

**Outcomes of
3-4 April WHO informal
consultation on vaccines
in preparation for global mercury
treaty**

Dr Elwyn Griffiths and WHO Secretariat

12 April 2012



**World Health
Organization**

Mercury treaty and vaccines: context

- In 2009, the UN Environmental Programme (UNEP) Governing Council requested an Intergovernmental Negotiating Committee (INC) to prepare a global legally binding instrument on **mercury**.
- The members of the INC are governments, with intergovernmental organizations (eg WHO) and accredited non-governmental organizations able to participate as observers.
- The treaty is to include provisions to reduce the use of mercury in products and processes as part of the overall strategy to reduce risk to human health and the environment from mercury.
- Mercury-containing products used in health care include dental amalgam, thermometers and **thiomersal in vaccines**
- Potential policy options under consideration by the INC;
 - a "positive" list of mercury-added products to be banned
 - a "negative" list; all mercury-added products are banned, except those with specific exemptions
 - other options

WHO inputs

- WHO provided information on mercury in pharmaceuticals in a technical briefing prior to INC3 (Nairobi, Kenya, 2011)
- Countries asked for authoritative evidence on (a) alternative preservatives for vaccines, (b) economic, programmatic and manufacturing implications of moving (globally) to single dose, preservative free vaccines
- SAGE (Nov 2011) agreed:
 - WHO scientific meeting (3-4 April 2012) to review the evidence
 - SAGE discussion (12 April 2012) of immunization policy implications
 - IPAC review (18 April 2012) on immunization practice implications
 - GACVS review (June 2012) of safety of alternative preservatives
- UNEP agrees that WHO provides information to INC4 (June 2012)

Objectives of 3-4 April scientific meeting

(Chair Dr Elwyn Griffiths)

- To exchange information on alternative preservatives and alternative presentations for vaccines
- To develop conclusions based on state-of-the art knowledge
- To present the conclusions to the WHO SAGE, IPAC and GACVS Committees
- To publish the information presented in the consultation on the WHO website

WHO Informal Consultation to develop further guidance on Thiomersal in Vaccines (April 3-4)

- Open information session – objectives of the meeting explained, submissions heard from countries and NGOs.
- Scientific sessions – invited experts, as per WHO policy and practices.
- WHO has already discussed issue of Thiomersal in vaccines several times. In 2002 WHO developed guidance on regulatory expectations related to the elimination, reduction or replacement of Thiomersal in vaccines (WHO Technical Report Series 926, 2004)

Participants at April 3-4 Meeting

- EMA
- FDA
- Public Health Officials
- SAGE Member
- Academia
- Ministries of Health
- Ministries of Environment
- Health Systems Analysts
- PATH
- UNICEF
- Medicines sans Frontiers
- Safe Minds
- Bill & Melinda Gates Foundation
- GAVI Alliance
- IFPMA : DCVMN
- International Federation for Animal Health
- Veterinary vaccine manufacturers
- World Organization for Animal Health
- WHO (HQ, AFRO, AMRO, EMRO, EURO)

Alternatives Preservatives

(Sessions 1 and 2; Rapporteur, R Ball, GACVS member)

- **Current WHO position** on thiomersal used as a preservative in multi dose vials and in vaccine production
 - safety update on thiomersal; important to review latest data
- **Alternatives preservatives** for vaccines instead of Thiomersal
 - effectiveness and safety update on alternative preservatives
 - experience from other fields (biotherapeutics; veterinary vaccines; non-biological products)
 - pharmacopeial tests for alternative preservatives
 - R&D pipeline for alternative preservatives

Alternative Presentations

(Sessions 3 and 4; Rapporteur, C Morgan, IPAC member)

- Assess the impact of single dose presentations on the immunization supply chain
- Trends in use of multi-dose vials and vaccine supply
- Perspectives from immunization programme stakeholders



Sessions 1 and 2

Update on Safety of Thiomersal Alternative Preservatives

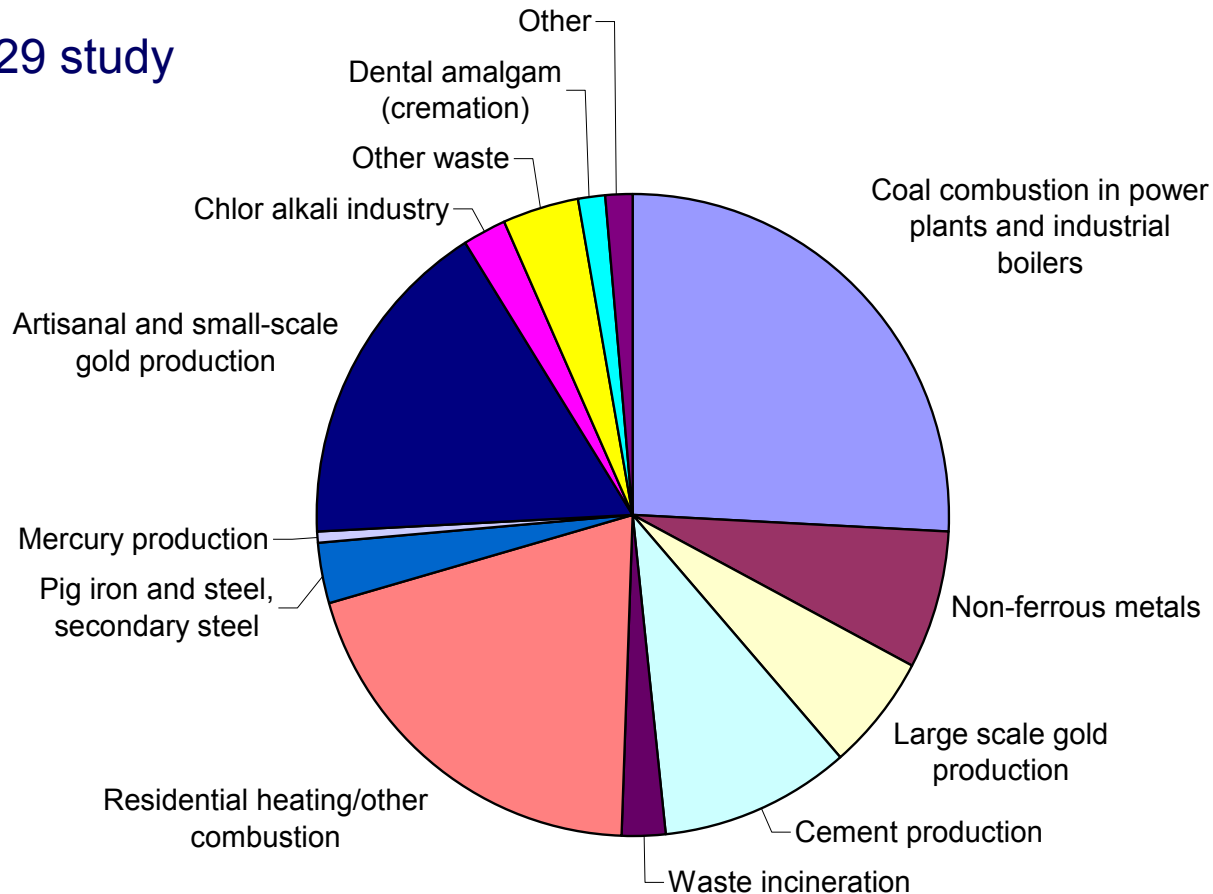


Current WHO position on the use of thiomersal in human vaccines

- The amount of mercury involved with thiomersal use in vaccines is exceedingly small compared to other sources of mercury
- There is no evidence that suggests a possible health hazard with the amounts of thiomersal currently used in human vaccines
- WHO recommends multi-dose vaccine vials for routine immunization programmes in many countries because they are safe and effective, they limit the required storage capacity and help reduce vaccine costs
- Alternative presentations would incur significantly higher costs in manufacturing procedures and new regulatory approvals, thereby limiting the ability to offer affordable vaccines

Greatest health gains will be made by addressing the main sources of mercury

UNEP para 29 study



World thiomersal production is small in comparison to other mercury sources

- World thiomersal production is small, estimated at 2,434 kg
 - 52% of which goes to human vaccines and
 - 36% to animal vaccines
 - Production volumes have been steadily decreasing
 - **May be only one single producer of pharmaceutical-grade thiomersal**
 - **Vaccine security issues**
- **Thiomersal = Ethyl mercury**



Safety of Thiomersal: update – Rob Mitkus, US FDA

- Numerous well-designed epidemiological studies conducted in many countries 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
- New mathematical models (e.g Complete Quantitative Risk Assessment model) being developed to further evaluate the kinetic and toxicological differences between ethyl and methyl mercury
 - important to continue to evaluate new data

Summary: benefits of vaccination with thiomersal containing vaccines outweigh any potential risk from thiomersal

Safety of thiomersal and alternative preservatives – Michael Pichichero, Univ. Rochester, USA

Methods: Medline search 2008 to present – thimerosal/ vaccines/autism

- Blood and hair mercury measurements – Argentina, China, Amazon
 - half life of thiomersal much shorter than for methyl mercury
 - autistic disorder children had similar total mercury in blood compared w/ unaffected controls
 - Thiomersal contribution to total blood mercury very low compared to methyl mercury
- Epidemiological studies – US, Amazon, Italy, Poland
 - Some studies found no association between thiomersal 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 macaques)
 - Some studies found associations between thiomersal exposure and adverse behavioral, histopathological, or neurochemical outcomes; 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)
 - thiomersal exposures varied by body weight; in vitro model showed interactions of very high dose thiomersal with various biological molecules; exploratory principal component analysis

**Summary: no new evidence questioning safety of thiomersal
as a preservative in multi-dose vials**



Experience with alternatives to thiomersal from other fields

International Alliance for Biologicals

- Survey of members of IABS; response rate 10%, Europe and “Rest of World”
- Uses of Thiomerosal
 - Human vaccines – preservatives, **manufacturing eg inactivating agent for pertussis vaccine**
 - Veterinary vaccines – anti-microbial in multi-dose vials; inactivating agent.
 - Sera (anti-venoms) – used as a preservative in production
 - Biotherapeutics – not used; methylparabenz or metacresol instead
- Alternative to thiomerosal?
 - Single dose vials; strict GMP; 2-PE in DTaP, IPV; phenol in typhoid vaccine and anti-venoms; Benzethonium chloride in anthrax vaccines
- Required properties of a preservative?
 - Antimicrobial compatibility with formulation
 - No negative effect on antigens
- Why has thiomersal not been replaced?
 - Technical constraints
 - No market pressure (especially for veterinary vaccines except for cat vaccines)
 - Regulatory consequences – high costs for approval, no harmonization
- Does anti-microbial testing reflect need?
 - **Most preservatives seem to work, but no data on how the testing requirements are related to effectiveness in field**
 - In some countries no request for microbial testing for veterinary vaccines; need stability testing



Efficacy of alternative preservatives, review of testing practices – Gwenael Cirefice, EMA

- Human Vaccines
 - Thiomersal is the only preservative in EMA centrally authorized human vaccines
 - Alternative preservatives in some nationally registered vaccines
 - Evolution toward elimination of preservatives through switching to single dose vials
 - Except thiomersal in multi dose vials for pandemic influenza vaccines
 - **Little comparative data available with alternatives**
 - **Risk with replacement**
 - High concentration of alternative preservative may be needed
 - Uncertainty regarding processing/quality/safety/efficacy
- Alternative preservatives
 - Few published papers with varying results
 - Ph.Eur adapted criteria for preservatives since alternative preservatives did not meet previously established anti-microbial effectiveness criteria despite safe use of the vaccines for many years

The R and D pipeline for alternative preservatives

- Published literature on alternative preservatives is limited
- Different standards and assays make comparison difficult
- **There is no “real” R and D pipeline.**
- **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
- Development is cost-intensive, time consuming, trial and error, unpredictable, case-by-case, not considered a priority by industry for replacements because no incentive
- Key problems
 - No selective affinity of preservatives
 - Tough anti-microbial effectiveness test criteria/Regulatory criteria
 - Allergy, hypersensitivity/product quality and potency concerns
 - **Vaccines are sensitive substrates** – narrow range for pH etc, interference due to excipients and protein immunogens
- Potential Strategies
 - Enhance selective affinity?
 - New compounds? Cationic antimicrobial peptides – not ready to go
 - Rely on characteristics of active ingredients (antigen or antigen carriers),
 - Benzyl alcohol is “new” non-vaccine preservative that might be applicable to vaccines but depends on antigen

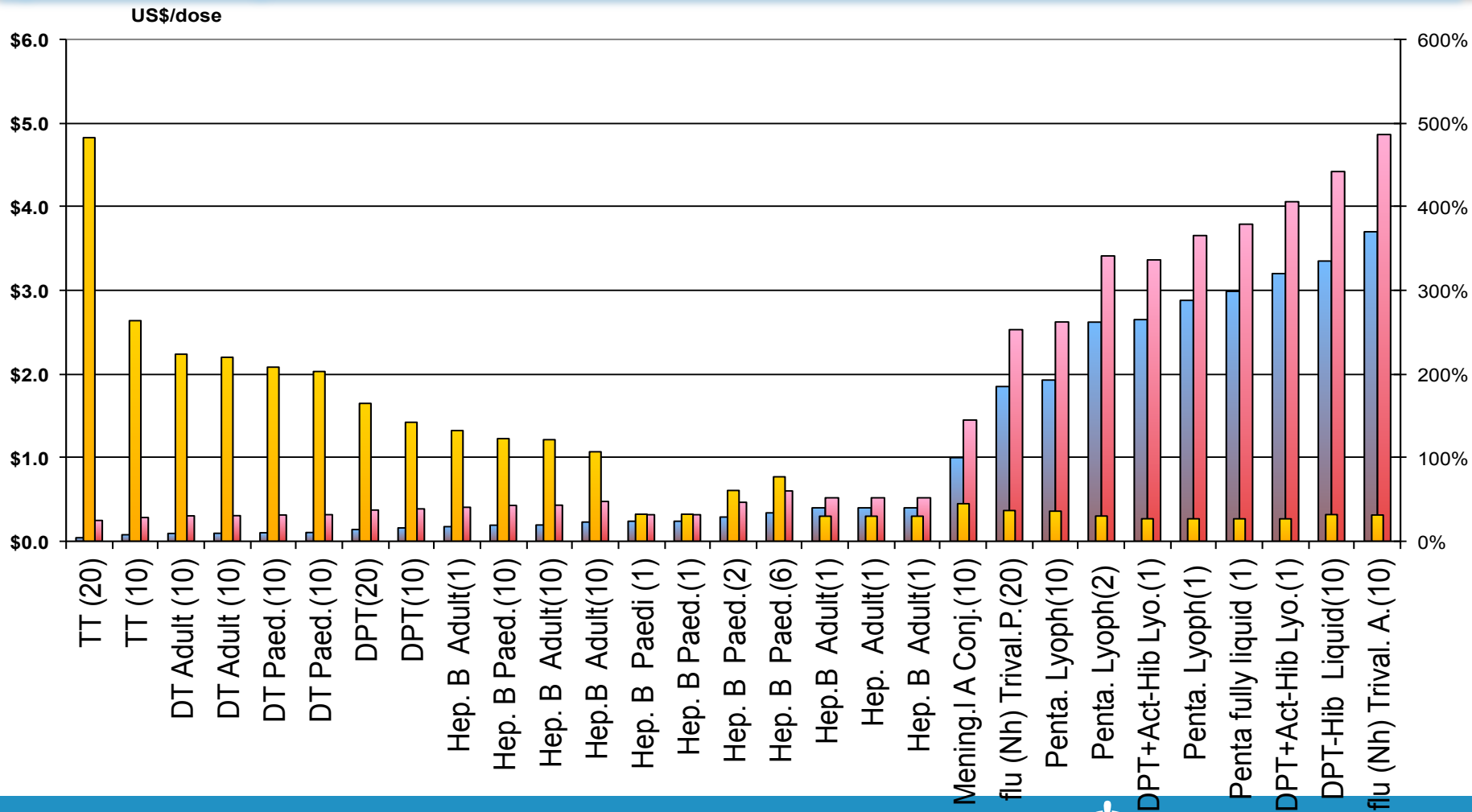
Sessions 3 and 4

Single dose thiomersal-free presentations Operational issues

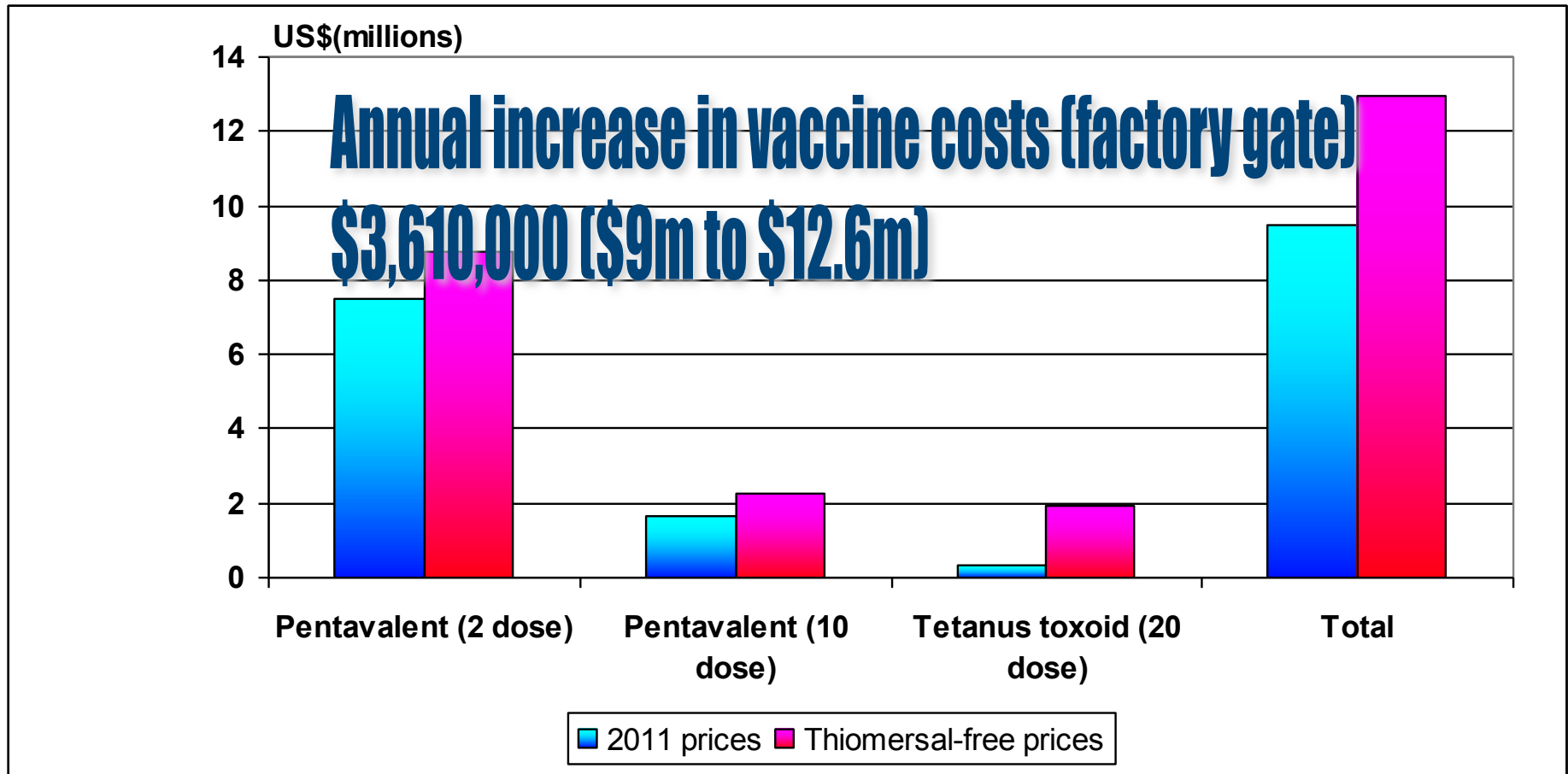
Costs, storage and waste implications of switching to single-dose thiomersal free vaccines

- Development costs and time are substantial
 - Transition may take 10 years, including clinical trials, licensing, expansion of manufacturing capacity, then WHO pre-qualification
- Storage volume requirements will more than triple
 - The increases affect raw materials suppliers, manufacturers, procurers and distributors and users in countries.
 - Some estimates may be up to nine-fold – particularly when considering the increases required at national and subnational levels
- Waste management implications are of the order of a tripling of impact, with additional vaccine vial waste and production outputs.
- Disproportionately greater impact for cheaper traditional vaccines

Cost implications: price per dose for Thiomersal free

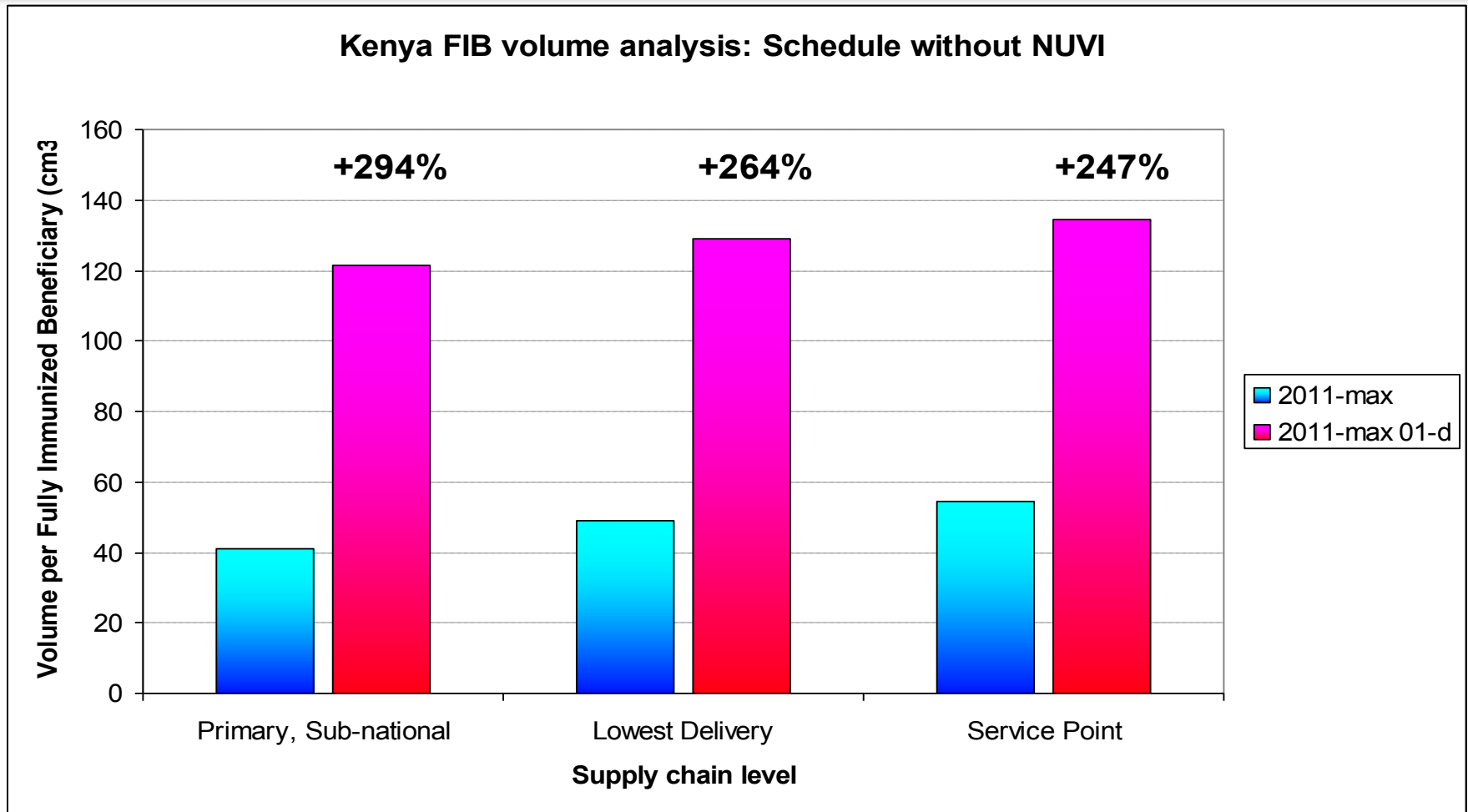


Example of country level (Kenya) vaccine cost increase that would be required by single-dose preservative-free vaccines



Note: Kenya is in transition from 2-dose liquid-lyo pentavalent to 10-dose fully liquid.

Example of country level volume increase requirements that would be required by single-dose preservative-free vaccines



NUVI=New and Underutilised Vaccine Introduction



Operational implications of preservative-free (no multi-dose)

- Workload implications – a project "Optimize" time-motion study shows single dose immunizations as 38% slower
- Intensive work would be required to seek regulatory approval of preservative free formulations, similar to that required for alternative preservatives
- Potential for interruption to vaccine supply and coverage
 - “Campaign” style operations likely to be compromised, whether for influenza, pandemic preparedness, meningococcal vaccine, or routine intensification activities
 - Other routine settings may be compromised, if storage and supply is disrupted

Country and procurer perspectives

- Included China, Sri Lanka, UNICEF, PAHO
 - Despite the availability of single-dose presentations, 10 dose vials are most commonly used and there is no evidence of increasing use of 1 dose vials
 - Multi-dose vials are commonly used in UNICEF procuring countries and are likely to continue to be a vital part of immunization programs
- Confirm continued demand for multi-dose vaccines
 - Driven by operational uses and also by need to accommodate newer vaccines
- A ban on thiomersal would disproportionately affect the ‘basic’ vaccines and diseases of significance to adult and child survival in LMICs
- Case study from Chile on
 - “a political problem requiring a technical solution”
 - resulting in a shift to thiomersal free vaccines, and other changes in the programme (OPV to IPV),
 - Illustrating the point that such shifts should not be made in isolation but accompanied by other decisions on vaccine programme with major resource implications

Manufacturers perspectives DCVMN and IFPMA

- Confirm large investment of time and money that would be needed to seek an alternative preservatives, or a switch to preservative-free
- Switch to single dose formulations may decrease manufacturing capacity, commercial viability and ultimately vaccine supply
- Call for evidence-based policy, balancing public health risks and long-term planning if any switch is contemplated

Veterinary vaccines

- Veterinary vaccines are also highly regulated, because they need to account for food chain issues,
- They are provided in high volumes (up to 100-dose presentations) and settings where single-dose formulations are not feasible
- Thiomersal is used in manufacture as well as a preservative and occupies a unique place in animal health products. As with human vaccines, there is no satisfactory alternative candidate preservative
- Consequences if thiomersal is withdrawn include
 - Compromised animal health
 - Compromised human health (including zoonoses) and food chain
 - Impact on economic development / Environmental consequences
- Emphasizes the need for thiomersal to be maintained as a global resource for animal health

Based on presentation by Barbara Freischem



Decisions have consequences: coordinated communication is essential to maintain public confidence

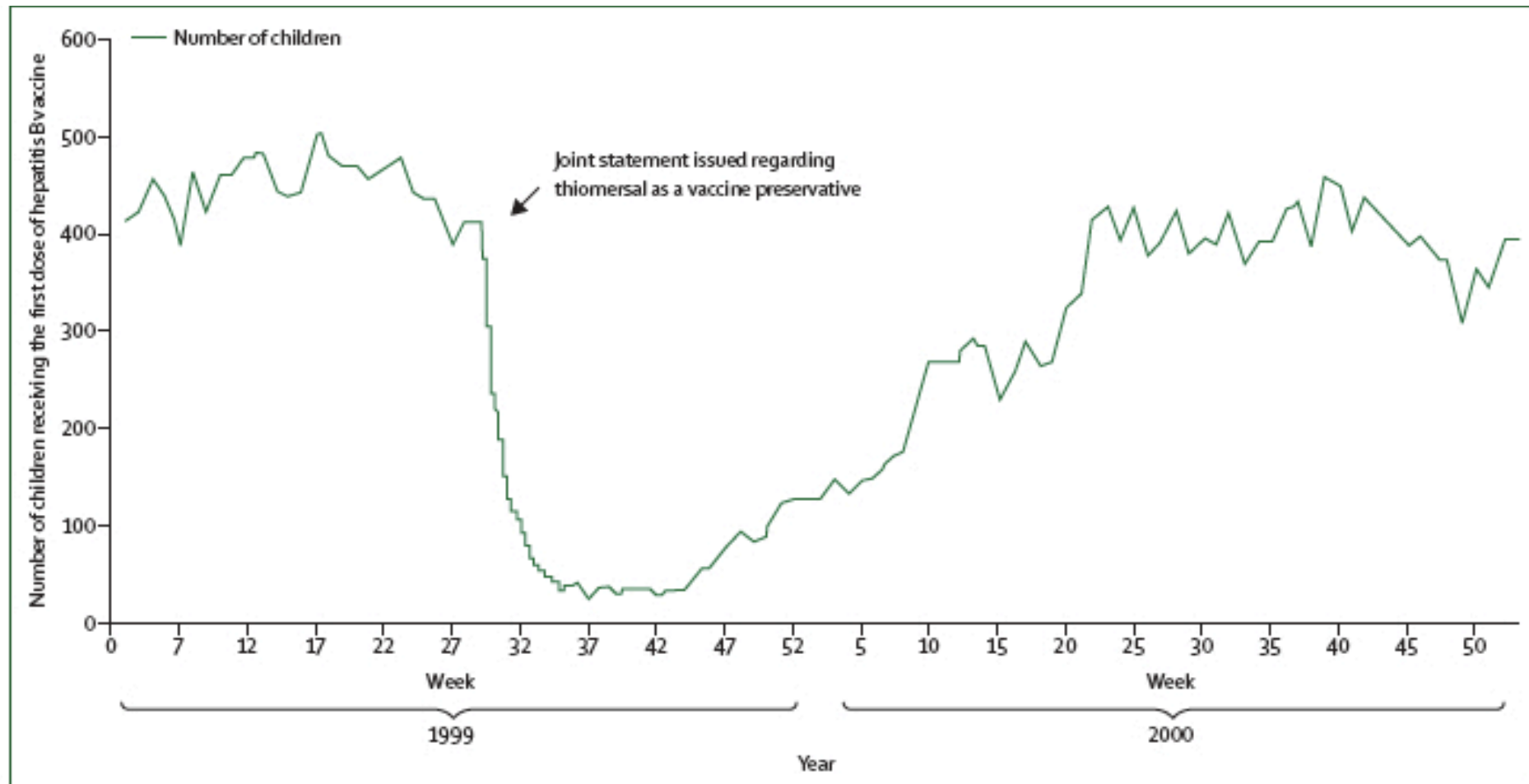


Figure 1: Number of children who received the first dose of hepatitis B vaccine less than 5 days after birth (USA, 1999–2000)
Data from the US Centres of Disease Control and Prevention's morbidity and mortality weekly report.³⁸

Conclusions from Session 1 and 2

- Need for preservative for multi (5- or 10-) dose vials for specific vaccines
- Well-designed studies have **failed** to find a causal relationship between prenatal, neonatal, or postnatal exposures to thiomersal 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

Conclusions from Session 1 and 2

● Alternative Preservatives

- Published literature on preservatives is limited
- Preservatives have variable anti-microbial effectiveness, which differs by vaccine
- Concerns that alternative preservatives might have their own toxicity issues
- 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
- Regulatory requirements for substituting alternative preservatives are substantial and would likely require a long implementation time

Session 3 and 4 conclusions

- A shift to single dose preservative-free vaccines would have major implications:
 - Multi-fold increases in costs of vaccines, storage and waste
 - Potential disruptions to supply of vaccines
 - Other operational disruption with potential for fewer vaccinations for both human and animal health
- Need for multi-dose formulations will continue
 - strengthen support for current preservative supply, noting the vulnerability of the sole manufacturer
 - Continue long-term search for alternative preservatives

Session 3 and 4 conclusions

- **Communications are important** and need careful coordination to emphasize
 - Country and agency concerns expressed in this meeting
 - Work for a unified position rather than country by country
 - That the position on safety of Thiomersal remains unchanged, although monitoring will continue
 - Removing Thiomersal could have major negative impact on vaccine supply and global public health

Spare slides

Geographic distribution of participants (non-WHO)

- Australia
- Belgium
- Brazil
- Chile
- France
- Germany
- India,
- Indonesia
- Jordan
- Nigeria
- People's Republic of China
- Sri Lanka
- Switzerland
- The Netherlands
- United Kingdom
- United States of America

