

- 1 Status Quo
- 2 T- letter - state a part ——— 2 cts
- 3 Situational **Communications Considerations Regarding Thimerosal**
use DRAFT - not for distribution
July 3, 1999
4. Modified use of
vaccines.

706 353 6680

I. Communications Situation: What's 'new' here?

- Recent Food and Drug Administration Modernization Act assessment activities have led to a recognition of a *new* exposure to Hg not previously appreciated
- For infants up to 6 months, Hg exposure from vaccines given according to the U.S. vaccination schedule may exceed some methylmercury exposure recommendations.
- This concern/exposure results from the recommended vaccination schedule, which over the years (i.e., since 1976 or the year of the FDA's safety assessment of thimerosal) has expanded in order to provide children with protection from more vaccine preventable diseases. It does not arise from the amount of thimerosal in any given individual vaccine.
- It appears the recommendation to vaccinate children against Hep B is what created the potential for Hg exposure from vaccines to exceed some methylmercury exposure recommendations; although in some instances, an influenza vaccination may also do this.
- This issue provides toxicologists and others who advocate for zero exposure to Hg a new forum or opportunity to espouse their position.

II. There are a number of target audiences that we need to reach with our thimerosal-related communications. They include:

- Physicians
- Nurses
- Parents
- The public
- State and local grantees / State and local health departments
- Our immunization-service delivery partners
- Our immunization education and promotion partners
- Policy makers and legislators
- Vaccine manufacturers
- The media
- WHO
- European public health officials

SafeMinds

Property of
SafeMinds

*Best
Brand
choice.*

*Serious
comm &
problems
all.*

III. In communicating with our target audiences, it is very important we have a "bottom-line" vaccine-related behavior message. There are four potential behavioral recommendations regarding thimerosal-containing vaccines:

1. Maintain the status quo (i.e., "thimerosal-containing vaccines are not a problem, and can be safely administered to children regardless of age or circumstance")
2. Recommend thimerosal-free vaccines over thimerosal-containing vaccines (i.e., essentially discontinue use of thimerosal-containing vaccines)
3. Situational use for thimerosal-containing vaccines (i.e., these vaccines are okay in these circumstances, but not so good in these circumstances. For example, "you can use them without concern for children 6 months or older" or "avoid thimerosal-containing Hep B vaccines for infants under 6 months").
4. (Slightly) Modified use in line with the current childhood immunization schedule (i.e., "Physicians and parents should use prudent product or brand choice to reduce ethylmercury exposure to levels below those provided by the EPA's mercury exposure guidelines.")

IV. Communication Implications and Potential Ramifications of each Alternative:

Alternative #1:

This recommendation is problematic for a number of reasons, including:

- a. It seemingly puts our childhood immunization schedule in conflict with the EPA guidelines; which is a status that will require us to have a sound or better scientific foundation than the EPA with regard to Hg exposure.
- b. Its scientific foundation is essentially "We have no evidence or data that indicates there is a problem." A statement that will likely then spur lots of people to produce evidence illustrating that this is a real problem (even only through the use of theories) as well as generate a number of adverse event reports alleging a wide range of adverse effects.
- d. Relatedly, we have little data or science to support our position— leaving us particularly vulnerable to the advocates of reduced or zero mercury exposure, who do have some published data to reference.
- c. We will be perceived as "nonresponsive," "uncaring about the health of children," and doing what's best for vaccine manufacturers.

Alternative #2:

This recommendation is also problematic for a number of reasons, including:

- a. We have no evidence or data that indicates a serious or widespread health problem has arisen from the use of thimerosal-containing vaccines.
- b. This position puts the CDC in conflict with FDA. Further, the FDA has been monitoring and working to reduce thimerosal exposure, and thus has more data/science than CDC.
- c. The vaccine manufacturers, while supporting the concept of thimerosal-free vaccines, would likely point out that it is the CDC's childhood immunization schedule—not the individual vaccines—that are the source of the potential problem. In defending their products, they could suggest that ACIP and CDC were negligent in their processes by not considering additive exposure or levels when they made additions to the childhood immunization schedule.
- d. This position could be interpreted as an implicit concession that there is a health-risk associated with thimerosal—a perception that would likely fuel anti-mandatory vaccination sentiment and generate a large number of adverse event reports and injury compensation claims related to thimerosal-containing vaccines—especially Hep B.

Alternative #3:

This recommendation has superficial appeal but the reality will likely be:

- a. The creation of two categories of vaccines—good vaccines (i.e., thimerosal free) and bad vaccines (i.e., thimerosal containing).
- b. Once physicians, parents, the public, and others have decided two categories exist, then we essentially end up with the implications noted under Alternative #2.

Alternative #4:

From a communications perspective, this appears to be the best course of action.

- a. It puts the focus on the childhood immunization schedule, which is the crux of the issue.
- b. It can be framed as a logical, responsible, and science-based next step toward the eventual removal of thimerosal from all vaccines.
- c. It resolves the apparent conflict between our childhood immunization schedule and the EPA's Hg exposure guidelines.
- d. It enables us to reference the EPA's guidelines, and by implication, the scientific basis that underlies those guidelines (vs. having to develop our own scientific foundation in very short order).
- e. Relatedly, it enables us to reference and utilize the FDA's science and activities surrounding thimerosal, including the 1976 review, the vaccine clinical trial data, FDAMA, etc.
- f. Thanks to c, d, and e, this recommendation becomes science-based (vs. based on

- hypotheses, speculation, and extrapolation)
- g. It will likely earn the endorsement and cooperation of vaccine manufacturers.
 - h. This course of action may not completely appease those who advocate actions that will more immediately reduce Hg exposure from vaccines to zero, but the concept of "prudent product or brand choice" does provide physicians and parents the ability to accomplish that goal if they so desire. Further, as the course of events in the last week suggest, some of toxicologists and other advocates will see this as an opportunity to espouse their position to the media.
 - i. This alternative will likely fuel those opposed to mandatory hepatitis B vaccination of infants and children for school entry, but all the alternatives are likely to do that.
 - j. Ideally, this course of action should have the endorsement of the ACIP so that we are consistent with our processes for changing or modifying the country's immunization recommendations. This endorsement could come from ACIP at their next scheduled meeting.

NOTE:

In light of this issue and rotavirus, we should anticipate more attention being directed to state immunization laws. After all, the primary messages of those advocacy groups are:

- The government doesn't know enough about how infants metabolize vaccines.
- Many of the additives in vaccines are potentially dangerous.
- The process used to formulate and approve childhood immunization recommendations is highly flawed (e.g., there's not enough data to support the recommendations).
- The benefits of vaccination may often outweigh the risks, but given the uncertainties that surround the value, efficacy, and safety of many of the vaccines, parents— not the government— should be the final arbiters of childhood vaccine use.

Table 1

Examples of Possible Vaccine Combinations and Resulting Thimerosal Exposures during the First 6 Months of Life

All infants* should receive the recommended doses of vaccines to protect them against seven diseases in the first 6 months of life. These vaccination combinations assure full vaccination while maintaining a level of thimerosal exposure below reference guidelines. It assumes that background levels of exposure to mercury are negligible in the first 6 months of life.

All children should receive 2 or 3 doses of inactivated polio vaccine and 3 doses of rotavirus vaccine during the first 6 months of life in accordance with the Recommended Immunization Schedule. These vaccines do not contain thimerosal.

Using the 5th percentile for weight, the cumulative methyl mercury exposure by 6 months of age, based on reference guidelines (EPA), should not exceed 80 ug. Large safety margins have been built into the reference guidelines. The larger amounts of micrograms of cumulative exposure that would be allowable for children above the 5th percentile for weight are not provided here.

DTaP	Hib	Hepatitis B	Cumulative Hg
ACEL-IMUNE	Comvax	Comvax**	75 ug
Certiva	Comvax	Comvax**	75 ug
Tripedia	Comvax	Comvax**	75 ug
Infanrix	ActHiB	Engerix-B	37.5 ug
Infanrix	ActHiB	Recombivax HB	37.5 ug
Infanrix	HibTITER (single dose)	Engerix-B	37.5 ug
Infanrix	HibTITER (single dose)	Recombivax HB	37.5 ug
Infanrix	OmniHIB	Engerix-B	37.5 ug
Infanrix	OmniHIB	Recombivax HB	37.5 ug
Infanrix	Pedvax HIB (liquid)	Engerix-B	37.5 ug
Infanrix	Pedvax HIB (liquid)	Recombivax HB	37.5 ug
Infanrix	ActHiB	Engerix-B***	25 ug
Infanrix	ActHiB	Recombivax HB***	25 ug
Infanrix	HibTITER (single dose)	Engerix-B***	25 ug
Infanrix	HibTITER (single dose)	Recombivax HB***	25 ug
Infanrix	OmniHIB	Engerix-B**	25 ug
Infanrix	OmniHIB	Recombivax HB***	25 ug
Infanrix	Pedvax HIB (liquid)	Engerix-B***	25 ug
Infanrix	Pedvax HIB (liquid)	Recombivax HB***	25 ug
Infanrix	Comvax	Comvax**	0 ug

*See Table 2 for hepatitis B immunization of preterm infants.

**Comvax may not be administered before 6 weeks of age.

***Administer the 3rd dose on or after 12 months of age (see 1999 harmonized schedule).

Introduction

The key issue to consider is not whether a vaccine contains thimerosal as there is no inherent value in whether or not this is present or in whether an infant receives any vaccine that contains thimerosal or has a mercury exposure of zero. The focus should not be on what the vaccines do or do not contain but rather on whether a child is being exposed to a level of mercury that is defined as being potentially harmful. By focusing on the child and not the vaccine one can address the most important issue to both the pediatrician and the parent: protecting the child both from disease and from any potential toxicity.

The acceptable levels for mercury are defined by the EPA and WHO as levels below which there is no risk (or minimal likelihood) of mercury toxicity. Although these levels were defined for exposure to methyl mercury, data suggest similar toxicities for methyl and ethyl mercury, the form present in thimerosal. In fact, the defined cutoffs were established with a substantial margin of safety built in to assure that no toxicity occurs. Within the first 6 months of life, for a child of average weight, both WHO and EPA define this cutoff as a cumulative exposure of about 100 ug. By two years of age, a cumulative exposure to about 550 ug is acceptable for a child of average weight. Note that both ATSDR and the FDA define 3- and 4-fold higher levels of exposure, respectively, as acceptable.

Goals

1. Vaccinate children with all recommended antigens for optimal disease prevention.
2. Assure that exposure to mercury does not exceed EPA and WHO defined cutoffs for cumulative exposure, especially within the first 6 months of life.
3. Maintain the ability of the immunization program to provide safe vaccination regimens to all children in both the private and public sectors.
4. Maintain public and provider confidence in the safety of the vaccination program.

Approach

Vaccination providers should be instructed to provide a combination of vaccines that will result in complete immunization of infants while not exceeding the accepted, safe level of mercury exposure. There are several options for accomplishing this, with only minimal changes in the vaccination schedule:

- ▶ Vaccinate a child who is not at high risk for hepatitis B (e.g., not born to a surface antigen positive mother or with household exposure to hepatitis B) with a thimerosal containing hepatitis B vaccine at 2, 4, and 12 months. This small change in the vaccination schedule is unlikely to decrease protection (and may actually improve immunogenicity as boosting is greater with a longer interval between doses). Because the concentration of thimerosal in hepatitis B vaccines is lower than other products, the cumulative dose in <6 month old children who receive 2-doses would be 25 ug.
- ▶ Vaccinate a child with either a thimerosal containing DTaP and a thimerosal free

Hib or vice versa. There is one thimerosal free DTaP (Infanrix) and 3 thimerosal free Hib vaccines (ActHIB, PedvaxHIB [liquid], and Comvax which also contains hepatitis B vaccine). The cumulative exposure in <6 month old children would be 75 ug, or 50 ug if the Merck 2-dose Hib vaccine were used with Infanrix.

- ▶ For an infant at high risk of hepatitis B, provide the first dose of thimerosal containing hepatitis B vaccine at birth, followed by 2-doses of Comvax at 2 and 4 months, and thimerosal containing DtaP for a cumulative exposure in <6 month old children of 87.5 ug.
- ▶ No IPV vaccines contain thimerosal so that this vaccine would not contribute any mercury exposure.

Given the above scenarios, the cumulative exposure for a fully immunized child would range between 75 ug and 100 ug, both within the defined safe level of cumulative exposure for a 6 month old child. Moreover, allowing vaccine providers to combine a variety of vaccines to assure a safe cumulative exposure would provide flexibility and minimize the potential for product shortages.

Communications

When the focus of the communication was on the vaccine product rather than the child, there was an inherent contradiction: why are we moving to thimerosal free vaccines if vaccines containing this product are safe? Parents inevitably would want vaccines that don't contain thimerosal, leading to shortages, deferral of vaccination, and receipt of mercury concentrations that exceed the cutoff by some children. The communication problem is avoided by presenting child-focused messages.

Key communications message:

Physicians and parents all want to protect children from threats to their health. On-time vaccinations protect children from serious diseases such as Hib meningitis and pertussis (whooping cough). Every child can receive all recommended vaccines, some of which may contain thimerosal, and not be exposed to mercury levels that exceed the level defined by EPA and WHO as safe. In fact, this level was chosen with a very wide margin of safety so that the possibility of an adverse effect would be very remote.

The concept of a safe level of exposure is one that is familiar both to physicians and to the public. For example, physicians test children for blood lead levels and only intervene (e.g., with chelation therapy) when the level exceeds a defined cutoff. For other heavy metals, such as zinc or cadmium, physicians would only become concerned when a child's exposure exceeded a defined cutoff. For the public also, the idea that there is a level below which no harmful effects occur also makes sense. People choose to eat tuna and other products that contain low levels of mercury because they know that this level of exposure will not result in any toxicity.

If vaccinations can be completely and safely given now, why is the FDA encouraging vaccine manufacturers to remove thimerosal from their products? One answer is that by increasing the

number of thimerosal free products, it will be easier for vaccine providers to purchase and provide vaccines. Currently, there are some regimens that would exceed defined cutoffs. When more products are thimerosal free, physicians will have more flexibility and it will be easier to assure that no child receives a regimen that could possibly result in some toxicity. Moreover, by increasing flexibility, the possibility of shortages would be decreased assuring that all children are able to receive needed immunizations. Also, greater availability of thimerosal free products would further increase the margin of safety, particularly for premature and low birth weight infants for whom the defined cutoff may be lower. Finally, this change would reassure the public that the PHS and vaccine manufacturers are continuing to do whatever possible to assure optimal safety and maintain public confidence in the vaccination program.

This approach also would protect vaccination programs in the developing world. It would be possible to provide all recommended vaccines, including Hib and hepatitis B without exceeding the defined cutoff or, if this cutoff is exceeded, still remaining well within the margin of safety. In the developing world, where the risk of mortality or severe morbidity from vaccine preventable diseases is much greater, the balance between the risks associated with non-vaccination and exposure to a mercury level that is below the cutoff or within a safe margin of that cutoff is clearly in favor of vaccination. By focusing on the child, rather than defining a specific vaccine product as being better or worse, one avoids the problem of having to avoid certain products. This is particularly important because inclusion of thimerosal prevents contamination of multi-dose vials and is important to protect against potentially severe bacterial infections occurring with contaminated vaccine.

Calculation of total dose exposure for the first 6 months, at 5th percentile for weight.

"FDA" method:

Birth = 2.5kg

6 months = 4.1kg

Average = $(2.5+4.1)/2 = 3.3\text{kg}$

Dose allowed over 6 months = $3.3\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 26\text{wks} = 60.1\mu\text{g}$

"CDC" method:

Age	Boys (kg)	Girls (kg)
0-1mo	2.54	2.36
1-2mo	3.16	2.97
2-3mo	3.80	3.58
3-4mo	4.43	4.18
4-5mo	5.00	4.71
5-6mo	5.60	5.25
6-7mo	6.20	5.79

Weighted: 4.08 3.84 (6 months)

Dose allowed over 6 months (allowing for immunization up to 7 months):

Boys: $4.08\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 30\text{weeks} = 85.9\mu\text{g}$

Girls: $3.84\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 30\text{weeks} = 80.68\mu\text{g}$

FDA limit: 0.48

NTSAR : 0.3

\therefore Minimum = 180 μg

Reasonable = 242 μg

Liberal = 300 +

Calculation of total dose exposure for the first 6 months, at 5th percentile for weight.

"FDA" method:

Birth = 2.5kg

6 months = 4.1kg

Average = $(2.5+4.1)/2 = 3.3\text{kg}$

Dose allowed over 6 months = $3.3\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 26\text{wks} = 60.1\mu\text{g}$

"CDC" method:

Age	Boys (kg)	Girls (kg)
0-1mo	2.54	2.36
1-2mo	3.16	2.97
2-3mo	3.80	3.58
3-4mo	4.43	4.18
4-5mo	5.00	4.71
5-6mo	5.60	5.25
6-7mo	6.20	5.79

Weighted: 4.08 3.84 (6 months)

Dose allowed over 6 months (allowing for immunization up to 7 months):

Boys: $4.08\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 30\text{weeks} = 85.9\mu\text{g}$

Girls: $3.84\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 30\text{weeks} = 80.68\mu\text{g}$

Varying the exposure limits away from EPA to FDA/ATSDR

FDA calculations for weight of 3.3kg and 6 months:

ATSDR (0.3) = $180.2\mu\text{g}$

FDA (0.48) = $288.3\mu\text{g}$

CDC calculations for weight of 3.84kg and 7 months:

ATSDR = $241.9\mu\text{g}$

FDA = $387.1\mu\text{g}$

etc...

Calculation of total dose exposure for the first 6 months, at 5th percentile for weight.

"FDA" method:

Birth = 2.5kg

6 months = 4.1kg

Average = $(2.5+4.1)/2 = 3.3\text{kg}$

Dose allowed over 6 months = $3.3\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 26\text{wks} = 60.1\mu\text{g}$

"CDC" method:

Age	Boys (kg)	Girls (kg)
0-1mo	2.54	2.36
1-2mo	3.16	2.97
2-3mo	3.80	3.58
3-4mo	4.43	4.18
4-5mo	5.00	4.71
5-6mo	5.60	5.25
6-7mo	6.20	5.79

Weighted: 4.08 3.84 (6 months)

Dose allowed over 6 months (allowing for immunization up to 7 months):

Boys: $4.08\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 30\text{weeks} = 85.9\mu\text{g}$

Girls: $3.84\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 30\text{weeks} = 80.68\mu\text{g}$

Calculation of total dose exposure for the first 6 months, at 5th percentile for weight.

"FDA" method:

Birth = 2.5kg

6 months = 4.1kg

Average = $(2.5+4.1)/2 = 3.3\text{kg}$

Dose allowed over 6 months = $3.3\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 26\text{wks} = 60.1\mu\text{g}$

"CDC" method:

Age	Boys (kg)	Girls (kg)
0-1mo	2.54	2.36
1-2mo	3.16	2.97
2-3mo	3.80	3.58
3-4mo	4.43	4.18
4-5mo	5.00	4.71
5-6mo	5.60	5.25
6-7mo	6.20	5.79

Weighted: 4.08 3.84 (6 months)

Dose allowed over 6 months (allowing for immunization up to 7 months):

Boys: $4.08\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 30\text{weeks} = 85.9\mu\text{g}$

Girls: $3.84\text{kg} \times 0.1\mu\text{g/kg/day} \times 7\text{days} \times 30\text{weeks} = 80.68\mu\text{g}$

Varying the exposure limits away from EPA to FDA/ATSDR

FDA calculations for weight of 3.3kg and 6 months:

ATSDR (0.3) = $180.2\mu\text{g}$

FDA (0.48) = $288.3\mu\text{g}$

CDC calculations for weight of 3.84kg and 7 months:

ATSDR = $241.9\mu\text{g}$

FDA = $387.1\mu\text{g}$

etc...

Interim Schedule Options*

Thimerosal Below Standards	First year	Second year	Manufacturer
----------------------------	------------	-------------	--------------

1. Separate Hib and hepatitis B

Infanrix (DTaP)	2, 4, 6 months	15-18 months	SKB
PedvaxHib (liquid)	2, 4 months	12-15 months	Merck
ActHiB	2, 4, 6 months	12-15 months	PMC
HibTITER (single dose)	2, 4, 6 months	12-15 months	Lederle
OmniHiB	2, 4, 6 months	12-15 months	SKB
Engerix-B	2, 4 months	12-18 months	SKB
Recombivax HB	2, 4 months	12-18 months	Merck
IPV	2, 4, 6-18* months	6-18* months	PMC
MMR		12-15 months	Merck
Varicella		12-18 months	Merck

TOTAL MERCURY	25 micrograms	12.5 micrograms
---------------	---------------	-----------------

Issues

Retains some mercury, but low level and maximal on any visit is 12.5 micrograms

Supply of Infanrix