



Update on Equine Respiratory Disease

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Agenda

- ▶ Equine herpesvirus-1 & (EHV-4)
 - Overview of current outbreak in cutting horses
 - EHV facts
 - EHV protection
- ▶ Equine Influenza (EIV facts and protection)
- ▶ Respiratory disease (bacterial)
- ▶ Therapeutic intervention (update on antibiotics)
- ▶ Questions



How common is acute infectious upper respiratory disease in horses?

A National Estimate of Acute Infectious Upper Respiratory Disease (IURD) and Risk Factors Associated with Infection for Horses in the United States During 1998-1999

Diane K. Gross, DVM; Paul S. Morley, DVM, PhD, Diplomate ACVIM; et al.
AAEP Proceedings, vol 46, 2000



How common is acute infectious upper respiratory disease in horses?

- ▶ To determine the rate of undifferentiated IURD (+ strangles) in horses in the US
- ▶ NAHMS- 1034 operations with 3+ resident horses (racetracks not included)
- ▶ Signs; cough, nasal discharge, fever, depression, anorexia...
- ▶ Results; 1.5 ± 0.2 horses developed IURD out of every 100 horses.
- ▶ Relied on owners/trainers to report occurrence

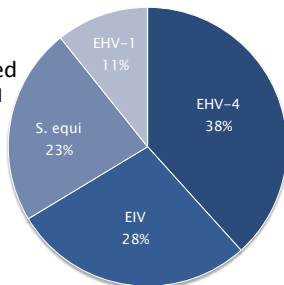
Surveillance programme for important equine infectious respiratory pathogens in the USA

N. Pusterla, P. H. Kass, S. Mapes, C. Johnson, D. C. Barnett, W. Vaala, C. Gutierrez, R. McDaniel, B. Whitehead, J. Manning

Downloaded from veterinaryrecord.bmj.com on June 29, 2011

US Equine Respiratory Pathogens

- ▶ 24 month study
- ▶ 761 samples submitted
 - fever, coughing or nasal discharge
- ▶ 201/761 (26.4%)
 - PCR positive for one or more pathogens
 - EHV-4 (82 cases)
 - EIV (60 cases)
 - S. equi (49 cases)
 - EHV-1 (23 cases)



Voluntary Surveillance Program for Important Equine Infectious Respiratory Pathogens in the United States
 Nicola Pusterla, DVM, Diplomate ACVIM, et al.
 2010 AAEP Proceedings

Equine Herpes Virus



- ▶ Commonly affects younger horses - weaning to 2-3 years
- ▶ Spread via inhalation & direct contact (ubiquitous in equine populations)
- ▶ Natural immunity is short lived (60 days)
- ▶ EHV-1 & 4 primary concern to horses- latent in lymph nodes of respiratory tract (EHV1) and trigeminal nerve ganglia (EHV4)
- ▶ Once infected, they carry the virus for life
- ▶ EHV 2 & 5 new players?

Differences between EHV-1 & EHV-4

- ▶ EHV-1 and EHV-4 are 70% genetically similar
- ▶ EHV-1
 - Upper respiratory
 - Abortion
 - Newborn Still Birth
 - Neurological
 - Mainly D₇₅₂ point mutated EHV-1 strain
- ▶ EHV-4
 - Mainly Upper Respiratory



EHV Risk factors

- Horses under stressful situations
- Horses in large groups



Slide Dr. Julie Wilson

EHV: Recognizing the Signs

- ▶ Fever and/or cough
- ▶ Nasal discharge
- ▶ Mild Limb edema
- ▶ Poor appetite and depression
- ▶ Abortion
- ▶ Poor anal / tail tone
- ▶ Inability to retract penis
- ▶ Ataxia
- ▶ Bladder paresis
- ▶ Fecal incontinence
- ▶ Muscle fasciculation
- ▶ Increased respiratory rate
 - (> 14 b/min)



Dr. Julie Wilson- Slide

Equine Herpes Virus (EHV)

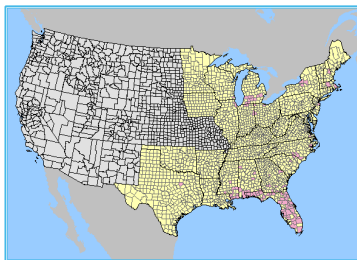
–Utah outbreak summary

- ▶ 421 primary exposures
 - 1685 secondary/tertiary exposures
- ▶ 88 confirmed EHV-1 or EHM cases
 - 58 from primary exposures
 - 30 from secondary/tertiary exposures
- ▶ 12 dead or euthanized
 - 10 from primary exposures
 - 2 from secondary exposures

EEE–though December 28, 2010

231 cases

- 1 – Maryland
- 1 – New Jersey
- 1 – Virginia
- 10 – New York
- 4 – Massachusetts
- 1 – New Hampshire
- 57 – Michigan
- 4 – Ohio
- 8 – Alabama
- 20 – Mississippi
- 93 – Florida
- 24 – GA, IL, IN, TX, WI



http://diseasemaps.usgs.gov/eee_us_veterinary.html

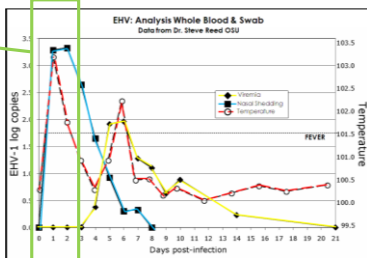
EHV: To test or not to test.....

- ▶ Normally would reserve testing for individuals showing clinical signs
 - Non-clinical horses have been documented to shed EHV-1 via respiratory secretions
- ▶ However, there is benefit to testing clinically normal individuals if there has been EHV exposure
 - If individual has 2 consecutive negative tests, 7-10 days apart, the horse can be considered free of disease

Submit Blood and Nasal Swab-PCR

Viral presence (blood vs. nasal swab) will vary depending on stage of disease

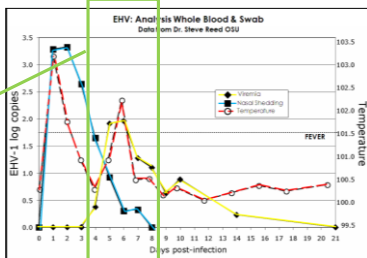
- ▶ Early in disease
 - Nasal swab (+)
 - Blood (-)
- ▶ Mid-disease
 - Nasal swab (+)
 - Blood (+)
- ▶ Late in disease
 - Nasal swab (+/-)
 - Blood (+)



Submit Blood and Nasal Swab-PCR

Viral presence (blood vs. nasal swab) will vary depending on stage of disease

- ▶ Early in disease
 - Nasal swab (+)
 - Blood (-)
- ▶ Mid-disease
 - Nasal swab (+)
 - Blood (+)
- ▶ Late in disease
 - Nasal swab (+/-)
 - Blood (+)



Equine Herpesvirus

- ▶ There is no vaccine labeled for the neurologic form of EHV-1, but.....
 - Will help establish a level of protection via improved herd immunity
 - Vaccination can reduce the level of viral shedding during an outbreak
 - Stimulates mucosal antibodies
 - Very short-lived phase of immunity
 - Two vaccines have been shown to suppress viremia in experimental challenge with D₇₅₂ strain

EHV Challenge Study

Colorado State University

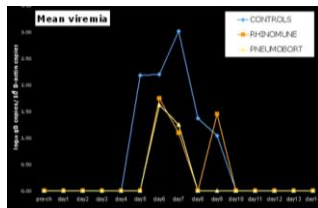
- ▶ Evaluate immunity
 - challenge with Findlay 03, 5×10^7 pfu
- ▶ Blinded, randomized challenge trial
- ▶ 8 ponies in each group
- ▶ Treatments:
 - Pneumabort K
 - Rhinomune
 - Placebo



Control of EHV-1 viremia and nasal shedding by commercial vaccines
 L.S. Goehring, B. Wagner, R. Bigbie, S.B. Hussey, S. Rao, P.S. Morley, D.P. Lunn
Vaccine, 28 (2010) 5203–5211

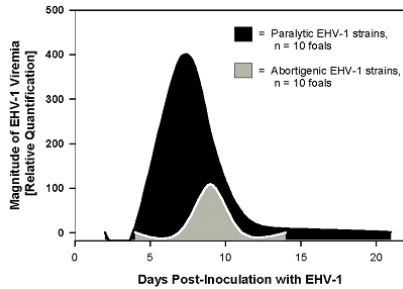
Viremia post-challenge with Findley OH03

- ▶ Control
 - 6/8 viremic
 - 13 total viremic days
- ▶ Rhinomune
 - 4/8 viremic
 - 5 total viremic days
- ▶ Pneumabort K
 - 2/8 viremic
 - 3 total viremic days



Control of EHV-1 viremia and nasal shedding by commercial vaccines, Goehring, et al
Vaccine 28 (2010) 5203–5211

Hypervirulence of EHV-1 Neurologic Strain



New EHV-1 study-Cornell

Wagner, B., Wimer, C., Freer, H., Osterrieder, N., Erb, H.N.

Infection of peripheral blood mononuclear cells with neuropathogenic equine herpesvirus type-1 strain Ab4 reveals intact interferon- induction and induces suppression of anti-inflammatory interleukin-10 responses in comparison to other viral strains



Veterinary Immunology and Immunopathology (2010), doi:10.1016/j.vetimm.2011.06.032

- ▶ RaL11 (respiratory strain)
- ▶ NY03 (abortogenic strain)
- ▶ Ab4 (neurotropic strain)

Equine Influenza

- ▶ Influenza virus
 - (A1 & A2)
- ▶ Highly contagious
 - Horses inhale virus
- ▶ Particularly prevalent in young horses
 - Generally seen in horses 2 years of age and older
- ▶ Major concern in areas of high horse population density
- ▶ Disease increases risk of secondary bacterial infection



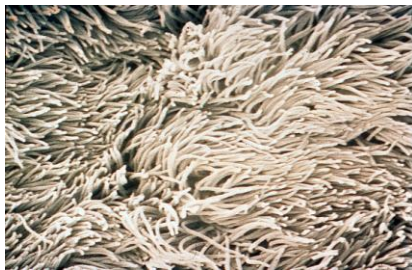
Equine Influenza

- ▶ Infects & replicates in ciliated epithelial cells in upper & lower respiratory tract
- ▶ Results in de-ciliation of large areas w/in 4 to 6 days
- ▶ Incubation period= 1 to 3 days
- ▶ Fever, harsh dry cough= release of large amounts of virus
- ▶ Serous...mucopurulent nasal discharge, myalgia, inappetance, enlarged Inn.



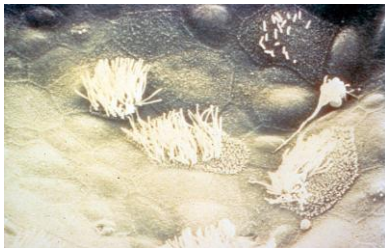
Normal trachea

▶ Image courtesy of Dr. Issel and Gluck Center



Trachea after cilia destroyed by flu

▶ Image courtesy of Dr. Issel and Gluck Center

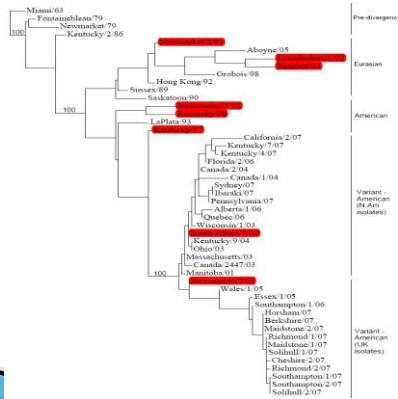


Immunological Protection from EIV- Summary

- ▶ Dependent on different immune mechanisms at both local and systemic level
- ▶ Systemically- IgG_a and IgG_b responses associated w/ protection and likely depends on an INF γ mediated Th1 immune response
- ▶ Mucosally- production of IgA critical and typically depends on Th2 immune response

Vaccination

- ▶ Primary goals; (1) to reduce clinical signs, (2) shorten convalescent period, (3) reduce shedding
- ▶ Ideally; provide long-term immunity, efficient memory response & cross protection
- ▶ Vaccine efficacy= clinical protection, absence of pyrexia, cough and discharge
- ▶ Virological protection= absence of virus in secretions



Relatedness of Equine Influenza Virus (EIV) A/Equine/Kentucky/97 with Recent Circulating EIV and Canine Influenza Virus (CIV) Based on Comparison of Hemagglutinin Gene Sequences

Accession # of EIV A/Equine/Kentucky/97: AF197249
 Accession # of EIV A/Equine/Kentucky/02: DQ124191
 Accession # of EIV A/Equine/Ohio/03: DQ124192
 Accession # of CIV A/Canine/Florida/03: DQ124157
 Accession # of CIV A/Canine/Florida/04: DQ124190
 Accession # of CIV A/Canine/Texas/04: DQ124196

Virus	% Homology
EIV A/Equine/Kentucky/02	99.4
EIV A/Equine/Ohio/03	98.8
CIV A/Canine/Florida/03	98.4
CIV A/Canine/Florida/04	98.2
CIV A/Canine/Texas/04	98.0

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	Intervet	Calveza	Prestige	Fit. start	Recombinet /Bio
Manufacturer	Pfizer	Boehringer Ingelheim	Intervet	Intervet	Merial
Influenza Strain	Kentucky 97	Kentucky 95 Newmarket 93 Ohio 03	Kentucky 93 O'Warrior Newmarket 93 Kentucky 02	Kentucky 91	Kentucky 94 Newmarket 93 (HA only)
Antigen Type	Killed	Killed	Killed	Modified Egg	Recombinant
Adjuvant	Metasim (Lipid)	Carbopol	Hyabegon (Carbopol)	None	Carbopol
Route of Administration	Intramuscular	Intramuscular	Intramuscular	Intranasal	Intramuscular
Combination Vaccine Available	Yes	Yes	Yes	No	No
EIV Types in combination	EHV 1 & 4	EHV 1	EHV 1 & 4	None	None
Labelled initial number of doses required	2	3	2	2	2
Challenge Studies	Yes	Yes	Yes	Yes	Yes
Influenza Strain	Kentucky 99 Kentucky 01 Ohio 03	None w/ new Calveza 03	None with new KY 02	Kentucky 91 Kentucky 98	Sussex 89 Newmarket 03
Duration of Challenge Studies	3 and 7 months	None with Calveza 03	None with KY 02	3 and 6 months	14 day (SNM0); 5 mo (Sussex 89)
Minimum Age for Vaccination	None	4 months (KY 99); 6-12 months (Sussex 89) with old Calveza	4 months	12 mo - 3 doses (Sussex 89)	4 months

Bacterial Pneumonia

Definition

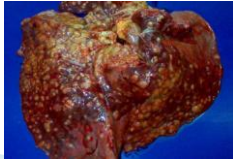
- ▶ The colonization of pulmonary parenchyma by pathogenic organisms
- ▶ Characterized by :
 - influx of inflammatory cells (esp. neutrophils)
 - tissue destruction
 - loss of function
- Disease results from interaction of 1 or more agents (virus, bacteria) in a stressed or adverse environment



BACTERIAL PNEUMONIA

PATHOGENESIS

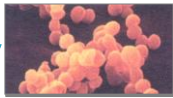
- ▶ The lower airways are normally sterile.
- ▶ Myriad defenses remove and destroy potential pathogens.
- ▶ Disease requires compromise of defense mechanisms.
- ▶ Immune defense compromised by:
 - Stress
 - Viral infections



Streptococcus zooepidemicus is the bacteria most commonly implicated in equine LRT

"Strep zoo"

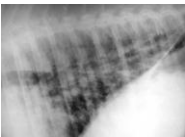
- A universal URT commensal and most frequently isolated bacteria pathogen of equine LRT Infections^{11,12}
- In the North American field efficacy study,* 373 horses had a pretreatment TTW
 - 259 animals (70%) had *Strep zoo* isolated from the pretreatment TTW
 - 208 had > 1,000 colony forming units/mL
- A 2008 Canadian study evaluated >1,300 clinical equine cases for 6 years¹³
 - *S. zooepidemicus* leading URT and LRT bacterial isolate of horses
 - Had 99% in vitro susceptibility to ceftiofur



Equine Study 1553C-60-06-208

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If initial URT infection progresses-
Abscesses, Interstitial & Pleural Disease



Treatment Modalities

- Directed at causative agent
- Directed at host's inflammatory /immune response
- Directed at enhancing pulmonary defenses/immunity
- Directed at secondary pathophysiologic processes



The Question?

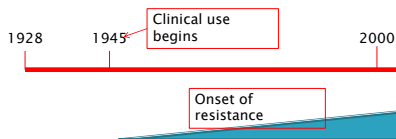
- When were Antibiotics first discovered and when were they first used?



Impact of the accelerating use of antimicrobials

Increased use corresponds to reduced efficacy, growing resistance

- **1928** – Alexander Fleming discovers penicillin
- **1945** – Widespread clinical use of antimicrobials begins; no reported resistance
- **2000** – Antimicrobial use is commonplace; non-judicious use frequently occurs; resistance is widespread



Few antimicrobials are approved for use in Horses

▶ The arsenal of injectable antimicrobials approved for systemic use in horses is limited

- Ampicillin
- Penicillin G (procaine)
- Ceftriaxone (Naxcel® sterile powder, Excede® sterile suspension)
- Trimethoprim-sulfonamide

▶ Clinicians often resort to extra-label use of human drugs or those approved for other animal species*



*The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) allows veterinarians to prescribe extra-label uses of certain approved animal drugs and approved human drugs for animals under certain conditions.

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Non-compliance is a leading cause of treatment failure

▶ Missed or late doses can result in:

- Poor therapeutic response
- Recurrence of infection
- Bacterial resistance

▶ Compliance influenced primarily by convenience of protocol

▶ Key contributors to inconvenience: multi-dose regimens, longer treatment regimen



The greater the inconvenience of a treatment protocol, the worse compliance becomes

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Beta-lactam antibiotics

- Penicillin- Procaine penicillin G, Na or K penicillin
- Synthetic penicillins- ampicillin, amoxicillin, ticarcillin
- Cephalosporins-
 - First generation- cefazolin, cephalexin
 - Third generation- ceftiofur, ceftazidime
 - Fourth generation- cefepime
 - all have extended gm (-) activity
 - increased resistance to B-lactamase org.
- Most infections in horses caused by B-hemolytic strep. (uniformly susceptible to penicillins).

What's New In Antibiotic Therapy In Horses

EXCEDE®
A New Sustained-Release Injectable
Antibiotic for Horses



EXCEDE (ceftiofur crystalline free acid) Sterile Suspension: An equine-approved antimicrobial

Indication - Pfizer recently received FDA approval for use of EXCEDE (ceftiofur crystalline free acid) Sterile Suspension in horses for the treatment of LRT disease caused by susceptible strains of *Streptococcus equi*/ssp. *Zooepidemicus*.

Dosage and administration - Two IM injections at 6.6 mg/kg (3.0 mg/lb) 4 days apart. Therapeutic drug concentrations are maintained for a total of 10 days from initiation of treatment.

Dose-volume equivalent - Administered at 1.5 mL per 100 lbs bodyweight, with a maximum dose of 20 mL per injection site (≤10 mL per site is recommended).



EXCEDE is available in a ready-to-use 100 mL vial.

When administered by an attending veterinarian, 2 doses of EXCEDE provide a full course of therapy and treatment compliance is assured

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The unique EXCEDE formulation

Ceftiofur crystalline free acid (CCFA) is incorporated into a special oil base formulation



This formulation creates a depot of CCFA *in situ*



This depot gradually releases CCFA from injection site, thereby creating the sustained release effect



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Per Os in the Hoss

- ▶ Gastric pH very variable (1.0 to 7.5) with periods of spontaneous alkalinization...
- ▶ Volume of fluids in GI tract; humans=5-10L per day total; horses=24L/day + 1.6L/hr of gastric, duodenal & pancreatic secretions
- ▶ Feeding- changes pH, alters gastric emptying and GI motility, > secretion of bile
- ▶ < oral absorptions noted with sulfa's, doxycycline, rifampin, erythromycin



Trimethoprim-Sulfonamide

- Considered -cidal at high concentrations.
- Lipophilic and penetrates tissues well (CNS).
- Broad-spectrum coverage (gm (+), (-) and some anaerobes.
- Interfere with synthesis of folic acid from PABA with sulfonamides competitively inhibiting PABA.
- Purulent fluids rich in protein and PABA, this will decrease TMS activity.





Trimethoprim-Sulfonamide

- ▶ Good activity against many *Strep* organisms- although some resistance noted despite susceptibility results. (**)
- ▶ Potentiated sulfas **Not** recommended for initial treatment of *S. equi* infections;
Verheven K, Newton J et al. Elimination of guttural pouch infection and inflammation in asymptomatic carriers of *Streptococcus equi*. *Equine Vet J*. 2000; 32: 527-532.
- ▶ Excellent GI absorption although reduced substantially by feeding....(delay feeding).
- ▶ Lack of clinical activity against anaerobes.
- ▶ 3.75g/50kg is the dose once a day No crushing tablets (as top dress)



Potentiated Sulfas

- ▶ $t_{1/2}$ = sulfamethoxazole 3.5–5 hrs.
- ▶ $t_{1/2}$ = sulfadiazine 3–4 hrs.
- ▶ $t_{1/2}$ = trimethoprim 2–3 hrs.
- ▶ BID PO dosing is necessary to attain therapeutic plasma concentrations of trimethoprim

(Dowling in Bertone, 2004)



Trimethoprim–Sulfonamide

- ▶ Oral formulation containing TMP with sulfadiazine in a 1:5 ratio commonly dosed at 20 to 30mg/kg BID.
- ▶ In horses– rapid elimination of TMP leads to >persistence of sulfonamide and changes optimal ratio. Therefore, potentiated sulfonamides should be dosed BID.



Newer Macrolides

- ▶ Pharmacokinetic advance over erythromycin.
- ▶ Azithromycin– high oral bioavailability. $T_{1/2}$ = 20 hrs. Concentration in BAL cells \pm 150 x serum.
- ▶ Clarithromycin– more effective than azithro against *R. equi* in vitro. Improved efficacy in severe *R. equi* pneumonia as compared to erythro or azithromycin. (Giguere ACVIM 2003)
- ▶ Tilmicosin– $T_{1/2}$ = 18hrs. \pm against *R. equi*



Tulathromycin Draxxin-Pfizer

- ▶ New injectable macrolide for tx of pulmonary dz in cattle and swine
- ▶ Lung concentrations above MIC₉₀ for 15 days for *P. multocida*
- ▶ Study in foals; 2.5mg/kg IM Q 7 days (#37 foals with lung abscesses)
- ▶ Results; tulathromycin well tolerated for tx of pulmonary abscesses in foals (NOT *R. equi!*)

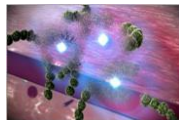
*NB- very pH sensitive- strong distribution in lung tissue- inactive in acidic environments

Gamithromycin (Zactran)

- ▶ Initial studies (*in vitro*) are promising
- ▶ investigated activity against *S. zooepidemicus* & *R. equi*
- ▶ 6 mg/kg IM (foals) maintained concentrations above MIC for both organisms for approximately 7 days

Combination use of beta-lactams + aminoglycosides

- Empirical treatment with a beta-lactam + an aminoglycoside often given¹
- Provides broad coverage, and potential synergistic effect^{15,16}
- β-lactam's MOA is disruption of cell-wall synthesis
- Aminoglycosides have poor cell-penetrating ability
- β-lactam + aminoglycoside may have a potentially synergistic effect – β-lactam degrades cell wall, allowing aminoglycoside to penetrate for a dual antimicrobial effect



Antimicrobial associated diarrhea (AAD)

- ▶ Most frequently observed AE of antimicrobial therapy
- ▶ Antimicrobials alter gut flora, allowing commensal enteropathogens (e.g., *C. difficile*) to proliferate
- ▶ 2009 study results*
 - ▶ >4,900 horses treated with antimicrobials for non-GI signs and presenting with diarrhea
 - ▶ Probable AAD diagnosed in 32 (0.65%)
 - ▶ Antimicrobials most commonly associated:
 - gentamicin n=12 (10 in combo)
 - enrofloxacin n=8 (1 in combo)
 - penicillin n=8 (8 in combo)
 - doxycycline n=6 (2 in combo)
 - ▶ AAD-associated mortality 6/32 (18.8%), *C. difficile* (2), doxycycline (3), enrofloxacin (2), TMS (1)
 - ▶ Conclusion: Any antimicrobial class can potentially cause AAD



*Reported at 2010 AAEP Annual Convention, publication pending, data on file, Pfizer Inc.

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Godzillacillin !!

- Does 'cutting edge' medicine mean finding uses for the hot new drug in human medicine?
- The empirical use of enrofloxacin or vancomycin in horses is a MAJOR concern.
- Can we be effective stewards of public health and avoid regulatory action by FDA?

Questions?



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