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
Number of Visits per Month

Visits per month

2008 2009 2010 2011 2012 2013
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 with public health practitioners in 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

Routes by which zoonoses are acquired

From Cohen & Powderly, 2003
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

Thursday, 28 March, 2013, 5:58am

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

[Diagram showing the transmission cycle of West Nile Virus with images of birds and horses]
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 $\rightarrow$ SP6 transcribe to RNA

5' YF WN YF 3'

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**

- 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®

2005

2006

2007

Intervet Introduces PreveNile™ West Nile Virus Vaccine

Horse Vaccines
Comparison of WN vaccines in horses

<table>
<thead>
<tr>
<th>Vaccine group</th>
<th>Clinical signs</th>
<th>Fever</th>
<th>Death</th>
<th>Virus isolation</th>
<th>Histopathic lesions</th>
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<tbody>
<tr>
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<td>0/6</td>
<td>0/6</td>
<td>1/6&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>3/6</td>
<td>6/6</td>
<td>6/6</td>
<td>6/6&lt;sup&gt;g&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Cases of horses with criteria for vaccinated and control horses after intrathecal WNV challenge.

<sup>b</sup> Canarypox vectored WN (Merial) 2 doses

<sup>c</sup> 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
♦ CAMEL: 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

![FY04-33 RVF Vaccine Titer Graph](image)
Safety and immunogenicity of recombinant Rift Valley fever MP-12 vaccine candidates in sheep

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

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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
- Avian influenza
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- Brucellosis
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- 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
A Henipavirus Vaccine in Sight

Veronika von Messling¹ and Roberto Cattaneo²

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 negative-strand RNA viruses of coronaviruses, paramyxoviruses, and others.

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).
Hendra and Nipah Vaccine Interventions

Hendra

Vaccinate horses to prevent horse & human cases

Nipah

Vaccinate pigs to prevent pig & human cases
# Hendra and Nipah Vaccines

<table>
<thead>
<tr>
<th>Virus</th>
<th>Vaccine type</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Hendra</td>
<td>Subunit G protein</td>
<td>Licensed Hendra vaccine for horses</td>
</tr>
<tr>
<td></td>
<td>Canarypox vector</td>
<td>Immunogenic, protective in swine</td>
</tr>
<tr>
<td></td>
<td>VLPs (G, F and M proteins)</td>
<td>Preclinical (mice)</td>
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<tr>
<td></td>
<td>Subunit G protein</td>
<td>Preclinical (mice)</td>
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<tr>
<td>Both</td>
<td>VEE replicon</td>
<td>Preclinical (mice)</td>
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<tr>
<td></td>
<td>VSV vector</td>
<td>Preclinical (mice)</td>
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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

Spirochete killing in tick

Bait vaccine (rec E. coli-OspA)
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!