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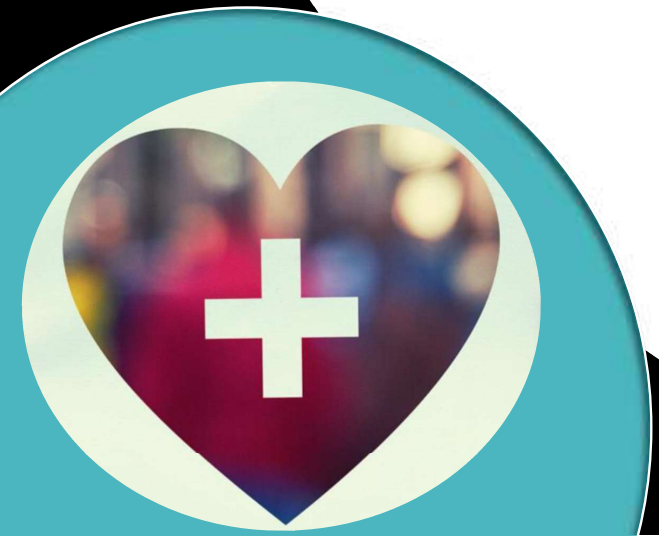
Health Science Committee



New peer-reviewed publication

Open Access | Review

The Novelty of mRNA Viral Vaccines and Potential Harms: A Scoping Review

by Matthew T.J. Halma [1,*], Jessica Rose [2] and Theresa Lawrie [1]

[1] EBMC Squared CIC, 11 Laura Place, Bath BA2 4BL, UK

[2] Independent Researcher

* Author to whom correspondence should be addressed.

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(This article belongs to the Section Public Health & Healthcare)

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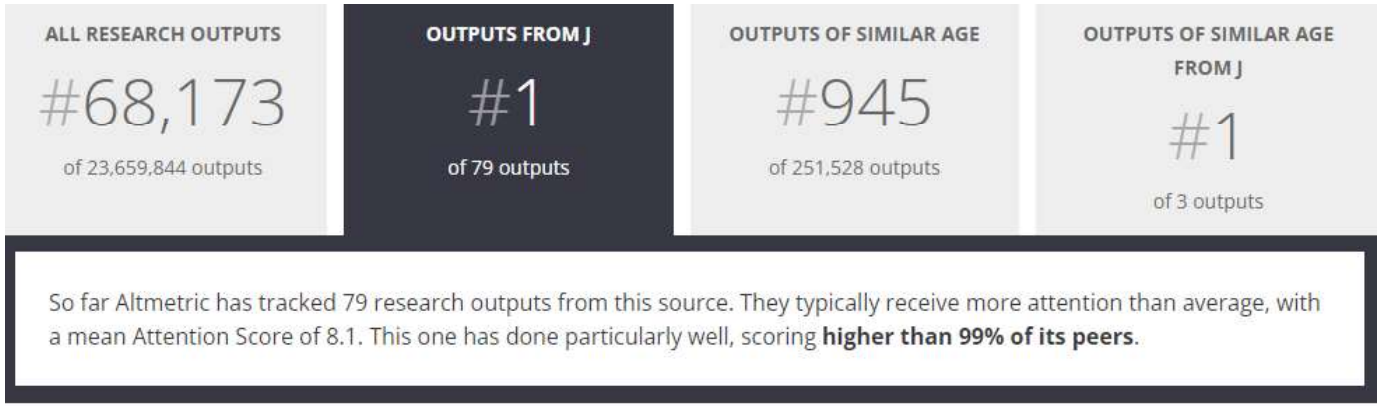
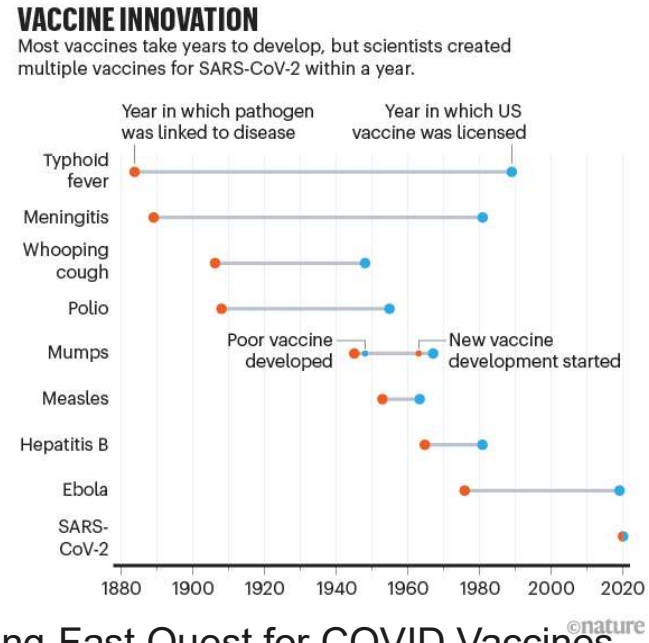
Meta Points

- Barriers overcome
  - ‘Irregularities’ in publishing
- A new science
  - Setting research priorities
- Positive reception
  - Most viewed article from journal (MDPI J)



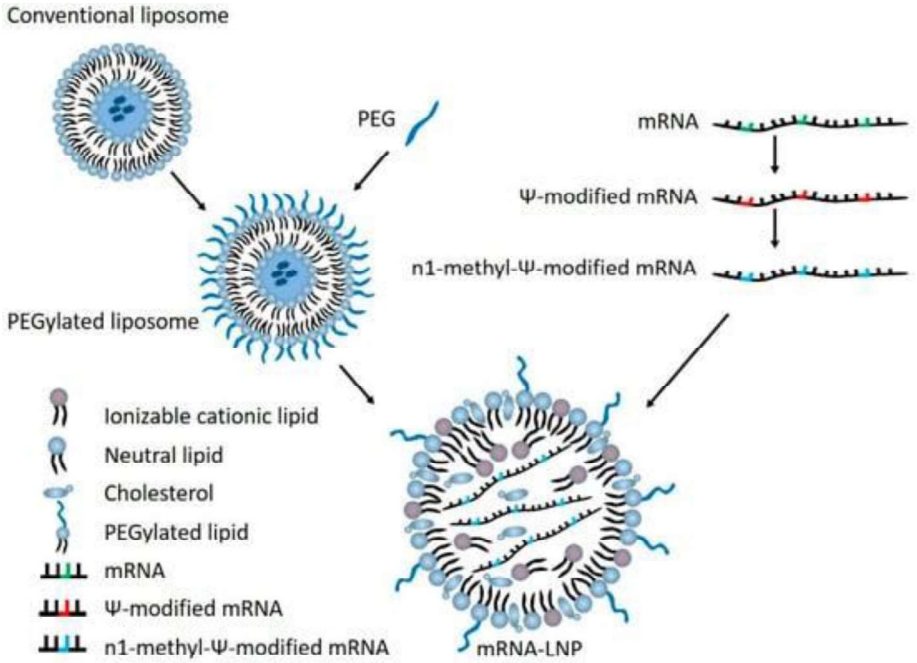
Main points

- Limited and countervailing evidence before approval
- Unprecedented platform (mRNA)
- Unprecedented target (coronavirus)
- Unprecedented speed of development



Ball, P. The Lightning-Fast Quest for COVID Vaccines—And What It Means for Other Diseases. *Nature* **2020**, *589*, 16–18.

Elements



Halma, M.T.J.; Rose, J.; Lawrie, T. The Novelty of mRNA Viral Vaccines and Potential Harms: A Scoping Review. *J* **2023**, *6*, 220-235.

Individual elements and harms

- Lipid nanoparticle
  - Can be inflammatory by themselves
  - Moghimi, S.M.; Simberg, D. Pro-Inflammatory Concerns with Lipid Nanoparticles. *Molecular Therapy* **2022**, *30*, 2109–2110

- Poly-ethylene glycol
  - Allergen for some
  - Increases residence time of PEG in body ->inhibits breakdown

- Other elements: DSPC, SM-102
  - Only briefly cover DSPC
  - Limited safety data

Individual elements (cont.)

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- Chemical modification of mRNA
  - N1-methyl-pseudouridine

Lipid Nanoparticles

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- Developed as a delivery mechanism for RNA to avoid immune activation and degradation of RNA
  - Enables entry into cells
- PEGylation further evades body breakdown
- Some concerns over immunogenicity, inflammation

History of Synthetic mRNA

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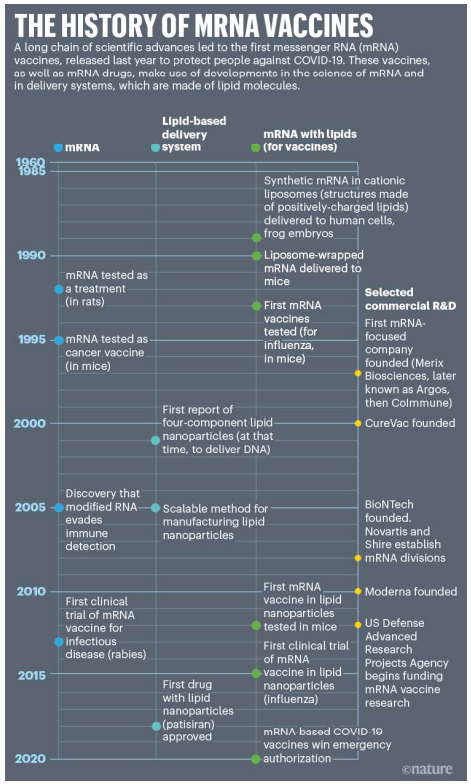
- A bit of history
- Robert Malone in 1987 mixes RNA with lipids and expressed proteins in human cell lines
  - Issues: RNA quickly breaks down
- Katalin Kariko in 2005 uses modified RNA (pseudouridinylated) to evade host immune response
  - Much longer breakdown time
  - Differences ion protein translation



Nature **597**, 318-324 (2021)

History of Synthetic mRNA (cont.)

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- N1-methyl-Pseudouridinylated RNA
  - Exists naturally in 18S rRNA (ribosomal RNA) in archaea
  - Some earlier characterization studies, only studied for biological effect from 2015 on
    - Andries, O.; Mc Cafferty, S.; De Smedt, S.C.; Weiss, R.; Sanders, N.N.; Kitada, T. N(1)-Methylpseudouridine-Incorporated MRNA Outperforms Pseudouridine-Incorporated MRNA by Providing Enhanced Protein Expression and Reduced Immunogenicity in Mammalian Cell Lines and Mice. *J Control Release* **2015**, *217*, 337–344,

Clinical trials- mRNA

- Data on 285 study participants
- 14% Severe adverse event (SAE) rate (requir8ing medical attention)
- Comparison: Post marketing observation of SAEs after influena vaccines is 0.16%
  - *Hum. Vaccines Immunother.* **2020**, *16*, 1762–1771.

LNP delivery of RNA expressing foreign antigen	Rabies	rabies virus glycoprotein	CureVac AG	CV7201	NCT02241135 (2013-2018)	(79/101, 78%) [10/101, 10%]	Bell's Palsy (1/101, 1%)	[3]
	Rabies	rabies virus glycoprotein	CureVac AG	CV7202	Phase 1: NCT03713086 (2018-2021)	(9/10, 90%) [5/10, 50%]	Lack of appetite (3/10) Night sweats (2/10) Dizziness (1/10) Tachycardia (1/10)	[4]
	Chikungunya virus	Chikungunya virus antigens	Moderna	VAL-181388 / mRNA-1388	Phase 1: NCT03325075 (2017-2020)		No data available	
	Cytomegalovirus	Pentameric complex and	Moderna	mRNA-1647	Phase 1:		No data available	
		B glycoprotein			NCT03382405 (2017-2021) Phase 2: NCT04232280 (2020-2022*)			
	Metapneumovirus and parainfluenza virus type 3 (MPV/PIV3)	MPV and PIV3 F glycoprotein	Moderna	mRNA-1653	Phase I: NCT03392389 (2017-2019)		No data available	
	Respiratory Syncytial Virus (RSV)	F glycoprotein	Moderna	mRNA-1345	Phase 1: NCT04528719(2020-2023*)		Recruiting	
	Zika Virus (ZIKV)	Pre-membrane and envelope glycoprotein	Moderna	mRNA-1893	Phase I: NCT04064905 (2019-2021)		No data available	
	Influenza H7N9	Haemagglutinin	Moderna	mRNA-1851	Phase 1: NCT03345043 (2016-2018)	(53.3-73.3%) 30/90, 20-30%]		[5,6]
	Influenza H10N8	Haemagglutinin	Moderna	mRNA-1440	Phase 1: NCT03345043 (2016-2018)	(~80%) [5/84, 6%]		[5,6]
	HIV-1		Arcos Therapeutics	AGS 004	Phase II: NCT00672191 (2008-2011)	(23/35, 72%) lower than placebo arm [0/35, 0%] No difference in viral load between arms.	Local site reactions,	[7]

Coronavirus vaccines

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- Data on 179 vaccine recipients, 4% SAE rate

Table 1. Summary of human trials of non-COVID-19 coronavirus vaccines. Adapted from [117].

Platform	Vaccine	Group	Status	Severe Adverse Events	NCT ID
		SARS Vaccine Clinical Trials			
Inactivated virus	Inactivated SARS-CoV vaccine (ISCV)	Sinovac	Phase I, completed	[0/24, 0%]	No NCT ID
DNA vaccine	VRC-SRSDNA015-00-VP	NIAID	Phase I, completed	[0/9, 0%]	NCT00099463
		MERS Vaccine Clinical Trials			
DNA vaccine	GLS-5300 (INO-4700)	GeneOne Life Science/Inovio Pharmaceuticals/International Vaccine Institute	Phase I, completed	[0/75, 0%] Infections in 36% of participants	NCT02670187
DNA vaccine	GLS-5300 (INO-4700)	GeneOne Life Science/Inovio Pharmaceuticals/ International Vaccine Institute	Phase I/IIa, completed	No results available	NCT03721718
Viral vector vaccine	MVA-MERS-S	CTC North GmbH & Co. KG	Phase I, completed	[0/23, 0%]	NCT03615911
Viral vector vaccine	MVA-MERS-S_DF1	CTC North GmbH & Co. KG	Phase Ib, not yet recruiting	No data	NCT04119440
Viral vector vaccine	ChAdOx1 MERS	University of Oxford	Phase I, recruiting	[1/24, 4%]	NCT03399578
Viral vector vaccine	ChAdOx1 MERS	King Abdullah International Medical Research Center/University of Oxford	Phase I, recruiting	[6/24, 25%]	NCT04170829
Viral vector vaccine	BVRS-GamVac-Combi	Gamaleya Research Institute of Epidemiology and Microbiology/Acellena Contract Drug Research and Development	Phase I/II, recruiting	No data	NCT04128059
Viral vector vaccine	BVRS-GamVac	Gamaleya Research Institute of Epidemiology and Microbiology	Phase I/II, recruiting	No data	NCT04130594

Summary

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- Unprecedented technology
- Limited evidence for safety
- Strong evidence against safety
- Violation of precautionary principle

Public health needs the public trust

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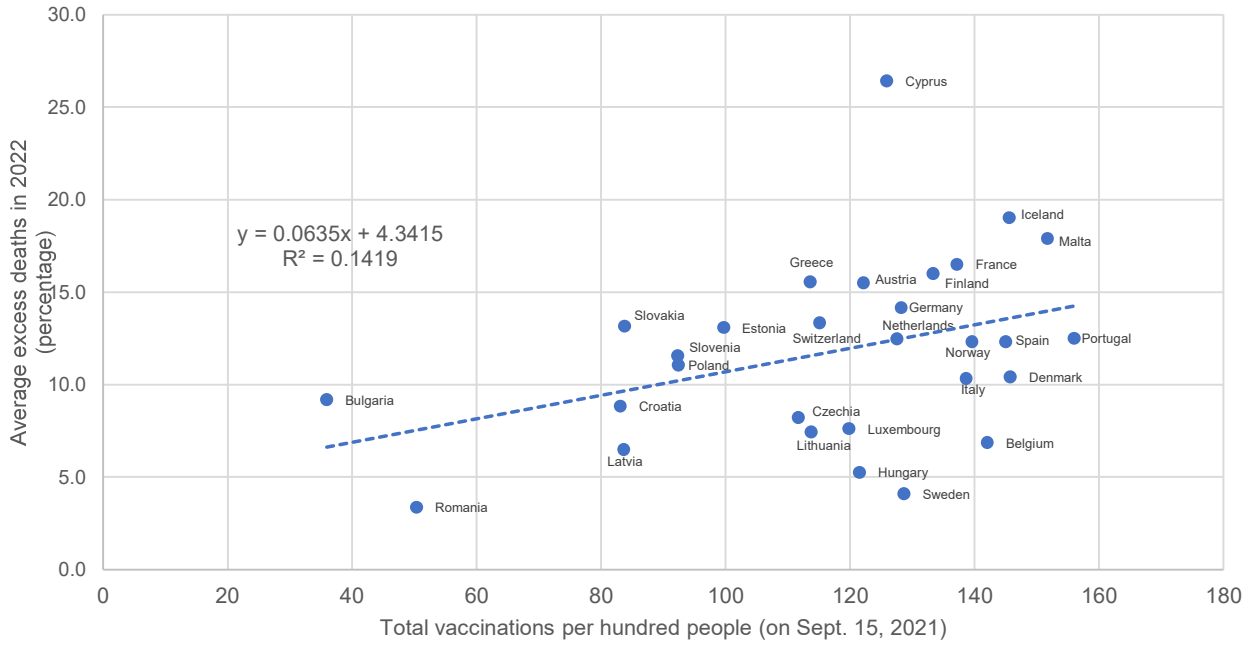

Therapeutics for long covid and vaccine injury

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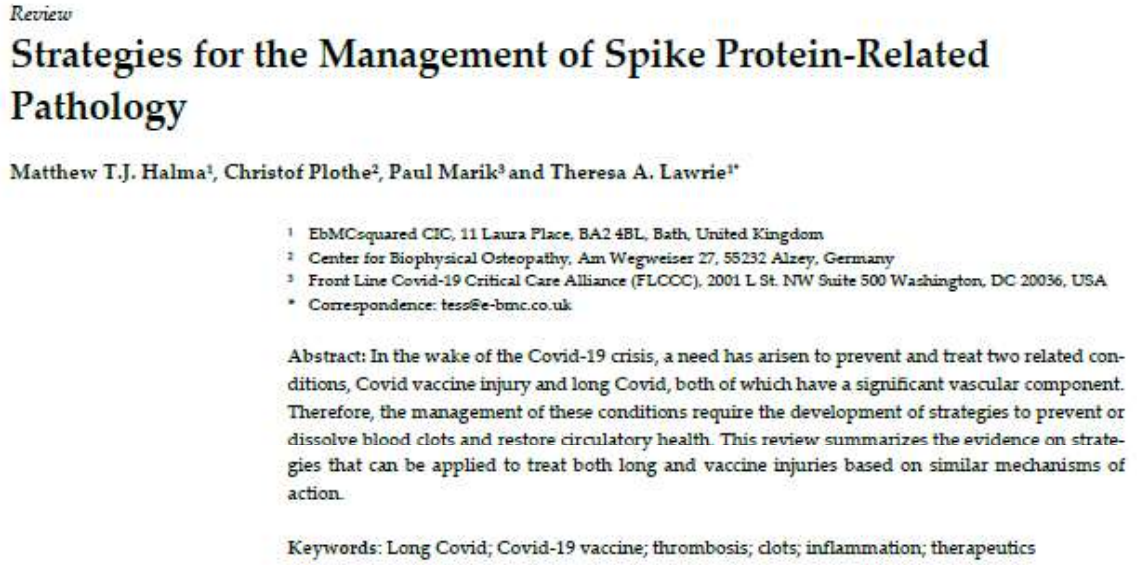
- Seeks to summarize:
  - clinical diagnosis and patient factors affecting outcomes (age, sex, etc.)
  - Cause/Etiology (focus on spike protein related pathology)
  - Therapeutic mechanisms
    - Inhibit spike
    - Clear spike
    - Heal damage
      - Lower inflammation
      - Restore mitochondrial energy production



Review

Strategies for the Management of Spike Protein-Related Pathology

Matthew T.J. Halma[1], Christof Plothe[2], Paul Marik[3] and Theresa A. Lawrie[1*]

[1] EbMCsquared CIC, 11 Laura Place, BA2 4BL, Bath, United Kingdom
[2] Center for Biophysical Osteopathy, Am Wegweiser 27, 55232 Alzey, Germany
[3] Front Line Covid-19 Critical Care Alliance (FLCCC), 2001 L St. NW Suite 500 Washington, DC 20036, USA
* Correspondence: tess@e-bmc.co.uk

Abstract: In the wake of the Covid-19 crisis, a need has arisen to prevent and treat two related conditions, Covid vaccine injury and long Covid, both of which have a significant vascular component. Therefore, the management of these conditions require the development of strategies to prevent or dissolve blood clots and restore circulatory health. This review summarizes the evidence on strategies that can be applied to treat both long and vaccine injuries based on similar mechanisms of action.

Keywords: Long Covid; Covid-19 vaccine; thrombosis; clots; inflammation; therapeutics