

ORIGINAL ARTICLE

Patients with positive patch test to formaldehyde can be safely vaccinated with formaldehyde-containing vaccines

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Abstract

Background: Prophylactic vaccination against influenza and other epidemic viruses is recommended for citizens above 65 years. Several vaccines may contain traces of formaldehyde and are contra-indicated in patients hypersensitive (in the broadest possible meaning) to formaldehyde. Thorough knowledge on the various subtypes of hypersensitivity is sparse among non-dermatologists and non-allergists, and therefore many patients are prevented from vaccination based on a positive patch test to formaldehyde. The purpose of this retrospective study was to investigate whether patients with positive patch test to formaldehyde subsequently receiving a formaldehyde-containing vaccine and developed a severe adverse reaction.

Methods/Materials: From January 2000 to June 2021, 169 patients (>50 years) had a positive formaldehyde patch test at the Department of Dermatology and Allergy Center, Odense University Hospital and were included into this retrospective study. The electronic medical record was assessed for receipt of a formaldehyde-containing vaccine after patch test and for subsequent contact with the Acute Ward in the Region of Southern Denmark within 14 days after vaccination.

Results: Of the 158 patients residing in the Region of Southern Denmark, 130 patients were vaccinated with one or more formaldehyde-containing vaccines of whom 123 received an influenza vaccine. No contacts to the acute wards were identified.

Discussion: Although prospective studies would be beneficial, patients with positive patch test to formaldehyde can be safely vaccinated with formaldehyde-containing vaccines.

KEYWORDS

formaldehyde, influenza vaccination, patch test, type IV reaction

1 | INTRODUCTION

Sensitization to formaldehyde most frequently manifests as contact dermatitis although rare cases of systemic symptoms upon exposure to

formaldehyde in vaccines have been described.^{1–4} Vaccination against viral diseases such as influenza often elicit local or systemic adverse reactions both of hypersensitivity and non-hypersensitivity nature, but are rarely severe and should only in severe cases, for example, severe

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cutaneous adverse reactions or anaphylaxis prevent the patient from revaccination.^{3–6} The risk of elicitation an adverse reaction to a vaccine must certainly in every patient be balanced against the risk for life threatening viral disease in the unvaccinated patient.

Licensed drugs must label all constituents in the formulation of the final product; thus, potential presence of residues arising from the manufacturing process must be mentioned, even if the amount is very minute (<https://fmk-online.dk/Secured>, accessed January 2022 [in Danish language]). Therefore, formaldehyde is labelled as an ingredient in the majority of commercially available virus vaccines in Denmark. Labelling includes the sentence ‘Hypersensitivity to the ingredients, egg and chicken proteins, ovalbumin, gentamicin, formaldehyde, cetyltrimethylammonium-bromide or polysorbat 80’ (author’s translation). Thorough knowledge on differences between immediate type (type 1) reactions, delayed type (type IV) reactions, other t-lymphocyte mediated reactions and other types of adverse reactions is sparse among colleagues without dermatological or allergological training. Although the word ‘hypersensitivity’ probably refers to severe reactions only, physicians and patients in many cases misinterpret the labelling, preventing life protecting vaccinations. Legislation requires, that the licensed health person ask the patient for possible ‘allergy to vaccines or constitutions herein’ prior to administration of the vaccination and therefore patients with contact allergy to formaldehyde answer affirmatively and either abstain from receiving vaccinations (FMK-online), or the patients are excluded from vaccination by the health personnel.

Formaldehyde is a toxic and carcinogenic auxiliary substance, widely used in many vaccines and in a number of manufacturing processes, including textiles, paints, plastics, gloves, and the leather industry as well as cosmetics, hair, and nail products.⁷ The purpose of adding formaldehyde to vaccines in the manufacturing process is to inactivate bacteria and viruses in the vaccines. Subsequently, formaldehyde is removed from the vaccines during various purification processes, but small trace amounts <0.1 mg^{6,8} may remain in the final product. Formaldehyde in vaccines is considered to be safe for two reasons: First, formaldehyde is an essential intermediate in human metabolism and is required for the synthesis of pyrimidines, purines, and amino acids so all human beings have detectable quantities of formaldehyde in the circulation. Second, quantities of formaldehyde at least 600-fold higher than that contained in vaccines have been administered safely to animals.⁸

Assessment of safety of a given medical procedure should ideally include investigations on the most sensitive group of patients at risk. Since we failed to identify a more suitable patient group than patients with a prior positive patch test reaction to formaldehyde, since these patients are often misunderstood by health personel in context to vaccination and since these data were readily available in our internal database, this patient group was chosen for this retrospective study.

2 | PATIENTS

From January 2000 to June 2021 (inclusion period), 169 patients >50 years (59 men and 110 women) had a positive patch test for

formaldehyde at the Department of Dermatology and Allergy Center, Odense University Hospital. At the time of the first positive formaldehyde patch test, 83 patients were between 50 and 59 years old, 51 patients were between 60 and 69 years old, and 35 patients were between 70 and 93 years old. Twenty-three patients died during the study period.

3 | METHODS

Patch testing with formaldehyde was performed using TRUE-test^R including formaldehyde (180 µg/cm²) and formaldehyde 2% in aqueous solution (Chemotechnique Diagnostics, Vellinge, Sweden), in Finn Chambers 1.⁹ We use TRUE-test^R as part of our baseline series, and supplement with extra allergens in the European baseline series tested in Finn Chambers. Patch tests were applied on the patient’s back for 2 days and test reactions were evaluated on Day 3 or Day 4 and Day 7 by trained personnel. Reactions were graded as negative, irritant reaction, doubtful or positive (+, ++ or +++) according to the recommendations of the European Society of Contact Dermatitis.⁹ Positive reactions only were included.

Data on all publicly administered vaccines are stored in a nationwide health registration system for all citizens residing in Denmark (FMK-online). One hundred fifty-eight included patients were manually checked in FMK-Online for receipt of a formaldehyde-containing vaccine prior to or subsequent to testing patch test positive to formaldehyde.

Subsequently, the electronic patient file was assessed for contact with an acute ward in the Region of Southern Denmark up to 14 days after vaccination and, in the affirmative, the reason for contact. Out of 169 patients with formaldehyde contact allergy, 158 patients were residents in the Region of Southern Denmark, whereas 11 patients came from other Danish regions and their patient files could not be evaluated, for legislative (GDPR) reasons.

4 | ETHICS

The study was approved by the Danish Data Protection Agency (no. 20/53636).

5 | RESULTS

5.1 | Patch testing

In total, 169 patients were positive for formaldehyde by patch testing (85: +, 76: ++, 8: +++); 44 had a positive reaction to formaldehyde in TRUE-test^R only, 72 had a positive reaction to formaldehyde from Chemotechnique only, and 53 were positive to both tests—discrepancies between test methods have been described previously.¹⁰ Eight patients had positive formaldehyde tests 2–3 times within the 20-year period.

FIGURE 1 The number of vaccinations with formaldehyde-containing vaccines administered to patients with positive patch test to formaldehyde during the study period. Out of the total population of 169, 130 patients had received at least one vaccine.

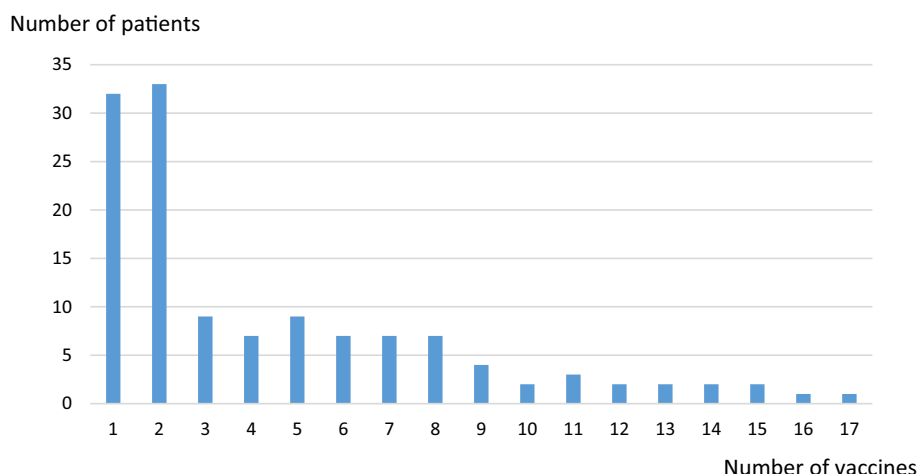


TABLE 1 Vaccines containing formaldehyde.

Influenza vaccines	Manufacturer	ATC-code
Vaxigriptetra (4-valent vaccine mod influenza A og B), s.c. or i.m.	Sanofi	J07BB02
Vaxigrip	Sanofi	J07BB01
Fluarix	GSK	J07BB02
DiTeKiPol/Act-Hib (tetanus, diphtheria, polio, Haemophilus influenzae)	AJ Vaccines	J07CA06
Pentavac (diphtheria, pertussis, polio, tetanus, Haemophilus influenzae)	Sanofi	J07CA06
Other formaldehyde-containing vaccines	Manufacturer	ATC-code
DiTeBooster (tetanus, diphtheria)	AJ Vaccines	J07AM51
DiTeKiBooster (tetanus, diphtheria, pertussis)	AJ Vaccines	J07AJ52
Vaqta (Hepatitis A)	MSD	J07BC02
TicoVac, TBE-virus	Pfizer	J07BA01
Dukoral (cholera)	Valneva Sweden	J07AE01
Typhim VI (typhus)	Sanofi	J07AP03
HBVAXPRO (Hepatitis B)	MSD	J07BC01

Note: The table list the currently available formaldehyde-containing vaccines on the Danish market.

5.2 | Results of vaccination

A total of 130/158 patients with a positive formaldehyde patch test residing in the Region of Southern Denmark had received a formaldehyde-containing vaccine (123 received an influenza vaccine) (Figure 1). Twelve patients (having received 1 to 13 formaldehyde-containing vaccines, average 5 vaccines after positive formaldehyde test) died of unrelated diseases during the observation period. None of the patients residing in the Region of Southern Denmark were subsequently in contact with the local acute ward due to acute adverse reaction of any nature elicited by vaccination.

Two patients had been visiting an emergency hospital clinic on the same day they received a formaldehyde-containing vaccination. However, both were boosted with the tetanus vaccine in relation to an acute wound and therefore not considered to have an adverse vaccination reaction.

Twenty-two patients have not received vaccines other than COVID-19 vaccines after testing.

Of the 120 patients aged <65 years at the time of inclusion, 80 patients received at least one influenza vaccination during the study period. Of the remaining 40 patients, 23 were still less than 65 years of age in January 2022 and thus were not offered vaccination free of charge. The remaining 17 patients had turned 65 years but no records of vaccination were found.

Thirty-one patients, of whom 23 had also received influenza vaccine, were vaccinated with other formaldehyde-containing vaccines (Table 1)—(24, 2, 3, 2 patients receiving 1, 2, 3, 4 vaccines, respectively).

In total, the 130 vaccinated patients had received 590 formaldehyde-containing vaccines.

6 | DISCUSSION

A prospective study following all patients with contact allergy to formaldehyde, gentamicin and other excipients in vaccines with respect to adverse reactions including hypersensitivity reactions to subsequent vaccinations with formaldehyde-containing vaccines would be ideal, but would necessitate a follow up period of several years. We, therefore, chose apply a retrospective design confined to—for legislative reasons—severe adverse reactions to virus vaccines requiring hospital evaluation. The purpose was to gather evidence on safety of vaccination of patients with positive patch test to formaldehyde for use as evidence in the subsequent dialogue with the authorities, delabeling formaldehyde—and logically other similar excipients—as contraindications for vaccination. Influenza vaccines is the numerically predominant formaldehyde-containing vaccine in Denmark, but in order to include the highest possible number of vaccinations we

chose to enrich the number by including other formaldehyde-containing vaccines into the study.

National recommendations for influenza vaccination focus primarily on citizens above the age of 65 years. We chose to include patients above the age of 50 years due to the prolonged study period of 21 years. No records of contact with the acute wards were obtained subsequent to vaccination, and therefore we conclude that no severe hypersensitivity—or other—reactions were elicited.

Whether vaccination of patients with positive patch tests to formaldehyde experience an increased frequency and/or severity of side effects after vaccinations remains unknown, but since no severe reactions were identified, it seems feasible and safe to vaccinate formaldehyde-positive patients with formaldehyde-containing vaccines, although risks always must be weighed against benefits. The fact that most patients had received more than one formaldehyde-containing vaccine after the positive formaldehyde patch test further supports the statement.

A possible explanation of our findings could be the trace amount of formaldehyde in vaccines^{6,8} insufficient to elicit a reaction—in fact, the amount is lower than natural exposure and uptake from many products found in the environment.^{7,8} Leventhal et al.⁶ and Offit et al.⁸ investigated the residual amounts of formaldehyde in various vaccines such as influenza and DiTePol and found that the residual quantities did not exceed 0.1 mg formaldehyde. Furthermore, severe reactions such as Sweets Syndrome elicited by virus vaccines remains extremely rare, averaging 1 per 1 500 000 doses, and formaldehyde-containing vaccines cause most often only less severe, local symptoms.^{4–7} In most cases, patients developed a maculo-papular reactions on the chest, shoulders, antecubital fossa or arms.⁷ Furthermore, immunizations are highly effective in preventing infectious diseases and therefore an indispensable public health measure.⁵

7 | LIMITATIONS

The study is retrospective and only include severe adverse reactions to vaccination requiring hospitalization. Whether this patient group experience an increased frequency and/or severity of less severe side effects remains unknown. Further, some patients died for other reasons or were resident in regions, where legislation prevented us from obtaining vaccination data, reducing the cohort by a significant number.

8 | CONCLUSION

In conclusion, citizens >50 years of age, who have tested positive for formaldehyde by patch test, can be safely vaccinated with formaldehyde-containing vaccines without experiencing severe reactions requiring hospitalization. This recommendation of course does not extend to patients reporting anaphylaxis to a formaldehyde-containing vaccine.

AUTHOR CONTRIBUTIONS

Ulla Bindslev-Jensen: Investigation; writing – original draft; validation; writing – review and editing; formal analysis; data curation. **Charlotte G. Mortz:** Supervision; writing – review and editing; methodology. **Klaus E. Andersen:** Methodology; writing – review and editing. **Carsten Bindslev-Jensen:** Conceptualization; writing – review and editing; project administration; supervision; resources; methodology.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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