

Summary of the Workshop on Thimerosal in Vaccines

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At the Lister Hill Center Auditorium, NIH, Bethesda, MD

Written by Robert Pless, M.D.
National Immunization Program, CDC

The purpose of the meeting was to get everyone "on the same page" regarding the issue of mercury in vaccines, not to set policy, but to exchange information.

Unfortunately, there is limited experience regarding the toxicity of thimerosal and the content of mercury it presents, despite the long history of use. Summarizing the issues as follows:

1. Use of a preservative
Is it necessary?
Which one? Are adequate substitutes available?
2. What do we know of the toxicology of thimerosal?
3. What is the impact of the current concern on confidence in vaccines?
4. Plans to reduce thimerosal?
5. What to do during a transition to thimerosal-free products?
6. What are the research priorities?

1. The need for a preservative

Historically, there have been disasters related to contamination of vaccines leading to infection and death of recipients.

FDA regulations stipulate that a preservative is required in multipuncture, multidose vials.

The nature of this preservative is not addressed by FDA, rather the US Pharmacopeia provides guidance in how to measure the effectiveness of the product as "cidal" for bacterial challenge and "static" for yeasts and molds. The USP demands that the minimum amount be used that is effective against challenge organisms, to minimize toxicity.

There is no language addressing preservatives for single dose vials. Single dose vials may contain thimerosal if they are filled from the same bulk as multidose vials.

2. Manufacturer perspective

Concern was raised that this issue appeared to be a crisis, and yet there was no new data ever presented to suggest it was a crisis.

Rather, there is much uncertainty:

- standards (EPA vs FDA) for mercury exposure
- guidelines (PHS vs AAP) for thimerosal in vaccines
- an abstract published last year suggested that premature infants had a much greater rise in blood Hg after Hep B vaccination than term babies. However, the hep B vaccine was used in infants less than 1kg and over 2.5kg with no group from 1-2.5kg. Vaccinating neonates less than 2kg is already considered something to avoid, if possible (not born of sAg +ve moms).
- The only new thimerosal-containing vaccine recently added to the infant schedule was hepatitis B.
- The toxicity of methylmercury, used as proxy for ethyl, was derived from 2 studies that disagreed with each other.
- The quality of the other preservative most used (2-phenoxyethanol) is variable. Thimerosal performs better in some cases.

Problems switching relate to:

- impact on vaccination programs
- alternatives may not be as effective
- reliance on aseptic filling techniques: no safety net
- reformulations necessary: would slow production of influenza vaccine for example
- loss of multi-dose presentations of vaccine (developing world, higher costs, ...)

Good manufacturing practices continue to improve but may not end up perfect. Also, there is WHO requirement for a preservative to be present.

Bottom line: manufacturers will remove thimerosal, but it will take time.

3. International perspective

We all agree that Hg exposure is something we do not want.

Preservatives in multi-dose vials are essential; alternatives unclear at the moment.

The scientific process has not clarified the concerns: safe cutoff limits vary, toxic effects have not been proven at vaccine dose levels.

WHO's joint expert committee on food (?JECFA) reaffirmed the exposure limit (food) at 3.3mcg/kg/wk, except for pregnant women and nursing mothers (where exposure should be reduced by a factor of 5, though this was not made a specific recommendation).

Global vaccine supply may be affected:

- local production may stop
- supplies would dry up
- cold chain may not be able to cope with single dose vials

The price of vaccines would go up by 6-10x. One encouraging note is a disposable pouch and needle for delivery of hepatitis B vaccine.

Impact on disease:

For example: China would see an increase of 10-15% of neonatal hepatitis B infections if birth dose not given.

To this point, there has been little impact on vaccination programs after the announcement (i.e., joint statement of the American Academy of Pediatrics and US Public Health Service on Thimerosal and Vaccines released on July 7, 1999)

Bottom line: There is no turning back from multi-dose vials, and no way to eliminate human error

Audience comment: integrity of immunization programs are an issue, don't want them to be seen as adding to the exposure of Hg already present.

4. Toxicology issues

Thimerosal chosen because it is water soluble and compatible with biological

systems.

In reality, beyond the early approval days (1930's) little work has been done. Few studies on thimerosal exist.

- renal toxicity in animals
- acute toxicity from overdose: experiences in humans (1 suicide attempt, 1 episode of drug contamination - chloramphenicol-containing 1000 times the amount, due to a gross error in production - that led to severe nephrotoxicity)
- does not appear to be carcinogenic, no teratogenicity detected
- in a chronic dosing study, major pathology is renal, Hg accumulated in inorganic form (less likely to cross BBB).

5. Thimerosal in vaccines

The reason for action was not evidence for lack of safety, but lack of data, given that exposure amounts for the vaccine schedule exceed EPA guidelines.

The current FDA initiative does not call necessarily for the total elimination of thimerosal. the goal is to reduce where feasible: remove, replace, reduce.

6. Pharmacokinetics and toxicity: ethyl and methyl

Review of EPA's report to congress on scientific issues related to studies of the health effects of methyl mercury.

Findings:

- Hg is a developmental neurotoxin
- Developing fetus is 10x more sensitive than adult
- low level exposure difficult to evaluate
- more studies are needed to sort this out.

Based on studies of acute methylmercury exposure in Iraq, and the Seychelle and Faroe islands.

Iraq (81 maternal/child pairs), 50-400mcg / 6 months, motor retardation seen with maternal hair at 10-20ppm.

Seychelles - fetal exposure, continuous. No effect with maternal hair at 0.5-27 ppm.

Faroe - fetal exposure, episodic. Domain specific effects at 0.2-39ppm hair. Confounders may have included age at testing and test measures used. PCB's were present in the Faroes and not Seychelles...

Ethylmercury: de-ethylation is faster than de-methylation in methylmercury.

Therefore faster conversion to inorganic Hg and potentially less exposure of the brain.

7. Guidelines on Hg exposure

- not black and white, not "safe"/ "unsafe". Rather a screening level beyond which one might want to look more closely at exposures and minimize them.
- the margin is for chronic exposure, not acute. This still needs to be reconciled.

- There is a variable and large margin of safety associated with them.

Concept is that of a safe daily exposure, estimated from data with uncertainty factors added on, that in a lifetime of ingestion would not harm.

Use most vulnerable populations as the "goal" of setting the level.

8. Impact on hepatitis B

Survey of birthing hospitals

83% aware of joint statement, 79% of them had policy to vaccinate at birth

Of those, 9.3% stopped all vaccination, 66.5% stopped vaccinating seronegative moms, 24% no change.

BUT: only 36% changed policy to ensure better testing of pregnant mothers for sAg.

Estimates:

200 preventable infections compared with program to vaccinate all infants

246 new early childhood infections

Conclusions: need to ensure testing of pregnant women. Unfortunately, there is already evidence that the vaccination policy changes operationalized in light of the new AAP/PHS "guidelines" has placed infants at some risk of infection.

Audience: one health department has already documented 3 infections in infants who would otherwise have received vaccine.

9. Impact on pertussis and hib

Risk remains among those unimmunized, the organisms still circulate.

Vaccine protects better than herd immunity.

Estimates of actual burden of illness given impact of thimerosal concern is difficult to compute.

10. The European Agency for the Evaluation of Medicinal Products (EMEA) response to the issue

Developed concern about mercury exposure due to vaccines and other medicinal products and referred the issue to the safety working party. Issues were neurotoxicity and sensitization, there was not enough data to conclude on nephrotoxicity.

Recommended:

- warning labels
- encourage thimerosal-free products for infants and toddlers
- move towards addressing removal/reduction of thimerosal

They are working with relevant and interested parties to ensure continuity of vaccine supply.

OUTCOMES

Many speakers echoed similar needs for research and further work.

The following concepts were underlined:

- vaccines are not perfect
- good manufacturing practices not perfect
- we cannot live in a mercury-free environment, the goal is to decrease exposure overall
- the stated guidelines for exposure are not cut-offs, they are screening levels to be used to consider the individual exposure and whether action should be considered

Research needs:

- data on which to comment on the long term impact of "vaccine-level" exposure (from existing data sources or novel data sources)
 - need to get better data on toxicology and pharmacokinetics of ethyl mercury.
- There is too much we do not yet know: is bolus dose = chronic exposure (can an exposure limit be applied to vaccination); how is ethyl mercury handled upon injection, etc.?
- need to know how to communicate controversial and inconclusive data while maintaining confidence in immunization programs.

Added concerns:

- if thimerosal replaced, how safe are alternatives

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