# Perceived high risk of COVID-19 vaccination: the revealing power of placebo.

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*Perceived high risk of COVID-19 vaccination: the revealing power of placebo.*

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To the Editor

Self-limiting mild adverse events (AEs) after COVID-vaccination are common and should not contraindicate revaccination[1]. Unfortunately, these are too often erroneously labeled as hypersensitivity reactions (HRs), precluding revaccination[2]. A patient with a history compatible with an immediate HR to the vaccine should be offered allergologic evaluation with the excipients of these vaccines based on the respective type[3,4]. In contrast, in the diagnostic work-up of patients with subjective symptoms or multiple unverified drug hypersensitivities a placebo-controlled challenge should be considered[5].

In this study, we assessed the reoccurrence rate (RR) of AEs after vaccination or unrelated to the vaccine in COVID-19-vaccine naïve patients. We report data on 69 individuals who attended the outpatients' clinic of the Antwerp University Hospital from April 1 to July 1, 2022, for risk stratification concerning COVID-19 vaccination. Patient characteristics are summarized in table 1.

All patients were administered a placebo, either as primary diagnostic (n=52) or after negative skin testing (n=17). The main reason for referral was symptoms after previous COVID-19 vaccination (n=41). Twenty-eight patients were COVID-19-vaccine naïve and reasons for referral are shown in table 1. Seventeen of the 69 patients were offered allergologic evaluation including skin tests (STs) with the concerning excipients or the COVID vaccine, based on clinical suspicion. In 1 patient a polysorbate allergy was diagnosed. She suffered from a so called 1-1-1-urticaria[6] after administration of the first dose of Vaxzevria®. In all other patients, allergologic evaluation was negative. All 69 patients were (re)vaccinated in a placebo-controlled manner. In 11 patients previously vaccinated with Spikevax® (n=3); Jcovden® (n=3) or Vaxzevria (n=5) a switch was made to Comirnaty® either due to practical reasons of availability of vaccines in our center (n=10) or because of confirmed hypersensitivity (n=1).

Out of the 41 patients who reported symptoms after previous dose, 14 reported symptoms after placebo administration and were vaccinated uneventfully afterwards. Two patients had symptoms after re-exposure to the vaccine: 1 patient experienced dyspnea with urticaria that was considered anaphylaxis, 1 patient had urticaria immediately after the vaccination with Comirnaty®. Both did not meet criteria for mast cell activation[7]. Of the 28 COVID-19-vaccine naïve patients, 5 had symptoms after administration with placebo and were later vaccinated uneventfully. In total, 19 out of 69 patients (27.54%) experienced symptoms after placebo. Overall, 67 of 69 patients were vaccinated uneventfully without premedication and the RR of AEs was 1 in 20 (4.88%). Details regarding allergologic evaluation and vaccination are shown in table 2.

The aim of this study was dual: first, to evaluate the RR of presumed AEs after vaccination and second, to evaluate the rate of AEs unrelated to the vaccine in COVID-19-vaccine naïve patients. A recent meta-analysis stated that 13.65% of individuals experience reoccurrence of nonlife-threatening symptoms after a second dose[8]. In our cohort, the RR of AEs was 4.88%. The difference might be explained by the fact that placebo administration enabled to distinguish the effective reoccurrence of vaccine-induced symptoms from nocebo effect[9,10]. Actually, after exposure to placebo 28% of patients experienced symptoms (similar to the symptoms that occurred upon previous exposure to the vaccine). Placebo-controlled provocation is an important part of drug provocation tests (DPTs) but has not been described before in the context of possible vaccination hypersensitivity. Previous studies on placebo and nocebo effects in DPTs demonstrate that patients with symptoms after exposure, anxiety and/or depression are prone to nocebo effects[11].

We conclude that the RR of AEs after COVID-19 vaccination is low. A thorough history and clinical details regarding symptoms and timing are essential for correct risk stratification. The use of placebo is of great value and should be considered in drug provocation tests, especially in patients with a history of symptoms after previous exposure and in patients with anxiety or depression.

| Demographics | Demographics | Demographics |
|---|---|---|
| | M/F | M/F |

| Demographics | Demographics | Demographics |
|---|---|---|
| | Mean age (range) | Mean age (range) |
| Relevant clinical history | Relevant clinical history | Relevant clinical history |
| | Asthma | Asthma |
| | Chronic urticaria | Chronic urticaria |
| | Aeroallergy | Aeroallergy |
| | Hypothyroidism | Hypothyroidism |
| | Celiac disease | Celiac disease |
| | Chronic pain | Chronic pain |
| | Diabetes mellitus type II | Diabetes mellitus type II |
| | Breast carcinoma | Breast carcinoma |
| Reason for referral | Reason for referral | Reason for referral |
| | Anxiety | Anxiety |
| | Multiple anaphylaxis | Multiple anaphylaxis |
| | Refused by vaccination center | Refused by vaccination center |
| | | Suspected hypersensitivity to unrelated drugs |
| | | Suspected hypersensitivity to macrogol |
| | | Anaphylaxis to diclofenac (which contains tromethamine) i |
| | | Possibly angio-edema after unknown vaccine, more than 10 |
| | Symptoms after 1st or 2nd dose (+) | Symptoms after 1st or 2nd dose (+) |
| | | (Pre)syncope, hypotension, palpitations immediate after va |
| | | Dyspnea immediate after vaccination |
| | | Dysphagia immediate after vaccination |
| | | Hoarseness immediate after vaccination |
| | | Nausea immediate after vaccination |
| | | Headache immediate after vaccination |
| | | Pruritus immediate after vaccination |
| | | Flushing immediate after vaccination |
| | | Urticaria immediate after vaccination |
| | | Urticaria $>$ 1 day after vaccination |
| | | Unspecified skin rash |
| | | Angio-edema / sensation of swelling immediate after vacci |
| | | Angio-edema / sensation of swelling $>$1 day after vaccinati |
| | | Measurement of acute serum tryptase |

Table 1: Patient characteristics

(+) 17 patients showed signs and symptoms compatible with an immediate HR after administration of the vaccine.

| Skin testing (limited to patients with diagnosis of anaphylaxis) | Skin testing (limited to patients with diagnosis of anaphyl |
|---|---|
| | Polysorbate positive |
| | Polysorbate negative |
| | Macrogol negative |
| | Tromethamine negative |
| Administered vaccine | Administered vaccine |
| | Comirnaty® |
| | Jcovden® |
| | Vaxzevria® |
| Symptoms immediately after vaccination | Symptoms immediately after vaccination |

| | |
|---|---|
| Skin testing (limited to patients with diagnosis of anaphylaxis) | Skin testing (limited to patients with diagnosis of anaphyl |
| Symptoms after administration of placebo | Symptoms after administration of placebo |
| Symptoms after placebo per referral group | Symptoms after placebo per referral group |

Table 2: Details regarding allergologic evaluation and vaccination.

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