

NEW VACCINES FOR PATHOGENS INFECTING ANIMALS AND HUMANS: ONE HEALTH

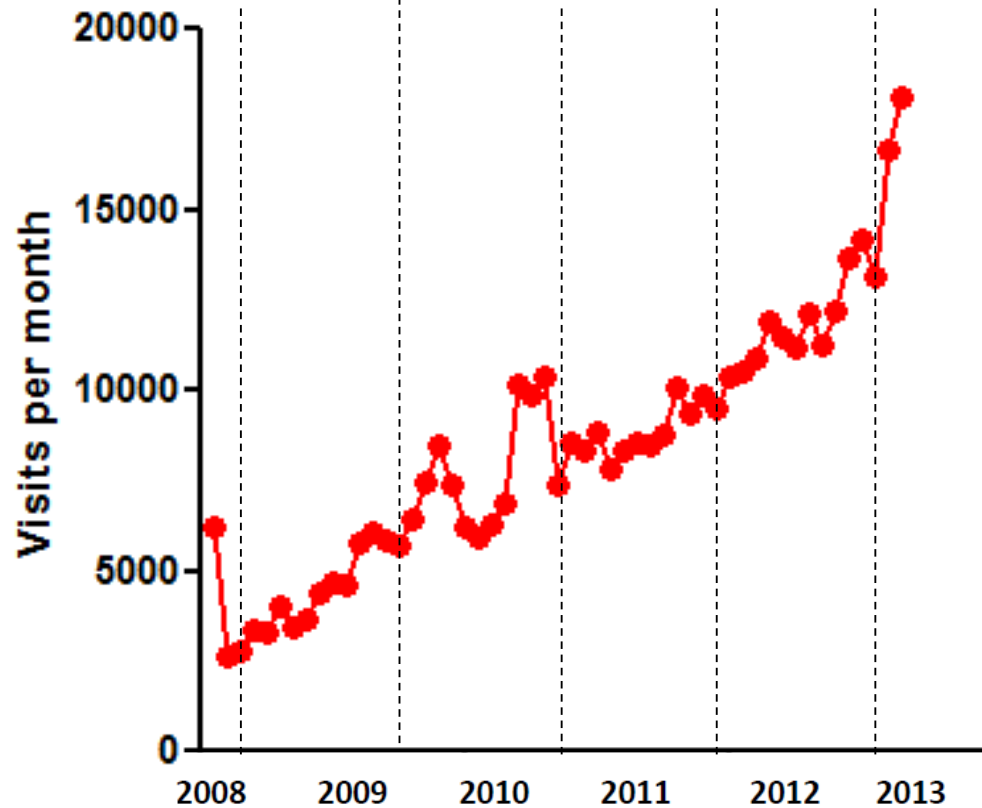
Thomas P Monath MD

What is the One Health Initiative?

- Movement to forge interdisciplinary collaboration between medical, veterinary, and environmental health disciplines
- Enhance biomedical research, public health, education, and clinical care
- Endorsed by AMA, AAP, AVMA, CDC, USDA, NEHA, FAO, ASTMH, and many other groups

One Health Initiative website www.onehealthinitiative.com

Number of Visits per Month



Initiative Aims to Merge Animal and Human Health Science to Benefit Both

Medical and veterinary science are like siblings who have grown apart. But now, there's a flurry of efforts to reunite them. Proponents of this idea, called "one medicine" or "one health," say that breaking down the walls between the two fields will help fight diseases that jump from animals to humans, such as SARS and avian influenza, and advance both human and animal health.

In April, the American Veterinary Medical Association (AVMA) decided to establish a 12-member task force to recommend ways in which vets can collaborate

rural areas, versus more than 140, mostly urban-based, schools of medicine.

The benefits of collaboration could go beyond zoonoses, says Jakob Zinsstag of the Swiss Tropical Institute in Basel. For instance, in Chad, Zinsstag has helped introduce joint vaccination campaigns for livestock and humans, which has helped

raise vaccination rates of hard-to-reach nomadic populations. In the United Kingdom,

It's all connected. Human and animal medicine should grow closer together, One Health supporters say.



One Health Interactions

75% of emerging infections are zoonoses

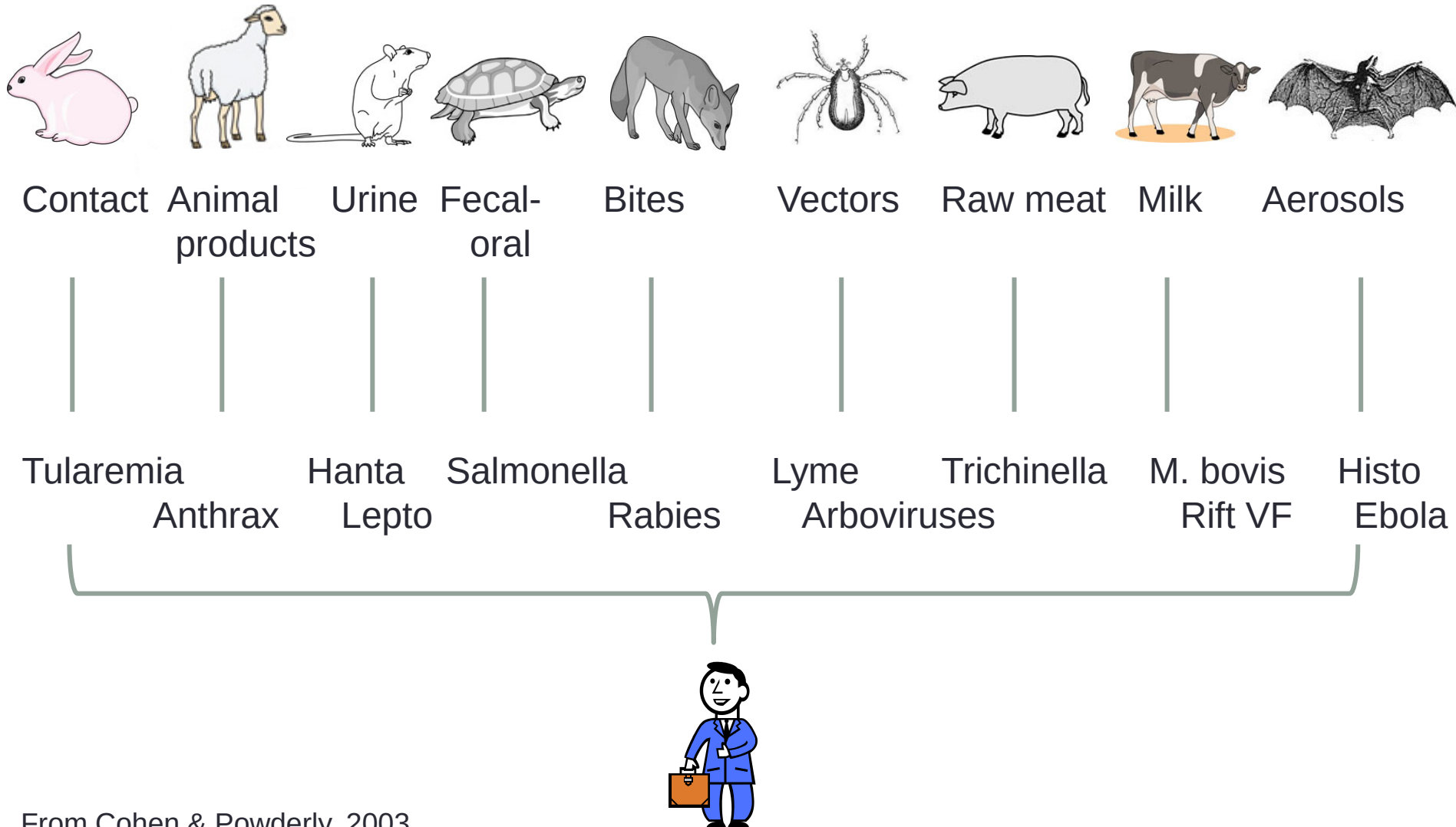


Impact of Zoonotic Diseases

- High correlation between poverty, livestock keeping, and endemic zoonoses
- 56 zoonotic diseases responsible for:
 - 2.5 billion cases of human disease/year
 - 2.7 million deaths/year
 - Reductions in livestock production

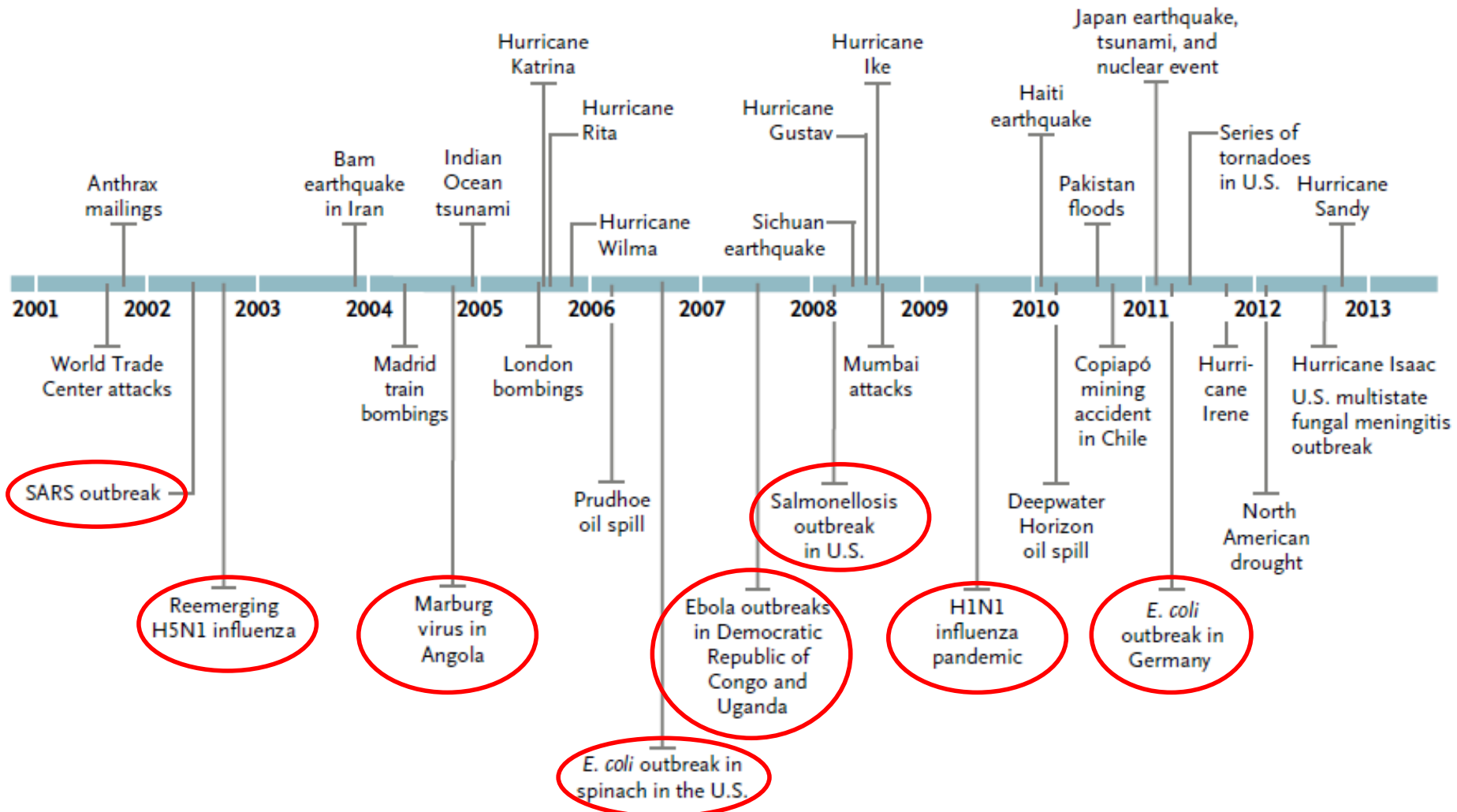
Grace D, Mutua F, Ochungo P, et al. Mapping of poverty and likely zoonoses hotspots. ILRI report to the Department of International Development, UK. Available at: mahider.ilri.org/handle/10568/21161.

Routes by which zoonoses are acquired



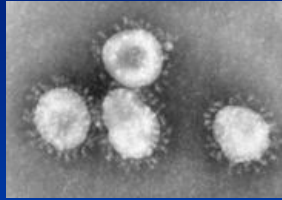
Public Health Emergencies

Lurie N et al. NEJM 2013;368:1251





SARS



NIPAH



EBOLA



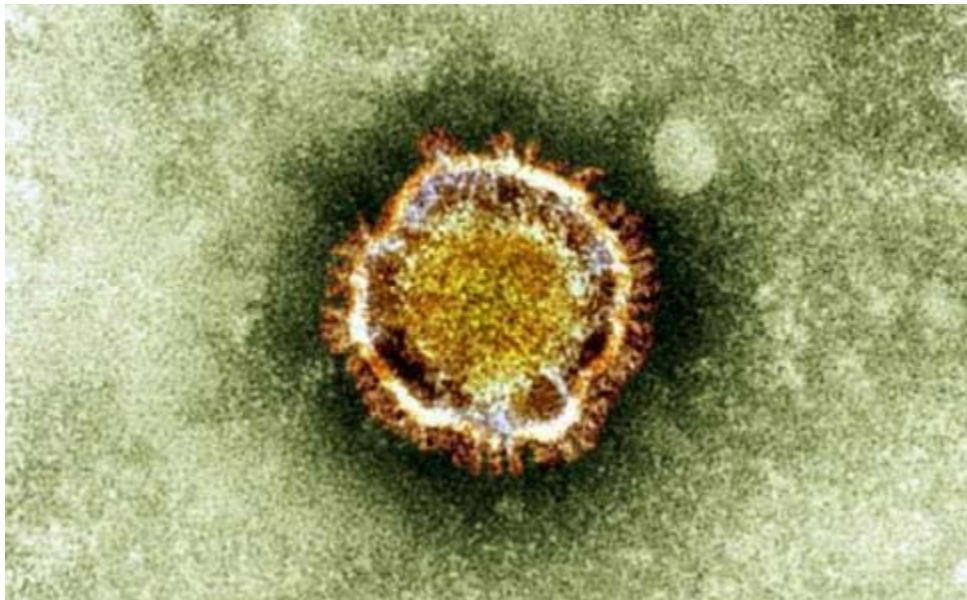
New coronavirus appears deadlier than Sars, says HKU

Mysterious coronavirus, though not less infectious, has a higher mortality rate and infects many species, Hong Kong researchers find

Emily Tsang

emily.tsang@scmp.com (<mailto:emily.tsang@scmp.com>)

Thursday, 28 March, 2013, 5:58am



- 17 confirmed cases in Middle East
- 56% CFR
- Pantropic infection
- Likely reservoir bats
- Other intermediate animal hosts

First human infections with avian influenza H7N9 virus

4 April 2013



Fourteen people in China have been infected with avian influenza H7N9 virus, leading to five deaths. This avian influenza virus has never been isolated from humans.

Influenza A viruses with the H7 hemagglutinin protein circulate among birds, and some, such as H7N2, H7N3, and H7N7, have been previously found to

Vaccines: Nexus of Human and Animal Health

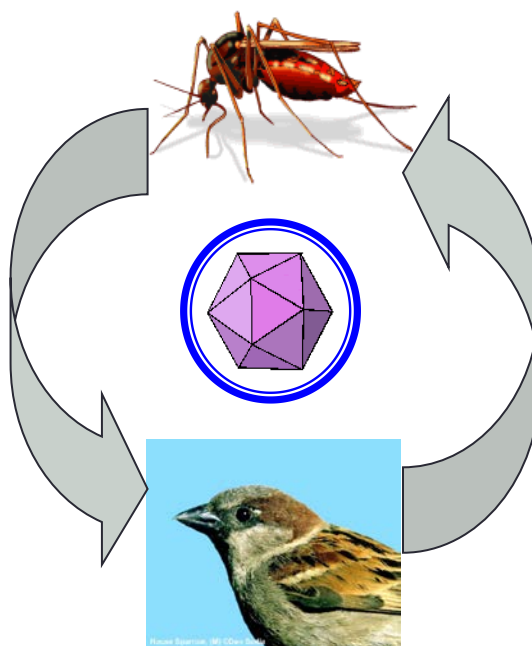
- Vaccinate humans and domesticated animals to prevent disease in both
 - Humans and domesticated animals are dead-end hosts
- Vaccinate domesticated animals to prevent disease in humans and domesticated animals
 - Diseases transmissible from domesticated animals to humans
- Vaccinate wild animals to prevent disease in humans and domesticated animals
- Vaccinate wild animals to prevent disease in wild animals
- Vaccinate humans to prevent infection of domesticated animals
- Vaccinate domestic animals to prevent disease in domestic animals and promote human health, well-being, and the economy

Role of Vaccines in Disease Prevention

Vaccinate humans and domesticated animals to prevent disease in both

- West Nile
- Japanese encephalitis
- Lyme disease
- Q fever

West Nile Virus: Transmission Cycle



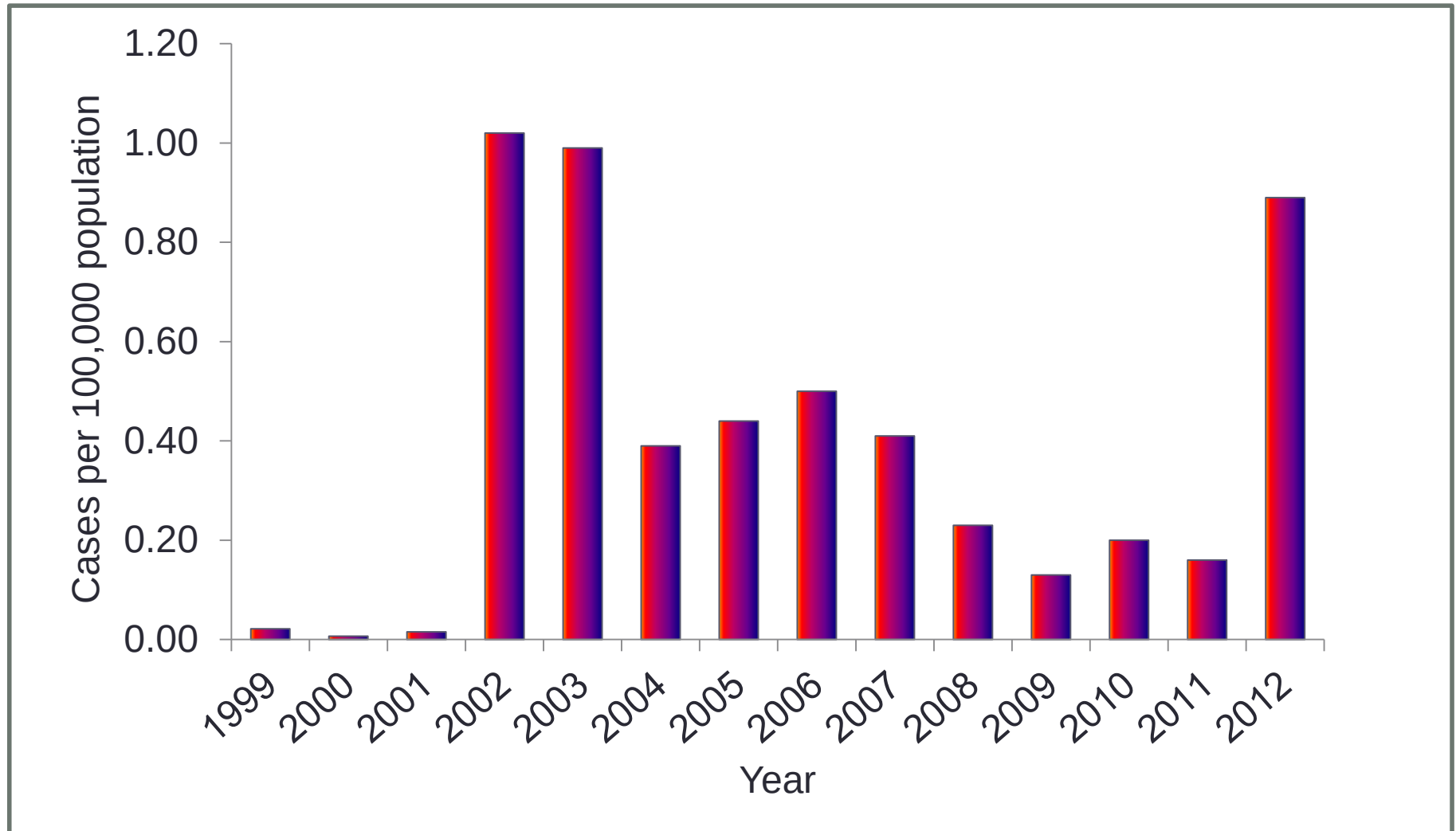
Epidemic



Epizootic



Incidence WN Neuroinvasive Disease, United States, 1999-2012



West Nile in Equids

- Many outbreaks in Africa and Europe
- Over 25,000 cases reported in US since 1999
- Since 1999, 694 equids affected per 100,000 (vs. 10 per 100,000 humans)
- 33% CFR
- 40% of surviving animals with sequelae
- Large economic impact
- Vaccines for horses marketed since 2001
- Marked reduction in cases due to vaccine and natural immunity



West Nile Vaccines

Human
vaccines

Baxter
Intercell
Crucell
Inviragen
NIH
Vical

Horse
vaccines

Ft Dodge
Merial
Novartis

Human &
horse
vaccines

Acambis
(licensed to
Intervet for
horses and
sanofi for
humans)

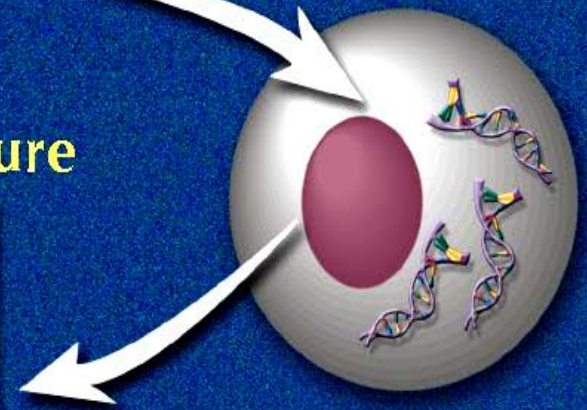
Construction of Chimeric Virus

Full length cDNA → SP6 transcribe to RNA

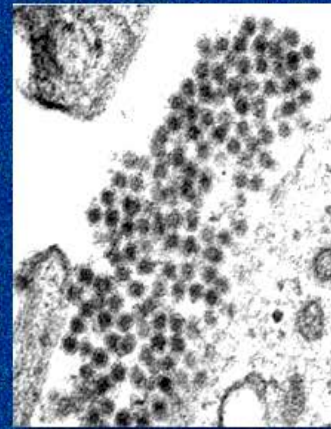
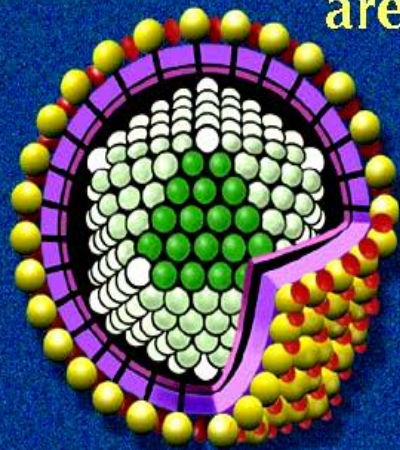
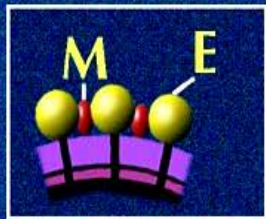


Transfect RNA
(Electroporation)

Grow virus
in Vero cell culture



Envelope
proteins
are WN

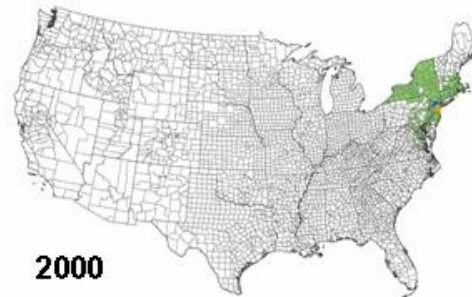


Replicative 'engine' is YF 17D

Chronology of Development of ChimeriVax™-WN

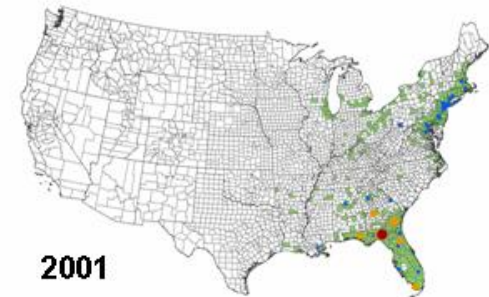


- YF 17D vector with WN99 transgene constructed (4Q99)



- Attenuating mutations inserted
- Preclinical studies (mice)

Year 1

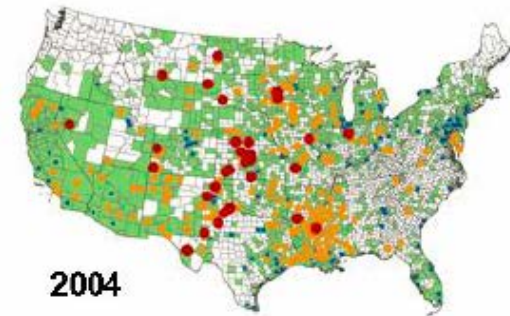
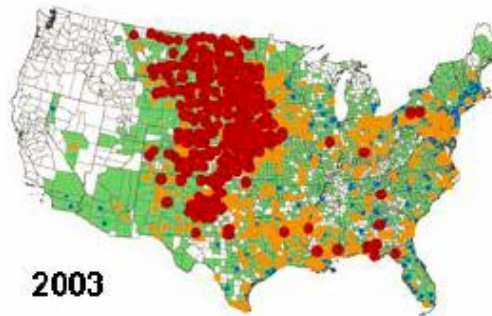
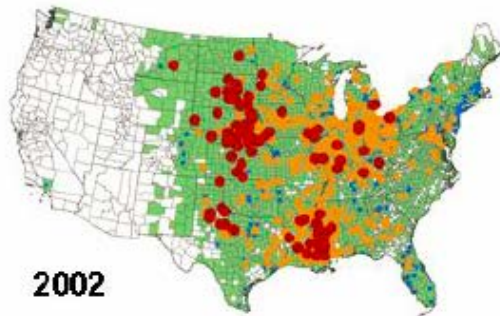


- GMP manufacturing
 - Preclinical studies (monkeys)
 - Horse immunization, challenge
 - Virus-vector studies
- Year 2

• .01-9.99 • 10-99.99 • >=100

■ Any WNV activity (birds, mosquitoes, horses, humans)

Chronology of Development of ChimeriVax™-WN



- GMP vaccine clinical trial material
- GLP Toxicology
- Intervet licenses horse vaccine

Year 3

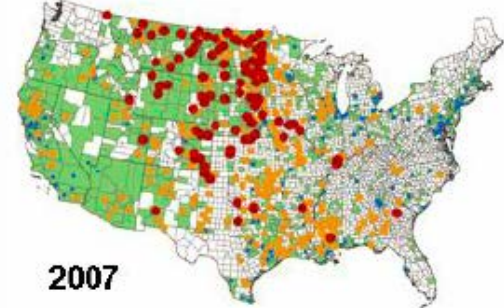
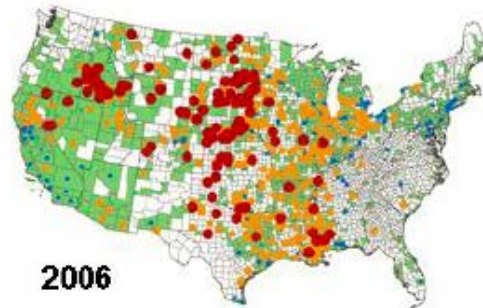
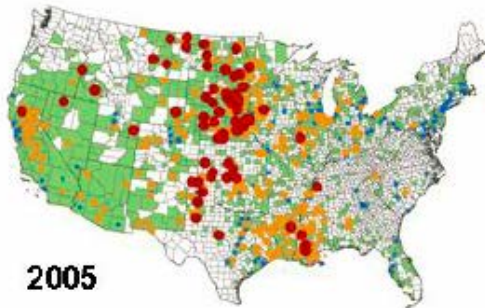
- IND filed
- Phase 1 initiated

Year 4

- Phase 1 completed
- Vaccine re-engineered & plaque purified
- Preclinical re-evaluation (hamsters, NHP)
- Repeat GLP Tox

Year 5

Chronology of Development of ChimeriVax™-WN



- IND amended
- Phase 2 initiated

Year 6

- Phase 2 completed
- PreveNile®



Intervet Introduces PreveNile™ West Nile Virus Vaccine

Horse Vaccines

Comparison of WN vaccines in horses

TABLE 1. Summarization of case criteria for vaccinated and control horses after intrathecal WNV challenge

Vaccine group	No. of horses with criterion ^a				
	Clinical signs	Fever ^e	Death ^f	Virus isolation	Histopathic lesions
ChimeriVax-WN	0/6	0/6	0/6	0/6	1/6 ^h
Recombitek® ¹	1/5 ^b	1/5	0/5	0/5	1/5 ^h
Innovator® ²	4/6 ^c	1/6	0/6	0/6	3/6 ^h
Controls	6/6 ^d	3/6	6/6	6/6	6/6 ^g

¹ Canarypox vectored WN (Merial) 2 doses

² Inactivated whole virion (Ft Dodge) 2 doses

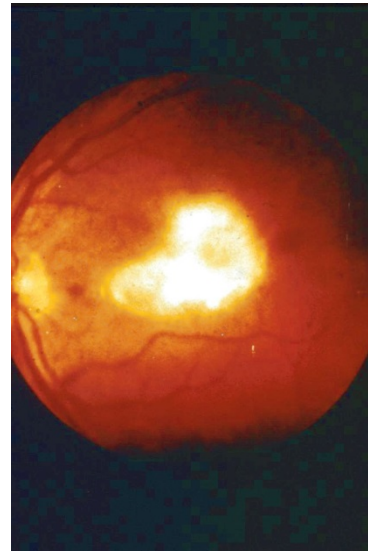
Role of Vaccines in Disease Prevention

Vaccinate domesticated animals to prevent disease in humans and domesticated animals

- Rabies
- Avian influenza
- Rift Valley fever
- Brucellosis
- Japanese encephalitis
- Venezuelan equine encephalitis
- Hendra and Nipah
- Q fever
- *Bartonella henselae*
- Highly effective
- In use, ?effective
- Theoretical
- Strong evidence for
- Largely impractical
- Field evidence for
- Theoretical
- Poorly effective
- Withdrawn (poor sales)

Rift Valley Fever

- Mosquito-borne *Phlebovirus* disease of humans and livestock
- Major outbreaks in Africa, Middle East
- Also transmissible by contact and aerosol from livestock to humans
- Hemorrhagic fever
- Bioterrorism threat agent
- No approved vaccines for humans
- Older vaccines for livestock poorly effective or have significant side effects (abortion in ewes)



RVFV IN DOMESTIC ANIMALS

- ◆ SHEEP: ~20-30% mortality, abortion
- ◆ CATTLE: ~10-15% mortality, abortion
- ◆ GOATS: ~5-10% mortality, abortion
- ◆ CAMELS: survive, low viremia, ?abortion
- ◆ WATER BUFFALO: survive, low viremia
- ◆ AFRICAN BUFFALO: survive, abortion
- ◆ OTHER AFRICAN UNGULATES: Antibody only

Mortality depends on breeds, other health and stress factors

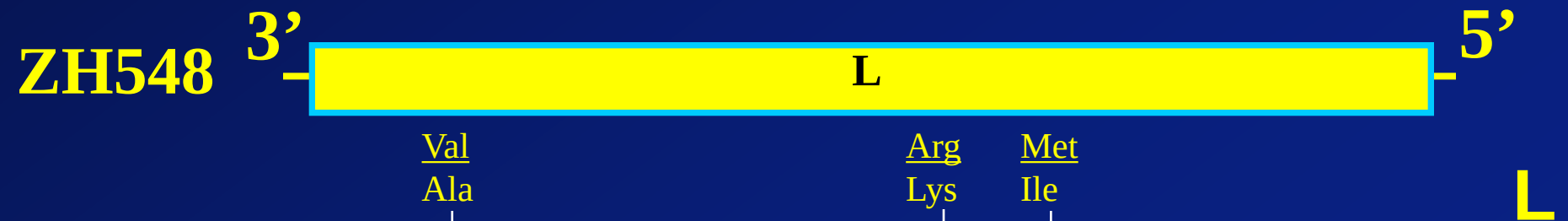
Infections of adult animals end in death if viremia high.

Immature animals have higher viremias and mortality.

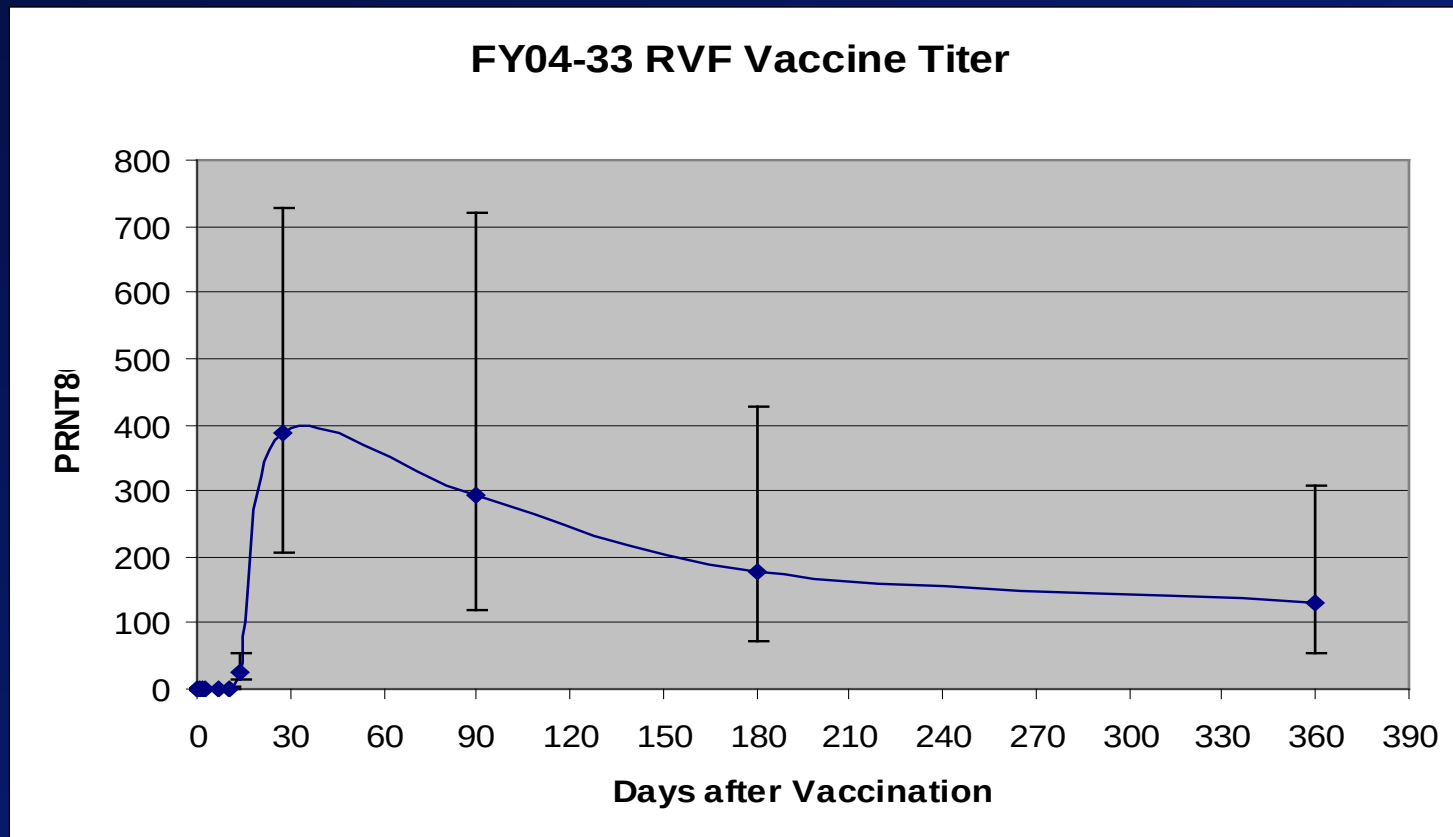
Abortion seems to be a complication of most viremic infections.

MP-12 RVF VACCINE

- ◆ Developed by USAMRIID for humans
- ◆ ZH-548 strain passaged in the presence of 5FU in mid-1980's
- ◆ 12th mutagen cycle selected for development and passed all FDA-required preclinical testing including Rhesus neurovirulence, reversion in lambs
- ◆ Tested in 62 humans at USAMRIID
- ◆ Single dose safe and highly immunogenic
- ◆ Safe, immunogenic and protective vs challenge in livestock including pregnant ewes
- ◆ Licensed to Pfizer Animal Health for protection of cattle and sheep



Neutralizing antibody response to RVF MP12 vaccine in humans





Contents lists available at SciVerse ScienceDirect

Vaccine 31 (2013) 559–565

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



Safety and immunogenicity of recombinant Rift Valley fever MP-12 vaccine candidates in sheep[☆]

John C. Morrill^{a,*}, Richard C. Laughlin^b, Nandadeva Lokugamage^a, Roberta Pugh^b, Elena Sbrana^a, William J. Weise^b, L. Garry Adams^b, Shinji Makino^a, C.J. Peters^a

^a Department of Microbiology and Immunology, The University of Texas Medical Branch at Galveston, 301 University Blvd., Room 4.142B MRB, Galveston, TX 77555-1019, USA

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Red=infected

Virus activity



ELSEVIER

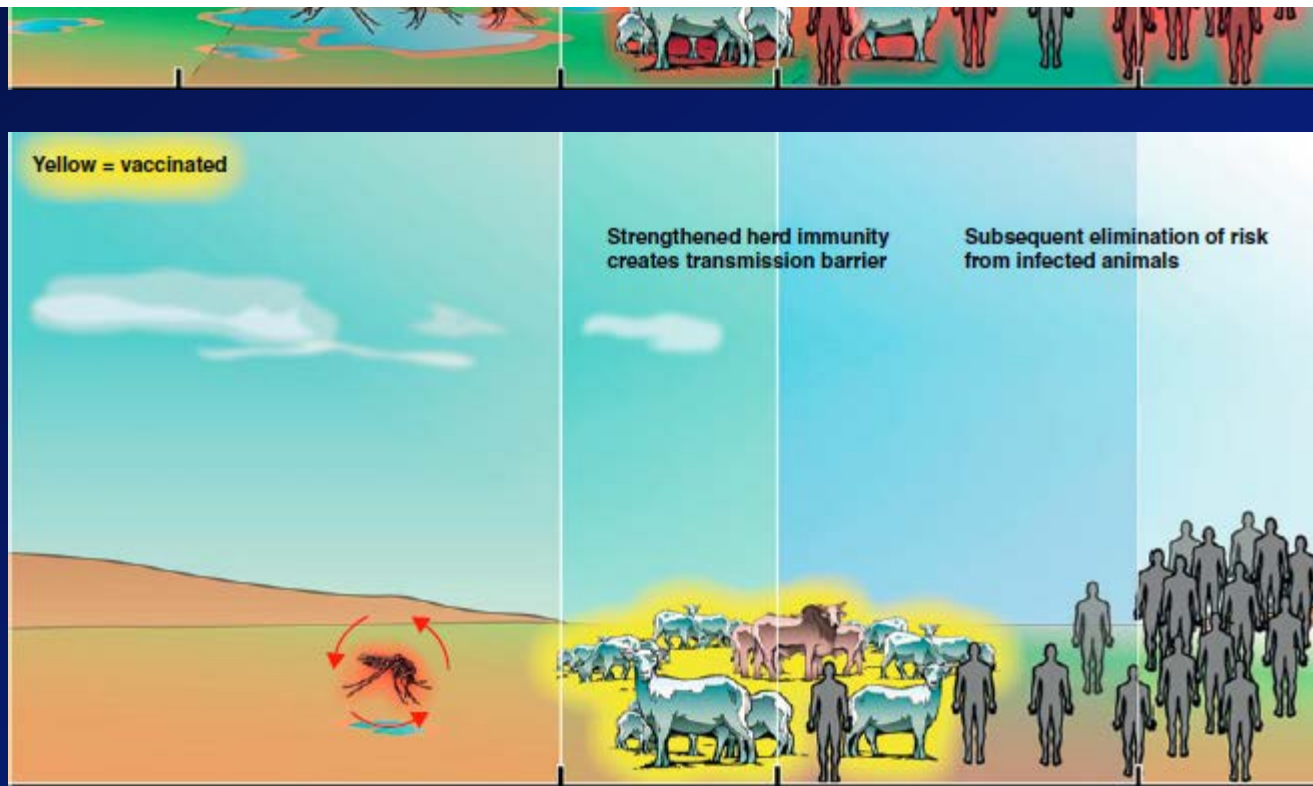
Available online at www.sciencedirect.com

Current Opinion in Virology 2012, 2:315–323

Current Opinion in
Virology

Breaking the chain: Rift Valley fever virus control via livestock vaccination[☆]

Brian H Bird and Stuart T Nichol



Role of Vaccines in Disease Prevention

Vaccinate domesticated animals to prevent disease in humans and domesticated animals

- Rabies
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- Brucellosis
- Japanese encephalitis
- Venezuelan equine encephalitis
- Hendra and Nipah
- Q fever
- *Bartonella henselae*

Hendra and Nipa Viruses

(Henipavirus, *Paramyxoviridae*)

Hendra

- Australia
- Bat-bat enzootic cycle
- Severe (lethal) respiratory and neurological illness
- Bat→horse→human
- Vets refusing to treat sick horses and exiting practice

Nipah

- SE Asia
- Bat-bat enzootic cycle
- Severe (lethal) encephalitis in humans and swine
- Bat → human via saliva contaminated food
- Bat→ Swine → human
- Nosocomial person-person

VIROLOGY

Science 2012;337:651-2

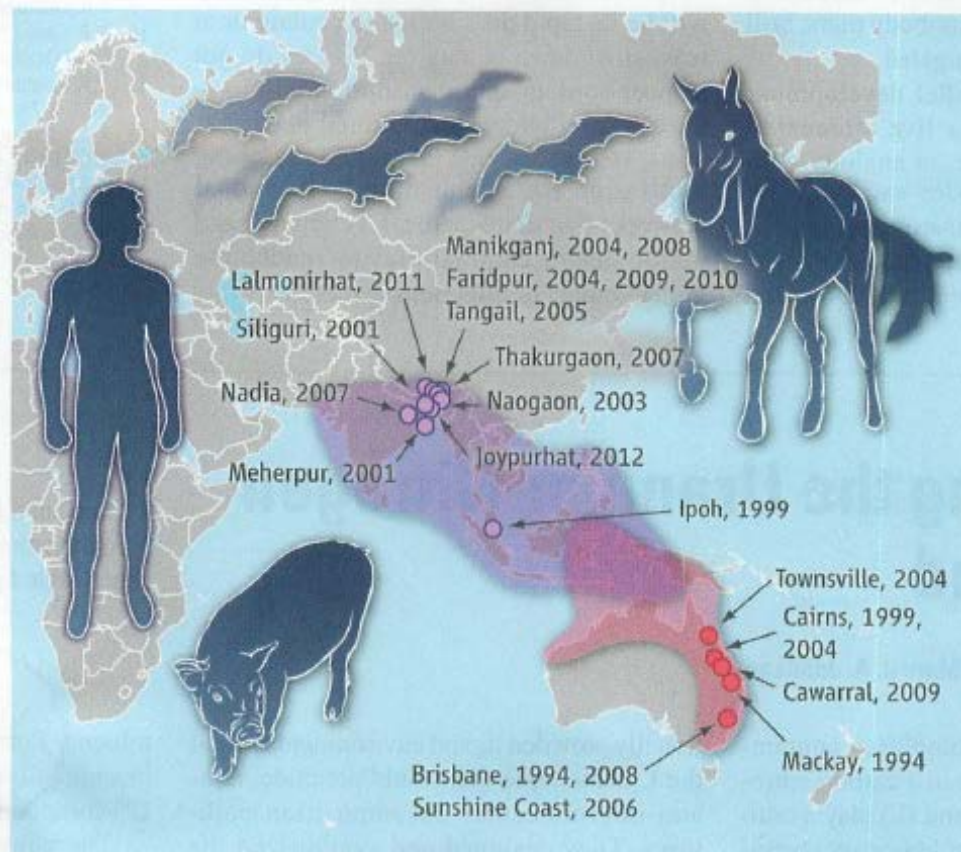
A Henipavirus Vaccine in Sight

Veronika von Messling¹ and Roberto Cattaneo²

A candidate vaccine against Nipah and Hendra viruses, recently emerging zoonotic threats, looks promising.

Nipah virus emerged in pig farms in Malaysia in the 1990s. Outbreaks were difficult to miss: The cough of infected animals could be heard 1 mile away from the farms. It soon became clear that Nipah is an important zoonotic threat. Fruit bats can transmit the virus to many mammals, including humans (1). The frequency of recurring Nipah virus outbreaks is on the rise (2). These outbreaks, which often affect Bangladesh or India, have caused more than 300 human fatalities since 1999 often due to encephalitis.

A related virus named Hendra emerged in 1994 in Australia. Also carried by bats, Hendra causes fatal disease, especially in humans and horses (3). Together, Hendra and Nipah form the new *Henipavirus* genus (2) of the Paramyxoviridae, a family of

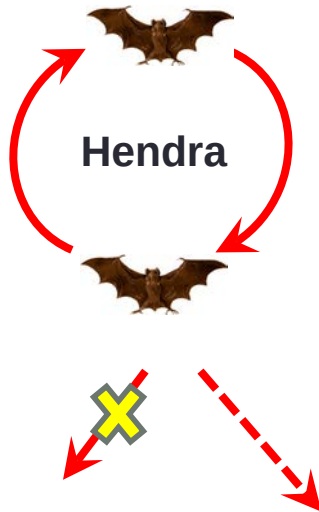


Outbreak. Recent and recurring outbreaks of Nipah (blue) and Hendra (red) viruses in human, bat, pig, and horse have been observed in Southeast Asia, India, and Australia (3, 15).

ited market may not attract large pharmaceutical companies provides a unique opportunity for local leadership in vaccine development.

Producing the vaccine first for veterinary use, as planned in Australia for Hendra protection (8), may reduce infection in domestic animals and thereby the spread to humans. Such a subunit vaccine may be a primer for an integrated approach to control airborne zoonotic diseases by targeting the animal reservoir, emulating strategies successfully used to reduce the disease burden associated

Hendra and Nipah Vaccine Interventions



Vaccinate horses to prevent horse & human cases



Vaccinate pigs to prevent pig & human cases

Hendra and Nipah Vaccines

Virus	Vaccine type	Status
Hendra	Subunit G protein	Licensed Hendra vaccine for horses
Nipah	Canarypox vector	Immunogenic, protective in swine
	VLPs (G, F and M proteins)	Preclinical (mice)
	Subunit G protein	Preclinical (mice)
Both	VEE replicon	Preclinical (mice)
	VSV vector	Preclinical (mice)



MEDIA RELEASE

EMBARGO LIFTS 12.01AM AEDT, THURSDAY 01 NOVEMBER 2012

Vaccine arrives to boost the fight against deadly Hendra virus

*International collaborative partnership develops vaccine to combat one of
Australia's most lethal viruses*

Brisbane, Australia – 01 November 2012: From today, Australian horse owners and the equine industry will receive an important boost in their fight against the deadly Hendra virus with the introduction of Equivac[®] HeV vaccine. Available under permit from accredited veterinarians, the vaccine will also assist in breaking the cycle of transmission that puts humans at risk of contracting this potentially lethal virus.

Role of Vaccines in Disease Prevention

Vaccinate wild animals to prevent disease in humans and domesticated animals

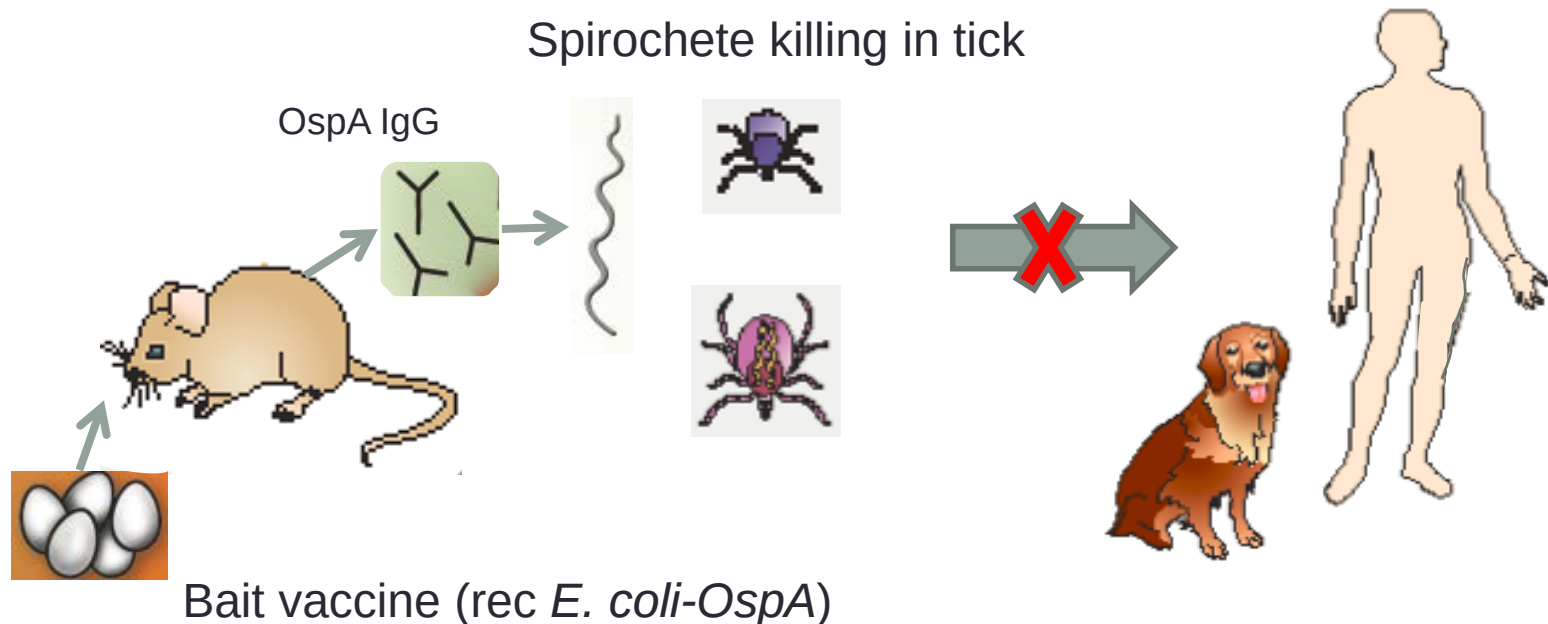
- Rabies
- *Mycobacterium bovis*
- *Brucella abortus*
- Lyme disease
- Widely used, effective
- Field trials, effective
- Targeted use
- In development

Immunization of field mice to prevent LD in humans and dogs

Oral vaccine that breaks the transmission cycle of the Lyme disease spirochete can be delivered via bait

Maria J.C. Gomes-Solecki^{a,b,*}, Dustin R. Brisson^c, Raymond J. Dattwyler^{a,b}

Vaccine 24 (2006) 4440–4449



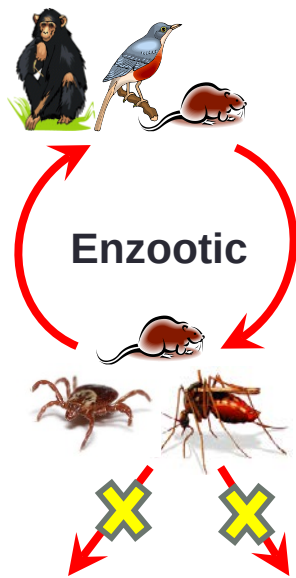


LymeShield™

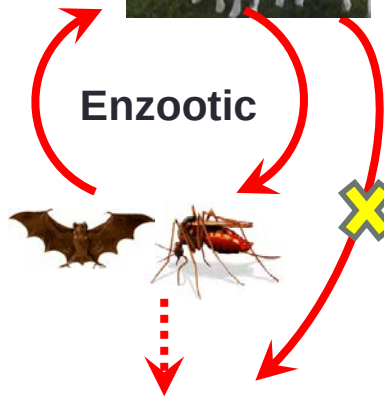
US BIOLOGIC is implementing an innovative solution that prevents the transmission of Lyme disease.



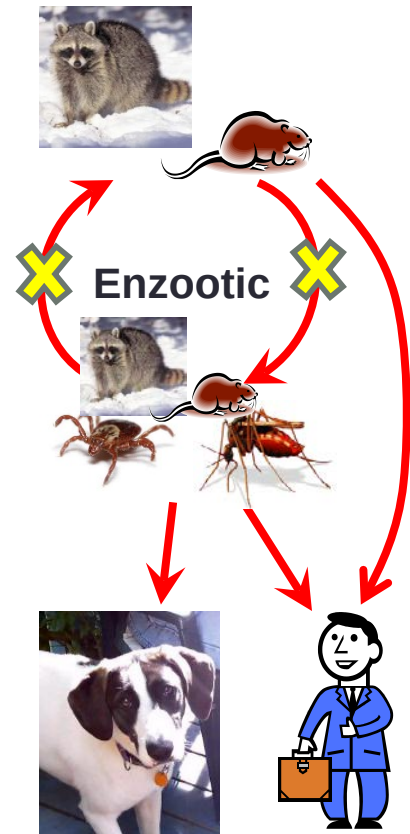
Patterns of Disease Transmission and Vaccine Interventions



Vaccinate humans and affected domestic animals



Vaccinate domestic animals to protect humans



Vaccinate wild animals to protect humans and domestic animals

Conclusions

- Integrated approach required to the prevention and control of infectious diseases of humans and animals
- Coordination across human and animal health divisions in biopharma
- Dual use technologies spanning human and animal health
- Prove and implement immunization of livestock for preventing zoonotic infection
- Novel methods for immunization of wildlife

Thank you!