maciviva
COLD CHAIN INDEPENDENT VIROSOME-BASED VACCINES

MYMETICS

# EU H2020 - MACIVIVA project

# Developing Cold Chain Independent Virosomal Vaccines

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# Need Worldwide Convenient Vaccines

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**MACIVIVA**

PAST

PRESENT

FUTURE

- Reducing cold chain dependence
- Developing ready to use vaccines


Need to explore:

- New galenic formulations
- New stabilization methods
- New manufacturing methods

Thermostable vaccines supporting exposures from -20°C to 40°C

Liquid
(4°C)

Liquid or Lyophilized
(4°C to -20°C)

- Most vaccines are heat and/or freeze-sensitive
- Cold chain dependent for preserving bioactivity
- Frequent inadequate shipment and/or storage temperature in developing countries





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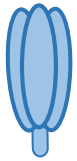
# Challenge: Preserve Virosome & Antigens

## Making the MACIVIVA Proof of Concept with the liquid virosomes

From solubilized inactivated influenza



Native Hemagglutinin

Native Neuraminidase

Native phospholipids

Vaccine components

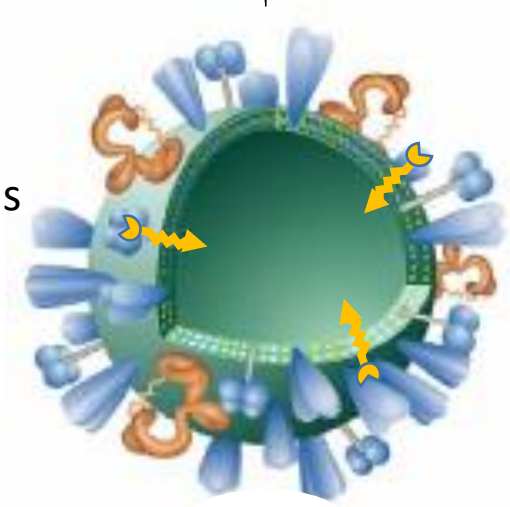
Vaccinal antigen

± Synthetic phospholipids

± Adjuvant

*In vitro* assembly of Influenza virosome as carrier of vaccinal antigens

Antigens and adjuvants on the SAME particle



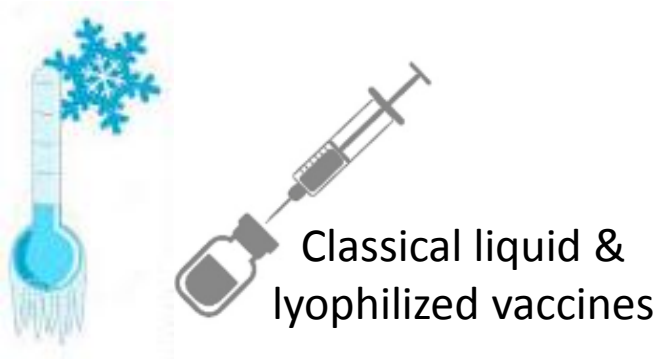
Tested in clinical trials

- Influenza HA and NA (commercialized)
- HIV-1 derived antigens (rgp41 & P1)
- Malaria *Pf* AMA-1, CSP-1, others
- *Candida albicans* Sap2
- Others

**Virosomes = Reconstituted Viral Membranes = VLPs**

# MACIVIVA Project - Innovations & Benefits

- Developing new GMP Pilot line(s)
- Manufacturing virosomal vaccines under new solid dosage form(s)
- Cold chain independent vaccines
- No need of reconstitution with liquid – **Direct administration**
- Needle free vaccination: **Painless & may be self-administered**
- Favor **mucosal immunity**



Classical liquid & lyophilized vaccines

**New solid vaccine dosage forms**

-Sublingual pills
-Oral enteric coated pills
-Nasal powder spray

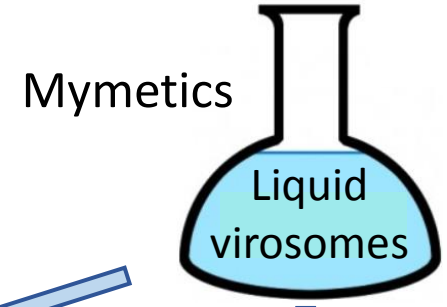
**Refrigerator/Freezer (≤ 8°C)**

- Complex logistic
- Required for preserving vaccine potency

**Cold chain independent (10°C to 40°C)**

- Greatly simplified logistics
- Vaccines resistant to heat or freeze exposures

# New Solid Dosage Forms of Virosomal Vaccines




Next generation of virosomes:
- Solid powder form(s)
- Thermostable
- Cold-chain independent

Promising preliminary data

**Pilot Line no. 1**
Freeze/Freeze drying
**Catalent:** Sublingual tablets

**Pilot Line no. 2**
Heat Spray drying
**Upperton**: Capsules - oral delivery

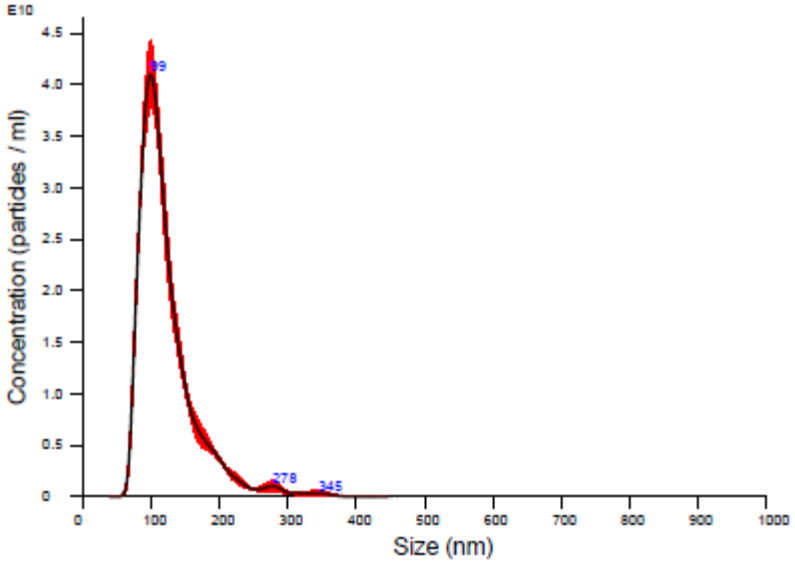
**Pilot Line no. 3**
Heat Spray drying
**Upperton:** Nasal spray

Mucosal vaccine delivery is expected to favor local (site of delivery) and distant mucosal antibody response, together with the systemic antibody response

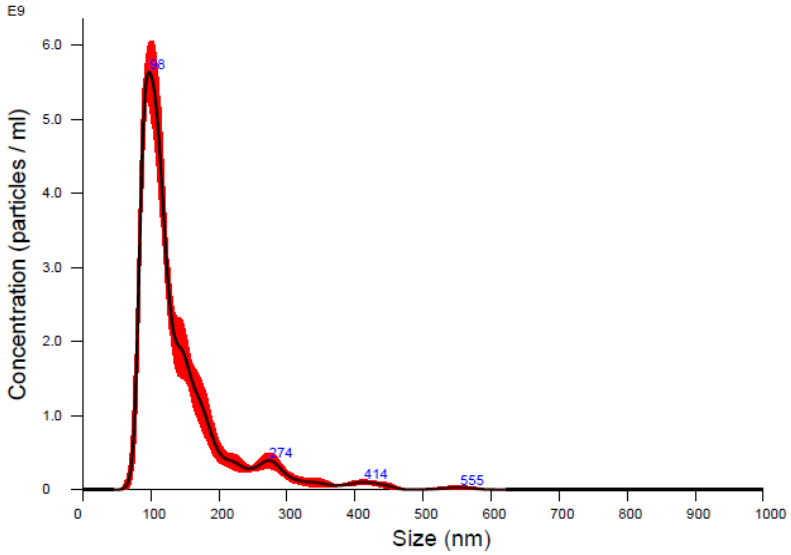
# Spray Drying Preserve Virosome Structure and Size

- Nanoparticle tracking analysis (NTA) on virosomes before and after downstream processing
- Mean virosome particle size: about 100 nm

MYM-V212 Lot 170130-1
(Liquid before spray drying)



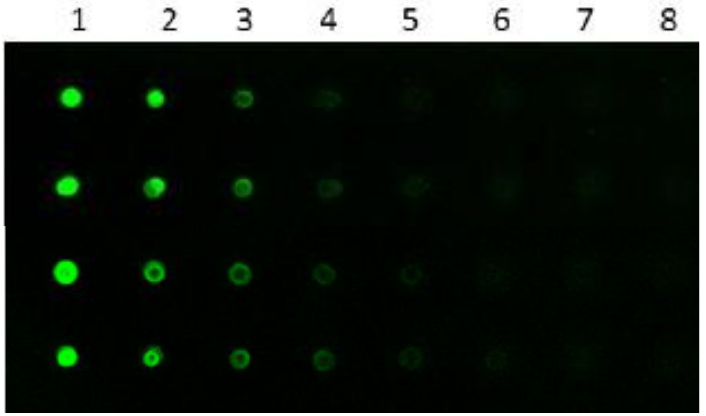

MYM-V212 Lot 170130-1
(Powder after spray drying)



# Spray Drying Preserve Antigens on Virosomes

- Spot blot maintains the antigens mostly in their native state
- No significant differences found for P1, rgp41 and HA between liquid and spray dried powder

Two-fold dilutions



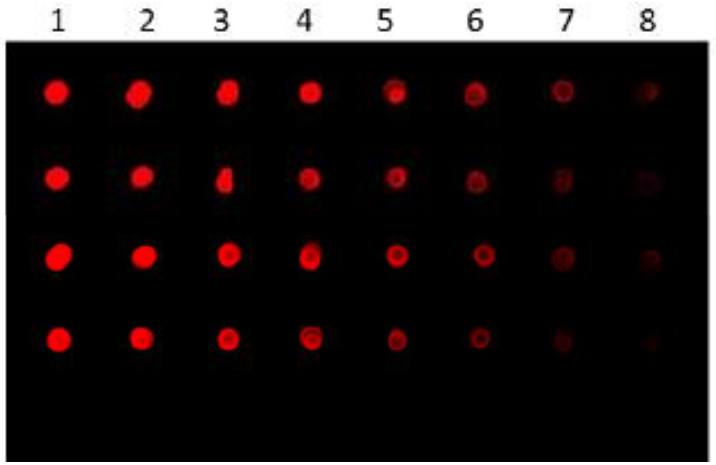

MYM-V201 liquid virosomes

MYM-V202 liquid virosomes

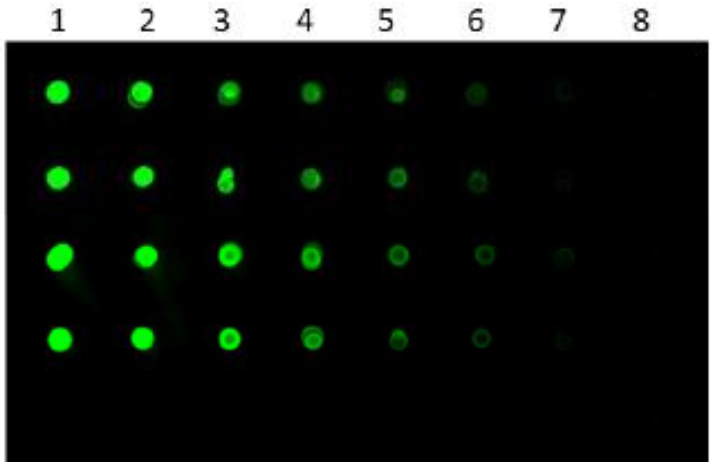
Spray dried powder with adjuvant

Spray dried powder without adjuvant

Anti-HA mAb




Anti-rgp41 serum




Anti-P1 mAb

MYM-V201 liquid virosomes

MYM-V202 liquid virosomes

Spray dried powder with adjuvant

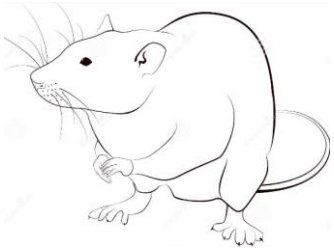
Spray dried powder without adjuvant

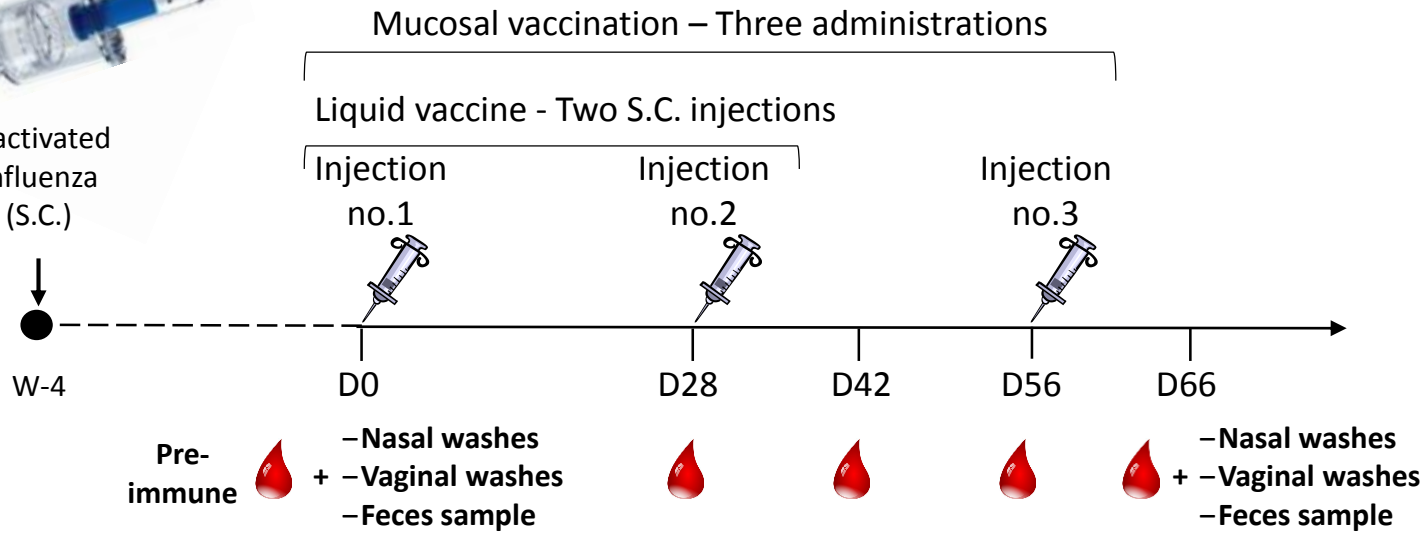
Negative control virosomes

# Animal study - Vaccination Schedule

- Wistar rats (2-months at start of the study)
- Subcontractor: Preclinics (Germany)
  - Group 1 – Liquid vaccine + adjuvant
  - Group 4 – Intranasal vaccine + adjuvant
  - Group 5 – Intranasal vaccine no adjuvant

| Vaccine component | MYM-V202 | 056#111 | 056#112 |
|---|---|---|---|
| | Liquid vaccine with adjuvant | Nasal spray with adjuvant | Nasal spray without adjuvant |
| | µg/ 0.1 mL | µg/10 mg | µg/10 mg |
| P1 | 5.0 | 5.0 | 5.0 |
| rgp41 | 11.5 | 11.5 | 11.5 |

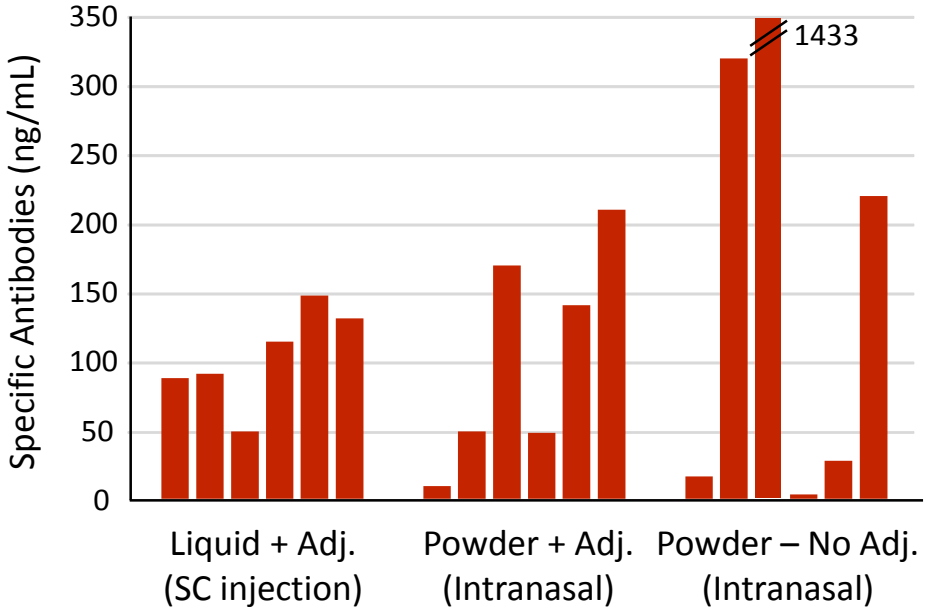




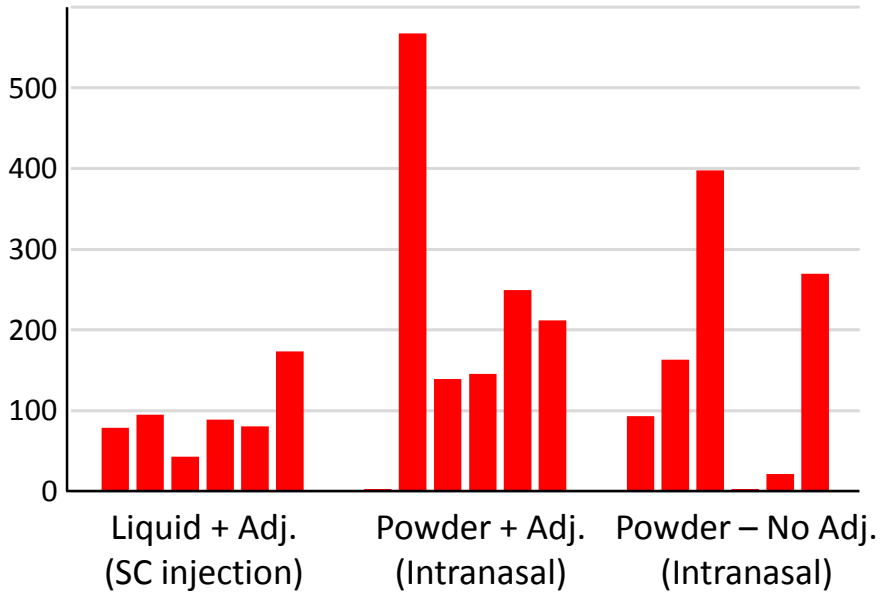
# Serum Antibody Concentrations After Vaccination

Spray dried powders elicit comparable or higher levels of specific serum antibodies as compared to the liquid virosome formulation

Serum anti-rgp41
D42: 14 days after 2nd vaccination




Serum anti-rgp41
D56: 28 days after 2nd vaccination

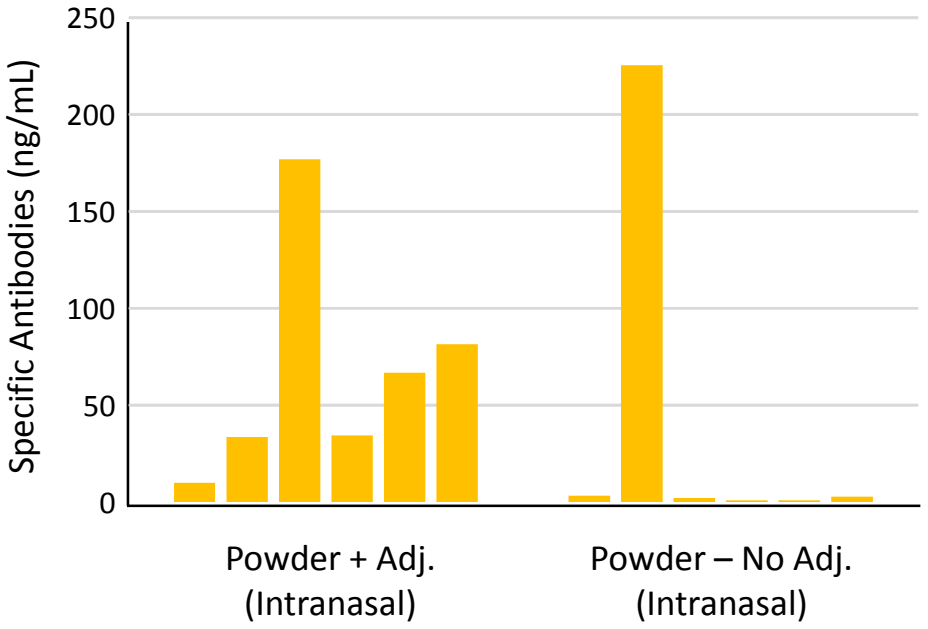


# Mucosal Antibody Concentrations After Vaccination

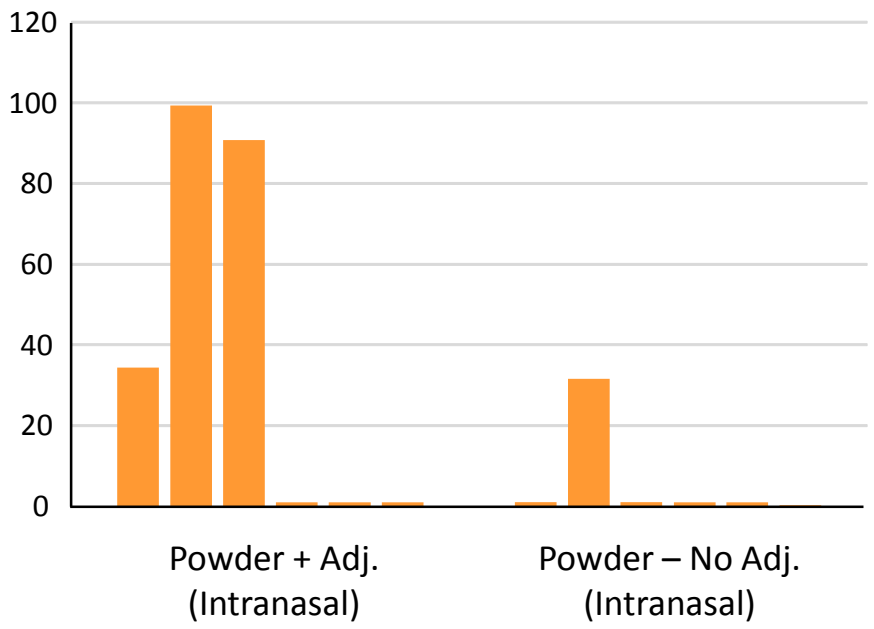
Overall, adjuvanted spray dried powder elicits higher levels of mucosal specific antibodies than unadjuvanted nasal formulation

D66: 10 days after 3rd vaccination

Nasal anti-rgp41 antibodies




Nasal anti-P1 antibodies

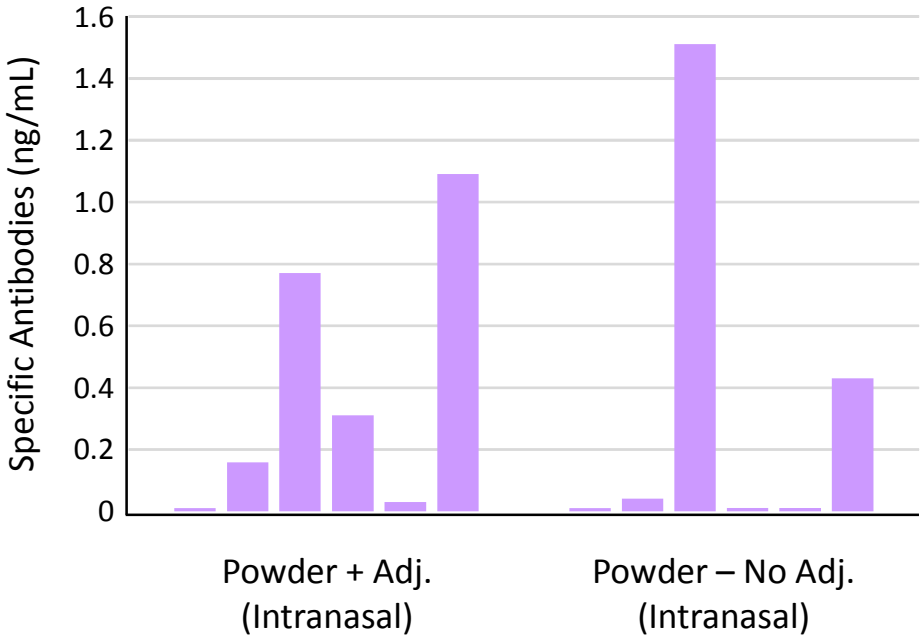


# Mucosal Antibody Concentrations After Vaccination

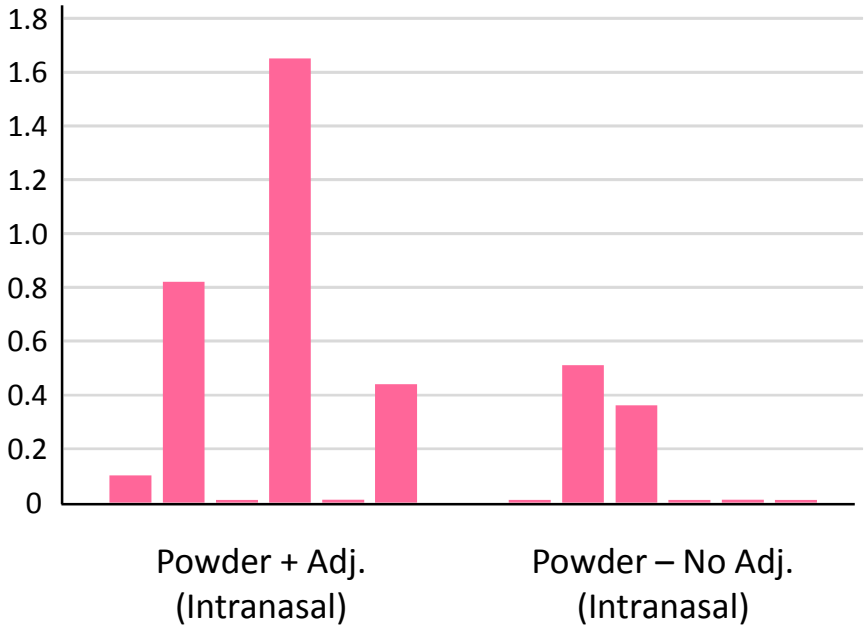
Overall, adjuvanted spray dried powder elicits higher levels of mucosal specific antibodies than unadjuvanted nasal formulation

D66: 10 days after 3rd vaccination

Vaginal anti-rgp41 antibodies




Vaginal anti-P1 antibodies




0.3 ng/mL of antibodies = 1.1 x $10^9$ antibody molecules/mL

# Conclusions

- Pilot lines were developed - optimization ongoing

- Intranasal spray powder preserved virosome immunogenicity
  - ✓ Serum antibodies
  - ✓ Nasal antibodies
  - ✓ Vaginal antibodies
  - ✓ Rectal antibodies (not shown)

  Serum > Nasal > Vaginal > Rectal

- Adjuvant improves the nasal powder vaccine-induced antibodies

- Preliminary results with oral capsules and sublingual tablets with virosomal HIV-1 vaccines: Preservation of virosomes and antigens confirmed (data not shown). Vaccine delivery conditions need to be further optimized.

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