MEASLES AEROSOL VACCINE

Initiative for Vaccine Research

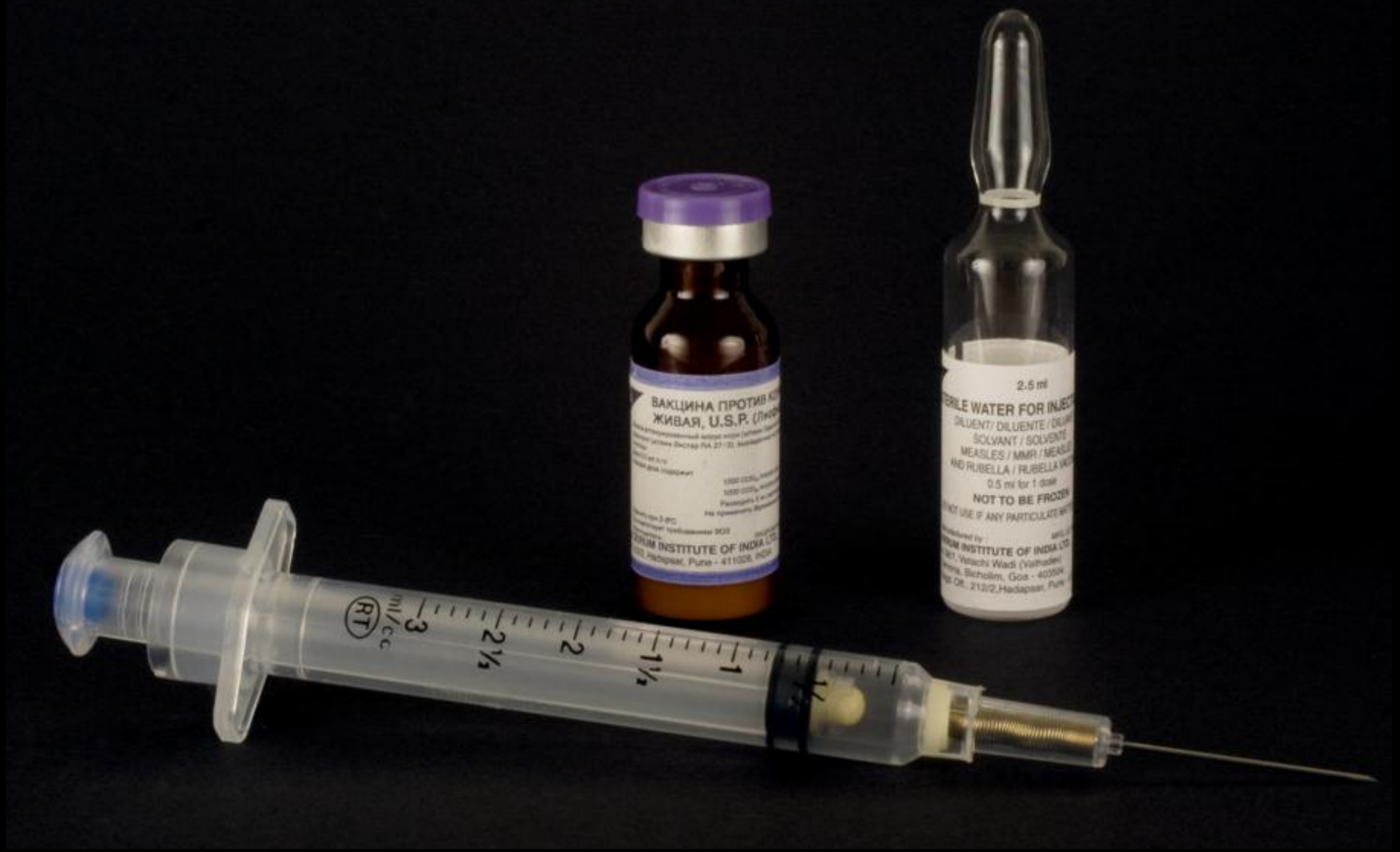
World Health Organization

....On 14 May 1796, Jenner inoculated James Phipps .....

A new route of administration

- Why?
- Injection safety – waste management
- Lessons learned from polio campaigns

So, should we change the dominant logic for measles vaccine?



INJECTABLE MEASLES VACCINE

Requires trained health staff to give injections

+

Creates unsafe waste

+

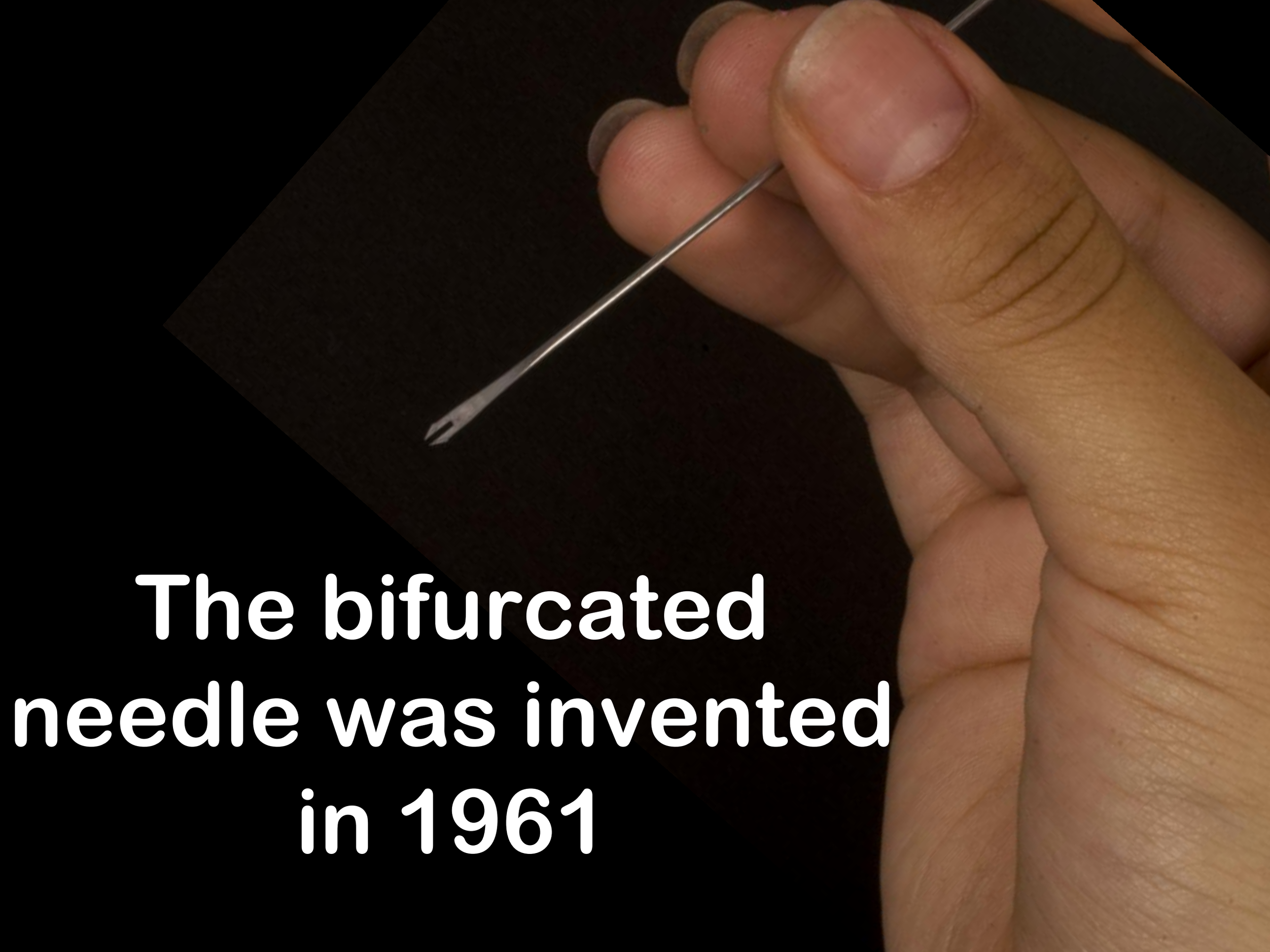
Requires infrastructure to dispose of waste

- Slide on challenges link to injection safety and waste management: HIV, HBVB, HCV infections,

40 children vaccinated

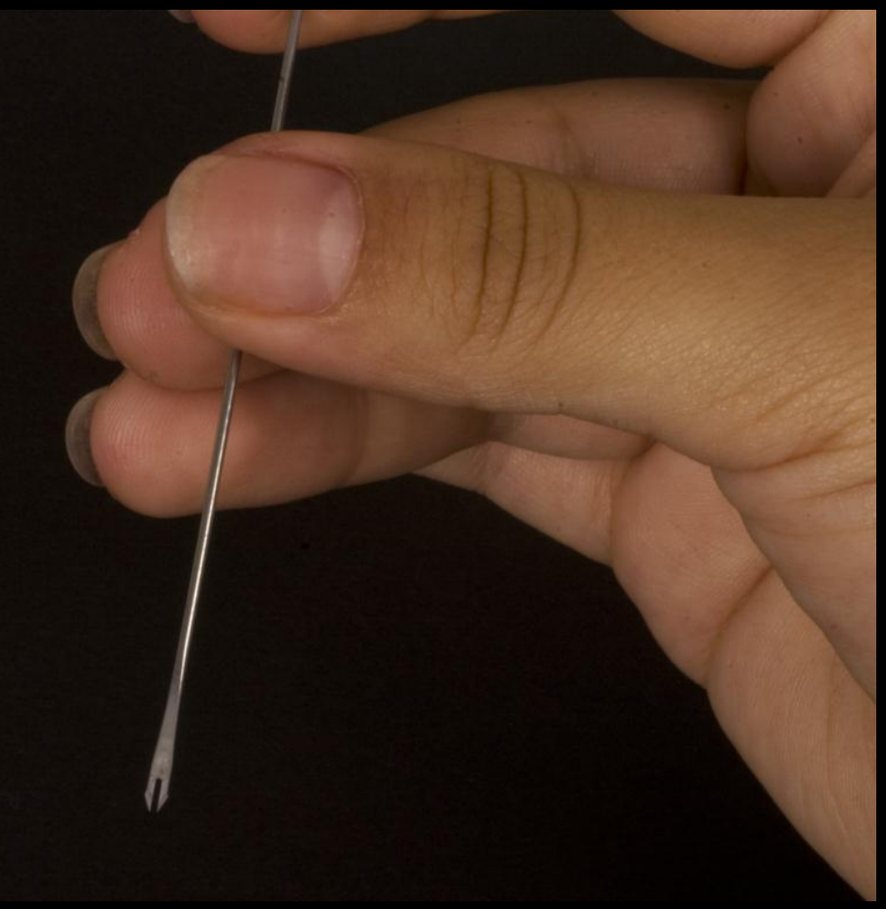
Injectable route

Aerosol route


The bifurcated needle was invented in 1961

Smallpox was eradicated 30 years ago

Lessons learned from polio campaigns
House to house vaccination in Mexico.
Mass campaign Egypt
Ethiopia



easy to
administer

can be given by
trained
volunteers

no unsafe waste

Smallpox
bifurcated needle

Poliomyelitis
oral polio vaccine

Measles Aerosol Vaccine

Is it suitable for field use?

Is it safe?

Dr. Sabin at the National Institutes of Health, Ca. mid-1980's

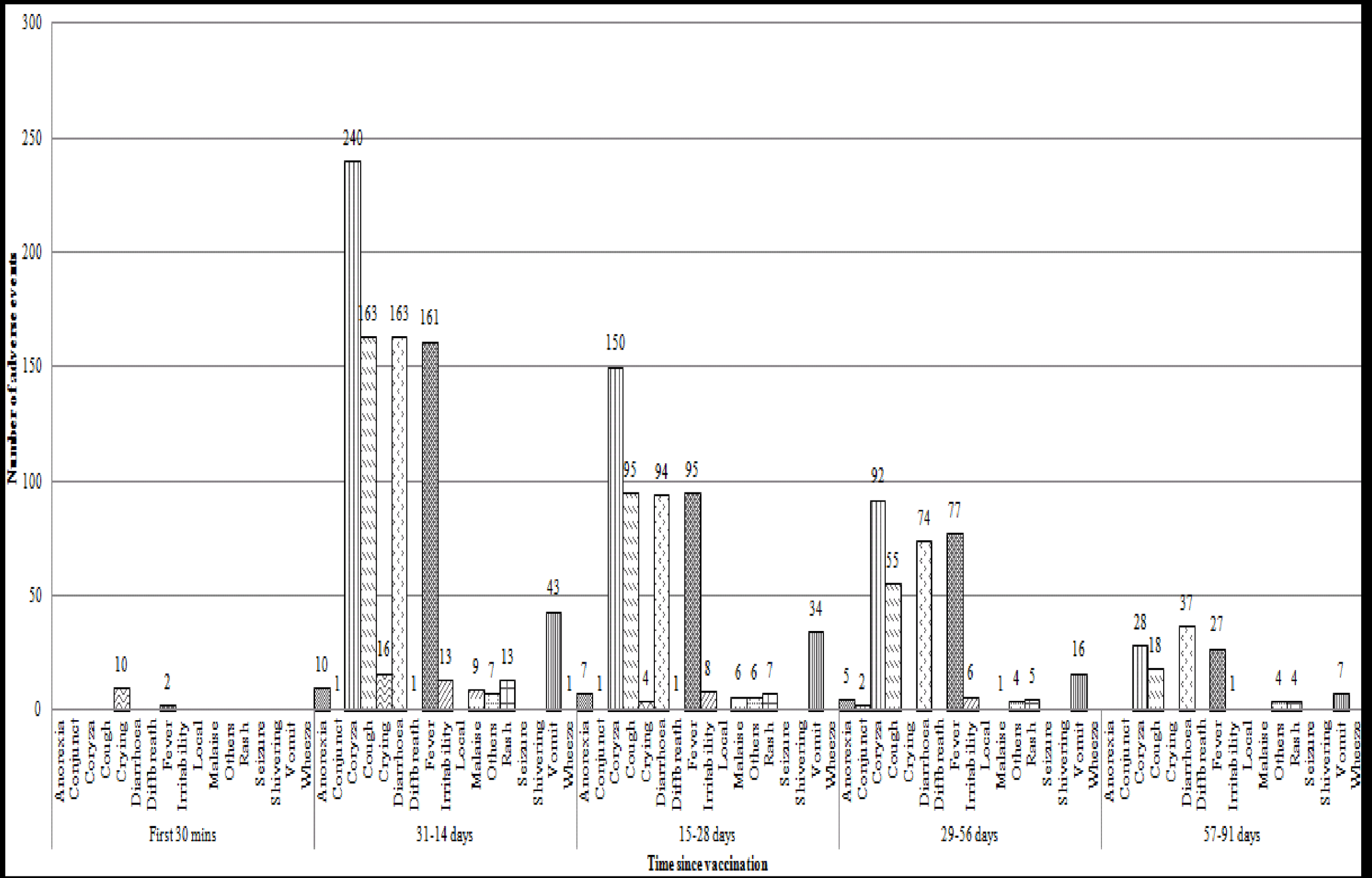
"Mass immunization of almost of all susceptible children in a short period of time, has the potential of rapidly eliminating measles as a public health problem. Immunization by **inhalation of aerosolized measles vaccine** provides a procedure that could make such a mass programme possible, especially in parts of the world where measles continues to be a serious problem..."

Measles aerosol vaccine safety data from previous studies

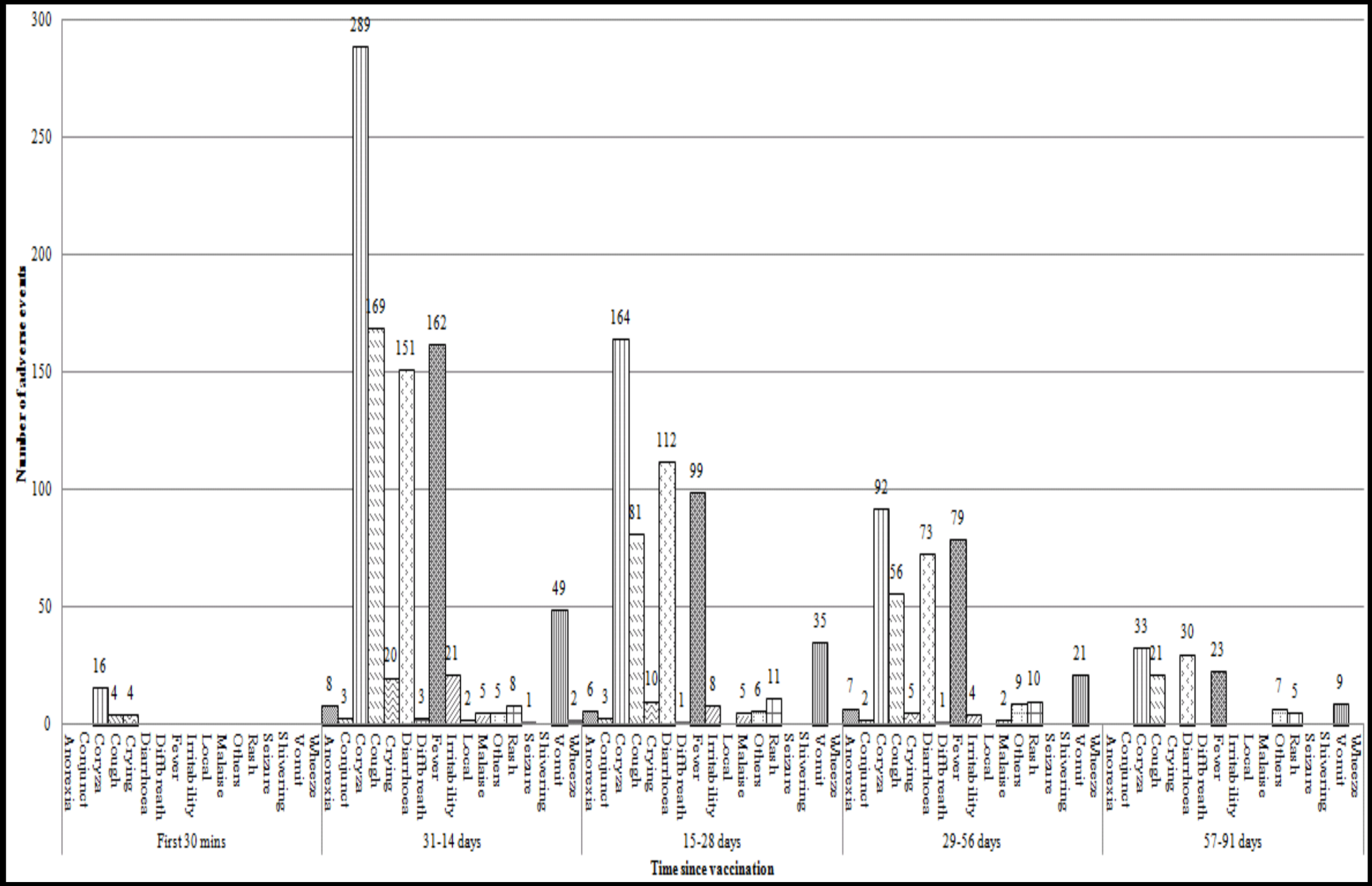
- No SEVERE adverse events (AE) reported
- Fever was the most common AE
- Cough was reported as an AE < 3 weeks post vaccination
- Rhinitis was also a common reported AE

Low N et al 2007

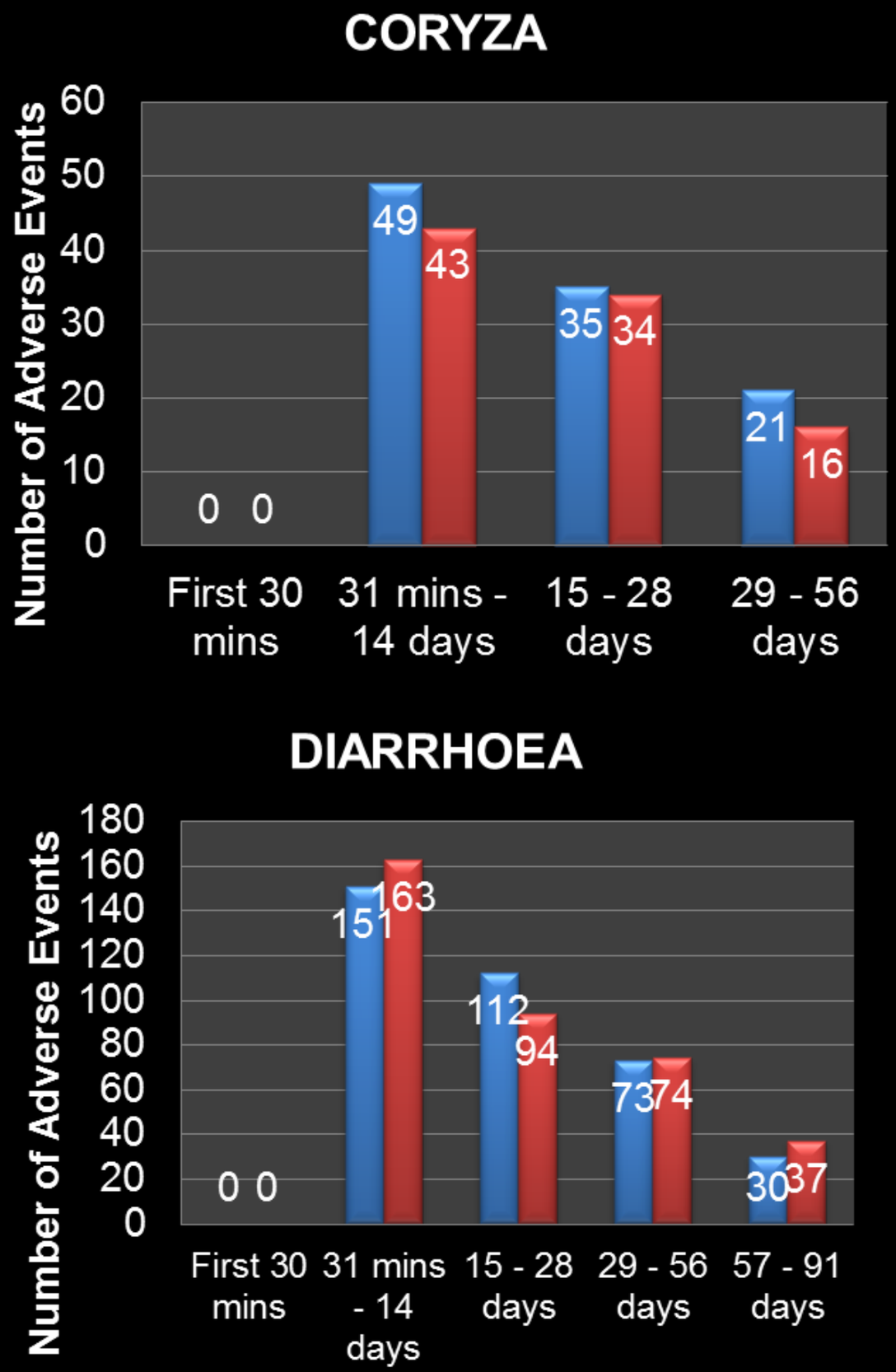
Distribution of all AEs by time since vaccine administration – S/C group

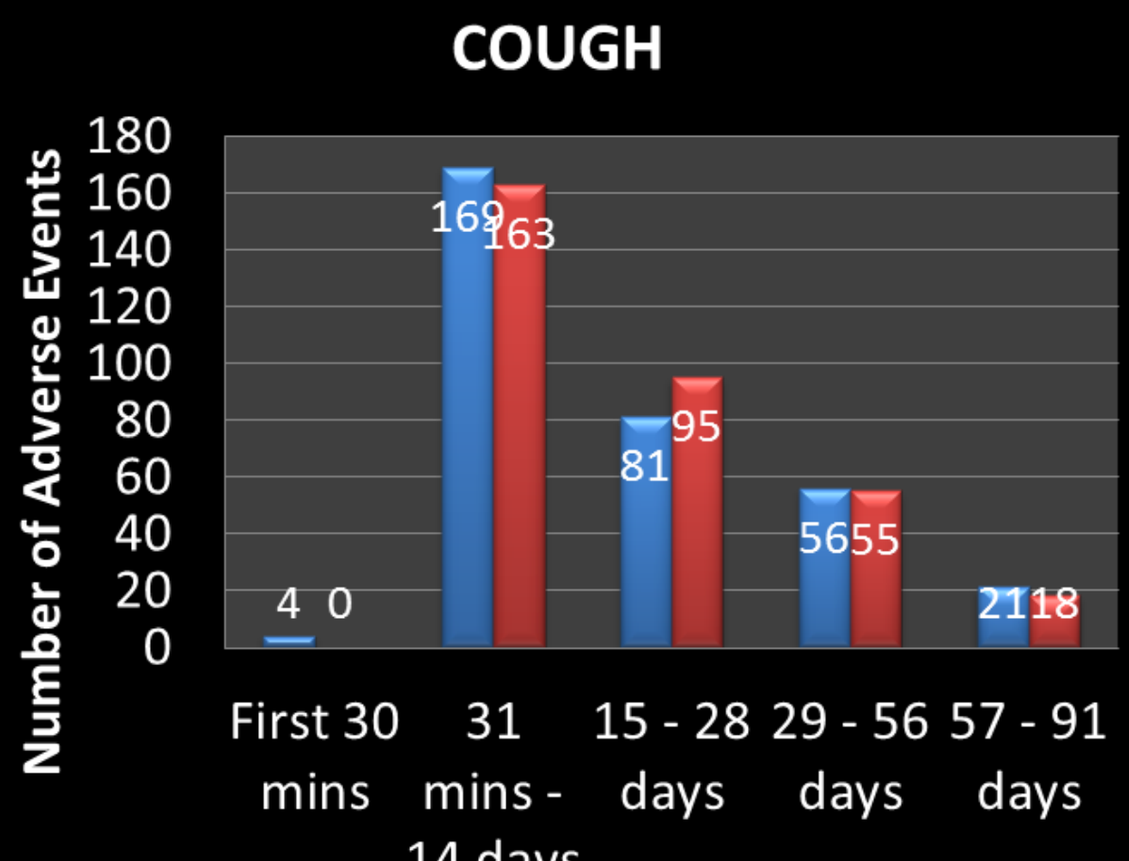


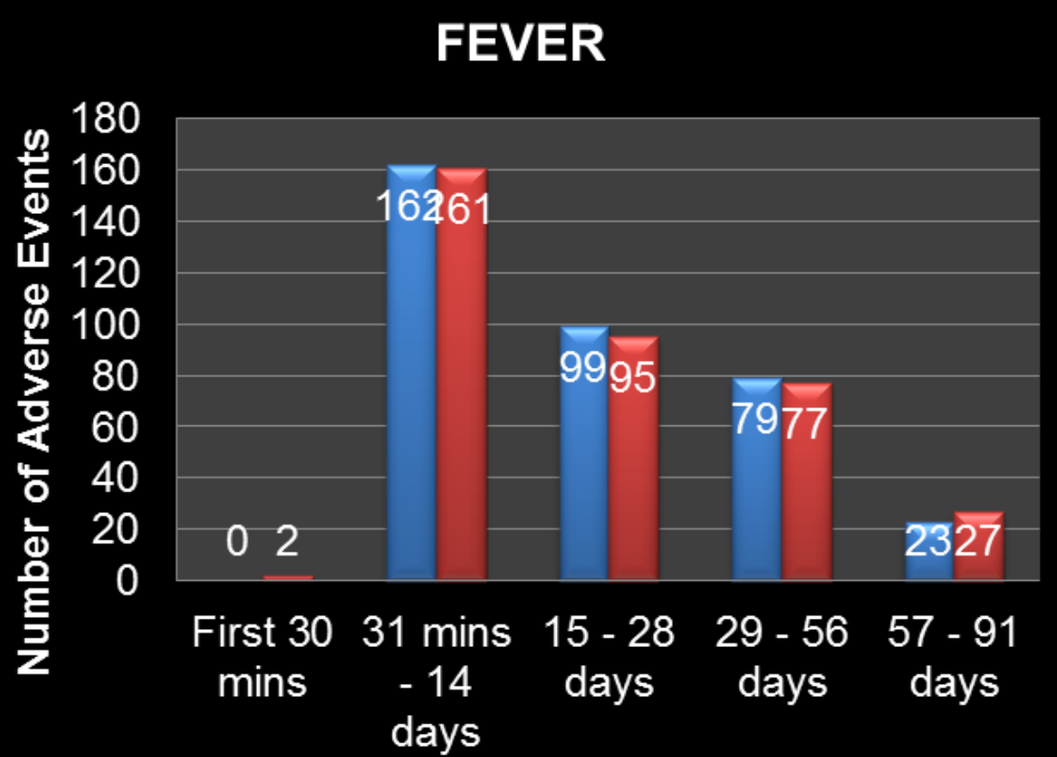
Distribution of all AEs by time since vaccine administration – Aerosol group



Adverse Events according to time since cir







DSMB Overall Conclusions

- Based on the information presented in the Final Safety Report dated June 2012 the DSMB have **no concerns regarding the safety profile** of the aerosolized measles vaccine.

- The DSMB concluded that the adverse event profile of the aerosol vaccine **was similar** to that of the subcutaneous vaccine.

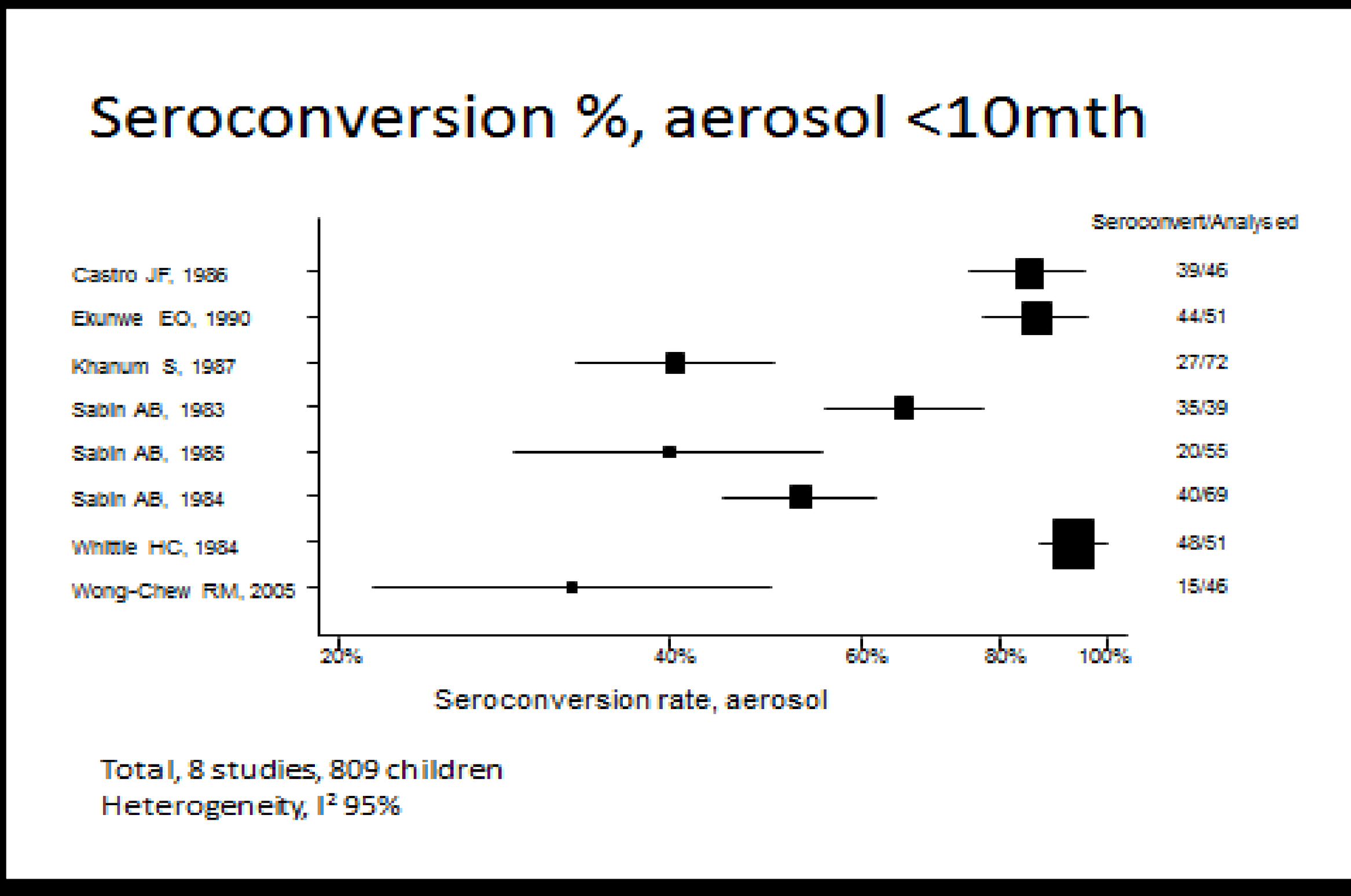
DSMB Overall Conclusions

- The DSMB noted the **differences in symptoms and behaviour** between the two groups during vaccine administration with a lower percentage of children crying, struggling or exhibiting shallow breathing in the aerosol group, suggesting better immediate tolerability.

- Aerosol administration was, however, associated with coughing in a minority.

Is the measles aerosol vaccine efficacious and effective ?

Serological response following measles aerosol vaccine, by age



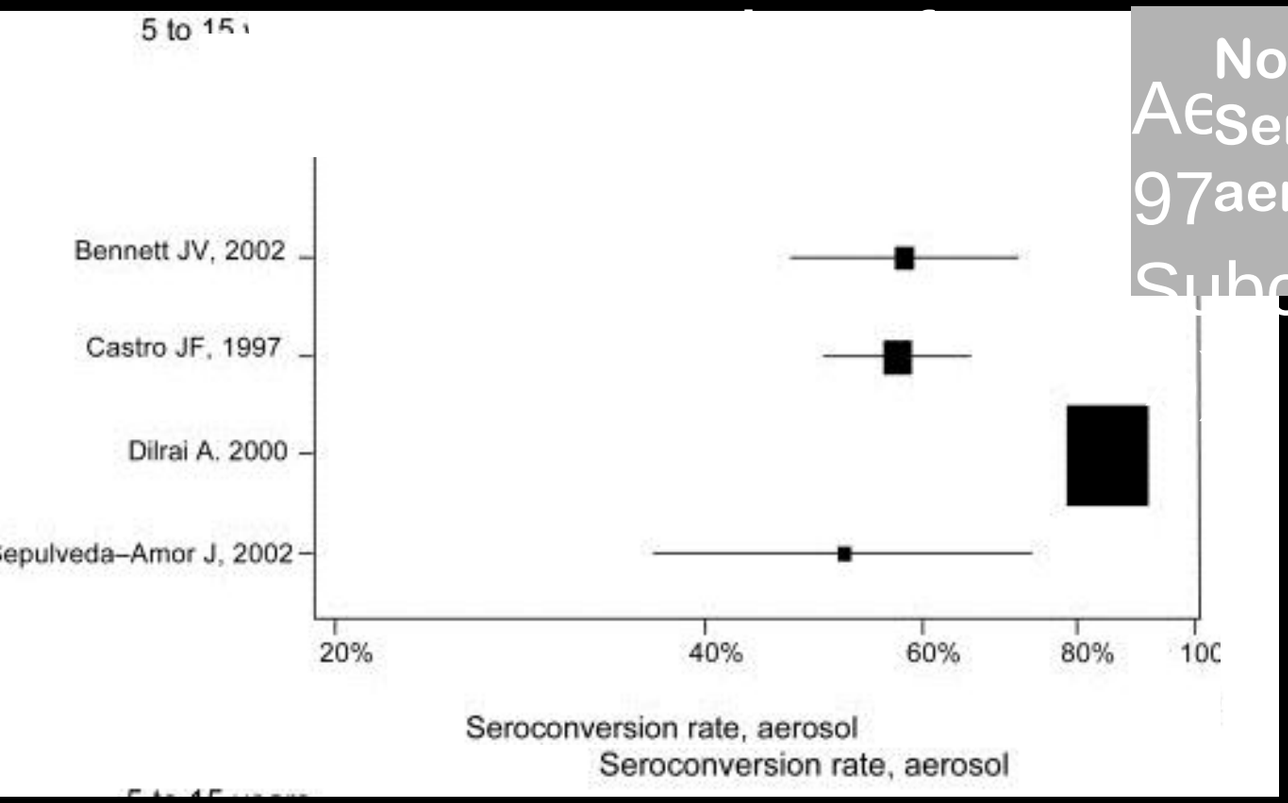
Total, 8 studies, 809 children
Heterogeneity, I^2 95%

Serological response following measles aerosol vaccine, by age

Summary weighted seroconversion

No pooled results because of heterogeneity: Seroconversion rates were higher with aerosol than with subcutaneous vaccine

Ae
97
Subcutaneous - 97.1% (92.4% - 100



Low N et al 2008

Field effectiveness of live attenuated measles-containing vaccines: a review of published literature

- 75 studies on VE after one dose

- at 9–11 months of age ---- 77.0% (IQR, 62%–91%)
- at 12 months of age ---- 92.0% (IQR, 86%–96%)

- If restricted to include only estimates for which vaccination history was verified and cases were laboratory confirmed
  - at 9 months ---- 84.0% (IQR, 72.0%–95.0%)
  - at 12 months ---- 92.5% (IQR, 84.8%–97.0%)

- Pivotal study
- to evaluate the immunogenicity and safety of a measles vaccine given by aerosolized inhalation:
- randomized controlled trial

OBJECTIVES

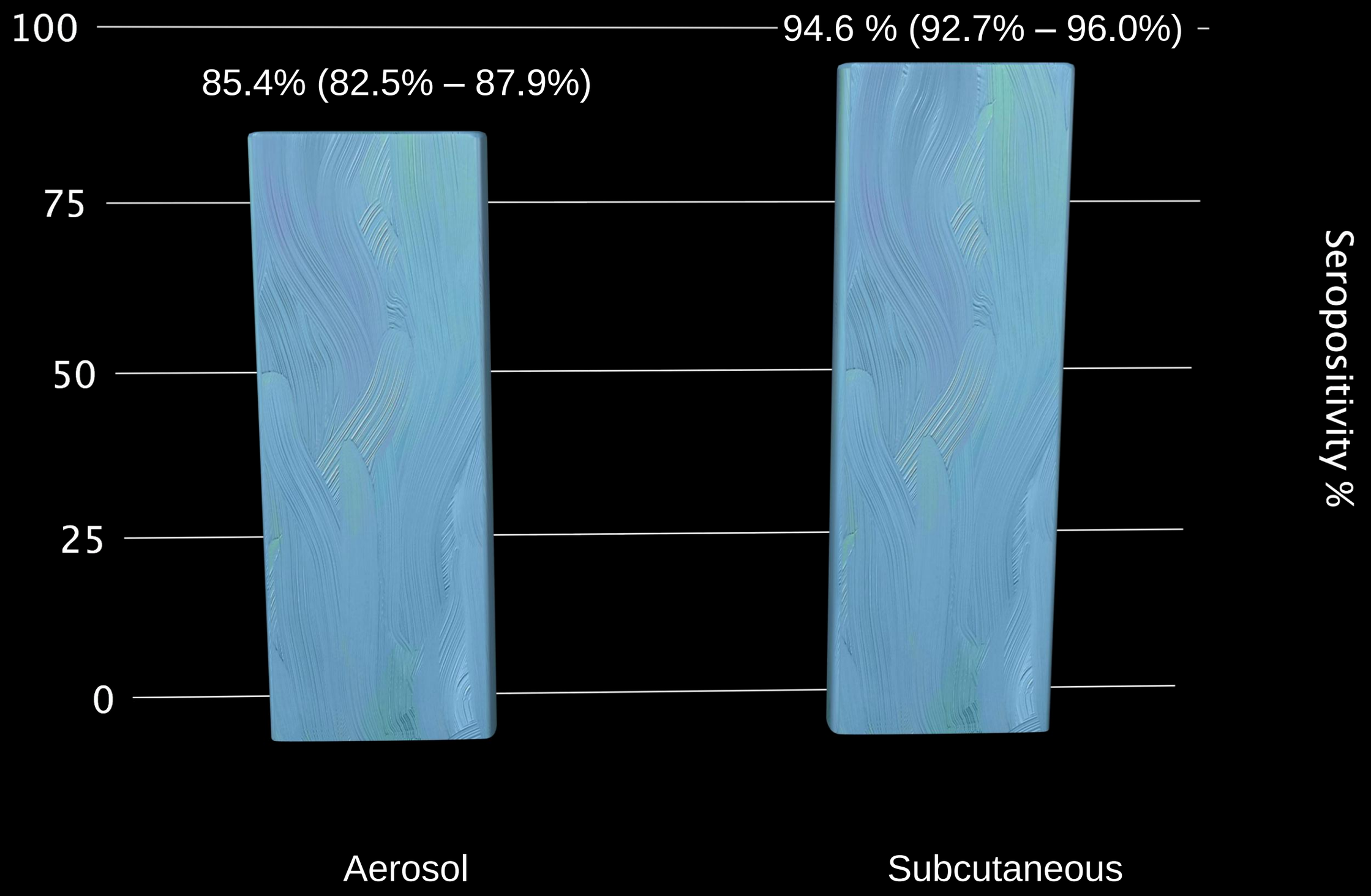
- IMMUNOGENICITY
  - •To assess the immunogenicity of measles vaccine delivered via a nebulizer/vaccine combination product
- SAFETY
  - –To describe the frequency of adverse events following measles aerosol and subcutaneous vaccination

PRIMARY OUTCOME

- IMMUNOGENICITY
- Measles Seropositivity at day 91 post-vaccination

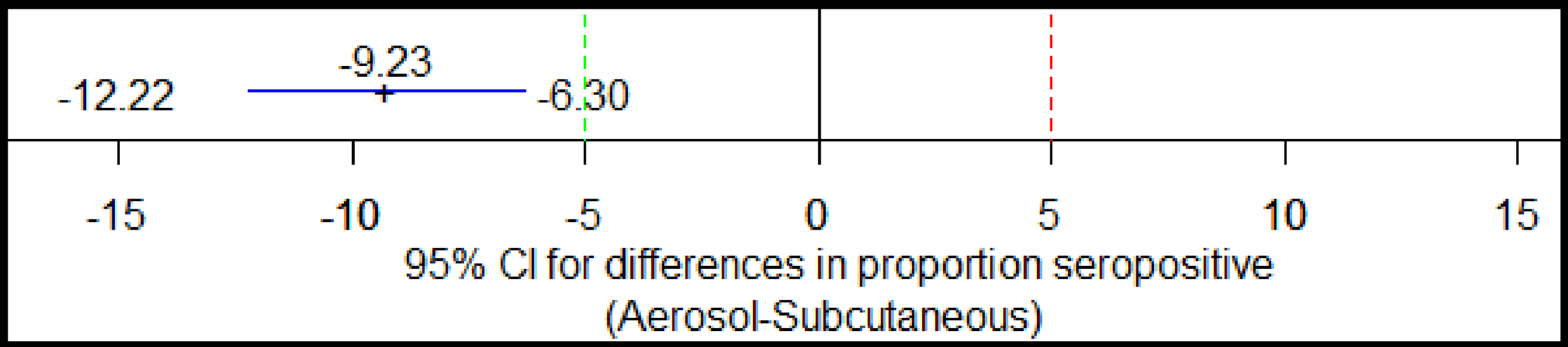
- SAFETY
- AEs up to day 91 post-vaccination
- AEs including acute clinical reactogenicity, other AEs, and SUSARs
-

Seropositivity by study arm

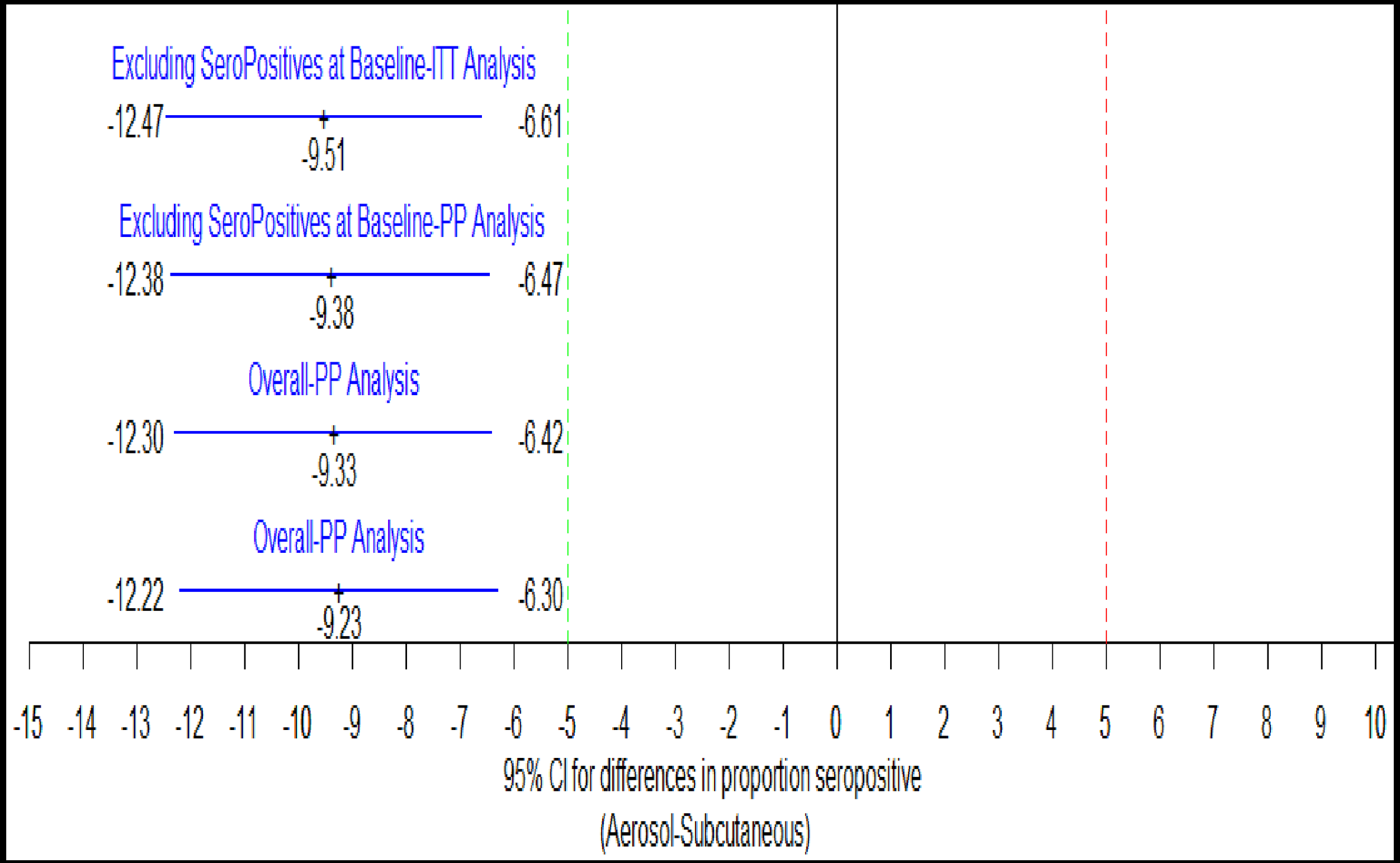


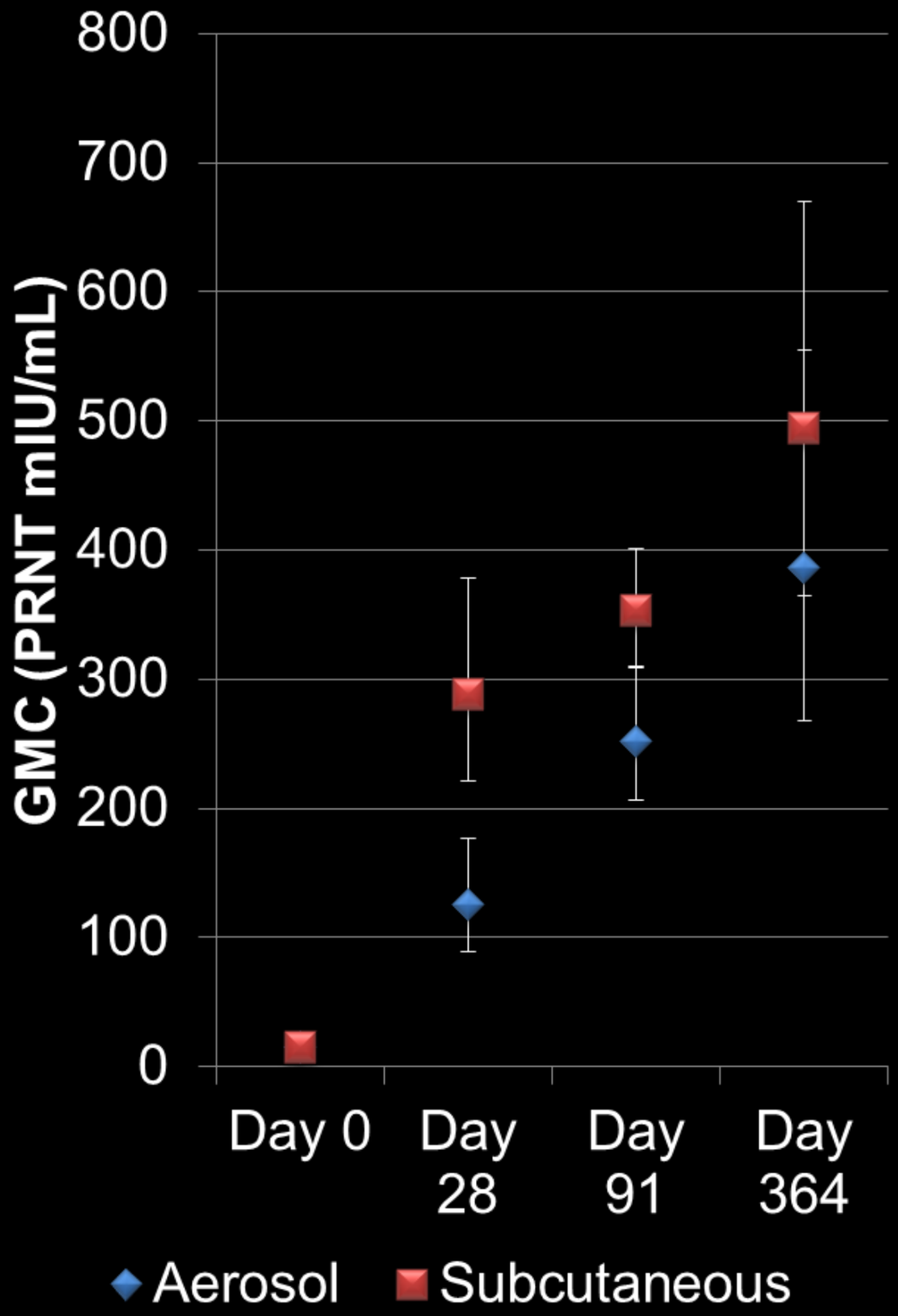
- Difference in Sero-positivity between study arms
- Per Protocol cohort

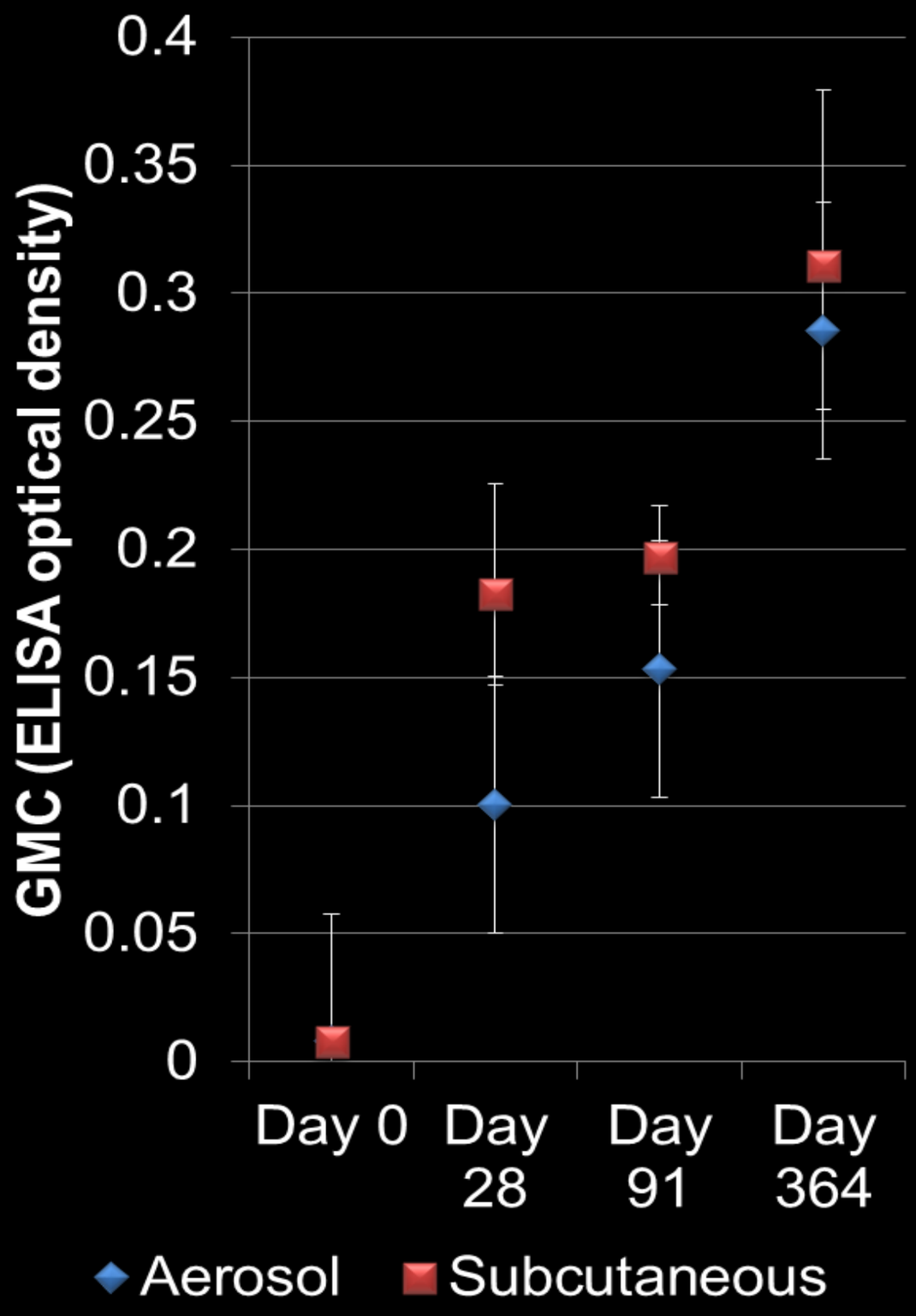
	AER n/N	AER%, 95% CI	SC n/N	SC%, 95% CI	Difference (AER-SC) 95% CI
Seropositive at day 91	662/775	85.42 (82.53-87.90)	743/785	94.65 (92.79-96.05)	-9.23 (-12.22 to -6.30)



Summary of primary outcomes




800
700
600
500
400
300
200
100
0
GMC (PRNT mIU/mL)
Day 0
Day 28
Day 91
Day 364
Aerosol
Subcutaneous


0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
GMC (ELISA optical density)
Day 0
Day 28
Day 91
Day 364
Aerosol
Subcutaneous

Slide on

Immunogenicity when administered as a second dose

Long term persistence of antibodies after aerosol vaccine

Slide on

- Measles aerosol vaccine during outbreaks.

Immunogenicity- Measles vaccine (SC)

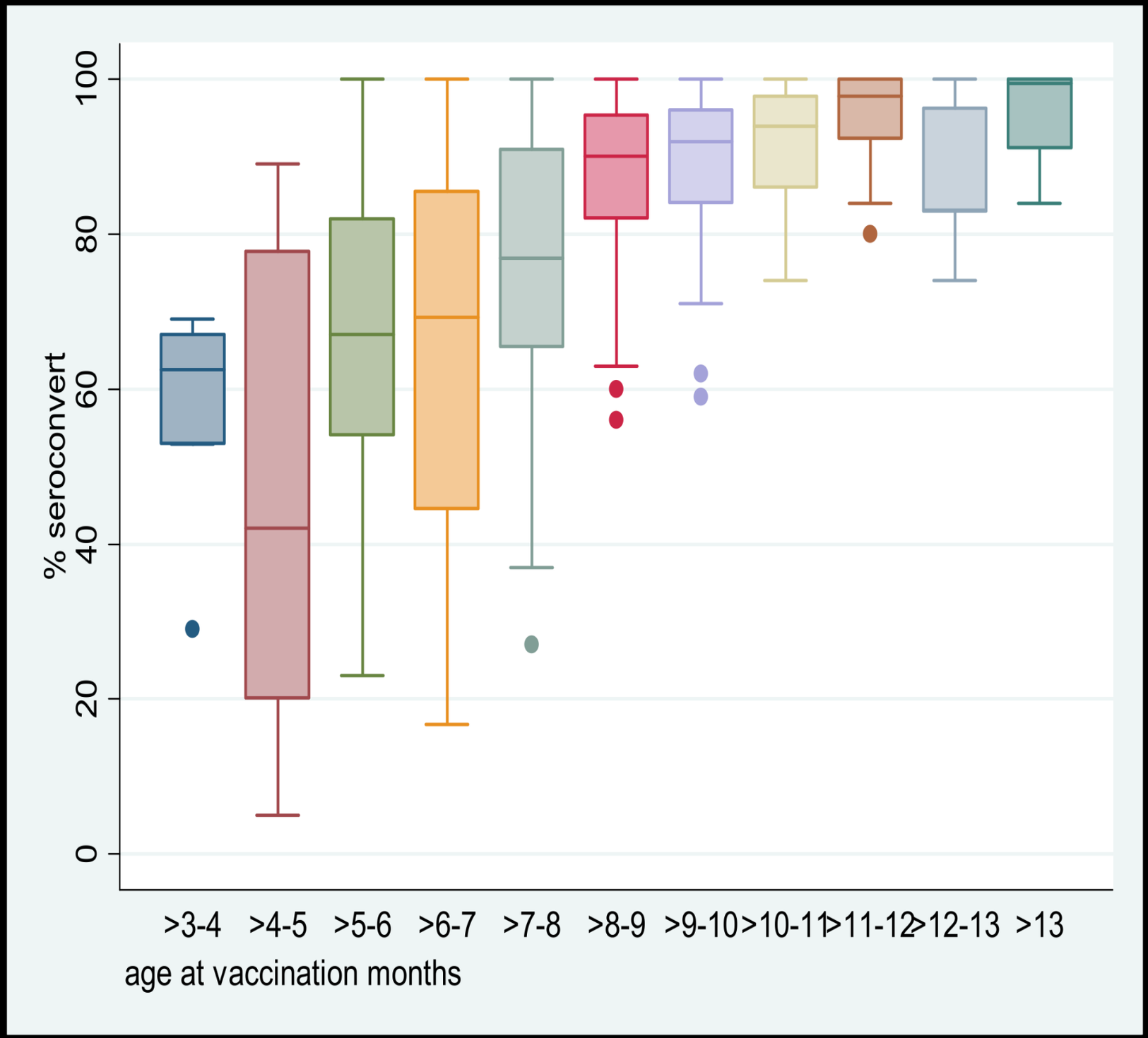
- Global review

- 65 studies
- 1973-2002

- 90% (IQR: 82-95) at
- 9 months

- 96% (IQR: 88-100) at
- 12 months

- Study variations limit interpretation



Susana Scott* et al
*London School of Hygiene and Tropical Medicine

Using Cost-Effectiveness Analysis to Support Research and Development Portfolio Prioritization for Product Innovations in Measles Vaccination (Garrison L et al 2011)

- 4 technologies evaluated: aerosol delivery, needle-free injection, inhalable dry powder, and early administration DNA vaccine.
- 4/4 to have a small absolute impact in terms of reducing the number of measles cases in most scenarios because of already improving vaccine coverage.
-
- 3/4 are projected to reduce unit cost per dose by $0.024 to $0.170 and would improve overall cost-effectiveness.
- 4/4 will require additional investments to reach the market.
- Over the next 40 years, the aggregate cost savings could be substantial, ranging from $98.4 million to $689.4 million.

An evaluation of respiratory administration of measles vaccine for retention of acute lower respiratory infections in children (Higginson D et al , 2011)

- systematically reviewed the literature PLUS an expert opinion exercise by inviting 20 experts
-
  - –mixed feelings about an aerosol measles vaccine.
  - –low levels of optimism regarding the likelihood of efficacy and low cost of development (scores around 50%);
  - –moderate levels of optimism regarding answerability, low cost of production, low cost of implementation and affordability (score around 60%); and
  - –high levels of optimism regarding deliverability, impact on equity and acceptability to health workers and end-users (scores over 80%). this intervention will have a modest but nevertheless important impact on reduction of burden of disease due to childhood pneumonia (median: 5%, interquartile range 1-15%, minimum 0%, maximum 45%).
  - –a feasible candidate strategy in the campaign for global elimination of measles.
- an unique opportunity to decrease the overall burden of disease due to severe pneumonia in young children.

Incremental cost effectivennes

- Preliminary results.

Usability + Acceptability

Oman, 2009
>30 end users
4 immunization sessions

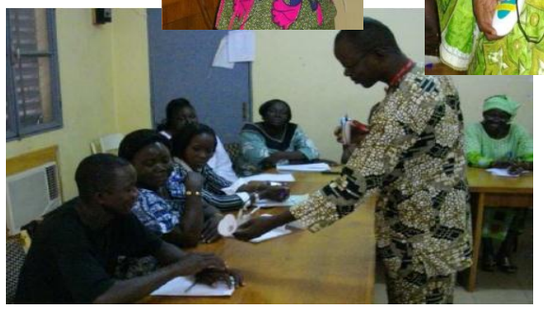
Guyana, 2008
>50 end users
5 immunization sessions

TechNet 21, 2007
25 logisticians

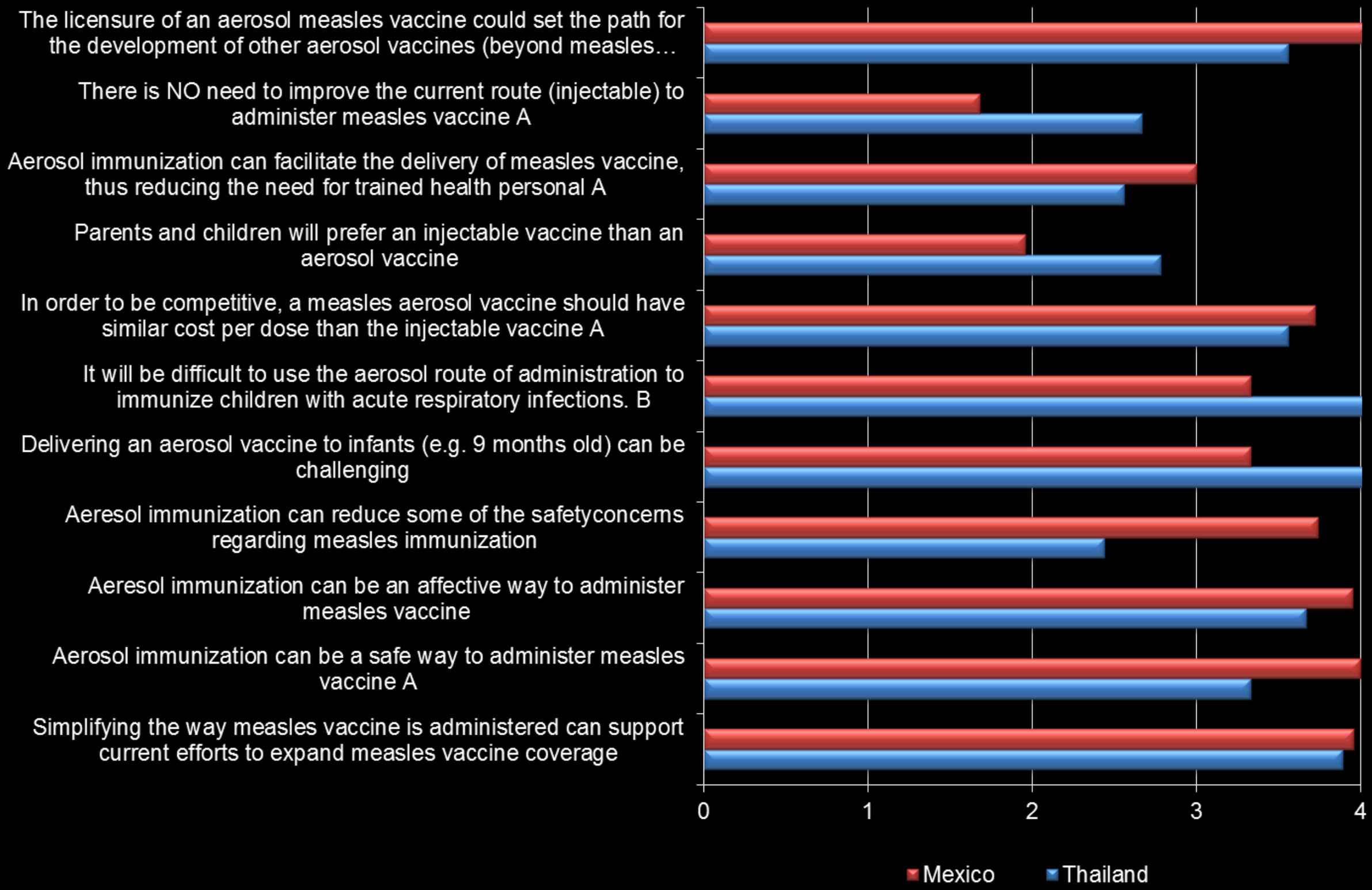
VietNam, 2011
>40 end users
10 immunization sessions

Burkina Faso, 2010
>60 end users
21 immunization sessions

GVRF, 2006
> 50 vaccine researchers



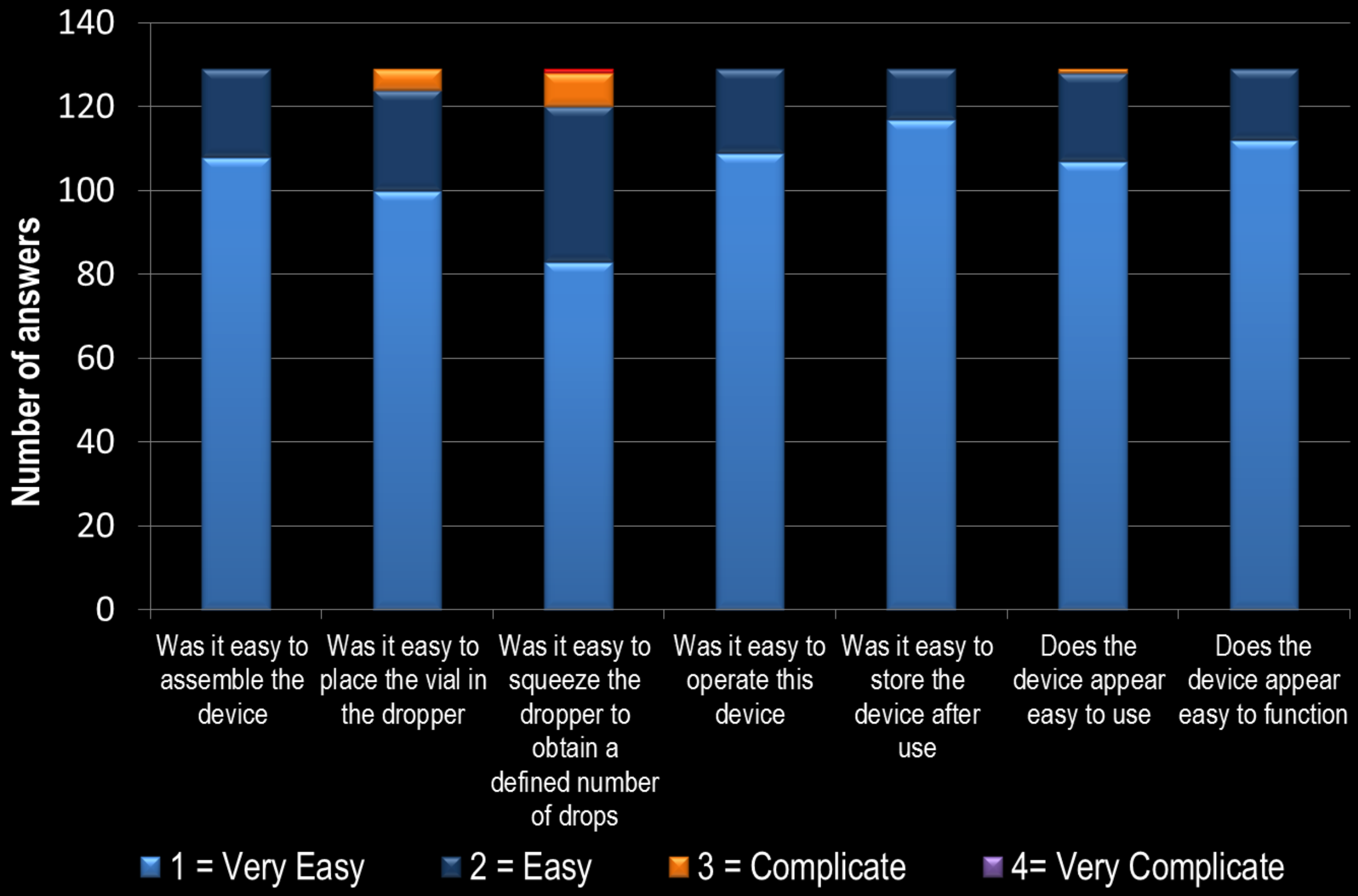
Focus Groups - Results



	Guyana 2007 N=50	Oman 2009 N =93	Burkina Faso 2010 N=92	Vietnam 2010 N=65	
Advantages				Vaccinators	Parents
Pain free	√	√	√	√	√
Reduced injection safety risk	√	√		√	√
Physical aspect of the device			√		√
Ease of use if cost ~to SQ	√		√	√	√
Strengthen HR by recruiting volunteers			√	√	
High acceptance among parents		√		√	√
Time saved in campaigns	√			√	
Easy to transport	√			√	
Easy to manage vaccination waste			√	√	
Fewer AEs	√				√
More sterilized than injection					√
Potential to use with combination vaccines	√				

	Guyana 2007 N=50	Oman 2009 N =93	Burkina Faso 2010 N=92	Vietnam 2010 N=65	
Disadvantages				Vaccinators	Parents
Reliability of the device		√	√		
Increased "difficulty" in estimating vaccine efficacy		√	√	√	√
Concerns on possible side effects		√	√		√
Risks of cross contamination		√		√	√
Young children may be reluctant	√			√	
Implementing 3 routes for vaccination (oral, Injection, aerosol) at the same time				√	
Not familiar with maintaining electric equipment				√	
Longer time for vaccination					√
Potential to use with other combination vaccines		√			

Vaccinators opinion



- In general, the results from these studies supported the introduction of measles aerosol vaccine on the grounds of it being pain free, easier to use, cause less anxiety for parents and removal of injection safety concerns and waste management requirements.

- However, results also included health workers concerns related to potential difficulty to ensure the required dose is administered and; parents/community members concerns about potential risk of cross-contamination. Managers were interested in learning more about costs of introduction and feasibility of effective implementation of an additional route of vaccine administration.

Slide on Aerosol MR and MMR

Potential additional research

11th Meeting of the WHO Product Development Group for Measles Aerosol Project 23-24 Aug 2012

- The analysis of risk factors did not show any evidence that any of the factors investigated had a significant association to remaining seronegative.

- Data available suggest that there may be differences in the kinetics of the immune responses between the aerosol and subcutaneous routes.

- However, PDG lacked the data that would allow a clear interpretation that these differences exist and of the potential relevance.

-

11th Meeting of the WHO Product Development Group for Measles Aerosol Project 23-24 Aug 2012

- They noted that the evidence available is insufficient to evaluate its potential efficacy in older children for primary vaccination or as a second dose of measles vaccine.
- They recommended that additional studies should be considered to further evaluate the measles aerosol vaccine, namely: immunogenicity in older children (e.g. >12 months of age) and; evaluation of the immune response using other immunological criteria including the assessment of the kinetics and duration of antibodies, and the differences in T cell responses.
-

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- They noted that shall individual countries consider moving forward with the licensure and introduction of the measles aerosol vaccine, other key factors besides the immunogenicity results should be included in the assessment such as:
- the incremental cost effectiveness analysis ;
- the evidence on its acceptability and usability;
- the potential performance of the measles aerosol vaccine in older children and in mass campaigns,
- its likely use for the administration of the second dose of measles vaccine and,
- the potential device improvements to facilitate its use in low resource environments.

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- They noted that the results of this trial should be considered in a context of a change in global measles immunization policies and goals, which encompasses
  - –recent recommendations for a widespread introduction of a second dose of a measles vaccine,
  - –primary vaccination at 12 months of age in countries with high levels of coverage or in the elimination phase and,
  - –recommendations for introduction of rubella vaccine.

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- Lastly, the PDG members reiterated that
- 1) the current subcutaneous measles vaccination is safe and effective, and
- 2) a safe and effective aerosol delivery of a measles vaccine could potentially support current global control and elimination efforts and consequently support future studies in this area of work.

Acknowledgments

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Serum Institute of India Ltd
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