

HUMAN CHALLENGE STUDIES IN HEALTHY VOLUNTEERS: PRACTICAL CONSIDERATIONS AND OUTCOMES OF INFLUENZA TRIALS



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WHEN YOU NEED TO BE SURE

SGS

- Influenza challenge studies in healthy volunteers
 - Disease modeling \Rightarrow testing novel therapies.
 - Synchronized disease onset \Rightarrow timed intervention
 - Non seasonal influenza \Rightarrow “à volonté” \Rightarrow Clinical development

- Optimal model : virulent species
 - high infectivity - relevant symptoms
 - no safety concerns

- Optimal methods
 - virus preparation and inoculation
 - sample management and data analysis

- Experience of SGS/CPU with influenza trials
 - Viral Challenge Unit / CPU Antwerpen
 - Challenge agents manufacturing project (CHAMP)

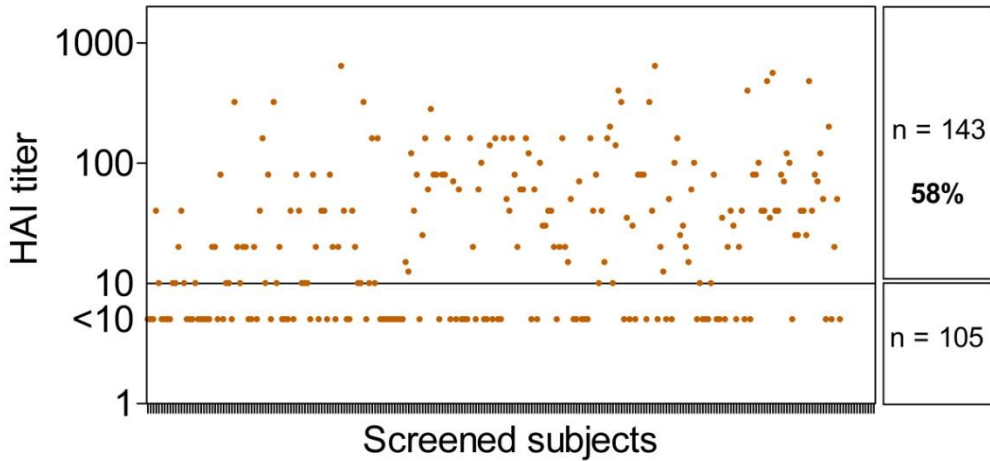
- 2 influenza A challenge models investigated

	H1N1 (Phase 2a)	H3N2 (Phase 1)
Immunity to challenge agent	Hemagglutination inhibition (HAI) ≤ 10	Microneutralisation (MNT) ≤ 20
Adventitious agents: day -2	Biofire FilmArray Respiratory Panel	
Challenge agent inoculation	0.25 mL/nostril (10 ⁵ -10 ⁷ TCID ₅₀ /mL)	
ILI twice daily	Symptoms Score Card (SSC)	
Nasal mucus weight	Tissue paper collection	
Viral shedding in airways	Nasopharyngeal swabs: qPCR, qCulture	

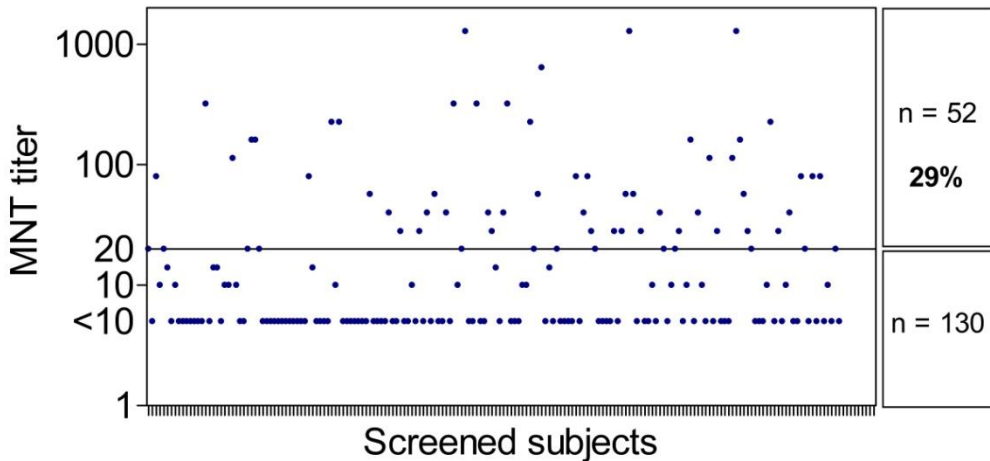
qPCR: quantitative polymerase chain reaction / qCulture: quantitative viral culture

- Regulatory framework (CA, IEC, Biosafety)
- State of the art VCU: **keep in / keep out** ⇒ key to success
- Rescue medications
- Well-trained staff: data collection, sample manipulation

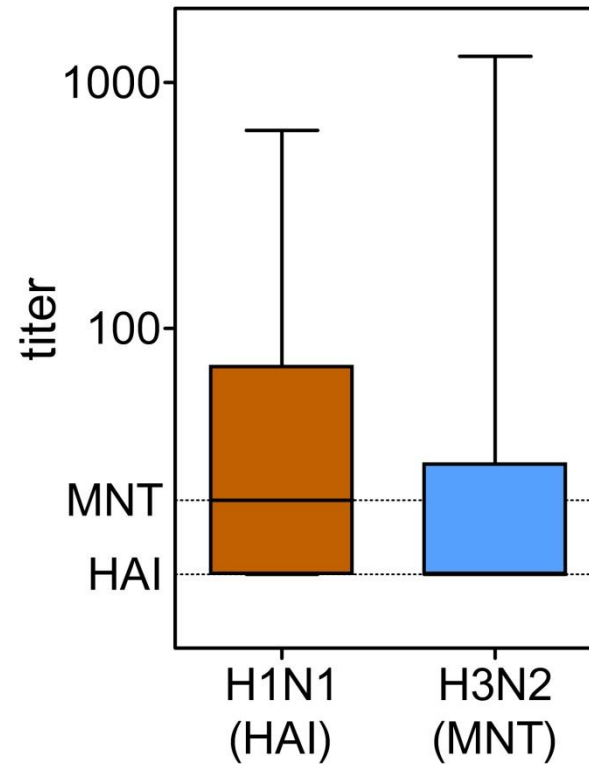
HAI - H1N1 study



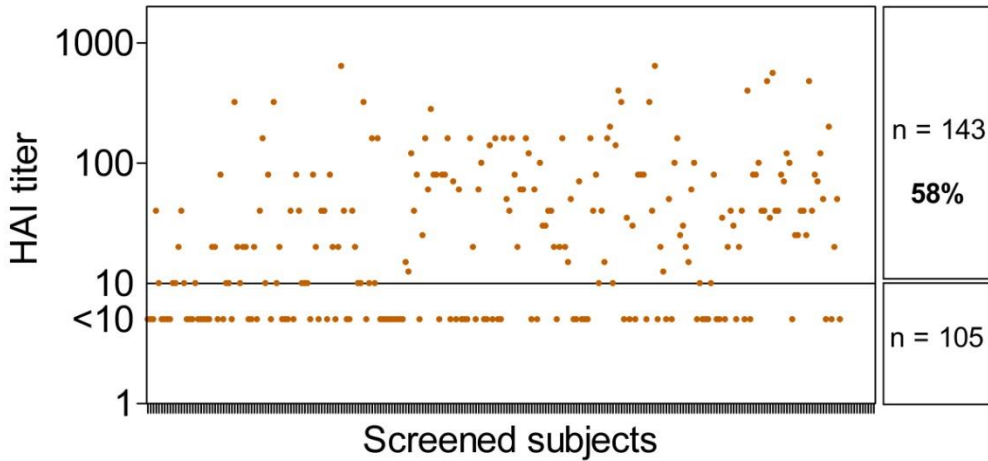
MNT - H3N2 study



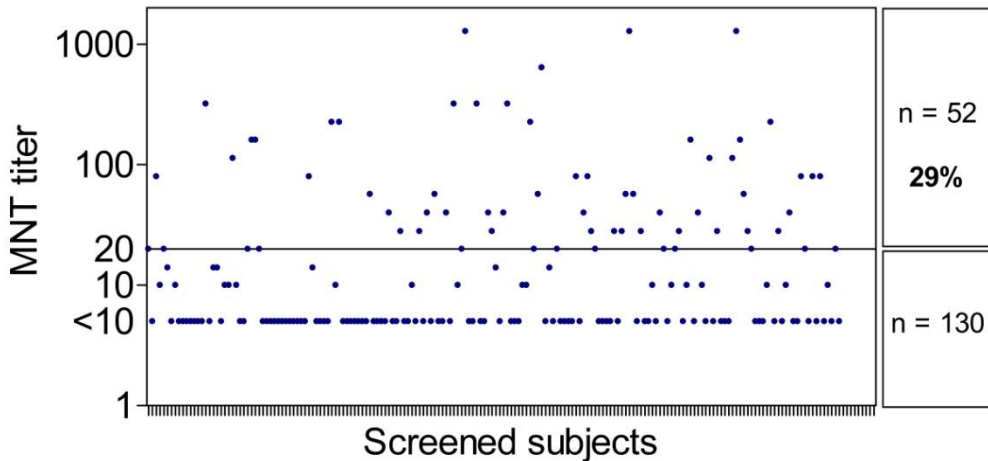
Screening HAI MNT



HAI - H1N1 study



MNT - H3N2 study



■ Success rate 1st screen

- 42% HAI
- 71% MNT
- No / Low Ab titer: likelihood symptoms development



■ Inoculation

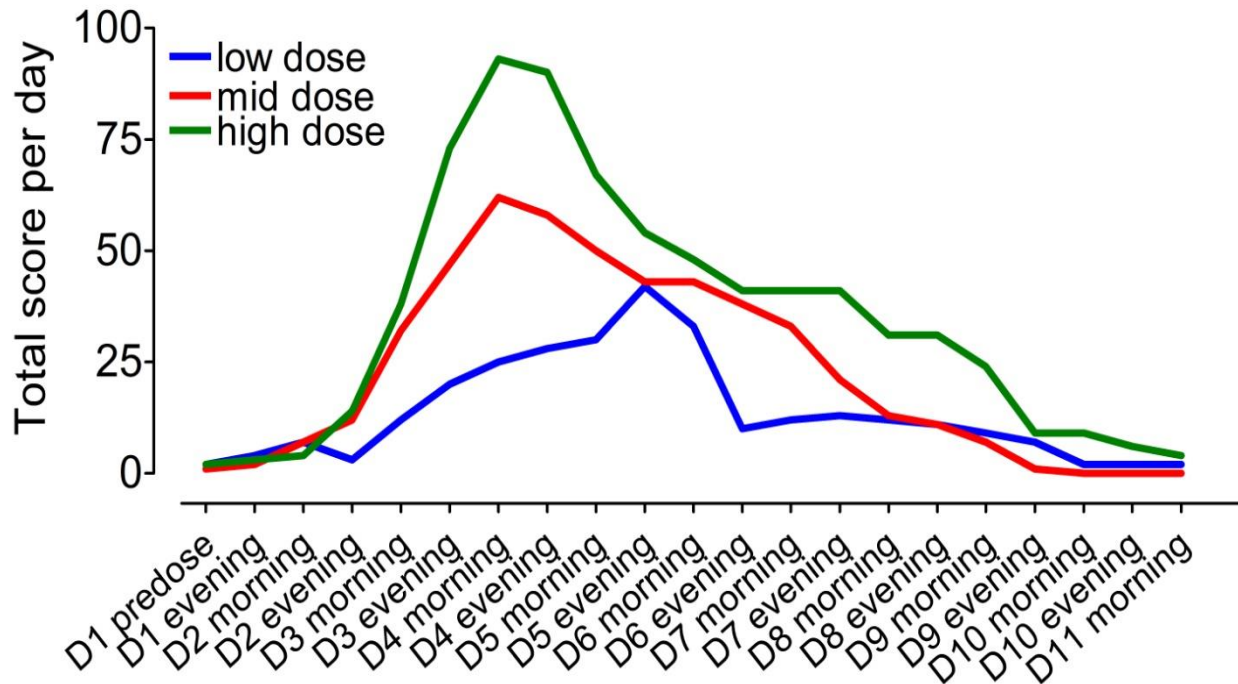
- H1N1: Eppendorf pipette
- H3N2: VaxINator device

■ VaxINator device

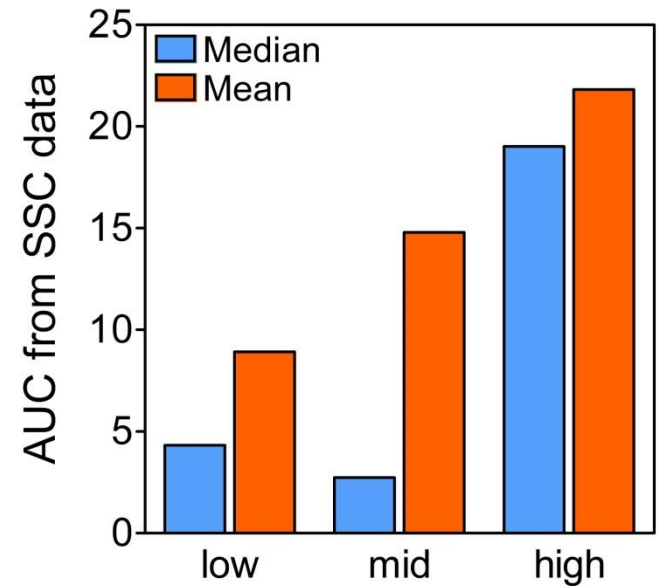
- sprays challenge agent
- handy lock-system => 0.25 mL
- much appreciated

- **dose-dependent ILI** observed 3 to 5 days post-inoculation

ILI symptoms score H3N2

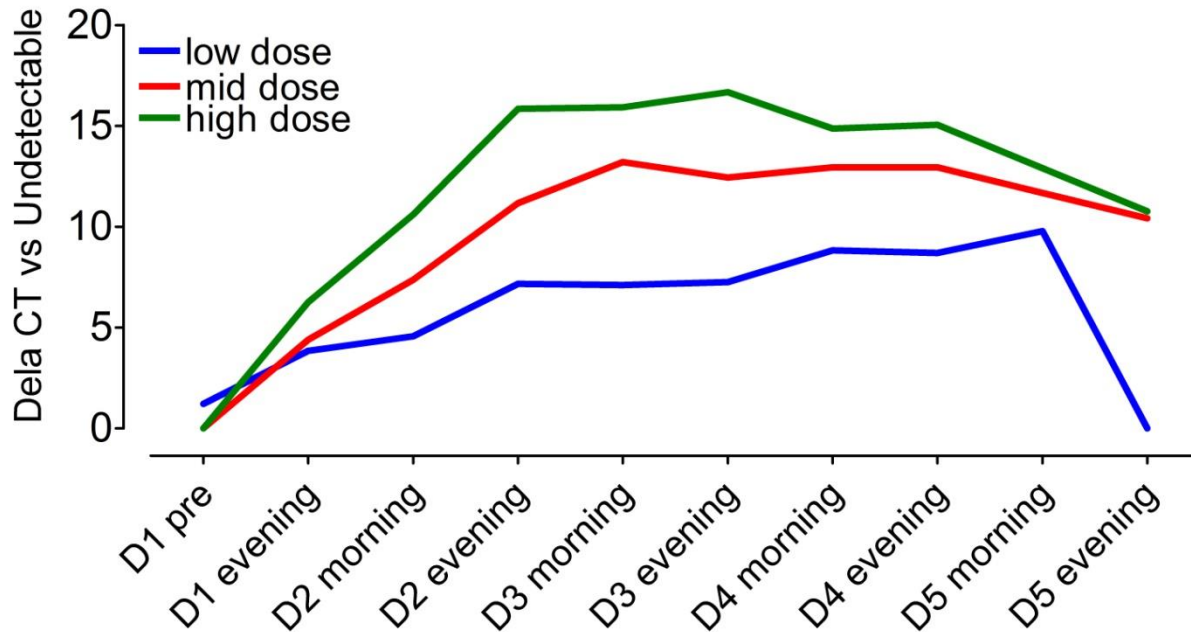


Symptomology H3N2

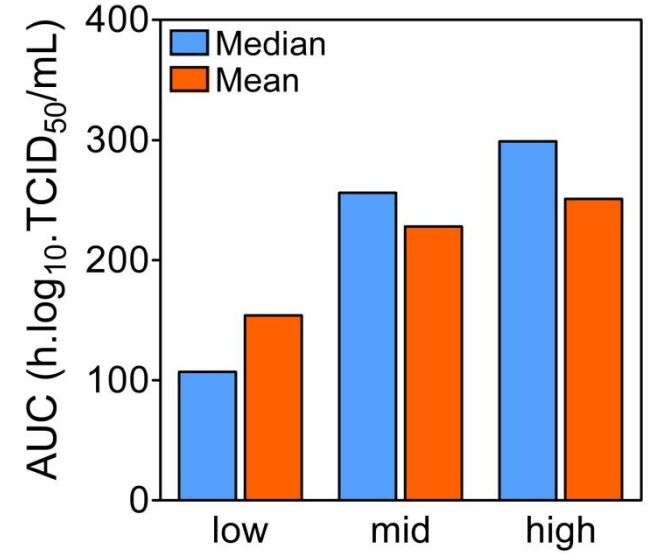


■ dose-dependent viral loads

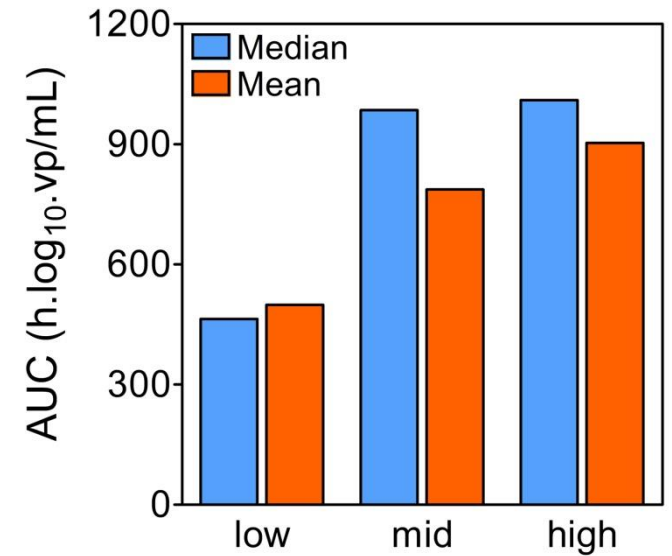
H3N2 viral load in NPS



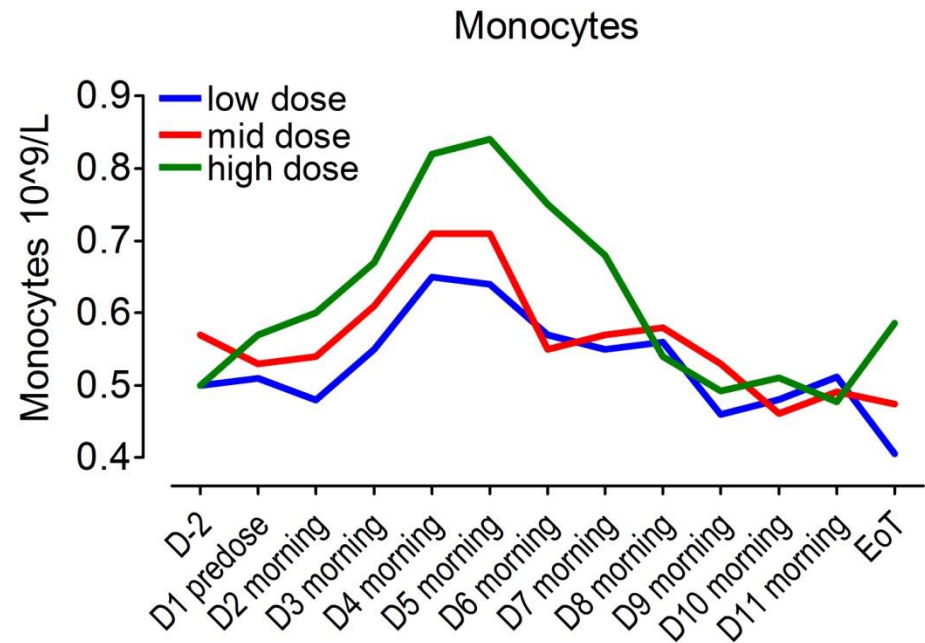
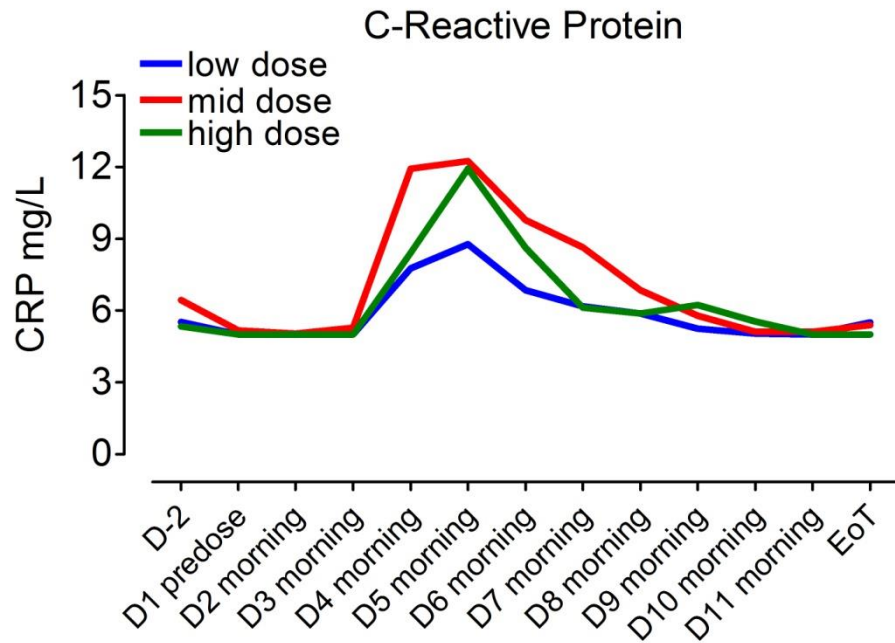
Viral shedding H3N2 culture



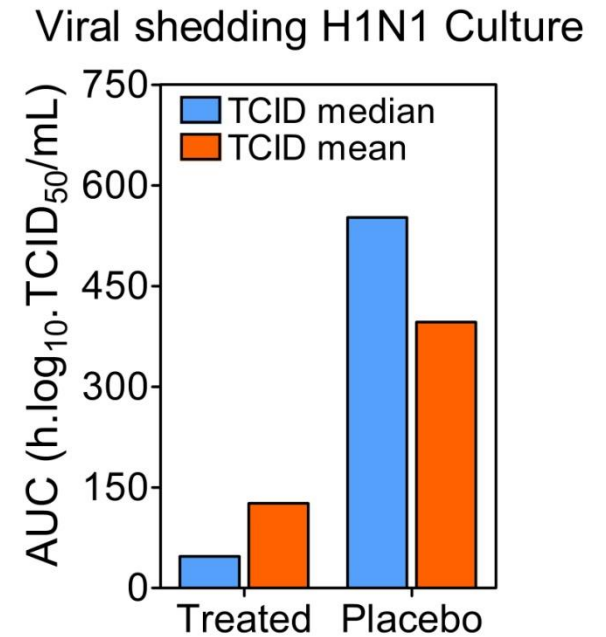
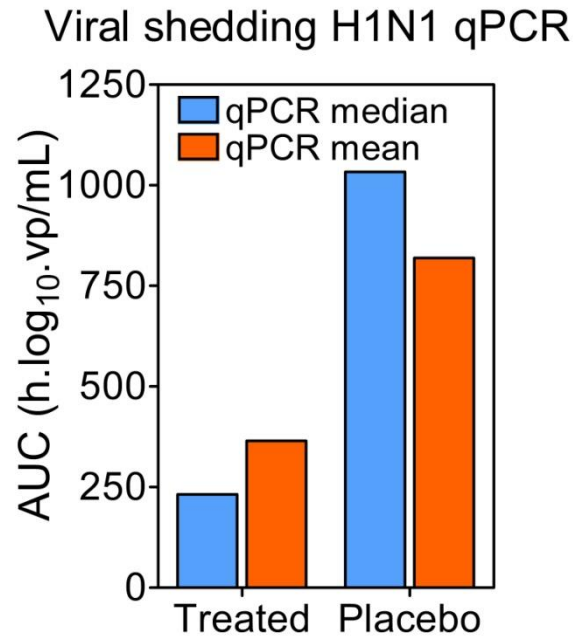
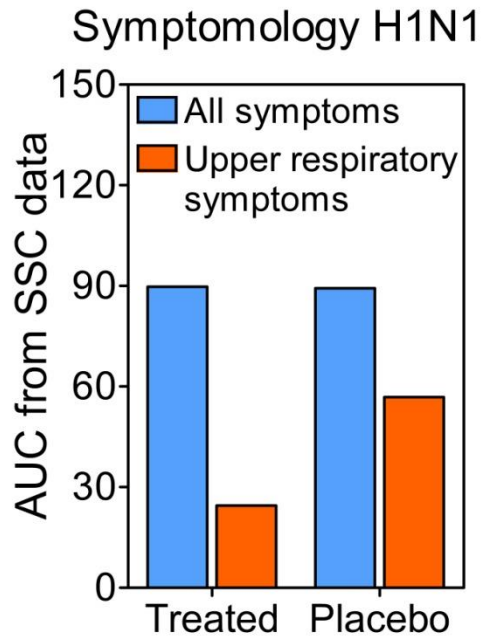
Viral shedding qPCR H3N2



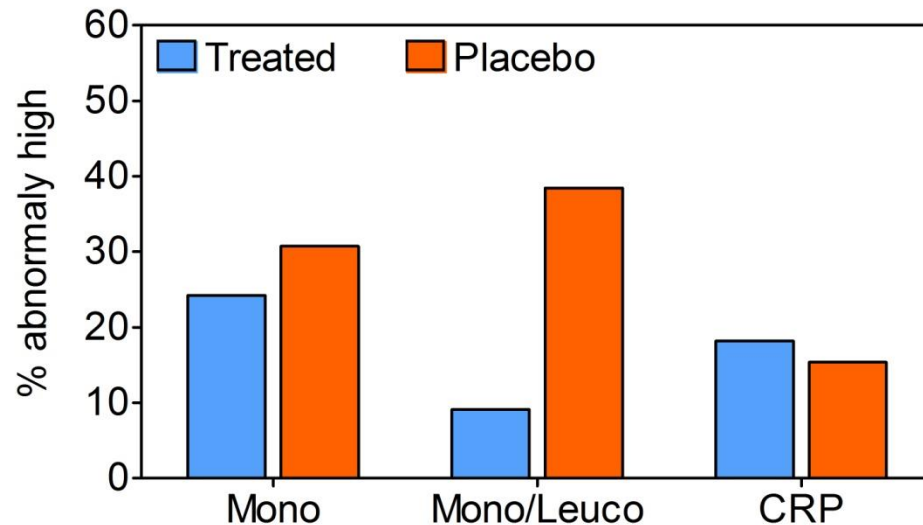
■ Concordant biology



- Segregation of **Treated** vs **Placebo** subjects by 3 methods



- Segregation of **Treated** vs **Placebo** subjects by biology (% abnormality high)



Mono: absolute monocytes counts

Mono/Leuco: monocytes to leucocytes ratio

CRP: C-reactive protein

- Human challenge studies
 - intensive processes
 - close monitoring and optimal techniques
 - delivery of reliable data
- Both influenza trials provided **expected outcomes** while following **standardized methods**.
- A new interventional H3N2 trial is currently initiated, and its recruitment is consistent with current data

ACKNOWLEDGEMENTS

- Volunteers
- SGS/CPU staff (RO, CTA, CTN, CRC, PM, CRA, CRP)

- Sponsors  

- Labs 
knows your target



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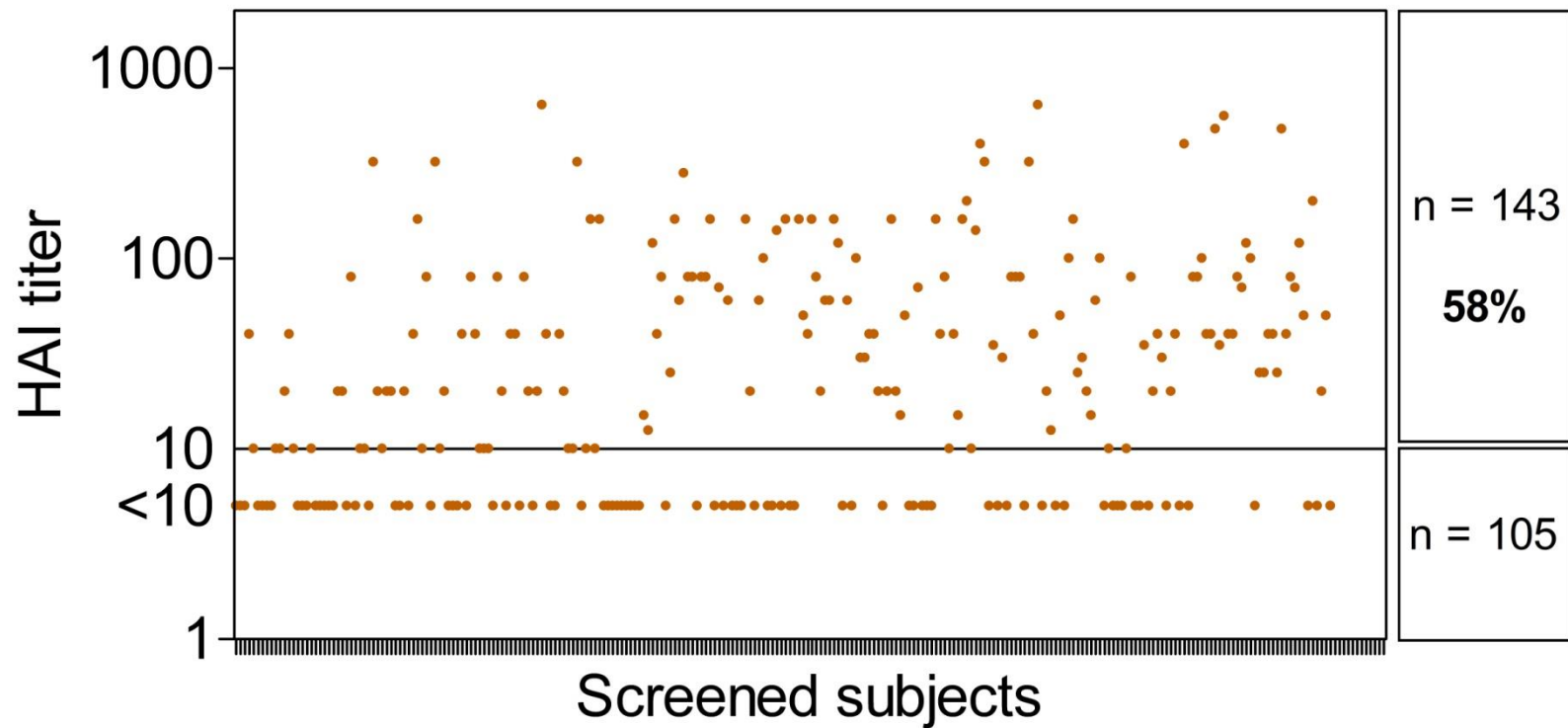
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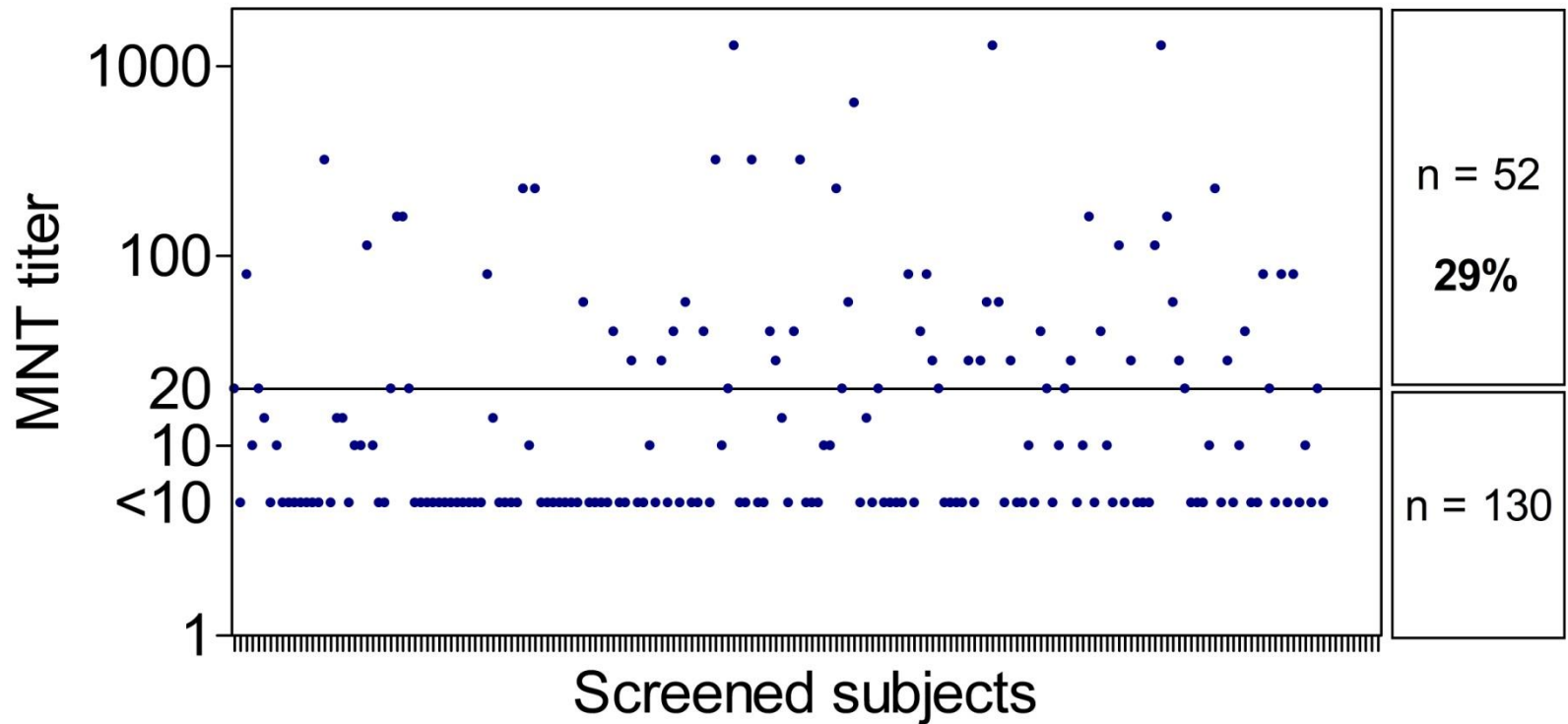
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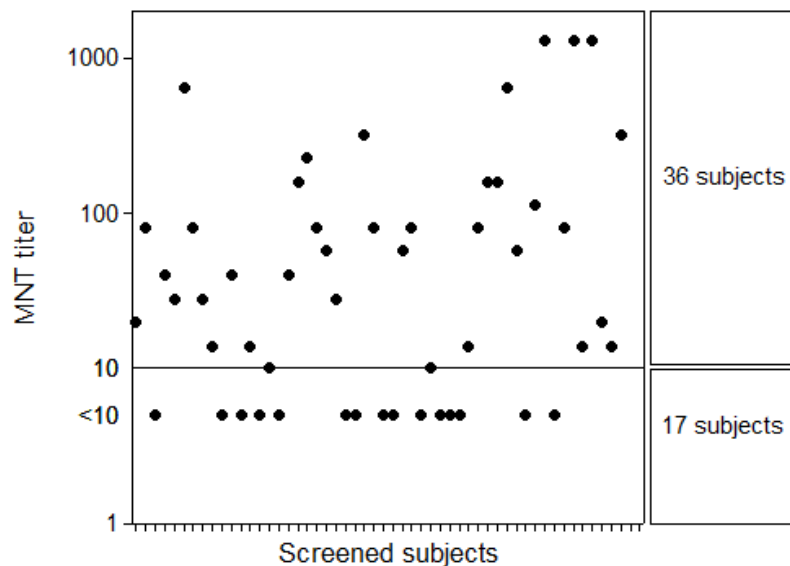
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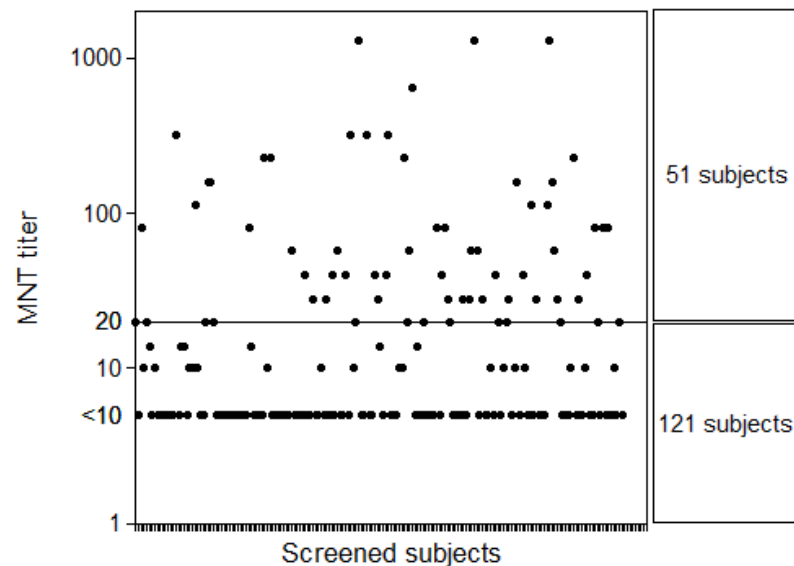
MNT - H3N2 study



MNT - VENTALEON - Gr1



MNT - CHAMP study - Gr1,2,3



	VENTALEON	CHAMP
Success rate MNT	32.1%	70.4%
Failure rate MNT	67.9%	29.6%
MNT treshhold	10	20
Effect treshhold swap on success rate MNT	+7 (+13%)	-18 (-10.5%)