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Alternatives to thiomersal as preservatives for vaccines

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

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Alternatives to thiomersal as preservatives for vaccines

- Thiomersal is the only preservative used in centrally authorised human vaccines (mainly Influenza pandemic vaccines)
- Alternative preservatives in some human vaccines registered nationally or via MRP/DCP (e.g. phenol in Typherix®, Typhim Vi®, Pneumovax II®, 2-phenoxyethanol in Tetravac®, Pediacel®, Revaxis®, Repevax®)
- Evolution towards the **elimination** of preservatives in vaccines → monodose presentations
- Most new vaccines presented as preservative-free, single dose presentations
- Multidose vaccine without preservative: Celvapan®/Vepacel®
  - After opening, Celvapan®/Vepacel® are to be used within 3 hours
  - In comparison, Pandemrix® and Focetria® should be used within 24 hours

Alternatives to thiomersal as preservatives for vaccines (cont' d)

- Use of thiomersal mainly based on historical experience rather than comparison (e.g. Influenza vaccines)
- Little comparative data available between use of thiomersal and an alternative preservative
- Risk with replacement:
  - Substituting an efficacious preservative by an alternative which may require higher concentration
  - Uncertainty with regard to effect on processing / stability / efficacy when preservative in existing vaccine is changed

Thiomersal-preserved human vaccines (centralised procedure)

Vaccine	Vaccine type	Amount of thiomersal	Presentations
Pandemrix®	H1N1 pandemic vaccine	5 µg/dose	10-dose vial
Focetria®	H1N1 pandemic vaccine	50 µg/dose	10-dose vial
Daronrix®	H5N1 mock up vaccine	50 µg/dose	Monodose vial or ampoule 10-dose vial or ampoule
Pandemic Influenza vaccine H5N1 GSK®	H5N1 mock up vaccine	5 µg/dose	10-dose vial
Pumarix®	H5N1 mock up vaccine	5 µg/dose	10-dose vial
Foclivia®	H5N1 mock up vaccine	50 µg/dose	10-dose vial
Prepandrix®	H5N1 pre-pandemic vaccine	5 µg/dose	10-dose vial
Tritanrix hepB®	DTwP-HBsAg combination vaccine	8 µg/dose	2-dose or 10-dose vial

Alternatives to thiomersal as preservatives for veterinary vaccines

- Thiomersal is the only preservative used in centrally authorised veterinary vaccines (mainly large animals)
- Alternative preservatives in some veterinary vaccines registered nationally or via MRP/DCP (e.g. methyl parahydroxybenzoate in Bovilis BVD®, formaldehyde in Rotavec Corona®)
- There are modern multidose vaccines authorised not containing thiomersal (e.g. Bovilis BTV 8®)
- Use of thiomersal also mainly based on historical experience rather than comparison
- Risk of replacement has not been addressed

Thiomersal-preserved veterinary vaccines (centralised procedure)

Vaccine	Vaccine type/species	Amount of thiomersal	Presentations
Bluevac BTV8®	Bluetongue vaccine/ sheep + cattle	200 µg/dose sheep 400 µg/dose cattle	26, 50, 126 doses in sheep 13, 25, 63 doses in cattle
Circovac®	Porcine circovirus vaccine/ pigs (gilts, sows and piglets)	200 µg/dose sows 50 µg/dose piglets	5, 25 doses in gilts, sows 20 and 100 doses in piglets
Coxevac®	Coxiella burnetii vaccine/ cattle + goats	440 µg/dose cattle 220 µg/dose goats	10, 25 doses in cattle 20, 50 doses in goats
Gripovac 3/ Respiporc 3®	Swine influenza vaccine/ pigs	210 µg/dose	10, 25, 50 doses
Neocolipor®	*E. coli* vaccine/ pigs	200 µg/dose	5, 10, 25, 50 doses
Netvax®	*Clostridium perfringens* vaccine/ chickens	35-50 µg/dose	1000 doses

Thiomersal-preserved veterinary vaccines (centralised procedure)

Vaccine	Vaccine type/species	Amount of thiomersal	Presentations
Suvaxyn Aujeszky 783+ O/W®	Aujesky's disease vaccines/ pigs	150 µg/dose	10, 50, 100 doses
Suvaxyn PCV®	Porcine circovirus vaccine/ pigs (piglets)	100 µg/dose	10, 50, 125 doses
Zulvac 1 Bovis®	Bluetongue vaccine/ cattle	200 µg/dose	10, 50 and 120 doses
Zulvac 1 Ovis®	Bluetongue vaccine/ sheep	200 µg/dose	10, 50 and 120 doses
Zulvac 1+8 Bovis®	Bluetongue vaccine/ cattle	200 µg/dose	10, 50 and 120 doses
Zulvac 1+8 Ovis®	Bluetongue vaccine/ sheep	200 µg/dose	10, 50 and 120 doses
Zulvac 8 Bovis®	Bluetongue vaccine/ cattle	200 µg/dose	10, 50 doses
Zulvac 8 Ovis®	Bluetongue vaccine/ sheep	210 µg/dose	50, 120 doses

Considerations for veterinary vaccines

- Amount of thiomersal per dose is generally higher for veterinary vaccines than human vaccines but doses administered are generally higher

- Thiomersal is referred to in the Regulation (EC) 37/2010 (Maximum Residue Limit regulation) as allowed only in multidose vaccines up to a concentration of 0.02%

- The multidose presentations for veterinary vaccines exceed human multidose presentations by 10 fold or more

Use of an alternative antimicrobial preservative in vaccines

All vaccines must comply with the current European Pharmacopoeia (Ph. Eur.) general monograph 0153 - "Vaccines for Human Use"

The *antimicrobial preservatives* section of monograph 0153 requires that the efficacy of the antimicrobial preservative is evaluated as described in Ph. Eur. chapter 5.1.3 – "Efficacy of antimicrobial preservation".

Courtesy of Dr. Emmanuelle Charton, EDQM

Acceptance criteria in chapter 5.1.3

In chapter 5.1.3, the criteria for evaluation of antimicrobial activity are given in terms of the log reduction of viable microorganisms

Table 5.1.3-1 Acceptance criteria for parenteral preparations

		Log reduction				
		6 h	24 h	7 d	14 d	28 d
Bacteria	A	2	3	-	-	NR
	B	-	1	3	-	NI
Fungi	A	-	-	2	-	NI
	B	-	-	-	1	NI

NR: no recovery.

NI: no increase ► in number of viable micro-organisms compared to the previous reading. ◄

The A criteria express the recommended efficacy to be achieved. In justified cases where the A criteria cannot be attained, for example for reasons of an increased risk of adverse reactions, the B criteria must be satisfied.

Courtesy of Dr. Emmanuelle Charton, EDQM

If neither the A nor B criteria in chapter 5.1.3 are satisfied

The general vaccines monograph (0153) also states:

If neither the A criteria nor the B criteria (in chapter 5.1.3) can be met, then in justified cases the following criteria are applied to vaccines for human use

- bacteria, no increase at 24 h and 7 days, 3 log reduction at 14 days, no increase at 28 days;
- fungi, no increase at 14 days and 28 days.

Courtesy of Dr. Emmanuelle Charton, EDQM

Reasons for additional criteria

The criteria in monograph 0153 were included when the current antimicrobial preservatives section was introduced in 2001 (Ph. Eur. edition 4.0) because the preservatives in many vaccines on the market did not comply with criteria A or B of chapter 5.1.3 although they had been satisfactorily used for many years.

Courtesy of Dr. Emmanuelle Charton, EDQM

Comparative antimicrobial effectiveness of vaccine preservatives in scientific literature

Thiomersal vs. 2-phenoxyethanol (2-PE)

• 2-PE (2.5 mg/dose) and thiomersal (50 µg/dose) were equally effective in inactivating challenge doses of a yeast, Gram-negative and -positive bacteria in a DTwP vaccine (USP method)

Lowe I and Southern J, The antimicrobial activity of phenoxyethanol in vaccines, Lett. Appl. Microbiol. 1994, 18, 115-116

• 2-PE (0.5% w/v) showed lower antimicrobial activity than thiomersal (0.01% w/v) against yeast and mould at low temperature (4C) in an adsorbed DTaP vaccine (JP method)

Komatsu E et al., Influence of temperature on the efficacy of 2-phenoxyethanol as a preservative for adsorbed diphtheria-purified pertussis-tetanus combined vaccine, J Health Sc 48(1) 89-92 (2002)

Comparative antimicrobial effectiveness of vaccine preservatives in scientific literature (cont'd)

2-PE vs. thiomersal vs. other preservatives (phenol, m-cresol, methyl- and propyl-parabens)

- 2-PE (5.0 mg/dose) met the Ph. Eur. acceptance criteria (B) and provided a superior antimicrobial effectiveness in a Prevenar 13 formulation

- Thiomersal (0.01%) or other preservatives did not meet the Ph. Eur. acceptance criteria (A/B). The rate of growth inhibition of thiomersal on S. aureus was significantly lower in single and multi-challenge studies.

Khandke L et al., Preservative of choice for Prevenar 13 in a multi-dose formulation, Vaccine 29 (2011) 7144-7153

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