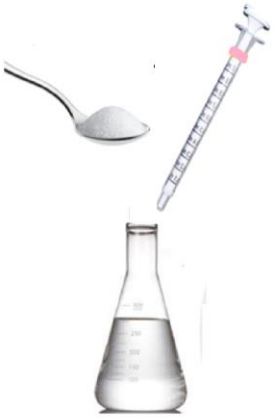
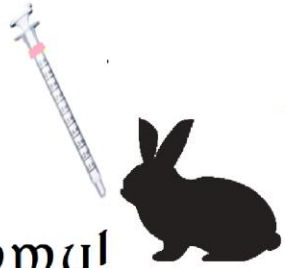
Just a Spoonful of Sugar





Yummy!

Emergency vaccination clinics for RHDV2 (Rabbit Hemorrhagic Disease)

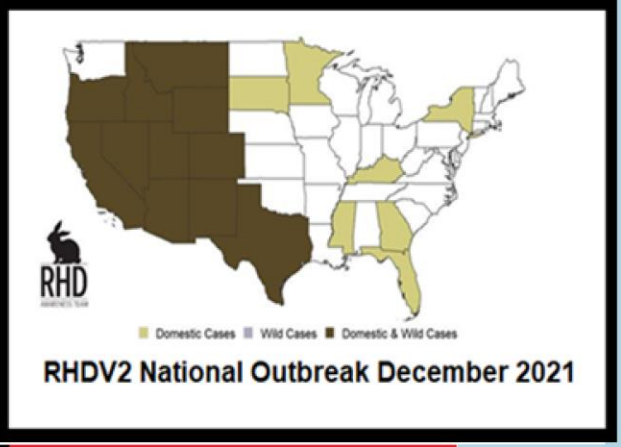
Pain & Distress 66%

Adverse Events 14%

EVIDENCE-BASED IMPROVED CARE

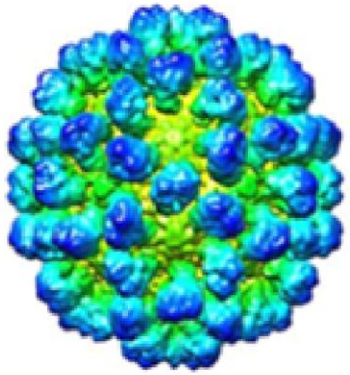
1ml Oral Sucrose given to domestic rabbits
2 minutes before vaccination & microchipping

2020-2021 outbreak of Foreign Animal Disease: Rabbit Hemorrhagic Disease (RHDV2)



RHDV2 National Outbreak December 2021

RHDV2



Morbidity 80%

Mortality 90%

No cure or treatment

NATIONAL EMERGENCY

1) Need safe, humane protocols to protect millions of domestic and wild rabbits/hares & ecosystems
2) Need mass vaccination clinics prioritizing local outbreak areas

PROBLEM

No known evidence-based protocols for needle prick procedures in rabbits nor standard outcome measures

2020

Outbreak RHDV2

CONCERNS

- Clinic RHDV2 Biosecurity
- Resource Stewardship
- Preventing Pain/Distress
- Tracking Adverse Events
- First emergency use of vaccine
- Human Safety: COVID-19

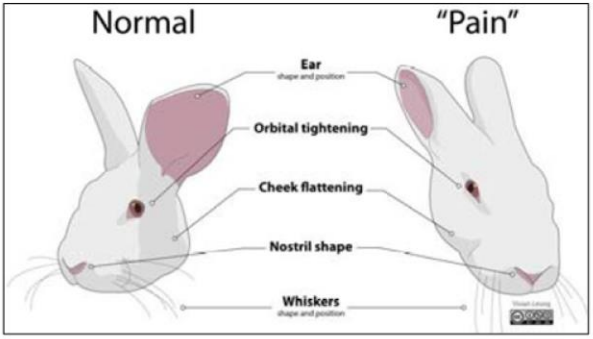
OPPORTUNITY

1) Observe thousands of procedures under similar conditions during vaccination clinics with microchipping
2) **Pioneering research: USA rabbits have never been vaccinated for any disease**

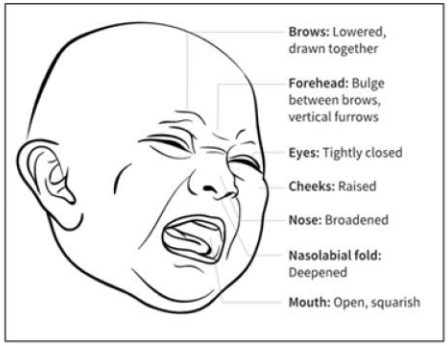
Scientific Questions

1) DETECTION of PAIN/DISTRESS:

Similar to human infant studies, during clinic-based needle prick, will rabbits display behavioral or facial grimace signs consistent with pain/distress from validated laboratory-based scales?



International Association for the Study of Pain
Inspired by AALAS webinar of July 7th, 2020
"Facial Expression Scales for Pain Assessment in Laboratory Animals"
– Dr. Daniel Pang



Bettercare Learning Program

Scientific Questions

2) RISK:

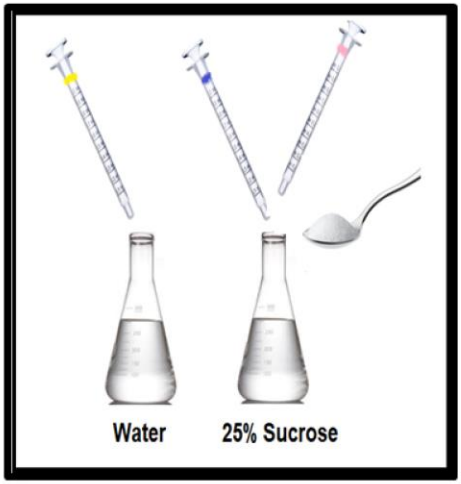
Will certain demographics (breeds, ages, sex) have higher pain/distress scores or incidence of Adverse Events?

3) CORRELATION:

Will pain/distress scores directly correlate with increased incidence of Adverse Events (AEs) scores from Owner-Reported Outcome Measure (OROM) surveys?

4) HARMS & BENEFITS of SUCROSE:

Like proven in translational human infant studies, will rabbits that receive 1 ml 25% oral sucrose 2 minutes prior to needle prick demonstrate a significant decrease in pain/distress and subsequent Adverse Events?



Standard Definitions

PAIN: "**An unpleasant sensory and emotional experience** associated with or resembling **actual or potential tissue damage**" *International Association for the Study of Pain (2020)*

DISTRESS: Aversive state in which an animal fails to cope or adjust to various stressors. Distress may not induce immediate or observable pathological or behavioral alteration making it difficult to evaluate or monitor the animal's state when it is present." *Association for Assessment & Accreditation of Laboratory Animal Care International (AAALAC)*

ADVERSE EVENTS (AEs): Negative outcomes occurring during study after an intervention, **with or without causation** - *Brighton Collaboration*

Owner Reported Changes

- Physical Activity
- Personality
- Food or Water Consumption
- Excrement (type/amount)
- Hotter to touch
- Hard or soft bump
- Swelling
- Vet diagnosis

Veterinarian Diagnoses

Viral/Bacterial Infections
Torticollis "Head tilt"
Anaphylaxis
Gastric Statis
Death (necropsy at University)

HYPOTHESES

1) DETECTION of AE (classified by SNOWMED)

99% of OROM surveys indicated 1+ AE sign

"Very common" >10% of population

Changes: excrement, food, water, personality, activity

All pain / distress signs (*except vocalization = 0)

"Common" 1-10%

Changes: temperature, new bump or swelling, illness

2) RISK IS DISPROPORTIONATE

Male	n=459 (**54%** of pop.)	**72%** of P/D	**82%** of severe AE
Dwarf	n=144 (**15%** of pop.)	**68%** of P/D	**75%** of severe AE
Elder	n=68 (**8%** of pop.)	**61%** of P/D	**62%** of severe AE

3) CORRELATIONS

One-way ANOVA

Pain/Distress $F(3,19)=5.54$, $p<.05$

Adverse Events $F(3,39)=5.17$, $p<.05$

Significant difference between control group and 3 intervention groups.

REGRESSION $F(1,7)=82.18$, $p<.01$, $r^2=.93$

SIGNIFICANT PREDICTION:

Pain/Distress **Adverse Events**

4) BENFITS of SUCROSE: Post hoc Tukey's Test

1 ml sucrose compared to control is significant ($p<.05$) for both pain/distress and AEs. Others not significant

HARMS: No serious Adverse Events attributed to sucrose

METHODS:
Double Blind, Random Control Trial

Because the same rabbits would return in 3 weeks, for dose 2, recruit for oral sucrose intervention study

Clinic 1: Baseline survey, veterinary well-check screening
Observe enrolled study population **(N=850)**

Clinic 2: Add 3 intervention groups (n=280+)

Analysis: Conduct One Way ANOVA then Tukey HSD tests to compare pain/distress between intervention groups. Repeat to compare AEs. Conduct regression analysis to determine if pain/distress scores predict AEs.

Control Variables

- Same vaccine & microchip
- Same 22 needle gauge & 1 inch length
- Trained vet staff with same protocols, scoring
- Same rabbits & owners
- Same site / day

1000+ rabbits pre-registered for clinic;
850 enrolled in oral sucrose study
21 Veterinarians
5 Vet techs 8 Vet students
2 dedicated staff to draw up vaccine

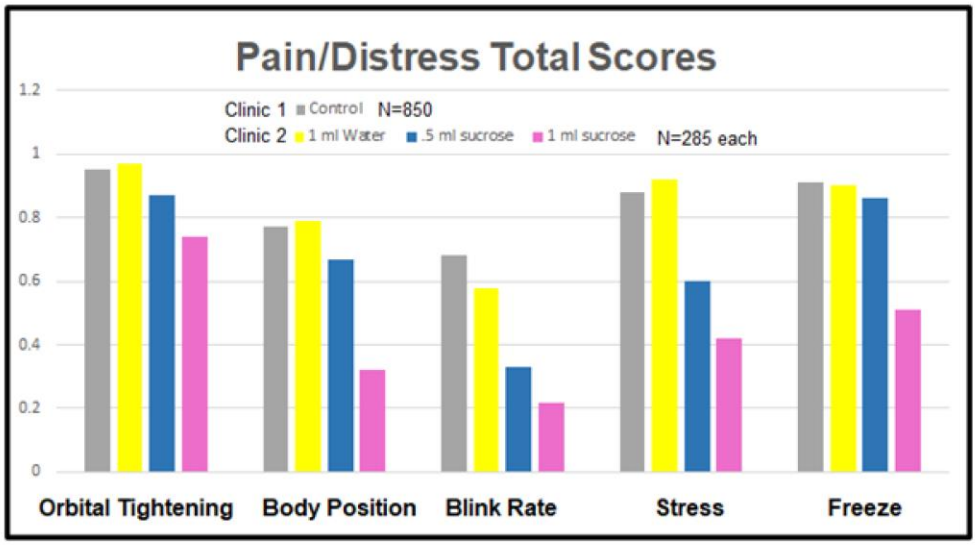
All biosecurity and humane protocols reviewed by advisory team with members from Board of Animal Health, USDA, Board of Veterinary Medicine and clinic medical director

Adapt Procedures Used with Human Infants

Over 70 studies have been conducted in human infants using oral sucrose before needle prick using validated human facial grimace scales which are similar to validated scales in rabbits. Mammals share similar nervous system frameworks which lead to my hypothesis that these translational study results in humans will be mirrored in this domestic rabbit study.

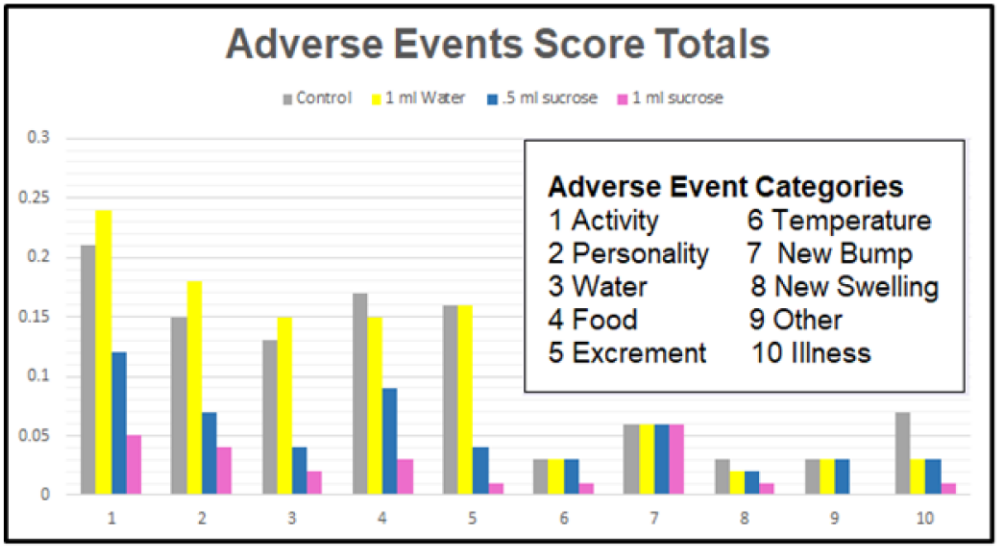
Outcomes for <u>25% Oral Sucrose for Human Neonates</u>
Fewer signs of pain/distress at time of procedure
Faster recovery to baseline
Less incidence of Total Adverse Events
Less incidence of Severe Adverse Events

RESULTS



Grey: Control – Clinic 1	**Yellow: water 1ml**
Blue: sucrose.5 ml	**Pink: sucrose 1 ml**

INCIDENCE: Pain/Distress	**Control**	**1 ml sucrose**	**Decrease**	**Proportion**
Orbital Tightening	0.95	0.74	0.21	0.78
Body	0.77	0.32	0.45	0.42
Blink Rate	0.68	0.22	0.46	0.32
Stress	0.88	0.42	0.46	0.48
Freeze	0.91	0.51	0.4	0.56
TOTAL SCORE	4.19	2.21	1.98	0.53
AVERAGE	1.40	0.74	**0.66**	**0.53**



	INCIDENCE: AEs - Noting Changes	Control	1 ml sucrose	Decrease	Proportion
1	Activity	0.21	0.05	0.16	0.24
2	Personality	0.15	0.04	0.11	0.27
3	Water Consumption	0.13	0.02	0.11	0.15
4	Food Consumption	0.17	0.03	0.14	0.18
5	Excrement	0.16	0.01	0.15	0.06
6	Temperature	0.03	0.01	0.02	0.33
7	New Bump	0.06	0.06	0.00	1.00
8	New Swelling	0.03	0.01	0.02	0.33
9	Other	0.03	0.01	0.02	0.33
10	Illness	0.07	0.01	0.06	0.14
	TOTAL	1.04	0.25	0.79	0.24
	AVERAGE	0.19	0.05	**0.14**	**0.24**

CONCLUSIONS

EVIDENCE-BASED HUMANE CARE:

Just like in human infants, recommend administration of 1 ml 25% oral sucrose solution 2 minutes before procedures that are expected to yield pain/distress

-Decreased average pain/distress scores by 66%

-Decreased subsequent Adverse Events by 14%

Oral sucrose is a humane, inexpensive, easy-to-administer, low-risk step to help prevent pain/distress with needle prick showing potential for use in other small mammals.

In addition to companion rabbits, consider sucrose during vaccination of endangered wild rabbits and hares in endemic areas and for at-risk New England Cottontail populations.

PREDICTION for PREVENTION

These screenings for pain/distress can help veterinarians to PREDICT which rabbits have more risk of Adverse Events. Channeling resources can help prevent the most severe AEs by providing additional education, close monitoring, and early intervention while promoting good stewardship of resources.