




# From zoonosis to pandemic: are we prepared?

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One Health Journal

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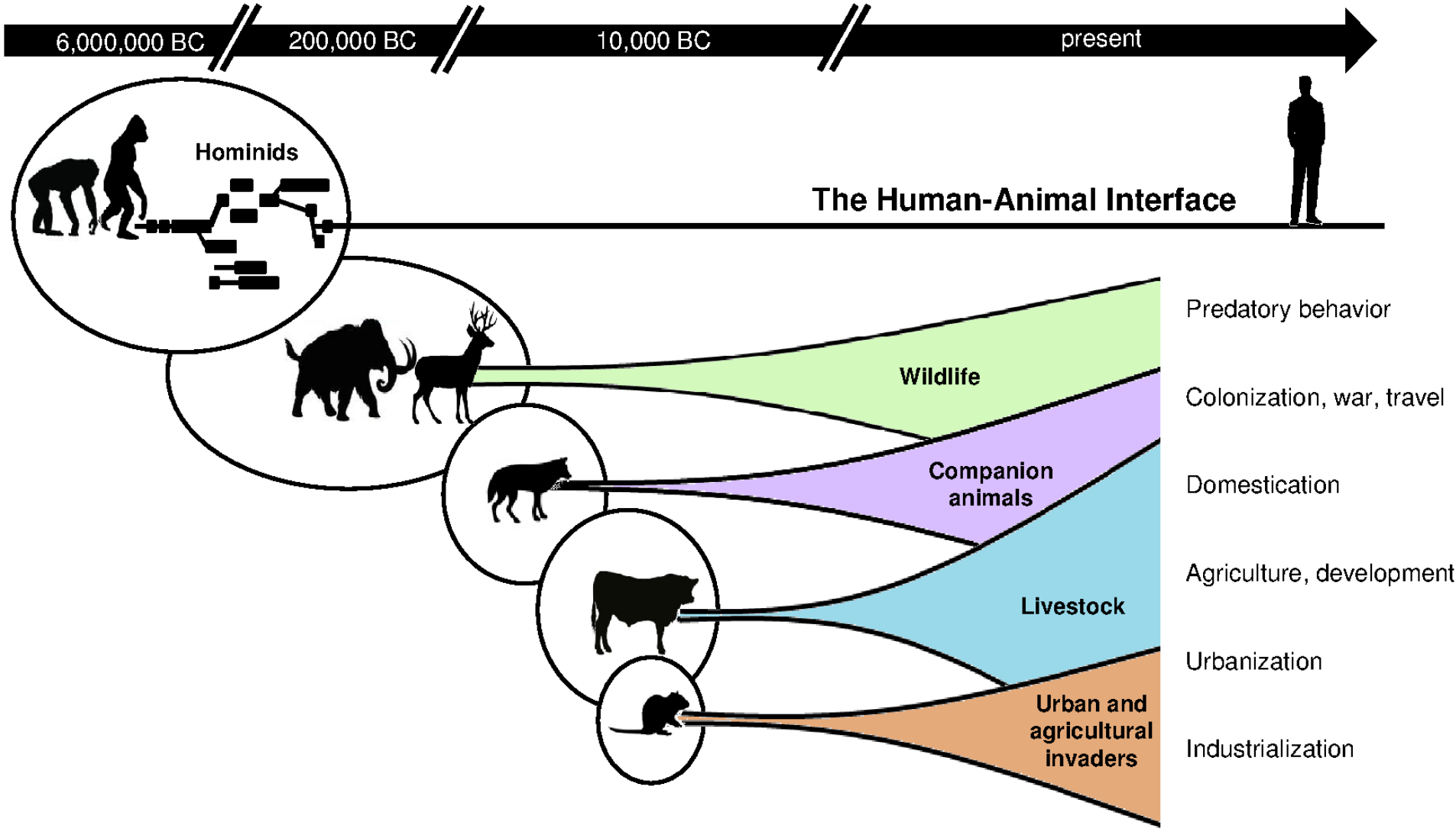
**CSO Viroclinics-Biosciences BV (NL)**

**Chair ESWI (EU)**





# The human-animal interface through ages




*Reperant LA, Cornaglia G, Osterhaus AD  Curr Top Microbiol Immunol.2013*

The importance of understanding the human-animal interface: from early hominins to global citizens

# *Emerging viruses in prehistory: Domestic animals at the human-animal interface*

## *'CROSSING THE SPECIES BARRIER'*

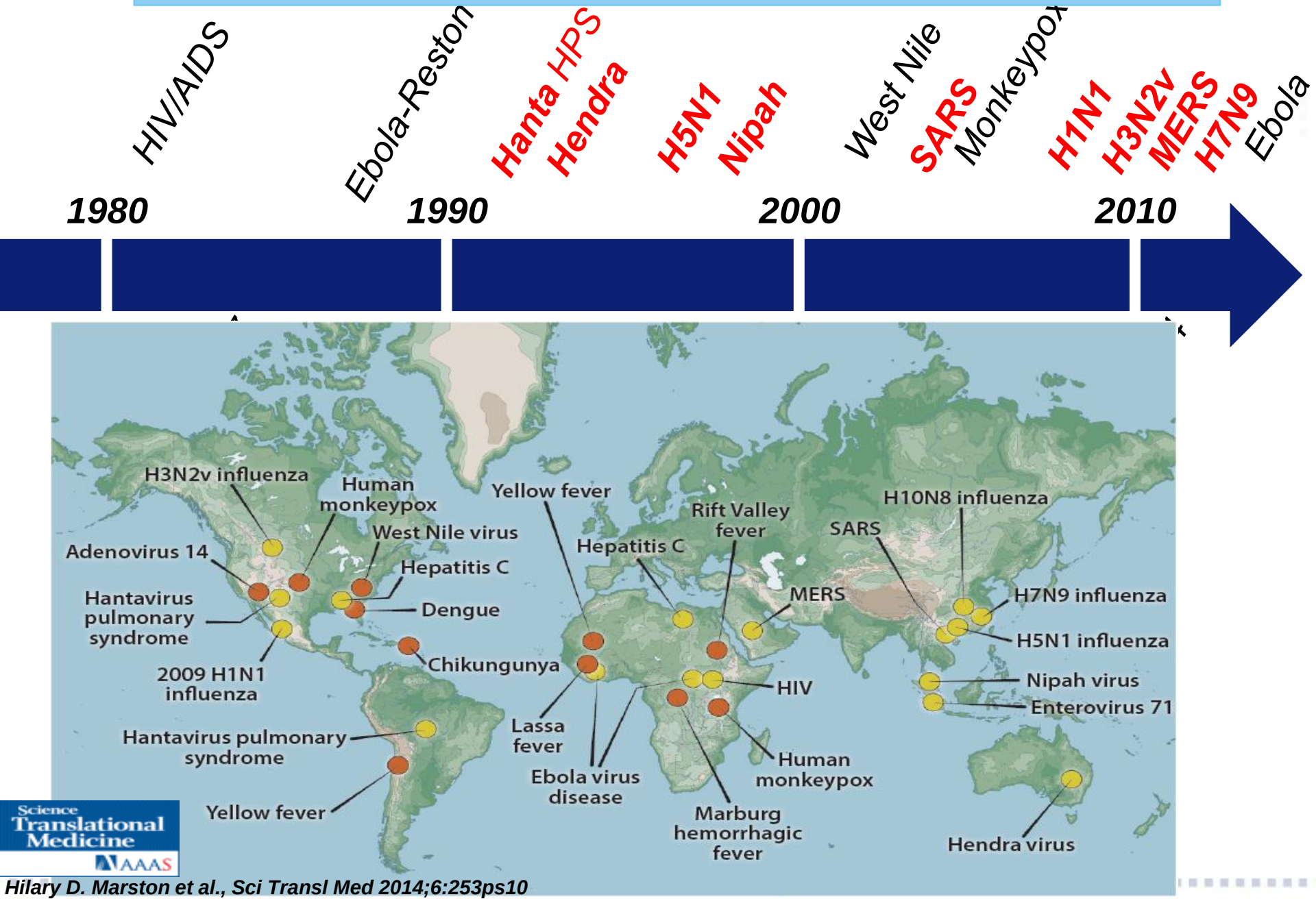
***Emergence of some of the major plagues of humankind:***

- ***Measles** virus related to rinderpest virus of **cattle***
- ***Mumps** virus related to **porcine** rubulavirus*
- ***Smallpox** virus related to **camel**pox and **gerbil**pox viruses*
- ***Rota**viruses related to those of **cattle** and **pigs***
- ***Calici**viruses related to those of **cattle** and **pigs***

*Reperant et al.,CTMI 2013*

A

# The Paradox of the past decennia

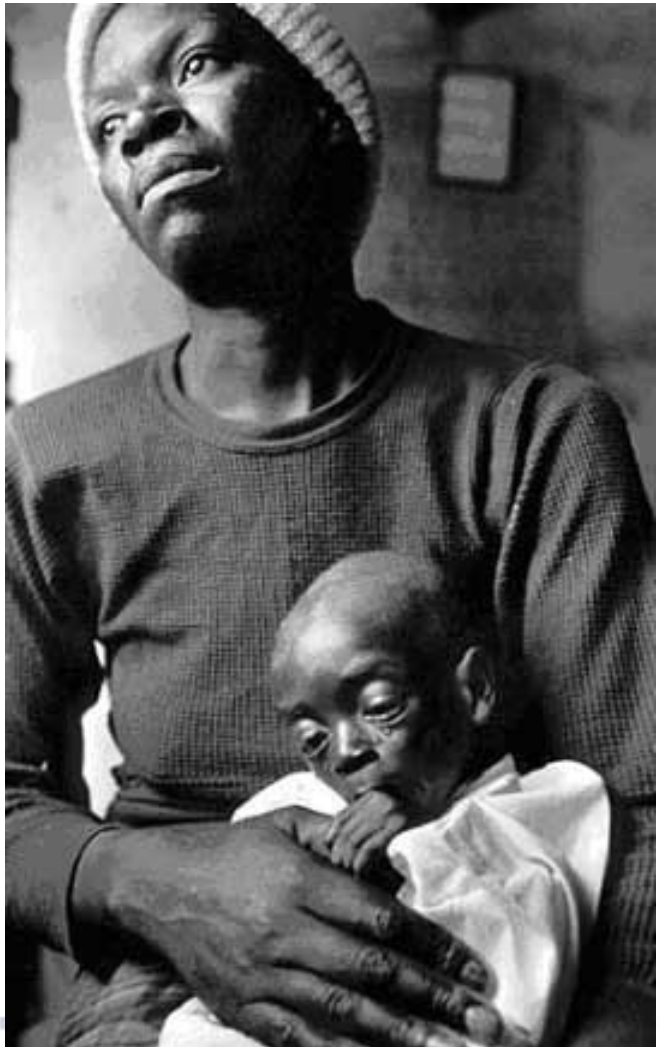



Science Translational Medicine AAAS

*Hilary D. Marston et al., Sci Transl Med 2014;6:253ps10*

# The AIDS pandemic: started 30 years ago

**>55 million infected, >20 million deaths, >1.5 million die each year!**



**Complex mix of pre-disposing factors**



**Animal contacts (bush meat consumption)**
**Behaviour (changing taboos, mores, i.v. drug abuse)**
**Demography (urbanisation…)**
**Mobility (air travel, wars …)**
**Poverty (vs wealth)**
**Medical practices (iatrogenic transmission)**
**Virus adaptation (mutation, recombination)**

# Since the eradication smallpox:
## more animal poxvirus infections in humans?




Wolfs et al. E.I.D. 2002

Zijlstra et al BMJ 2013




*Figure 1. African child with disseminated monkeypox. Note postauricular adenopathy (courtesy of Leo Lanoie, Prince Albert Parkland Health Region, Saskatchewan, Canada).*




ProMED-mail 9 Jan 2003




Pelkonen et al. E.I.D. 2003; 9:1458-1461

**Stittelaar *et al*., Nature, 2006**

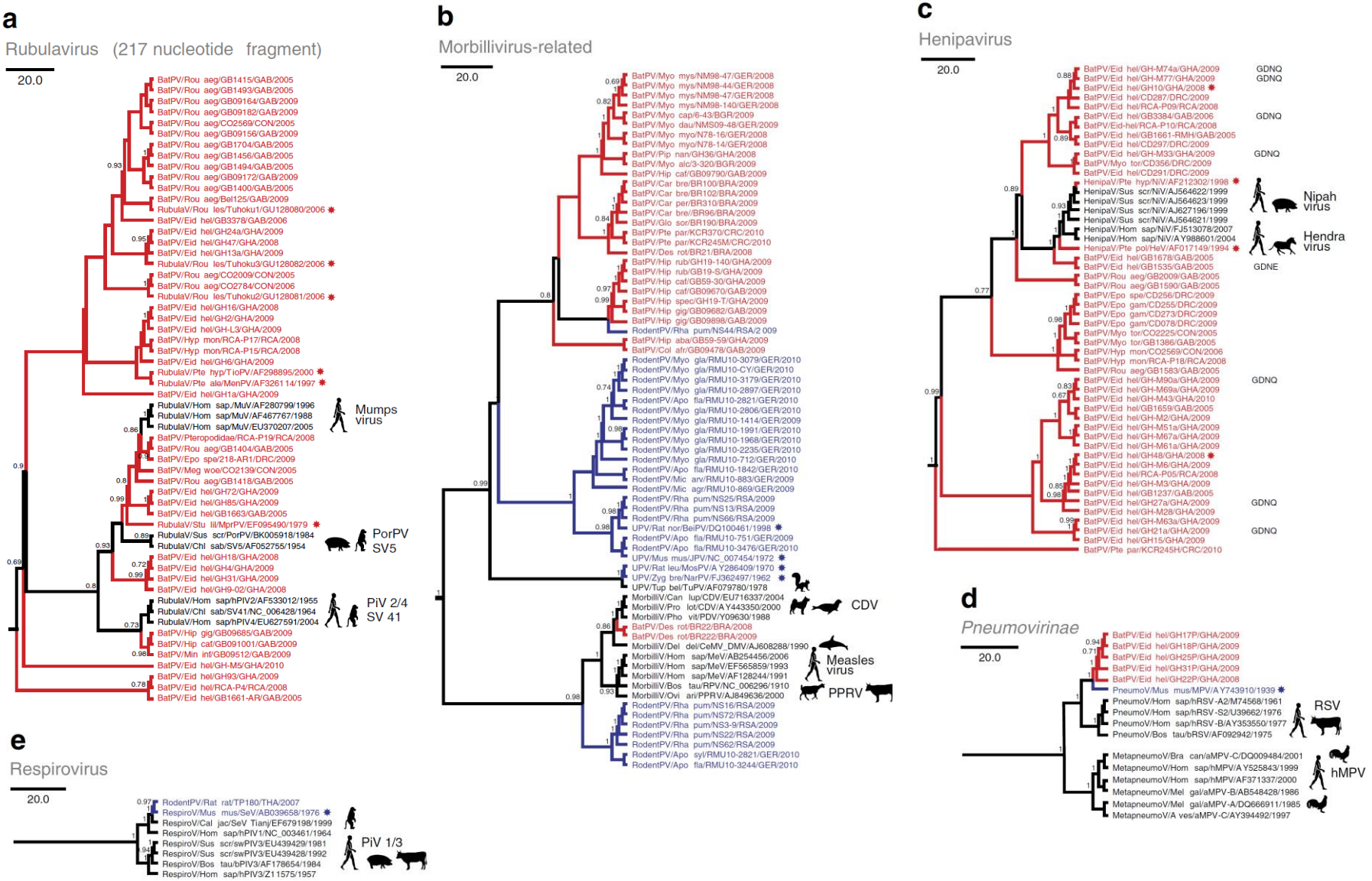
# Novel paramyxoviruses continue to be identified

nature COMMUNICATIONS

ARTICLE

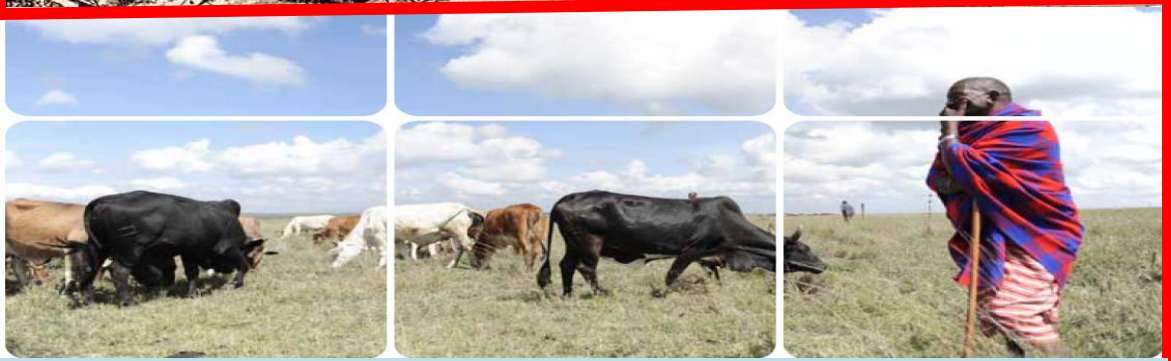
Received 14 Sep 2011 | Accepted 19 Mar 2012 | Published 24 Apr 2012 DOI: 10.1038/ncomms1796

Bats host major mammalian paramyxoviruses



**Rinderpest: morbillivirus disease of cattle**
**Animal husbandry catastrophes 17th Century Netherlands**





***Rinderpest eradication: lessons for measles eradication?***
***de Swart RL, Duprex WP, Osterhaus** AD.*
*Curr Opin Virol. 2012*

## PROGRESS TOWARDS RINDERPEST GLOBAL FREEDOM

Last outbreak **2001**

2002

2003

2004

2005

Vaccination stopped and provisional freedom from rinderpest **2006**

2007

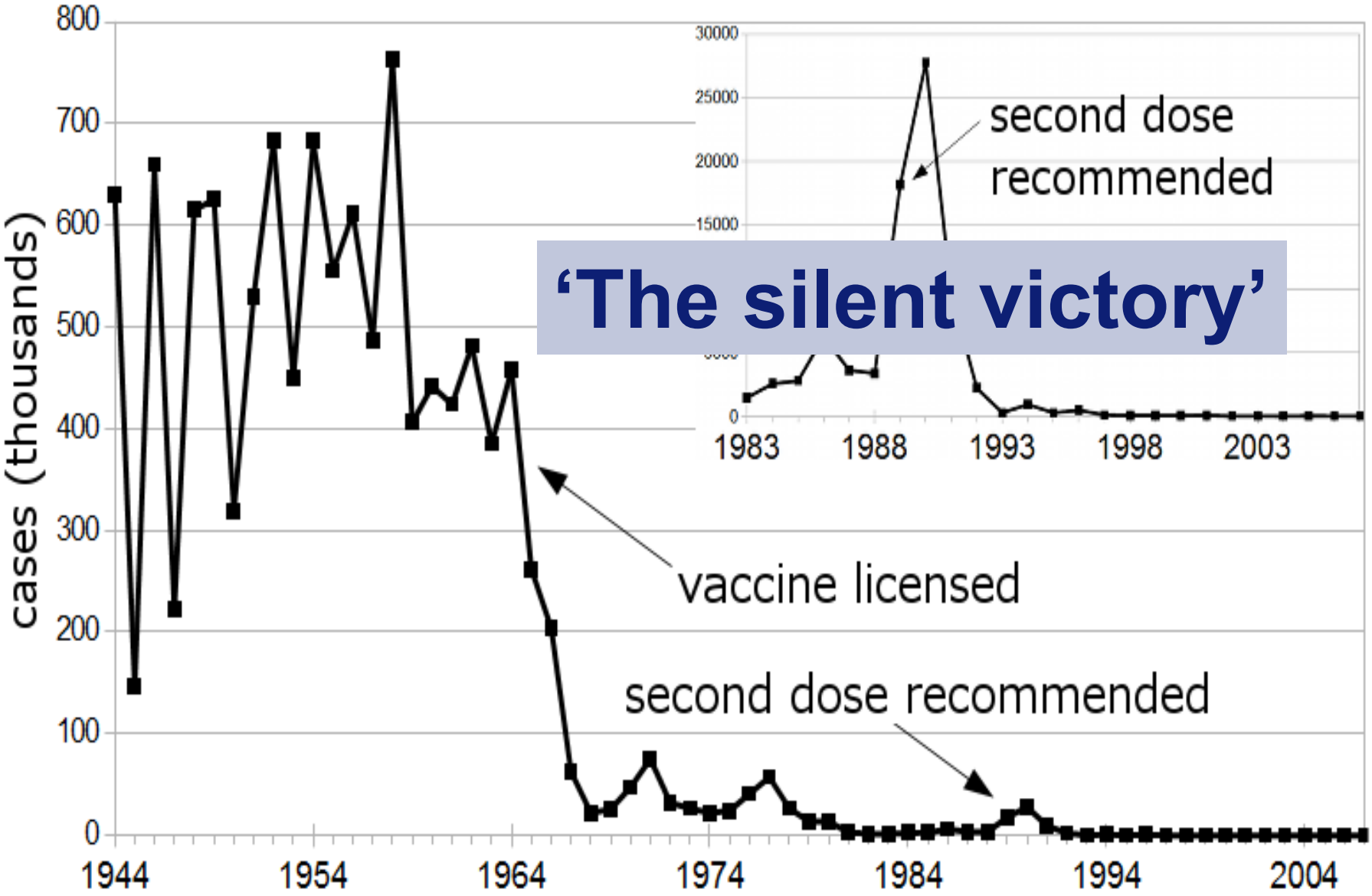
2008

Targeted surveillance exercise **2009**

End of the field operations **2010**

Global declaration **2011**

# Measles cases in the United States, 1944-2007




**‘The silent victory’**

Source: ://www.infectionlandscapes.org/

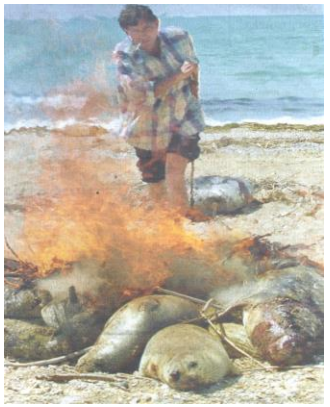
# Morbilliviruses crossing species barrier



**PDV in European Harbour seals**
**Nature 1988 / Science 2002**




**CDV in Baikal seals**
**Nature 1988**



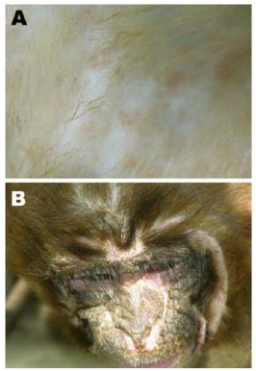
**CDV in Caspian seals**
**EID 2000**



**CDV in Serengeti lions**
**Vaccine 1994**



**DMV in Med. monk seals**
**Nature 1997**

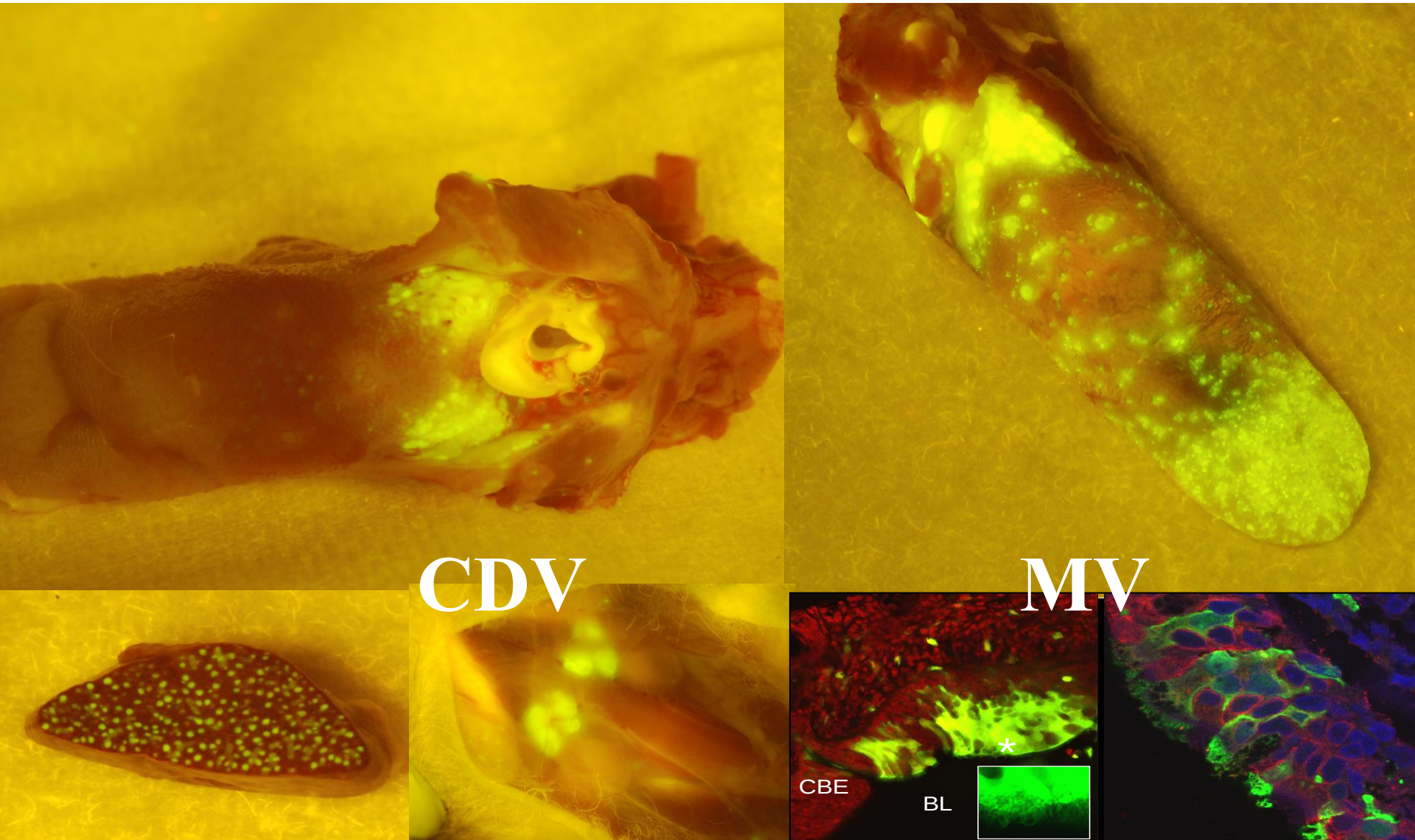



**CDV in macaques**
**China, EID 2011**

**Should we continue measles vaccination for ever?**

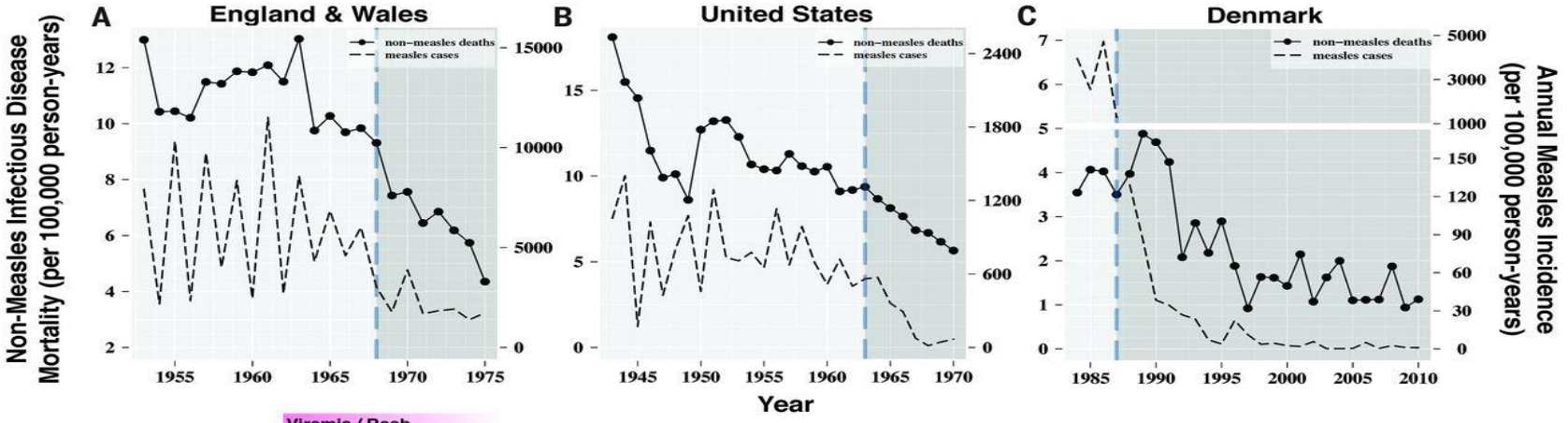
# Experimental morbillivirus infections of macaques

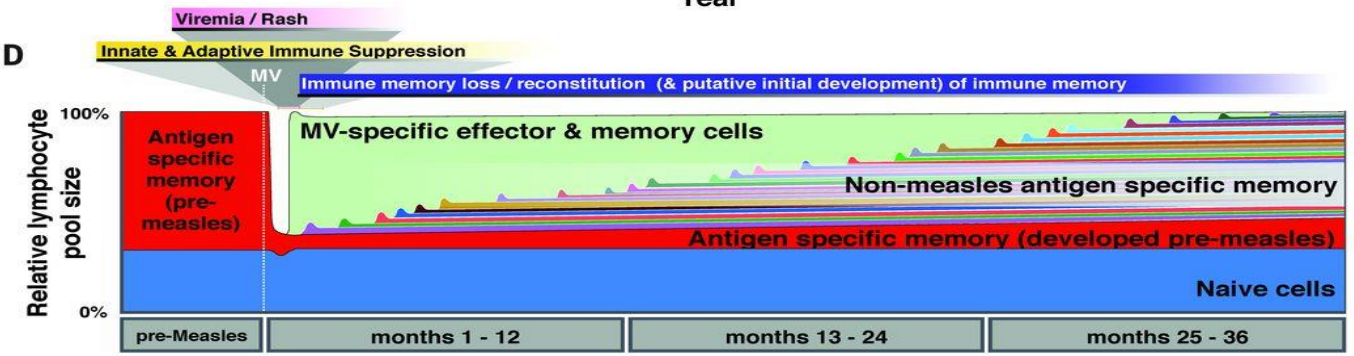
De Vries, et al., PLoS Path 2013
CD150 versus nectin-4 receptor usage?

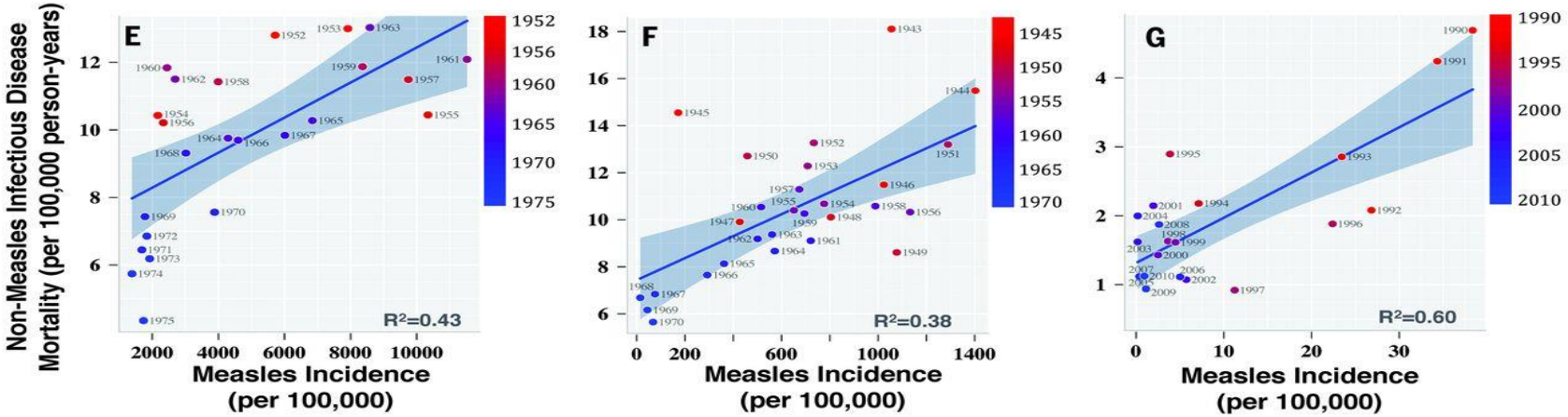


# *Measles incidence, non-measles infectious disease mortality, and measles-induced immunomodulation.*

*Mina, Metcalf, de Swart, Osterhaus and Grenfell. Science 2015;348:694-699*



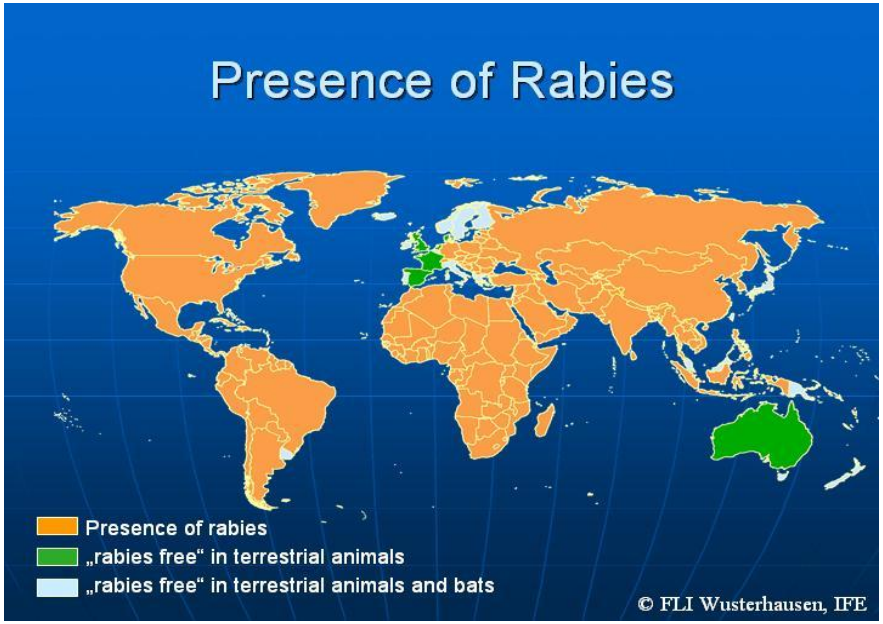



# Duvenhage (rabies) virus infection in The Netherlands: ‘out of Africa’

## Treatment failure of a traveller In The Netherlands!

- van Thiel et al., Euro surveill., 2008
- van Thiel *et al*., Plos Negl. Trop. Dis. 2009






Annual number of rabies deaths between 50,000 and 60,000

**Vaccines don’t protect: vaccination does !!!**

Vaccine 32 (2014) 2020–2021

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Discussion

# Development of a multivalent paediatric human vaccine for rabies virus in combination with Measles–Mumps–Rubella (MMR)☆

Anthony R. Fooks[a,b,*], Penelope Koraka[c], Rik L. de Swart[c], Charles E. Rupprecht[d,e], Albert D.M.E. Osterhaus[c]

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[b] University of Liverpool, Department of Clinical Infection, Microbiology and Immunology, Liverpool L3 5TQ, UK
[c] Erasmus MC, Department of Viroscience, PO Box 2040, 3000 CA Rotterdam, The Netherlands
[d] Ross University School of Veterinary Medicine, PO Box 334, Basseterre, Saint Kitts and Nevis
[e] The Global Alliance for Rabies Control, Manhattan, KS, USA

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# Response to imported case of Marburg hemorrhagic fever, The Netherlands

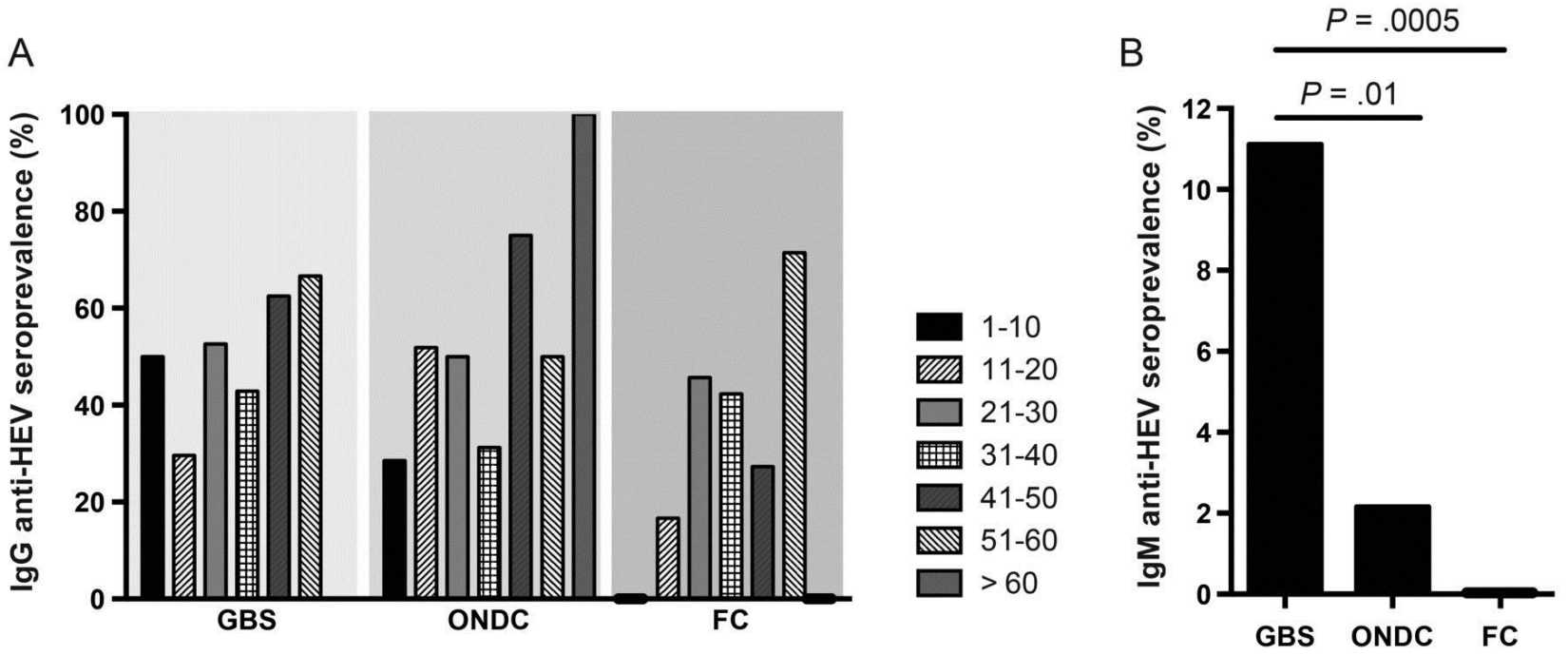
***Timen et al., Emerg Infect Dis. 2009***
***van Paassen et al., Lancet ID, 2009***

Table. Control measures targeting contacts with risk for exposure to Marburg virus, the Netherlands, 2008*

| Type of contact | Date of exposure, Jul | No. persons | Risk for exposure | Measures | | |
|---|---|---|---|---|---|---|
| | | | | Temperature monitoring 2×/day | Daily temperature reporting to health authorities | Asked to limit travel and to not leave the country |
| Household/family contacts | 2–8 | 4 | High | Yes | Yes | Yes |
| Persons exposed in hospital ward | 5–7 | 6 | High | Yes | Yes | Yes |
| GP of the index case-patient | 5 | 1 | High | Yes | Yes | Yes |
| Healthcare workers, Elkerliek Hospital | 7 | 33 | High | Yes | Yes | Yes |
| Local laboratory workers | 5–7 | 18 | High | Yes | Yes | Yes |
| Ambulance staff | 7 | 2 | Low | Yes | No | No |
| Health care workers, LUMC | 7–11 | 66 | Low | Yes | No | No |

*GP, general practitioner; LUMC, Leiden University Medical Centre.

# Anti–hepatitis E virus (HEV) immunoglobulin G (IgG) and immunoglobulin M (IgM) seroprevalence.

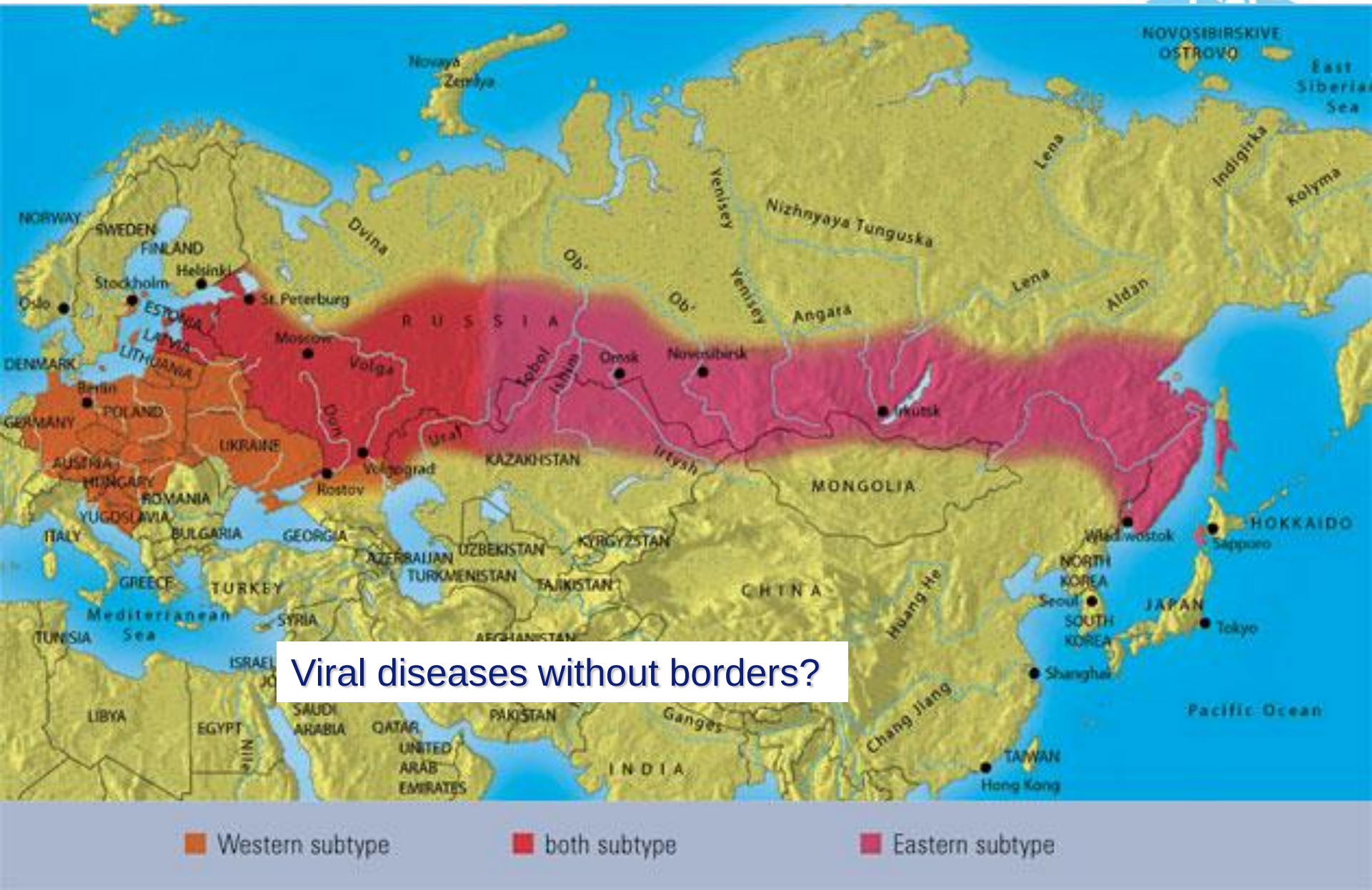



**Expect the unexpected**

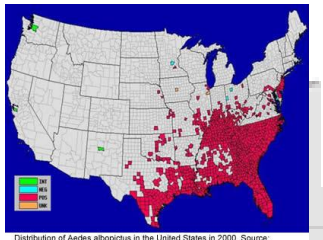
***GeurtsvanKessel C H et al. Clin Infect Dis.2013***

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# TICK-BORNE ENCEPHALITIS
## -geographical distribution-



# Chikungunya virus (alpha virus) and *Aedes albopictus*



Distribution of Aedes albopictus in the United States in 2000. Source: http://www.cdc.gov/ncidod/dvbid/arbor/albopic_97_sm.htm; accessed September 28, 2006.

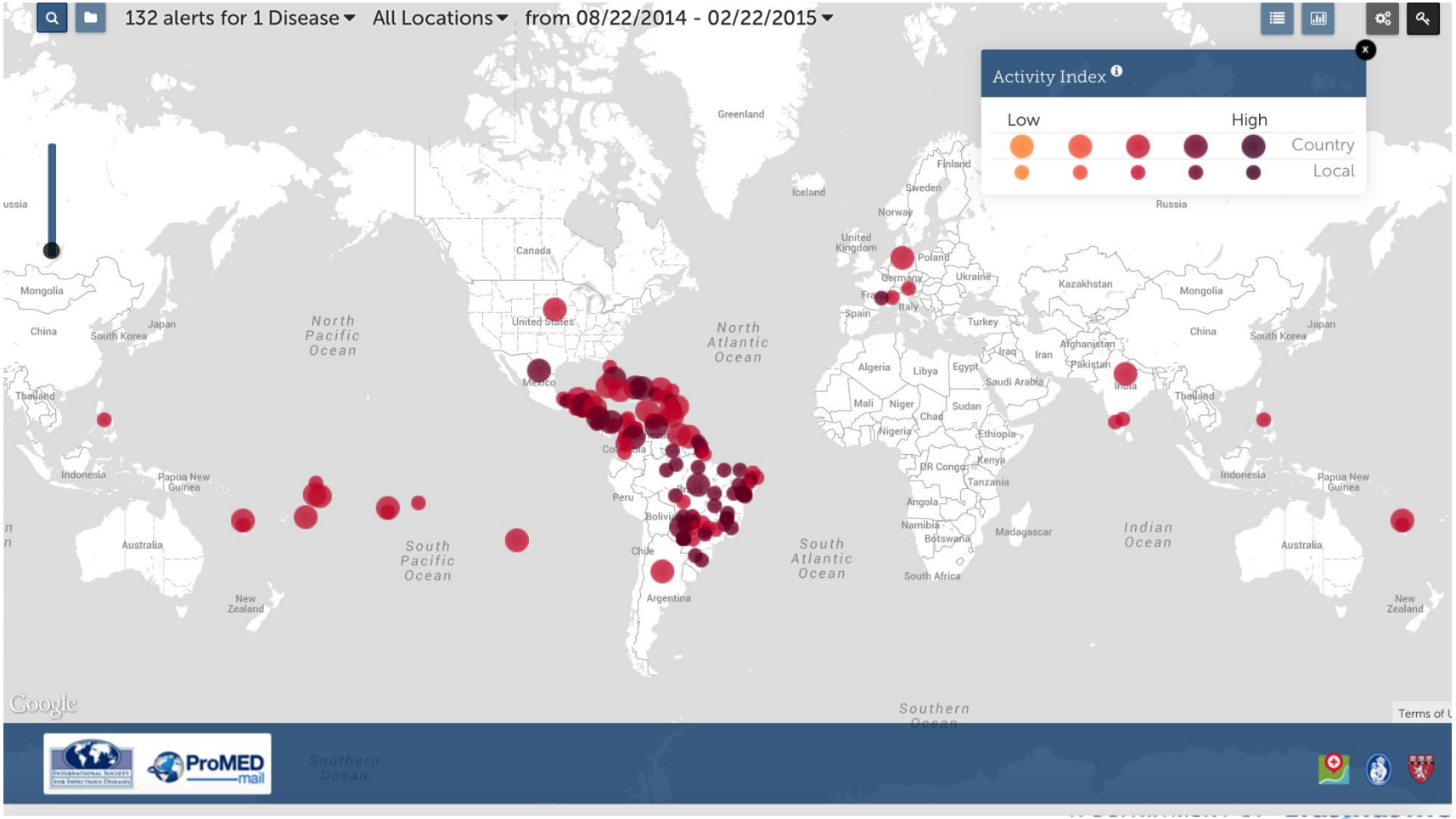
***Aedes albopictus* In the USA**

Chikungunya virus variants

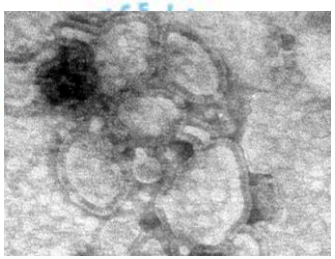
- Western African
- Central African
- Eastern and southern African
- Indian Ocean
- Asian



# Chikungunya virus
## Past six months



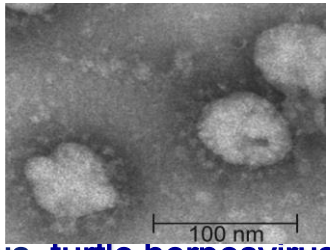
# Identification of new viral pathogens ErasmusMC



1995 CDV as the cause of mass mortality in Serengeti lions
1996 γ-herpesvirus in seals (phocid herpesvirus-2)
1997 monk seal morbilliviruses (MSMV-WA/G)
1997 influenza A (H5N1) virus in humans
1998 lentivirus from Talapoin monkeys (SIVtal)
1999 influenza B virus in seals
2000 human metapneumovirus (hMPV)
2002 re-emerging PDV in Europe
2003 SARS CoV cause of SARS in humans (Koch`s postulates)
2003 influenza A (H7N7) virus in humans
2004 fourth human coronavirus (CoV NL)
2005 H16 influenza A viruses (new HA!) in black headed gulls
2008 dolphin herpesvirus
2009 deer astrovirus
2010 human astrovirus, human picobirnavirus
2011 ferret coronavirus, ferret HEV, porcine picobirnavirus, stone marten anellovirus.
influenza A (H1N1) virus in dogs
2012 human calicivirus, HCoV-EMC, boa arenaviruses
2013 seal parvovirus, seal anelloviruses, deer papillomavirus, fox hepevirus, fox parvovirus, turtle herpesvirus
2014 canine bocavirus, porcine bocavirus, python nidovirus, camel circovirus, phocid herpes virus-7, influenza A (H10N7) virus in seals…

**novel molecular techniques**

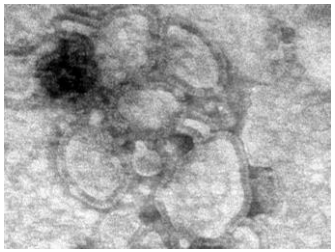
**FP7 funding: EMPERIE; ANTIGONE; PREPARE…**
**NL funding: VIRGO-FES…**

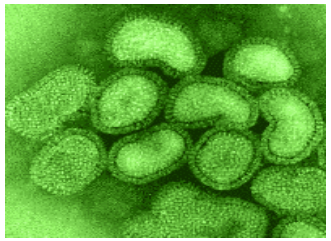


# Newly identified human respiratory viruses in last 15 years alone

| | | |
|---|---|---|
| HPAI-H5N1 * | influenzavirus | 1997 |
| Hendra-/NipahV | paramyxovirus | 2001 |
| hMPV * | paramyxovirus | 2001 |
| SARS-CoV * | coronavirus | 2003 |
| HPAI-H7N7 * | influenzavirus | 2003 |
| HCoV-NL63 * | coronavirus | 2004 |
| HCoV-HKU1 | coronavirus | 2005 |
| HBoV | parvovirus | 2005 |
| KI/WU-PyV | polyomavirus | 2007 |
| MelV(KamV) | orthoreovirus | 2007 |
| H1N1 pand | influenza virus | 2009 |
| HPBV * | picobirnavirus | 2010 |
| H3N2 porcine | influenza virus | 2011 |
| MERS-CoV * | coronavirus | 2012 |
| LPAI-H7N9 | influenzavirus | 2013 |
| -H9, -H10, -H6… | influenzavirus | 2013-15 |

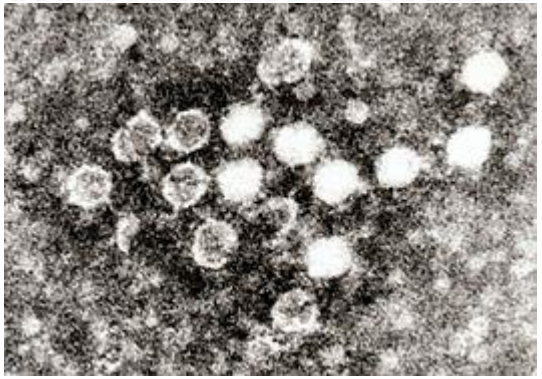






* Erasmus MC discovery

# Parvoviruses: wide spectrum of disease in humans and animals alike





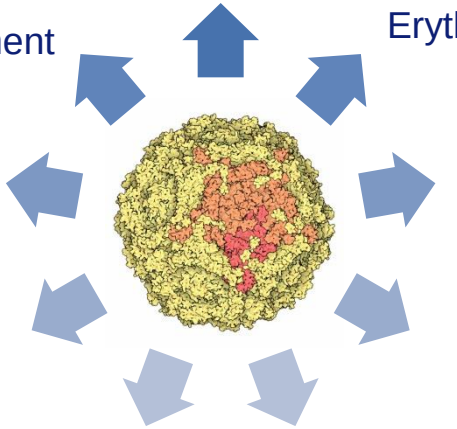

Brain involvement



Asymptomatic

Erythema infectiosum (Human B19)





Immune disorders
(Aleutian mink disease, Human B19)



Anemia
(Human B19,
non-human primate erythroviruses)

Hepatitis, myocarditis
(Canine parvovirus, Goose parvovirus, B19)

Respiratory disease
(Human bocavirus,
Canine bocavirus)



Fetal hydrops
(Human B19, Porcine parvoviruses)



Gastro-enteritis
(Canine parvovirus, Human bocavirus, Bufavirus)



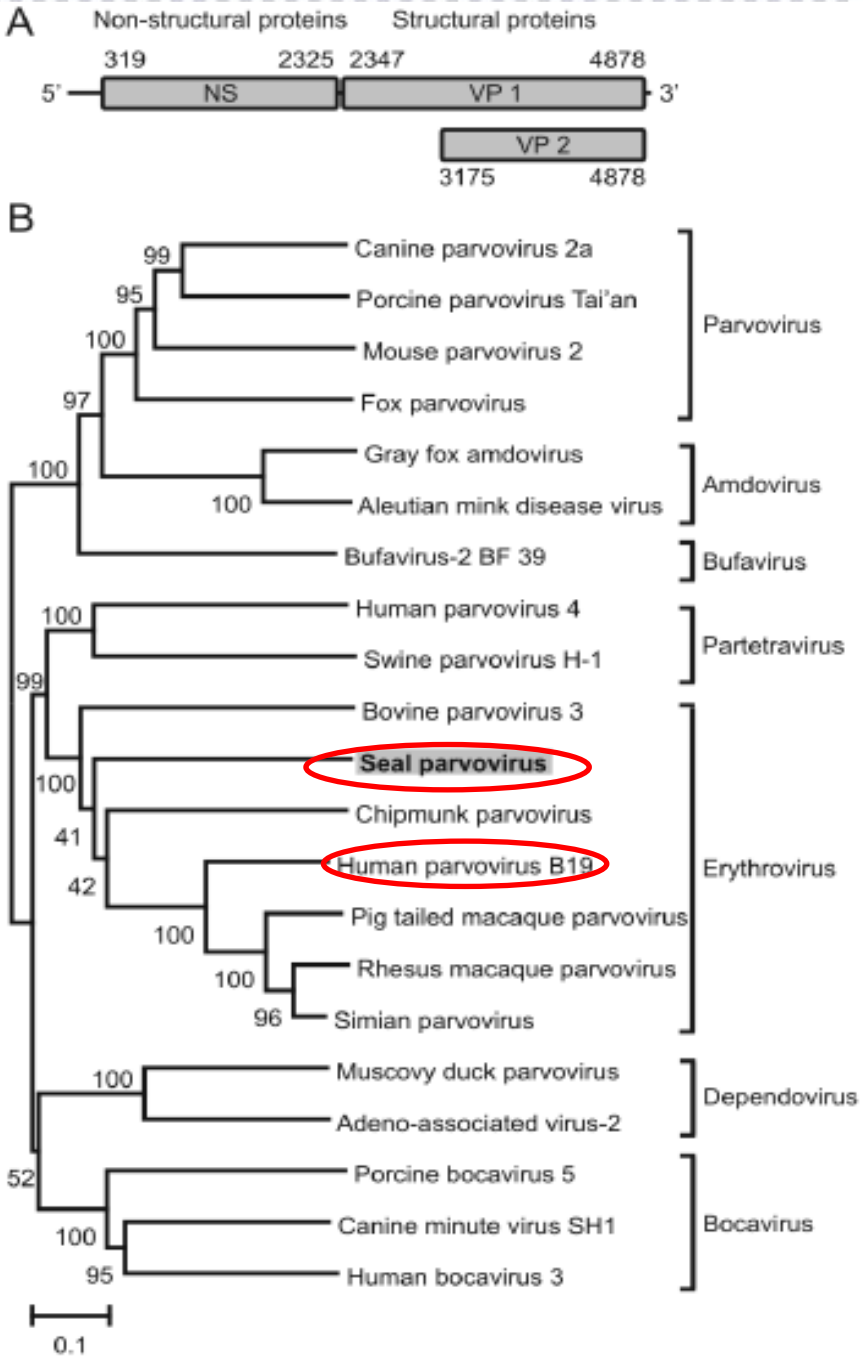
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# Harbour seal with CNS disease

**Sequences of a novel parvovirus detected**

**→ same genus as Human parvovirus B19, different from Canine parvovirus**






*Bodewes et al., PLoS One 2013*

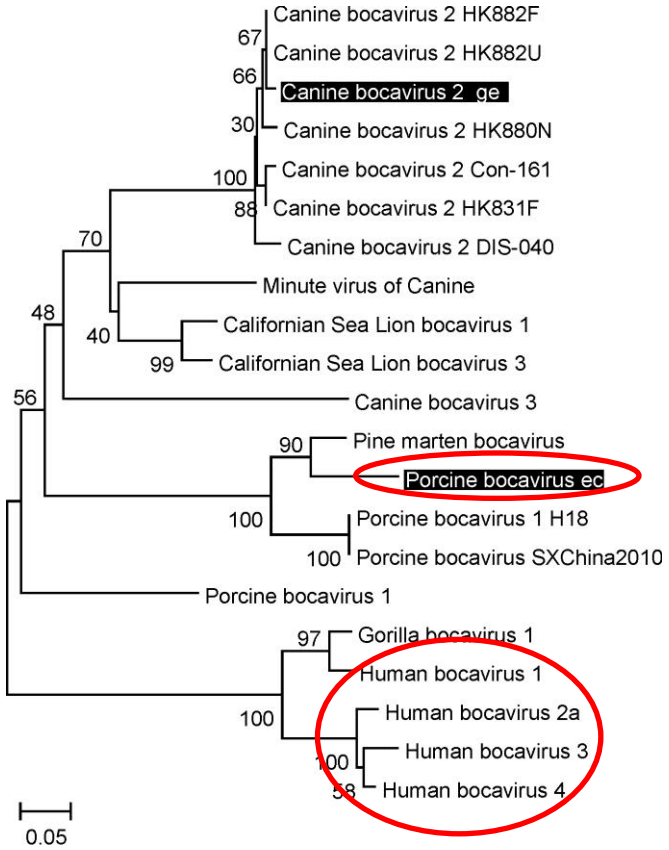
# Virus discovery in a pig with encephalitis

- **Various other causes of encephalitis of pigs excluded by PCR**

  **→ Virus discovery brain tissue**

➢ **Novel porcine bocavirus**

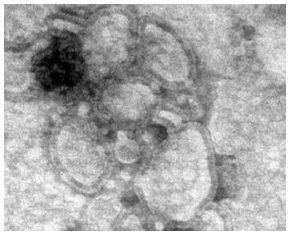




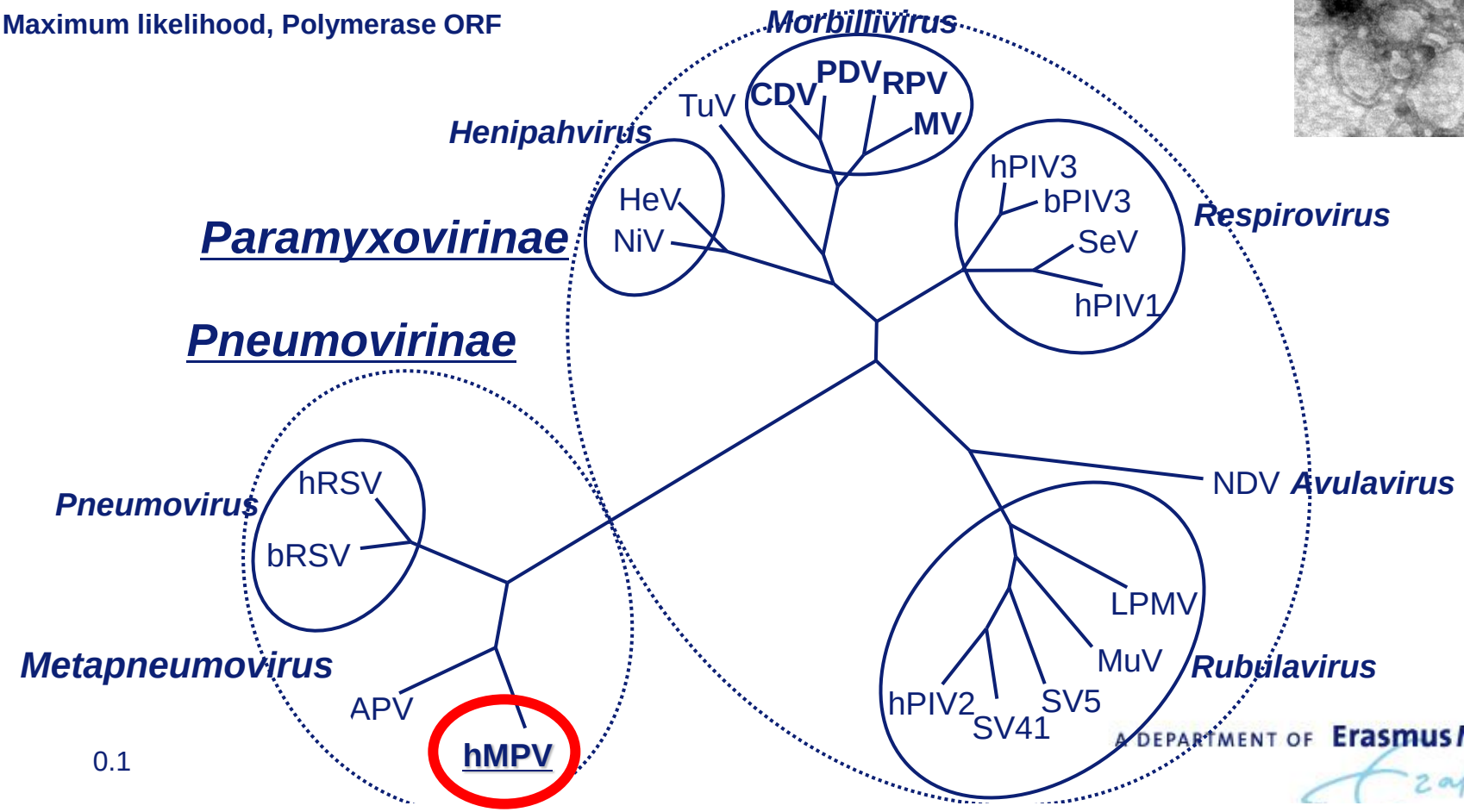

*Bodewes et al., in prep.*

# Order *Mononegavirales*, family *Paramyxoviridae:* "discovery of another human paramyxovirus"

*v.d.Hoogen et al., Nat.Med. 2001*



DNA Maximum likelihood, Polymerase ORF




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**MRCA of APV and HMPV: about 200 years ago** (M.v.d.Graaf et al.)

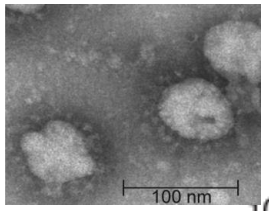
# SARS-CoV
## - Phylogeny -

Drosten et al., NEJM 2003
Rota et al., Science 2003
v.d. Hoek et al., Nature Med., 2004
Fouchier et al., PNAS 2004
Woo et al., J.Virol., 2005






hMPV as the cause?



Fouchier et al.,Nature 2003
Kuiken et al., Lancet 2004




**Press conference of**

# SARS etiology

**network**

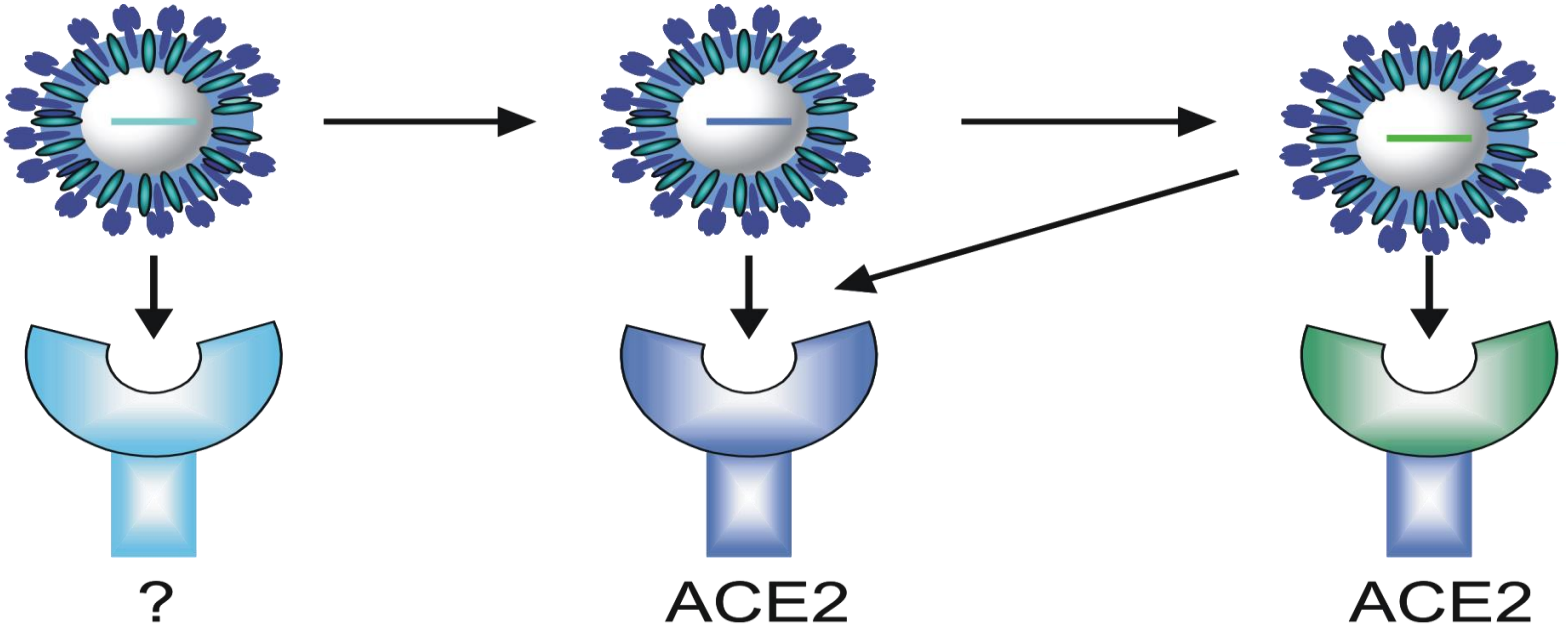
**Official declaration of SARS-CoV as the etiologic agent**

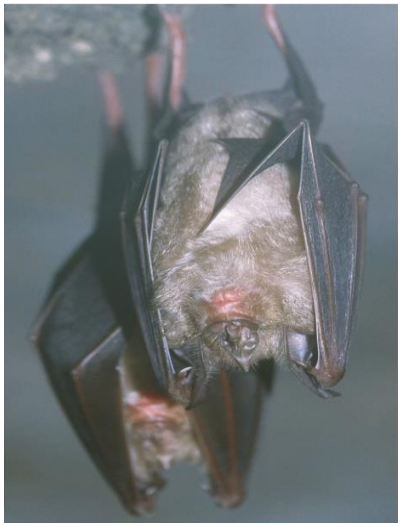
## Short- and mid-term objectives:

- clarification of transmission routes and natural history
- establishment and evaluation of diagnostic tools



# Zoonotic transmission of SARS-CoV

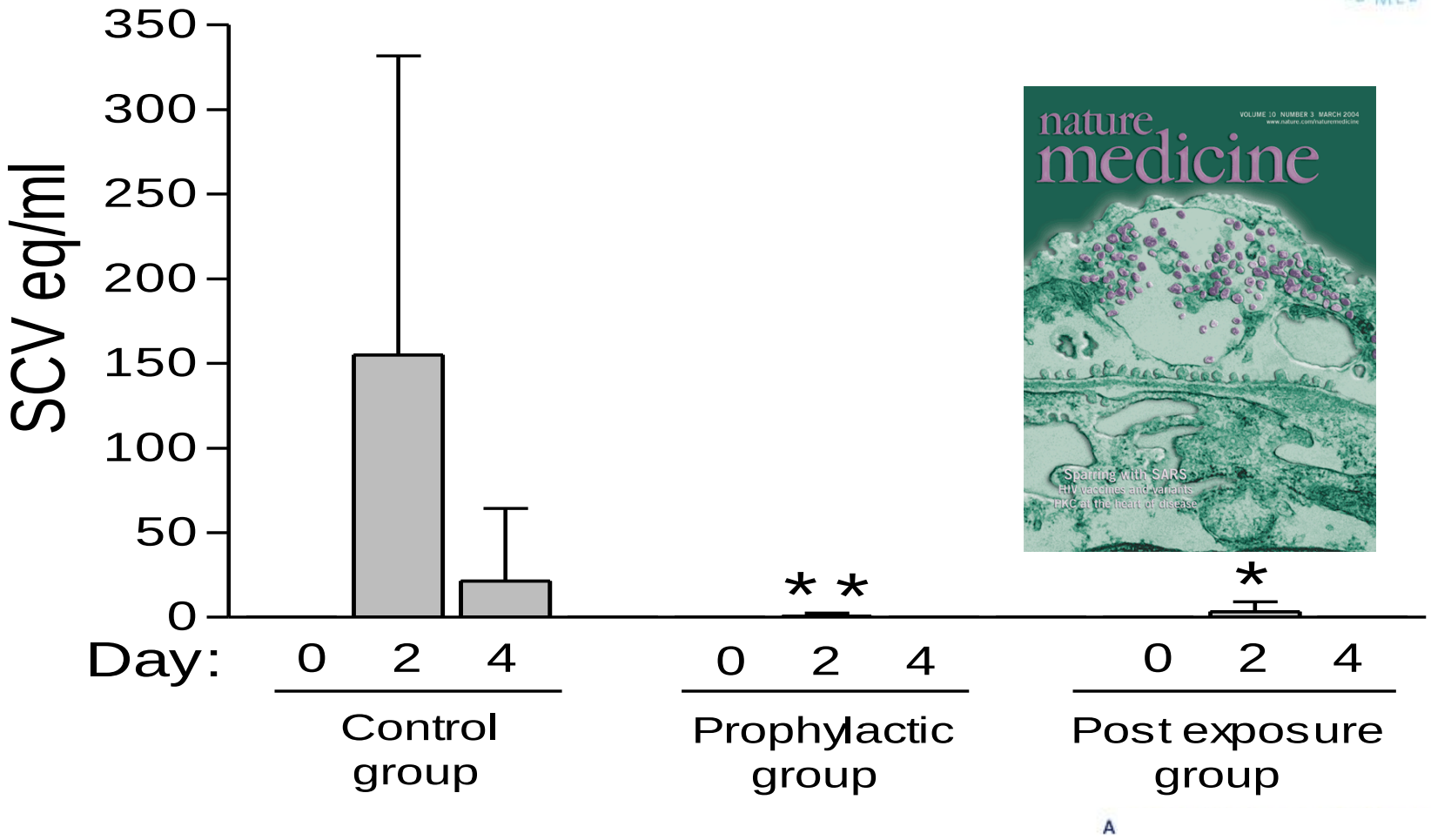






# IFN-*a* treatment macaques: SARS-CoV excretion from pharynx

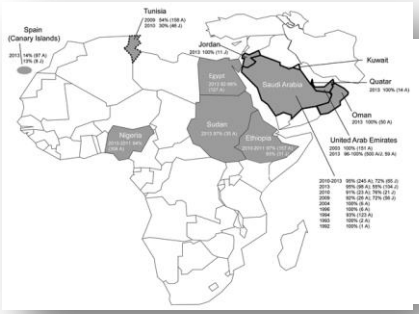






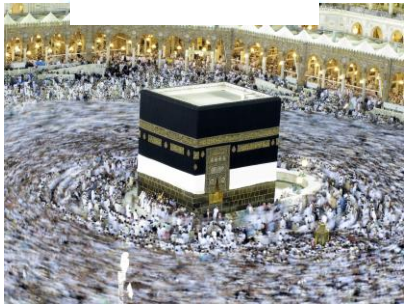
Haagmans et al., Nature Med. 2004

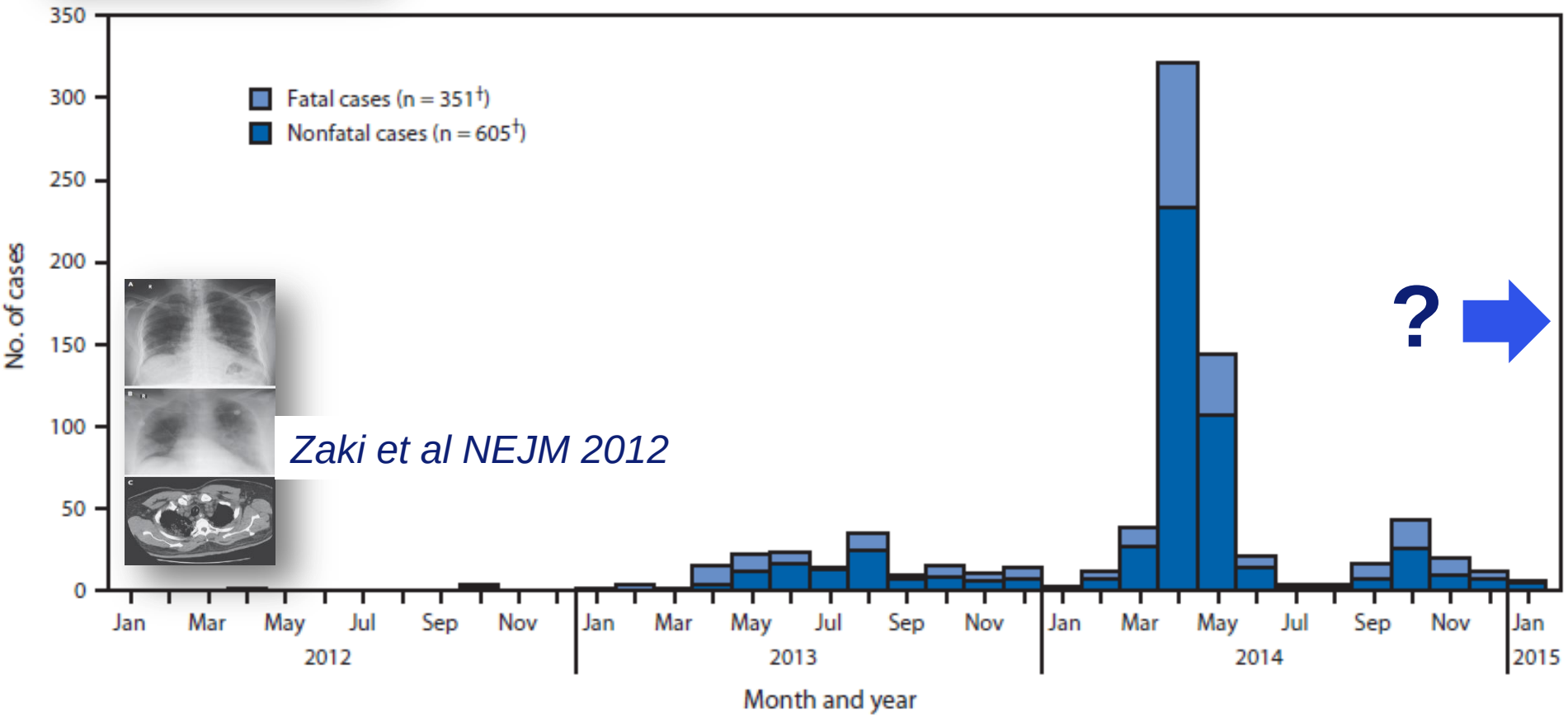
# MERS-CoV human cases




**To date: estimated 900 cases in >20 countries with 385 deaths**

Saudi Arabia, Malaysia, Jordan, Qatar, Egypt, the United Arab Emirates, Kuwait, Oman, Algeria, Bangladesh, the Philippines, Indonesia (none confirmed), UK, and USA

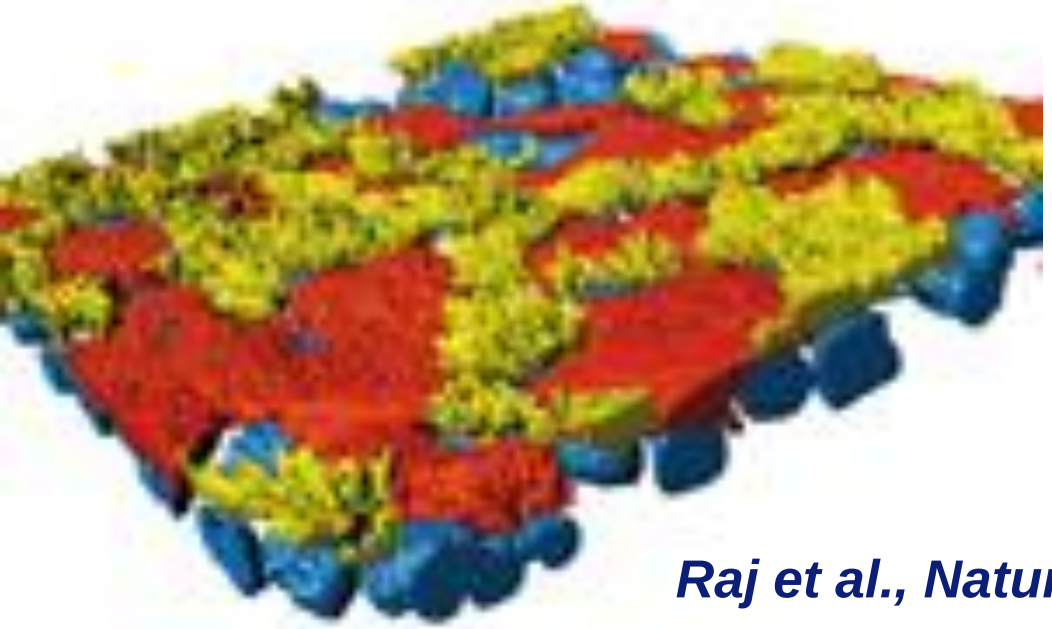


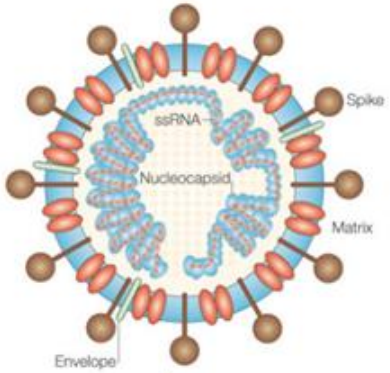


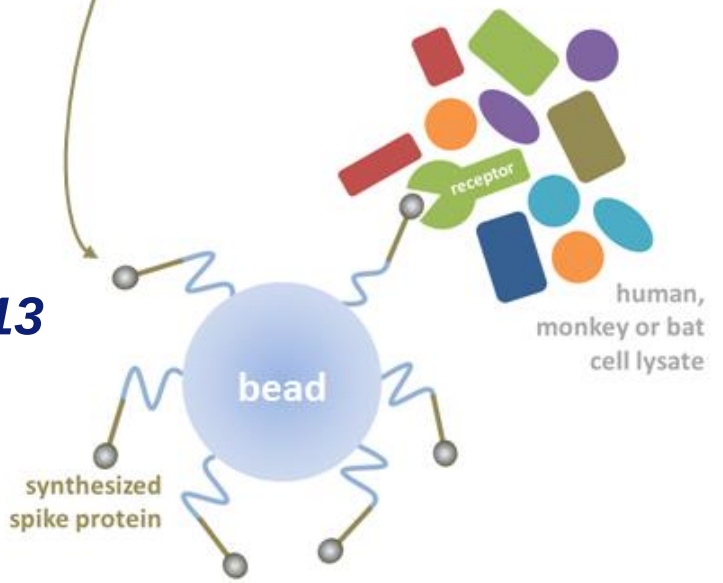



*Zaki et al NEJM 2012*

# CD26: receptor MERS-CoV

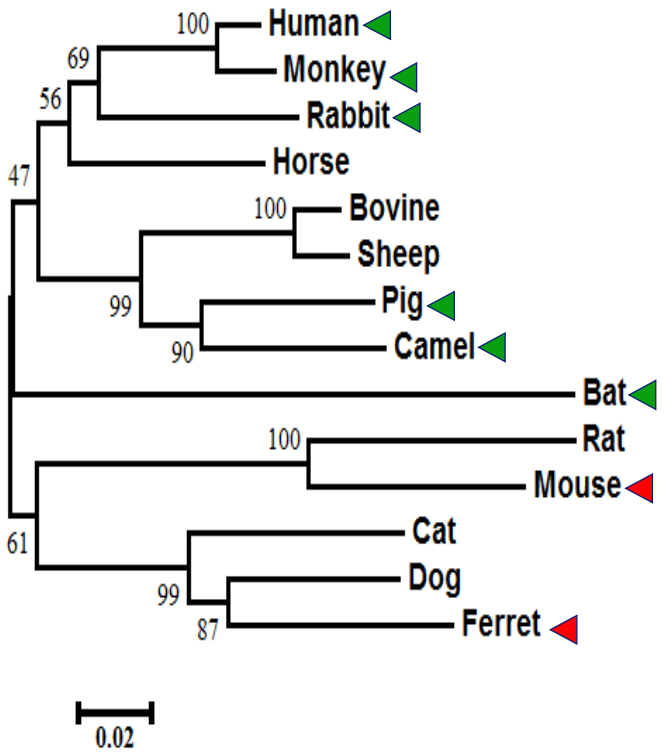


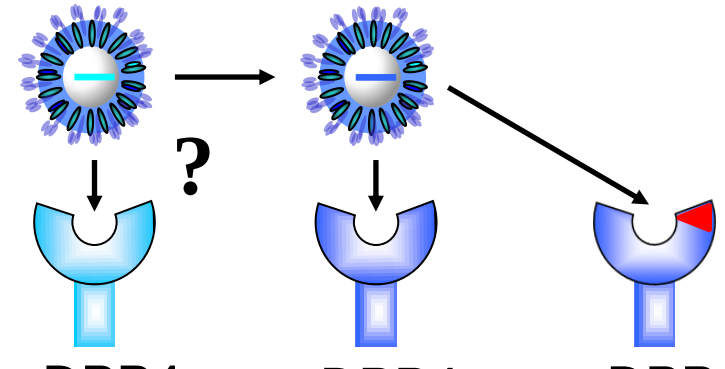


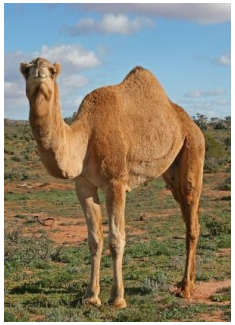

*Raj et al., Nature 2013*

# Zoonotic transmission of MERS-CoV









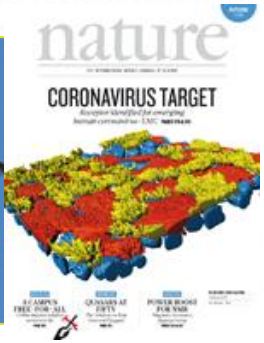
## Antibodies in dromedary camels

**(Reusken et al Lancet ID 2013)**

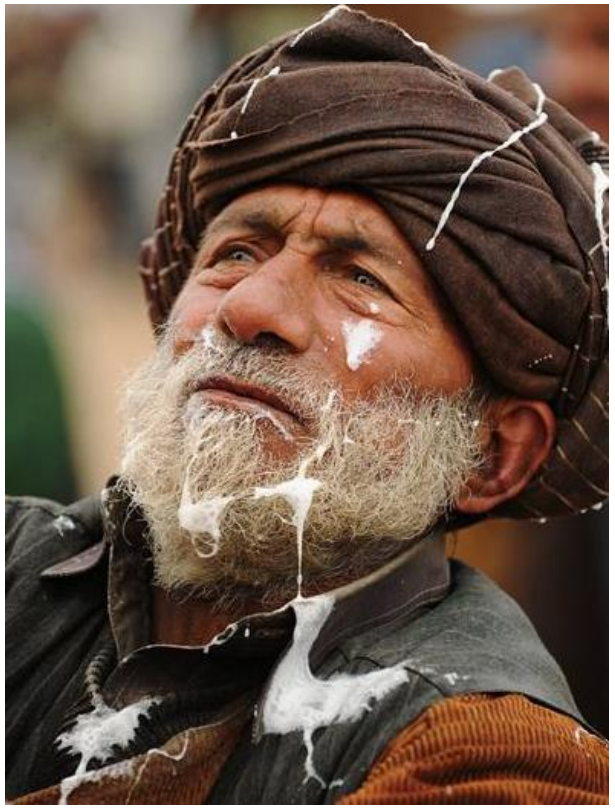
## Dromadary camels: carriers of MERS-CoV

**(Haagmans et al., Lancet ID 2013)**







## Identification of the CD 26 MERS-CoV receptor

**(Raj et al., Nature 2013)**

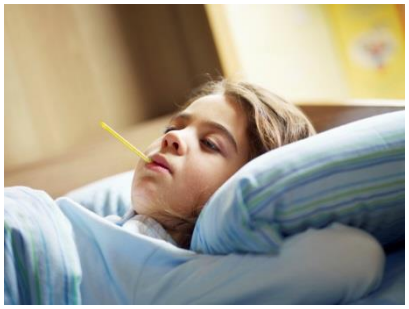
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# MERS: PREVENTION AT THE SOURCE?



# Seasonal influenza is a serious and life-threatening disease worldwide



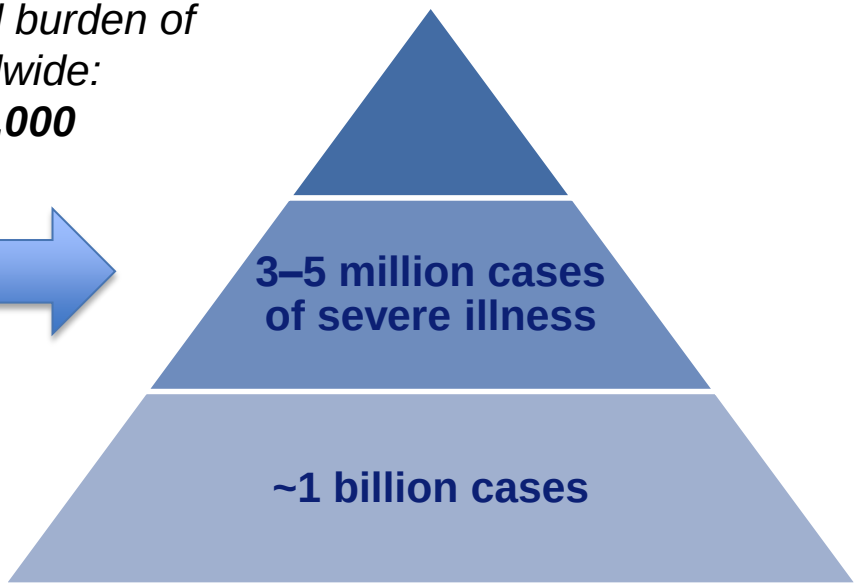







*Annual burden of influenza in the **USA: 30,000–40,000 deaths**[1]*

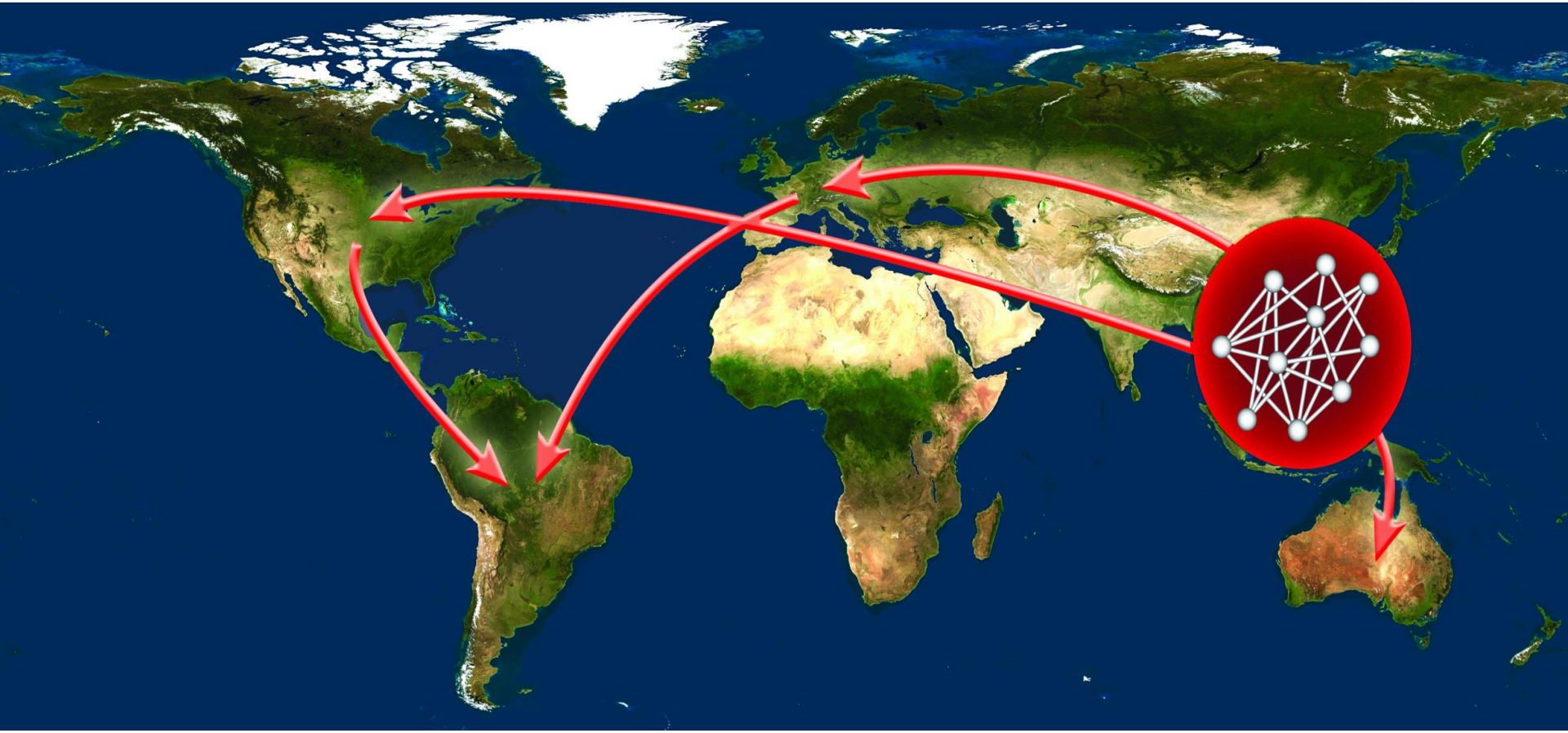
*Extrapolated annual burden of influenza worldwide: **300,000–500,000 deaths**[1]*




1. WHO. Influenza. 2008. www.who.int/immunization/topics/influenza/en/index.html. Accessed April 2014

# The Global Circulation of Seasonal Influenza A (H3N2) Viruses

Science
AAAS



*Russell et al. 2008*

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

*BF Koel et al, Science. 2013 Nov 22;342(6161):976-9*

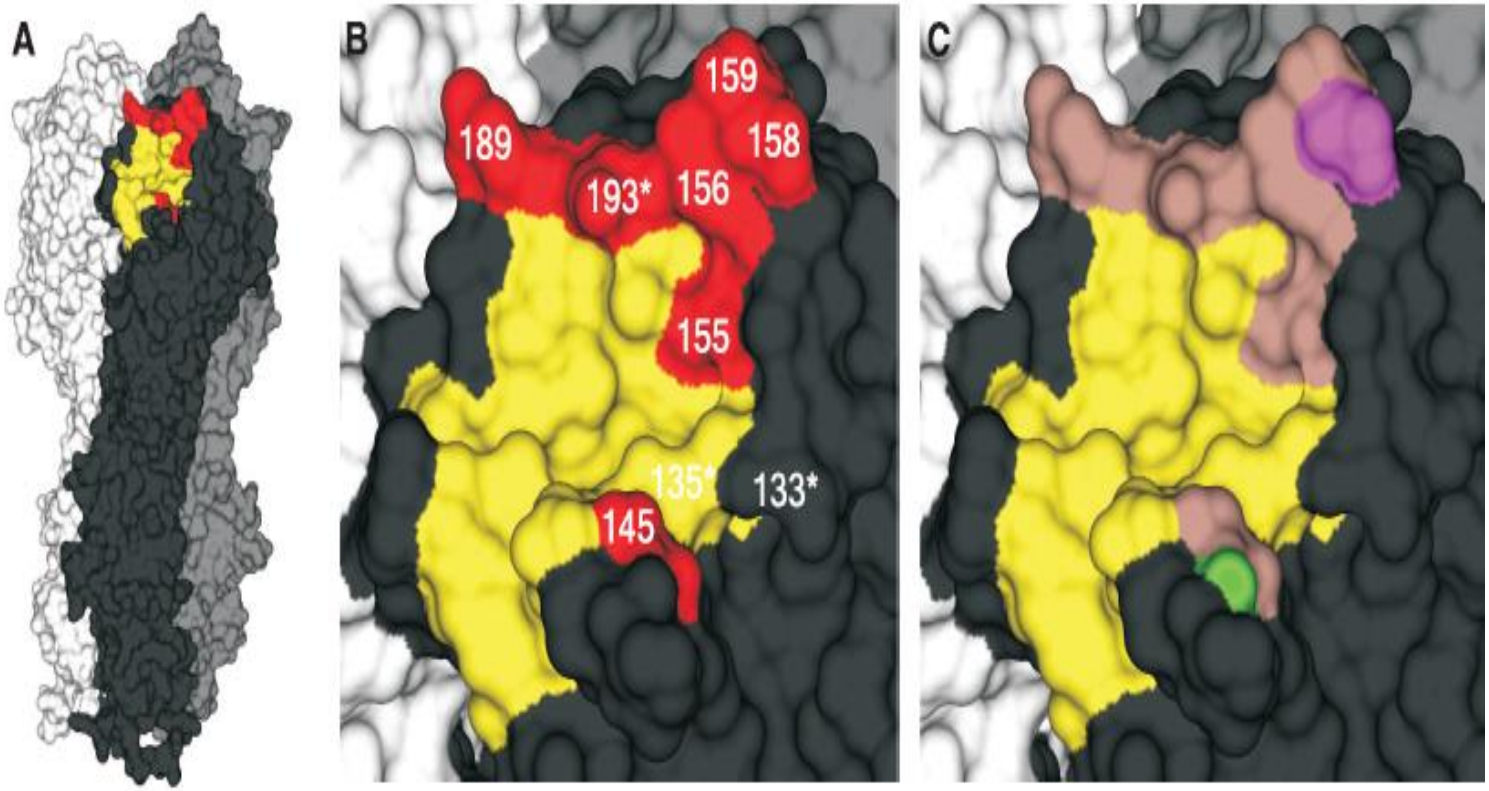
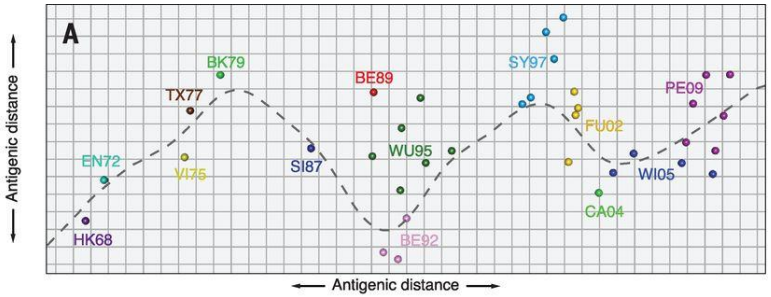
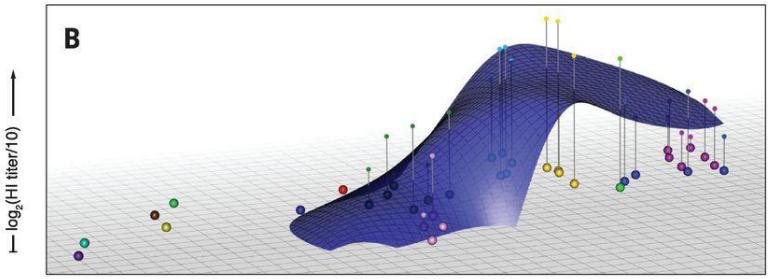



**Fig. 2. Positions of the cluster-transition amino acid substitutions indicated on an A/Aichi/2/1968 HA trimer.** The three monomers are shown in black, white, and gray; the RBS is in yellow. (**A** and **B**) The positions responsible for A/H3N2 cluster transitions are shown in red. An asterisk indicates 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.

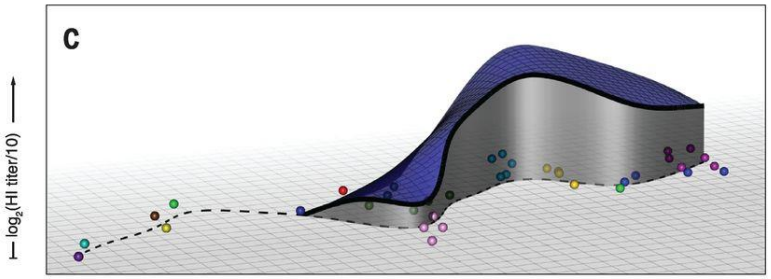
# *Creating an antibody landscape*



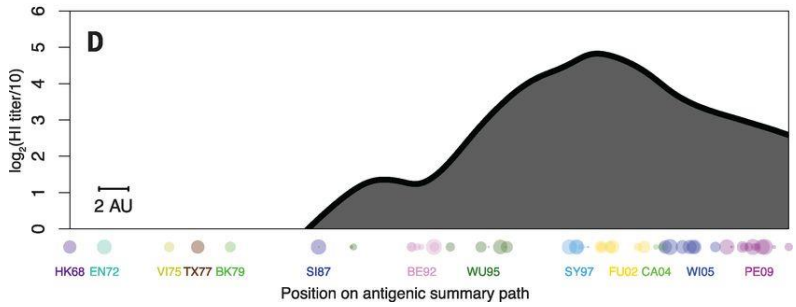

*A) Antigenic map of A/H3N2 showing virus strains color-coded by antigenic cluster.*




*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*

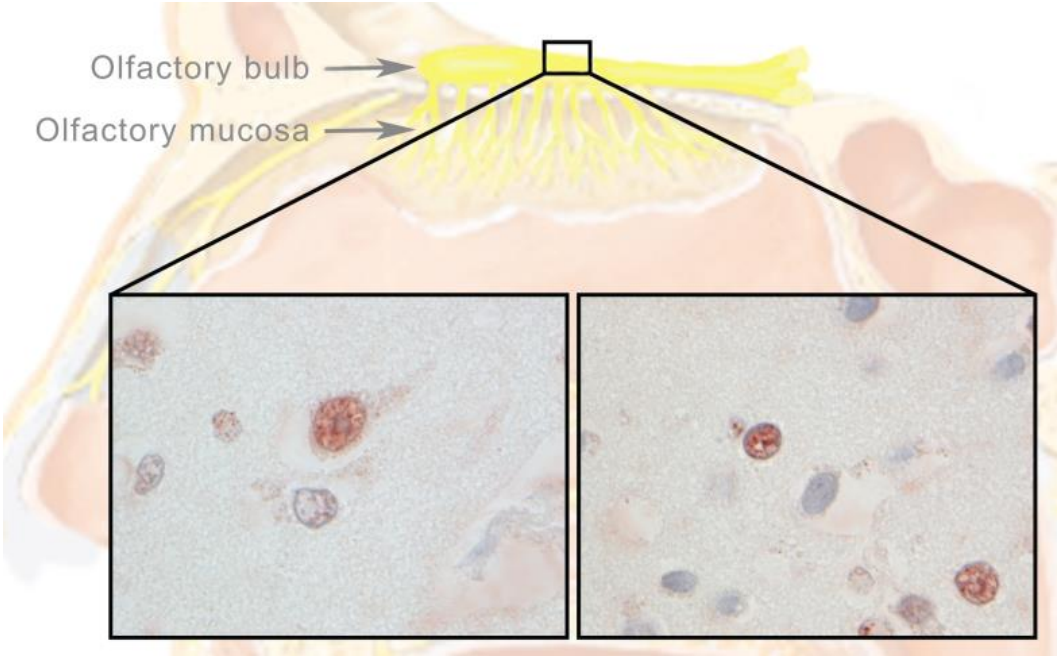



*D) The height of the landscape along the antigenic summary path in (C) is plotted to create a rotation-independent two-dimensional summary visualization of the landscape*

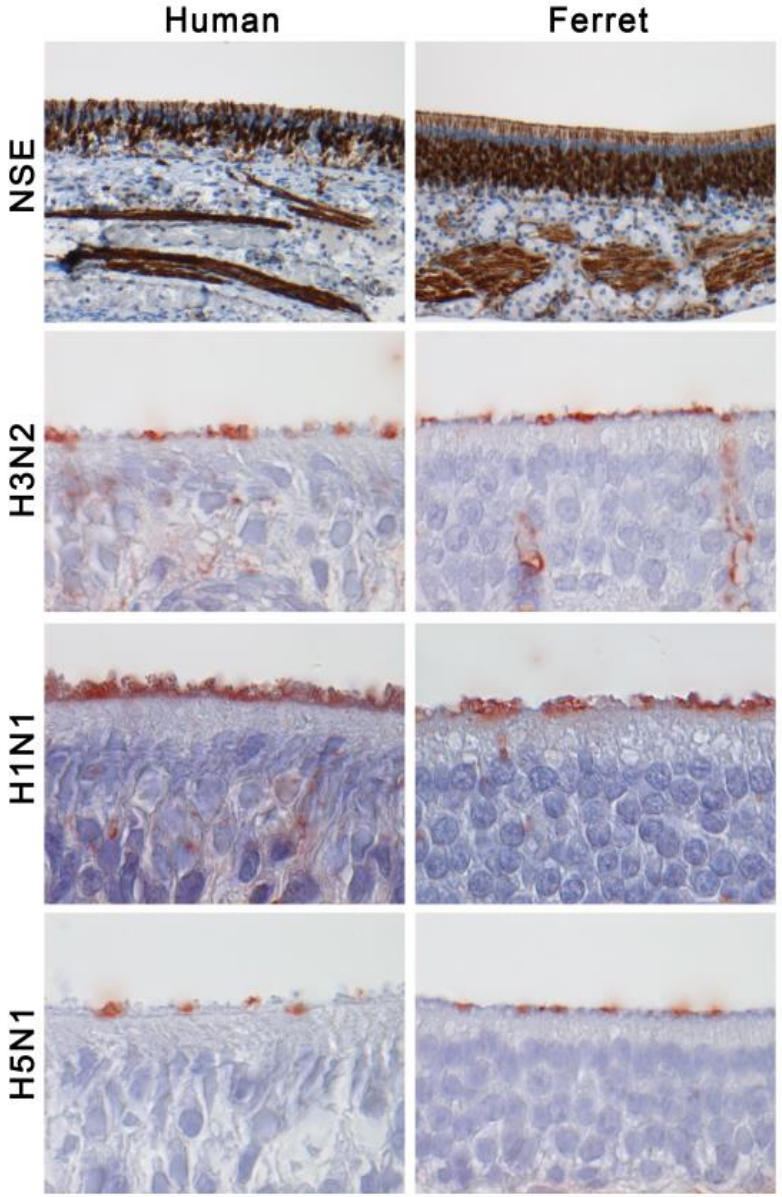


***J. M. Fonville et al. Science 2014;346:996-1000***

# The olfactory nerve as route of entrance into the CNS



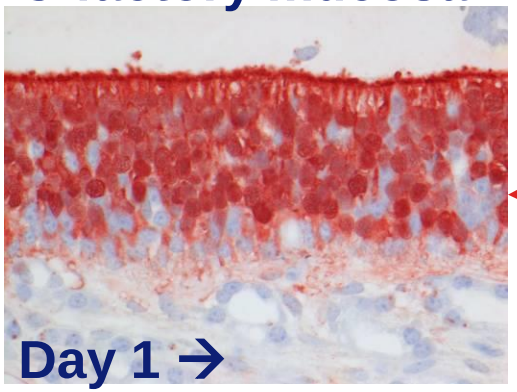

**Detection of influenza in the olfactory bulb of an immunocompromised child**

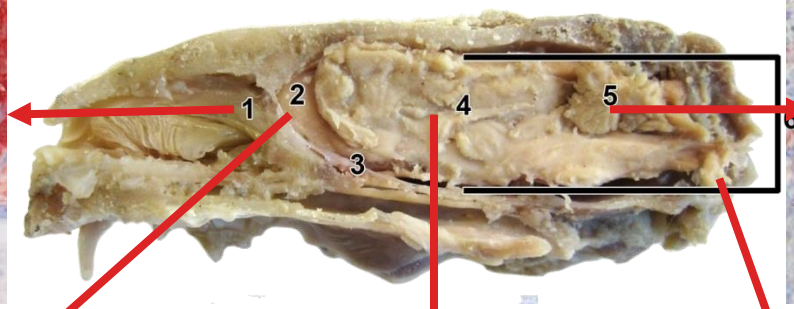


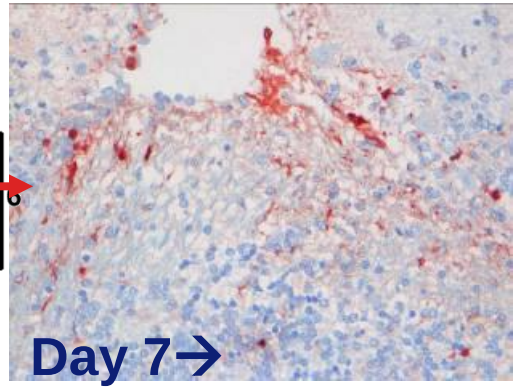

**Different influenza viruses attach to the olfactory mucosa**

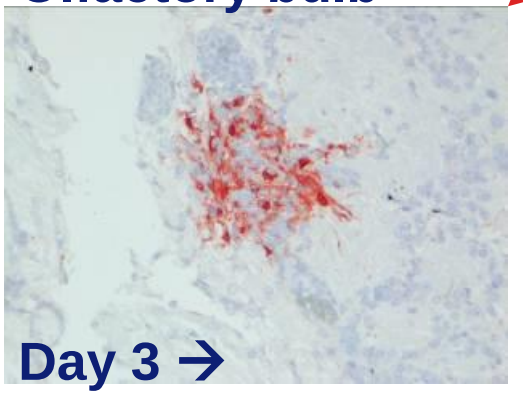
van Riel et al., **Evidence for Influenza Virus CNS Invasion Along the Olfactory Route in an Immunocompromised Infant.**
**J Infect Dis. 2014**

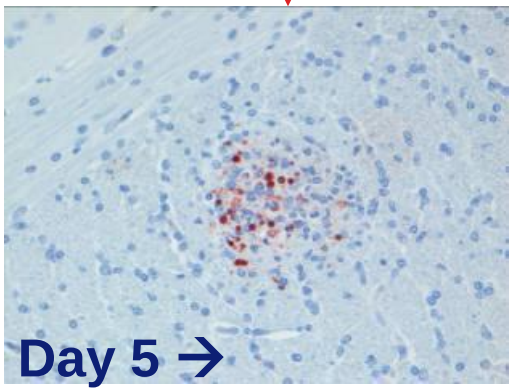
# H5N1 virus CNS invasion via the olfactory nerve

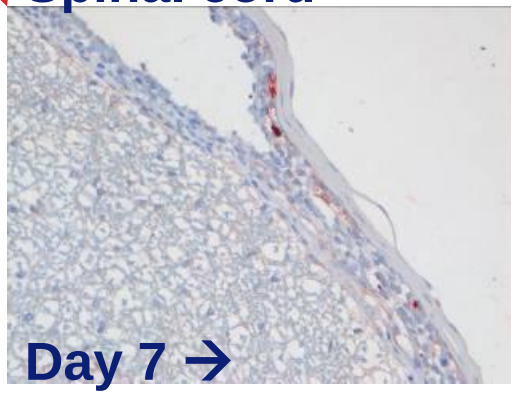


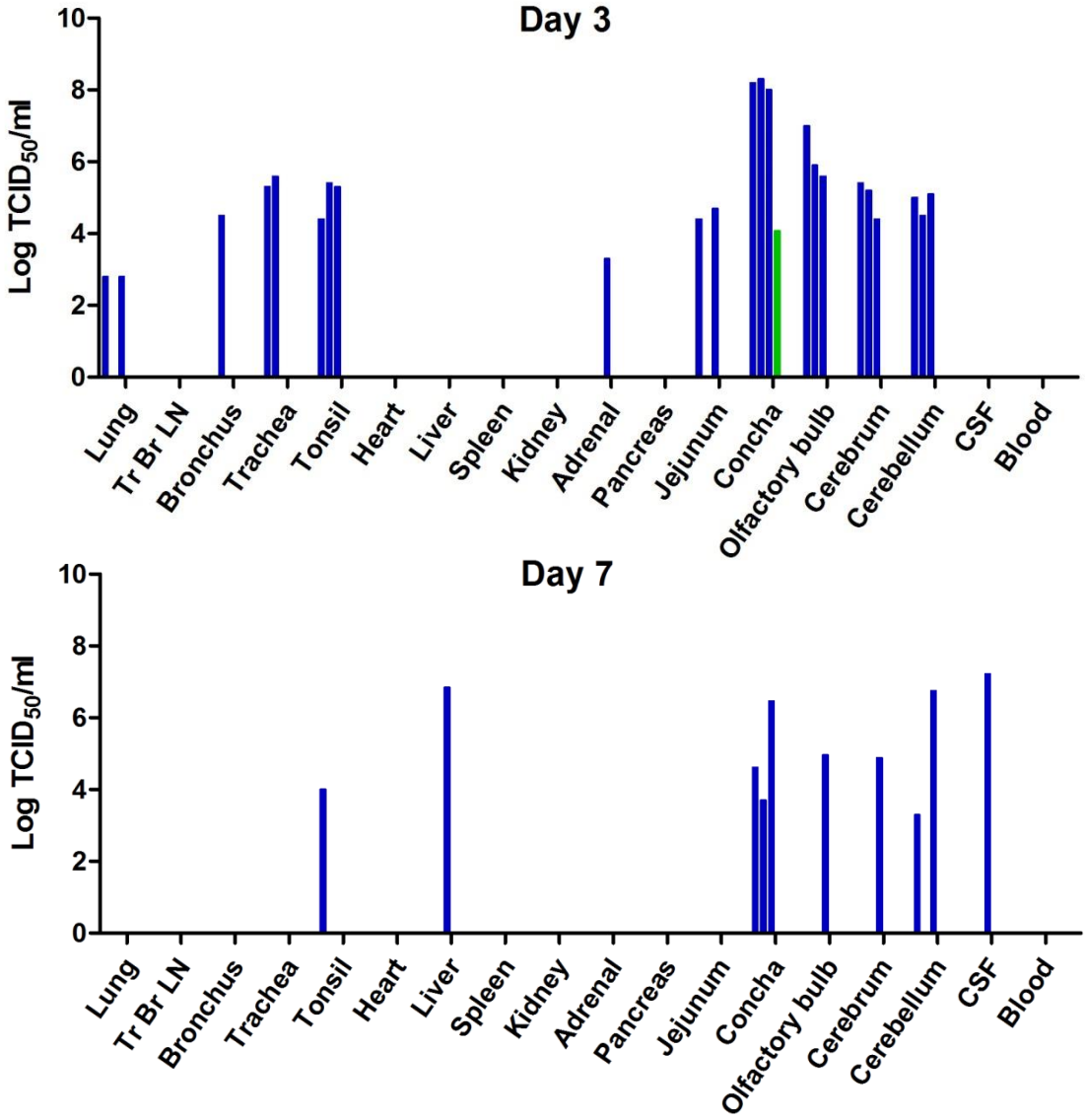



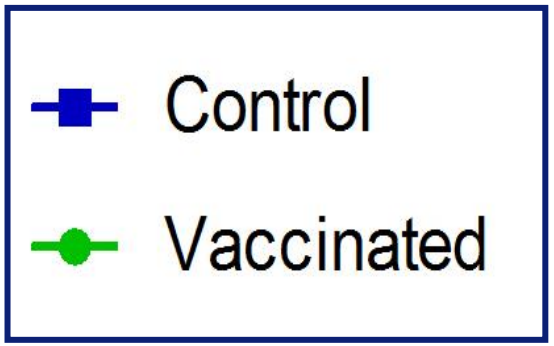




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*Schrauwen & van Riel 2012 J Virol*

# Results - Virus titers in tissues

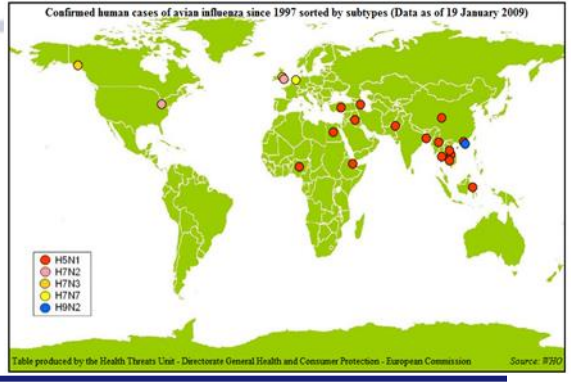



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# INFLUENZA A VIRUS

## Recent zoonotic transmissions from birds -confirmed human cases-



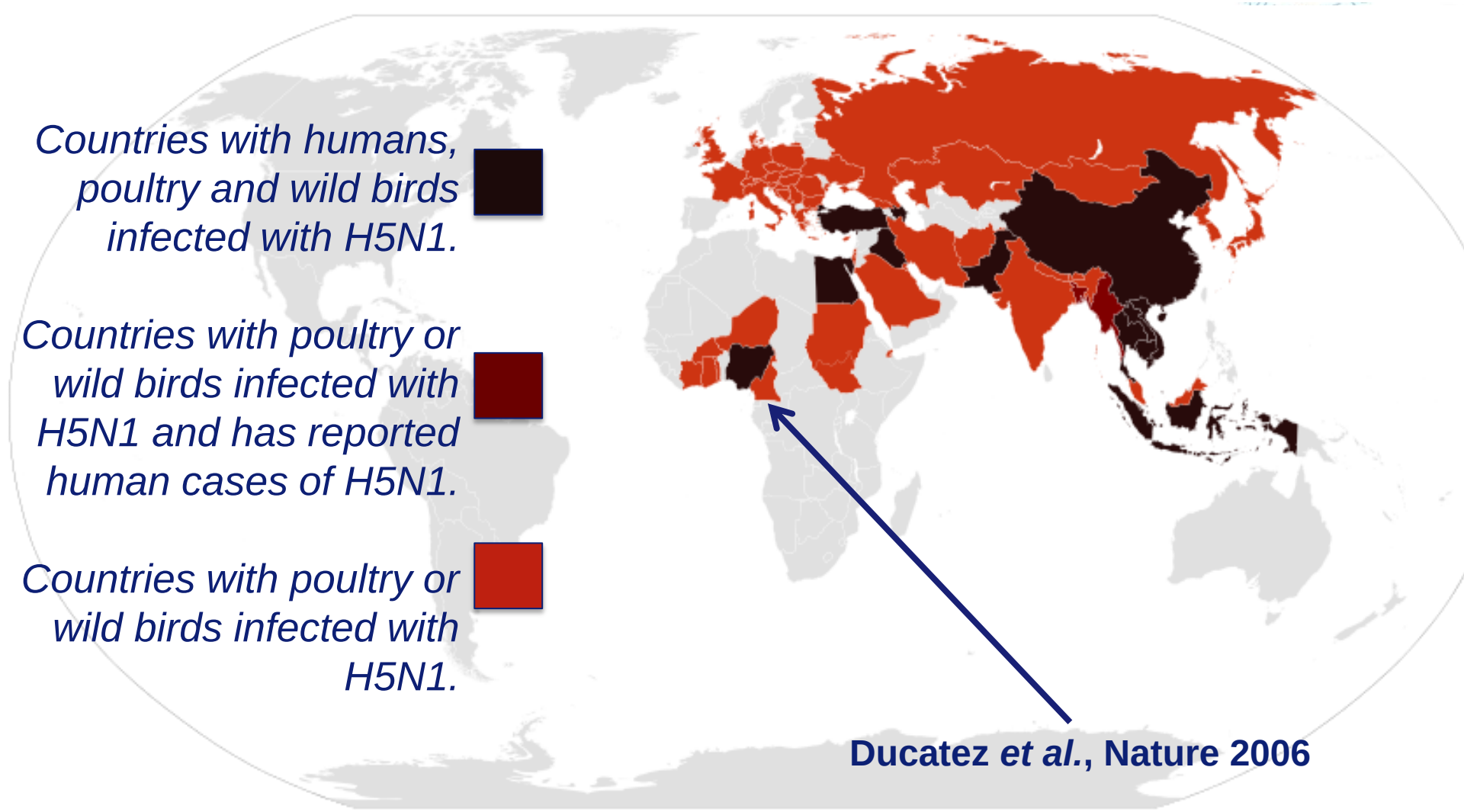

| Subtype | Country | Year | # Cases | # Deaths |
|---|---|---|---|---|
| H7N7 | UK | 1996 | 1 | 0 |
| H5N1 | Hong Kong | 1997 | 18 | 6 |
| H9N2 | SE-Asia | 1999 | >2 | 0 |
| H5N1 | Hong Kong | 2003 | 2? | 1 |
| H7N7 | Netherlands | 2003 | 89 | 1 |
| H7N2 | USA | 2003 | 1 | 0 |
| H7N3 | Canada | 2004 | 2 | 0 |
| H5N1 | SE-Asia/M-East/ Europe/W-Africa | 2003-15* *CFR ~ 60% | >700 (increasing) | >400 |
| H7N9 | PR China | 2013 | >600 | >100 |
| H9, H10, H6.. | Asia… | ongoing | <5 | <5 |

# Highly pathogenic avian influenza A virus H5N1

*Countries with humans, poultry and wild birds infected with H5N1.*

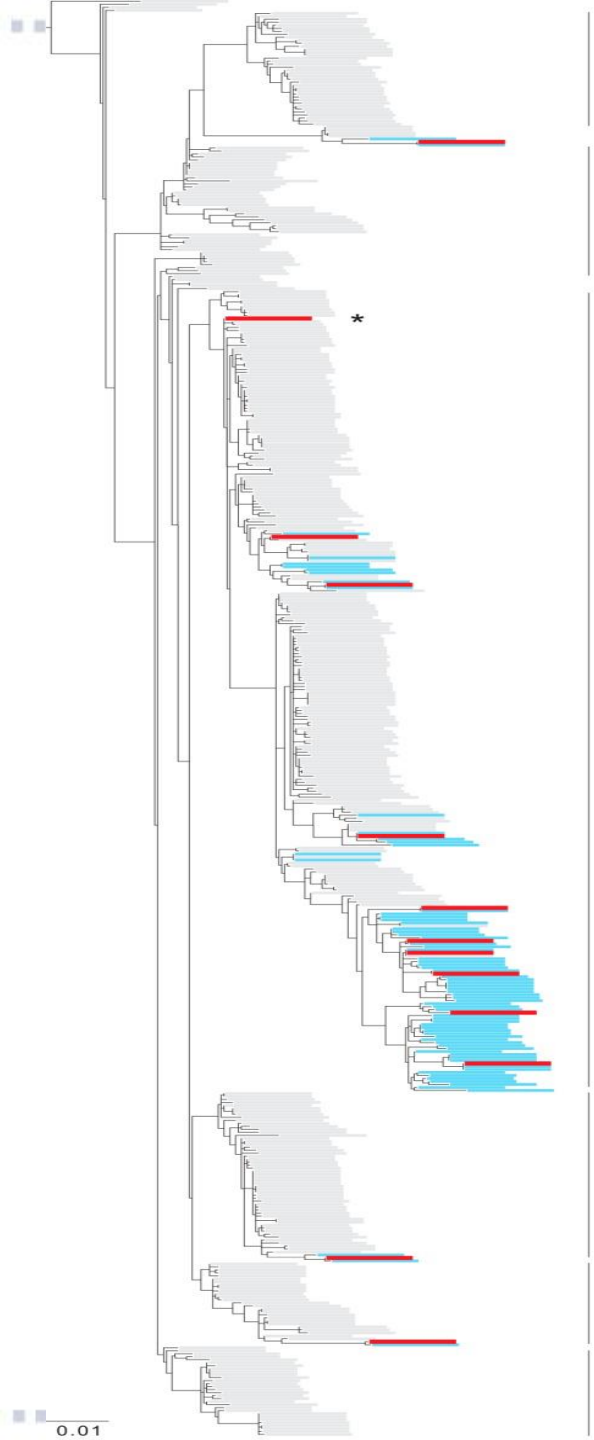
*Countries with poultry or wild birds infected with H5N1 and has reported human cases of H5N1.*

*Countries with poultry or wild birds infected with H5N1.*



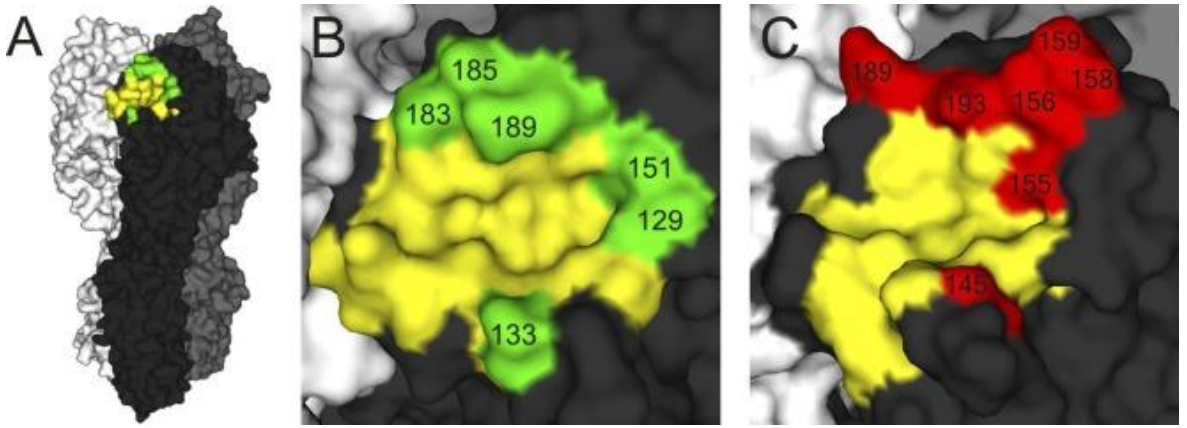
**Ducatez *et al.*, Nature 2006**

*Wikipedia, as of 29 May 2013*




***Antigenic Variation of Clade 2.1 H5N1 Virus Is Determined by a Few Amino Acid Substitutions Immediately Adjacent to the Receptor Binding Site***

*Björn F. Koel, et al.,* ***mBio 2014***



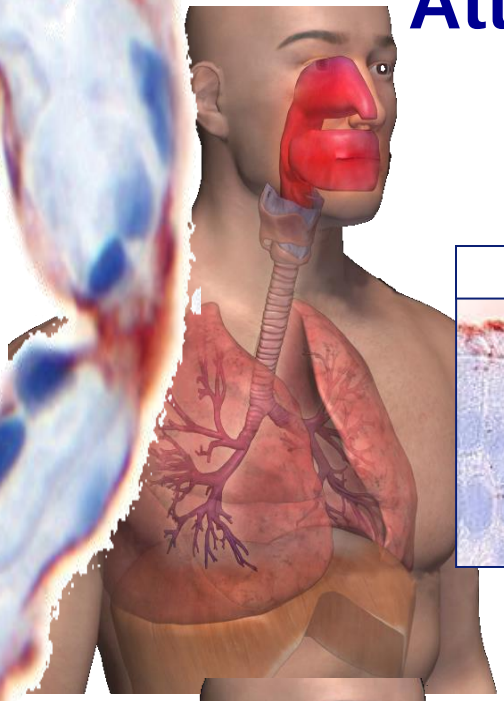


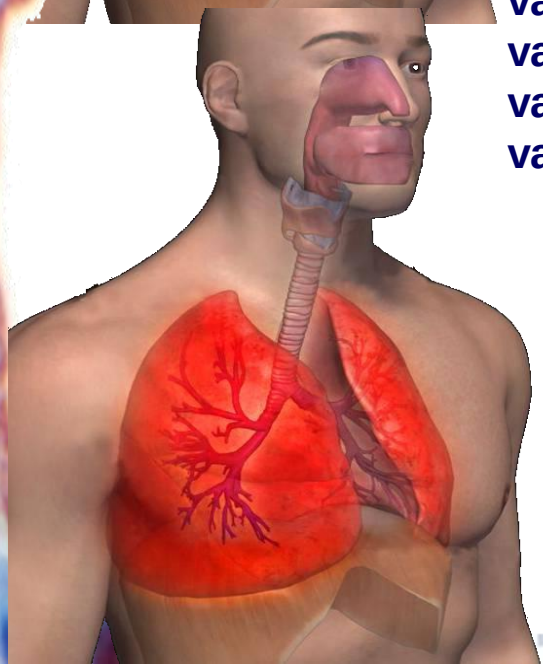
© J. HABEL/CORBIS

# Feline friend or potential foe?

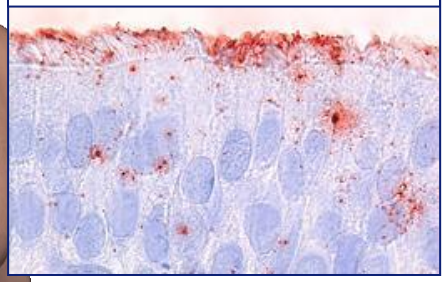
What role do cats play in the epidemiology of the H5N1 avian flu virus? We don't yet have all the answers, but it's time to consider new precautions, argue **Thijs Kuiken**, **Albert Osterhaus**, **Peter Roeder** and their colleagues.

# Attachment to upper or lower respiratory tract

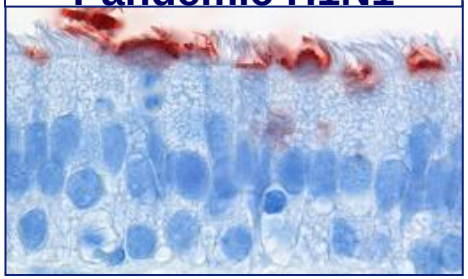




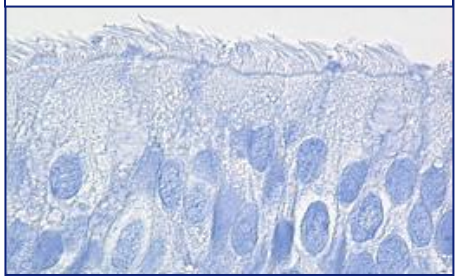
**Seasonal H3N2**



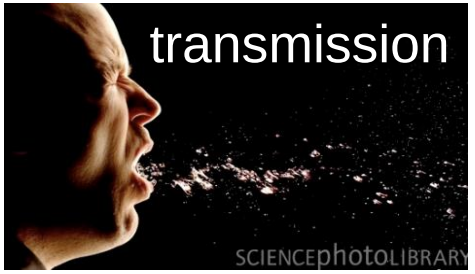
**Pandemic H1N1**



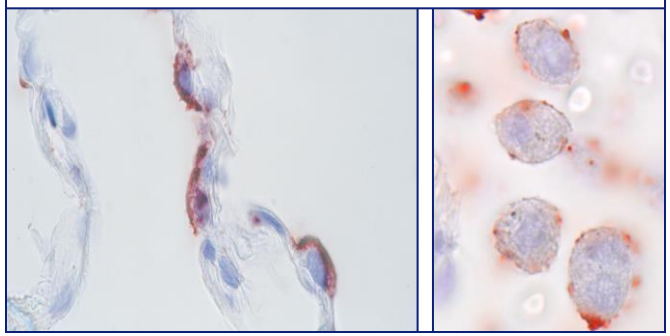
**HPAIV H5N1**

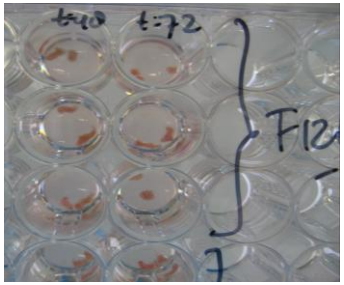


van Riel et al.,Science 2006
van Riel et al., Am J Pathol 2007
van Riel et al., Am J Pathol 2009
van Riel et al., Am J Pathol 2010
van Riel et al.,PLoS Path. 2011



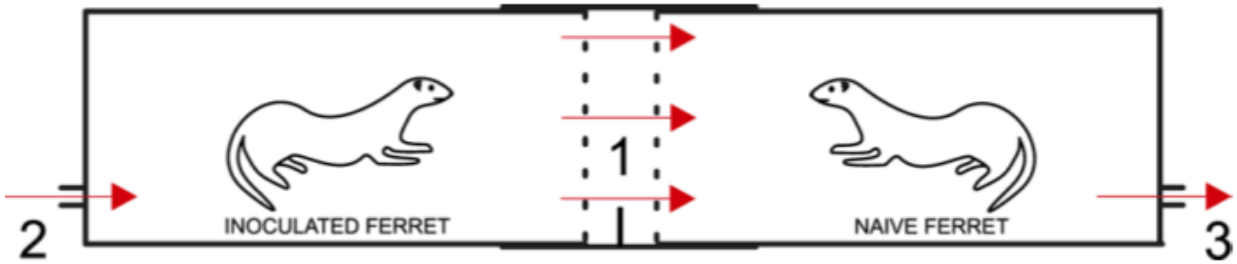

**HPAIV H5N1**

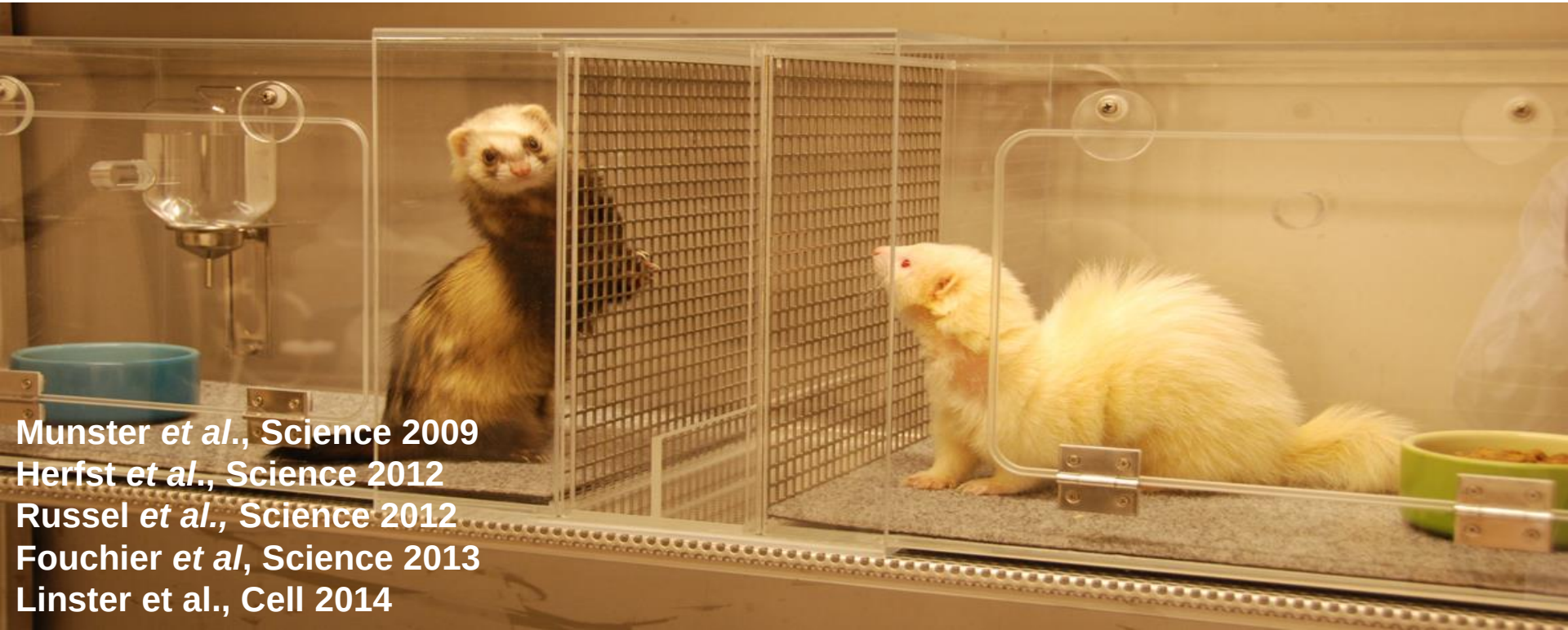





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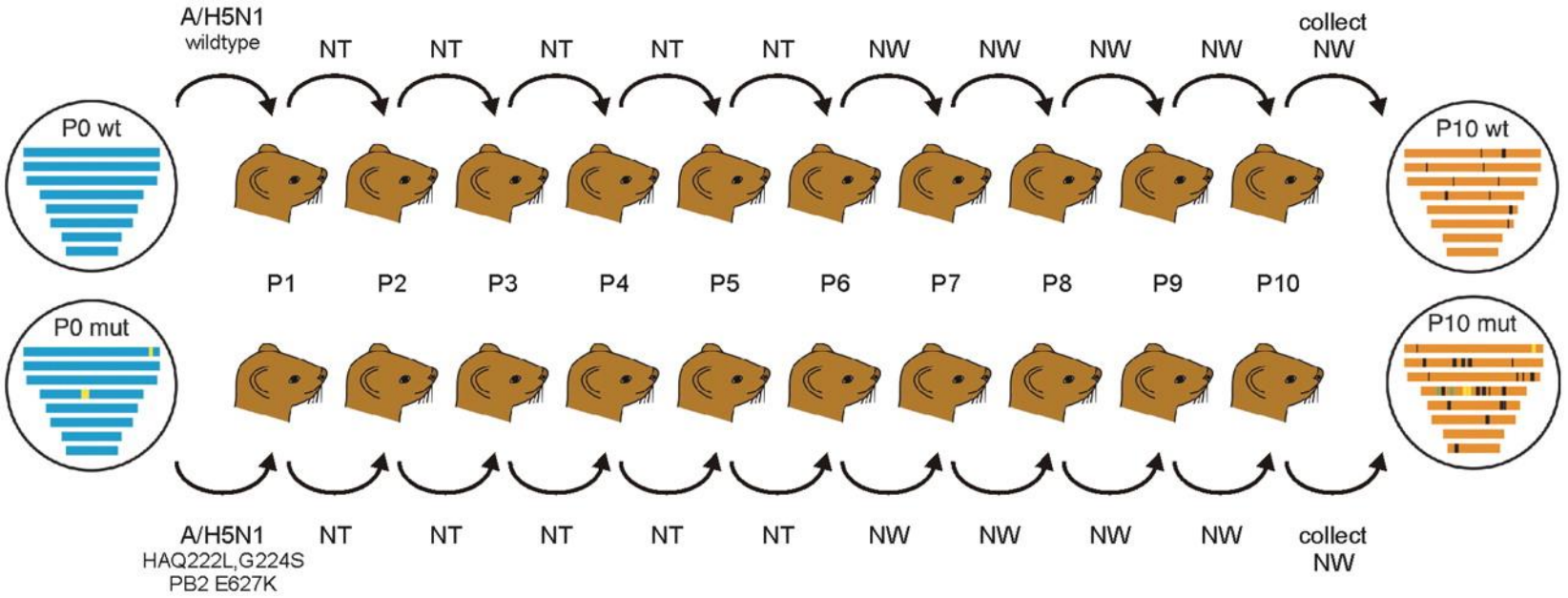
# Transmission set up
## - Ferrets -



Munster *et al*., Science 2009
Herfst *et al*., Science 2012
Russel *et al*., Science 2012
Fouchier *et al*, Science 2013
Linster et al., Cell 2014

***Fig. 2 Experiment 3, virus passaging in ferrets (P1 to P10, passages 1 to 10).***




***Sander Herfst et al. Science 2012;336:1534-1541***

**H5N2 and H5N8 virus detections in poultry and wild birds in 2014.The almost simultaneous detection of closely related viruses in Asia, Europe, and North America suggests linkage with wild bird migration via a large region in Russia.**



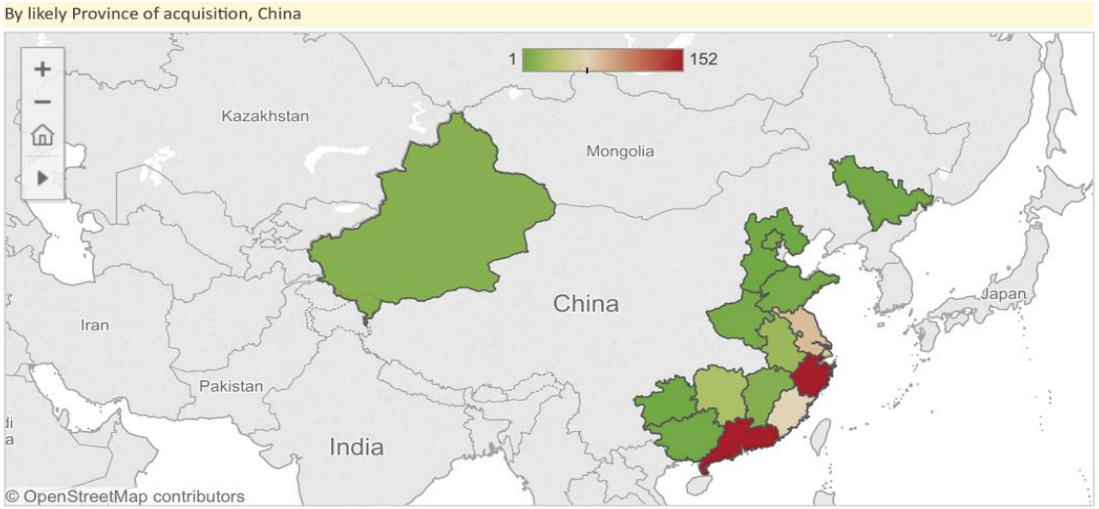

*Josanne H. Verhagen et al. Science 2015;347:616-617*

Science

AAAS

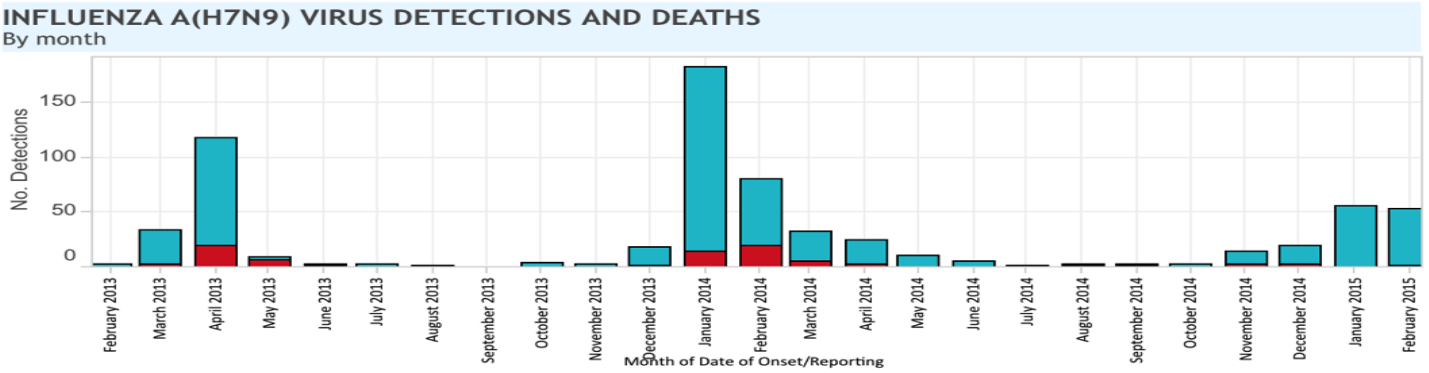
*Published by AAAS*

# Low pathogenic avian influenza A virus H7N9




*Laboratory confirmed:* *593*
*Deaths:* *105*
*Recoveries:* *488*

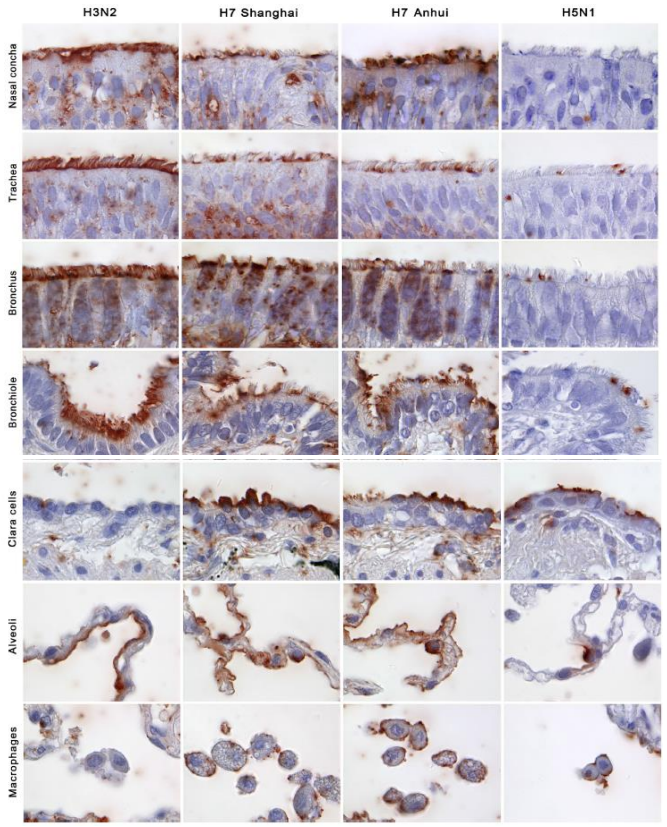
Influenza A(H7N9)A virus laboratory confirmed detections worldwide by time.
Data are from FluTrackers, the World Health Organization and Ministries of Health from the provinces and municipalities across China.




http://virologydownunder.blogspot.com.au/2014/11/influenza-ah7n9-virus-detection-numbers.html

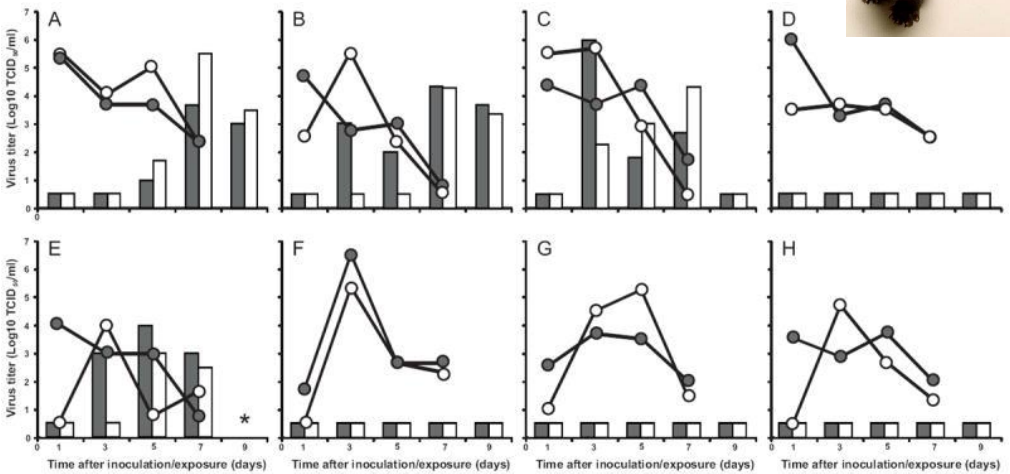
# Novel avian-origin influenza A (H7N9) virus attaches to epithelium in both upper and lower respiratory tract of humans.

***D van Riel et al. Am J Pathol. 2013 Oct;183(4):1137-43***




Richard M*. et al.*, ***Limited airborne transmission of H7N9 influenza A virus between ferrets.*** Nature. 2013.





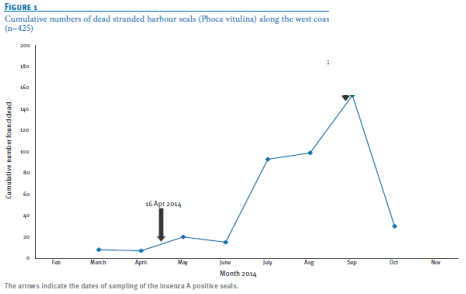

**Limited human-to-human transmission:**
**Small clusters!**

Chen Z, et al., Emerg Infect Dis. 2014

# Avian influenza A/H10N7 virus-associated mass deaths among seals




425 deaths March- October 2014




152 deaths June-August 2014 (Anholt)

About 1400 deaths September-November 2014

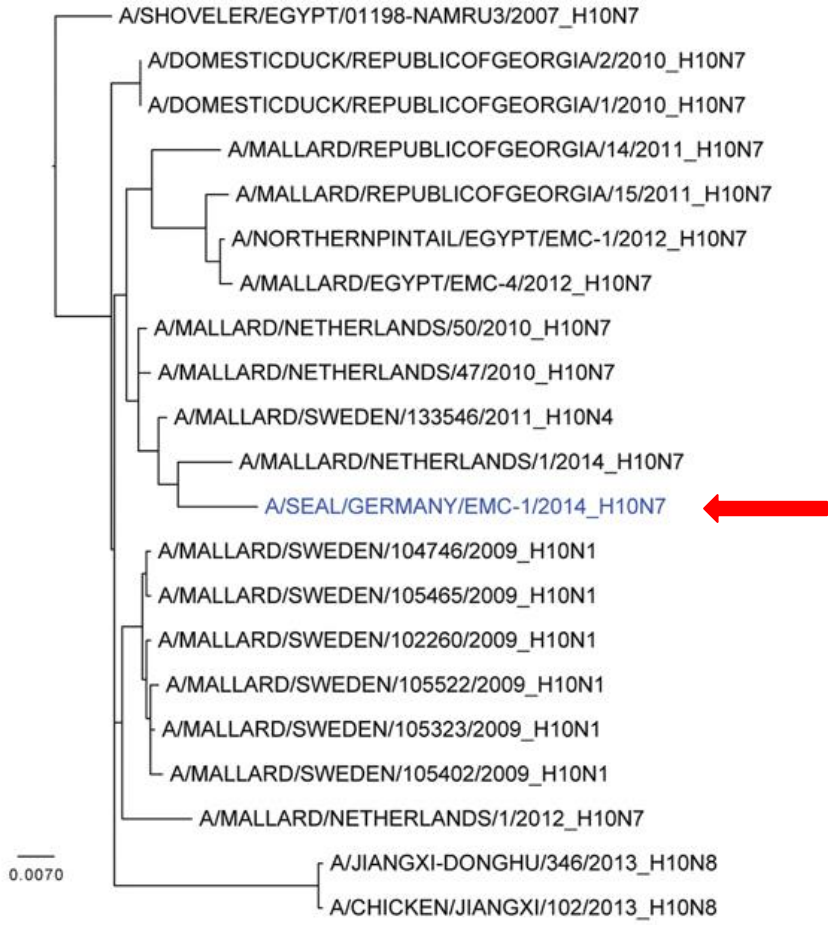
First cases in the Netherlands: November 2014,



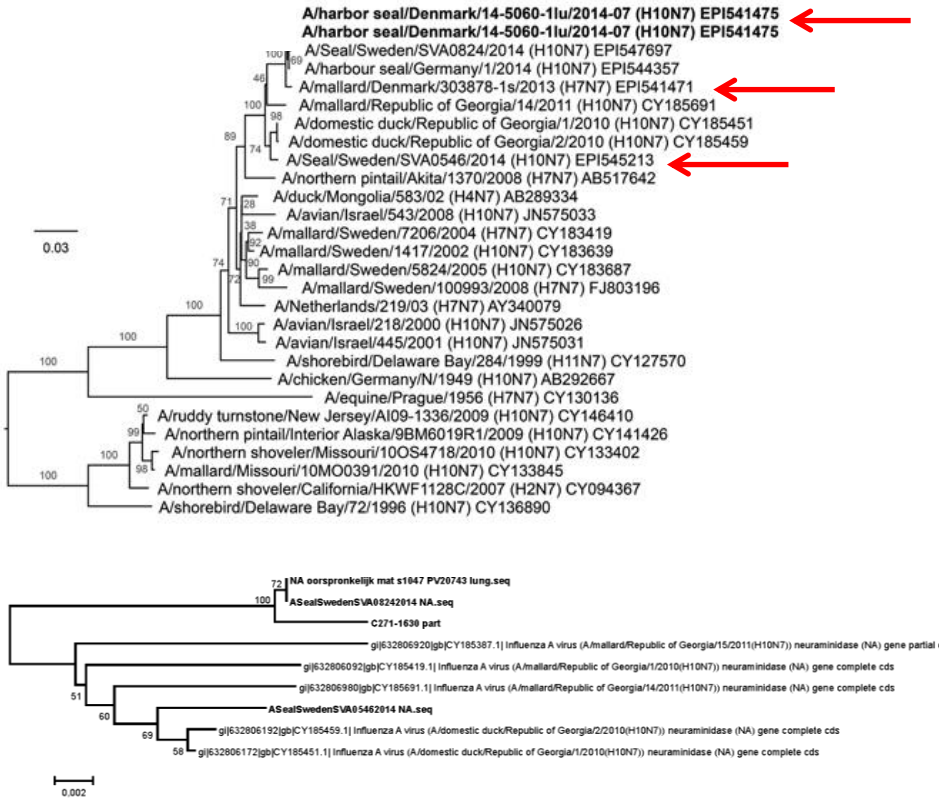
*Zohari et al Eurosurveillance 2014, Krog et al EID 2015, Bodewes et al EID 2015*

# Origin of the virus? HA & NA

HA




NA




*Zohari et al Eurosurveillance 2014, Krog et al EID 2015, Bodewes et al EID 2015*

# AVIAN FLU: PREVENTION AT THE SOURCE?



(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

A DEPARTMENT OF Erasmus MC

# Crucial preparedness elements to be developed in 'peace time'

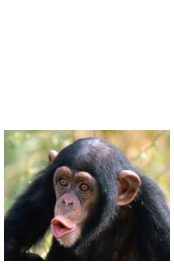
*Reperant et al., Science 2015*



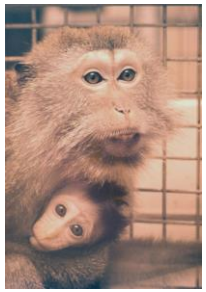


- **Syndrome surveillance** in humans & animals
- **Virus discovery** / identification platforms for humans & animals
- **Animal reservoirs and models** (BSL3/4)
- **Pathogenesis** platforms for new infections (transmission…!)
- **Koch's postulates**
- **Receptor identification**
- **Pathogenesis**
- **Intervention strategies** at the source?







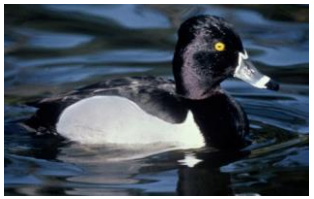




**International collaboration and coordination**

- using all available technology (classic and novel!!!)
- are of key importance for their control !!!

# Emerging virus research at Erasmus MC
## - The team leaders -



| | |
|---|---|
| Prof. R. Fouchier / Dr.S.Herfst | Mol.Virology |
| Prof. T. Kuiken | Pathology |
| Prof. M. Koopmans /Dr.C.Reusken | Epidemiology |
| Prof. C. Boucher / Dr,E. vd Vries | Antiviral research |
| Drs A. van der Eijk / P. Fraaij / Prof. E van Gorp | Clinical / Pediatric research |
| Prof. G. Rimmelzwaan | Viro-Immunology |
| Dr. B. Haagmans | Viro-pathogenesis |
| Drs. M. Schutten / S.Pas | Diagnostics |
| Dr. A. Andeweg | Genomics |
| Dr. J. Kreijtz | Vacinology |
| Dr.K.Stittelaar | Anim. models |







EU FP7: NOVAFLU; FLUBIRD; ERC; ARCAS; FLUPIG; EMPERIE; ANTIGONE;
NIAID: CEIRS. NWO: VIRGO; FES



# ACKNOWLEDGEMENTS:


**EU FP7-HEALTH**

NOVAFLU*
NEWFLUBIRD*

**EMPERIE***
**ANTIGONE***
**FLUNIVAC***
**PREPARE**
**COMPARE**
**ASKLEPIOS***
**imi ZAPI***
**ERC FLUPAN***

**NIH-NIAID**

**CEIRS***






* Erasmus MC coordinated

Ministerie LNV / ELI*