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
None; the Meta-Research Innovation Center at Stanford (METRICS) has been funded with grants from the Laura and John Arnold Foundation.

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

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D. Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

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%

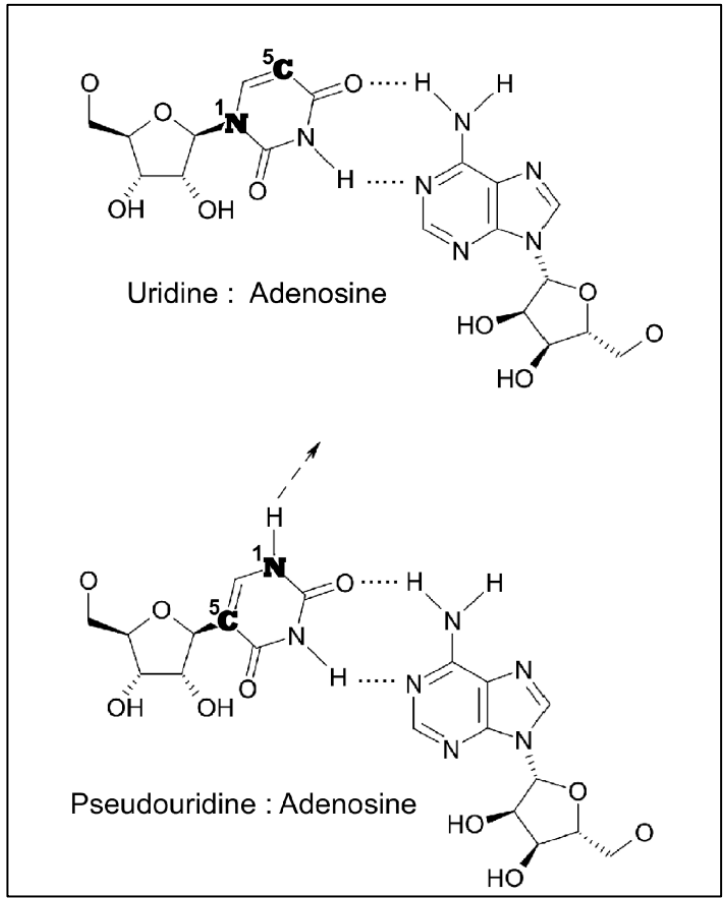
modRNA-Technologie

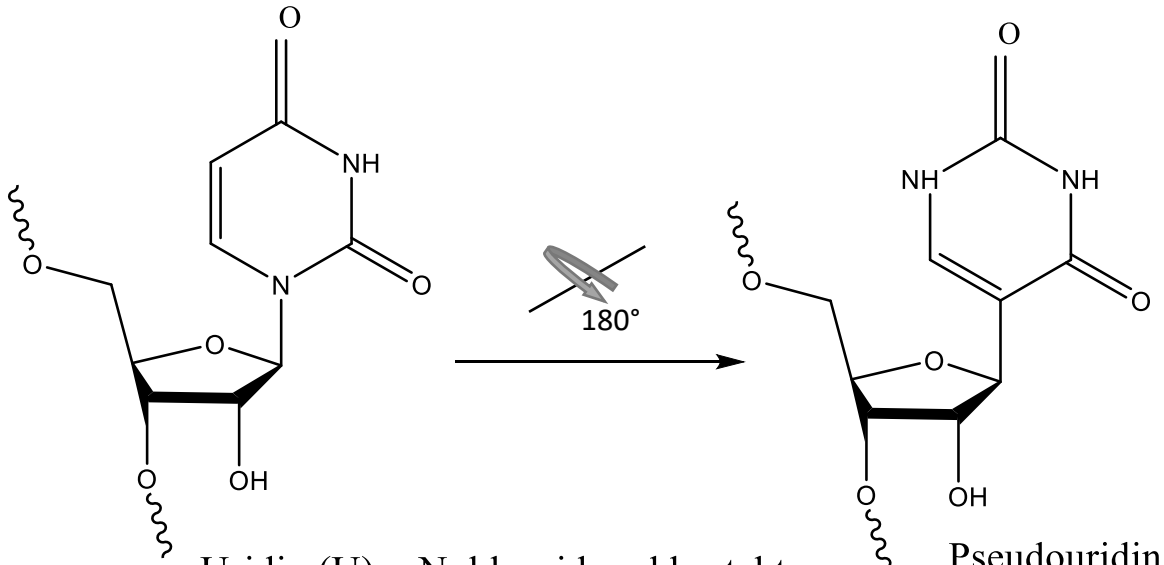
- Wirksamkeit
- Qualität
- Inhaltsstoffe
- Probleme

GDCh-Wissenschaftsforum Chemie (WIFO) Leipzig 4. – 6. September 2023:
Plenarvortrag: **Revolutionizing mRNA for Life** S. Fakih, Tübingen/D

Warum mRNA und nicht modRNA
oder
mod mRNA ?

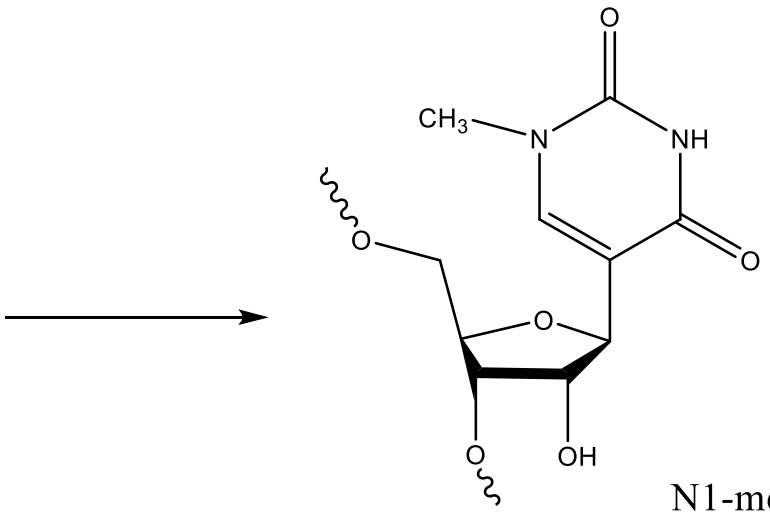
Modifizierung: Uridin → N1-methyl Pseudouridin





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

Pseudouridin (Ψ)



N1-methyl-Pseudouridin (N1-methyl-Ψ)

Published online 3 August 2011 *Nucleic Acids Research, 2011, Vol. 39, No. 21* **9329–9338**
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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Received April 17, 2011; Revised June 27, 2011; Accepted June 30, 2011

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

Yuri V. Svitkin[1,2,*], Yi Min Cheng[3], Tirtha Chakraborty[3], Vladimir Presnyak[3], Matthias John[3] and Nahum Sonenberg[1,2,*]

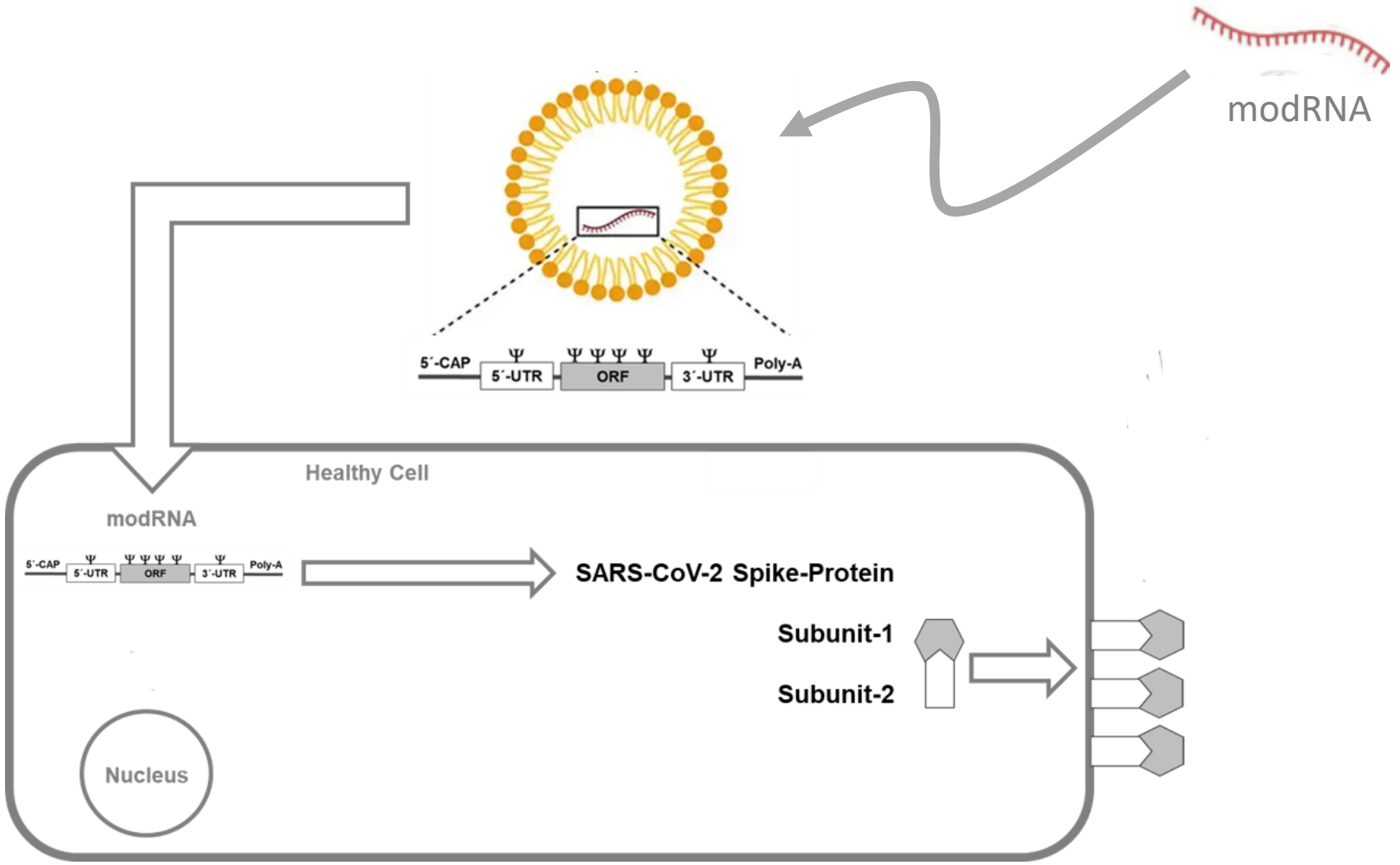
[1]Department of Biochemistry, McGill University, Montréal, Québec H3A 1A3, Canada, [2]Rosalind and Morris Goodman Cancer Research Centre, Montréal, Québec H3A 1A3, Canada and [3]Moderna Therapeutics, Cambridge, MA 02139, USA

Received January 18, 2017; Editorial Decision February 12, 2017; Accepted February 20, 2017

ABSTRACT

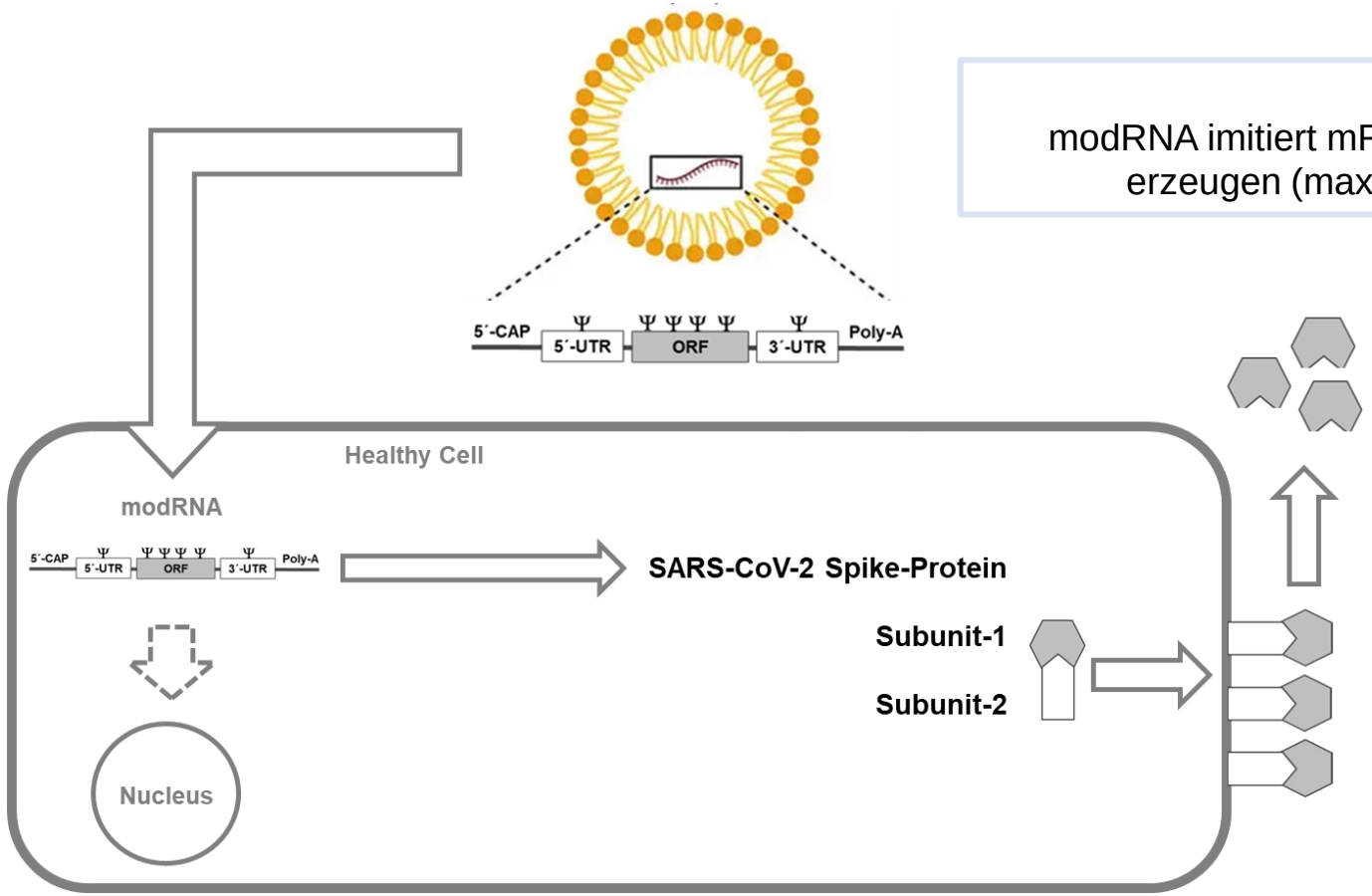
Certain chemical modifications confer increased stability and low immunogenicity to *in vitro* transcribed mRNAs, thereby facilitating expression of therapeutically important proteins. Here, we demonstrate that N1-methyl-pseudouridine (N1mΨ) outperforms several other nucleoside modifications and their 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

modRNA Technik Prinzip



modRNA basierte Injektionen erzeugen vielfältige Schäden

1. Das trojanische Pferd
Lipid Nanopartikel imitieren Exosome => biologische Barrieren werden überwunden und modRNA wird in die Zellen geschmuggelt (giftige Lipide).



2. Das vermeintlich Gute
modRNA imitiert mRNA und zwingt gesunde Zellen ein fremdes virales Protein zu erzeugen (maximal lang mit maximaler Effizient und höherer Fehlerrate)

5. Giftstoffe
Omnipräsenz eines fremden Antigens im Körper führt zur hyper-inflammation.

4. Das Todesurteil
Präsentation des fremden Antigens auf der Oberfläche wandelt die Zelle von Freund zu Feind .

3. Größter anzunehmender Unfall
Integration der modRNA in DNA (in vitro: : https://doi.org/10.3390/cimb44030073)

Weitere Probleme bei der Proteinbiosynthese

Article

N^1-methylpseudouridylation of mRNA causes +1 ribosomal frameshifting

https://doi.org/10.1038/s41586-023-06800-3

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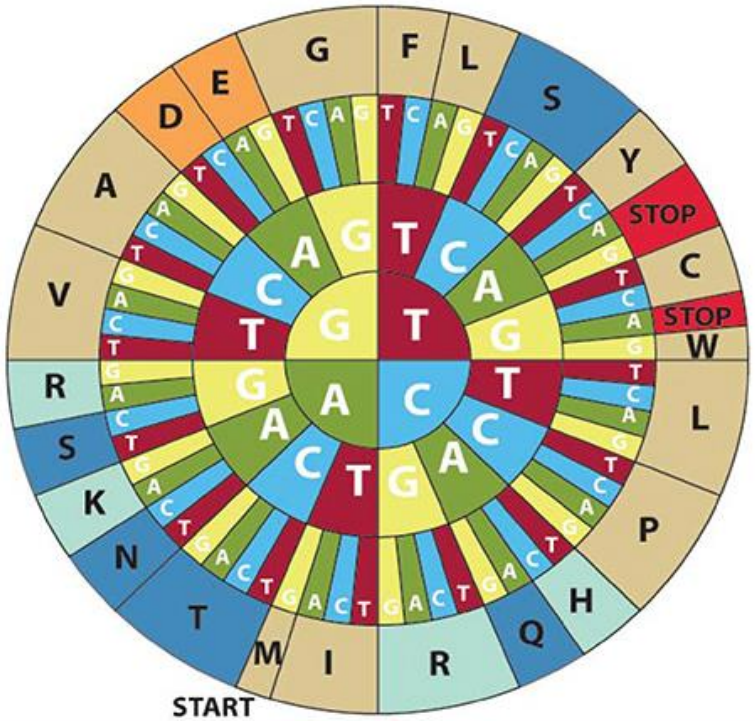
Open access

Thomas E. Mulroney[1], Tuija Pöyry[1], Juan Carlos Yam-Puc[1], Maria Rust[1], Robert F. Harvey[1], Lajos Kalmar[1], Emily Horner[1], Lucy Booth[1], Alexander P. Ferreira[1], Mark Stoneley[1], Ritwick Sawarkar[1], Alexander J. Mentzer[2], Kathryn S. Lilley[3], C. Mark Smales[4,5], Tobias von der Haar[4], Lance Turtle[6], Susanna Dunachie[7,8,9], Paul Klenerman[7,10], James E. D. Thaventhiran[1,11]✉ & Anne E. Willis[1,11]✉

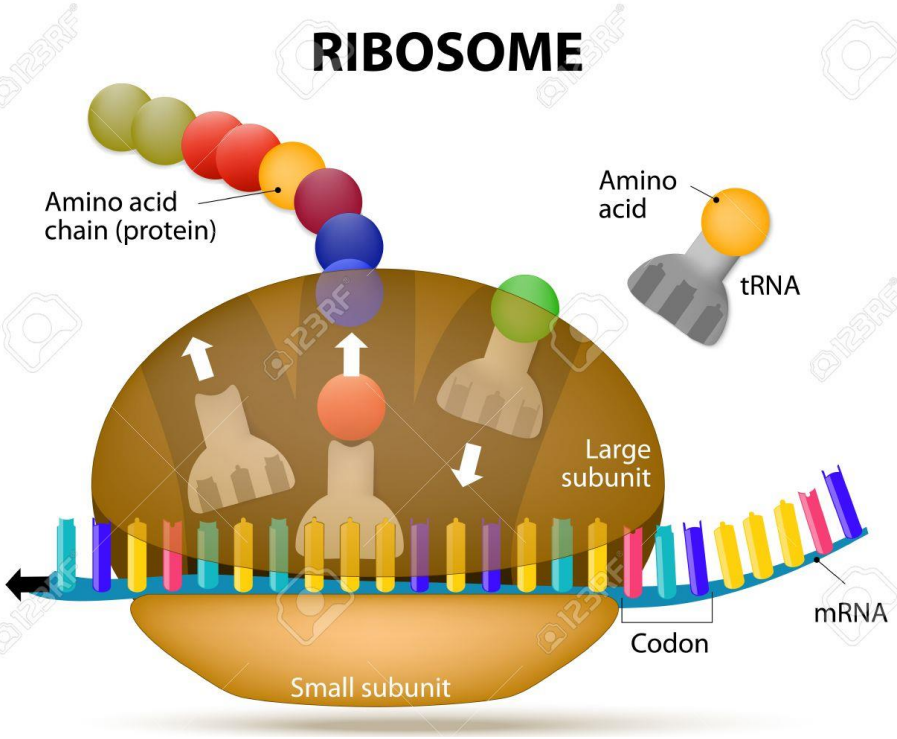
explored. Here we demonstrate that incorporation of N^1-methylpseudouridine into mRNA results in +1 ribosomal frameshifting in vitro and that cellular immunity in mice and humans to +1 frameshifted products from BNT162b2 vaccine mRNA translation occurs after vaccination. The +1 ribosome frameshifting observed is probably a

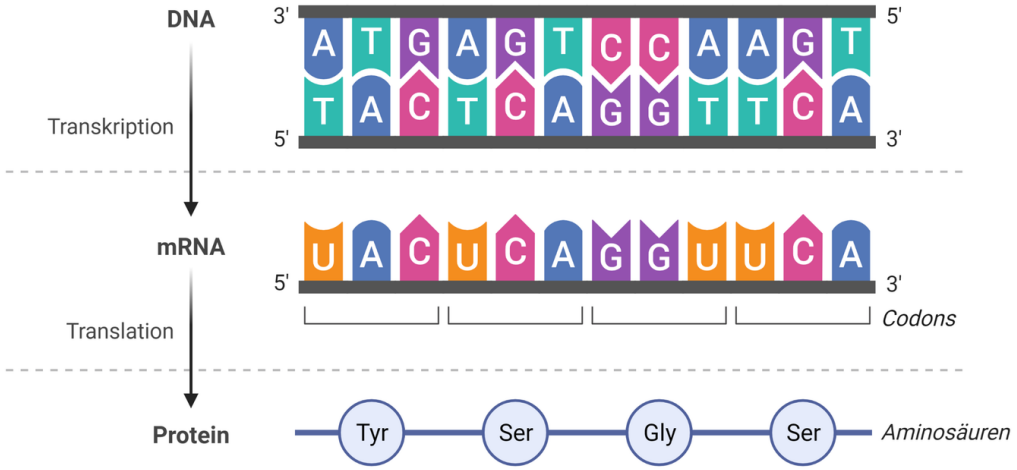
Proteinbiosynthese



Amino acid code

A - Alanine	G - Glycine	M - Methionine	S - Serine
C - Cysteine	H - Hisitidine	N - Asparagine	T - Threonine
D - Aspartic Acid	I - Isoleucine	P - Proline	V - Valine
E - Glutamic acid	K - Lysine	Q - Glutamine	W - Tryptophan
F - Phenylalanine	L - Leucine	R - Arginine	Y - Tyrosine





Auswirkung des Verrutschens des Leserahmens (ribosomaler shift)

UAC UCA GGU UCA => Tyrosin-Serin-Glycin-Serin

1-Shift => * ACU CAG GUU CA => Threonin-Glutamin-Valin-*

- Nach dem Verrutschen des Leserahmens werden irgendwelche anderen Aminosäuren eingebaut

  => Proteine unbekannter Funktion

  => Immunreaktion gegen diese Proteine

  => Amyloid Ablagerungen?

Wirksamkeit?

thebmjopinion Latest Authors Topics

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%

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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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?

modRNA der Zulassungsstudie ist nicht modRNA für die Anwendung

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 February 2021
EMA/707383/2020 Corr.1*[1]
Committee for Medicinal Products for Human Use (CHMP)

Seite 18 / 140

Assessment report

Comirnaty

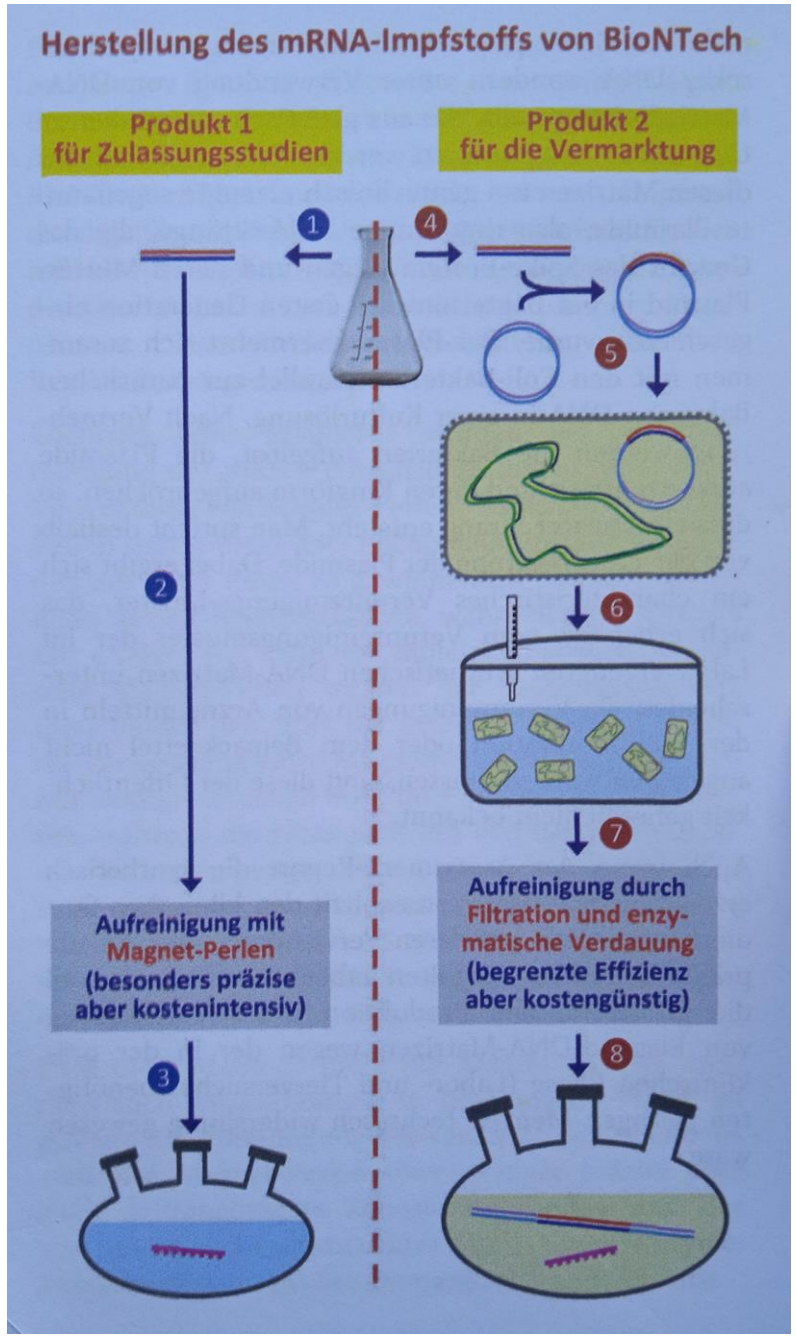
Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/0000

Manufacturing process development

Process development changes were adequately summarised. Two active substance processes have been used during the development history; Process 1 (clinical trial material) and Process 2 (commercial process). Details about process differences, justification for making changes, and results from a comparability study are provided. The major changes between active substance process versions were described in the dossier.

Herstellung des mRNA-Impfstoffs von BioNTech



Produkt 1 für Zulassungsstudien

1. Laborsynthese der DNA-Matrize des Gens für das Spike-Protein als Vorlage für die mRNA-Sequenz und deren Vervielfältigung
2. Laborsynthese der mRNA unter Verwendung der DNA-Matrize und anschließende präzise aber kostenintensive Aufreinigung unter Verwendung von Magnet-Perlen
3. Bereitstellung der aufgereinigten mRNA (magenta) für die Verpackung in Lipid-Nanopartikel

Produkt 2 für die Vermarktung

4. Laborsynthese der Gens für das Spike-Protein als DNA
5. Integration des DNA-Gens in ein Bakterien-Plasmid und dessen gentechnisce Einbringung in die erste Bakterien-Generation
6. Vermehrung des genetisch veränderten Bakteriums (Folgegenerationen) in technischen Großanlagen
7. Gewinnung des Bakterien-Plasmids und dessen Linearisierung als DNA-Matrize, RNA-Synthese und kostengünstige groß-technische Aufreinigung
8. Bereitstellung der aufgereinigten mRNA (magenta) für die Verpackung in Lipid-Nanopartikel, jedoch mit vielfältigen Verunreinigungen, u.a. DNA einschließlich der linearisierten Plasmid-Matrize mit dem Spike-Gen (in der Abbilung eine mehrfarbige lineare Struktur)

Verwendete Symbole

- Synthetisch hergestellte DNA-Matrize
- mRNA des Impfstoffs
- Bakterien-Plasmid vor gentechnischer Manipulation
- Bakterien-Plasmid mit gentechnisch eingefügtem Spike-Gen
- Coli-Baktierium mit dem gentechnisch manipulierten Plasmid neben der eigenen DNA (grün)
- linearisiertes Bakterien-Plasmid als DNA-Matrize für die großtechnische Produktion

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 159, 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 11.7 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**

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

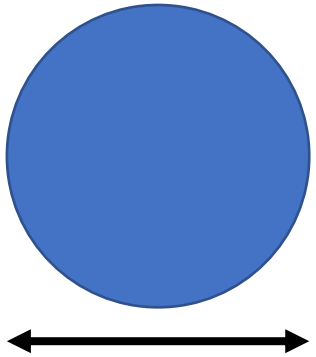
⇒ **Gesamtvolumen circa 1285 nm^3**

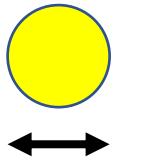
⇒ **Volumen einer Kugel mit Radius 6.74 nm**

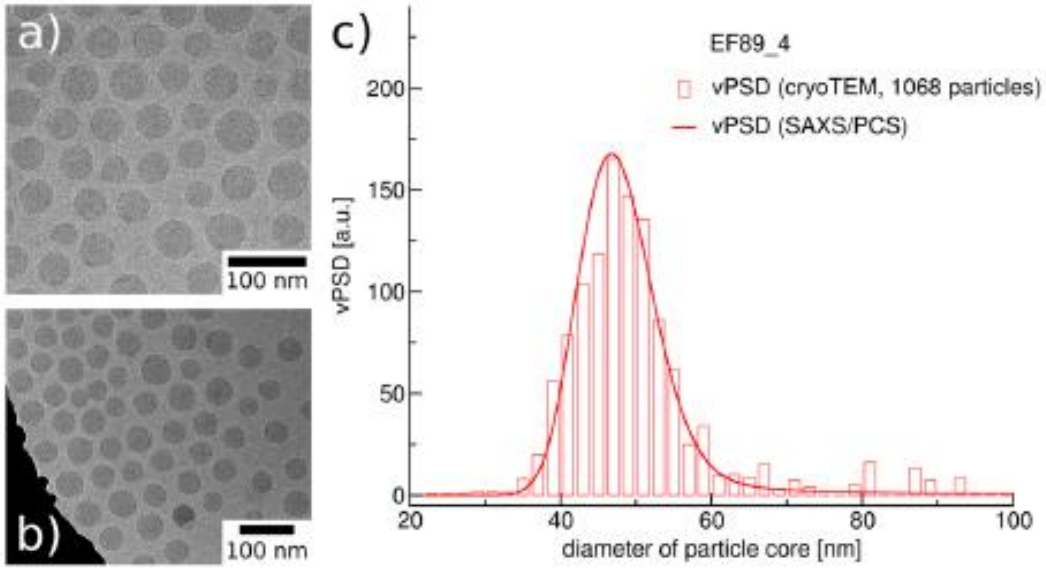
⇒ **Durchmesser der modRNA circa 13.5 nm**

Anzahl modRNA pro Partikel

- Teilchengröße der Nanopartikel: 40 - 180 nm







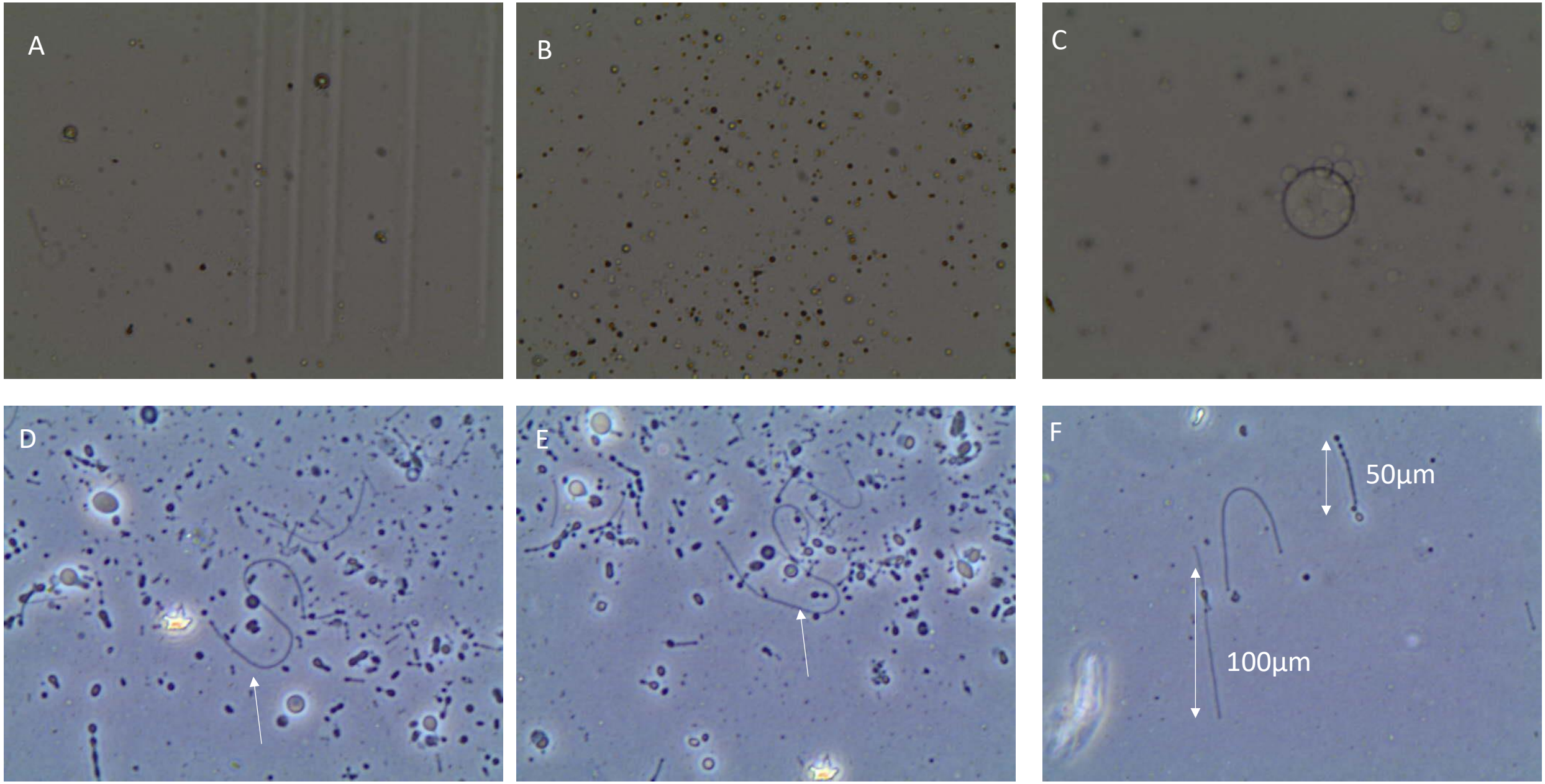
=> Bei den kleinen Nanopartikeln circa 1 modRNA Molekül pro Partikel

=> Pro Injektion circa 10 Billionen beladene Partikel

=> Enorme Schadwirkung

T. Unruh, K. Götz, C. Vogel, E. Fröhlich, A. Scheurer, L. Porcar, F. Steiniger, *ACS Nano,* **2024**, *18*, 9746-9764.

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



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?

Rest-DNA-Gehalt?

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

Paul-Ehrlich-Institut

Ihre Fragen 1-3 beantworten wir wie folgt:

Mit der Zulassung der COVID-19-mRNA-Impfstoffe wurde festgelegt, welche Spezifikationen welcher Parameter vor der In-House-Freigabe jeder einzelnen Impfstoffcharge durch den Hersteller erfüllt werden müssen. Erst bei Erreichen der erforderlichen Spezifikationen kann der Hersteller einen Chargenprüfungsantrag bei der Arzneimittelprüfbehörde stellen. Im Fall zentral zugelassener Impfstoffe wie den COVID-19-mRNA-Impfstoffen ist die zuständige Arzneimittelprüfbehörde das für die behördliche Chargenprüfung des jeweiligen Impfstoffprodukts vorgesehene amtliche Arzneimittelkontrolllabor (Official Medicines Control Laboratory, OMCL) im europäischen OMCL-Netzwerk.

Zu den in der Zulassung festgelegten Spezifikationen gehört ein Rest-DNA-Grenzwert und jeder Hersteller eines in der EU zugelassenen COVID-19-mRNA-Impfstoffprodukts hat also die Pflicht, bei der Herstellung für jede Charge zu prüfen, ob der in der Zulassung festgelegte entsprechende Grenzwert eingehalten wird.

Das Europäische Direktorat für die Qualität von Arzneimitteln (European Directorate for the Quality of Medicines, EDQM), das die Chargenprüfung im OMCL-Netzwerk koordiniert, veröffentlicht Leitfäden, in denen festgelegt ist, welche der in der Zulassung festgelegten Grenzwerte allein vom Hersteller oder vom Hersteller und von den OMCL-Laboren zusätzlich zu prüfen sind.[1]

Bei den Parametern wie dem Rest-DNA-Gehalt im Impfstoff, die nur vom Hersteller experimentell geprüft werden, überprüft das OMCL die Testergebnisse des Herstellers daraufhin, ob die in der Zulassung festgelegten Grenzwerte in jeder Charge eingehalten wurden.

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?

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 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, for the 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

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
Thrombosis	3,899	3,951	98.7
Deep vein thrombosis	2,275	2,297	99.0
Pulmonary thrombosis	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

medicina

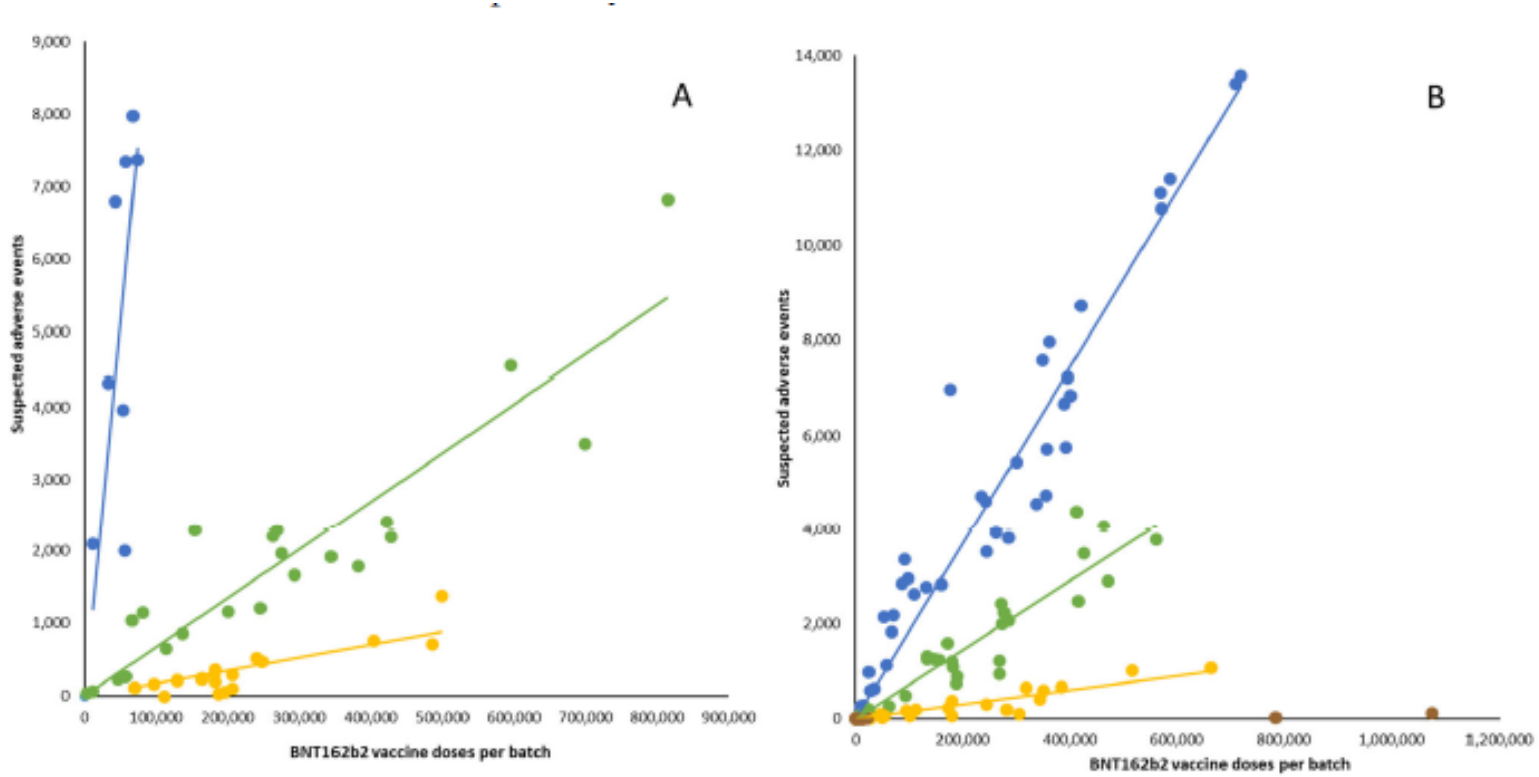
MDPI

Article

Reports of Batch-Dependent Suspected Adverse Events of the BNT162b2 mRNA COVID-19 Vaccine: Comparison of Results from Denmark and Sweden

Vibeke Manniche [1], Max Schmeling [2], Jonathan D. Gilthorpe [3] and Peter Riis Hansen [4,5,*]

Chargenabhängigkeit der Nebenwirkungen



PERIODIC SAFETY UPDATE REPORT #1
for
ACTIVE SUBSTANCE: COVID-19 mRNA vaccine (nucleoside modified) (BNT162b2)

Table 9. Most Frequently Reported Lot Numbers

Lot Number	Number of Cases
EL1484	16077
EJ6797	11168
EK9788	10139
EM0477	9214
EJ6136	7034
EJ6134	7029
EJ6795	7010
EJ6796	4942
EJ6788	4421
EL0725	3870
ER1741	3692
EP9598	2750
EL1491	2621
EJ3002	2602
EP9605	2461
EK1768	2157

Kommt dies überraschend?

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

Joseph Fraiman [a], Juan Erviti [b], Mark Jones [c], Sander Greenland [d], Patrick Whelan [e], Robert M. Kaplan [f], Peter Doshi [g,*]

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!

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

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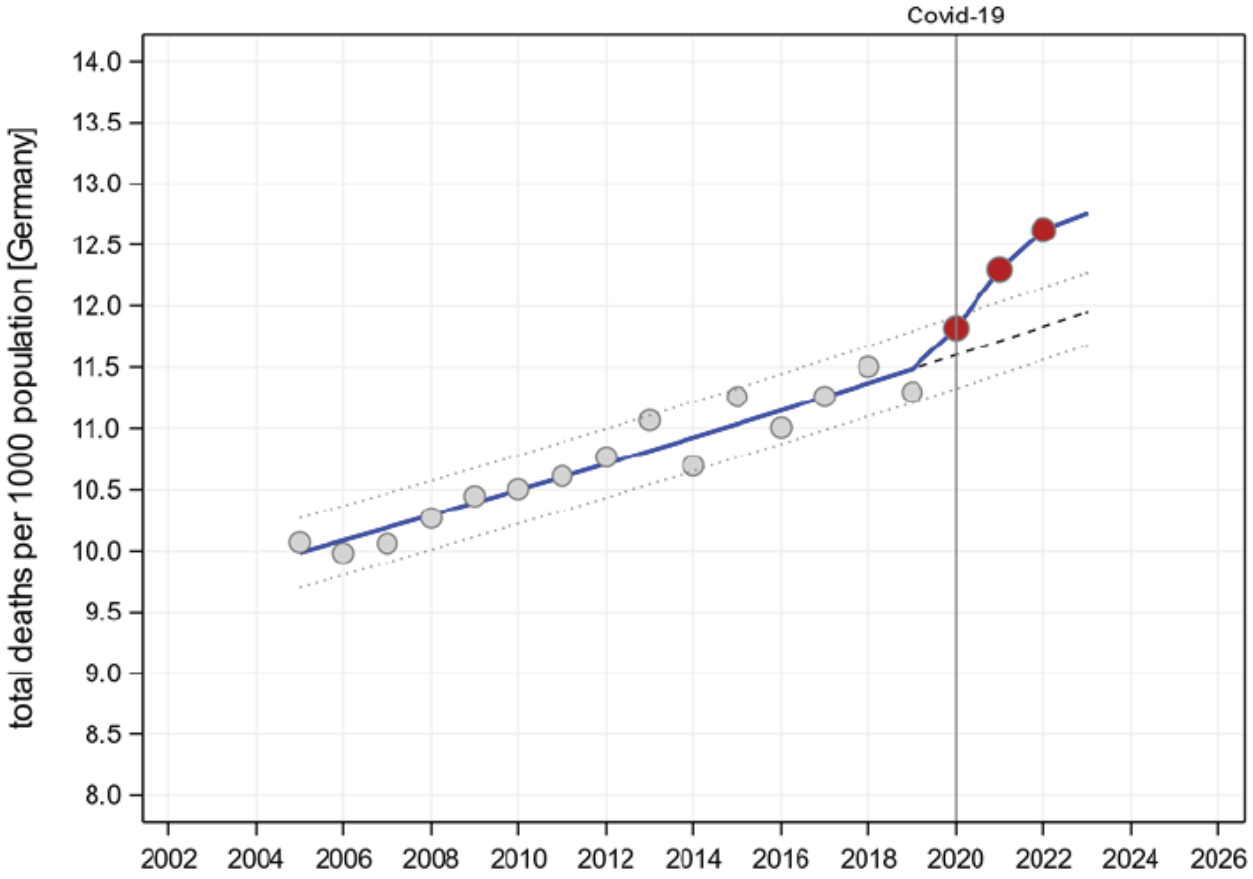
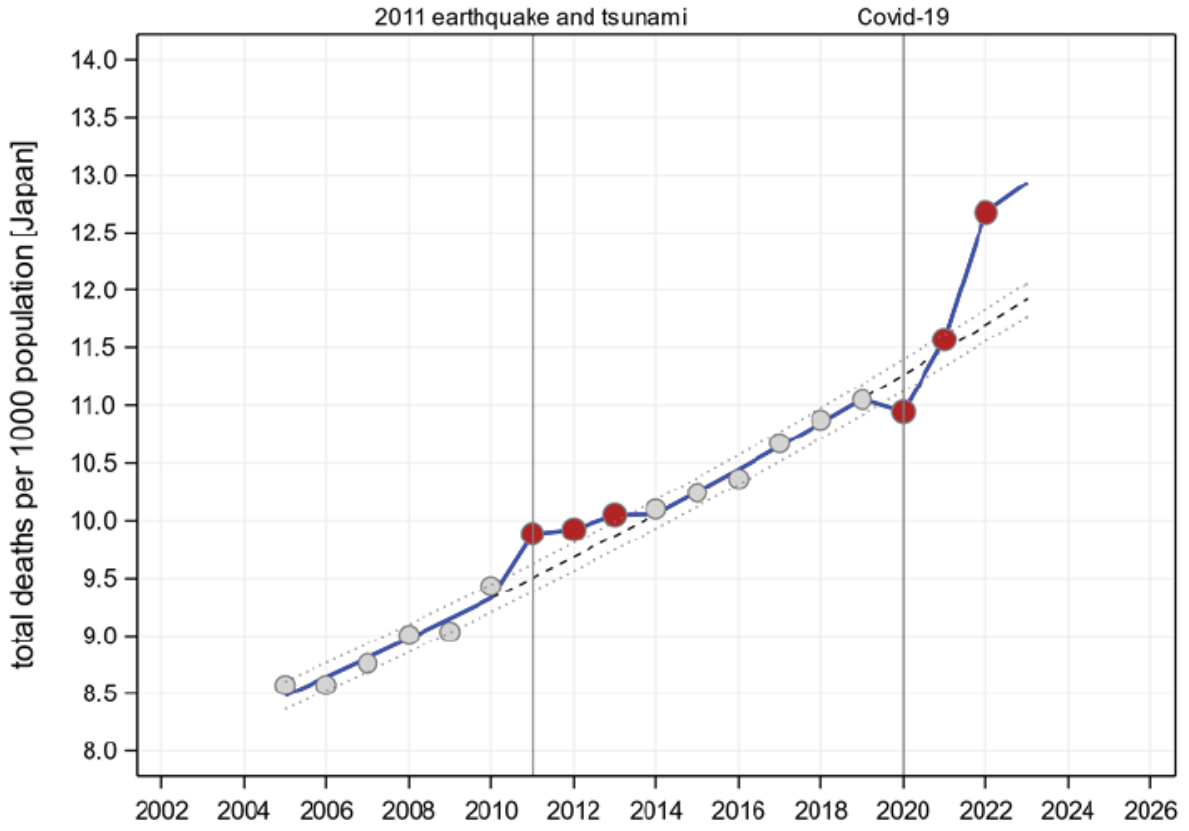


Gesamtzahl Todesfälle in Deutschland pro 1000 Einwohner (gepunktete Linien: 95%-Vorhersageband)



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)

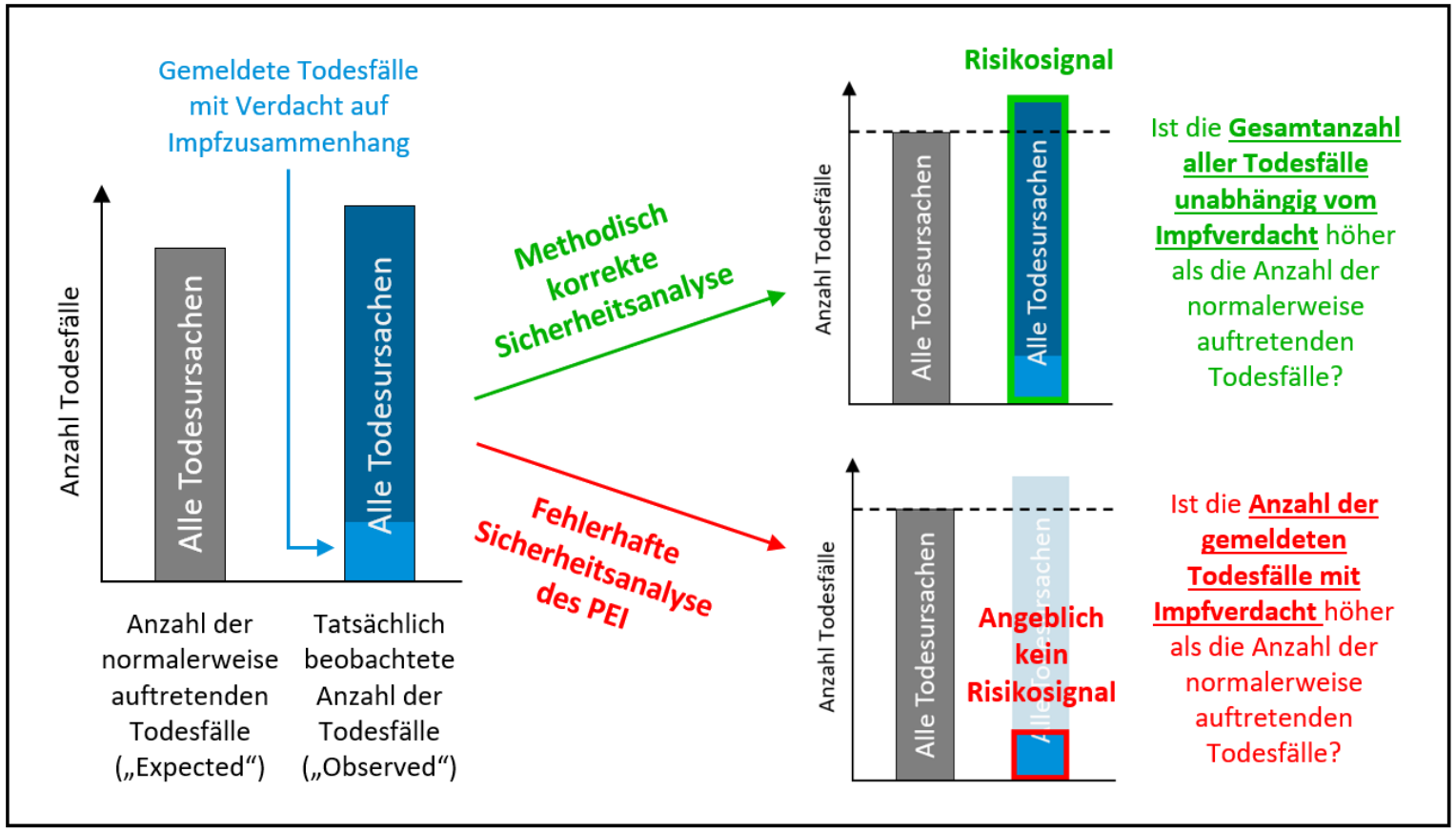


Illustration der methodisch korrekten Anwendung der Observed-versus-Expected Sicherheitsanalyse und der fehlerhaften Anwendung durch das Paul-Ehrlich-Institut.

=> 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

Fazit

- Sofortiges Aussetzen der Impfempfehlung der STIKO
    - Kosten / Nutzen der modRNA Technologie müssen geklärt werden
    - Offenlegung der Prüfprotokolle etc.
    - Entflechtung von Medizin und Pharmaindustrie