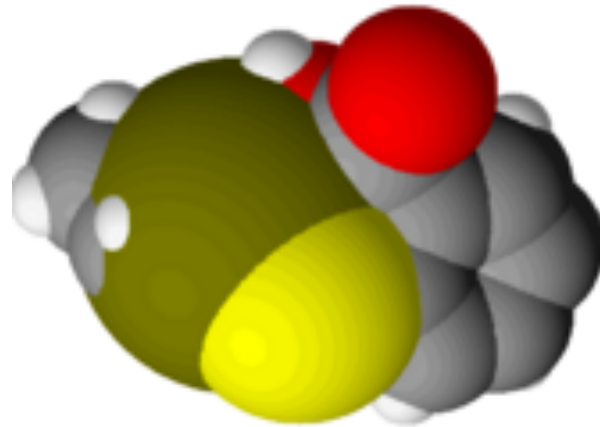


Indicative operational, financial and environmental impact of Thiomersal-free vaccines



Anthony Battersby & Andrew Garnett
FBA Health Systems Analysts



Methodology

- Questionnaire sent to 35 vaccine manufacturers:
23 of 35 WHO-prequalified manufacturers responded. (66% response)

WHO questionnaire on thiomersal-containing vaccines February 2012

Manufacturer:

Respondent:

Email address for correspondence:

1 Please list all your vaccine and presentation combinations which currently contain thiomersal. Include any products made by subsidiary companies. Insert additional rows if needed.

Product	Presentation. Choose from list, or specify alternative	Quantity produced in 2011 (doses)	Price per dose 2011 (USD)

2 Do you manufacture thiomersal-free versions of any vaccines and sera listed above?

If YES, please complete the following table. Insert additional rows if needed.

Product	Presentation. Choose from list, or specify alternative	Quantity produced in 2011 (doses)	Price per dose 2011 (USD)

3 Could any of your current range of vaccines use Phenoxylethanol instead of Thiomersal?

If YES, please list these products

Product

4 Are there any other mercury-free preservatives that you could use?

If YES, please list these preservative options

Preservative

5 Would phenoxylethanol or another preservative give the same shelf life as the thiomersal?

If NO, please comment on likely shelf life:

6 Are there any other techniques, such as physical barriers which could allow preservative-free multi-dose vials to be used safely in accordance with the existing WHO multi-dose vial policy?

7 What would be the likely development cost of replacing thiomersal with another preservative or barrier device?

8 Alternatively, what would be the likely development cost of introducing a preservative-free range of vaccines?

9 How long would it require for you to be able to apply for a licence for vaccines without thiomersal?

10 How long would re-licencing take?

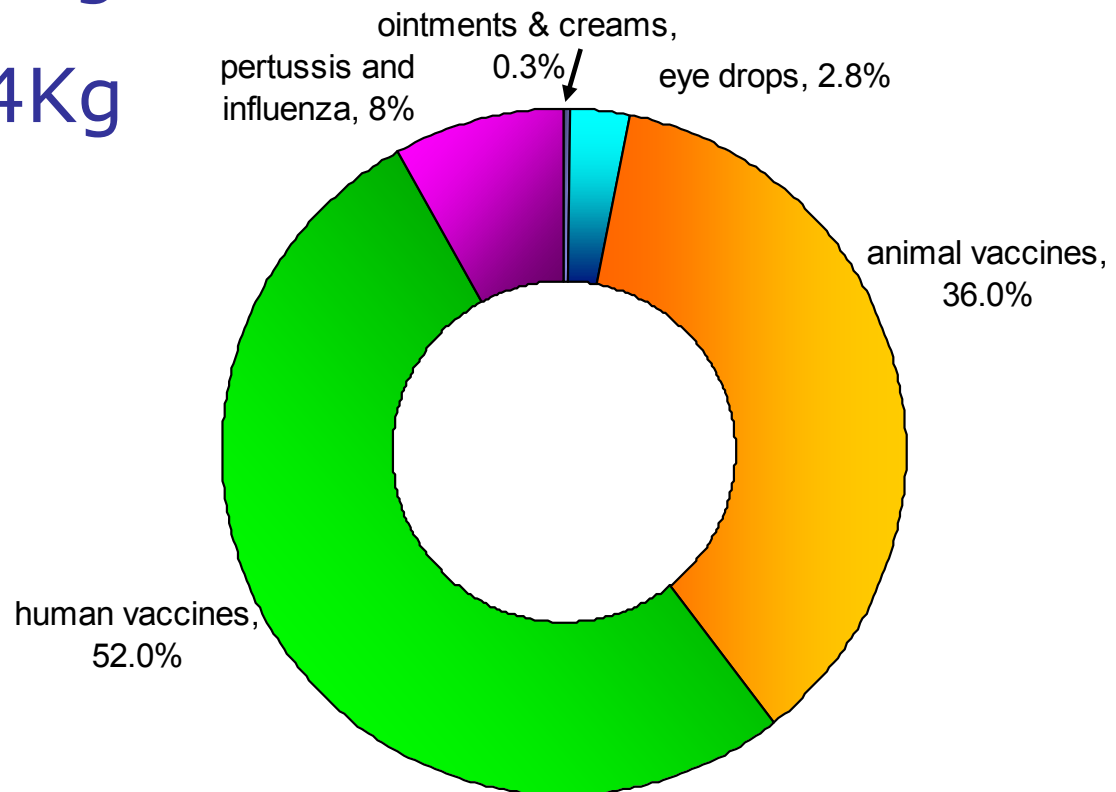
11 What would be the likely affect be on the cost of the vaccine (percent increase or decrease)

Methodology

- Discussions with vaccine and Thiomersal manufacturers
- Modelling based on PAHO-UNICEF 2011 procurement quantities and world data extrapolated from *State of the World's Children 2011*
- Case study based on one country data
- Infrastructure costs from PQS, cold room manufacturer and other sources

World production of Thiomersal

- 1 manufacturer of pharmaceutical grade Thiomersal?
- 1993: 10,000Kg
- 2011: 2,434Kg



Vulnerabilities

- Single manufacturer of pharmaceutical grade Thiomersal.
- Declining market for Thiomersal
- One year's assured stock of Thiomersal
- Basle Convention on movement of hazardous waste may prevent movement of raw material (mercuric chloride)
- In 2012 UNICEF has interruptions in supply for DPT, YF, PCV & RV.

Development COSTS to go Thiomersal-free

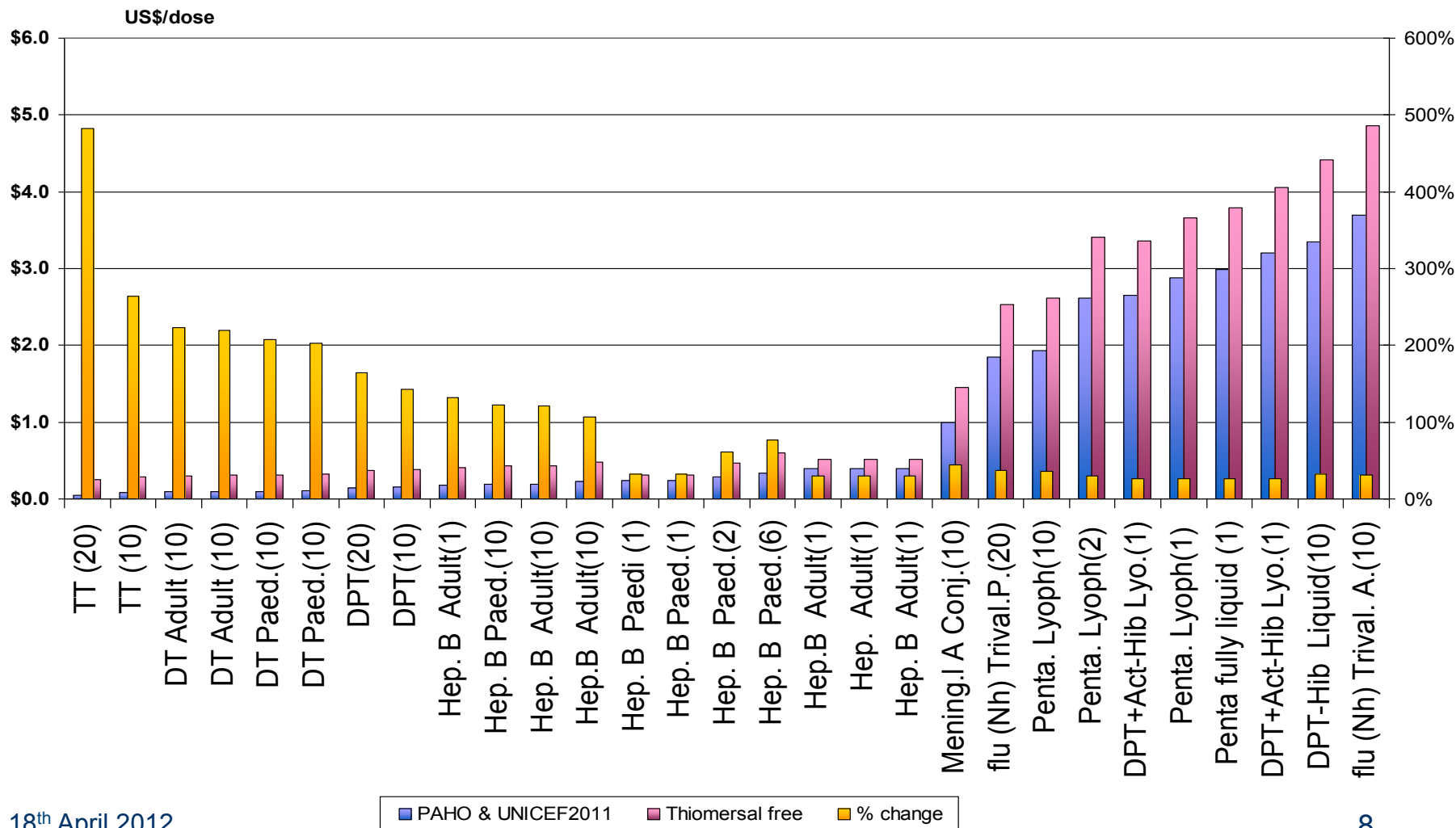
- Clinical trials and licencing, 16 pre-qualified manufacturers and 67 vaccines, indicative cost of “at least \$1,000,000” per vaccine
- Expansion of production plant, additional land, high speed filling, cost unknown, indicated cost “millions of \$”
- Assurance and/or soft loans will be required from purchasers before manufacturers will commit.
- Market uncertainty may cause smaller vaccine manufacturers to stop production of Thiomersal-containing vaccines

Development TIME to go Thiomersal-free

- Clinical trials may take 2-5 years
- Licencing may take 1-2 years for an individual manufacturer and 4-5 years for world-wide coverage
- Full expansion of manufacturing capacity probably will not take place until trials are completed and may take 1-2 years
- WHO pre-qualification cannot take place until vaccines are licenced
- Complete transition may take 10 years or more
- Transition will inevitably result in some eventual redundancy which will have to be paid for, because existing Thiomersal lines will be needed during transition

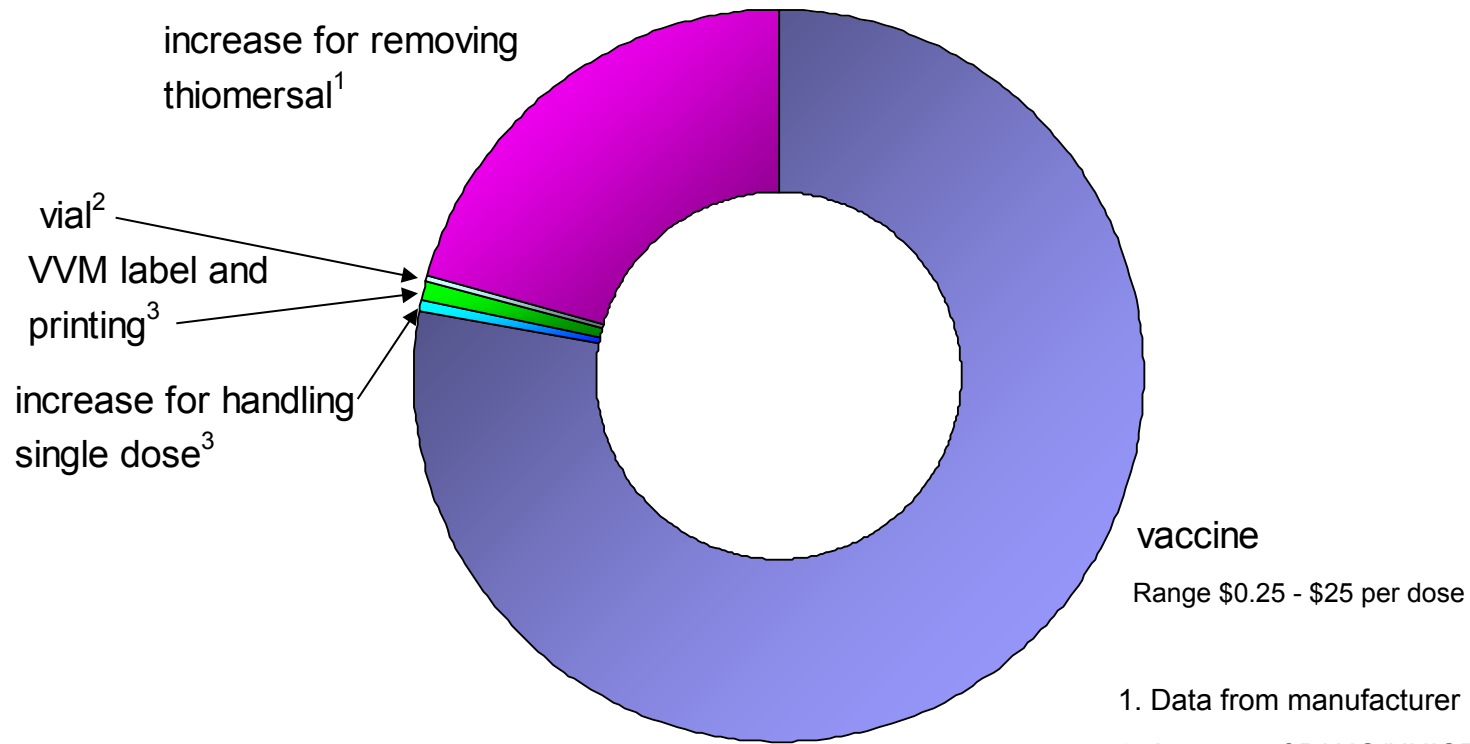
Cost implications of removing Thiomersal

Price per dose for Thiomersal-free



Cost implications of removing Thiomersal

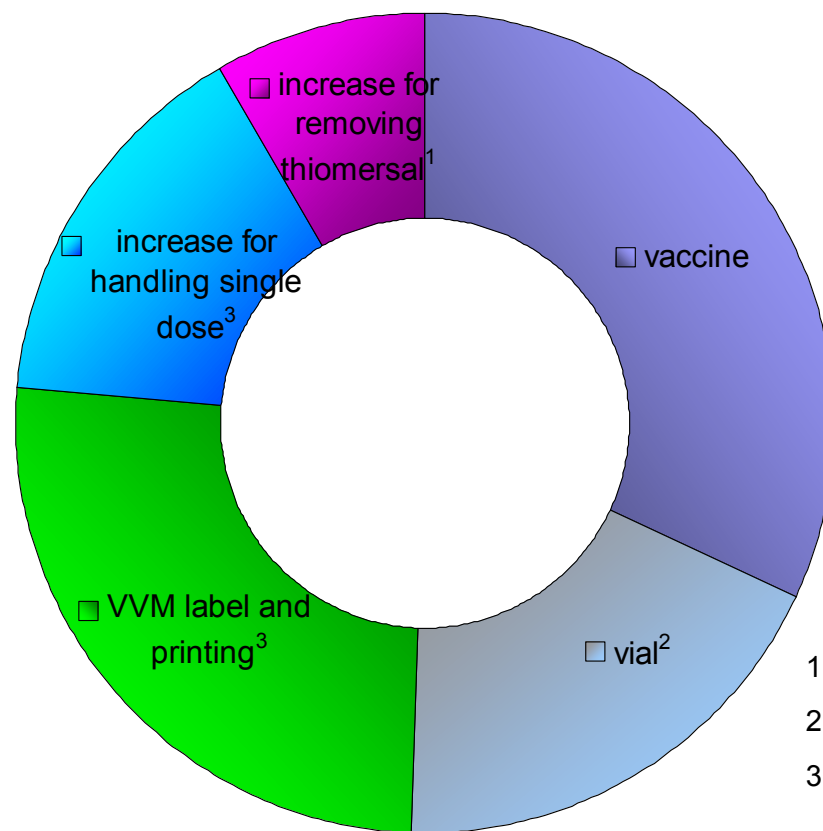
Proportional breakdown of cost per vial for expensive vaccines



1. Data from manufacturer
2. Average of PAHO/UNICEF 2011 mix
3. Data from manufacturers

Cost implications of removing Thiomersal

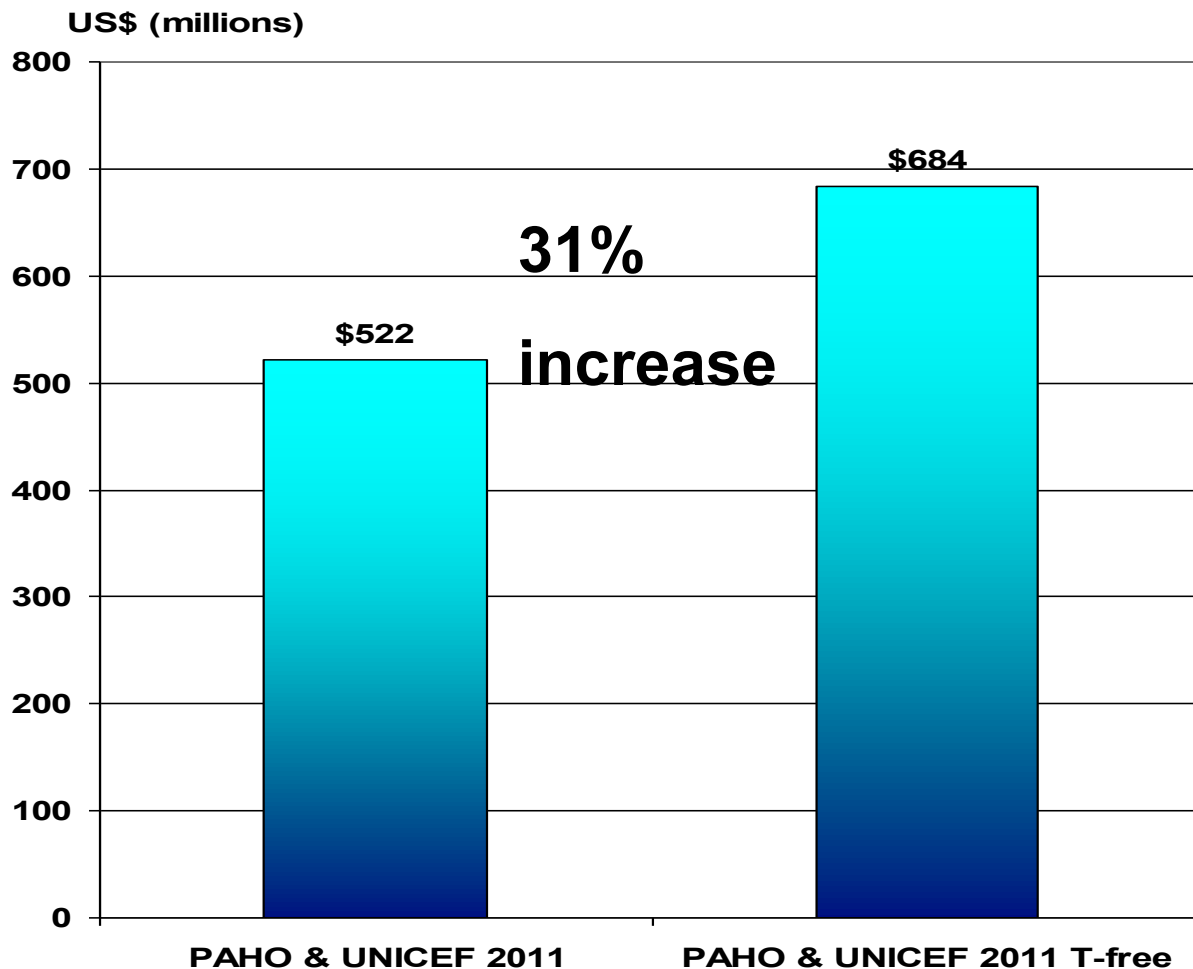
Proportional breakdown of cost per vial for cheapest vaccines



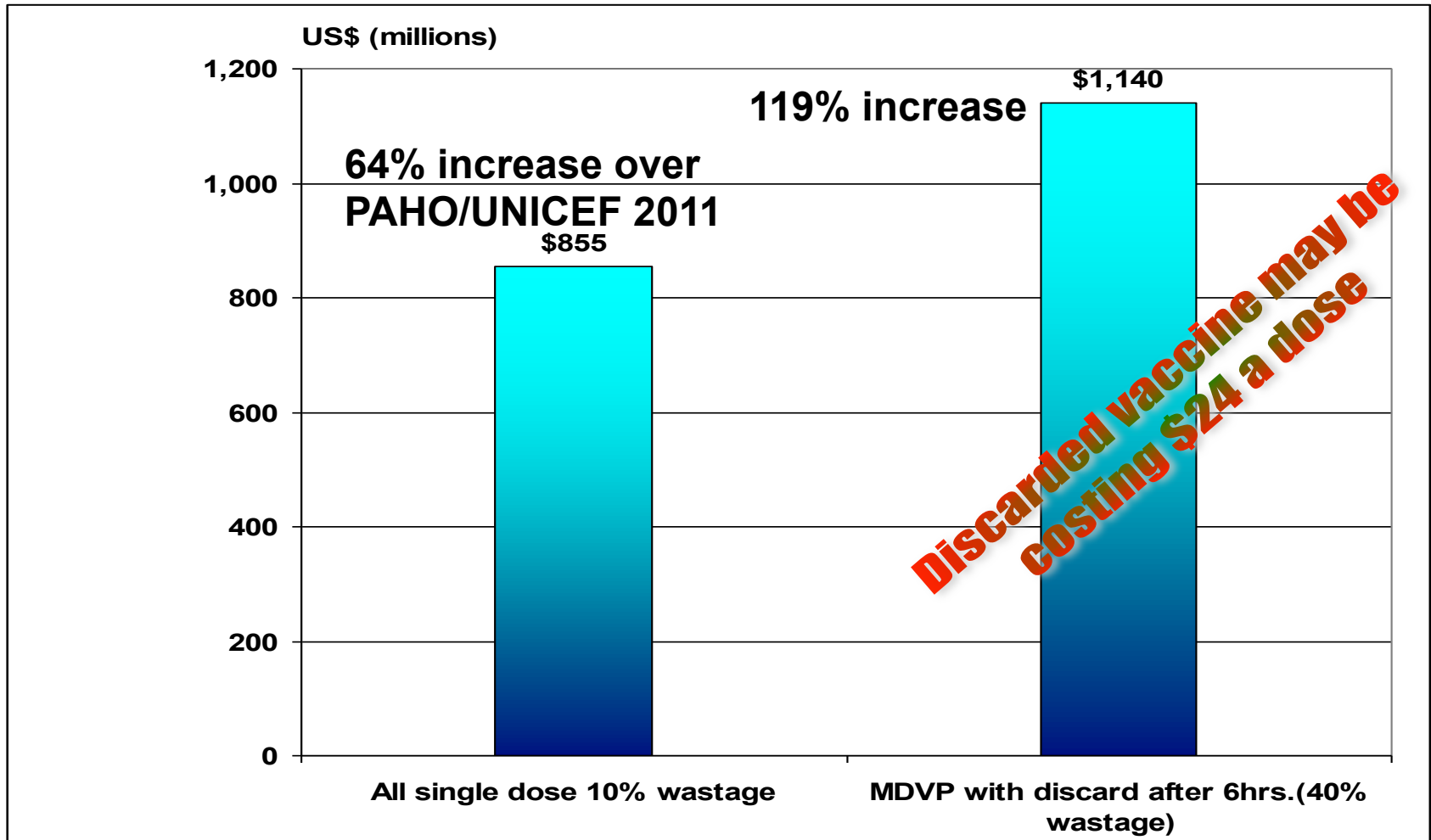
1. Data from manufacturer
2. Minimum of PAHO UNICEF 2011 mix
3. Data from manufacturers

Cost implications of change: global

PAHO/UNICEF 2011 supply. Existing total v Thiomersal-free equivalent

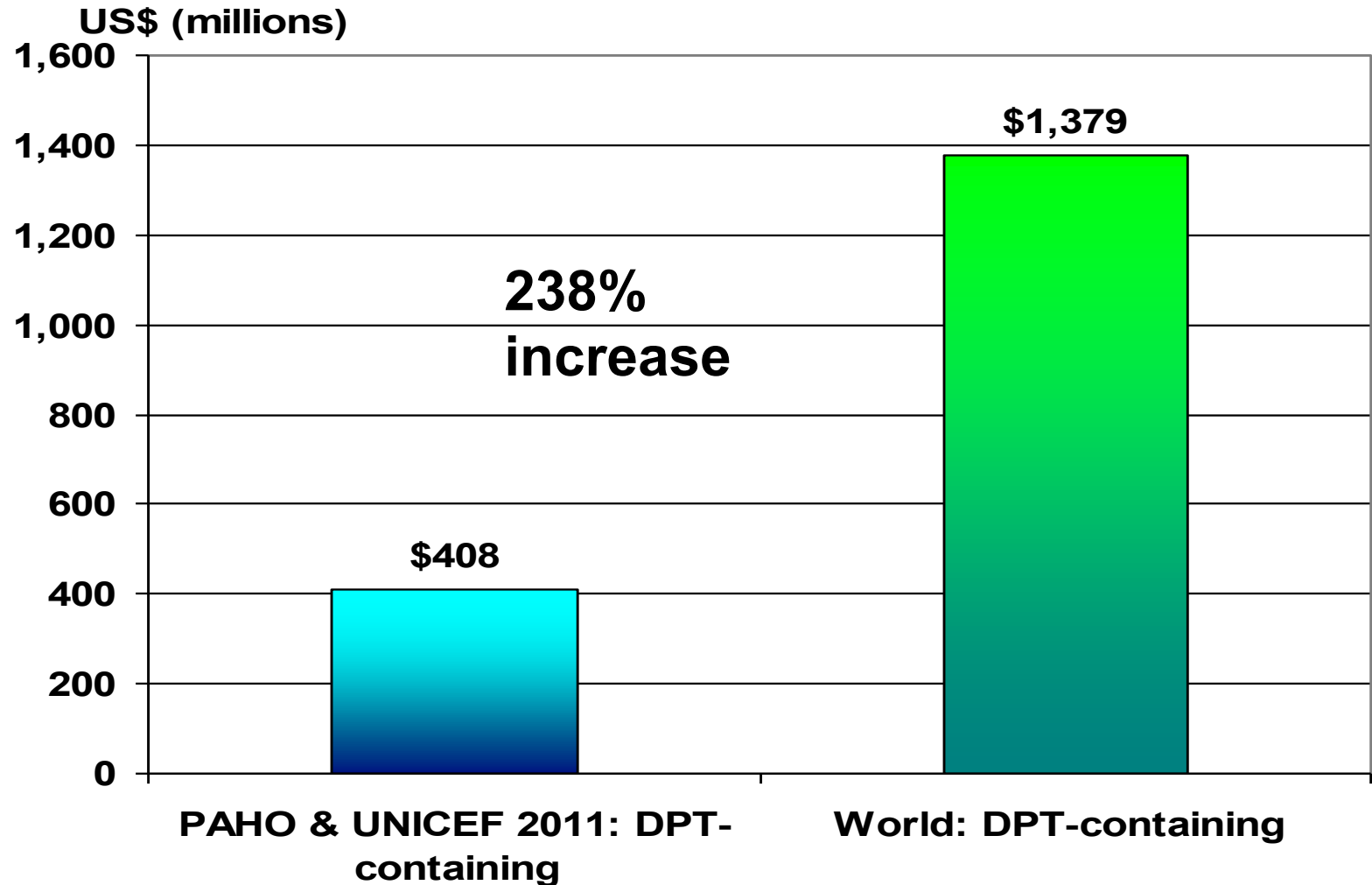


Cost implications of change: global



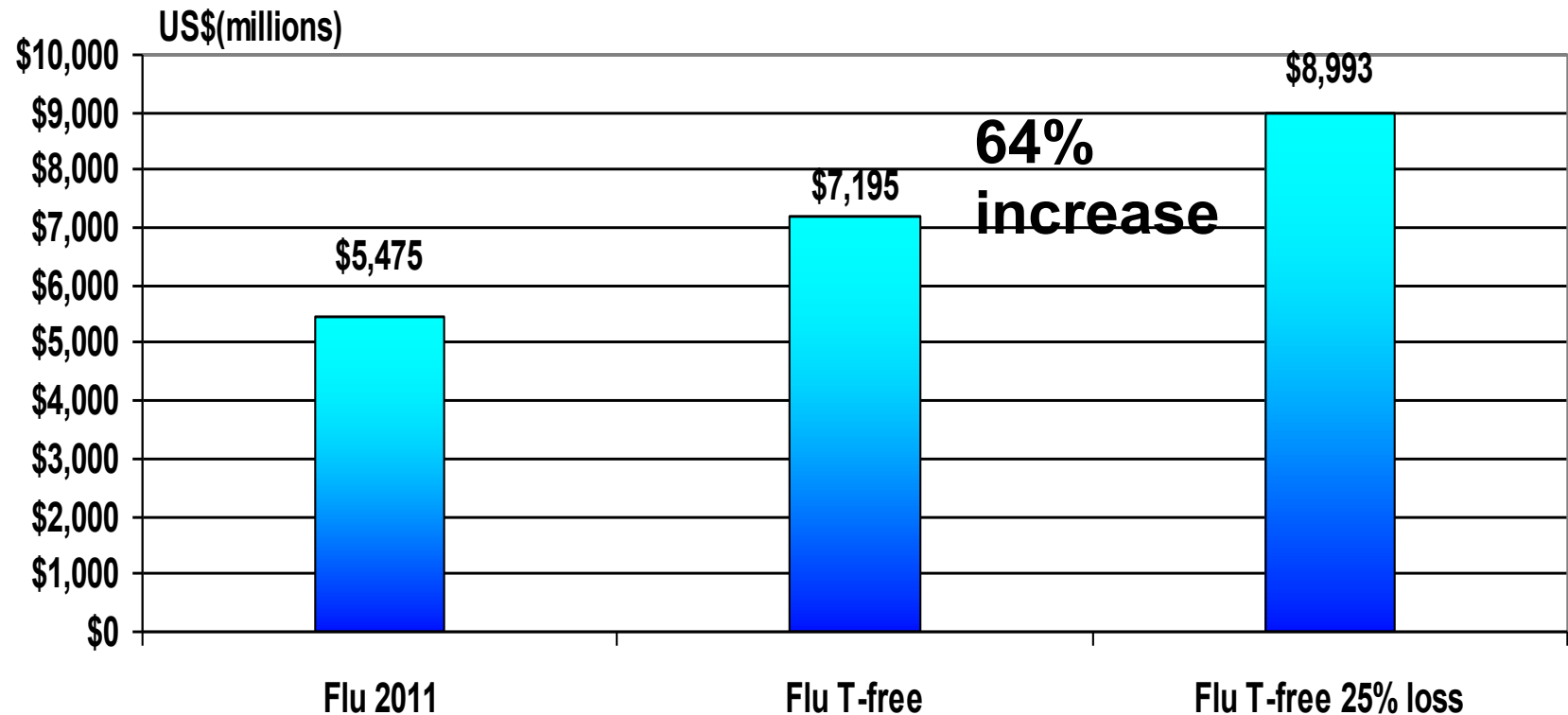
10% wastage on single dose presentation because in-country studies indicate that 5% is not enough

Cost implications of change: global



Cost implications of change: global

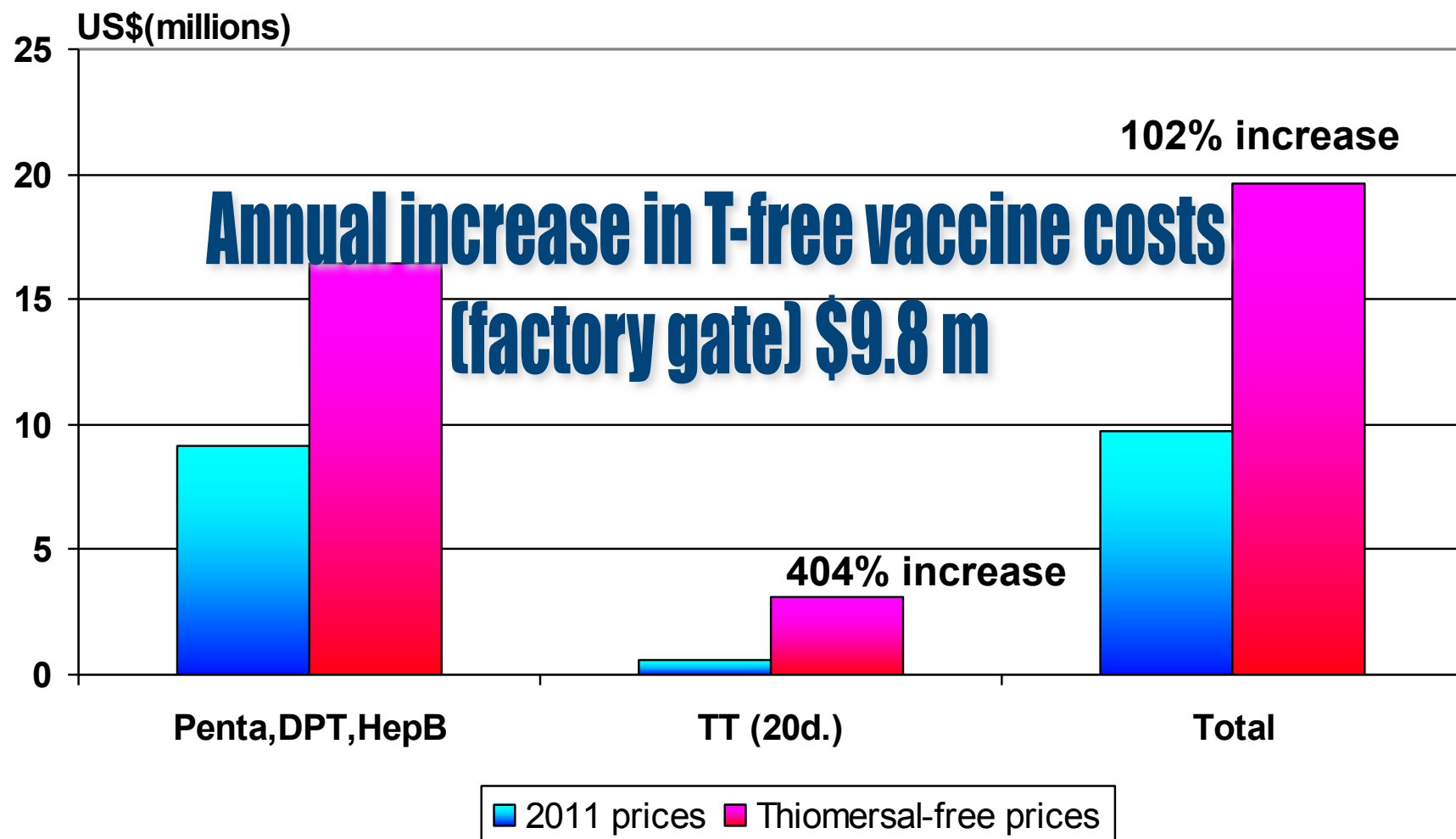
World: Influenza vaccine



Based on: PAHO price of \$3.7 per dose in 10 dose vials

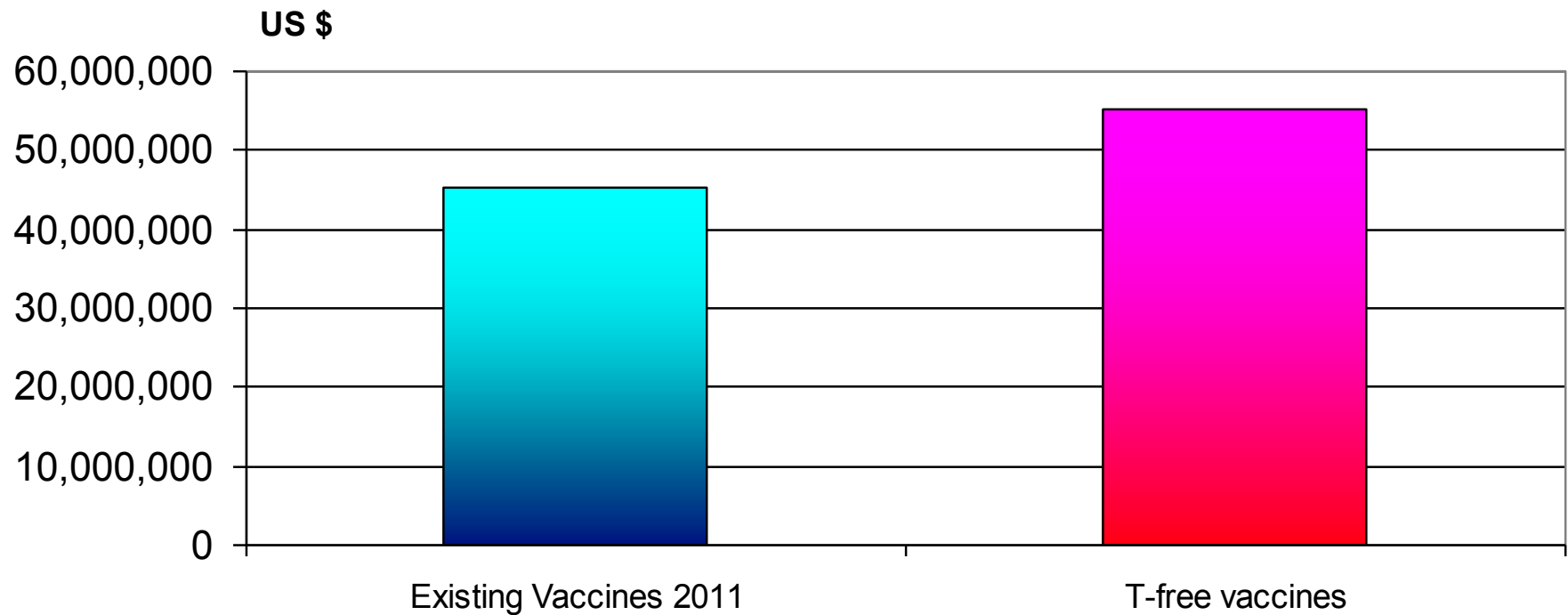
1.5 billion doses annually. Source: manufacturer

Cost implications of change: Country A



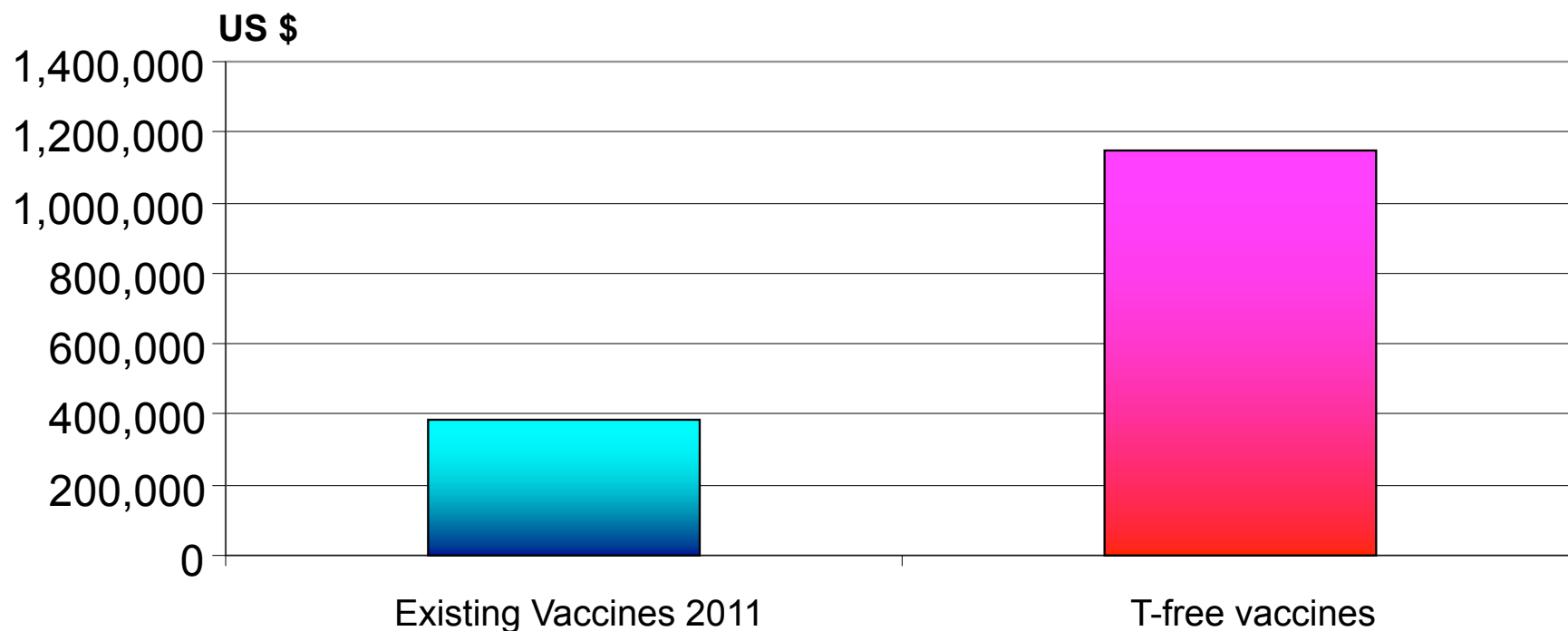
Cost implications – Country A example

Total Annual Vaccine Cost



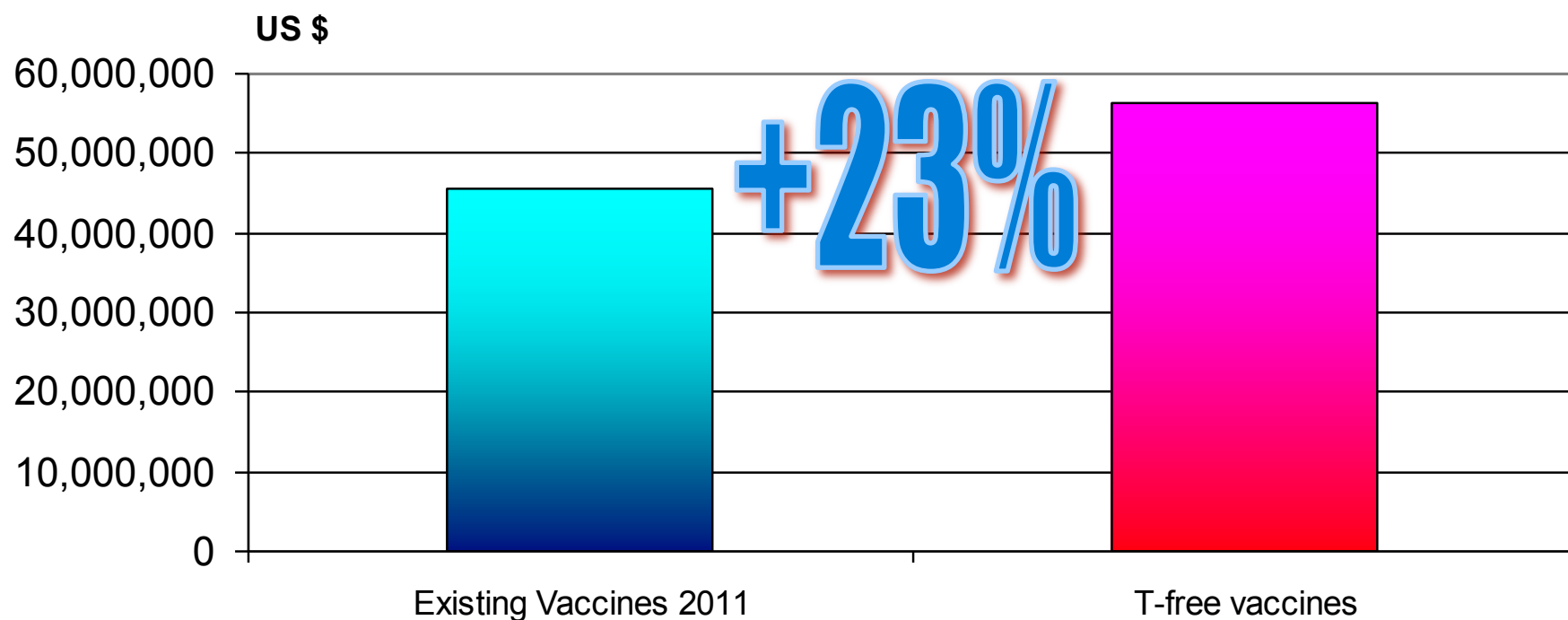
Cost implications – Country A example

Total Annual Shipping Cost



Cost implications – Country A example

Total Annual Landed Cost



Volume implications - global

Based on PAHO-UNICEF 2011 procurement:
compared with total volume for 2011 mix

- Range of single dose vial sizes 9.7 cm³ to 40.1 cm³ *
- Maximum volume-per-dose for current single dose: **+324%**
- Minimum vial size (all 9.7 cm³ per dose): **+165%**

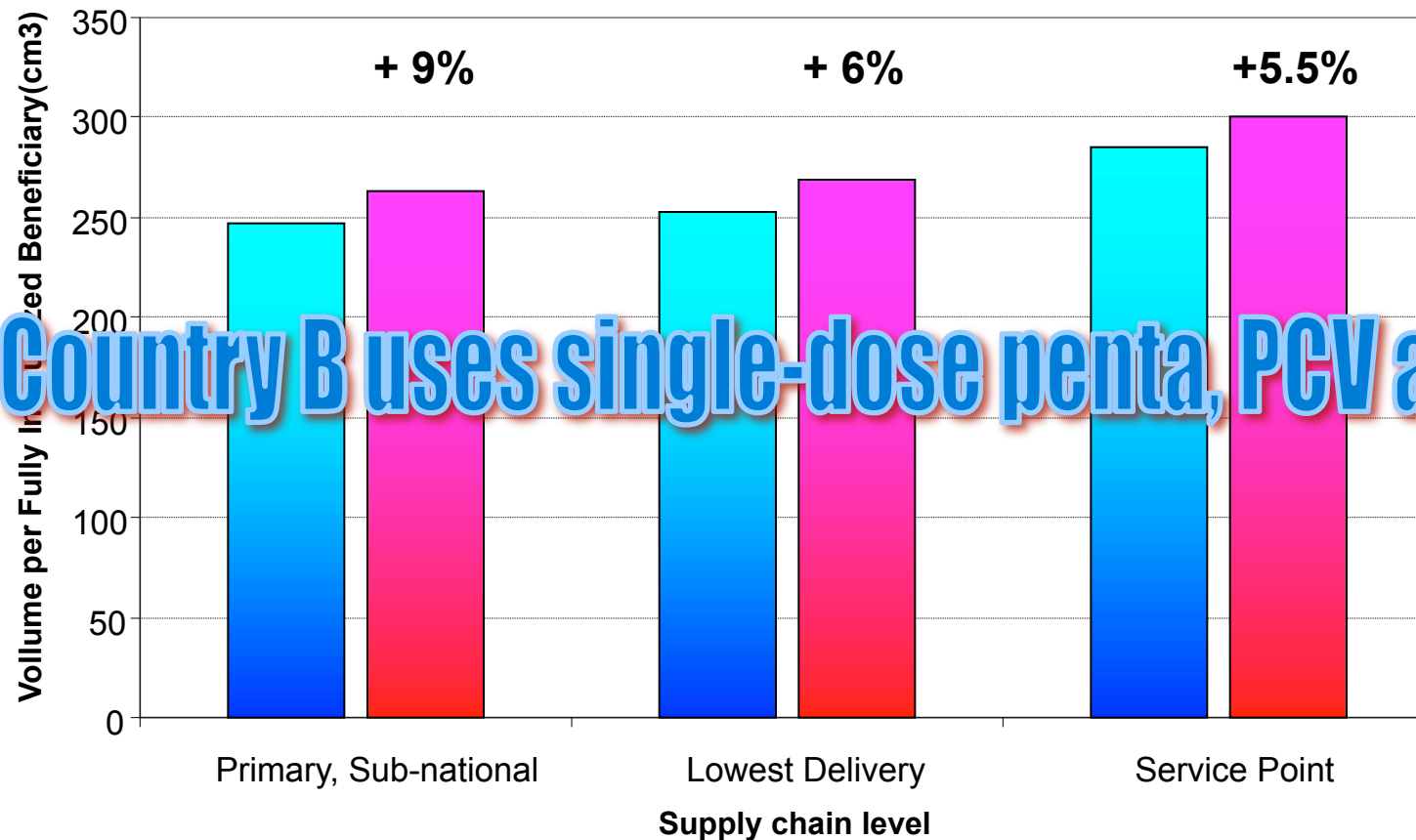
Impact on cold chain equipment:

- *Example from Country A* : indicative estimate \$1,032,000 of additional equipment and the buildings to house that equipment

* Source of vaccine volume data: Optimize packaging study

Volume implications – Country B example

Country B FIB volume analysis: Schedule without NUVI

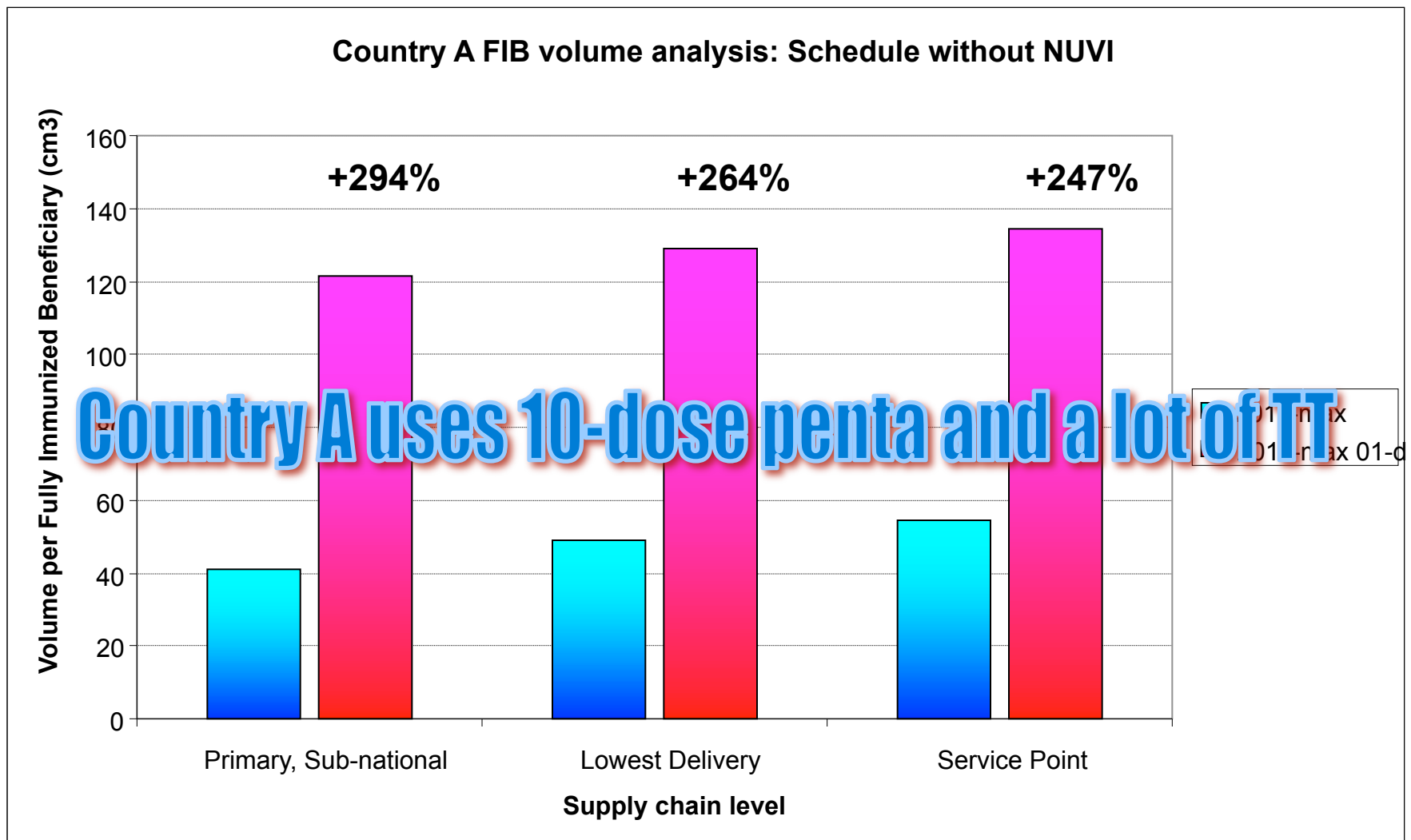


Country B uses single-dose penta, PCV and Rota

NUVI=New and Underutilised Vaccine Introduction

18th April 2012

Volume implications – Country A example



NUVI=New and Underutilised Vaccine Introduction

International air shipment implications

Source: Boeing – based on hold capacity data for 747-400 passenger aircraft
2010 Guidelines to Defra / DECC's GHG Conversion Factors for
Company Reporting: Methodology Paper for Emission Factors



65



85



230

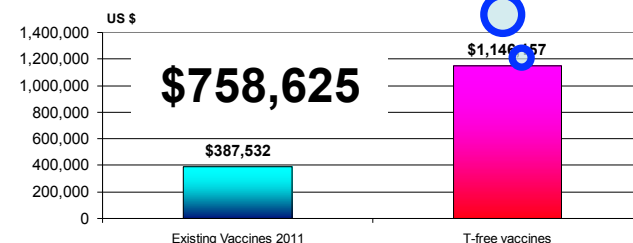
International air shipment implications

Source: Boeing – based on hold capacity data for 747-400 passenger aircraft
2010 Guidelines to Defra / DECC's GHG Conversion Factors for
Company Reporting: Methodology Paper for Emission Factors

57 GAVI
countries

590 tonnes
CO₂e
282% increase

Country A Annual Shipping Cost



Workload implications

Increased workload with single-dose vials:

- For storekeepers having to manage much larger volumes.
- For nurses with larger session sizes, additional staff may be required?
- For supervisors and trainers
- Health workers and storekeepers will need training in management and use of smaller presentations.

presentation	Time taken to administer 30 injections (seconds)					Difference from	
	vaccinator 1	vaccinator 2	vaccinator 3	vaccinator 4	average	using 10 dose	
1 dose	1,016	1,552	932	1,167	1,167	38%	slower
2 dose	829	932	852	871	871	3%	slower
10 dose	767	729	1,039	845	845	0%	
Uniject™	492	577	551	540	540	36%	faster

Source: Lorensen K, Kristensen D. *Time and Motion Study with Potential Human Papillomavirus (HPV) Vaccine Product Presentations*. Seattle: PATH; 2009

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Workload implications

Carrying vaccines during collections and outreach:

Larger capacity or multiple vaccine carriers will be needed for routine outreach. Volume and weight become an issue.

For country A ~ 4,000 additional vaccine carriers

Administered doses						gross vol of Vaccine Carriers								
Outreach	target pop	WCBA	Penta	TT	all other vax	visit /yr	existing doses incl waste	new doses incl waste	existing pres.cc ³	new pres.cc ³	existing vol Lt.	new vol Lt.	Nbr. Of 1.7lt VC	Weight (Kg.)
A	942	942	514	229	1,057	6	211	202	10.92	39.17	1.0	6.2	4	16
B	242	242	217	200	449	6	118	107	10.92	39.17	0.6	3.7	3	12

But it is not only vaccines that have to be carried:

Workload implications



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T-free outreach load

Outreach operations

Can preservative-free vaccines safely be used outside the cold chain for:

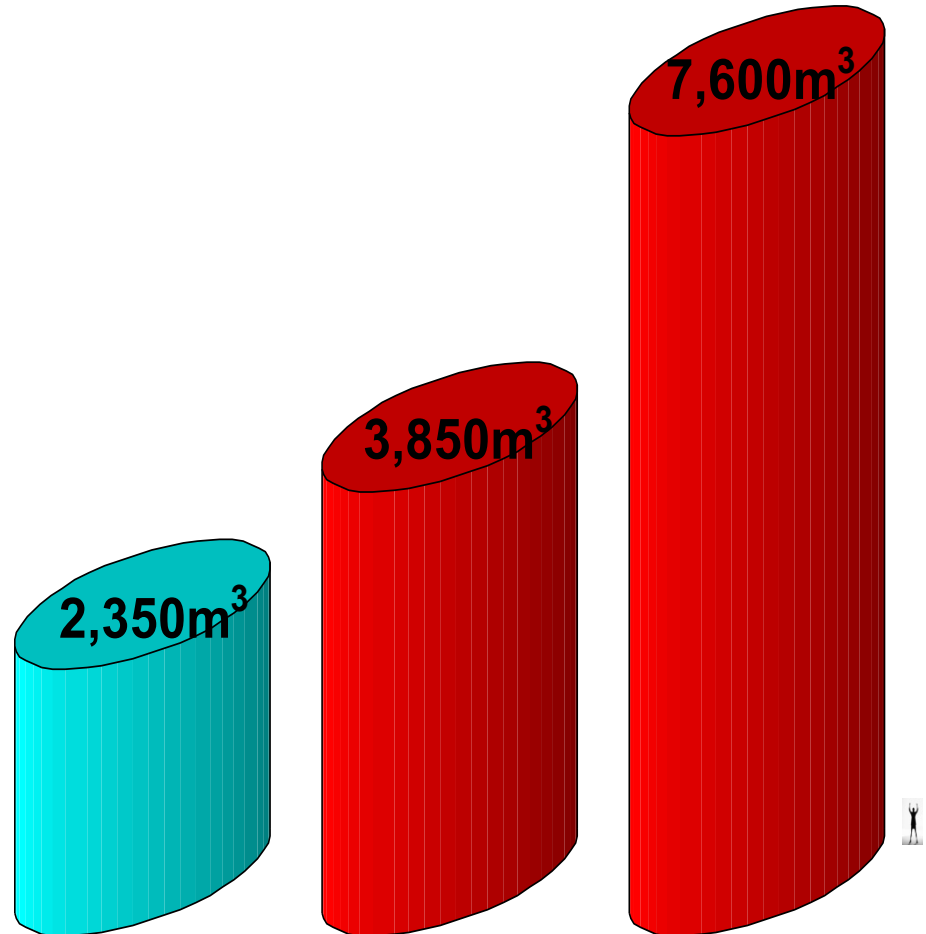
- Extended outreach?
- Birth-dose HepB?
- Campaigns - e.g. Meningococcal A (MenAfriVac®) 300 million people by 2015

..... stability and safety profiles need to be assessed

Waste management implications

Based on 2011 PAHO-UNICEF procurement data:

- Current discarded vaccine vials contain ~ 9 kg Hg
- Discarded syringes from 2011 contain ~ 0.25 kg Hg (~ 275 million syringes)
- With single-dose vials, vial waste would increase from 2,350 m³ to between 3,850 m³ and 7,600 m³



Waste management implications

Based on 2011 PAHO-UNICEF procurement data:

..... if Thiomersal is retained what happens if US-type legislation is extended globally?

Managing Excess Vaccines

PUB-WA 841-11



Waste & Materials Management
P.O. Box 7921
Madison, WI 53707-7921

How Should I Manage Excess Vaccines?

Depending on vaccine ingredients, discarded vaccines may be infectious waste, hazardous waste or non-hazardous solid waste (regular trash).



Vaccines that may be infectious waste when discarded

As of September 2011, the following vaccines that contain live attenuated virus are infectious waste when discarded, according to the Wisconsin Division of Public Health:

- Seasonal Influenza – only FluMist®
- MMR — M-M-R® II
- MMR-Varicella — ProQuad®
- Rotavirus — RotaTeq® and Rotarix®
- Typhoid Fever — only Vivotif®
- Varicella Zoster — Varivax® and Zostavax®
- Yellow Fever — YF-Vax®

Here are your options for managing excess live virus vaccine:

- Contact the manufacturer to see if it can be returned for proper management. For excess live virus vaccine that is not returned to the manufacturer, see the following options.
- Send it to an infectious waste treatment facility for disinfection and subsequent management as regular trash. (Lists of infectious waste transporters are available at dnr.wi.gov/org/aw/wm/faclists); or
- Disinfect it yourself according to ss. NR 526.11

and 526.12, Wis. Adm. Code (www.legis.state.wi.us/rsb/code/nr/nr526.pdf). Be sure to keep records. Manage the disinfected vaccine as regular trash.

Vaccines that may be hazardous waste when discarded

Some vaccines are preserved with 1:10,000 or 0.01 percent Thimerosal (see the vaccines in the table titled "Thimerosal Content in Some U.S. Licensed Vaccines" at www.vaccinesafety.edu/thi-table.htm that have .01% in the Thimerosal Concentration column). Thimerosal contains about 50 percent mercury by weight. Vaccines with 1:10,000 or 0.01 percent Thimerosal have about 50 mg/L mercury, which exceeds the 0.2 mg/L hazardous waste toxicity characteristic regulatory level for mercury. According to state and federal hazardous waste management requirements, discarded Thimerosal-preserved vaccines may need to be managed as hazardous waste, using the waste code D009 (mercury).

NOTE: One mercury-containing fever thermometer contains the same amount of mercury (1/2 gram) as 20,000 adult doses of Thimerosal-preserved vaccine. While bulk mercury (e.g., in a mercury fever thermometer) is a bigger threat to human health and the environment compared to a Thimerosal-preserved vaccine, it is still important to manage these discarded vaccines properly.

It is illegal to manage Thimerosal-preserved vaccines as infectious waste or regular trash.

Here are your options for managing excess Thimerosal-preserved vaccines:

- Ship *unexpired* vaccines to the manufacturer for use or proper management (with prior permission from the manufacturer),
- Manage the vaccines under the state of Wisconsin hazardous waste management contract,

Harmonising vial sizes and packaging

Define target product profiles:

- Minimum possible vial sizes
- Compatibility with high-speed filling machines
- Dimensionally coordinated primary, secondary and tertiary packaging
- Good ergonomic design
- Continued ability to carry out shake test
- Clear and consistent labelling
- Allow space for future bar coding
- Minimum airfreight weights and volumes*

*Current insulated shipping container weights per dose for single-dose vial presentations range from 10.0 grams for a single-dose HepB vaccine up to 41.0 grams for a 2 vial pentavalent liquid-lyo vaccine

Initial conclusions

Removal of Thiomersal will result in:

- Major impact on vaccine manufacturing.
- Higher international and national distribution costs.
- Higher carbon emissions
- Higher vaccine costs
- Greater workload for both logistic and nursing staff
- Greater volume of waste
- A transition period of up to 10 years to complete clinical trials, obtain licences & WHO pre-qualification, retool vaccine production plants, upgrade in-country cold chains and recruit and retrain staff.
- Countries may begin to question the cost-benefit of immunisation

Initial conclusions

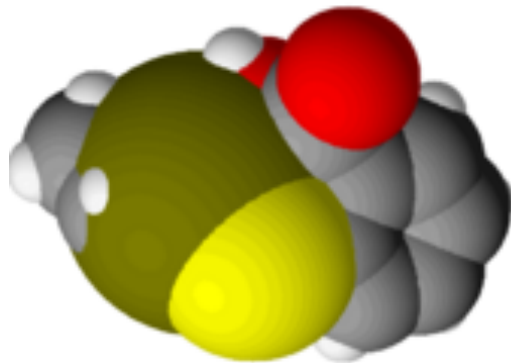
If Thiomersal removal is implemented:

- There is high risk of serious programme disruption, brought about by demand for Thiomersal-free vaccine before it is available, and during the transition. (Already raised at INC3)
- The cost changes will require a re-examination of the relative cost-effectiveness of immunisation as a public health intervention and countries will have to reassess where to invest their scarce health resources.
- A consultative body will need to be established to reach agreement on: the transition programme, enable financing, identify detailed operations research, coordinate production, explain the transitional arrangements and obtain buy-in by all stakeholders.

Further detailed study is needed to support a definitive decision.

Whatever that decision is, there will have to be major advocacy to ensure that all parties support the decision.

This is all to do with the balance of risk - what will achieve the greatest good for the most people?



Removing this molecule from all vaccines will be very disruptive,
time consuming and expensive

Questions not yet completely quantified

- Is there only a single manufacturer of pharmaceutical grade Thiomersal?
- How vulnerable is that manufacturer?
- Does the Basle Convention on movement of hazardous waste prevent movement of raw material (mercuric chloride)?
- What are the cost implications for manufacturers?