Assessing and updating recombinant live vectored and inactivated vaccines to provide protection against antigenic drift of HPAI viruses

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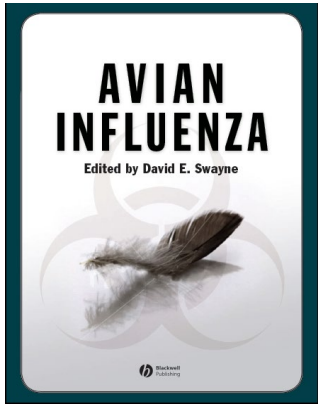
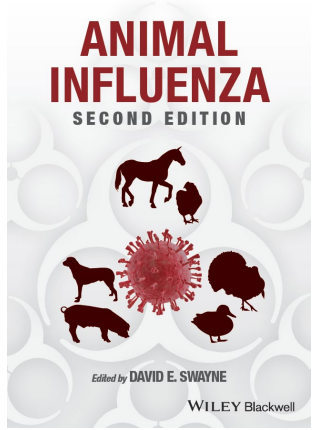
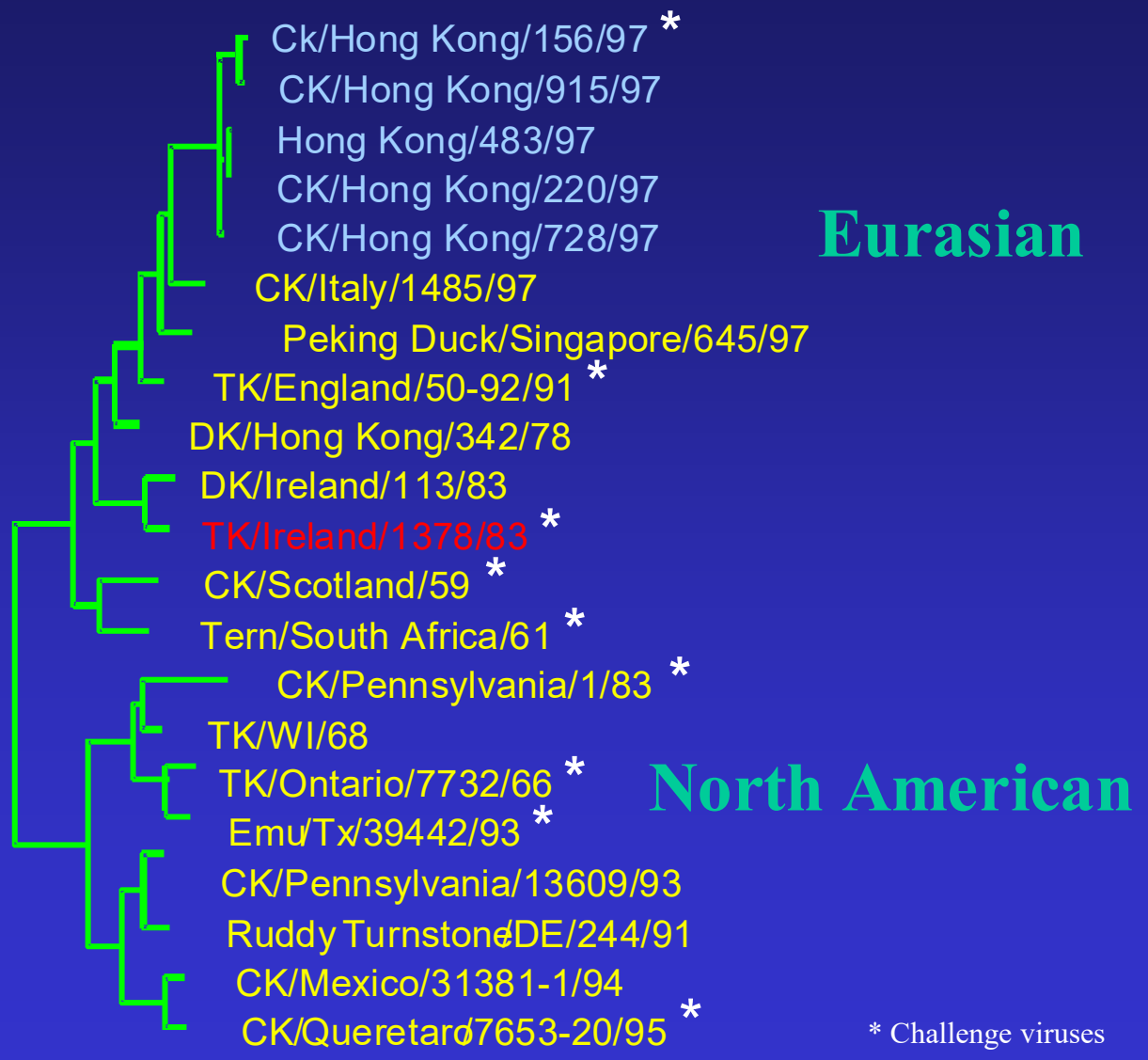


Acknowledge Contributions: M. Criado, K. Bertran, D.H. Lee, E. Spackman, D. Suarez, R, Fouchier, D. Smith, X Wan



H5 HPAI Vaccine Protection up to Late 1990's

- Historically, AI vaccines in poultry had broad protection within hemagglutinin subtype
- Pre-Gs/GD lineage H5N1 vaccination program
  - Fowl pox with H5 AIV gene insert Tk/Ireland/1378/83
  - Different challenge viruses (87.3-100% aa sequence similarity)



(Swayne et al., Vaccine 18:1088-1095. 2000)

H5 HPAI Vaccine Protection up to Mid-2000's

Homosubtypic Hemagglutinin Protection by AI Vaccines

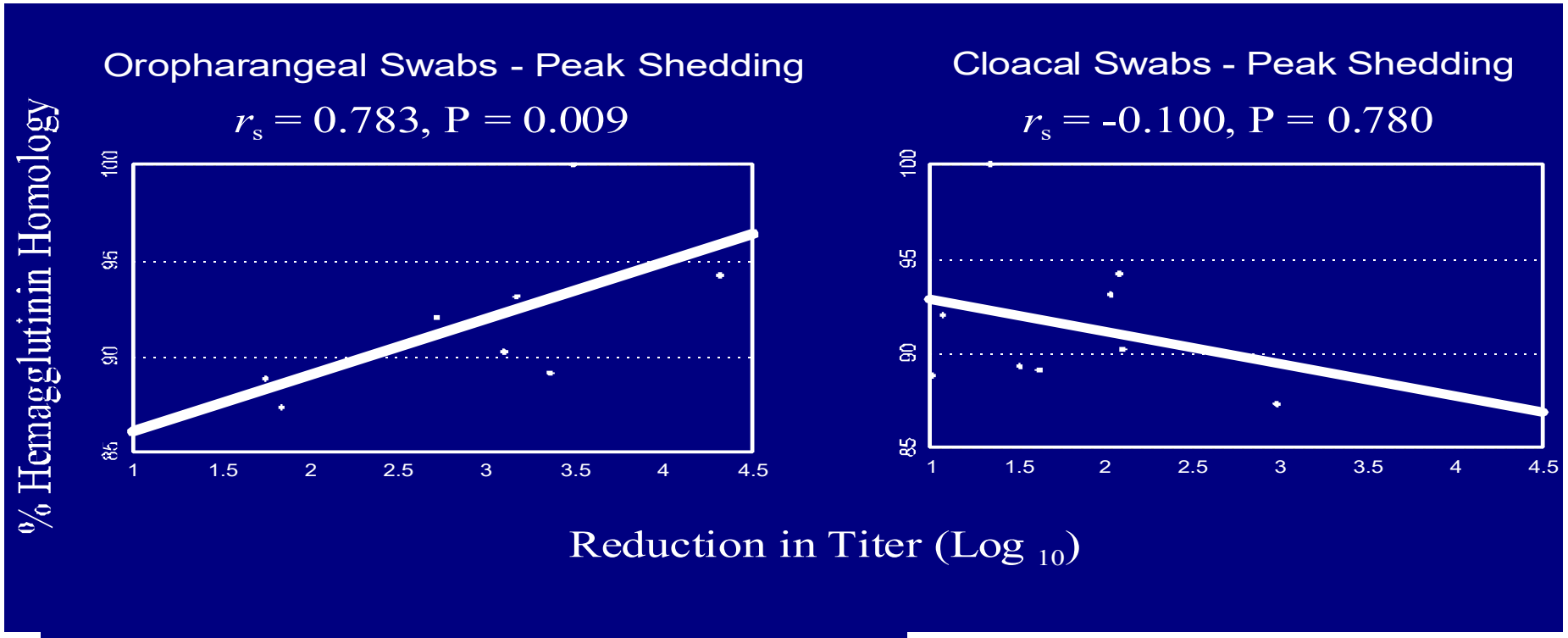
Chickens vaccinated SQ 1d with rFP-H5-Ire/83 and IN challenged at 3 wks with 10^{5-6} EID_{50} of HPAIV

Challenge Virus	Subtype	HA Similarity to Tk/Ire/83	Mortality (MDT)
Ck/Scotland/59	H5N1	92	0/10
Tern/S. Afr/61	H5N3	93.1	0/10
Tk/Ontario/66	H5N9	89.1	0/10
Ck/PA/83	H5N2	87.3	0/10
Tk/Ireland/83	H5N8	100	0/10
Tk/England/91	H5N1	94.2	0/10
Ck/Queretaro/95	H5N2	89.3	0/10
HK/156/97	H5N1	90.2	0/10
Ck/S. Korea/03	H5N1	89.9	0/10
ck/Vietnam/04	H5N1	88.4 est	0/22
WS/Mongolia/05	H5N1	89.7	1/8
Control	-	-	80-100%

- **Excellent, broad, homosubtypic protection from mortality by H5 AIV vaccine**

Protection in the Face of Changing H5 HPAIV

- 100% protection from clinical signs and death
- Variable reduction in shedding of challenge virus



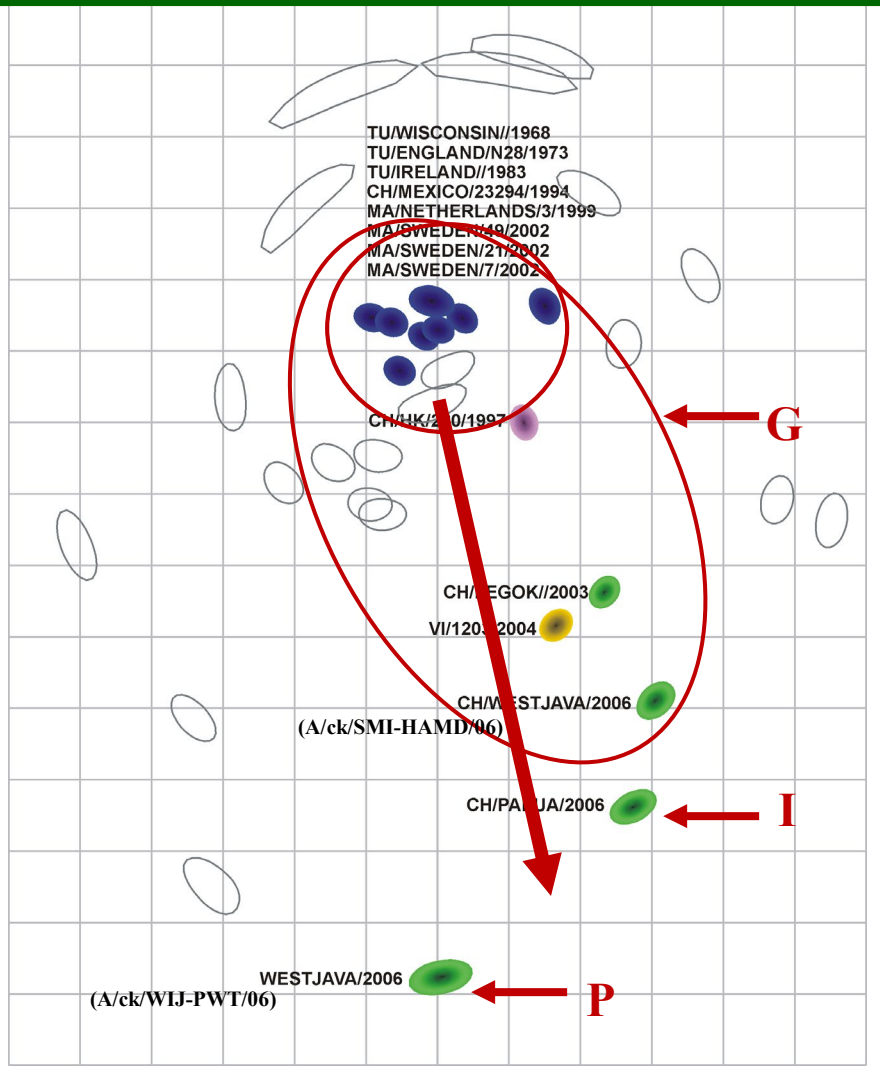
(Swayne et al., Vaccine 18:1088-1095. 2000)

Antigenic Drift in Gs/GD H5 HPAIV Lineage: Impact on Vaccine Efficacy

Antigenic Drift (Changing Virus):

Inactivated Vaccine Seed Strains - Indonesia

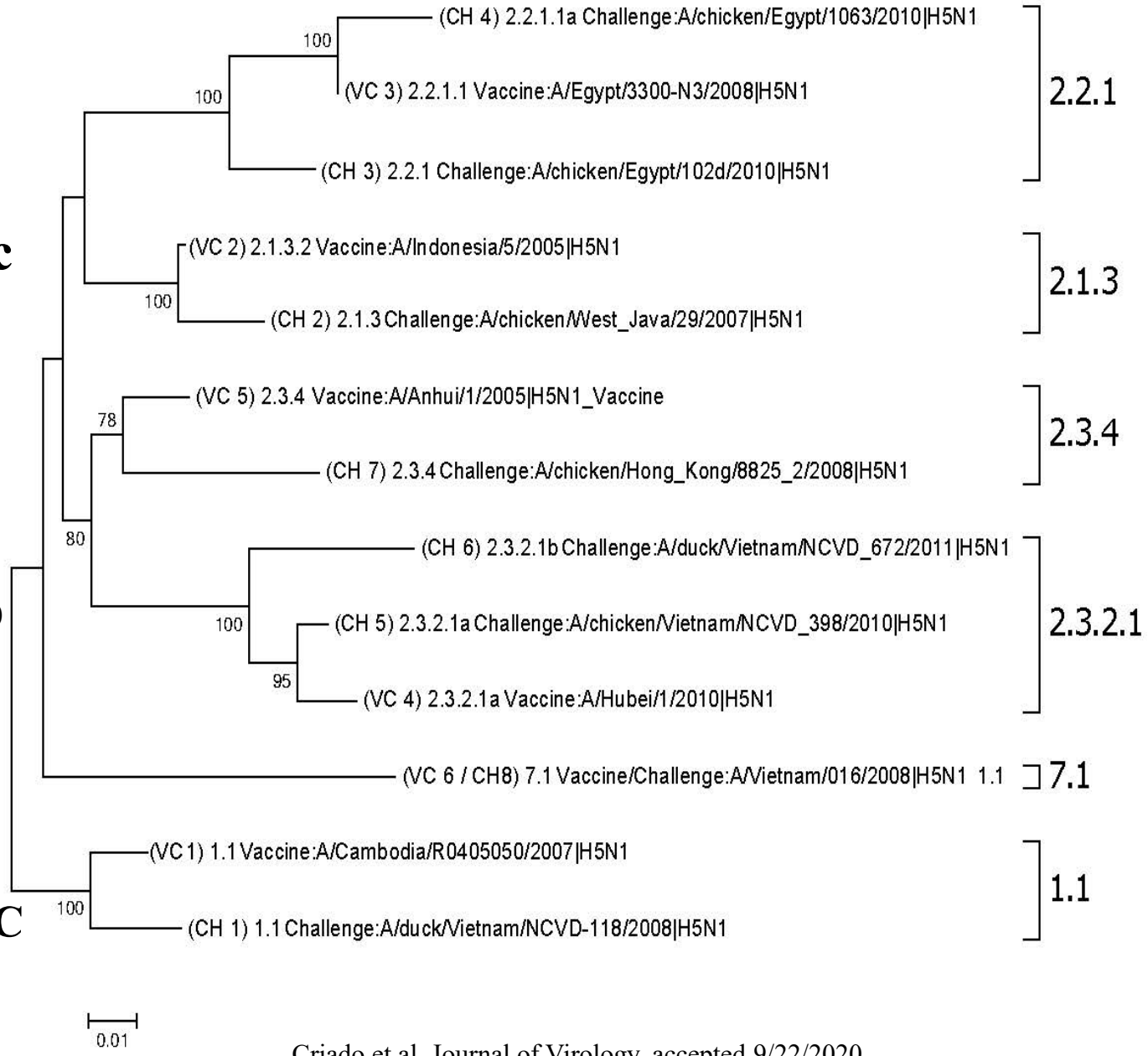
- Historical H5 Vaccines – Similar antigenicity
- Drifting of HA away from root
  - Good protection: Ck/HK/220/97, Ck/Legok/03, VN/1203/04, Ck/WJ/HAMD/06
  - Intermediate protection: Ck/Papua/06
  - Poor protection: PWT/06



Swayne et al. J. Virol 2015

1. Protection in early 2010's: Inactivated Vaccine Study

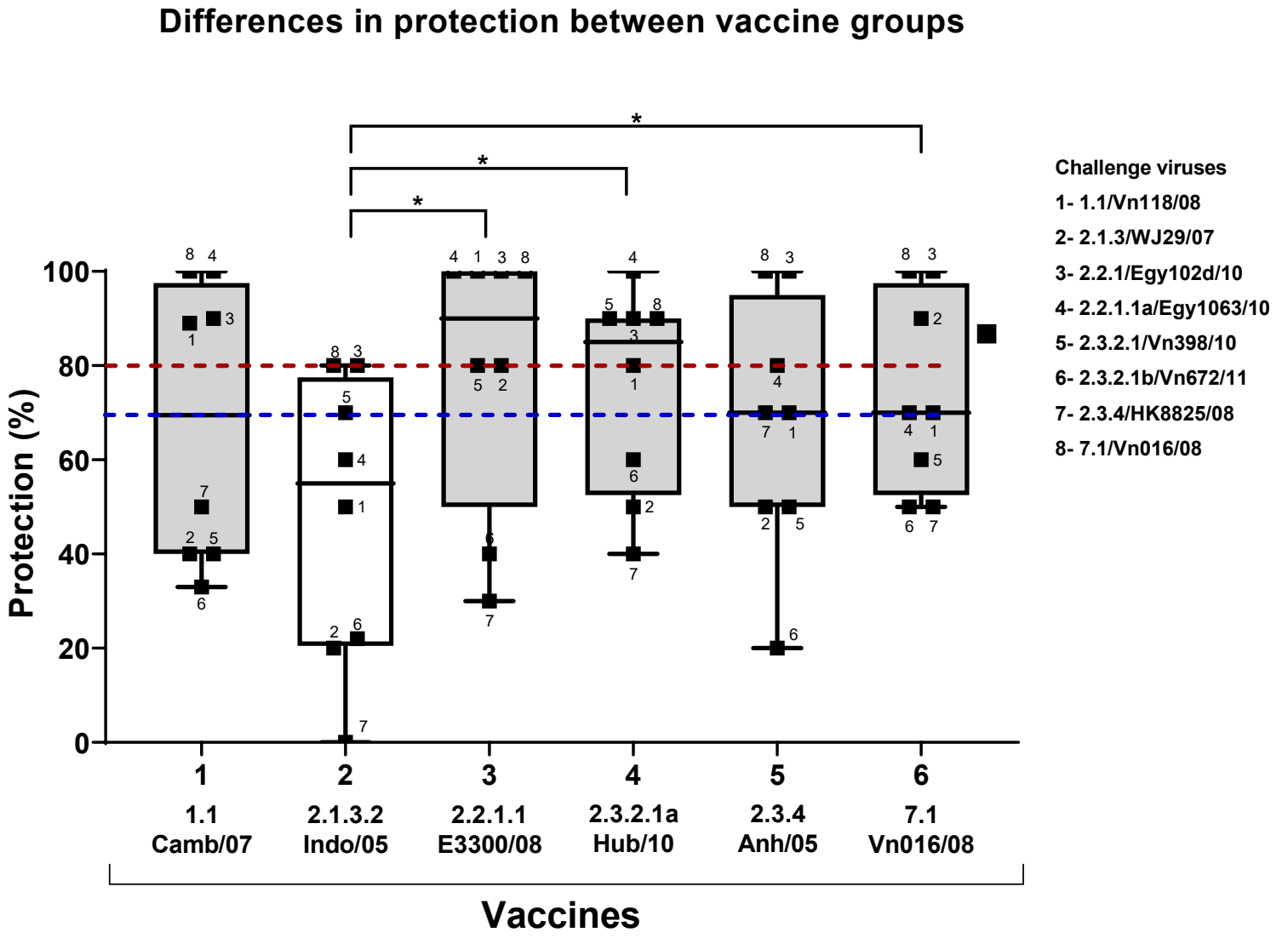
- Examine antigenically diverse Gs/GD H5 vaccines seeds (WHO prepandemic seeds) and diverse challenge viruses
- Experimental Design:
  - 6 vaccine seeds – vaccinated 3 wk-old WL chickens (512 HAU), oil-in-water emulsified vaccine
  - 8 challenge viruses – challenged 10^6 EID_{50} 6 wk-old and terminated 8 wk-old
  - Clinical signs, mortality and mean death times
  - Collected serum day of challenge and 14 DPC for HI titers (vaccine and challenge virus), and oropharyngeal swabs on 2 DPC for qRRT-PCR (minimum detection 1.7-2.5log10 EID_{50})



Criado et al. Journal of Virology, accepted 9/22/2020

Protection in early 2010's: Inactivated Vaccine Study

- Nearly half (47.92%, n=23) of the forty-eight combinations of vaccine/challenge viruses examined had bird protection (survival) of 80% or above
- 2.1.3.2 had narrowest protection
- 2.2.1.1 had the broadest protection
- Most vaccinated groups had prolonged mean death time (MDT)



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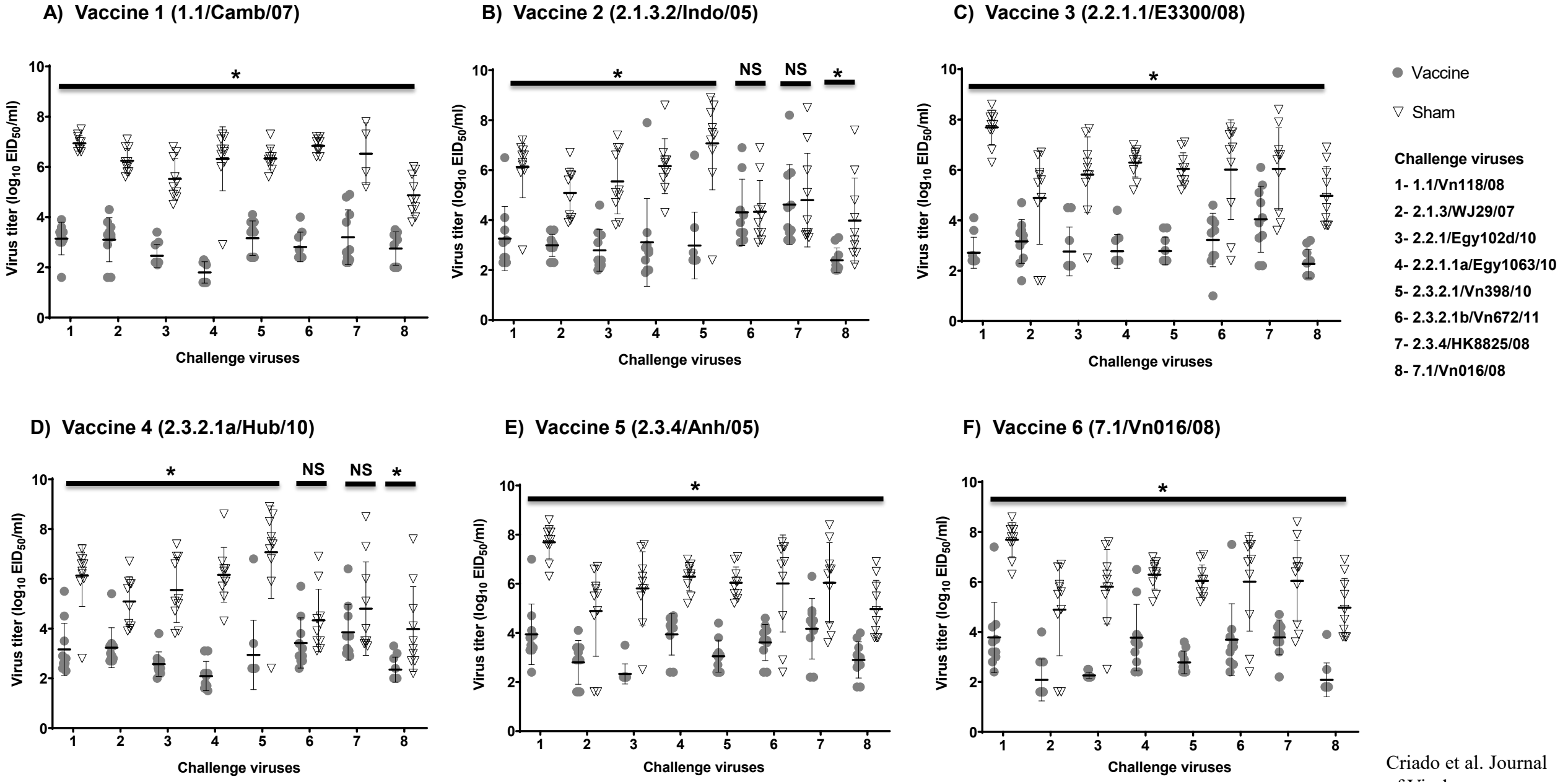

In most groups - virus shedding titers were significantly lower compared to the sham group ($p \leq 0.05$)

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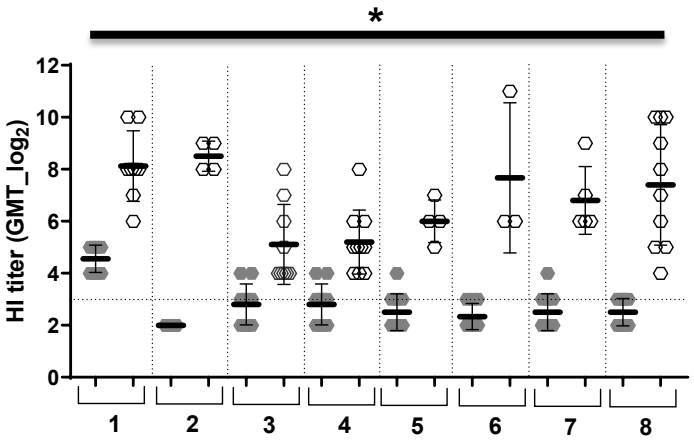
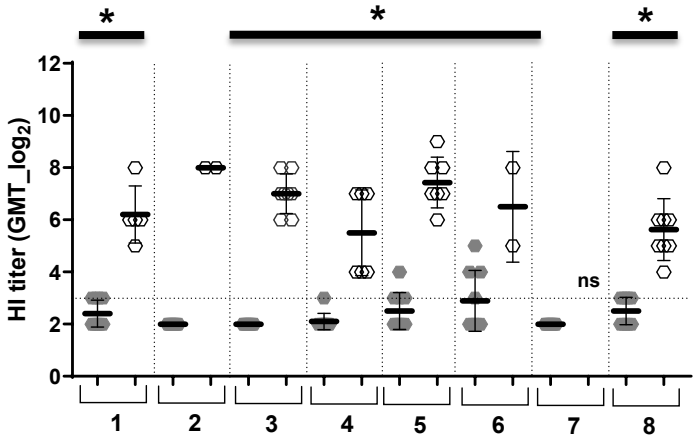
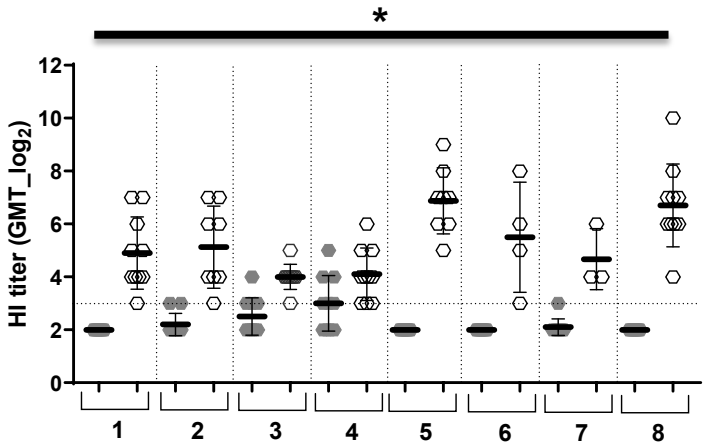
A) Vaccine 1 (1.1/Camb/07): challenge virus as antigen



B) Vaccine 2 (2.1.3.2/Indo/05): challenge virus as antigen



C) Vaccine 3 (2.2.1.1/E3300/08): challenge virus as antigen



Pre-challenge sera

Post-challenge sera

Challenge viruses

1- 1.1/Vn118/08

2- 2.1.3/WJ29/07

3- 2.2.1/Egy102d/10

4- 2.2.1.1a/Egy1063/10

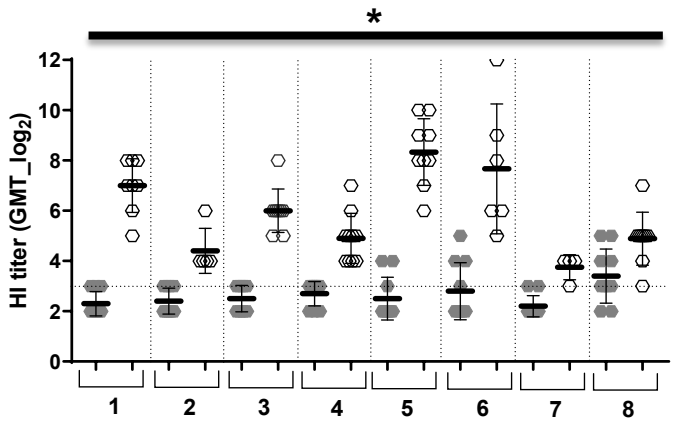
5- 2.3.2.1/Vn398/10

6- 2.3.2.1b/Vn672/11

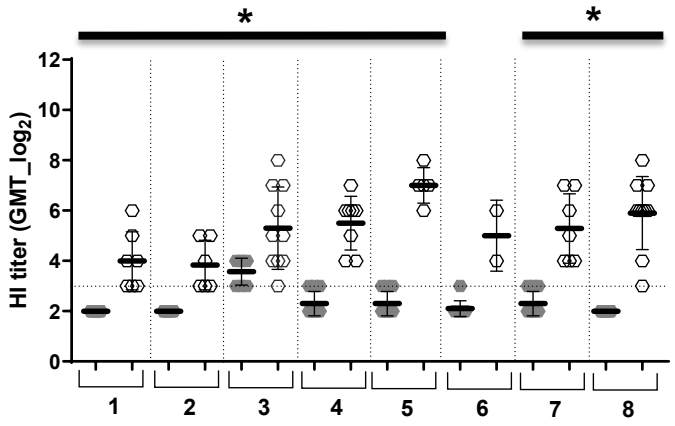
7- 2.3.4/HK8825/08

8- 7.1/Vn016/08

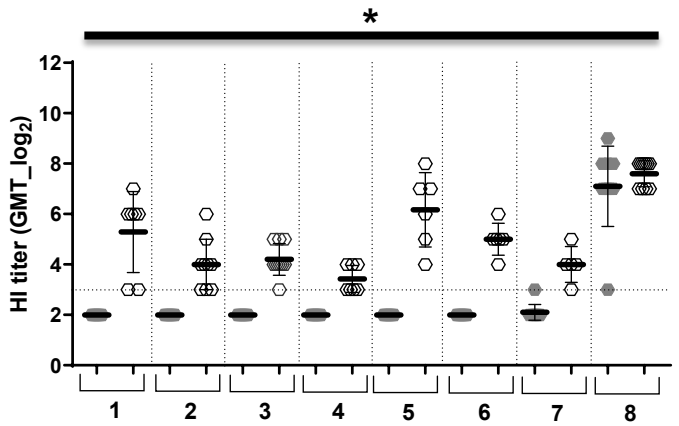
D) Vaccine 4 (2.3.2.1a/Hub/10): challenge virus as antigen



E) Vaccine 5 (2.3.4/Anh/05): challenge virus as antigen



F) Vaccine 6 (7.1/Vn016/08): challenge virus as antigen



- **Most vaccinated birds had high HI antibody titers against homologous vaccine antigen**
- **Most vaccinated birds had lower or no antibody titer against the challenge virus antigen**

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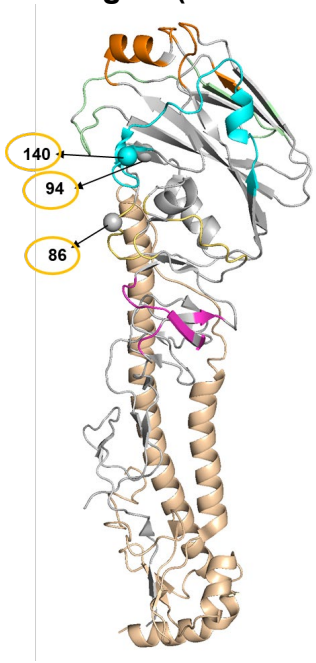
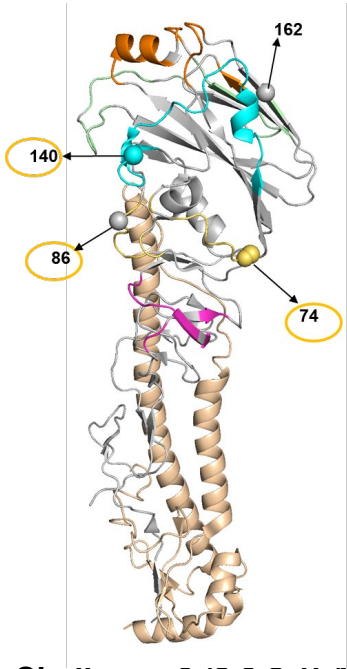
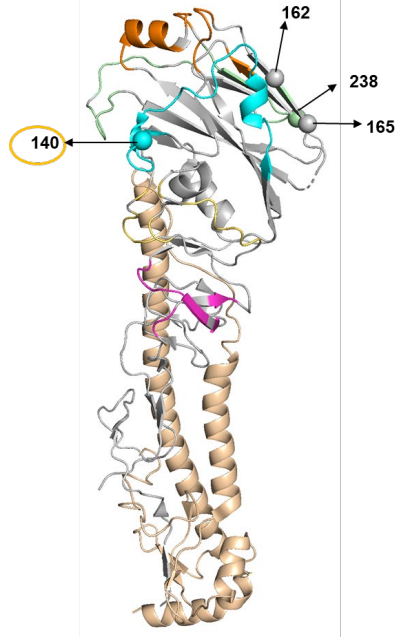
Challenge 1 (1.1/Vn118/08)



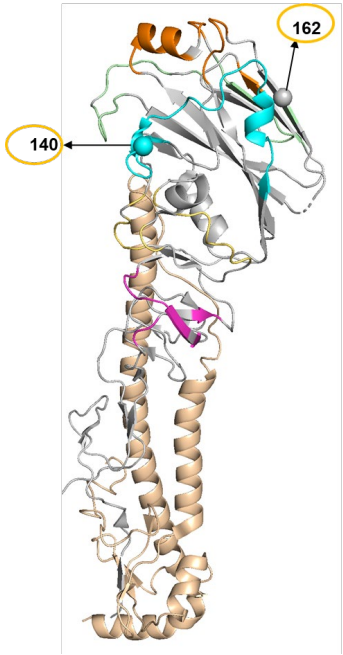
Challenge 2 (2.1.3/WJ29/07)



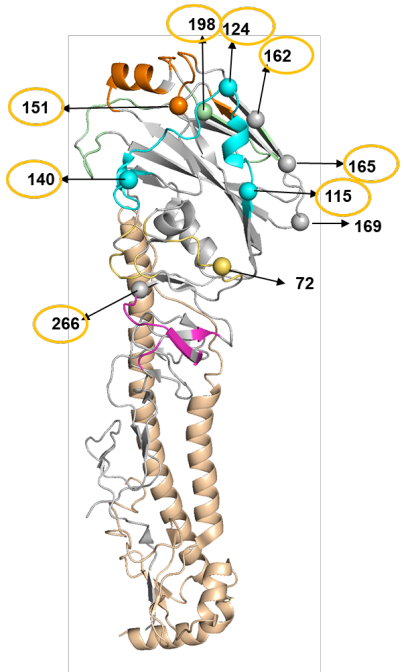
Challenge 4 (2.2.1.1a/Egy1063/10)



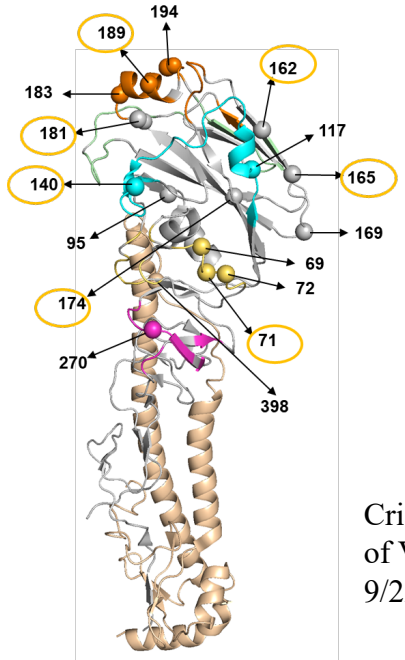
Challenge 5 (2.3.2.1/Vn398/10)



Challenge 6 (2.3.2.1b/Vn672/11)



Challenge 7 (7.1/Vn016/08)



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Antigenic changes associated with resistance:

- **Antigenic changes spread across epitopes A-E and adjacent sites of hemagglutinin - amino acid changes in 27 specific locations**
- **Previously reported antigenic changes were identified in positions 86, 94, 124, 140, and 189 plus an additional 22 sites**
- **Position 140 were predominant and strongly associated with the loss of vaccine protection**
- **Position 162 were also detected and negatively associated with vaccine protection**
- **Changes in glycosylation sites that potentially mask antigenic epitopes**

Determine if live vectored vaccine can provide broader protection than inactivated vaccine across diverse lineages of H5 HPAI challenge

Vaccines

Inactivated whole influenza vaccine (rgH5N1) – PR8 Backbone **HA** gene from **A/Gyrfalcon/Washington/40188-6/2014, H5N8 clade 2.3.4.4, HPAIV**
Live vectored vaccine (rHVT-H5) **HA** from **A/Gyrfalcon/Washington/40188-6/2014, H5N8 clade 2.3.4.4, HPAIV**

Challenge Viruses (H5 HPAIV)

1- A/turkey/Minnesota/12582-1/2015, H5N2 clade **lineage 2.3.4.4a**

2- A/chicken/Vietnam/NCVD-14-A324/2014, H5N6 clade lineage **2.3.4.4d**

3- A/duck/Vietnam/NCVD_672/2011, H5N1 clade lineage **2.3.2.1b**

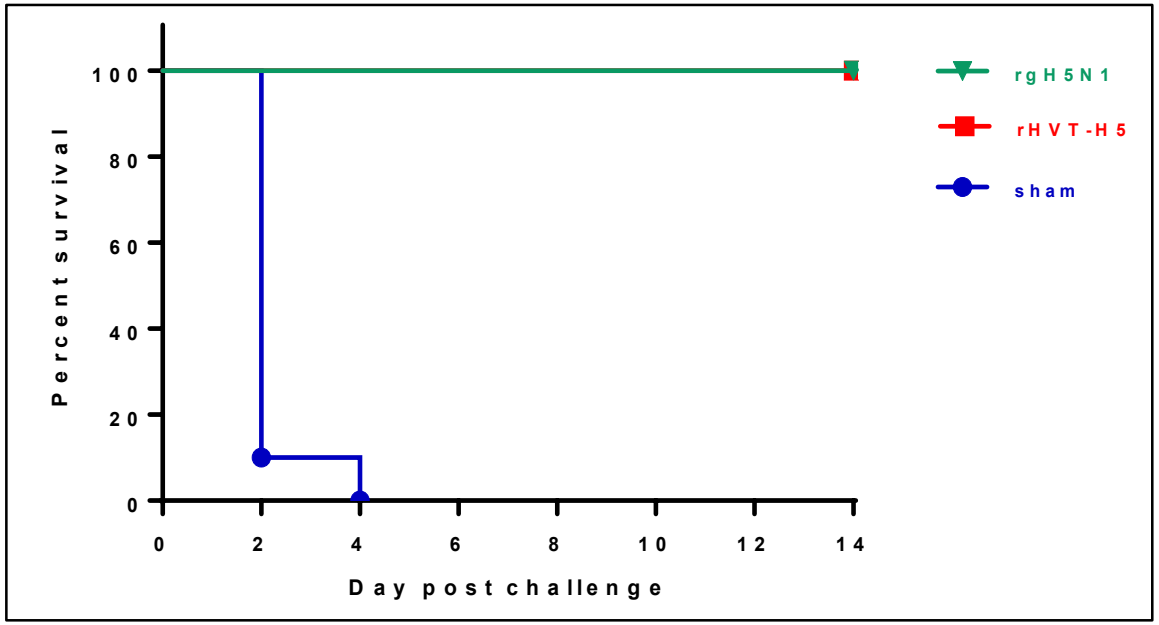
4- A/chicken/West_Java/29/2007, H5N1 clade lineage **2.1.3**

5- A/chicken/Queretaro/14588-19/1995, H5N2 **Mexican lineage**

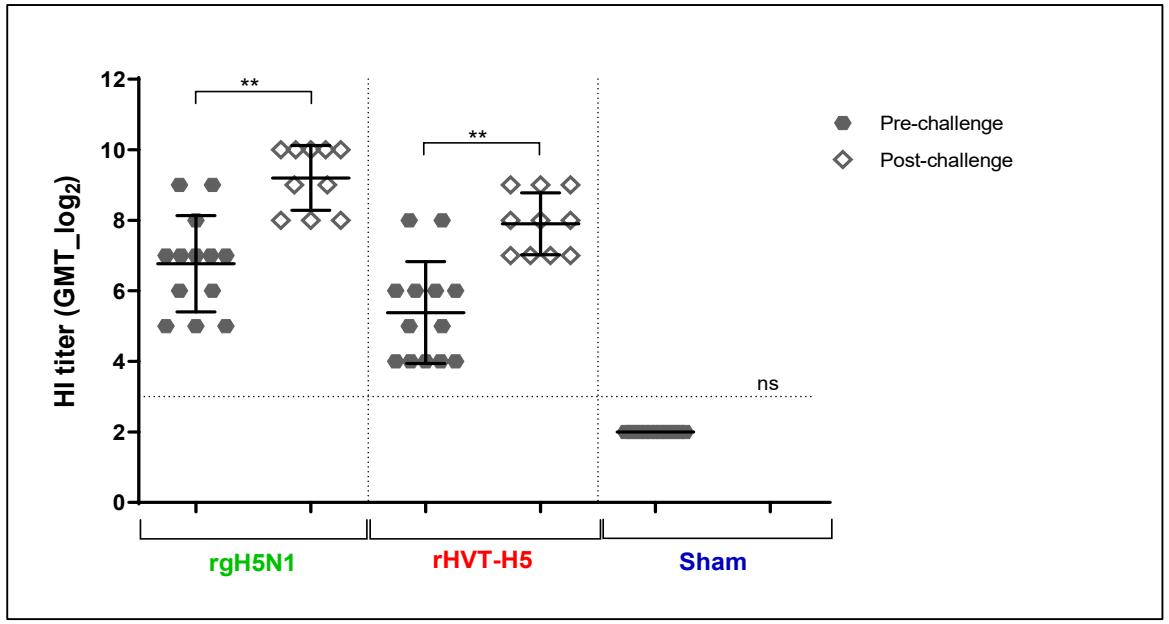
Similar results were observed for SPF WL chickens challenge with

A/chicken/Vietnam/NCVD-14-A324/2014 (2.3.4.4d), H5N6 HPAIV and

A/chicken/Queretaro/14588-19/1995 (N. American), H5N2 HPAIV



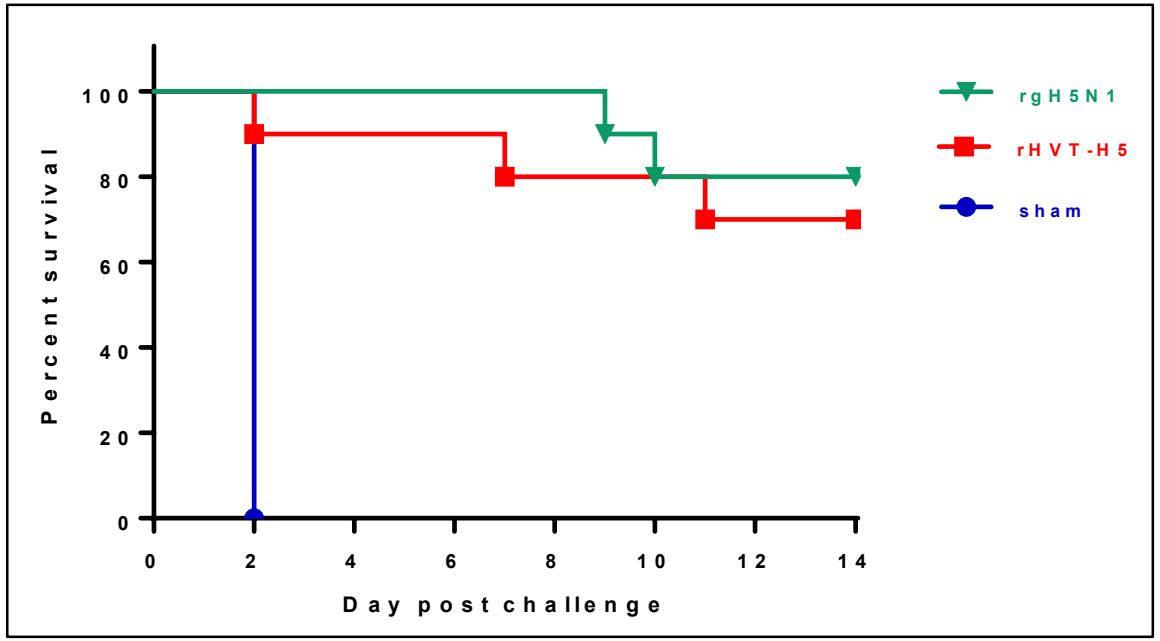
Vaccinated birds were protected against mortality and morbidity of HPAIV.



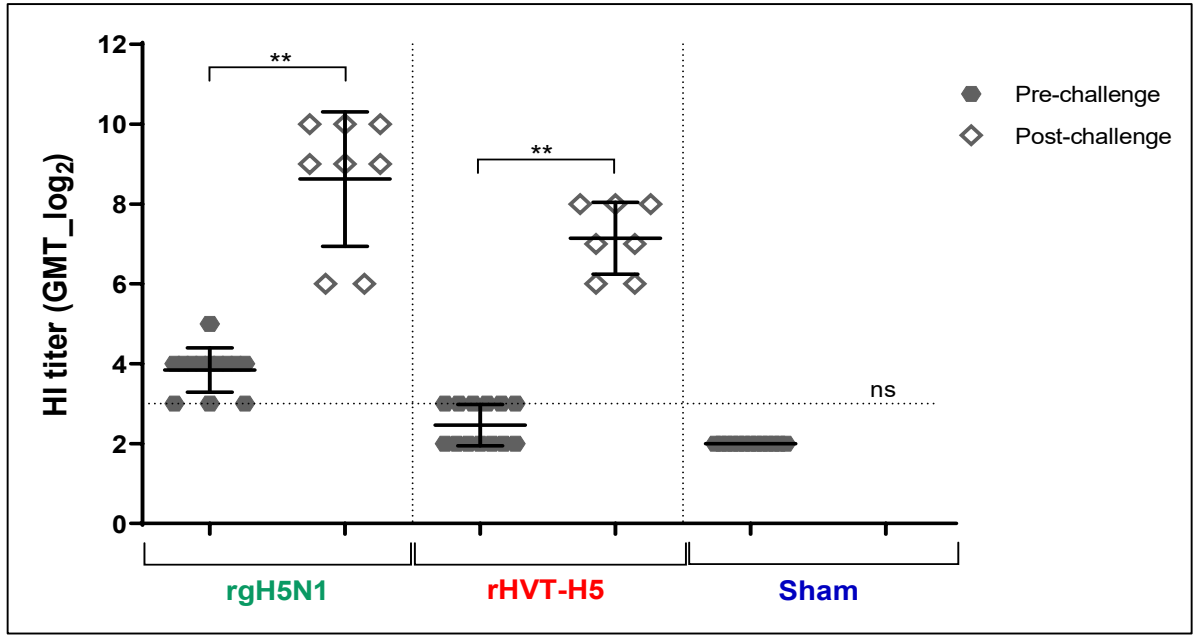
Vaccinated birds had pre- and post-challenge HI antibodies against the challenge antigen, which were protective.

SPF WL chickens challenged with A/chicken/West Java/29/2007 (2.1.3), H5N1 HPAIV

Mortality and morbidity



Antibody levels

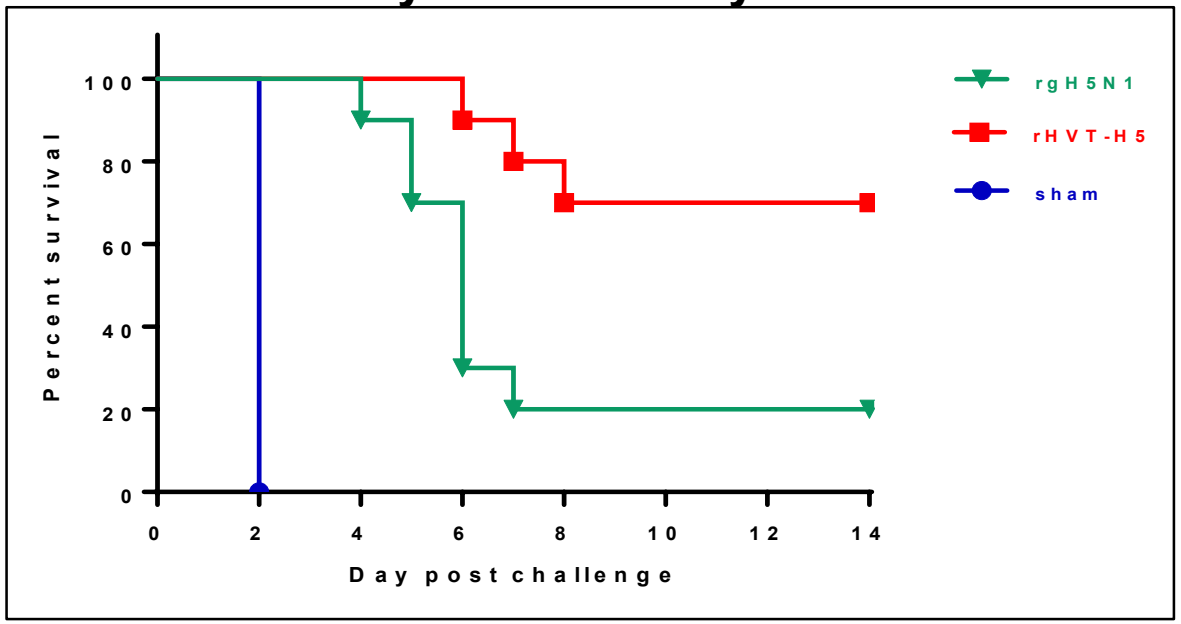


The rgH5N1 vaccinated birds had 80% protection and rHVT-H5 vaccinated birds provided 70% protection against the challenge virus.

Vaccinated birds had low levels of pre- challenge antibodies against the challenge antigen. Birds that survived had significant increase in the post-challenge antibody levels compared to pre-challenge.

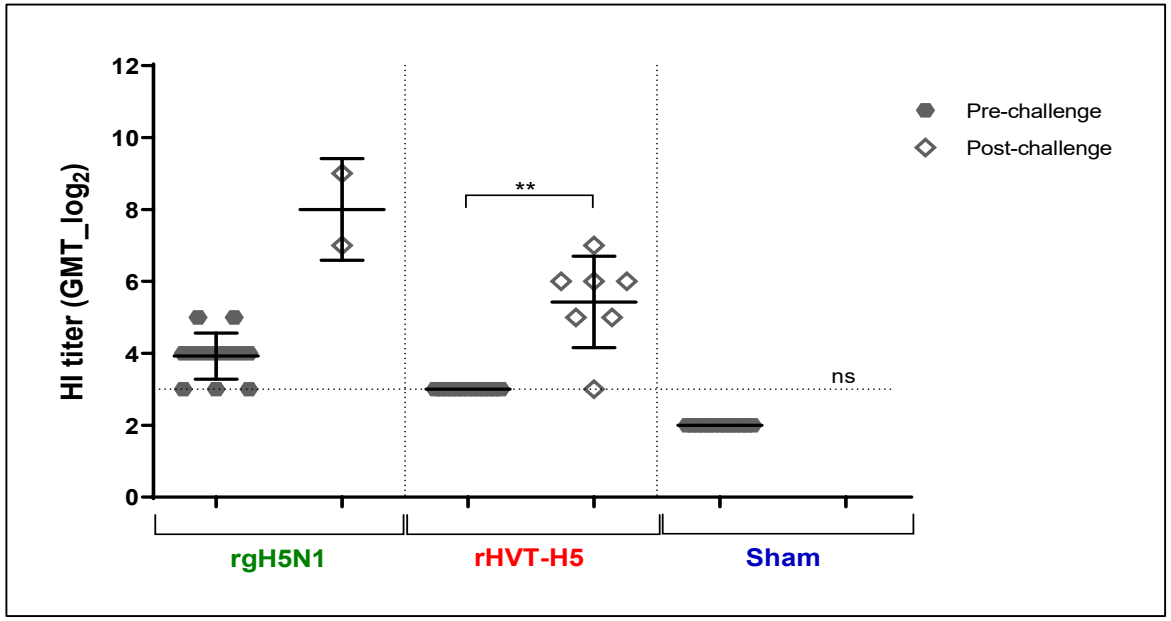
SPF WL chickens challenged with A/duck/Vietnam/NCVD-672/2011 (2.3.2.1b), H5N1 HPAIV

Mortality and morbidity



The rgH5N1 vaccinated birds had 20% protection and rHVT-H5 vaccinated birds provided 70% protection against the challenge virus.

Antibody levels



Vaccinated birds had low levels of pre- challenge antibodies against the challenge antigen. Birds that survived had increase in the post-challenge antibody levels compared to pre-challenge.

SUMMARY

1- Results showed all challenge groups vaccinated with the rHVT-H5 had 70-100% protection. In contrast, the inactivated vaccine (rgH5N1) provided protection ranging 20-100%.

2- Independent of the vaccine and challenge virus used the OP and CL shedding was significantly reduced compared to the sham group.

3- The presence of pre-challenge antibodies titers was associated with protection, but lack of titers, especially in recombinant vaccinated chickens, was not associated with mortality

Biotechnology to Address Genetic Drift

Homosubtypic HA Protection by AI Vaccines

Chickens vaccinated SQ 1d with recombinant fowlpox vaccines and IN challenged at 3 wks with 10^6 EID_{50} of HPAIV A/turkey/Italy/4580/1999 [H7N1])

Vaccine Group	Morbidity	Mortality (MDT)	Virus Isolation(Log_{10} EID_{50} titer/ml)	
			oral	cloacal
rFP-H7-Vic/85	8/10	8/10 (4.0)	ND	ND
rFP-H7-It/00	1/10	1/10 (5.0)	$6/10^{a}(2.1^{A})$	$2/10^{a}$ (1.3^{A})
rFP-F7-VA/02	8/10	8/10 (3.3)	ND	ND
rFP	10/10	10/10 (2.3)	$10/10^{a}$ (6.7^{B})	$9/10^{b}$ (3.5^{B})

- **Continental lineages of H7 AIV with limited homosubtypic protection with H7 HA subtypes**

Conclusions:

- **Close antigenic-matched field viruses to inactivated AI or recombinant vectored vaccines containing hemagglutinin gene inserts provide the best protection**
- **Pre-2002, H5 vaccine studies demonstrated broad protection within the same hemagglutinin subtype against genetically diverse H5 HPAI outbreak viruses**
- **H5Nx Gs/GD lineage and Mexican H7N3 lineage have seen unprecedented use of vaccines in poultry accompanied by drift of field viruses such that inactivated vaccine seed strains and recombinant vaccines have had to be changed to maintain protection**
- **Live recombinant vaccines have given broader protection against antigenically diverse challenge viruses compared to inactivated AI vaccines**
- **Live recombinant vaccines may need less frequent changes in hemagglutinin inserts than inactivated vaccine seed strains**

Thank you for your attention!