



Short communication

Vaccination of yeast sensitive individuals: review of safety data in the US vaccine adverse event reporting system (VAERS)

Lauren DiMiceli^{a,*}, Vitali Pool^a, John M. Kelso^{b,1},
Sean V. Shadomy^{a,2}, John Iskander^a, V.A.E.R.S. Team^a

^a Immunization Safety Branch, NIP/CDC, Mail Stop E61, Atlanta, GA 30333, USA

^b Allergy Division, Naval Medical Center, San Diego, CA 92134, USA

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Abstract

The preparation of recombinant hepatitis B vaccines involves using cellular cultures of *Saccharomyces cerevisiae*, otherwise known as baker's yeast. Prior to vaccine licensure, clinical trials were performed to address whether residual yeast proteins in the vaccines could induce anaphylaxis, including testing for IgE anti-yeast antibody levels. 1–2% of subjects had anti-yeast IgE antibodies before immunization, but demonstrated no significant rise in IgE after HBV. We searched reports in the Vaccine Adverse Event Reporting System (VAERS) for those that mentioned a history of allergy to yeast and then reviewed the adverse events described in these reports for potential anaphylactic reactions. Probable anaphylaxis was defined as the presence of one or more dermatologic symptoms and one or more respiratory, gastrointestinal, or cardiovascular symptoms with onset within 4 h of Hepatitis B vaccination. Possible anaphylaxis was defined in one of two ways: (1) cases that described dermatologic or respiratory symptoms (but not both) occurring within 4 h of vaccination; or (2) cases that described one or more dermatologic and/or respiratory symptoms occurring 4–12 h post vaccination. Among the 107 reports of pre-existing “yeast allergies,” 11 reports described probable or possible anaphylaxis after HBV. Four additional cases were described after other vaccines. The majority of vaccinees who met the case definitions and had a history of yeast allergies were female, ages ranged from 10 to 64, and symptom onset ranged from 15 min to 5 h after vaccination. No deaths were reported. The small number of reports to VAERS may be partly due to health care professionals observing current contraindications by not vaccinating yeast sensitive individuals. Nevertheless, yeast associated anaphylaxis after HBV in sensitized patients appears to be a rare event.

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1. Introduction

In the United States, two kinds of hepatitis B vaccines (HBV) have been produced and distributed. Plasma-derived HBV are no longer manufactured in the United States; all current HBV are produced by recombinant methods [1]. Modern genetically engineered HBV are highly effective and safe products [2]. They are prepared by harvesting hepatitis B surface antigen from cell cultures of recombinant strains of

Saccharomyces cerevisiae (common bakers' yeast) that carry the surface antigen gene of hepatitis B virus. As a result of biochemical and biophysical purification, there is no detectable yeast DNA and only trace amounts of yeast proteins (1–5%) in the final vaccine products [3–7]. Two polysaccharide vaccines, HibTITER and Prevnar, include a conjugating protein (CRM197) isolated from cultures of *Corynebacterium diphtheriae* grown in a yeast extract-based medium. However, the final vaccine products do not contain yeast protein [8,9]. Whether these residual yeast proteins in HBV could act as antigens or allergens in vaccinees was evaluated early in vaccine development. To address this issue, testing for both IgG and IgE antibodies against yeast proteins were performed in small subsets (50–133 subjects) of volunteers participating in clinical trials [10–12]. Hundred percent of subjects had IgG

* Corresponding author. Tel.: +1 404 325 3310.

E-mail address: bqw6@cdc.gov (L. DiMiceli).

¹ Co-corresponding author.

² Present address: Meningitis and Special Pathogens Branch, NCID/CDC, Mail Stop C09, Atlanta, GA 30333, USA.

antibodies against yeast even before vaccination, presumably due to prior exposure by, for example, eating bread. The titers of these IgG antibodies rose, fell, or remained unchanged after immunization, but showed no consistent pattern and were not related to any clinical complaints after vaccination. 1–2% of subjects had anti-yeast antibodies of the IgE class even prior to immunization, but received the vaccine uneventfully and had no significant rise in the titer of these antibodies. It was concluded from these studies that the small amounts of yeast proteins in recombinant HBV do not provoke immune reactions in vaccine recipients or cause allergic reactions in the rare subjects with pre-existing anti-yeast IgE antibodies. Further, IgE-mediated allergy to yeast as an aeroallergen or food allergen is actually quite rare, although it may have some immunologic cross-reactivity with other fungi [13–15]. In a study of 193 bakery workers, including 104 filing claims for baker's asthma, none had positive skin tests to baker's yeast [15]. A potentially confounding circumstance is the belief by some patients and practitioners in the “yeast hypersensitivity syndrome” [16]. In this “syndrome,” a wide range of ill-defined symptoms is attributed to exposure to the yeast, *Candida albicans*. This organism is actually part of normal human flora, and the condition lacks biologic plausibility and has been deemed unproven. Patients who believe they suffer from this malady may think of themselves as “allergic to yeast”, but even the proponents of this entity do not claim it is IgE mediated or causes anaphylaxis. Nonetheless, hypersensitivity to yeast is listed in HBV package inserts as a contraindication for HBV administration [4–8].

In the US, a nationwide post-marketing monitoring system for vaccine safety known as the vaccine adverse event reporting system (VAERS) has been in place since 1990. The goal of this review was to find if adverse events (AE) have been reported to VAERS following vaccination of individuals reportedly allergic to yeast. We were particularly interested in identifying and describing possible IgE-mediated anaphylactic reactions.

2. Methods

VAERS is a spontaneous reporting system for adverse events following vaccination with US licensed vaccines that is maintained by the U.S. Department of Health and Human Services [17,18]. VAERS accepts AE reports from vaccine providers, other healthcare workers, vaccinees or their parents, and other reporters, either directly or via vaccine manufacturers. The VAERS form provides space for comments regarding the vaccinee's pre-existing physician-diagnosed allergies and other medical conditions (Box. 19, see VAERS form at <http://vaers.hhs.gov>). Free text information from VAERS reports is entered into a searchable database and coded using medical classification terms assigned to each report by using the coding symbols for thesaurus of adverse reaction terms (COSTART). In addition to the standard VAERS form, the reporters may submit relevant medi-

cal documentation pertaining to the reported adverse event. These documents are scanned into an image database and are also available for review. We queried the VAERS database for mention of the key word “yeast” anywhere in the report record. These reports with accompanying medical documentation were then manually reviewed to find cases that mentioned a history of allergy to yeast. A limitation exists because the majority of VAERS reports did not specify the species of yeast the vaccinee was reportedly allergic to. The AE described in the VAERS reports in patients with a reported allergy to yeast were then characterized. We defined cases as *probable anaphylaxis* following vaccination if the following criteria were met: presence of one or more dermatologic symptoms (urticaria, angioedema, pruritus) and one or more respiratory (dyspnea, bronchospasm, nose/eye symptoms), gastrointestinal (nausea, vomiting, diarrhea), or cardiovascular symptoms (hypotension, tachycardia, palpitation, loss of consciousness) occurring within 4 h of vaccination [19]. *Possible anaphylaxis* was defined as either one or more dermatologic or respiratory symptoms (but not both) occurring within 4 h after vaccination, or as one or more dermatologic and/or respiratory symptoms occurring 4–12 h after vaccination. There is no universally accepted definition of anaphylaxis [20]. We chose a definition that has been used in previously published reports of the evaluation of anaphylactic reactions to vaccines [19].

3. Results

From July 1, 1990 through July 1, 2004, there were 180,895 adverse event reports submitted to VAERS. Additionally, the Centers for Disease Control and Prevention biologics surveillance data from 1991–2001 indicate a distribution of more than 276 million doses of HBV in the United States [18]. Among VAERS reports, we identified 107 reports that mentioned a history of allergy to yeast that was present prior to vaccination and occurrence of adverse symptoms. Eighty-two of these 107 reports involved vaccinees who received HBV (alone or in combination with other vaccines), while the other 25 reports involved recipients of vaccines other than HBV. Eleven of the 82 reports involving HBV recipients described probable or possible anaphylaxis; 10 cases occurred after HBV administered alone and one case after HBV along with measles–mumps–rubella vaccine. Four of the 25 reports involving recipients of vaccines other than HBV described probable or possible anaphylaxis; two cases after influenza, one case after typhoid fever and tetanus–diphtheria, and one case after varicella. Thus, a total of 15 of the 107 reports that mentioned a history of allergy to yeast describe probable or possible anaphylaxis (11 HBV + 4 other vaccines). The other 92 reports described symptoms such as injection site reactions, pain, headache, fever, chills or fatigue. Details on the 15 potential anaphylaxis cases among vaccinees reportedly allergic to yeast are presented in Table 1. The majority of vaccinees in this case series were females

Table 1
Cases of probable and possible anaphylaxis after vaccination in yeast sensitive individuals, VAERS, 1990–2004

No.	Case	Vaccine	Dose	Age (years)	Sex	Time of onset after vaccination	Symptoms
1	prob	HBV	2	35	f	1–2 h	Angioedema, arthralgia, chest pain, hoarseness, tachycardia, mottling of skin, nausea, rash, tongue swelling, urticaria, hives, edema of face
2	poss	HBV	1	48	f	5 h	Asthma-like reaction, vomiting, nausea, shortness of breath, sweating, dizziness, blurred vision, increased blood pressure
3	poss	HBV	2	Unknown	f	2 h	Urticaria
4	prob	HBV	1	Unknown	f	45 min	Difficulty breathing, swelling and hives of the upper and lower lips
5	poss	HBV	1	50	f	1 h	Flushed, chilled, experienced “a strange sensation coming up her throat through her chest”, and had grey colored streaks around nose and mouth; no problems on receipt of 2nd dose
6	poss	HBV	2	20	m	1 h	Slight swelling of both hands and severe itching of the backs of his hands
7	prob	HBV	ns	28	f	2–3 h	Rash all over body, angioedema, vomiting, diarrhea, severe chest pain, irregular heartbeat, joint pain
8	prob	HBV	3	12	m	30 min	Nausea, vomiting, severe headache, photophobia, urticarial rash on face
9	poss	HBV	2	Unknown	f	Immediately	Hives, high fever, rash
10	poss	HBV	1	10	f	15 min	Shortness of breath 15 mins post injection, soreness in joints
11	poss	HBV MMR	1	13	m	i	Shortness of breath; hives appeared six hours later
12	poss	TYP+Td	ns	37	m	5 h	Angioedema of face and lips, rash or hives, “allergic reaction”
13	poss	Flu	ns	64	f	15–45 min	Itchy watery eyes, oral edema; inj site skin reaction 24 h later
14	poss	Flu	ns	29	f	20 min	Difficulty breathing, tachycardia, numbness
15	prob	Varicella	ns	35	f	1 h	Tachycardia, dyspnea, urticaria, pruritus, oropharyngeal edema, nasal congestion

prob: Probable anaphylaxis case; poss: possible anaphylaxis case; i: immediately; ns: not stated; HBV: hepatitis B vaccine; MMR: measles, mumps, and rubella vaccine, live; Flu: influenza vaccine, inactivated; Typ: typhoid vaccine; Td: tetanus, diphtheria vaccine, adsorbed; Var: varicella vaccine, live.

($n = 11$ or 73%), in accord with the VAERS dataset in which the majority of vaccinees with AE reported are women [18]. Ages ranged from 10 to 64 years. The onset of initial symptoms ranged from 15 min to 5 h after vaccination. Six cases prompted a doctor and/or emergency room visit. There were no deaths reported.

4. Discussion

Reviews of post-marketing experience with recombinant HBV have confirmed a favorable safety profile for these vaccines [21–23]. Cases and case-series of various severe adverse reactions occurring in temporal association with HBV have been described in the literature. Some of them, e.g. neurological and autoimmune conditions, have caused controversy; however, the consensus today is that even if some of

these reactions are causally related to HBV, the rate of these reactions is very small and does not outweigh the benefits of vaccination [2]. Severe anaphylactic reactions following vaccination, including with HBV, are also extremely rare. In a study using automated health records from four large health maintenance organizations in the US, Bohlke et al. have determined the risk of anaphylaxis following hepatitis B vaccinations in children and adolescents to be 1.1 per million doses [24,25].

Few attempts have been made to determine whether yeast proteins could have been a possible cause of hypersensitivity reactions following HBV. Brightman et al. described a 30-year-old woman who had developed injection site edema within several hours following vaccination with HBV (Engerix-B) [26]. The next day, the entire arm was swollen and she experienced paresthesia, chest tightness and epigastric pain. No other dermatological, respiratory or GI symp-

toms were noted. The patient was treated with chlorpheniramine and symptoms gradually subsided over the next 10 days. On the basis of a positive skin-prick test with baker's yeast and the clinical history, the authors presumed that the woman had an IgE-mediated reaction to traces of *S. cerevisiae* in the vaccine. Hudson et al. reported a 24-year-old woman with a history of recurrent idiopathic urticaria, and cold air, exercise and aspirin-induced asthma since childhood [27]. She was asymptomatic for several months prior to vaccination and developed acute urticaria within 30 min after receipt of the first dose of HBV (Engerix-B). The same patient developed throat tightness and acute urticaria 10 min after receiving the second dose of HBV (Hevac B). Subsequent immunoblot testing was negative for anti-yeast IgE and the authors state that they were "not able to implicate a specific inciting agent".

In this review of AE spontaneously reported to VAERS over a period of 14 years, we identified only 15 cases of potentially IgE-mediated anaphylactic reactions following vaccination of individuals with a reported history of yeast allergy. Of these, 11 received HBV that contain trace amounts of yeast proteins. It is possible that in some of these 11 cases, sensitivity to yeast played a role in the development of the vaccine adverse reaction. However, since no allergy testing was done in these subjects to confirm sensitivity to yeast, the role of other allergens in these vaccines cannot be ruled out. For example, latex from vaccine vial closures could theoretically contaminate the vaccines and cause an anaphylactic reaction. Immediate hypersensitivity reactions have been reported, although rarely, to VAERS following vaccination of latex sensitive individuals [28]. None of the vaccinees in this case series mentioned having allergy to latex prior to vaccination. One patient in this review (#11) also received MMR vaccine at the time of HBV administration. The MMR vaccine manufactured by Merck and Co. Inc., contains gelatin, and allergic reactions due to gelatin in vaccines have been described previously [19,29]. This could also possibly explain the reactions in patients #13, #14, and #15, since they also received vaccines that may contain gelatin. Evaluation of potentially allergic reactions to vaccines by an allergist should include skin testing with the whole vaccine and any potentially allergenic components [30]. Additional laboratory investigation of such reactions may include IgE immunoassays to demonstrate and characterize allergens.

The majority of allergic reactions in reportedly yeast-sensitive vaccinees in this case series (11 out of 15) followed the receipt of HBV. Such predominance could be explained by a reporting bias, e.g. vaccinees or vaccinators who believe themselves or their patients to have "allergy to yeast" or the "yeast hypersensitivity syndrome" might be more likely to report an allergic event following a vaccine "grown in yeast". The vaccine information statement (VIS) may contribute to the bias because it states that people who have had a severe allergic reaction to baker's yeast should not receive HBV [31].

VAERS data are subject to limitations common to all voluntary reporting systems. The extent of underreporting is unknown for most reported AE but reporting is generally higher for more serious adverse events such as anaphylaxis compared to minor AE [32]. There may also be a reporting bias leading to underreporting of "yeast allergy" as a pre-existing condition for reports describing AE to vaccines not listing yeast allergy as a contraindication. Another limitation of VAERS is frequent lack of details regarding the adverse event, pre-existing conditions, laboratory findings, recovery status, and other clinical information. It is possible that some of the patients described in this case-series were misclassified. However, this misclassification could occur in both directions.

In conclusion, the evidence from passive surveillance for vaccine safety, as well as from the medical literature, suggests that recombinant yeast derived HBV pose minimal risk of allergic reactions in yeast sensitive individuals. The small number of reports to VAERS may be partly due to health care professionals observing current contraindications by not vaccinating yeast sensitive individuals. Nevertheless, yeast associated anaphylaxis in sensitized patients appears to be a rare event. If potential recipients of the hepatitis B vaccine indicate that they are "allergic" or "hypersensitive" to yeast, they should be further queried about the nature of their reactions to yeast. Only for those who would rarely respond with a convincing history of a potentially mast cell-mediated reaction within minutes of inhalation or ingestion of yeast should the vaccine be withheld.

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