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\((2\text{-mercaptobenzoato-(2-)O,S})\) 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 allergenic 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 vac-
cines (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 associ-
ated 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 pos-
sibility 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 autis-
tic 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 nine-
ties by the Center for Disease Control and Prevention
(CDC) epidemiologist Dr. Thomas Verstraeten. These
results presented on the conference of Epidemic Intel-
ligence 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 reevaluation 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 Immuni-
zation Safety Review: Vaccines and Autism, the above
mentioned Committee concluded: “The committee
also concludes that the body of epidemiological evi-
dence favors rejection of a causal relationship between
thiomersal-containing vaccines and autism. The com-
mittee 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 con-
taining 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 associa-
tion between the vaccination with thiomersal-con-
taining vaccines and autism. Possibility of develop-
ment 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 Hu-
man 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. Contra-
indications: “Hypersensitivity to any compound of the
medicinal product”. In PL the CHMP recommendations
were expressed by following statements: “This medi-
cinal 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 to 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>
<thead>
<tr>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Thiomersal content per dose</th>
<th>Mercury content per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP</td>
<td>IBSiS BIOMED S.A. (Cracow)</td>
<td>max. 50 μg</td>
<td>max. 25 μg</td>
</tr>
<tr>
<td>DT</td>
<td>IBSiS BIOMED S.A. (Cracow)</td>
<td>max. 50 μg</td>
<td>max. 25 μg</td>
</tr>
<tr>
<td>D</td>
<td>IBSiS BIOMED S.A. (Cracow)</td>
<td>max. 50 μg</td>
<td>max. 25 μg</td>
</tr>
<tr>
<td>d</td>
<td>IBSiS BIOMED S.A. (Cracow)</td>
<td>max. 50 μg</td>
<td>max. 25 μg</td>
</tr>
<tr>
<td>T</td>
<td>WSiS BIOMED Sp. z o. o. (Warsaw)</td>
<td>max. 50 μg</td>
<td>max. 25 μg</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Thiomersal content per dose</th>
<th>Mercury content per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodivac</td>
<td>IBSiS BIOMED S.A. (Cracow)</td>
<td>max. 1 μg</td>
<td>max. 0,5 μg</td>
</tr>
<tr>
<td>Tetana</td>
<td>IBSiS BIOMED S.A. (Cracow)</td>
<td>max. 1 μg</td>
<td>max. 0,5 μg</td>
</tr>
</tbody>
</table>
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 thimerosal-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 thimerosal-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 thimerosal-containing vaccines.

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