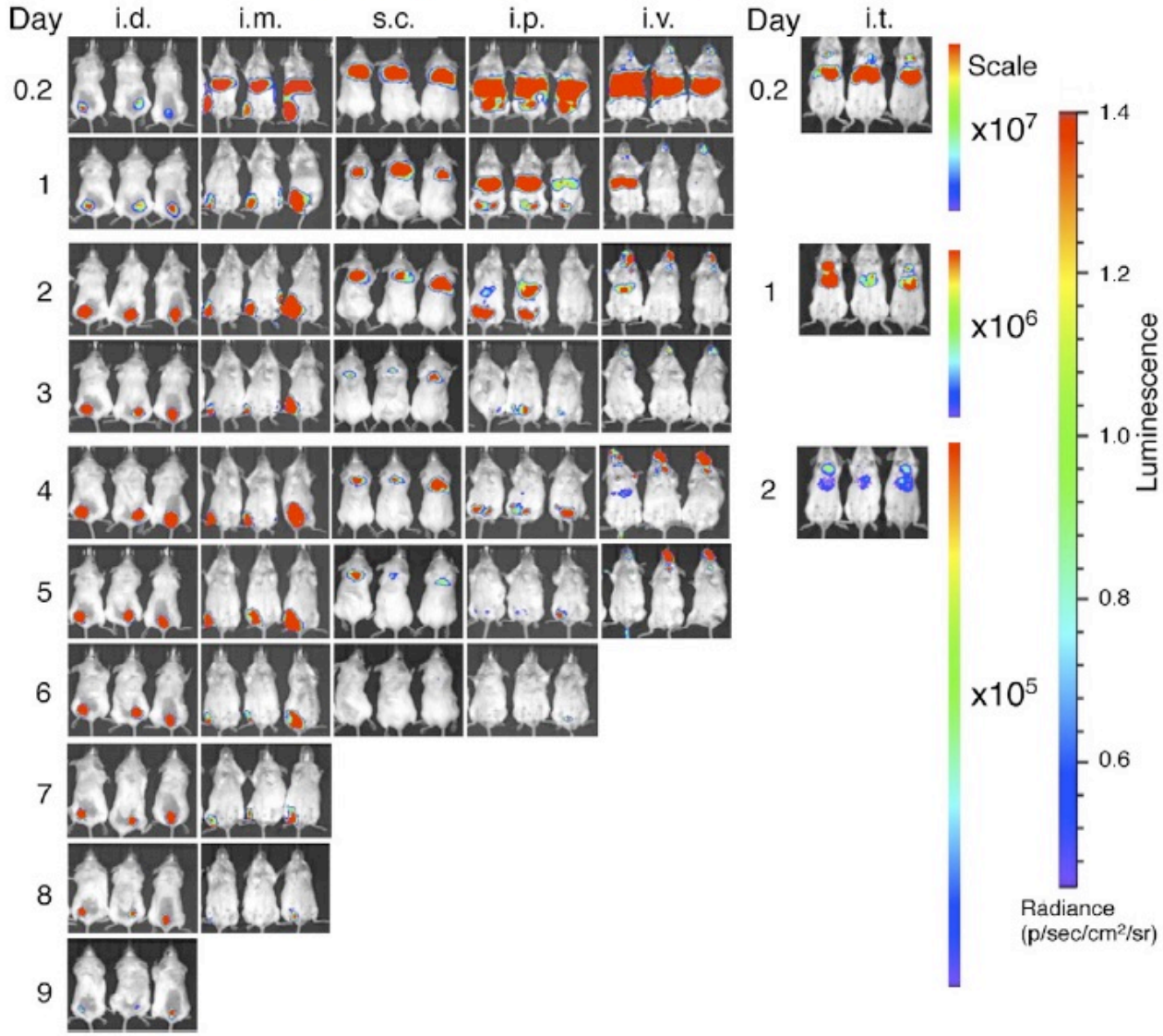


Fig. 2. Duration and translational pattern of mRNA-LNPs in mice injected by various routes. Representative IVIS images of groups of 3 BALB/c mice injected with 5.0 μg mRNA-LNPs by the intradermal (i.d.), intramuscular (i.m.), subcutaneous (s.c.), intravenous (i.v.), intraperitoneal (i.p.) and intratracheal (i.t.) routes. Relative luminescence plot is shown and the scale of luminescence is indicated.

5. Conclusion

The expression profile of *in vitro* and *in vivo* delivered HPLC-purified, 1-methylpseudouridine, LNP-encapsulated firefly luciferase encoding mRNA was evaluated in this study. mRNA-LNP was efficiently taken up by immortalized, as well as, primary cells in vitro. Our major finding is the outstanding ability of mRNA-LNPs for in vivo mRNA delivery. To our knowledge, this is the first demonstration that a single injection of low dose (0.005–0.250 mg/kg) mRNA administered by various injection routes translated at high levels for up to 10 days depending on the dose and the site of the delivery. Our findings clearly show that mRNA is a promising non-viral delivery platform that has a bright future as a potent therapeutic and that delivery by LNPs that have performed well in clinical trials offers a clear step towards research application and clinical development.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jconrel.2015.08.007.

Swedish Public Health Agency reporting has distorted mortality rates for the unvaccinated and the vaccinated

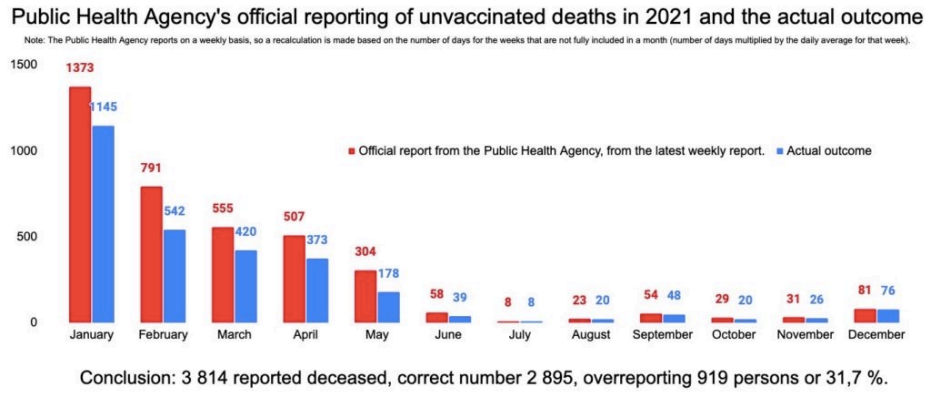
https://lakaruppropet.se/public-health-agency-reporting-has-distorted-mortality-rates-for-the-unvaccinated-and-vaccinated/

should have been counted in vaccinated group, which thus increases by 919 persons or 135%.

Number of deaths per month in Sweden in 2021 in covid-19 in the group of unvaccinated persons and three groups of vaccinated persons

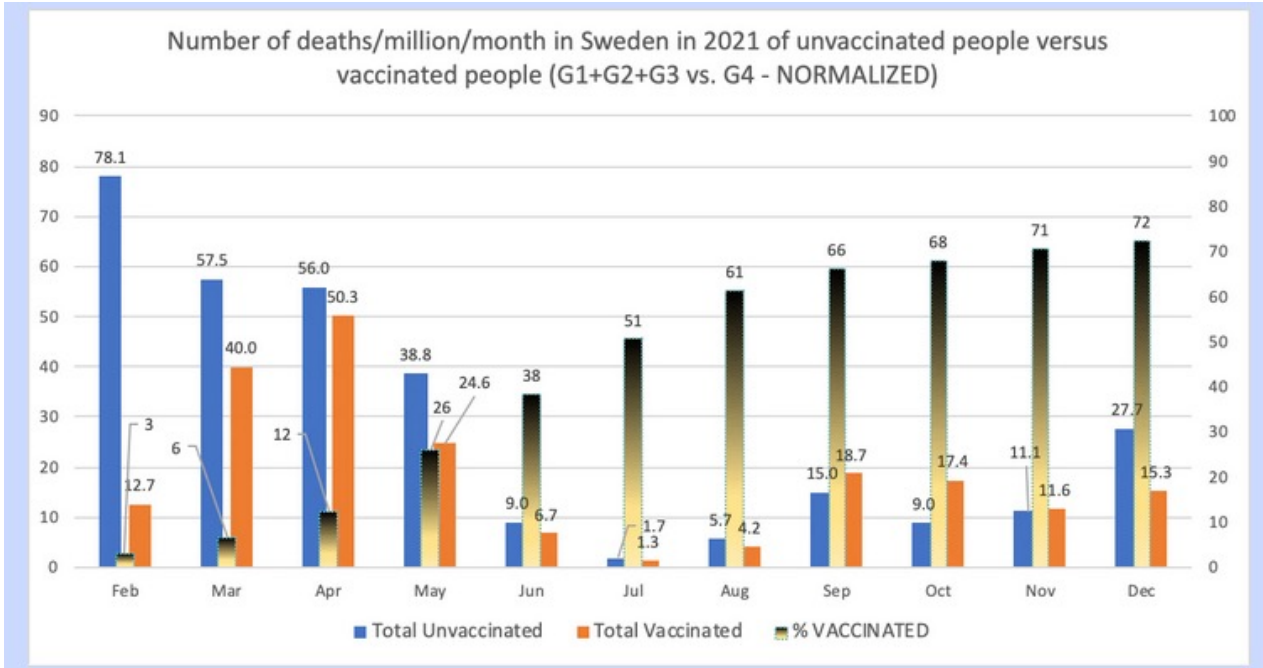
Months/ groups	1. Completely unvaccinated	2. Have received dose 1 and < 21 days have passed	3. Partially vaccinated	4. Fully vaccinated	Totally per month
January.	1145	219	9	0	1373
February.	542	191	54	4	791
March.	420	89	50	27	586
April.	373	84	53	65	575
May.	178	67	53	67	365
June.	G1 39	G2 10	G3 9	G4 27	85
July.	8	1	0	7	16
August.	20	1	2	27	50
September.	48	0	5	129	182
October.	20	2	8	124	154
November.	26	1	7	86	120
December.	76	1	3	116	196
Totally per group	2895	666	253	679	4493

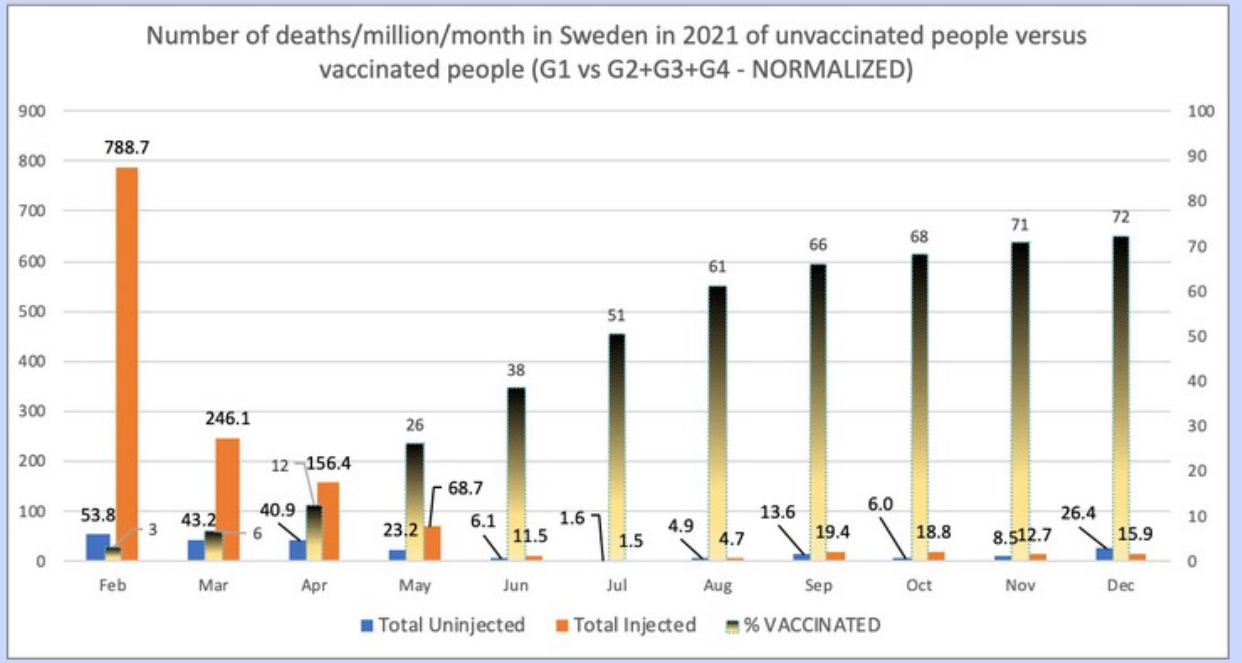
The following chart shows a comparison the data provided by the Agency in its latest weekly report on the number of deaths in the unvaccinated group with the data we received [2].



Conclusion: 3 814 reported deceased, correct number 2 895, overreporting 919 persons or 31,7 %.

=> Unter Berücksichtigung der Impfquote ergibt sich folgendes Bild:





Hochfragwürdige Studie des Imperial College London: Gekaufte Forschung ??

Global impact of the first year of COVID-19 vaccination: a mathematical modelling study

Oliver J Watson*, Gregory Barnsley*, Jaspreet Toor, Alexandra B Hogan, Peter Winskill, Azra C Ghani

Summary

Background The first COVID-19 vaccine outside a clinical trial setting was administered on Dec 8, 2020. To ensure global vaccine equity, vaccine targets were set by the COVID-19 Vaccines Global Access (COVAX) Facility and WHO. However, due to vaccine shortfalls, these targets were not achieved by the end of 2021. We aimed to quantify the global impact of the first year of COVID-19 vaccination programmes.

Methods A mathematical model of COVID-19 transmission and vaccination was separately fit to reported COVID-19 mortality and all-cause excess mortality in 185 countries and territories. The impact of COVID-19 vaccination programmes was determined by estimating the additional lives lost if no vaccines had been distributed. We also estimated the additional deaths that would have been averted had the vaccination coverage targets of 20% set by COVAX and 40% set by WHO been achieved by the end of 2021.

Findings Based on official reported COVID-19 deaths, we estimated that vaccinations prevented 14·4 million (95% credible interval [CrI] 13·7–15·9) deaths from COVID-19 in 185 countries and territories between Dec 8, 2020, and Dec 8, 2021. This estimate rose to 19·8 million (95% CrI 19·1–20·4) deaths from COVID-19 averted when we used excess deaths as an estimate of the true extent of the pandemic, representing a global reduction of 63% in total deaths (19·8 million of 31·4 million) during the first year of COVID-19 vaccination. In COVAX Advance Market Commitment countries, we estimated that 41% of excess mortality (7·4 million [95% CrI 6·8–7·7] of 17·9 million deaths) was averted. In low-income countries, we estimated that an additional 45% (95% CrI 42–49) of deaths could have been averted had the 20% vaccination coverage target set by COVAX been met by each country, and that an additional 111% (105–118) of deaths could have been averted had the 40% target set by WHO been met by each country by the end of 2021.

Interpretation COVID-19 vaccination has substantially altered the course of the pandemic, saving tens of millions of lives globally. However, inadequate access to vaccines in low-income countries has limited the impact in these settings, reinforcing the need for global vaccine equity and coverage.

Funding Schmidt Science Fellowship in partnership with the Rhodes Trust; WHO; UK Medical Research Council; Gavi, the Vaccine Alliance; Bill & Melinda Gates Foundation; National Institute for Health Research; and Community Jameel.

Lancet Infect Dis 2022

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See Online/Comment https://doi.org/10.1016/S1473-3099(22)00417-0

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Einschätzung Kuhbandner zur hochfragwürdigen Studie des Imperial College London

Liebe Alle,

da gerade eine hochfragwürdige Studie des Imperial College London durch die Mainstream-Medien geistert, die angeblich zeigt, dass die Impfungen 20 Millionen Todesopfer verhindert hätten, hier ein paar hilfreiche Argumente um die zutiefste Fragwürdigkeit dieser Studie aufzudecken:

1) Eine gute Zusammenfassung kritischer Punkte findet man hier:

https://brownstone.org/articles/did-covid-vaccines-save-tens-of-millions-of-lives/

Hier in Kürze ein paar Punkte:

- es handelt sich mal wieder um eine evidenzfreie mathematische Modellierung
- es wird unter anderem nicht beachtet, dass die neueren Virusvarianten eine deutlich geringere Sterblichkeit aufweisen, dass die hoch vulnerablen Personen bereits vorher verstorben sind und kein zweites Mal versterben können, dass sich eine natürliche Immunität aufgebaut hat und dass sich die Behandlungsmöglichkeiten verbessert haben
- Interessant ist auch, wer die Studie finanziert hat: u.a. Global Alliance for Vaccines Initiative (GAVI), the Bill and Melinda Gates Foundation, Rhodes Trust...

2) Hier ein Twitter Beitrag, welcher die Fragwürdigkeit der Modellierung in der Studie, auf welcher die Aussage beruht, visuell sehr einfach auf den Punkt bringt: