

**WHO Informal Consultation to develop further guidance
on vaccines for the UNEP-convened Intergovernmental
Negotiating Committee Meeting 4 (INC4)**



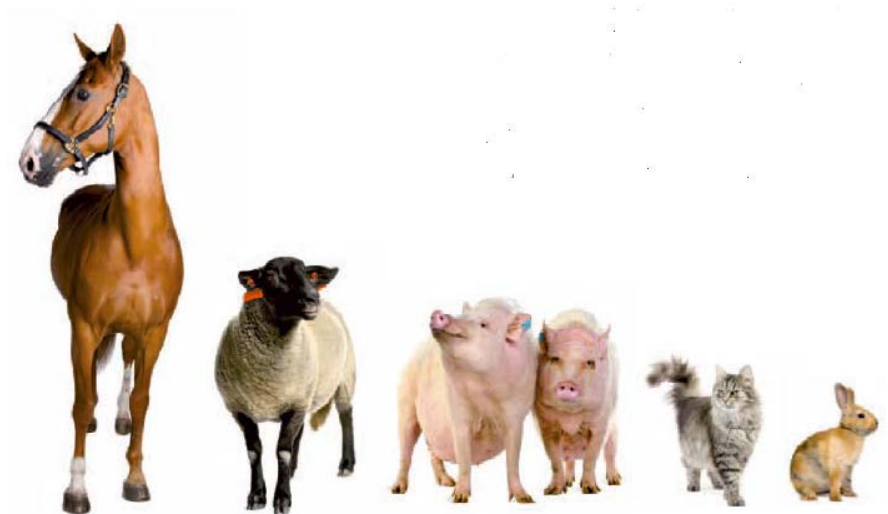
Manufacturing perspectives on alternatives to thiomersal – animal health

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Presentation outline

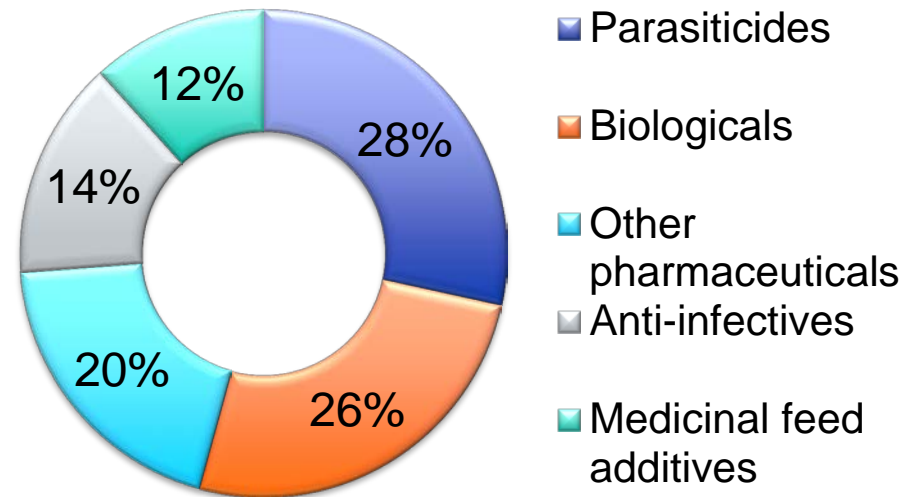
- 'Our' world
- Thiomersal in animal health products
- Environmental consideration
- Consequences of thiomersal becoming unavailable
- Alternatives to thiomersal
- Summary



Vaccination in animal health

- Prevention is key in animal health
- Distinct animal population dynamics, different vaccination strategies
 - Companion animals
mostly individual patients
single-dose vaccines
 - Livestock animals
Mostly groups of animals
multi-dose vaccines
 - Wildlife
May be scattered and difficult to access
- Our products prevent disease in animals and
 - reduce animal suffering
 - stop zoonotic diseases from infecting people
 - help maintain the supply of nutritious animal-derived food

% share of global AH market



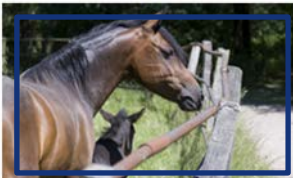
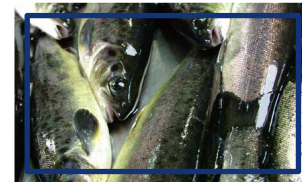
Vaccination in animal health versus human health

- Many more different vaccines in animal health than in human health
- Billions of animals are vaccinated on an annual basis (short life cycles)
- Most production animals are held in groups, many kept in difficult to access areas, single-dose presentations are not feasible (increased weight of bottles, increased waste, increased time for vaccinations),
- Many species would be left unprotected without thiomersal
- Many diseases are zoonoses; vaccination not only prevents humans from being infected, it also interrupts reservoir cycles
- Highly regulated, as for human biologicals
- Pertinent differences:
 - Different clinical settings & sanitary conditions
 - Differences in animals' immune systems allow for slightly different purity requirements
 - Need to think about human safety:
 - Operator safety / Food safety (residues of e.g. adjuvants, preservatives)



'Our' world

Some of our clients



How (where) are livestock animals vaccinated? Some examples



Diseases prevented by thiomersal containing vaccines

- Usually high morbidity or high mortality
- **High morbidity** disease examples:
Foot-and mouth disease – cattle
Infectious bronchitis - poultry
- **High mortality** examples:
Rinderpest – cattle
Newcastle disease (some strains)
- poultry



Rinderpest in 1900



Foot-and-mouth disease



Infectious bronchitis



Newcastle disease



Foot and mouth symptoms (photo courtesy USDA)



Exotic Newcastle disease

Thiomersal in animal health products

A unique substance

- Thiomersal has undergone assessment for human food safety (in the EU with the conclusion that up to 0.02% in the finished product no MRLs are necessary and above 0.02% is therefore not allowed);
- Thiomersal uses start with manufacture: thiomersal actively contributes to inactivation or stabilisation of some antigens and can facilitates filtration (little risk of release into the environment);
- Legal requirement for preservatives in multi-dose presentations of inactivated vaccines to avoid cross-contamination of the vaccinated animals;
- Veterinary vaccines often are less purified than human vaccines,
 - a higher protein load leads to reduction of preservative efficacy;
 - only thiomersal can cope well enough with these negative factors;
- Thiomersal is the only generally applicable preservative;
 - other preservatives work only well in a few individual vaccines;
 - antibiotics may be an alternative, but not acceptable;



Environmental considerations

Animals, people, environment

- *How much thiomersal do animals receive during vaccination?*

From 0.1-2 µg/kg bw (cattle, pigs, horses) up to 30 µg/kg bw (poultry); in the EU vaccines may contain up to 0.02% thiomersal; in cattle a vaccine dose of 5 ml would add 0.001 mg thiomersal per animal, equivalent to 0.0005 mg HG.

- *Does thiomersal accumulate in animals?*

Available data indicate that ethylmercury, the metabolite of thiomersal, is well excreted, mostly in faeces and the rest in urine.

- *Do animals normally take up mercury and what is the added burden through thiomersal in vaccines?*

Normal uptake in animal varies: grass-fed cattle (Netherlands) take up 0.2 mg HG/day. When fed on diets including fish meal, the normal intake would likely be higher. One vaccination would add 0.25% to the daily intake.

- *So, the environment?* Well, at most one dose would add 0.25% HG to the normal excretion. On the other hand sick animals are less productive, effectively wasting natural resources (feed, water) while producing more effluents per animal-derived food.

- *What about the mercury in the product?*

A 500 ml bottle of vaccine at most contains 0.1 mg thiomersal, i.e. 0.05 mg HG.
Vets try to use up all vaccines in a multi-dose container.



Alternatives to thiomersal

Criteria to be considered for alternatives (*not exhaustive*)

- Inherent reactivity with actives and excipients
- Solubility within effective ranges
- Analytical methods
- PET
- Concentration required
- Storage criteria
- Worker safety issues
- Method of sterilization
- Mechanism of action
- Effective pH range
- Shelf life and stability in the final product
- Safety to the target animals
- Human food safety – MRLs will need to be set
- Intellectual property
- Regulatory acceptance



Alternative candidates?

- No single other substance can do what thiomersal does, for some products suitable alternatives are not known; needs to be a bactericide
 - Complication of manufacturing processes
- Food safety assessment a pre-requisite (e.g. MRL assessment in the EU)
=> 2-phenoxy-ethanol has **not** been assessed in the EU
- Issues with current alternatives in animal health products (e.g. toxicity, antimicrobial resistance development)
- Significant hurdles to overcome
 - A large number of different vaccines for different species exist in animal health
 - Investigation of viable alternatives without compromising product quality, efficacy and stability
 - Redeveloping the production processes for all animal vaccines concerned
 - Developing regulatory dossiers for alternative preservatives
 - Gaining regulatory approval for changes products
- Changing to other preservatives not always possible, will take time and may not be economically viable



Consequences

If thiomersal were to become unavailable

- Animal health would be compromised
 - Many animal vaccines contain thiomersal
 - Single dose presentations not feasible for livestock vaccines
- Human health would be compromised
 - Stop zoonotic disease in animals before it affect humans
 - Challenge to ensure a good supply of highly nutritious animal derived food if animals are unprotected and die or become less productive
- Human economic development would be compromised
 - Livestock in many countries around the world is a means of economic development – of the individual as well as of a country's economy
- Environmental consequences
 - Compromised animal health has negative effects on the environment
 - Direct waste of resources through animal death
 - Higher demand on resources through less effective production – more animals need more feed and water to produce the same amount of food
 - higher waste – more animals produce more waste for the same amount of food



Thiomersal in animal health products

- Disease prevention through vaccination is a major aspect of animal health
- Vaccines for livestock by necessity are multi-dose presentations, where preservatives are needed
- Single dose presentations are not feasible for livestock vaccines due to logistical challenges and increased waste
- Additional exposure to mercury through food is minuscule, added environmental release as well (0.25% of estimate intake in feed added by vaccination)
- Replacement by other preservatives comes at significant costs
 - costs to manufacturers to find alternative, carry out the required testing, and request regulatory approval,
 - costs in animal lives to carry out the tests,
 - costs to agricultural productivity if vaccines were discontinued,
 - Costs to economic development.



Thank you for your attention!

