Measles Vaccination by Aerosol

Innovative Administration Systems for Vaccines
Rockville --- Dec 18-19, 2003

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Mexico-INSP

Measles aerosol immunization

SAFE ☑ no serious AEFIs, fewer than SC route

IMMUNOGENIC
- ☑ induced >80% response among infants < 9 months of age
- ☑ 86-100% response in studies (1961-2002) among ≥ 9 months & school-aged children
- ☑ **good response with rubella vaccine**

EFFECTIVE ☑ lower attack rate (outbreak Mexico 1988-90):
- immunized with aerosol *(0.8%)*
- immunized with s-c *(14%)*
- unvaccinated group *(26%)*

EZ strain retains potency during nebulization process

Measles Aerosol Project

GOAL:

To develop & license at least one method (vaccine & delivery device) for respiratory delivery of currently licensed measles vaccines

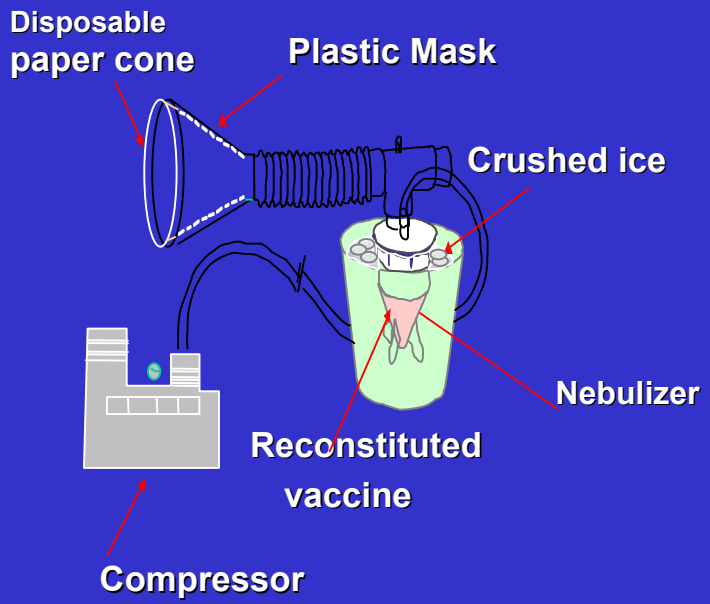
- **a measles vaccine that is cheaper, safer and easier than percutaneous administration**
- **at least three devices for aerosol administration of reconstituted vaccine tested**
- if feasible, a **dry powder** method will enter the initial studies

Current device options

➔ Nasal spray systems

CDC-Creare

➔ Vibrating mesh nebulizers



➔ Jet nebulizers

Devices : selection & development

- Develop methods & characterise the “Classical” Mexican devices
- Define optimal logistics & usability criteria; validate in the field

- Identify existing devices that fulfil set criteria
- Work with device developers to obtain “optimal” device(s)

- Complete toxicology studies with “optimal” device(s)
- Carry out Phase 1 & Phase 2 studies with “optimal” device(s)
- Manage a portfolio of device options

Measles Aerosol Project Workplan

Years 6, 7 ...

Phase 4 & post-licensure

Licensure

Year 5
2006-07

Additional Phase 2 trials

Years 3, 4
2005-06

Phase 2 trials

Year 2
2003-05

Phase 1 trials, India
Phase 2 trial, Mexico
Economic assessment

Year 1
2002-03

Draft protocols for clinical evaluation
Review of potential safety concerns
Device selection & characterisation
Pre-clinical studies: Bench, Animal & Tox studies
Organization of PDG & mgmt procedures

Measles Aerosol Management Group (MAMG)

Members

Dr M Grabowsky	-- American Red Cross, USA
Dr S Chu	-- Centers for Disease Control & Prevention, USA
Dr M P Kieny	-- WHO - Initiative for Vaccine Research

Measles Aerosol Product Development Group (PDG)

Chairperson

Prof Felicity Cutts	-- MRC-The Gambia & LSHTM, UK

Members

Dr John Bennett	-- Rollings School of Public Health, USA
Prof Allan Coates	-- The Hospital for Sick Children, Canada
Dr Jorge Fernandez de Castro	-- Nat Inst of Public Health, Mexico
Prof Myron Levine	-- Center for Vaccine Development, USA
Dr Mark Papania	-- CDC, USA
Dr Ajay Tahlan	-- Central Research Institute, India
Dr Jose Luis Valdespino	-- Nat Inst of Public Health, Mexico
Dr Jennifer Welbeck	-- Medical School, Ghana

Ad-hoc Members

Dr Nirmal Ganguly	-- Indian Council of Medical Research, India
Dr Mark Miller	-- Fogarty Int Center, NIH, USA

Measles Aerosol Partners

Bill and Melinda Gates Foundation

Serum Institute of India, Limited, India

Sabin Vaccine Institute, USA

International Society for Aerosols in Medicine

Johns Hopkins Univ, Univ of Maryland, MRC ……..

Limitations of Devices used in Previous Measles Aerosol Vaccination Studies

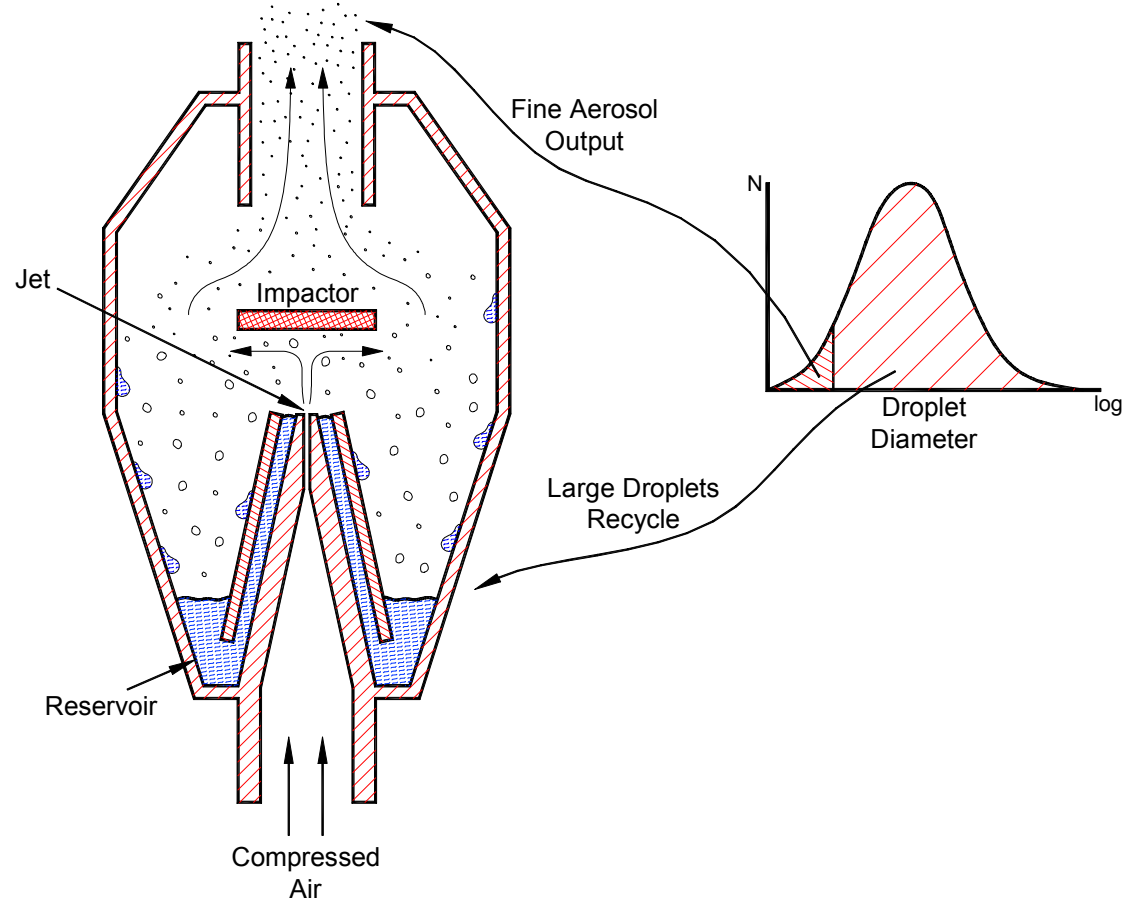
- Power requirements
- Need for crushed ice
- Cumbersome equipment – not standardized
- Delivered dosage not precisely known
- Dosage timing (30 seconds) – requires time piece
- Loss of virus potency with Schwarz strain
- Potential contamination of device with spread of respiratory pathogens to vaccinees
- Environmental vaccine virus aerosol –
  Risk to vaccinators and others?

Goal – Mimic the aerosol output of previous devices with a device that does not have these limitations

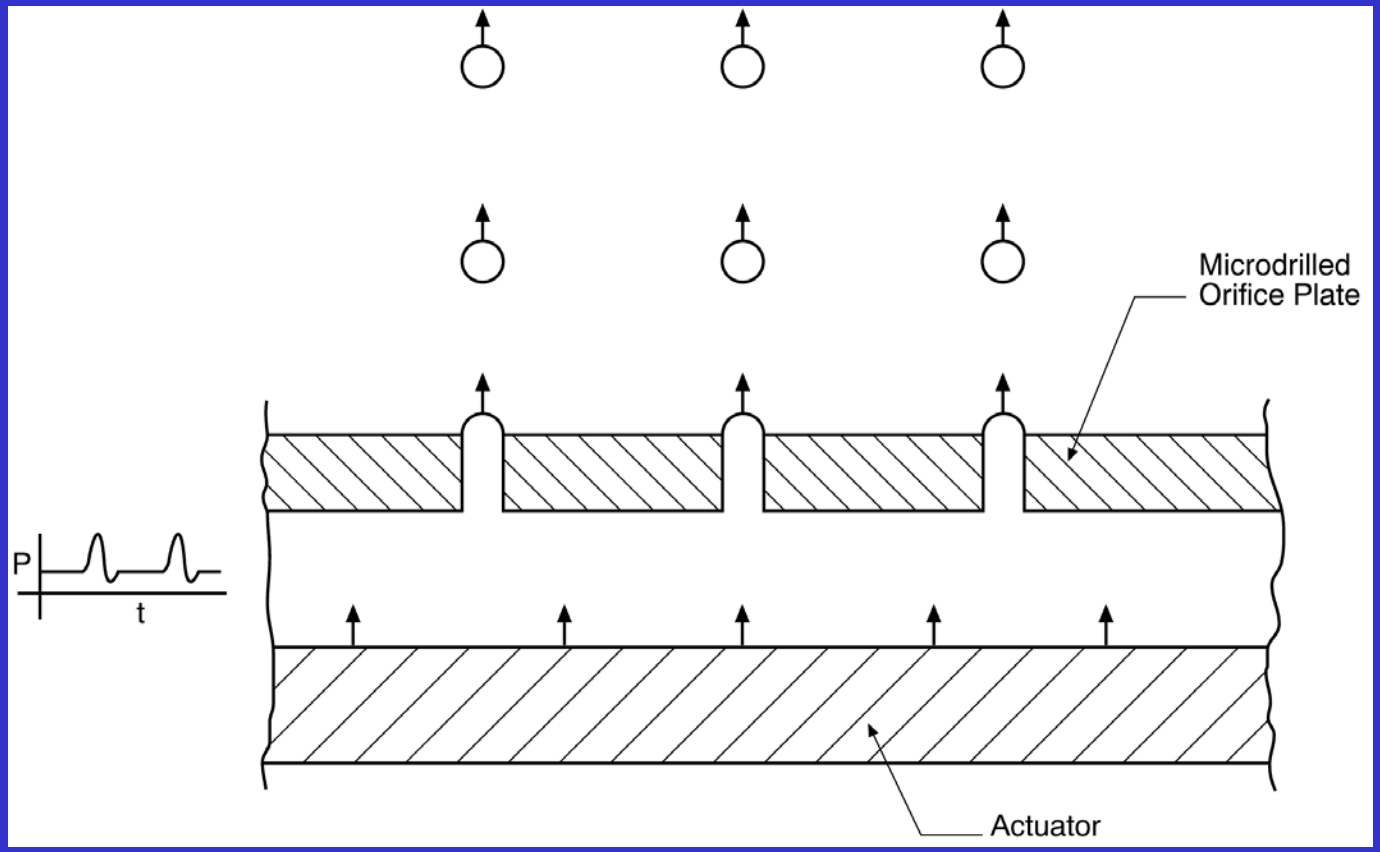
Basic Aerosol Vaccination Science

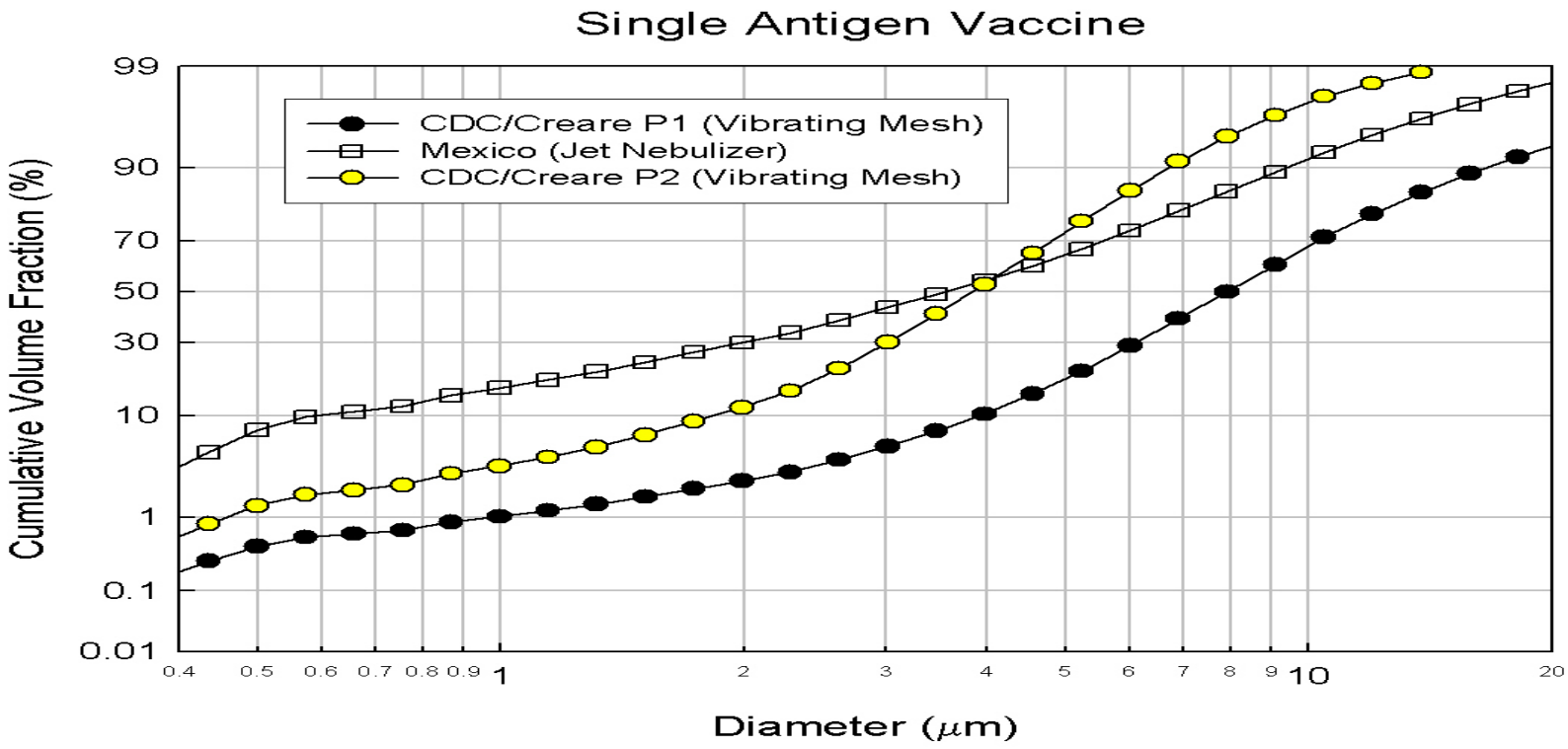
- The particle size distribution, particle speed and route of administration are the most important factors in determining where the administered aerosol deposits
- It is critical for the live vaccine virus to survive aerosolization

Jet Nebulizer Design and Function

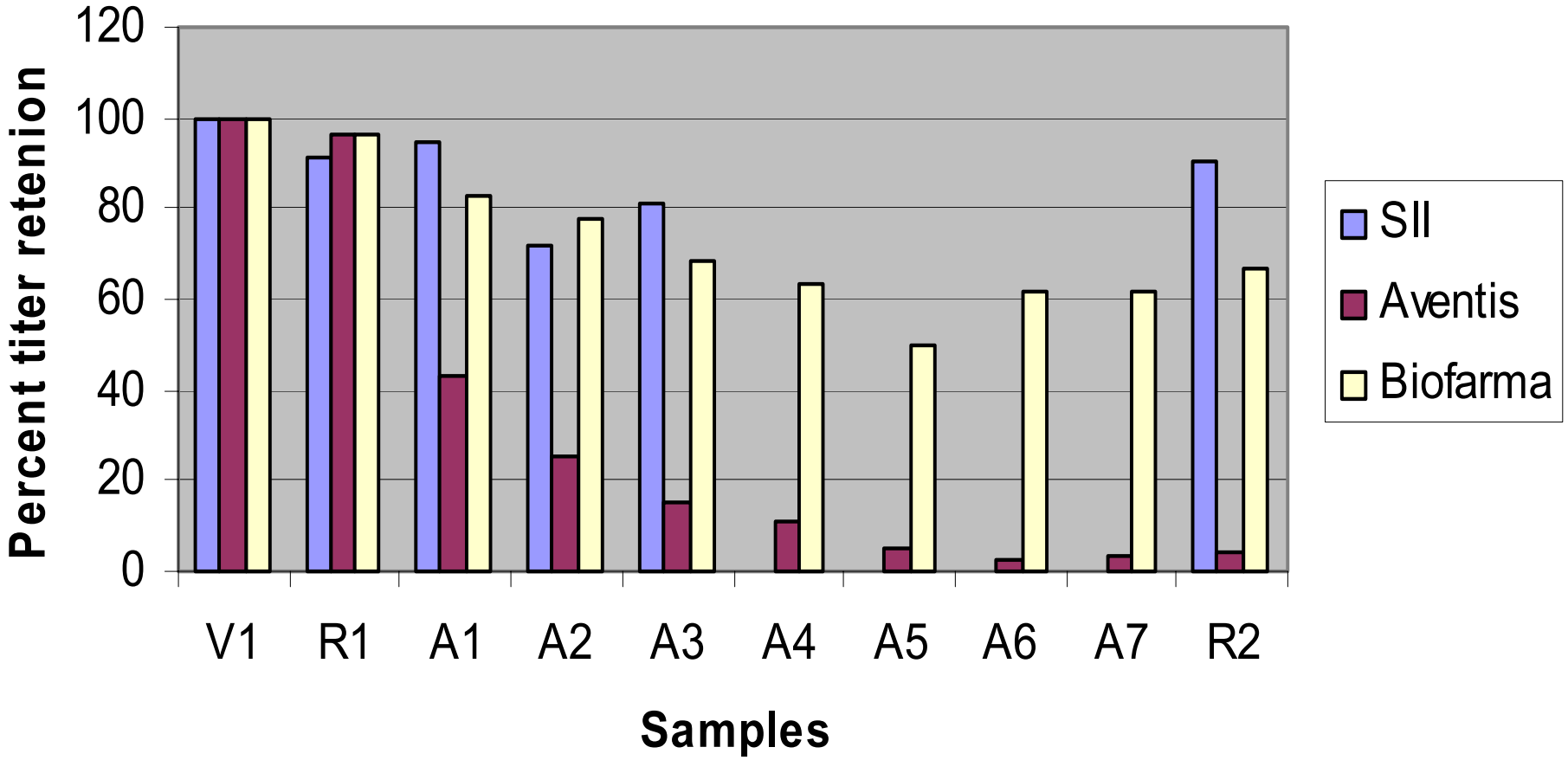


CDC/Creare Device - Vibrating Mesh Direct Droplet Generation

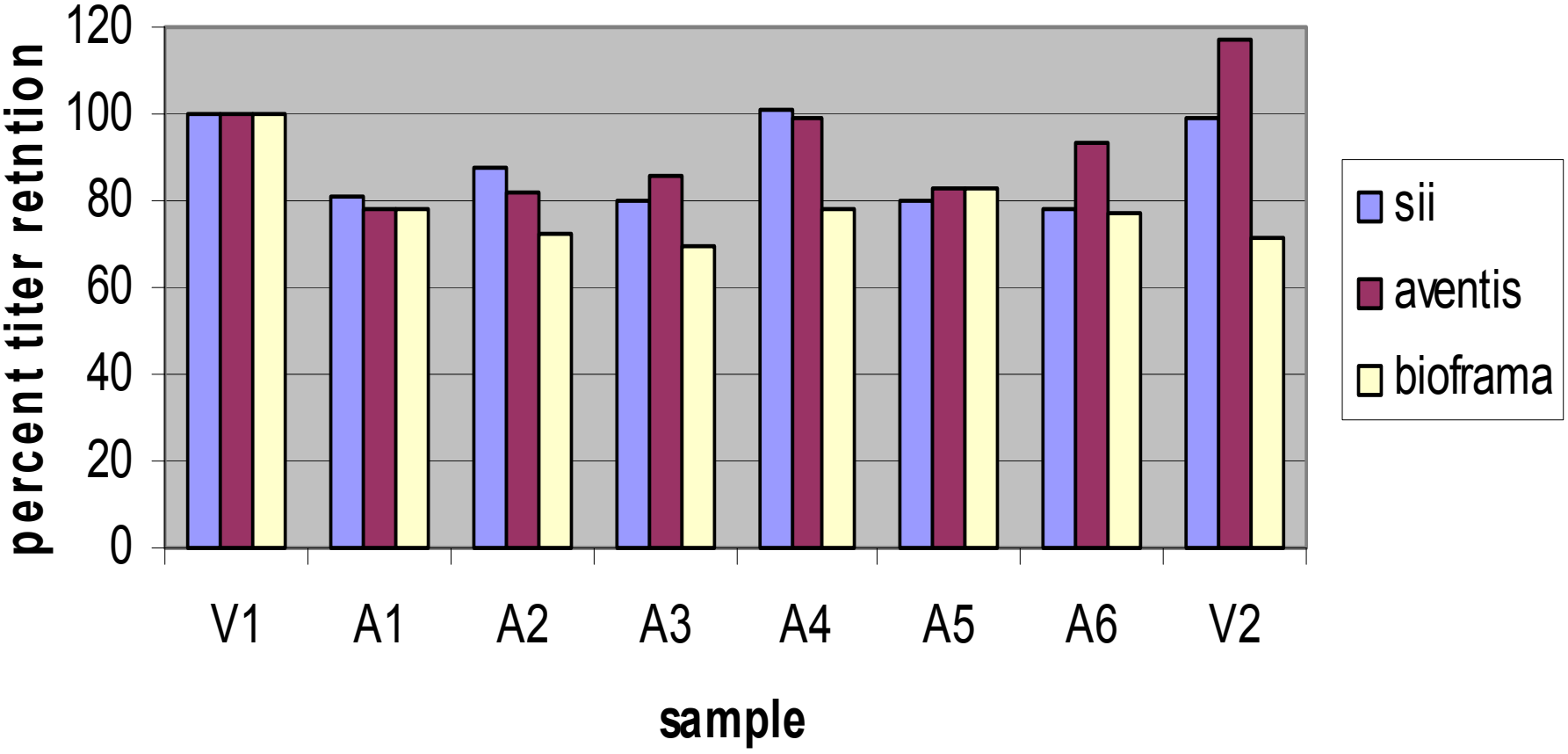



Single Antigen Vaccine
CDC/Creare P1 (Vibrating Mesh)
Mexico (Jet Nebulizer)
CDC/Creare P2 (Vibrating Mesh)
Cumulative Volume Fraction (%)
99
90
70
50
30
10
1
0.1
0.01
0.4
0.5
0.6
0.7
0.8
0.9
1
2
3
4
5
6
7
8
9
10
20
Diameter (μm)

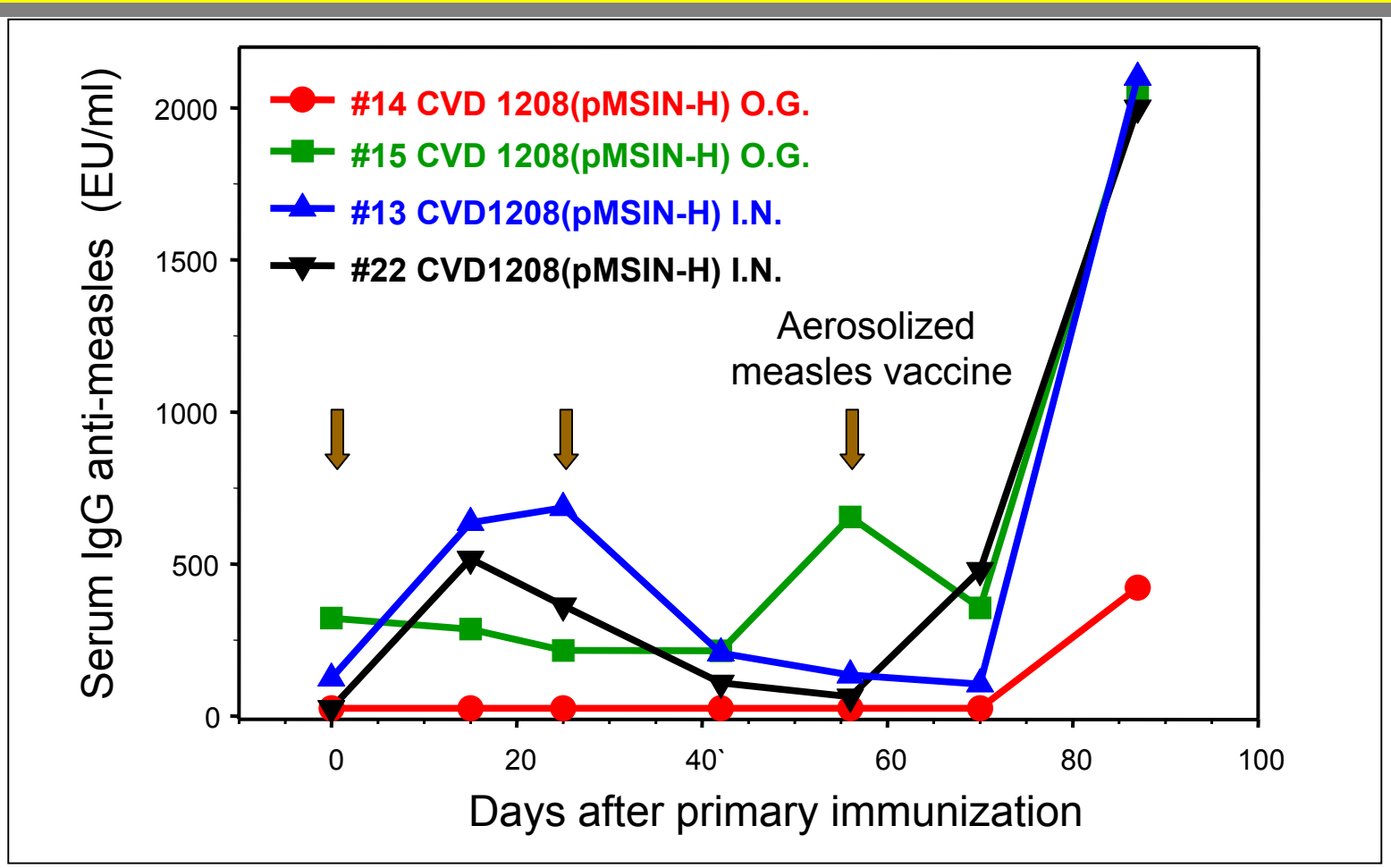
Measles Vaccine Virus Potency Retention
Mexican Jet Nebulizer with Crushed Ice



Measles Vaccine Virus Potency Retention
CDC/Creare Device (no ice)



SERUM ANTI-MEASLES IgG FOLLOWING MUCOSAL ADMINISTRATION TO JUVENILE MACAQUES OF *S. FLEXNERI* 2A CVD 1208 CARRYING A DNA VACCINE ENCODING MEASLES HEMAGGLUTININ



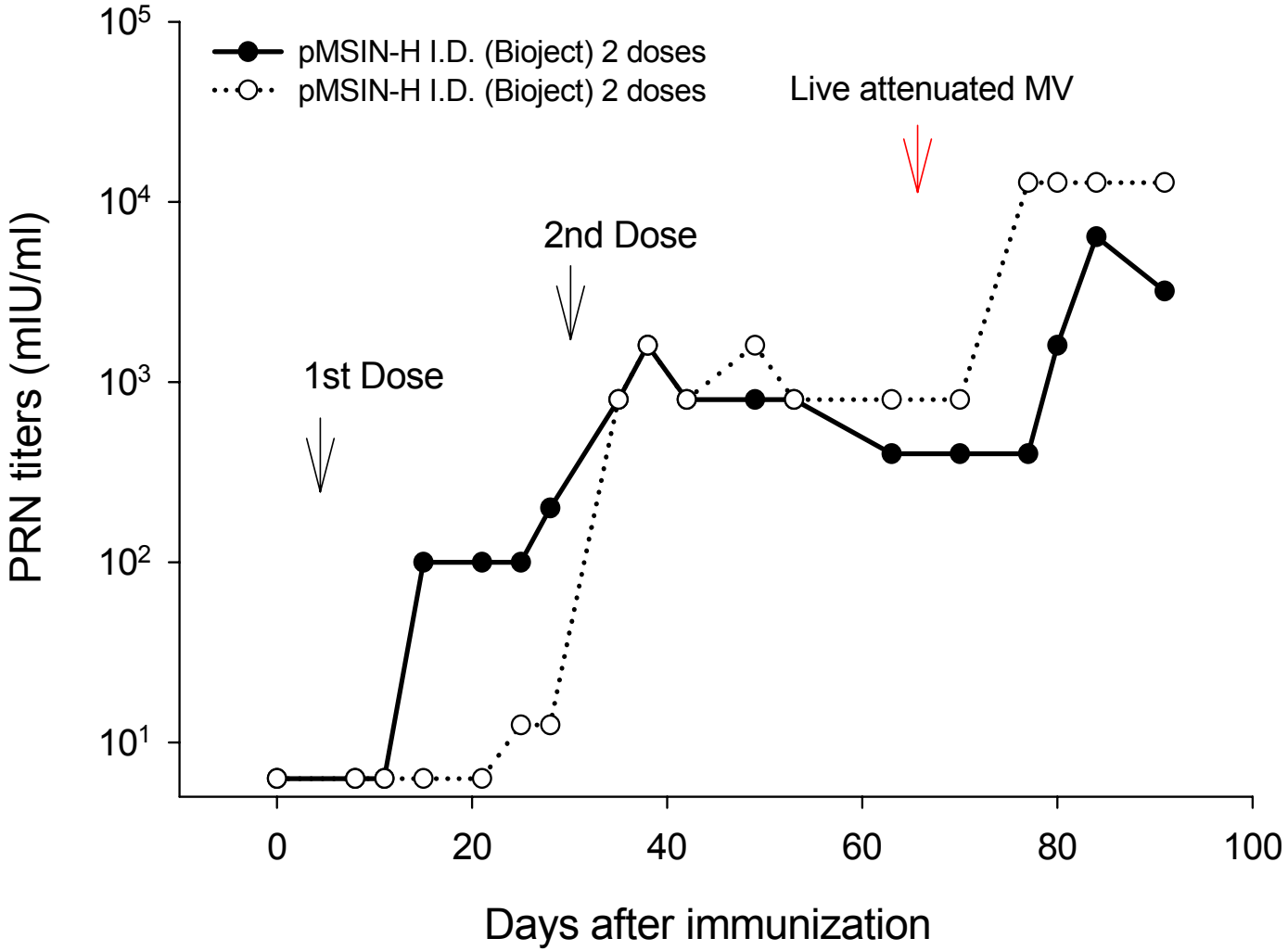
CVD

JUVENILE RHESUS MODEL – SERUM MEASLES PLAQUE REDUCTION NEUTRALIZING ANTIBODIES AFTER PRIMING WITH *S. flexneri* 2A CVD 1208 CARRYING pMSIN-H DNA VACCINE ENCODING MEASLES H & AEROSOL MEASLES VACCINE BOOST

Aerosol boost ↓ Challenge

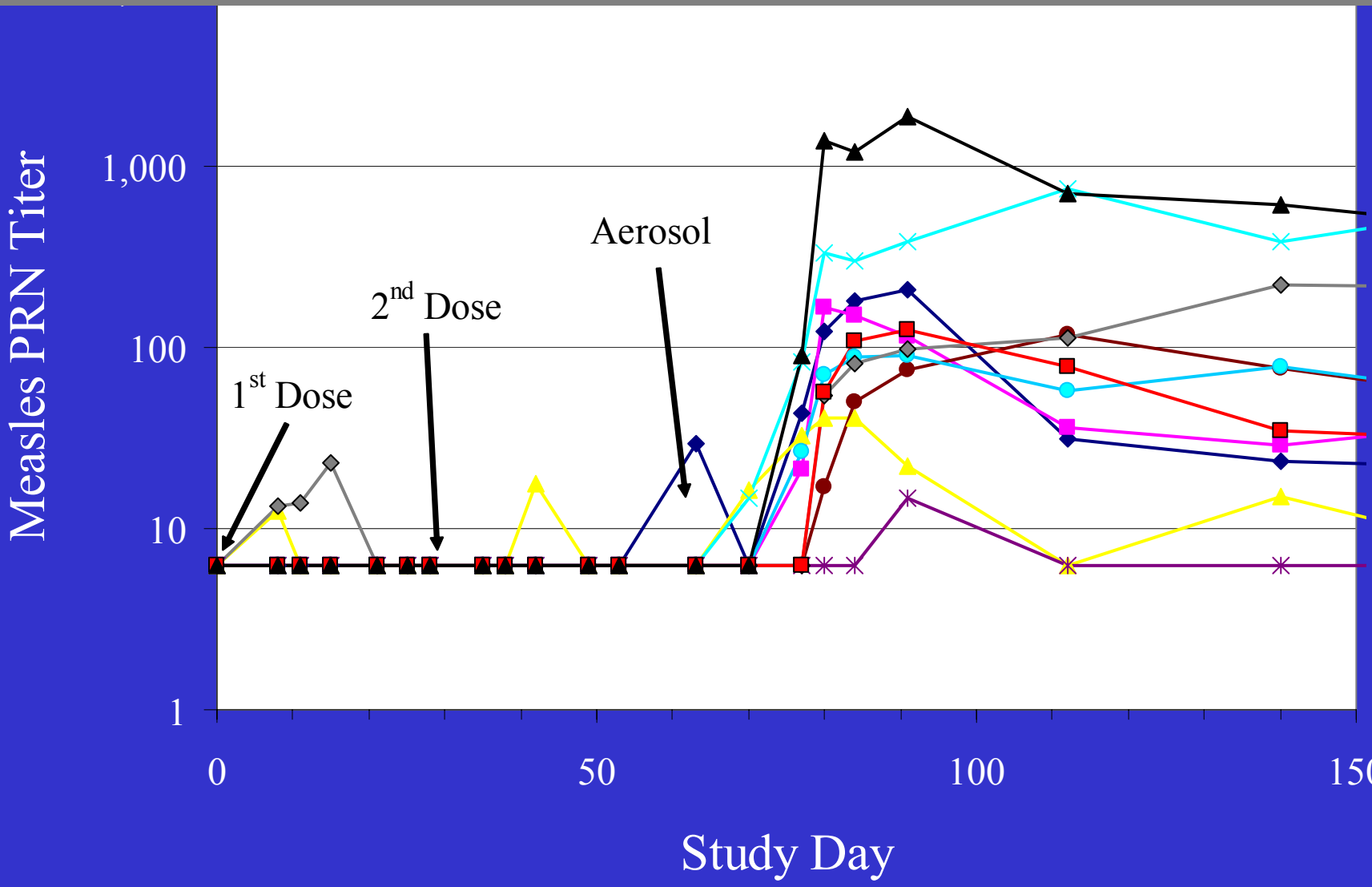
Monkey	ELISA showed priming	Day 0	Day 56	Day 116	Day 366	Viremia $TCID_{50}$ per 10^6 PBMC*
13 (i.n.)	yes	<10	<10	752	218	0 (well)
22 (i.n.)	yes	<10	482	563	210	0 (well)
15 (o.g.)	modest	<10	<10	87	<10	$10^{4.8}$ (ill)
14 (o.g.)	no	<10	<10	<10	<10	$10^{4.8}$ (ill)

Measles PRN Titers Following Priming with pMSIN-H DNA Vaccine Administered by Biojector 2000 Needle-free Injector and Following Boost with EZ Measles Vaccine Administered by Aerosol Device



CVD

Measles PRN Titers Following Priming with Mucosal Vaccines and Boost with EZ Measles Vaccine Administered by Aerosol Device



CVD

CVD MEASLES VACCINE PROJECT

***Shigella* vectors:**	Eileen Barry
DNA vaccines:	Man Ki Song, Mahender Singh, Jeffrey Ulmer & John Polo (Chiron)
Clin. Microbiol:	James Nataro, Sophie Livio
Aerosol measles:	Mark Papania (CDC)
Immunology:	Marcela Pasetti, Marcelo Sztein, Sandra Medina-Moreno, Yu Leung Lim
Rhesus monkey challenge	Diane Griffin (JHU), Fernando Pollack (JHU), Robert Adams (JHU)
PI Coordination:	Mike Levine
Funding:	Bill and Melinda Gates Foundation

CVD

CDC/Creare Aerosol Vaccination Device

- Vibrating membrane technology has very low energy requirements- Outlet electricity only needed for charging batteries every 1000 doses
- Particle size closely matches “Mexican” device that has been successful in clinical trials
- Particle size flexibility (simply change plate)
- Viability retained for all strains without crushed ice
- Demonstrated “proof of principle” – Immunogenic with no adverse events in rhesus macaques
- Triggered dosing with variable dose duration
- Vaccine delivered direct from vial
- Minimal environmental contamination with optional nasal or oral prong

Next Steps

- Second Generation Prototypes
- Formal toxicology studies to assess safety in macaques
- Phase 1 and 2 Clinical trials