

## Sensitization to thimerosal (Merthiolate) is still present today

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The results on thimerosal (Merthiolate) hypersensitivity of a retrospective study, together with the relevant data on thimerosal hypersensitivity referred to in the literature up to 1993, are presented. Positive patch test reactions to thimerosal (0.1% pet.) were observed in 32 (1.3%) of 2461 adult patients with suspected contact allergy examined in the period 1987-1992. 20 (0.8%) patients had a solitary positive patch test to thimerosal. The observed incidence is low. Clinical symptoms related to thimerosal hypersensitivity were observed in only 3 patients. The collected results are discussed with emphasis on the clinical implications of sensitization to thimerosal. It appears that a positive patch test to thimerosal is frequently clinically irrelevant.

**Key words:** thimerosal; Merthiolate; CAS 54-64-8; preservatives; delayed-type hypersensitivity; epidemiology; clinical relevance; vaccinations. © Munksgaard, 1994.

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Thimerosal (Merthiolate) is a relatively non-toxic preservative that has been used for many decades, but it is also a hidden sensitizer. Like phenylmercuric salts, thimerosal is bacteriostatic against gram-positive and gram-negative bacteria and also active against fungi and yeasts by inhibiting sulfhydryl-containing enzymes (1-3). Thimerosal is mainly metabolized into inorganic mercury in the liver and kidneys and there is also some uptake in other organs including the skin (1, 4). Thimerosal at concentrations of 0.001 to 0.1% has numerous applications (Table 1a).

The objective of this study was to investigate the incidence and clinical relevance of thimerosal hypersensitivity in our department (I) and to review the relevant data on thimerosal hypersensitivity in the literature up to 1993 (II).

### RETROSPECTIVE STUDY OF THIMEROSAL HYPERSENSITIVITY 1987-1992

#### Materials and Methods

The European standard series and an additional series including thimerosal 0.1% in white petrolatum (pet.) were used for patch testing 2461 adult patients suspected of having contact allergy in the period 1987-1992. In 536 other patients, the ad-

ditional series was omitted because of lack of clinical indication. Plastic test chambers and test substances from van der Bend (Trolab), Brielle, The Netherlands, were used. Test procedures were performed according to the protocol described by Cronin (3). The available information on the patients with a positive patch test to thimerosal was retrospectively evaluated.

#### Results

32 (1.3%) out of the 2461 patients tested had a positive patch test to thimerosal (Table 2). Thimerosal was listed 19th of the 46 substances patch tested (Table 3). This group consisted of 19 women (mean age 37.3 years) and 13 men (mean age 39.5 years), with a range of 19-56 years for each sex. The highest number of positive reactors fell into the 4th and 5th decades of life, taking into account that in our study, the number involved of those in the 2nd decade was very limited. 12 patients with positive patch tests to thimerosal also reacted to other substances: nickel sulfate ( $n=5$ ), fragrance mix ( $n=4$ ), balsam of Peru ( $n=3$ ), ethylenediamine ( $n=3$ ), isoeugenol ( $n=2$ ) and 10 other different substances ( $n=10$ ).

24 patients with positive patch tests to thimerosal had an eczematous reaction suspected of being



Table 1

(a) Applications of thimerosal (Merthiolate) (at concentration 0.001 to 0.1%) as cited in the literature reviewed

vaccines: diphtheria, tetanus, pertussis, mumps, hepatitis B, influenza, tick-born encephalitis, staphylococcus, salmonella and meningococcus A  
several immunoglobulins  
extracts and diluents for: routine intracutaneous allergy tests; intracutaneous testing for candida, coccidioidin, histoplasmin, mumps and (old) tuberculin; hyposensitization therapy  
blood and plasma products  
topical medication for: the eyes, ENT area and skin (including in some corticosteroids, phenylbutazone ointment, amphotericin cream and elase)  
storing and cleaning solutions for soft contact lenses  
disinfectant for skin and mucous membranes (tincture and solution)  
cosmetic creams and lotions  
toothpastes and mouthwashes  
pesticides

(b) Applications of thimerosal (Merthiolate) as mentioned in the Dutch drug information system of 1993

tetanus vaccine, one of the 3 influenza vaccines, hepatitis B and staphylococcus vaccines  
some immunoglobulins  
many topical treatments for the eyes and ears  
Elase® (fibrinolysin and desoxyribonuclease) oleagel/powder  
ethacrynic acid powder for injection  
Varidase® (streptokinase and streptodornase) powder

Table 2. Patients with positive patch tests to thimerosal ( $n=32$ )\* and the separate subgroup with solitary positive patch tests to thimerosal ( $n=20$ )\*\*

Year	No. patients*	(%)	No patients**	(%)
1987	6/394	1.5	4	1.0
1988	1/421	0.2	1	0.2
1989	4/436	0.9	3	0.7
1990	2/408	0.5	0	0.0
1991	7/393	1.8	4	1.0
1992	12/409	2.9	8	2.0
1987-1992	32/2461	1.3	20/2461	0.8

contact allergy, while another 6 had urticarial or angio-edematous reactions. 3 patients who used contact lenses had (peri-)ocular symptoms.

In a subgroup of 20 patients (0.8%), an isolated positive patch test to thimerosal was observed. This subgroup consisted of 9 women aged 19-47 years (mean age 36.2 years) and 11 men aged 23-56 years (mean age 40.8 years). In 10 patients with a solitary positive patch test to thimerosal, eczema on the hands was observed. In 6 of these cases, eczema was even restricted to the hands. (Peri-)ocular symptoms were observed in 4 cases. 1 patient suffered from a chronic external otitis. In 9 cases, skin reactions were observed elsewhere, whereas there was no skin reaction in 1 other case. The duration of symptoms varied considerably between patients.

Table 3. The 20 highest scores of positive patch tests to test substances of the \* European standard series ( $n=2997$ ) and \*\* additional series ( $n=2461$ )

	No. of patients	Mean %
nickel sulfate*	537	17.9
fragrance mix*	276	12.5
cobalt chloride*	156	5.2
wood tar**	112	4.6
para-aminoazobenzene**	100	4.1
balsam of Peru*	111	3.7
isoeugenol**	83	3.4
colophony*	95	3.2
formaldehyde*	91	3.0
Kathon CG*	91	3.0
potassium dichromate*	86	2.9
thiuram mix*	81	2.7
oak moss**	60	2.4
para-phenylenediamine*	60	2.0
cinnamic aldehyde**	45	1.8
para-tertiary-butylphenol-formaldehyde resin*	55	1.8
epoxy resin*	48	1.6
carba mix**	37	1.5
thimerosal**	32	1.3
neomycin*	39	1.3

Some had symptoms varying from days to weeks, others from months to even years. A few patients had exacerbation or progression of symptoms which had persisted for a longer period.

3 patients were also tested for mercury, ammoniated mercury and phenylmercuric nitrate, resulting in one irritant reaction to the latter. The overall results with these mercury substances tested in the period 1987-1992, with the restriction that these were only tested if indicated, revealed 4 positive cases, who all had a negative patch test to thimerosal.

A relationship between thimerosal hypersensitivity and the presenting symptoms was very likely in 3 patients, based on the clinical outcome (Table 4).

## LITERATURE REVIEW

### Delayed-type Hypersensitivity and Cross-sensitization

Organic mercury, in particular, can be responsible for delayed-type hypersensitivity, but an important rôle for the other constituent of thimerosal, thiosalicylate, is uncertain (Fig. 1) (2, 4-12). The ethyl mercury radical appears to be the allergic determinant of the thimerosal molecule (4, 12). Cross-sensitization to a few organic mercurials, and even to a few inorganic and metallic mercurials, has been observed (4, 6, 13); however, these observations have not been confirmed in many other reports (4, 5, 8-10). It has to be stressed that hypersensitivity to thimerosal does not necessarily imply true mercury allergy (4). 3 groups of patients are



Table 4. Patients with a solitary positive patch test to thimerosal and clinical symptoms very likely to be related to thimerosal hypersensitivity

Patient no.	Age (years)/Sex	Patch test reaction to thimerosal	Clinical symptoms	Product responsible	Clinical recovery after avoiding contact
1	37/F	+++	relapsing conjunctivitis	eye medication	yes
2	47/F	++	dyshidrotic hand eczema (hand-eye drops contact)	eye medication	yes
3	35/M	++	dyshidrotic hand eczema	pesticides	yes

to be considered: (a) positive to thimerosal, but negative to mercurials and thiosalicylic acid; (b) positive to thimerosal and some other mercurials, but negative to thiosalicylic acid; (c) positive to thimerosal and thiosalicylic acid, but negative to other mercurials (2). Products containing thimerosal may also cause photohypersensitivity to piroxicam, a non-steroidal antiinflammatory drug, probably as a result of cross-reactivity between thiosalicylate and a degraded photoproduct of piroxicam (14, 15).

In patch test procedures, thimerosal has been tested in petrolatum (pet.) as well as in aqueous and alcoholic solutions. Evaporation from the latter 2 vehicles may result in concentrations that cause irritation (16). Although the patch test concentration of 0.1% thimerosal (pet.) is generally accepted, in many cases, the positive patch test reaction can be interpreted as irritant (5, 11, 12). At a concentration of 0.05% (pet.), Aberer (9) observed 65 strongly positive and 27 weak positive patch test reactions in 100 patients with established (0.1% pet.) thimerosal hypersensitivity. Lisi et al. (11) compared 0.05% with 0.01% (pet.) in patch testing and 0.01% (0.025 ml) in intradermal testing, including the strength of the reactions related to time, in order to determine the minimum eliciting patch test concentration in 40 patients with previously demonstrated thimerosal hypersensitivity (0.1% pet.). A positive patch test to 0.05% and 0.01% was observed in 5 and to 0.05% alone in 15 patients, while 24 patients, particularly among the

latter 2 subgroups, had a positive intradermal test reaction. Here, the optimal test concentration for patch testing appeared to be 0.05% (pet.). In contrast, others suggested that a negative patch test does not exclude possible thimerosal hypersensitivity and that intradermal testing may be more sensitive (17).

### Epidemiology

The availability and usage of thimerosal-containing products differ between various countries. Data on sensitization to thimerosal in the general population, however, are not available. The frequencies reported, mostly concerning selected groups, vary from 1 to 18%. All ages may be involved, but there is a predominance in young adults, especially those in the 3rd decade of life (4, 5, 9–11, 13, 18–22). Möller (4) observed a mean frequency of 3.7% in a Department of Dermatology in Sweden during a 5-year period (1970–1974).

The frequency in children may be 2–4% (18, 23). A frequency of 10% has also been observed, but the group was much smaller ( $n=74$ ) (4). In Portugal, sensitization to thimerosal was observed as the 2nd highest ( $n=13$ , 2.3%) after neomycin ( $n=16$ , 2.9%) in 562 unselected schoolchildren. Results from questionnaires indicated papular urticaria in 19.8%, atopy-related stigma in 18.1%, pityriasis alba in 18.1%, asthma in 9.4% and allergic rhinitis in 4.9%, of the children, but there was no correlation between any of these conditions and the incidence of positive patch tests (23).

Occasionally, sensitization peaks of up to 26% have been observed in military recruits, medical students and student nurses without skin manifestations (4, 5). In Italy, 28 (4.7%) individuals sensitized to thimerosal were observed among 593 military recruits without any skin or eye disorder (24). Sensitization to thimerosal appears to occur more frequently in individuals without skin lesions than in patients suspected of having allergic contact dermatitis (5, 20, 21, 24). The prevalence of allergy to thimerosal in contact lens wearers is not known exactly, but the frequencies of ocular adverse reactions to thimerosal alone or in combination with

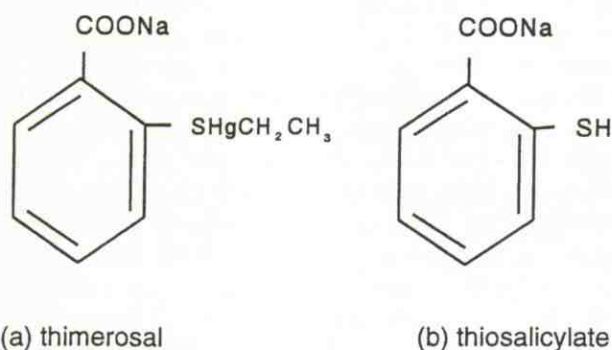


Fig. 1. Chemical structures.



other preservatives range from 2 to 45% (21, 25). In this respect, prior patch testing had no clinically predictive value (26).

### Clinical Manifestations in Thimerosal Hypersensitivity

Clinically, proven thimerosal hypersensitivity can be related to contact dermatitis, particularly as pompholyx on the hands, and sometimes also to contact urticaria (4). In soft contact lens wearers, any combination of perilimbal conjunctival hyperemia, corneal infiltrates, punctate epithelial keratopathy and corneal pseudodendrites may develop due to thimerosal used as a preservative in cleaning, soaking, rinsing and comfort solutions. The symptoms may be more advanced in one eye and eczema on the eyelids is often absent. Consequently, the diagnosis of allergic contact conjunctivitis may be missed (17, 21, 27-31). Fräki et al. (32) observed thimerosal to be one of the commonest sensitizers, besides antibiotic compounds, in a group of 142 patients with chronic external otitis. 8 (5.7%) of the 57 patients with 1 or more positive patch tests reacted to thimerosal. Preservatives such as thimerosal, especially if used concomitantly with alcohol or detergent, are able to cause sensorineural deafness (33).

Local reactions due to vaccination may occur, but as investigated in inoculation with tetanus vaccine, these were not simply caused by thimerosal hypersensitivity (34). Systemic allergic reactions seem to be very rare, but may be underdiagnosed. Acute disseminated urticaria or exanthema, eczema and an associated increase in body temperature have been reported (4, 20, 35). However, a positive patch test to thimerosal alone does not definitively prove a causative relation. Acute laryngeal obstruction developed in a 58-year-old man after repeated use of a thimerosal (0.033%) containing spray for a sore throat. Subsequently, he had a strong positive patch test reaction to thimerosal (36).

Iatrogenic sensitization by thimerosal-containing vaccines and its clinical relevance are the major bone of contention in the literature. In general, the intra- and epicutaneous routes of administration are at a much higher risk for sensitizing, as compared with the subcutaneous and intramuscular routes (34). It has been proposed that thimerosal-contaminated outer surfaces of needles may even increase the risk of sensitization (20).

The rôle of thimerosal (0.01%) in tetanus vaccine was investigated in cutaneous reactions in 876 military recruits. Local reactions occurred in 2-3% of the group and were not necessarily caused by thimerosal hypersensitivity. Of interest is that the

number of local reactions did not increase in 2 separate subgroups with previously positive tests to thimerosal, i.e., on patch testing ( $n=33$ ) and intracutaneous testing ( $n=16$ ), respectively. In addition, in a subgroup ( $n=15$ ) with negative patch tests, compared with a subgroup ( $n=26$ ) with positive patch tests, the incidence of positive patch tests to thimerosal did not increase after vaccination (34). Similar conclusions were drawn by means of questionnaires to 50 (1%) patients with positive patch tests to thimerosal at a contact dermatitis unit in the UK during a 5-year period and matching them to 50 controls. No difference in reactions to the usual vaccinations was reported between the 31 respondents of each group (13). Aberer (9) observed a correlation between frequent vaccinations against tick-born encephalitis (TBE) with vaccine containing 0.05 mg thimerosal and a positive patch test to thimerosal (0.1% pet.) in 50 (77%) of 65 thimerosal-hypersensitive patients with clinical eczema. This vaccine was administered intramuscularly, which should virtually eliminate the risk of sensitization (34). Only 2 patients who had received the vaccine subcutaneously developed untoward reactions at the injection site. Of interest is that the growing number of individuals in Austria immunized against TBE since 1974 parallels an increase in the number of individuals sensitized to thimerosal. Wong et al. (37) did not observe any local reaction after vaccination with thimerosal-containing hepatitis B vaccine during a campaign in Singapore. Moreover, a positive patch test to thimerosal was observed in none of 50 patients receiving hyposensitization therapy with thimerosal-containing extracts for more than 6 months (38). Förström et al. (20) observed no reactions after subcutaneous injection with 0.1 ml of a 0.01% thimerosal solution in a subgroup of 45 eczema patients with positive patch tests to thimerosal. However, after subcutaneous exposure to 0.5 ml (corresponding the amount and concentration of thimerosal used in tetanus vaccine), an adverse reaction was noted in 9 (20%) patients. 5 patients had a local reaction at the site of the injection, 3 patients had an eczematous reaction on the upper extremities and 1 patient showed generalized eczema with fever.

Attention has been focussed on the possible rôle of aluminium, contained in some of the vaccines (e.g., DPTP and DTP), in local and even systemic reactions. In view of the common exposure to aluminium, there are only rare reports of contact allergy to this metal. Cox et al. (39) reported 3 children with persistent symptoms at the injection site, who had a positive patch test to aluminium and 1 of them also to thimerosal. Therefore, they advocated that an aluminium salt and that, if alu-



minium test chambers are used, a single blank chamber should be added to the standard series. It should also be realized that mercury in thimerosal is able to catalyze oxidation of aluminium material, resulting in the production of local heat (2).

### Discussion

The mean incidence of sensitization to thimerosal of 1.3% during a 6-year period (1987–1992) is low as compared with figures reported previously (4, 5, 9–11, 13, 19–22, 37). Young individuals have the obligate opportunity for iatrogenic sensitization via the usual inoculations (4, 5). This means, in principle, that there should not exist a significant difference between the sexes (11, 37). In our population, we observed a predominance of females like a few others (9, 13), whereas Möller (4) observed a slight predominance of males.

In the total group of patients with a positive patch test, the clinical meaning was difficult to establish. Information about previous inoculations was not available at all. Although eye and ear medications, nasal sprays, other topical therapeutical products and cosmetics had been used widely, only 2 cases of eczema of the hands and 1 of ocular symptoms could be related to thimerosal hypersensitivity. Our data firmly support the view that thimerosal hypersensitivity should be considered as just an accidental finding in the majority of cases in routine patch testing. The patients concerned have been sensitized in the past with unidentified agents. Recurrent contact with the allergen does not necessarily evoke clinical symptoms because of the very low concentrations (4, 5, 7, 9, 10, 19, 20, 34, 37, 38).

Considering contact lens wearers with eye symptoms, one should also be aware of a possible interaction between thimerosal and the contact lens material (17, 30, 40).

Despite experiences and reports in the past, including the fact that thimerosal is only weakly bacteriostatic and mildly fungistatic, it is still used today. The lack of an adequate alternative is evidently the most important reason. Reisman (38) advocated the use of an alternative, e.g., phenol. Meanwhile, new preservatives might have become available, but have not been introduced. The Dutch drug information system of 1993 reveals that thimerosal is present in some pharmaceuticals (Table 1b).

The alternative for soft contact lens care is the disposable use of sterile single unit-dose preservative-free saline with thermal disinfection (28–30) or the use of a special preservative-free care system containing only a low concentration (0.6%) of hydrogen peroxide (Titmus H202® Ciba Vision).

In the European Community, mercury and its

compounds (proposed zero tolerance level of 1 mg/kg) are prohibited in cosmetics except for phenylmercuric salts and thimerosal, both organic mercury, in creams, shampoos, eye cosmetics and solutions for contact lenses. In The Netherlands, as distinct from elsewhere, contact lenses are considered as cosmetics. Illegal use of mercury and its compounds has been found in usually very low contents in decorative cosmetics, as mercuric iodine in disinfectant detergents and ammoniated mercury in skin bleaching products (source: Keuringsdienst van Waren (Food Administration), District Enschede, The Netherlands).

Based on the data reviewed and our own data, some conclusions on thimerosal hypersensitivity can be drawn.

Patch testing with thimerosal should probably be performed with a concentration lower than 0.1% pet., but a more extended comparative (preferably double-blind) study is recommended before a definite concentration can be introduced. In view of clinical symptoms after the use of an aluminium-containing vaccine, the addition of a patch test with an aluminium salt is indicated. A positive patch test to thimerosal should frequently be considered as an accidental finding with no clinical relevance. As a consequence, inoculation with a thimerosal-containing vaccine in individuals who have a previously positive patch test to thimerosal should not be considered absolutely contra-indicated, particularly when the subcutaneous or intramuscular route is used.

Special attention is indicated in the case of (peri-)ocular symptoms in relation to the use of contact lenses, as well as to any topical treatment of the eyes, and in the case of prolonged external otitis during any topical treatment of the ears. Alternatives for soft lens care are available.

Although it looks worthwhile to reduce the use of thimerosal as much as possible, it appears not to be necessary to eliminate it completely. More information on the development of incidence and prevalence of thimerosal hypersensitivity among the general population and contact lens wearers should be obtained. An adequate list (data system) should, besides drugs, also provide information on over-the-counter and other products containing mercury and its compounds. In The Netherlands, the number of thimerosal-containing vaccines is limited and thereby the risk of iatrogenic sensitization in youth. Nevertheless, sensitization to thimerosal is still present today.

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