WHO INC 4 Consultation Session 1 and 2 Summary

Robert Ball MD, MPH, ScM

April 4, 2012

WHO INC 4 Consultation Session 1
WHO Position on Thimerosal – David Wood

- Greatest health gains will be made by addressing main sources of mercury
  - combustion, gold production, etc
  - fish is main source of methyl mercury exposure in environment
- Vaccines are highly regulated: safety, efficacy, quality
- Thimerosal containing vaccines are essential medicines
  - 120 countires, 64% of global birth cohort: DTP, HiB
  - 1.4 million child deaths averted
  - epidemic: influenza and meningitis (Africa)
- High quality studies conducted in several countries conclusively show that vaccines that contain thimerosal are very safe
  - no credible scientific evidence that thimerosal-containing vaccines cause autism
- There is little evidence that a range of vaccines can be preserved with alternatives
- Thimerosal free vaccines will increase cost of vaccines; switch to single dose vials alone would require more raw materials, more energy for production and transport, and more waste = increased environmental impact
- Vaccines that contain thimerosal are manufactured in 40 countries; potential barriers to trade could lead to limitations of access to life saving vaccines

WHO INC 4 Consultation Session 1 Update on Thimerosal – Rob Mitkus

- Well-designed epidemiological studies have failed to find a causal relationship between prenatal, neonatal, or postnatal exposures to thimerosal in vaccines and a host of neuropsychological outcomes, including autism
- Complete Quantitative Risk Assessment model accounting for the kinetic and toxicological differences between ethyl and methyl mercury might be a useful area of further research
  - Preliminary evidence of neurotoxicity in neonatal rat and macaque has been published, but studies have limitations so replication is required before they could be used to characterize ethylmercury toxicity in animals
  - Would incorporate any future rigorously conducted and confirmed animal studies demonstrating toxicity from thimerosal
  - Contribute to cumulative toxicity assessment from exposure to multiple mercury species
- Benefits of vaccination with thimerosal containing vaccines outweigh any potential risk from thimerosal

WHO INC 4 Consultation Session 2
Safety of thimerosal and alternative preservatives – Michael Pichichero

Safety of Thimerosal - Methods: Medline search 2008 to present – thimerosal/ vaccines/autism

- Blood and hair mercury measurements – Argentina, China, Amazon
  - half life of thimerosal much shorter than for methyl mercury
  - autistic disorder children had similar total mercury in blood compared w/ unaffected controls
  - Thimerosal contribution to total blood mercury very low compared to methyl mercury
- Epidemiological studies – US, Amazon, Italy, Poland
  - Some studies found no association between thimerosal in vaccines and neurodevelopmental problems including autism; other studies found an association.
  - Dr. Pichichero's review suggested that the latter studies had flaws in study design invalidating their conclusions
- Animal studies (mice, rats and macacques)
  - Some studies found associations between thimerosal exposure and adverse behavioral, histopathological, or neurochemical outcomes and others did not
  - Dr. Pichichero's review suggested that those that found associations were either at doses or dosing intervals that weren't relevant to human situation, or study design or execution or outcome made results preliminary and requiring confirmation
- Miscellaneous (3 studies)
  - thimerosal exposures varied by body weight; in vitro model showed interactions of very high dose thimerosal with various biological molecules; exploratory principal component analysis
- Summary of Dr Pichichero: no new evidence questioning safety of thimerosal as a preservative in multi-dose vials.

WHO INC 4 Consultation Session 2
Safety of thimerosal and alternative preservatives – Michael Pichichero

- **Alternative Preservatives (2 published studies reviewed)**
  - Neither 2 PE nor thimerosal met all criteria by all regulatory authorities and performance varied by vaccine studied (hepatitis B vaccine and Prevnar)

WHO INC 4 Consultation Session 2
Experience with Alternatives to Thimerosal from other Fields – Johannes Lower

- Survey of members of International Alliance of Biological Standardization about alternatives to thimerosal from other fields, response rate 10%, Europe and "Rest of World"
- Other (than preservative) uses of thimerosal?
  - Human vaccines – preservatives, manufacturing, inactivating agent for pertussis vaccine
  - Veterinary vaccines – protect against microbial growth prior to use in many vaccines; inactivating agent.
  - Sera (anti-venoms) – used as a preservative in production
  - Biotherapeutics – methylparabenz or metacresol
- Alternative to thimerosal?
  - Single dose vials, strict GMP, replacement of thimerosal; 2-PE in DTaP, phenol in anti-venoms; Benzachromium chloride
- Required properties of a preservative?
  - Antimicrobial
  - Compatibility with formulation
  - No negative effect on antigens
- Why not replaced with an alternative preservative?
  - Technical constraints
  - No market pressure (veterinary vaccines except for cats rabies vaccines)
  - Regulatory consequences – high costs for approval, no harmonization
- Does Anti-microbial testing reflect need?
  - Most preservatives seem to work, but not good data on how the AME requirements are related to effectiveness in field
  - Veterinary vaccines don't need AME, but need stability testing

WHO INC 4 Consultation Session 2
EMA - Efficacy of alternative preservatives, review of testing practices – Gwenael Cirefice

- Human Vaccines
  - Thimerosal is the only preservative in centrally authorized human vaccines
  - Alternative preservatives in some nationally registered vaccines
  - Evolution toward elimination of preservatives in single does vials
    - Thimerosal in multi dose vials in pandemic vaccines
  - Little comparative data available with alternatives
  - Risk with replacement
    - Higher concentration of alternative may be needed
    - Uncertainty wrt processing/quality/safety/efficacy
- Veterinary vaccines
  - Thimerosal is only preservative in centrally authorized vaccines
  - Alternatives in some nationally authorized vaccine
  - Replacement has not been addressed
  - Higher amounts per dose, but higher volumes injected
- European Pharmacopeia
- Alternative preservatives
  - A few published papers found with varying results

WHO INC 4 Consultation Session 2
WHO procedure for multi-challenge assay for preservatives - Drew Meek

- Designed to better reflect "multi-puncture" that occurs in the field
- Adequately preserved vaccines can be kept for use in subsequent sessions up to 28 days from first use (WHO Multi Dose Vaccine Policy)
- Study using this method showed
  - DTP / Hep B containing thimerosal, from 16 – 100 ug/dose demonstrated preservative efficacy
  - Limited data with IPV + 2 PE suggested it was less efficacious;
  - Single study arm with Ph Eur method suggested 2PE more effective against Staph. Aureus than thiomersal but less effective against Aspergillus niger.

WHO INC 4 Consultation Session 2
The R and D pipeline for alternative preservatives – Geert V Bossche

- Published literature on alternative preservatives is limited
- Different standards and assays make comparison difficult
- There is no "real" R and D pipeline. Effort is to look at alternatives preservatives used for other products.
- Completely new concepts for preservatives may have unintended consequences.
- Pragmatic approach
  - No ideal alternative preservative
  - No "gold standard" for vaccines because of specificity for each vaccine
- Key problems
  - No selective affinity
  - Tough anti-microbial effectiveness test criteria/Regulatory criteria
  - Allergy, hypersensitivity/product quality and potency
  - Vaccines are tough substrates – narrow range for pH etc, interference due to excipients and protein immunogens
- Potential Strategies
  - Enhance selective affinity?
  - New compounds? Cationic antimicrobial peptides (CAP)
    - In between a disinfectant and antibiotic. Interesting, but not ready to go.
  - Rely on characteristics of active ingredients (antigen or antigen carriers), but depends on antigen
  - Benzyl alcohol is "new" non-vaccine preservative that might be applicable to vaccines
- Development is cost-intensive, time consuming, trial and error, unpredictable, case-by-case, not considered a priority by industry for replacements because no incentive

WHO INC 4 Consultation
Session 1 and 2 Conclusions

- Preservative is required for multi-dose vials
- Well-designed studies have failed to find a causal relationship between prenatal, neonatal, or postnatal exposures to thimerosal in vaccines and a host of neuropsychological outcomes, including autism
  - Evaluation of data on safety that emerges in the future should continue
  - Quantitative Risk Assessment framework might be useful
- Alternative Preservatives
  - Published literature on alternative preservatives is limited
  - Alternative preservatives have variable anti-microbial effectiveness, which differs by vaccine, and have different compatibility with antigens and excipients
  - Alternative preservatives might have concerns about their own toxicity
  - Different anti-microbial effectiveness standards and assays make comparison difficult and relationship of standards to field performance is unclear
  - There is no “real” R and D pipeline but CAP’s and preservatives used for other products might be options in the future
    - But completely new concepts for preservatives may have unintended consequences
  - Regulatory requirements for substituting alternative preservatives are substantial and would likely require a long implementation time