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THIOMERSAL-CONTAINING VACCINES – A REVIEW OF THE CURRENT STATE OF KNOWLEDGE

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ABSTRACT

Thiomersal is an organomercury compound known for its antiseptic and antifungal properties and used as an antibacterial agent in pharmaceutical products, including vaccines and other injectable biological products.

In recent years, concerns about the possible link between immunization with thiomersal-containing vaccines and autism development have grown. Many case-control and cohort studies have been conducted on a number of populations, and none of them have confirmed the hypothetical relation between thiomersal and increased risk of autism spectrum disorders (ASDs) development. It is also confirmed by the fact, that since 1999, number of thiomersal-containing vaccines used worldwide is decreasing year by year, while the prevalence of ASDs cases is rising.

There are no contraindications to the use of vaccines with thiomersal in infants, children and non-pregnant women. The risk of serious complications associated with the development of diseases in unvaccinated individuals far outweighs the potential risk of adverse consequences associated with immunization with thiomersal-containing vaccines.

Key words*: inactivated vaccines, thiomersal, mercury, autism*

INTRODUCTION

Thiomersal, commonly known also as thimerosal or Merthiolate (Eli Lilly and Company trade mark name) is an organomercury compound providing antiseptic and antifungal properties. Widely proven antimicrobial activity of thiomersal resulted in its marketing in a range of pharmaceutical products, including vaccines and other injectable biological products since 1930s (1). This pharmaceutical compound containing 49.55% of mercury has been proven in effective clearing a broad spectrum of pathogens in pharmaceutical products in concentrations ranging from 0,001% to 0,01%. If presents in vaccines recommended for children, its concentration varies from 0,005% to 0,01% (12,5 μg Hg to 25 μg Hg per 0,5 ml dose) (2). Thiomersal and other organo-mercurial compounds are not used in live vaccines due to their negative interactions on the active substance. However in inactivated vaccines they might be added during some of production steps, such as harvest or formulation of final bulk, or their residual content in the final formulation comes from preservation of some production stages eg. inactivation of some antigens (i.e. whole cell or acellular pertussis vaccines) (1, 3).

In late-1990s the U.S. Food and Drug Administration after deep research issued a statement, pointing out that infants during the first six months of life immunized according to the U.S. recommended schedule might receive, depending on the vaccine formulation used and the infant weight, such amounts of ethylmercury that exceed limits approved by Environmental Protection Agency for exposure to methylmercury (0,0001 mg/kg-day) (4). As a precautionary recommendation, the American Academy of Pediatric and the Public Health Service issued also a joint statement in 1999 calling for removal of mercury-containing preservatives from all vaccines administered to infants and children as soon as possible and advised to conduct the study aimed to investigate the potential risks associated with ethylmercury exposure from thiomersal-containing vaccines (5). These recommendations have raised however general concerns, even if the potential harmful effects of vaccines with thiomersal have not been confirmed (1, 6).

TOXICITY OF MERCURY

The toxicity of mercury is complex and depends on the form, route of entry, dosage and age of the person at exposure. Mercury might occur in three forms: the metallic element, inorganic salts and organic compounds (i.e. methylmercury, ethylmercury and phenylmercury). According to the chemical nomenclature given by International Union of Pure and Applied Chemistry (IUPAC) thiomersal is an ethyl(2-mercaptobenzoato-(2-)-*O*,*S*) mercurate(1-) sodium metabolized to ethyl form of mercury and thiosalicylate. The association between possibility of causing autism by thiomersal-containing vaccines has been raised mainly by public media in recent years. It has been originated from biological plausibility of ethylmercury with methylmercury, where initial data published on methylmercury showed some potential risk of toxic effects resulting from its adsorption and accumulation in brain (7). This controversial data raised further suspicions of induction of adverse effect risk in children who were exposed to methylmercury at levels previously considered as safe (7). It should be remembered that in 1999 the toxicological profile of ethylmercury was unknown and expected to resemble at observed for methylmercury (8). Since then a lot of scientific evidence has been gathered proving that ethylmercury (metabolite of thiomersal) has not been associated with such consequences as caused by methylmercury due to its shorter half-life in the human body and differences in pharmacodynamic and pharmacokinetic properties (9, 10, 11). The main difference between ethyl- and methylmercury relates to active excretion of ethylmercury into the gut (8). The thresholds for neurologic effects due to methylmercury and ethylmercury were estimated to be approx. 200 mcg/L and from 1000 to 2000 mcg/L respectively (12). Research aimed to measure concentrations of mercury in blood, urine and stool of infants aged 2-6 months who received vaccines containing thiomersal clearly indicated that administration of thiomersal-containing vaccines does not raise blood concentrations of mercury above widely accepted safe values. Elimination of ethylmercury from blood via the stool was found quite effective, with estimated blood half-life ranging from 4 to 10 days (13). Nevertheless, lack of the data on the possibilities of blood-brain barrier crossing by ethylmercury raise public doubt (8).

There are a few reports available on the neuro- and nephro-toxicity caused by accidental poisoning of ethylmercury, however induced with doses of several times exceeding the lethal dose in rats (LD_{50}: 60 mg/kg) – thus significantly and enormously higher than those presented in vaccines in use (14).

Up to now, there is no proven evidence that thiomersal may cause any potential harm except an allergic responses e.g. delayed-type local hypersensitivity reactions such as redness and swelling at the injection site, mainly regarded as mild and lasting only for a few days. Sensitization to this compound was estimated in an about 1-5% of vaccinated adolescents and adults (1, 2).

In the scope of the current knowledge and available data published, general attention should be rather paid into its positive effects i.e. reducing the risk of contamination of opened multi-dose vaccines rather than into unproven negative effects of thiomersal (8).

SAFETY OF THIOMERSAL-CONTAINING VACCINES

Over the past several years much concern has been raised regarding the potential links of childhood vaccination with the development of autism or autism spectrum disorders (ASD) (6). Autism classified as a pervasive developmental disorder (PDD) is characterized by impaired social interaction and verbal/non-verbal communication (15). Although a causation of autism is still unknown, its genetics and environmental factors might hypothetically be involved (9, 11). The available data suggesting, that genetic variation in neuronal circuitry might affect synaptic development, further imply that pathogenesis of autism has rather nothing in common with exaggerated or inappropriate immune response to vaccination (15).

Thiomersal containing vaccines, especially diphtheria, tetanus and whole-cell pertussis vaccines, frequently blamed as one of possible environmental source of mercury, are constantly receiving widespread critical media interest (6, 9, 11). It should be stressed out, that theoretical association between vaccination and autism is getting far form the truth consequently, as the number of thiomersal-containing vaccines used worldwide is decreasing year by year, while the prevalence of ASDs cases is rising (15). Such observation was found in research conducted in Denmark where number of autism cases did not decrease even after the discontinuation of thiomersal use in vaccines administered to children between mid-1980s and late-1990s (16).

In the meantime, several case-control and cohort studies have been conducted on a very numerous populations and none of them supported a causal relationship between the use of thiomersal-containing vaccines in children and development of autistic spectrum disorders or found higher risk of autism (10, 16 - 21). Moreover, according to the available data, a vaccine dose-response association with autism was also not confirmed. One of the US case-control study, using immunization registries, medical charts and parents interviews of 246 children with spectrum disorders of autism, compared with 752 controls organized in 3 medical centers pub-

lished in 2010 did not find an increased risk of ASDs in children vaccinated with thiomersal-containing vaccines (19). Other study performed in a large population of children delivered in 1991-1992 in United Kingdom also did not revealed any link between thiomersal and neurological or psychological disorders and finally proved no autism risk in children younger than 6 months vaccinated with thiomersal-containing vaccines (17). From the other side, it was found that the risk associated with the use of contaminated multidose vials in the absence of thiomersal far outweigh any other potential risks. Subsequently, dozens of studies published from countries around the world, did not confirm the possibility of any linkage between vaccines containing thiomersal and neurodevelopmental disorders (22). Recently published meta-analysis of case-control and cohort studies on potential autism rates and childhood vaccination from various countries, showed also no evidence of any risk of development of autism or autistic spectrum disorders after administration of vaccines containing thiomersal (6).

Despite the above arguments, media discussion, doubting thiomersal safety and supporting again a link between vaccinations and autism, began to appear in March 2014. This attention was resulted from looking up upon the results on the negative effects of thiomersal-containing vaccines on children, conducted in the nineties by the Center for Disease Control and Prevention (CDC) epidemiologist Dr. Thomas Verstraeten. These results presented on the conference of Epidemic Intelligence Service (EIS), when reassessed once again in detail, were found lacking many interfering factors (bias), influencing the final analysis result. Many had forgotten that in 2003 improved and in-depth analysis of this controversial study confirming no relationship between thiomersal in vaccines and the incidence of autism in children was finally published in "Pediatrics" (21). Moreover, the revaluation of T. Verstraeten study by an independent commission from Emory University finally resulted in official statement of Dr Verstraeten, rejecting his initial thesis as not supported (21, 23, 24).

All together, scientific data coming from analyses performed by different study groups were expressed in a position paper of the expert panel of Institute of Medicine of The National Academies (23). In Immunization Safety Review: Vaccines and Autism, the above mentioned Committee concluded: "The committee also concludes that the body of epidemiological evidence favors rejection of a causal relationship between thiomersal-containing vaccines and autism. The committee further finds that potential biological mechanisms for vaccine-induced autism that have been generated to date are theoretical only. The committee does not recommend a policy review of the current schedule and recommendations for the administration of either the MMR vaccine or thiomersal-containing vaccines." (25).

The position papers on safety of vaccines containing thiomersal were also sequentially released by other international agencies and competent authorities including:

- A statement of the European Agency for the Evaluation of Medicinal Products (now European Medicines Agency) published on 24 March 2004 on thiomersal in vaccines for human use based on latest evidence relating to the safety of thiomersal-containing vaccines. The Committee for Proprietary Medicinal Products (CPMP) concluded that the latest epidemiological studies show no negative association between the vaccination with thiomersal-containing vaccines and autism. Possibility of development of specific neurodevelopmental disorders and the benefits of vaccination to the general population, including infants, far outweigh the risk, if any, of exposure to vaccines with thiomersal. Additionally CPMP stated that in order to reduce exposure to mercury, the development of vaccines containing the lowest possible level or no thiomersal or other mercury containing preservatives should continue to be promoted (26).
- The statement of the Global Advisory Committee on Vaccine Safety (GACVS) – an expert clinical and scientific advisory body established by WHO in 2012 proclaimed, that based on current evidence and published studies it is confirmed that half-life of ethyl mercury in blood is between 3 and 7 days. Thus levels on ethyl mercury attained in the blood and brain from cumulative doses of vaccines do not reach toxic levels and available evidence strongly supports the safety of the use of thiomersal as a preservative for vaccines administered to infants and children (27).

In order to determine the rules for identifying thiomersal content in medicinal products, in January 2007, the Committee for Medicinal Products for Human Use (CHMP) presented the necessity of updating of warning statement regarding the Summary of Product Characteristic (SPC) and Package Leaflet (PL), with regard to possible sensitization for medicinal products containing thiomersal. For vaccines in which thiomersal was used as a preservative, SPC was claimed to include the following information: In Section 4.8. Undesirable Effects: "This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitization reactions may occur (see Section 4.3.)." and in Section 4.3. Contraindications: "Hypersensitivity to any compound of the medicinal product". In PL the CHMP recommendations were expressed by following statements: "This medicinal product contains thiomersal as a preservative and

it is possible that <you/your child> may experience an allergic reaction." and "Tell your doctor if <you/your child> have/has any known allergies.".

For vaccines in which thiomersal was used during the manufacturing process, resulting in levels of thiomersal in the vaccine content below 40 nanograms per dose or undetectable levels, sensitization reactions to this compound are not expected to occur and no statements are recommended for SPC and PL. If residue of thiomersal used in the manufacturing process is greater than or equal to 40 nanograms per dose, the following information should be included in SPC: in Section 4.4 Special warnings and special precautions for use: "Thiomersal (an organomercuric compound) has been used in the manufacturing process of this medicinal product and residues of it are present in the final product. Therefore, sensitization reactions may occur." and in PL: "Thiomersal is present (in trace amounts) in this product, and it is possible that <you/your child> may experience an allergic reaction." and "Tell your doctor if <you/your child> have/has any known allergies." (28). All vaccines with thiomersal available on Polish market should be identified and described in accordance with the above guidelines.

THIOMERSAL-CONTAINING VACCINES AVAILABLE IN POLAND

Currently in Poland whole-cell vaccine against pertussis, diphtheria and tetanus (DTP; IBSiS BIOMED S.A.) is the only thiomersal-containing vaccines used in children during the first two years of life.

Derivatives of DTwP such as DT, D, T – containing thiomersal are used in children in special circumstances such as contraindications to vaccination against pertussis (see tab. I).

In Poland, according the annually updated Immunization Schedule, vaccination against diphtheria, tetanus and pertussis is mandatory. The compulsory vaccination with DTP vaccines consist of four doses at the second, 3-4, and 5-6 months of age as a primary vaccination and then at the 16-18 months of age fourth dose is administered as a booster (29). Because of the intervals between successive doses and rapid removal of ethylmercury from the organism, even four doses of DTwP vaccine during two first years of life, cause no possibility of its negative cumulative effect.

Clodivac and Tetana vaccines, recommended for teenagers and adults contain thiomersal only in trace amounts, as the residue of the manufacturing process (see tab. II).

Thiomersal is not present in vaccines against hepatitis B and influenza (single doses – prefilled syringe). Influenza vaccines may contain thiomersal as a preservative only in multidose presentations, which are currently not released on Polish market.

CONCLUSIONS

There are no contraindications to the use of thiomersal-containing vaccines in infants, children and non-pregnant adults. Any reliably and independently performed epidemiological studies, generally proved the lack of the link between vaccine-originated exposure to thiomersal and development of autism spectrum disorders. Before drawing the conclusion or interpretation of any of the study published, it should be remembered that only widely accepted methodology and pre-established criteria for reliable and valid epidemiological studies should be taken into account.

Growing number of autism cases seen in recent decades might be associated with increased attention

Table I. Vaccines containing thiomersal as a preservative registered in Poland

Trade name		Manufacturer	Thiomersal content per dose	Mercury content per dose
DTP	Diphtheria, tetanus and pertussis (whole cell) vaccine (adsorbed)	IBSiS BIOMED S.A. (Cracow)	max. 50 µg	max. 25 µg
DT	Diphtheria and tetanus vaccine (adsorbed)	IBSiS BIOMED S.A. (Cracow)	max. 50 µg	max. 25 µg
D	Diphtheria vaccine (adsorbed)	IBSiS BIOMED S.A. (Cracow)	max. 50 µg	max. 25 µg
d	Diphtheria vaccine (adsorbed, reduced antigen content)	IBSiS BIOMED S.A. (Cracow)	max. 50 µg	max. 25 µg
T	Tetanus vaccine	WSiS BIOMED Sp. z o. o. (Warsaw)	max. 50 µg	max. 25 µg

Table II. Vaccines registered in Poland in which thiomersal is used during the manufacturing process

Trade name:		Manufacturer:	Thiomersal content per dose:	Mercury content per dose:
Clodivac	Diphtheria and tetanus vaccine (adsorbed, reduced antigen content)	IBSiS BIOMED S.A. (Cracow)	max. 1 µg	max. 0,5 µg
Tetana	Tetanus vaccine (adsorbed)	IBSiS BIOMED S.A. (Cracow)	max. 1 µg	max. 0,5 µg

paid to the symptoms of autism and changes in autism disorders diagnostic criteria. Nevertheless, all available and reliable results shows independently that autism has nothing in common with thiomersal-contained vaccines, which quantity on the market since 1999 critically decreased.

Routine vaccinations provide protection against many serious diseases. Childhood vaccination should be performed in accordance with the Annual Immunization Schedule as early as possible to ensure the maximum protection.

It is extremely important to speak to the public about the facts, not about the myths of thiomersal-containing vaccines safety, using the results of reliable studies, in order to sustain the population confidence in the efficacy and safety of immunization programs. Risk associated with deaths and serious complications associated with the development of diseases in unvaccinated individuals far outweighs the potential risk of adverse consequences associated with immunization with thiomersal-containing vaccines.

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