



Human Respiratory Viruses:

'new kids on the block'

Ab Osterhaus DVM PhD

Director Research Center for Emerging Infections and Zoonoses (RIZ)

University of Veterinary Medicine Hannover

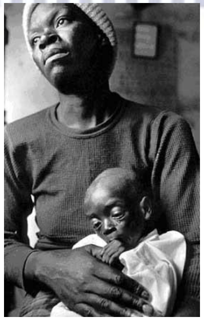
Chair One Health Platform

Chair ESWI

10th GVN network meeting

Fondation Merieux, les Pensieres

November 2018



HIV/AIDS

Ebola-Reston

Hanta HPS
Hendra

H5N1
Nipah

West Nile
SARS

Monkeypox
H1N1
H3N2v
MERS
H7N9
Ebola
ZIKA
Ebo

1980 ***1990*** ***2000*** ***2010***

Lyme
E. Coli O157:H7
BSE

vCJD

EHEC O104:H4

Past decades: zoonoses at the origin of major human disease outbreaks

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

Clinical and Developmental Immunology
Volume 2013, Article ID 210490, 8 pages
http://dx.doi.org/10.1155/2013/210490

Clinical Study

Epidemiology of Human Respiratory Viruses in Children with Acute Respiratory Tract Infections in Jinan, China

Yanqin Lu,[1,2] Shifu Wang,[3] Lehai Zhang,[3] Chao Xu,[1,2] Cuirong Bian,[4] Zhaoxia Wang,[5] Yanhui Ma,[6] Ke Wang,[1,2] Lixia Ma,[6] Chen Meng,[6] Caiyun Ni,[6] Jiabei Tong,[1,2] Gongchao Li,[1,2] and Jinxiang Han[1,2]

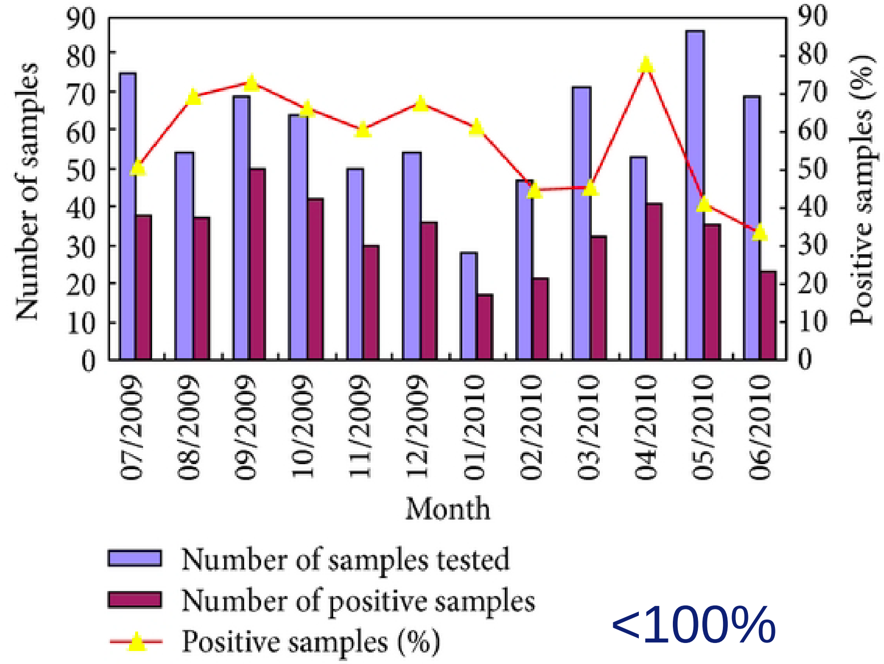


Figure 1: Number of recruited patients and the numbers of positive samples for viral infections.

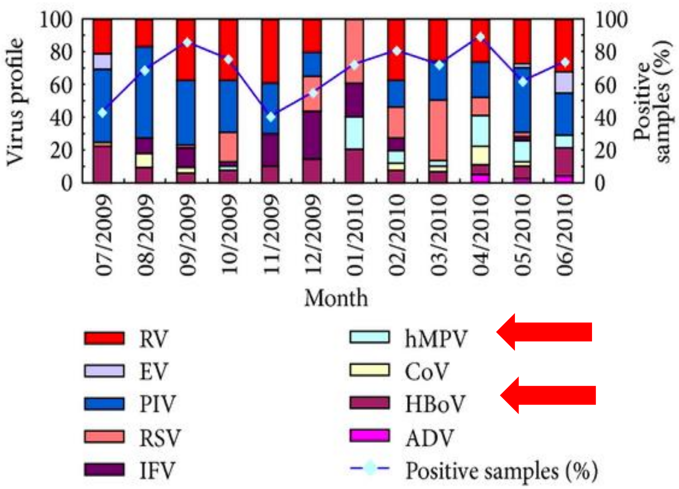


Figure 3: Number of positive results for various viruses in patients with acute lower respiratory tract infections.

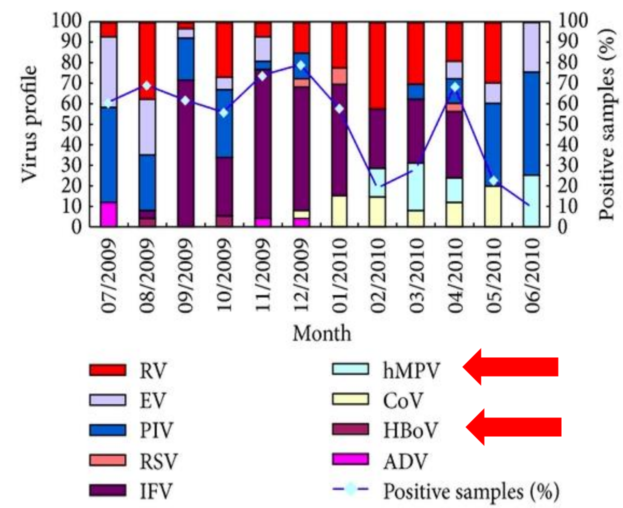
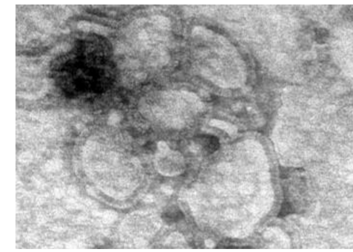


Figure 2: Number of positive results for various viruses in patients with acute upper respiratory tract infections.

Identification of viral pathogens based on surveillance activities: ErasmusMC / RIZ TiHo

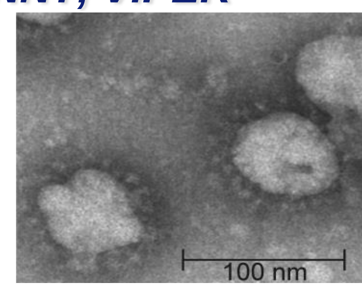
1995 CDV as the cause of mass mortality in Serengeti lions
1996 γ-herpesvirus in seals (phocid herpesvirus-2)
1997 monk seal morbilliviruses (MSMV-WA/G)
1997 influenza A (H5N1) virus in humans
1998 lentivirus from Talapoin monkeys (SIVtal)
1999 influenza B virus in seals
2000 human metapneumovirus (hMPV)
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 NL63)
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, MERS CoV, 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
2015 influenza A (H10N7) virus seals
2017… morbillivirus fin whale, hepadnavirus Tinamou, rec.canine circovirus, rec.canine bocavirus, herpesvirus sperm whale, Batai virus seal, avian metapneumovirus, novel pestivirus…

novel molecular techniques



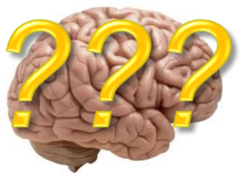
Funding:

EU: ***EMPERIE; ANTIGONE; PREPARE; COMPARE…***
NL: ***VIRGO-FES…***
DFG: ***N-RENNT; VIPER***



XXX human respiratory

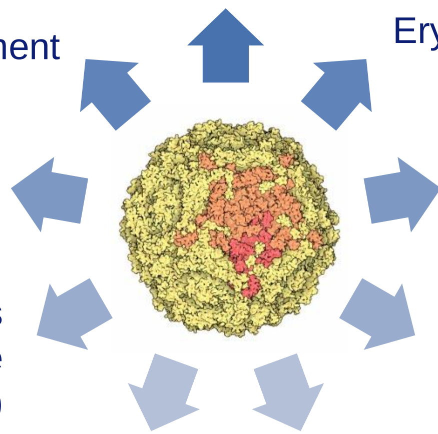
Parvoviruses: wide spectrum of disease in humans and animals alike



Asymptomatic

Brain involvement

Erythema infectiosum (Human B19)



Immune disorders
(Aleutian mink disease, Human B19)

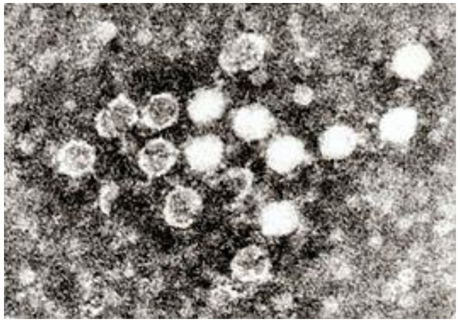
Anemia
(Human B19,
non-human primate erythroviruses)

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)

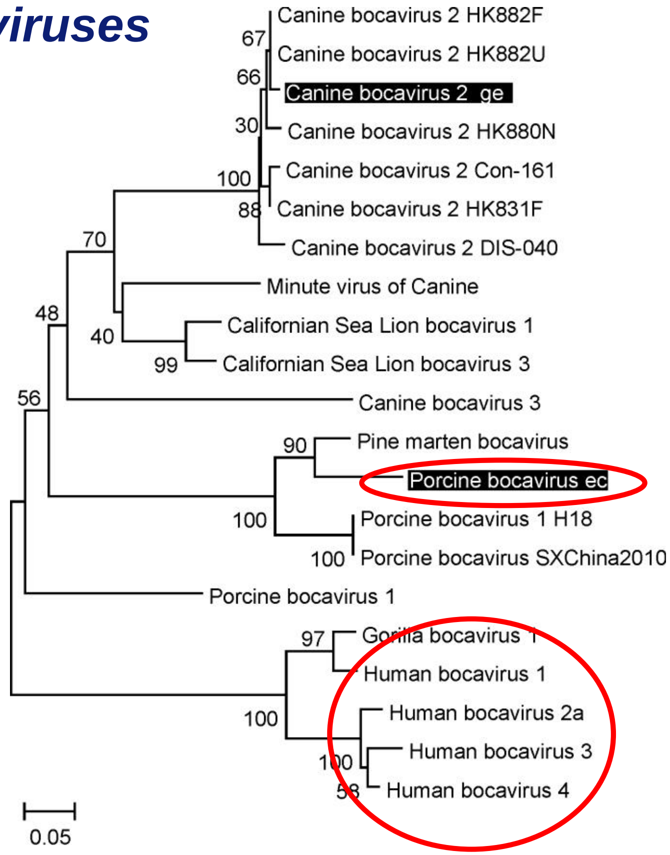


Virus discovery in pigs, dogs and seals with ENCEPHALITIS (comparative virology)

Novel (recombinant) canine bocaviruses

Novel porcine bocavirus

novel seal parvovirus



Bodewes et al., PLoS One 2013 / 2014; Vet Microbiol.2014
Piewbang et al., Vet Pathol. 2018

Moesker F. *et al.*, Clin Microbiol Infect 2016

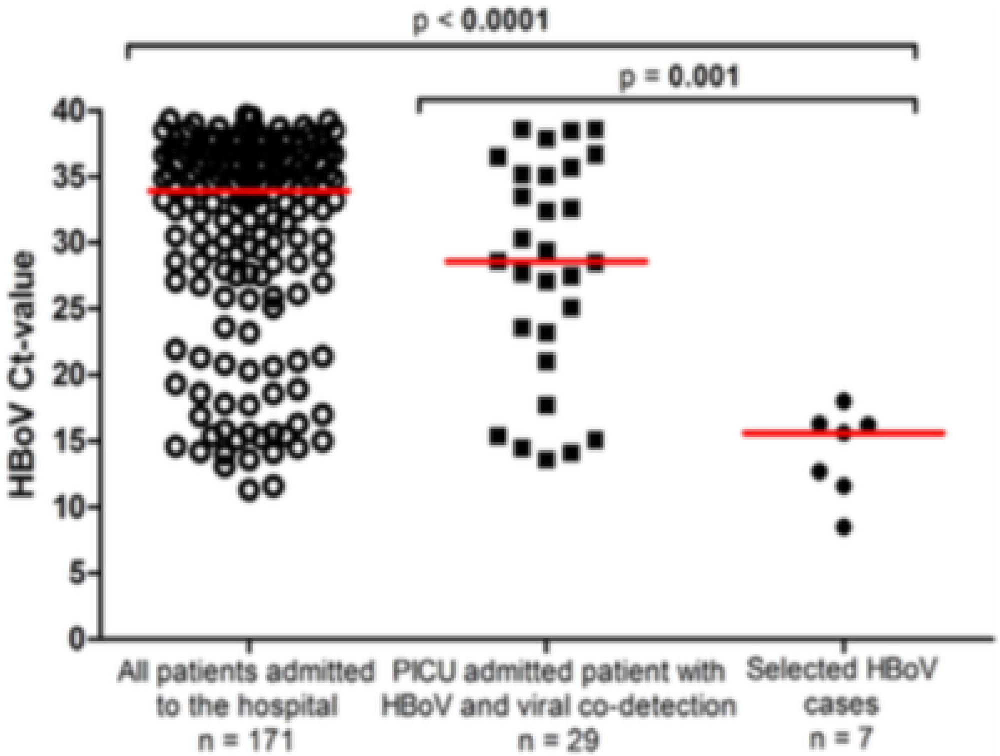


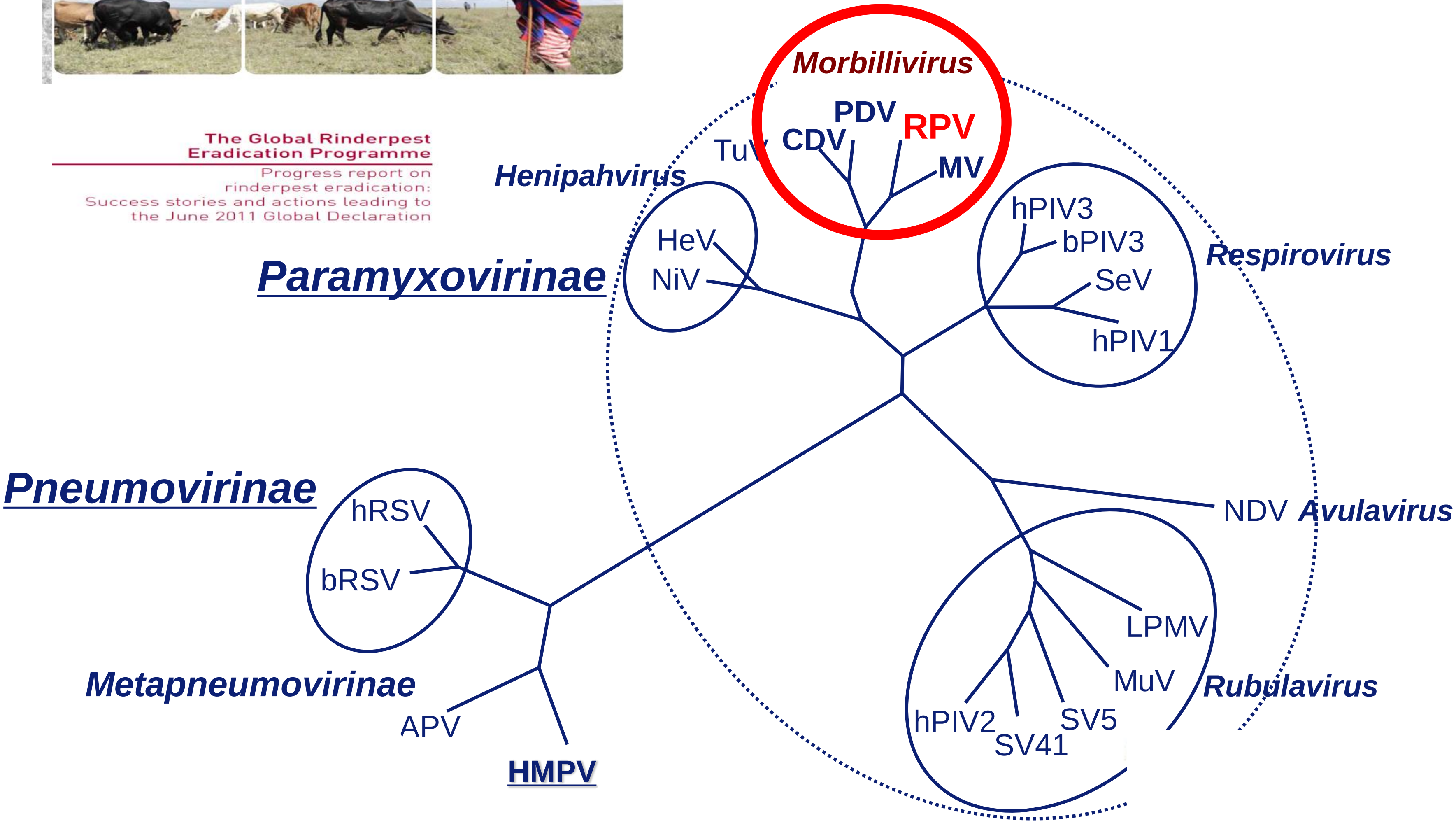
FIG. 2. Comparison between median Ct-values of human bocavirus (HBoV) RT-PCR-positive respiratory tract samples of paediatric patient admitted to the Erasmus MC-Sophia from 2007 to 2012; all hospital-admitted paediatric patients versus patients admitted to the paediatric intensive care unit (PICU) with HBoV and viral co-detection versus PICU-admitted patients with a single HBoV infection. Horizontal bars represent group medians.

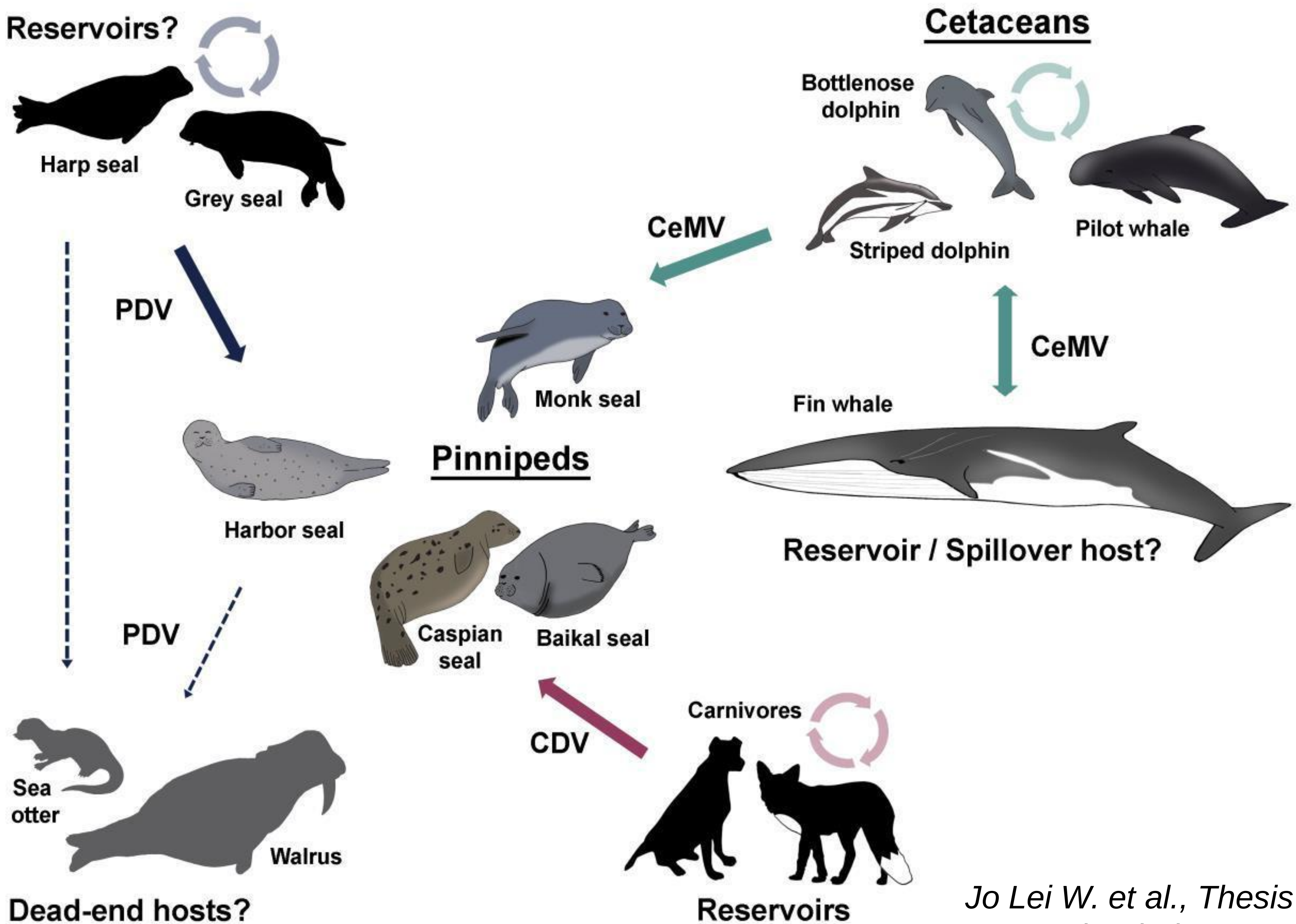
Rinderpest eradication: lessons for measles eradication?

de Swart RL, Duprex WP, Osterhaus AD. *Curr Opin Virol. 2012*

The Global Rinderpest Eradication Programme

Progress report on rinderpest eradication: Success stories and actions leading to the June 2011 Global Declaration



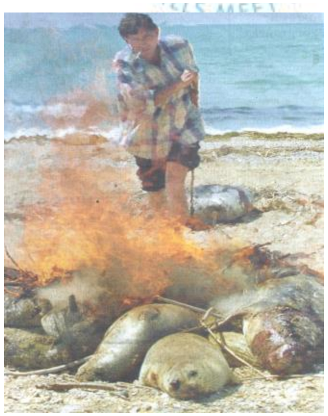


Jo Lei W. et al., Thesis & Curr.Opin.Virol. 2018

Morbilliviruses crossing species barriers a pandemic risk after measles eradication?

PDV: European Harbour seals
Nature 1988 / Science 2002

CDV: Baikal seals
Nature 1988



CDV: Caspian seals
EID 2000

DMV:
Fin Whale Denmark
JWD 2016

DMV:
Med. monk seals
Nature 1997

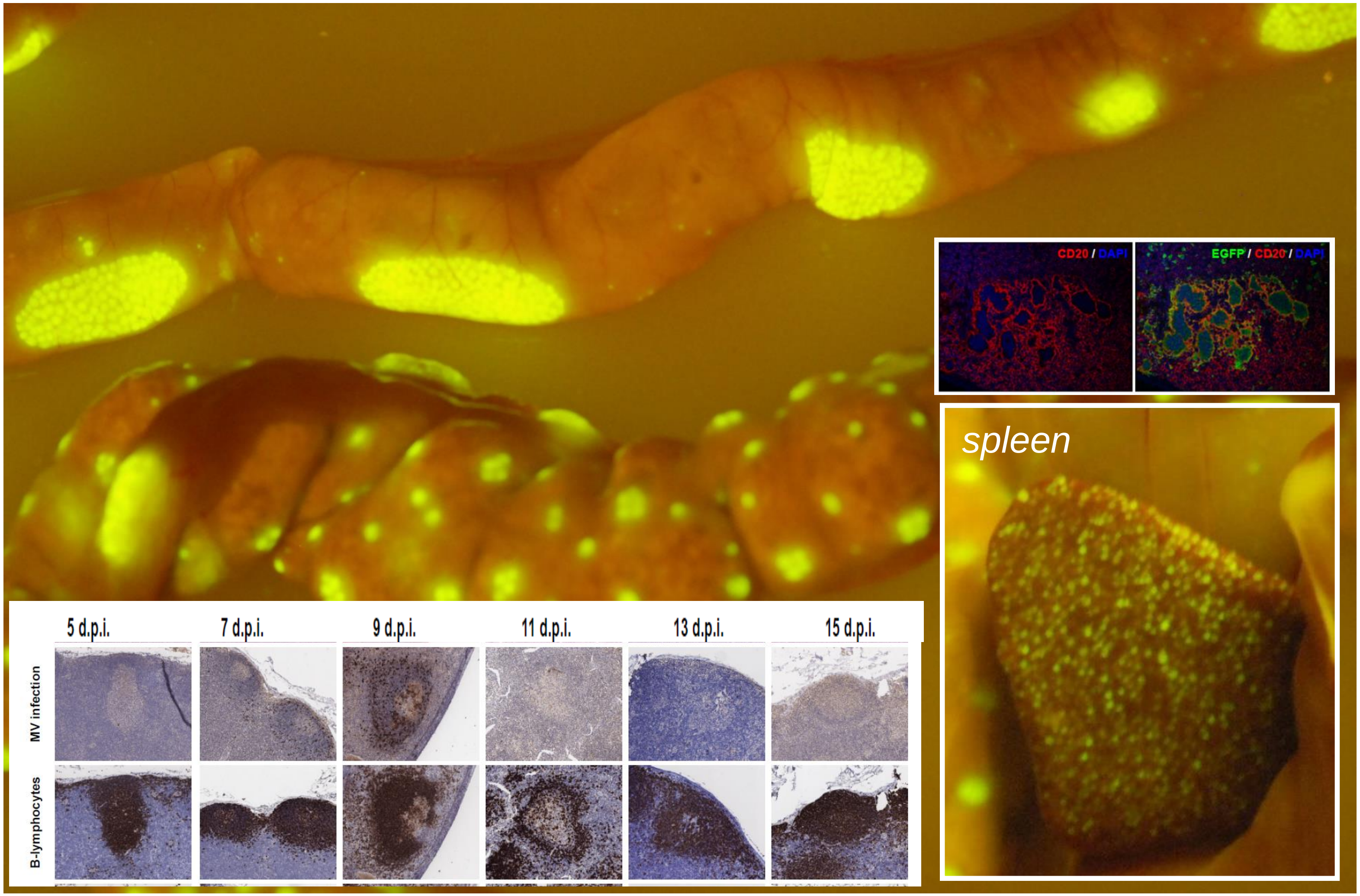
CDV: Serengeti lions
Vaccine 1994

CDV:
Rhesus macaques
China, EID 2011

Should we continue measles vaccination for ever?

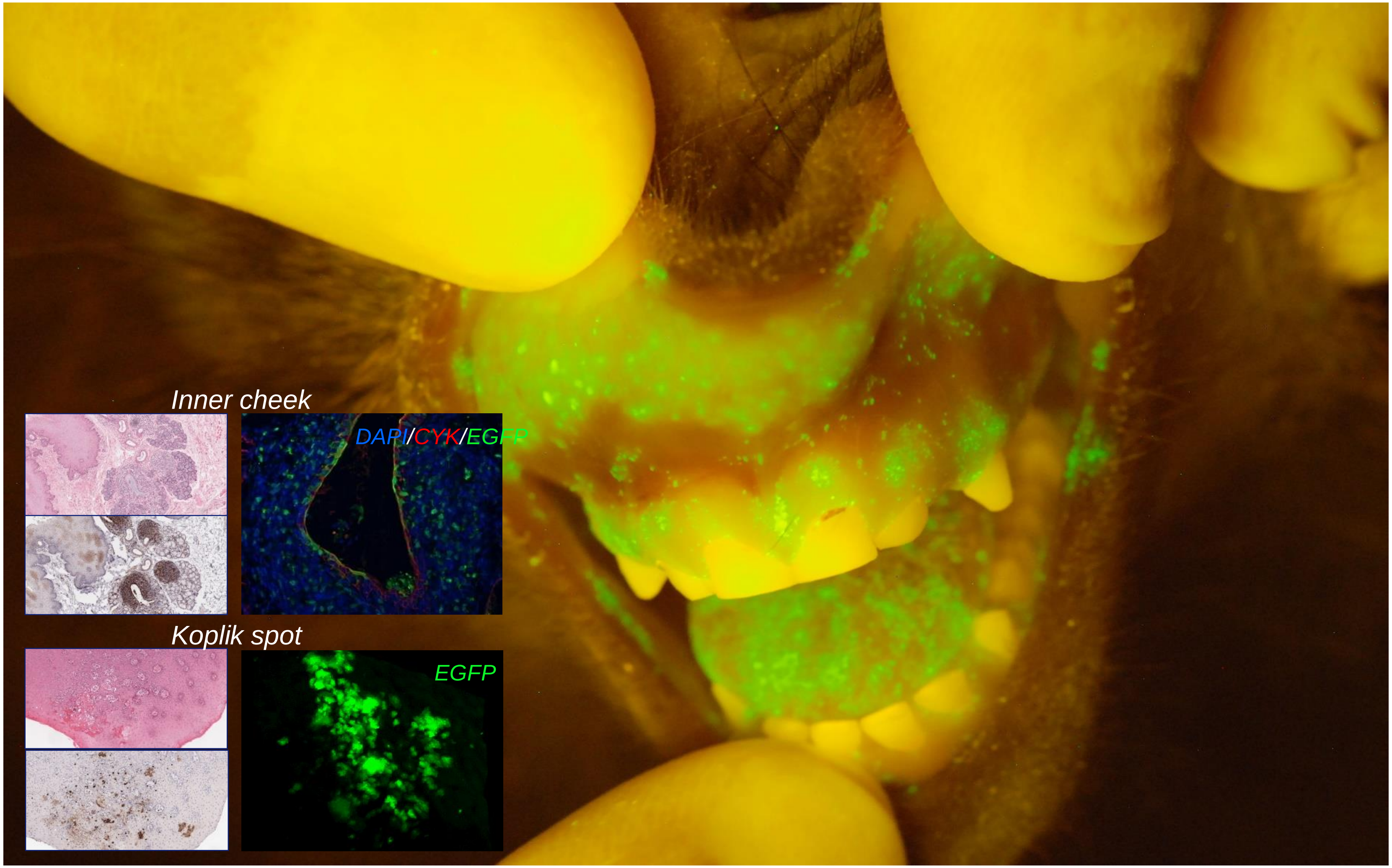
CD150 is the primary morbillivirus entry receptor

de Vries RD, et al., PLoS Pathog. 2012



PVRL4 is the morbillivirus receptor on epithelial cells

de Vries RD, et al., PLoS Pathog. 2012

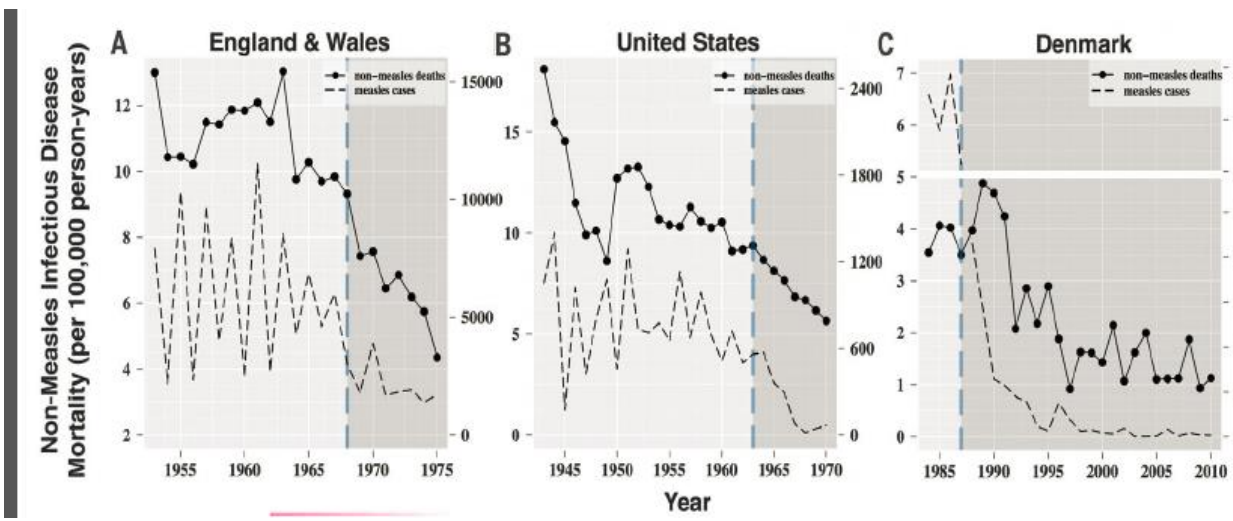


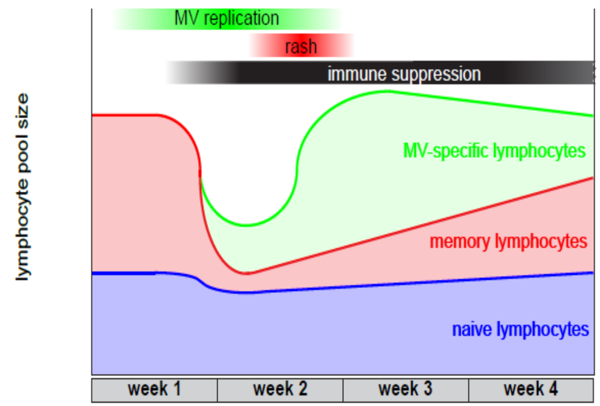
REPORT

VACCINES

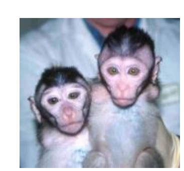
Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality

Michael J. Mina,[1,2*] C. Jessica E. Metcalf,[1,3] Rik L. de Swart,[4]
A. D. M. E. Osterhaus,[4] Bryan T. Grenfell[1,3]





Measles immune suppression; lessons from the macque model.
de Vries RD, et al., PLoS Pathog. 2012
CD45RA(-) memory T-lymphocytes and follicular B-lymphocytes killed



nature COMMUNICATIONS

Article | OPEN | Published: 23 November 2018

Studies into the mechanism of measles-associated immune suppression during a measles outbreak in the Netherlands

Brigitta M. Laksono, Rory D. de Vries, R. Joyce Verburgh, Eline G. Visser, Alwin de Jong, Pieter L. A. Fraaij, Wilhemina L. M. Ruijs, David F. Nieuwenhuijse, Henk-Jan van den Ham, Marion P. G. Koopmans, Menno C. van Zelm, Albert D. M. E. Osterhaus & Rik L. de Swart

Nature Communications **9**, Article number: 4944 (2018) | Download Citation

Fig. 5

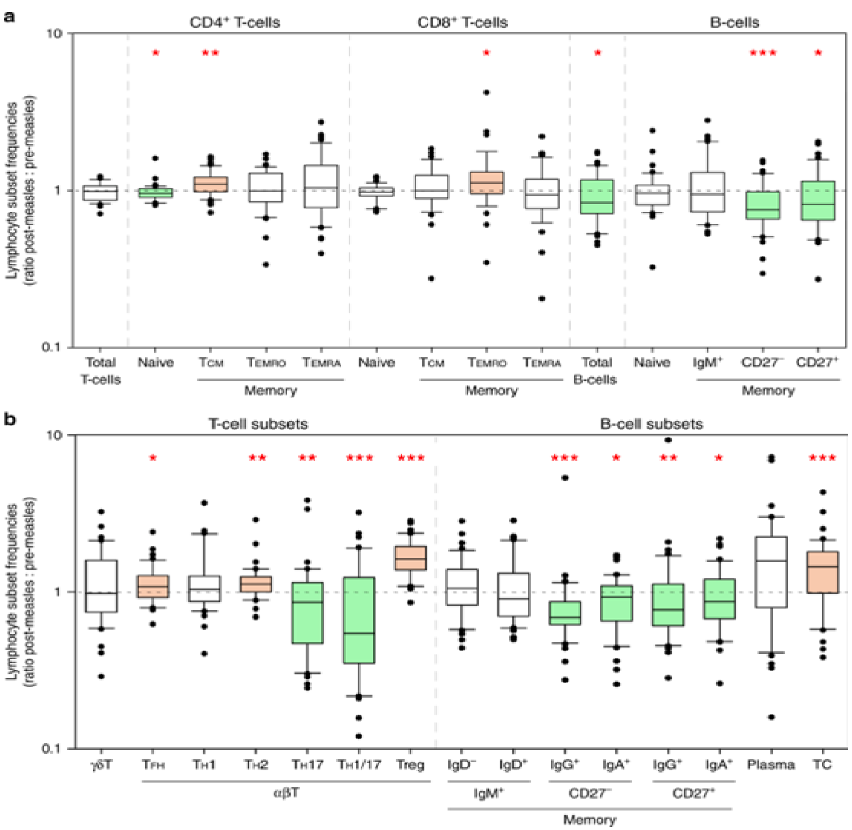


Fig.5

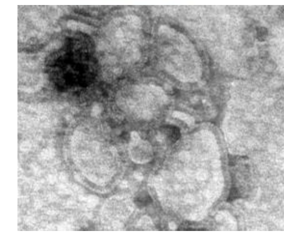
Significant changes in the frequencies of different lymphocyte subsets after measles. Frequency ratios of **a** **naive or memory lymphocyte subsets** or **b** **functionally distinct T and B cell subsets** ($n = 42$ paired samples). The ratio was calculated as the frequency of a subset after measles divided by the frequency of the same subset before measles. Horizontal dashed line indicates no changes ('ratio = 1') in frequency after measles. Ratio '>1' indicates increase and ratio '<1' indicates decrease in lymphocyte subset frequency after measles. Vertical dashed lines separate different lymphocyte subsets. TH1/17: TH1TH17 cells. $CD27^{+}IgM^{+}IgD^{-}$ B cells are also known as IgM-only memory B cells. $CD27^{+}IgM^{+}IgD^{+}$ B cells are also known as natural effector cells. TC: transitional B cells. Green box represents significant decrease. Orange box represents significant increase. Statistical differences in frequencies of lymphocyte subsets before and after measles were analysed by two-tailed paired *t*-test or Wilcoxon signed-rank test. Centre lines of the box plots represent medians. Lower and upper boundaries of the boxes represent first and third quartiles, respectively. Lower and upper whiskers represent the 10th and 90th percentiles of the data, respectively. Dots represent outliers. $*P < 0.05$; $**P < 0.01$; $***P \leq 0.001$

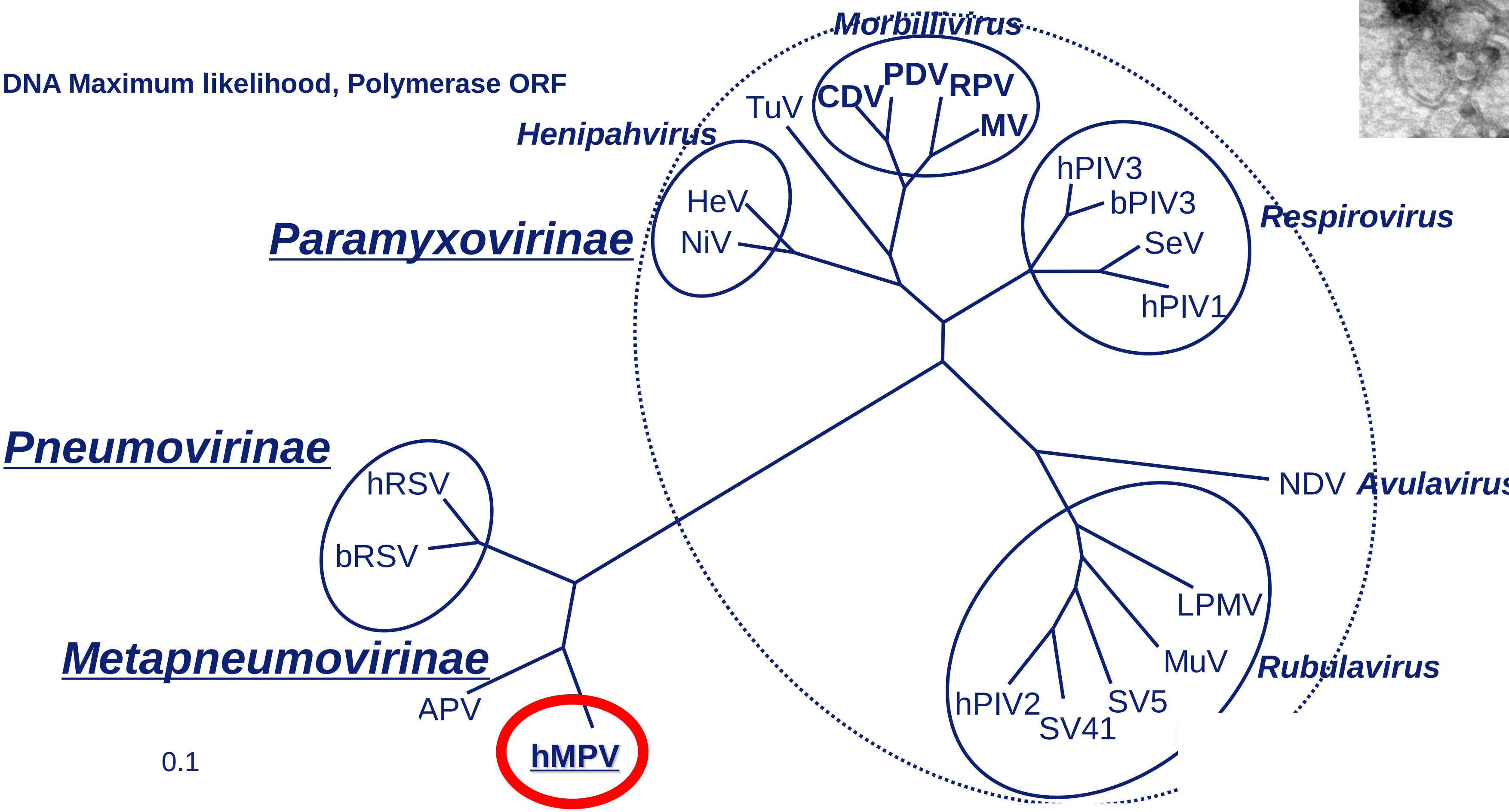
nature medicine

Article | Published: 01 June 2001

A newly discovered human pneumovirus isolated from young children with respiratory tract disease

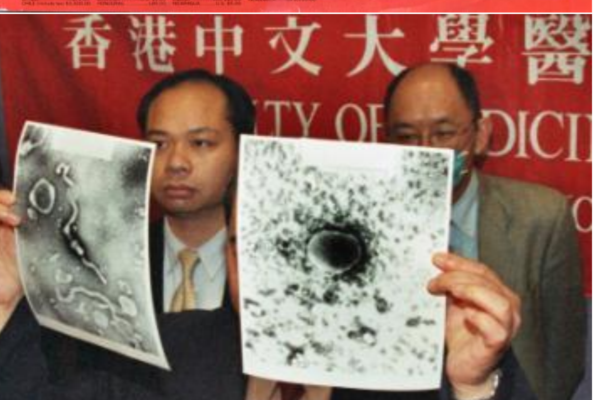
Bernadette G. van den Hoogen, Jan C. de Jong, Jan Groen, Thijs Kuiken, Ronald de Groot, Ron A.M. Fouchier & Albert D.M.E. Osterhaus



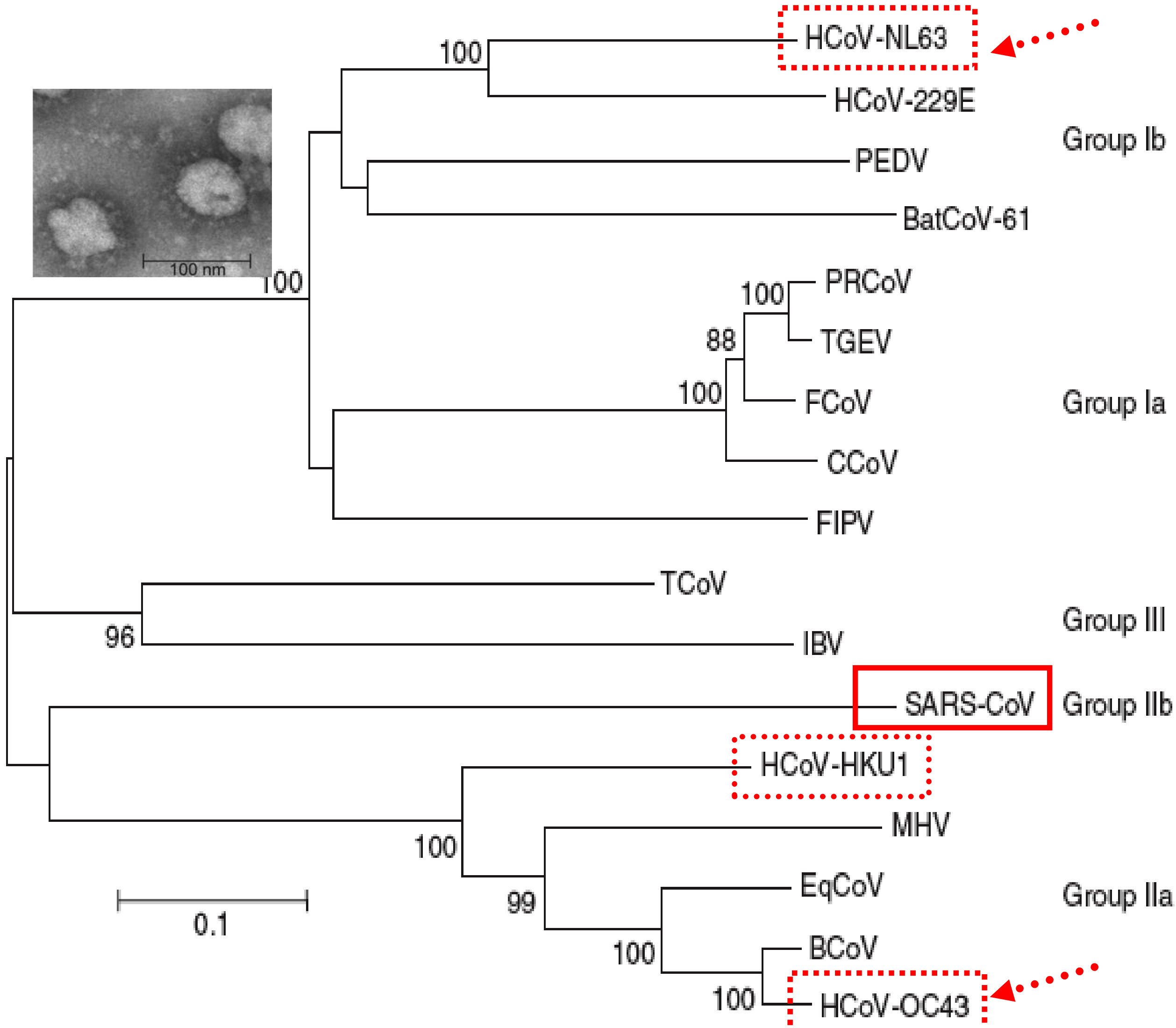


SARS-CoV
- Phylogeny -

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?



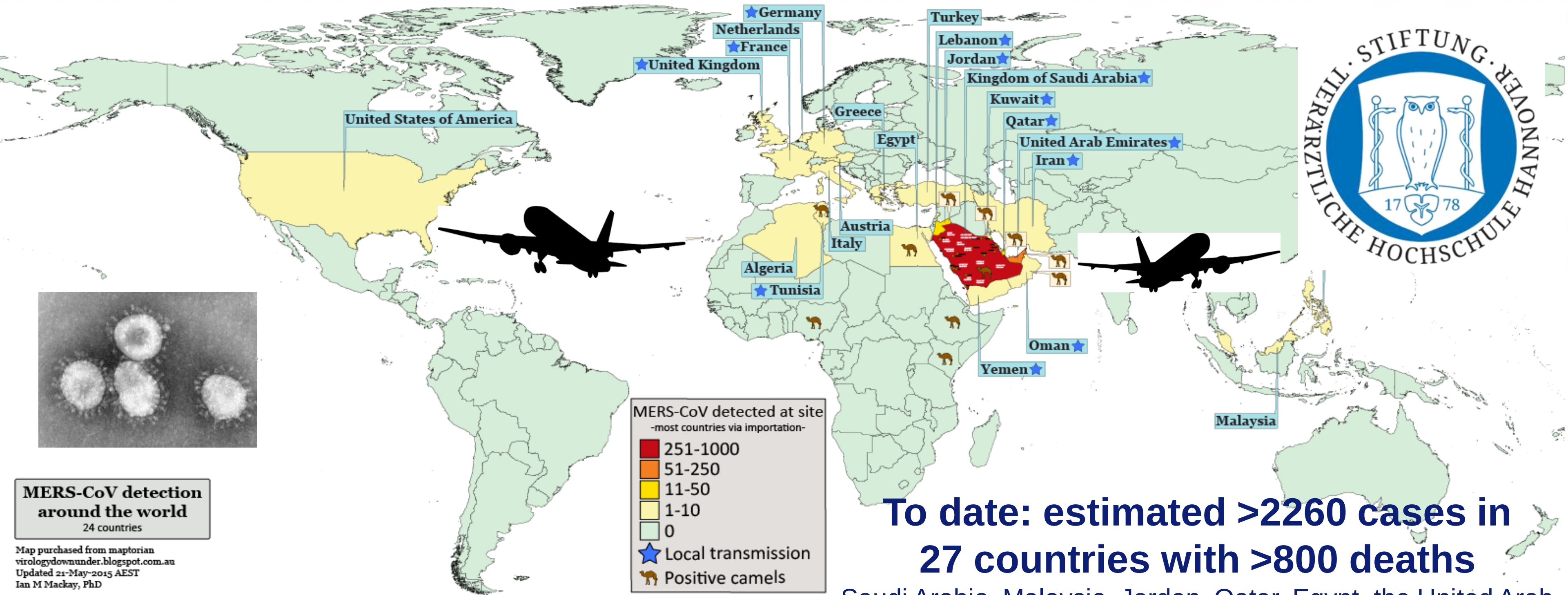
Fouchier et al.,Nature 2003
Kuiken et al., Lancet 2004

Press conference of
SARS etiology
network

Official declaration of SARS-CoV as the etiologic agent

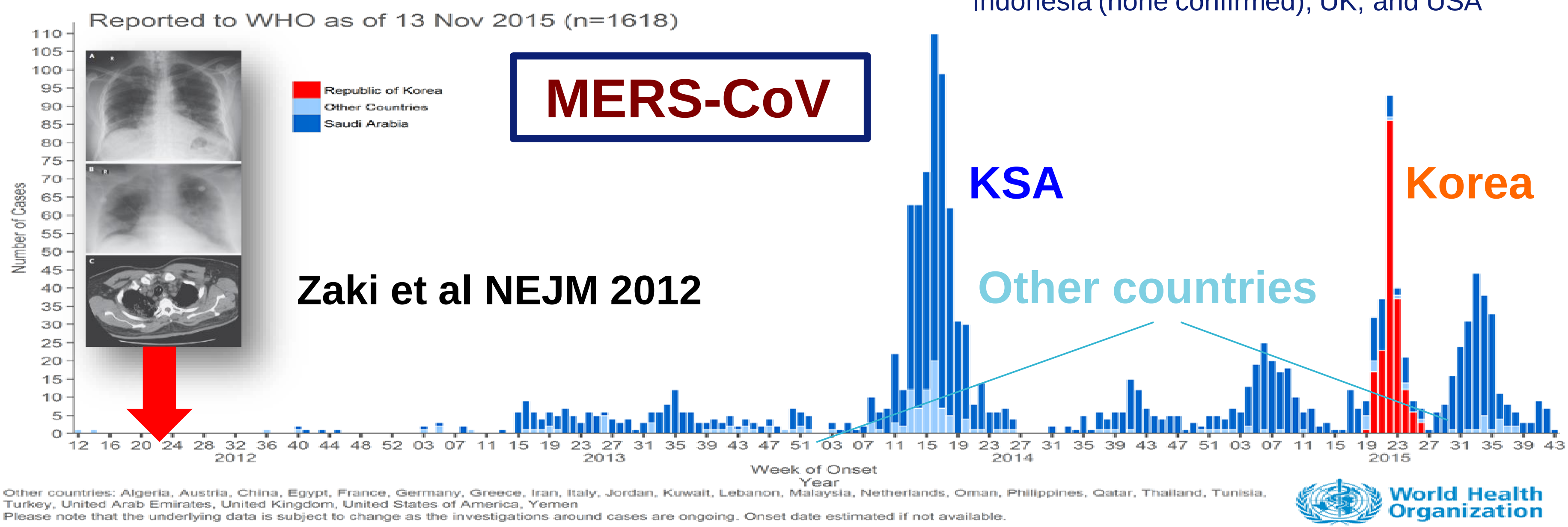
Short- and mid-term objectives:

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



To date: estimated >2260 cases in 27 countries with >800 deaths

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



MERS-CoV

Zaki et al NEJM 2012

Antibodies in dromedary camels

(Reusken et al Lancet ID 2013)

Dromedary camels: carriers of MERS-CoV

(Haagmans et al., Lancet ID 2013)

Identification of the CD 26 MERS-CoV receptor

(Raj et al., Nature 2013)

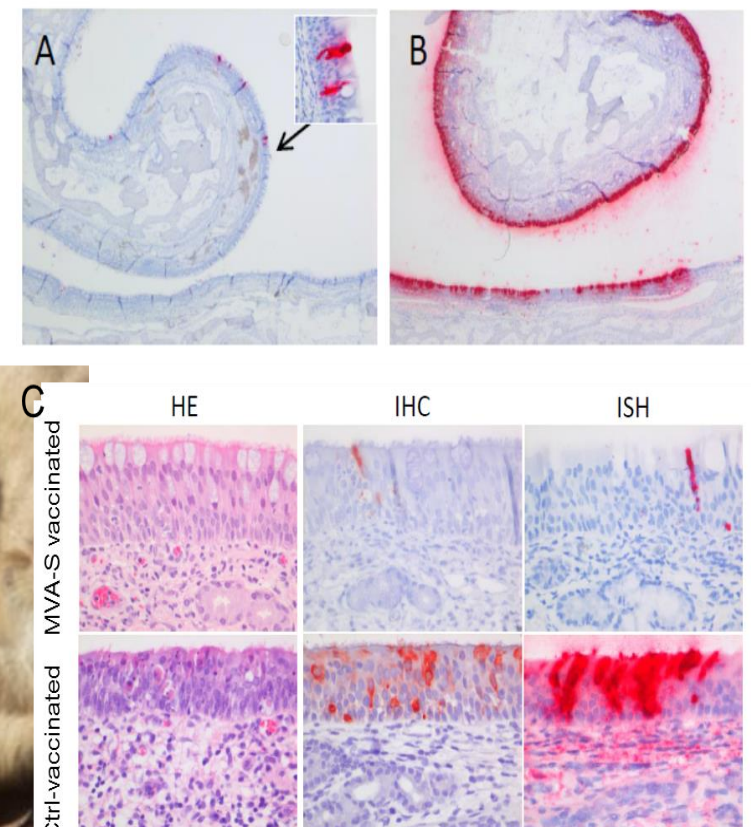
MVA expressing the MERS-CoV spike protein:

PREVENTION AT THE SOURCE?

A ONE HEALTH APPROACH

Science AAAS

Fei Song et al. JV 2013



Haagmans et al., Science 2016

MERS-CoV MVA vaccination: ‘one stone - two birds’ approach

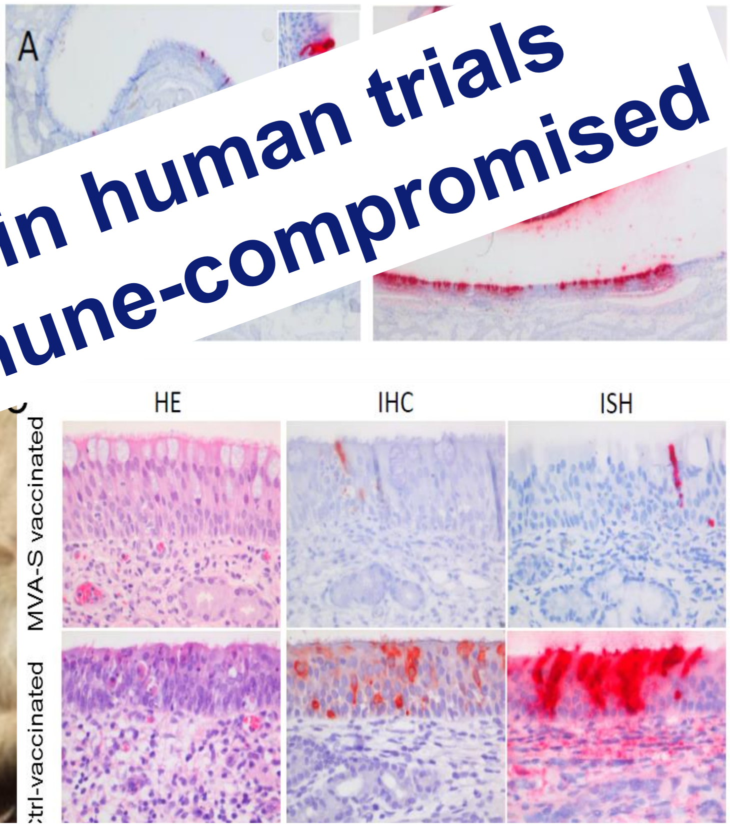
PREVENTION AT THE SOURCE?

Science AAAS

Fei Song et al. JV 2013

A ONE HEALTH APPROACH

MVA MERS-S vaccine now in human trials (HCW’s, camel handlers, immune-compromised



Haagmans et al., Science 2016

Science Advances | AAAS
SIGNIFICANT RESEARCH, GLOBAL IMPACT

Sci Adv. 2018 Aug; 4(8): eaas9667.
Published online 2018 Aug 8. doi: 10.1126/sciadv.aas9667

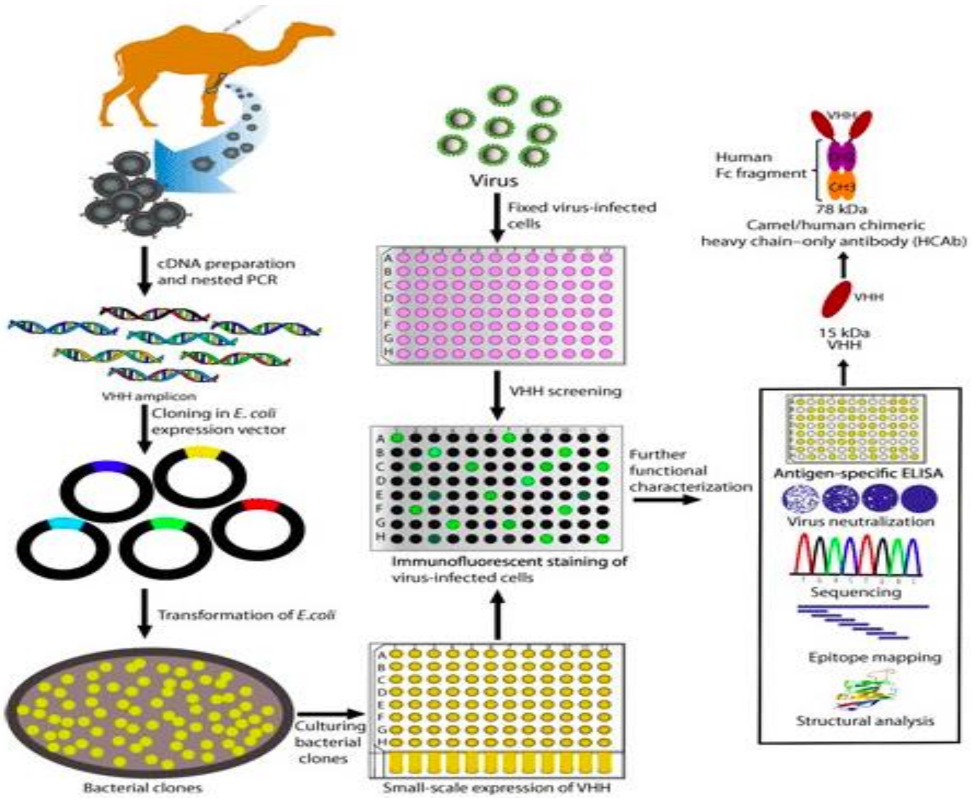
PMCID: PMC6082650
PMID: 30101189

Chimeric camel/human heavy-chain antibodies protect against MERS-CoV infection

V. Stalin Raj,[1,*†‡] Nisreen M. A. Okba,[1,*] Javier Gutierrez-Alvarez,[2] Dubravka Drabek,[3] Brenda van Dieren,[4] W. Widagdo,[1] Mart M. Lamers,[1] Ivy Widjaja,[4] Raul Fernandez-Delgado,[2] Isabel Sola,[2] Albert Bensaid,[5] Marion P. Koopmans,[1] Joaquim Segalés,[6,7] Albert D. M. E. Osterhaus,[8,9] Berend Jan Bosch,[4] Luis Enjuanes,[2] and Bart L. Haagmans[1,‡]

IMI-ZAPI

SEVENTH FRAMEWORK PROGRAMME



Schematic overview of VHH identification by direct cloning using bone marrow from immunized dromedary camels.

Last four pandemics

Credit: US National Museum of Health and Medicine

1918

"Spanish Flu"

>40 million deaths

A(H1N1)

1957

"Asian Flu"

1-4 million deaths

A(H2N2)

1968

"Hong Kong Flu"

1-4million deaths

A(H3N2)

2009

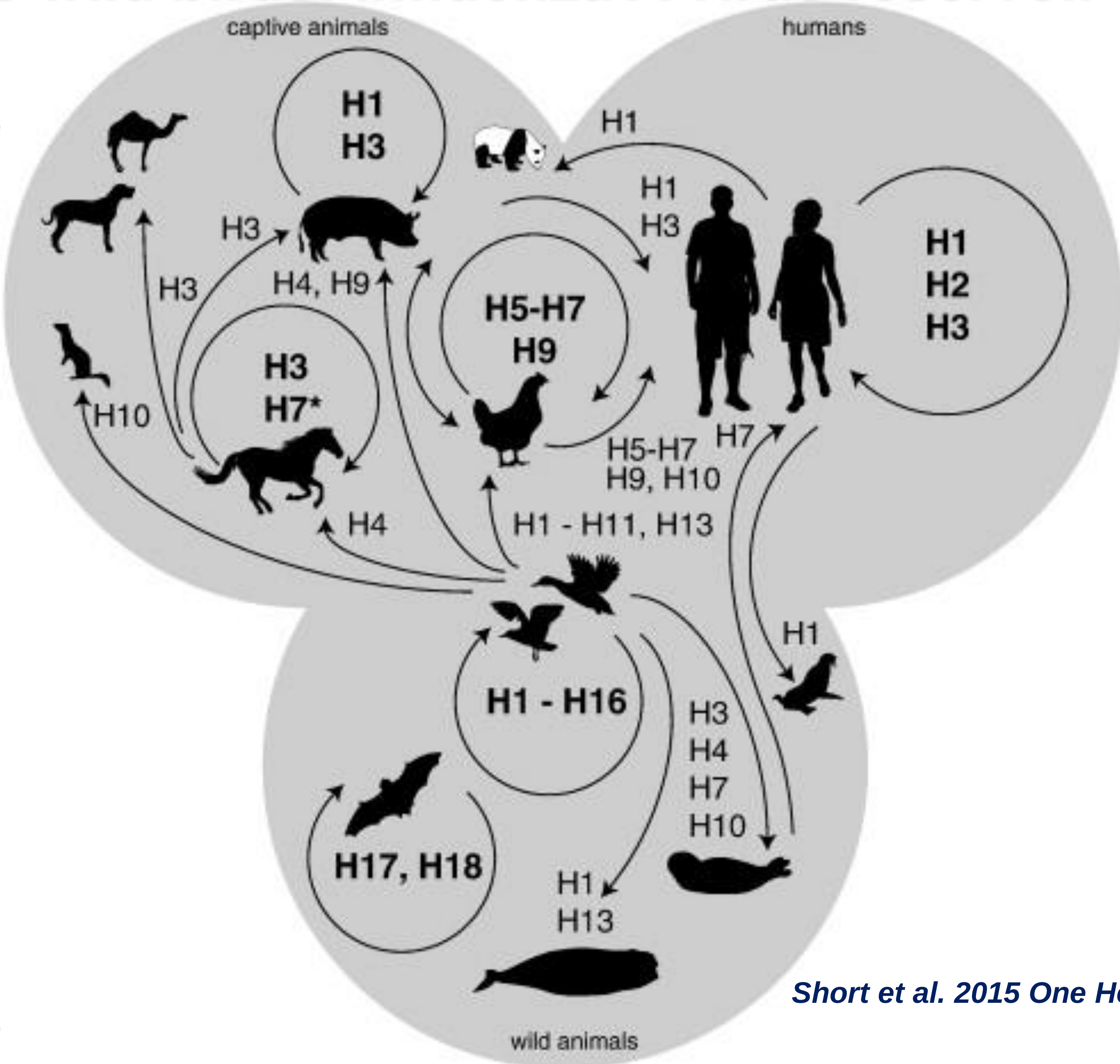
"Mexican flu"

0.2-0.3 million deaths

A(H1N1)

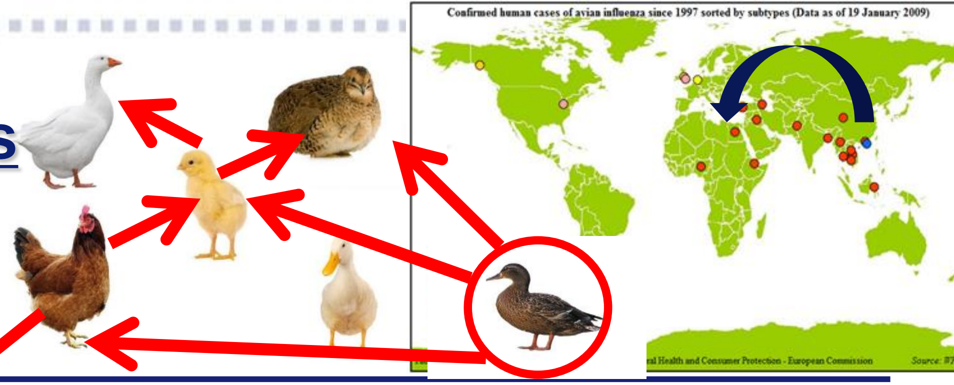
A

Aquatic wild birds: Influenza A virus reservoir



Short et al. 2015 One Health 2015

Recent zoonotic transmissions from birds -confirmed human cases-

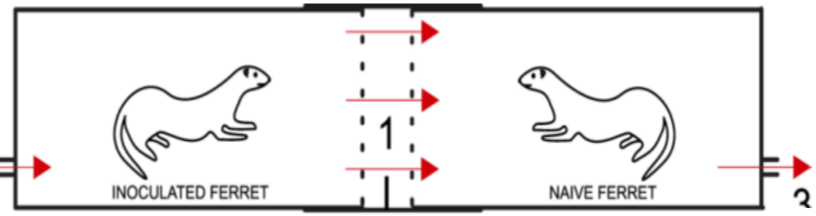


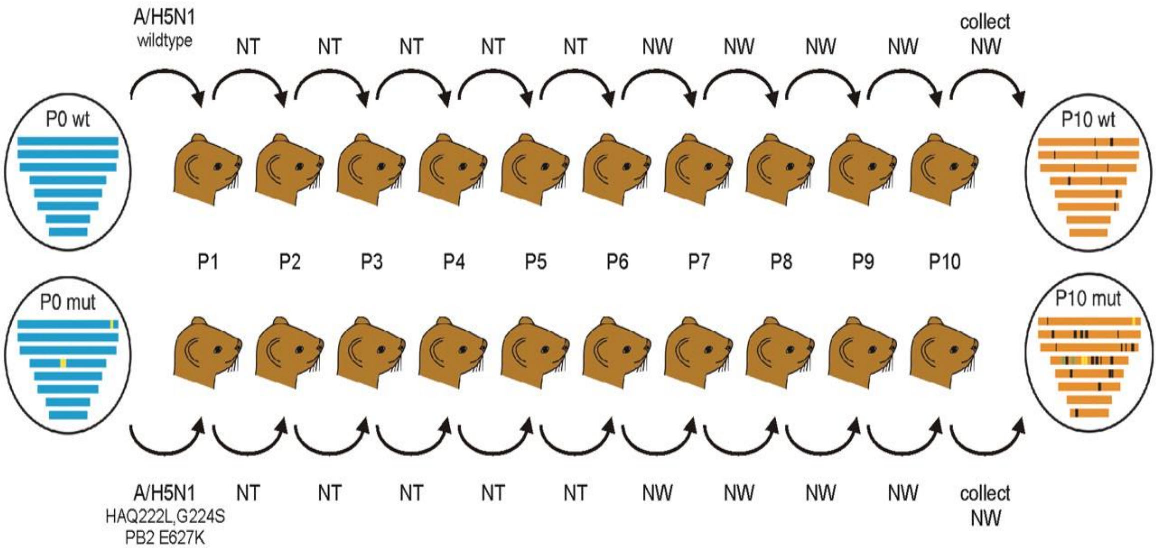
Subtype	Country	Year	# Cases	# Deaths
H7N7	UK	1996	1	0
H5N1	Hong Kong	1997	18	6
H9N2	SE-Asia	1999	>2	0
H5N1	Hong Kong	2003	2?	1
H7N7	Netherlands	2003	89	1
H7N2	USA	2003	1	0
H7N3	Canada	2004	2	0
H5N1	SE-Asia/M-East/ Europe/W-Africa	2003-18*	>840	>450 (increasing)
H7N9	PR China	2013-18	>1500	>600
H9, H10, H6..	Asia…	ongoing	<10	<10

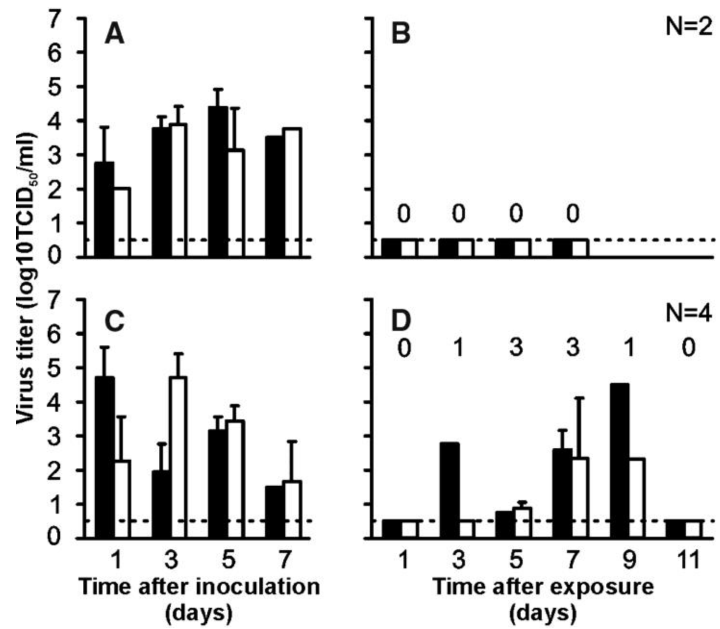
*CFR ~ 55%

Avian Influenza: Asia
‘live bird markets’

Virus passaging in ferrets (P1 to P10, passages 1 to 10).





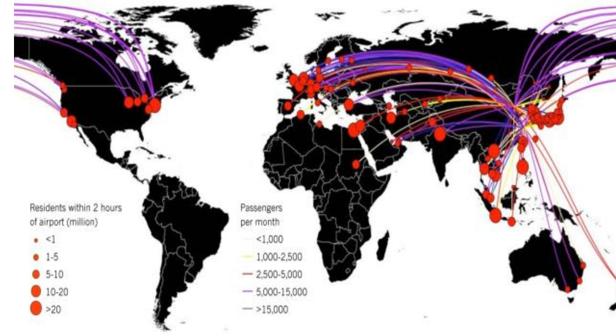


Sander Herfst et al. Science 2012

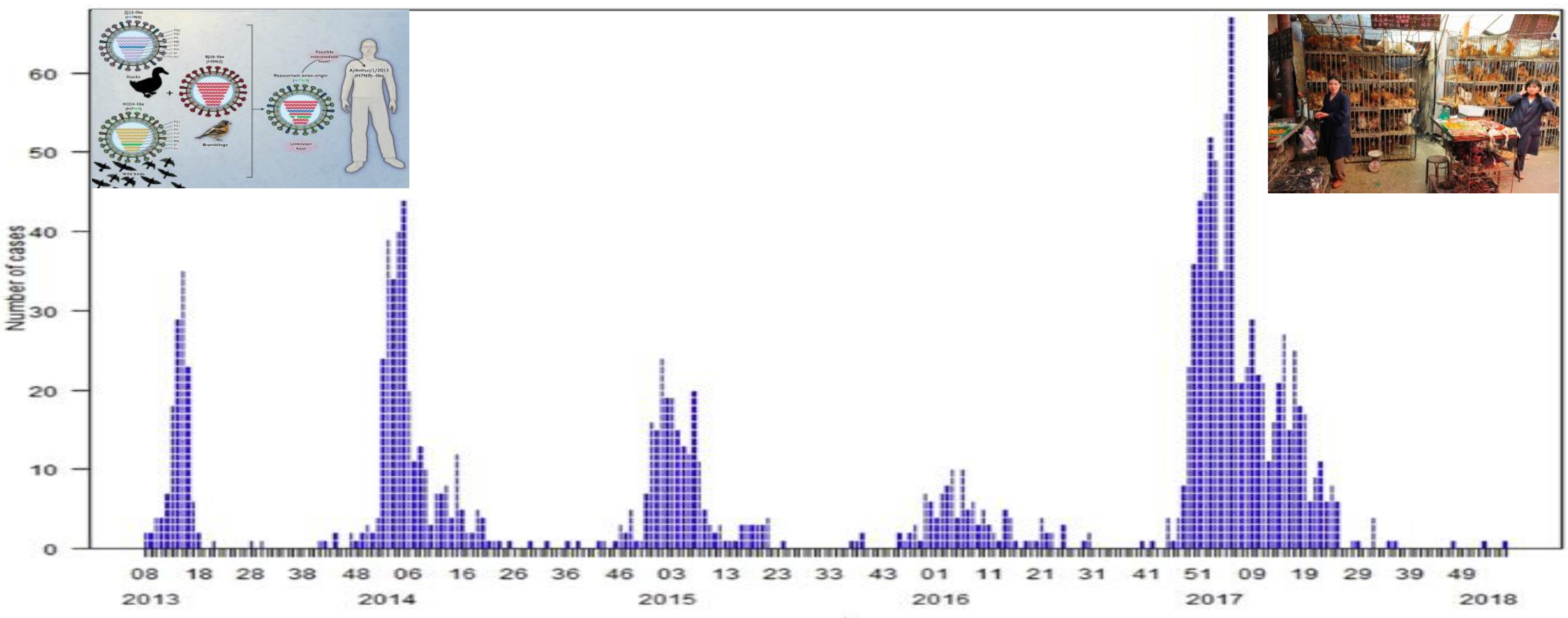
Munster et al., Science 2009
Russel et al., Science 2012
Linster et al., Cell 2014

High and low pathogenic avian influenza A viruses H7N9

Laboratory confirmed: 1584
Deaths: 612
Recoveries: 972



Number of Confirmed Human H7N9 Cases by week as of 2018-8-31



Source: FAO

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

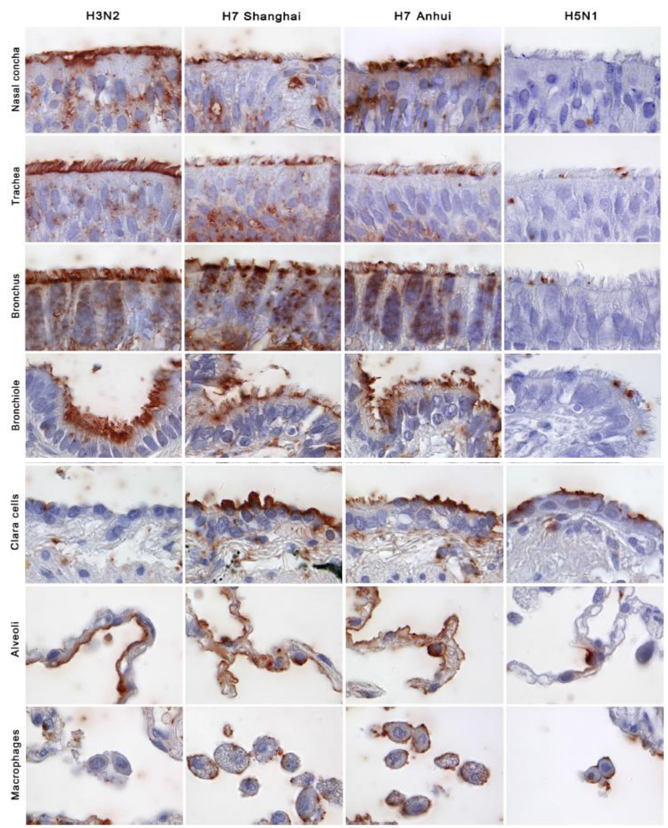
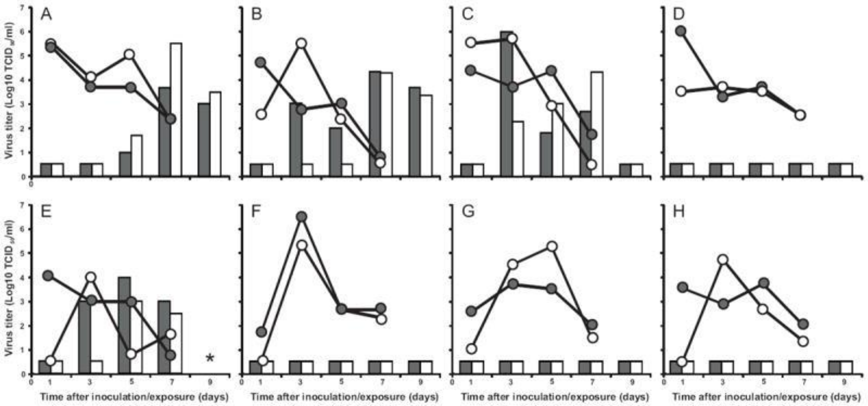


Figure 1 Attachment of two reassortant viruses containing hemagglutinin of either influenza virus A/Shanghai/1/13 (H7 Shanghai) or A/Anhui/1/13 (H7 Anhui) to different parts of the upper and lower human respiratory tract. The attachment of a human seasonal influenza virus (H3N2) and a highly pathogenic avian influenza virus (H5N1) is shown for comparison.

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

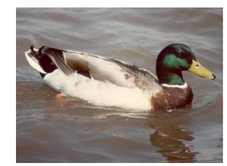


Limited human-to-human transmission: Small clusters!

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

Crucial preparedness elements for emerging viruses to be developed in 'peace time':


- **Disease surveillance** in humans & animals
- **Virus surveillance / genetic characterization** for humans & animals
- **Diagnostics** development and distribution <u>platforms</u>
- **Mathematical modeling** capacity
- **Animal model** capacity (BSL3/4)
- **Pathogenesis and transmission** <u>platforms</u>
- **Preventive intervention** <u>platforms</u> (societal, vaccination, antiviral)
- **Therapeutics discovery** <u>platforms</u> (antivirals, antibodies, BRM's...)
- **Healthcare** preparedness
- **Communication and distribution** strategies


Of key importance for their control:

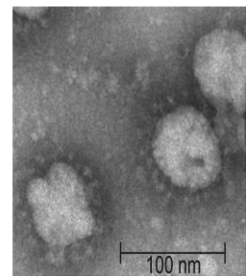
❖ International collaboration and coordination

❖ Using all available technology and information

Acknowledgements

Respiratory Viruses Erasmus MC and TiHo

R. Fouchier/M.Ludlow	Mol.Virology
W.Baumgärtner	Pathology
M. Koopmans	Epidemiology
C. Boucher/E.vd Vries	Antiviral research
A vd Eijk/ P.Fraaij/E van Gorp	Clinical / Pediatrics
G. Rimmelzwaan/G.Verjans	Viro-Immunology
B. Haagmans	Virology
M.Ludlow/R.Bodewes/W.Jo/E.vd Vries	Virus discovery studies



SARS collaborations

Drosten C.	Bonn University Germany
Lim W	QM Hospital Hongkong
Peiris M	University of Hongkong
Guan Y	University of Hongkong
Tam JS	Hongkong Polytech. University
Rottier PJ	Utrecht University Netherlands
Rota PA	CDC Atlanta
Stöhr K	WHO Geneva
Tashiro M	NIC Tokyo
v.d. Werf S	Pasteur Paris
Zambon MC	PHE London

MERS and Flu collaborations

Drosten C.	Bonn University Germany
Farag E	Supreme Health Council Qatar
Bosch BJ	Utrecht University Netherlands
Sutter G	Max. Univ. Münich Germany
Segalis Q	CRESA Barcelona Spain
Zambon MC	PHE London
Neubert A	IDT

Forthcoming conferences dealing with outbreak preparedness