Sweden's no lockdown policy WAS right and countries that enforced them had 'significantly worse outcomes', report by its government finds

- **Sweden has completed a report into the nation's handling of Covid-19**
- **The report praises the decision to avoid a full lockdown like other countries**
- **The authors said some restrictions could have been implemented sooner**

By DARREN BOYLE FOR MAILONLINE
PUBLISHED: 02:07 GMT, 26 February 2022 | **UPDATED:** 08:18 GMT, 26 February 2022

Sweden made the correct decision by avoiding a full Covid-19 **lockdown** and relying on their population's common sense, a commission into the handling of the virus has claimed.

Despite praising keeping the country open, the commission said some restrictions should have been introduced earlier.

Swedish experts said repeated lockdowns in other European countries were neither 'necessary' nor 'defensible'.

Verstoorde bloedsuikerspiegels bij diabetespatiënten na coronavaccinatie

24-02-2022

Diabetespatiënten kunnen na een coronavaccin tijdelijk last hebben van schommelende bloedsuikerspiegels. Zowel verlaagde als verhoogde bloedsuikerspiegels werden gemeld. Het komt niet vaak voor.

Meldingen

Tot 12 november 2021 ontving Bijwerkingencentrum Lareb 279 meldingen van een verstoorde bloedsuikerspiegel na een coronavaccinatie. Het is niet duidelijk of er verschillen zijn tussen mensen met diabetes type 1 of type 2, en tussen mensen die wel of geen insuline gebruiken.

In verhouding tot het aantal toegediende vaccins, werden de meeste meldingen gedaan na vaccinatie met een AstraZeneca vaccin. In enkele gevallen was de bloedglucosespiegel erg moeilijk onder controle te krijgen en duurde dat ook erg lang.

Vragenlijstonderzoek coronavaccins

Lareb heeft ook vragenlijstonderzoek gedaan onder gevaccineerden. Van de 1316 deelnemers met diabetes rapporteerden 22 (1,7%) schommelende bloedsuikerspiegels. Het komt dus niet vaak voor, maar kan bij sommige patiënten wel veel impact hebben.

Lees hier het artikel in Pharmaceutisch Weekblad.

Vergrote lymfeklieren relatief vaker na coronaboostervaccinaties

04-02-2022

Vergrote lymfeklieren (lymfadenopathie) is een bekende bijwerking van de coronavaccins. Na de boostervaccinatie wordt het relatief vaker gemeld dan andere bijwerkingen vergeleken met de 1e en 2e prik. Ook ontstaan ze sneller na de vaccinatie, houden ze iets langer aan en hebben melders er meer last van.

Vergrote lymfeklieren

Lymfeklieren in de hals, oksel, lies en rondom het sleutelbeen kunnen opzwellen bij een ontsteking, een infectie, auto-immuunziekte of na vaccinatie. Dit komt doordat de immuuncellen in de lymfeklieren actief worden.

Vaker na boostervaccinatie

Over het algemeen worden de veelvoorkomende bijwerkingen van de coronavaccinatie even vaak gemeld bij de 1e en 2e prik of boosterprik. Vergrote lymfeklieren worden relatief wel vaker gemeld dan andere bijwerkingen na de boostervaccinatie vergeleken met de 1e en 2e prik. Dit geldt ook voor reacties op de prikplaats.

Sneller, langer en meer last

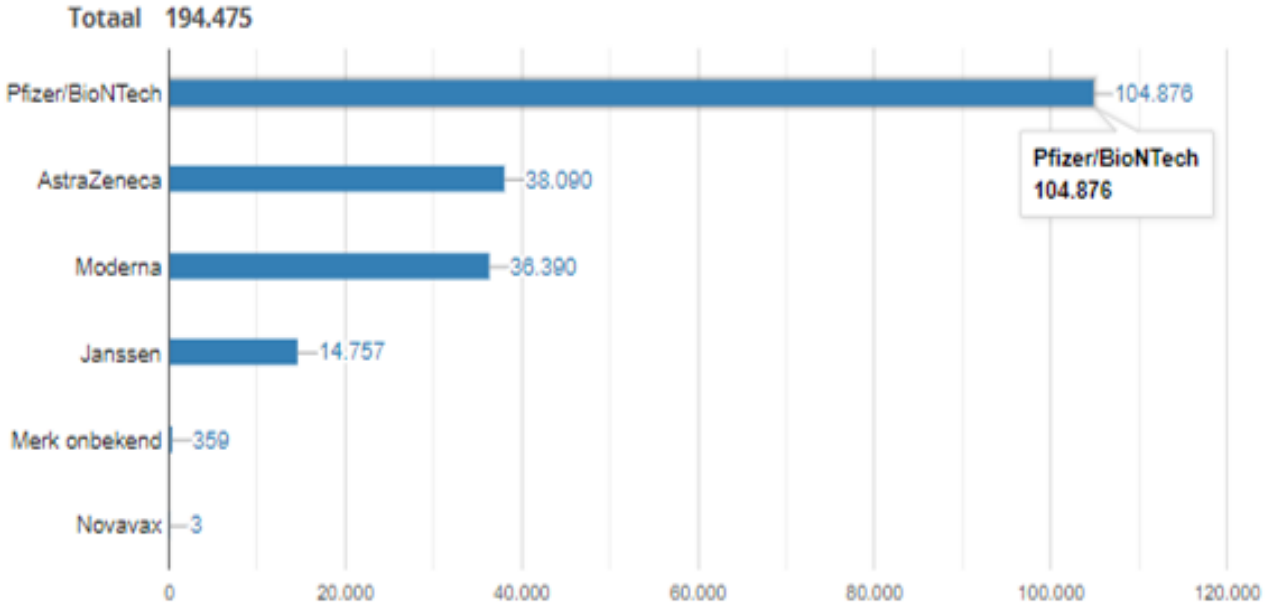
Na de boostervaccinatie ontstonden de vergrote lymfeklieren gemiddeld 1 dag na de vaccinatie. Bij de 1e en 2e vaccinatie was dit na 2 tot 3 dagen. Meestal verdwijnen de klachten na een week. De klachten duurden gemiddeld ook een halve dag tot een dag langer dan na de 1e en 2e vaccinatie. Melders hebben er gemiddeld ook meer last van. Sommige melders vergeleken de grootte van de lymfeklieren met een tennis- of golfbal of avocado. Het is verstandig om naar de huisarts te gaan als de klieren langer dan 2 weken vergroot blijven.

Bekijk hier het overzicht van de meldingen (in het Engels).

Belangrijk! Lees eerst deze toelichting

- Een gemelde bijwerking **hoeft niet altijd door het vaccin veroorzaakt te zijn**.
  Klachten of aandoeningen kunnen ook door een andere oorzaak na de vaccinatie zijn ontstaan.
- Het **aantal meldingen zegt niets** over **hoe vaak** een bijwerking optreedt.
- Onderstaande gegevens kunnen niet gebruikt worden om de bijwerkingen per vaccin te vergelijken.
- De verschillende coronavaccins worden in wisselende hoeveelheden en bij verschillende doelgroepen gebruikt.
- De getoonde meldingen zijn afkomstig van patiënten, zorgverleners en fabrikanten van de vaccins.
- Eén melding kan meerdere bijwerkingen betreffen die afzonderlijk in het overzicht getoond worden. Het aantal bijwerkingen is dus hoger dan het aantal meldingen.
- Wilt u gegevens over de meldingen gebruiken in publicaties of media? Dit kan uitsluitend **na overleg met Lareb**.
  Dit in verband met de juiste interpretatie en benodigde toelichting van deze gegevens.

Aantal meldingen



vaccinatiecampagne tijdens een pandemie zal ontvangen. Behalve dat het scenario nog niet duidelijk is hangt het af van andere omstandigheden, zoals de aandacht in de media, de bekendheid met melden, de bereidheid tot melden en het bijwerkingenprofiel van de vaccins. Voor de monitoring van vaccin moet vooraf een inschatting gemaakt worden van de deelname. Tijdens de H1N1 campagne werden zo'n 4000 gevaccineerden gevolgd in de monitoring.

Op dit moment wordt uitgegaan van deze inschatting:

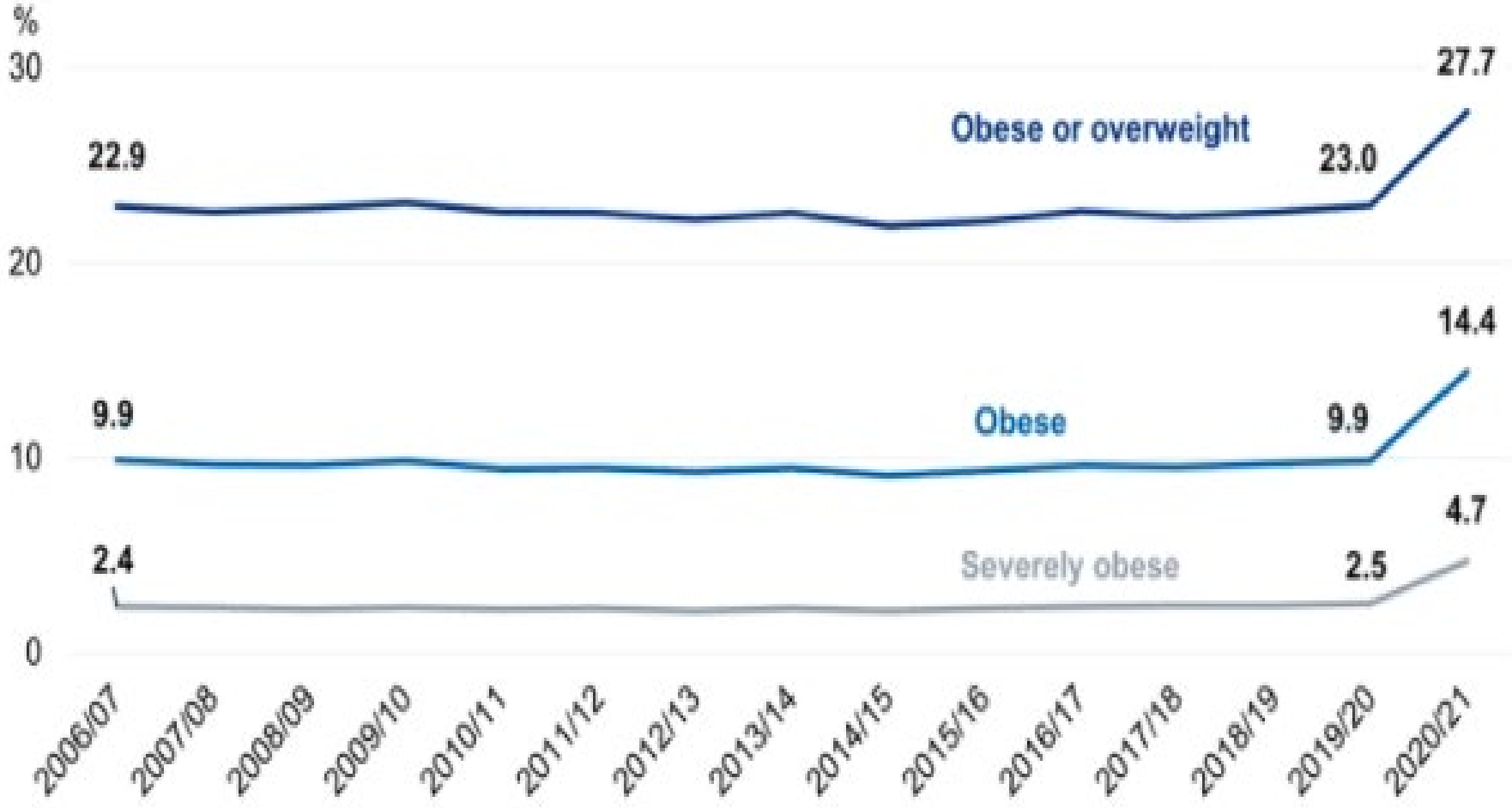
Extra meldingen vaccins	15.000, waarvan 600 ernstig
Deelnemers monitoring vaccin	4.000

Rapportage overzichten en signaaldetectie.

De query's voor de analyses voor de rapportages van meldingen en in LIM gerapporteerde bijwerkingen, dienen voor aanvang van de campagne geprogrammeerd te worden.

numbers

Prevalence of obese, severely obese, and obese or overweight Reception children, 2006/07 to 2020/21

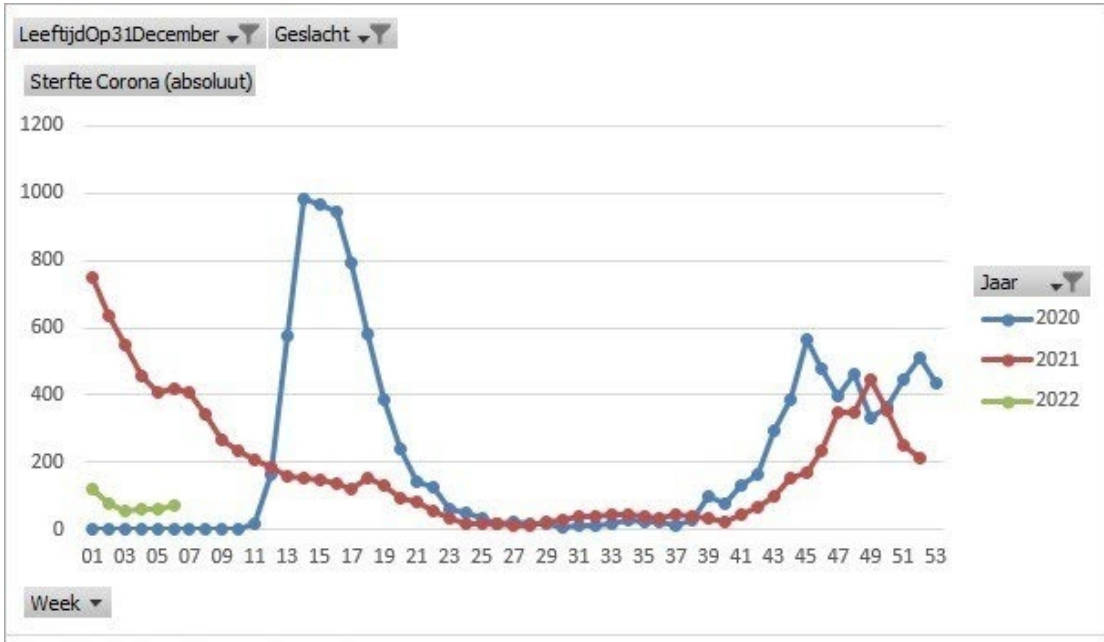


For more information: Table 2 National Child Measurement Programme, England, 2020/21 school year

Could Omicron be even LESS deadly than seasonal flu? Scientists believe ultra-infectious strain may kill 100 TIMES fewer people than Delta (and mortality rates were ALREADY similar to influenza before the variant emerged)

- Researchers expect the ultra-infectious variant to kill between 97 and 99 per cent fewer people than Delta
- UK advisers estimate the infection-fatality rate (IFR) it stood at 0.25 per cent before Omicron emerged
- Others suggested it could be 0.1 per cent — similar to flu— compared to 1 per cent before the vaccine rollout
- But experts queried 99 per cent estimate, insisting it does not look plausible and there too much uncertainty

By STEPHEN MATTHEWS HEALTH EDITOR FOR MAILONLINE and EMILY CRAIG HEALTH REPORTER FOR MAILONLINE
PUBLISHED: 16:13 GMT, 7 January 2022 | **UPDATED:** 23:25 GMT, 7 January 2022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1000
800
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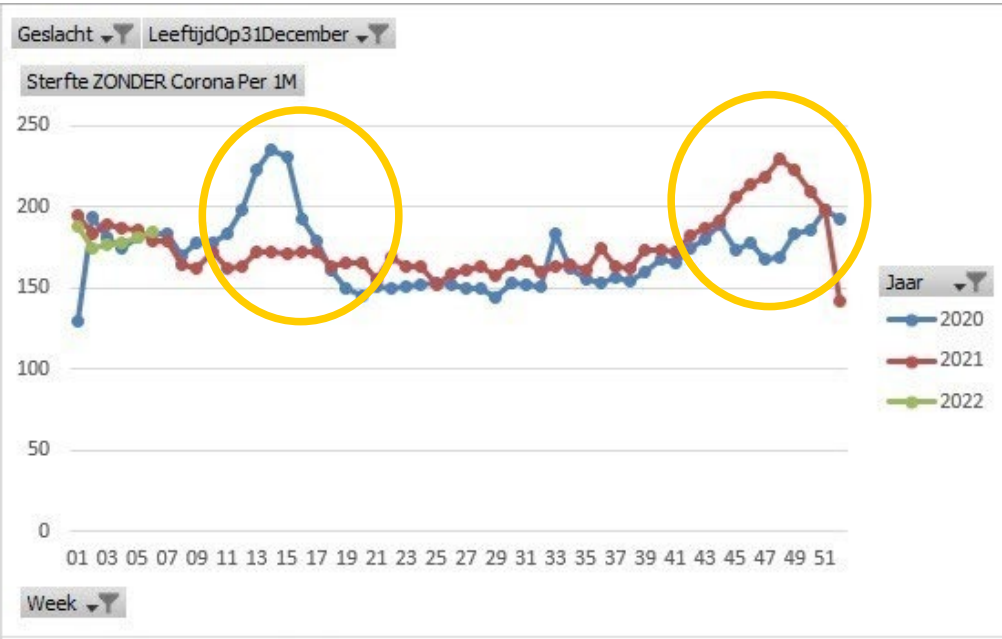
01 03 05 07 09 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53
Jaar
2020
2021
2022
Week


Geslacht
LeeftijdOp31December
Sterfte ZONDER Corona Per 1M
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200
150
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Jaar
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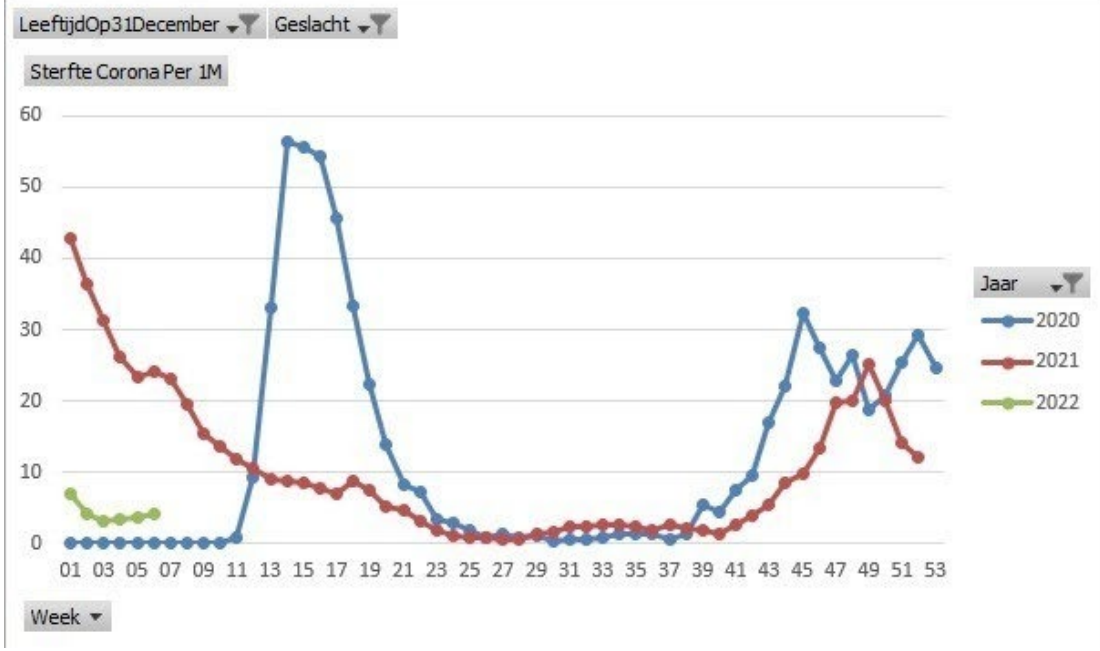
Week


LeeftijdOp31December
Geslacht
Sterfte Corona Per 1M
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50
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Jaar
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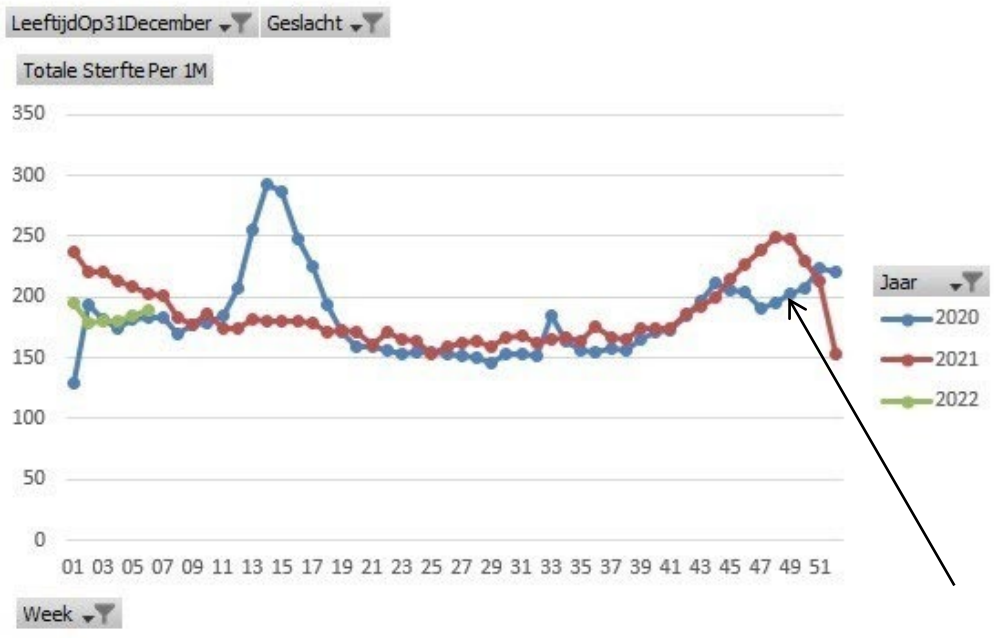
2022
Week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Geslacht
Totale Sterfte Per 1M
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300
250
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150
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Jaar
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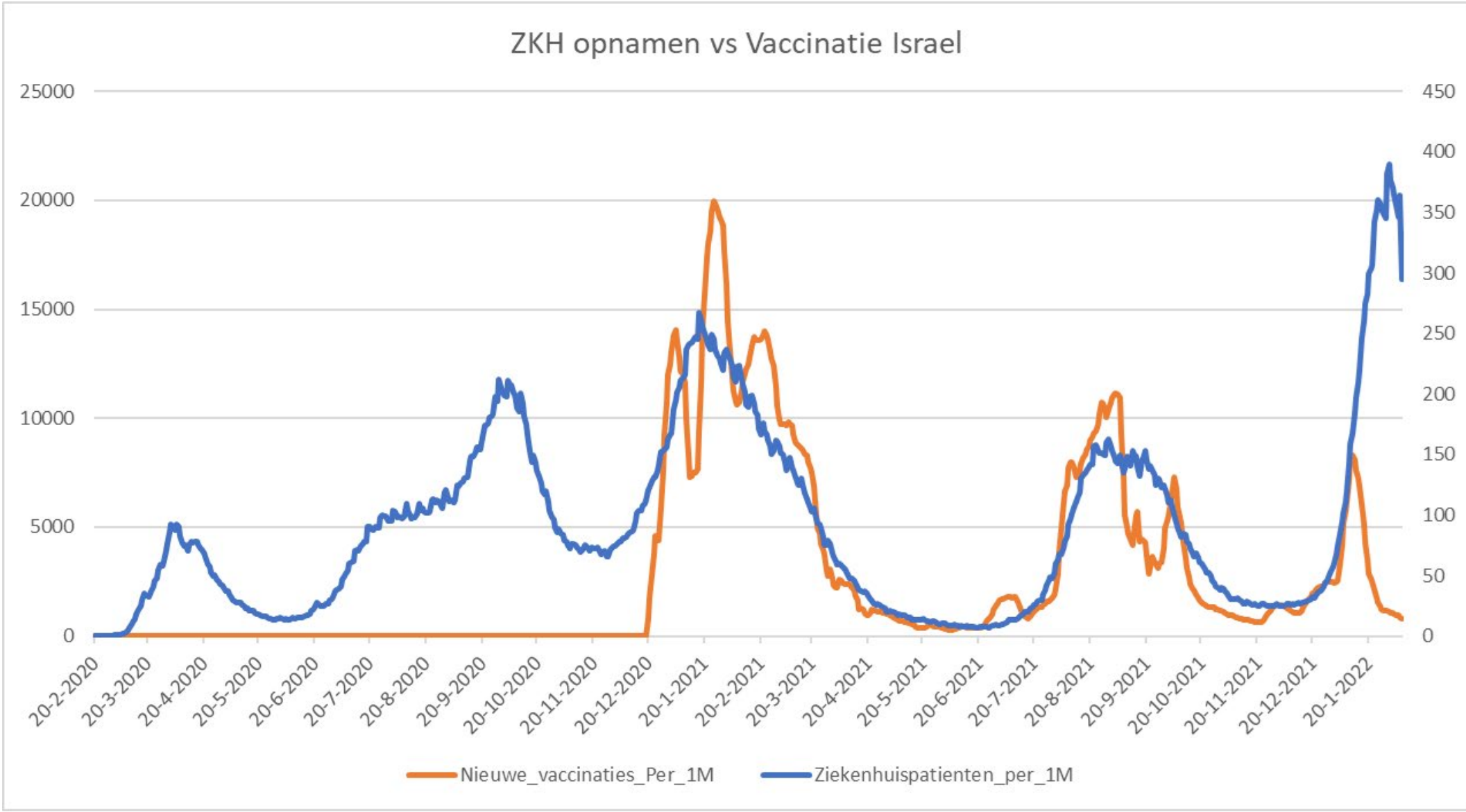
ZKH opnamen vs Vaccinatie Israel
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20-3-2020
20-4-2020
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20-8-2020
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20-12-2021
20-1-2022
Nieuwe_vaccinaties_Per_1M
Ziekenhuispatienten_per_1M

Natuurlijke immuniteit

ORIGINAL ARTICLE

Protection against SARS-CoV-2 after Covid-19 Vaccination and Previous Infection

Victoria Hall, F.F.P.H., Sarah Foulkes, M.Sc., Ferdinando Insalata, M.Sc., Peter Kirwan, B.Sc., Ayoub Saei, Ph.D., Ana Atti, M.Sc., Edgar Wellington, M.Sc., Jameel Khawam, M.Sc., Katie Munro, M.Sc., Michelle Cole, D.B.M.S., Caio Tranquillini, M.D., Andrew Taylor-Kerr, M.P.P., et al., for the SIREN Study Group*

February 16, 2022
DOI: 10.1056/NEJMoa2118691

39 References

CONCLUSIONS

Two doses of BNT162b2 vaccine were associated with high short-term protection against SARS-CoV-2 infection; this protection waned considerably after 6 months. Infection-acquired immunity boosted with vaccination remained high more than 1 year after infection. (Funded by the U.K. Health Security Agency and others; ISRCTN Registry number, ISRCTN11041050.)

Real-world studies have shown the short-term effectiveness of vaccines with respect to symptomatic and asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the severity of coronavirus disease 2019 (Covid-19), and secondary transmission.[1-4] The duration of this protection over longer periods remains uncertain and warrants ongoing study.

The population uptake of two doses of Covid-19 vaccines in the United Kingdom (in persons >12 years of age) as of February 2022 was 84.5%,[5] and it has now been more than 6 months since the second dose was administered to prioritized groups (health care and social workers and clinically vulnerable persons). Given the sustained high levels of community infection[5] and concerns about the potential waning of immunity,[6-10] the government of the United Kingdom initiated a rollout of booster vaccination in prioritized groups in September 2021.[11] Improved understanding and characterization of

Protection of COVID-19 vaccination and previous infection against Omicron BA.1 and Delta SARS-CoV-2 infections, the Netherlands, 22 November 2021- 19 January 2022

Stijn P. Andeweg, Brechje de Gier, Dirk Eggink, Caroline van den Ende, Noortje van Maarseveen, Lubna Ali, Boris Vlaemynck, Raf Schepers, RIVM COVID-19 surveillance and epidemiology team, Susan J.M. Hahné, Chantal Reusken, Hester E. de Melker, Susan van den Hof, Mirjam J. Knol

doi: https://doi.org/10.1101/2022.02.06.22270457

Abstract

Given the emergence of the SARS-CoV-2 Omicron BA.1 variant and the roll-out of booster COVID-19 vaccination, evidence is needed on protection conferred by primary vaccination, booster vaccination and previous SARS-CoV-2 infection against Omicron BA.1 compared with Delta infection.

We employed a test-negative design and used multinomial logistic regression on data from

medication

Original Investigation

ONLINE FIRST FREE

February 18, 2022

Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities

The I-TECH Randomized Clinical Trial

Steven Chee Loon Lim, MRCP[1]; Chee Peng Hor, MSc[2,3]; Kim Heng Tay, MRCP[4]; et al

» Author Affiliations | Article Information

JAMA Intern Med. Published online February 18, 2022. doi:10.1001/jamainternmed.2022.0189

COVID-19 Resource Center

Visual Abstract

Related Articles

Key Points

New JAMA paper show Ivermectin blows the COVID vaccines out of the water

Whoops! How embarrassing! The CDC gave you bad advice. If you want to survive COVID, you should use the drug they said to avoid, and avoid the drug they said to use.

Steve Kirsch
5 hr ago

Remember that "horse dewormer" that the FDA, CDC, NIH, CNN, and Sanjay Gupta all told you not to use? A new paper recently published in the Journal of the AMA (JAMA) shows that Ivermectin works way better than the COVID vaccine in keeping you from dying from COVID.

The data

The lower the p-value, the more significant the result is. A Chi-squared test was used. Data came from the JAMA paper appendix.

Vaccine:

➞ Ivermectin group: protection against death=10% | p=0.94
➞ Control group: protection against death=24% | p=0.67
➞ Overall: protection against death=23% | p=0.64

Deaths	Vaccinated	Not Vaccinated	Vaccine Effectiveness Against Death	p-value
Ivermectin	1.2%	1.3%	10%	0.94
Control	3.6%	4.8%	24%	0.67
Total	2.4%	3.1%	23%	0.64

Ivermectin:

➞ Non-vaccinated group: protection against death=72% | p=0.21
➞ Vaccinated group: protection against death=67% | p=0.15
➞ Overall: protection against death=69% | p=0.06

Deaths	Ivermectin	Control	IVM Effectiveness Against Death	p-value
Not Vaccinated	1.3%	4.8%	72%	0.21
Vaccinated	1.2%	3.6%	67%	0.15
Total	1.2%	4.0%	69%	0.06

Gain of function

SCIENCE GENETIC DATABASE

"We should get rid of the idea that our genome belongs to us alone"

Published on 09/11/2020 | Reading time: 9 minutes

By **Norbert Lossau**
Chief Science Correspondent

DNA helix: The genomDE initiative is committed to the digital storage of the genetic material of the German population

Source: Getty Images

VERMELDING VAN NATUURLIJKE OORSPRONG

Onderzoekers vinden coronavirussen bij vleermuizen

Bij vleermuizen werden naaste verwanten van Sars-CoV-2 gevonden
Foto: foto alliantie / blickwinkel/AGAMI/T. douma

door: **ASTRID-MARIA BOCK**
17-02-22 - 12:32 uur

Komt Sars-CoV-2 van vleermuizen? Dat suggereren althans nieuwe bevindingen. Onderzoekers van het Pasteur Instituut in Parijs hebben drie virustypes gevonden bij vleermuizen in Laos die voor bijna 97 procent genoomcorrespondentie hebben met het pandemische virus.

In hun studie , gepubliceerd in het tijdschrift Nature, leggen de onderzoekers uit dat ze bij in totaal 645 vleermuizen speeksel-, ontlasting- en urinemonsters hebben genomen en onderzocht. Ze vonden de virussen die zo lijken op SARS-CoV-2 in drie soorten

Article | Published: 16 February 2022

Bat coronaviruses related to SARS-CoV-2 and infectious for human cells

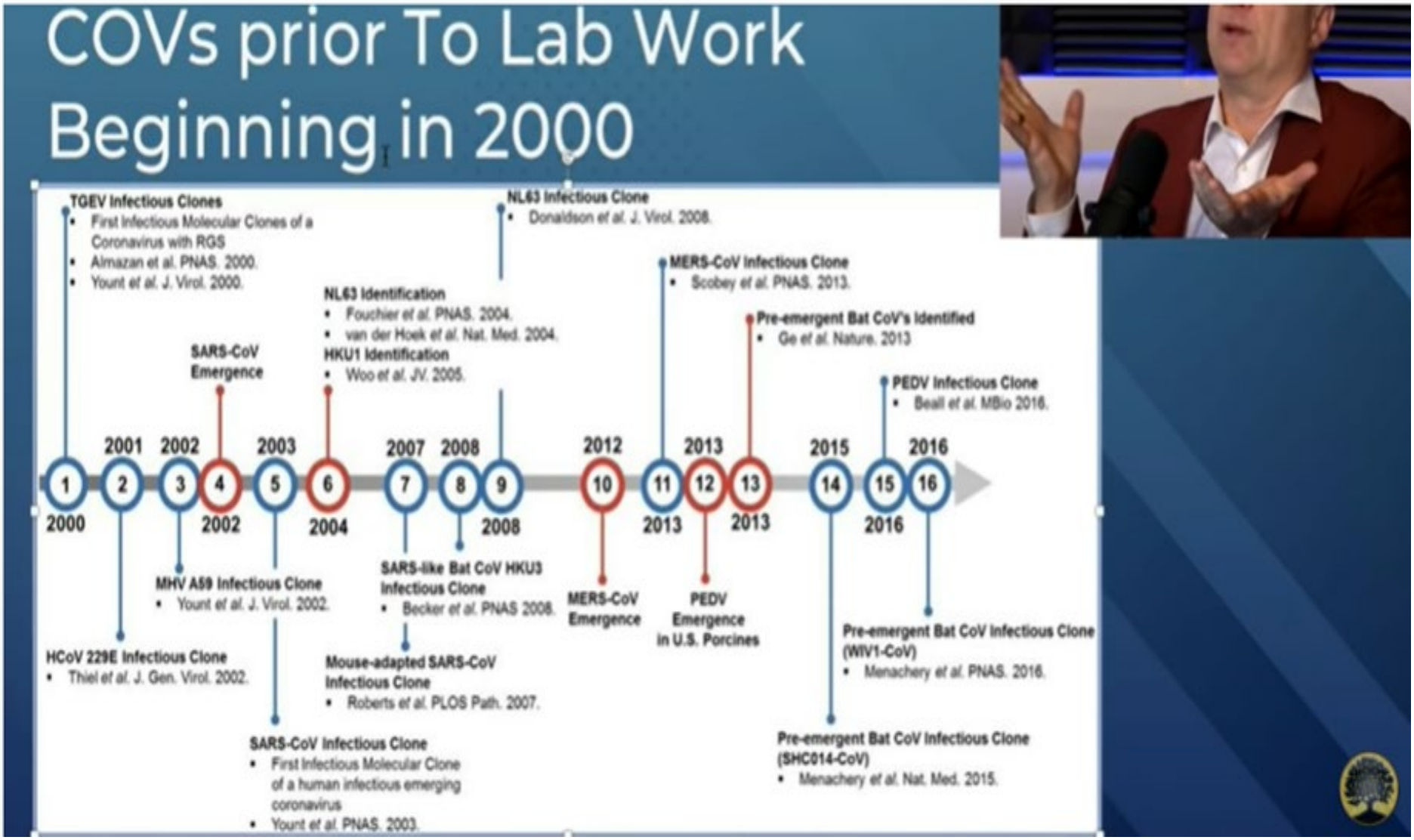
Sarah Temmam, Khamsing Vongphayloth, ... Marc Eloit ✉ + Show authors

Nature (2022) | Cite this article

627 Altmetric | Metrics

Abstract

The animal reservoir of SARS-CoV-2 is unknown despite reports of various SARS-CoV-2-related viruses in Asian *Rhinolophus* bats[1–4], including the closest virus from *R. affinis*, RaTG13[5,6] and in pangolins[7–9]. SARS-CoV-2 presents a mosaic genome, to which different progenitors contribute. The spike sequence determines the binding affinity and accessibility of its receptor-binding domain (RBD) to the cellular angiotensin-converting enzyme 2 (ACE2) receptor and is responsible for host range[10–12]. SARS-CoV-2 progenitor bat viruses genetically close to SARS-CoV-2 and able to enter human cells through a human ACE2 pathway have not yet been identified, though they would be key in understanding the origin of the epidemics. Here we show that such viruses indeed circulate in cave bats living in the limestone karstic terrain in North Laos, within the Indochinese peninsula. We found that the RBDs of these viruses differ from that of SARS-CoV-2 by only one or two residues at the interface with ACE2, bind more efficiently to the hACE2 protein than the SARS-CoV-2 Wuhan strain isolated in early human cases, and mediate hACE2-dependent entry and replication in human cells, which is inhibited by antibodies neutralizing SARS-CoV-2. None of these bat viruses harbors a furin cleavage site in the spike. Our findings therefore indicate that bat-borne SARS-CoV-2-like viruses potentially infectious for humans circulate in *Rhinolophus* spp. in the Indochinese peninsula.



https://www.youtube.com/watch?v=18d9-8m9B3U

Adding Furin Cleavage Sites

to use human ACE2 and grow in human cells. *S2 Proteolytic Cleavage and Glycosylation Sites:* After receptor binding, a variety of cell surface or endosomal proteases[68-71] cleave the SARS-CoV S glycoprotein causing massive changes in S structure [72] and activating fusion-mediated entry[64,73]. We will analyze all SARSr-CoV S gene sequences for appropriately conserved proteolytic cleavage sites in S2 and for the presence of potential furin cleavage sites[74,75]. SARSr-CoV S with mismatches in proteolytic cleavage sites can be activated by exogenous trypsin or cathepsin L. Where clear mismatches occur, we will introduce appropriate human-specific cleavage sites and evaluate growth potential in Vero cells and HAE cultures. In SARS-CoV, we will ablate several of these sites based on pseudotyped particle studies and evaluate the impact of select SARSr-CoV S changes on virus replication and pathogenesis. We will also review deep sequence data for low abundant high risk SARSr-CoV that encode functional proteolytic cleavage sites, and if so, introduce these changes into the appropriate high abundant, low risk parental strain. *N-linked glycosylation:* Some glycosylation events regulate SARS-CoV particle binding DC-SIGN/L-SIGN, alternative receptors for SARS-CoV entry into macrophages or

The Punchline

The absence of CTCCTCGGCGGGCACGTAG from any eukaryotic or viral genome in the BLAST database makes recombination in an intermediate host an unlikely explanation for its presence in SARS-CoV-2. A human-codon-optimized mRNA encoding a protein 100% homologous to human MSH3 could, during the course of viral research, inadvertently or intentionally induce mismatch repair deficiency in a human cell line, which would increase susceptibility to SARS-like viral infection. Infection of SEQ ID11652-MSH3-transduced

```
LOCUS       HZ246785               3414 bp    DNA     linear   PAT 26-NOV-
2015
DEFINITION  JP 2015518816-A/7089: MODIFIED POLYNUCLEOTIDES FOR THE PRODUCTION
            OF ONCOLOGY-RELATED PROTEINS AND PEPTIDES.
ACCESSION   HZ246785
VERSION     HZ246785.1
KEYWORDS    JP 2015518816-A/7089.
SOURCE      synthetic construct
  ORGANISM  synthetic construct
            other sequences; artificial sequences.
REFERENCE   1  (bases 1 to 3414)
  AUTHORS   Hatala,P., Wood,K.M., Ejebe,K., Elbashir,S.M., John,M., Roy,A.,
            Whoriskey,S., Fougerolles,A.D., Guild,J., Schrum,J.P.,
            Ellsworth,J.L., Chakraborty,T. and Bancel,S.
  TITLE     MODIFIED POLYNUCLEOTIDES FOR THE PRODUCTION OF ONCOLOGY-RELATED
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  JOURNAL   Patent: JP 2015518816-A 7089 06-JUL-2015;
            MODERNA THERAPEUTICS
COMMENT     OS   Artificial Sequence
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https://www.frontiersin.org/articles/10.3389/fviro.2022.834808/full

EMA emails

In addition, during an evaluation EMA's scientific committees may request inspections of the medicine's manufacturing sites, of the site where a non-clinical or clinical study was performed or of the pharmacovigilance (safety monitoring) processes involved in the application and such inspections would then be carried out as part of the assessment.

Based on the outcome of any inspection and the assessment of the extensive information provided by the companies, EMA decides whether or not a medicine is safe, effective and of good quality and is therefore suitable for use in patients.

Once a vaccine has received approval, batches can only be marketed and released following quality control testing if the product is in line with the specifications that were approved as part of the respective Marketing Authorisation. This control is carried out by the manufacturer. EMA does not carry out its own analysis. However, for most centrally authorised vaccines EU legislation requires that a Member State's Official Medicines Control Laboratory performs an additional independent control for each batch before it is put on the EU market. This independent control is referred to as Official Control Authority Batch Release (OCABR[1]) and includes testing of agreed quality parameters and a compliance check of the manufacturer's own test results.

2) Does EMA have a mechanism on which it acts upon specific requests sent to EMA substantiated by independent laboratories analyses on eventual breakage of the content declaration of medical products? If yes, please provide details on how to proceed with application of such request to the EMA formally.

https://ivsincic.eu/objave/moji-razgovori-s-emom-treci-dio/

The mentioned medicinal products have been classified as vaccines based on the European Pharmacopeia, EU legislation and scientific guidelines, listed below:

-European Pharmacopeia, Monograph of Vaccine for human use:

Vaccines for human use are preparations containing antigens capable of inducing a specific and active immunity in man against an infecting agent or the toxin or antigen elaborated by it. Immune responses include the induction of the innate and the adaptive (cellular, humoral) parts of the immune system. Vaccines for human use shall have been shown to have acceptable immunogenic activity and safety in man with the intended vaccination schedule.

Vaccines for human use may contain: whole micro-organisms (bacteria, viruses or parasites), inactivated by chemical or physical means that maintain adequate immunogenic properties; whole live micro-organisms that are naturally avirulent or that have been treated to attenuate their virulence whilst retaining adequate immunogenic properties; antigens extracted from the micro-organisms or secreted by the micro-organisms or produced by genetic engineering or chemical synthesis. The antigens may be used in their native state or may be detoxified or otherwise modified by chemical or physical means and may be aggregated, polymerised or conjugated to a carrier to increase their immunogenicity. Vaccines may contain an adjuvant. Where the antigen is adsorbed on a mineral adjuvant, the vaccine is referred to as 'adsorbed'.

Assessments of medicines for human use are carried out by the Agency's Committee for Medicinal Products for Human Use (CHMP). For an application of a new medicine, two Committee members – known as rapporteur and co-rapporteur – from different countries are appointed to lead the assessment. The names of the rapporteur and co-rapporteur are published in the assessment report of the medicine (which can be found through the links provided above).

The rapporteurs for the vaccines are as follows:

Comirnaty: Rapporteur: Filip Josephson Co-Rapporteur: Jean-Michel Race

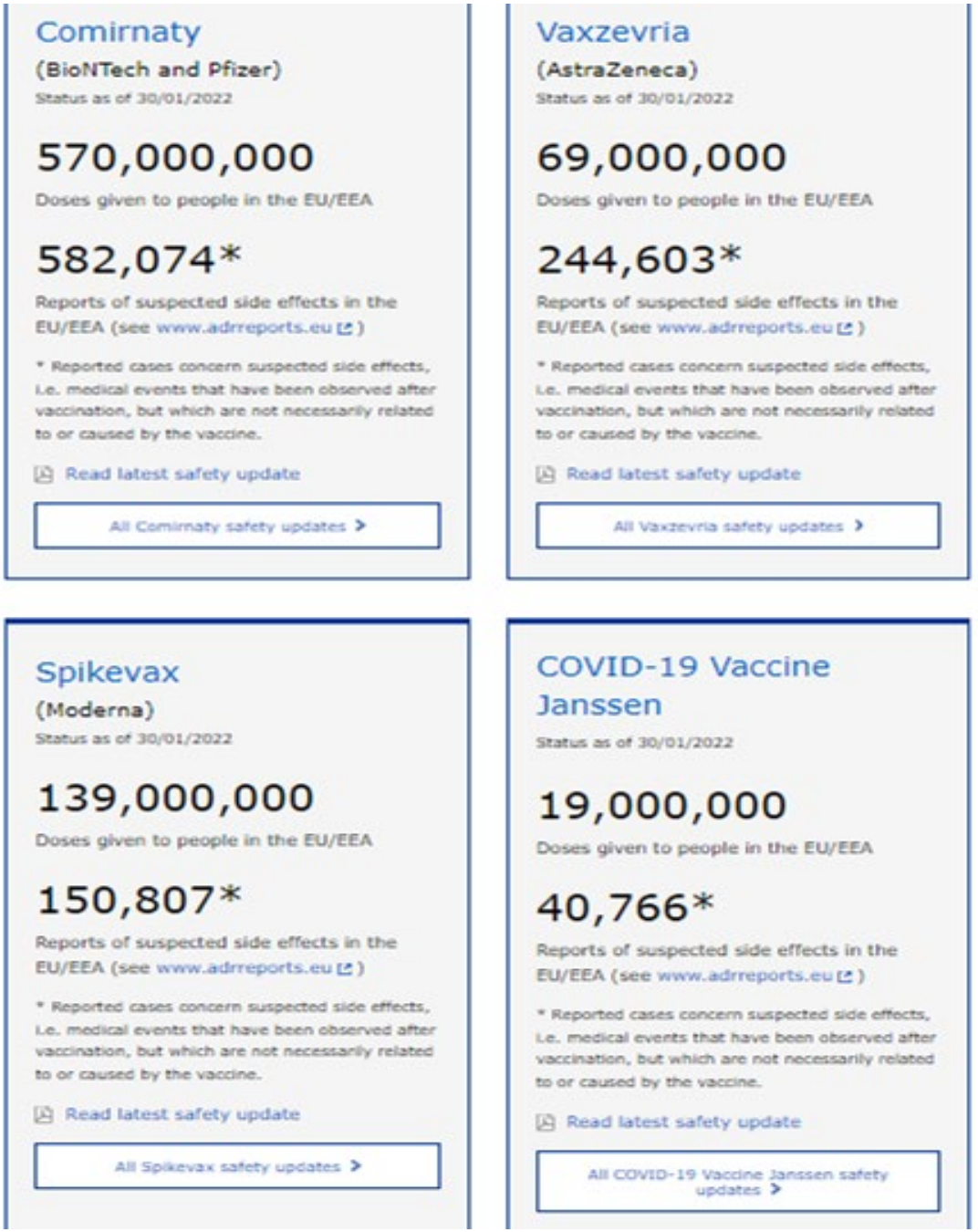
COVID-19 vaccine Janssen: Rapporteur: Christophe Focke Co-Rapporteur: Sol Ruiz

Spikevax: Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Andrea Laslop

Vaxzevria: Rapporteur: Sol Ruiz Co-Rapporteur: Johann Lodewijk Hillege

The benefit-risk evaluation and decision for a medicine is taken collectively by the entire CHMP committee after discussion of the rapporteur and co-rapporteur assessment reports.

This is the list of the current CHMP members: https://www.ema.europa.eu/en/committees/chmp/members.



https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/safety-covid-19-vaccines

-----Original Message-----
From: Wathion Noel <Noel.Wathion@ema.europa.eu>
Sent: Thursday, 19 November 2020 19:12
To: Cooke Emer <Emer.Cooke@ema.europa.eu>; Sweeney Fergus <Fergus.Sweeney@ema.europa.eu>; Nolte Alexis <Alexis.Nolte@ema.europa.eu>; Boone Hilde <Hilde.Boone@ema.europa.eu>; Dias Monica <Monica.Dias@ema.europa.eu>; Cavaleri Marco <Marco.Cavaleri@ema.europa.eu>
Subject: Some reflections after today's TC with the Commissioner

Dear all,

Since Alexis and Monica were no longer connected when we had our short discussion after today's TC with the Commissioner, a brief summary of what I already said together with some additional reflections.

As a minimum we can say that the TC was interesting, the atmosphere was rather tense, at times even a bit unpleasant, and provides a hint on what EMA may expect if the expectations are not being met, irrespective if such expectations are realistic or not.

The real added value of today's TC in my view is that we have more clarity now on what may not be easily acceptable for the EC, ie a delay of several weeks between an authorisation granted by the FDA/ MHRA (under whatever form) and a CMA opinion issued by EMA. The political fall-out seems to be too high, even if the "technical" level at the MSs (as it was referred to by the Commissioner) could defend such a delay in order to make the outcome of the scientific review as robust as possible.

Although we know that whatever we do (speeding up the process to align as much as possible with the "approval" timing by FDA/MHRA versus taking the time needed to have robust assurance in particular as regards CMC and safety) EMA will have a very big challenge addressing questions and criticism from various parties (EC, MSs at political level, EP, media, the general public) in case of a delay of several weeks.

Even if it can not be excluded now that at the end we are aligned with the FDA/MHRA (both in the outcome of the scientific review and the timing), the opposite certainly can not be excluded at this moment so we need to prepare for the worst case scenario. So how do we go from here? Are the current measures enough? In my view, probably not. We will be overwhelmed from all fronts and be in the middle of the storm. And on who's support will we be able to count? I hope it will not be a rethorical question...

What can we do on top, without creating the perception that we are interfering outside our "technical" mandate?
A non-exhaustive list:
1. Explaining the EMA process and what it will deliver:
- A public event is organised on 11/12: I think we need to critically review if we will achieve what is needed, taking into account the already brought forward date and the content related aspects.
- Making better use of social media tools as referred to by Emer today: we urgently need a dedicated strategy. However the resources in Comms are so stretched already that they have at this moment enormous difficulties to cope with the high influx of (media) queries. Reaching out to a specialist company to help out?
2. Explaining the differences between US/U.K. EUA and CMA: although the general public and the media will not (necessarily) understand the nuances between the 2 concepts we have to finalise this exercise which is currently ongoing ASAP, and then, more importantly, decide how to make best use of it. CMC, responsibility and accountability are certainly elements to be considered in my view.
3. Making the CMA process adapted as much as possible to the current pandemic situation: this exercise is ongoing but (1) the time gained may be limited and (2) any changes may be too late for the Pfizer/BioNTech vaccine. Nevertheless I think we should finalise ASAP if only to demonstrate that we did our utmost.

I hope these reflections can contribute to coming to a decision how to best address the important challenges ahead.

KR,

Noel

Nolte Alexis

Mon 23/11/2020 10:48

Sent Items

To:

Korakianiti Evdokia;

Evdokia,

One way to understand how the lower mRNA level in the finished product translates to efficacy would be to measure whether it affects significantly levels of protein expression. It could be that the level of antigenic protein expressed is not significantly affected. However, I don't know whether there is a test that would allow to predict impact on efficacy without clinical trial for comparability.

Alexis

Korakianiti Evdokia

Mon 23/11/2020 10:38

Inbox

Dear Colleagues,

This email is for awareness and to flag an important comparability issue with the BioNTech vaccine that needs to be addressed prior to approval.

Issue: A significant difference in %RNA integrity / truncated species has been observed between the clinical batches (~ 78% mRNA integrity) based on which the Interim analysis was performed and the proposed commercial batches (~ 55%).

The company claims that the efficacy of the drug product is dependent on the expression of the delivered RNA, which requires a **sufficiently intact RNA molecule.** The root cause for for the lower %RNA integrity at commercial batches has not yet been identified

Impact: The potential implications of this RNA integrity loss in commercial batches compared to clinical ones in terms of both safety and efficacy are yet to be defined. Whether or not the observed comparability issues could be a blocking point will depend on the relevance of these observations to safety and efficacy and the company will be requested to fully justify the lower %RNA integrity (and other differences noted).

Point for discussion will be whether the comparability issues can be solved only by Quality data (additional functional/ in vitro biological data + available non-clinical) or that further clinical data (bridging studies are/will be performed) will be needed. It is difficult to make any projections on this.

Way forward: This issue and other MO (but in our view not blocking to a potential approval) have been raised at ETF and are being discussed at BWP this week and in a TC with FDA on Wednesday

With many thanks to Ton who's is the Quality specialist for this vaccine together with Brian looking after the chemical elements

Best regards

Evdokia

Ext. 7150

From: Jekerle Veronika <Veronika.Jekerle@ema.europa.eu>
Sent: 24 November 2020 12:02
To: Korakianiti Evdokia <Evdokia.Korakianiti@ema.europa.eu>
Cc: Facchini Claudio <claudio.facchini@ema.europa.eu>; Moseley Jane <Jane.Moseley@ema.europa.eu>; van der Stappen Ton <ton.vanderstappen@ema.europa.eu>; Dooley Brian <Brian.Dooley@ema.europa.eu>; Rager Irene <Irene.Rager@ema.europa.eu>; Seguin Vanessa <Vanessa.Seguin@ema.europa.eu>
Subject: update from BWP meeting on BioNTech

Dear Evdokia,

The BWP has just discussed the BioNTech BWP and below you will find the main conclusions:

The Dossier is generally of good quality considering the speed in development and compilation.

- 3 major objections are agreed:

- **MO1**: GMP distant assessments for US manufacturing sites (Note: Distance assessment on the Wyeth, Andover site (DS, QC DS, QC DP) and on the Pfizer, Chesterfield site (QC DS, QC DP) are ongoing → interim reports expected 11 Dec 2020, MO reworded to allow statement of GMP)
- **MO2**: Differences in the level of mRNA integrity; comparability between clinical and commercial material, DS and DP is questioned (Note: root cause analysis ongoing an 2 additional PPQ batches manufactured with a slightly adjusted process – waiting for results, if RNA integrity is improved back to initial levels this could be accepted / characterisation data requested to understand protein variability from mRNA fragments → potential impact on safety).
- **MO3**: Pending PPQ-batches for DP: comparability, process validation and stability (Note: as above: 2 PPQ batches manufactured and currently undergoing testing).
- Note that full information on two novel excipients (lipid in the nanoparticles) is not yet provided. This data is expected in the next CMC wave.

Conclusions: a number of major concerns remain that impact the benefit/risk of the vaccine (efficacy/safety) most notably the comparability issue around % mRNA integrity. These concerns are shared by most member states. **An approval by the end of the year could potentially be possible, if these concerns + GMP will be resolved**. Any remaining Quality issues will need to be considered in the context of overall B/R (& could potentially be addressed via specific obligations/Annex II conditions/recommendations).

The BWP report reflecting these conclusions is undergoing written adoption today.

With thanks to Ton, Brian and Claudio,

Kind regards,

Veronika

Veronika Jekerle, PhD

Head of Pharmaceutical Quality Office

Quality and Safety of Medicines

Office: 09-N-02

Extension: 8438

Nolte Alexis

Thu 12/11/2020 14:04

Inbox; Sent Items

Colleagues,

See below Radhouane's briefing (thanks!) from the COVID SC yesterday. Lots of info that is relevant.

On the quality/inspections dashboard and the request to extend to clinical aspects: I had the same thought when seeing the dashboard: great job Evdokia and your team. I'm wondering is the PPO can be of help here and if capacity allows. Michael, could your team look into this with Irene and Marco?

Thanks,

Alexis

- OPEN initiative: meeting scheduled this Friday to finalise the document. Agnes mentioned that for the time being the pilot is on COVID only and involves participation of experts in ETF and CHMP.

- Redaction of PPD: Agnes mentioned that she is working on specific arrangement that would allow us not to redact documents shared with HC. She will f/u on this topic.

- Hilde provided an update on the EC legal proposal to extend EMA's mandate. Press release published today (EC press release with links to legal proposals): resource estimate to implement the proposal will have to be discussed with Emer. EC estimates: 40 FTEs by 2024 (never discussed with EMA). Timing of implantation: 2nd half of 2021 (should go through co-decision very fast) with immediate implementation. Will have an impact on the 2021 work program. Emer asked for an update on Monday next week. This will be followed by a discussion on November 17th with Christa and MB topic coordinators. EXB adoption: 24 November.

- Safety monitoring plan and guidance on risk management planning for COVID-19 vaccines: endorsed (no major comments)

Workstream 1 Therapeutic Response

- Biontech: FDA preparing for EUA by the end of December and is targeting an advisory committee on December 18th provided that the company submits data by November 26th (FDA has asked for all safety data available). It was mentioned that the EUA requirements that FDA will put in place are more stringent than what we would accept for the CMA. The Agency will try to align and get the CMA completed by the end of the year (currently planned in January).

- Moderna: They have more than 100 cases and could trigger an interim analysis anytime now. The CMC package looks more straightforward than the Biontech one. We could try to compress the timelines but not as much as for Biontech.

- AZ: FDA wants to wait for US data as they do not want to use data from Brazil and UK. This is the application r for which we will have most likely differences with FDA.

- Noel message (for discussion at EXB tomorrow): make sure that CMA concept is agile and that because of administrative requirements we do not finalise the application 6 weeks after the finalising the rolling-review for Biontech and Moderna.

- Lilly's mab: FDA might go for an EUA for the product. Another Mab from Regeneron could come as well (both for use in outpatient setting with mid disease).

- Reflection paper on COVID-19 vaccines: should be adopted by ETF this week. We will check with Harald if CHMP wants to endorse the document before publication.

- Sharing of information with CTFG: it was agreed that SA letters can be shared.

Workstream 2 Supply chain

- Dashboard - overview of Qual/Insp issues for COVID vaccines and Therapeutics: very positive feedback from the SG. Noel asked if a similar dashboard should be developed for clinical aspects. Marco will explore.

Communication:

- A GA is scheduled on Friday November 20th. Another one is scheduled in December. Noel will discussed with Emer what is her preferred date for an update from the COVID 19 SG to staff.

- Proposal for Public Stakeholder Meeting on COVID-19 vaccines on 15 December. Should be discussed at EXB tomorrow.

Cavaleri Marco

ma 23/11/2020 15:31

Hilde

I think we may want to say that we need first to understand if this can be actually done as it is really compressed and there are still a number of uncertainties not last when the CY can submit and how the CMC gaps are evaluated

Marco

Boone Hilde

ma 23/11/2020 15:00

Dear Irene, this is the Eudralink with the Excel timetable that Florian sent to us, and which already sets the CHMP opinion on 21 December – hence my questions below.

They need our feedback by 18h today.

Kind regards, Hilde

Rager Irene

ma 23/11/2020 14:57

Dear Hilde

To bring it even forward to 21 Dec will be very difficult, so I would be better to not yet promise this – even though we are going to do our best, of course!

I would suggest that we will wait for the updated submission proposal from BNT/Pfizer this late afternoon, as this will make fine tuned planning much easier.

Thanks and Kind Regards,

Irene.

Boone Hilde

ma 23/11/2020 14:26

Dear Marco & Irene,

In the EC table, CHMP opinion is presented for 21 December, whereas this morning 23rd was mentioned as per current timetable, I understand.

But, indeed we agreed trying to bring Opinion forward by a few days eg to 21 or even 18 Dec.

So, what response should we give back to EC now:

Current EMA planning is 23 Dec for Opinion, but we are looking into bringing adoption forward?

Or

Do we already say that 21 Dec for Opinion, as listed in the EC table, is correct, but that we are looking into bringing adoption forward even more?

I take it that the Eudralink TT request that we just received, replaces Olga's question below (as it is in essence the same).

Best, Hilde

'Vaccines'

WELT+ CORONA VACCINATIES

Vraagteken op het mRNA-vaccin

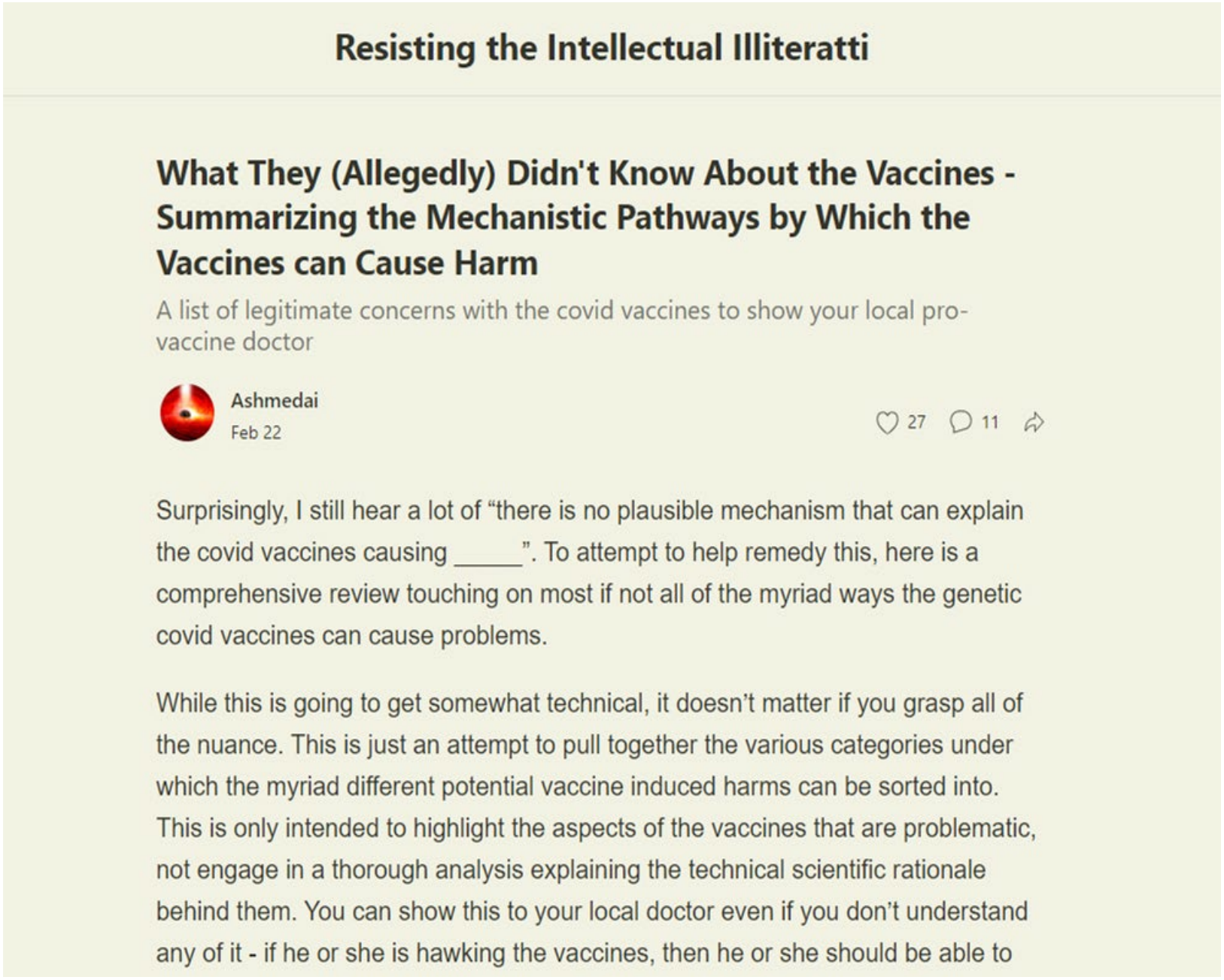
Vanaf 18:44 uur | Leestijd: 7 minuten

Door **Elke Bodderas** , Cornelia Stolze

Bron: Getty Images/skaman306

14 maanden na de eerste vaccinatie zijn Biontech en Moderna nog steeds zonder de juiste goedkeuring - omdat essentiële onderzoeken ontbreken. Het proces is ongebruikelijk. Artsen en apotheekexperts hebben vragen.

Inmiddels zijn zo'n 62 miljoen Duitsers ingeënt, waarbij de preparaten



Resisting the Intellectual Illiteratti

What They (Allegedly) Didn't Know About the Vaccines - Summarizing the Mechanistic Pathways by Which the Vaccines can Cause Harm

A list of legitimate concerns with the covid vaccines to show your local pro-vaccine doctor

Ashmedai
Feb 22

27 11

Surprisingly, I still hear a lot of “there is no plausible mechanism that can explain the covid vaccines causing _____”. To attempt to help remedy this, here is a comprehensive review touching on most if not all of the myriad ways the genetic covid vaccines can cause problems.

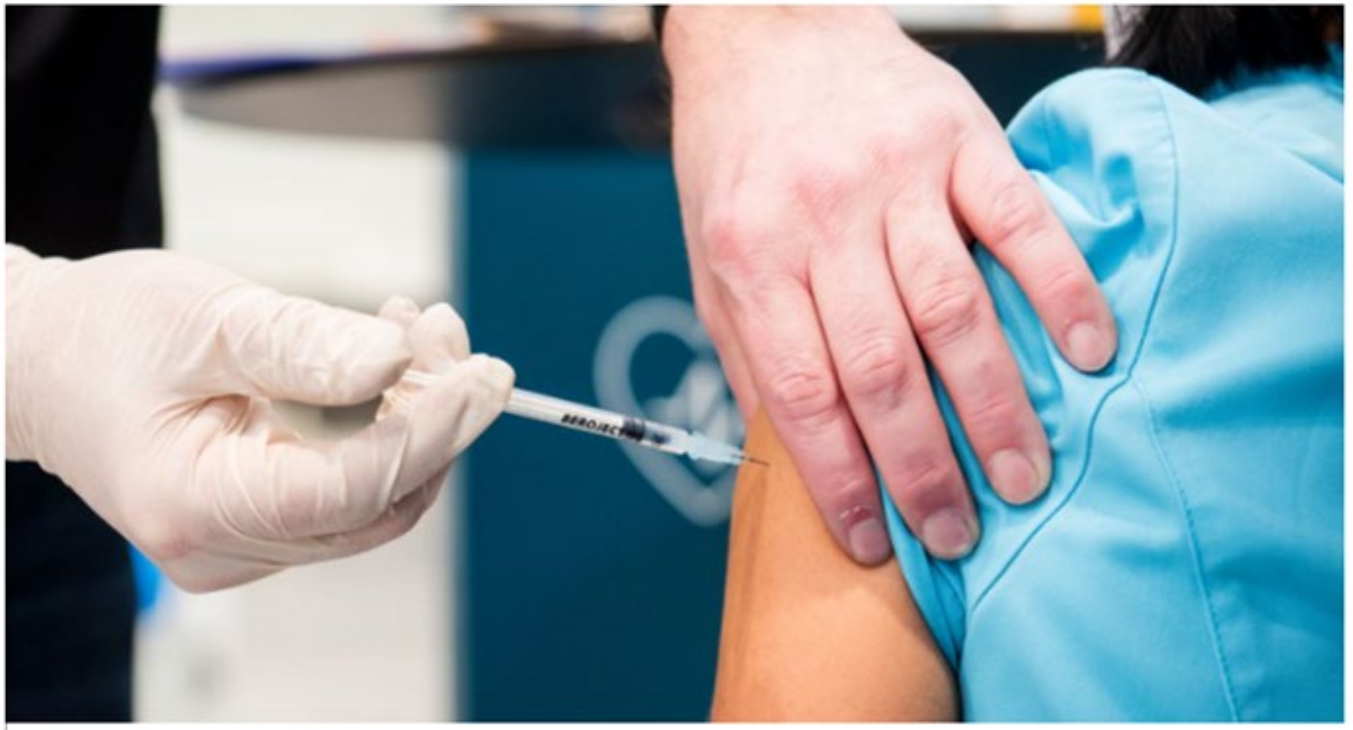
While this is going to get somewhat technical, it doesn’t matter if you grasp all of the nuance. This is just an attempt to pull together the various categories under which the myriad different potential vaccine induced harms can be sorted into. This is only intended to highlight the aspects of the vaccines that are problematic, not engage in a thorough analysis explaining the technical scientific rationale behind them. You can show this to your local doctor even if you don’t understand any of it - if he or she is hawking the vaccines, then he or she should be able to

https://ashmedai.substack.com/p/what-they-allegedly-didnt-know-about?utm_source=url

aspiration

STIKO beveelt aspiratie voor COVID-19-vaccinatie aan als voorzorgsmaatregel

vrijdag 18 februari 2022



/foto alliantie, Daniel Bockwoldt

Berlijn – In tegenstelling tot de algemene aanbevelingen voor vaccinaties, adviseert het Permanent Vaccinatiecomité (STIKO) van het Robert Koch Instituut (RKI) aspiratie bij intramusculaire toediening van een COVID-19-vaccin. Dit is bedoeld om de veiligheid van vaccins verder te vergroten.

STIKO wijst hierop in de 18e update van het COVID-19 vaccinatieadvies van 15 februari. In diermodellen trad perimyocarditis op na directe intraveneuze toediening van een mRNA-vaccin. Ze konden zowel klinisch als histopathologisch worden aangetoond.

pregnancy

EVERYTHINGNEWS FEBRUARY 4, 2021 / 9:21 PM / UPDATED A YEAR AGO

Fact check: Available mRNA vaccines do not target syncytin-1, a protein vital to successful pregnancies

By Reuters Staff

5 MIN READ

Numerous posts have falsely claimed that mRNA vaccines used against COVID-19 target a protein called syncytin-1, which is needed for placental formation and successful pregnancies. Many of these posts also baselessly imply that the vaccines will make people infertile. These claims are untrue; no available mRNA vaccines target a protein called syncytin-1.

nature microbiology

ARTICLES

https://doi.org/10.1038/s41564-021-00908-w

The furin cleavage site in the SARS-CoV-2 spike protein is required for transmission in ferrets

Thomas P. Peacock[1,5], Daniel H. Goldhill[1,5], Jie Zhou[1,5], Laury Baillon[1,5], Rebecca Frise[1,5], Olivia C. Swann[1], Ruthiran Kugathasan[1], Rebecca Penn[1], Jonathan C. Brown[1], Raul Y. Sanchez-David[1], Luca Braga[2], Maia Kavanagh Williamson[3], Jack A. Hassard[1], Ecco Staller[1], Brian Hanley[4], Michael Osborn[4], Mauro Giacca[2], Andrew D. Davidson[3], David A. Matthews[3] and Wendy S. Barclay[1]✉

SARS-CoV-2 entry requires sequential cleavage of the spike glycoprotein at the S1/S2 and the S2′ cleavage sites to mediate membrane fusion. SARS-CoV-2 has a polybasic insertion (PRRAR) at the S1/S2 cleavage site that can be cleaved by furin. Using lentiviral pseudotypes and a cell-culture-adapted SARS-CoV-2 virus with an S1/S2 deletion, we show that the polybasic insertion endows SARS-CoV-2 with a selective advantage in lung cells and primary human airway epithelial cells, but impairs replication in Vero E6, a cell line used for passaging SARS-CoV-2. Using engineered spike variants and live virus competition assays and by measuring growth kinetics, we find that the selective advantage in lung and primary human airway epithelial cells depends on the expression of the cell surface protease TMPRSS2, which enables endosome-independent virus entry by a route that avoids antiviral IFITM proteins. SARS-CoV-2 virus lacking the S1/S2 furin cleavage site was shed to lower titres from infected ferrets and was not transmitted to cohoused sentinel animals, unlike wild-type virus. Analysis of 100,000 SARS-CoV-2 sequences derived from patients and 24 human postmortem tissues showed low frequencies of naturally occurring mutants that harbour deletions at the polybasic site. Taken together, our findings reveal that the furin cleavage site is an important determinant of SARS-CoV-2 transmission.

In 2019, SARS-CoV-2 entered the human population and by March 2020 was declared a pandemic by the World Health Organization[1–3]. Coronaviruses enter host cells via their spike glycoprotein which is synthesized as an inactive precursor that must be cleaved to mediate membrane fusion. Depending on the sequence of spike at the S1/S2 junction, the cleavage can occur: (1) during trafficking in the producer cell by host furin-like enzymes; (2) by serine proteases such as the transmembrane protease, serine 2 (TMPRSS2), at the cell surface during attachment; or (3) by cathepsin proteases in the late endosome/endolysosome[4,5]. Upon SARS-CoV-2 has been repeatedly shown to rapidly lose this polybasic CS upon passage in Vero cells, a popular cell line for isolating and propagating the virus[22–28]. In addition, there are isolated reports of CS mutants sequenced directly from clinical swabs[22,24]. Several different mutants in this region are described, including total deletions of the CS, loss of arginine substitutions within the CS making it less polybasic or deletions of flanking regions leaving the polybasic tract intact but potentially affecting accessibility to protease.

In this study, we use a combination of lentiviral pseudotypes (PVs) with spike CS mutations and Vero-passaged SARS-CoV-2

express TMPRSS2 (refs. [30,31]), and syncytia formation was compared with SARS-CoV and MERS-CoV spikes. As described before[18], SARS-CoV spike expression resulted in poor syncytia formation, while MERS-CoV spike produced appreciable levels of syncytia (Fig. 1b and Extended Data Fig. 1). SARS-CoV-2 WT spike gave an intermediate level of syncytia formation that was ablated in the monoCS or ΔCS/Δflank mutants. The H5CS spike bearing the optimized furin CS produced a higher level of syncytia formation than SARS-CoV-2 WT, similar to MERS-CoV.

To investigate the differences in spike cleavage efficiency in producer cells between the mutants, PVs with each mutant spike protein were concentrated and probed by western blot (Fig. 1c, left panel). Equal amounts of PV particles were loaded as indicated by p24 content. Anti-spike S2 antibody detected two bands in PVs, consistent with cleaved and uncleaved spike. For PVs expressing WT SARS-CoV-2 spike, the stronger band corresponded to the cleaved S2 product. H5CS spike was more efficiently cleaved while SARS-CoV WT spike and SARS-CoV-2 monoCS and deletion mutants were largely uncleaved. Consistent with PV, authentic SARS-CoV-2 virus harboured both uncleaved and cleaved S2, whereas ΔCS mutant virus only contained uncleaved spike (Fig. 1d). Overall, these data are consistent with previous work that has shown the polybasic CS of SARS-CoV-2 is a suboptimal furin CS[11,18,19].

The furin CS of SARS-CoV-2 spike protein promotes entry into epithelial cell lines and cultures but adversely affects entry into Vero and 293T cells. To investigate a role for the S1/S2 furin CS of SARS-CoV-2 in virus replication in different cell types, we performed competition assays, taking a mixed SARS-CoV-2 population containing 70% ΔCS mutant and 30% WT (as determined by

was detected at any time point.

Next, we probed the ability of PVs with different mutant spike proteins to enter different human cell lines: 293T cells expressing human ACE2, Caco-2 cells or Calu-3 cells (Fig. 2d–f). PVs bearing the envelope of amphotropic murine leukaemia virus (MLV-A) or Indiana vesicular stomatitis virus glycoprotein (VSV-G), or produced without any viral glycoproteins (bald), were used as positive and negative controls throughout. As in the Vero E6 cells (Fig. 1e), a clear negative correlation was seen between efficiency of furin cleavage of the spike and entry in 293T-ACE2 cells (Fig. 1h). PVs with WT SARS-CoV-2 spike entered 293T-ACE2s less efficiently than SARS-CoV, while SARS-CoV-2 spike mutants without furin cleavage (monoCS/ΔCS/Δflank) entered cells significantly more efficiently (>3-fold compared with WT). Introduction of the optimized furin CS (H5CS) dramatically decreased entry (~10-fold lower than WT; $P<0.001$). In Caco-2 and Calu-3 cells, the opposite trend was observed in accordance with the efficiency of virus replication in Caco-2, Calu-3 and primary HAE cells (Fig. 1i,j). Mutants unable to be cleaved by furin, including ΔCS, entered cells significantly less efficiently than WT and H5CS (>2-fold lower in Caco-2 and ~5-fold lower in Calu-3 cells).

Entry of SARS-CoV-2 into 293T cells is dependent on cathepsins while entry into Caco-2, Calu-3 and primary HAE cells is dependent on TMPRSS2. As well as at the S1/S2 junction, coronavirus spike proteins require cleavage by host cell proteases at the S2′ site to enable viral–host cell membrane fusion. To investigate whether the different cell entry phenotypes seen in 293T-ACE2/Vero versus Caco-2/Calu-3/HAE cells were due to differences in protease usage, we performed PV entry assays in the presence of protease inhibitors: camostat, which inhibits serine proteases such as TMPRSS2,

Fig. 1 | The suboptimal furin CS of SARS-CoV-2 spike enhances entry into mucosal epithelial and primary human airway cells. a, Amino acid sequence alignment of coronavirus furin CS mutants used in this study. Mutants with potential S1/S2 furin CSs are shown in shades of orange while mutants without furin CSs are shown in shades of blue. **b**, Syncytia formation due to overexpression of different coronavirus spike proteins in Vero E6 cells. Percentage indicates the proportion of nuclei in each field that have formed clear syncytia. Data are plotted as mean + s.d. of three independent repeats. Statistical significance was determined by one-way ANOVA with multiple comparisons against SARS-CoV-2 WT. ****$P<0.0001$. An extended figure of representative fields shown is in Extended Data Fig. 1. **c**, Western blot analysis of concentrated lentiviral PVs with different coronavirus spike proteins. Levels of lentiviral p24 antigen shown as loading control. Representative blot shown from $n=3$ independent repeats. **d**, Western blot analysis of concentrated WT and ΔCS SARS-CoV-2 viruses. Levels of nucleocapsid (N) protein shown as loading control. Representative blot shown from $n=2$ independent repeats. **e**, SARS-CoV-2 competition assay growth curve between WT and ΔCS virus in Vero E6 and Caco-2 cells. Cells were infected at an MOI of 0.1. Starting inoculum ratio is shown on the left-hand bar, while proportions of virus as determined by deep sequencing at 72 h post-inoculation are shown on the right. Virus titres determined by plaque assay at 72 h post-inoculation are shown in superimposed white data points. All results indicate triplicate repeats plotted as mean + s.d. **f**, SARS-CoV-2 competition assay growth curve between WT and ΔCS virus in HAEs. Cells were infected at an MOI of 0.1. Starting inoculum ratio shown at time 0; proportions of virus determined by deep sequencing. All time points were taken from triplicate

flanking amino acids but retains the tribasic CS (Δflank). The mutations were engineered into a spike expression plasmid to enable cell surface expression and generation of coronavirus lentiviral PVs. In addition, to study the importance of the PRRAR motif in the context of live virus, we used a naturally occurring Vero-cell-adapted mutant SARS-CoV-2, ΔCS[26]. This variant and the wild-type (WT) virus from which it was derived were cloned by limiting dilution to enable studies using individual genotypes.

Furin cleavage of coronavirus spike proteins has been shown to correlate with syncytia formation when spike is overexpressed at neutral pH (refs. [7,18,19]). Therefore, we transiently expressed the SARS-CoV-2 mutant spike proteins in Vero E6 cells, which do not express TMPRSS2 (refs. [30,31]), and syncytia formation was compared with SARS-CoV and MERS-CoV spikes. As described before[18], SARS-CoV spike expression resulted in poor syncytia formation, while MERS-CoV spike produced appreciable levels of syncytia (Fig. 1b and Extended Data Fig. 1). SARS-CoV-2 WT spike gave an intermediate level of syncytia formation that was ablated in the monoCS or ΔCS/Δflank mutants. The H5CS spike bearing the optimized furin CS produced a higher level of syncytia formation than SARS-CoV-2 WT, similar to MERS-CoV.

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The furin CS of SARS-CoV-2 spike protein promotes entry into epithelial cell lines and cultures but adversely affects entry into Vero and 293T cells. To investigate a role for the S1/S2 furin CS of SARS-CoV-2 in virus replication in different cell types, we performed competition assays, taking a mixed SARS-CoV-2 population containing 70% ΔCS mutant and 30% WT (as determined by deep sequencing of the S1/S2 CS; Fig. 1e) inoculated onto Vero E6 cells; human intestinal Caco-2 cells; or air–liquid interface, differentiated human airway epithelial cell (HAE) cultures at a low multiplicity of infection (MOI) enabling multicycle replication. By 72 h, the ΔCS mutant outcompeted WT in Vero E6 cells, whereas WT became predominant in the Caco-2 cells. In primary HAE cultures, the WT rapidly outcompeted the ΔCS virus which was almost undetectable after 72 h (Fig. 1f). We also infected Calu-3 (human lung) cells with clonal WT or ΔCS virus at an MOI of 0.1 (Fig. 1g). WT virus replicated robustly and reached peak titres greater than 10^5 plaque-forming units (p.f.u.) after 48 h. Conversely, ΔCS virus was unable to productively infect Calu-3 cells and no infectious titre was detected at any time point.

Next, we probed the ability of PVs with different mutant spike proteins to enter different human cell lines: 293T cells expressing human ACE2, Caco-2 cells or Calu-3 cells (Fig. 2d–f). PVs bearing the envelope of amphotropic murine leukaemia virus (MLV-A) or Indiana vesicular stomatitis virus glycoprotein (VSV-G), or produced without any viral glycoproteins (bald), were used as positive and negative controls throughout. As in the Vero E6 cells (Fig. 1e), a clear negative correlation was seen between efficiency of furin cleavage of the spike and entry in 293T-ACE2 cells (Fig. 1h). PVs with WT SARS-CoV-2 spike entered 293T-ACE2s less efficiently than SARS-CoV, while SARS-CoV-2 spike mutants without furin cleavage (monoCS/ΔCS/Δflank) entered cells significantly more efficiently (>3-fold compared with WT). Introduction of the optimized furin CS (H5CS) dramatically decreased entry (~10-fold lower than WT; $P<0.001$). In Caco-2 and Calu-3 cells, the opposite trend was observed in accordance with the efficiency of virus replication in Caco-2, Calu-3 and primary HAE cells (Fig. 1i,j). Mutants unable to be cleaved by furin, including ΔCS, entered cells significantly less efficiently than WT and H5CS (>2-fold lower in Caco-2 and ~5-fold lower in Calu-3 cells).

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Fig. 1 | The suboptimal furin CS of SARS-CoV-2 spike enhances entry into mucosal epithelial and primary human airway cells. a, Amino acid

REPORT

IFITM proteins inhibit placental syncytiotrophoblast formation and promote fetal demise

JULIAN BUCHRIESER, SÉVERINE A. DEGRELLE, THÉRÈSE COUDERC, QUENTIN NEVERS, OLIVIER DISSON, CAROLINE MANET, DANIEL A. DONAHUE, FRANÇOISE PORROT, KENZO-HUGO HILLION, [...] OLIVIER SCHWARTZ +10 authors Authors Info & Affiliations

SCIENCE • 12 Jul 2019 • Vol 365, Issue 6449 • pp. 176-180 • DOI: 10.1126/science.aaw7733

Placenta formation and fetal demise

A critical step of placental development is the fusion of trophoblast cells into a multi-nucleated syncytiotrophoblast layer. Trophoblast fusion is mediated by syncytins, encoded by endogenous retrovirus–derived envelope glycoproteins. Buchrieser *et al.* report that interferon-induced transmembrane (IFITM) proteins inhibit syncytin-mediated syncytiotrophoblast formation, restricting placental development and triggering fetal demise (see the Perspective by Kellam and Weiss). The results provide a molecular explanation for the placental dysfunctions observed in interferon-mediated disorders such as intrauterine growth retardation, TORCH (toxoplasmosis, other, rubella, cytomegalovirus, and herpes) infections, and some forms of preeclampsia.

Science, this issue p. 176; see also p. 118

TORCH (toxoplasmosis, other, rubella, cytomegalovirus, and herpes) infections, and some forms of preeclampsia.

Science, this issue p. 176; see also p. 118

Abstract

Elevated levels of type I interferon (IFN) during pregnancy are associated with intrauterine growth retardation, preterm birth, and fetal demise through mechanisms that are not well understood. A critical step of placental development is the fusion of trophoblast cells into a multinucleated syncytiotrophoblast (ST) layer. Fusion is mediated by syncytins, proteins deriving from ancestral endogenous retroviral envelopes. Using cultures of human trophoblasts or mouse cells, we show that IFN-induced transmembrane proteins (IFITMs), a family of restriction factors blocking the entry step of many viruses, impair ST formation and inhibit syncytin-mediated fusion. Moreover, the IFN inducer polyinosinic:polycytidylic acid promotes fetal resorption and placental abnormalities in wild-type but not in *Ifitm*-deleted mice. Thus, excessive levels of IFITMs may mediate the pregnancy complications observed during congenital infections and other IFN-induced pathologies.

downregulation

Innate Immune Suppression by SARS-CoV-2 mRNA Vaccinations: The role of G-quadruplexes, exosomes and microRNAs

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Abstract

The mRNA SARS-CoV-2 vaccines were brought to market in response to the widely perceived public health crises of Covid-19. The utilization of mRNA vaccines in the context of infectious disease had no precedent, but desperate times seemed to call for desperate measures. The mRNA vaccines utilize genetically modified mRNA encoding spike proteins. These alterations hide the mRNA from cellular defenses, promote a longer biological half-life for the proteins, and provoke higher overall spike protein production. However, both experimental and observational evidence reveals a very different immune response to the vaccines compared to the response to infection with SARS-CoV-2. As we will show, the genetic modifications introduced by the vaccine are likely the source of these differential responses. In this paper, we present the evidence that vaccination, unlike natural infection, induces a profound impairment in type I interferon signaling, which has diverse adverse consequences to human health. We explain the mechanism by which immune cells release into the circulation large quantities of exosomes containing spike protein along with critical microRNAs that induce a signaling response in recipient cells at distant sites. We also identify potential profound disturbances in regulatory control of protein synthesis and cancer surveillance. These disturbances are shown

vaccine in comparison with natural infection." The authors found there to be many qualitative similarities though quantitative differences [2]. Jhaveri (2021) suggests that mRNA vaccines do what infection with the virus does: "The protein is produced and presented in the same way as natural infection" [3]. The U.S. Centers for Disease Control and Prevention (CDC) makes the case based upon antibody titers generated by prior infection vs. vaccination, in addition to production of memory B cells, to argue that the immune response to vaccination is analogous to the response to natural infection [4]. It is this similarity in the humoral immune response to vaccination vs natural infection, paired with both trial and observational data demonstrating reduced risk of infection following vaccination, that stands as the justification for the mass vaccination campaign.

In this paper we explore the scientific literature suggesting that vaccination with an mRNA vaccine initiates a set of biological events that are not only different from that induced by vaccination but are in several ways demonstrably counterproductive to both short- and long-term immune competence and normal cellular function. These vaccinations have now been shown to downregulate critical pathways related to cancer surveillance, infection control, and cellular homeostasis. They introduce into the body highly modified genetic material. A medRxiv preprint has revealed a remarkable difference between the characteristics of the immune response to an infection with SARS-CoV-2 as compared with the immune response to an mRNA vaccine against COVID-19 [5]. Differential gene expression analysis of peripheral dendritic cells revealed a dramatic upregulation of both type I and type II interferons (IFNs) in COVID-19 patients, but not in vaccinees. One remarkable observation they made was that there was an expansion of circulating hematopoietic stem and progenitor cells (HSPCs) in COVID-19 patients, but this expansion was notably absent following vaccination. A striking expansion in circulating plasmablasts observed in COVID-19 patients was also not seen in the vaccinees. All of these observations are consistent with the idea that the vaccines actively suppress type I IFN signaling, as we will discuss below. In this paper we will be focusing extensively, though not exclusively, on vaccination-induced type I IFN suppression and the myriad downstream effects this has on the related signaling cascade.

mitochondrial

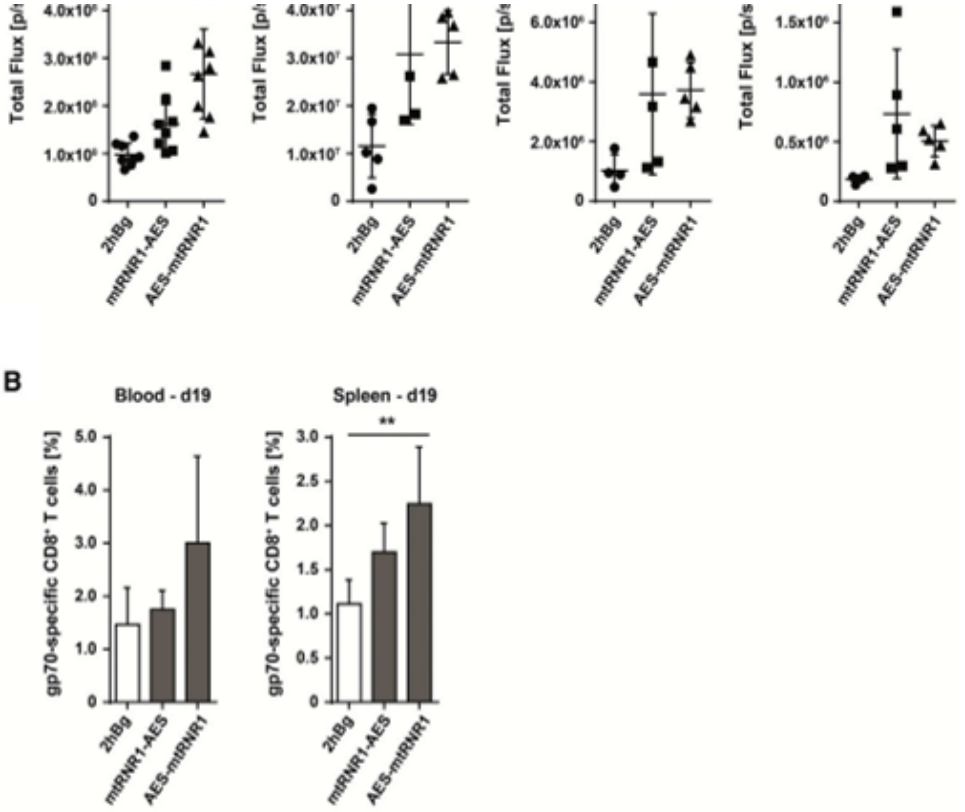
3'-UTR

Like the 5'-UTR the 3'-UTR (UTR= untranslated region) is just extra RNA that can confer stability to the mRNA as a whole. There are two elements in the Pfizer/BioNTech mRNA SARS-CoV2 vaccine, derived from the *amino-terminal enhancer of split (AES)* and the *mitochondrial 12S RNA* genes. Both were described as conferring stability to the mRNA, as well as enhancing the production of the encoded protein, and are common features in mRNA based therapeutics and vaccines (von Niessen et al. 2019). These features help the information in the mRNA stay around the cell a bit longer and create more of the important protein that activates the immune response against SARS-CoV2 coronavirus if /when it actually arrives.

poly (A) Tail

The poly A part of the diagram simply is a modification that helps keep the mRNA from being digested by cellular enzymes. Just about all mRNAs in the cell are decorated with this terminal extension, the "tail" of the mRNA. The tail helps

https://kevinfolta.medium.com/anatomy-of-the-pfizer-covid19-mrna-vaccine-eb29beff7aa3

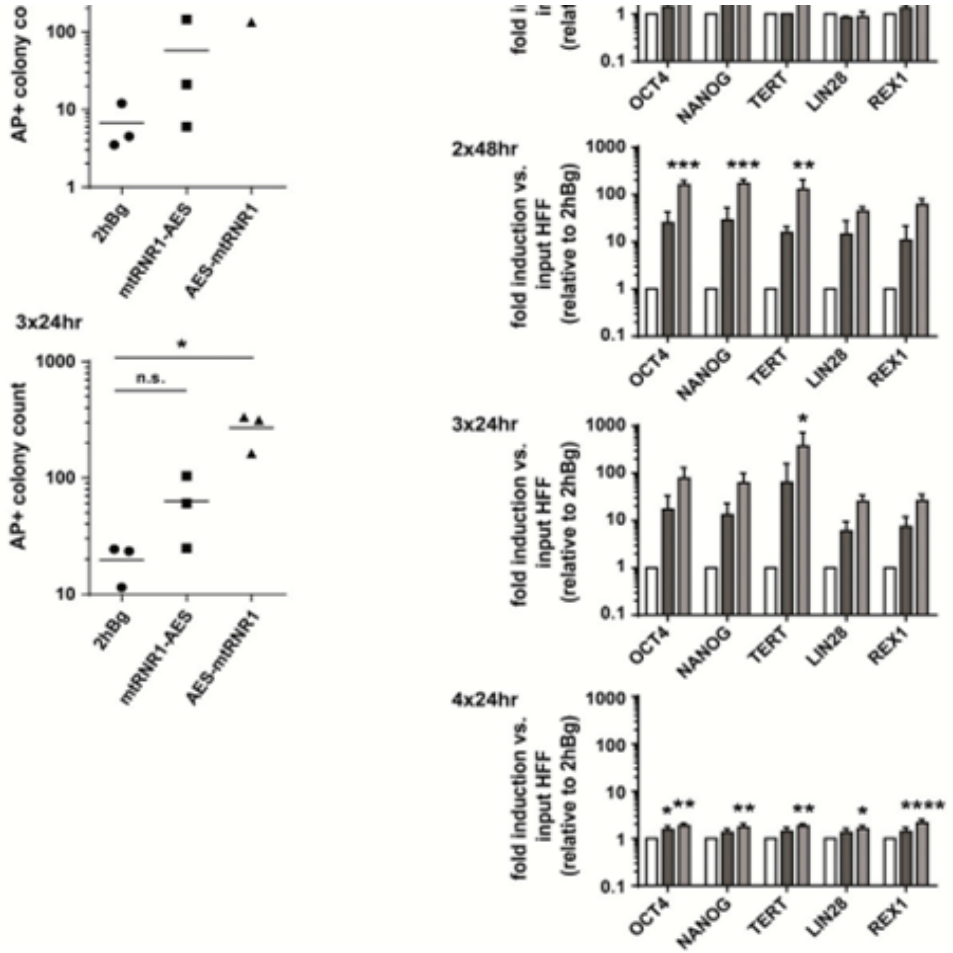


Over 50% of the sequences enriched by several selection rounds were represented by 15 distinct motives defined by identical core areas but diverse 5′/3′ ends. Six of the motives mapped to mRNAs (AES, PLD3, PTRF, CCDC124, PTMA, and MYH9), which are known to have a high median mRNA half-life.[22] The selection rounds enriched for motives mapping to the UTR of the respective mRNAs, but not to their on average much longer coding regions. Altogether, these findings indicate a directed and efficient evolution.

The AES-mtRNR1 and mtRNR1-AES combination motives that we determined functionally as the best performers have a far lower number of putative miRNA-binding sites as compared to the other dUTRs we had discovered and tested. This is in line with reports that mRNA translation decreases with a higher number of miRNAs binding to the 3′ UTR.[45]

mtRNR1- and AES-derived motives were previously not known to stabilize mRNA. mtRNR1 is the mitochondrially encoded non-coding 12S rRNA, which is involved in the translation of the 13 mtDNA protein-coding genes in mitochondria.[46] Mutations in mtRNR1 are associated with deafness.[47] AES is a distinct member of the Groucho/Transducin-like enhancer of split gene family, and it regulates androgen receptor transcriptional activity and Notch and Wnt signaling and acts as a tumor suppressor gene.[48–50]

We validated the identified 3′ UTR motives in two common applications for mRNA-based gene delivery. First, we studied their usefulness for vaccination with antigen-encoding mRNA. Vaccine antigen-encoding mRNA can be administered by different routes, e.g., subcutaneously, intradermally, into lymph nodes, or systemically. Each route aims to deliver the mRNA into professional antigen-presenting cells. As our lab has developed and clinically translated systemic targeting of lymphatic compartments by mRNA encapsulated in liposomal nanoparticles, we used this model. By doing so, we demonstrated that AES-mtRNR1 and mtRNR1-AES tagging improved expression of the mRNA in mouse lymphatic compartments as compared to the 2hBg 3′ UTR. The optimized expression translated into stronger induction of antigen-specific immune responses in the vaccinated mice. Future studies have to explore whether the discovered elements also improve



post-test; ****$p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, relative to 2hBg (three independently performed experiments).

expression and immune responses of mRNA delivered by routes used by others for cancer vaccination.

Second, we studied the efficiency and robustness of cellular reprogramming of human fibroblasts to iPSCs with mRNA-encoded transcription factors, which is considered to benefit from prolonged mRNA stability.[17,51] Our initial screening had enriched elements for augmented transcript stability in hDCs, which are the target cells of gene delivery for vaccination. Due to the cell type-specific expression of *trans*-acting factors, such as miRNAs and RNA-binding proteins, we had not expected that mtRNR1-AES and AES-mtRNR1 3′ UTRs would be profoundly superior in conveying transcript stability in human fibroblasts, which are broadly used target cells for iPSC generation-directed gene delivery.

Alphaviral self-replicating RNA is an alternative vector for fast reprogramming, which requires only one transfection.[52,53] It, however, comes with the disadvantage that clinical grade iPSCs have to be free of residual contaminations of self-replicating vectors. With mRNAs tagged with the AES-mtRNR1 3′ UTR, two transfection rounds were sufficient for the generation of iPSC colonies from human neonatal fibroblasts. One of the implications of this improvement is to make refractory cell lines or cell types like EPCs that require even more rounds of transfections amenable to iPSC generation. Optimized 3′ UTRs further increase the efficiency of a potent, simple, safe, and good manufacturing

Open Access Article

Intracellular Reverse Transcription of Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 In Vitro in Human Liver Cell Line

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Abstract

Preclinical studies of COVID-19 mRNA vaccine BNT162b2, developed by Pfizer and BioNTech, showed reversible hepatic effects in animals that received the BNT162b2 injection. Furthermore, a recent study showed that SARS-CoV-2 RNA can be reverse-transcribed and integrated into the genome of human cells. In this study, we investigated the effect of BNT162b2 on the human liver cell line Huh7 in vitro. Huh7 cells were exposed to BNT162b2, and quantitative PCR was performed on RNA extracted from the cells. We detected high levels of BNT162b2 in Huh7 cells and changes in gene expression of long interspersed nuclear element-1 (LINE-1), which is an endogenous reverse transcriptase. Immunohistochemistry using antibody binding to LINE-1 open reading frame-1 RNA-binding protein (ORFp1) on Huh7 cells treated with BNT162b2 indicated increased nucleus distribution of LINE-1. PCR on genomic DNA of Huh7 cells exposed to BNT162b2 amplified the DNA sequence unique to BNT162b2. Our results indicate a fast up-take of BNT162b2 into human liver cell line Huh7, leading to changes in LINE-1 expression and

https://www.mdpi.com/1467-3045/44/3/73

future studies.

In the BNT162b2 toxicity report, no genotoxicity nor carcinogenicity studies have been provided [26]. Our study shows that BNT162b2 can be reverse transcribed to DNA in liver cell line Huh7, and this may give rise to the concern if BNT162b2-derived DNA may be integrated into the host genome and affect the integrity of genomic DNA, which may potentially mediate genotoxic side effects. At this stage, we do not know if DNA reverse transcribed from BNT162b2 is integrated into the cell genome. Further studies are needed to demonstrate the effect of BNT162b2 on genomic integrity, including whole genome sequencing of cells exposed to BNT162b2, as well as tissues from human subjects who received BNT162b2 vaccination.

Human autonomous retrotransposon LINE-1 is a cellular endogenous reverse tran-

4. Discussion

In this study we present evidence that COVID-19 mRNA vaccine BNT162b2 is able to enter the human liver cell line Huh7 in vitro. BNT162b2 mRNA is reverse transcribed intracellularly into DNA as fast as 6 h after BNT162b2 exposure. A possible mechanism for reverse transcription is through endogenous reverse transcriptase LINE-1, and the nucleus protein distribution of LINE-1 is elevated by BNT162b2.

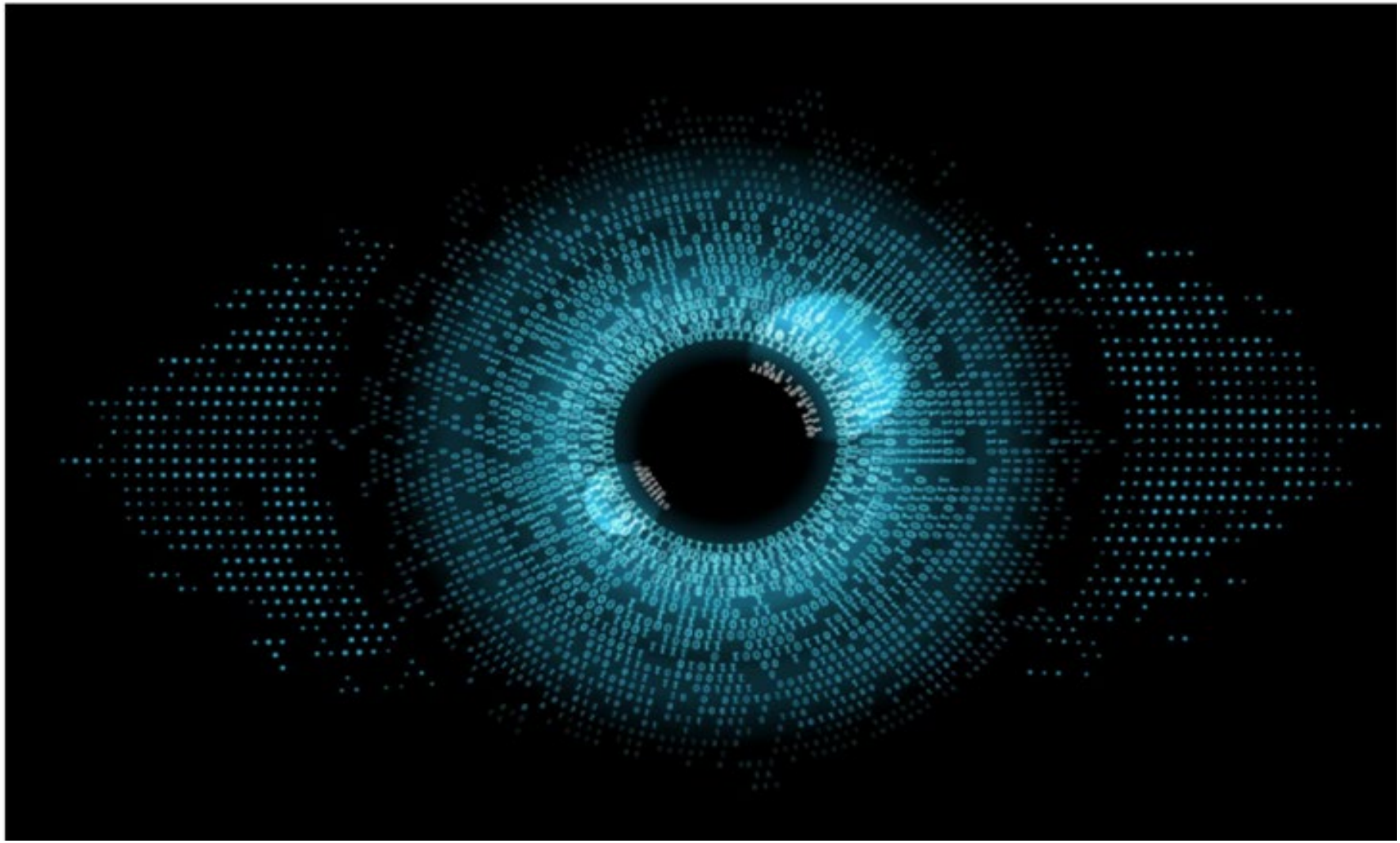
Intracellular accumulation of LNP in hepatocytes has been demonstrated in vivo [36].

freedom , vaccination # digitization , health , vaccination , new , top topic , WHO

WHO commissions transnational digital vaccination card

CDU MdB: Vaccination register in Germany planned for autumn

RELEASED 27 Feb 2022 289 comments



Forbes

EDITORS' PICK | Feb 24, 2022, 10:40am EST | 489,690 views

A National Vaccine Pass Has Quietly Rolled Out – And Red States Are Getting On Board

Suzanne Rowan Kelleher Forbes Staff
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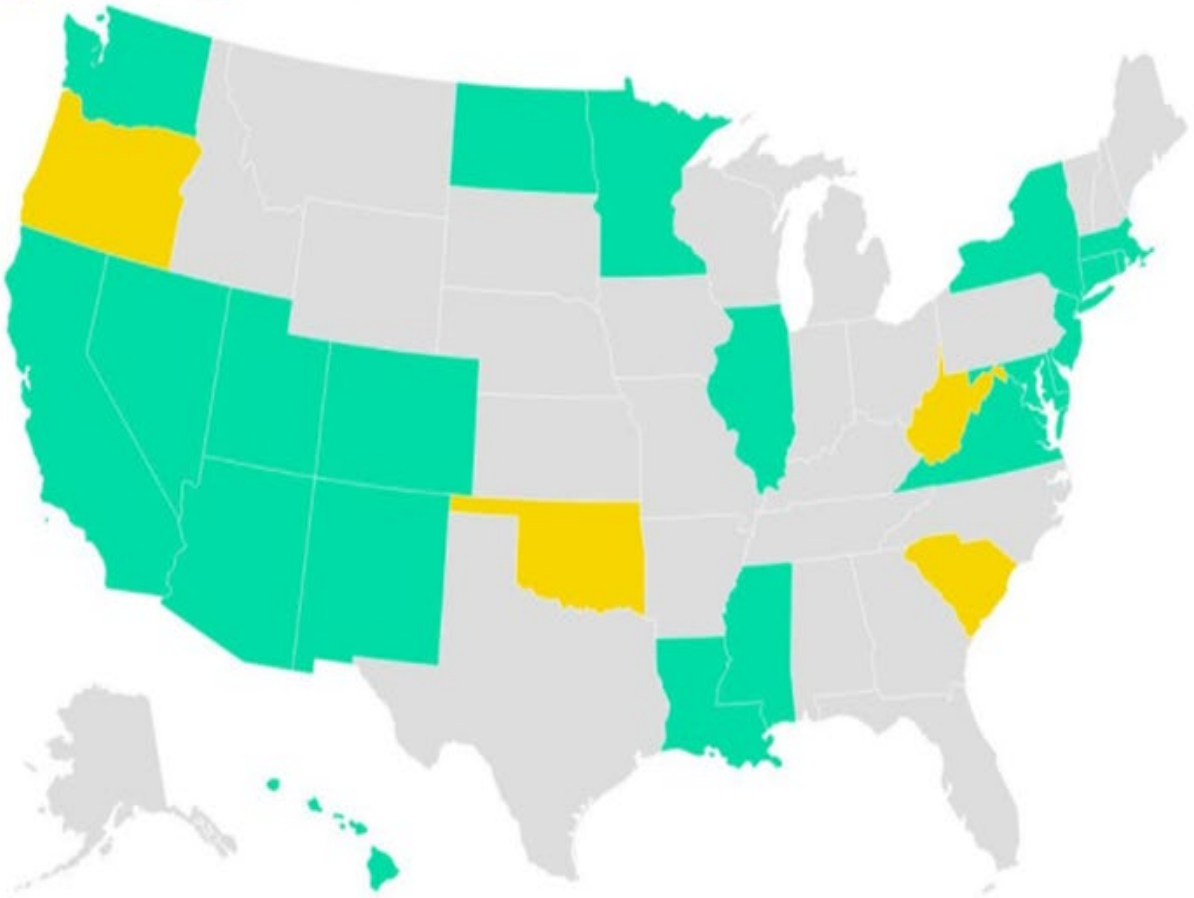
digital health physician at MITRE.

SMART Health Card Accessibility by State

States that have rolled out SMART Health Cards

Coming Soon SMART Health Card



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