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A first-in-human study of a novel adjuvant for increased immunogenicity and dose-sparing of seasonal influenza vaccines

UZ GENT UNIVERSITEIT GENT harmony CLINICAL RESEARCH LITEVAX INDIGO Affordable Flu Vaccines

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Overview

Influenza

Influenza Vaccines

Adjuvants

- Litevax Adjuvant & CMS

TETRALite-1, a first-in-human trial

- Objectives
- Study Design
- Study Population

Safety & Reactogenicity of CMS

Humoral & Cellular Immunogenicity of CMS

Conclusions & Future Directions

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Influenza

Increased risk for severe disease and complication in

- Pregnant women
- Children <5 years
- Older adults
- Immunosuppressive conditions

Seasonal epidemic (Winter)

- 1 billion infections/year worldwide
- 3-5 million severe cases
- 300,000 – 650,000 deaths/year

Vaccination remains the most effective way of preventing disease

- Effectiveness is low: 60% to as low as 10%

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Influenza

Influenza types A,B,C & D

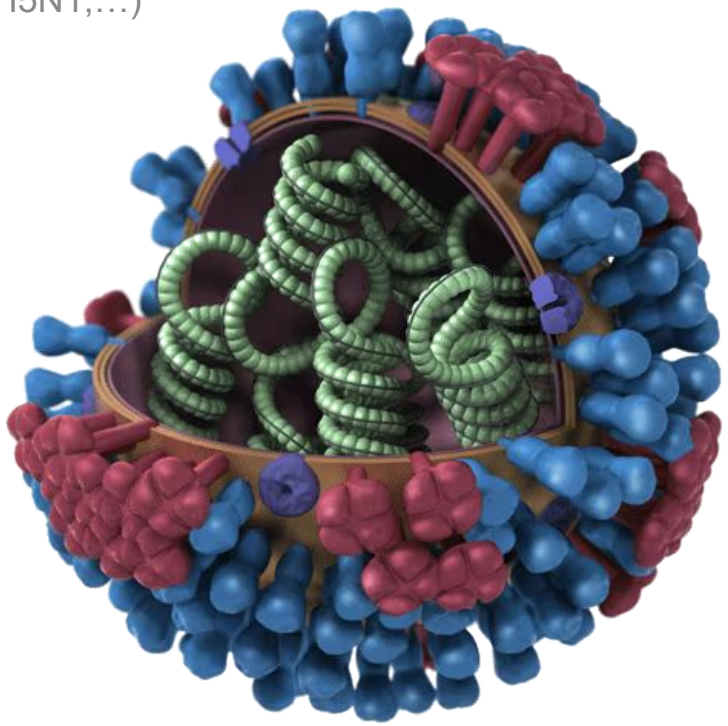
- Influenza A causes disease and pandemics
  - Subtyping based on Hemagglutin & Neuramidase (H1N1, H3N1, H5N1,…)
- Influenza B causes disease
  - 2 lineages: Victoria & Yamagata
- Influenza C & D less important for human disease

Antigenic drift decreases Vaccine Effectiveness

- Mutations in HA and NA genes

Immunosenescence decrease immunogenicity

- Ageing causes an ‘exhausted’ immune system
- Vaccine-induced immune responses are less adequate



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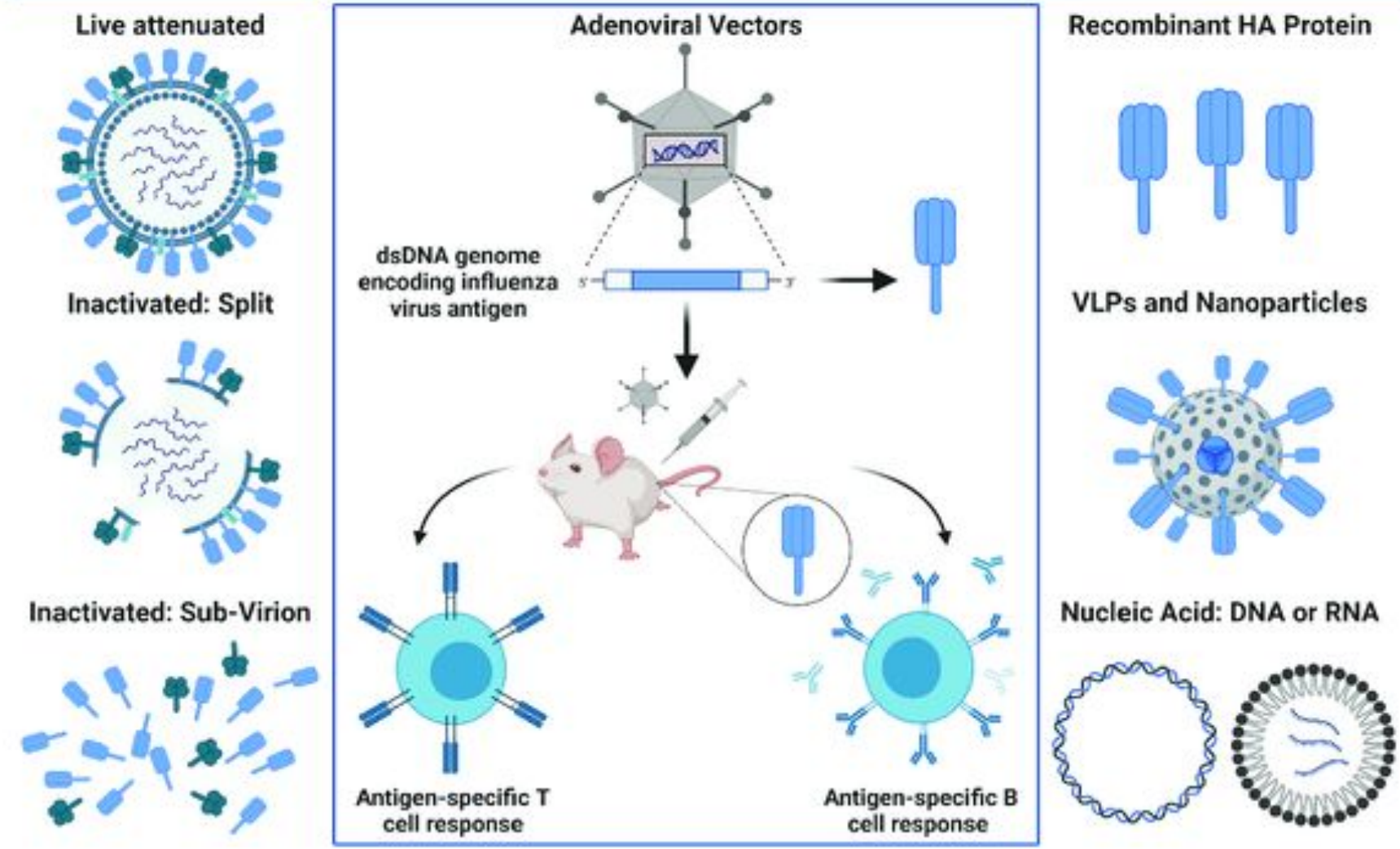
Influenza Vaccines in use & in development

Licensed Vaccines

- Tetravalent (4 influenza types)
- Inactivated split most used in Belgium

Vaccines in development

- mRNA
- Nanoparticles



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Lucas J. Kerstetter. "Adenoviral Vectors as Vaccines for Emerging Avian Influenza Viruses (2021)

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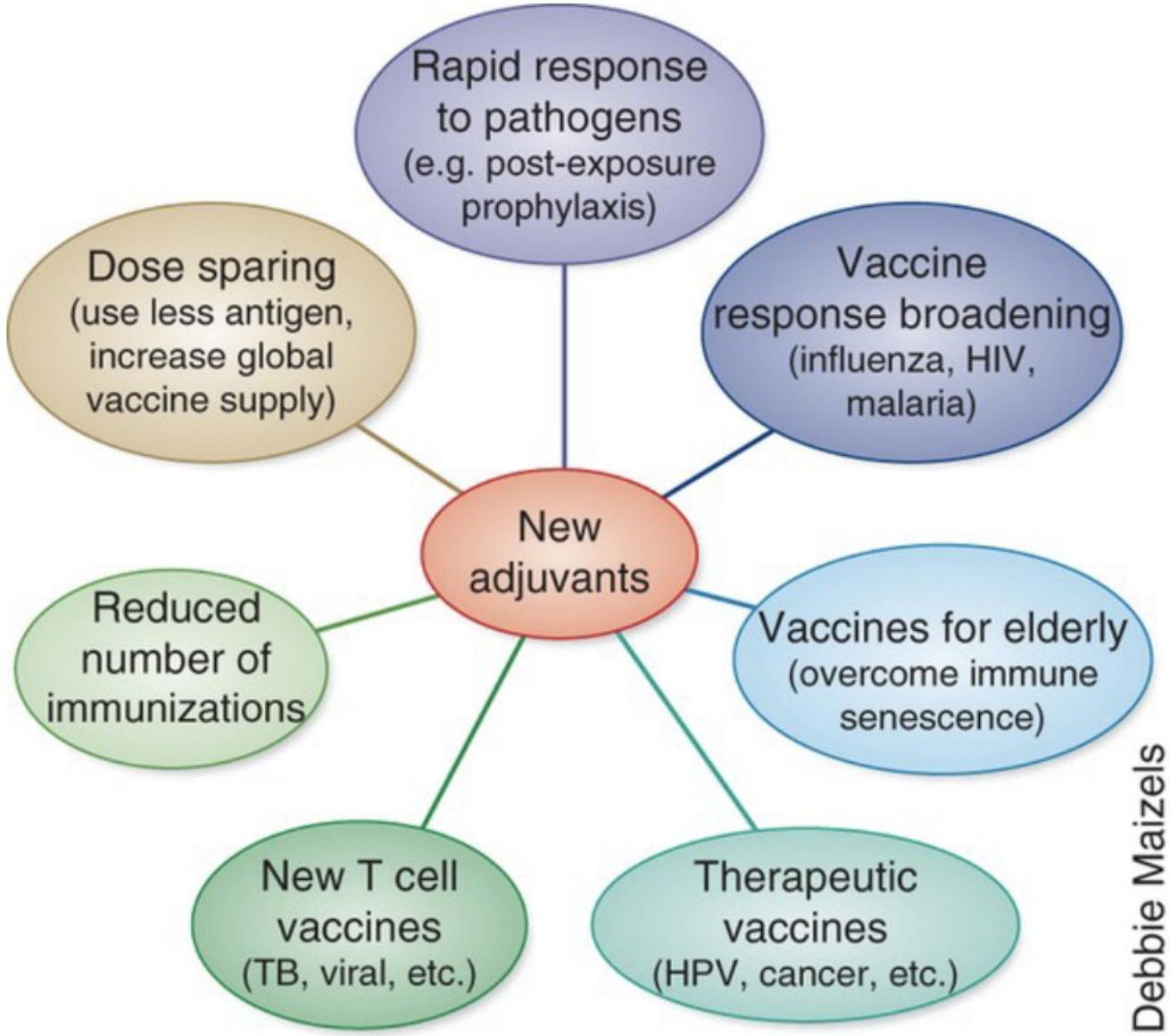
Adjuvants

An adjuvant is any substance (or a mixture of substances) that enhances the immune response to an antigen with which it is mixed

- Increased immunogenicity for OA
- Dose-sparing

Only 7 adjuvants are licensed for human use



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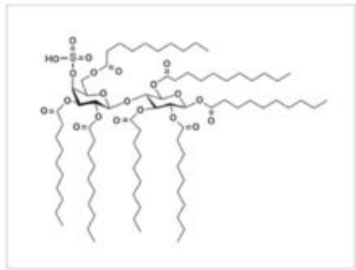
Litevax Adjuvant / CMS

- CMS: fully synthetic molecule, organic synthesis
  - Carbohydrate fatty acid Mono Sulphate ester (CMS) is the active ingredient of LiteVax Adjuvant (LVA)



- LVA: formulated CMS; oil-in-water emulsion
  - Aqueous solution, ready-for-use
  - Ingredients: CMS, synthetic squalane, Polysorbate 80, PBS
  - No preservatives, sterile emulsion
  - Storage 2-8 °C, up to 25 °C possible
  - Stable emulsion: GMP batch >2 years, ongoing
  - Use for single dose vaccines

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LITEVAX

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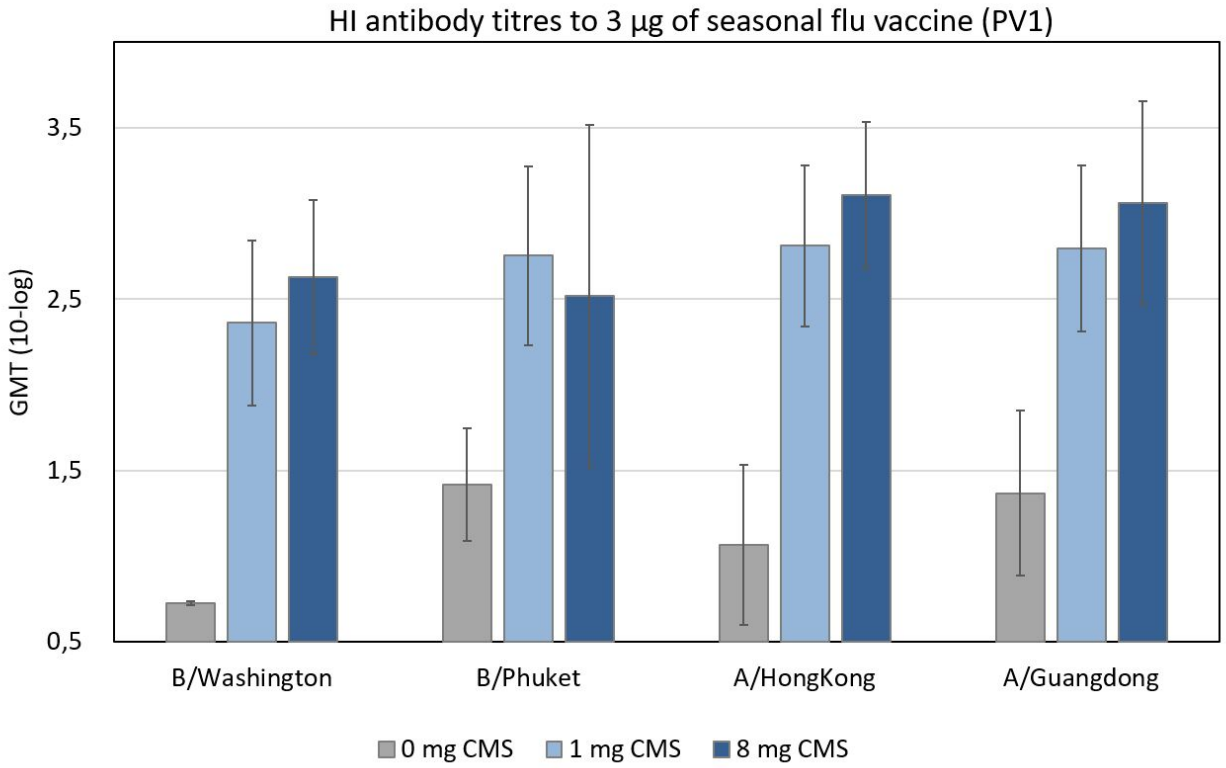
Litevax Adjuvant / CMS

Immunogenicity TETRA^{LITE} in ferrets



*Platenburg et al, Vaccine.2023.10.017

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LITEVAX

Litevax Adjuvant / CMS

Mode of action

- O/W emulsions (MF59, AS03, GLA-SE)
- No TLR4-activation; receptor not known
- Strong G-CSF, KC, IL-5, IL-6 (mice)
- Increased WBCs: neurophils & monocytes
- Muscle & dLN: clustering DC/lymphocytes/macrophages
- *In vitro*: DC activation; CD80/CD86 upregulation
- Many unknows, role of CMS

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TETRA^{LITE} - 1

First-in-human trial in which a single intramuscular injection with TETRA^{LITE} containing **1/5th of the standard dose of VaxigripTetra® plus 2 or 0.5 mg of LiteVax Adjuvant (LVA)** was tested in healthy adult volunteers and compared with a **normal dose of VaxigripTetra® without adjuvant**

VaxigripTetra (season 2022-2023)

- A/H1N1
- A/H3N2
- B/Victoria
- B/Yamagata

	Empty vial	Antigen	Diluent	Adjuvant	Vaccine
		Vaxigrip Tetra prefilled syringe 0.5 mL contains 4x 15 µg HA	Saline 0.9% NaCl	Vial with 1.2 mL of 20 mg/mL	0.5 mL Per injection
					
Cohort 1.	0.5 mL Vaxigrip Tetra				0.5 mL vaccine 15 ug HA + 0 mg LVA
Cohort 2.	0.5 mL Vaxigrip Tetra	1.75 mL 0.9% NaCl	0.5 mL LVA		0.5 mL vaccine 3 µg HA + 2mg LVA
Cohort 3.	0.5 mL Vaxigrip Tetra	1.0 mL 0.9% NaCl	0.125 mL LVA		0.5 mL vaccine 3 µg HA + 0.5mg LVA

Direct injection using the prefilled syringe

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Objectives

Primary
To evaluate **safety and tolerability** of a single administration of TETRALITE (3 µg VaxigripTetra + 0.5 mg or 2 mg adjuvant) versus 15 µg VaxigripTetra without adjuvant in healthy participants (18-50 years).
Secondary
To evaluate the **humoral immune responses** of a single administration of TETRALITE (3 µg VaxigripTetra + 0.5 mg or 2 mg adjuvant) versus 15 µg VaxigripTetra without adjuvant in healthy participants (18-50 years).
Exploratory
To evaluate the **cellular (T cell) immune responses** of a single administration of TETRALITE (3 µg VaxigripTetra + 0.5 mg or 2 mg adjuvant) versus 15 µg VaxigripTetra without adjuvant in healthy participants (18-50 years).

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Study Design

Randomized, active-controlled, double-blind, single-center, first-in-human Phase 1 trial

3 Cohorts

- Cohort 1: 15 µg VaxigripTetra (commercial vaccine) = control vaccine
- Cohort 2: 3 µg VaxigripTetra + 2 mg LVA
- Cohort 3: 3 µg VaxigripTetra + 0.5 mg LVA

Staggered design & Sentinel participants for safety

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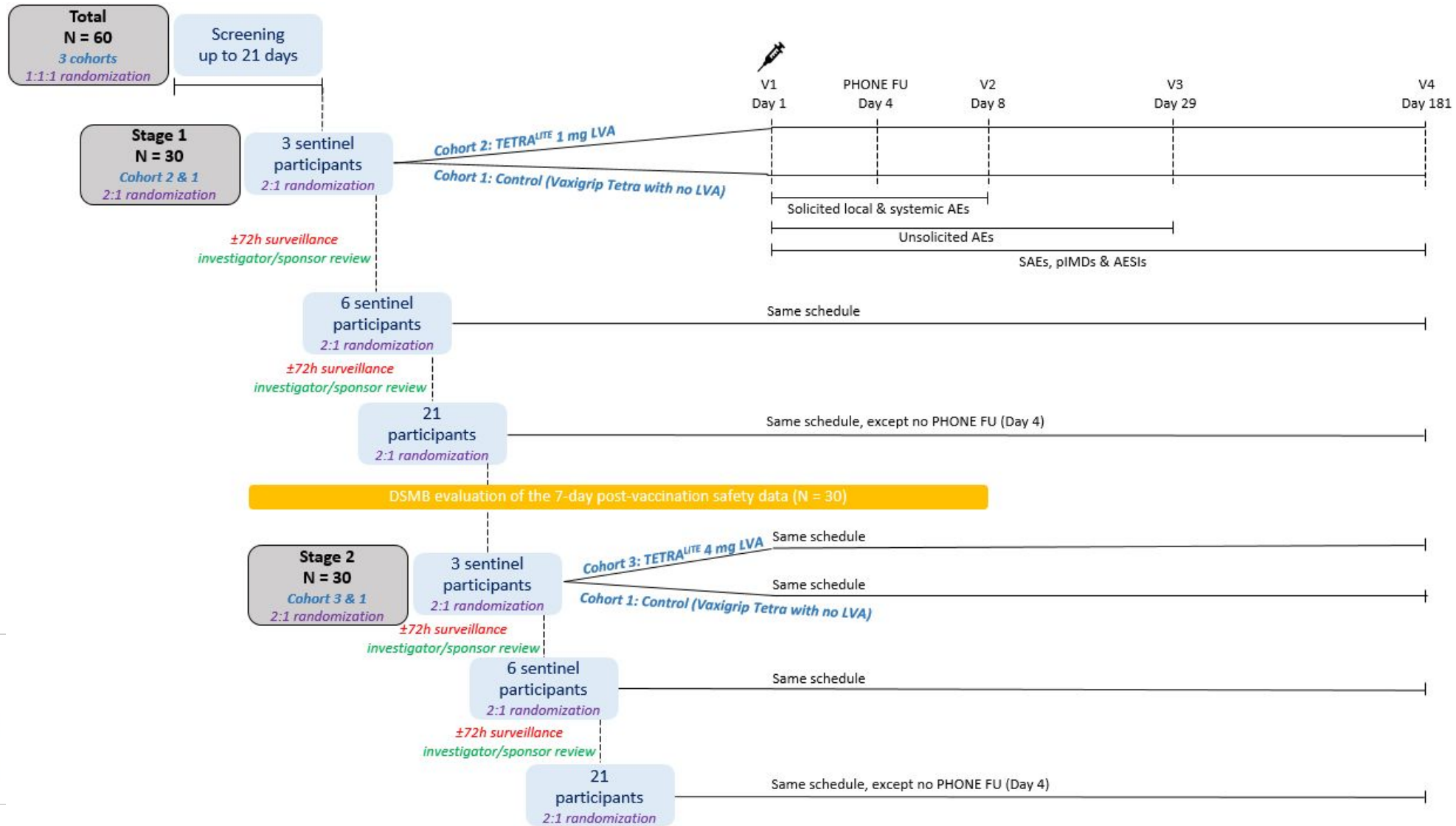
Study Design



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Study Population

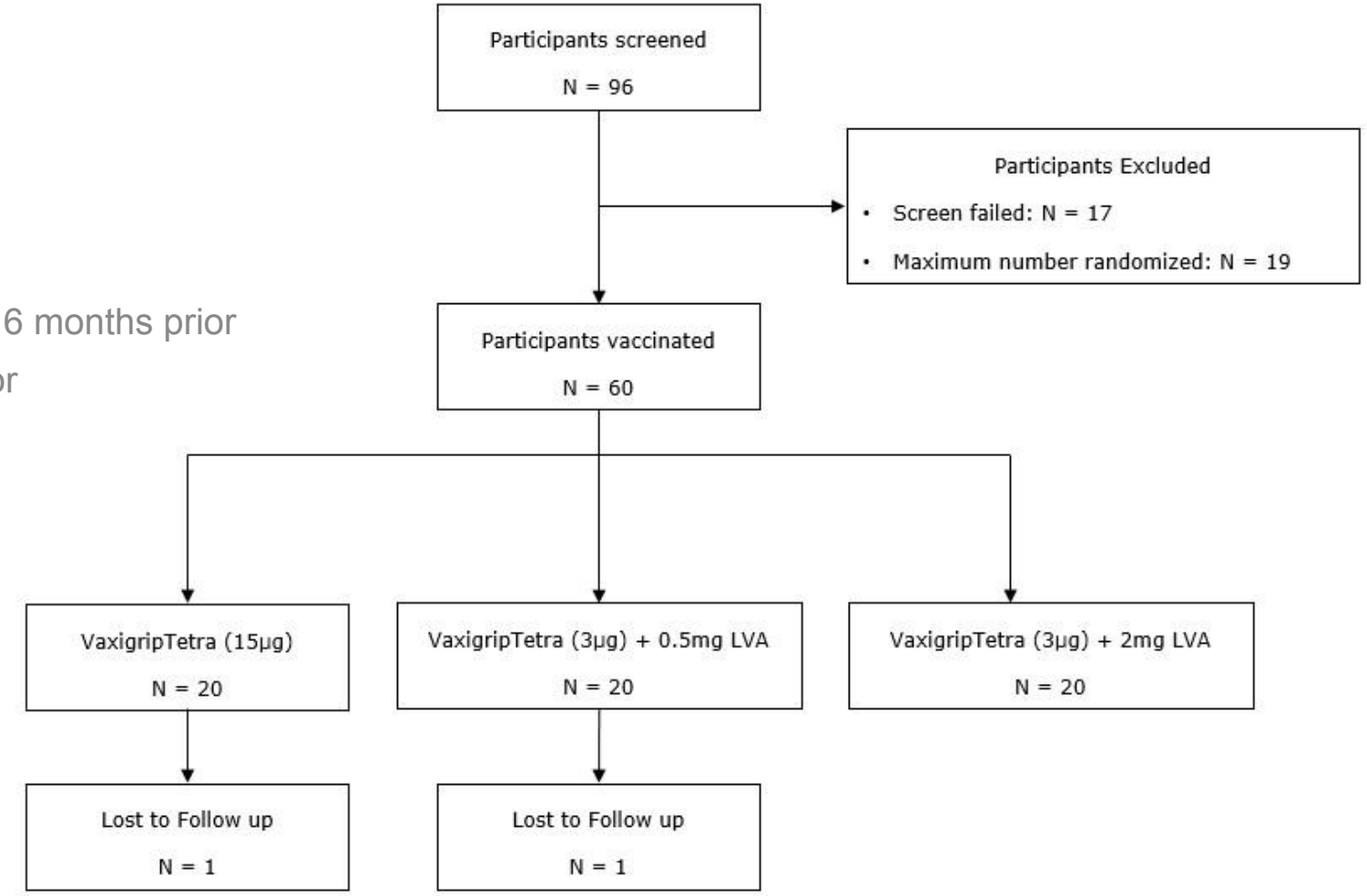
N = 60 participants

- N = 20 per cohort

Healthy adults

- No active disease/medication
- No seasonal influenza vaccine 6 months prior
- No other vaccines 1 month prior

18 – 50 years of age



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Study Population

		VaxigripTetra (15µg) (N=20)	VaxigripTetra (3µg) + 0.5 mg CMS (N=20)	VaxigripTetra (3µg) + 2 mg CMS (N=20)	Total (N=60)
Age (years)		39.8 (9.8)	38.9 (10.0)	34.1 (10.0)	37.6 (10.1)
Gender	Female	12 (60.0%)	14 (70.0%)	16 (80.0%)	42 (70.0%)
	Male	8 (40.0%)	6 (30.0%)	4 (20.0%)	18 (30.0%)
Race	White	20 (100.0%)	19 (95.0%)	18 (90.0%)	57 (95.0%)
	Black or AA	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (1.7%)
	Asian	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (1.7%)
	Other	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (1.7%)
Weight (kg)		74.34 (13.4)	73.96 (12.78)	68.49 (8.68)	72.26 (11.91)
BMI (kg/m^2)		24.33 (3.43)	24.33 (3.07)	23.84 (2.69)	24.17 (3.03)

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Safety and Reactogenicity

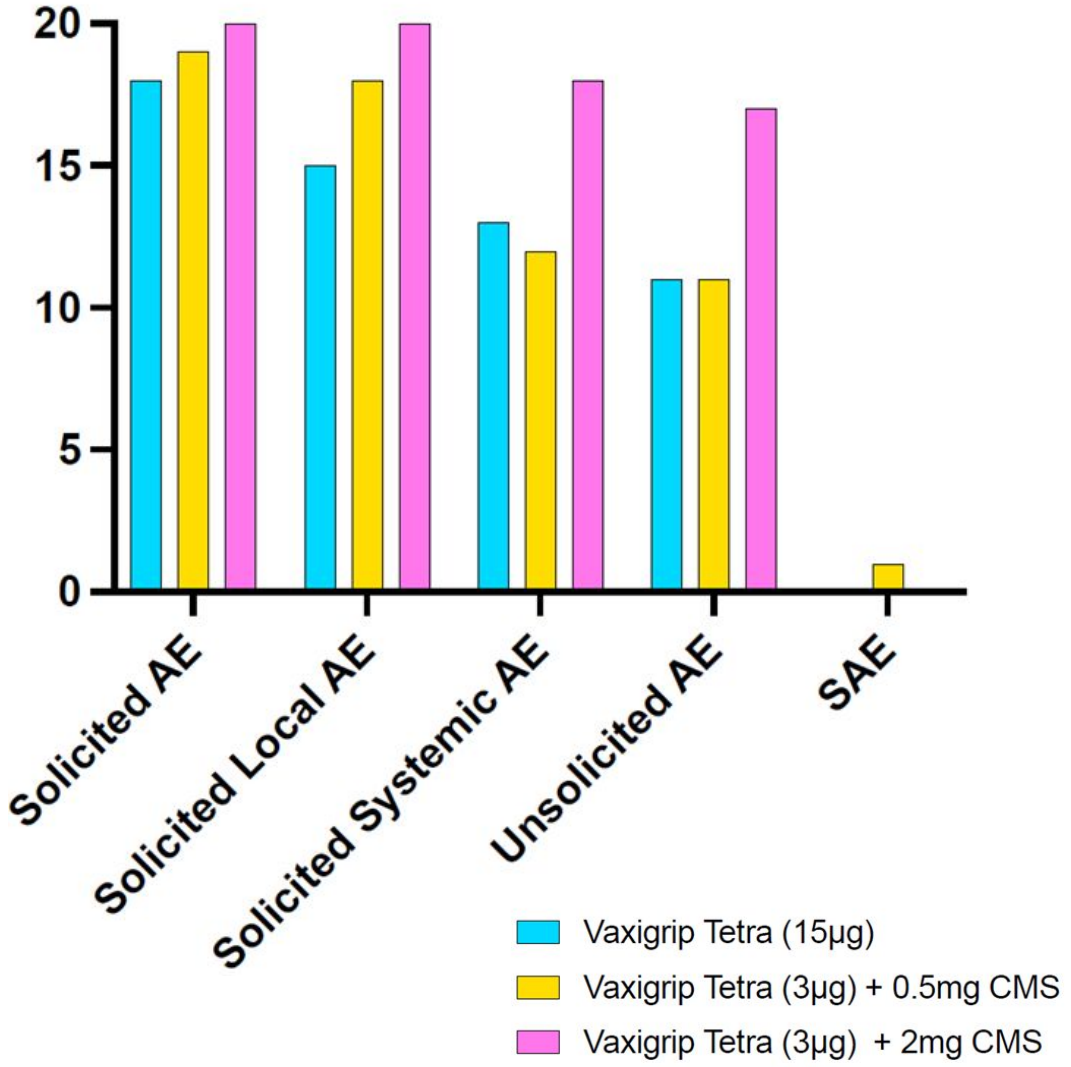
Solicited Adverse events

- 7 days after vaccination
- Local
  - Pain, Redness, Swelling, Induration
- Systemic
  - Headache, Fatigue, Malaise, Arthralgia, Myalgia, Fever

Unsolicited Adverse events

- 28 days after vaccination

Severe Adverse events & potential Immune-mediated diseases



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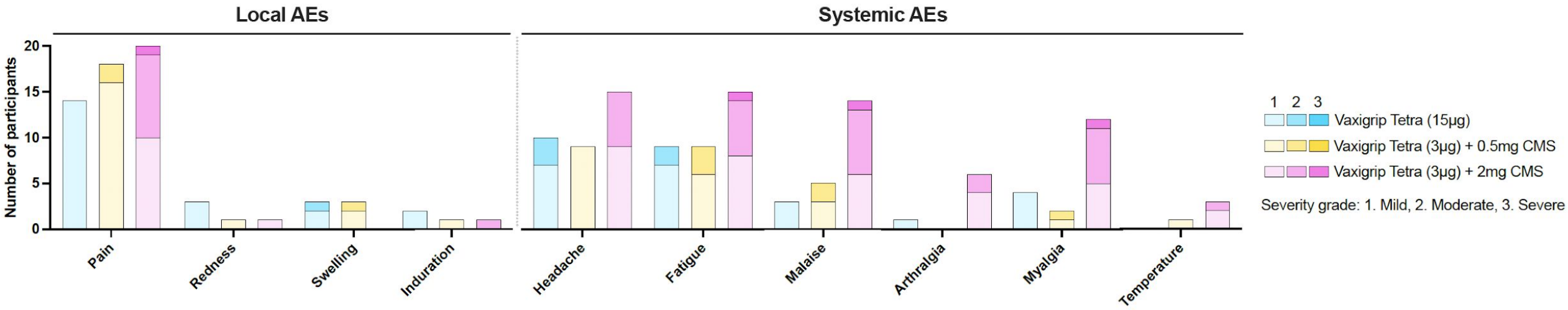
Safety and Reactogenicity

Reactogenicity is acceptable for all doses

- Higher reactogenicity for 2mg CMS
- Higher severity for AEs for 2mg CMS
- 2mg CMS is maximum dose for humans
  - Lower reactogenicity expected for OA



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Humoral Immunogenicity

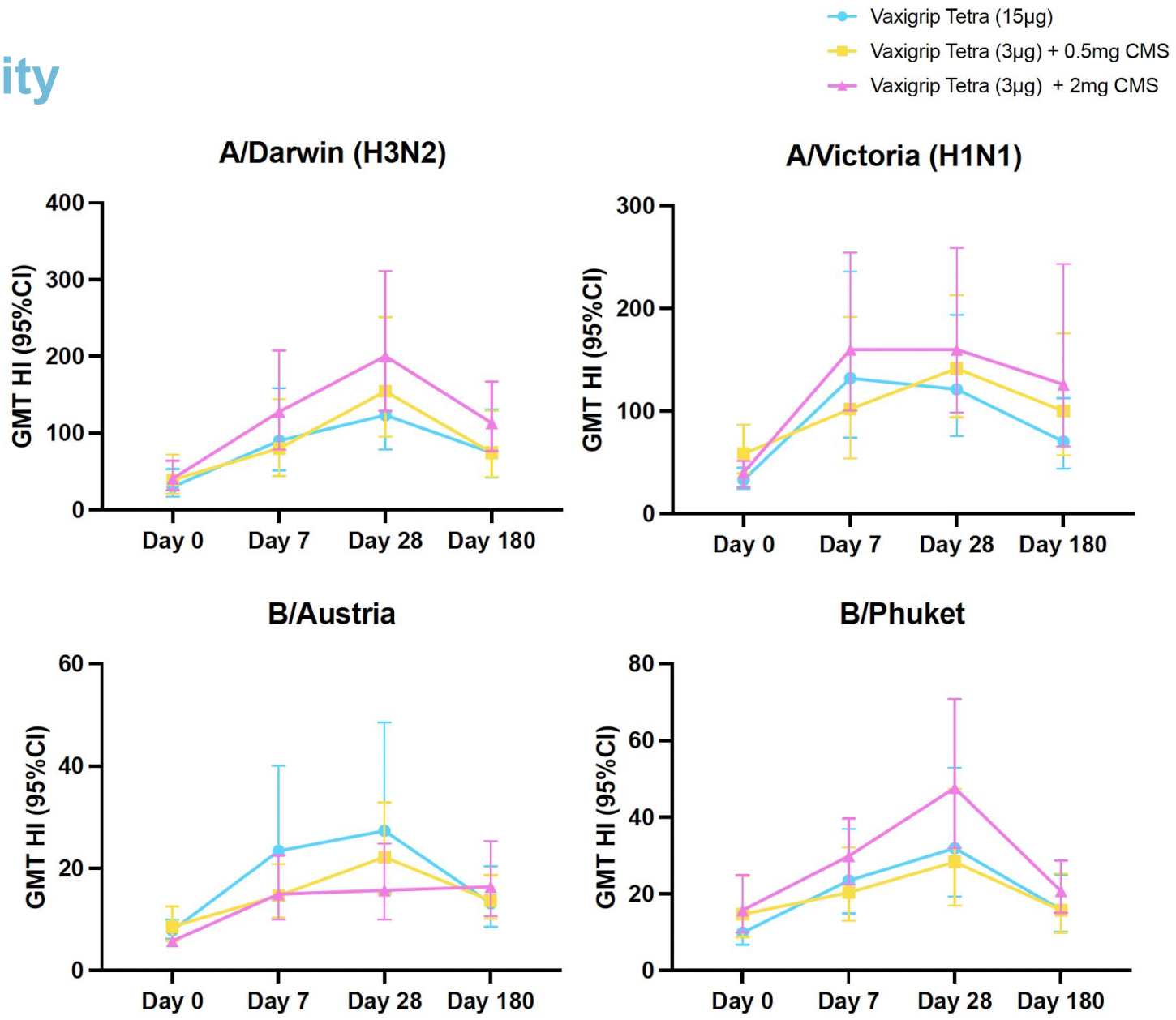
Hemagglutinin inhibition titer

- Surrogate measure for protective immunity
- Defined using serial dilutions of serum & its ability to bind to HA antigen

No differences in HI titers between 3 cohorts

- HI titers are as high for adjuvanted 1/5th antigen dose as full antigen dose

Peak on Day 28, decrease after 6 months but higher than baseline



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Cellular Immunogenicity

Intracellular Cytokine Staining & Flow Cytometry

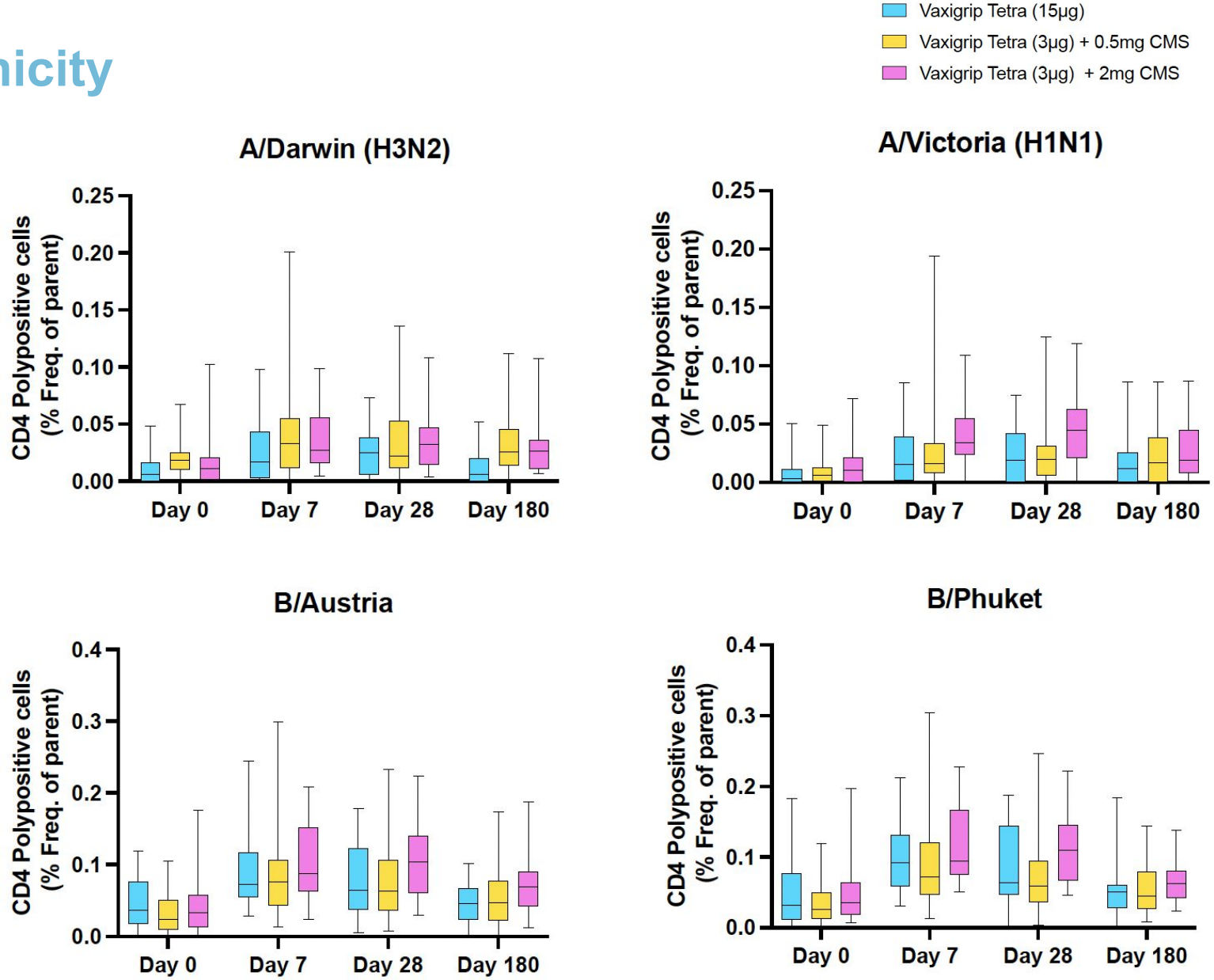
- CD3, CD4, CD8
  - Extracellular markers
- CD40L, IFNγ, IL-2, TNFα
- Polypositive cells
  - CD4 OR CD8 positive AND
  - Positive for at least 2 intracellular markers

CD4+ polypositive cells

- No significant differences
- Peak at Day 7

CD8+ polypositive cells

- Same trend but lower than LOD



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Conclusion

- CMS is safe in humans
  - Higher reactogenicity of 2mg CMS compared to 0.5mg CMS or control.
- Humoral and cell-mediated immunogenicity was similar for adjuvanted and control vaccines
  - Even with 1/5th antigen dose
- CMS can have beneficial implications in low-resource settings or in a pandemic context.
  - Studies in older adults are needed

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Future Directions

- CMS can have beneficial implications in low-resource settings or in a pandemic context.
  - Phase 1 clinical trial in India
  - Dose-sparing in YA can have beneficial impact
    - 1 Vaccine = 5 vaccinations

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	EU - Phase 1	IN - Phase 1
Age	18-50y	18-50y
Antigen	Vaxigrip Tetra (‘22-’23)	VaxiFlu-4 (‘24-’25)
Adjuvant	CMS	CMS
Vaccine 1	15µg *(n = 20)*	15µg *(n = 25)*
Vaccine 2	3µg + 2mg LVA *(n = 20)*	3µg *(n = 25)*
Vaccine 3	3µg + 0.5mg LVA *(n = 20)*	3µg + 1mg LVA *(n = 25)*

Control

IMP

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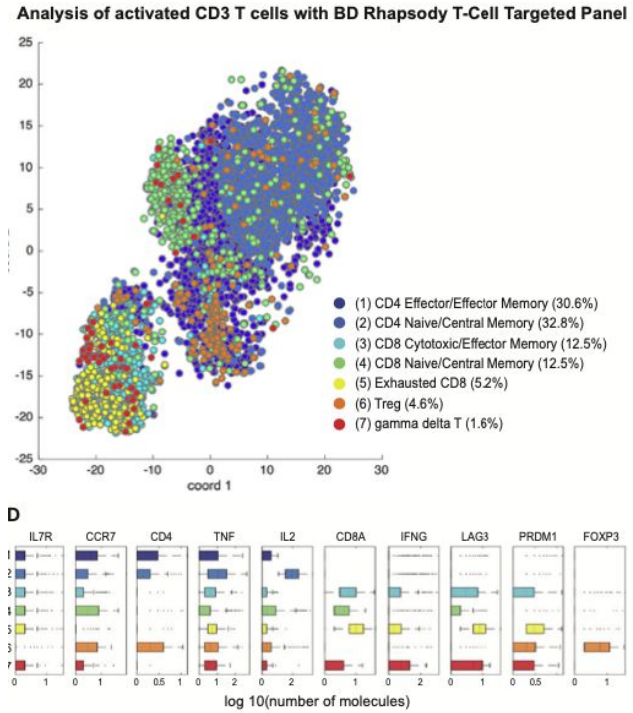
Future Directions

- Studies in older adults are needed
  - Phase 1b trial started
  - There is a clear effect of LVA (1/5th dose = similar immunogenicity)
    - What are the mechanisms of action?
      - A systems vaccinology approach: single cell RNA sequencing techniques
  - In a non-dose sparing context, can LVA help enhance the immune response in older adults?



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A Beautiful Collaboration

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