Identificación y manejo de la Influenza Aviar

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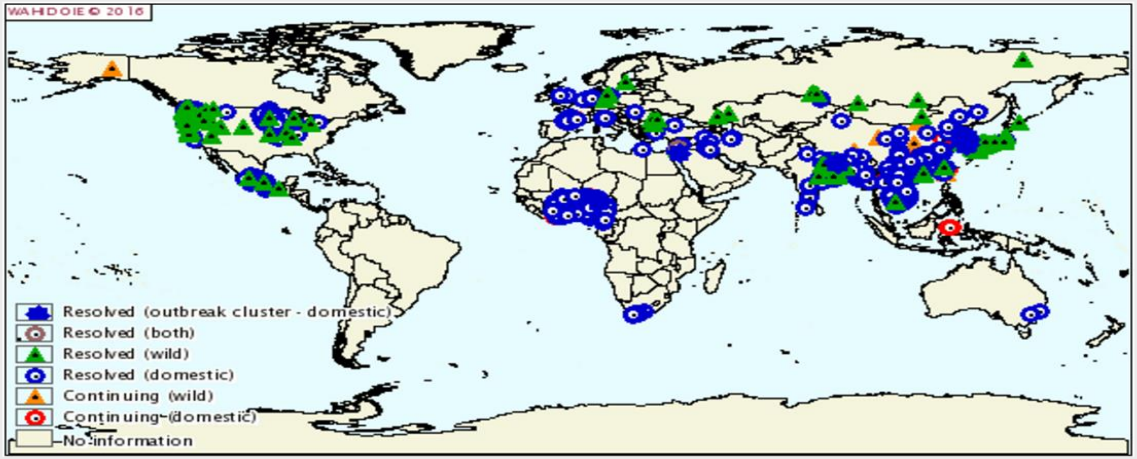
1. Conceptos básicos de la IA

Importancia de la IA

- Enfermedad económicamente devastadora que afecta a aves y mamíferos, incluidos los humanos
- Brotes reportados mundialmente en aves domésticas y salvajes
- Enzoótica en algunos países de Asia, África y América (México, Guatemala, El Salvador)



Brotes IAAP 2011-2016

World Health Organization

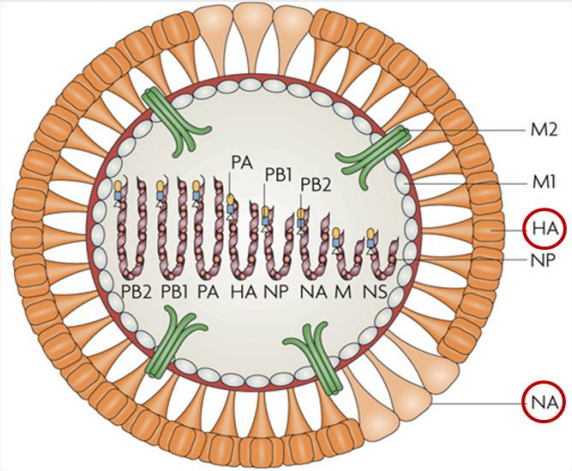
Etiología: virus IA

Família: *Orthomyxoviridae*

Género: **Influenzavirus A**: aves y mamíferos

Influenzavirus B: humanos

Influenzavirus C: humanos y suínos



Subbarao 2007 Nature Reviews Immunology

Constante evolución

Subtipos: **16 HA y 9 NA**

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Bioseguridad

Aves acuáticas silvestres

American green-winged teal (*Anas carolinensis*)

American wigeon (*Anas americana*)

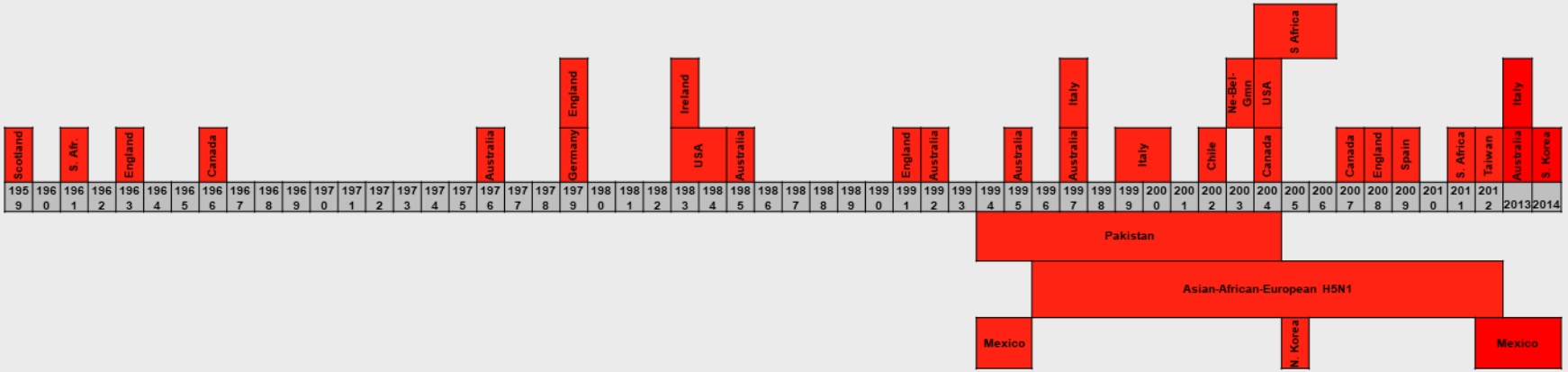
Mallard (*Anas platyrhynchos*)

Northern pintail (*Anas acuta*)

Gadwall (*Anas strepera*)

Wood duck (*Aix sponsa*)

Frecuencia de brotes en el tiempo.



Swayne

Principales problemas

Riesgo de convertirse en problema de salud humana.
Fenómenos de deriva y cambio antigénico IABP-IAAP.
Pérdidas económicas asociadas (mortalidad por tapón caseoso para cepas de BP).
Lineamientos de la OIE y regulatorios.
Ausencia de cobertura de pérdidas/ ocultamiento de brotes.

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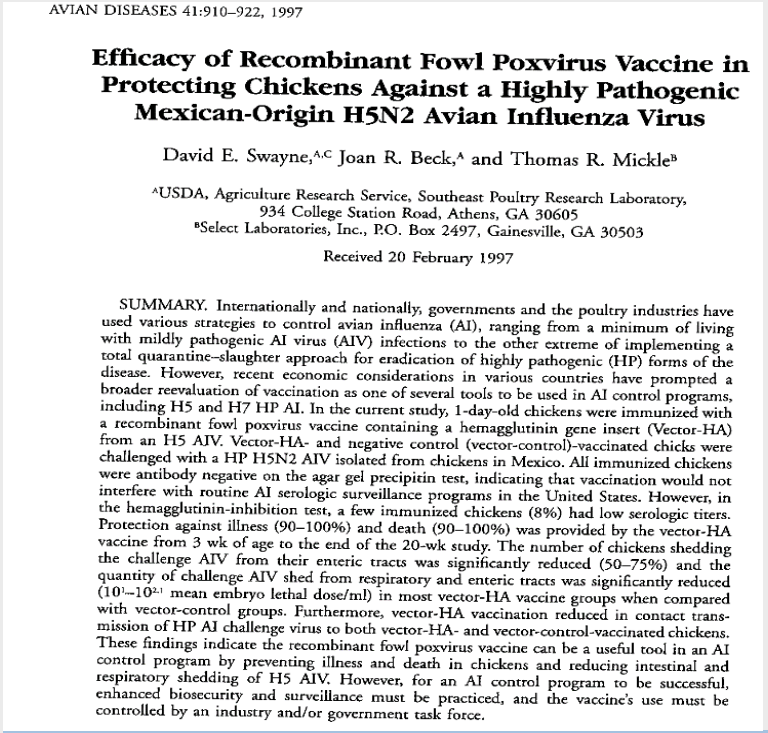
Historia



AVIAN DISEASES 41:910–922, 1997

Efficacy of Recombinant Fowl Poxvirus Vaccine in Protecting Chickens Against a Highly Pathogenic Mexican-Origin H5N2 Avian Influenza Virus

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Received 20 February 1997

SUMMARY. Internationally and nationally, governments and the poultry industries have used various strategies to control avian influenza (AI), ranging from a minimum of living with mildly pathogenic AI virus (AIV) infections to the other extreme of implementing a total quarantine–slaughter approach for eradication of highly pathogenic (HP) forms of the disease. However, recent economic considerations in various countries have prompted a broader reevaluation of vaccination as one of several tools to be used in AI control programs, including H5 and H7 HP AI. In the current study, 1-day-old chickens were immunized with a recombinant fowl poxvirus vaccine containing a hemagglutinin gene insert (Vector-HA) from an H5 AIV. Vector-HA- and negative control (vector-control)-vaccinated chicks were challenged with a HP H5N2 AIV isolated from chickens in Mexico. All immunized chickens were antibody negative on the agar gel precipitin test, indicating that vaccination would not interfere with routine AI serologic surveillance programs in the United States. However, in the hemagglutinin-inhibition test, a few immunized chickens (8%) had low serologic titers. Protection against illness (90–100%) and death (90–100%) was provided by the vector-HA vaccine from 3 wk of age to the end of the 20-wk study. The number of chickens shedding the challenge AIV from their enteric tracts was significantly reduced (50–75%) and the quantity of challenge AIV shed from respiratory and enteric tracts was significantly reduced (10^{3}–$10^{2.1}$ mean embryo lethal dose/ml) in most vector-HA vaccine groups when compared with vector-control groups. Furthermore, vector-HA vaccination reduced in contact transmission of HP AI challenge virus to both vector-HA- and vector-control-vaccinated chickens. These findings indicate the recombinant fowl poxvirus vaccine can be a useful tool in an AI control program by preventing illness and death in chickens and reducing intestinal and respiratory shedding of H5 AIV. However, for an AI control program to be successful, enhanced biosecurity and surveillance must be practiced, and the vaccine's use must be controlled by an industry and/or government task force.

Swayne

- H5N2 BP oficialmente reconocido en 1994 (circulaba tiempo atrás).
- Mutación IAAP a finales de 94-95.
- Aprobación oficial para el uso de VME en 1995 vs lineamientos de OIE (Pronabive 94).
- Aprobación del uso de una vacuna recombinante vector viruela en 1998 (Trovac).
- Erradicación de brotes de AP, pero persiste como BP a la fecha, expandiéndose a Guatemala y El Salvador.

Historia

Se vacunó vs lineamientos de la OIE

Control de brotes de IAAP a mediados del 95.

Presión del gobierno para retirar la vacuna.

Reinfección de aves susceptibles.

Deriva antigénica importante para el 2000.

Acciones del gobierno lentas para actualizar la semilla vacunal.

Deriva antigénica

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Escorcia *et al. BMC Veterinary Research* 2010, **6**:57
http://www.biomedcentral.com/1746-6148/6/57

BMC Veterinary Research

RESEARCH ARTICLE Open Access

Impact of antigenic and genetic drift on the serologic surveillance of H5N2 avian influenza viruses

Magdalena Escorcia[1], Karol Carrillo-Sánchez[2], Santiago March-Mifsut[2], Joaquin Chapa[3], Eduardo Lucio[3], Gerardo M Nava[4*]

Abstract

Background: Serologic surveillance of Avian Influenza (AI) viruses is carried out by the hemagglutination inhibition (HI) test using reference reagents. This method is recommended by animal health organizations as a standard test to detect antigenic differences (subtypes) between circulating influenza virus, vaccine- and/or reference- strains. However, significant discrepancies between reference antisera and field isolates have been observed during serosurveillance of influenza A viruses in pig and poultry farms. The objective of this study was to examine the effects of influenza virus genetic and antigenic drift on serologic testing using standard HI assays and reference reagents. Low pathogenic AI H5N2 viruses isolated in Mexico between 1994 and 2008 were used for phylogenetic analysis of AI hemagglutinin genes and for serologic testing using antisera produced with year-specific AI virus isolates.

Results: Phylogenetic analysis revealed significant divergence between early LPAI H5N2 viruses (1994 - 1998) and more recent virus field isolates (2002 - 2008). Results of the HI test were markedly influenced by the selection of the AI H5N2 virus (year of isolation) used as reference antigen for the assay. These analyses indicate that LPAI H5N2 viruses in Mexico are constantly undergoing genetic drift and that serosurveillance of AI viruses is significantly influenced by the antigen or antisera used for the HI test.

Conclusions: Reference viral antigens and/or antisera need to be replaced constantly during surveillance of AI viruses to keep pace with the AI antigenic drift. This strategy should improve the estimation of antigenic differences between circulating AI viruses and the selection of suitable vaccine strains.

Vacunación.

Cross Protection of Commercially Vaccinated Birds to Different LPAI Challenge

Challenge virus	DPI[a]	Oropharyngeal Viral Titers Vaccinated	Control
Vaccine strain Jalisco Lineage	3DPI	1.66 (5/10)	4.5 (5/5)
	5DPI	0.98 (4/10)	3.1 (5/5)
CK/AG/124-3705/98 Lineage A	3DPI	4.44 (10/10)	4.2 (5/5)
	5DPI	2.14 (8/10)	2.4 (5/5)
CK/Guatermala/194573/02 Lineage B	3DPI	4.86 (10/10)	4.9 (5/5)
	5DPI	3.62 (10/10)	3.4 (5/5)

Suarez 2002

¿Es necesario actualizar la semilla vacunal?

Típicamente se emplea una semilla oficial (Pronabive 94 y posteriormente 2006). Se está en proceso de aprobar una semilla nueva (2015).

Deriva antigénica

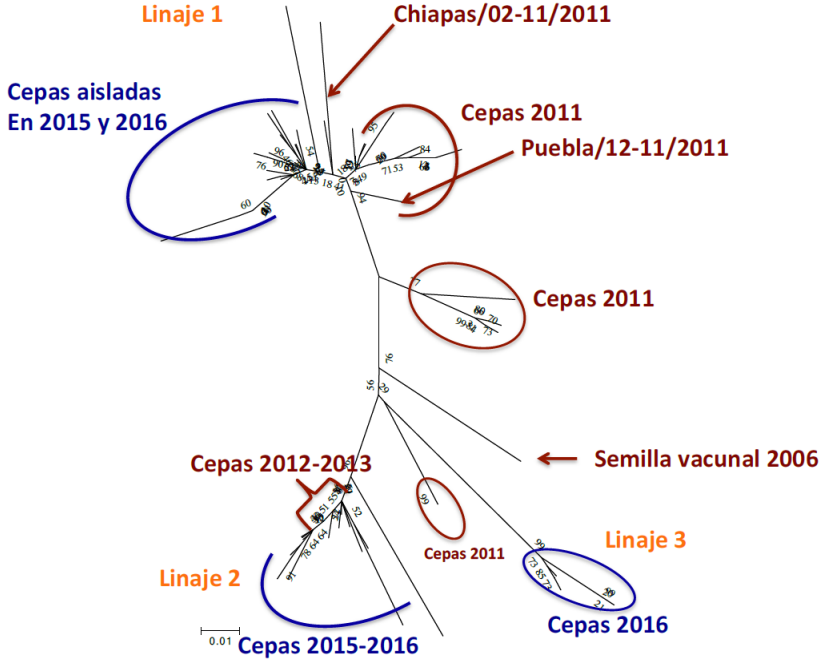
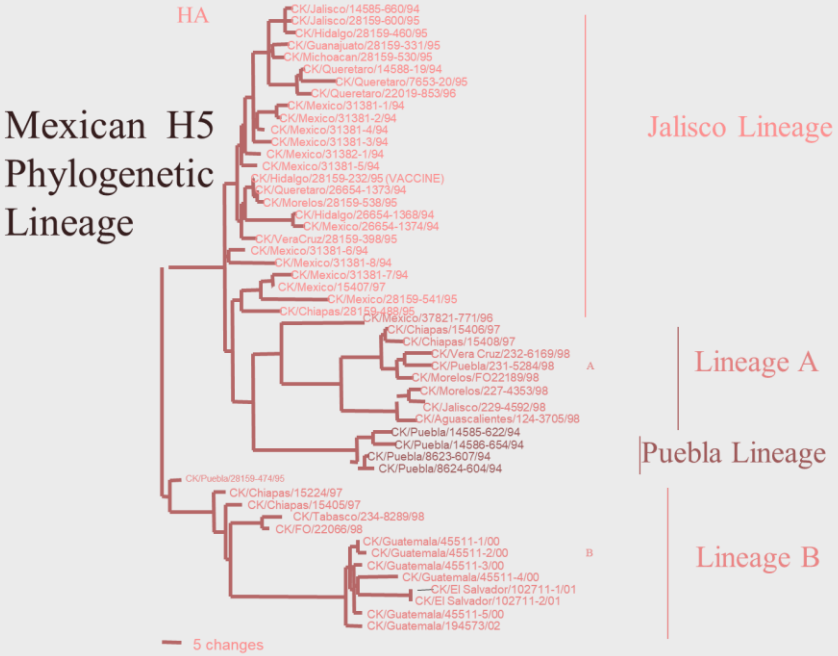


Figura 1. Historia evolutiva en forma lineal de cepas del virus de influenza aviar subtipo H5 aislados en México.



Sueros de aves vacunadas con Pronabive 94

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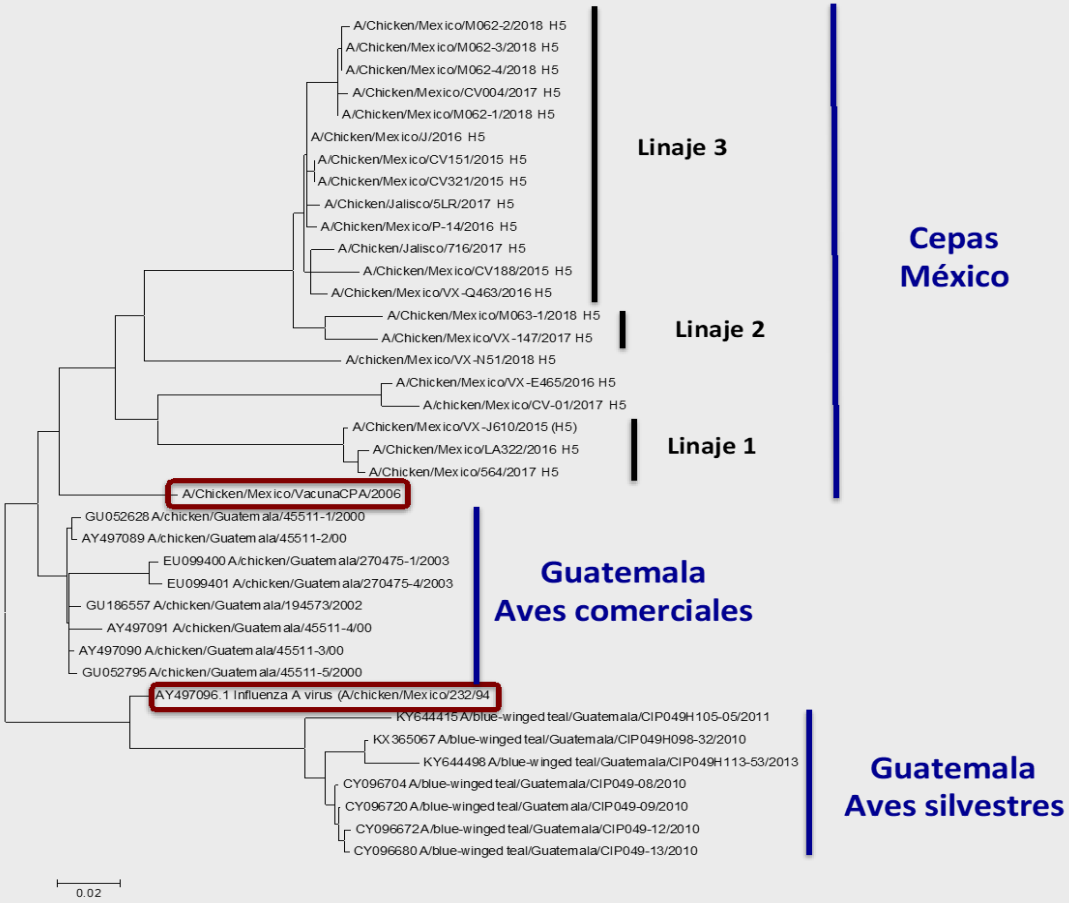
Isolate	Pathotype	Clevage site sequence	Genotype[b]	HI titer[c]
CK/Hidalgo/28159-232/94-vaccine seed	LP	RETR/G	Jalisco	640
CK/Mexico/31381-7/94	LP	RETR/G	Jalisco	256
CK/Queretaro/7653-20/95	HP	RKRKRKTR/G	Jalisco	320
CK/Jalisco/28159-600/95	LP	RETR/G	Jalisco	640
CK/Mexico/15407/97	LP	RETR/G	Jalisco	512
CK/Puebla/14585-622/94	HP	RKRKTR/G	Puebla	256
CK/Puebla/14586-654/94	HP	RKRKTR/G	Puebla	160
CK/Mexico/37821-771/96	LP	RETR/G	A	320
CK/Chiapas/15406/97	LP	KETR/G	A	160
CK/Morelos/FO22189/98	LP	KETR/G	A	128
CK/Puebla/28159-474/95	LP	RETR/G	B	512
CK/Guatemala/45511-1/00	LP	RETR/G	B	40
CK/El Salvador/102711-1/01	LP	RETR/G	B	40
CK/Guatemala/194573/02	LP	RETR/G	B	40

Información Gene bank.



Vacunas muertas emulsionadas.

Excreción viral relacionada a niveles de anticuerpos y homología de la semilla vacunal con el virus de campo.

.-Títulos más altos correlacionan con menor excreción viral.

.-Mayor homología correlaciona con menor excreción viral.

.-Títulos 1:40 con 100% homología

.-Títulos de 1:320 con 85% homología

.-Títulos de 1:40 con 85% homología

Títulos de anticuerpos altos.

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Bursal Disease Field Vaccines on Avian Influenza Vaccination Immunity

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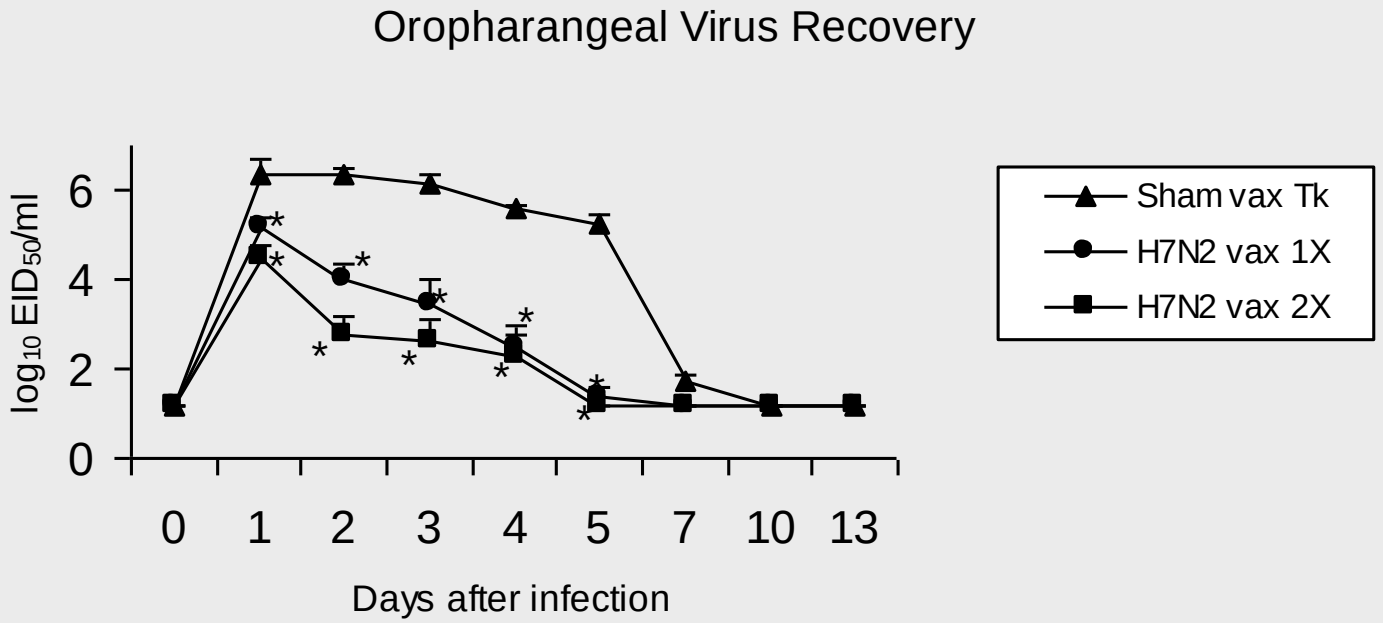
Key words ABSTRACT: IBD vaccine, H5N1, chickens

Traditional live Infectious Bursal Disease virus (IBDV) vaccines were thought to have some degree of adverse effect on the bursa of fabricous of chickens, which in turn may interfere with antibody production against other poultry vaccines. In this study, 15 broiler flocks vaccinated against avian influenza (AI) virus were sampled for serum. The flocks have received IBDV vaccination either from the conventional live vaccines or with the new recombinant subunit vaccine. Haemagglutination inhibition (HI) test was carried on sera using different AI antigens. Sera measured by the variant A/chicken/Egypt/VRLCU67/2011 (H5N1) isolate showed significant difference ($P<0.05$) between mean HI titers of bird vaccinated by traditional IBDV vaccines and titers of those vaccinated with the subunit vaccine. Results indicate that live IBDV vaccines may affect the efficacy of AI vaccine, and the study encourages the use of the field AI isolates for reliable interpretation of HI test results.

Títlos de anticuerpos altos

Vaccine (4 & 6 wks): A/chicken/Pennsylvania/21342/97 (H7N2)
Challenge (8 wks): A/turkey/Virginia/158512/02 (H7N2)



Programas de vacunación.

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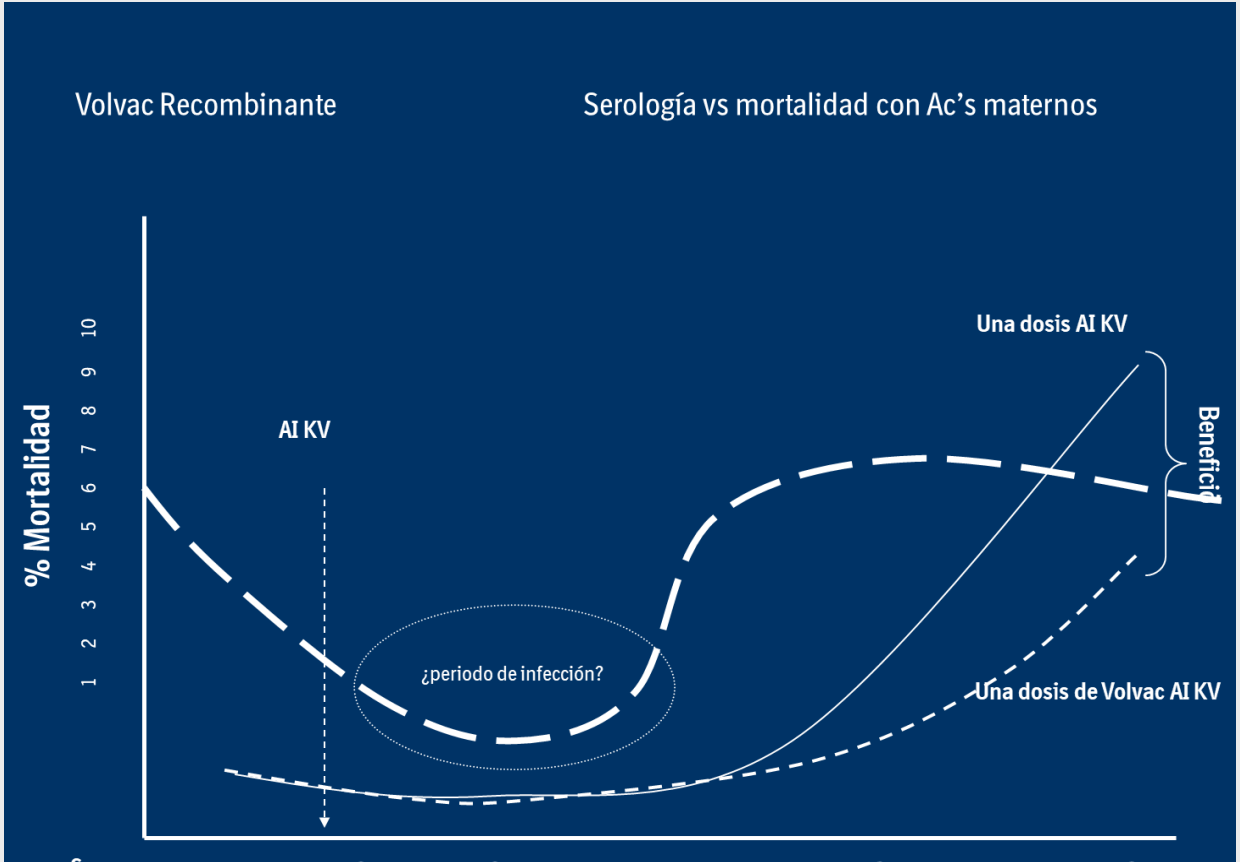
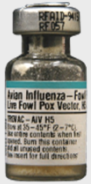


Programas de vacunación

PROGRAMA PRIME BOOST

D0



D10-21

1. Vacunación en incubadora con una vacuna viva vectorizada

2. Vacunación en campo con una vacuna muerta emulsionada.

- 2 tipos de vacuna
- 2 respuestas inmunes
  - Humoral
  - Celular

Programas de vacunación

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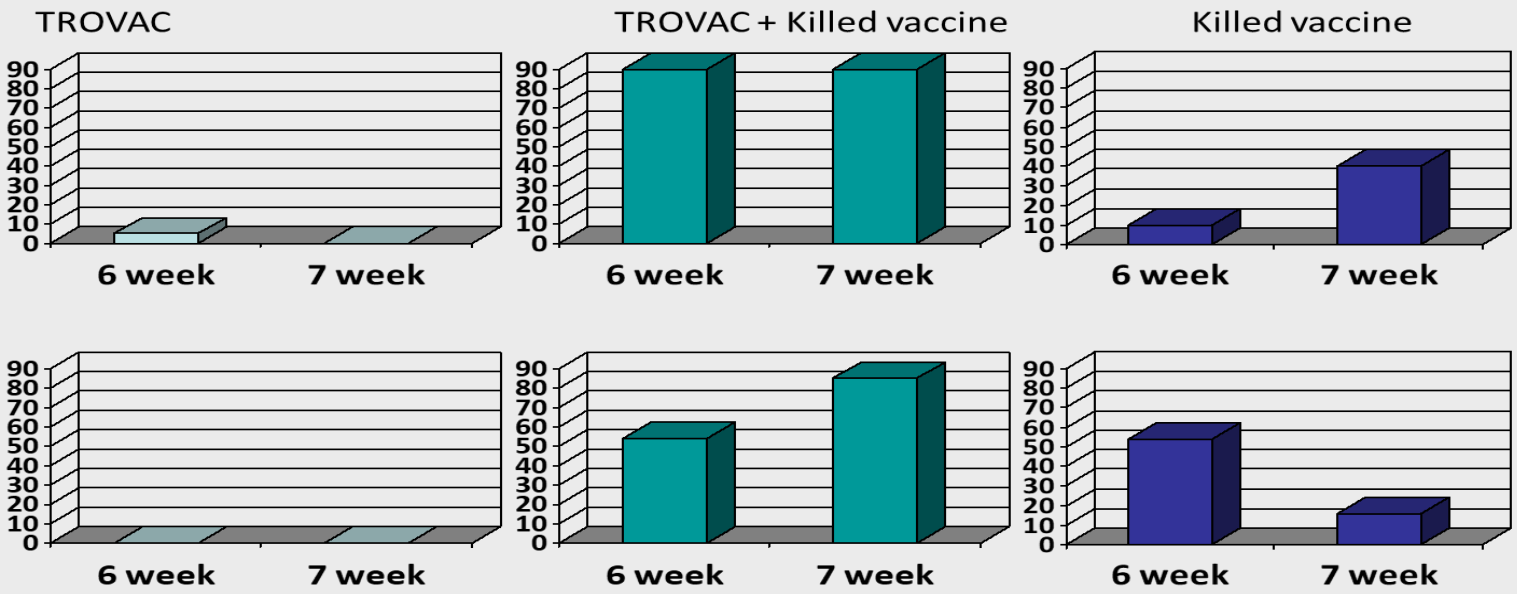
PRIME BOOST



Farm 1 vs. Farm 2
TROVAC 1 day old SC;
Serology 6, 7 weeks old

Inactivated AI vaccine - 15 days old - SC

Programas de vacunación

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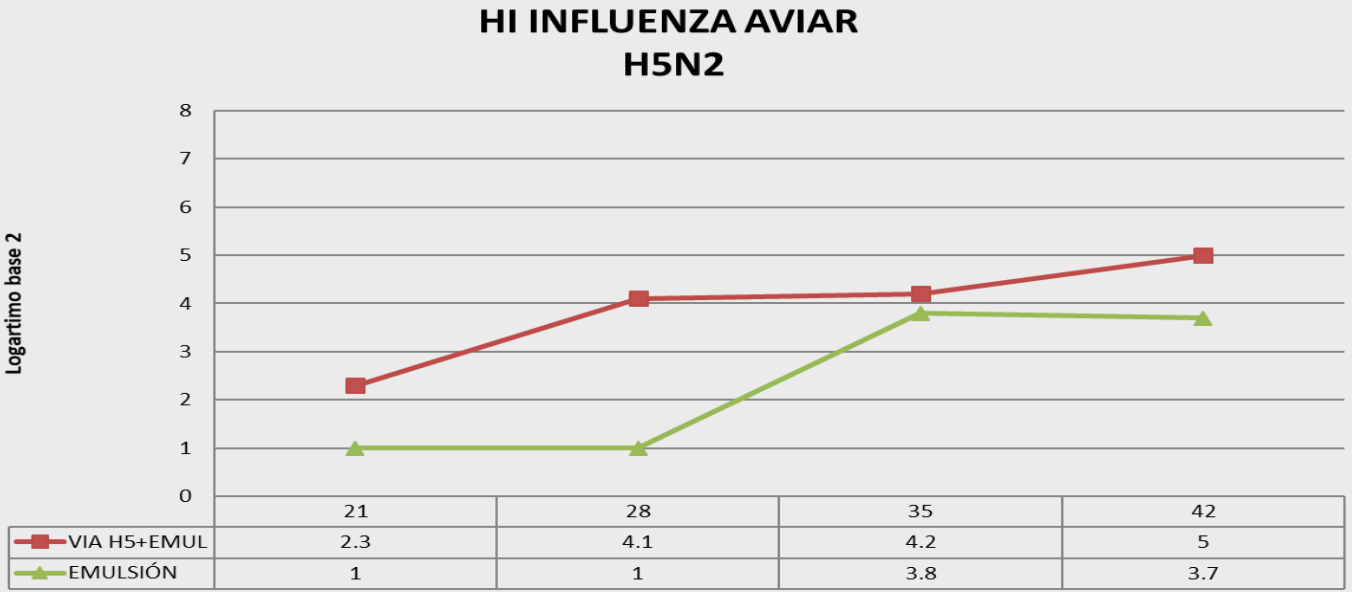
RESULTADO SEROLOGÍA
TROVAC + EMULSIÓN vs EMULSIÓN



1 día	12 días
Marek HVT+TROVAC VIA-H5	Emulsión ND+IA
Marek HVT	Emulsión ND-IA

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Prime-Boost (It-H5N9) **protection with FP MDA**

Richard-Mazet *et al.* (2014)
Vet. Res. 45:107

- **D0 / D14:** Vaccination of **SPF & FP MDA+** chicks
- **D28:** chall. with **A/ck/West Java (Spg)/29/2007 H5N1**

MDA	Vaccination		H5N8 HI titers D28	Protection (chall. at D28)
	V1 - D0	V2 - D14		
-	-	-	-	0/10 (0%)
-	vFP89	-	5.5 (100%)	1/10 (10%)
FP	-	H5N9 inact.	5.1 (100%)	5/9 (56%)
FP	**vFP89**	**H5N9 inact.**	**8.1 (100%)**	**9/9 (100%)**

USDA ARS
D. Swayne

Synergistic effect of prime-boost on HI titers and protection in birds with anti-vector (FP) MDAs

Programas de vacunación.

Resultado

1er. prueba

2da. prueba

- La respuesta serológica para Influenza Aviar H5N2 fue mejor y más rápida,(21 días) posterior a la aplicación de vacuna emulsiona en las aves vacunadas con TROVAC VIA.H5

Programas de vacunación.

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2ª prueba comparativa mar-may 2017

Parámetro	Con Trovac	Sin Trovac	Diferencia
Aves recibidas	145,916	102,917	
Edad a venta (días)	44	43	1
% Mortalidad	6.65	9.46	-2.81
Hembras	5.28	7.87	-2.59
Machos	8.99	15.38	-6.39
Peso promedio (Kg)	2.584	2.551	33
Ganancia diaria (g)	60	59	1
Conversión*	1.780	1.768	12
Hembras	1.753	1.737	16
Machos	1.817	1.863	-46
Indice de producción	315	304	11

Participación del mercado.

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AI TOTAL MARKET

Broilers

1,672 Millones

-34% POBLACION NO VACUNABLE

1,104 Millones

UNIVERSO

Millones

Incubadora

TROVAC H5 — 100% — 1,104

Dosis Única

Granja

INACTIVADAS — 100% — 1,656

1.5 Dosis

Pollita Comercial

101.6 Millones

-17% POBLACION NO VACUNABLE

83 Millones

UNIVERSO

Millones

Incubadora

TROVAC H5 — 100% — 83

Dosis Única

Granja

INACTIVADAS — 100% — 332

4 Dosis

Potencial para TROVAC H5	1,104	+	83	1,187 Millones de DOSIS	702.7 Millones	75%
Potencial para Volvac AI+ND KV Concentrada 2.5K Dosis	1,656	+	332	1,998 Millones de DOSIS	189 Millones	19.5%

Penetración en Dosis 2017

Otras vacunas vectorizadas.

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AVIAN DISEASES 54:239–241, 2010

Protective Dose of a Recombinant Newcastle Disease LaSota–Avian Influenza Virus H5 Vaccine Against H5N2 Highly Pathogenic Avian Influenza Virus and Velogenic Viscerotropic Newcastle Disease Virus in Broilers with High Maternal Antibody Levels

David Sarfati-Mizrahi,[A] Bernardo Lozano-Dubernard,[A] Ernesto Soto-Priante,[AC] Felipa Castro-Peralta,[A] Ricardo Flores-Castro,[B] Elizabeth Loza-Rubio,[B] and Manuel Gay-Gutiérrez[A]

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Received 27 March 2009; Accepted and published ahead of print 1 September 2009

Table 2. Protection conferred against mortality after challenge with VVNDV or HPAIV 21 days postvaccination.

	Vaccine						
	rNDV-LS/AI-H5 (dose)				LaSota (dose)		None
Challenge viruses	4.8[A]	5.8	6.8	7.8	5.8	6.8	0
NDV	55%[B]	80%	90%	100%	75%	90%	0%
AIV	80%	85%	90%	100%	10%	0%	20%

[A]Log_{10} chicken embryo infective doses given by eye drop at 10 days of age.
[B]Percentage of protection from mortality within the 10-day observation period.

LAB	PRODUCT	YTD FEB'17 MIO	YTD FEB'18 MIO	Growth %	Growth MIO
BIAH	VAC VIRUELA MERIAL	$ 14.00	$ 17.78	27.0%	$ 3.8
BIAH	VAXXITEK HVT + IBD 4000 DS X 1	$ -	$ 12.04	100.0%	$ 12.0
CEVA	VECTORMUNE HVT AIV	$ 19.52	$ 10.07	-48.4%	-$ 9.5
CEVA	VECTORMUNE FP LT	$ 8.10	$ 9.40	16.0%	$ 1.3
CEVA	VECTORMUNE HVT NDV 4000 DS	$ 1.65	$ 8.37	407.8%	$ 6.7
MSD	NOBILIS IB 4-91	$ 5.82	$ 6.41	10.1%	$ 0.6
BIAH	VAXXITEK HVT + IBD 2000 DS	$ 25.29	$ 6.34	-75.0%	-$ 19.0
MSD	COCCIVAC D	$ 1.68	$ 5.49	226.3%	$ 3.8
BIAH	VOLVAC ND MLV (LASOTA)	$ 3.55	$ 4.14	16.6%	$ 0.6
BIAH	GALLIMUNE ND DAY OLD	$ 4.86	$ 3.93	-19.2%	-$ 0.9

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Influenza: una carga epidemiológica importante

- Cada año en el mundo: / ***7,324,782,000***

  - ✓ 5 – 10% de los adultos se ven afectados por infecciones del tracto respiratorio superior por influenza
  - ✓ 20 – 30% de los niños presentan influenza anualmente
  - ✓ 3 a 5 millones de casos de enfermedad severa
  - ✓ 250,000 a 500,000 muertes

WHO Fact sheet N° 248, Octubre 2015. http: www.who.int/mediacentre/factsheets/fs211/en/ Acceso en Oct 28 , 2015
http://populationpyramid.net/es/mundo/2015/

Influenza Humana

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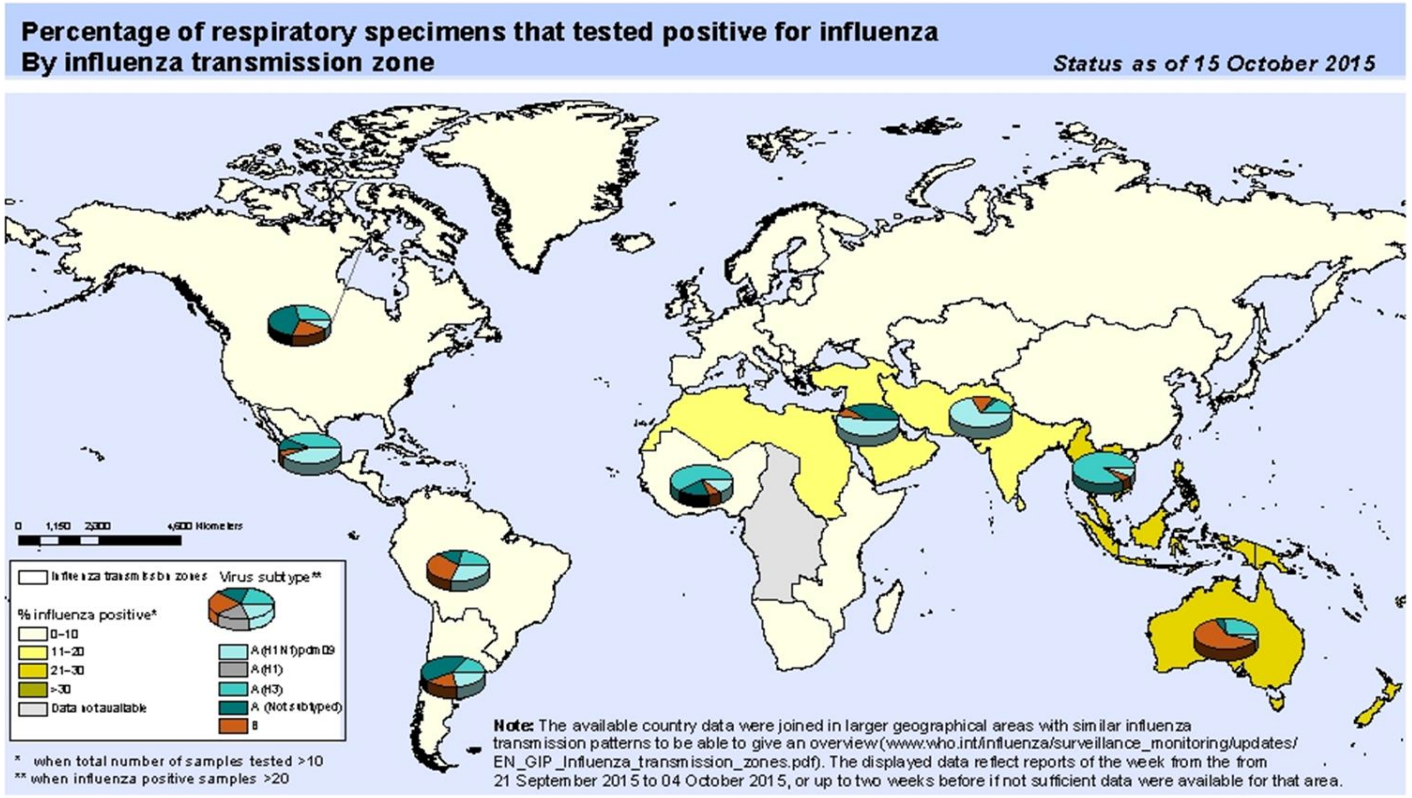

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Global Influenza Surveillance and Response System (GISRS), FluNet (www.who.int/flunet),

World Health Organization

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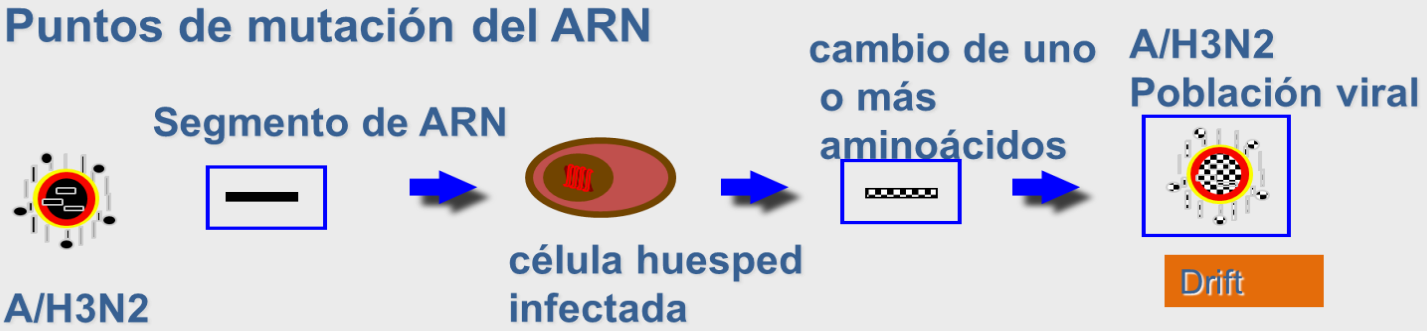
Cambios antigénicos “Drift”
cambios menores en HA o NA

- Afecta virus influenza A y B
- Ocurre cada año o varios años dentro de un subtipo de influenza
- Las mutaciones afectan los aminoácidos del ARN
- No ocasionan nuevos subtipos
- Pueden provocar epidemias significatívas



Betts FR, Douglas RG, Mandell G.L., Douglas R. G., Bennett J.E., Principles and practice of infectious diseases, 3rd ed., 1990;39:1306-25

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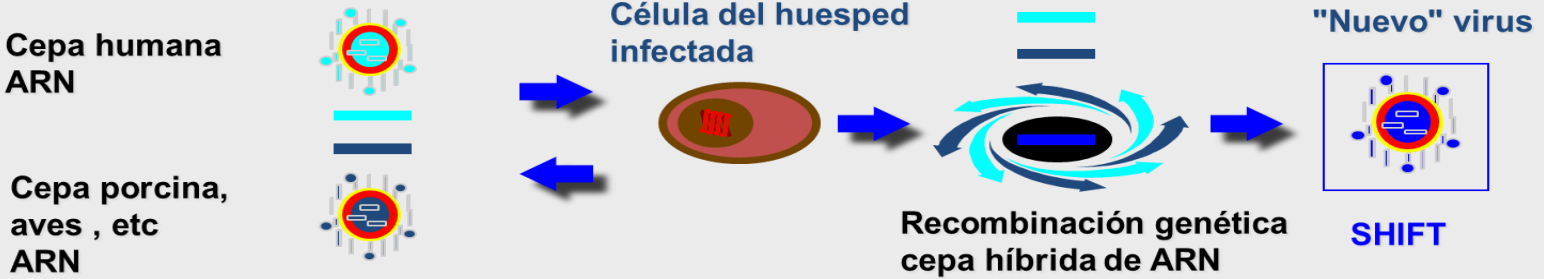
Cambios Antigénicos Mayores (Shift)

- Afecta sólo al virus Influenza A
- Variaciones genéticas grandes y repentinas en HA y/o NA
- No hay inmunidad en la población
- Resulta en pandemias cada 10 a 40 años

Recombinación de ARN



Resulta en un nuevo subtipo: "nueva" HA y/o "nueva" NA

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Pandemias de Influenza

1918: "Influenza Española"

> 50 millones de muertes

1957: "Influenza Asiática"

1-4 millones de muertes

- En los últimos 100 años han ocurrido 4 pandemias

1968: "Influenza Hong Kong"

1 – 4 millones de muertes

2009: "Influenza Mexicana"

575,400*

Lancet, 2009. Influenza H1N1 Albert Osterhaus

Lancet Infectious Diseases 2012. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Dawood Fatima.

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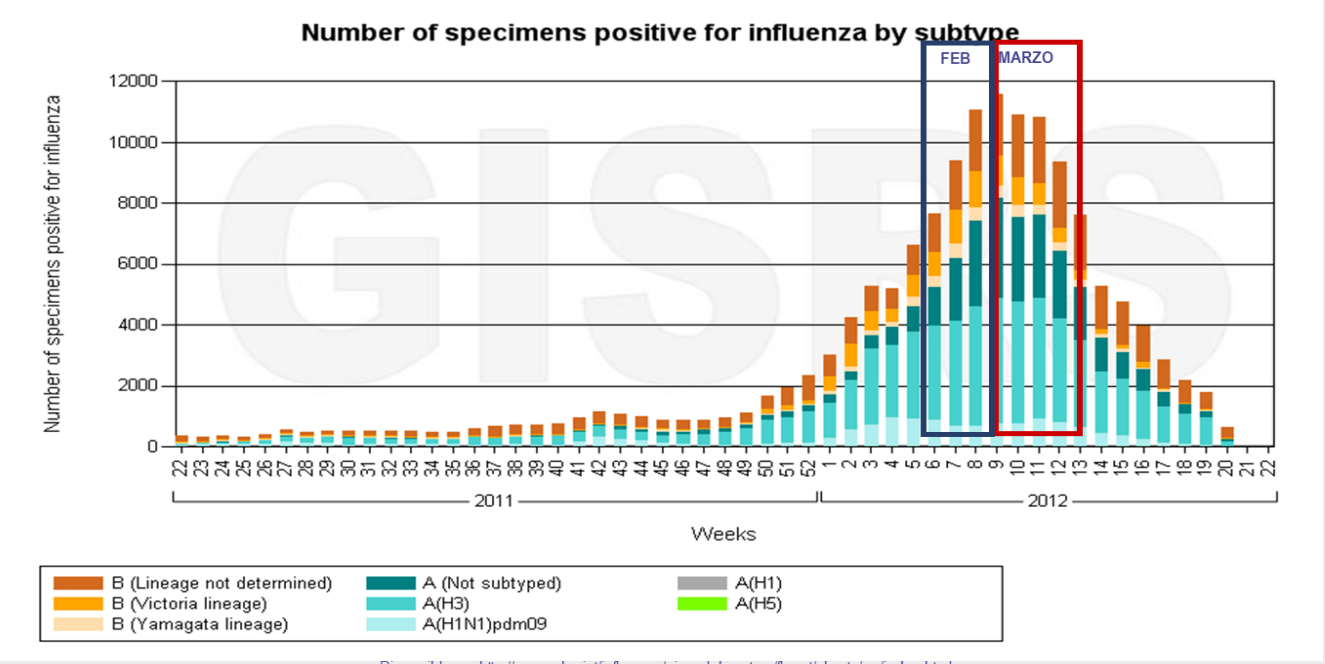
Distribución de los virus circulantes por semana epidemiológica, México , 2012



Disponible en: http://www.who.int/influenza/gisrs_laboratory/flunet/charts/en/index.html

Influenza Humana

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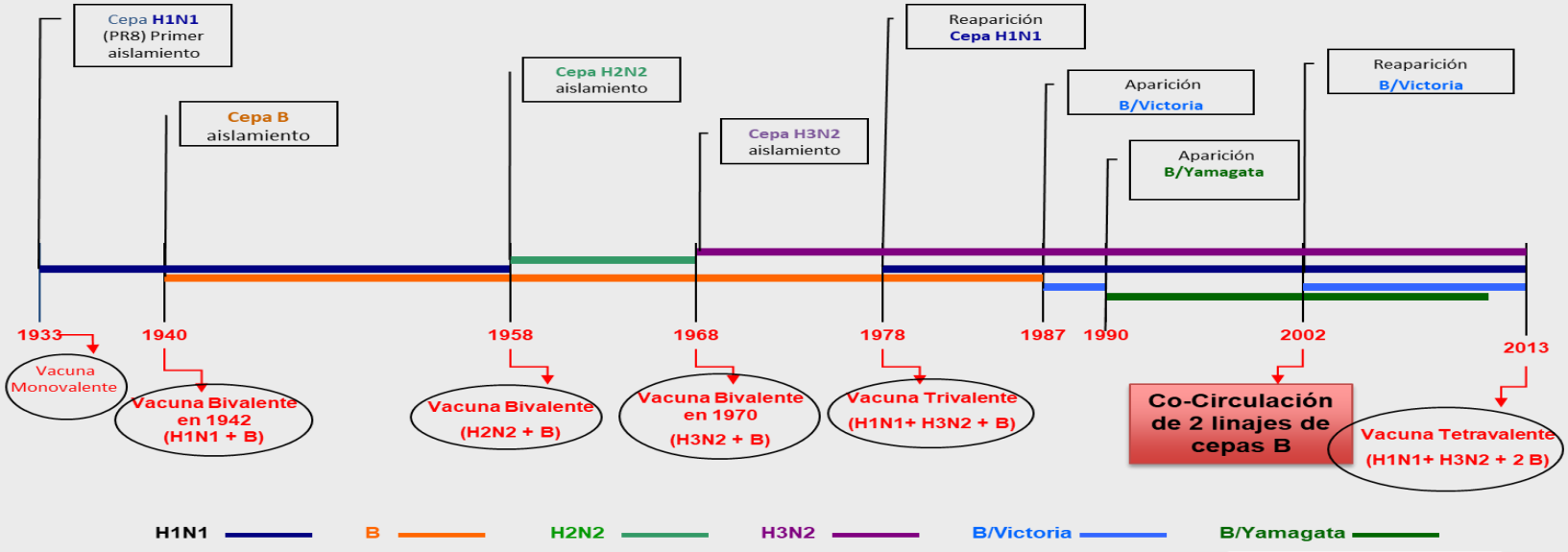
Evolución del virus de Influenza y co circulación
Racional para el desarrollo de vacunas



Las vacunas deben evolucionar paralelamente para mantener el nivel de protección

Figura adaptada de Hannoun, Expert rev. Vaccines 12(9), 1085-1094 (2013)

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Recomendación de la Vacunación Universal contra Influenza

- ACIP recomienda la vacunación anual contra influenza para todas las personas de 6 meses de edad en adelante, incluyendo todos los adultos, al menos que haya contraindicación[1]

  Niños de 6 meses a <9 años de edad que requieren 2 dosis, si no han sido adecuadamente primovacunados

- Esta recomendación universal es en el reconocimiento de los siguientes hechos[1]:
  - ✓ ***Todo el mundo tiene riesgo de tener influenza***
  - ✓ ***Cada caso de influenza puede conducir a resultados médicos graves***
  - ✓ ***Cada caso de influenza es potencialmente prevenible***

[a] ACIP = Advisory Committee on Immunization Practices.

Reference: 1. Centers for Disease Control and Prevention (CDC). Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on

Futuro no muy lejano.

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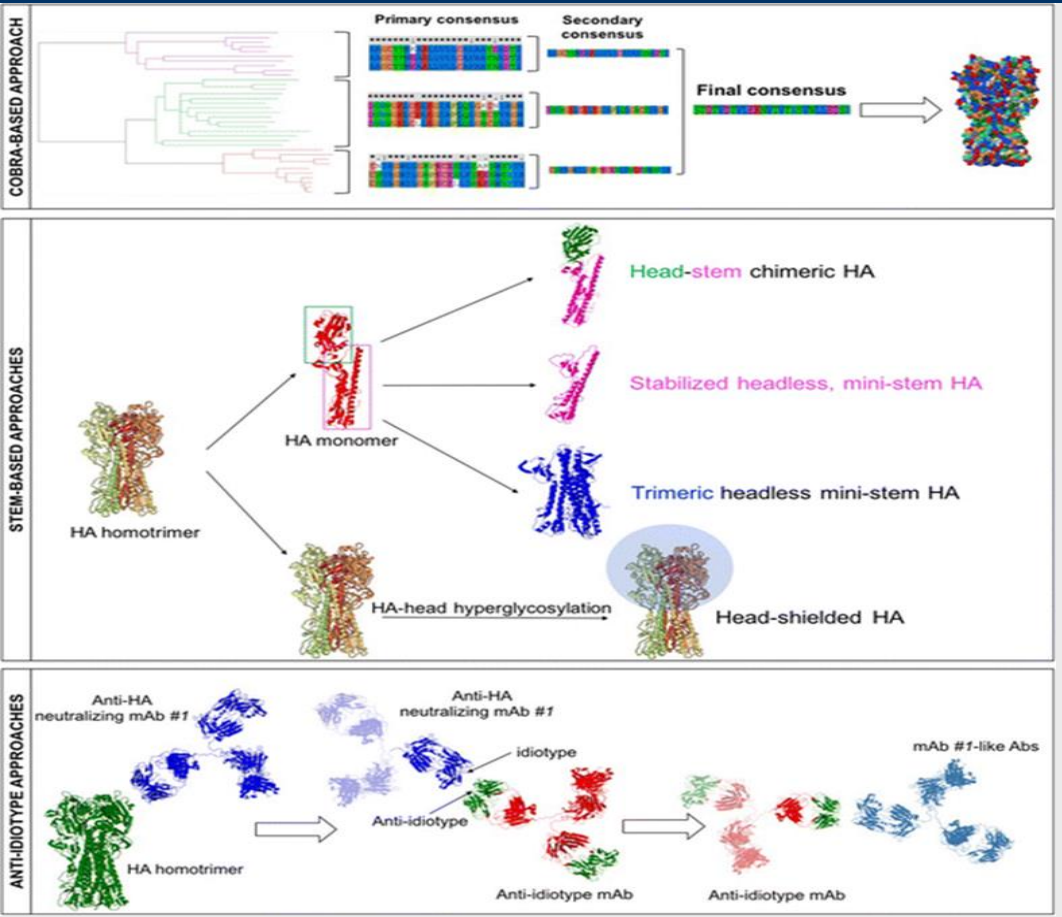

Aportando valor...

Unidades de aislamiento

Conclusiones

Es necesario modificar el marco regulatorio (estimular el reporte de brotes y adoptar estrategia de vacunas de la IH).

Se debe monitorear la deriva antigénica de los virus de campo de manera constante.

La deriva antigénica obliga a la actualización constante de la semilla vacunal.

El programa prime boost Pox/H5 + emulsión actualizada es el que mejor resultado ha obtenido en término de protección.

El usar el virus de campo como antígeno en la prueba de HI es un buen predictor de la protección.