

1 **Allergic reactions to the first COVID-19 vaccine: a potential role of Polyethylene**
2 **glycol?**

3

4 Beatriz Cabanillas¹, Cezmi Akdis^{2, 3} and Natalija Novak^{4*}

5

6 1. Department of Allergy, Research Institute Hospital 12 de Octubre, Avenida de
7 Córdoba s/n, 28041 Madrid, Spain

8 2. Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich,
9 Davos, Switzerland.

10 3. Christine Kühne-Center for Allergy Research and Education, Davos,
11 Switzerland

12 4. Department of Dermatology and Allergy, University Hospital Bonn, Venusberg
13 Campus 1, 53127 Bonn, Germany.

14

15

16

17

18

19 *Corresponding author: Univ.-Prof. Dr. Natalija Novak

20 Department of Dermatology and Allergy, University Hospital, Bonn, Venusberg
21 Campus 1, 53127 Bonn, Germany.

22 Email: natalija.novak@ukbonn.de

23

24

25 **Keywords:** BNT162b2; COVID-19; Polyethylene glycol; SARS-CoV-2; Vaccine

26 **To the Editor:**

27 The COVID-19 vaccine developed by Pfizer and BioNTech was approved by the
28 Medicines and Healthcare Products Regulatory Agency (MHRA) in the United
29 Kingdom (UK) on December 2nd 2020.¹ MHRA is therefore the first regulator agency
30 in the world to approve a vaccine to prevent coronavirus disease (COVID-19), which is
31 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a virus that
32 is responsible for a global pandemic.

33 The vaccine, named BNT162b2, is a messenger ribonucleic acid (mRNA) vaccine
34 produced as a highly purified single-stranded, 5'-capped mRNA that has been generated
35 through *in vitro* transcription in cell-free conditions from the corresponding DNA. The
36 mRNA encodes the viral spike (S) from SARS-CoV-2.¹ (Fig. 1) The approval by MHRA
37 was based on the results of a phase-III-trial involving 44,000 participants, which
38 showed that BNT162b2 was 95% effective 28 days after the administration of the first
39 dose.² On December 8th 2020, the vaccine BNT162b2 was started to be administrated to
40 the population at risk for COVID-19 in the UK. On the second day of the vaccination
41 program, the National Health System (NHS) in England informed that two workers of
42 the NHS experienced adverse allergic symptoms shortly after receiving the vaccine,
43 which prompted MHRA to advise healthcare providers not to administrate the vaccine
44 to subjects with a significant history of allergic reactions.³

45 According to MHRA, vaccine BNT162b2 for COVID-19 prevention contains the
46 following excipients: ALC-0315 = (4-hydroxybutyl) azanediyl)bis (hexane-6,1-
47 diyl)bis(2-hexyldecanoate), ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-
48 ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3-phosphocholine, cholesterol,

49 potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium
50 hydrogen phosphate dihydrate, sucrose, water for injections.¹ From all the excipients
51 officially declared one with the ability to cause allergic reactions is ALC-0159 since it
52 contains polyethylene glycol (PEG) or macrogol (Fig. 1). PEG is a hydrophilic polymer
53 that is frequently used as an excipient in everyday products including medicines,
54 cosmetics, or foods. Although anaphylactic reactions to PEG have not been frequently
55 reported, in the last years an increased number of adverse allergic reactions to PEG has
56 been described in individuals due to the administration of certain drugs or due to the use
57 of certain products for personal hygiene.⁴⁻⁶ Recently, the largest case series of allergic
58 reactions to PEG was described in individuals that developed anaphylactic reactions to
59 medications containing this compound. PEG was described as a high-risk hidden
60 allergen in drug and food items that can induce allergic reactions difficult to detect by
61 health care providers and might be therefore underdiagnosed.⁷ Cross-reactivity of PEG
62 with Polysorbat 80 due to the shared chemical moiety: $-(\text{CH}_2\text{CH}_2\text{O})_n$ has been
63 described as well.^{8,9} Skin prick testing and intradermal testing with different dilutions of
64 PEG, basophil activation test as well as oral provocation testing are recommended in
65 suspected individuals. Since even severe anaphylactic reactions during skin testing have
66 been described, testing of suspected individuals should be carefully done following
67 published algorithms in specialized allergy centers.⁷ Recently, specific IgE to PEG has
68 been detected with the help of a dual cytometric bead assay,¹⁰ such non-invasive
69 methods would be helpful as additional diagnostic tools to screen for potential
70 individuals at risk. Since even non-IgE mediated hypersensitive reactions to PEG have
71 been described in the literature, double-blind placebo-controlled oral challenges might
72 be necessary in a subgroup of individuals.

73 For patients tested positive, avoidance of PEG as well as PEG analogues is strictly
74 recommended.

75 Although the trigger of the adverse allergic reactions suffered by the two NHS workers
76 after receiving the vaccine BNT162b2 against COVID-19 has yet to be determined, the
77 potential role of the excipient ALC-0159 containing PEG as a high-risk hidden trigger
78 of dangerous allergic reactions should be carefully taken into account before advising
79 the administration of BNT162b2 vaccine.

80

81

82

83

84

85

86

87

88

89

90

91

92

93

94

95

96

97

98

99

100 **References**

- 101 1. Government of the United Kingdom. Health and social care [https://www.gov.uk/
102 government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-
103 covid-19](https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19) Accessed December 9, 2020
- 104 2. Mahase E. Covid-19: UK approves Pfizer and BioNTech vaccine with rollout
105 due to start next week. *BMJ*. 2020; 371:4714. doi: 10.1136/bmj.m4714.
- 106 3. Reuters. Healthcare & Pharma [https://www.reuters.com/article/health-
107 coronavirus-britain-vaccine-idUSKBN28J1D1](https://www.reuters.com/article/health-coronavirus-britain-vaccine-idUSKBN28J1D1) Accessed December 9, 2020
- 108 4. Bordere A, Stockman A, Boone B, Franki AS, Coppens MJ, Lapeere H, et al. A
109 case of anaphylaxis caused by macrogol 3350 after injection of a corticosteroid.
110 *Contact Dermat*. 2012;67:376–378.
- 111 5. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene
112 glycols: a review. *Clin Exp Allergy*. 2016;46:907–922. doi:10.1111/ cea.12760.
- 113 6. Wylon K, Dölle S, Worm M. Polyethylene glycol as a cause of anaphylaxis.
114 *Allergy Asthma Clin Immunol*. 2016;12:67. doi: 10.1186/s13223-016-0172-7.
115 PMID: 27999603; PMCID: PMC5155397.
- 116 7. Sellaturay P, Nasser S, Ewan P. Polyethylene Glycol-Induced Systemic Allergic
117 Reactions (Anaphylaxis). *J Allergy Clin Immunol Pract*. 2020: S2213-
118 2198(20)31007-2. doi: 10.1016/j.jaip.2020.09.029
- 119 8. Stone CA Jr, Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, Hemler JA,
120 Phillips EJ. Immediate Hypersensitivity to Polyethylene Glycols and
121 Polysorbates: More Common Than We Have Recognized. *J Allergy Clin
122 Immunol Pract*. 2019;7:1533-1540.e8. doi: 10.1016/j.jaip.2018.12.003.

- 123 9. Calogiuri G, Foti C, Nettis E, Di Leo E, Macchia L, Vacca A. Polyethylene
124 glycols and polysorbates: Two still neglected ingredients causing true IgE-
125 mediated reactions. *J Allergy Clin Immunol Pract.* 2019;7:2509-2510. doi:
126 10.1016/j.jaip.2019.05.058.
- 127 10. Zhou ZH, Stone CA Jr, Jakubovic B, Phillips EJ, Sussman G, Park J, Hoang U,
128 Kirshner SL, Levin R, Kozlowski S. Anti-PEG IgE in anaphylaxis associated
129 with polyethylene glycol. *J Allergy Clin Immunol Pract.* 2020;17:S2213-
130 2198(20)31231-9. doi: 10.1016/j.jaip.2020.11.011.

131

132

133

134

135

136

137

138

139

140

141

142

143

144

145

146

147

148

149

150 **Conflict of interest**

151 The authors declare no conflict of interest

152

153

154 **Figure legend.**

155 **Figure 1.** Schematic representation of the vaccine for COVID-19: BNT162b2,
156 describing the full list of ingredients that contains the vaccine, and the potential role of
157 PEG as high-risk hidden allergen.