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Institut für Virologie und Immunologie IVI

UNIVERSITÄT BERN

Experimental release of rVSVΔG(HA): Vaccination of zoo birds in Bern and Basel

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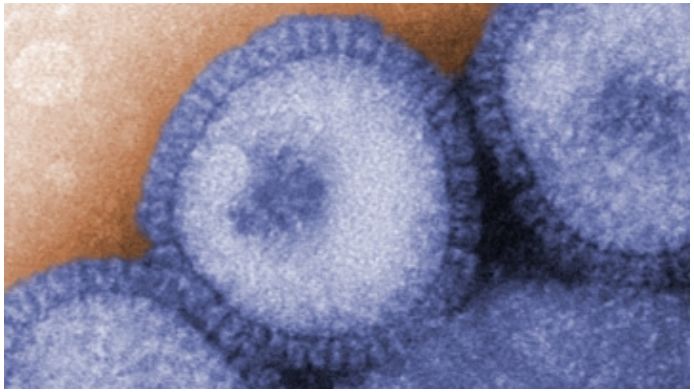
Influenza A virus



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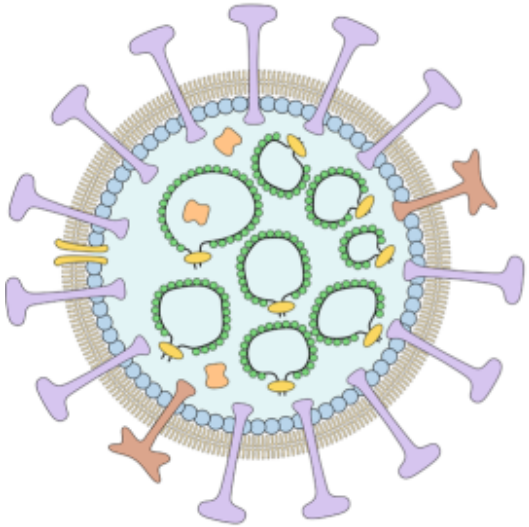
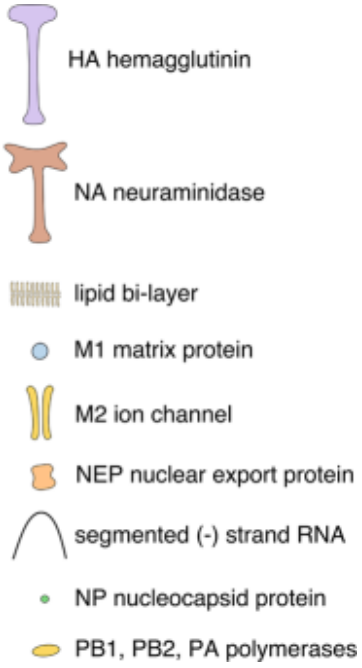
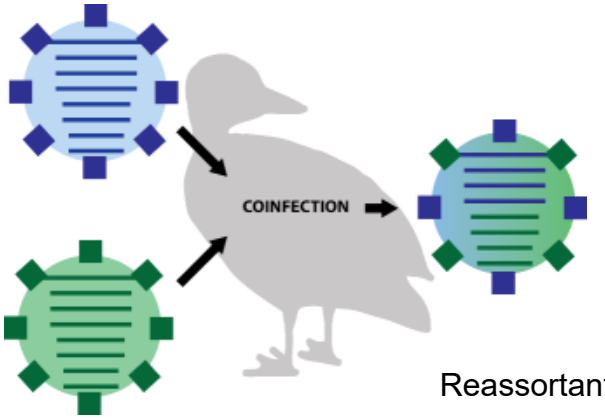




Wild waterfowl represent the natural influenza A virus reservoir

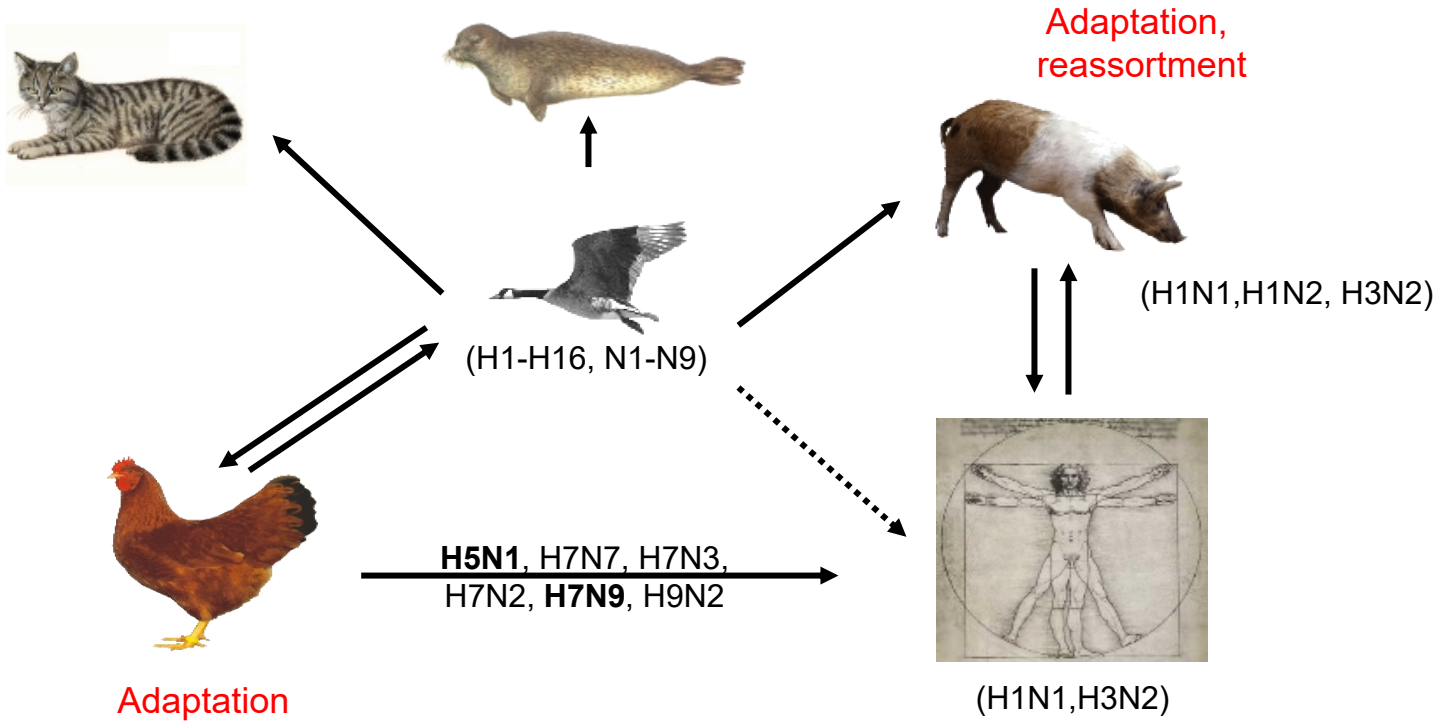


16 HA subtypes (H1-H16)
9 NA subtypes (N1-9)

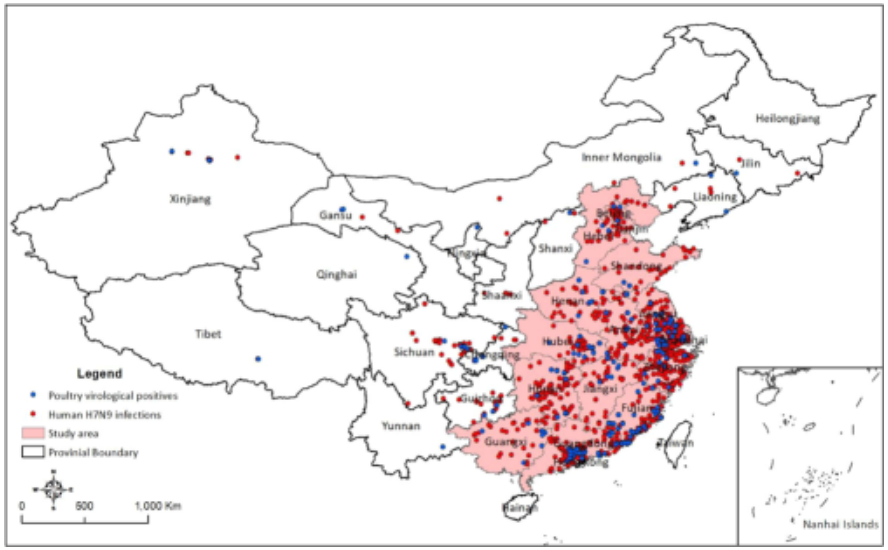
Multiple combinations, e.g. H5N1, H9N2 etc.

Most avian influenza viruses are perfectly adapted to their natural hosts and are low-pathogenic!

Transmission of avian influenza viruses to other species

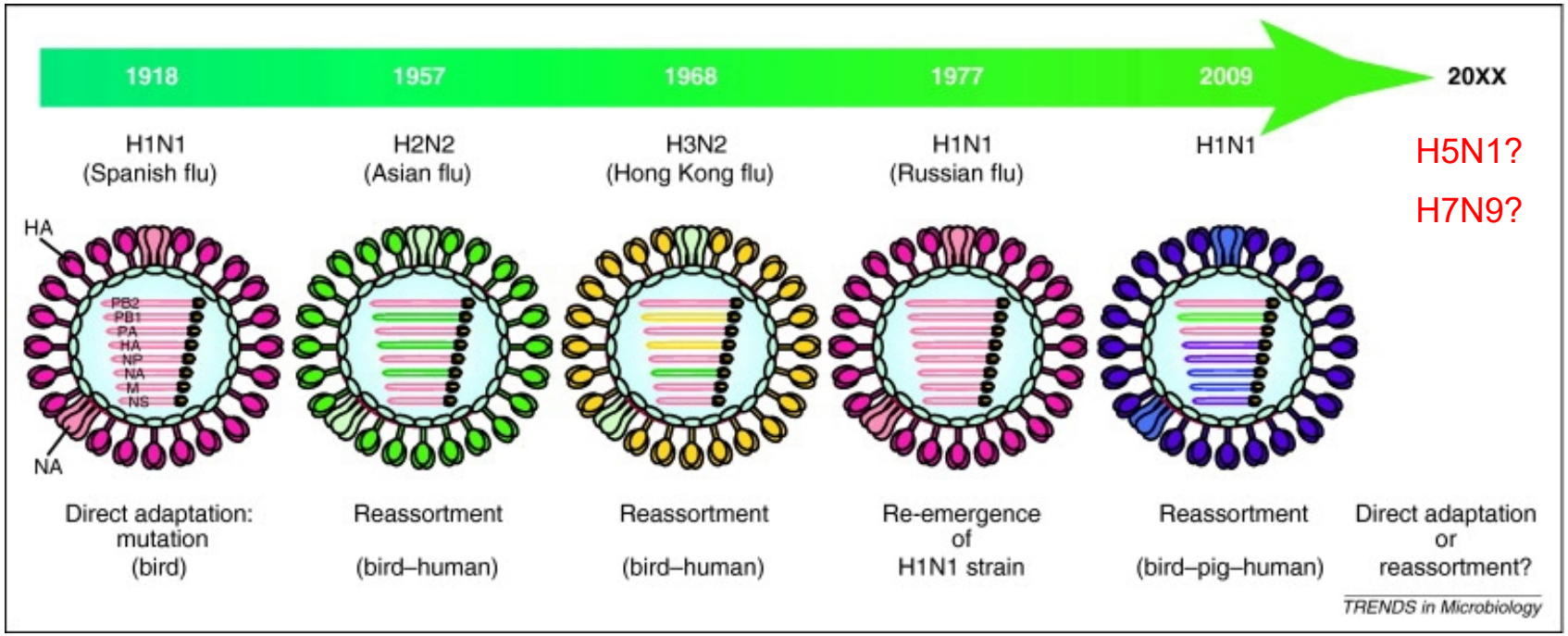


Avian influenza viruses have zoonotic potential



- LPAIV H7N9
- In 2/2013 - 6/2017 1533 confirmed human infections, 592 with lethal outcome
- Adaptive mutations detected
- Air-borne transmission in ferrets
- Rare human-to-human transmission
- A vaccination campaign controlled H7N9 circulation in poultry and successfully stopped transmission to humans (Zeng et al 2018).

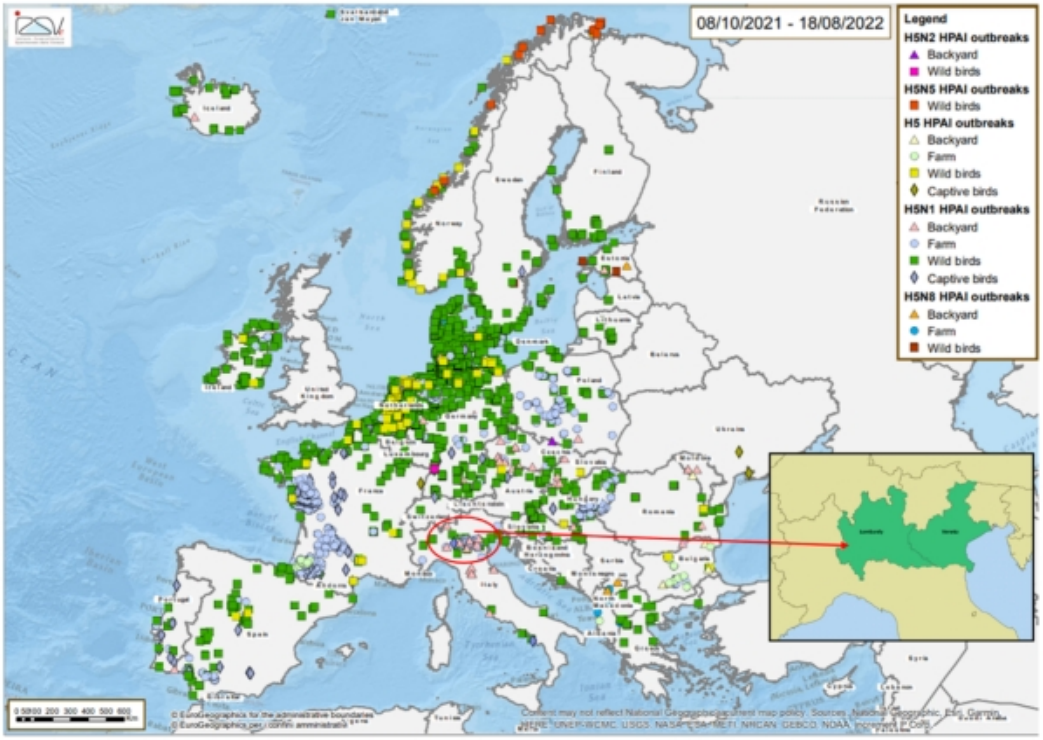
Avian influenza viruses were involved in all previous influenza pandemics



Highly pathogenic avian influenza viruses

- Subtypes H5Nx and H7Nx
- Evolve from LPAIV through mutations in the HA gene
- Systemic infection
- Mortality rate in poultry up to 100% (“fowl plague”)
- Some duck species are resistant to the disease and serve as “trojan horses”

In 2021-2022 Europe was hit by the largest H5N1 outbreak ever seen

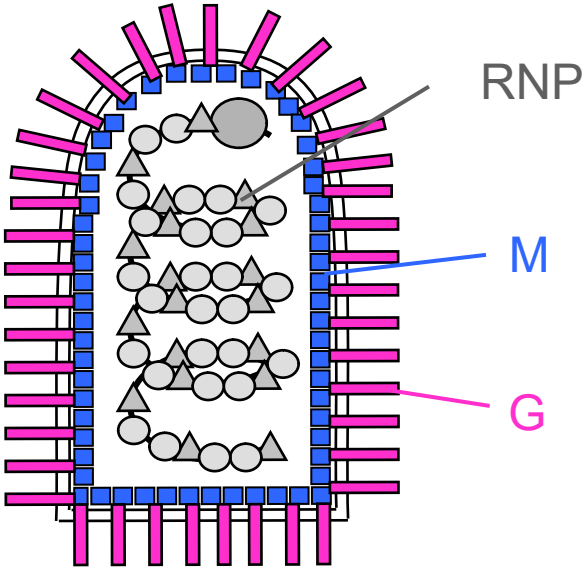


- 3600 infections in wild bird populations recorded
- 2500 outbreaks on poultry farms
- Culling of 50 millions birds
- Outbreaks also in the summer season
- Spread to North America in 2022
- Infection of mammalian species recorded (seals, porpoise, foxes, bears)

Several countries currently pursue a non-vaccination policy

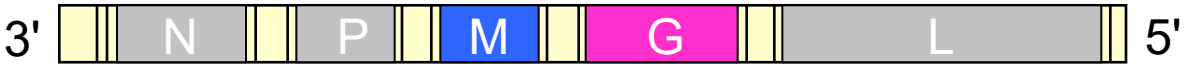
- Outbreaks of HPAIV occurred only sporadically in the past and could effectively be controlled.
- Conventional AIV vaccines do not allow simple serological differentiation between vaccinated and infected animals (DIVA).
- Immunized animals may not show symptoms when infected with HPAIV, but may still excrete infectious virus.
- Trade restrictions
- At initiative of several EU member states, the European commission will allow vaccination against H5 and H7 influenza viruses

VSV is an enveloped virus with a single-stranded negative-sense RNA genome



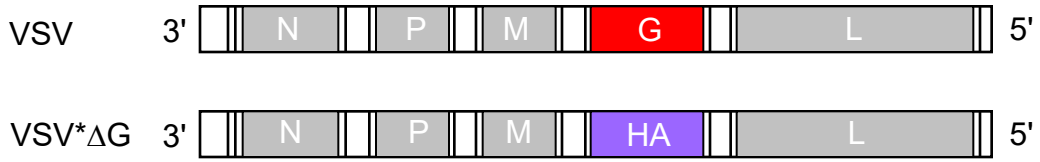
- Member of the *Rhabdoviridae*
- Characteristics *in vitro*:

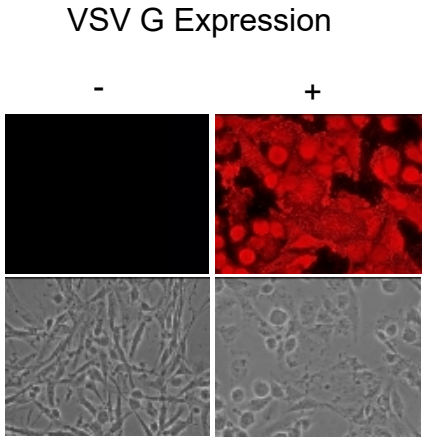
  - Broad cell tropism (G protein) - High titers (10^9 pfu/ml)
  - Highly cytotoxic (M and G)
  - Highly sensitive to IFN



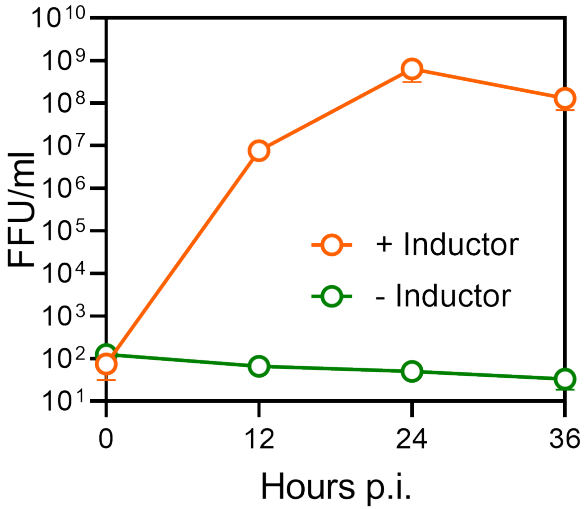
~ 11,200 nt

VSVΔG(HA) replicon particles

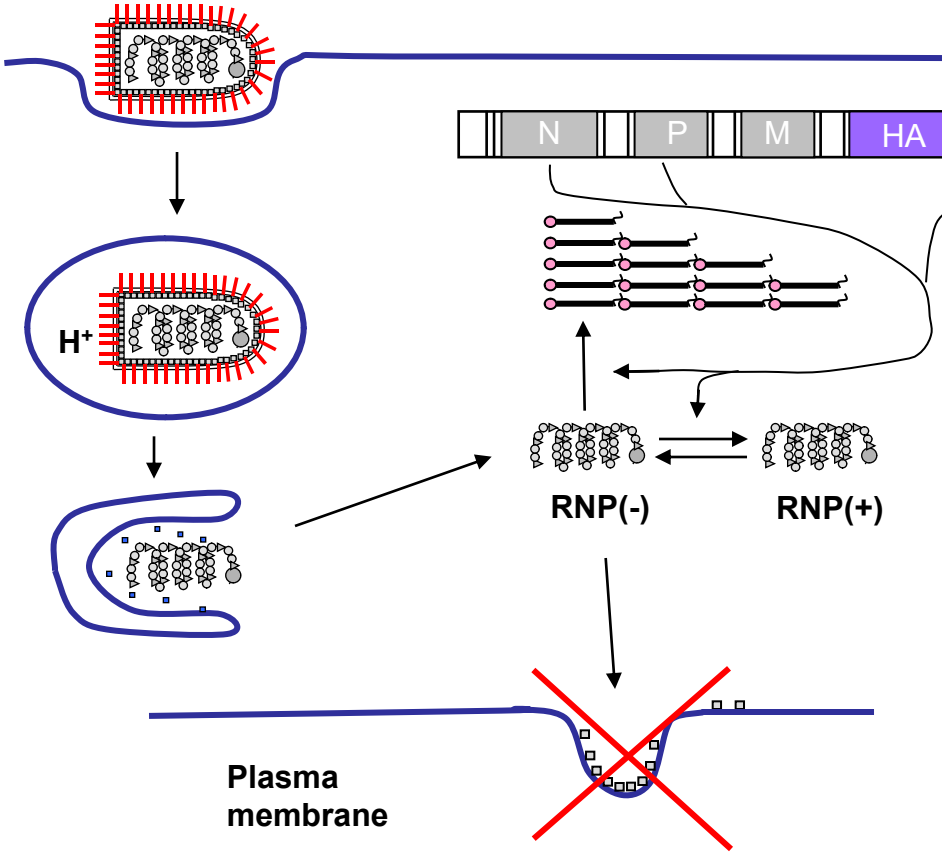




Helper cell line



RNA-Replicons: Self-replicating RNA



- Efficient delivery
- Transcription/replication in cytoplasm!
- RNA amplification → high HA antigen level
- Viral RNA → stimulates the innate immune system!
- Inability to replicate → safety!

Dose-dependent induction of virus-neutralizing antibodies

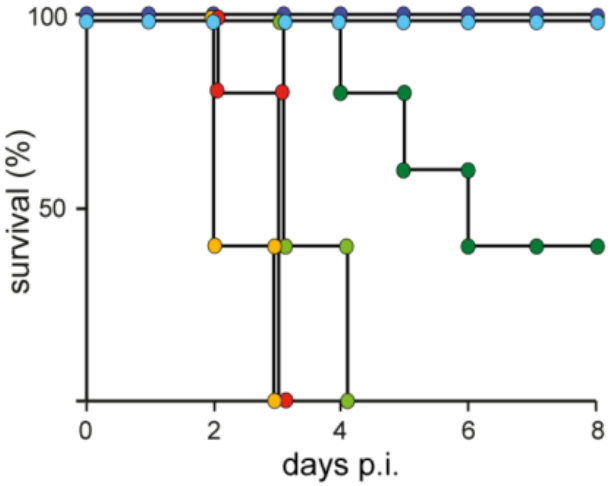
VRP	Number of immunizations	Vaccine dose (ffu)	ND_{50}/ml Chicken no. #1	#2	#3	#4	#5
VSV*ΔG	2	$2x10^8$	<100	<100	<100	<100	<100
VSV*ΔG($HA_{H5\text{-}HP}$) + UV	2	-	<100	<100	<100	<100	<100
VSV*ΔG($HA_{H5\text{-}HP}$)	1	$2x10^8$	1350	400	141	283	200
	2	$2x10^8$	12800	51200	9050	9050	9050
VSV*ΔG($HA_{H5\text{-}HP}$)	1	$2x10^7$	<100	<100	<100	<100	<100
	2	$2x10^7$	283	141	<100	<100	<100
VSV*ΔG($HA_{H5\text{-}HP}$)	2	$2x10^6$	<100	<100	<100	<100	<100

[a]A/whooper swan/Mongolia/3/2005 (H5N1)

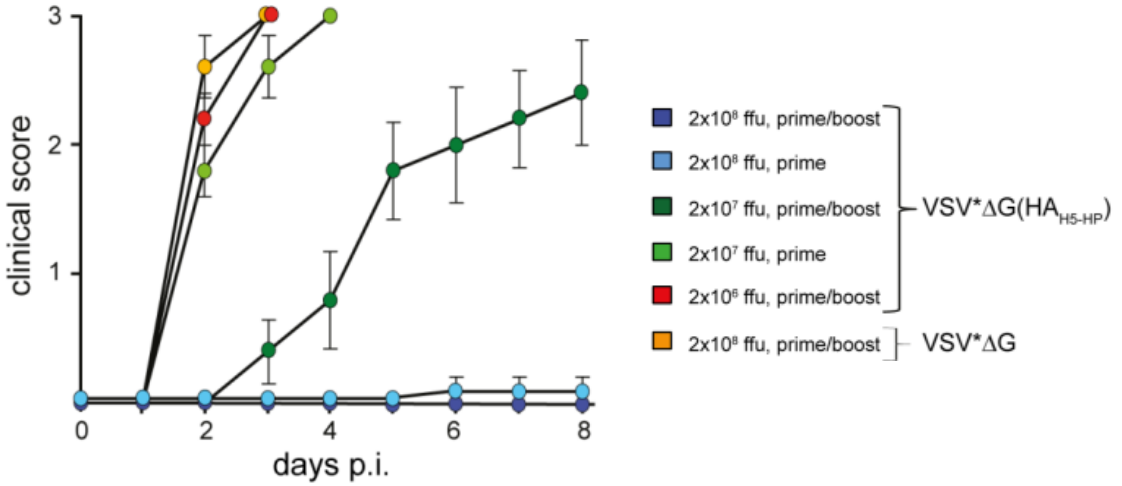
Boosting of the antibody response!

A single, high vaccine dose is sufficient to protect chickens against HPAIV (H5N1)

Survival

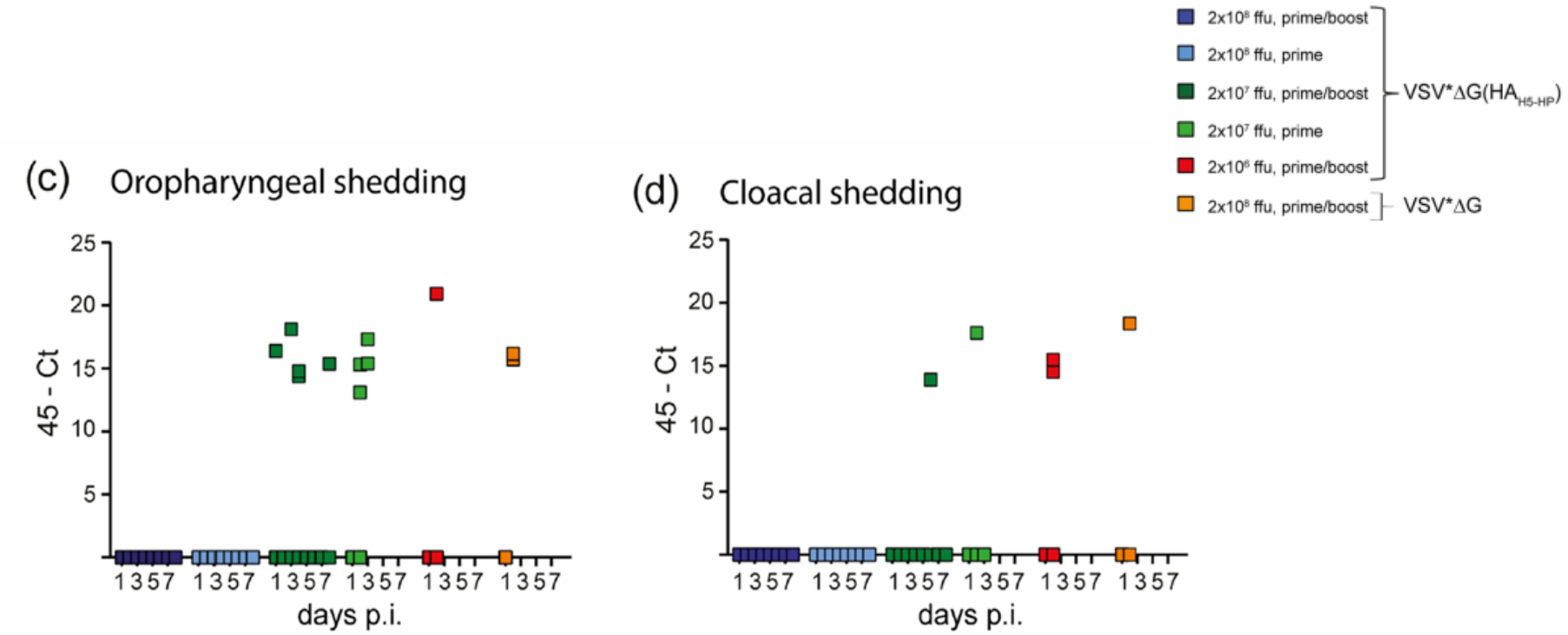


Clinical symptoms



Challenge with: A/whooper swan/Mongolia/3/05 (H5N1)

Immunized animals do not excrete H5N1



Halbherr *et al*. (2013) Plos One 8:e66059

Serological differentiation of immunized from infected animals

		NP-ELISA		H5-ELISA	
	Survival	Pre-challenge	Post-challenge	Pre-challenge	Post-challenge
VSVΔG-GFP	0/6	0/6	ND	0/6	ND
Sentinel	0/6	0/6	ND	0/6	ND
VSVΔG-HA	6/6	0/6	5/6	6/6	6/6
Sentinel	6/6	0/6	0/6	0/6	0/6

Vaccinated: NP(-)/H5(+)
Infected: NP(+)/H5(+)

Halbherr *et al*. (2013) Plos One 8:e66059

Summary

- VSVΔG(HA) is propagation-defective, single-cycle vaccine vector with a high biosafety profile.
- A single high vaccine dose administered intramuscularly confers full protection of chickens against challenge with a lethal dose of HPAIV H5N1.
- Excretion of challenge virus is abrogated and sentinel animals protected.
- Animals immunized with VSVΔG(HA) can be serologically distinguished from infected animals (DIVA).
- Adjuvants are not required.
- Adverse effects have not been observed.

The extraordinary biosafety and efficacy profile of VSVΔG(HA) justifies its use for experimental vaccination of birds in the zoos of Bern and Basel.

Thank you for your attention!