L'INSOSTENIBILE IMPREVEDIBILITA' DEI VACCINI COVID-19

Marco Cosentino

Medico Chirurgo, Dottore di Ricerca in Farmacologia e Tossicologia
Professore Ordinario di Farmacologia
nella Scuola di Medicina dell'Università degli Studi dell'Insubria

22 Agosto 2022

L'INSOSTENIBILE IMPREVEDIBILITA'
DEI VACCINI COVID-19

1) **Farmacologia dei vaccini a RNA**
   Ovvero: giocare a dadi con la spike

2) **Analisi di laboratorio negli studi autorizzativi**
   Cosa comporta il fatto che non siano state svolte?

3) **Curare il COVID-19**
   Ruolo delle cure nella valutazione dell'efficacia vaccinale

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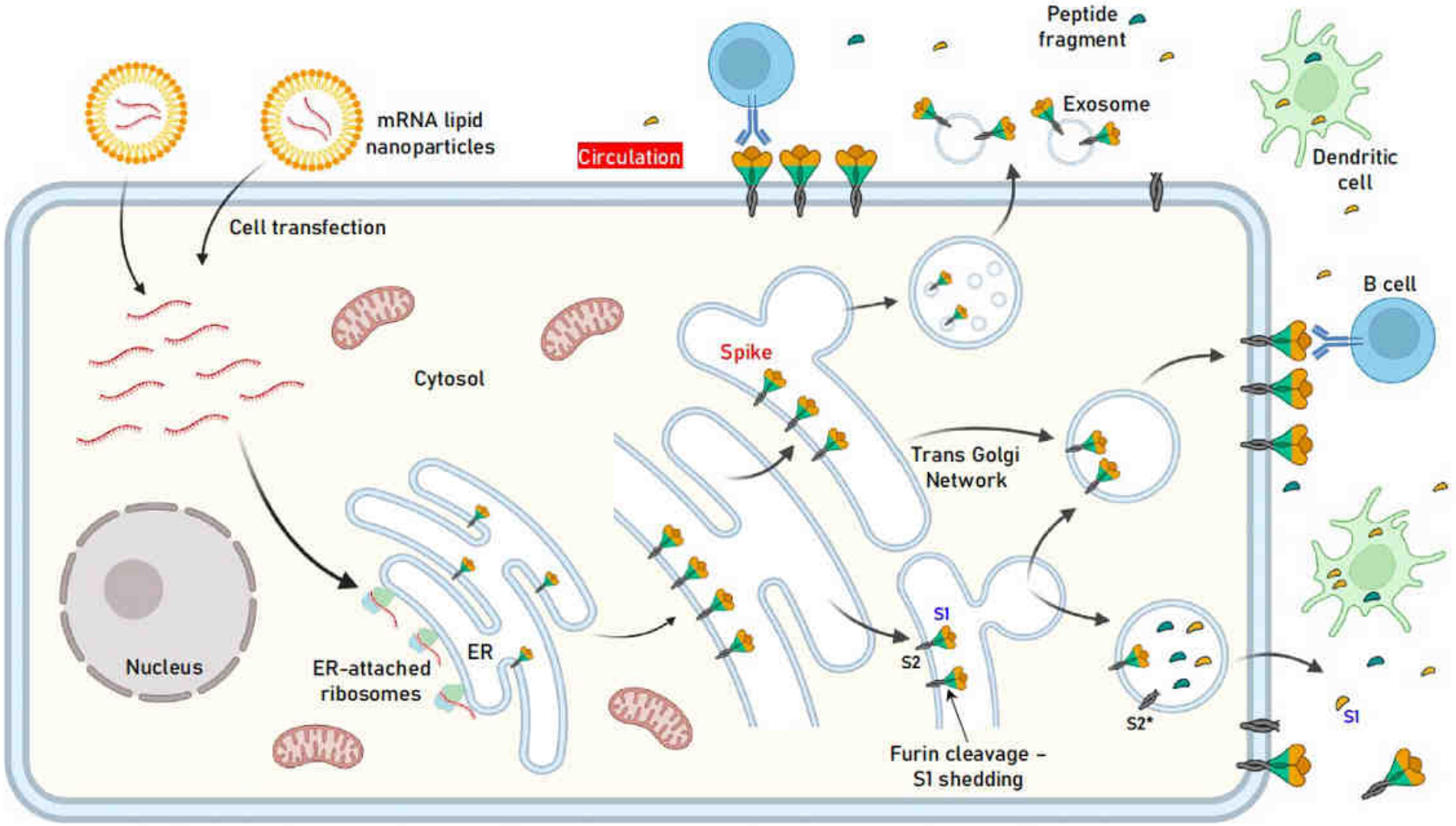
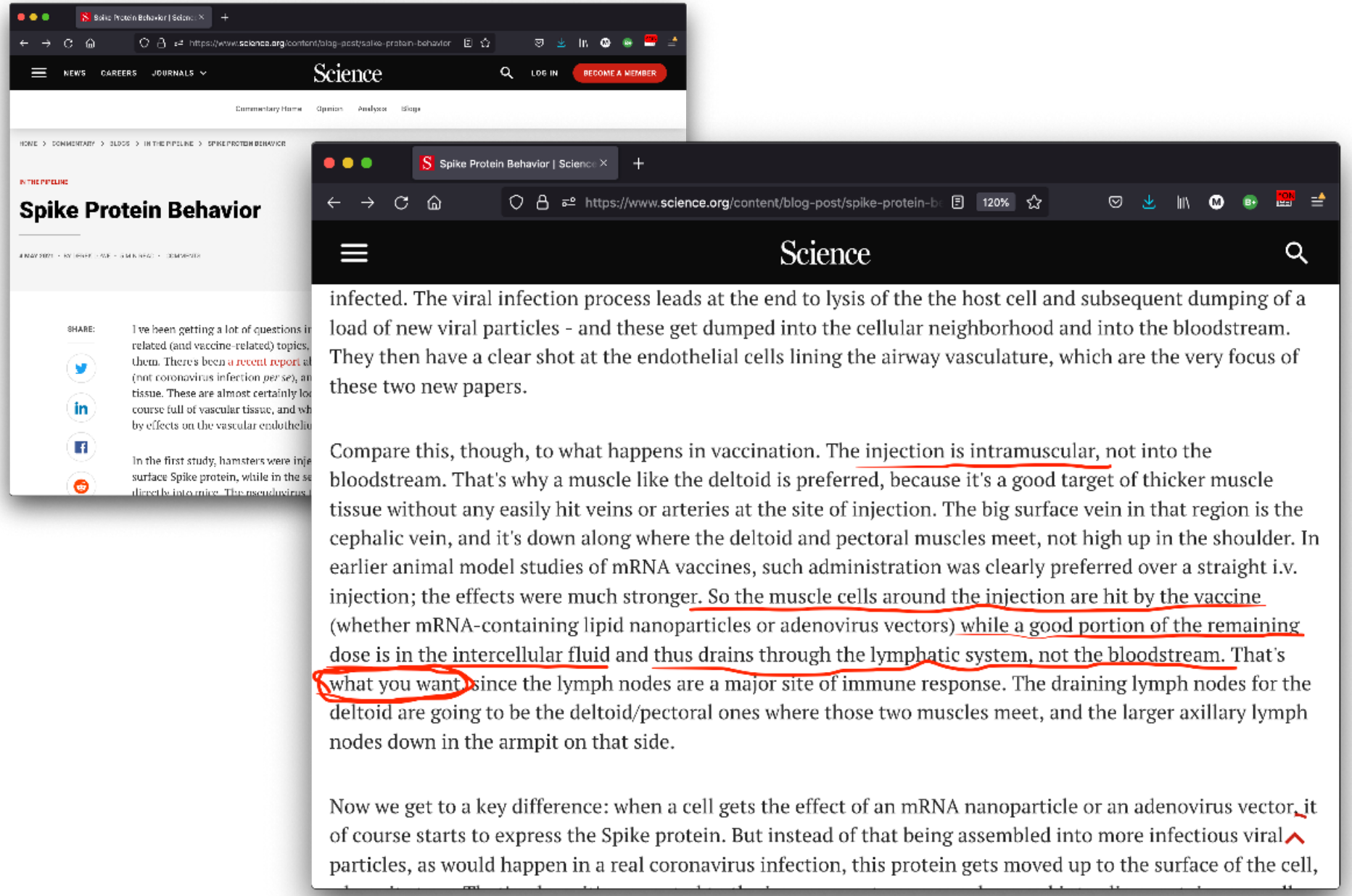
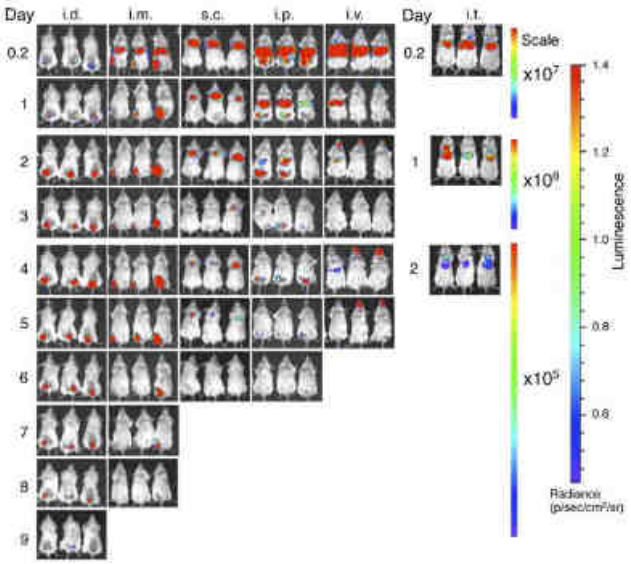
Antigen expression-localization following cell transfection with S protein mRNA-containing lipid nanoparticles (LNPs) used in anti-SARSCoV-2 mRNA vaccines



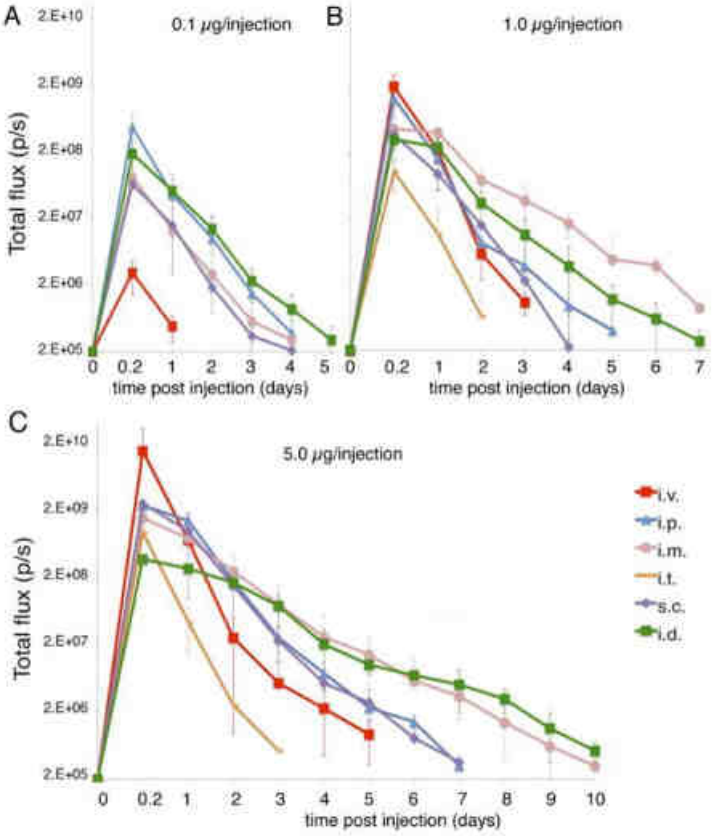
Trougakos, I.P. et al. (2022) **Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis.** *Trends Mol. Med. (in press)*



https://www.science.org/content/blog-post/spike-protein-behavior



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



Translational kinetics of mRNA-LNP delivered by different routes in vivo. Quantification of the bioluminescent signal measured in BALB/c mice injected with (A) 0.1 µg, (B) 1.0 µg or (C) 5.0 µg mRNA-LNPs by intradermal (i.d.), intramuscular (i.m.), subcutaneous (s.c.), intravenous (i.v.), intraperitoneal (i.p.) and intratracheal (i.t.) routes. Error bars are standard error of the mean (SEM).

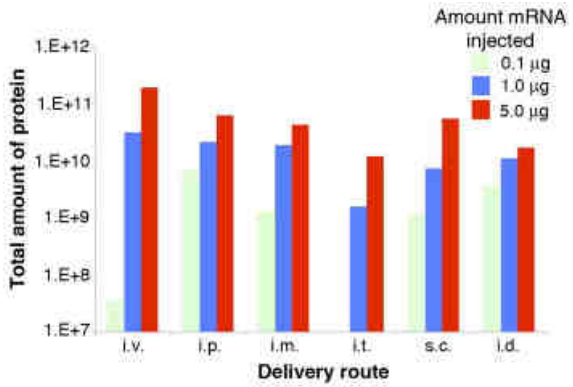


Table 1

Half-life of protein production

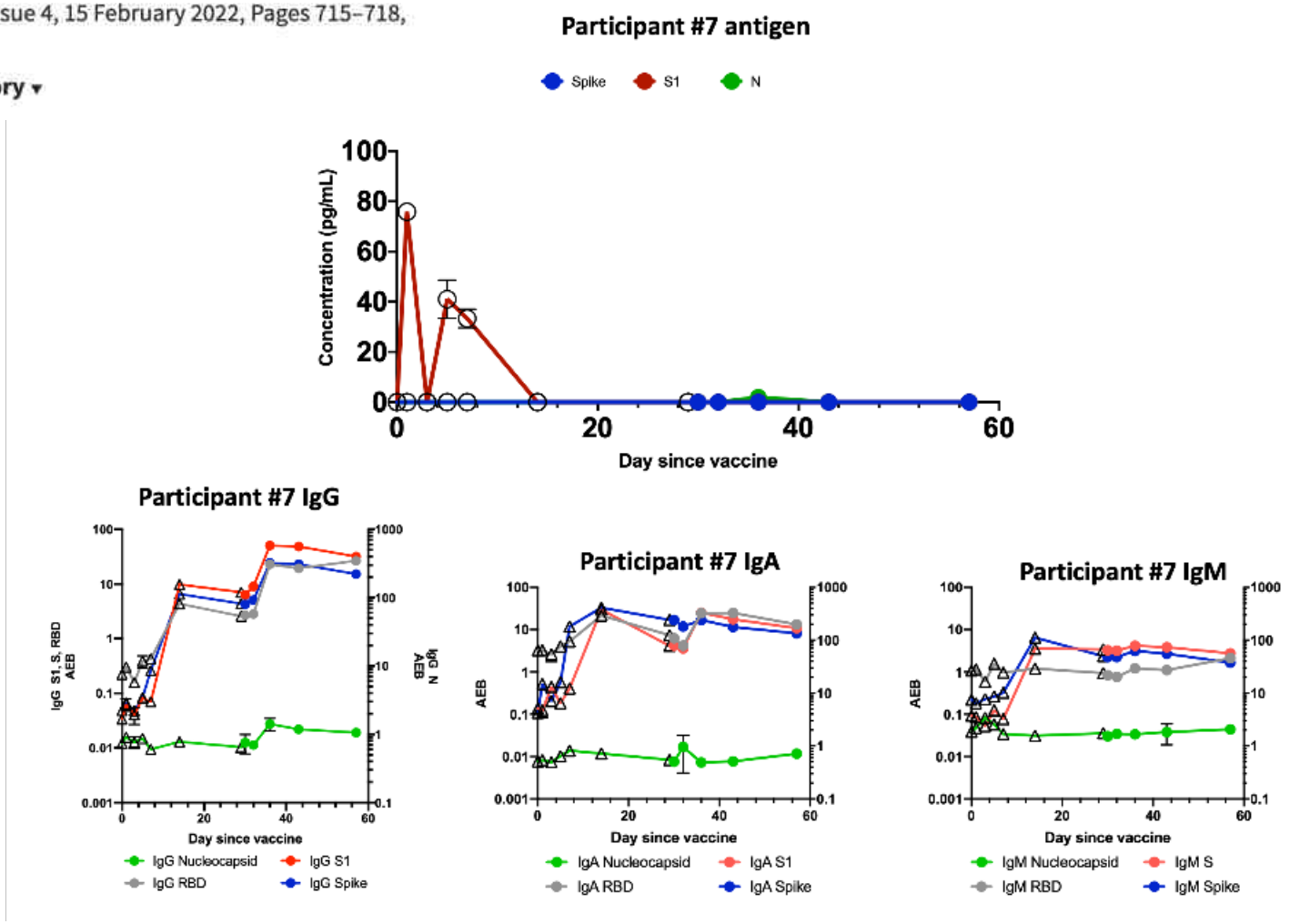
Delivery site	Half-life of mRNA translation (hours)
intradermal	29.6
intramuscular	20.6
subcutaneous	14.7
intravenous	6.8
intraperitoneal	14.8
intratracheal	7.5

Pardi, N. et al. (2015) **Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes.** *J. Control. Release. 217, 345-351*

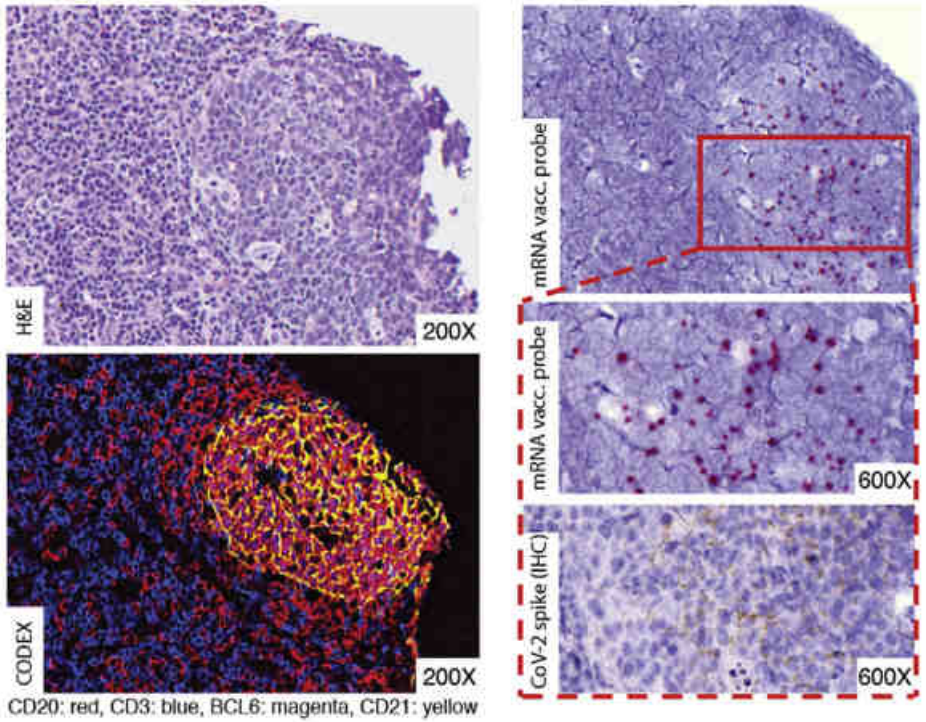
Circulating Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients

Alana F Ogata, Chi-An Cheng, Michaël Desjardins, Yasmeen Senussi, Amy C Sherman, Megan Powell, Lewis Novack, Salena Von, Xiaofang Li, Lindsey R Baden ... Show more
Author Notes

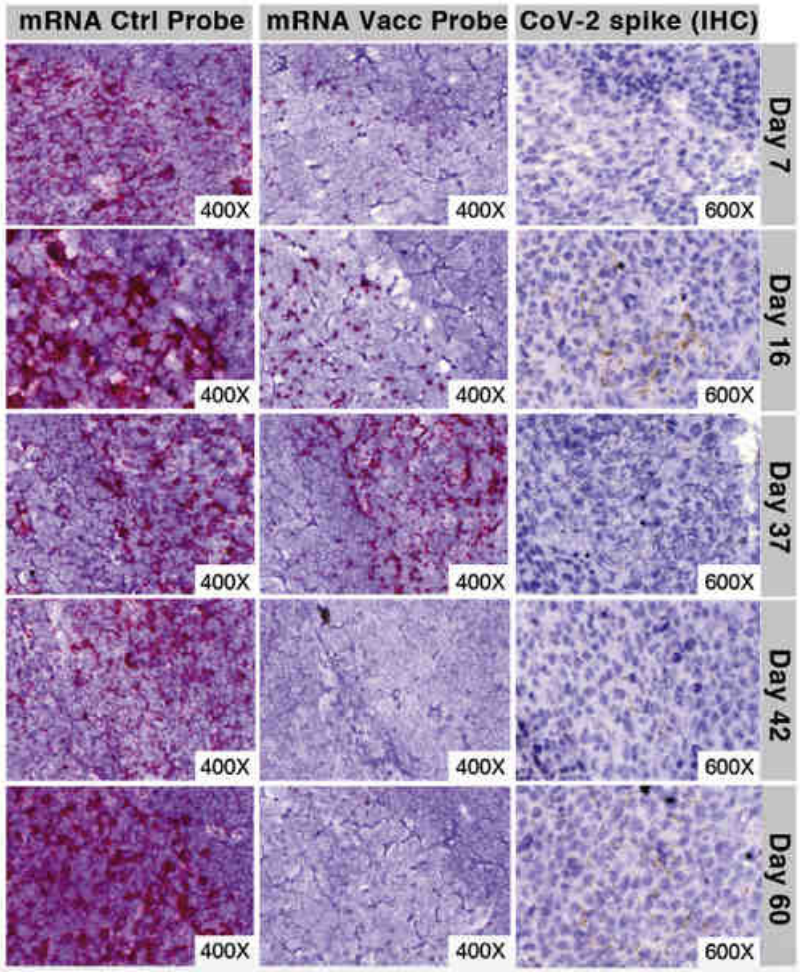
Clinical Infectious Diseases, Volume 74, Issue 4, 15 February 2022, Pages 715–718,
https://doi.org/10.1093/cid/ciab465
Published: 20 May 2021 **Article history**



Ogata, A.F. et al. (2022) **Circulating Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients.** *Clin. Infect. Dis. 74, 715-718*



Representative LN GC after mRNA vaccination showing hematoxylin and eosin staining (upper left), four-color Codex staining (lower left), in situ hybridization of a SARS-CoV-2 mRNA vaccine-specific probe (upper right [lower magnification] and middle right [greater magnification]), and immunohistochemical (IHC) staining for spike antigen (lower right). Vaccine mRNA probe hybridization was visualized by colorimetric development with Fast Red chromogen, and positive IHC staining for spike antigen was visualized as granular brown color from 3,3′-diaminobenzidine (DAB) reagent.



Representative in situ hybridization of an RNAScope control probe (left panels) and SARS-CoV-2 mRNA vaccine-specific probe (middle panels) within ipsilateral axillary core needle LN biopsies of female patients 7–60 days after second mRNA-1273 or BNT162b2 dose. Probe hybridization is indicated by red chromogen spots. IHC signal for spike antigen (right panels) is detected as granular brown staining.

Röltgen, K. et al. (2022) **Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination.** *Cell 185, 1025-1040.e14*

RESEARCH LETTER

blood advances

TO THE EDITOR:

SARS-CoV-2 spike-dependent platelet activation in COVID-19 vaccine-induced thrombocytopenia

Jacob Appelbaum,[1] Donald M. Arnold,[2] John G. Kelton,[2] Terry Gernsheimer,[1] Stefan D. Jevtic,[2] Nikola Ivetic,[2] James W. Smith,[2] and Ishac Nazy[2]

[1]Division of Hematology, Department of Medicine, University of Washington School of Medicine, Seattle, WA; and [2]Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada

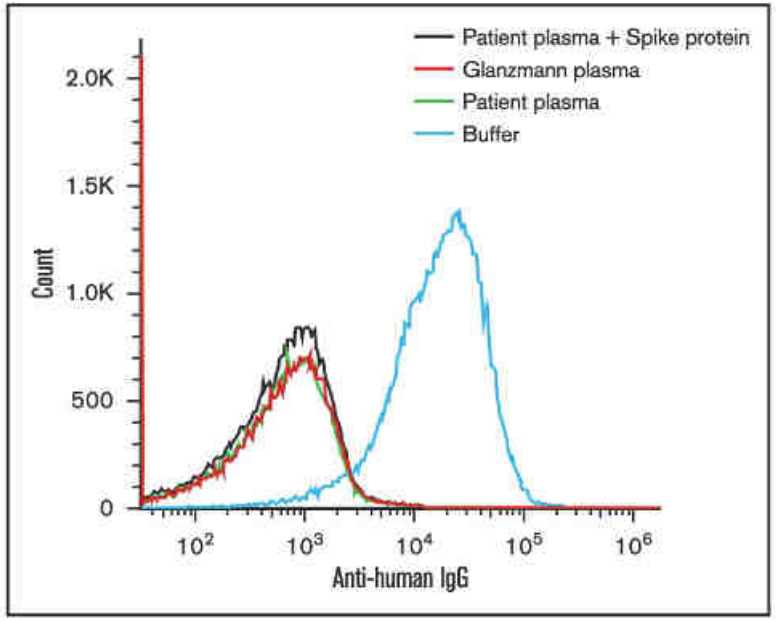


Figure 2. Flow cytometry of IgG binding to the platelet surface. Platelets incubated with plasma sample from our patient (green) failed to show IgG binding with exogenous spike protein administration (red). Negative buffer control (black) and positive Glanzmann thrombasthenia (blue) are shown for comparison.

Appelbaum, J. et al. (2022) **SARS-CoV-2 spike-dependent platelet activation in COVID-19 vaccine-induced thrombocytopenia.** *Blood Adv. 6, 2250-2253*

International Journal of
Molecular Sciences

MDPI

Article

Intramyocardial Inflammation after COVID-19 Vaccination: An Endomyocardial Biopsy-Proven Case Series

Christian Baumeier [1,*], Ganna Aleshcheva [1], Dominik Harms [1], Ulrich Gross [1], Christian Hamm [2,3], Birgit Assmus [3], Ralf Westenfeld [4], Malte Kelm [4], Spyros Rammos [5], Philip Wenzel [6], Thomas Münzel [6], Albrecht Elsässer [7], Mudather Gailani [8], Christian Perings [9], Alae Bourakkadi [10], Markus Flesch [11], Tibor Kempf [12], Johann Bauersachs [12], Felicitas Escher [1,13,14] and Heinz-Peter Schultheiss [1]

Citation: Baumeier, C.; Aleshcheva, G.; Harms, D.; Gross, U.; Hamm, C.; Assmus, B.; Westenfeld, R.; Kelm, M.; Rammos, S.; Wenzel, P.; et al. Intramyocardial Inflammation after COVID-19 Vaccination: An Endomyocardial Biopsy-Proven Case Series. *Int. J. Mol. Sci.* 2022, *23*, 6940. https://doi.org/10.3390/ijms23136940

Academic Editors: Loredana Frasca and Steven Fiering

Received: 8 April 2022
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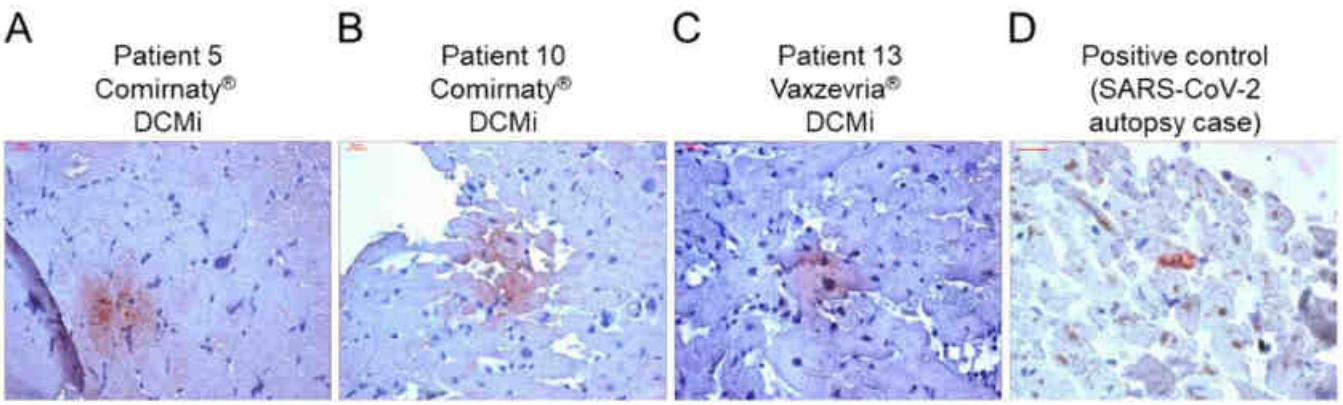

Figure 2. Evidence of SARS-CoV-2 spike protein in cardiac tissue after COVID-19 vaccination. (**A**–**C**) Representative immunohistochemical stainings of SARS-CoV-2 spike protein in EMBs from patients diagnosed with DCMi after receiving Comirnaty® (panel A and B, patients 5 and 10) or Vaxzevria® (panel C, patient 13). (**D**) SARS-CoV-2-positive cardiac tissue served as positive control. Magnification 400×. Scale bars 20 µm.

vaccines

MDPI

Case Report

Clinical and Molecular Characterization of a Rare Case of BNT162b2 mRNA COVID-19 Vaccine-Associated Myositis

Eli Magen [1,2,*,†], Sumit Mukherjee [3,4,†], Mahua Bhattacharya [3], Rajesh Detroja [3], Eugene Merzon [2,5], Idan Blum [1], Alejandro Livoff [6], Mark Shlapobersky [6], Gideon Baum [3], Ran Talisman [7], Evgenia Cherniavsky [8], Amir Dori [9,10] and Milana Frenkel-Morgenstern [3,*]

check for updates

Citation: Magen, E.; Mukherjee, S.; Bhattacharya, M.; Detroja, R.; Merzon, E.; Blum, I.; Livoff, A.; Shlapobersky, M.; Baum, G.; Talisman, R.; et al. Clinical and Molecular Characterization of a Rare Case of BNT162b2 mRNA COVID-19 Vaccine-Associated Myositis. *Vaccines* **2022**, *10*, 1135. https://doi.org/10.3390/vaccines10071135

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Lane no	Description
1	Positive control after 1st PCR
2	Positive control after 2nd PCR
M	50bp marker
-	Empty
3	PBMC after 1st PCR
4	1/2 tissue sample after 1st PCR
5	3/2 tissue sample after 1st PCR
M	50bp marker
-	Empty
M	50bp marker
6	PBMC after 2nd PCR
7	1/2 tissue sample after 2nd PCR
8	3/2 tissue sample after 2nd PCR
14	50bp marker

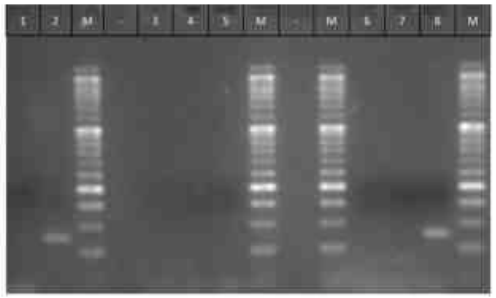
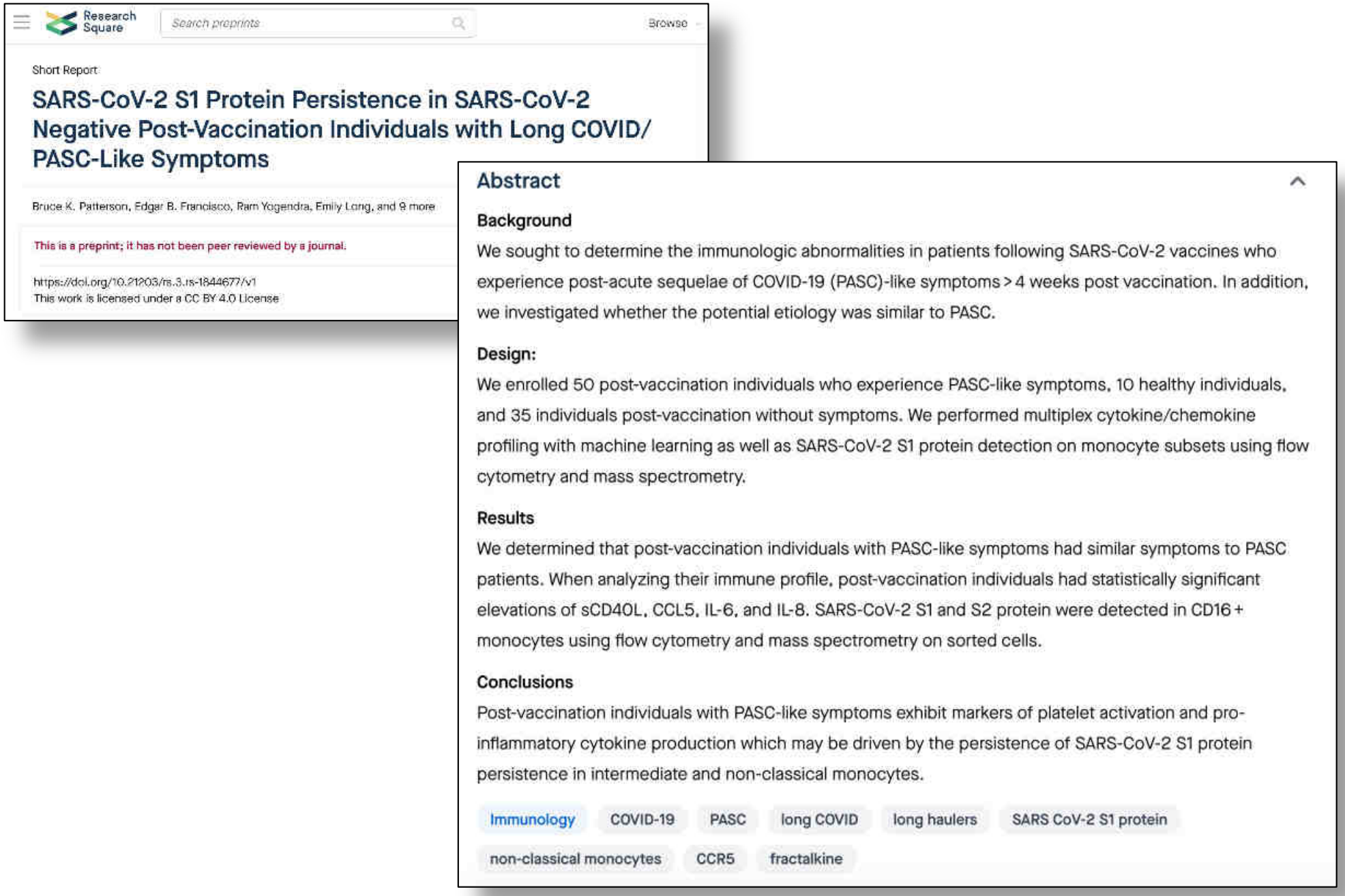


Figure 3. (**I**) Distribution of mapped RNA-seq reads across spike mRNA. (**II**) PCR validation of vaccine spike mRNA expression in the patient's muscle tissue biopsy samples one-month post-vaccination.



https://www.researchsquare.com/article/rs-1844677/v1

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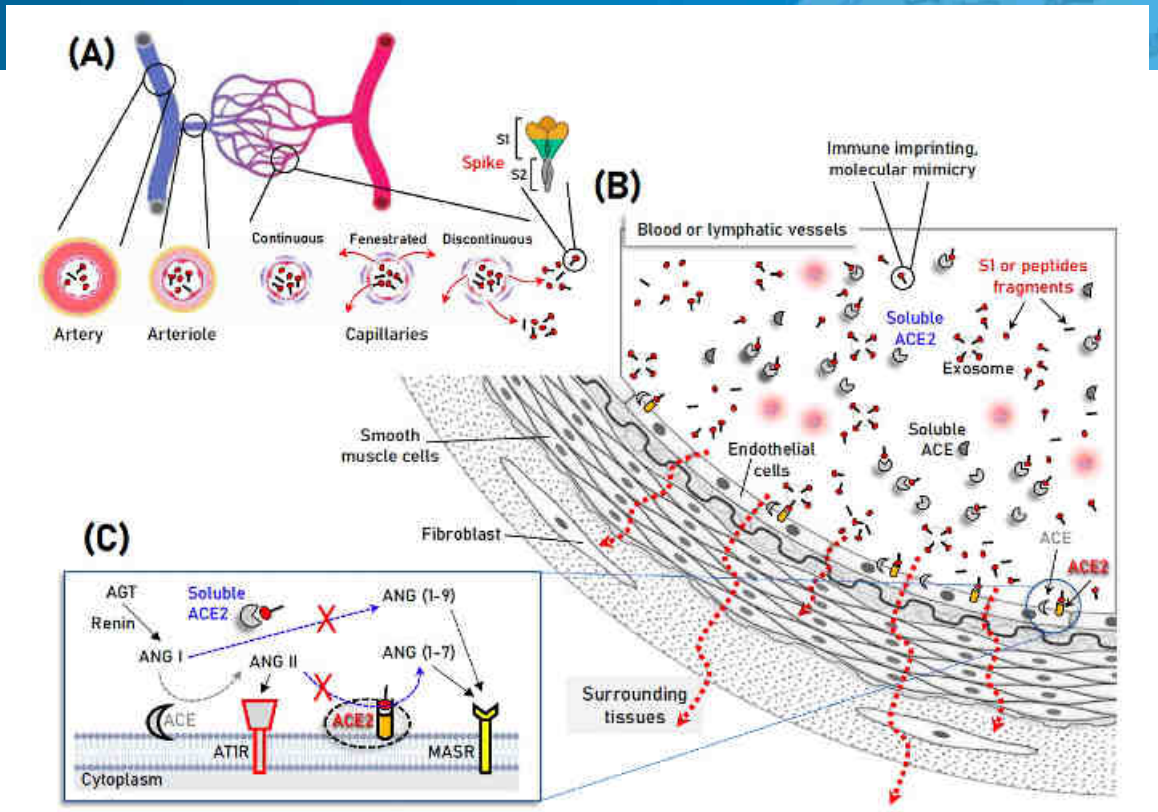
OPINION | VOLUME 28, ISSUE 7, P542-554, JULY 01, 2022

Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis

Ioannis P. Trougakos • Evangelos Terpos • Harry Alexopoulos • ... Efstathios Kastritis • Evangelos Andreakos • Meletios A. Dimopoulos • Show all authors

Published: April 20, 2022 • DOI: https://doi.org/10.1016/j.molmed.2022.04.007 • Check for updates



Schematic of the vasculature components showing vaccination-produced S protein/subunits/peptide fragments in the circulation

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Letter

The spike hypothesis in vaccine-induced adverse effects: questions and answers

Marco Cosentino [1,*] and Franca Marino [1]

1) Evidence for systemic biodistribution of COVID-19 vaccine induced S protein

2) Adverse effects following COVID-19 vaccination: too much S protein, for too long and/or in the wrong place?

3) COVID-19 mRNA vaccines: pharmaceutical drugs rather than conventional vaccines

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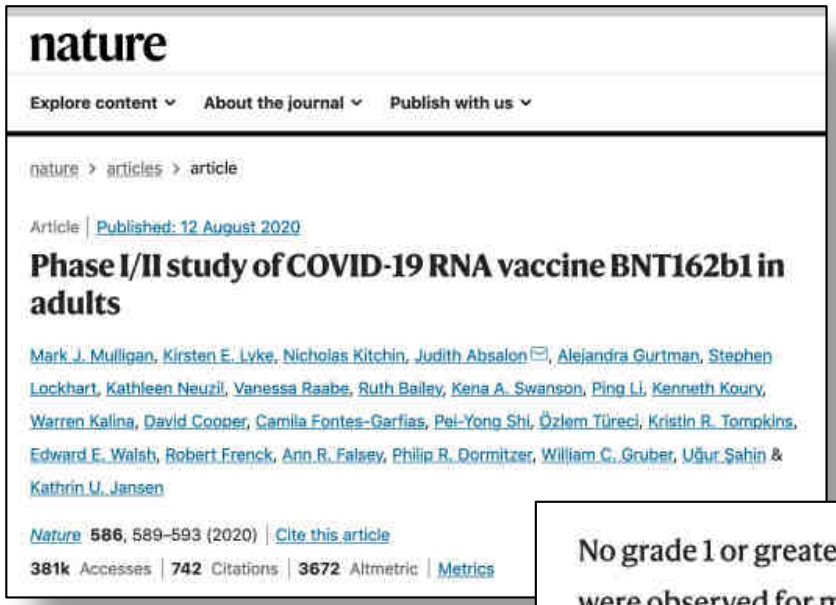

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Article | Published: 12 August 2020

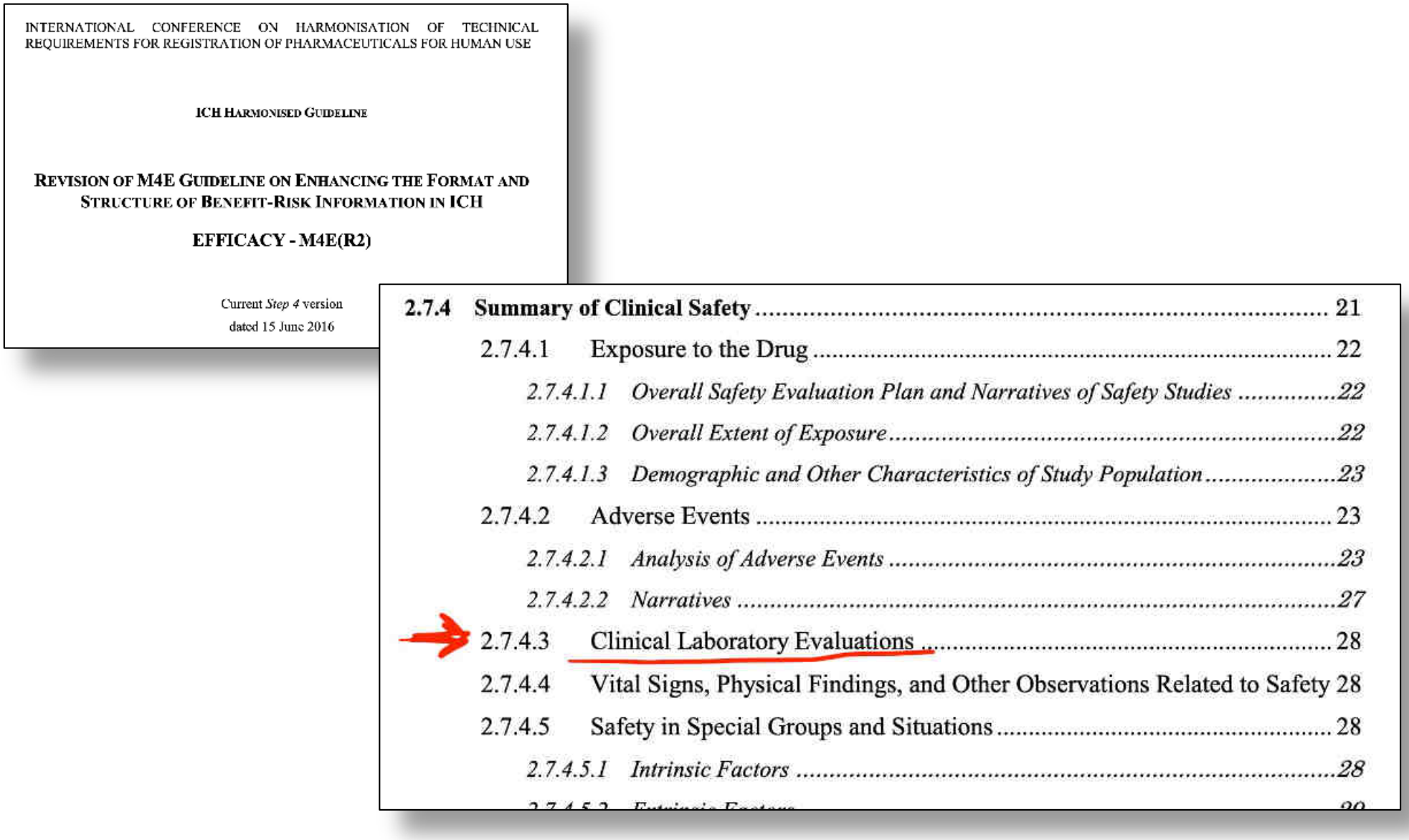
Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults

Mark J. Mulligan, Kirsten E. Lyke, Nicholas Kitchin, Judith Absalon ✉, Alejandra Gurtman, Stephen Lockhart, Kathleen Neuzil, Vanessa Raabe, Ruth Bailey, Kena A. Swanson, Ping Li, Kenneth Koury, Warren Kalina, David Cooper, Camila Fontes-Garfias, Pei-Yong Shi, Özlem Türeci, Kristin R. Tompkins, Edward E. Walsh, Robert Frenck, Ann R. Falsey, Philip R. Dormitzer, William C. Gruber, Uğur Şahin & Kathrin U. Jansen

Nature **586**, 589–593 (2020) | Cite this article

No grade 1 or greater change in routine clinical laboratory values or laboratory abnormalities were observed for most participants after either of the BNT162b1 vaccinations. Of those with laboratory changes, the largest changes were decreases in the lymphocyte count after the first dose in 8.3% (1 out of 12), 45.5% (5 out of 11) and 50.0% (6 out of 12) of participants who received 10 µg, 30 µg and 100 µg BNT162b1, respectively. One participant each in the 10-µg (8.3% (1 out of 12)) and 30-µg (9.1% (1 out of 11)) groups and 4 participants in the 100-µg group (33.3% (4 out of 12)) had grade 3 decreases in the lymphocyte count. These decreases in lymphocyte count after the first dose were transient and returned to normal 6–8 days after vaccination (Extended Data Fig. 1). In addition, grade-2 neutropenia was noted 6–8 days after the second dose in 1 participant each in the 10-µg and 30-µg BNT162b1 groups. These two participants continue to be followed in the study, and no adverse events or clinical manifestations of neutropenia have been reported to date. None of the post-vaccination abnormalities observed were associated with clinical findings.

https://www.nature.com/articles/s41586-020-2639-4



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

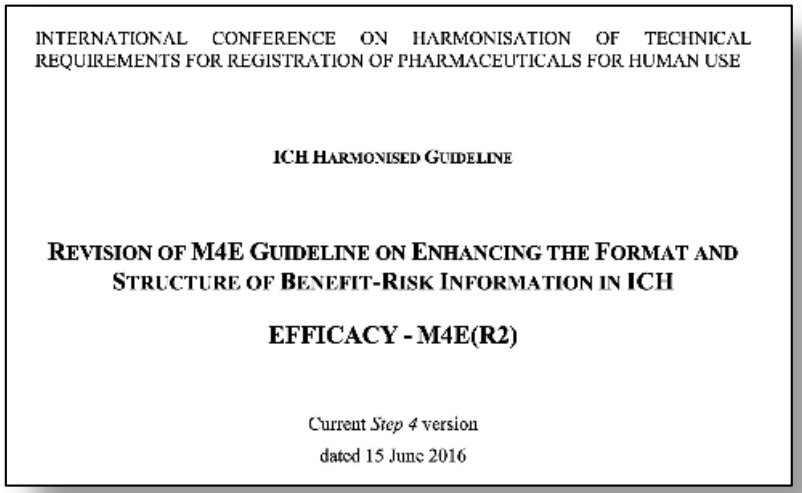
ICH HARMONISED GUIDELINE

REVISION OF M4E GUIDELINE ON ENHANCING THE FORMAT AND STRUCTURE OF BENEFIT-RISK INFORMATION IN ICH

EFFICACY - M4E(R2)

Current *Step 4* version
dated 15 June 2016

https://database.ich.org/sites/default/files/M4E_R2__Guideline.pdf



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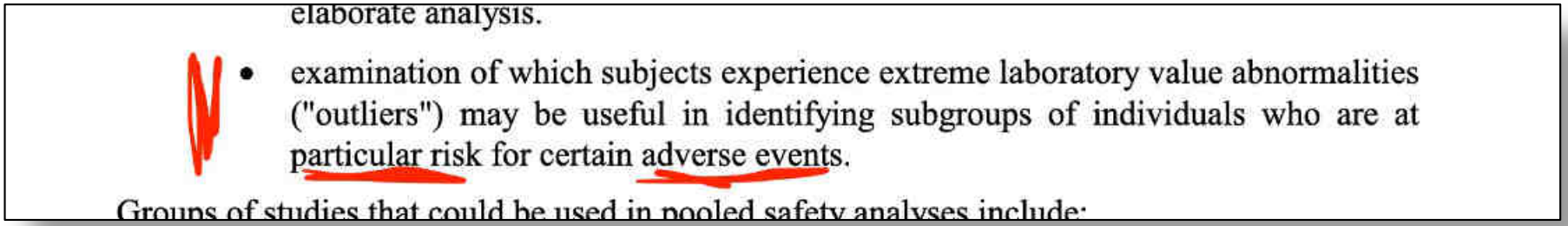

elaborate analysis.

- examination of which subjects experience extreme laboratory value abnormalities ("outliers") may be useful in identifying subgroups of individuals who are at particular risk for certain adverse events.

Groups of studies that could be used in pooled safety analyses include:

https://database.ich.org/sites/default/files/M4E_R2__Guideline.pdf

There is an urgent need to assess any patterns of clinical laboratory findings occurring in subjects before and following vaccination, as it could be of major help:

- **in the assessment, prediction and prevention of individual risk, allowing the identification of subgroups of individuals who are at particular risk for AE as well as the better understanding of the pathophysiological mechanisms underlying specific AE;**

- **in the evaluation of suspect AE following vaccination, contributing to the definition of any eventual relationship between AE and the vaccines and encouraging the spontaneous reporting of the AE to the pharmacovigilance systems;**

- **in general, in reassuring the public about the safety assessment process of these COVID-19 vaccines, consequently leading to a more safe and effective use of these vaccines and to the overcoming of vaccine hesitancy.**

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REPORT ESTESO ISS

COVID-19: SORVEGLIANZA, IMPATTO DELLE INFEZIONI ED EFFICACIA VACCINALE

Aggiornamento nazionale
17/08/2022 - ore 12:00

DATA PUBBLICAZIONE 19/08/2022

Prodotto dall'Istituto Superiore di Sanità (ISS), Roma, 17 agosto 2022

TABELLA 5 - TASSO DI INCIDENZA DI DIAGNOSI DI INFEZIONE DA SARS-CoV-2, DI OSPEDALIZZAZIONE, DI RICOVERO IN TERAPIA INTENSIVA E DI DECESSO PER 100.000 E RISCHIO RELATIVO PER STATO VACCINALE E FASCIA DI ETÀ

Gruppo	Fascia di età	Tasso (per 100,000)				Rischio relativo		
		Non vaccinati	Vaccinati con ciclo completo >120 giorni	Vaccinati con ciclo completo ≤120 giorni	Vaccinati con ciclo completo + dose aggiuntiva/booster	Non vaccinati rispetto a vaccinati con ciclo completo >120 giorni	Non vaccinati rispetto a vaccinati con ciclo completo ≤ 120 giorni	Non vaccinati rispetto a vaccinati con ciclo completo + dose aggiuntiva/booster
Diagnosi tra 15/07/2022-14/08/2022	12-39	2.947,1	1.653,5	2.572,1	2.426,6	1,8	1,1	1,2
	40-59	2.554,5	2.173,4	3.702,5	2.710,6	1,2	0,7	0,9
	60-79	3.446,3	4.233,5	3.329,5	2.764,5	0,8	1,0	1,3
	80+	5.100,0	2.355,2	2.637,2	2.395,6	2,2	1,9	2,1
	Totale	**3.124,9**	**2.546,2**	**3.152,0**	**2.603,4**	**1,2**	**1,0**	**1,2**
Diagnosi tra 01/07/2022-31/07/2022 con ospedalizzazione	12-39	31,9	13,4	16,2	12,5	2,4	2,0	2,6
	40-59	25,8	16,1	30,0	15,0	1,6	0,9	1,7
	60-79	153,6	95,8	97,9	51,3	1,6	1,5	3,0
	80+	1.124,4	301,5	382,4	224,4	3,7	2,9	5,0
	Totale	**153,5**	**59,7**	**72,7**	**41,2**	**2,6**	**2,1**	**3,7**
Diagnosi tra 01/07/2022-31/07/2022 con ricovero in TI	12-39	0,9	0,4	0,7	0,4	2,2	1,3	2,2
	40-59	1,7	0,7	4,1	0,8	2,4	0,4	2,1
	60-79	13,0	5,7	1,7	2,9	2,3	7,6	4,5
	80+	28,5	4,0	14,9	5,4	7,1	1,9	5,3
	Totale	**6,6**	**2,2**	**3,3**	**1,6**	**3,0**	**2,0**	**4,1**
Diagnosi tra 24/06/2022-24/07/2022 con decesso	12-39	0,2	0,1	0,0	0,1	2,0	Inf	2,0
	40-59	2,2	0,7	0,0	0,5	3,1	Inf	4,4
	60-79	19,1	11,6	16,2	5,3	1,6	1,2	3,6
	80+	327,2	75,2	90,1	48,2	4,4	3,6	6,8
	Totale	**33,4**	**9,6**	**11,8**	**5,6**	**3,5**	**2,8**	**6,0**

Note: Per maggiori dettagli vedere Nota metodologica paragrafo 4
- Il tasso relativo alla popolazione complessiva ("Totale") equivale al tasso standardizzato rispetto alla popolazione 2022 (https://demo.istat.it/)
- Il tasso di incidenza degli ultimi 30 giorni potrebbe essere sottostimato in quanto considera a rischio tutte le persone, tranne quelle che sono state diagnosticate e riportate alla sorveglianza negli ultimi 3 mesi. A causa dell'elevato numero di nuove infezioni, spesso non diagnosticate o autodiagnosticate e quindi non riportate alla sorveglianza, il numero delle persone a rischio considerate per il calcolo del tasso di incidenza è quindi verosimilmente sovrastimato, in particolare nelle fasce 12-39 e 40-59. È inoltre verosimile la presenza di una più elevata sottonotifica delle diagnosi nella popolazione non vaccinata e vaccinata da oltre 120 giorni. (Per maggiori dettagli vedere Nota metodologica paragrafo 4)

Prodotto dall'Istituto Superiore di Sanità (ISS), Roma, 17 agosto 2022

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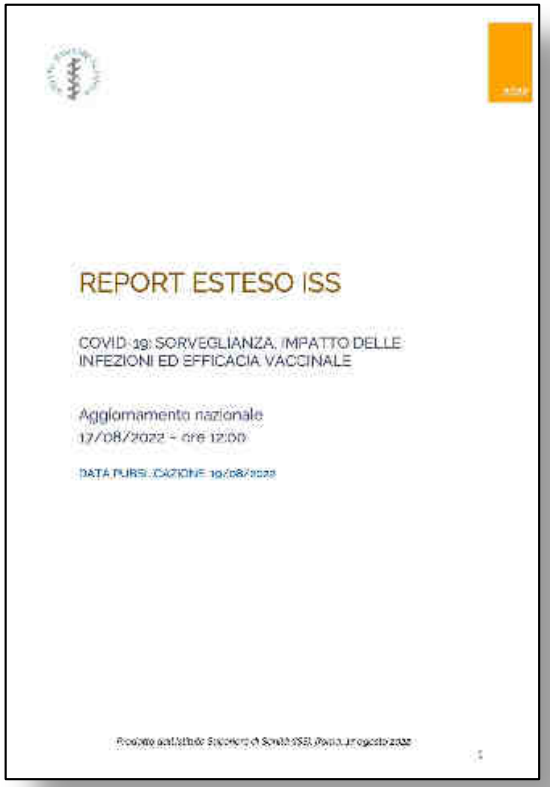
https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_17-agosto-2022.pdf



REPORT ESTESO ISS

COVID-19: SORVEGLIANZA, IMPATTO DELLE INFEZIONI ED EFFICACIA VACCINALE

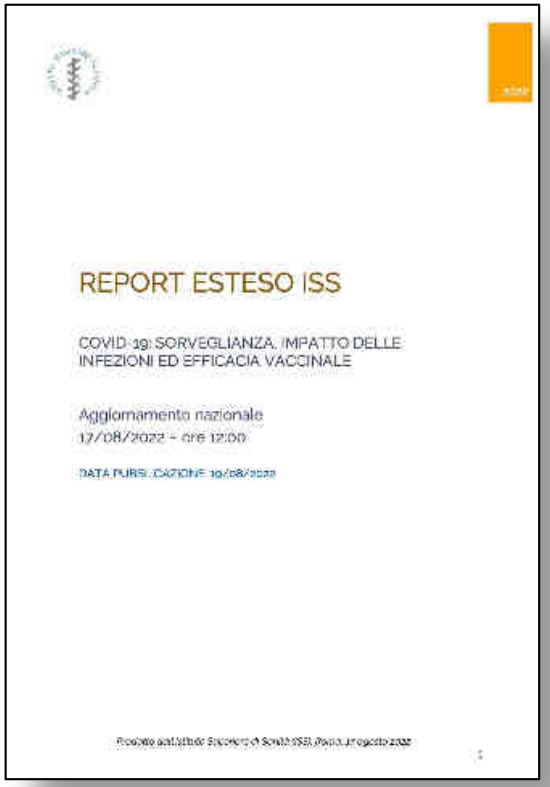
Aggiornamento nazionale
17/08/2022 - ore 12:00

DATA PUBBLICAZIONE 19/08/2022

Gruppo	Fascia di età	Non vaccin
Diagnosi tra 15/07/2022-14/08/2022	12-39	2.947
	40-59	2.554
	60-79	3.448
	80+	5.100
	Totale	**3.124**
Diagnosi tra 01/07/2022-31/07/2022 con ospedalizzazione	12-39	31
	40-59	25
	60-79	153
	80+	1.124
	Totale	**153**
Diagnosi tra 01/07/2022-31/07/2022 con ricovero in TI	12-39	0
	40-59	1
	60-79	13
	80+	28
	Totale	**6**
Diagnosi tra 24/06/2022-24/07/2022 con decesso	12-39	0
	40-59	2
	60-79	19
	80+	327
	Totale	**33**

Note: Per maggiori dettagli vedere Nota

https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_17-agosto-2022.pdf



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Remote management of COVID-19 patients at home: the neglected role of drugs

Marco Cosentino[1]*, Veronica Vernocchi[2]*, Franca Marino[1], Mauro Rango[2]

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*: these authors provided equal contributions to the study.

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DEI VACCINI COVID-19

1) **Farmacologia dei vaccini a RNA**
   Ovvero: giocare a dadi con la spike

2) **Analisi di laboratorio negli studi autorizzativi**
   Cosa comporta il fatto che non siano state svolte?

3) **Curare il COVID-19**
   Ruolo delle cure nella valutazione dell'efficacia vaccinale

Umanità e Ragione