



# Heartland Virus in the South Central Region

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# Heartland Virus (HRTV) Background

- **Novel Phlebovirus**
  - Single-stranded RNA viruses in Bunyaviridae family
- **First identified in two patients in Missouri in 2012**
  - Heartland Regional Medical Center

*The NEW ENGLAND JOURNAL of MEDICINE*

BRIEF REPORT

## A New Phlebovirus Associated with Severe Febrile Illness in Missouri

Laura K. McMullan, Ph.D., Scott M. Folk, M.D., Aubree J. Kelly, M.S., Adam MacNeil, Ph.D., Cynthia S. Goldsmith, M.G.S., Maureen G. Metcalfe, B.S., Brigid C. Batten, M.P.H., César G. Albariño, Ph.D., Sherif R. Zaki, M.D., Ph.D., Pierre E. Rollin, M.D., William L. Nicholson, Ph.D., and Stuart T. Nichol, Ph.D.

# HRTV Confirmed Case

## Clinically compatible illness

**1.** Fever ( $\geq 100.4^{\circ}\text{F}$  or  $38^{\circ}\text{C}$ )

– AND –

**2.** Leukopenia (WBC  $> 4,500$  cells/ $\text{mm}^3$ )

– AND –

**3.** Thrombocytopenia  
(Platelet  $< 150,000$  cells/ $\text{mm}^3$ )

(w/o another explanation)

## + Laboratory evidence of recent HRTV infection

**1.** Detection of viral RNA by RT-PCR in blood or tissue

– OR –

**2.** A  $\geq 4$ -fold rise in virus-specific plaque reduction neutralization antibody titers between acute and convalescent serum

# Investigation Timeline

September: TDH notified of  
+ HRTV

2013

2014

2015

# Investigation Timeline

**July: Case #1 hospitalized**

**August: Case #1 died**

**September: TDH notified of  
+ HRTV**

2013

2014

2015

# Case #1 Background

- 80 year old male
- Chief Complaint: weakness, recurrent falls, confusion
- Presented to a local ED for progressive weakness and recurrent falls. Subjective fever at home.
- History of multiple tick bites.
- Transferred to VUMC on hospital day 2.

## PMH/PSH

- COPD
- Cirrhosis
- Chronic EtOH use
- DVT
- MVC s/p L BKA
- Chronic back pain

## Medications

- Coumadin
- Demerol

## Social History

- Married. 3 Children.
- Lived on a farm. Active outdoors.
- Studied PhD in Music in Spain

# Case #1 Clinical Findings

- **Notable exam findings:**

- Gen: Ill-appearing
- CV: Tachycardic
- Resp: Tachypneic, bilateral crackles
- Skin: Vesicular rash and mottling on RLE, abdomen and anterior chest; round lesion with central clearing

- **Notable lab findings:**

- WBC 1,100 cells/mm<sup>3</sup> (4,500-10,000 cells/mm<sup>3</sup>)
- Platelets 35,000 cells/mm<sup>3</sup> (150,000-400,000 cells/mm<sup>3</sup>)
- Sodium 126 mEq/L (135-145 mEq/L)
- AST 626 / ALT 166 U/L (8-48 / 7-55 U/L)
- All cultures (blood, urine); Lyme, Ehrlichia, RMSF titers; and Ehrlichia PCR negative

# Case #1 Clinical Course

- **Within hours of arrival to VUMC transferred to MICU for respiratory distress**
  - Intubated 7/26 – 7/31
  - Pressor support (levophed) 7/26 – 7/28
  - Treated with doxycycline, zosyn and vancomycin
  - Course complicated by cardiac strain, atrial fibrillation with RVR, GI bleed requiring cauterization of gastric ulcers , acute kidney injury, aspiration pneumonia
- **Despite clinical improvement, had ongoing severe delirium**
  - Palliative Care consulted 7/30
  - Progressive decline. Family declined aggressive measures. Passed away 8/6/2013
  - Autopsy performed

# Investigation Timeline

July: Case #1 hospitalized

August: Case #1 died

September: TDH notified of  
+ HRTV

2013

2014

2015

August: TDH notified of  
+ HRTV

# Investigation Timeline

July: Case #1 hospitalized

August: Case #1 died

September: TDH notified of  
+ HRTV

2013

2014

2015

July: Case #2 hospitalized  
& died

August: TDH notified of  
+ HRTV

# Case #2 Background

- 68 year old male
- Chief Complaint: confusion and falls
- Presented to a local ED 7/12 for new rash and pain in LLE. Rx'ed doxycycline and sent home.
- Developed progressive weakness, nausea & vomiting and recurrent falls – returned to local ED 7/16.
- Transferred to regional medical center and ultimately to VUMC 7/19.
- History of multiple tick exposures.

## PMH/PSH

- Localized melanoma
- Hypertension
- h/o small stroke (2013)

## Medications

- Lisinopril

## Social History

- Married. 2 Children.
- Lived in a rural area.
- Landscaper. Worked outside on multiple properties daily.

# Case #2 Clinical Findings

- **Notable exam findings:**

- Gen: Jaundiced
- CV: Tachycardic
- Skin: Purple/red, nonblanching rash over left lower extremity

- **Notable lab findings:**

- WBC 31,100 cells/mm<sup>3</sup> (4,500-10,000 cells/mm<sup>3</sup>)
- Platelets 15,000 cells/mm<sup>3</sup> (150,000-400,000 cells/mm<sup>3</sup>)
- Sodium 127 mEq/L (135-145 mEq/L)
- AST 996 / ALT 352 U/L (8-48 / 7-55 U/L)
- Creatinine 3.24 mg/dL (0.7-1.3 mg/dL)
- Lactic acid 13.0 mg/dL (0.5-2.2 mg/dL)
- Ferritin 46,789 ng/mL (12-300 mg/mL)
- All cultures (blood, urine, CSF) and Lyme, Ehrlichia, RMSF titers negative

# Case #2 Clinical Course

- **Admitted directly to MICU at VUMC**
  - Intubated 7/18 – 7/22
  - Pressor support (levophed, vasopressin, phenylephrine) 7/19 – 7/22
  - Treated with doxycycline, meropenem and vancomycin
  - Course complicated by persistent shock, cardiac strain, atrial fibrillation with RVR, renal failure requiring dialysis, disseminated intravascular coagulation, delirium.
  
- **Despite maximal medical therapy, clinical status continued to deteriorate**
  - Family opted to transition to comfort measures
  - Passed away 7/22/2015
  - Autopsy performed

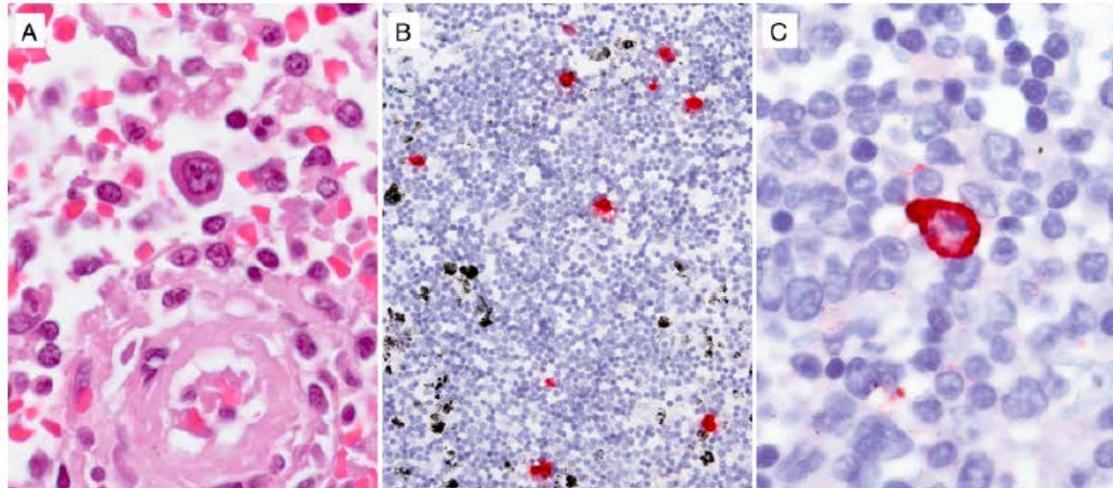
# Pathology Findings

- The Infectious Diseases Pathology Branch at the Centers for Disease Control and Prevention was consulted for additional evaluation of these unexplained deaths.
- Immunohistochemical (IHC) assays:
  - Heartland virus
  - *Ehrlichia*
  - *Anaplasma*
  - *Leptospira*
  - Spotted fever group *Rickettsia*



# IDPB Results

- **Case #1:**
  - IHC positive in spleen, mediastinal and mesenteric lymph nodes, whole blood and serum
- **Case #2:**
  - IHC positive in spleen and liver. Other testing pending.



**Figure 2.** Pathological features of fatal Heartland virus (HRTV) case. Spleen demonstrating white pulp depletion and scattered immunoblasts (A). HRTV antigen detected in large hematopoietic cells of lymph node (B) and spleen (C) by immunohistochemistry using fast red chromogen. Original magnifications:  $\times 158$  (A),  $\times 50$  (B), and  $\times 158$  (C).

# Investigation Timeline

July: Case #1 hospitalized

August: Case #1 died

September: TDH notified of  
+ HRTV

Field investigation

2013

May - August:  
Field investigation

2014

May & June:  
Field investigation

2015

July: Case #2 hospitalized  
& died

August: TDH notified of  
+ HRTV

August - September:  
Field investigation

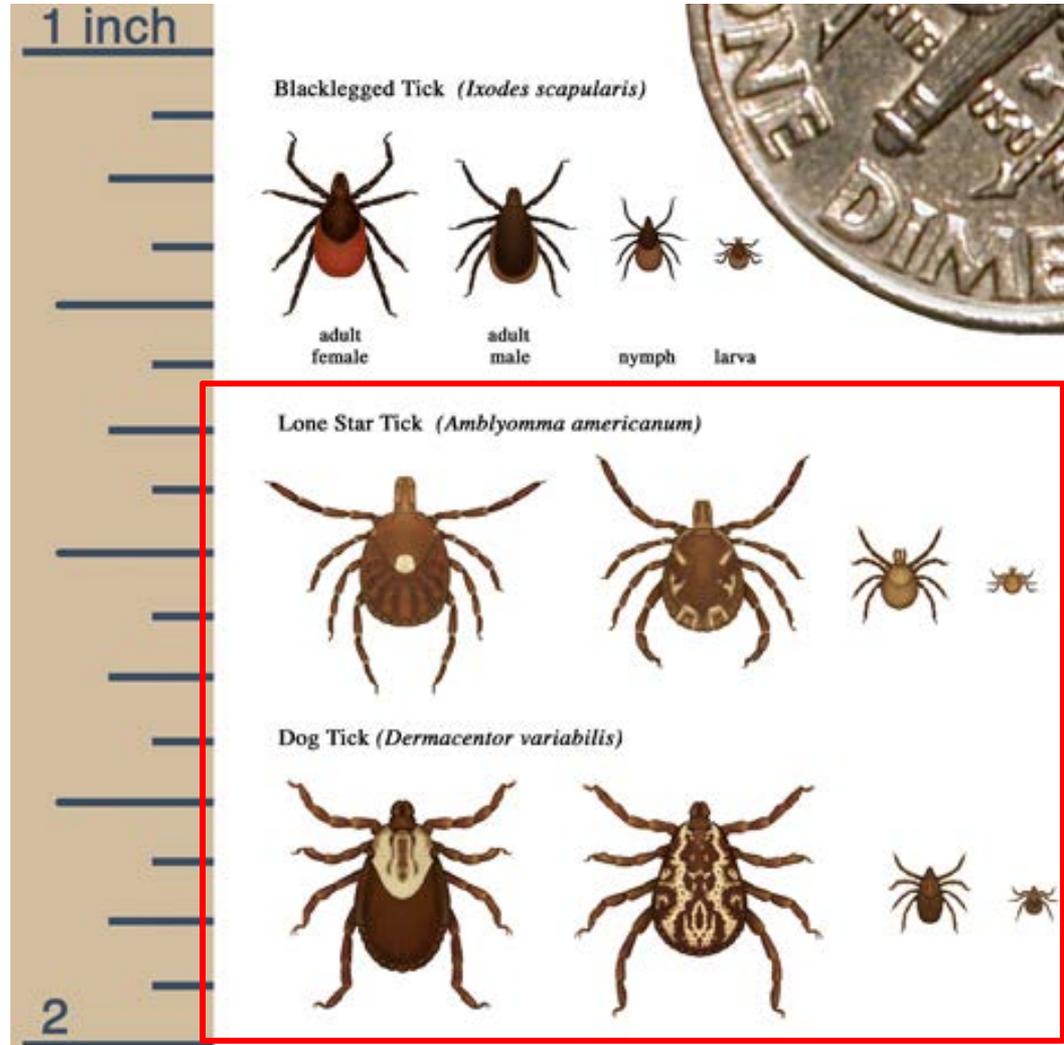
# Ticks in Tennessee



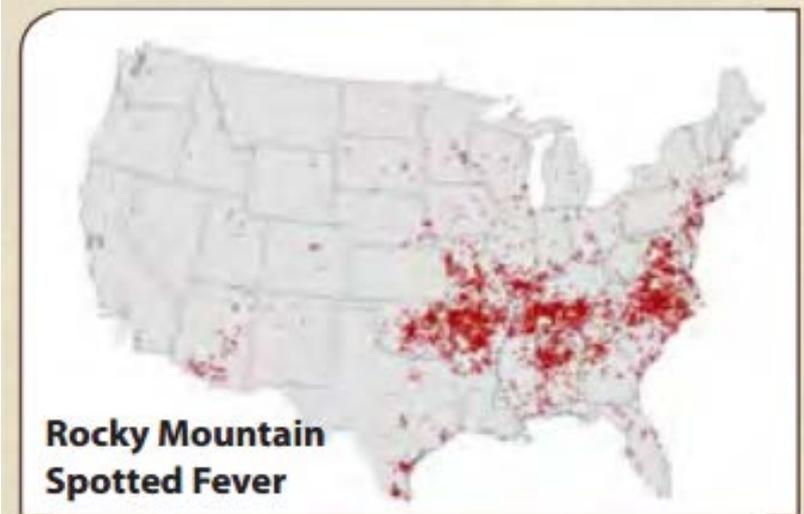
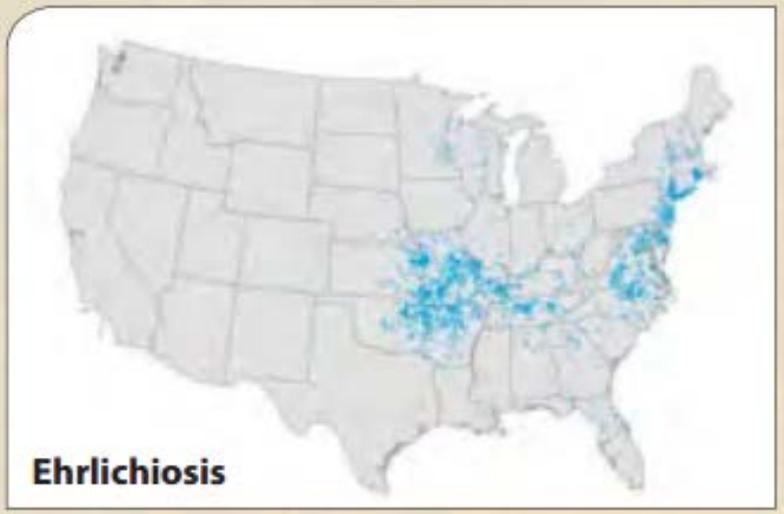
**LONE STAR TICK**  
*Amblyomma americanum*



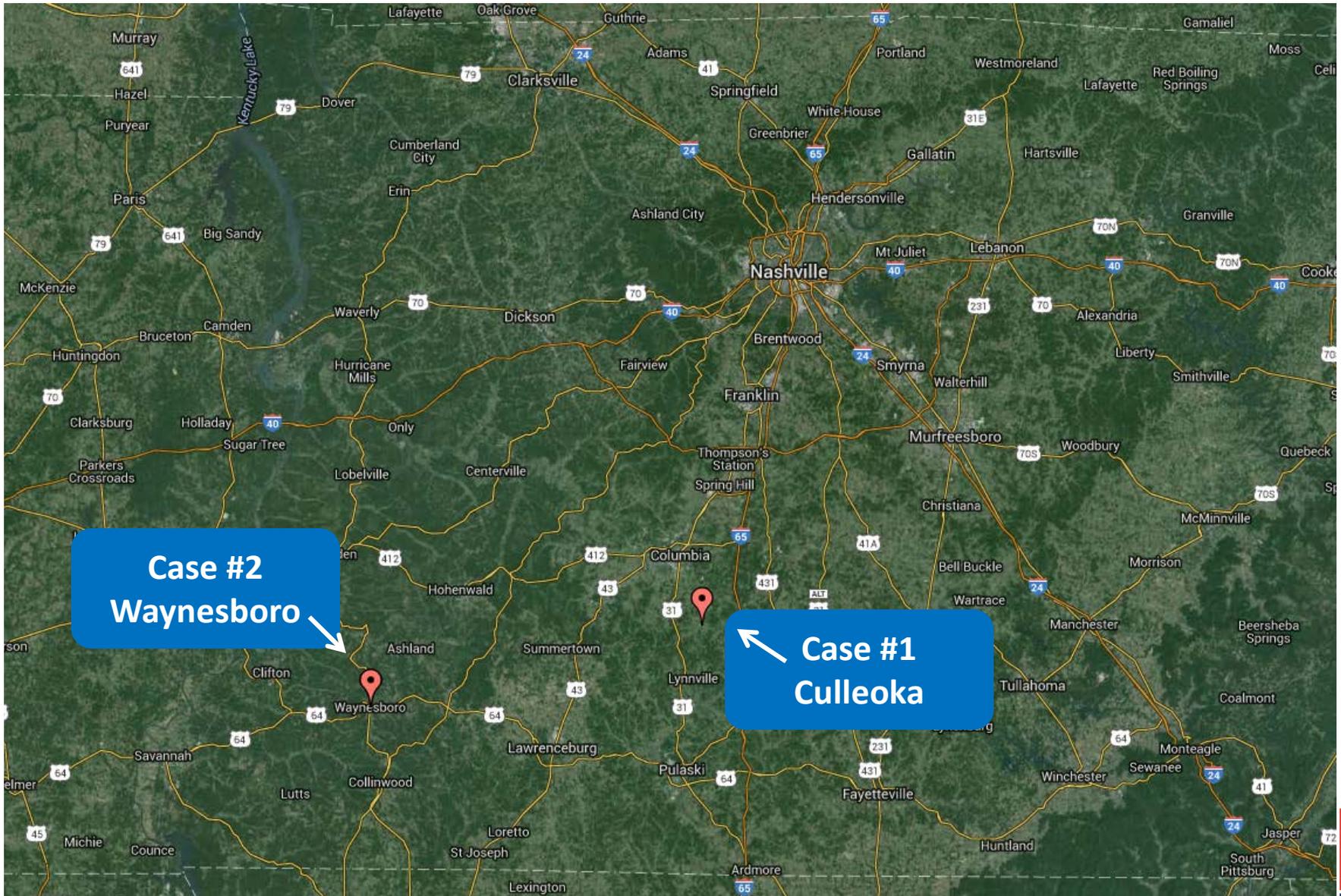
**AMERICAN DOG TICK**  
*Dermacentor variabilis*



# TN Tick Distribution



# Field Investigation



# Tick Dragging Basics



# Dragging Locations



# Tick Dragging in Action



**Julie Odom**

**Shannon Harney  
Abelardo Moncayo**



# Tick Dragging in Action



**Abelardo Moncayo**

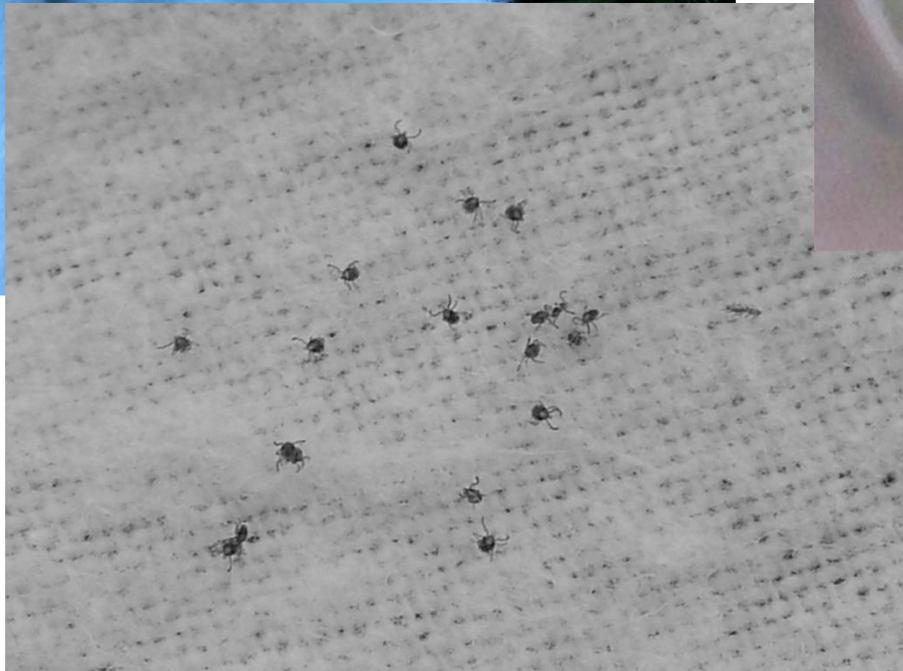
**Mary-Margaret Fill**



# Adults



# Larvae and Nymphs



# Results To Date

- Team (Central Office + SCR) dragged on **18** dates
  - May 2014 – August 2014 and May 2015 – September 2015
- Collected **~ 4000 ticks**

<i>A. americanum</i> (Lone Star)			<i>D. variabilis</i> (Dog Tick)		
<u>Adult</u>	<u>Nymph</u>	<u>Larvae</u>	<u>Adult</u>	<u>Nymph</u>	<u>Larvae</u>
356	1308	2352	48	0	0

- Yielded **237 testing pools**

# Testing

Ticks ID'd and  
separated:  
species, sex, stage

# Testing

Ticks ID'd and  
separated:  
species, sex, stage



Frozen in liquid N



# Testing

Ticks ID'd and  
separated:  
species, sex, stage



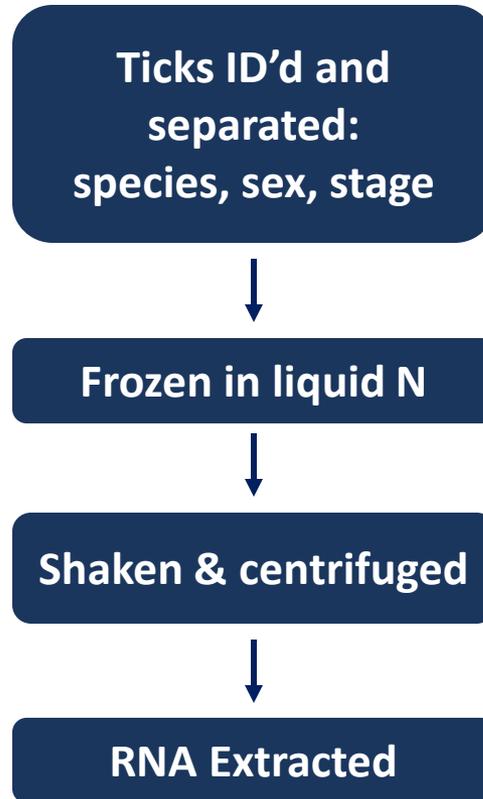
Frozen in liquid N



Shaken & centrifuged



# Testing



# Testing

Ticks ID'd and  
separated:  
species, sex, stage



Frozen in liquid N



Shaken & centrifuged



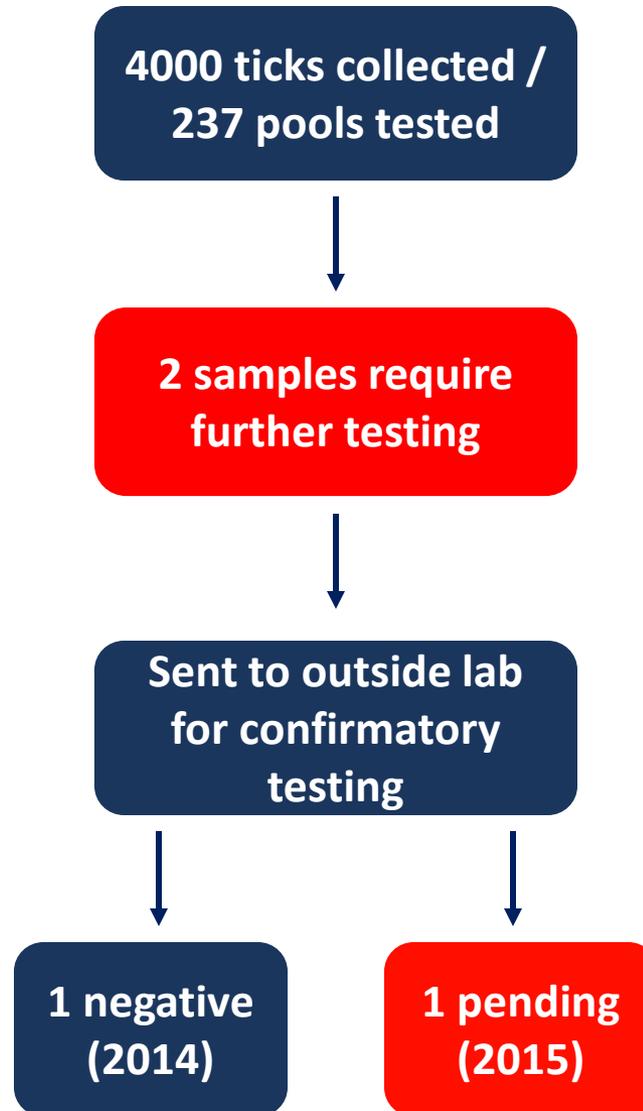
RNA Extracted



RT-PCR



# Testing Results



# For Reference:

*Am. J. Trop. Med. Hyg.*, 89(3), 2013, pp. 445-452  
doi:10.4269/ajtmh.13-0209  
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## First Detection of Heartland Virus (Bunyaviridae: *Phlebovirus*) from Field Collected Arthropods

Harry M. Savage,\* Marvin S. Godsey Jr., Amy Lambert, Nicholas A. Panella, Kristen L. Burkhalter,  
Jessica R. Harmon, R. Ryan Lash, David C. Ashley, and William L. Nicholson

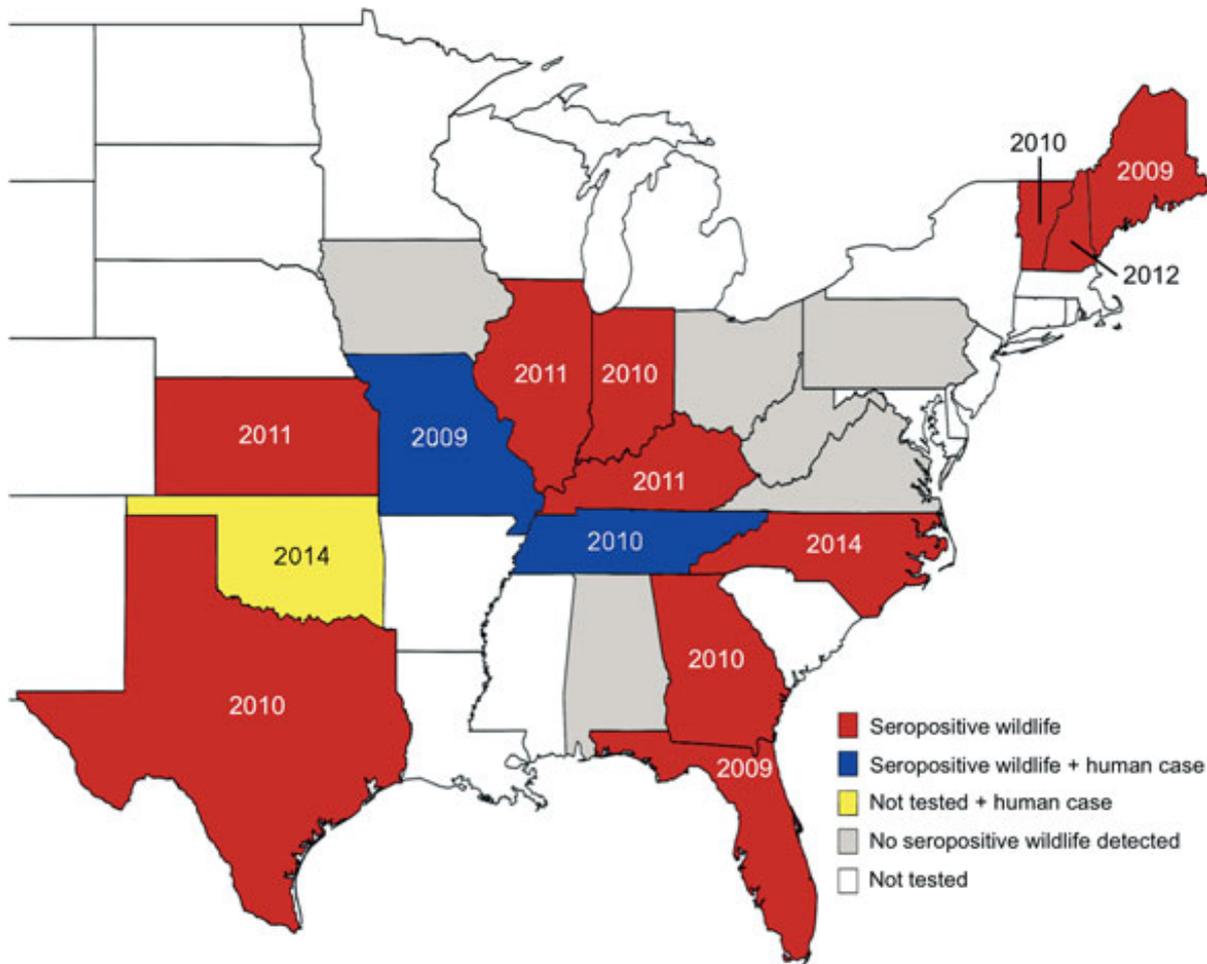
*Centers for Disease Control and Prevention, Fort Collins, Colorado; Centers for Disease Control and Prevention, Atlanta, Georgia;  
Department of Biology, Missouri Western State University, St. Joseph, Missouri*

- **Tested 56,428 ticks (~2000 pools)**
- **Only 10 pools positive for HRTV**
  - 8 pools yielded viable virus
- **All *A. americanum* nymphs**



# Recent HRTV Updates

## Heartland Virus Neutralizing Antibodies in Vertebrate Wildlife, United States, 2009–2014



# Additional Resources

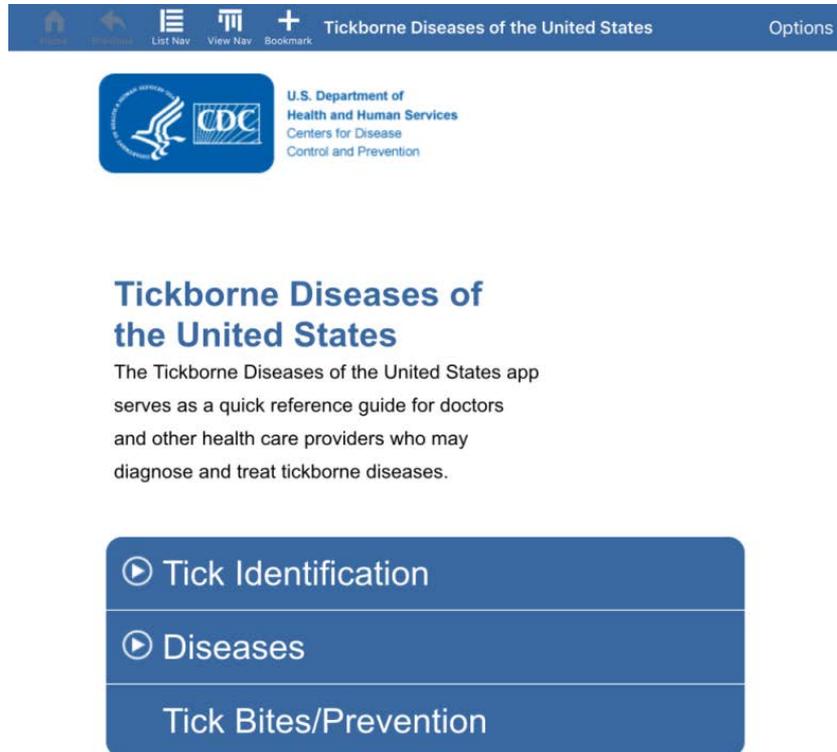
- **CDC has developed a mobile application for use by public health and healthcare providers**
- **Free in the App Store**
  - Apple or Android devices
- **Companion to manual “Tickborne Diseases of the United States”**

*Tickborne Diseases of  
the United States*



**U.S. Department of  
Health and Human Services  
Centers for Disease Control  
and Prevention**

# CDC Tick App



- Sections on tick identification, disease presentations and prevention
- Large color images of environmental and clinical features
  - Ticks
  - Rashes
- Treatment guidelines
- Standard prevention measures



# Future Directions

- **Testing samples from Pathogen Discovery Project**
  - *Ehrlichia* positive tested for coinfection with HRTV
- **Next generation sequencing of HRTV**
- **Plan to continue regular tick dragging in South Central Region**
  - May through August is peak time
- **Environmental testing**
  - Equine, other wildlife
- **Possible serosurvey**



**Thank You**