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LETTERS

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# Safety of Sars-Cov-2 vaccines administration for adult patients with hereditary fructose intolerance

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Dear Editor,

We have read with great interest the Letter to the editor written by Saborido-Fiaño et al. in an issue of *Human Vaccines & Immunotherapeutics*[1] concerning the article "Safety of vaccines administration in hereditary fructose intolerance", recently published by Maiorana et al.[2] in an issue of *Orphanet Journal of Rare Diseases.*

Maiorana et al.[2] performed a research from open sources, datasheets and Pharmaceutical Companies informations about the most common Italian and European vaccines, which are carried out in infancy and childhood, to clarify the safety of vaccines administration in pediatric patients with Hereditary fructose intolerance (HFI, OMIM 229600).

According to a recommendation of the *Istituto Superiore di Sanità* of Italy,[3] that consider a limit of 2.4 mg/kg/dose as a safe threshold for oral and parenteral (s.c./i.m.) route for HFI patients, the authors concluded that the majority of vaccines can be safely administered in infants and children affected by HFI with the exception of rotavirus vaccines.[2]

Saborido-Fiaño et al.[1] provided further relevant concerns on rotavirus vaccination in HFI patients, underlighting that recommendations to avoid rotavirus vaccinations in HFI patients are difficult to be respected since rotavirus vaccines are usually given prior to fructose-containing food introduction and therefore before the diagnosis of HFI.

The article of Maiorana et al.[2] was published before Sars-Cov-2 vaccines commercial production in Europe. Therefore, it does not report data about the safety of the new Sars-Cov-2 vaccines administration in HFI patients. Moreover, the work focused on pediatric vaccinations.

Attenuated, genetically modified or inactivated viruses are still the key active ingredients of many vaccines, despite recent progress in the use of virus-like particles or proteins in vaccine preparations. Maintaining the potency of these viral particles against degradation is a major challenge in providing proper immunization services. Typically, this requires keeping vaccines refrigerated at all times from production to administration, a major undertaking especially in remote regions of developing countries.[4]

The World Health Organization has identified the cold chain problem, the protection of vaccines from deterioration, as one of the most important challenges for the extension of global vaccination programs.[5]

There are two risk factors related to temperature that can inactivate vaccines: high temperature[6] and aluminum salt aggregation due to freezing.[7] Freezing risk is usually overcomed using stabilizers as sucrose, cyclodextrins, mannitol, and surfactants.[4,8–12]

It is well known that sugars and saccharides, such as sucrose, inulin, and dextran, can not only prevent the aggregation and denaturation of proteins in a liquid formulation but also preserve their structural integrity during freezing, drying, and storage in a solid state. In particular, sucrose, a disaccharide composed of the monomers glucose and fructose, is often added to the formulation to prevent aggregation during lyophilization.[11] Moreover, sucrose, as a cryoprotectant, reduces the perturbation caused by freezing.[12]

Cyclodextrins consist of (−1, 4)-linked glucopyranose units and contain a lipophilic central cavity and hydrophilic outer surface. Many chemically modified cyclodextrins have been developed.[13] In particular, hydroxypropyl-β-cyclodextrin (HP-β-CD) is commonly used in pharmaceutical formulation to improve drug substance solubility and delivery, thereby holding vast amount of safety profiles. In addition, compared to other CDs, HP-β-CD is more soluble in water while other CDs are not easily manipulated in various vaccine formulations.[14]

Mannitol, a sugar alcohol, is used less often as stabilizer.[15]

Despite having this fundamental role in vaccine formulation stabilization, sucrose can represent a problem for those people affected by HFI, a rare autosomal recessive disease caused by a deficiency of aldolase B (ALDOB), the main enzyme responsible for hepatic metabolism of fructose.[16] The signs and symptoms upon dietary exposure of HFI patients to fructose, sucrose, or sorbitol include clinical findings (nausea, vomiting, and abdominal distress; chronic growth restriction/failure to thrive) and metabolic disturbances (hypoglycemia, lactic acidemia, hypophosphatemia, hyperuricemia, hypermagnesemia, hyperalaninemia).-[17] Parenteral administration may cause death for severe hypoglycemia or acute hepatorenal failure.[18]

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For these reasons, individuals with HFI need to be treated life-long with a fructose-restricted diet and they should be aware of the presence of fructose, sucrose or sorbitol in certain medical formulations.[2]

Sucrose may be a key ingredient also in Sars-Cov-2 vaccines.

Until today the European Medicines Agency (EMA) has granted a conditional marketing authorization granted to the following covid vaccines: two messenger RNA vaccines (Comirnaty®, COVID-19 Vaccine Moderna) and two vector vaccine (COVID-19 Vaccine Janssen, Vaxzevria®),[19] the same have also been approved by the Food and Drug Administration (FDA)[20] and by the Medicines & Healthcare products Regulatory Agency in the United Kingdom.[21]

We performed a search on the sucrose content in the approved Sars-Cov-2 vaccines from the summary of product characteristics and the fact sheet for healthcare providers and we found that:

- Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 vaccine contains 30 mcg of a nucleoside modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2. Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl) bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and **6 mg sucrose.**[22]
- Each 0.5 mL dose of the Moderna COVID-19 vaccine contains a total lipid content of 1.93 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.31 mg tromethamine, 1.18 mg tromethamine hydrochloride, 0.043 mg acetic acid, 0.20 mg sodium acetate trihydrate, and **43.5 mg sucrose**.[23]
- Each 0.5 mL dose of the Vaxzevria vaccine contains not less than 2.5 × 108 infectious units Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein ChAdOx1-S, Excipients: L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80 (E 433), ethanol, sucrose, sodium chloride, disodium edetate (dihydrate), water for injections and **30 mg sucrose**.[24]
- Each 0.5 mL dose of Janssen COVID-19 vaccine is formulated to contain 5 × 1010 virus particles (VP) and the following inactive ingredients: citric acid monohydrate (0.14 mg), trisodium citrate dihydrate (2.02 mg), ethanol (2.04 mg), 2-hydroxypropyl-β-cyclodextrin (HBCD) (25.50 mg), polysorbate-80 (0.16 mg), sodium chloride (2.19 mg). Each dose may also contain residual amounts of host cell proteins (≤0.15 mcg) and/or host cell DNA (≤3 ng). No sucrose content is reported. [25]

In conclusion, among vaccines against Sars-Cov-2, Janssen COVID-19 Vaccine is the only one that contains as sugar cyclodextrin instead of sucrose.

The content of sucrose for each dose of Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, and Vaxzevria vaccine is safe for adult and adolescent HFI patients.

No vaccine contains isolated fructose or sorbitol.

To date, the Pfizer-BioNTech COVID-19 Vaccine is the only one authorized for use in in patients aged 12 to 15 years. If other Sars-Cov-2 vaccines would be approved for the pediatric age, the recommendation of Istituto Superiore di Sanità of Italy[3] should be considered to evaluate the safety of each dose according to the patient weight.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

## Contributions

All authors have made substantial contributions to all of the following: 1). the conception and design of the letter; 2). drafting the letter; 3). revising it critically for important intellectual content; 4). final approval of the submitted version.

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## References

1. Saborido-Fiaño R, Martinón-Torres N, Crujeiras-Martinez V, Couce ML, Leis R. Letter to the editor concerning the article 'Safety of vaccines administration in hereditary fructose intolerance'. Hum Vaccin Immunother. 2021 Mar;2:1–2. doi:10.1080/21645515.2021.1891816.
2. Maiorana A, Sabia A, Corsetti T, Dionisi-Vici C. Safety of vaccines administration in hereditary fructose intolerance. Orphanet J Rare Dis. 2020;15(1):274. doi:10.1186/s13023-020-01552-z.
3. Gallo G, Mel R, Ros E, Filia A (Ed.) Guida alle controindicazioni alle vaccinazioni (aggiornamento 2018). Roma (Italy): Istituto Superiore di Sanità; 2019. (Rapporti ISTISAN 19/3).
4. Pelliccia M, Andreozzi P, Paulose J, D'Alicarnasso M, Cagno V, Donalisio M, Civra A, Broeckel RM, Haese N, Jacob Silva P, et al. Additives for vaccine storage to improve thermal stability of adenoviruses from hours to months. Nat Commun. 2016;7:13520. doi:10.1038/ncomms13520.
5. Wolfson LJ, Gasse F, Lee-Martin SP, Lydon P, Magan A, Tibouti A, Johns B, Hutubessy R, Salama P, Okwo-Bele JM. Estimating the costs of achieving the WHO-UNICEF global immunization vision and strategy, 2006-2015. Bull World Health Organ. 2008;86(1):27–39. doi:10.2471/BLT.07.045096.
6. Lee BY, Cakouros BE, Assi TM, Connor DL, Welling J, Kone S, Djibo A, Wateska AR, Pierre L, Brown ST, et al. The impact of making vaccines thermostable in Niger's vaccine supply chain. Vaccine. 2012;30(38):5637–43. doi:10.1016/j.vaccine.2012.06.087.
7. Gupta CK, Leszczynski J, Gupta RK, Siber GR. Stabilization of respiratory syncytial virus (RSV) against thermal inactivation and freeze-thaw cycles for development and control of RSV vaccines and immune globulin. Vaccine. 1996;14(15):1417–20. doi:10.1016/S0264-410X(96)00096-5.
8. Croyle MA, Cheng X, Wilson JM. Development of formulations that enhance physical stability of viral vectors for gene therapy. Gene Ther. 2001;8:1281–90. doi:10.1038/sj.gt.3301527.
9. Evans RK, Nawrocki DK, Isopi LA, Williams DM, Casimiro DR, Chin S, Chen M, Zhu D-M, Shiver JW, Volkin DB, et al. Development of stable liquid formulations for adenovirus based vaccines. J Pharm Sci. 2004;93:2458–75. doi:10.1002/jps.20157.
10. Braga SS, Barbosa JS, Santos NE, El-Saleh F, Paz FAA. Cyclodextrins in antiviral therapeutics and vaccines. Pharmaceutics. 2021;13(3):409. doi:10.3390/pharmaceutics13030409.

11. Quaak SG, Haanen JB, Beijnen JH, Nuijen B. Naked plasmid DNA formulation: effect of different disaccharides on stability after lyophilisation. AAPS PharmSciTech. 2010;11:344–50. doi:10.1208/s12249-010-9391-2.
12. Yoshioka S, Miyazaki T, Aso Y, Kawanishi T. Significance of local mobility in aggregation of beta-galactosidase lyophilized with trehalose, sucrose or stachyose. Pharm Res. 2007;24:1660–67. doi:10.1007/s11095-007-9296-2.
13. Davis ME, Brewster ME. Cyclodextrin-based pharmaceutics: past, present and future. Nat Rev Drug Discov. 2004;3:1023–35. doi:10.1038/nrd1576.
14. Rincón-López J, Almanza-Arjona YC, Riascos AP, Rojas-Aguirre Y. Technological evolution of cyclodextrins in the pharmaceutical field. J Drug Deliv Sci Technol. 2021;61:102156. doi:10.1016/j.jddst.2020.102156.
15. Kim AI, Akers MJ, Nail SL. The physical state of mannitol after freeze-drying: effects of mannitol concentration, freezing rate, and a noncrystallizing cosolute. J Pharm Sci. 1998;87:931–35. doi:10.1021/js980001d.
16. Bouteldja N, Timson DJ. The biochemical basis of hereditary fructose intolerance. J Inherit Metab Dis. 2010;33(2):105–12. doi:10.1007/s10545-010-9053-2.
17. Gaughan S, Ayres L, Baker PR II. Hereditary fructose intolerance. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle: University of Washington; 2015 Dec 17. p. 1993–2021. [Updated 2021 Feb 18]; accessed 2021 April 24]. https://www.ncbi.nlm.nih.gov/books/NBK333439/; .
18. Cox TM. Aldolase B and fructose intolerance. FASEB J. 1994;8:62–71. doi:10.1096/fasebj.8.1.8299892.
19. EMA authorized vaccines. [accessed 2021 April 23]. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised#authorised-covid-19-vaccines-section; .
20. FDA authorized vaccines. [accessed 2021 April 24]. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines; .
21. British medicines & healthcare products regulatory agency authorized vaccines. [accessed 2021 April 23]. https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19;
22. Pfizer-BioNTech COVID-19 vaccine fact sheet for healthcare providers administering vaccine. [accessed 2021 May 19]. http://labeling.pfizer.com/ShowLabeling.aspx?id=14471 .
23. Moderna COVID-19 vaccine fact sheet for healthcare providers administering vaccine. [accessed 2021 May 19]. https://www.modernatx.com/covid19vaccine-eua/eua-fact-sheet-providers.pdf .
24. AstraZeneca ChAdOx1 nCoV-19 vaccine safety data sheet. [accessed 2021 May 19]. https://www.astrazeneca.com.au/content/dam/az-au/AZD1222%20SDS%2025943%20v1-1%2016SEP20.pdf .
25. The Janssen covid-19 Vaccine fact sheet for healthcare providers administering vaccine. [accessed 2021 May 19]. https://www.janssenlabels.com/emergency-use-authorization/Janssen+COVID-19+Vaccine-HCP-fact-sheet.pdf.