VTP-300: HBV Prime-boost therapeutic based on CD8+ T cell induction with concomitant checkpoint inhibition

Tom Evans MD

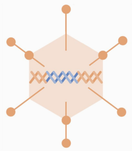
World Vaccine Congress Barcelona

ChAd-MVA provides powerful antigen-specific T cell responses

Leading CD8+ T cell-inducing platform in man
Platform safely mimics potent natural viral infections, using **heterologous** prime-boost

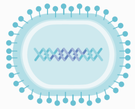
Prime

Chimpanzee Adenovirus Oxford 1 and 2 (ChAdOx)



1 – 12 weeks

Boost

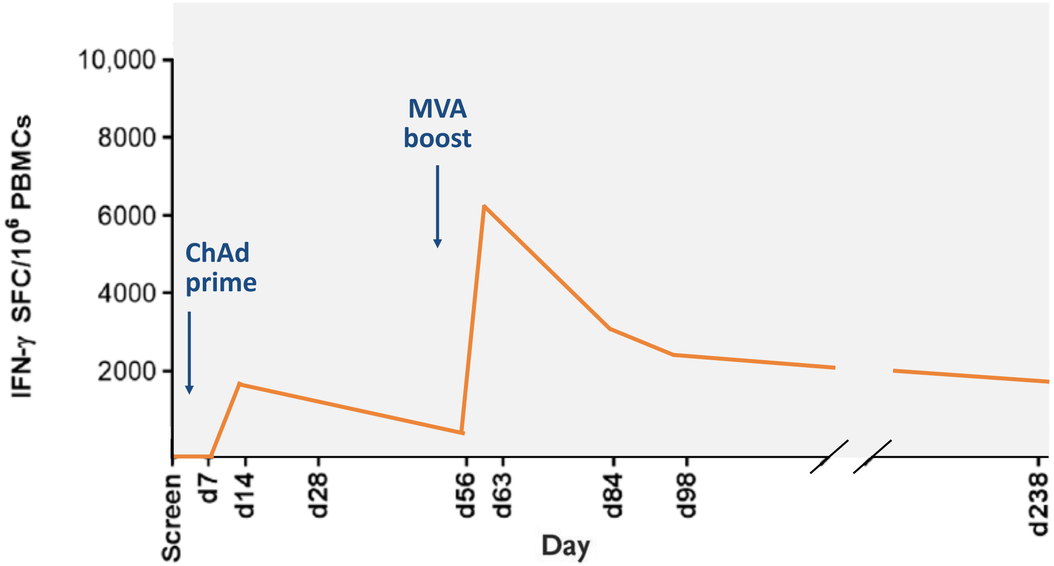


Avian-adapted Modified Vaccinia Ankara (MVA)

Key Platform Features:

- Vectors encode the same transgene
- Only boost target antigen responses
- No anti-vector immunity (unlike most human adenoviruses)

Indicative Human T cell response, HCV antigen, invariant chain[1]



Optimal immunogenicity

- Quantity: greater CD8+ T cell stimulation than other platforms
- Quality: T cells polyfunctional
- Duration: Sustained T cell levels

Demonstrable Tolerability Profile

- Neither vector can replicate in man

Convenient administration

- Intramuscular injection of each vector given 1 week to 3 months apart

1 Esposito et al (2020) *Science Translational Medicine*, Vol. 12, Issue 548 – Median T cell response in 10 healthy participants

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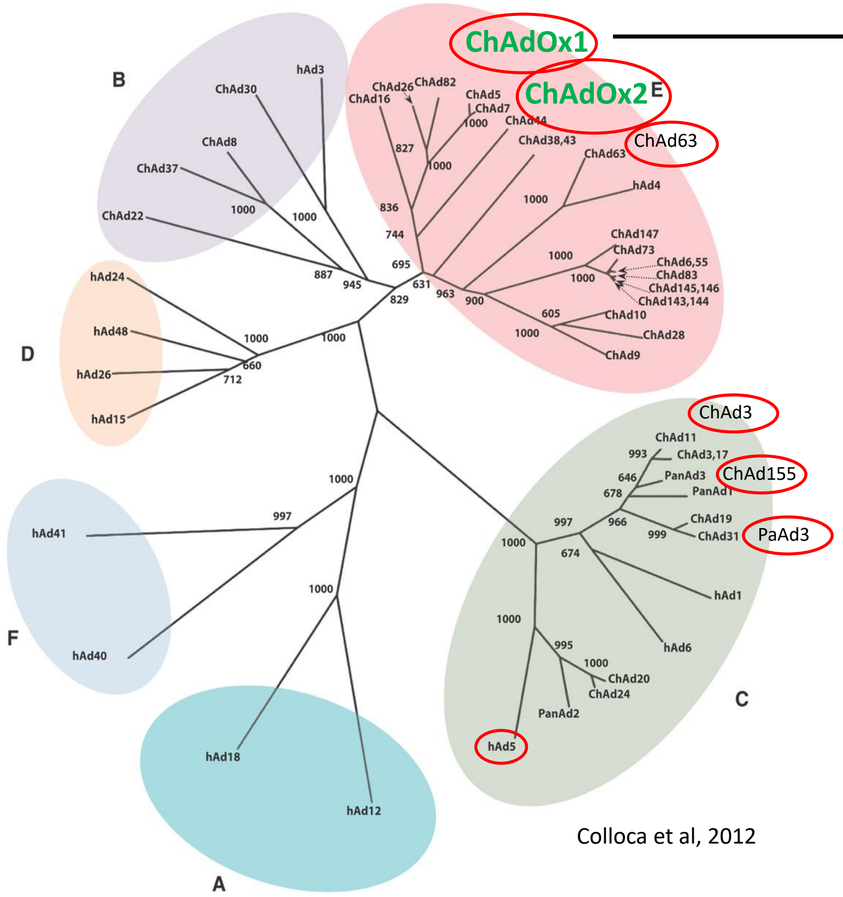
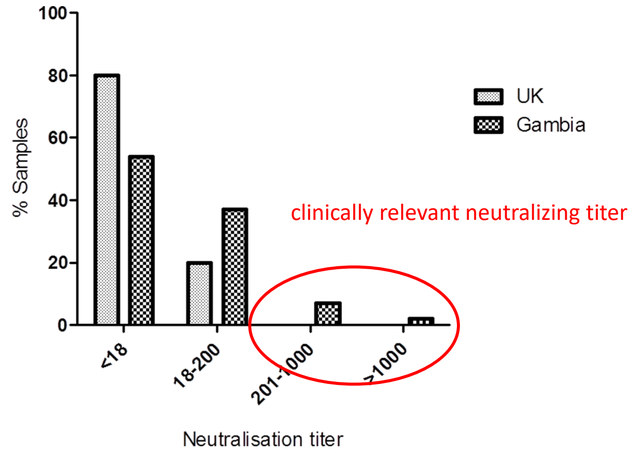
ChAdOx1: group E adenovirus from chimp isolate Y25

Adenovirus: non-enveloped DNA virus, genome size: 35-40kb,~38 proteins, subgroups (A-F) based on capsid sequence



Colloca et al, 2012

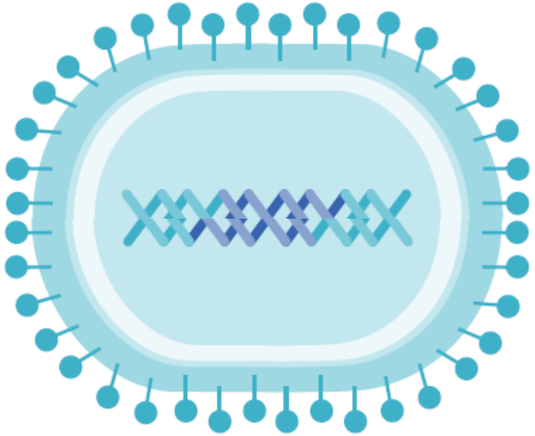
No/low pre-existing immunity



Anti-vector neutralising antibody titer in human sera from the UK (100 samples) and The Gambia (57 samples) (Dicks et al, 2012)

Modified Vaccinia Ankara (MVA)

- Derived from smallpox vaccine by >500 passages in avian cells
- No longer able to replicate in humans
- Administered to >130,000 without significant safety issues
- Licensed as a smallpox vaccine and as part of J&J Ebola vaccine
- Excellent boosting agent after Chimp adenovirus; Vaccitech uses a proprietary highly immunogenic F11 promoter
- Can accommodate carry large antigen inserts (25Kb)
- Stable for more than one year at 2-8C in appropriate formulations
- Can be produced in chicken embryonic fibroblasts or immortalized avian lines



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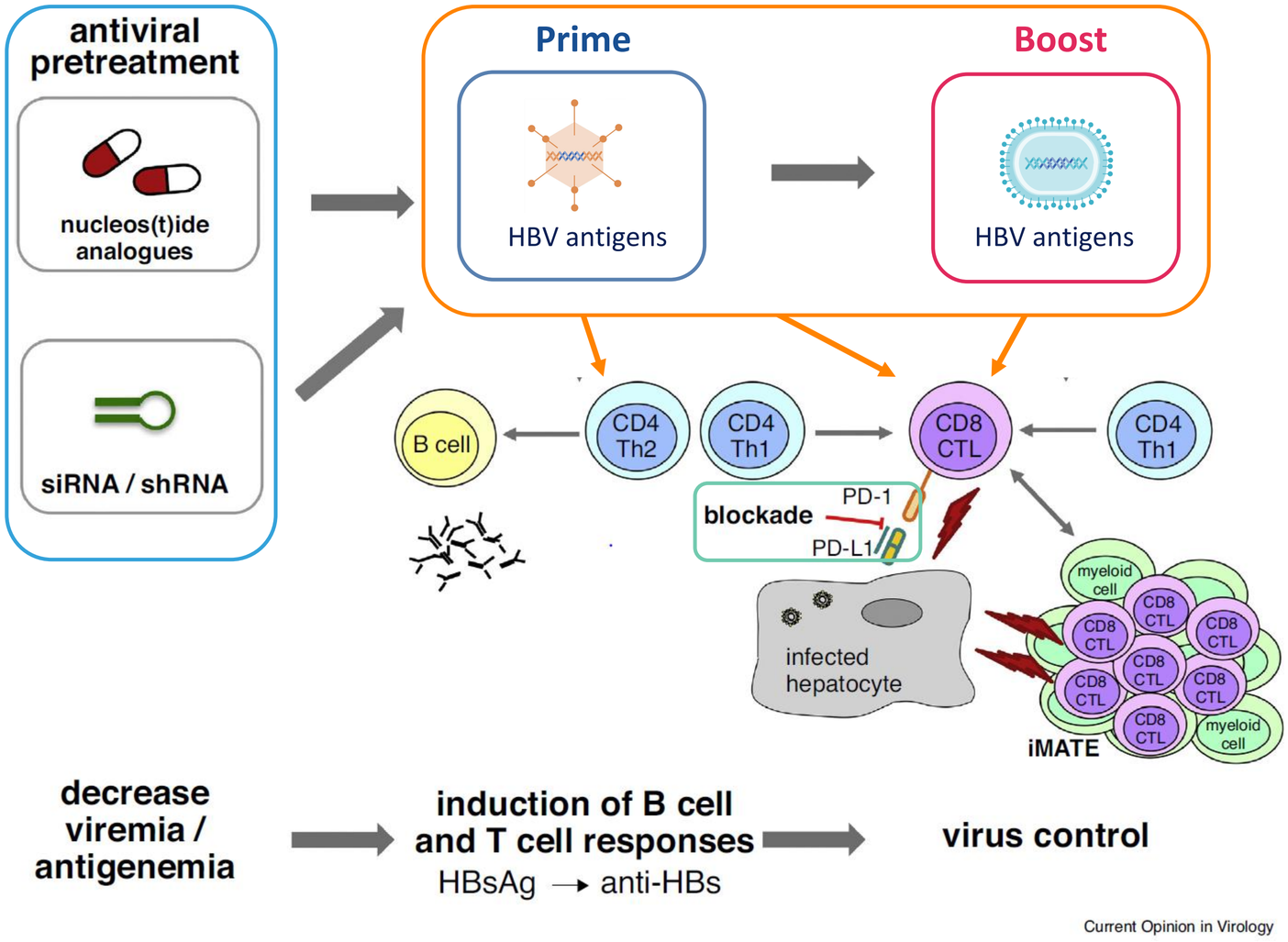
Prime-boost immunotherapy to reconstitute HBV immunity



Steps for combination therapeutic strategy include:

- **Antivirals and/or Direct Acting Agents** to suppress viremia and cccDNA
- **Immunotherapy to prime** anti-HBV T cells and antibodies to inhibit cellular infection
- **Immunotherapy to boost** functional T cell responses for lasting control of infection
- **Checkpoint inhibitors** to alleviate immune exhaustion

Adapted from Kosinska et al 2017 Current opinion in virology

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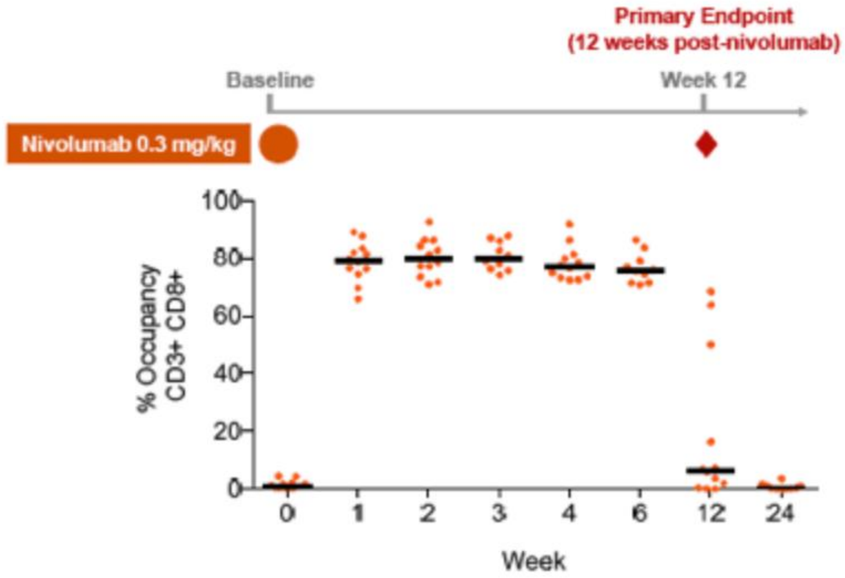
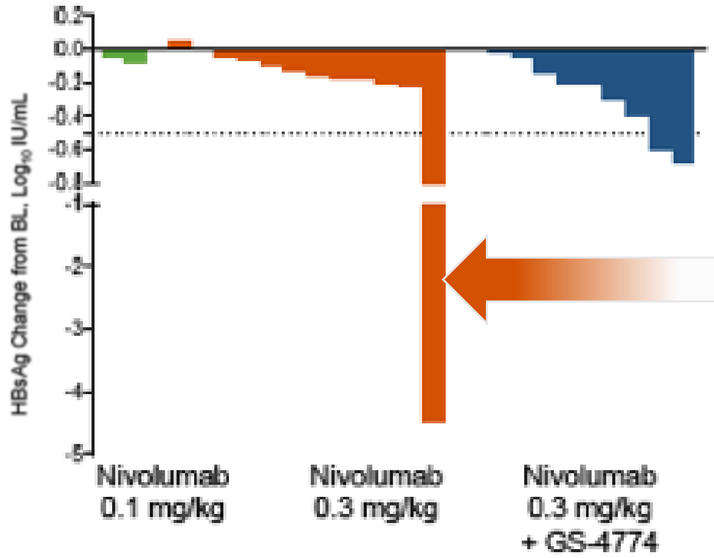
Checkpoint inhibitor and therapeutic vaccine in CHB patients

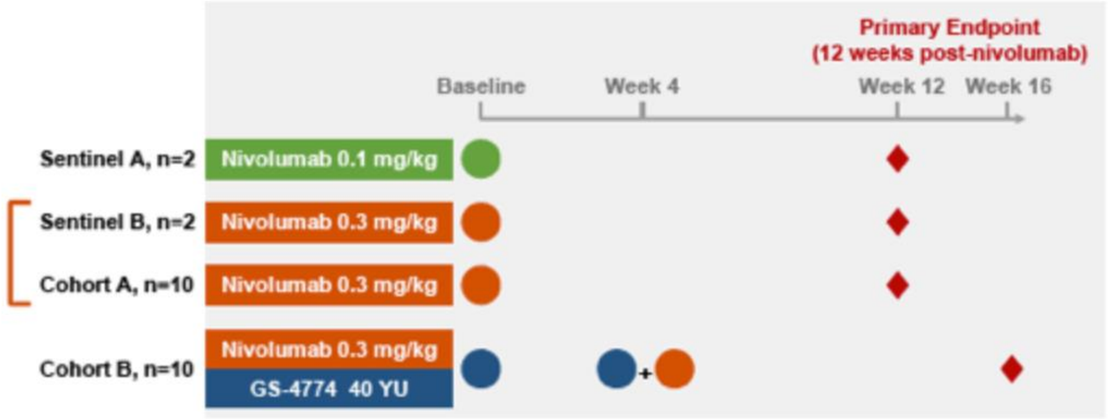
1 Optimal target occupancy with 1/10th of anti-PD1 licensed dose



2 Significant HBs Ag decline at wk 24
↓HBsAg >0.5 log^{10} in 3 patients



1 patient with **HBsAg loss** and **anti-HBs seroconversion** **30 weeks** after NUCs **discontinuation**



Unanswered questions

1. Therapeutic immunogenicity / Therapeutic schedule?
2. Timing of immune activation of T cells?
3. HBsAg Loss with ↑ALT: Immune activation or safety signal?

Ed Gane et al. J Hepatol 2019

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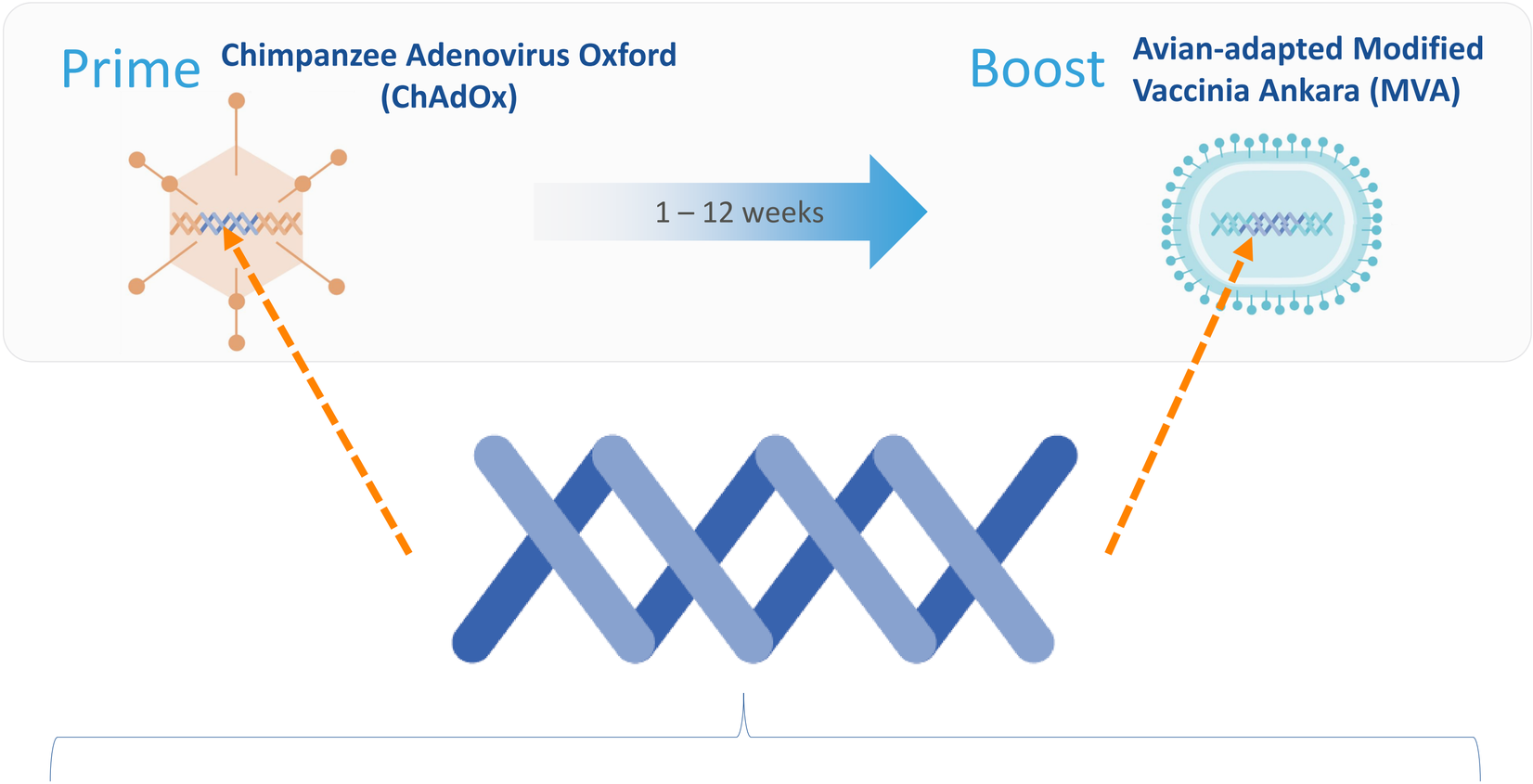
VTP-300 design includes full-length HBV sequence



- Full length surface (including Pre-S1, Pre-S2, modified polymerase, core)
- Consensus genotype C
- Proprietary promoters

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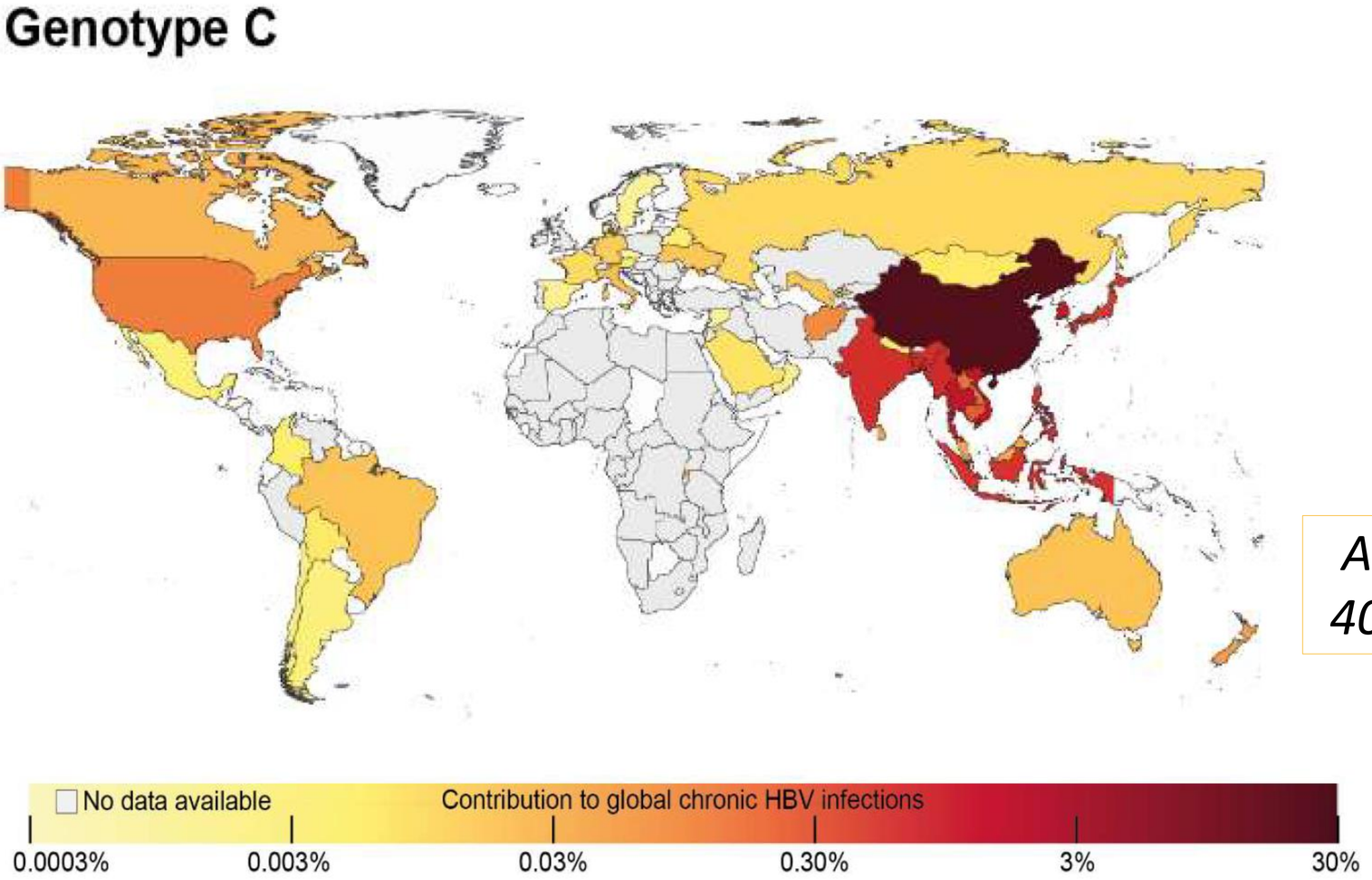
Genotype C Contribution to Chronic HBV Infections

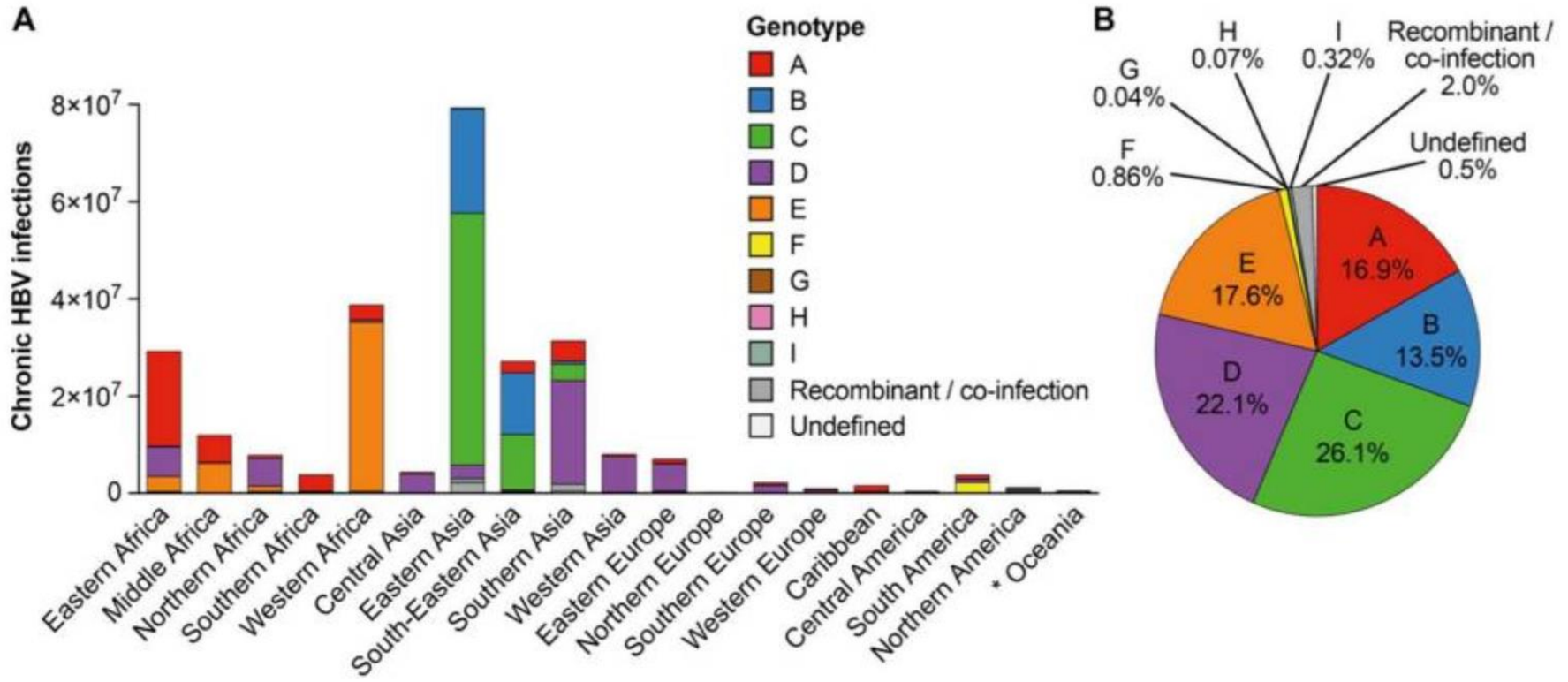


Australia and NZ – 40-50% Genotype C

Contribution of genotypes to global chronic HBV infections. The number of infections with each genotype in a respective country is illustrated as percentage of global chronic HBV infections.

Slide courtesy of PRAHealthSciences

Regional HBV Prevalence by Genotype

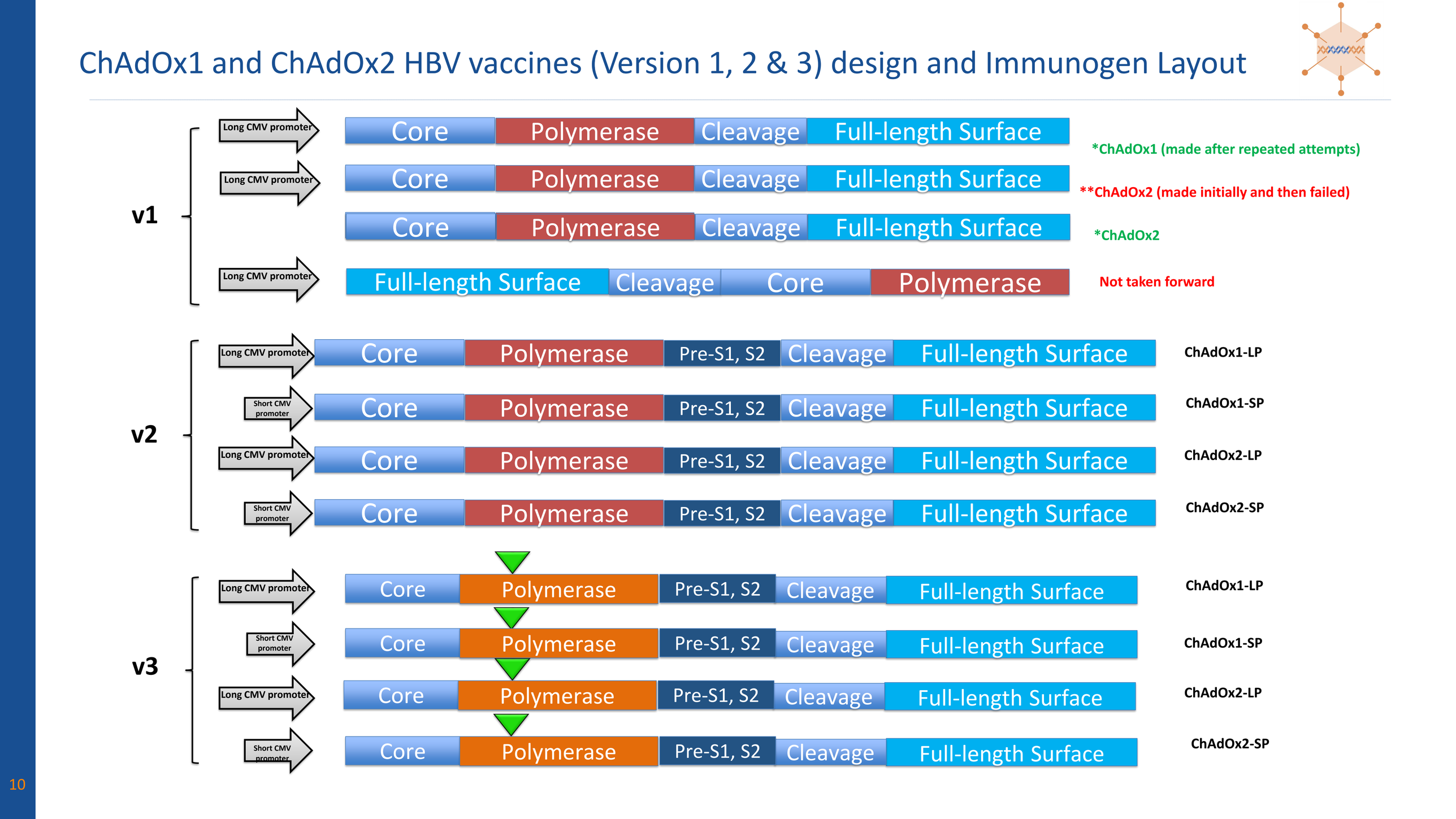


Approximation of the contribution of HBV genotypes to global burden of chronic HBV infection. (A) Estimation of the number of chronic infections with each genotype per world region. *: Oceania includes pooled data of Australia/New Zealand, Melanesia, Micronesia, and Polynesia. (B) Approximation of the genotype distribution within global chronic HBV infections. Values <2% are given with two decimals to prevent distortion of genotype distribution. Recombinant/co-infection: infection with an inter-genotype recombinant or with more than one HBV genotype; Undefined: genotype allocation not possible.

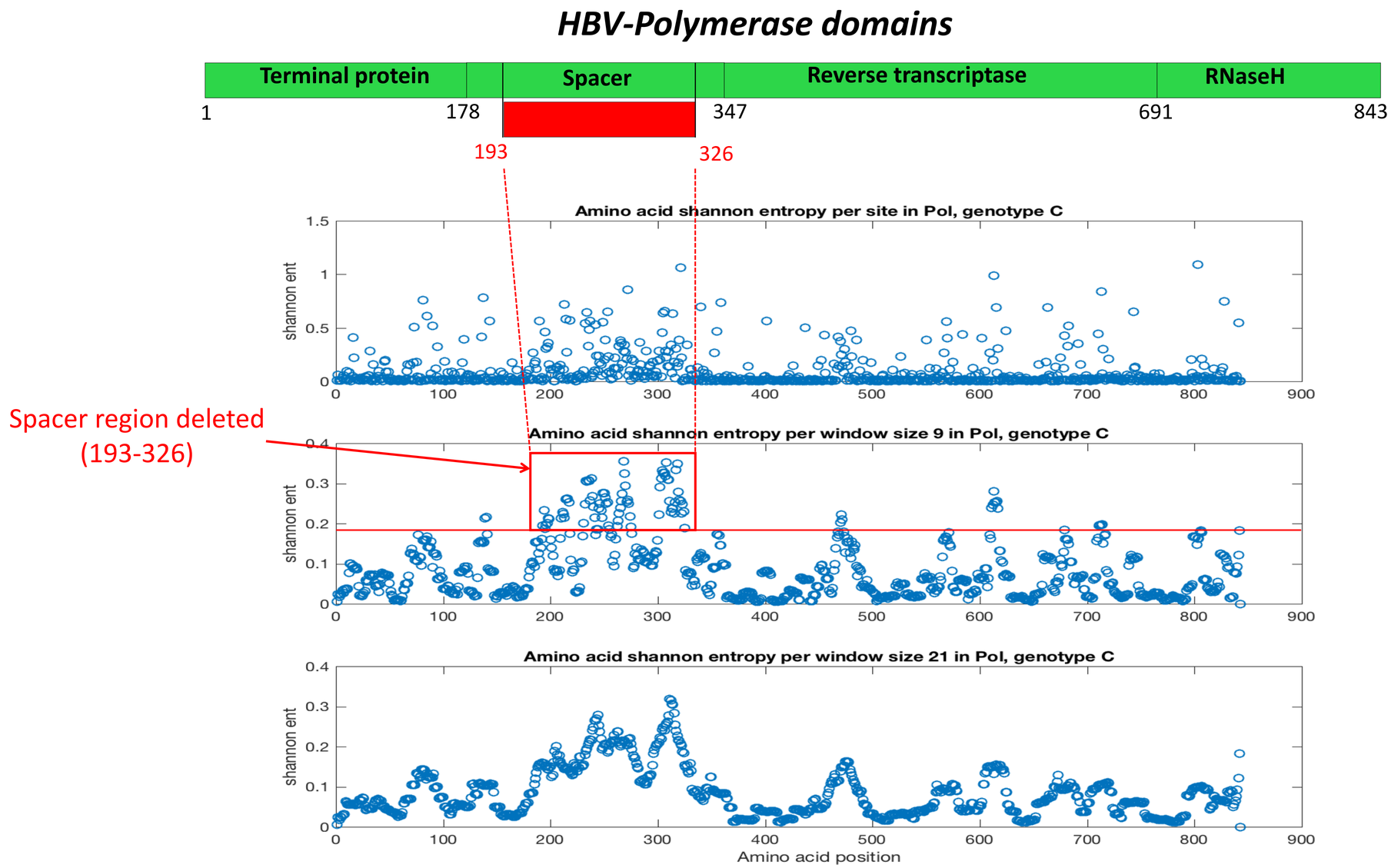
Slide courtesy of PRAHealthSciences

Velkov et al. Genes 2018

ChAdOx1 and ChAdOx2 HBV vaccines (Version 1, 2 & 3) design and Immunogen Layout

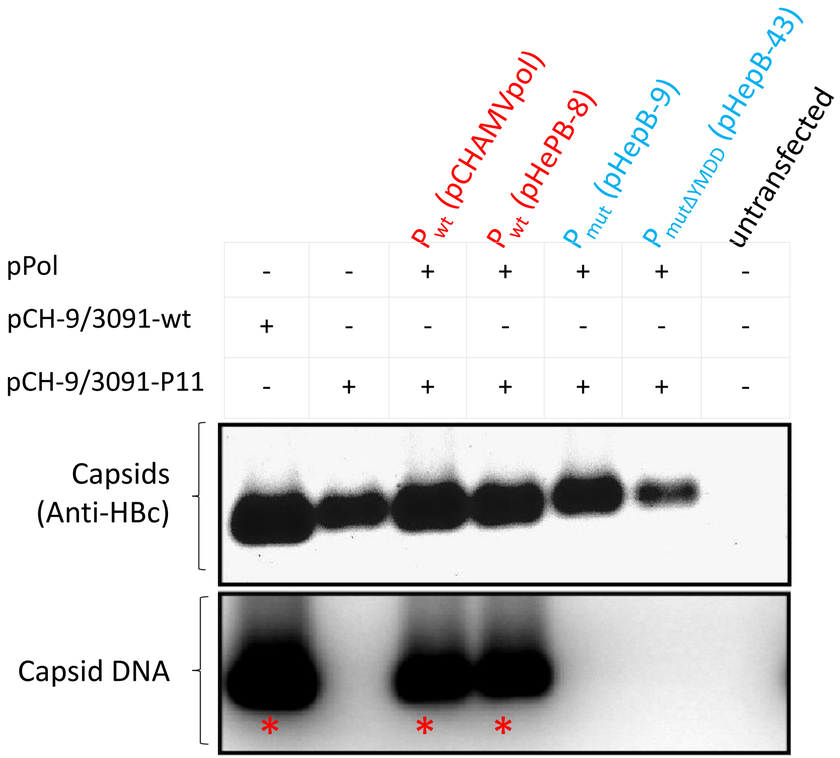


HBV Polymerase protein variability within 50 genotype C sequence

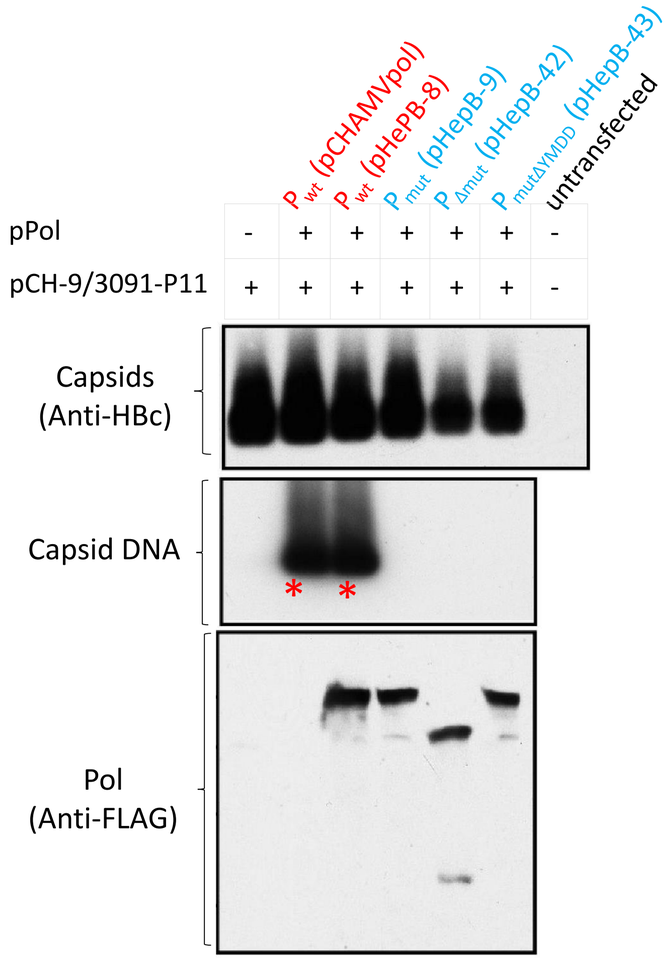


HBV Polymerase mutant (P_{mut}) is non-functional

Experiment 1



Experiment 2



*HBV DNA encapsidation associated with presence of functional HBV polymerase

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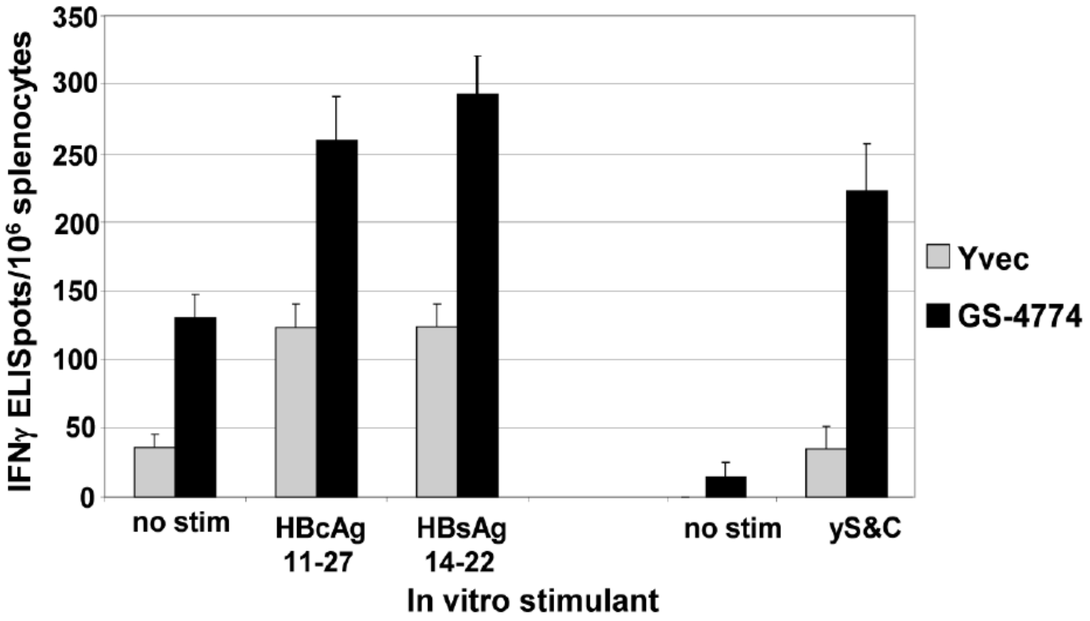
VTP-300 preclinical HBV-specific immunogenicity

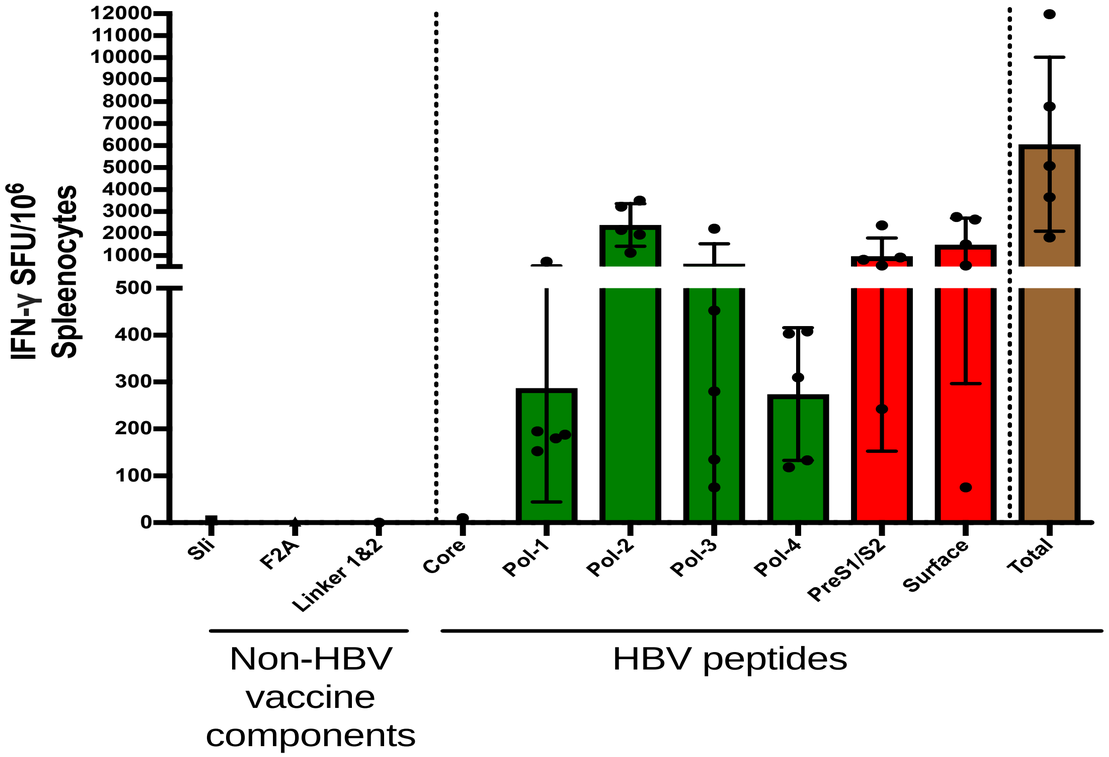
GS-4774 Yeast-based HBV vaccine[1]



1 King et al (2014) PLoS One, 9(7), p.e101904.

C57BL/6 mice vaccinated with GS-4774- or Yvec (empty vector control)

VTP-300



C57BL/6 mice vaccinated with ChAdOx-HBV and MVA-HBV[2]

2 Chinnakannan et al (2020) *Vaccines 2020, 8, 184*

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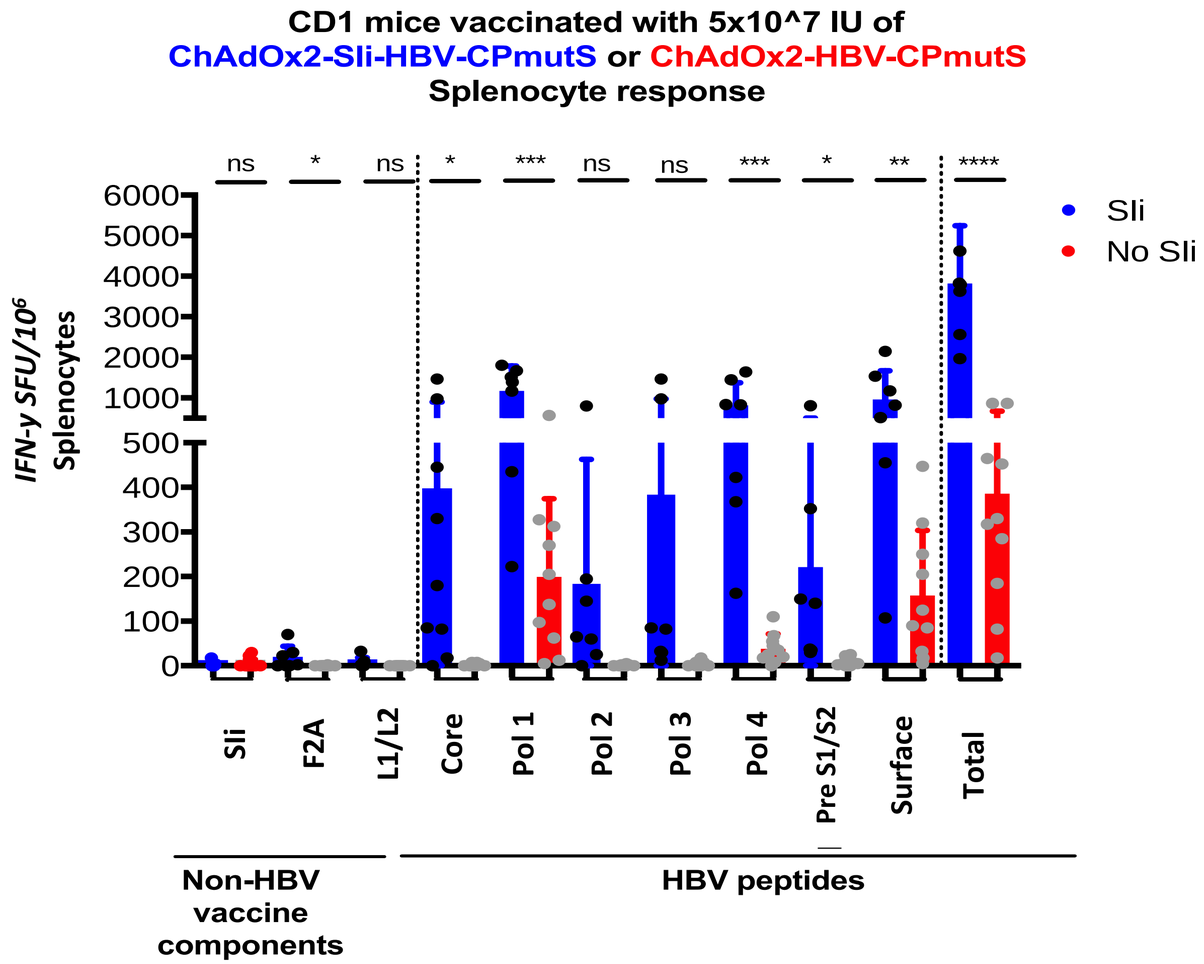
VTP-300: enhanced preclinical T cell and anti-HBs response

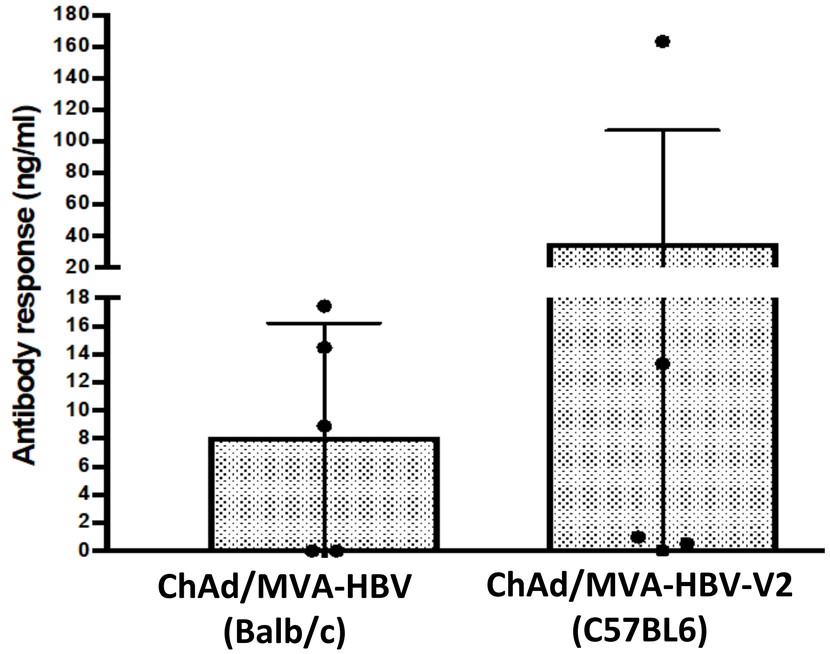
Enhanced immunogenicity

shark invariant chain (SIi) (in outbred mice)



Anti-HBs responses

(BALB/c and C57BL/6 mice)



Chinnakannan et al (2020) *Vaccines 2020, 8, 184*

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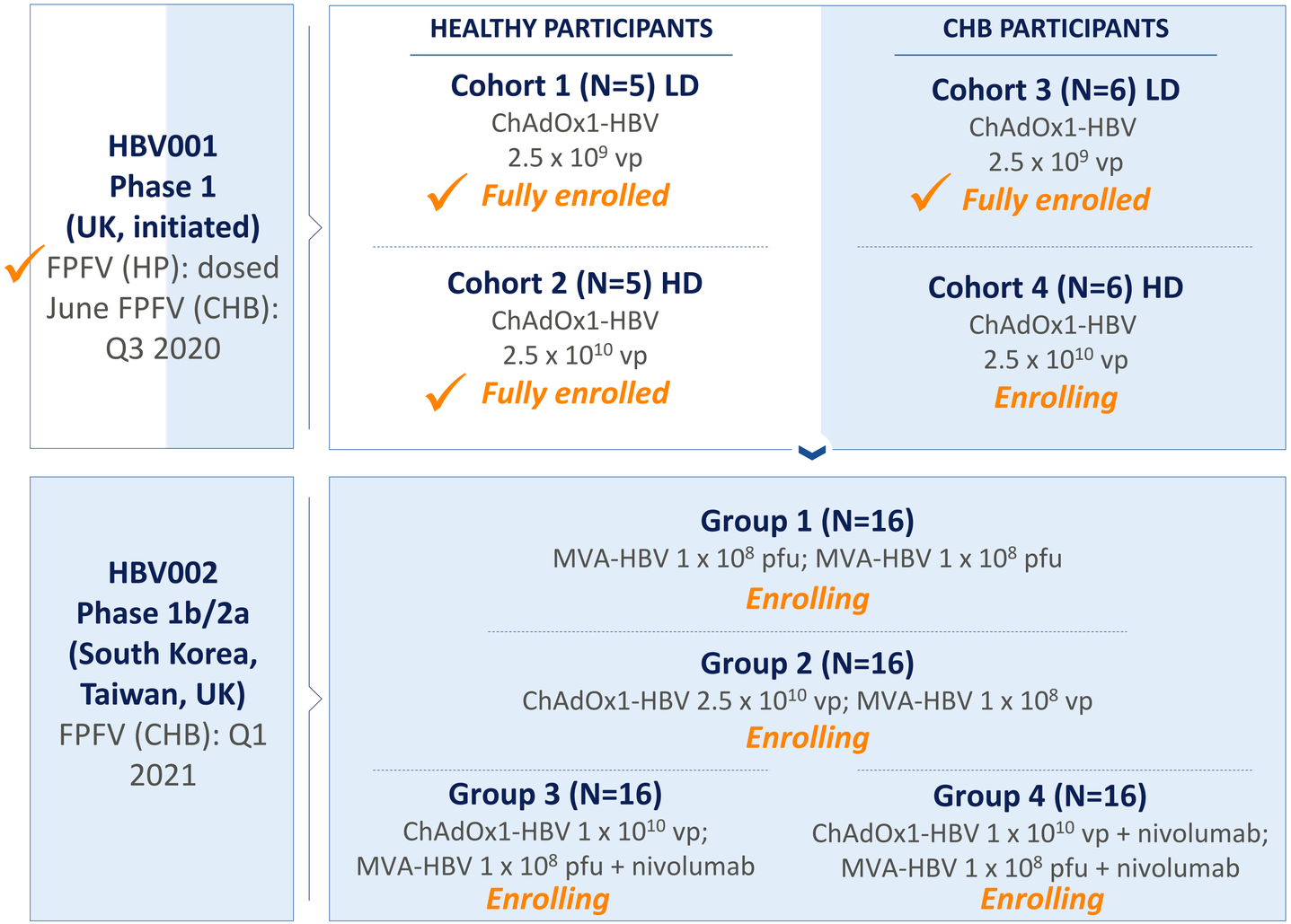
High Level Study Designs – HBV001 and HBV002



Inclusion Criteria

- HBV DNA <40 copies
- HBsAg <4,000 – 10,000 IU/mL
- On antivirals for 1 year

Study Outputs

- Safety and immunogenicity data from HBV001 and HBV002:
  - Healthy patients (HP) and CHB patients: Q4 2021

Healthy participants CHB participants

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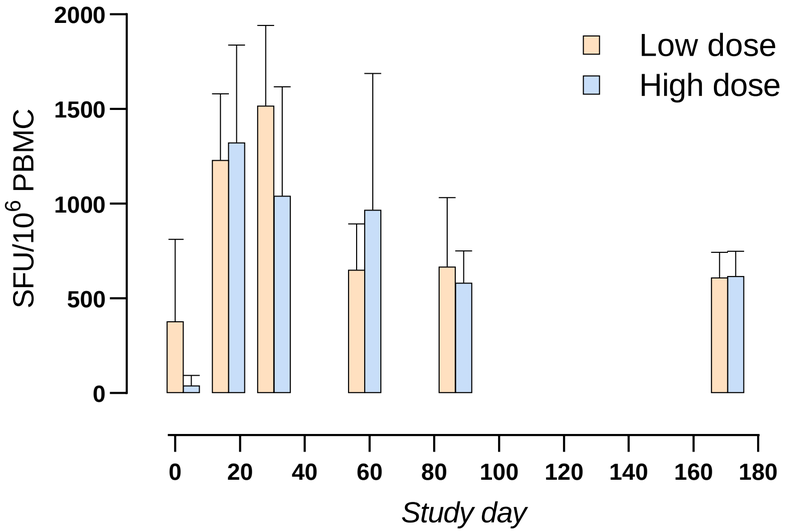
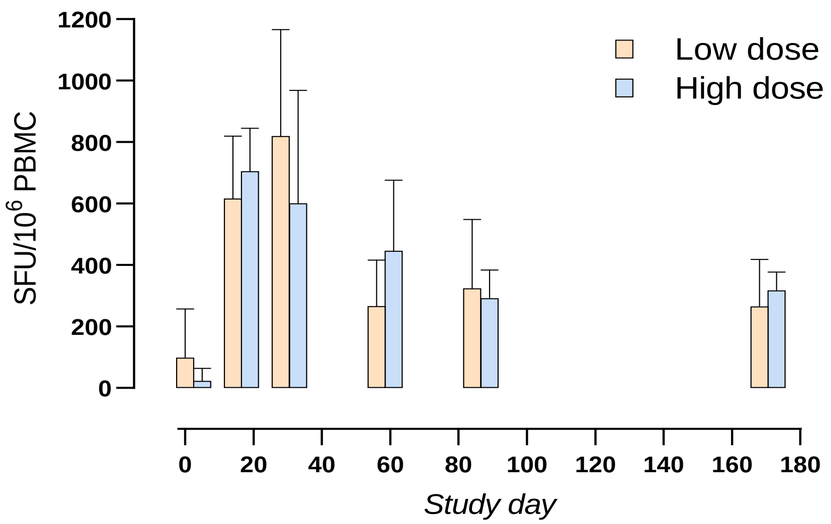
ELISPOT results HBV001 – Healthy controls

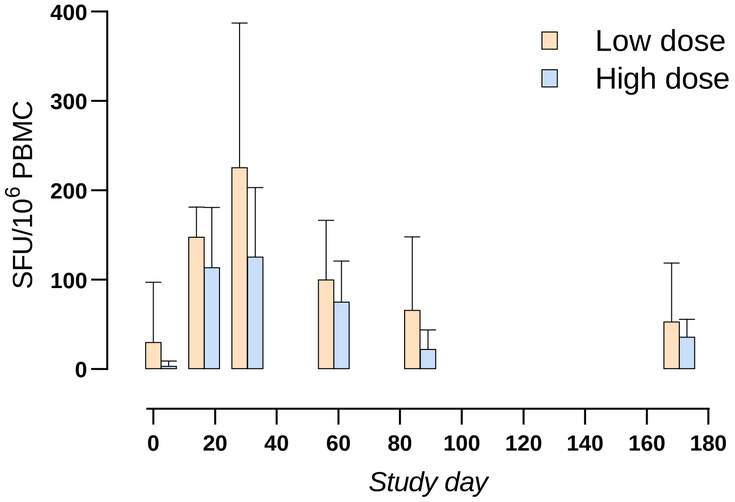
Summary data: total responses



Summary data: Core + Pol



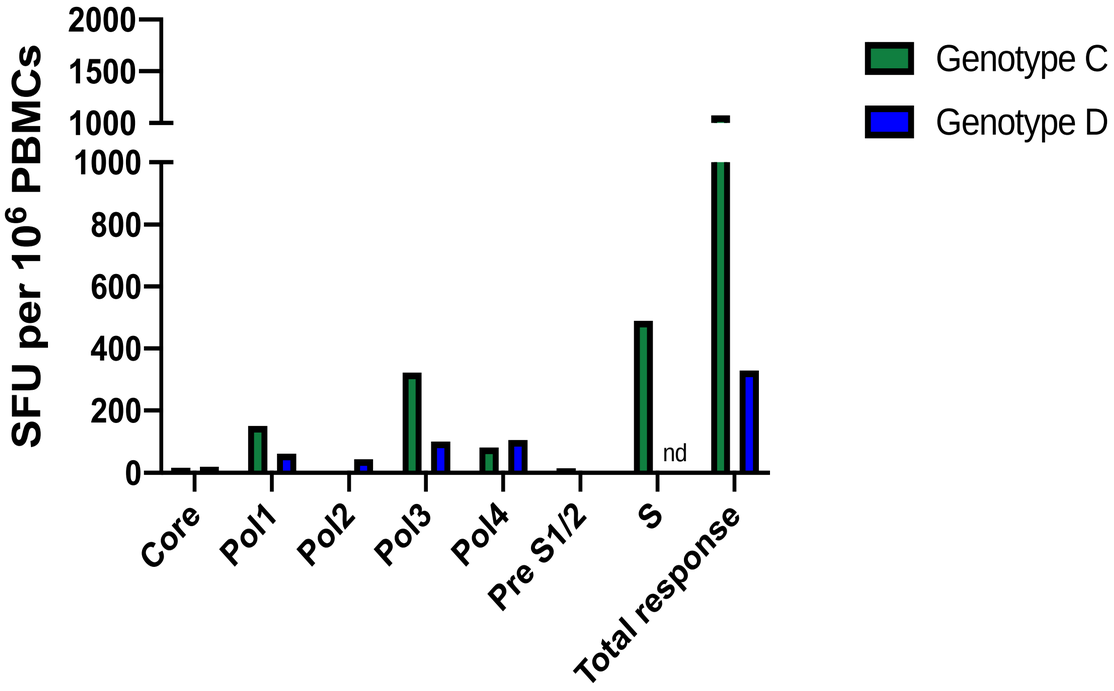
Summary data: Core alone

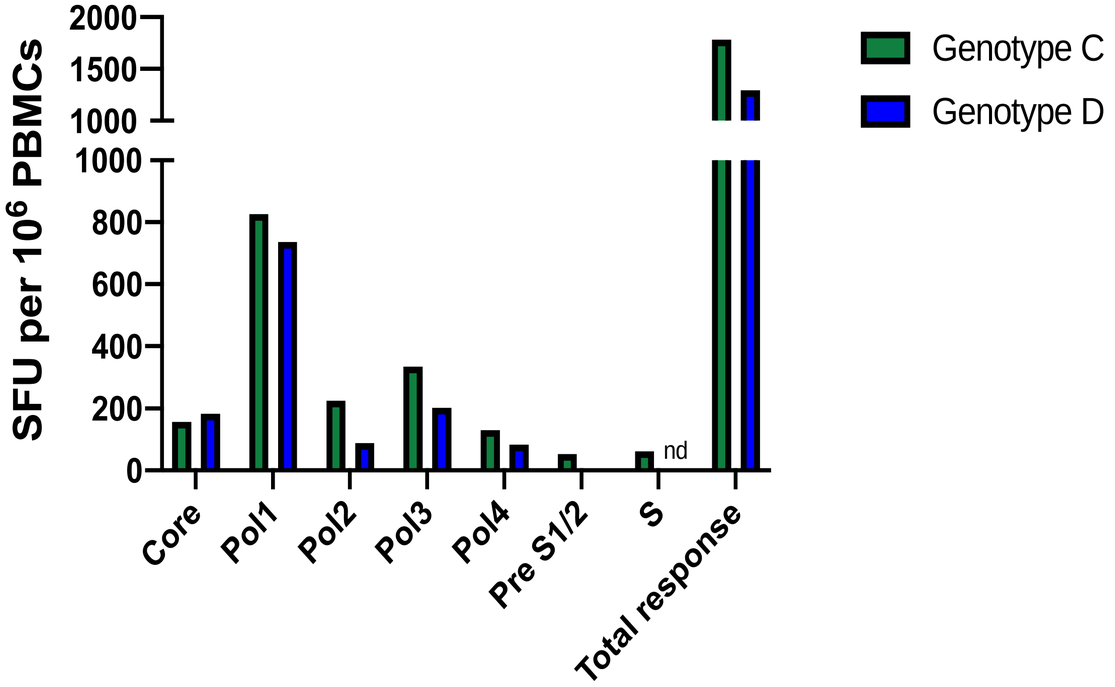


ELISPOT Results

- Single injection ChAdOx1-HBV resulted in a peak mean over 1,000 sfu/Million PBMCs
- No difference between high and low dose

ELISPOT results HBV001 – Healthy controls (two patients' fresh PBMC)





ELISPOT Results

- Fresh PBMCs Healthy volunteers d28 after high dose ChAdOx1-HBV
- ELISpot cross-reactivity between genotype C and genotype D peptide pools

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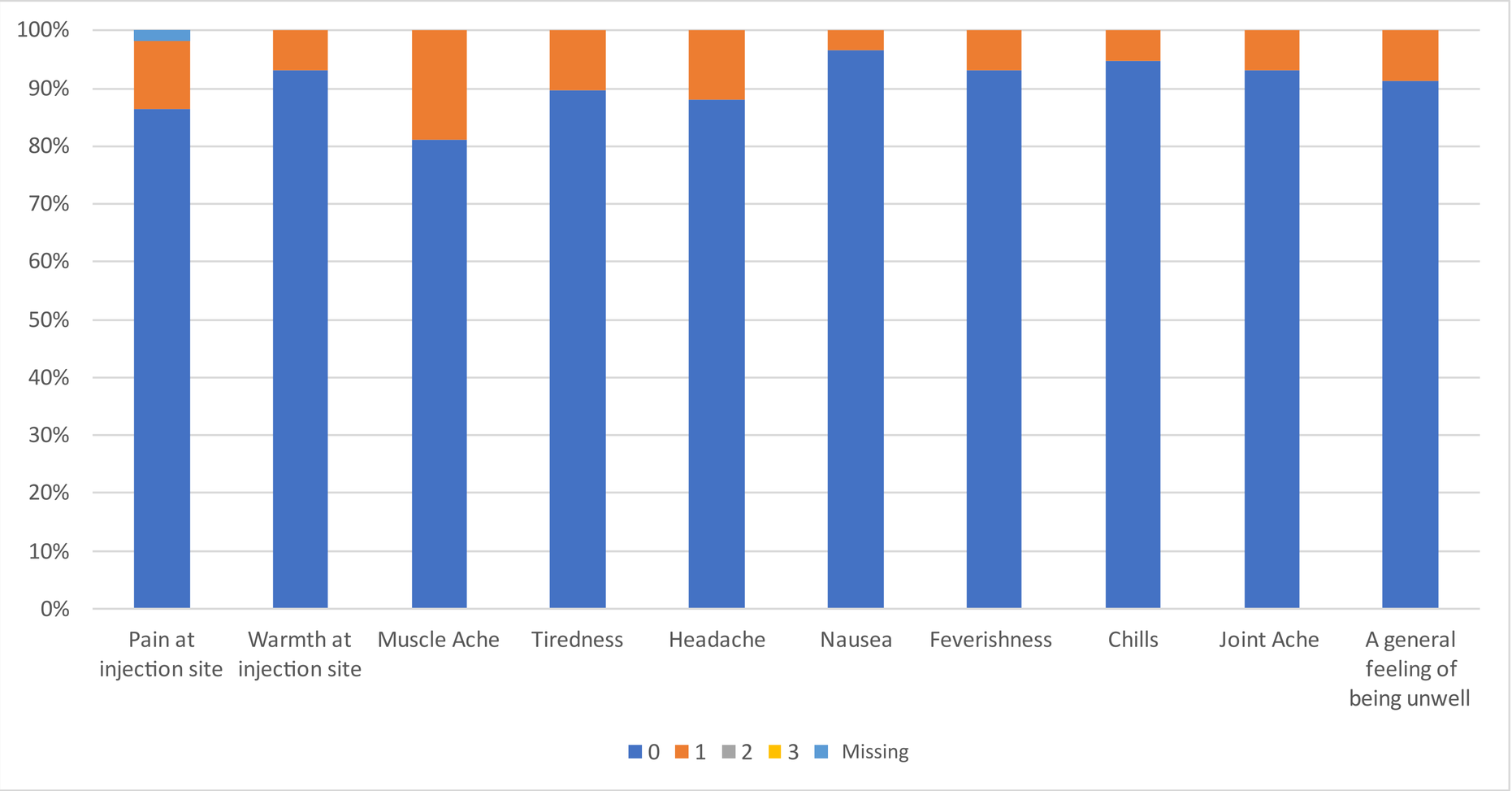
Post ChAdOx1-HBV (all days for group 2) in HBV002

All participants from Taiwan - 6 patients recorded 10 times over 7 days



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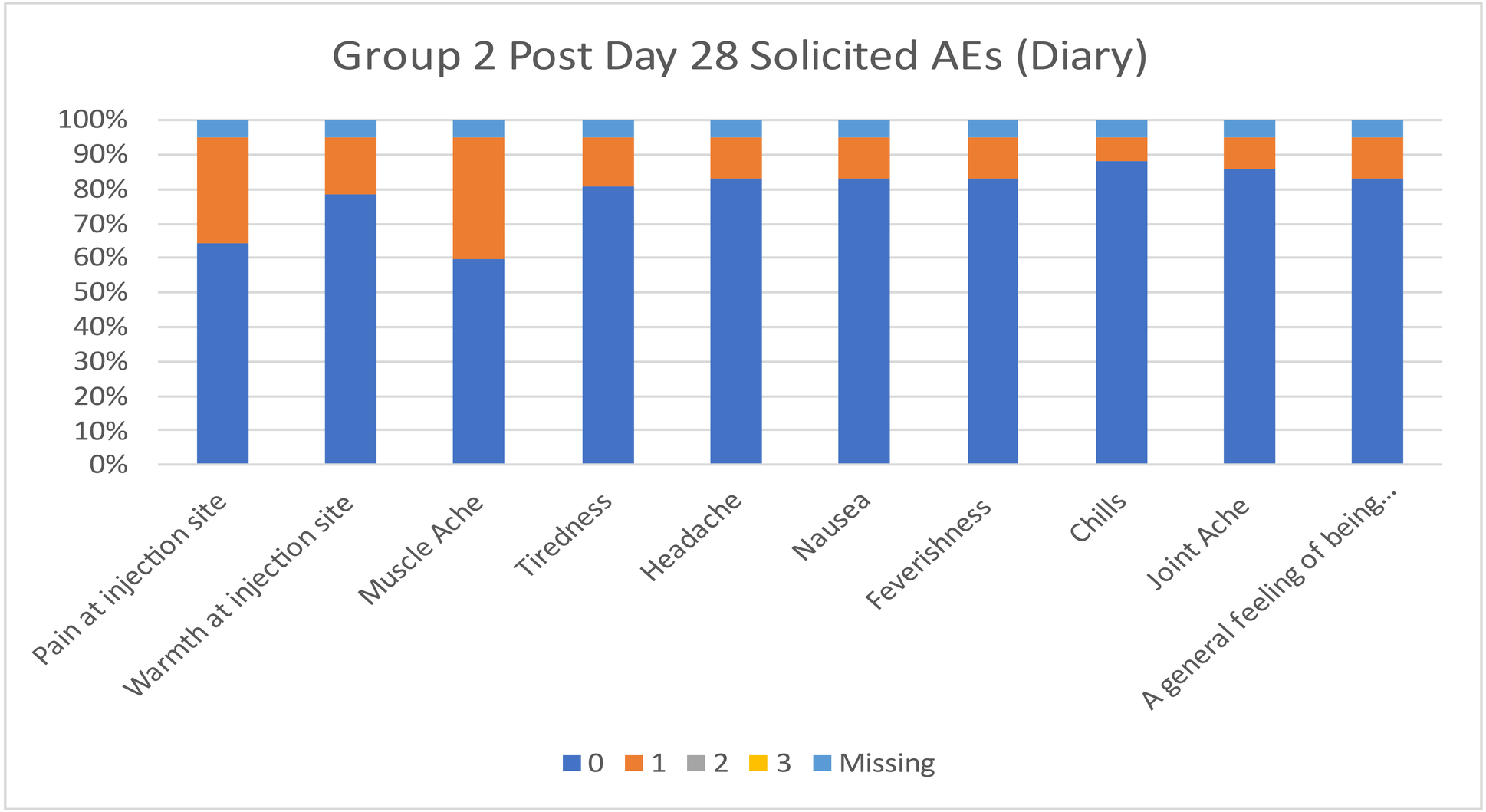
Post ChAdOx1-HBV (all days for group 2) in HBV002



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ChAdOx Anti-Vector Response is Transient, Not Impactful on Routine Vaccination

Real-World and Clinical Evidence

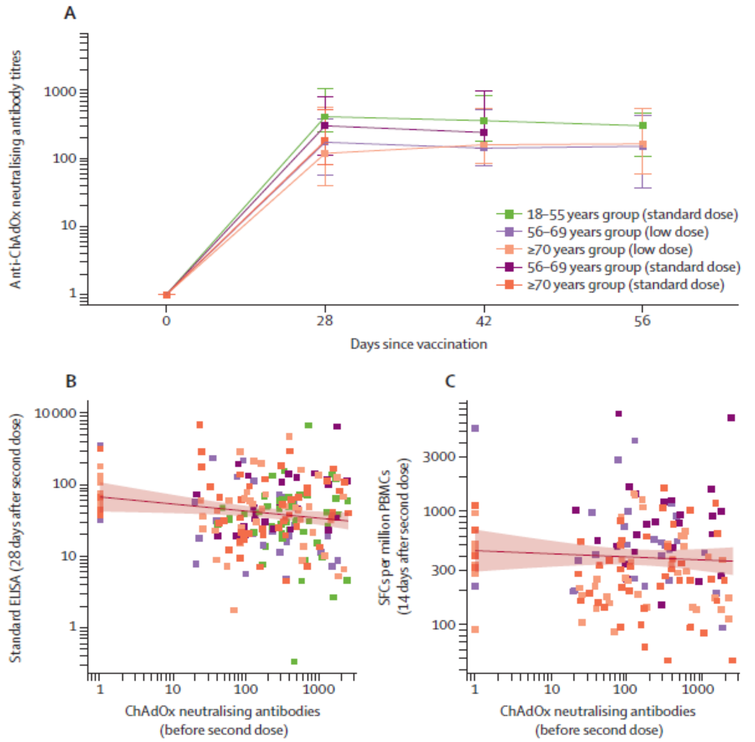
Growing real world and clinical evidence indicates:

- ChAdOx products can be boosted effectively using the same vector (COVID-19)
- The vector can be boosted against different diseases within a 12 week interval

'There was no difference in anti-spike antibody titres between individuals who had received a prior ChAdOx1 vectored vaccine and those who were naïve to ChAdOx1'

- Emary et al Lancet 2021

Anti-ChAdOx1 Vector Neutralising Titres After Prime and Boost Doses of Vaccine



The level of ChAdOx1 nCoV-19 neutralizing antibodies prior to vaccination is not associated with the subsequent response, especially prior to the second dose. This is true of all age groups

Source: Ramasamy et al., Lancet 2020

Summary of VTP-300 to date

HBV001

- 21 of 22 participants enrolled using ChAdOx1-HBV alone
- Initial presentation of full immunogenicity safety, and genotypic cross reactivity data, including CHB at AASLD

HBV002

- 30 patients enrolled in groups 1-4
- All 4 study arms now open
- Initial immunogenicity data AASLD

Study of VTP-300 with Arbutus-729 siRNA in advanced planning

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