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Update on Vaccine adjuvants

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Key points

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- Provide an update on licensed adjuvanted vaccines
- Examples of clinical benefits, specifically on the quality of the immune response
- Adjuvant and mRNA vaccines comparison

We use adjuvants for a purpose: to improve the immune response to vaccines

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Selection based on what provides optimal outcomes in terms of safety and immunogenicity

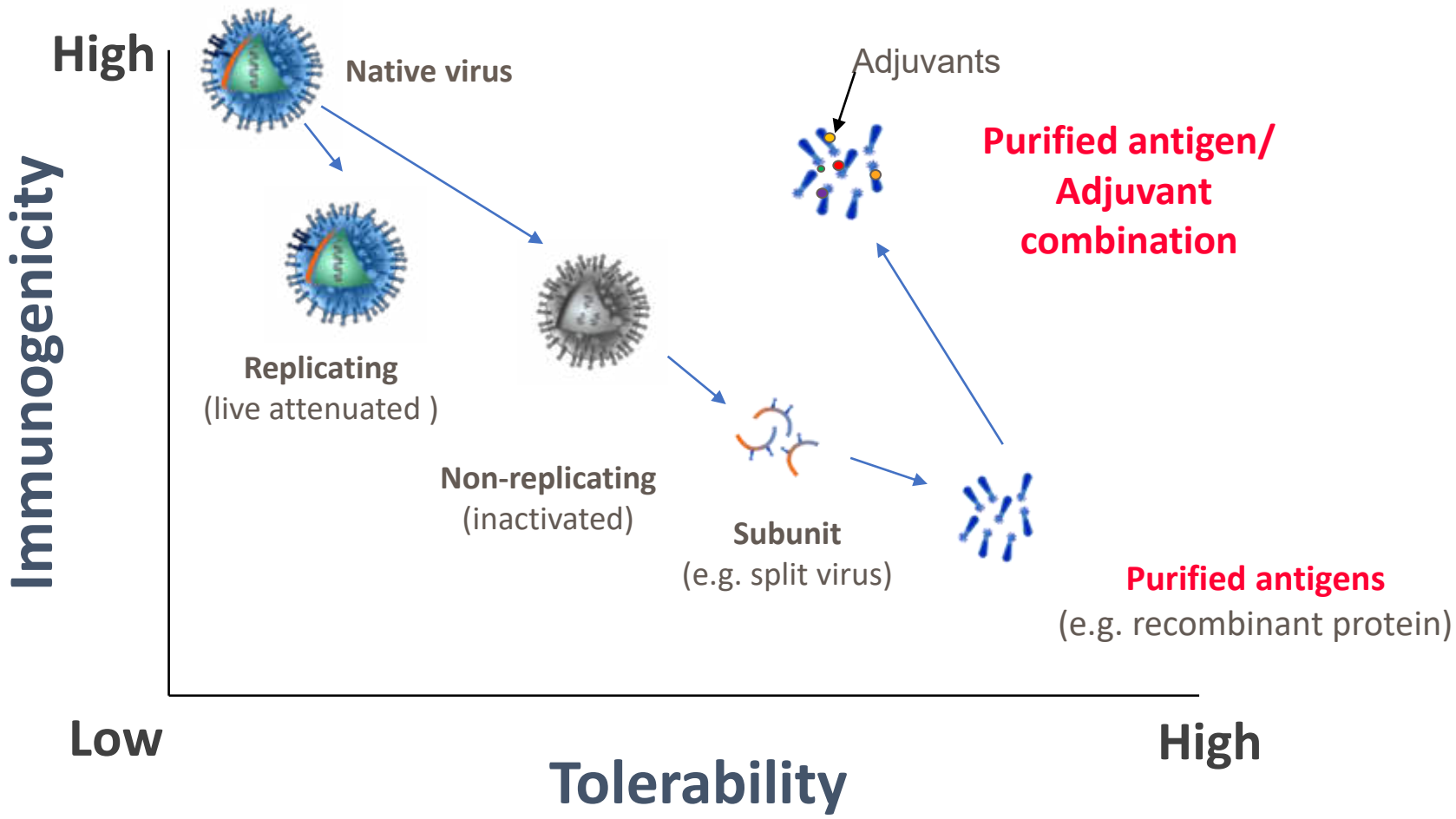

Figure adapted from Di Pasquale A et al. *Vaccines*. 2015;3:320-343.

Adjuvants come in different flavors and enigmatic names….

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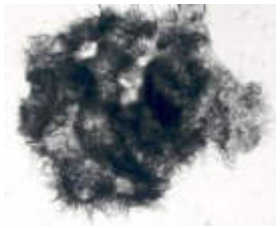
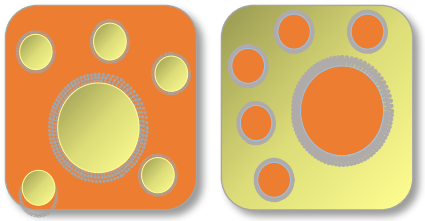
Delivery systems + Immunostimulants

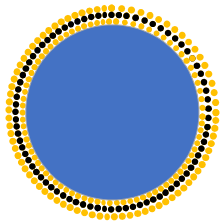
Aluminium salts



Emulsions

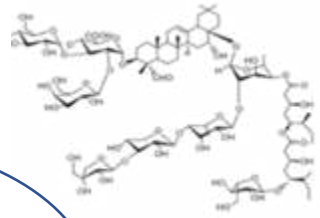


Liposome/ISCOMs

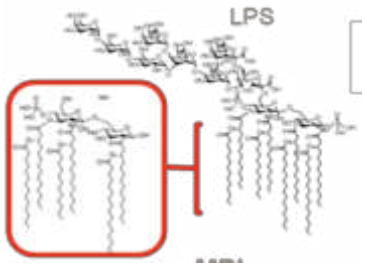


Excipients:
Span/tween
Vitamin E
Cholesterol…

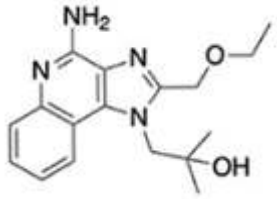
Saponin (QS21 & family)



MPL & TLR4L synthetics



TLR7/8L & friends



CpG & TLR9L friends

AF-X

AS-Xy

MF59

CAF-X

ALFQ

G/SLA-SE

SWE, SLQ..

Adjuvants in licensed vaccines..before and after COVID-19

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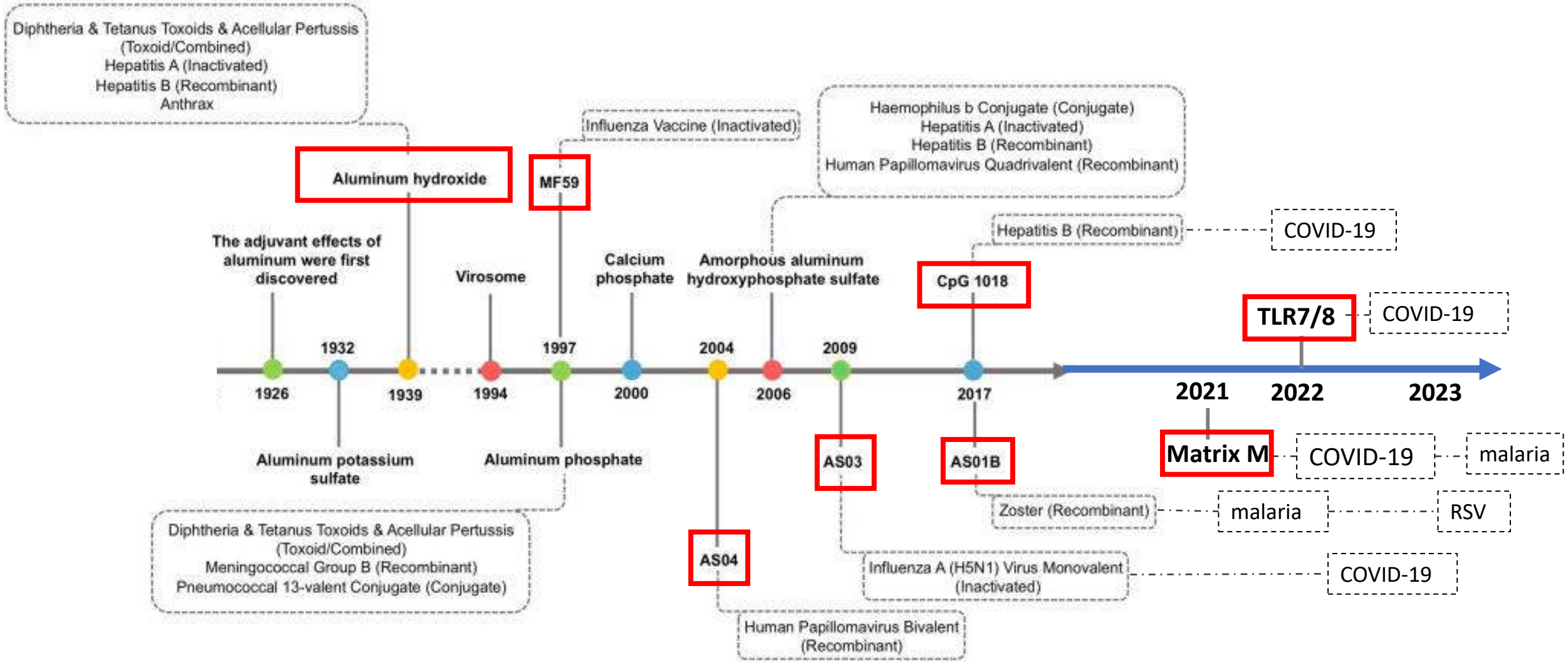
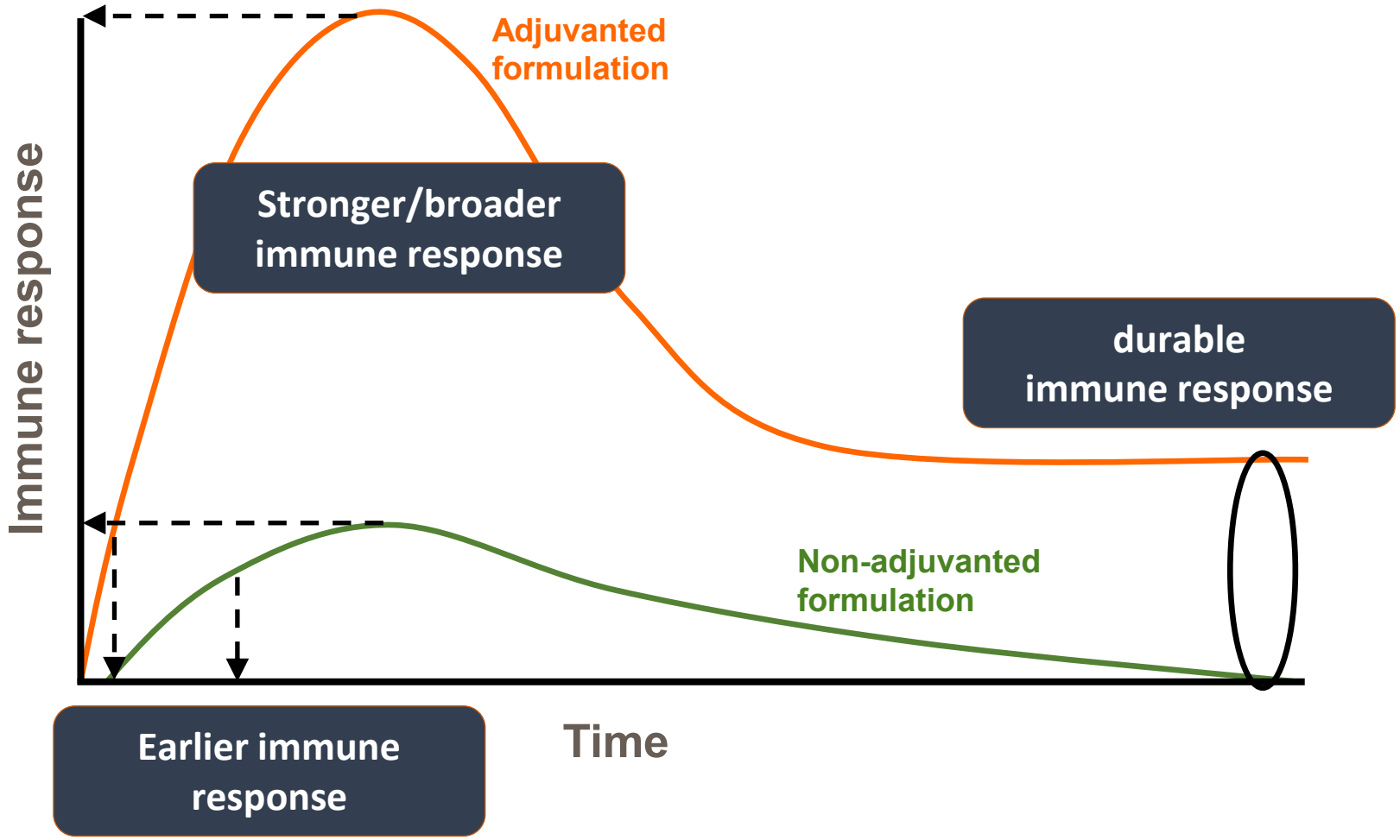


Shi, Vaccine, 2019; Pulendran et al. Nature Reviews Drug Discovery, 2021

Clinical benefits of adjuvanted vaccines

Adjuvant: expected impact on vaccine immune response



Garçon N, et al. Understanding modern vaccines, perspectives in vaccinology, Vol 1, Amsterdam: Elsevier; 2011

MF59 induces higher antibody responses in children (Seasonal Influenza vaccine)

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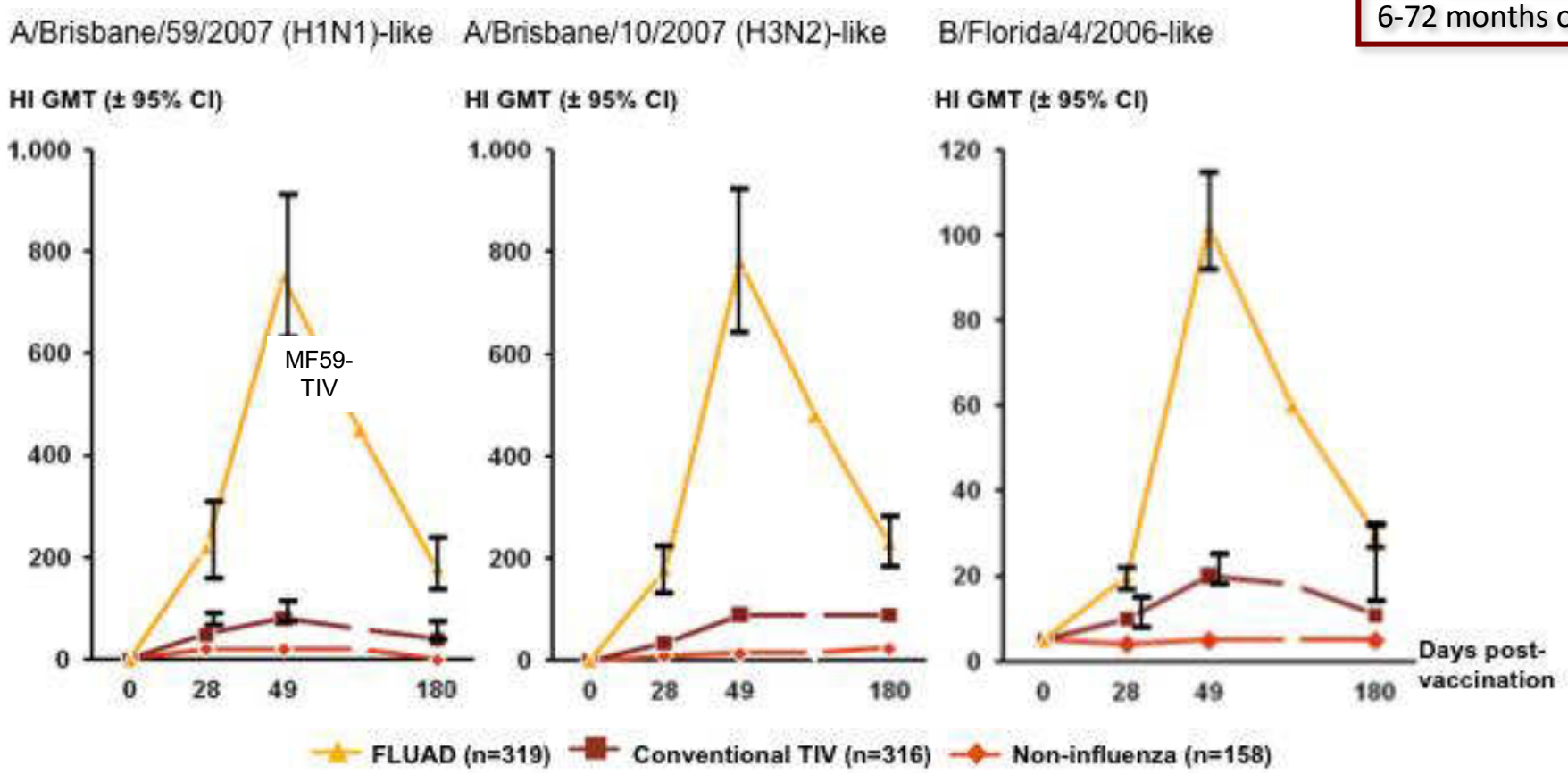
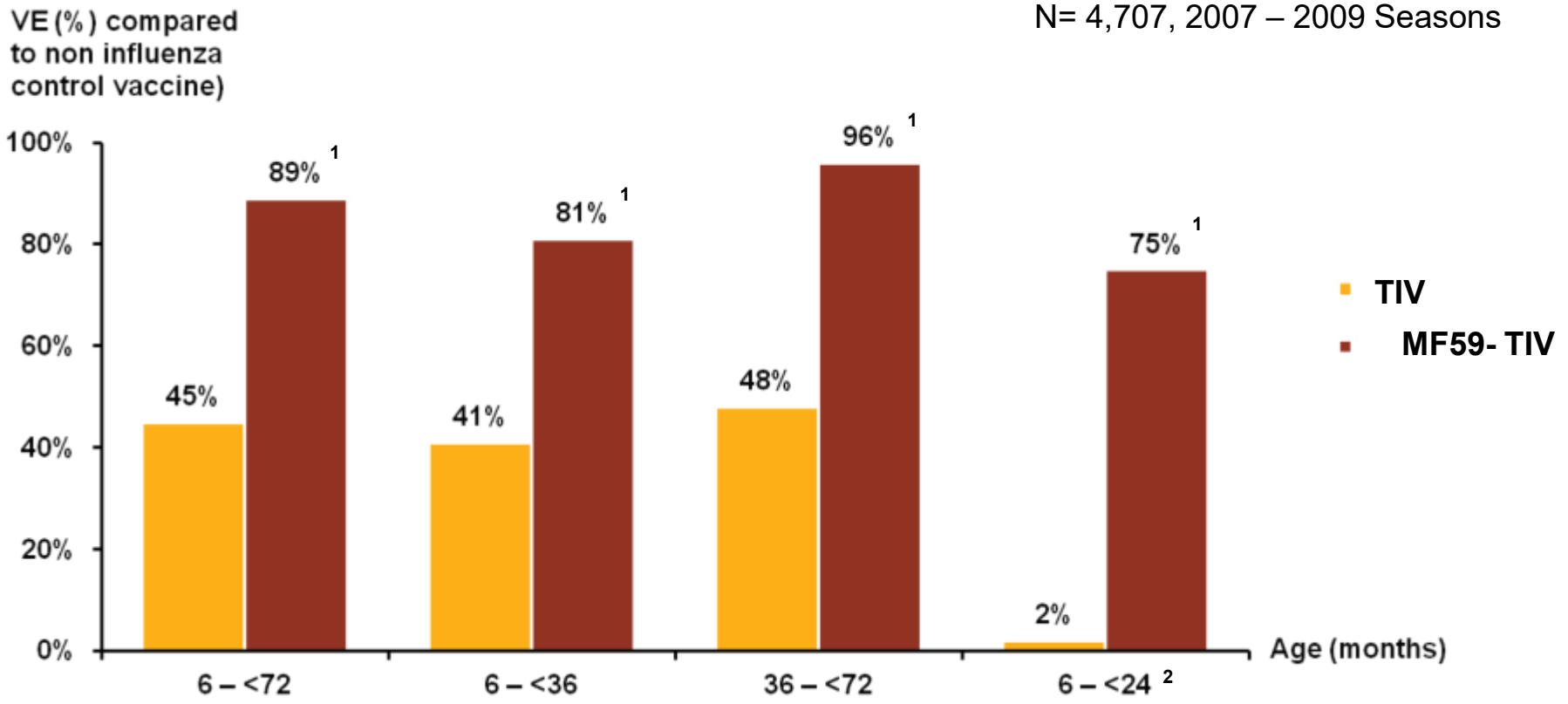
6-72 months old



Vesikari et al, NEJM 2011

Enhanced efficacy as compared to non adjuvanted vaccines



[1] *Statistically significant result.*

Vesikari et al, NEJM 2011

Emulsions can broaden antibody repertoire and promote affinity maturation (H5N1/AS03 or MF59)

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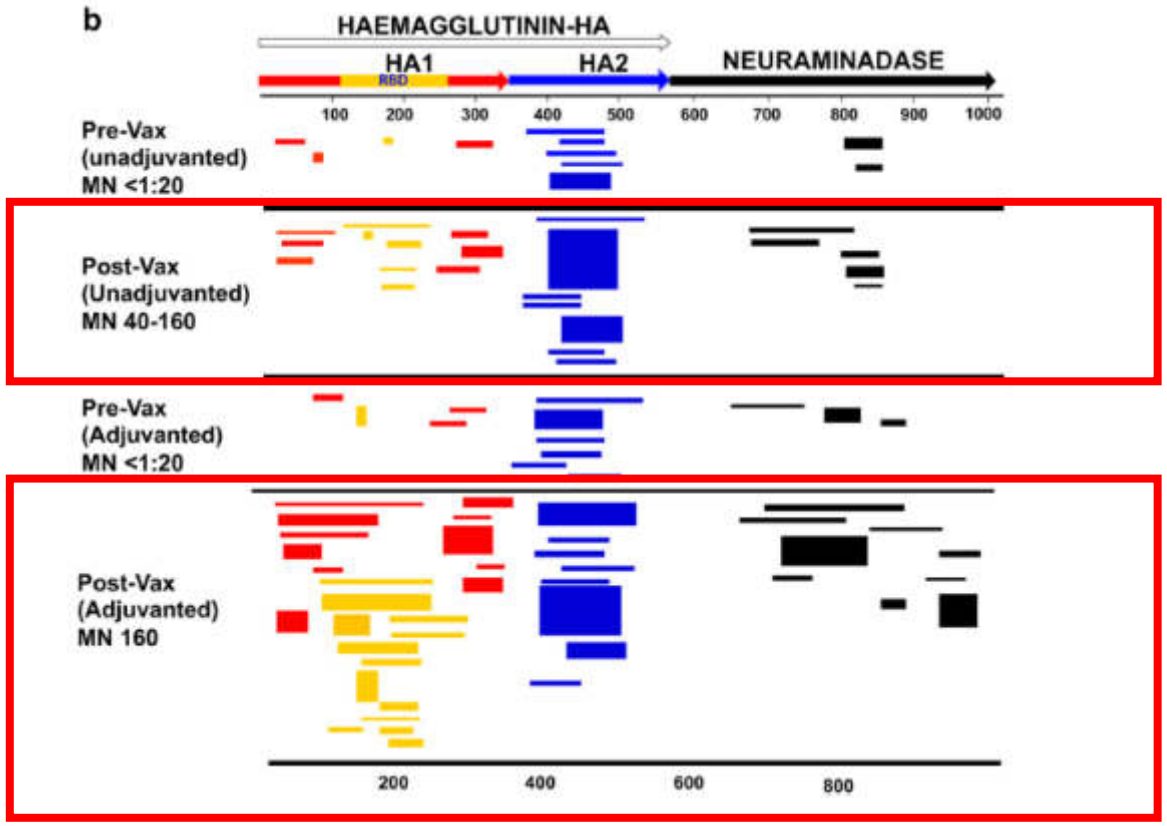
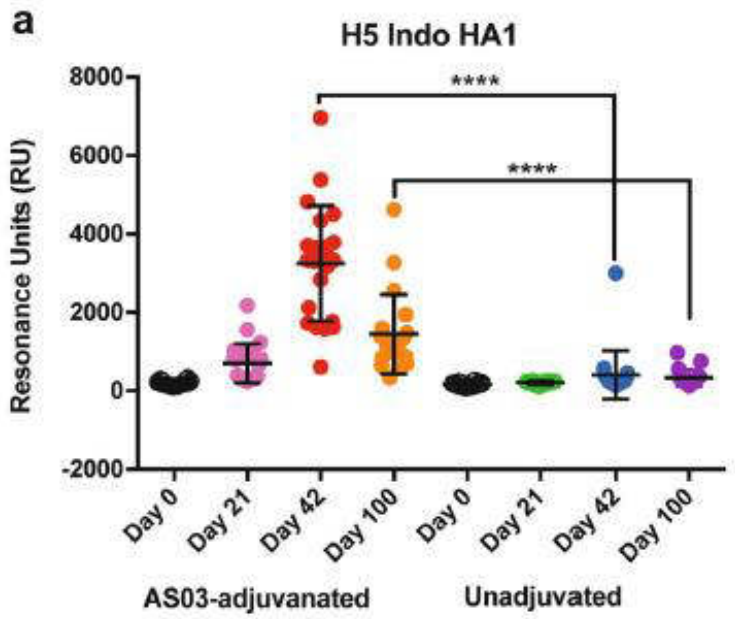
Increased Ab repertoire



Increased binding to HA



Similar data with MF59 (H5N1)

Khurana et al. Sci Transl Med. 2011; Npj Vaccine, 2018

The recombinant Zoster vaccine (VZV gE+ AS01) induces a durable immune responses in older individuals[1]

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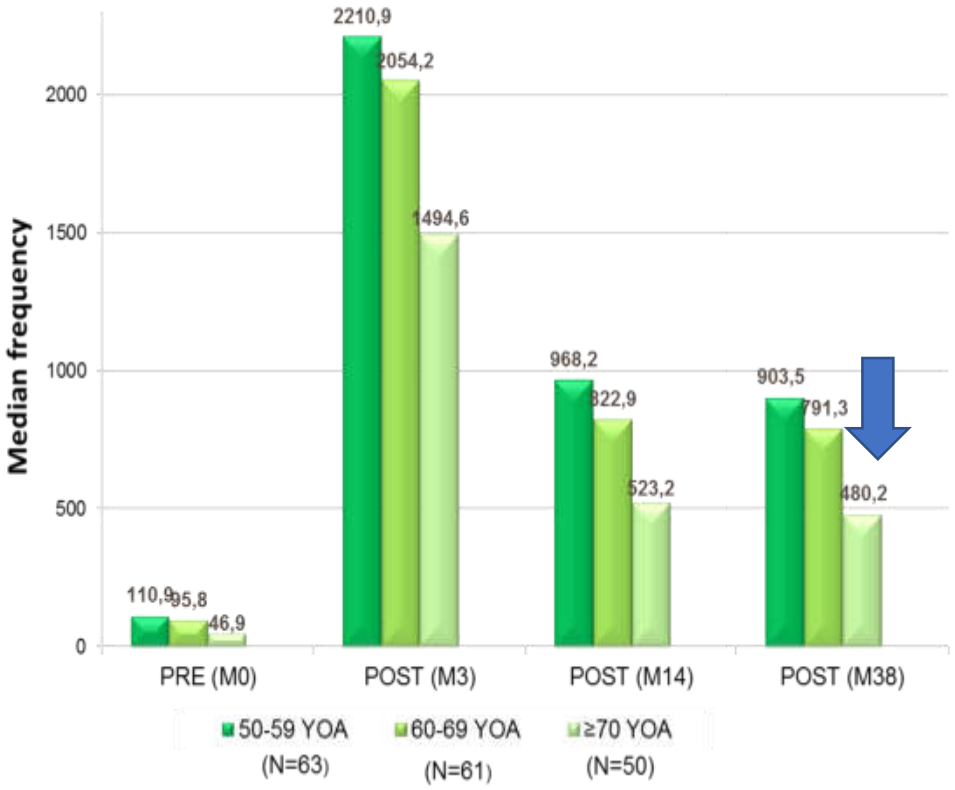
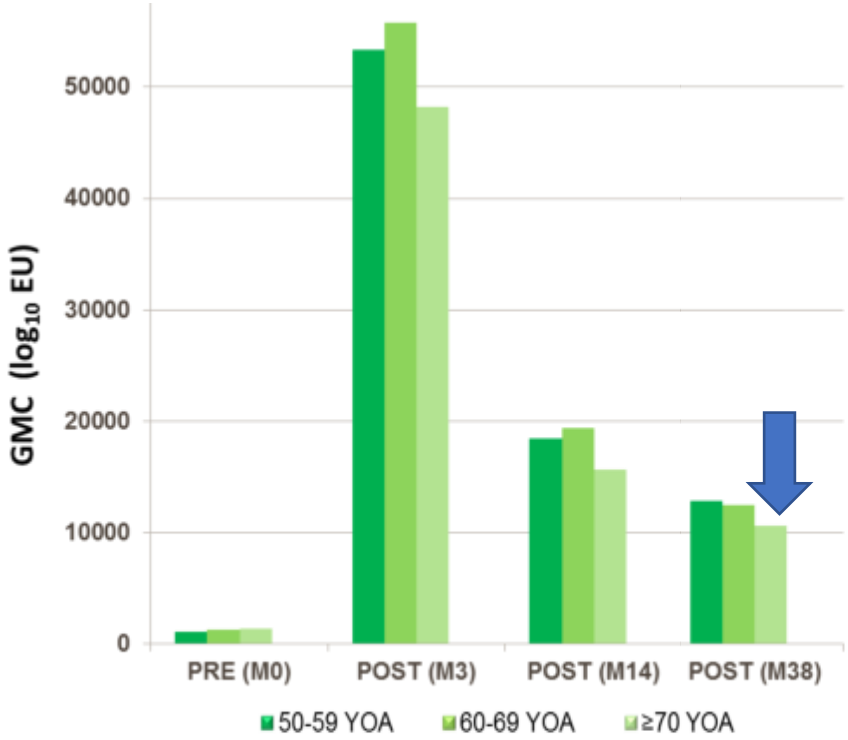
gE-specific CD4[2+] T cells



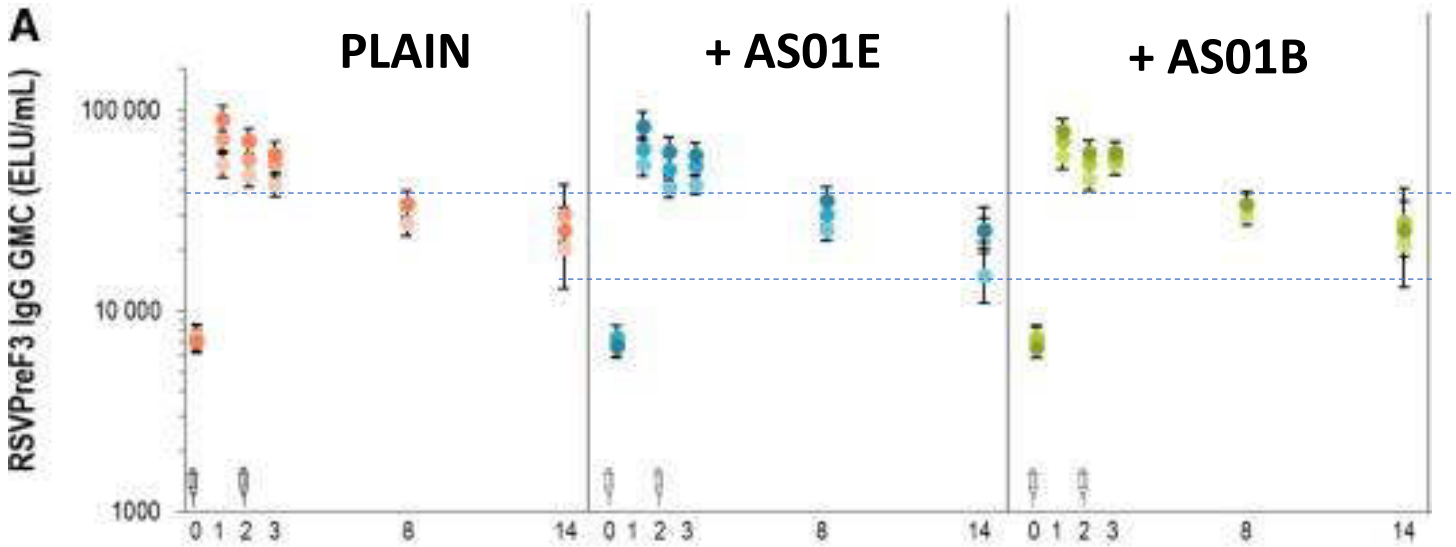
gE Antibodies

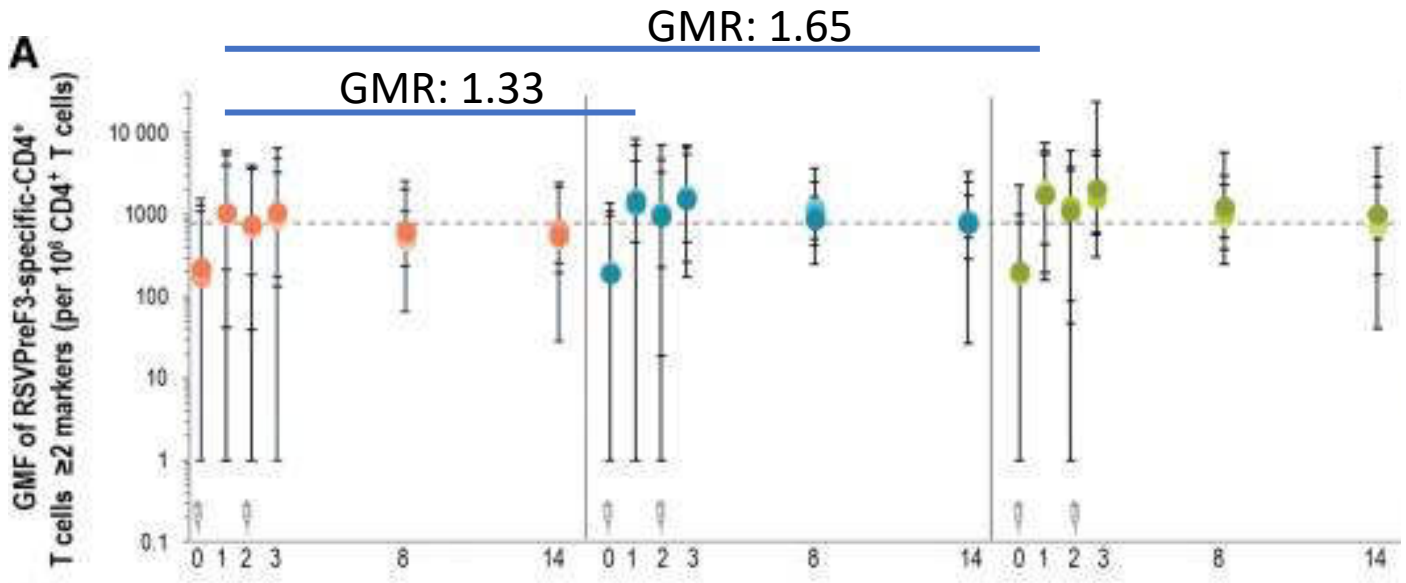


- 91% protection in vaccinees ≥80 years
- Vaccine efficacy sustained for at least 10-year follow-up[2]
- Immunogenicity and efficacy in immunocompromised patients

[1]Cunningham, J Infect Dis. 2018; [2]Strezova A; Open Forum Infect Dis 2022

Added value of AS01 is less obvious in the context of the RSV vaccine





Phase II
Older adults (60-80 YOA)
N=100/group

- 30 µg Plain
- 60 µg Plain
- 120 µg Plain
- 30 µg AS01$_E$
- 60 µg AS01$_E$
- 120 µg AS01$_E$
- 30 µg AS01$_B$
- 60 µg AS01$_B$
- 120 µg AS01$_B$

No dose sparing effect

Due to higher pre-existing immunity or intrinsic immunogenicity of the antigen?

Leroux-Roels, J Infect Dis. 2023

Observed Benefits of Adjuvants in Candidate or Licensed Adjuvanted Vaccines

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- Efficacy demonstrated for different antigen types Split (influenza), parasite-derived (malaria), viral glycoprotein (herpes zoster), viral particles (HPV)…

- Increase magnitude of the immune response but also quality: antibody breadth, cross-reactive T-cells and increased functionality of antibodies

- Benefits across the entire age spectrum (6-month-old infants to >80-year-old-adults) and in vulnerable populations (immunocompromsied) with acceptable safety outcomes

And some limitations….

- Fail to increase immunogenicity of conjugate vaccines
- Does not generally induce CD8+ T cell response
- The magnitude and persistence of the response **depends also on the antigen**
- Are more reactogenic than others vaccines, in particular in presence of pre-existing immunity- this has led to discontinuation of vaccine candidates.

Learnings on Safety

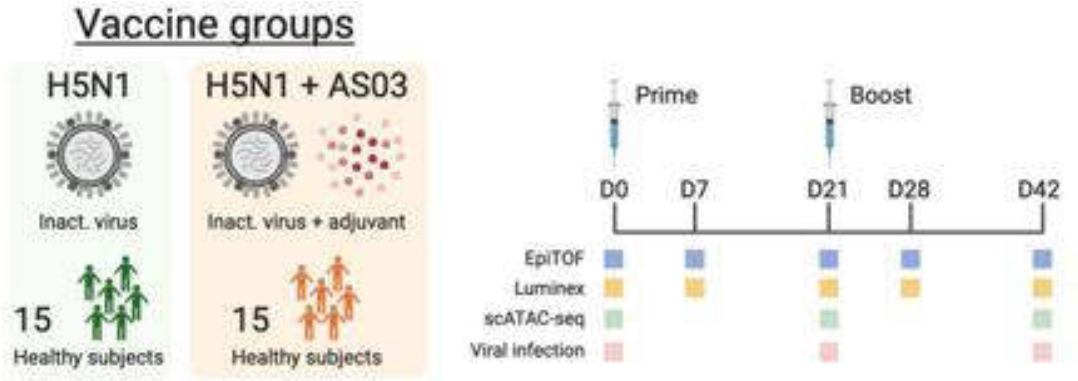
- pIMDs (potential immune-mediated disorders) are specifically monitored in clinical studies and in post-marketing surveillance

- Initial concerns of increased risk of inflammatory/autoimmune disease exacerbations is not supported by current data.

- Narcolepsy and AS03-adjuvanted H1N1 Flu vaccine: no evidence that the adjuvant is causing the issue (but may have contributed to increase an existing antigen-driven mimicry/immunopathological effect)

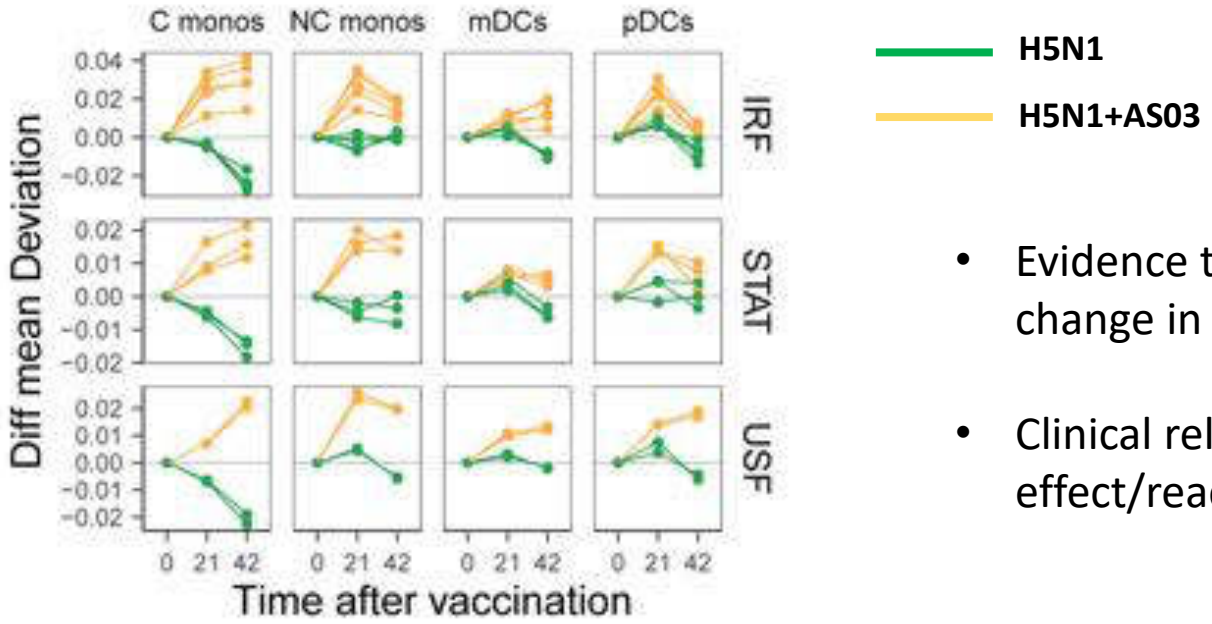
- GBS and adjuvanted Zoster vaccine (US CDC)-yet to be confirmed

Adjuvanted vaccines and “innate imprinting”- potential non-specific effect?



B	Biological insights	
Vaccine	**Gene accessibility**	**Trained immunity**
TIV H5N1+AS03	↓ AP-1	Reduction of inflammatory cytokine production (IL-1β, TNF-α, G-CSF)
H5N1+AS03	↑ IRF8,9,7 STAT1,2	Induction IFN response (antiviral program)
H5N1	↓ IRF8,9,7 STAT1,2	Reduction IFN response (antiviral program)

Change in transcription factor accessibility

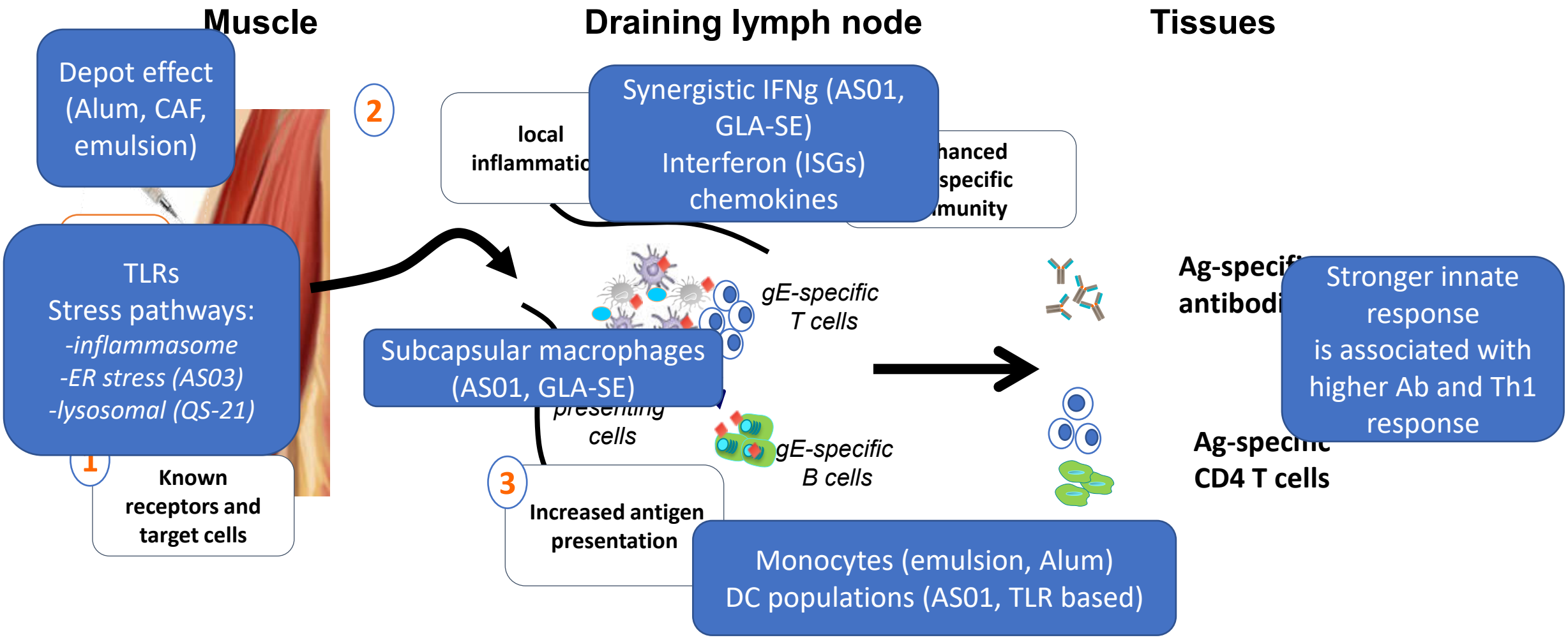


- Evidence that vaccination with adjuvants could induce a transient change in the responsiveness of innate cells to various stimuli
- Clinical relevance remains unclear but may contribute to non-specific effect/reactogenicity

Wimmers, Cell, 2021 ; Rescigno, Cell, 2021

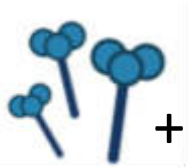
How do adjuvanted vaccines work and how to improve current adjuvants?

Adjuvants induce a Transient Stimulation of Innate Immunity, Which Is Required for the Adjuvant Effect



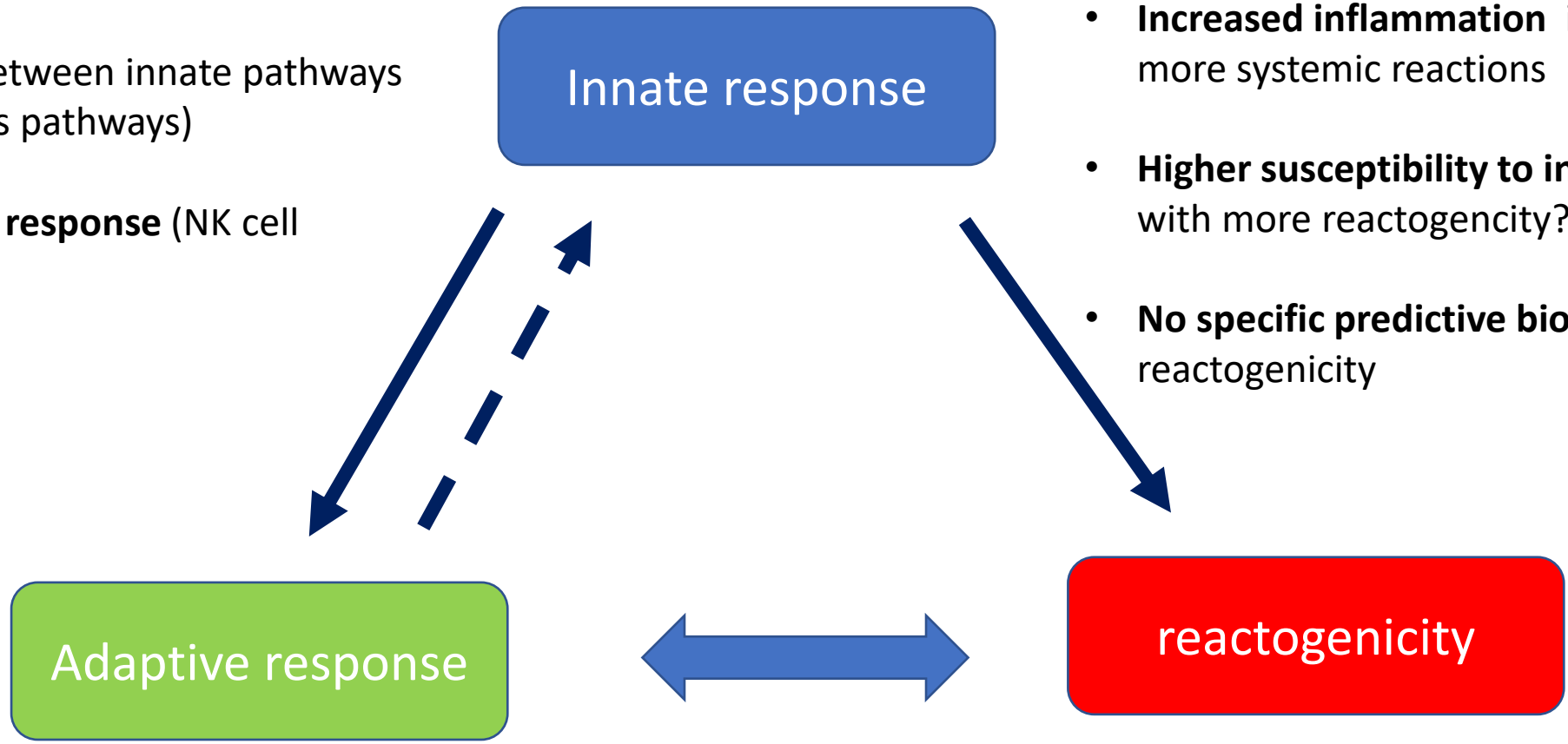
Didierlaurent AM, et al. *J Immunol*. 2014;193(4):1920-1930; Detienne S, et al. *Scientific Reports*. 2016;6:39475; Didierlaurent AM, et al. *Expert Rev Vac*. 2017;16(1):55-63; Coccia et al. *npj Vaccines*, 2017

Key innate pathways involved in adaptive response to adjuvanted vaccines



+ Adjuvant

- **Synergy** between innate pathways (TLR/Stress pathways)
- **Interferon response** (NK cell activation)
- **Monocyte**



- **Increased inflammation** is associated with more systemic reactions
- **Higher susceptibility to interferon** associated with more reactogencity?
- **No specific predictive biomarkers** of reactogenicity

Perspectives

- Development of small synthetic molecules to modulate immune response (Th17,therapeutic vaccines) or improve reactogenicity profile

- Emerging data suggest non-specific effect of adjuvanted vaccines through imprinting of the immune system (clinically relevant?)

- Several entities are and will be able to supply GMP-grade adjuvants (incl. open access)-> acceleration of adjuvanted vaccine development

- Head-to-head comparison with other platforms (e.g. mRNA) are needed

Comparison with mRNA

Adjuvanted versus mRNA-based vaccines

		antibodies		T cells		Adverse events	
1st vaccine	2nd vaccine	IgG	neutralizing	CD4	CD8	1st	2nd
NVX-Cov2373	NVX-CoV2373	++	+++	++	+/-	⇧	⇧⇧
BNT162b2	BNT162b2	+++	+++	++	++	⇧	⇧⇧
mRNA-1273	mRNA-1273	+++	+++	+++	++	⇧	⇧⇧

Hielscher, J. Clin Virol, 2022

Comparison on boosting with adjuvanted versus mRNA-based vaccines

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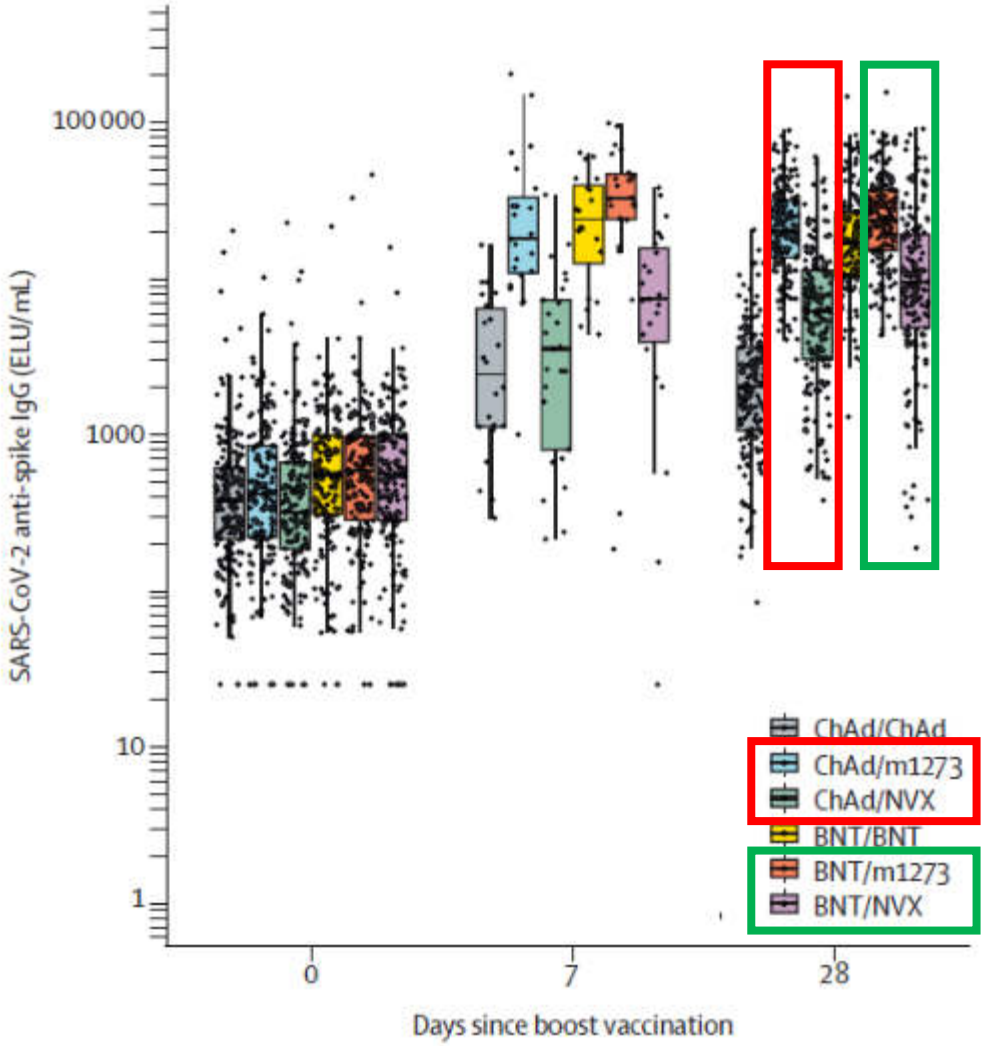
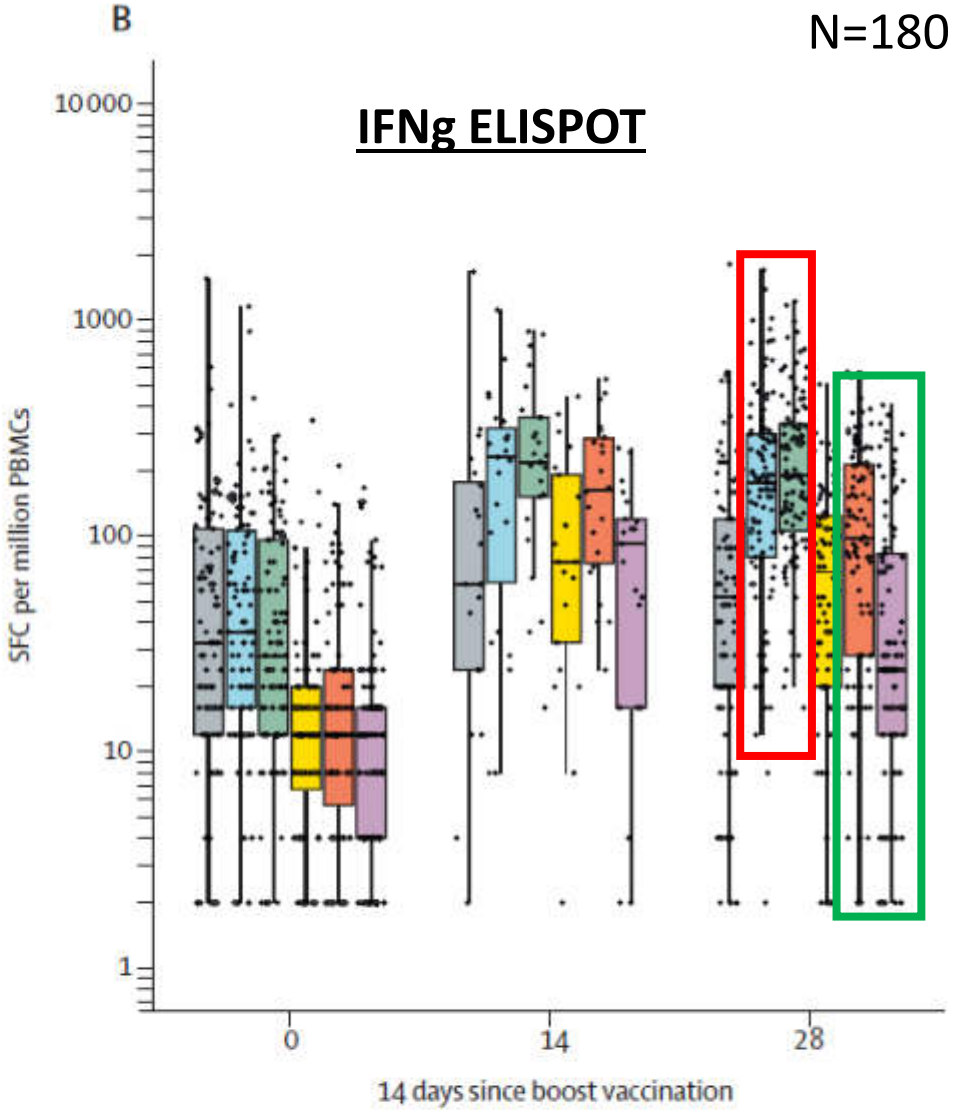
ComCov2 study (UK)
N=180 per gp, RCT

Binding antibodies



IFNg ELISPOT



Stuart, Shaw, Liu, The Lancet, 2022

Comparison on boosting with adjuvanted versus mRNA-based vaccines

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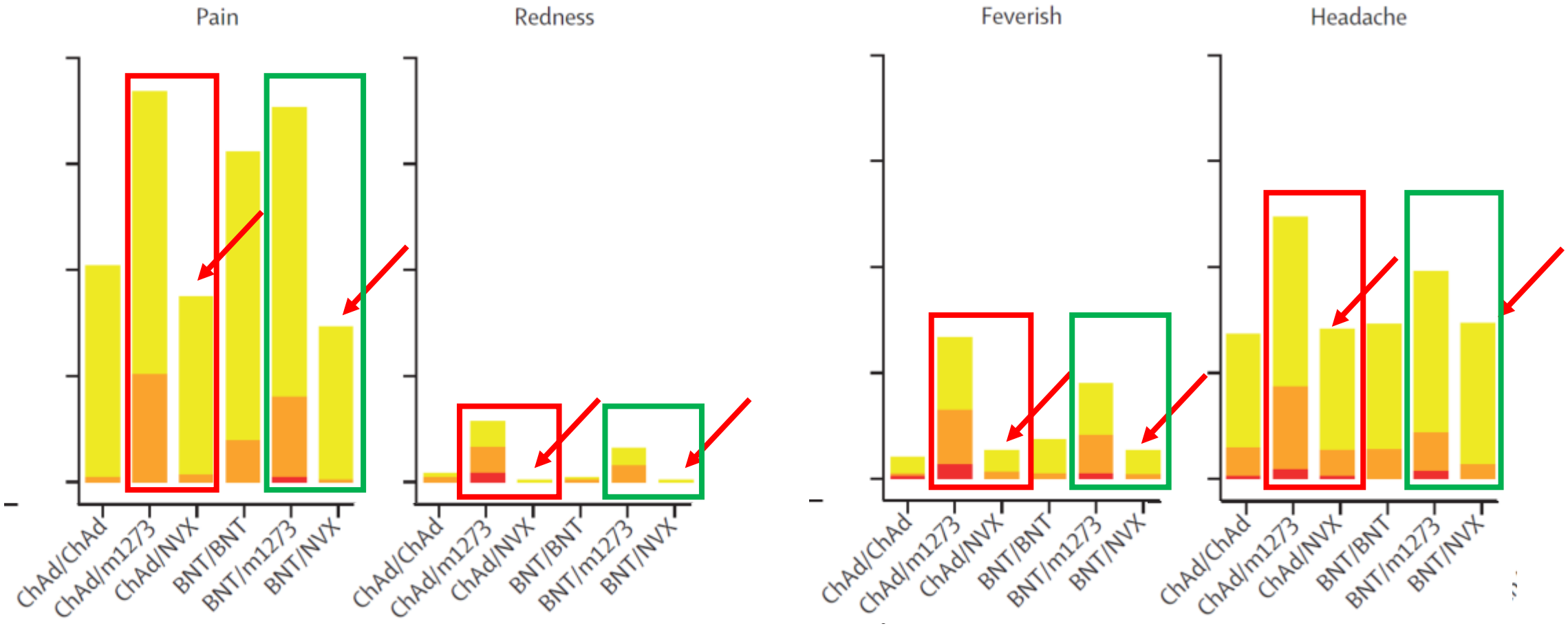
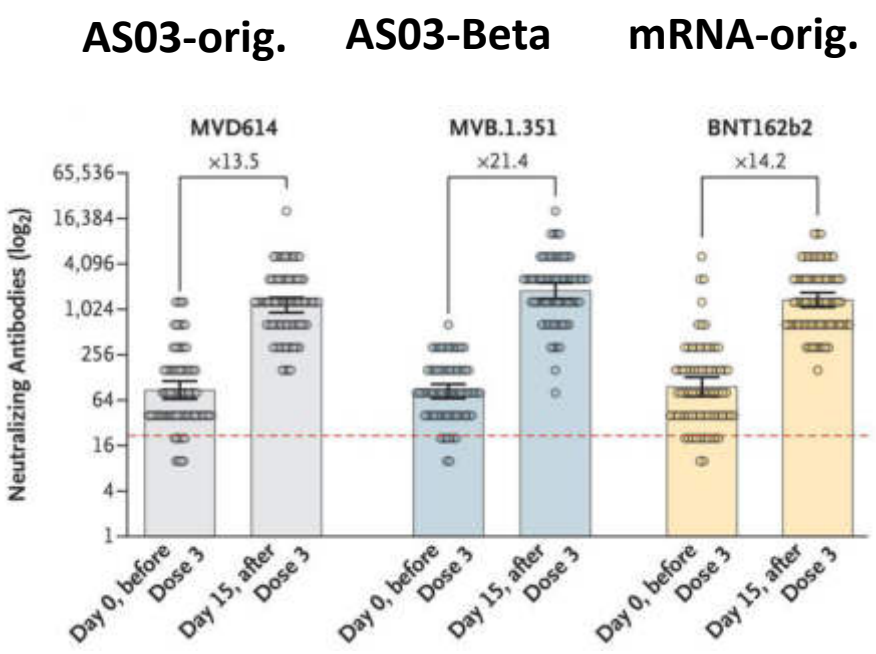
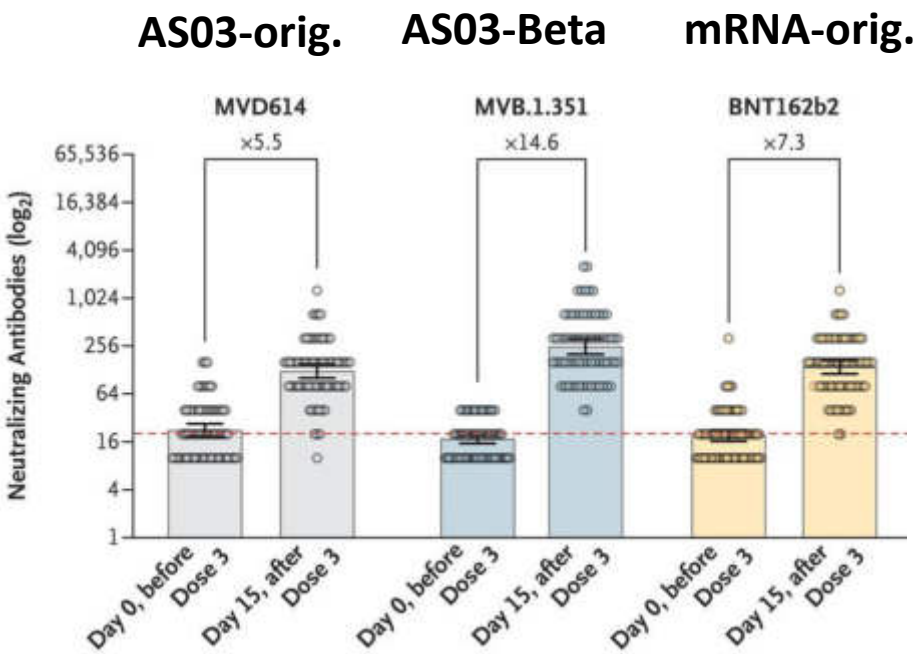


Stuart, Shaw, Liu, The Lancet, 2022

mRNA versus adjuvants: COVID-19 data on booster (3rd dose after mRNA primary series)

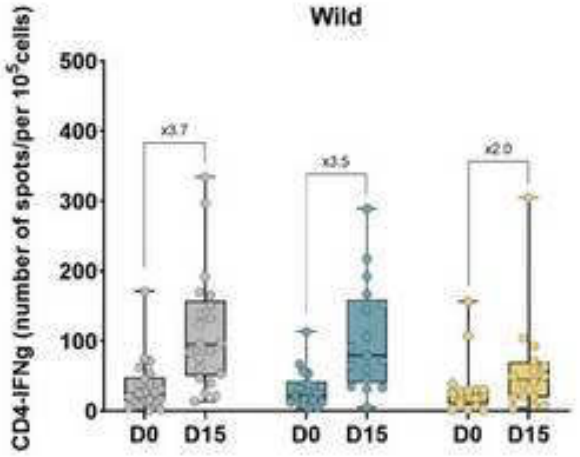


Nabs to **orig. strain**



Nabs to **omicron BA.1 strain**

Similar binding antibody, similar safety profile



Adapted from Launay et al. NEJM, 2022

mRNA versus adjuvants: pro and cons…

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	mRNA	Adjuvants

Immuno	• Strong antibody response but limited persistence and breadth?
	• CD4 and CD8 response demonstrated but
	  • Antigen-specific?
	  • Sustained CD4 T cell response?
		• Strong antibody response and evidence of increased breadth
		• Only CD4 T cells response
		  • Shown across many different antigens
		  • Persistence demonstrated

Safety	• Millions of doses administered with good safety profile but only 2 years of experience…. • High reacto- suitable for non COVID vaccines? • Not possible to distangle immune activation from antigen level (risk of low immuno/high reacto)	• Established safety across different vaccine antigens • High/medium reacto-tunable • Possible to reduce doses while keeping the same amount of antigen
Manufacturing	• Rapid, full synthetic • easy to change target antigen • Stability at RT?	• Could be complex • Usually excellent stability

Key points

- There are more several licensed adjuvanted vaccines than 5 years ago
- Clinical benefits of adjuvanted vaccines are demonstrated and emerging data show that adjuvants improve the quality of the immune response
- Head-to-head comparison of adjuvanted and mRNA-based vaccine are urgently needed to assess their respective potential/complementarity

Thank you

Pr. Arnaud Didierlaurent