THIOMERSAL IN VACCINES DCVMN PERSPECTIVE

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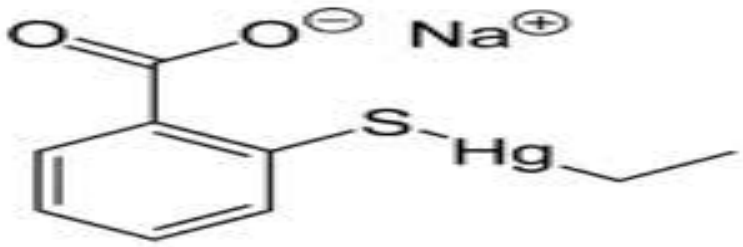
Dr. Suresh Jadhav
Executive Director
Serum Institute of India
ssj@seruminstitute.com

THIOMERSAL

- An organic mercury-based compound
- Has been used as a preservative in various vaccines and other biological and pharmaceutical products since the 1930's
- Since Year 1999, Under discussions and debate for possible safety risks. No consensus till date.
- Some countries including USA, have recommended vaccine formulations with either reduced thiomersal or with newer preservatives as precautionary measure.

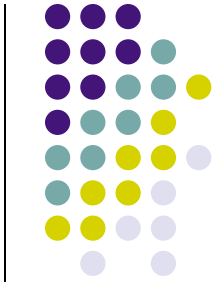


DCVMN Commitments

- DCVMN is committed to provide the highest quality vaccines for its use globally

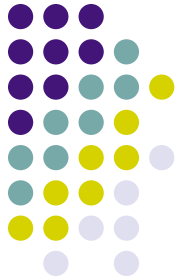
However, we need answers for some key questions

Key Questions



- Is there consensus that thiomersal poses a safety risk?
- Is there agreement on an effective substitute?
- If required, what might be an appropriate time frame for making all vaccines available in single dose containers without preservation ?

Safety of Thiomersal: Conclusions by Advisory Bodies



The safety of thiomersal has been consistently asserted by some of the world's most reputable medical advisory bodies.

- The National Institutes of Health
- WHO's Global Advisory Committee on Vaccine Safety
- The Center for Disease Control
- European Agency for the Evaluation of Medicinal Products
- UK Commission on Human Health

Conclusions by Advisory Bodies

- **Global Advisory Committee on Vaccine Safety (WHO)**

  - "No evidence of mercury toxicity in infants, children, or adults exposed to thiomersal in vaccines." (2000)

  - "…no reason to change current immunization practices with thiomersal-containing vaccines on the grounds of safety." (2000)

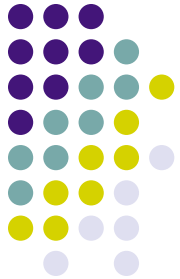
  - In 2008 GACVS again considered the thiomersal/safety issuer and reaffirmed the Year 2000 conclusions.

- **Institute of Medicine**

  - "The hypothesis that thiomersal exposure through the childhood immunization schedule has caused neurodevelopmental disorders is not supported by clinical or experimental evidence." (2000)

  - "The evidence favors rejection of a causal relationship between thiomersal containing vaccines and autism." (2004)

Conclusions by Advisory Bodies



- **European Medicines Agency**

  "The latest epidemiologic studies show no association between the vaccination with thiomersal-containing vaccines and specific neurodevelopmental disorders." (2004)

  "The benefits of vaccination far outweigh the risks, if any, of exposure to thiomersal-containing vaccines" (2004)

- **UK Commission on Human Medicines**

  Following the review of two independently conducted UK epidemiological studies on the safety of thiomersal-containing vaccines for infants in 2003, the CHM reinforced its 2001 position, stating that "… there is no evidence of neurodevelopmental adverse effects caused by levels of thiomersal in vaccines. The CHM also asserted that the balance of risks and benefits of thiomersal-containing vaccines is overwhelmingly positive.

Scientific research highlights

- Pichichero ME et al. Mercury levels in newborns and infants after receipt of thiomersal containing vaccines. *Pediatrics. 2008; 121(2): e208-e214.*

  Conclusions: ***The blood half-life of intramuscular ethylmercury from thiomersal in*** vaccines in infants is substantially shorter than that of oral methylmercury in adults. Increased mercury levels were detected in stools after vaccination, suggesting that the gastrointestinal tract is involved in ethylmercury elimination. Because of the differing pharmacokinetics of ethylmercury and methylmercury, exposure guidelines based on oral methylmercury in adults may not be accurate for risk assessments in children who receive thiomersal-containing vaccines.

- Barregard L et al. Toxicokinetics of mercury after long-term repeated exposure to thiomersal-containing vaccine. Toxicological Sciences. 2011; 120 (2):499-506.

  Conclusions: Mercury from thiomersal is not accumulated in blood in adults. This is in accordance with short half-lives and rapid metabolism of EtHg [ethylmercury] to inorganic mercury.

Scientific research highlights

- **Neurodevelopmental Effects**

  Burbacher TM et al. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thiomersal. *Environmental Health Perspective. 2005; 113:1015-1021.*

  Conclusion: MeHg [methylmercury] is not a suitable reference for risk assessment from exposure to thiomersal-derived Hg.

- Tozzi A et al. Neuropsychological performance 10 years after immunization in infancy with thiomersal-containing vaccines. *Pediatrics. 2009; 123(2):475-482.*

  Conclusions: *Given the large number of statistical comparisons performed, the few* associations found between thiomersal exposure and neuropsychological development might be attributable to chance. The associations found, although statistically significant, were based on small differences in mean test scores, and their clinical relevance uncertain.

Scientific research highlights

- **AUTISM**

  Schechter R, Grether J. Continuing increases in autism reported to California's developmental services system: mercury in retrograde. *Archives of General Psychiatry. 2008; 65(1):19-24.*

Conclusions:

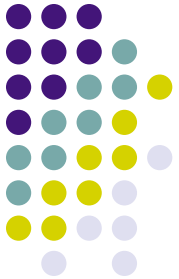
- *The DDS [Department of Developmental Services] data do not show any* recent decrease in autism in California despite the exclusion of more than trace levels of thiomersal from nearly all childhood vaccines.
- The DDS data do not support the hypothesis that exposure to thiomersal during childhood is a primary cause of autism.

Recent trends

- During the 2010-11 influenza season, more than 90 million vaccine doses of thiomersal containing influenza vaccine in multi-dose vials were distributed for vaccination of American citizens. Extensive safety studies showed that these vaccines were safe and effective.

- During Year 2010, UNICEF and PAHO revolving fund supplied 325 million doses of thiomersal containing vaccines for routine immunization against outbreaks of infectious diseases such as influenza or epidemic meningitis.

Recent trends



Thus, scientific research, reputed medical advisory bodies and long history of use suggest that thiomersal in vaccines does not cause nor contribute to autism

Options available to manufacturers:

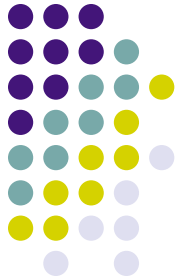
- Option 1: Replace thiomersal

  Is there a consensus on effective substitute

Or

Option 2: Shift to preservative free single dose presentations

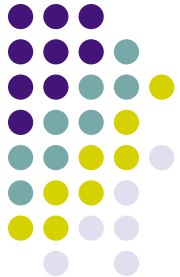
Option 1: Newer alternatives to thiomersal



- Will need consensus on alternative preservative.
- There are only a few tested, efficacious and safe alternatives to thiomersal-containing vaccines.

Preservative	Marketed Vaccines
Phenol (Phemerol)	•Typhoid Vi Polysaccharide (Typhim Vi; Sanofi Pasteur) Pneumococcal Polysaccharide (Pneumovax 23; Merck)
Benzethonium chloride	Anthrax (Biothrax, Emergent biodefense Operations Lansing Inc)
2-Phenoxyethanol	IPV (IPOL, Sanofi Pasteur, SA).

Do we have a universal preservative which could act as replacement

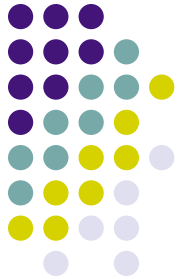


- Effectiveness: 2-Phenoxyethanol (2PE) a preservative which is currently in use in US at preservative levels 2.5mg/dose.
- WHO has conducted collaborative study on Preservative Efficacy Test (PET).

  It was reported that 2PE does not meet criteria “A” of *BP* for recovery study up to 24 hours.

- Safety concerns
  - Isolated report suggest (Year 2000; Archives of Toxicology Vol. 74) 2-PE has neurotoxic properties. Occupational exposure to this chemical for more than a year can lead to cognitive impairments.
  - In a recent report (Vaccine. 2011 Sep 22; 29(41):7144-53) concentration as high as 5mg/dose was reported to be comparable to thiomersal. Overall impact on safety of product including long term needs to be established.

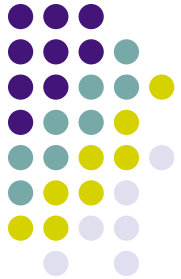
Do we have a universal preservative which could act as replacement



- Cost effectiveness
  - Use of 2PE at 2.5mg/dose concentration increases the cost of vaccine.
- No added benefit

- Reported dual use of Thiomersal in inactivation procedure of Pertussis).
- Research suggest low seroprotection and high no. of nonresponders in subjects injected with 2PE containing HB vaccine than those with Thiomersal containing vaccine.
- Thiomersal reported to have stabilizing effect on the HB surface antigen thus raising concerns over antigenic stability after deletion of Thiomersal as a preservative from the vaccine.

Option 2: Single dose presentations



- If forced, there will be shortage of vaccines as current vaccine manufacturing facilities will not be able to cope with increased requirements of containerization thereby disturbing the existing immunization program globally.

Option 2: Single dose presentations

A shift to single dose presentations will have major cost implications with increased requirement of raw materials, new production and storage facilities.

- More lots will need to be manufactured with increased production costs.
- Increased testing load for manufacturers and NCLs
- More waste will be generated carrying huge impact on environment.
- Need to establish new filling facilities. Increased space requirements for storage and transport
- Programmatic challenges for vaccination programs because of increased requirement of cold storage.
- Most importantly, cost per dose will increase manifolds for which governments will have to make necessary provisions.

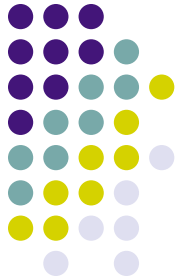
Time frame for such transition

- Obtaining regulatory approval for the new formulated thiomersal-reduced or-removed vaccines involves complex activities that are costly and time consuming and will involve preparing formulations, stability testing and preclinical toxicity testing and clinical trials which can take several years.

- This will be further challenging for DCVMN as we supply affordable vaccines with marginal profits which is made possible because of multi-dose containers.

Is this really required/ Is this a viable option.

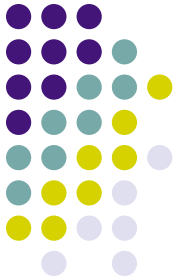
DCVMN position on Thiomersal containing vaccines



- DCVM provides more than 80 % of thiomersal containing vaccines to UN agencies at most affordable prices.
- This is possible because 90 % of vaccines are supplied in multidose containers. WHO recommends use of preservative in multi-dose containers.
- As of today, there is no universally accepted alternative to thiomersal.
- There will be huge economic, programmatic and technical challenges in following up either of option 1 or option 2.
- Till these challenges are overcome, use of thiomersal should continue globally otherwise existing immunization programs will be affected leading to global disaster, affecting childrens in the developing world.

DCVMN Expectation from SAGE

- SAGE takes into account existing scientific data on use of thiomersal and safety record in various vaccine preparations.
- SAGE takes into account the realistic situation in DCs where health budget are miniscule (NMT 2 % of total GDP) and international agencies have limited finances to procure product in single dose containers.
- We anticipate that SAGE will recommend continued use of thiomersal until above mentioned challenges are met or an equally efficient and safe alternative is available.



Thank you