

Vaccination hesitancy and the “myth” on mRNA-based vaccines in Italy in the COVID-19 era: Does urgency meet major safety criteria?

Salvatore Chirumbolo 

Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

Correspondence

Salvatore Chirumbolo, PhD, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Strada Le Grazie 9 37134 Verona, Italy.
Email: salvatore.chirumbolo@univr.it

Abstract

Coronavirus disease 2019 (COVID-19) vaccination campaign in Italy has started with a huge perplexity about vaccine efficacy, vaccine-borne adverse effects and vaccine clinical trial studies. In this commentary I tried to elucidate these issues, which represent a fundamental topic to be thoroughly addressed in COVID-19 pandemic.

KEYWORDS

administrative law, coronavirus, political science, public policy, social science, virus classification

1 | BACKGROUND

Coronavirus disease 2019 (COVID-19) pandemic still stands as a huge health concern, reaching more than 2.61 millions of cases and 90,618 victims worldwide on February 5th, 2021. To face at pandemic emergency, any Government is engaging a gigantic struggle against infectious contacts. Nations are currently adopting lockdown and several restrictions measures against usual social habits but are more frequently asking for crucial and urgent decisions from politics in setting the widest vaccination campaign against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^{1–3} Anyway, despite vaccination emergency is somewhat felt as a mandatory commitment to dampen infectious contacts, reduce COVID-19 hospitalization and come back to previous life customs, vaccination hesitancy, particularly on the more straightforward messenger RNA (mRNA)-based vaccines, still represents a fundamental concern.

In Italy, particularly for people usually refusing flu vaccines, hesitancy towards novel vaccine mRNA formulas is closely associated with increasing doubts on vaccination in general.⁴ By the way, public and institutional information about the many safety issues in the vaccination campaign are particularly weak in their persuasive potential. Questions were raised, for the many vaccine formulations available to date, on who could be vaccinated or not without any major health risk, such as elderly people with co-morbidities or

people living with HIV.^{5,6} The great complexity of topics regarding COVID-19 vaccines should deserve particular attention, as it deals with a global extent. Experts in the field focus their major concerns on allergy side effects and vaccination efficacy. For example, the ARIA-EAACI position paper about possible adverse effects caused by COVID-19 vaccination, such as hypersensitivity reactions, recently stated that, as regarding the vaccine BNT162b2, several cases of anaphylaxis occurred, but the Committee concluded that vaccination, held to overcome pandemic, is much more crucial than risking for anecdotic episodes of severe anaphylaxis.⁷ This position statement may sound as a cynic consideration about safety, yet the urgency in defeating COVID-19 pandemic is considered of the utmost importance.

The critical controversy between urgency in dampening SARS-CoV-2 infections and vaccine reliability is the real matter of debate about vaccination.

The mRNA based BNT162b2 vaccine has been recently questioned about its efficacy against SARS-CoV-2 variants, despite very recent reports showed neutralization efficacy on N501Y nCoV19 mutant and the UK variant.^{7–10} Actually, mRNA based vaccines represent a straightforward tool against infectious diseases and pandemic.^{11–14}

Widespread information about novel formulations, as mRNA-based vaccines, is particularly crowded and inflated by non

reviewed opinions and the debate can generate even alarming fakes about vaccination due to anecdotal news. As a matter of fact, people are commonly impressed by the emphasized tale of single, sporadic cases of adverse effects, without being correctly informed about the actual risk to undergo a severe damage upon a medical intervention. Estimating a risk to meet an adverse drug reaction (ADR) to vaccines, even by the mainstream information, is particularly crucial to warrant for a consolidated awareness of vaccination primacy among people. Whereas the US CDC reported 6 cases of anaphylaxis due to COVID-19 mRNA vaccines on 270,001 doses (Dec 19th, 2020), suggesting a risk <0.0023%, citizens could be ensured that this risk is really negligible in medical practice. Actually, undergoing a surgical intervention has a much higher mortality rate (0.71%) and 0.17% in elective surgery (10 times higher during emergency).¹⁵ On the contrary, the most correct information about vaccination is quite scanty in Italy, which prefers to mythologize COVID-19 vaccines as undisputable tools for health and well being, without any expanded debate about experts.¹⁶ Vaccine myth as well as vaccine distrust, are both regrettable attitudes.

A proper behavior towards vaccination is trusting vaccination as a medical expert practice and an outstanding and straightforward way to overcome infectious diseases. Trusting medicine should be a commonly positive feeling. Usually, a patient does not exhibit such burden of doubts and refusal against a simple therapeutic drug, despite even a simple pill, such as an antibiotic, may have adverse effects. The atavistic fear against vaccines dates back to Jenner, in the XVIII century, therefore, as people are convinced about vaccines as a source of “modified” harmful pathogens (yet, always pathogens) the concern of public vaccination is still far to be fully reassured.¹⁷

Therefore, which is the best approach to overcome this concern? To be much more properly and clearly informed.

2 | THE CURRENT DEBATE ABOUT COVID-19 MRNA VACCINES

In Italy, correct information about mRNA-based vaccines is scanty. Urgency in vaccination should not dampen the scientific debate.

Both BNT-162b2, produced by Pfizer-BioNTech and mRNA-1273 by Moderna, are simple molecules of ribonucleic acid, modified with pseudo-uridine (ΨU) and included in lipid nano-particle (LNPs) vehicles. RNA is endowed to be rapidly translated into nonfunctional SARS-CoV-2 S (spike) proteins, i.e. an S-proteins in a stable closed structure,¹⁸ so to trigger the immune response in the host without inducing damage due to its activity on the ACE2 receptor.^{18,19} As reported few lines ago, recent data are supporting the idea that these vaccine formulations have possible and significant adverse effects, particularly by highlighting the worrisome concern that anaphylaxis due to BNT162b1 vaccine accounts to 1:45,000, a ratio much higher than the usual allergic side effect percentage due to commonly used vaccines, that is, 1:1,000,000.²⁰ Estimated percentages need reappraisal on a global scale, however.

Briefly speaking, it is correct to state that some components should deserve caution, due to their assessed allergenicity.

Lipids used for LNPs may elicit allergy-related and immune responses.^{21,22} High molecular weight poly-ethylene-glycol, present in BNT162b2 as ALC0159 (2-[(polyethylene glycol)-2000]-N,N-di-tetradecyl-acetamide) is considered the leading cause of vaccine-caused anaphylaxis.²³ PEG presence, particularly in LNPs, is not yet a novelty in pharmacological science, anyway. PEG is contained in many commonly used medicines. Table 1 lists some major FDA approved drugs for human therapy, which contain PEG and may cause anaphylaxis. Considering that PEG is particularly frequent in several therapeutic formulas, the simple information about the anaphylactic potential of PEG should not exacerbate the civil debate about vaccines, at least because a huge deal of PEGylated therapeutic drugs is commonly used in the medical healthcare without bursting raw popular outcries. More correct information to ensure citizens about vaccine safety is mandatory, therefore. Considering the small number of anaphylaxis cases in US by CDC reports and the amount of ADRs to vaccine in US (101) on 158,000 vaccinated people,²⁴ the relative risk we calculated in our labs (SPSS software v 24.1) to meet a PEG-related anaphylaxis should be around 0.03, a very low value, even assessing previously reported evidence.²⁵ Yet, reports exist showing that PEG-caused anaphylaxis may be particularly dramatic for subjects,²³ and this may burst a serious public health concern.

In Italy, no clear warning about PEG-mediated ADRs regarding RNA-based vaccines has been ever forwarded by Government institutions, Scientific Committees or mainstream information, at least to organize a proper anti-anaphylaxis task force in the healthcare units. A sort of naïve mysticism around vaccination with BNT182b2 vaccine, as the only safe escape from restrictions to the social daily life and COVID-19 pandemic, has overcome any intelligent and moderate debate about the COVID-19 vaccination campaign.²⁶ The concerning results of this sort of misleading information about RNA-based vaccines is the high degree of vaccine hesitancy in the Italian population reached so far.²⁷ Common citizens, that is, people not engaged in healthcare jobs or medical activities, represent about a fifth (136,052 vs. 681,057) of the currently vaccinated Italian population: this rate is about one-third of the pro-vax people, that is, those individuals who trust vaccination as a safe way to rescue one's own wellbeing and health (data on January 13th 2021 from Ministry of Health, Italy).

Pandemic should revise our own attitude towards vaccination, at least theoretically. A study performed in China on 806 nurses during the period February 26th to March 31st, 2020, showed that more nurses changed their personal beliefs about vaccination from refusal/hesitancy to acceptance, respect to refusing or hesitant colleagues, that is, 15.5% versus 6.89% ($p < .001$) and 40% participants expressed a clear intention to accept a possible COVID-19 vaccine, if promptly available.²⁸ To date, though standing the availability of a straightforward vaccine formulation against COVID-19, the attitude has been quite reversed in the majority of people having experienced COVID-19 pandemic on their own lives.²⁹ Some reasons appear to elucidate how come many health professionals are critical towards

TABLE 1 List of major PEGylated drugs approved by FDA in 2020 and their allergic effects

Active principle	Drug commercial name	Company	Therapeutic use	Examples of reports showing allergic and adverse effects
Recombinant anti-hemophilic factor	Esperoct Turoctocog Aifa	Novo Nordisk	Haemophilia A	Pires S et al., <i>BMJ Case Rep.</i> 2018 Dec 14;11(1):e227426.
G-CSF	Ziextenzo (Pegfilgrastim)	Sandoz	Treating neutropenia during chemotherapy	Bustillo I, et al., <i>Cutan Ocul Toxicol.</i> 2009;28(4):181-4. Hanna GG, et al., <i>Clin Oncol (R Coll Radiol).</i> 2008 May;20(4):315-6
Recombinant phenyl-alanine ammonia lyase	Palylnziq (Pegvaliase)	BioMarin Pharmaceuticals	Phenylketonuria	Zori R, et al., <i>Mol Genet Metab.</i> 2018 Nov;125(3):217-227
L-Asparaginase	Aspartas	Servier Pharma	Leukemia	Fabry U et al., <i>Pediatr Res.</i> 1985 Apr;19(4):400-8.
Recombinant coagulation factor IX	Rebinyn	Novo Nordisk	Hemophilia B	Levy-Mendelovich S et al., <i>Blood Cells Mol Dis.</i> 2020 Feb;80:102370.
Recombinant anti-hemophilic factor	Adinovate	Baxalta	Hemophilia A	
PEGylated IFN- α	Sylatron Peginterferon-alpha-2b	Merck	Melanoma	Meller S et al., <i>Allergy.</i> 2015 Jul;70(7):775-83.
Anti-TNF- α	Cimzia (Cerulizumab-pegol)	UCB	Rheumatoid arthritis	McCabe E et al., <i>Rheumatology (Oxford).</i> 2020 Apr 1;59(4):908-910.
HGH (human growth hormone)	Somavert (Pegvisomant)	Pfizer	Acromegaly	Dadzie DD et al. <i>Pituitary.</i> 2012 Dec;15 Suppl 1:S68-71

Abbreviations: G-CSF, granulocyte colony-stimulating factor; INF, interferon; TNF, tumor necrosis factor.

the novel vaccines against COVID-19 made of a PEGylated LNP-encapsulated mRNA: (a) a too much shortening the scheduled clinical trial phases; (b) lacking of prospective studies about vaccine ADRs on a longest time interval.

So, how hesitancy is still present? This can be due to scarcely monitored information.

The complex issue of vaccinology, particularly during a worldwide emergency, should be taken into account as a fundamental educational mission for public health. For example, criticisms should be discussed within the exclusive realm of the expert community. Notwithstanding, some news, of commercial impact, reach the widest community, generating false expectations. The purported 95% efficiency of mRNA-based vaccines has been deeply criticized.^{30,31} Doshi's criticism raised against Pfizer-BioNTech and Moderna vaccines, on January 4th, 2021, regarded the reliability of data reported elsewhere.^{18,19} Despite mRNA technology for vaccine is a highly validated as excellent approach,^{10–14} one of Doshi's major criticism regards the observations that the number of recruited subjects for clinical trials were dwarfed by a significant amount of participants diagnosed as COVID-19 positive on the simple basis of symptomatology, as they were not polymerase chain reaction (PCR) confirmed, a number as high as 3410 total case, 1594 in the vaccine group and 1,816 in the placebo.³¹ Doshi will expand this consideration in a post dated February 5th, 2021 but his criticism, based on a FDA's report on Pfizer's vaccine, recalculated the Comirnaty, that is, BNT162b2 vaccine efficacy, around 19%–29%, instead of 95%.³¹

3 | HASTY VACCINE, BAD VACCINE?

Doshi recalculated BNT162b2 efficiency and therefore, besides to the many critical comments reported elsewhere about immunity, ethical abuse and ADRs,^{32,33} the quite hasty way by which the Pfizer-BioNTech vaccine was tested, due to the pandemic emergency, may reduce its purported and declared efficiency from 95% to a more real 29%.³⁴ One of the more concerning issue regarding these innovative, straightforward vaccines based on an mRNA approach, is the lacking of prospective surveys. These studies are mandatory not only to verify possible non immediate ADRs due to the innovative technique used for vaccination but also for the immune coverage within the population. In a recent paper, some authors analyzed 3296 subjects for plasma presence of COVID-19 IgGs and only 243 individuals (7.43%) have detectable SARS-CoV-2 IgGs in the serum.³⁵ Only 8 of them developed COVID-19 symptoms 30 days later, were SARS-CoV-2 RT-PCR positive but seven of them loss the specific IgGs.^{34–36}

So, besides to ADRs, the biggest burden of concerns regarding mRNA-based vaccines is the complete lacking of prospective studies. This can be comprehensible, if we would like to shut down pandemic worldwide: vaccines are an undelayable emergency need. Two main issues should make highly debating the need to set a prospective survey. The LNP-encapsulated mRNA has been never attempted

before as a vaccine tool and none can say anything about the consequences of introducing RNA inside the body. The increased ability of pseudouridinylated BNT162b2 mRNA or of mRNA1273 to be translated with relatively high efficiency, may cause endoplasmic reticulum stress (ER-stress) and an upregulation in chemokines mRNA because of a huge production of SARS-CoV-2 Spike (S) proteins.³⁷ However, ribonucleases (RNases) are highly conserved enzymes that exist intra-cellularly and extracellularly with high abundance. These RNases can rapidly and effectively degrade mRNAs, thereby eliminating long-term side effects of mRNA vaccines, at least theoretically.

Although this evidence regards SARS-CoV, the concern has never been raised so far. In this perspective it could be particularly hard to distinguish if a chemokines-induced inflammatory burst may come from a very recent SARS-CoV-2 infection or from vaccination.³⁸ Moreover, many criticisms were raised about the vaccine administration practice. A huge deal of misinformation, even regarding vaccine dosage, practice and temperature, might worsen the delay with which people should be vaccinated.³⁹ The hasty expectation to see brilliant outcomes following vaccination crushes against the paroxysmal crowd of objections.

4 | CONCLUSION

Which could be a conclusive remark of our debate herein reported? Outcry against vaccination, held by “scared” people, who are already stressed by pandemic caused fears, may be a real concern for any vaccination campaign, particularly if associated with long lasting hesitant and refusal attitudes of some individuals towards vaccination. Experts must be invited and encouraged, for ethical reasons, to build up a global task force with educational aims, to make aware people of what vaccination may hold for the human kind, in the COVID-19 era. Around novel, straightforward vaccine formulations, distrust dominates the scenery, so correct and honest information is mandatory. Medical science is never completely perfect to fit any puzzling question about how the human being can face at awful pathologies and pandemics, evenly occurring. Yet, any civil discussion about vaccines should be highly respectful of the huge efforts accomplished by current science and technology to bear the optimal solution to those concerns. Positive attitudes and trusting science are the best way to address vaccination as a safe practice. In this context, the scientific community must expose any critical comment, in the highest pro-active way, to expand a debate with the only purpose to get transparency from Big Pharmas and politics, so to ensure citizens and public opinion. If we altogether trust these fundamental keystones, then anyone can directly contribute in rendering our world much more pleasant and addressable.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ORCID

Salvatore Chirumbolo  <http://orcid.org/0000-0003-1789-8307>

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