




Disease Emergence
at the Animal-Human Interface

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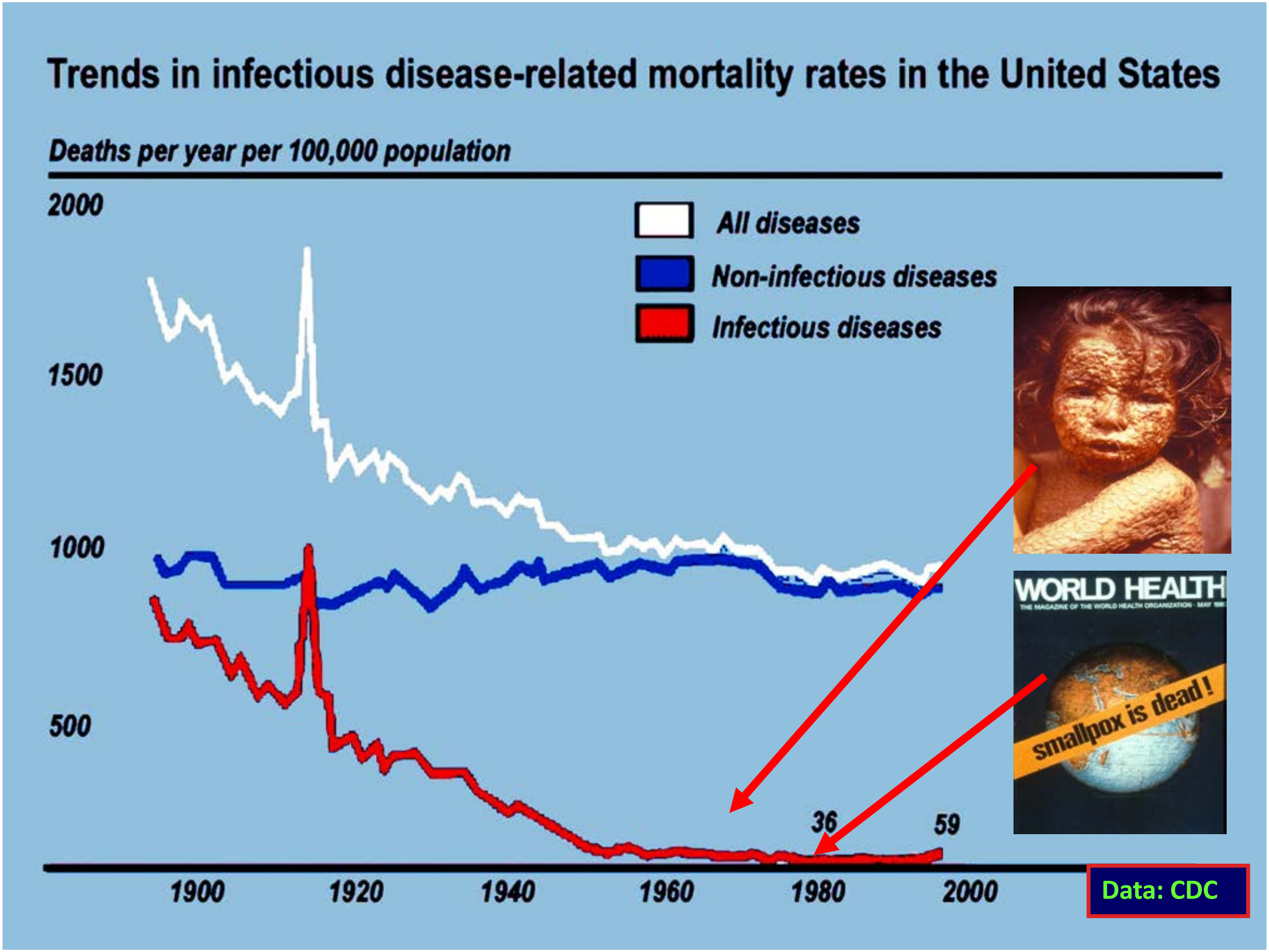
Chair One Health Platform

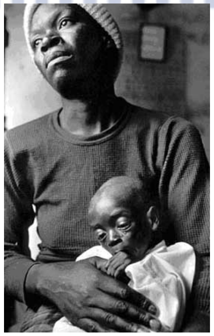
IMED 2018

• Vienna, Austria •

November 9-12, 2018


A
Plague of Athens: 17th century
Human factors at the basis
Black Death
14th century
C
Cholera 19th century
D
Morens et al.,
Lancet ID 2008
Zoonosis at the basis
Maori monument for the 1918 flu


Trends in infectious disease-related mortality rates in the United States
Deaths per year per 100,000 population
2000
1500
1000
500
All diseases
Non-infectious diseases
Infectious diseases
36
59
1900
1920
1940
1960
1980
2000
WORLD HEALTH
smallpox is dead!
Data: CDC



HIV/AIDS
Ebola-Reston
Hanta HPS
Hendra
H5N1
Nipah
West Nile
SARS
Monkeypox
H1N1
H3N2v
MERS
H7N9
Ebola
ZIKA
Ebol...

1980 — 1990 — 2000 — 2010

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

Lyme
E. Coli O157:H7
BSE
vCJD
EHEC O104:H4

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

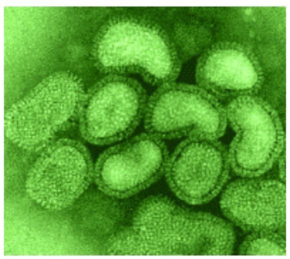
The importance of understanding the human-animal interface: from early hominins to global citizens

(Re-)emerging infectious diseases facilitated by

The Microbial Agent

Genetic adaptation and change

Polymicrobial diseases



The Human Host

Human susceptibility to infection

Human demographics and behavior

International trade and travel

Intent to harm (bioterrorism`

Occu… …posures

…priate use of …biotics

The Human Environment

Climate and wea…

Changi… …ems

… …development …nd use

Technology and industry

Poverty and social inequality

Lack of public / animal health services

Animal populations

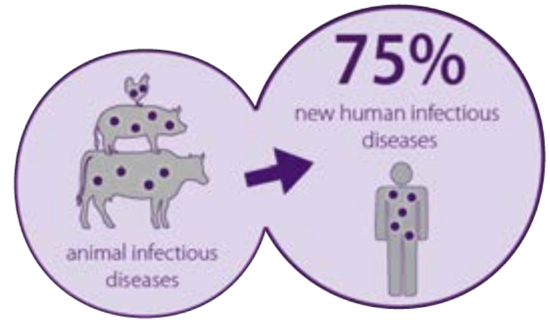
War and famine

Lack of political will

One Health approach to combat at the source

Morens DM et al., PLoS Pathog. 2013 July; 9(7)

The One Health Concept

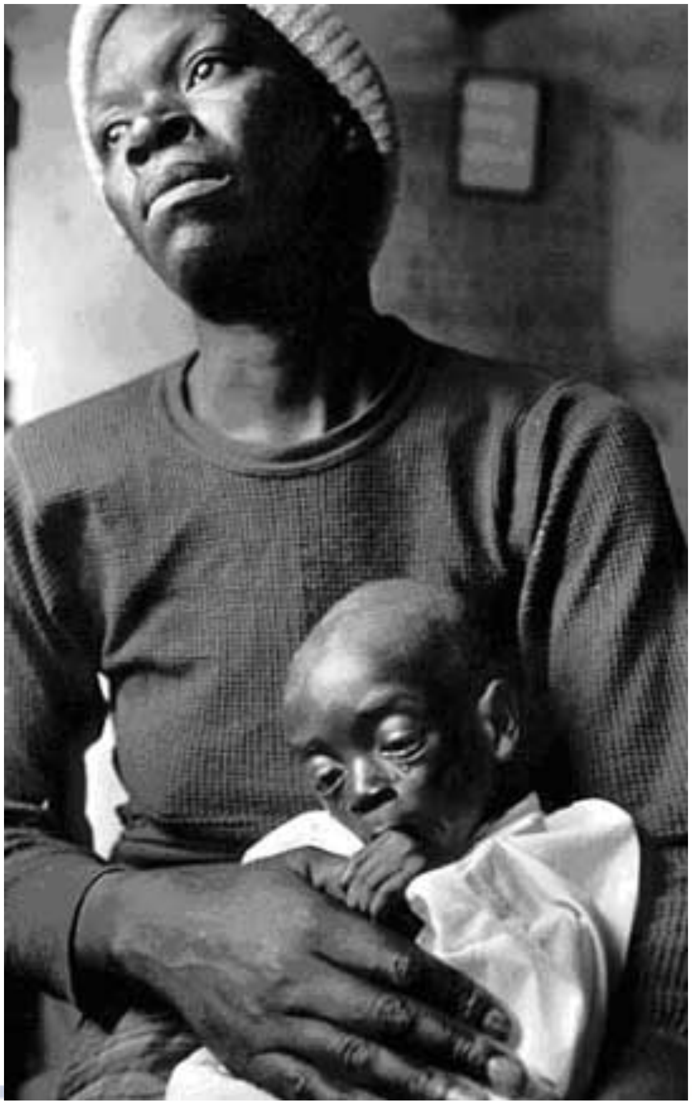


- **ONE HEALTH RECOGNIZES THAT THE HEALTH OF HUMANS, ANIMALS AND ECOSYSTEMS ARE INTERCONNECTED.**

- **A COORDINATED, MULTIDISCIPLINARY AND CROSS-SECTORAL APPROACH TO ADDRESS RISKS THAT ORIGINATE AT ANIMAL-HUMAN-ECOSYSTEMS INTERFACES.**

The AIDS pandemic: started 30 years ago

>55 million infected, >20 million deaths, 1.8 million infected and about 1 million die annually.



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)

UPDATED 30 AUGUST 2018

Experimental HIV vaccine shows promise in early trial

Scientists have created an experimental HIV vaccine that is able to neutralise HIV in animals.

0

An experimental HIV vaccine is safe and triggers strong immune responses in healthy adults and in monkeys, researchers report.

They say it also protected two-thirds of monkeys against an HIV-like virus.

Though results of animal studies are not always the same in humans, researchers are encouraged by this early-stage study, which included nearly 400 healthy people. For their next step, they are launching a new vaccine trial that will include 2 600 women in southern Africa who are at risk of HIV infection.

South Africa has the biggest HIV epidemic in the world.

According to Statistics South Africa, the

Since smallpox eradication:
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

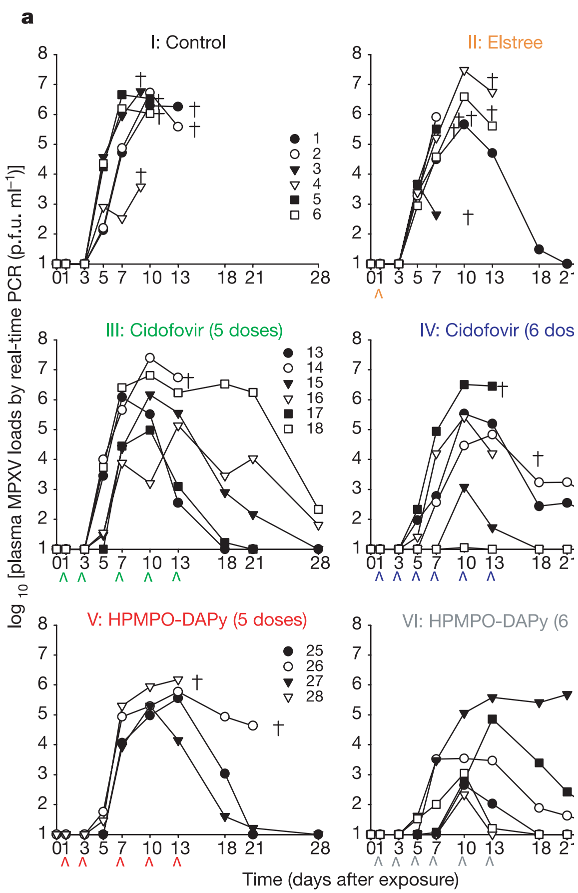
Pelkonen et al. E.I.D. 2003; 9:1458-1461

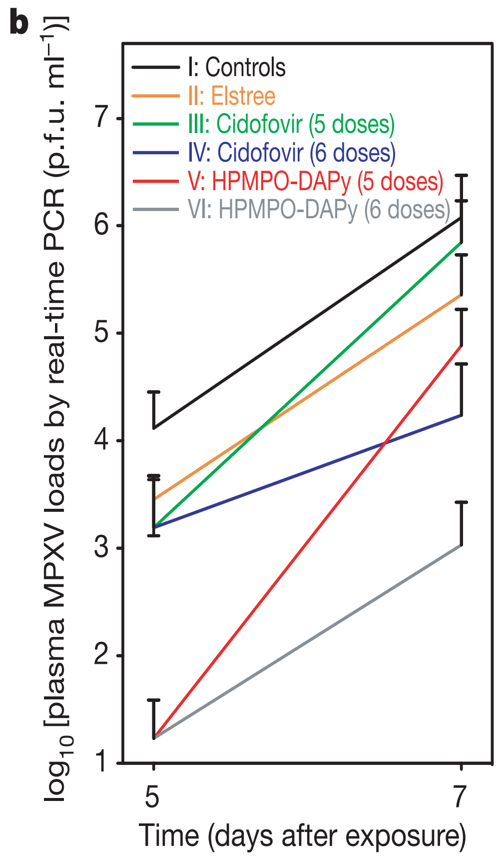
Stittelaar *et al*., Nature, 2006

Antiviral treatment is more effective than smallpox vaccination upon lethal monkeypox virus infection

Koert J. Stittelaar[1], Johan Neyts[3], Lieve Naesens[3], Geert van Amerongen[1,4], Rob F. van Lavieren[5], Antonin Holý[6], Erik De Clercq[3], Hubert G. M. Niesters[1], Edwin Fries[1], Chantal Maas[1], Paul G. H. Mulder[2], Ben A. M. van der Zeijst[4] & Albert D. M. E. Osterhaus[1]

Nature 2006





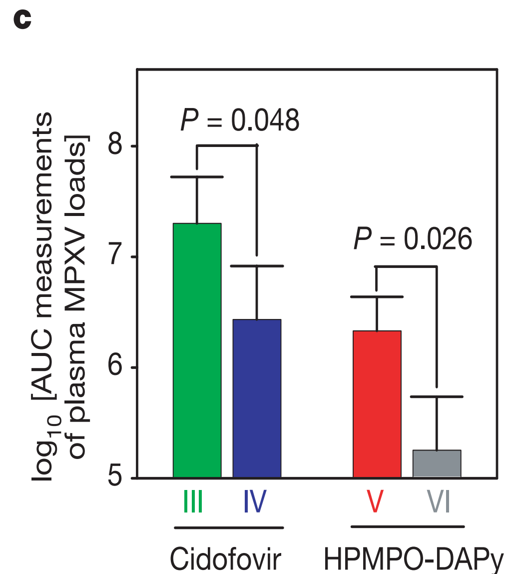
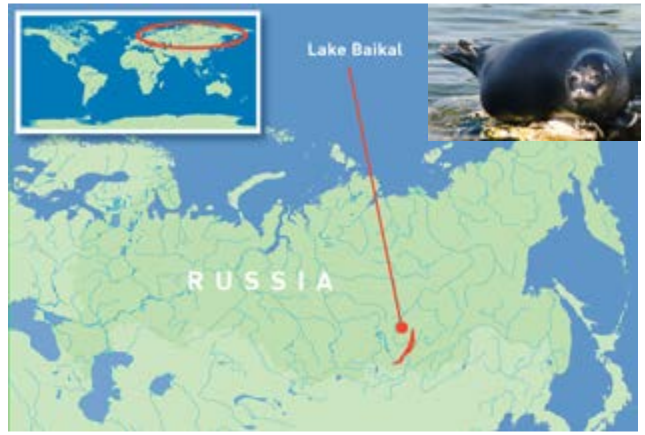


Figure 3 | Viral load profiles after infection with MPXV. a, Plasn loads of monkeys treated as described in Figs 1, 2. **b**, Plasma MPX monkeys (treated as described in Fig. 1) 5 or 7 days after infection. Data show average ± s.e.m. Statistical analysis of the pairwise comparisons of survival

Vaccine versus antiviral stockpiles for pox outbreak preparedness

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

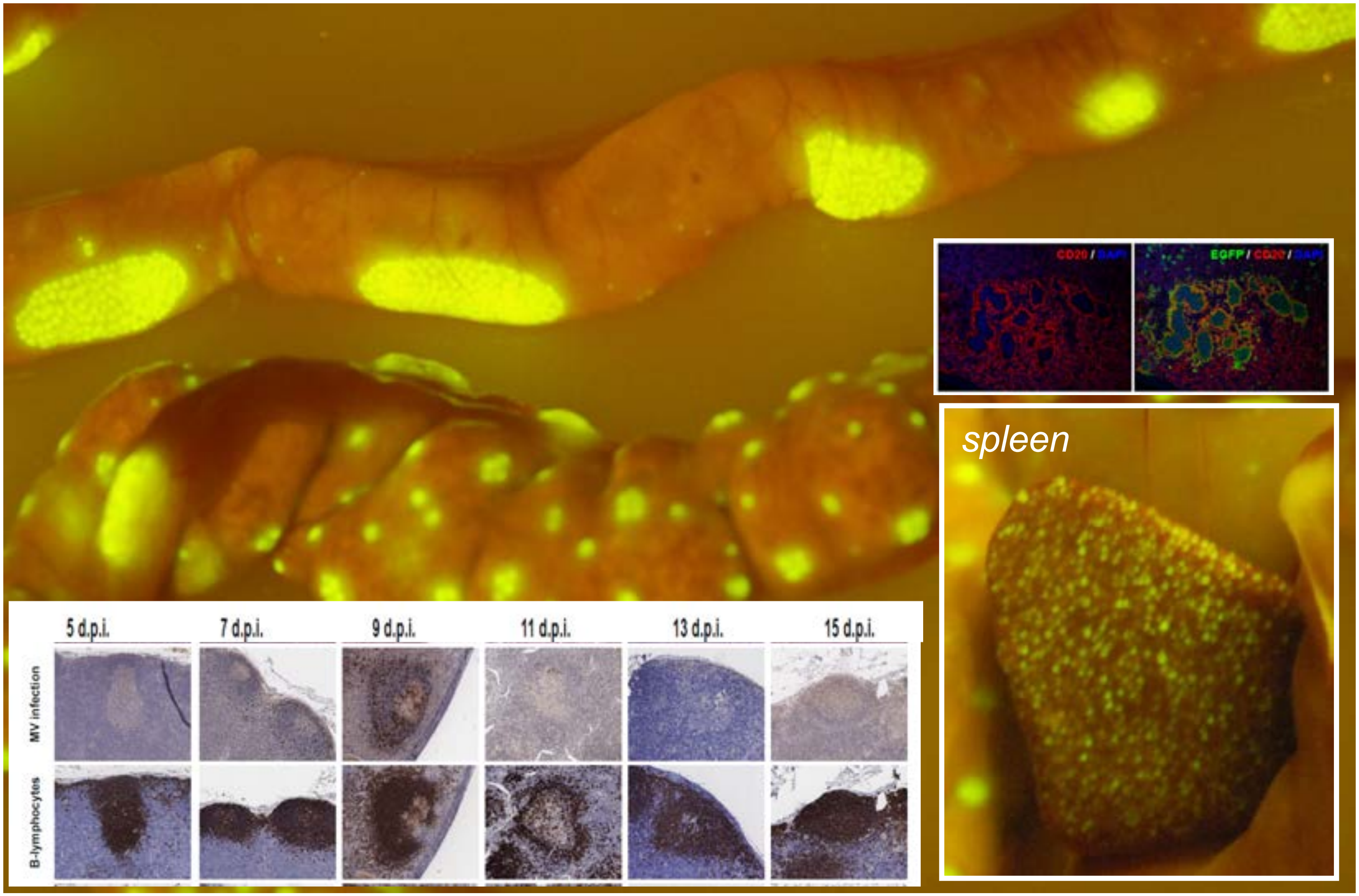
CDV: Serengeti lions
Vaccine 1994

CDV:
Rhesus macaques
China, EID 2011

Should we continue measles vaccination for ever?

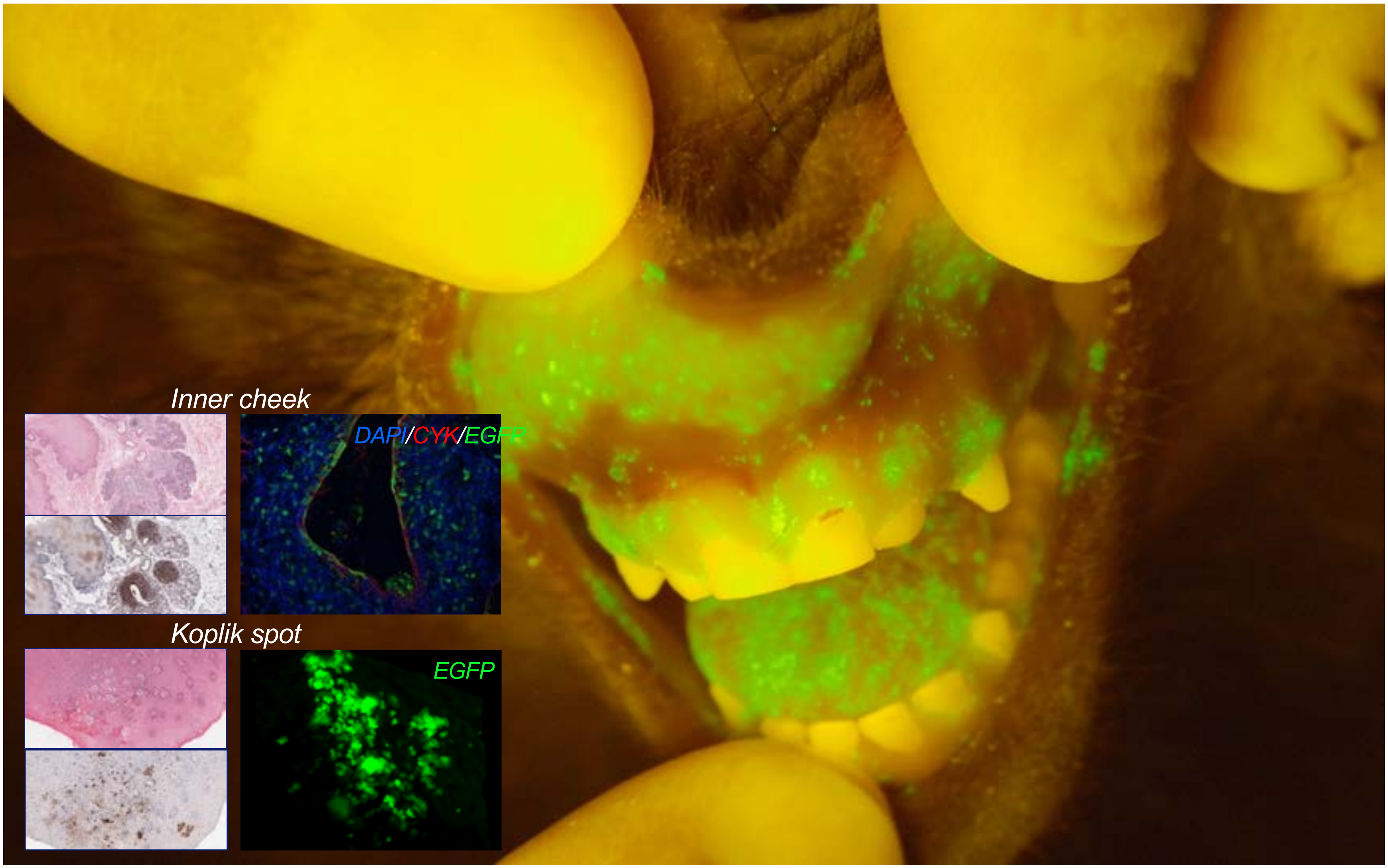
CD150 is the primary morbillivirus entry receptor

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



PVRL4 is the morbillivirus receptor on epithelial cells

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

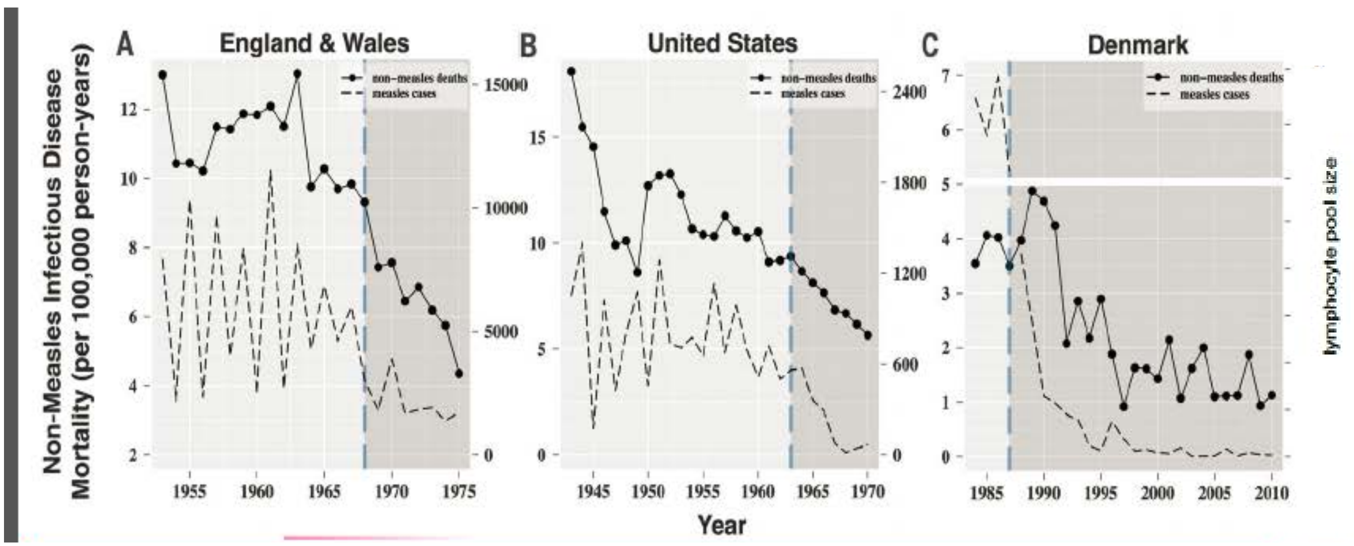


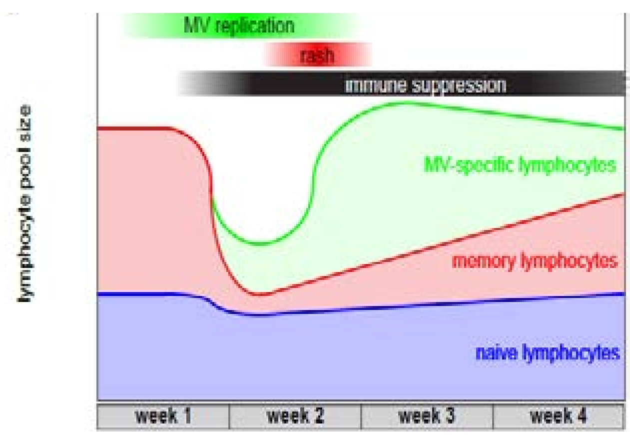
REPORT

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

Trump claims vaccines and autism are linked but his own experts vehemently disagree

The president has tweeted more than 20 times claiming – falsely – there is a link between vaccines and autism

Andrew Buncombe New York | @AndrewBuncombe | Saturday 5 May 2018 13:31 | 70 comments

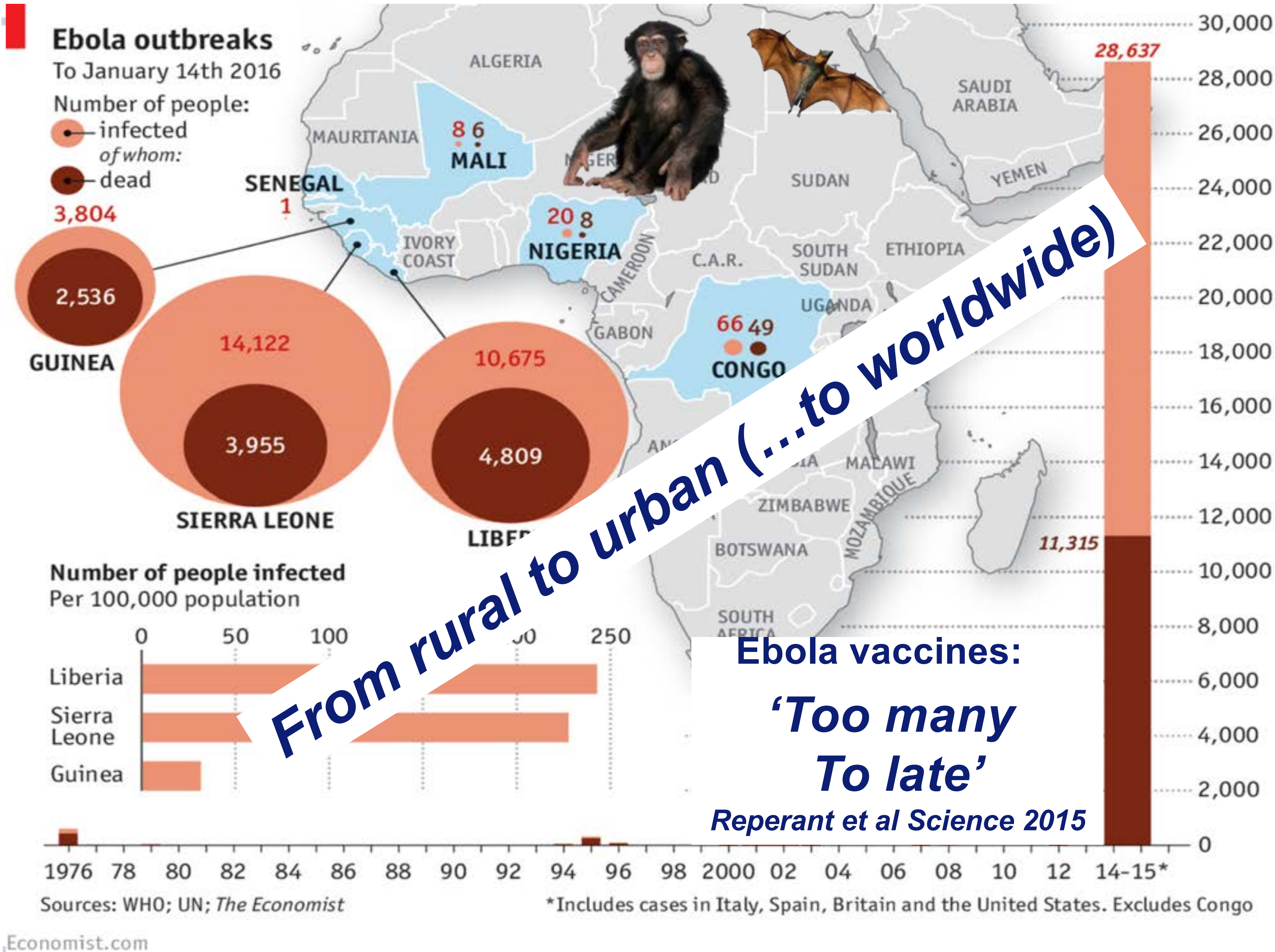
11118 shares

Like Click to follow The Independent US

Outbreaks of Ebola Virus Disease in Central Africa, 1976–2018.*			
Year of Onset	Country	Epicenter or Epicenters	No. of Cases (Case Fatality Rate [%])
1976	Zaire (current DRC)	Yambuku	318 (88)
1977	Zaire (current DRC)	Tandala	1 (100)
1994	Gabon	Mékouka, Ogooué-Ivindo Province	52 (60)
1995	Zaire (current DRC)	Kikwit	315 (81)
1996	Gabon	Mayibout, Ogooué-Ivindo Province	37 (57)
1996	Gabon	Booué, Ogooué-Ivindo Province	62 (75)
2001	Gabon and ROC	Mékambo, Ogooué-Ivindo Province (Gabon)	65 (82)
2001	ROC and Gabon	Mbomo, Kéllé, Cuvette Ouest Region (ROC)	59 (73)
2002	ROC	Mbomo, Kéllé, Cuvette Ouest Region	143 (89)
2003	ROC	Mbomo, Cuvette Ouest Region	35 (83)
2007	DRC	Luebo, Kasai Occidental Province	264 (71)
2008	DRC	Mweka and Luebo, Kasai Occidental Province	32 (47)
2014	DRC	Ikanamongo Village, Equateur Province	69 (71)
2017	DRC	Kagbono, Likati, Bas Uélé Province	8 (50)
2018	DRC	Ikoko-Impenge, Bikoro, Equateur Province	54 (61)
2018*	DRC	Mangina and Beni, North Kivu Province	74 (46)

* This outbreak was ongoing as of mid-August. Reported case numbers and case fatality rates are provisional. DRC denotes Democratic Republic of Congo, and ROC Republic of the Congo.

Munster V et al., NEJM 2018


Ebola outbreaks
To January 14th 2016
Number of people:
infected
of whom:
dead
3,804
2,536
GUINEA
14,122
3,955
SIERRA LEONE
10,675
4,809
SENEGAL
1
MALI
8 6
NIGERIA
20 8
CONGO
66 49
ALGERIA
MAURITANIA
IVORY COAST
CAMEROON
GABON
C.A.R.
SUDAN
SOUTH SUDAN
ETHIOPIA
UGANDA
SAUDI ARABIA
YEMEN
MALAWI
MOZAMBIQUE
ZIMBABWE
BOTSWANA
28,637
11,315
30,000
28,000
26,000
24,000
22,000
20,000
18,000
16,000
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0
Number of people infected
Per 100,000 population
0
50
100
250
Liberia
Sierra Leone
Guinea
1976 78 80 82 84 86 88 90 92 94 96 98 2000 02 04 06 08 10 12 14-15*
Sources: WHO; UN; The Economist
*Includes cases in Italy, Spain, Britain and the United States. Excludes Congo
Economist.com
From rural to urban (…to worldwide)
Ebola vaccines:
'Too many
To late'
Reperant et al Science 2015

Coltart *et al. BMC Medicine* (2015) 13:271
DOI 10.1186/s12916-015-0477-2

Medicine for Global Health

BMC Medicine

CORRESPONDENCE Open Access

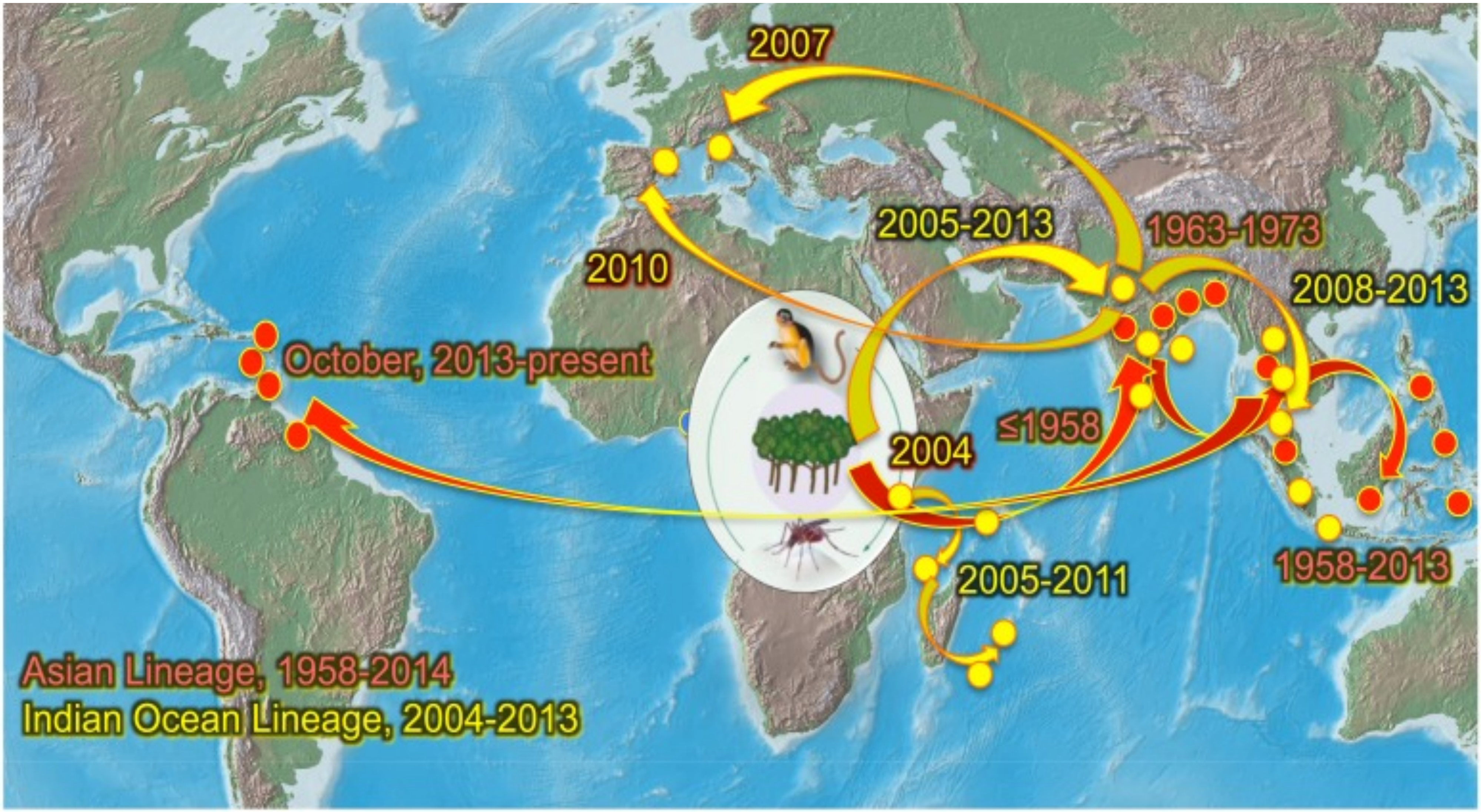
Role of healthcare workers in early epidemic spread of Ebola: policy implications of prophylactic compared to reactive vaccination policy in outbreak prevention and control

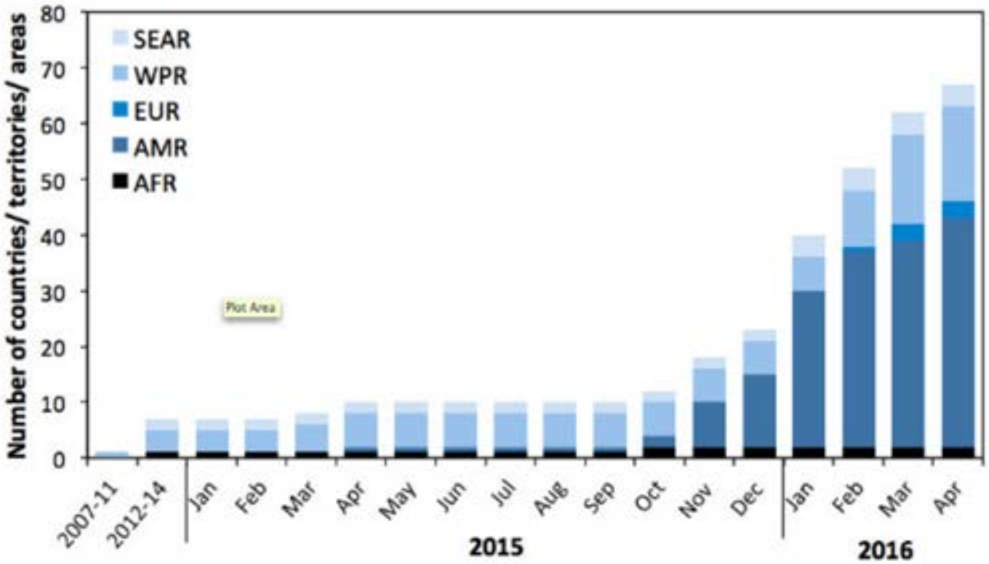
Table 3 Indicative proportion of early outbreak prevented by implementing different vaccination strategies: prospective versus reactive vaccination of healthcare workers

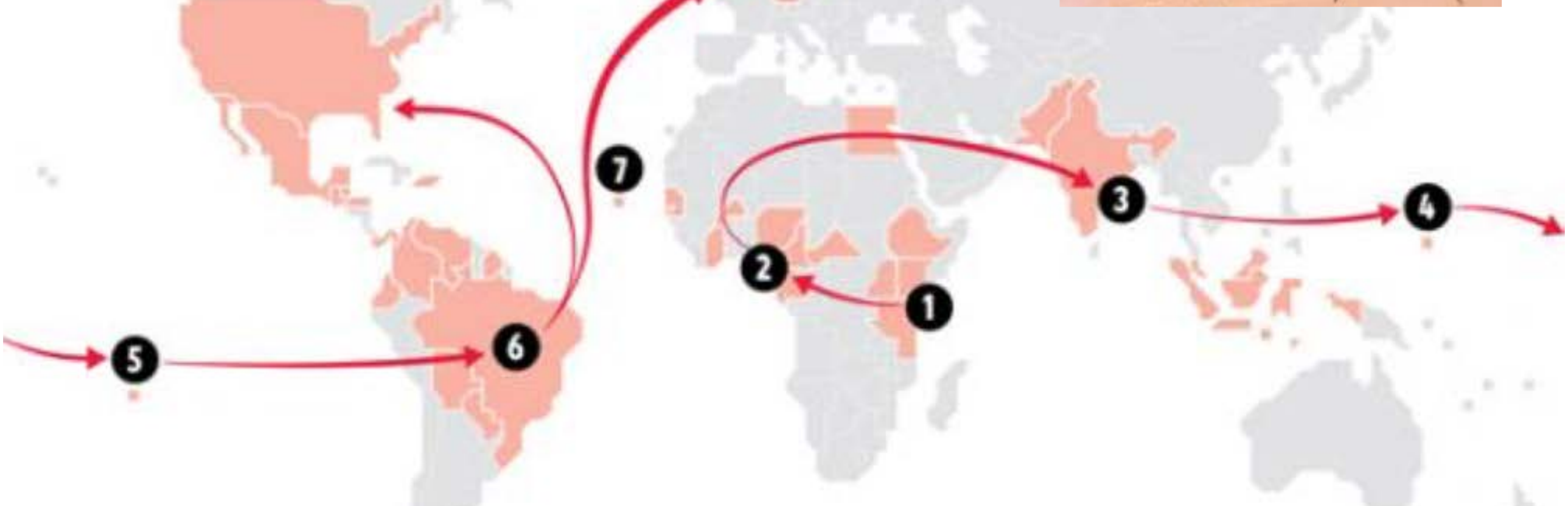
Epidemic	Country	Total number of cases [4]	Total number of deaths [4]	Cases included in epidemic tree	Percentage of initial outbreak prevented by vaccination strategy		
					Strategy 1: Vaccinate prophylactically (100 % coverage)	Strategy 2: Vaccinate prophylactically approx. 75 % of HCWs	Strategy 3: Vaccinate reactively (lag-time 42 days)
2014 West Africa	Guinea [22]	3,792	2,530	71	61 % (43/71)	36.6 % (26/71)	0
	Liberia [24–28]	10,672	4,808	9	67 % (6/9)	11 % (1/9)	0
	Sierra Leone [29–31]	13,683	3,953	NR	NR	NR	0
	Nigeria [23]	20	8	20	80 % (16/20)	50 %(10/20)	0
	Mali [32–34]	8	6	8	38 % (3/8)	13 % (1/8)	0
	USA [35]	4	1	4	75 % (3/4)	50 % (2/4)	0
	UK [36] and Spain [37]	2	0	2	100 % (2/2)	50 % (1/2)	0
	Senegal [38]	1	0	1	0	0	0
	Overall	28,183	11,306	115	63.5 % (73/115)	35.7 % (41/115)	
	(95 % confidence interval)				(0.54–0.72)	(0.27–0.45)	
Historic outbreaks	Kikwit [6, 39–43]	315	250	9	100 % (9/9)	NR	NR
	Mosango [44]	23	18	23	100 % (23/23)	74 % (17/23)	NR
	Yambuku [2]	318	280	45	44 % (20/45)	NR	NR
Total				192	65.1 % (125/192)	42.0 % (58/138)	0.0 % (0/609)
(95 % confidence interval)					(0.58–0.72)	(0.34–0.51)	

Cases numbers accurate as of 06/09/2015
NR, Not reported

Chikungunya virus
Past years

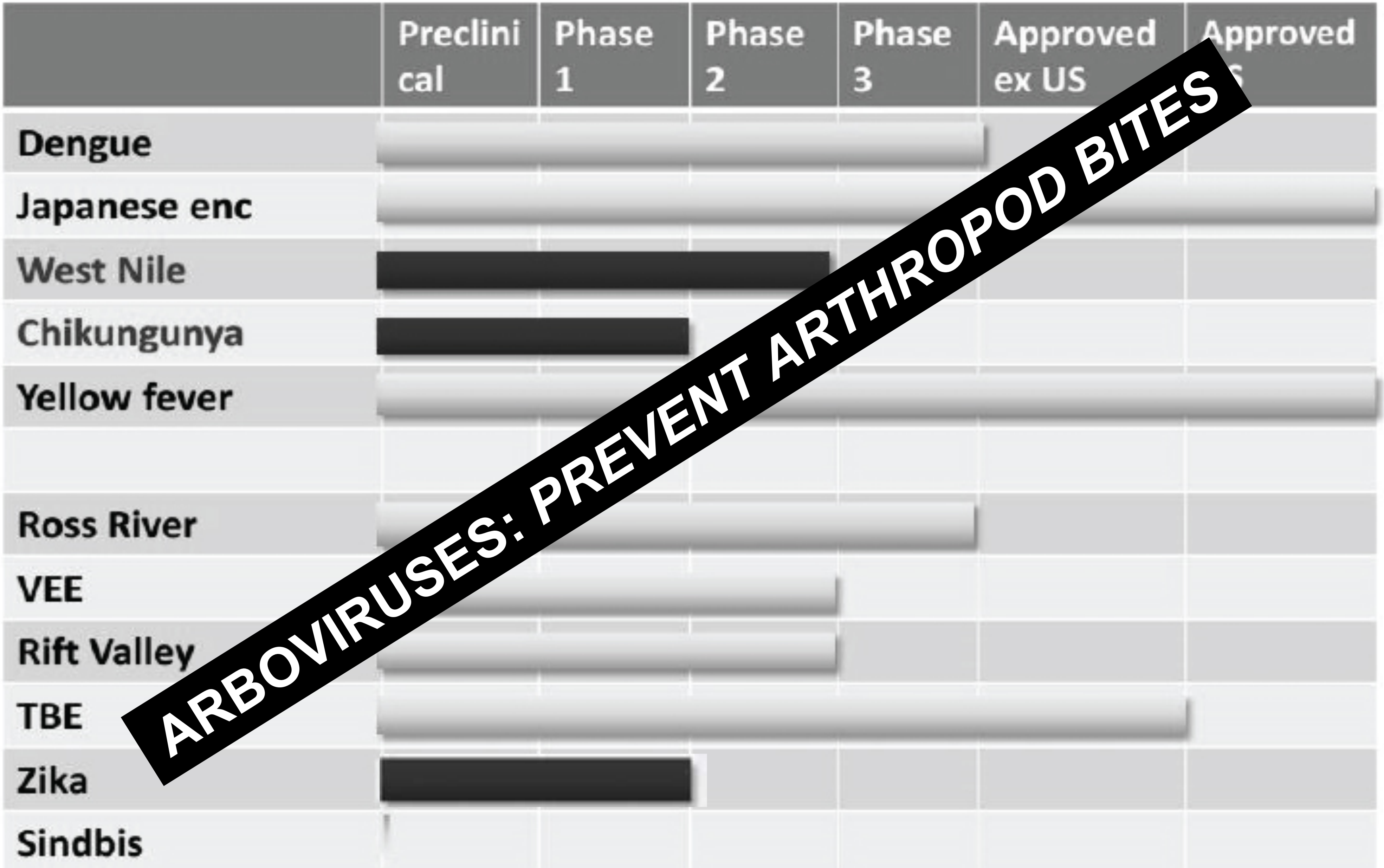






ZIKA: Out of Africa

Arbovirus vaccines: most are still lacking

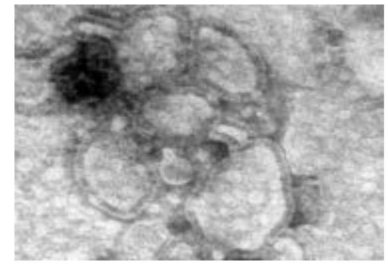


Identification of viral pathogens

ErasmusMC / RIZ TiHo

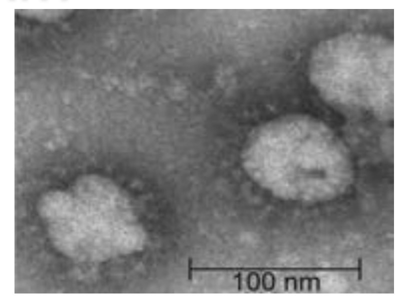
1995	CDV as the cause of mass mortality in Serengeti lions
1996	γ-herpesvirus in seals (phocid herpesvirus-2)
1997	monk seal morbilliviruses (MSMV-WA/G)
1997	influenza A (H5N1) virus in humans
1998	lentivirus from Talapoin monkeys (SIVtal)
1999	influenza B virus in seals
2000	human metapneumovirus (hMPV)
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 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, 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

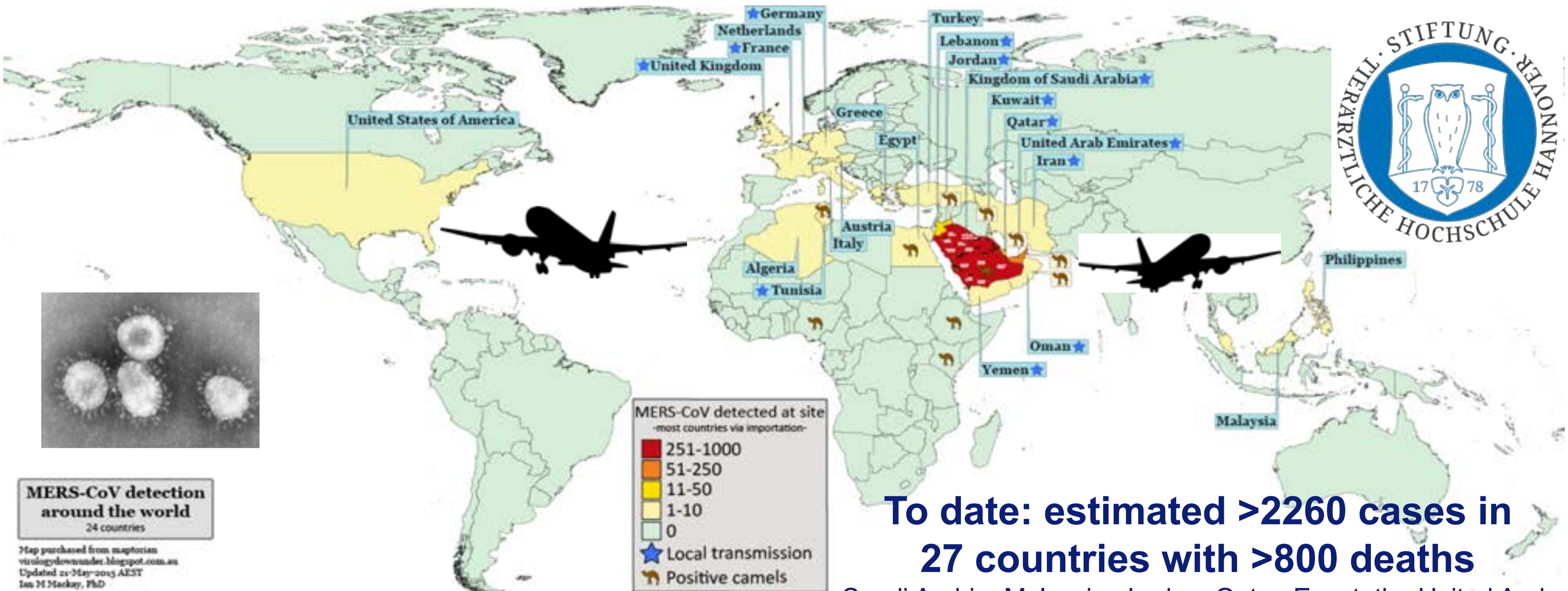


Fouchier et al.,Nature 2003
Kuiken et al., Lancet 2004

Press conference of
SARS etiology
network

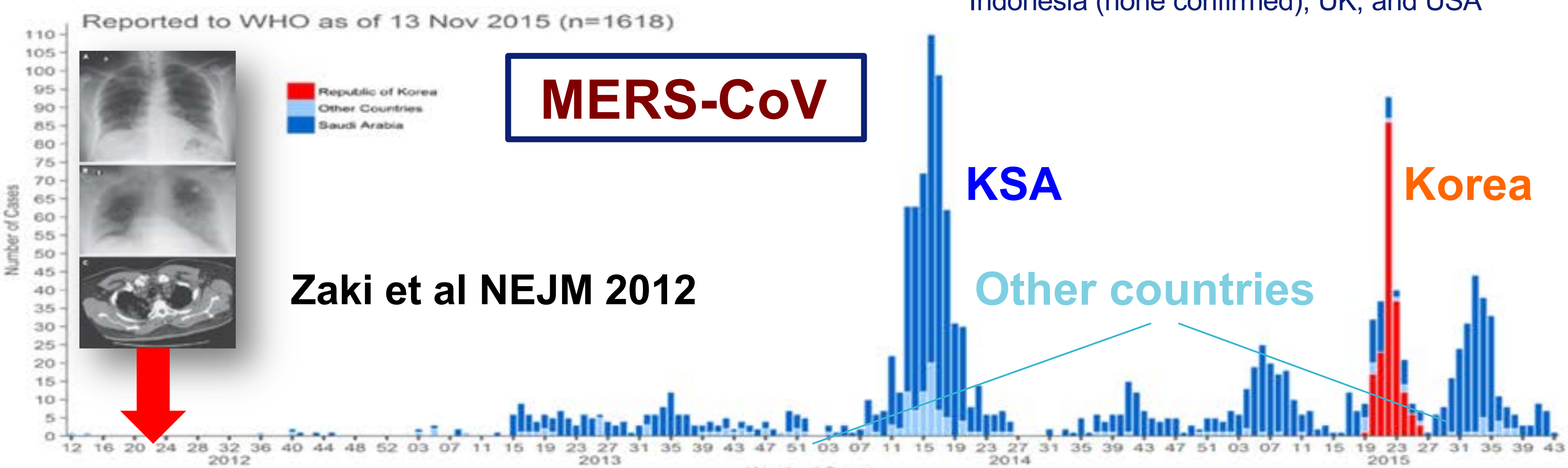
Official declaration of SARS-CoV as the etiologic agent

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



Other countries: Algeria, Austria, China, Egypt, France, Germany, Greece, Iran, Italy, Jordan, Kuwait, Lebanon, Malaysia, Netherlands, Oman, Philippines, Qatar, Thailand, Tunisia, Turkey, United Arab Emirates, United Kingdom, United States of America, Yemen
Please note that the underlying data is subject to change as the investigations around cases are ongoing. Onset date estimated if not available.

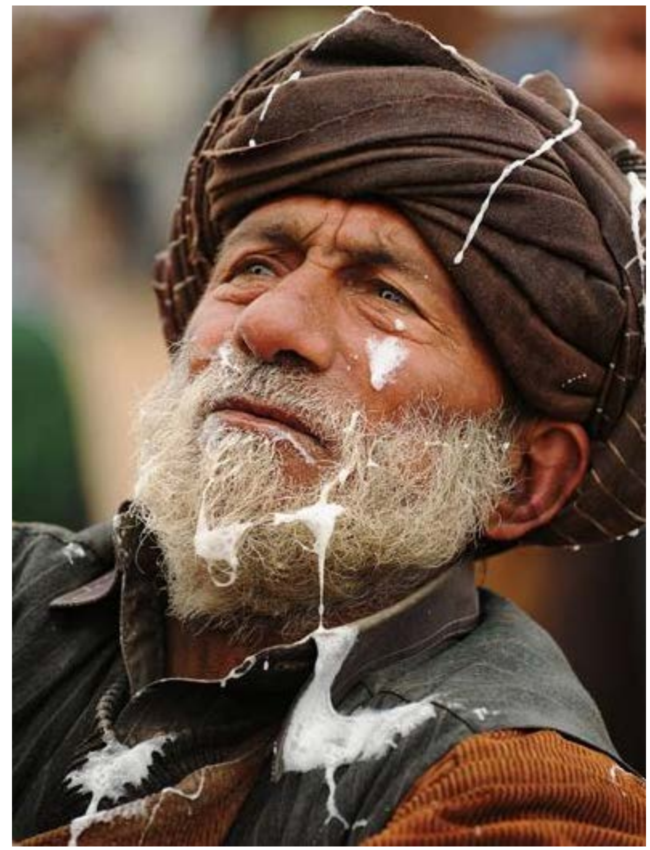
World Health Organization

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)

Food and Agriculture Organization of the United Nations

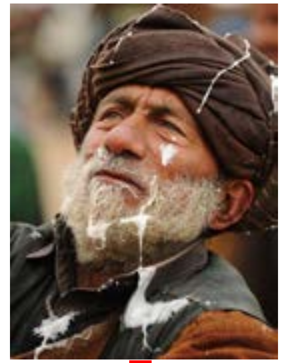
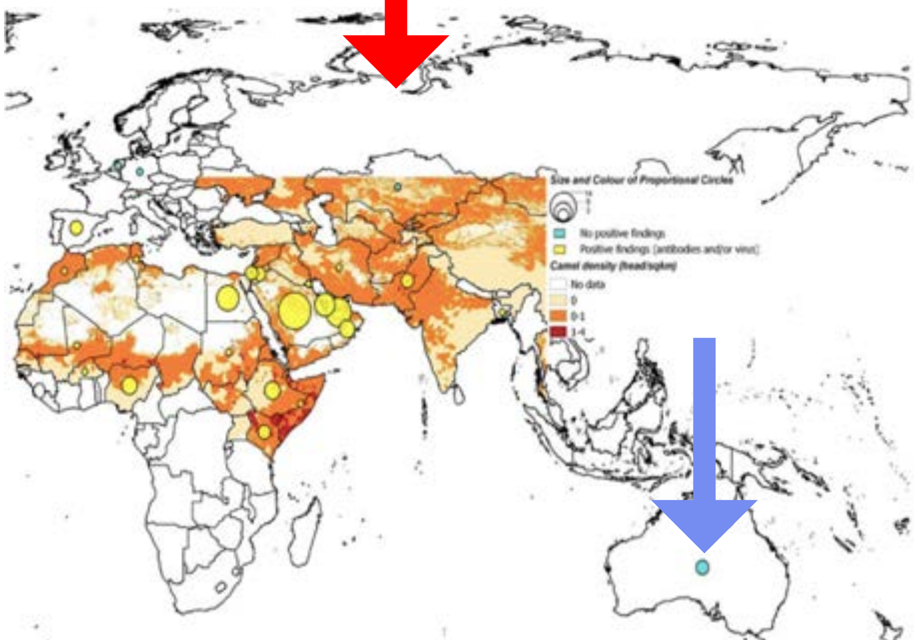
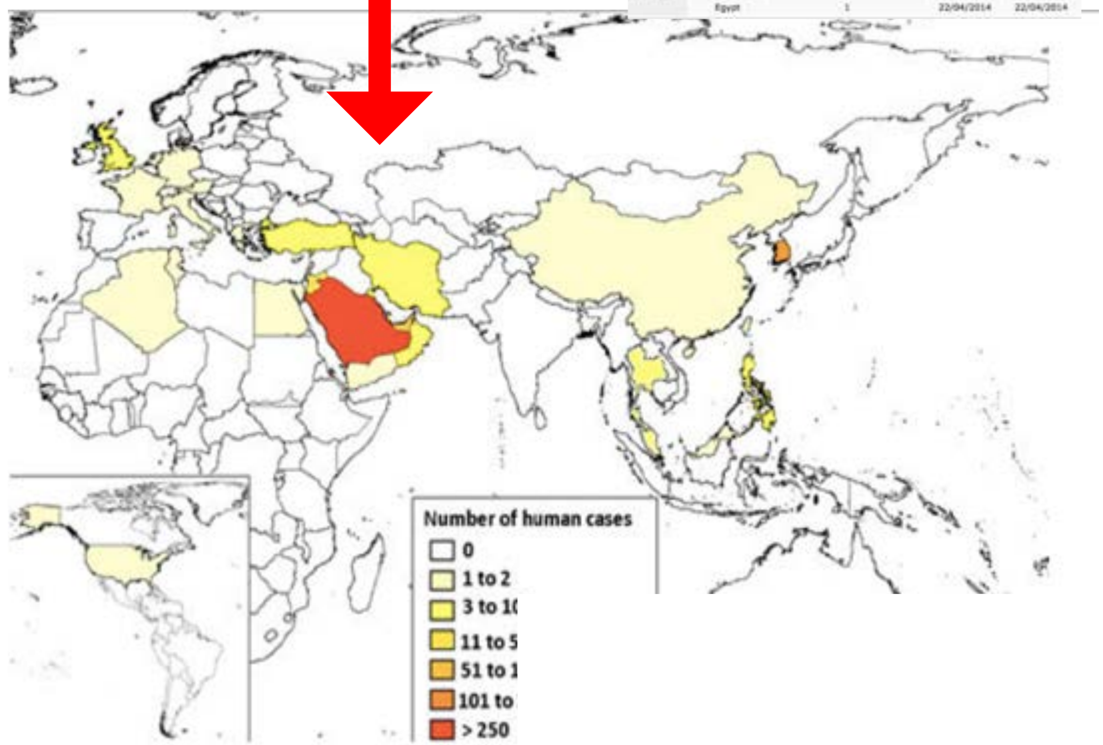


Table 1. *MERS-CoV cases in humans by country and dates of first and most recent observations*

	Country	Cumulative number of confirmed MERS-CoV human cases	First observation	Last Observation
Middle East	Saudi Arabia	1,886	13/06/2012	16/10/2018
	United Arab Emirates	88	19/03/2013	04/05/2018
	Jordan	26	02/04/2012	26/09/2015
	Qatar	19	15/08/2013	14/05/2017
	Oman	11	26/10/2013	23/02/2018
	Iran (Islamic Republic of)	6	11/05/2014	18/03/2015
	Kuwait	4	30/10/2013	06/09/2015
	Lebanon	2	22/04/2014	08/06/2017
	Yemen	1	17/03/2014	17/03/2014
	Bahrain (the Kingdom of)	1	04/04/2016	04/04/2016
Europe	United Kingdom	5	03/09/2012	16/08/2018
	Germany	2	05/10/2012	07/03/2015
	Netherlands	2	01/05/2014	05/05/2014
	France	2	23/04/2013	27/04/2013
	Austria	2	22/09/2014	08/09/2016
	Turkey	1	25/09/2014	25/09/2014
	Italy	1	25/05/2013	25/05/2013
	Greece	1	08/04/2014	08/04/2014
Asia	Republic of Korea	186	11/05/2015	26/08/2018
	Philippines	3	15/04/2014	30/06/2015
	Thailand	3	10/06/2015	25/07/2016
	China	1	21/05/2015	21/05/2015
	Malaysia	2	08/04/2014	24/12/2017
Americas	United States of America	2	14/04/2014	01/05/2014
Africa	Tunisia	3	01/05/2013	17/06/2013
	Algeria	2	23/05/2014	23/05/2014
	Egypt	1	22/04/2014	22/04/2014



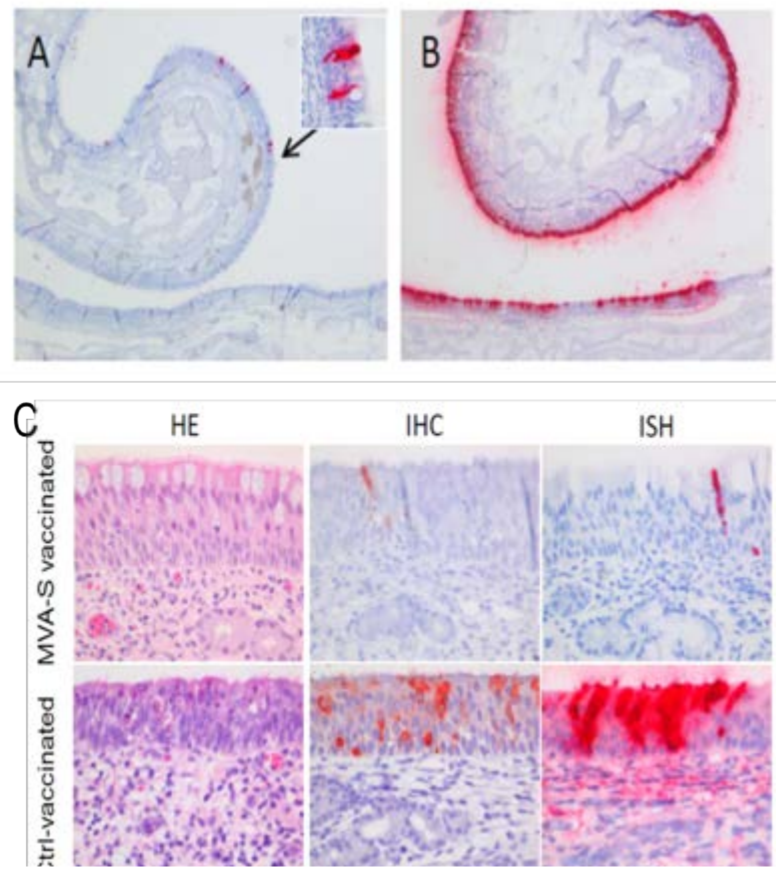
MERS-CoV livestock field surveys. Circles indicate countries in which field surveys have occured. Size is proportional to the number of studies in each country. Yellow circles indicate positive findings in livestock (antibodies or antigen), while turquoise circles represent the lack of positive findings. Please note that the circle in Spain indicates positive findings from the Canary Islands. The density map includes dromedary and bactrian camel distribution, and is an unpublished model based on the methodology described in Robinson et al. (2014) (http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0150424)



MVA expressing the MERS-CoV spike protein:

PREVENTION AT THE SOURCE?

Fei Song et al. JV 2013



Haagmans et al., Science 2016

MVA expressing the MERS-CoV spike protein:

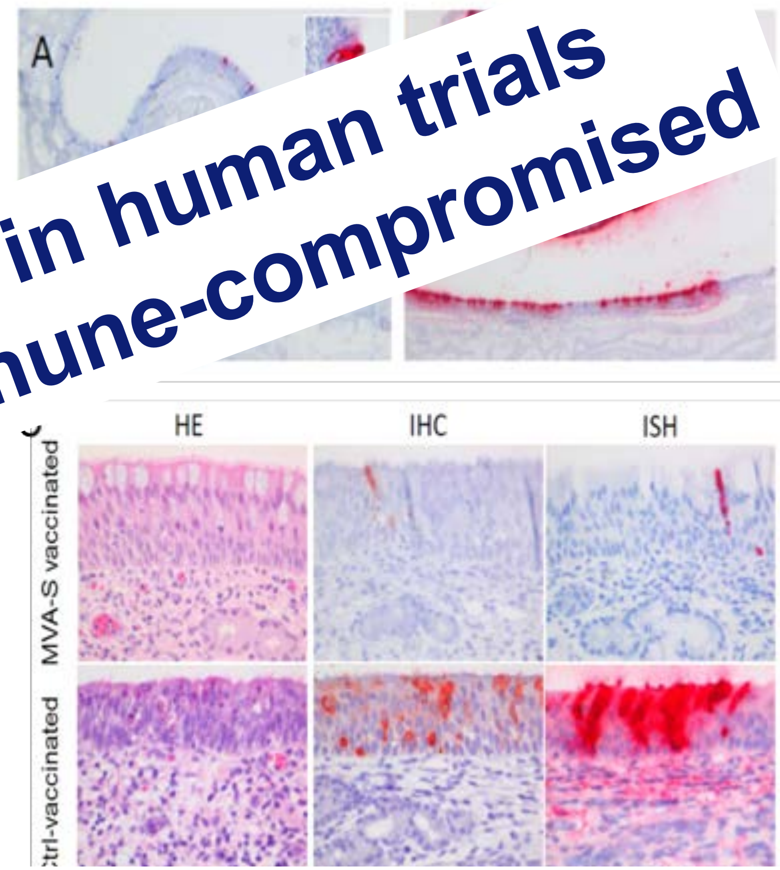
PREVENTION AT THE SOURCE?

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

MERS-CoV vaccine candidates
preclinical development and phase 1 trials

- *Plasmid DNA vaccine (Innovio/GeneOne)*
- *Plasmid DNA vaccine (NIAID, VRC)*
- *Virus like particles (Novavax)*
- *MVA vaccine (Sutter / Jenner Institute)*
- *Adenovirus based vectors (Jenner institute)*
- *RBD vaccine (Jiang)*

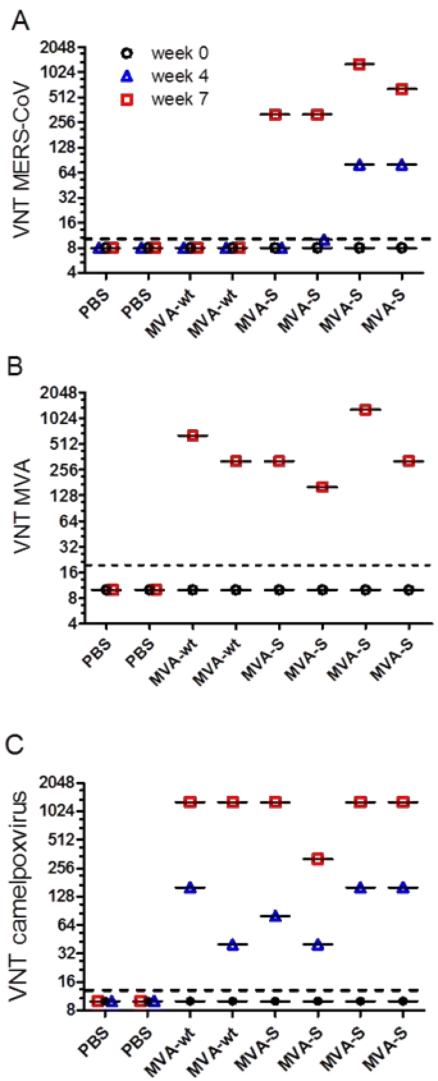
MVA expressing the MERS-CoV spike protein:

PREVENTION AT THE SOURCE

A ONE HEALTH APPROACH

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

Induction of antibodies that neutralize MVA but also camel pox virus



PRNT90 MERS-CoV virus neutralization titers

MVA neutralization

Camel pox virus neutralization

Haagmans *et al.*,Science 2016

Science Advances | AAAS
SIGNIFICANT RESEARCH, GLOBAL IMPACT

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PMCID: PMC6082650
PMID: 30101189

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

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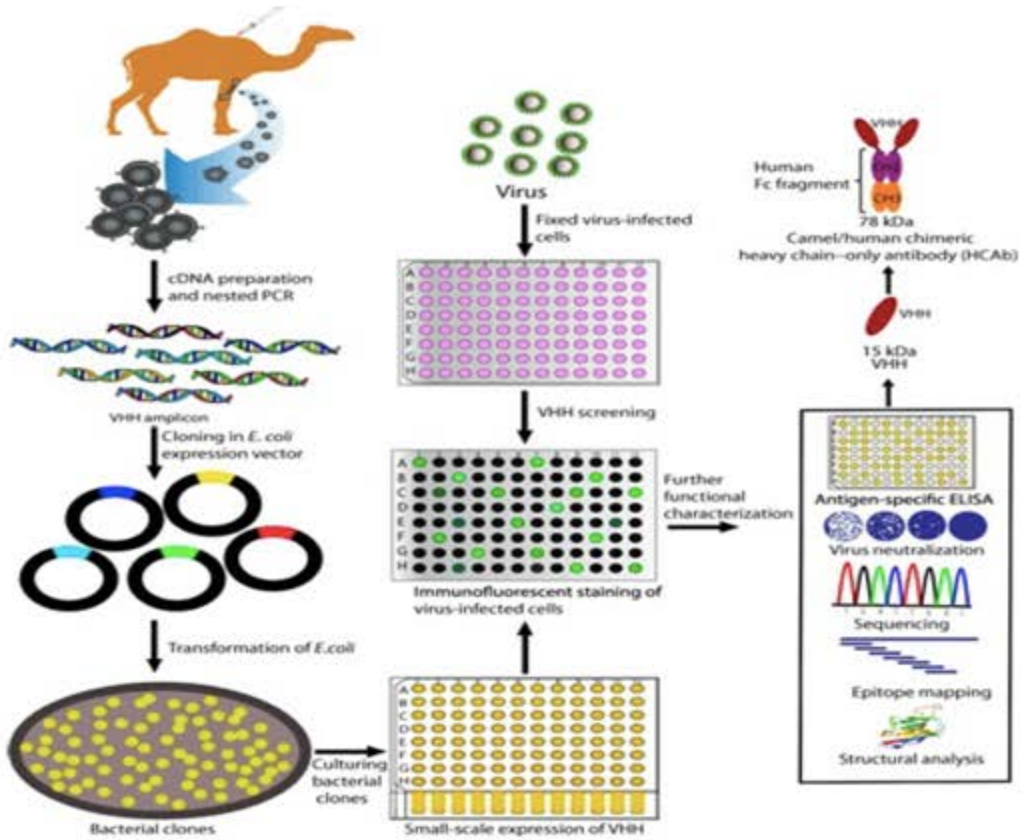
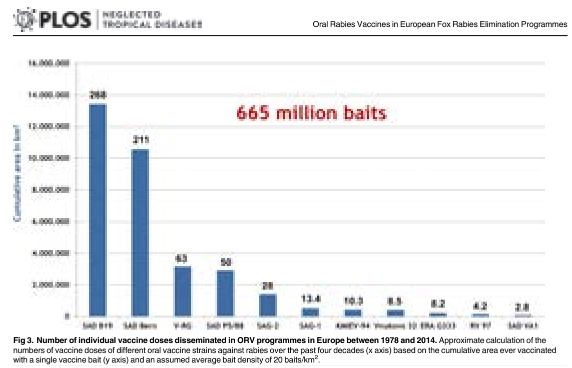
IMI-ZAPI

SEVENTH FRAMEWORK PROGRAMME



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



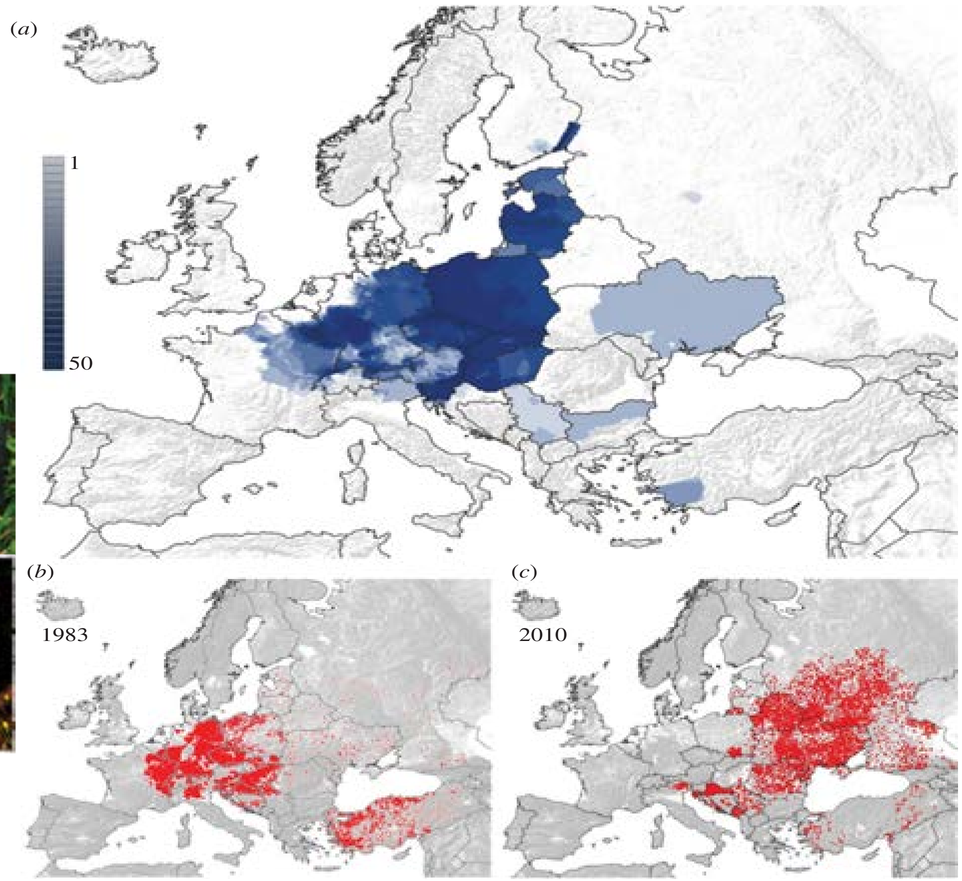


Figure 2. ORV effort and rabies cases. (*a*) Spatial extent of ORV area and the total number of ORV campaigns conducted in each country between 1978 and 2010. Reported rabies cases in (*b*) 1983 and (*c*) 2010.

Müller et al PLoS Negl Top Dis., 2015

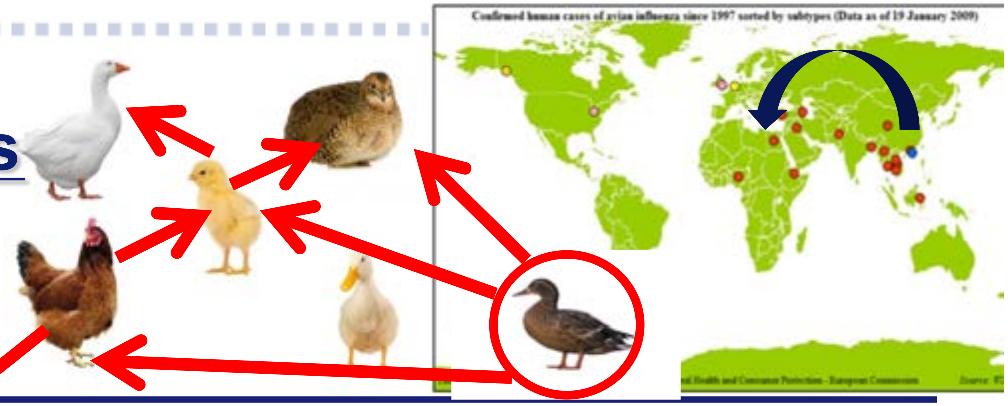
Last four pandemics

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)**

A

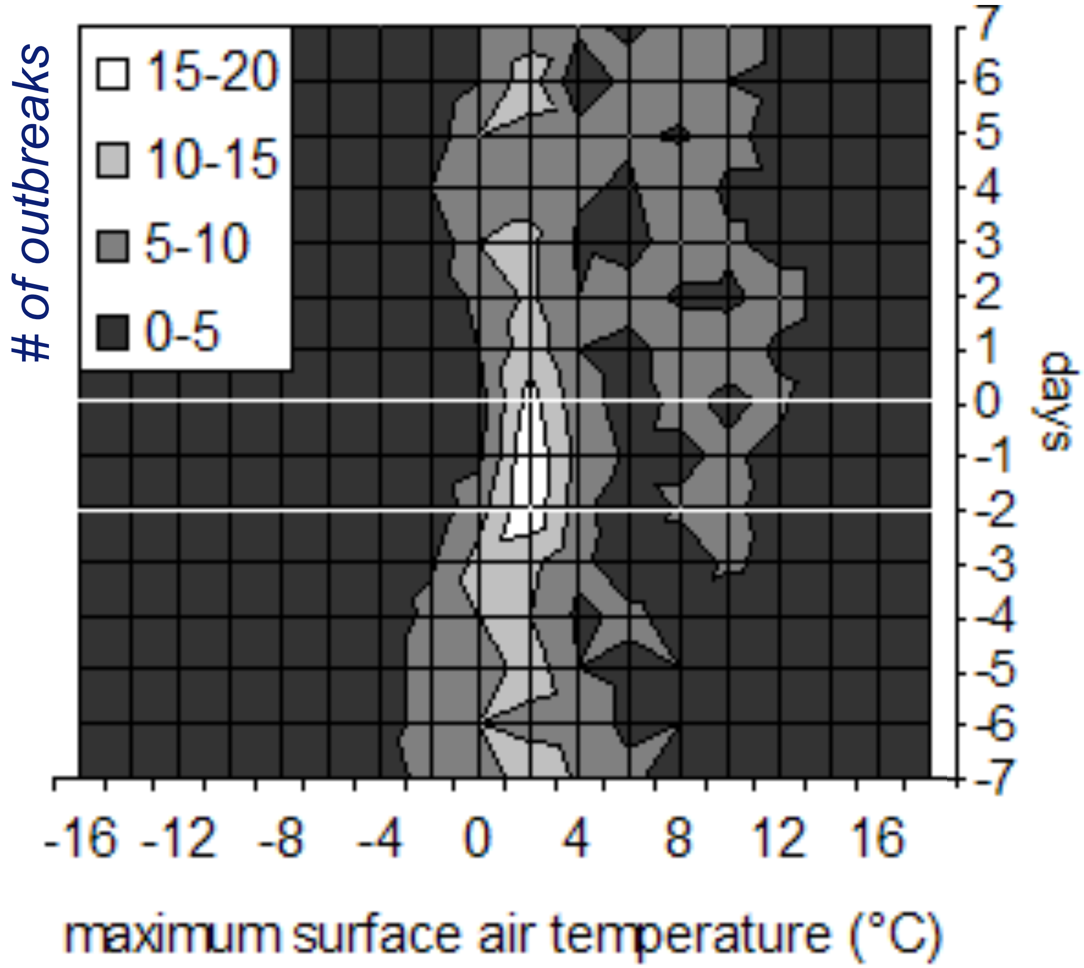
Recent zoonotic transmissions from birds -confirmed human cases-



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	<5	<5

*CFR ~ 55%

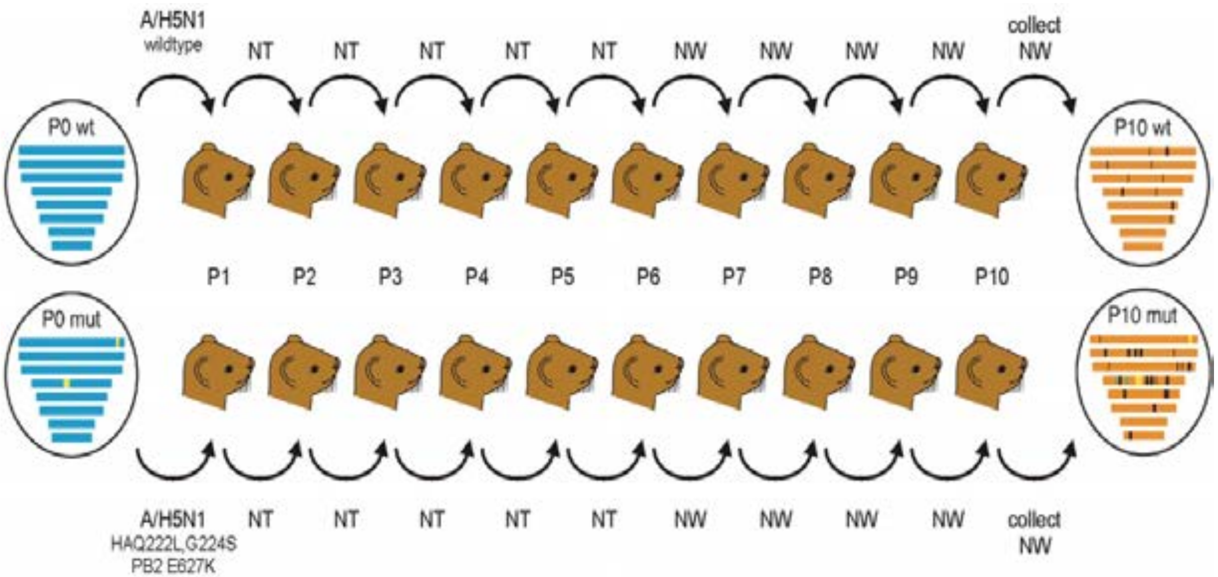
Most H5N1 outbreaks in European wild birds occurred where surface temperatures were just above freezing

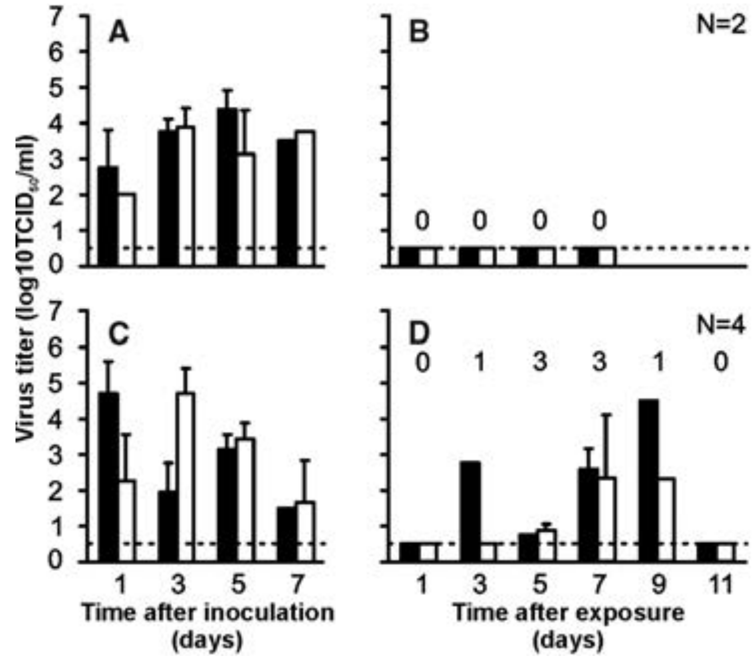


Reperant et al. 2010 PLoS Path.

Avian Influenza: Asia

HPAI H5N1 virus passaging in ferrets - toward transmissibility -





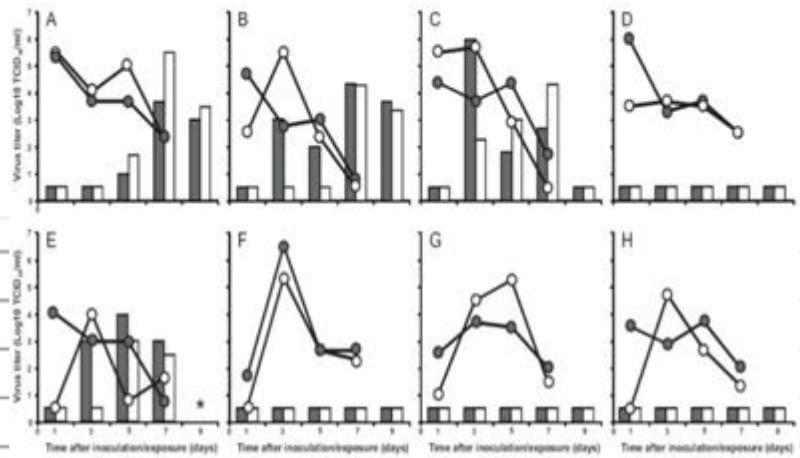
Five substitutions are sufficient for airborne transmission between ferrets

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

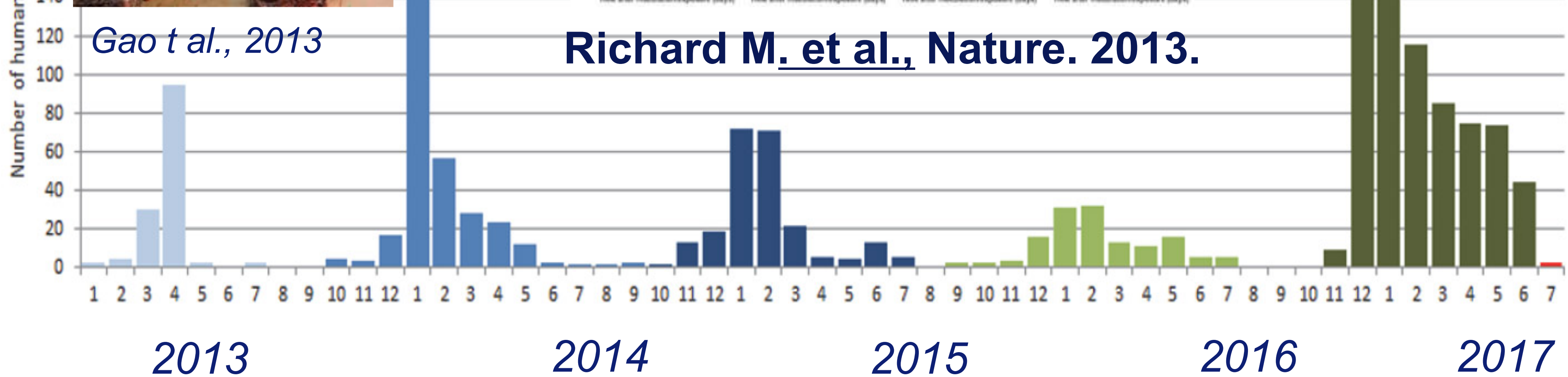
Low and highly pathogenic avian influenza A viruses H7N9

Laboratory confirmed: 1584
Deaths: 612
Recoveries: 972

Gao t al., 2013

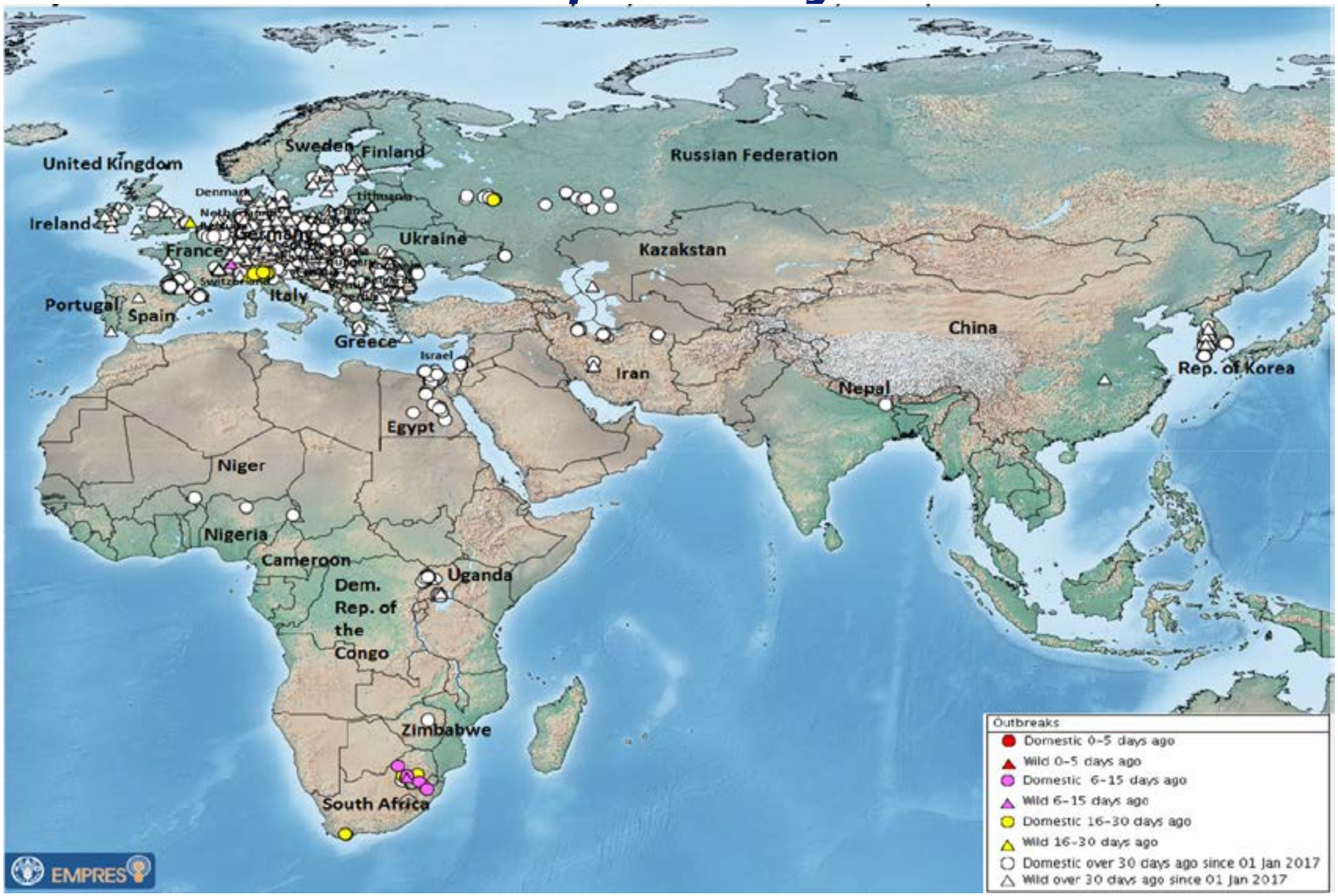


Richard M. et al., Nature. 2013.



Source: FAO, as of 23 Aug. 2017

Highly pathogenic avian influenza A virus in poultry/wild birds



H5N1
H5N2
H5N5
H5N6
H5N8
H7N3
H7N9

Source: FAO, as of 24 Aug. 2017

Crucial ‘peace time’ preparedness elements

Syndrome surveillance in humans & animals

Pathogen discovery / identification platforms for humans & animals

Diagnostics development and distribution platforms

Mathematical modeling capacity

Animal models capacity (BSL3/4)

Pathogenesis study platforms for new infections (transmission…!)

Preventive intervention platforms (societal, vaccination, antiviral)

Therapeutics discovery platforms (antivirals, antibiotics, BRM’s...)

Communication strategies

International collaboration and coordination

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

Crucial 'peace time' preparedness elements

Combatting emerging infections at the source in a One Health Approach

Syndrome surveillance in humans & animals

Pathogen discovery / identification platforms for human…

Diagnostics development and distribution pl…

Mathematical modeling capacity

Animal models capacity (B…

Pathogenesis st… …ections (transmission…!)

Preve… …ms (societal, vaccination, antiviral)

Therap… …ry platforms (antivirals, antibiotics, BRM's...)

Commu…ation strategies

International collaboration and coordination

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

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Respiratory Viruses Erasmus MC and TiHo

R. Fouchier / M.Ludlow	Mol.Virology
W.Baumgärtner	Pathology
M. Koopmans	Epidemiology
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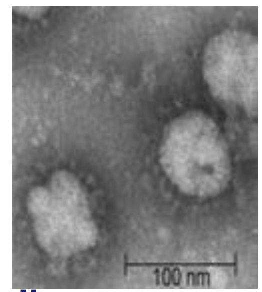
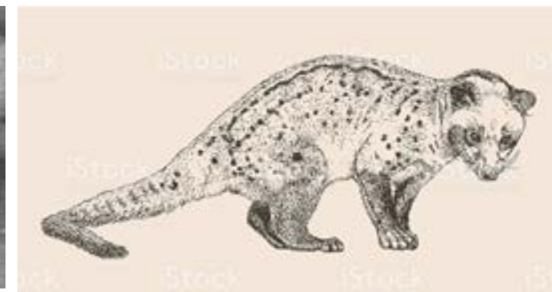
A vd Eijk / P.Fraaij / Prof. E van Gorp	Clinical / Pediatrics
G. Rimmelzwaan / G.Verjans	Viro-Immunology
B. Haagmans	Virology
G. Rimmelzwaan	Vaccinology
K.Stittelaar / R.Bodewes / E vd Vries	Animal / discovery studies





SARS collaborations

Drosten C.	Bonn University Germany
Lim W	QM Hospital Hongkong
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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
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Bosch BJ	Utrecht University Netherlands
Sutter G	Max. Univ. Münich Germany
Segalis Q	CRESA Barcelona Spain
Zambon MC	PHE London
Neubert A	IDT

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COMPARE
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ADITEC
FLUPIG
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IMI-ZAPI

NIH-NIAID

CEIRS

National (NL/DE)

Ministerie LNV / ELI
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DFG: N-RENNT / VECTORS
VolkswagenStiftung: FLAPchips
BMBF: TBENAGER
von Humboltstiftung


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