KEMENTERIAN PERTANIAN
DAN KETERJAMINAN MAKANAN

HUMAN AND VETERINARY VACCINOLOGY COURSE

(28 October – 1 November 2024)

OXFORD UNIVERSITY, UK

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TRAINING BACKGROUND

The Human and Veterinary Vaccinology course is a five-day course which covers all aspects of vaccinology.

The course includes contributions from world-leading experts.

The Programme provides state-of-the-art teaching in both human and veterinary vaccinology, drawing on the experience of Oxford University, the world-renowned The Jenner Institute based in Oxford, The Pirbright Institute (formerly the Institute for Animal Health - IAH) and partners in industry.

TRAINING BACKGROUND

Vaccinology is a cross-disciplinary subject and the most exciting developments in vaccinology have occurred when people from diverse research, business and medical backgrounds have used their skills to collectively tackle problems in vaccine design, manufacture and distribution.

This course consists of two parts which are taught by experts from the University of Oxford, academia and industry.

i. Human vaccinology
ii. Veterinary vaccinology

https://www.conted.ox.ac.uk/courses/human-and-veterinary-vaccinology

TRAINING BACKGROUND

Training course objectives:

i. An overview of the field of human and veterinary vaccinology, from Edward Jenner to modern day vaccines.
ii. An understanding of the immune system and immune mechanisms needed to provide protection from disease.
iii. An understanding of the recent advances that have been made in the vaccine field and appreciation of the impact of molecular immunology and pathogen genomics on vaccine development.
iv. An overview of the molecular methods used for the design and construction of vaccines.
v. An appreciation of the importance of pre-clinical testing and the many factors involved in the selection of animal models.
vi. The ability to understand and interpret the bioassays used to measure vaccine immunogenicity and to understand how immunogenicity correlates with protection.
vii. An understanding of the role of veterinary vaccines in animal heath, animal welfare, environmental protection and public health.
viii. An understanding of the vaccine development pathway - from bench to market.
ix. An overview of the ethical issues surrounding vaccine development and deployment.

How the training is conducted

There are 4 ways this training is conducted. This includes:

- Through an interactive presentation by the speaker
- In a face-to-face Q&A session between training participants and the speaker
- Through an online Q&A session between the training participants and the speaker
- Visit to the vaccine research and testing laboratory complex (The Pirbright Institute, UK)

Course Tentative

Date	Time	Speaker	Affiliation	Session
28 October 2024	09:00 - 09:20	Prof Sir Adrian Hill	Jenner Institute, University of Oxford	Welcome, Introductions and Course Overview
28 October 2024	09:20 - 10:20	Prof Sir Adrian Hill	Jenner Institute, University of Oxford	Prelude to human and veterinary vaccinology: scientific, manufacturing and regulatory synergies
28 October 2024	10:40 - 11:40	Dr Weng Ng	Diamond Light Source / Harwell	Introduction to vaccine design & structural vaccinology
28 October 2024	12:00 - 13:00	Dr Cesar Lopez-Camacho	Jenner Institute, University of Oxford	Introduction to pre-clinical immunology
28 October 2024	14:00 - 15:00	Prof Tom Hanke	Jenner Institute, University of Oxford	Antigen screening & selection processes
28 October 2024	15:20 - 16:20	Dr Liz Clutterbuck	Oxford Vaccine Group, University of Oxford	Immune defence mechanisms in humans & immunomonitoring in clinical trials
28 October 2024	16:40 - 17:40	Dr Mike Whelan	Novo Nordisk Institute for Vaccine Immunisation (NIVI)	Vaccine adjuvants: definitions and historical perspectives
28 October 2024	18:00 - 19:00	Prof Sir Adrian Hill	Jenner Institute, University of Oxford	Malaria vaccines
29 October 2024	10:30 - 11:30	Dr Ahmed Salman	Jenner Institute, University of Oxford	Preclinical efficacy testing of vaccines
29 October 2024	11:50 - 12:50	Dr Aadil El-Turabi	Jenner Institute, University of Oxford	Nanoparticles and VLPs in vaccine development

Date	Time	Speaker	Affiliation	Session
29 October 2024	13:50 - 14:50	Prof Jayne Hope	Roslin Institute, University of Edinburgh	Immune defence mechanisms in animals
29 October 2024	15:10 - 16:10	Prof Dan Peer (remotely)	NeoVac Ltd, Oxford	RNA vaccines
29 October 2024	16:30 - 17:30	Prof Florian Krammer (remotely)	Icahn School of Medicine at Mount Sinai, New York	Protein expression vaccine technologies
30 October 2024	08:00 - 10:15			Transfer to The Pirbright Institute
30 October 2024	10:15 - 11:15	Prof Bryan Charleston	Pirbright Institute, UK	An overview of veterinary vaccines and rational development of foot-and-mouth disease virus vaccines
30 October 2024	11:30 - 12:30	Dr Rebecca McLean	Pirbright Institute, UK	New vaccine platforms for Nipah virus and Natural infections of livestock and animals as models for human diseases
30 October 2024	14:00 - 15:00	Dr Julian Seago	Pirbright Institute, UK	Centre for Veterinary Vaccine Innovation and Manufacturing (CVIM)
30 October 2024	15:15 - 16:15	Dr Chris Netherton	Pirbright Institute, UK	Developing a vaccine against African Swine Fever
30 October 2024	16:30 - 17:30	Prof Munir Iqbal	Pirbright Institute, UK	Developing novel multivalent vaccines for poultry viral diseases

Date	Time	Speaker	Affiliation	Session
31 October 2024	09:00 - 10:00	Prof Susie Dunachie	Tropical Medicine & Global Health, University of Oxford	The clinical vaccine development process
31 October 2024	10:20 - 11:20	Prof Helen McShane	Jenner Institute, University of Oxford	Challenge Models in Vaccine Development
31 October 2024	11:40 - 12:40	Prof Tom Hanke	Jenner Institute, University of Oxford	HIV Vaccines
31 October 2024	13:40 - 14:40	Dr Carole Leung	Centre for Immuno-Oncology, University of Oxford	Therapeutic cancer vaccines
31 October 2024	15:00 - 16:00	Dr Gerardo Montalvo Zurbia Flores	Experimental Medicine Division, University of Oxford	Vaccines against Hepatitis C
31 October 2024	16:20 - 17:20	Dr Aadil El-Turabi	Jenner Institute, University of Oxford / University of Bern	Therapeutic vaccines based on virus like particles: from peanut allergy to Alzheimer disease
31 October 2024	17:40 - 18:40	Prof Rachel Tanner	Department of Biology, University of Oxford	Global progress in TB Vaccine development

Date	Time	Speaker	Affiliation	Session
1 November 2024	09:00 - 10:00	Dr Anita Milicic	Jenner Institute, University of Oxford	Novel vaccine delivery technologies
1 November 2024	10:20 - 11:20	Prof Sandy Douglas	Jenner Institute, University of Oxford	The vaccine manufacturing process
1 November 2024	11:40 - 12:40	Prof George Warimwe (remotely)	KEMRI Wellcome Trust Research Programme, Kilifi, Kenya	One Health Vaccinology
1 November 2024	13:00 - 14:00	Dr Simon Funnell	UK Health Security Agency	Vaccines in biodefence

KEMENTERIAN PERTANIAN
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VETERINARY VACCINOLOGY
(POULTRY)

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HISTORY OF VACCINE DEVELOPMENT

Edward Jenner (1749-1823)

- In 1796, Edward Jenner created the first successful smallpox vaccine using cowpox.
- A groundbreaking achievement that transformed medicine and paved the way for the eradication of a once-devastating disease.
- The word "vaccination" comes from the Latin word "vaca," meaning cow, referring to the use of cowpox in the process.

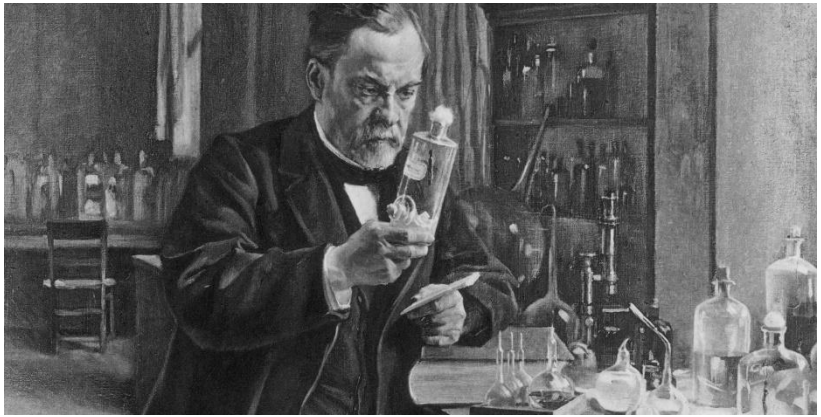
https://www.jenner.ac.uk/about/edward-jenner

Louis Pasteur (1822-1895)

- Louis Pasteur, a distinguished French chemist and microbiologist, made substantial contributions to the advancement of vaccines.

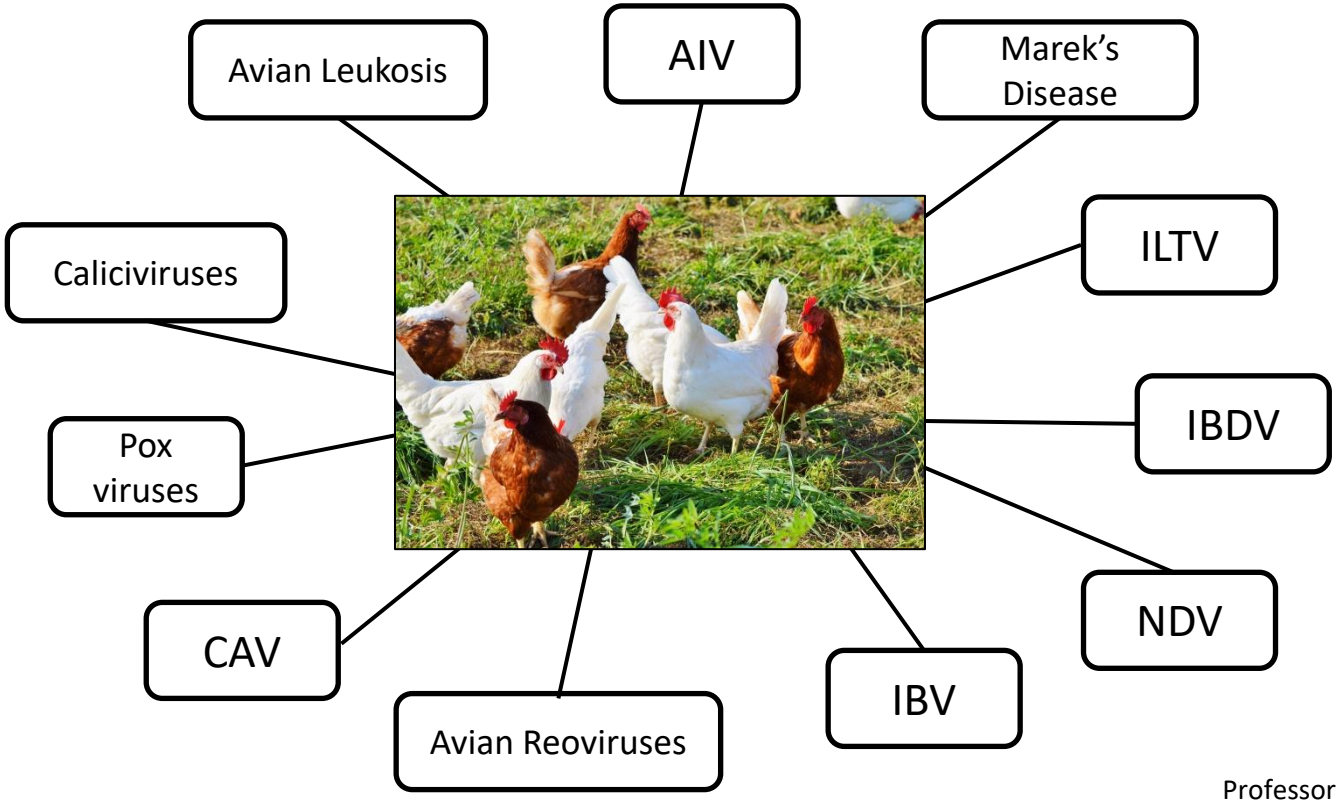
- In 1872, he developed the first laboratory-produced vaccine for fowl cholera and subsequently achieved success in rabies prevention through post-exposure vaccination in 1885.

- His research established the principle of employing attenuated (weakened) microbes to elicit an immune response, thereby marking a pivotal moment in the evolution of immunology and vaccination practices.



https://historyofvaccines.org/history/louis-pasteur-formemrs/overview

MULTITUDE OF VIRUSES EFFECTING POULTRY



Professor Munir Iqbal (2024)

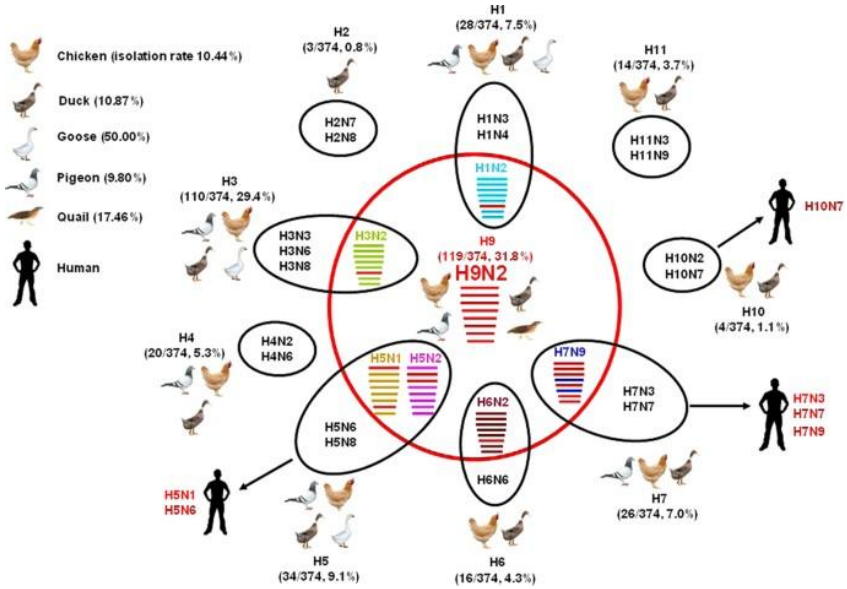
AVIAN INFLUENZA VIRUSES

H5 (Low and high pathogenicity)
- H5N1, H5N2, H5N3, H5N5, H5N6, H5N8, H5N9
- >30 HA gene clades and sub-clades

H7 (Low and high pathogenicity)
- H7N1, H7N2, H7N3, H7N4, H7N7, H7N9
- >25 HA gene clades and sub-clades

H9 (Low pathogenicity)
- H9N2
- 3 major HA lineages and >19 clades

H6 (Low pathogenicity)
- H6Nx



Wu *et al*. (2015), *Scientific Reports,* 5, 17508

High pathogenicity AIV infection in poultry	Low pathogenicity AIV infection in poultry
▪ H5 and H7 ▪ Sudden death (up to 100% mortality) ▪ Severe respiratory distress ▪ Excessive lacrimation ▪ Oedema of head ▪ Subcutaneous hemorrhage ▪ Diarrhoea ▪ Atypical neurological signs ▪ Cessation of egg laying	▪ H9N2 ▪ Mild respiratory disease with low mortality rate ▪ Ruffled feathers ▪ General depression ▪ Drop in egg production ▪ Reduced weight gain ▪ Tracheitis and blockage of trachea with mucus/pus

NEWCASTLE DISEASE VIRUSES

Different pathotypes of NDV

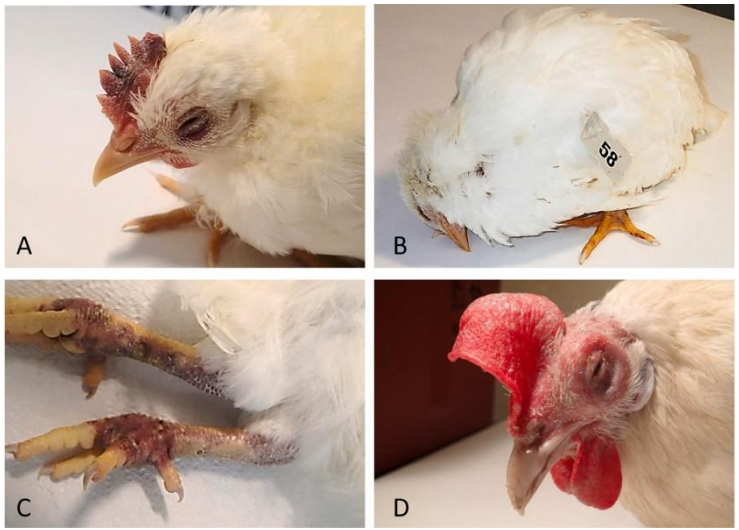
Velogenic (Viscero-tropic)
- Acute lethal infections, haemorrhagic lesions in the intestines

Velogenic (Neuro-tropic)
- High mortality following respiratory and neurological disease, gut lesions absent

Mesogenic
- Respiratory and neurological signs, with low mortality

Lentogenic
- Mild infections of the respiratory tract

Asymptomatic enteric
- Avirulent infections, replication primarily in the gut

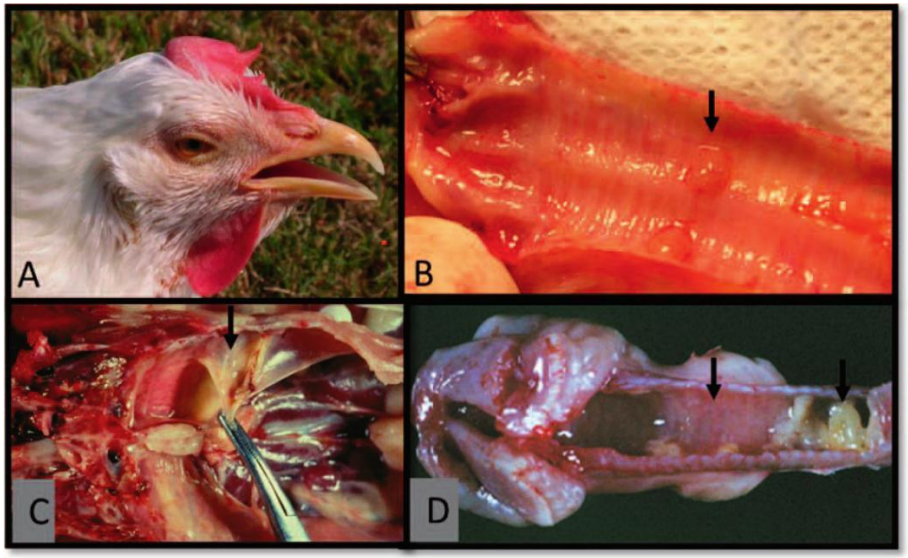


Dimitrov *et al.* (2019), *Virology,* 531, 203-218

INFECTIOUS BRONCHITIS VIRUSES

1. Major economically important disease of poultry
2. Infects all types of chicken flocks (broiler, breeder, and layers)

3. Clinical signs
   - Difficulty in breathing
   - Tracheal rales
   - Coughing
   - Sneezing
   - Watery eyes
   - Nasal discharge
   - Reduced egg production



Hoerr *et al.* (2021), *Avian Diseases,* 65, 600-611

INFECTIOUS BURSAL DISEASE VIRUSES

1. Major economically important disease of poultry
2. Causes atrophy bursa of Fabricius results immune suppressions that leads to secondary infection

3. Clinical signs
   - Depression
   - Watery diarrhoea
   - Ruffled feathers
   - Dehydration
   - High mortality (3-6 weeks of age)

Hemida *et al.* (2019), *Recent Advances in Animal Virology,* 237-252

Desirable formulation of vaccines

Potent

- Single dose induce faster, stronger and durable immunity against multiple pathogens

Effective

- Protect from clinical disease, reduced shedding and transmission

Affordable

- Cheap to produce and easy to deliver

Safe

- No adverse impact to host or environment

Stable

- Retain efficacy for at least 1 year at indicated temperature

Challenges facing vaccine efficacy

- Multiple subtypes of AIV (H5, H7, H9, H6) and their variants
- Virus evolution and antigenic diversity
- Emergence of new variants
- Co-circulation of multiple variants of same pathogens
- Poor quality vaccines (antigenic mismatch to the field challenge)
- MDA interference
- Mixed infection of different viruses (immunosuppressive pathogens)
- Sub-optimal vaccination practices (suboptimal delivery)

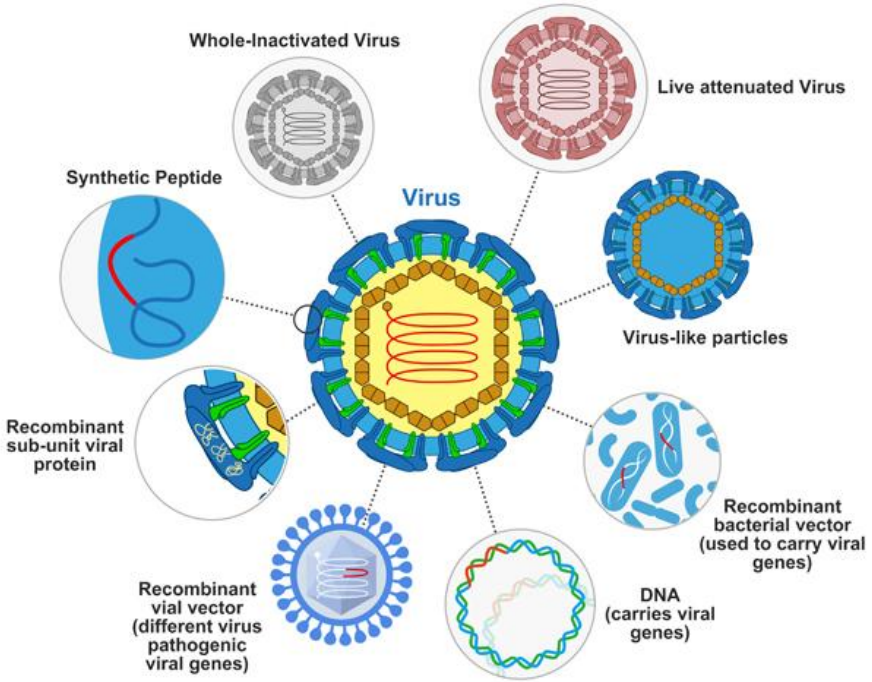
Vaccine and Vaccine efficacy

1. Vaccines work at an individual level to protect the immunised person against the specific disease, as well as at a population level to reduce the incidence of the disease in the population, thereby reducing exposure of susceptible persons and consequent illness.

2. Vaccine efficacy is a measure of how well a vaccine works when given in ideal, controlled conditions.

3. Vaccine effectiveness is a measure of how well a vaccine works under normal use in the real world, including in populations that may have been excluded from clinical trials, and is subject to biases inherent to observational studies.

VARIOUS TYPES OF VACCINE TECHNOLOGIES



Recombinant vaccine. Available at https://www.genscript.com/recombinant-vaccine.html

VIRAL VACCINE: TYPES AND CLASSIFICATIONS

Replicating/live vaccines	Non-replicating/replication restricted vaccines	DNA-based vaccines
Conventional attenuated live vaccines ▪ Naturally occuring attenuated strains ▪ Serial passage in heterologous host animals ▪ Serial passage in cell culture	Conventional inactivated vaccines	Reverse genetics
Live gene-deletion attenuation vaccines	Subunit vaccines	Chimeric viruses
Recombinant live vectored vaccines	Other forms of nonreplicating vaccines ▪ VLPs ▪ Plant made vaccines ▪ Synthetic peptide vaccines	▪ DNA vaccines ▪ RNA vaccines

Multivalent Vaccines

Mixture of inactivated viruses ▪ Produce separate whole virus antigens, measure antigen quantity, and combining two or more antigens as per requirement as a single dose ▪ AIV H5+H9, H9+IBV+NDV	**Poly vaccine** IB+ND+EDS+RT ▪ IBV strain M41 ▪ IBV strain D274 ▪ EDS76 ▪ NDV strain Clone 30 ▪ RT strain But1#8544
Viral vectors ▪ rHVT, expressing NDv (F) and IBDV (VP2); rNDV-H5HA or NDV-F	
Recombinant subunit ▪ Mixture of several immunodominant antigens	

Herpesvirus of Turkeys (HVT) and Duck Enteritis Virus (DEV) as vectors to deliver avian influenza protective antigens

i. Produced in cultured cells
ii. Single dose induces lifetime protection
iii. Induce immunity in the presence of maternal antibodies
iv. Safe, because it only infects avian species
v. Mass vaccination (*in ovo*) or day-old chicks at hatchery

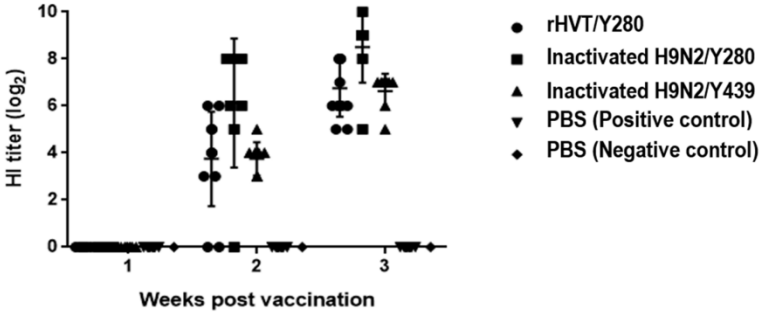


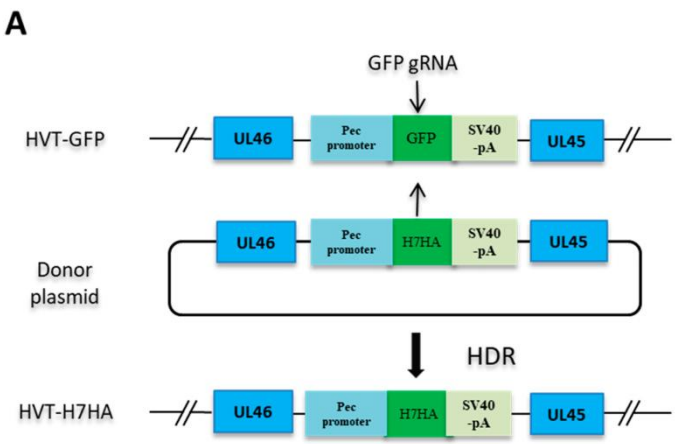
Table 1. Protective efficacy of the used vaccines against H9N2/Y280 challenge.

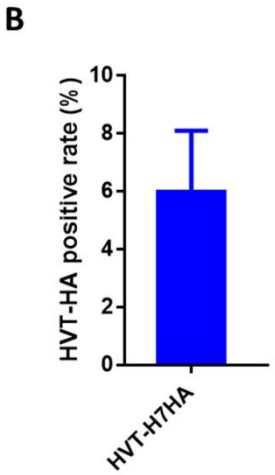
Group	Vaccination	Serology at 3 wpv (log_2 HI titer) [a]	Virus Shedding ($log_{10}EID_{50}$/0.1 mL) [b]				Virus Replication in Tissues ($log_{10}EID_{50}$/0.1 mL) [c]				
			3 dpi		5 dpi		5 dpi				
			OP	CL	OP	CL	Trachea	Lung	Bursa	Brain	Cecal Tonsil
A	rHVT/Y280	12/12 (6.8)	3/12 (0.5)	0/12 (−)	0/12 (−)	0/12 (−)	1/12 (0.1)	1/12 (0.1)	0/12 (−)	0/12 (−)	0/12 (−)
B	Inactivated H9N2/Y439	8/8 (8.5)	1/8 (0.3)	1/8 (0.2)	0/8 (−)	0/8 (−)	1/8 (0.1)	1/8 (0.2)	0/8 (−)	1/8 (0.2)	0/8 (−)
C	Inactivated H9N2/Y280	8/8 (6.9)	8/8 (4.0)	6/8 (1.4)	8/8 (1.8)	3/8 (0.6)	7/8 (2.0)	5/8 (1.4)	1/8 (0.2)	5/8 (1.2)	2/8 (0.5)
PC	PBS	0/10 (0)	10/10 (4.7)	8/10 (1.4)	10/10 (2.7)	9/10 (1.7)	10/10 (2.7)	7/10 (1.8)	5/10 (1.1)	6/10 (1.2)	6/10 (1.1)
NC	PBS	0/6 (0)	0/6 (−)	0/6 (−)	0/6 (−)	0/6 (−)	0/6 (−)	0/6 (−)	0/6 (−)	0/6 (−)	0/6 (−)

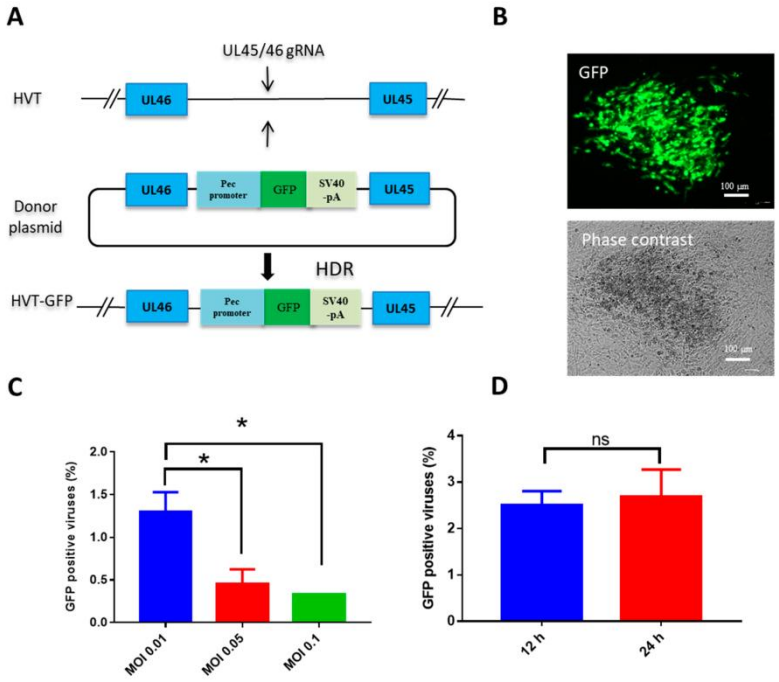
[a] Number of serology-positive/total survivors in the group (mean HI titer). [b] Number of virus-positive/total in the group. [c] Tissue collected at 5 dpi, showing virus-positive/total in the group (virus titers from pooled samples).

Zhang *et al.* (2021), *Animals, 14*, 872

BAC- and CRISPR/Cas9-based approaches for insertion of protective antigen genes into HVT and DEV

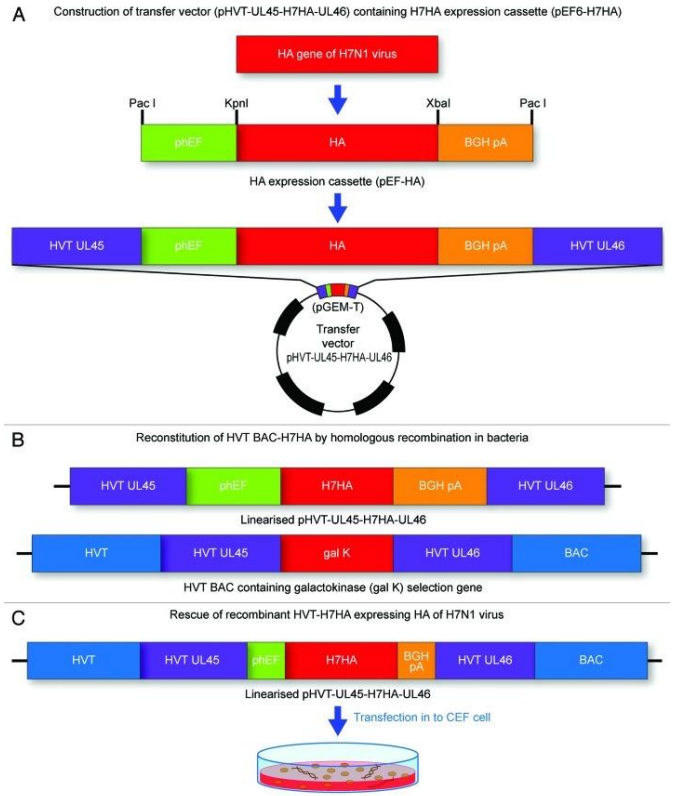






Chang *et al.* (2019), *Vaccines, 7*, 192

rHVT-AIV H7 vaccines

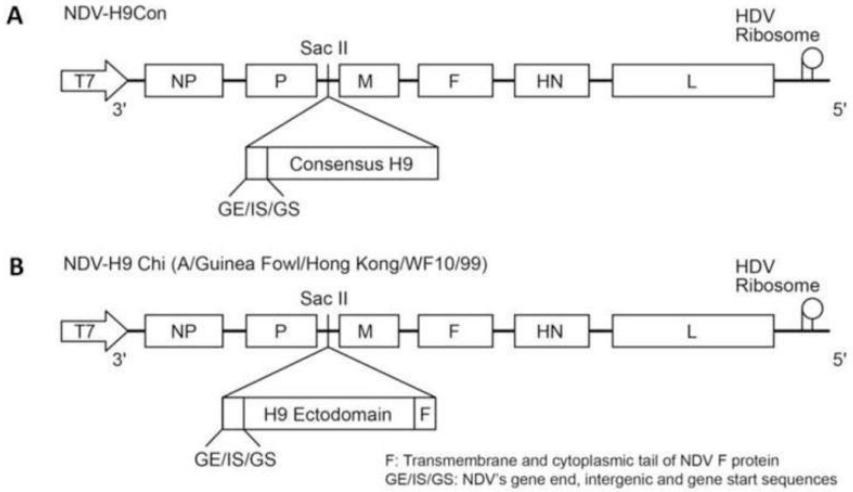


i. Cultured CEF cells infected with the rHVT-H7HA showed that HA was expressed and that the rescued rHVT-H7HA stocks were stable during several in vitro passages with no difference in growth kinetics compared with the parent HVT.

ii. Immunization of one-day-old chicks with rHVT-H7HA induced H7-specific antibodies and protected chickens challenged with homologous H7N1 virus against virus shedding, clinical disease and death.

Iqbal (2012), *Bioengineered, 3*, 222-226

rNDV-AIV H9 vaccines



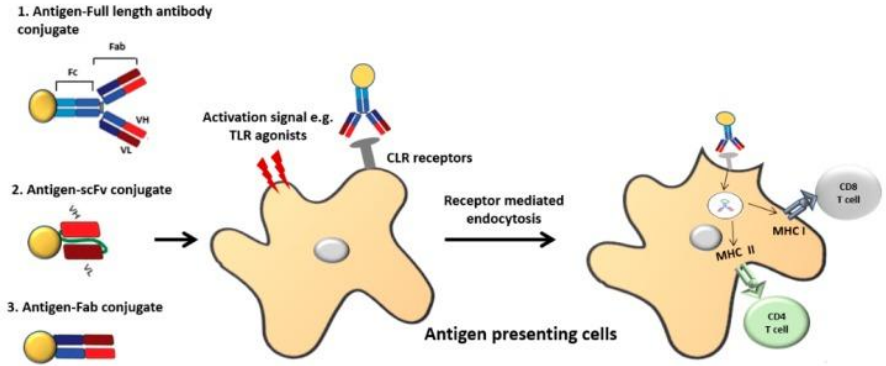
i. Both recombinant viruses expressed the inserted HA stably and grew to high titers.

ii. An efficacy study in chickens showed that both recombinant viruses were able to provide protection against challenge with a heterologous H9N2 virus.

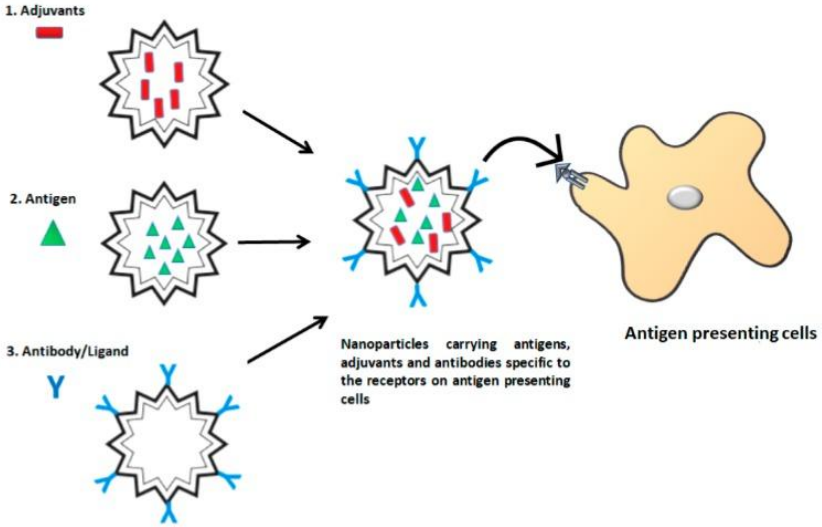
iii. Sera collected from birds immunized with either NDV-H9Con or NDV-H9Chi were able to cross-neutralize two different lineages of H9N2 viruses.

Nagy *et al.* (2016), *Vaccine, 34*, 2537-2545

Enhancing potency of poultry vaccines by targeted delivery of antigens to chicken antigen presenting cells (APCs)



Antibody-based antigen targeting

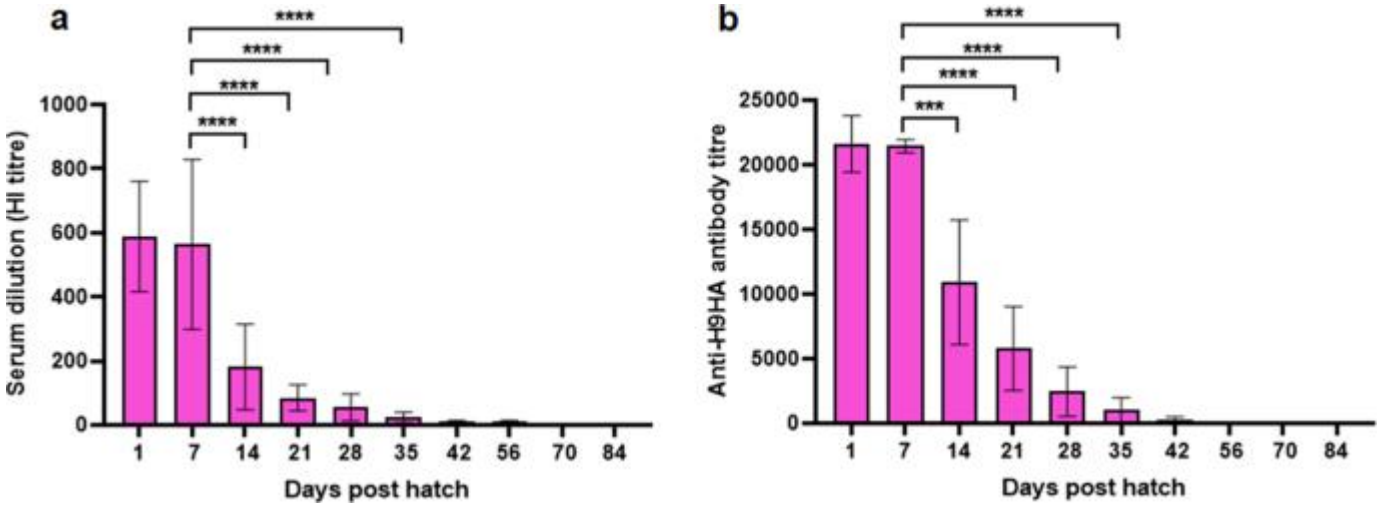


Nanoparticle-based antigen targeting

i. Induce rapid, potent and durable immunity
ii. Reduce amount and number of vaccine doses
iii. Broaden an immune response to antigenic variants

Shreshta *et al.* (2018), *Vaccines (Basel), 6*, 75

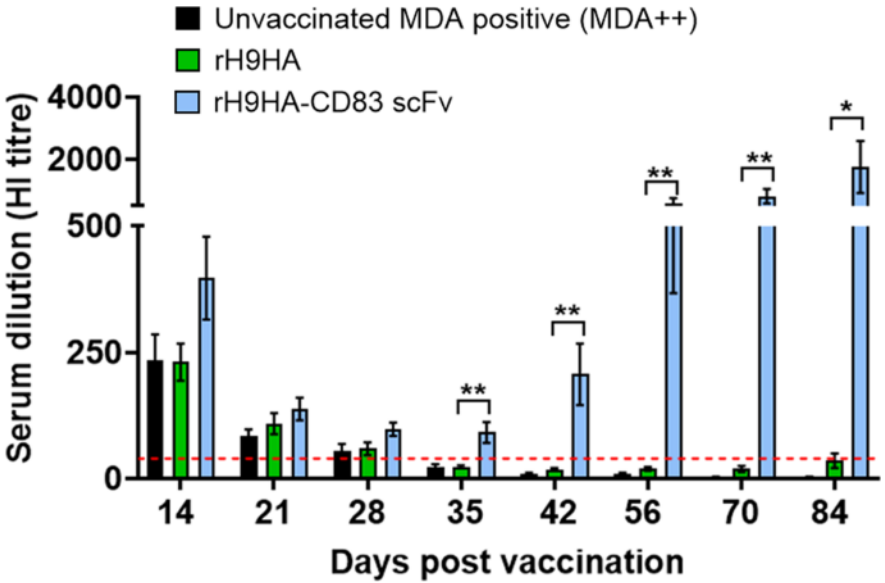
Targeted antigen delivery vaccine (TADV) overcomes MDAs interference



Anti-H9HA MDA level in the hatchlings reduces significantly by day 14 post hatch

Shreshta *et al.* (2022), *NPJ Vaccine, 7*, 33

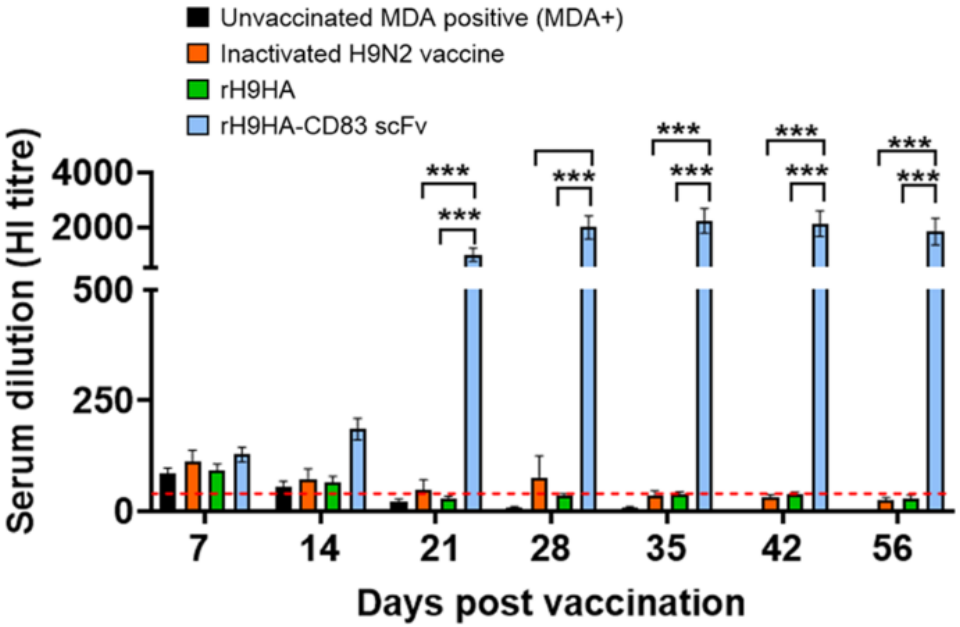
Vaccination to MDA++ chicks



Anti-H9HA antibody titres measured by HI assay in the serum of MDA++ chickens immunised with rH9HA and rH9HA-CD83 scFv vaccines

Shreshta *et al.* (2022), *NPJ Vaccine, 7*, 33

The rH9HA-CD83 scFv vaccine induces strong immunity in MDA+ chicks



Anti-H9HA antibody titres measured by HI assay in the serum of MDA+ chickens vaccinated with inactivated H9N2 vaccine, rH9HA and rH9HA-CD83 scFv

The rH9HA-CD83 scFv vaccine can overcome the interference of medium MDA levels (MDA+) compared to rH9HA and inactivated H9N2 vaccines

Shreshta *et al.* (2022), *NPJ Vaccine, 7*, 33

Summary

i. Effective vaccines can reduce the disease impacts and viral load shed into the environment, causing viral persistence
ii. Multivalent single dose vaccines can reduce costs and improve animal welfare
iii. TADV vaccines induce strong, broader and durable immunogenicity in poultry
iv. TADV vaccines can overcome MDA interference

SELECTED REFERENCES

i. Iqbal M. (2012). Progress toward the development of polyvalent vaccination strategies against multiple viral infections in chickens using herpesvirus of turkeys as vector. *Bioengineered*, *3*(4), 222–226. https://doi.org/10.4161/bioe.20476

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