



PEG allergy – A COVID-19 pandemic-made problem? A German perspective

Rebekka K. Bent MD, BSC, Valentina Faihs MD, Linda Tizek MPH, Tilo Biedermann MD, Alexander Zink MPH, MD, PhD and Knut Brockow MD*

ABSTRACT

Background: Polyethylene glycol (PEG) has been used for decades, but only caused allergic reactions exceptionally. Introduction of PEG-containing COVID-19 vaccines might have fostered public interest beyond medical reasoning.

Objectives: To investigate the impact of the SARS-CoV-2 pandemic on the public interest in PEG allergy in Germany and the published PEG allergy cases worldwide.

Methods: A retrospective longitudinal study was conducted to measure public interest in PEG allergy analyzing Google search volume in Germany from February 2018 to January 2022. Medically confirmed “PEG allergy” cases were analyzed by looking at the numbers of PubMed case reports and case series from 1977 until January 2022.

Results: Web results in Germany before COVID-19 show search volumes related to “PEG allergy/testing” was negligible, with 10 search queries per month. The pandemic led to a >200-fold increase from 250 queries 2 years before to 55 720 queries 2 years thereafter, reflecting tremendous public interest. Additionally, the maximum monthly search volume from before to during the pandemic increased immensely for “vaccination” (57-fold), “vaccination and adverse effects” (85-fold), “vaccination and allergy” (71-fold). In contrast, the increase of publication numbers for the search term “PEG allergy” was small from 2019 to 2021 (2.5-fold). Only a very low number of 211 cases with “PEG allergy” worldwide since 1977 could be identified.

Conclusion: PEG allergy became a topic of major public interest because of COVID-19 vaccination. Scientific publications have increased to a lesser extent, probably promoted by public awareness. Conversely, the overall number of cases published with PEG allergy remain very low. The current high demand for COVID-19 vaccination allergy testing is triggered by public interest instead of medical reasoning.

Keywords: Polyethylene glycol, PEG, COVID-19 pandemic, Public interest, Germany

INTRODUCTION

Polyethylene glycol (PEG) is a commonly used excipient in a huge amount of ubiquitously used cosmetics, drugs, and household products.¹ Most recently, PEG 2000 is being used in the artificial lipid layer of SARS-CoV-2 mRNA vaccines, namely Comirnaty[®] (BNT162b2 by Pfizer and BioNTech) and Spikevax[®] (mRNA 1273 by Moderna),¹ but not in the Johnson & Johnson or AstraZeneca COVID-19 vaccines. Multiple individuals reported anaphylaxis to COVID-19 vaccination,² with an incidence of 2.5 cases/mio doses for Moderna and 4.7/mio doses for Comirnaty[®] vaccinations, being 2-4 times higher than expected for other vaccinations.² The ingredient PEG has been discussed to cause allergic reactions and to be responsible for the increased incidence of anaphylaxis.^{3,4} However, recent data showed that anaphylaxis reaction rates to all PEG-containing and non-PEG-containing COVID-19 vaccines are similar to rates reported across several common other vaccines.⁵

Anaphylaxis to PEGs has been rarely reported before the pandemic,^{3,6} especially considering the widespread use in medicine.^{1,7} Additionally, the amount of PEG used in laxatives, eg, as Moviprep[®] (100 g PEG 3350) is multi-fold higher as compared to that used in COVID-19 vaccines. Comirnaty[®] contains 0.05 mg PEG 2000 and the amount in Spikevax[®] is not stated, but can be expected to be similar.⁸ However, it seems that broad media and internet coverage concerning the anaphylactic reaction following the Moderna and BioNTech/Pfizer vaccinations ratcheted public concern about the allergenic potential of PEG.²

The number of patients seeking testing for PEG allergy/COVID-19 vaccination allergy has been dramatically high. Furthermore, people have increasingly consulted the internet for health information in the last decades. It has become a key data source, also for public health promotion.^{9,10}

This study analyzed the impact of the SARS-CoV-2 pandemic on the increasing German public and scientific interest in PEG allergy. It investigates whether Google search volume in Germany can retrace the increased interest compared to the

evolution of PubMed case reported with PEG allergy worldwide.

METHODS

Google data

In this retrospective longitudinal study, we used Google Ads Keyword Planner to identify the average monthly search volume related to PEG allergy in Germany. Usually, the tool is used to optimise placements of advertisements but it also can be successfully employed for scientific purposes.¹⁰ When entering a specific word or phrase in the tool, it provides relevant keywords including their monthly number of searches for the last 48 months. Terms associated with "vaccination", "vaccination and adverse effects", "vaccination and allergy" and "PEG allergy" were categorized and subsequently quantitatively analyzed starting from February 2018 until January 2022.

Result for "adverse effects and vaccination" were being categorized in adverse effects resulting from the Moderna/BioNTech vaccination (both of whom include PEG) or from other vaccinations than these 2 (eg, rabies, measles, AstraZeneca). The Keyword volume "vaccination" was categorized into COVID-19 vaccination related (including BioNTech, Moderna, AstraZeneca, mRNA vaccination, COVID-19 vaccination) and not COVID-19 vaccination related terms (eg, hay fever allergy). Search results covering PEG containing vaccines were additionally extracted from the COVID-19 related group. Search results related to preexisting allergies such as "hay fever" or "penicillin allergy" and vaccinations in general (eg, "vaccination by existing poll allergy", "which vaccination for allergic sufferer", "vaccinate despite hay fever") were grouped as well, excluded allergies resulting from a vaccination. Furthermore, search volume for "PEG and Allergy" was analyzed and categorized into the disease "PEG allergy" including 23 PEG-allergy-related terms and terms related to diagnosing this disease.

Search volume was correlated to the German new corona infection numbers per month provided by the Robert-Koch-Institute (RKI)¹¹ and paired up with important pandemic events such

as the first vaccine release, STIKO (the Standing Committee on Vaccination at the German Robert Koch Institute), and World Health Organization (WHO) recommendations.

PubMed data

In February 2022, a systematic literature analysis for PEG allergy case reports from 1977 until February 2022 was performed, using the electronic biomedical literature databases PubMed, comprising citations from MEDLINE, life science journals, and online books (Table 1). Unconnected Keywords used were “PEG allergy”, “PEG and anaphylaxis”, and “PEG allergy and testing”. Single case reports of PEG allergy, for the period 1977–2016, were already summarized in the review by Wenande and Garvey and not separately listed.¹ References of the obtained articles were examined for cross references. The search was limited to articles in English, French, and German.

Articles reporting about the topic percutaneous endoscopic gastrostomy were excluded from the data. In addition, cases covering pegasparaginase allergy were not included in the data, as in the majority of those patients are allergic to the asparaginase rather than the PEG-moiety.^{12,13}

COVID-19 vaccine allergy cases were only included when further diagnostics (skin testing, oral provocation) proved a PEG allergy and not allergic reactions to an unknown culprit. Electronic medical records about PEG allergy or PEG allergy cases diagnosed by primary care providers without a further allergological work up were not included.^{14,15}

RESULTS

Google data

We included 741 vaccination-related keywords, which resulted in 134 433 230 queries over the last 4 years in Germany (Fig. 1a), including all vaccination related terms. The average interest in the topic vaccination was 561 108 queries per month February 2018 until January 2020 (Fig. 2a). An increase in search volume started in February 2020, parallel to the first COVID-19 case in Germany. Search volume remained stable until December 2020, the approval of the first

COVID-19 vaccination. Since then, search queries immensely increased up to a maximum of 22 291 480 queries in May 2021, 39-times higher than in the timeframe before COVID-19 pandemic. The maximum monthly search volume even increased up to 57-fold. Certain events such as the STIKO recommendation for COVID-19 vaccination or revaccination seemed to influence search volume more than actual COVID-19 infection numbers.

The search term “adverse effects and vaccination” resulted in 21 313 650 queries (Fig. 1a). In the first two years (February 2018 until January 2020), the total search volume of 1 448 430 queries was low compared to the last 2 years with a total search volume of 19 865 220 representing an increase of 13.7 times (Fig. 2b). Thereby a maximum monthly increase of 85-fold comparing March 2018 and May 2021 took place. Almost half of these queries were for PEG-containing vaccines such as BioNTech (n = 6 869 180) and Moderna (n = 2 266 270).

The 290 510 Google search queries for the terms “allergy and vaccination”, with a maximum monthly increase from July 2018 to May 2021 of 71-fold, were further categorized in “allergy to a COVID-19 Vaccination”, increased from zero up to a sum of 100 010 queries following December 2020 (Fig. 3a). “Allergy to PEG containing vaccines” and “PEG allergy” resulted in 64 700 queries.

The topic vaccination with a coexisting allergy, such as hay fever, was covered by 57 420 queries (Fig. 1a) in the 4 years. Before the pandemic, the search volume increased during the hay fever season, particularly in the months February until June 2019 and 2020 (average n = 216/month) compared to the remaining months (n = 61/month) (Fig. 3b). Thereafter, parallel to the 2020 vaccination start, the number of queries increased by 32-fold from 1510 queries in 2019 to 48 880 in 2021.

An even more drastic increase occurred with the 55 970 PEG allergy-related search queries (Fig. 4), of which only 250 occurred before February 2020. Overall, 44 230 search queries belonged to the disease category PEG allergy and 11 740 were related to PEG allergy testing, a search term not being searched before December 2020.

| Publication Year | Number of cases | Female (n) | Male (n) | Age range | Anaphylaxis | First author | Reference |
|--|-----------------|------------|----------|-------------|-------------|-----------------------|----------------|
| 2016 ^a | 37 | 23 | 14 | 24-86 | 28 (78%) | Wenande | 1 |
| 2016 | 1 | 1 | 0 | 46 | 1 (100%) | Wylon | 28 |
| 2016 | 1 | 0 | 1 | 39 | 1 (100%) | Lee | 29 |
| 2017 | 1 | 0 | 1 | 45 | 0 (0%) | Amsler | 30 |
| 2018 | 1 | 1 | 0 | 47 | 0 (0%) | Pator-Nieto | 31 |
| 2018 | 1 | 1 | 0 | 3 | 1 (100%) | Sari Gökay | 32 |
| 2019 | 1 | 1 | 0 | 65 | 1 (100%) | Giangrande | 33 |
| 2019 | 1 | 0 | 1 | 29 | 1 (100%) | Jover Cerda | 34 |
| 2019 | 53 | 26 | 27 | 2-87 (48,9) | 53 (100%) | Stone | 3 |
| Market introduction of PEG containing COVID-19 vaccination | | | | | | | |
| 2020 | 5 | 4 | 1 | 20-70 (47) | 5 (100%) | Sellaturay | 35,36,b |
| 2020 | 10 | n.s. | n.s. | n.s. | 0 | Ozkaya | 37 |
| 2020 | 1 | 0 | 1 | 76 | 1 (100%) | Rossi | 38 |
| 2021 | 10 | 3 | 7 | 12-77 | 10 (100%) | Brockow | 2,39 |
| 2021 | 10 | 4 | 6 | 18-64 | 8 (80%) | Bruusgaard | 40 |
| 2021 | 1 | 1 | 0 | 52 | 1 (100%) | Sellaturay | 41 |
| 2021 | 1 | 0 | 1 | 16 | 0 (0%) | Clark | 42 |
| 2021 | 2 | 1 | 1 | 33-59 (46) | 2 (100%) | Labella | 43 |
| 2021 | 1 | 1 | 0 | 24 | 1 (100%) | Pickert | 44 |
| 2021 | 1 | 1 | 0 | 30 | 1 (100%) | Rasmussen | 20 |
| 2021 | 1 | 1 | 0 | n.s. | 1 (100%) | Kuehn | 45 |
| 2021 | 1 | n.s. | n.s. | n.s. | 1 (100%) | Harper | 46 |
| 2021 | 1 | 0 | 1 | 57 | 1 (100%) | Caballero | 47 |
| 2021 | 1 | 1 | 0 | 28 | 1 (100%) | Vieira | 48 |
| 2021 | 1 | 1 | 0 | 38 | 1 (100%) | Paoletti | 49 |
| 2021 | 2 | 2 | 0 | 33 (27-39) | 2 (100%) | Rojas-Perez-Ezquerria | 50 |
| 2021 | 3 | 2 | 1 | 22-55 | 3 (100%) | Troelnikov | 51 |
| 2021 | 1 | 0 | 1 | 38 | 1 (100%) | Huynh | 52 |
| 2021 | 1 | 1 | 0 | 30 | 1 (100%) | Restivo | 53 |
| 2021 | 5 | n.s. | n.s. | n.s. | n.s. | Wolfson | 19 |

(continued)

| Publication Year | Number of cases | Female (n) | Male (n) | Age range | Anaphylaxis | First author | Reference |
|------------------|-----------------|------------|----------|---------------|-------------|--------------|--------------------|
| 2021 | 6 | 6 | 0 | 25-44 (36,4) | 6 (100%) | Cox | 7 |
| 2022 | 6 | 4 | 2 | 35-69 (50,16) | 6 (100%) | Picard | 26 |
| 2022 | 10 | 5 | 5 | 28-68 (53,7) | 10 (100%) | Bruunsgaard | 54 |
| 2022 | 10 | 4 | 6 | 16-63 (35,2) | n.s. | Bruunsgaard | 17 |
| 2022 | 1 | 1 | 0 | 50 | 1 (100%) | Habran | 55 |
| 2022 | 1 | 1 | 0 | 59 | 1 (100%) | Hennighausen | 56 |
| 2022 | 20 | n.s. | n.s. | n.s. | n.s. | Mortz | 57 |
| 2022 | 1 | 1 | 0 | n.s. | 1 (100%) | Kaplan | 58 |

Table 1. (Continued) Case reports of patients with PEG allergy in the period 1977–February 2022 ^aThis review summarises all cases reported from 1977 to 2015. ^bSame PEG patients compared to previous publication.

PubMed data

Seven hundred twelve scientific worldwide PubMed publications for “PEG allergy” (n = 510), “PEG and anaphylaxis” (n = 97) and “PEG allergy and testing” (n = 105) from 1977 to 2022 exist (Fig. 5, Table 1). The release of PEG containing COVID-19 vaccination went along with a 3.5-fold increase of publications on “PEG allergy” in 2021 compared to 2018 (Fig. 5).

The search term, “PEG allergy and anaphylaxis”, retrieved a peak in 2021 rising to >6.7 times; “PEG allergy and testing” did not show any increase in publication numbers.

Two hundred eleven cases with a diagnosed PEG allergy were found from 1977 until 2022 (Table 1). Ninety-eight patients were female, 77 male; no gender was given in 36 cases. Age ranged from 2 to 87 years. Wenande and Garvey already summarized 37 case reports starting 1977 until 2016;¹ therefore, we did not list these case reports separately. Stone and colleagues summarized another 53 PEG allergy cases.³ As far as possible, we tried not to list identical cases in more than one report or follow-ups twice. In almost all cases (n = 211) anaphylaxis due to PEG was reported. Overall 97 PEG allergy case published before the market introduction of PEG containing vaccines and 114 thereafter.

DISCUSSION

Google search volumes show an exponentially rising public interest in PEG allergy starting with the introduction of COVID-19 vaccination in Germany. Scientific publications on PEG allergy and PEG anaphylaxis, probably supported by public awareness, have only mildly increased 2.5- and 6.8-fold in 2021 worldwide compared to 2019. In strong contrast, only 211 PEG allergy cases have been known since 1977. Thus, the risk for patients without a typical allergic history remains negligible. German public interest in PEG allergy does not reconcile with the few PEG allergy case numbers published worldwide. The data thereby testify the public lack of knowledge on PEG allergy resulting in a current high demand for allergy testing before COVID-19 vaccination.

The outbreak of COVID-19 has left the world in a unique state of crisis leading to an unprecedented mass vaccination. The rapid development of COVID-19 vaccination induced German public concern about its safety, being reflected by an increase in Google search volumes. Search results for “vaccination” increased up to 39-fold, “adverse effects of vaccination” up to 14-fold. One hundred thousand ten search results were placed for “allergy to a COVID-19 vaccination” after the vaccination announcement, and 64 700 looked specifically into allergy to vaccination containing

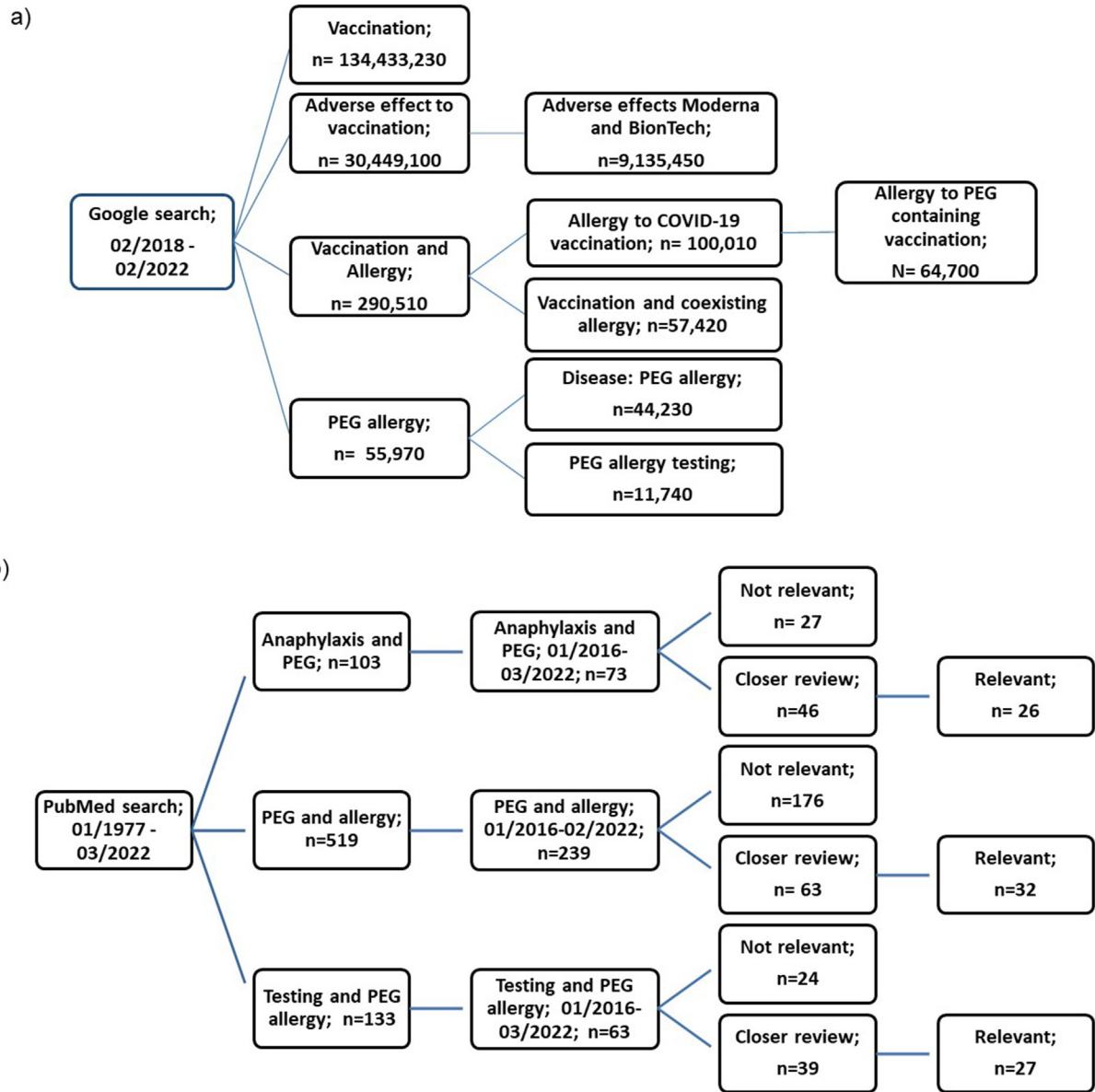


Fig. 1 Analysis of (a) Google Ads search results with the search volume per category (b) PubMed search results with the number of case reports per category

PEG. Before COVID-19 vaccination there was a negligible search volume for PEG allergy; it increased dramatically after March 2021, when AstraZeneca’s vaccine was temporarily halted and a general recommendation for COVID-19 vaccination was released. This is interesting, because AstraZeneca’s vaccine does not include PEG. However, media coverage, not even concerning PEG including vaccines, but rather COVID-19 vaccination in general, and political interventions, seem the main drivers of public interest, also shown in previous studies,^{10,16} and the actual

number of COVID-19 infections seem to play a subsidiary minor role.

PubMed case reports demonstrate a preexisting low scientific interest in PEG allergy before the pandemic worldwide with only few research papers and few case reports. Although this significantly peaked since the release of COVID-19 vaccines, coverage already had started to increase in 2016. PEG was already approved as a laxative since 1980 and nowadays is increasingly used in a huge variety of different medications and cosmetic

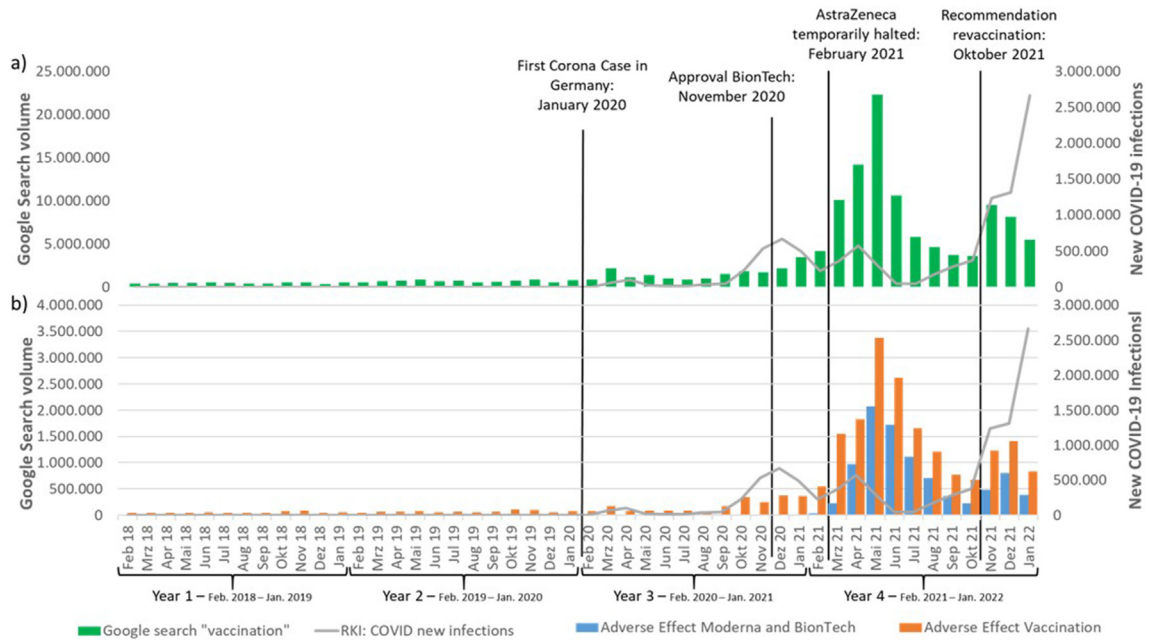


Fig. 2 Public interest measured by Google search volumes compared to the number of new infections per day during the COVID-19 pandemic in Germany for (a) “vaccination” (b) “vaccination” and “adverse effect”, “vaccination” and “adverse effects to Moderna and BionTech vaccine”

products.⁶ In contrast, the prevalence of PEG allergy case reports is as low as 211 cases in PubMed, although there has been a substantial increase of patient numbers in the last two years. Before that, PEG allergy was likely to be underreported,¹⁷ as it might had been a “hidden allergen” not known to physicians and

patients.^{1,3,17} It is likely that the broad media coverage of anaphylactic cases triggered public awareness for allergic reactions to vaccination and focusing on PEG as a possible culprit.¹⁸ In the beginning the reported allergy rate appears to be 2-4 times higher than expected for other vaccinations,² however new data show

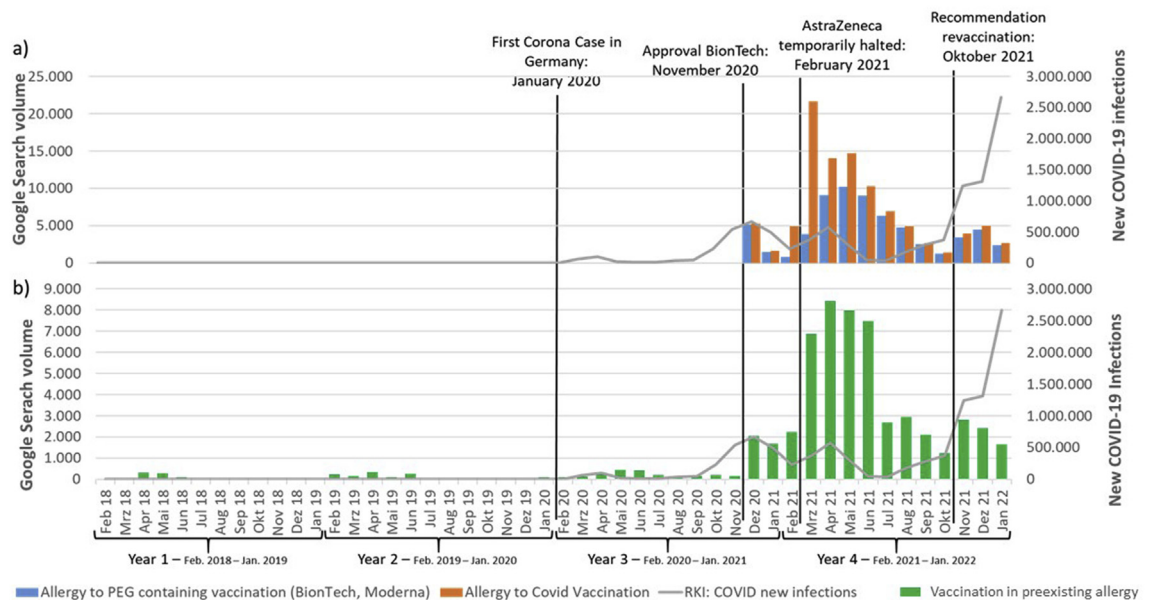


Fig. 3 Public interest measured by Google search volumes in Germany for (a) “COVID-19 vaccination” and “allergy” and (b) “vaccination” by preexisting allergy

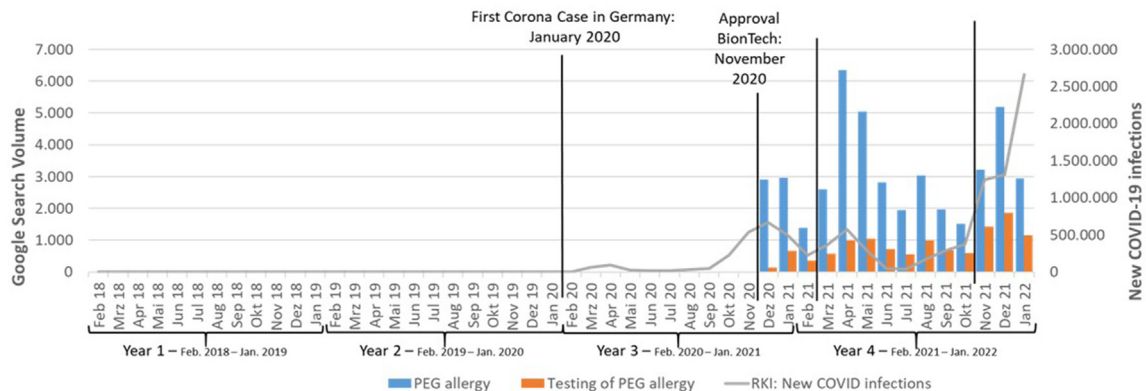


Fig. 4 Public interest on “PEG allergy” and “Testing for PEG allergy” as measured by Google Search Volumes compared to the number of new infections per day during the COVID-19 pandemic in Germany.

comparable anaphylaxis rates associated with COVID-19 vaccines to those of other vaccines, even ranking fifth in reported anaphylaxis rates, behind rabies, tick-borne encephalitis, measles-mumps-rubella-varicella, and human papillomavirus vaccines.⁵ The rarity of PEG allergy (<220 cases worldwide) strongly argues against a causal relationship for most cases with anaphylaxis and COVID-19 vaccination,² especially considering PEG being used in up to 1 million times higher concentrations in laxatives than it is used in vaccination.⁸

Furthermore, studies on allergic reactions to PEG-containing vaccines failed to identify PEG as the culprit in most cases.^{2,19,20} In these, re-vaccinations were normally well tolerated.^{21–25} In a Danish study with 199 377 vaccinated patients, only 0.03%

reported allergic reactions and of those only 3 had evidence for an allergy to ingredients of the vaccine after testing.²⁰ Additionally, several cases were reported where people with a known PEG allergy could be safely vaccinated.^{2,26} Other reasons for the higher number of reported allergy-like reactions following COVID-19 vaccination remain unknown. Furthermore, the reported allergies have highly subjective symptoms which may be explained at least partly through vasovagal or non-immune mediated mechanisms.²⁷ Public concerns might have driven anxiety and somatoform reactions, which may often not be distinguished from allergic reactions. The majority of people suspecting a PEG allergy before or after vaccination and wanting an allergological consultation did not have a clinical indication for allergological workup.^{2,19,20}

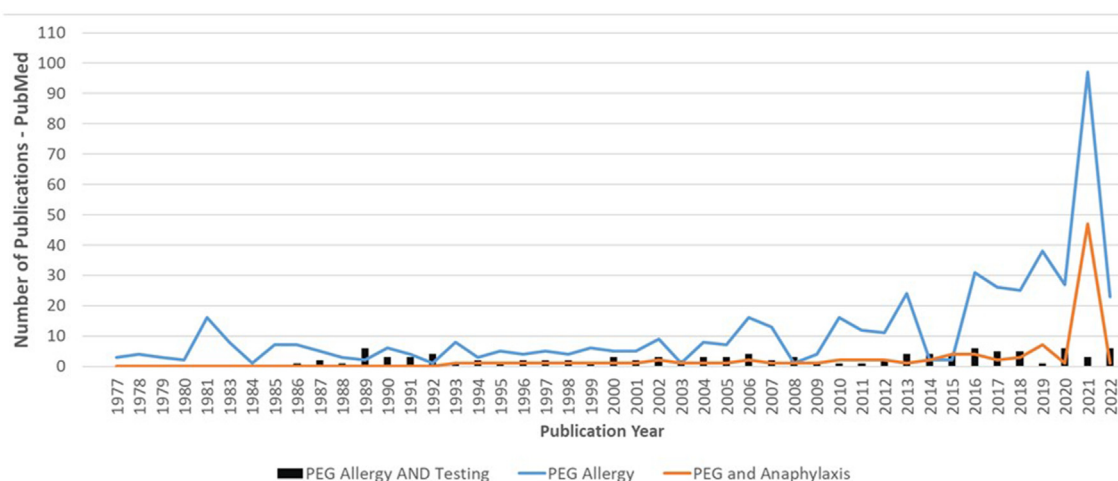


Fig. 5 Search Volume in PubMed for the topic “PEG allergy”, “Testing for PEG allergy” and “PEG anaphylaxis”

Furthermore, data showed a low seasonal interest in vaccination safety and coexisting allergy before the pandemic. In 2021, after pandemic started, this topic increased more than 32-fold compared to 2019 with no seasonal influences any more. For people having allergies there seems to be a high need for information especially on COVID-19 vaccination safety. This is also backed up by our experience in our clinical department.

Limitations concerning this study are the use of German Google data representing only a sub-population using Google for medical questions. Because Google AdWords Keyword Planner does not provide information on the user's demographics, no information about the examined population is available. The data only analyses German Google data. The situation may have been somewhat different in other industrialized countries, but exemplifies in Germany the disproportional public interest in PEG allergy, being strongly influenced by vaccine approvals, political recommendations or warnings concerning COVID-19, and spread of the COVID-19 infection. A further limitation might be the automatic completion of search terms provided by Google, which might bias people's search behavior. The interest in PEG allergy might be underestimated because not all patients suspecting an allergy consulted the internet. Furthermore, people might have searched with unspecific questions, not included in the specific google key terms. Additionally, PubMed PEG allergy case reports may not represent all existing PEG allergy cases. There might be an underreporting or a time delay. Due to a lack of knowledge on PEG allergy, previous PEG allergies before the pandemic might have been underdiagnosed.

CONCLUSION

German public interest in vaccination and PEG allergy strongly coincided with COVID-19 vaccine approval, heavy media coverage of the rare reports of anaphylaxis following COVID-19 vaccination and health authority recommendation for vaccination, even more than by the number of COVID-19 infections. Before the COVID-19 pandemic, PEG allergy was nearly unknown in the German population. This is especially interesting considering PEG's widespread and long-

lasting use in medicine and other preparations. The scientific community always have had some low-level interest in PEG allergy, which already increased after 2016 but significantly peaked after the PEG-containing vaccination availability. Although the numbers of patients with a reported PEG allergy substantially increased in the last 2 years, absolute numbers still remain low. Thus, the overrun of allergy departments by patients asking for PEG allergy testing is not and has never been medically justified. Scientific easily accessible and understandable online information about the very low frequency of PEG allergy seems of very great importance and need.

Abbreviations

COVID-19: Corona Virus Disease 2019; PEG: Polyethylene glycol; RKI: Robert-Koch-Institute; STIKO: Standing Committee on Vaccination at the German Robert Koch Institute; WHO: World Health Organization

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Author contributions

- Dr. Med. Rebekka K. BENT, B.Sc. Study conception, Formal Analysis, Investigation, Manuscript preparation, Project administration, Funding acquisition.
- Dr. Med. Valentina FAHS: Manuscript preparation.
- Dr. Phil. Linda TIZEK1, MPH: Data Analysis.
- Prof. Dr. Med. Tilo BIEDERMANN: Supervision, Funding acquisition.
- PD Dr. Med. Alexander ZINK MPH, MD, PhD: Supervision, Study concept, Funding acquisition.
- Prof. Dr. Med. Knut BROCKOW:" Study conception, Manuscript preparation, Supervision, Project administration, Funding acquisition.

Consent for publication

The authors consent to the publication of this article.

Ethics Statement

This study did not require ethics approval or patient consent.

Conflict of interest

None.

Author details

Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany.

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