



Why protect at-risk groups against influenza and how to improve Influenza vaccine effectiveness?



Prof. Ab Osterhaus DVM, PhD

Director Research Center for Emerging Infections and Zoonosis (RIZ)

University of Veterinary Medicine Hannover (D)

CSO Viroclinics-Biosciences BV (NL)

Chair One Health Platform

Chair ESWI



12.09.2017

Mena meeting Riga September 10th 2017





COI statement

- ***CSO Viroclinics Biosciences BV Rotterdam (NL)***
- ***Board Member Protein Sciences Corp. (USA)***
- ***Ad-hoc consultant / SAB member Pharma***

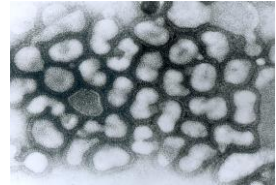


Influenza

-clinical symptoms -

- Acute onset
- Sore throat
- Coughing
- Redness of mucosae
- Fever $>39^{\circ} \text{C}$
- Myalgia
- Total malaise
- Shivers

Human influenza:



three appearances

Seasonal influenza

(A: H3N2, H1N1; B)

Avian influenza A:

H5, H6, H7, H9, H10...

Pandemic influenza

(A: H1N1, H2N2, H3N2, H1N1...?)



Global Circulation of Seasonal Influenza A (H3N2) Viruses



Asia is the epicenter for both influenza A/H1N1 and /H3N2 subtypes.

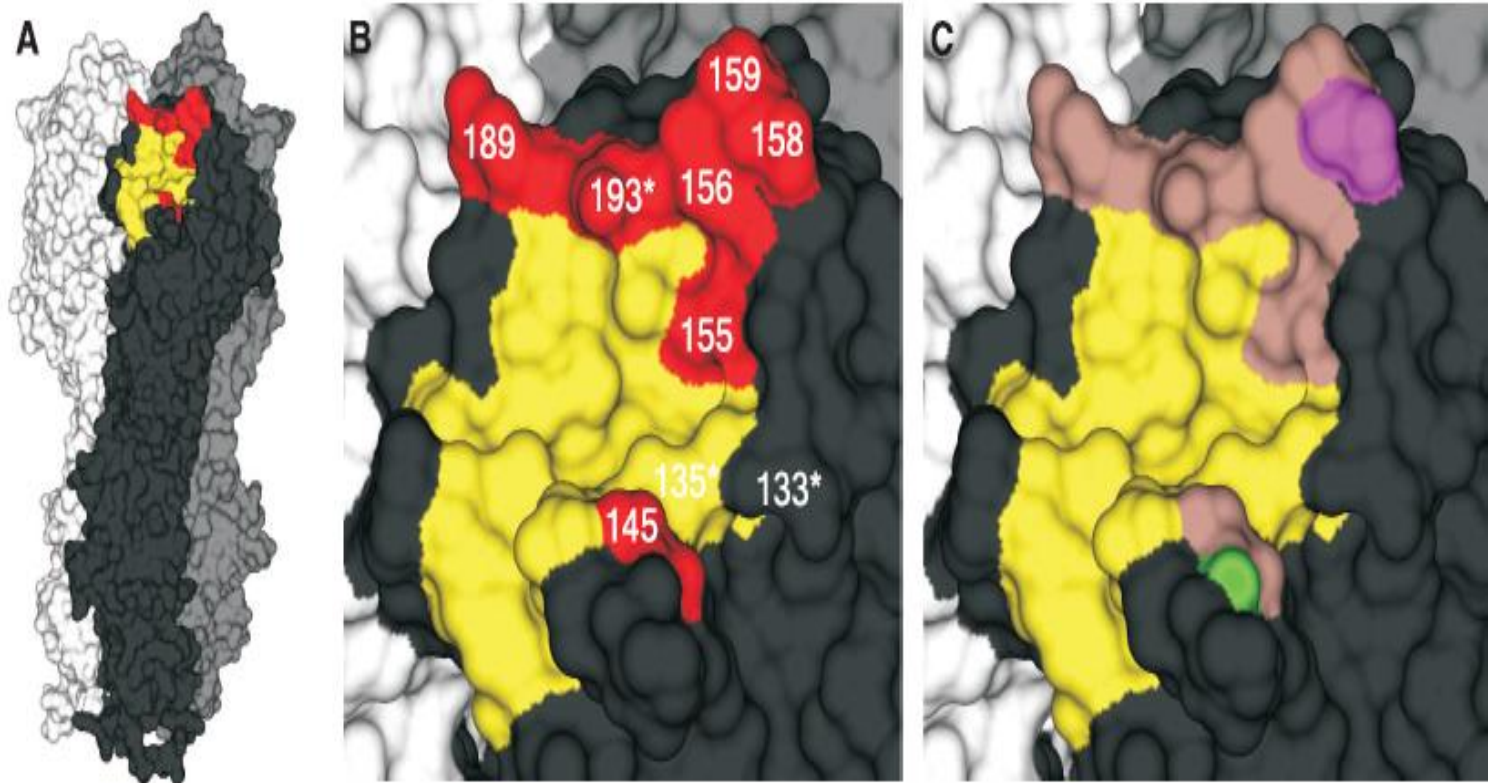
Russel et al. Science, 2008

But not for influenza B viruses. *van der Vries et al., submitted*

Substitutions near the receptor binding site determine major antigenic change during influenza virus evolution

BF Koel et al, Science. 2013

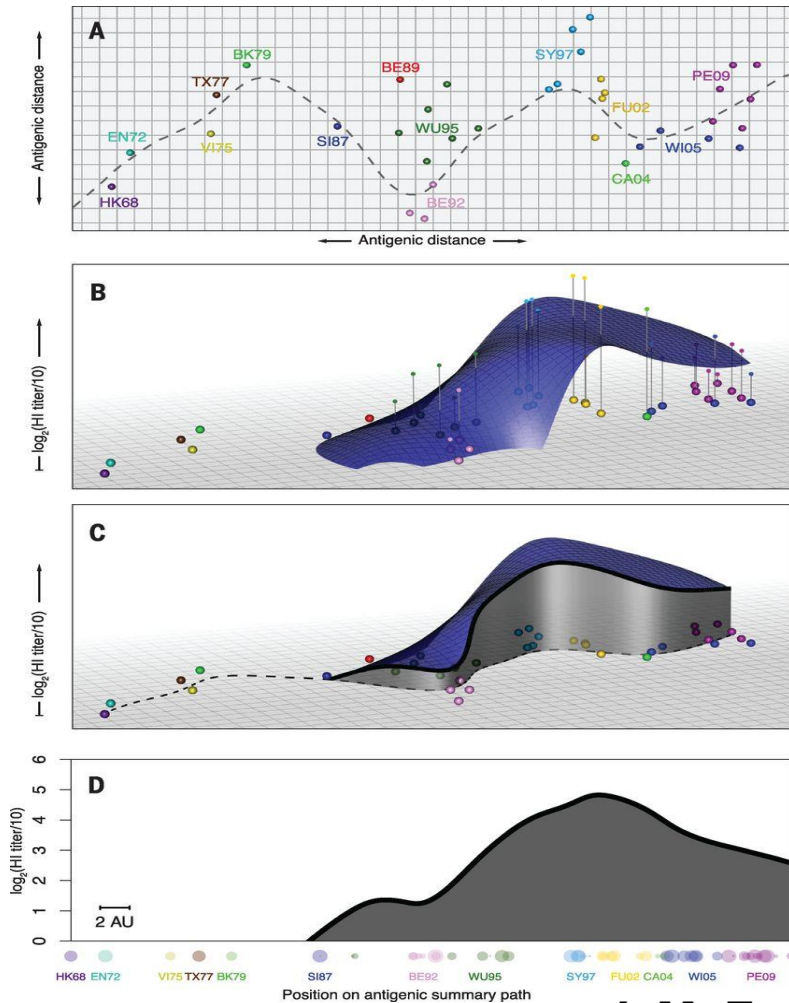
Fig. 2. Positions of the cluster-transition amino acid substitutions indicated on an A/Aichi/2/1968 HA trimer. The three monomers are shown in black, white, and gray, the RBS is in yellow. (A and B) The positions responsible for A/H3N2 cluster transitions are shown in red. An asterisk indicates accessory substitutions (fig. S10). Position 193 is both a cluster-transition substitution and an accessory substitution (Fig. 1B). (C) Positions of amino acid substitutions responsible for antigenic change of influenza A/H1N1 and B virus are shown in green and magenta, respectively. The positions responsible for cluster transitions of A/H3N2 virus are shown in light brown.



Creating an antibody landscape

Science

AAAS



A) Antigenic map of A/H3N2 showing virus strains color-coded by antigenic cluster.

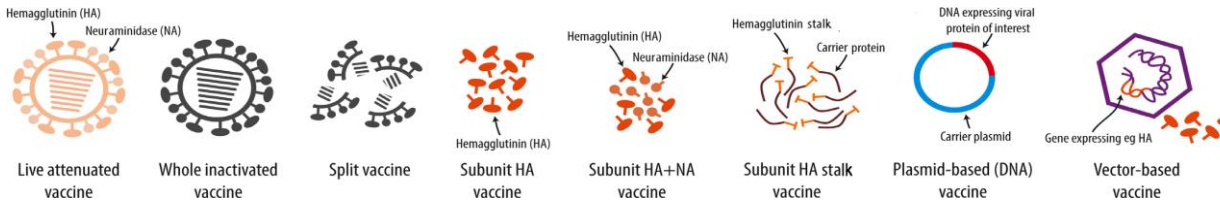
B) An additional dimension indicates the measured antibody titers as vertical impulses, and a smooth surface is fitted using locally weighted multiple linear regression

C) The height of the landscape along the path in (A) shows a slice through the landscape

D) The height of the landscape along the antigenic summary path in (C) is plotted independent two-dimensional space

J. M. Fonville et al. *Science* 2014;346:996-1000

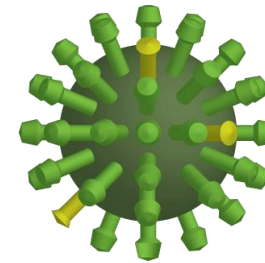
Figure 2. Range of current and new vaccine presentations against influenza A virus



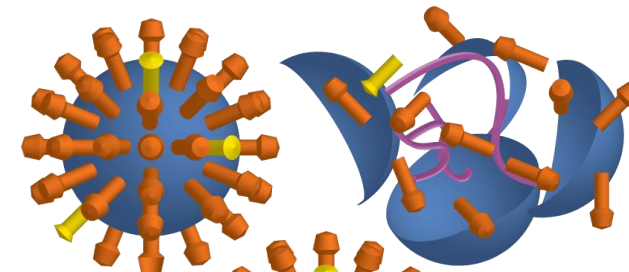
Types of registered human viral vaccines

<u>Type of vaccine</u>	<u>Examples</u>	<u>Correlate of protection</u>
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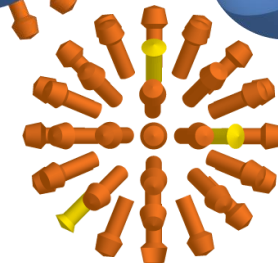
Live attenuated	Oral polio Measles Mumps Rubella Varicella Influenza	Antibody + CTL response (MHC-I processing of viral proteins after active replication)
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Whole inactivated / Split whole	Inactivated polio Influenza Hepatitis A	Antibody
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Subunit/Rec.protein	Hepatitis B Papilloma Influenza	Antibody
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Baculovirus Expression Vector System (BEVS)



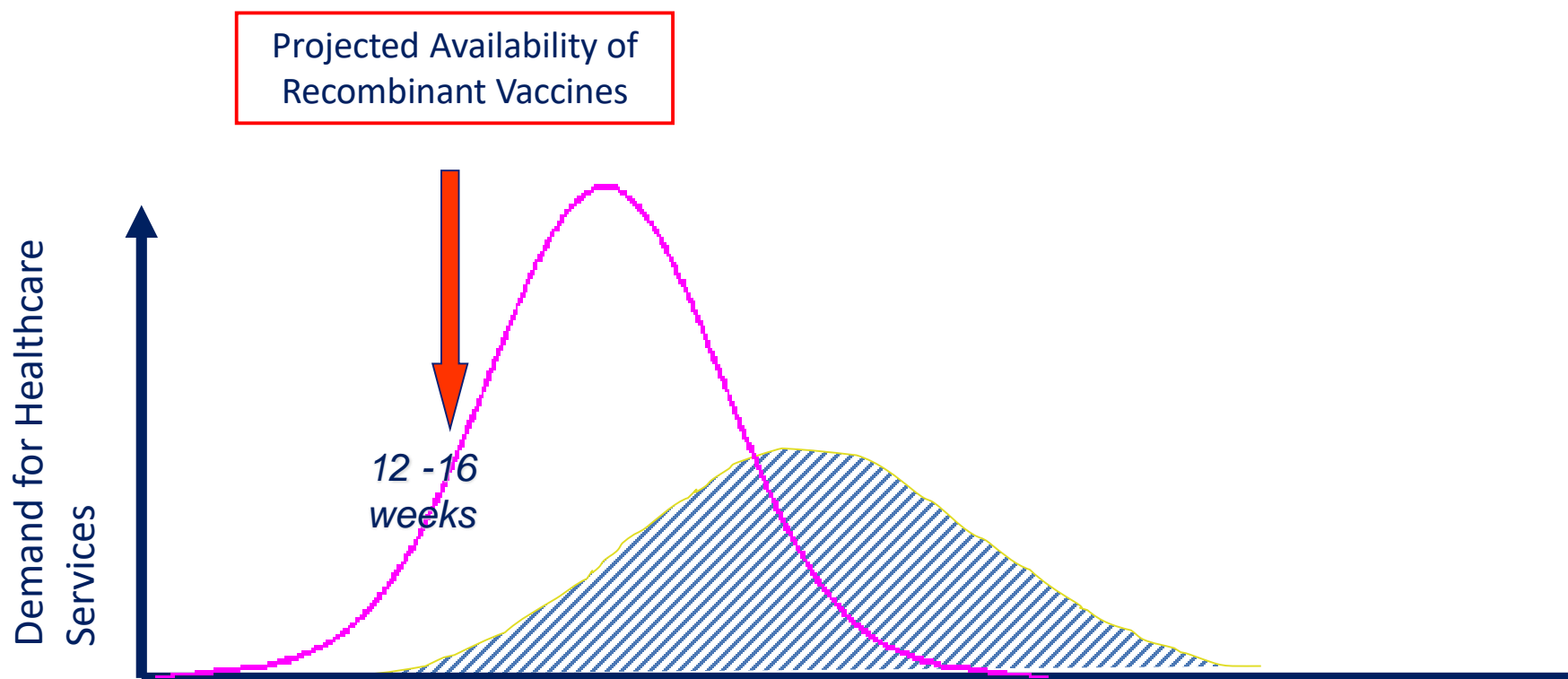
- n Engineer baculovirus with the gene of interest (e.g. Hemagglutinin)
- n Baculoviruses highly specific to insect cells
- n Powerful promoter generates high yield of protein of interest

- n Culture expression of insect cells in a fermenter
- n Infect cells with engineered virus
- n Incubate infection for ~48 - 72 hours

- n Protein forms rosettes
- n Purify protein to > 90% into final product
- n Formulate with PBS into vaccine

Flublok Approval → Validation

Recombinant pandemic influenza vaccines are projected to be available much sooner than those produced with egg-based technology.



Adapted from R. Robinson's presentation to FDA's VRBPAC on February 29, 2012

Flu risk groups 1/2



If you are over 65 years of age, or under 5, you have a higher chance of suffering ill side effects of influenza. Either your body and immune system are not yet developed enough to ward off the flu virus or your body has become weaker through age and your immune system may not be strong enough.



- Chronic lung diseases such as asthma
- Cancer
- Diabetes
- Heart disease
- Kidney, liver and blood disease
- Neurological and neuromuscular diseases

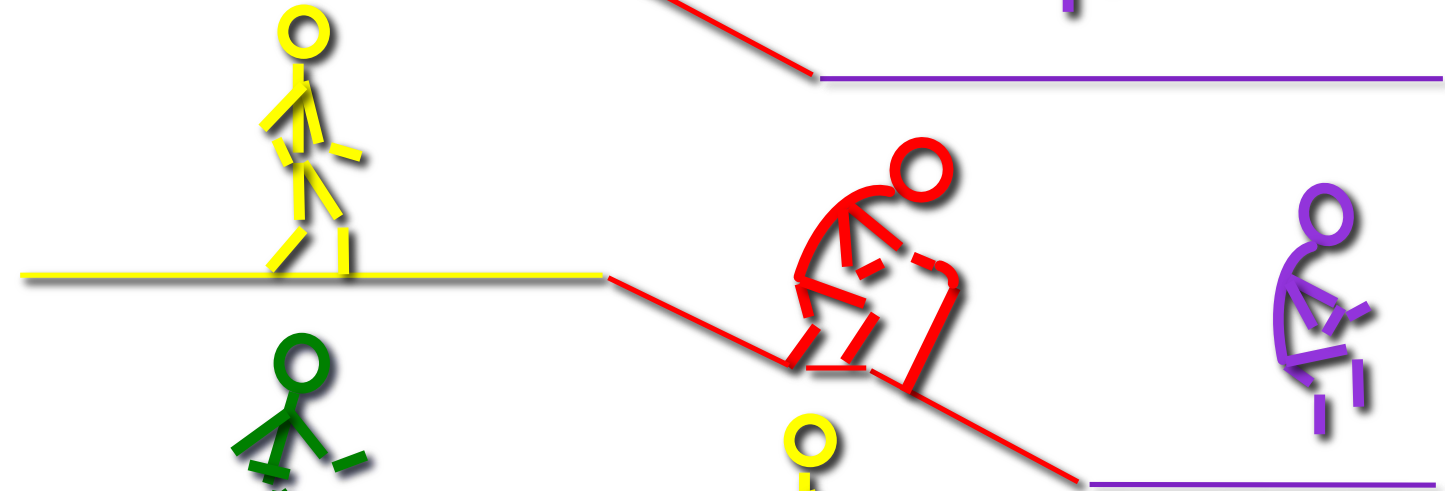
Seniors' Health: Adding Life To Years



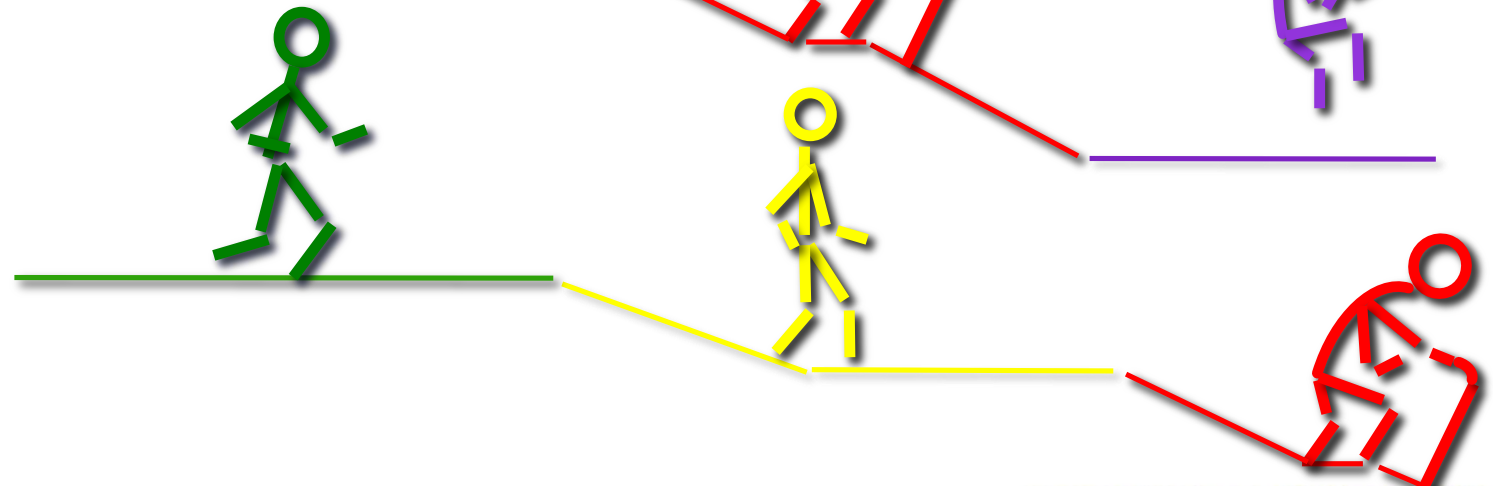
1980's



1990's



2000's



60

70

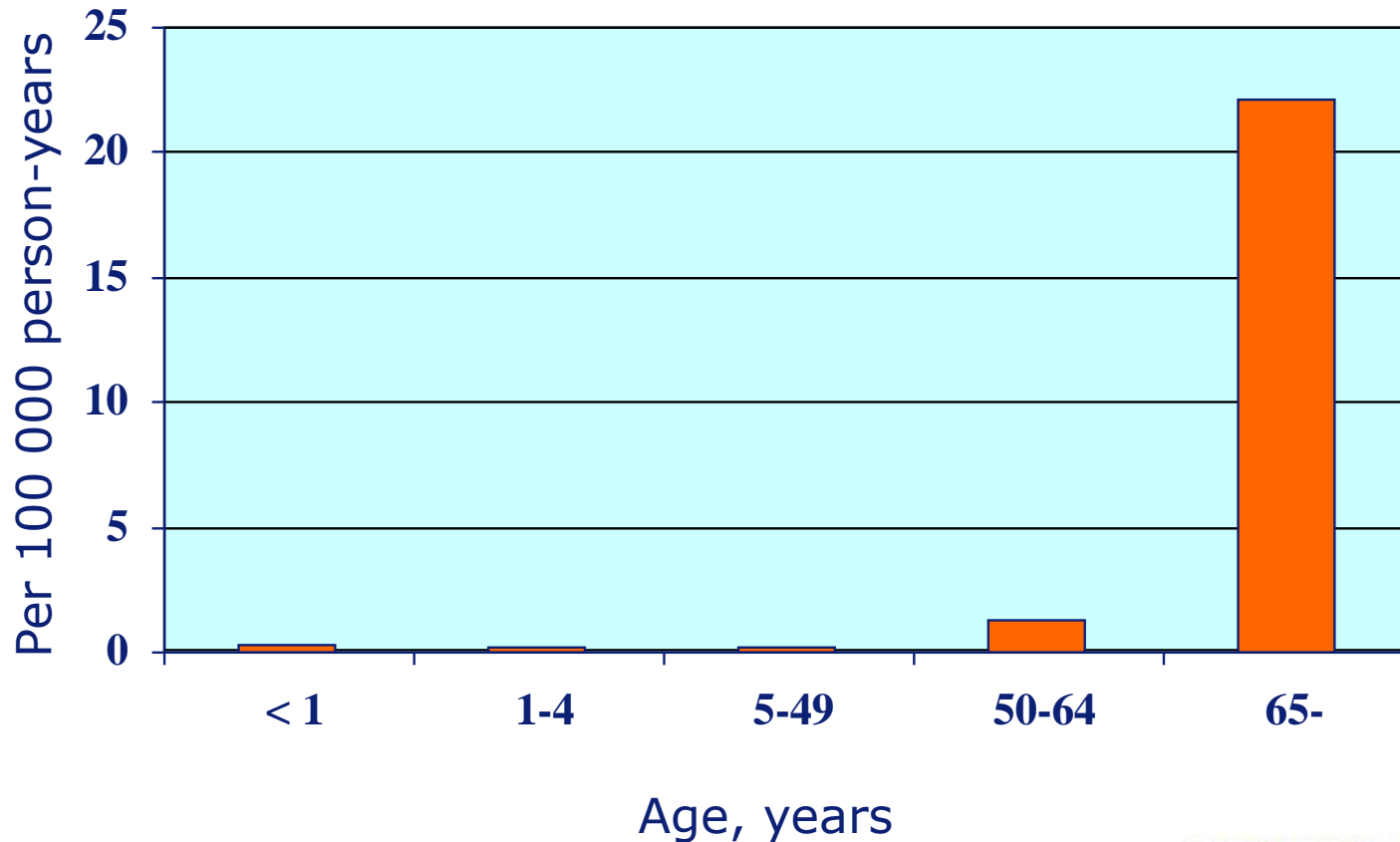
80

90

Age

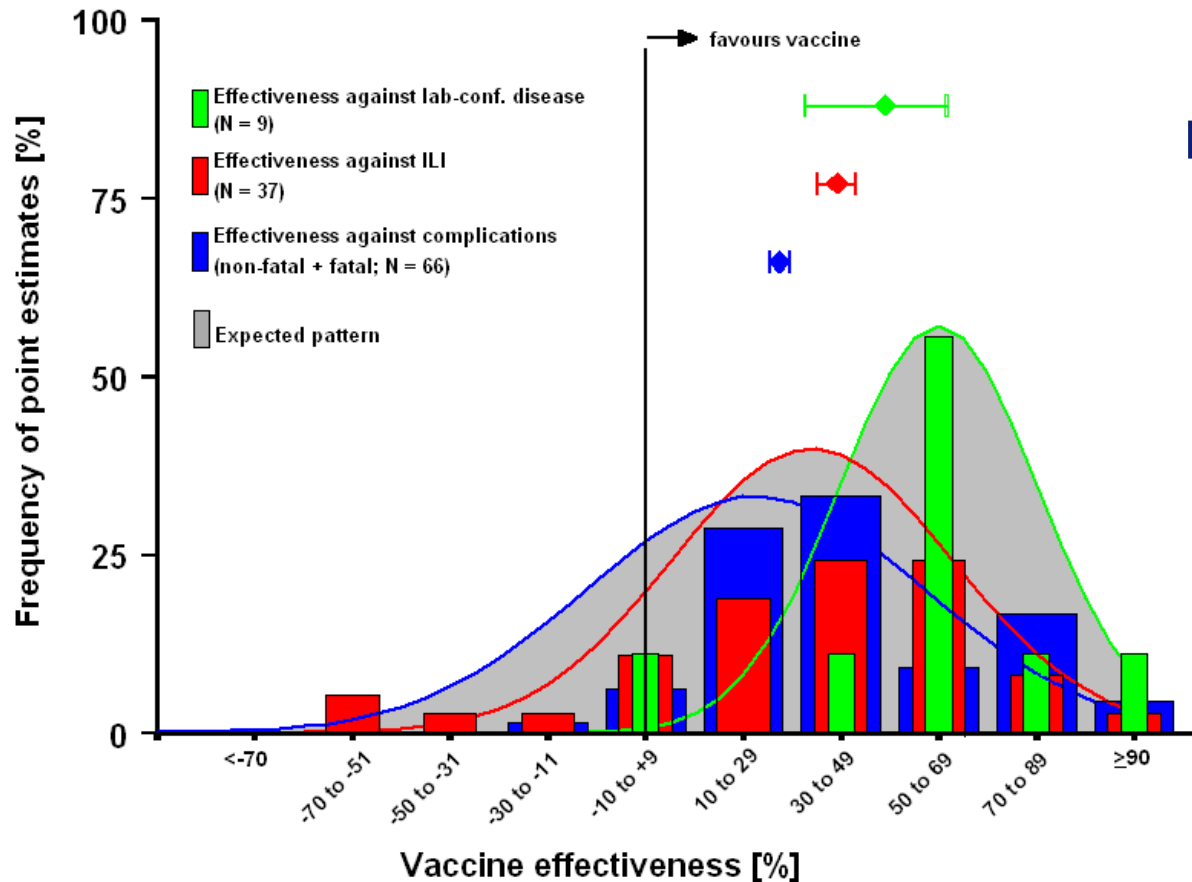
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Annual influenza-associated mortality rates



Thompson et al., JAMA 2003

Distribution of VE point estimates according to alternative outcome definitions.



Beyer et al., 2013 Vaccine:

‘Cochrane revisited’



Flu risk groups 2/2

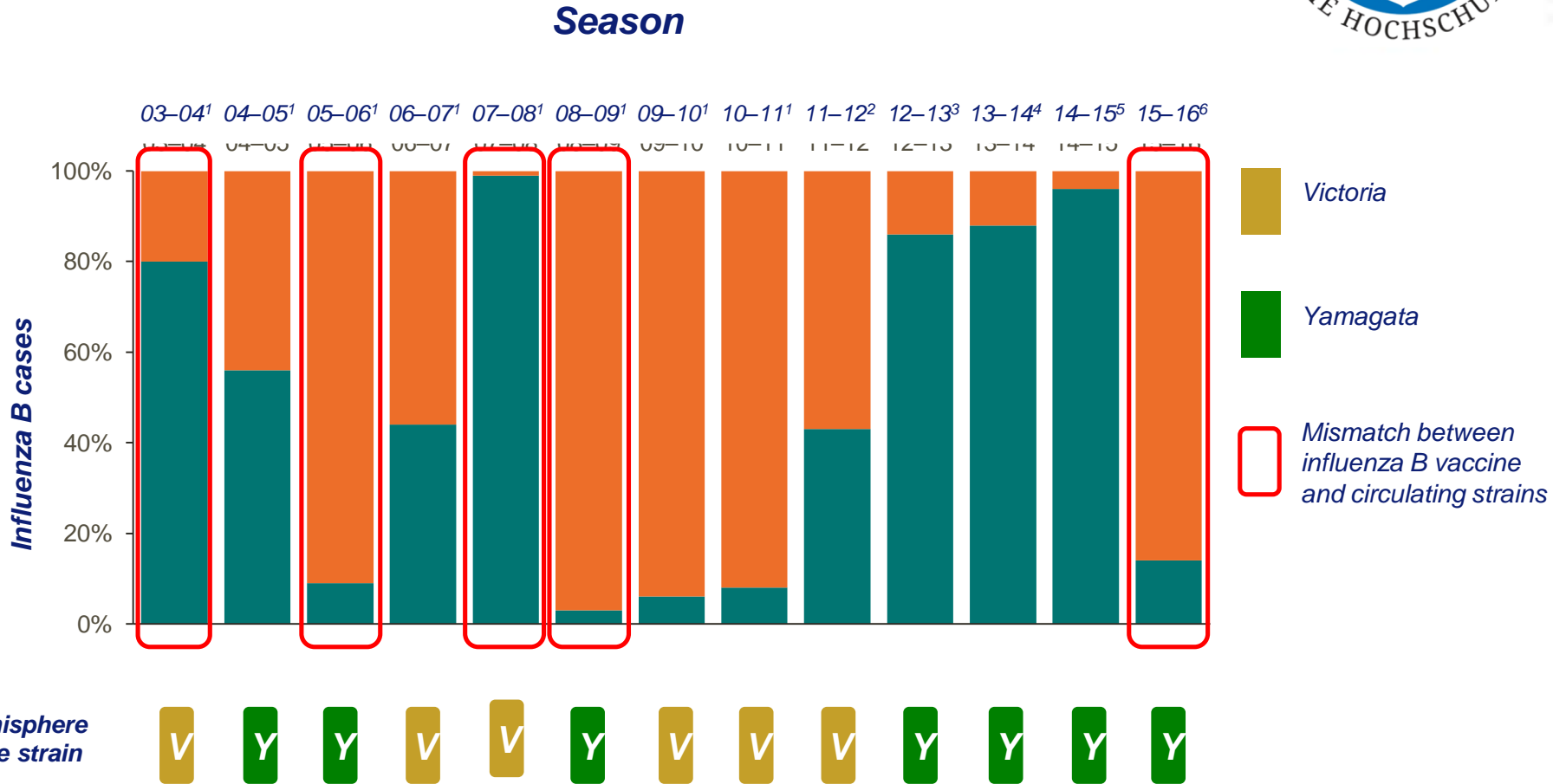


If you are suffering from a weakened immune system, you will be at greater flu risk. People with HIV or AIDS fall into this category, as these are diseases that directly attack and destroy the immune system.

If you are pregnant you may not have a strong enough immune system to ward off dangerous complications caused by the flu virus, both for yourself and your unborn baby.

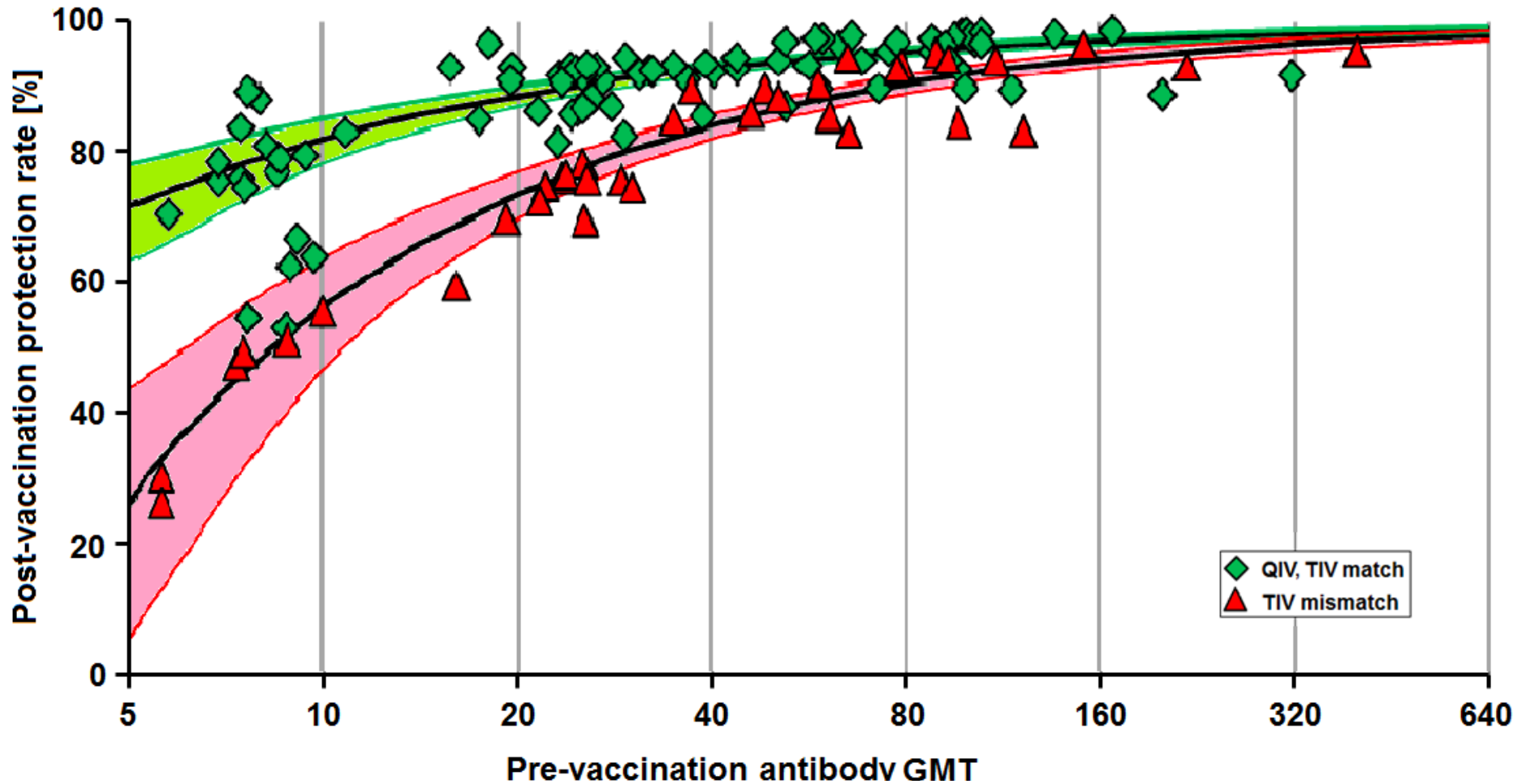
People who are in chemotherapy to treat cancer will be under tremendous stress due to the harmful effects of the treatment. While it is working to cure cancer, it also weakens the body's defence system, and thus contracting flu whilst undergoing chemotherapy can be very dangerous.

In Europe, 5/13 seasons had a mismatch between influenza B vaccine and circulating strains



1. Ambrose CS & Levin MJ. *Hum Vaccin Immunother* 2012;8:81-88; 2-6. European Centre for Disease Prevention and Control (ECDC), 2012-2016. Seasonal influenza risk assessments for each influenza season; 7-11. World Health Organization (WHO), 2011-2015. Recommended composition of influenza virus vaccines for use in the northern hemisphere for each influenza season.

Figure 3: Relationship between pre-vaccination GMT and post-vaccination protection rates, for match and B lineage mismatch.



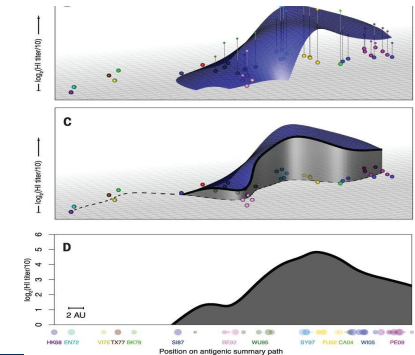
Impact of influenza B lineage mismatch and specific pre-seasonal immunity on the effectiveness of influenza vaccines. A meta-regression study on immunogenicity trials and controlled field trials.

New generation seasonal flu vaccines

Currently ongoing improvements:

Better strain selection and prediction

- Improved surveillance
- Dynamic strain mobility patterns
- Population-based antibody landscapes



Shorter vaccine production times

- Less drift-associated mismatch



Egg-independent production systems

- No egg-adaptation-associated mismatch
- Vectors
- Recombinant proteins

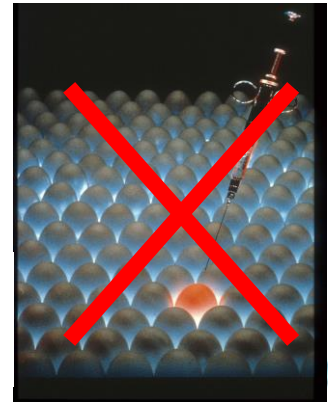
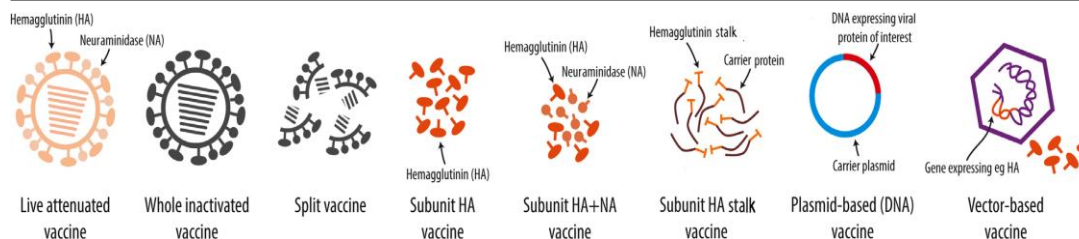


Figure 2. Range of current and new vaccine presentations against influenza A virus *Reperant et al., 2014*



Last four pandemics



Credit: US National Museum of Health and Medicine

1918

1957

1968

2009

“Spanish Flu”

“Asian Flu”

“Hong Kong Flu”

“Mexican flu”

>40 million deaths

1-4 million deaths

1-4million deaths

0.2-0.3 million deaths

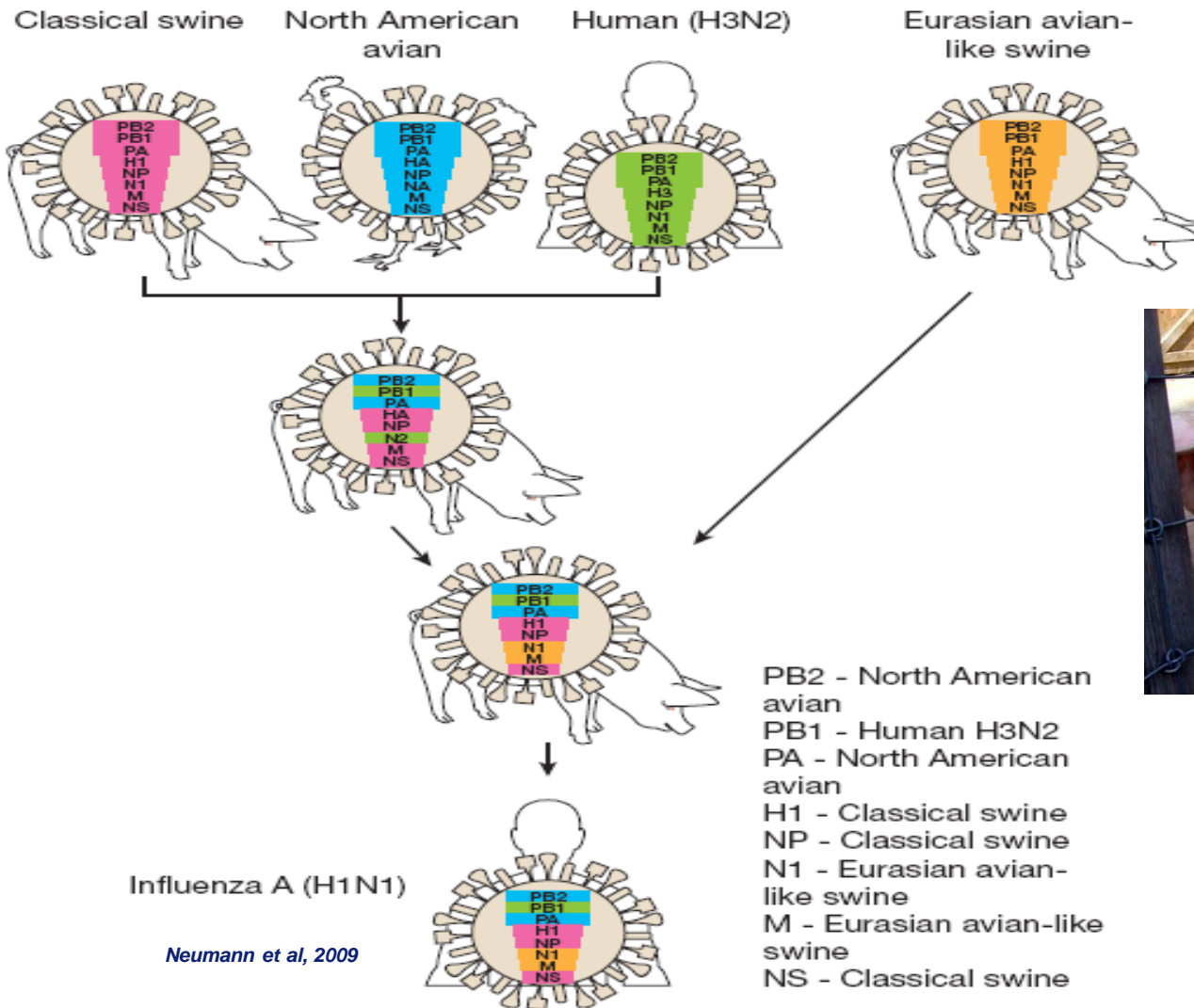
A(H1N1)

A(H2N2)

A(H3N2)

A(H1N1)

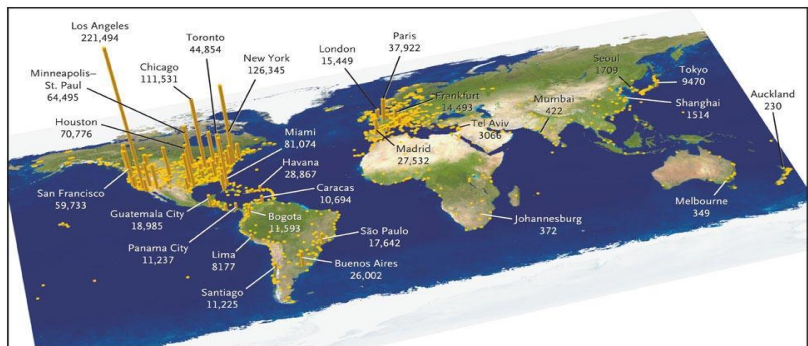
Origin of 2009 H1N1v pandemic virus



Within a few weeks, the 2009 H1N1 pandemic spread around the world affecting all countries



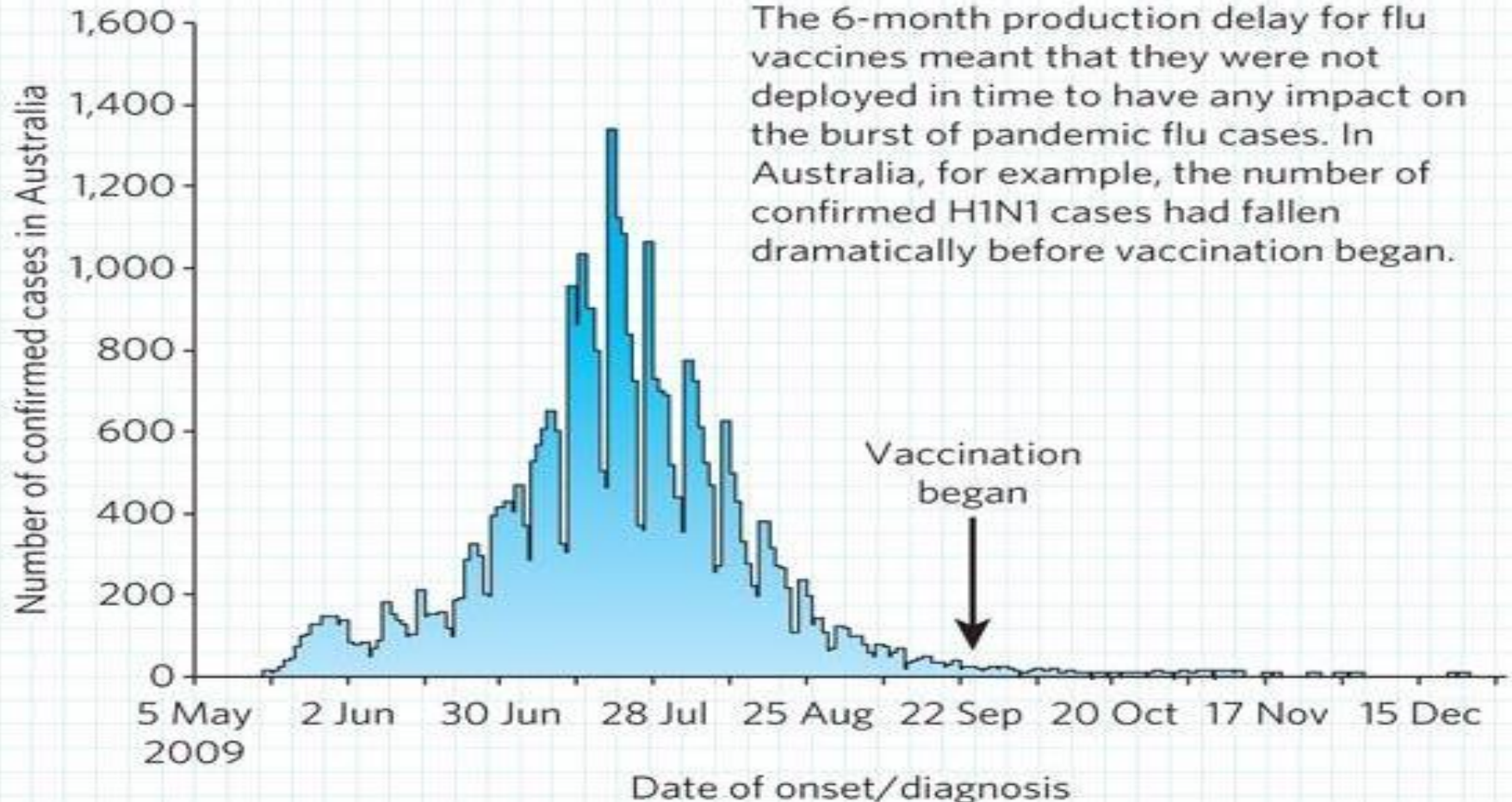
Air traffic from Mexico



2009(H1N1) pandemic vaccine preparation - response time -



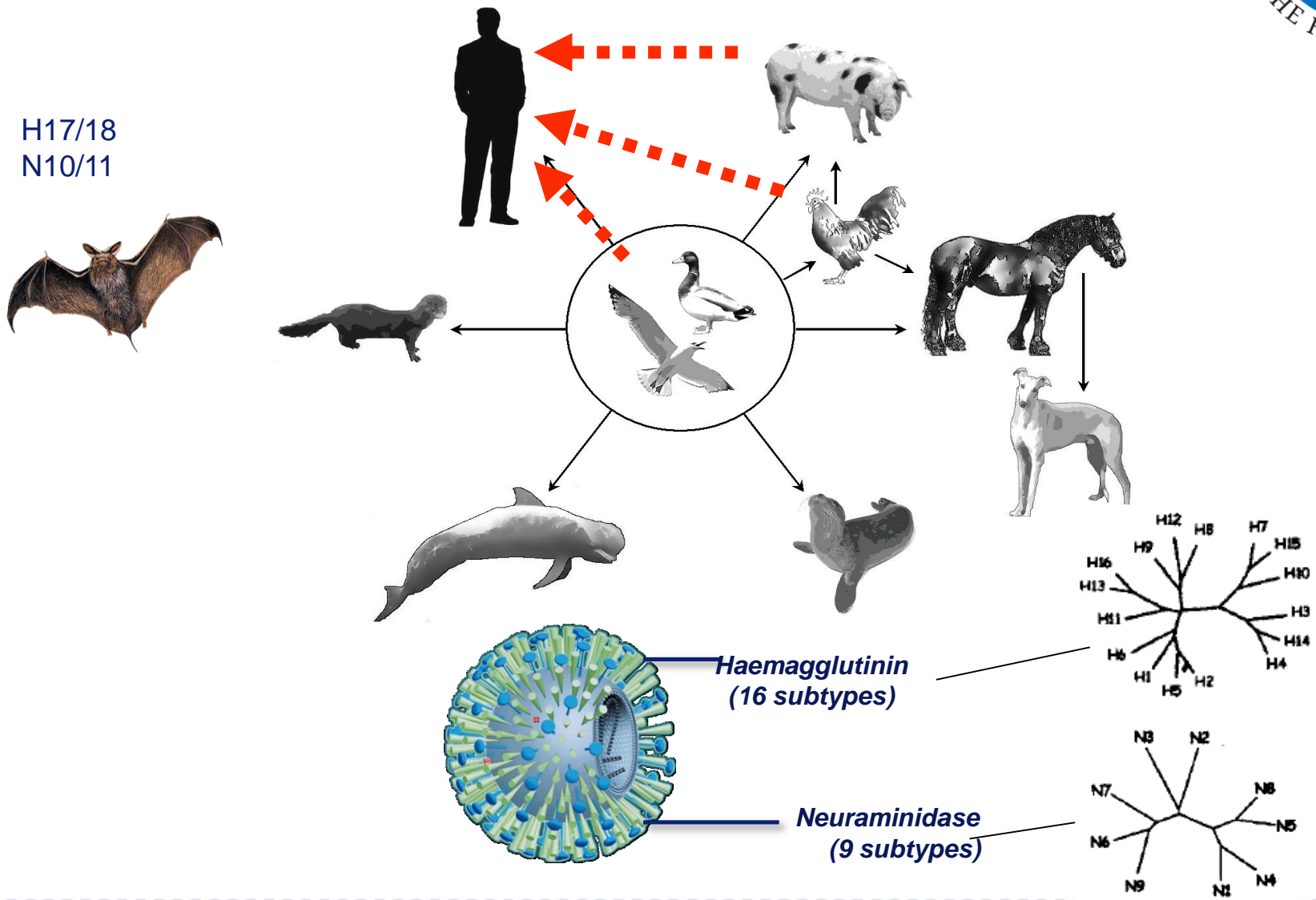
VACCINES ARRIVED TOO LATE



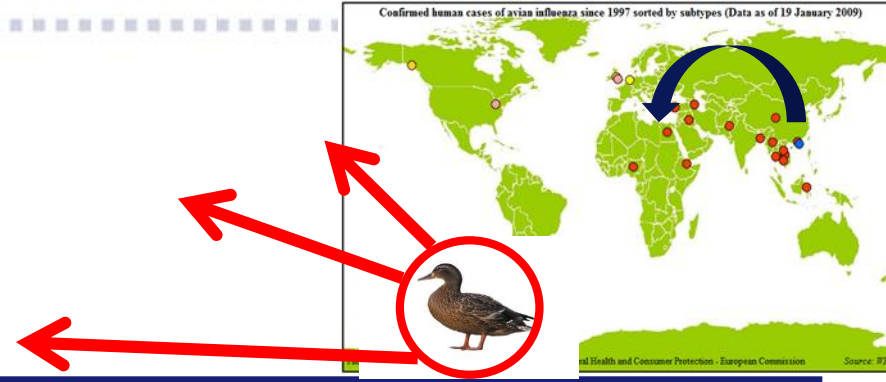
**It took too long to produce “tailor made” vaccines
for the southern hemisphere!**

Aquatic wild birds Influenza A virus reservoir

- De Jong et al., Nature 1997
- Claas & Osterhaus, Nat.Med 1998
- Fouchier et al., J Virol., 2005
- Munster et al., EID., 2005
- Olsen et al., Science., 2006
- BF Koel et al, Science. 2013



Recent zoonotic transmissions
from birds
-confirmed human cases-

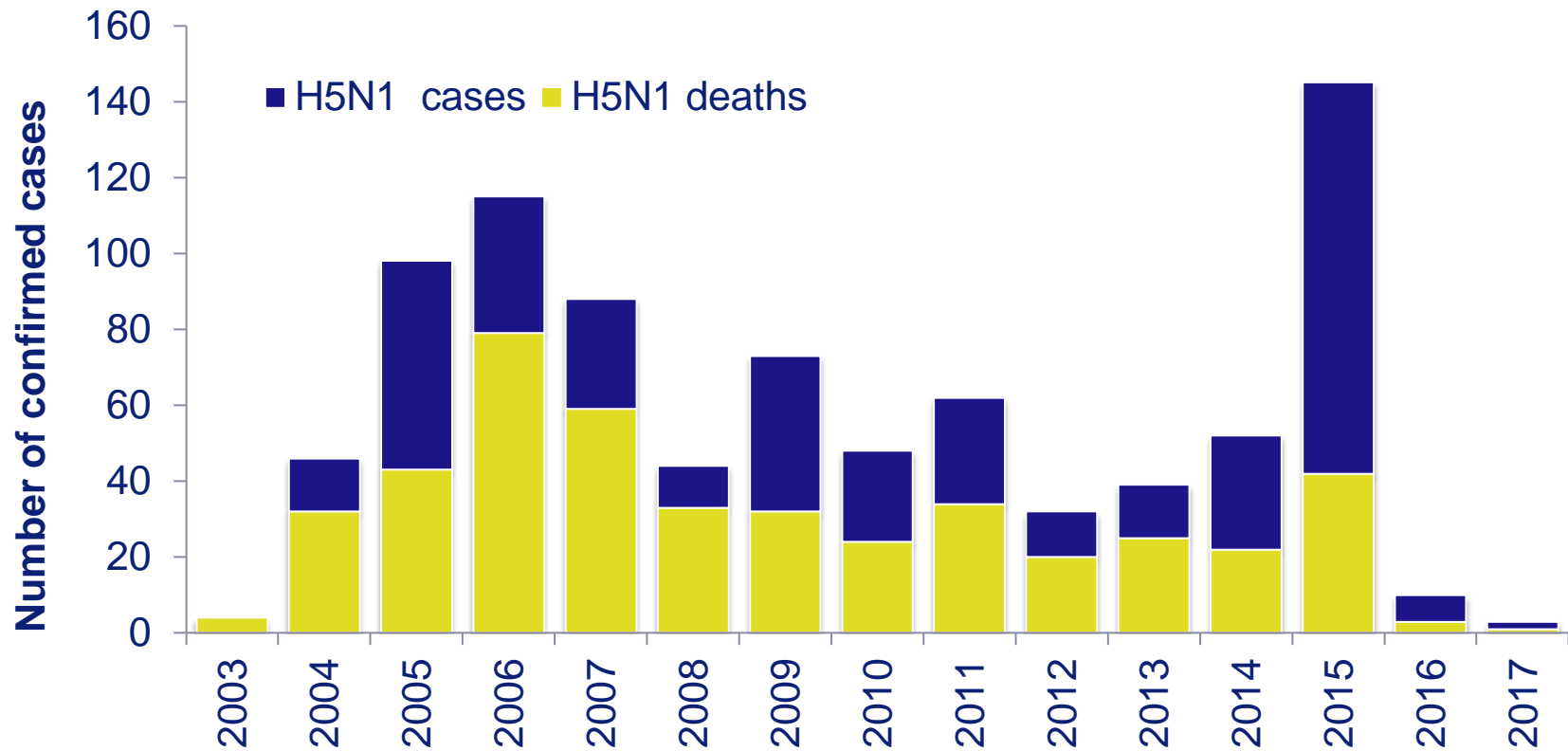


<i>Subtype</i>	<i>Country</i>	<i>Year</i>	<i># Cases</i>	<i># Deaths</i>
<i>H7N7</i>	<i>UK</i>	<i>1996</i>	<i>1</i>	<i>0</i>
<i>H5N1</i>	<i>Hong Kong</i>	<i>1997</i>	<i>18</i>	<i>6</i>
<i>H9N2</i>	<i>SE-Asia</i>	<i>1999</i>	<i>>2</i>	<i>0</i>
<i>H5N1</i>	<i>Hong Kong</i>	<i>2003</i>	<i>2?</i>	<i>1</i>
<i>H7N7</i>	<i>Netherlands</i>	<i>2003</i>	<i>89</i>	<i>1</i>
<i>H7N2</i>	<i>USA</i>	<i>2003</i>	<i>1</i>	<i>0</i>
<i>H7N3</i>	<i>Canada</i>	<i>2004</i>	<i>2</i>	<i>0</i>
<i>H5N1</i>	<i>SE-Asia/M-East/ Europe/W-Africa</i>	<i>2003-15*</i>	<i>>850</i>	<i>>450</i>
			<i>*CFR ~ 55%</i>	<i>(increasing)</i>
<i>H7N9</i>	<i>PR China</i>	<i>2013</i>	<i>>1500</i>	<i>>600</i>
<i>H9, H10, H6..</i>	<i>Asia...</i>	<i>ongoing</i>	<i><5</i>	<i><5</i>

Highly pathogenic avian influenza A virus H5N1



Laboratory confirmed: 859
Deaths: 453 CFR: ~53%
Recoveries: 406



Source: WHO/GIP, data in HQ as of 25 July 2017

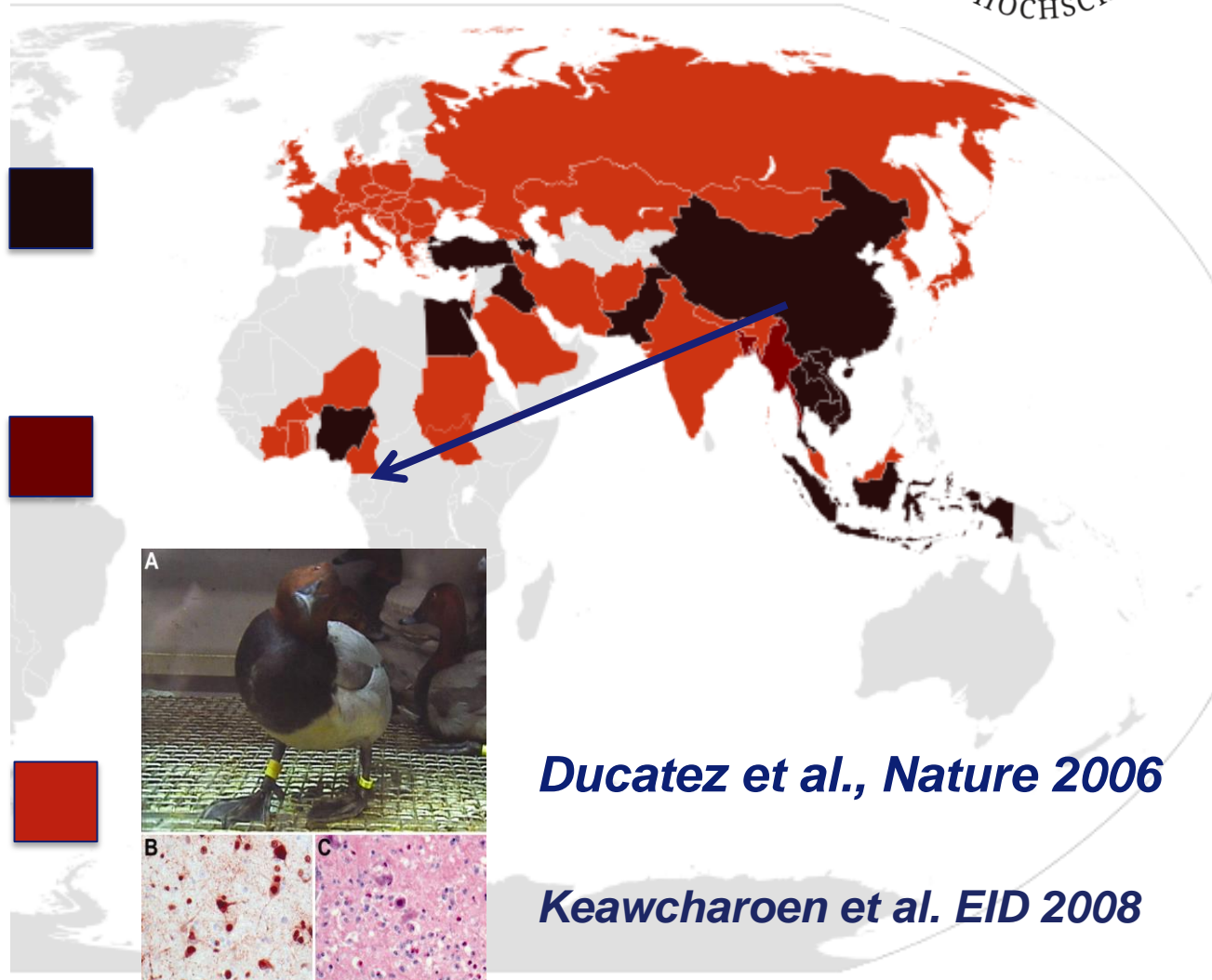
Highly pathogenic avian influenza A virus H5N1



Countries with humans, poultry and wild birds infected with H5N1

Countries with poultry or wild birds infected with H5N1 and has reported human cases of H5N1.

Countries with poultry or wild birds infected with H5N1.



Avian Influenza: Asia



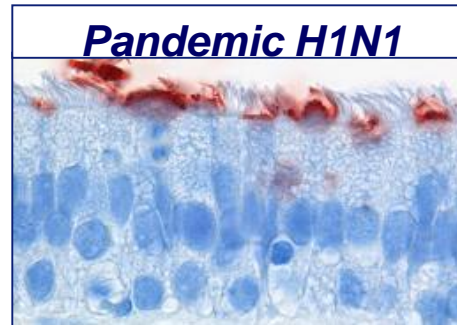
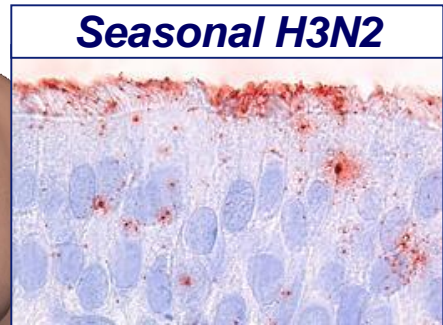
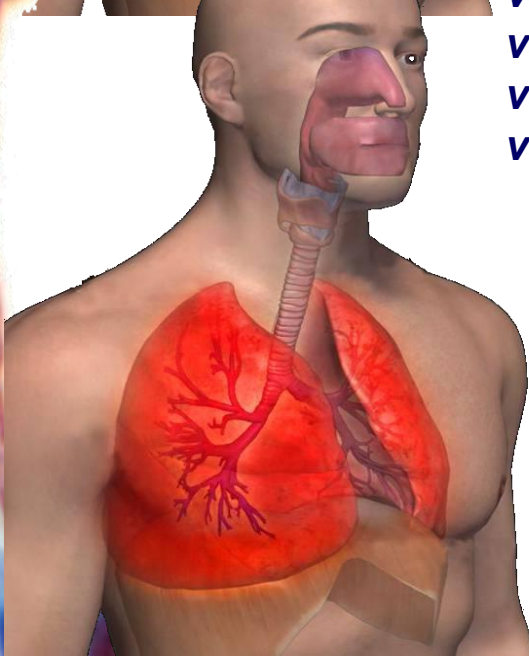
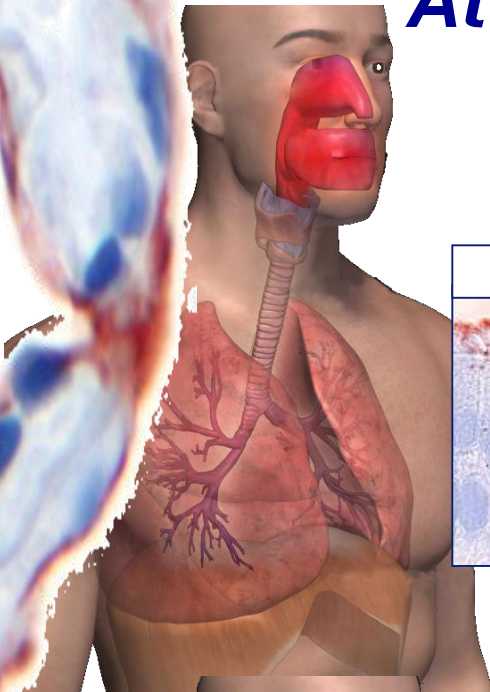
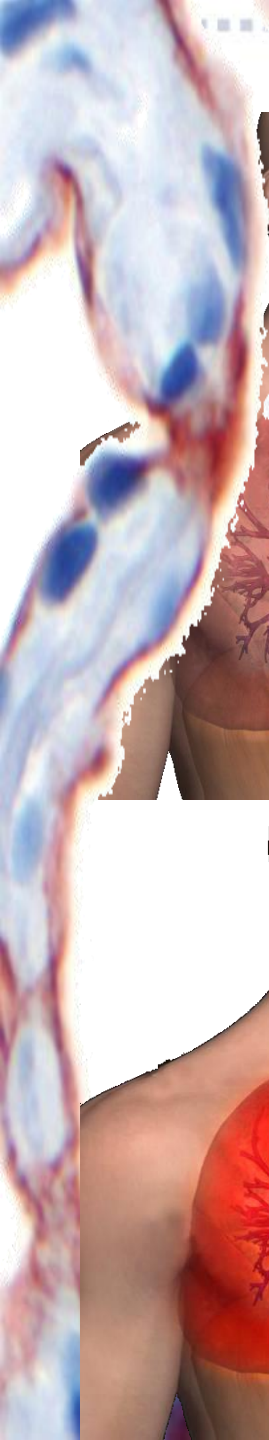


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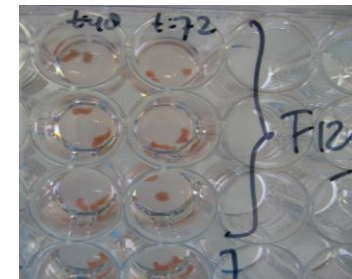
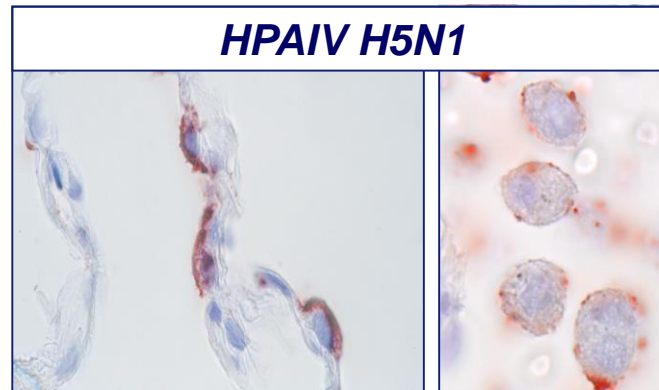
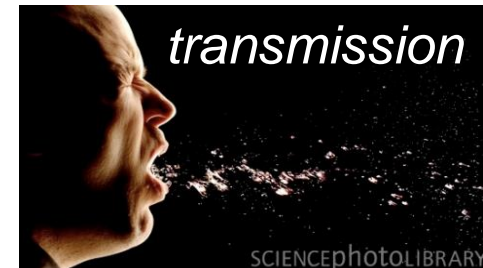
Feline friend or potential foe?

What role do cats play in the epidemiology of the H5N1 avian flu virus? We don't yet have all the answers, but it's time to consider new precautions, argue **Thijs Kuiken, Albert Osterhaus, Peter Roeder** and their colleagues.

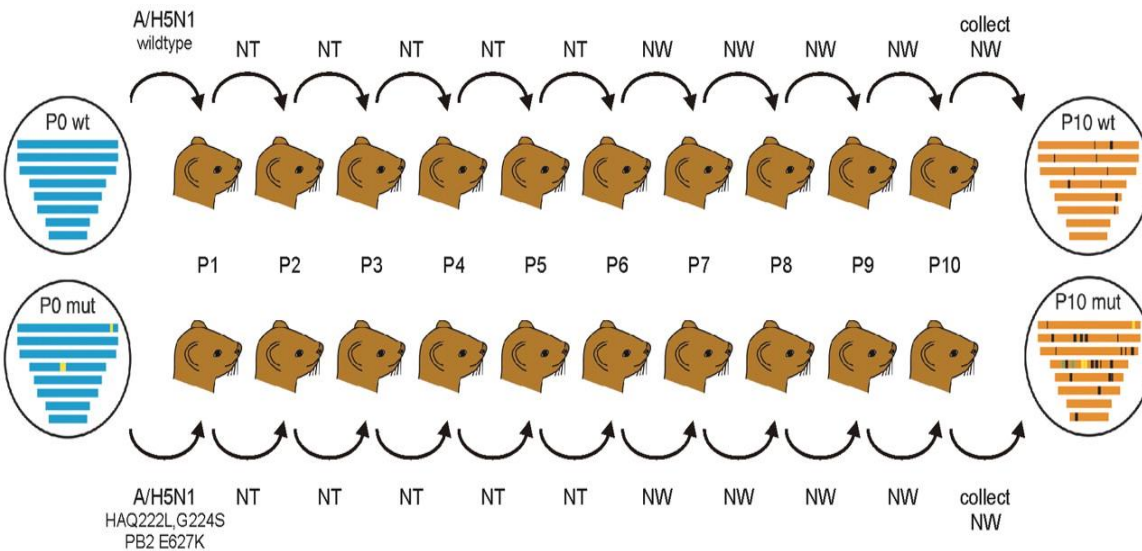
Attachment to upper or lower respiratory tract



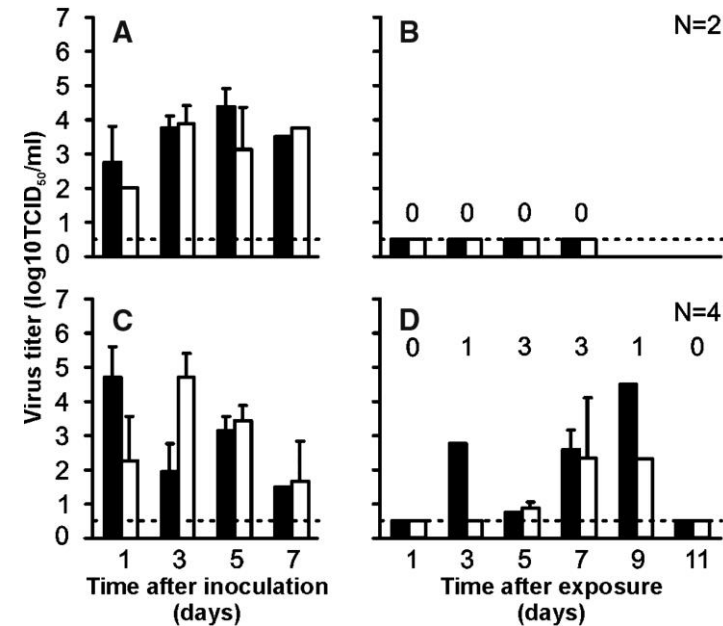
- van Riel et al., Science 2006
- van Riel et al., Am J Pathol 2007
- van Riel et al., Am J Pathol 2009
- van Riel et al., Am J Pathol 2010
- van Riel et al., PLoS Path. 2011



HPAI H5N1 virus passaging in ferrets - toward transmissibility -

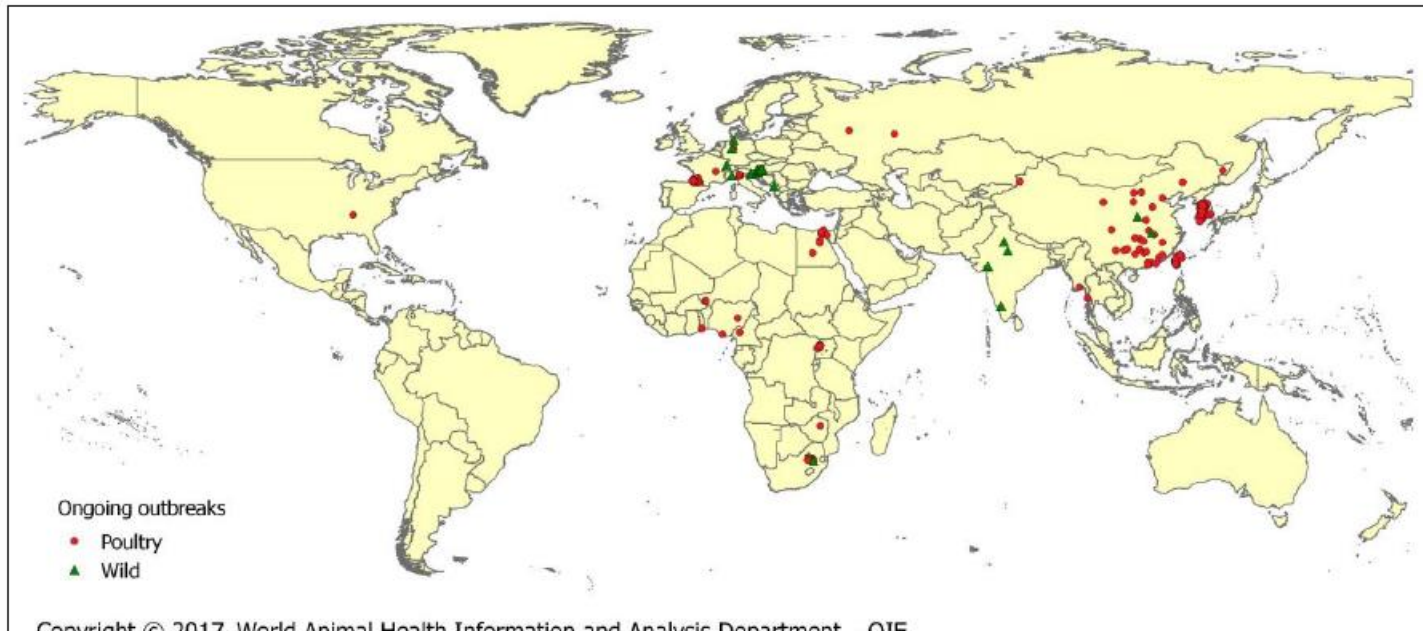


Five substitutions are sufficient for airborne transmission between ferrets



Munster et al., Science 2009
Herfst et al., Science 2012
Russel et al., Science 2012
Linster et al., Cell 2014

Highly pathogenic avian influenza A virus in poultry/wild birds



H5N1
H5N2
H5N5
H5N6
H5N8
H7N3
H7N9

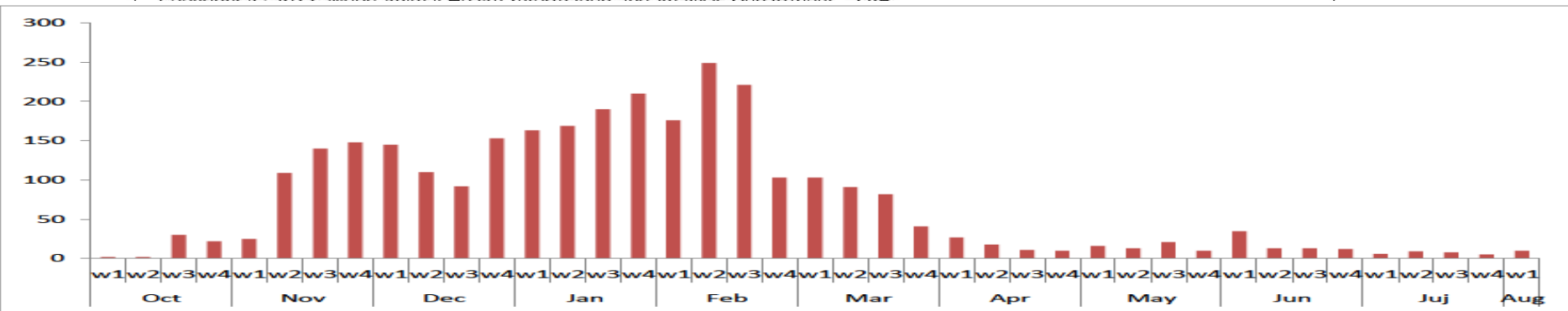
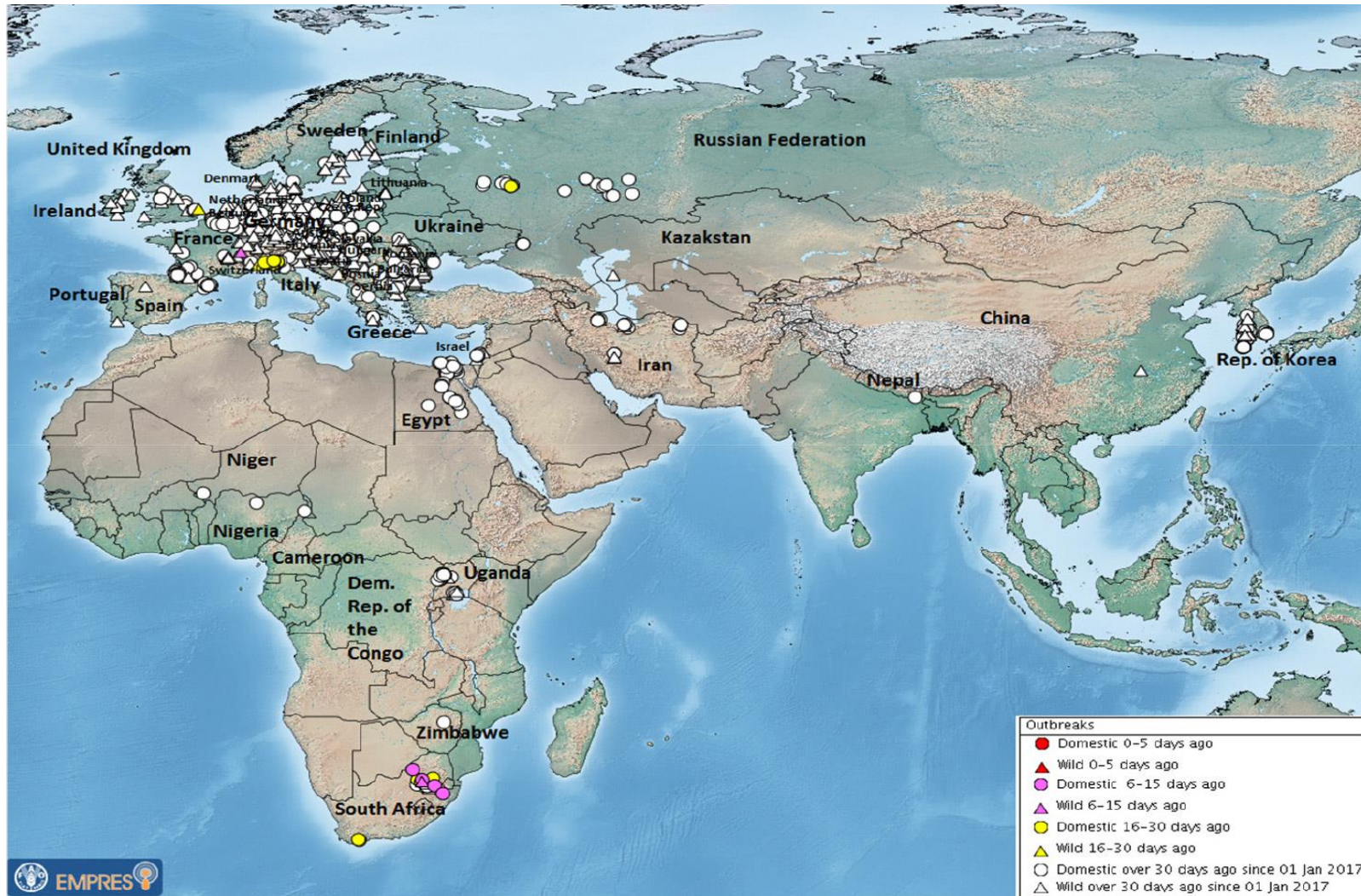


Figure 1. Epidemic curve showing the weekly incidence of outbreaks of Highly Pathogenic Avian Influenza since October 2016.

Source: OIE, as of 8 Aug. 2017

Highly pathogenic avian influenza A virus in poultry/wild birds



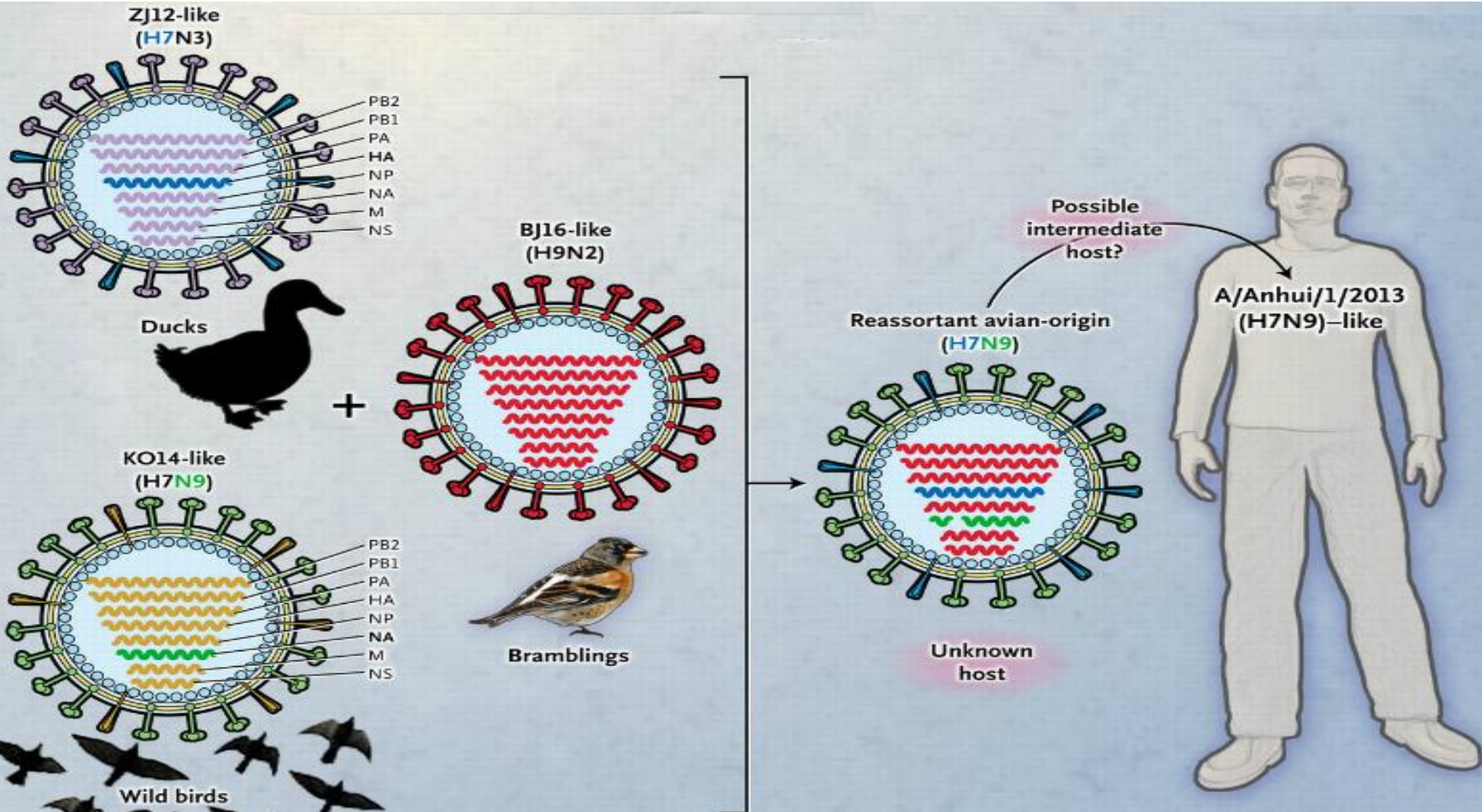
H5N1
H5N2
H5N5
H5N6
H5N8
H7N3
H7N9

Avian Influenza A H7N9-2013



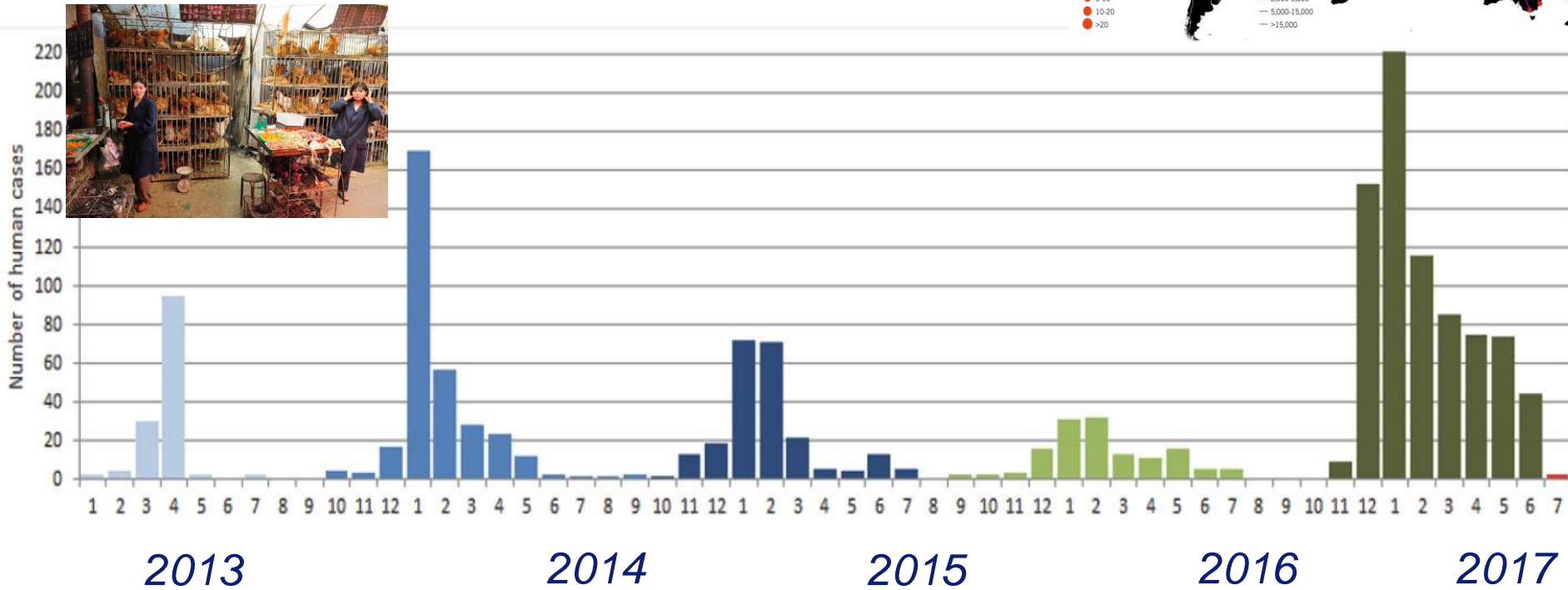
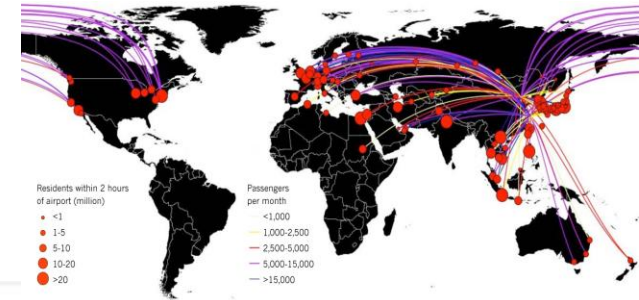
The NEW ENGLAND
JOURNAL of MEDICINE

Gao et al., 2013



High and low pathogenic avian influenza A viruses H7N9

Laboratory confirmed: 1584
 Deaths: 612 CFR: ~39%
 Recoveries: 972



Source: FAO, as of 23 Aug. 2017

High and low pathogenic avian influenza A viruses H7N9

SKILLS MEET TO



Pandemic influenza vaccines

- Improve efficacy; adjuvants & delivery systems -

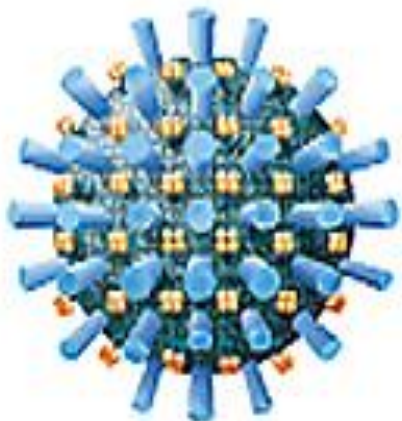


Adjuvants & antigen delivery systems

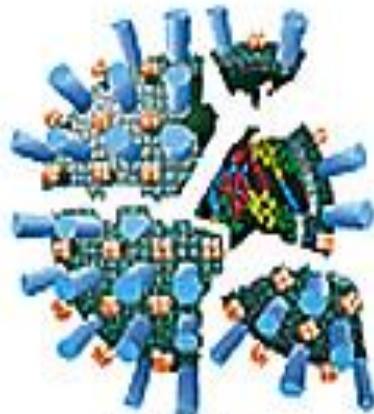
- Aluminum
- MF59
- ASO3
- Virosomes
- ISCOMs
- Others....

Variety of potential antigens

- Subunits
- Split vaccines
- Whole inactivated virus
- Live-attenuated virus
- Virus-like particles
- Recombinant proteins
- DNA vaccines
- Others....



Whole virus



Split virus



Subunit
(surface antigen)



Live attenuated

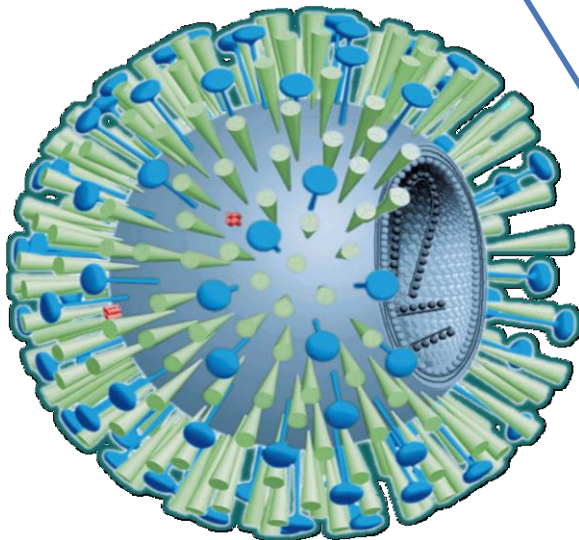
Basis for more universal influenza vaccines

- Conserved proteins or regions thereof -



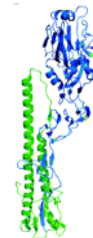
Viral targets for cross-reactive antibodies

- M2 protein
- Stalk region of HA
- NA
- NP ?



Viral targets for cross-reactive T cell responses

- All structural proteins in particular
 - NP
 - M1
- The non-structural proteins
 - NS1/NS2
 - PB1-F2, PA-X
- Polymerase proteins
 - PB1/PB2/PA



Achilles heel ??

(Pre)clinical testing MVA-based vaccines

- H5N1: Mice, macaques, humans
- 2009 (H1N1): Ferrets
- H7N9: Ferrets



- Kreijtz et al. *J. Inf. Dis.* 2007
- Kreijtz et al. *PLoS One.* 2009
- Kreijtz et al. *J. Inf. Dis.* 2009
- Kreijtz et al. *J. Gen. Virol.* 2010
- Kreijtz et al., *Lancet ID*, 2014



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Conclusions: Major Issues



Seasonal

- *Antigenic drift*
- *Vaccine mismatch*
- *Vaccine effectiveness*
- *Too low vaccination coverage in the high-risk groups*
- *Better vaccines expected*



Avian

- *Unprecedented global spread*
- *High human CFR (H5 & H7)*
- *Human-to-human spread: crucial mutations*

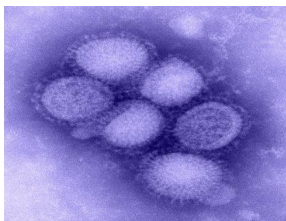


Pandemic

- *Unpredictable*
- *Intervention strategies needed*
- *Pandemic preparedness plans*
- *Universal vaccines wanted*

CONCLUSIONS influenza vaccines

- **Seasonal vaccines are safe, effective and cost-saving**
 - Healthy adults (e.g. HCWs) 70-90 % protection
 - HCWs should be vaccinated
 - Pregnant women should be vaccinated
 - Frail elderly only 30-40 % protection
 - Vaccination of healthy children indicated?
- **Novel and more universal vaccines are being developed**



Future human and animal flu vaccines

- Induce broader and longer protection against both epidemic and pandemic influenza
- Broaden correlates of protection beyond HI / VN antibody
 - *Induce cross-reactive antibodies (M2, HA-stem, NA...)*
 - *Induce CMI (CTL / Th) to conserved proteins (NP, M1...)*
 - *Use novel presentation forms (adjuvants, LAIVs, vectors...)*

