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A Leopard without Spots:
Clinical Diagnosis and Treatment of Rock Mountain Spotted Fever

Clinician Outreach and Communication Activity (COCA)

Webinar

April 12, 2018

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At the conclusion of the session, participants will be able to accomplish the following:

- Discuss clinical characteristics associated with early, intermediate, and late presentations of Rocky Mountain Spotted Fever, and those associated with higher risk of fatal outcome.
- Describe available diagnostic tests for RMSF, advantages and disadvantages of each, and the appropriate time points and specimens for collection.
- Explain the epidemiology of RMSF in Arizona and along the U.S.-Mexico border, and describe how it differs from other regions in the United States.

Today's First Presenter

Paige Armstrong, MD, MHS
LCDR, US Public Health Service
Medical Epidemiologist
Rickettsial Zoonoses Branch
National Center for Emerging & Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Today's Second Presenter

Naomi Drexler, MPH
Epidemiologist
Rickettsial Zoonoses Branch
National Center for Emerging & Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

A Leopard Without Spots: Clinical Diagnosis and Treatment of Rocky Mountain Spotted Fever

Dr. Paige Armstrong and Naomi Drexler
Rickettsial Zoonoses Branch
Centers for Disease Control and Prevention

Case: Pediatric Pyelonephritis

- 5 y/o F child presented in July with 2 days of fever (103.2^{o}F), headache, and flank pain.
  - Urinalysis negative, urine culture showed mixed flora
  - Mother reported faint rash

Case: Pediatric Pyelonephritis

- Day 4: returned and was admitted for persistent fever, abdominal pain, and earache
  - Urinalysis: +nitrites, - leuk, 10-13 WBCs, 8-10 RBCs
  - CBC: WBC 6.5, H/H 13.6/38.9, Plt 53k, Na 135
  - CXR: negative
  - Dx: pyelonephritis
  - Treatment: ancef and gentamycin

Case: Pediatric Pyelonephritis

- Day 5-6: severe abdominal pain, respiratory failure with hypoxia, acidosis, hypotension
  - Required intubation and transferred to tertiary care hospital
  - Dx: DIC, sepsis
  - Treatment: doxycycline and vancomycin
- Died on Day 6
  - RMSF confirmed by immunohistochemistry (IHC) and PCR

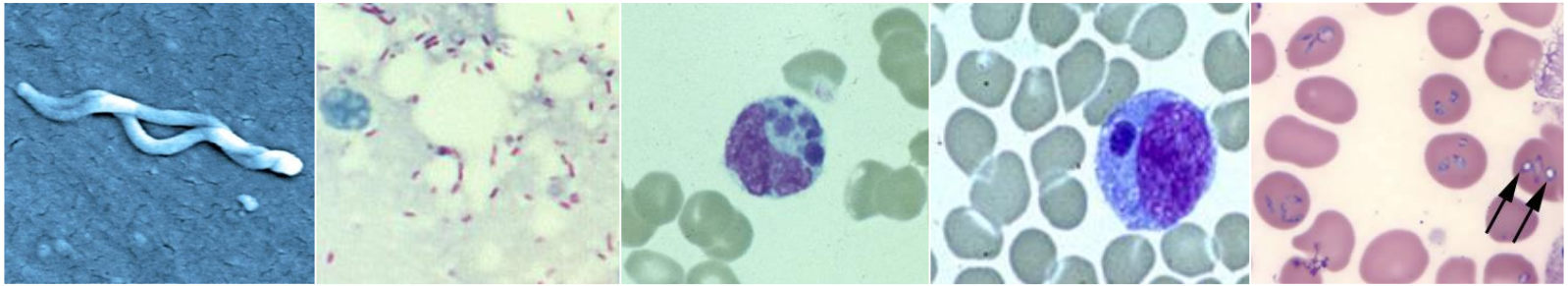
Lessons Learned

- Mimicked pyelonephritis
  - Urinalysis borderline
  - Common mimics: appendicitis, cholecystitis, upper respiratory tract infection
- Rapid decompensation
- Thrombocytopenia (plt 53k) is a red flag
- Close follow-up appointment should be scheduled

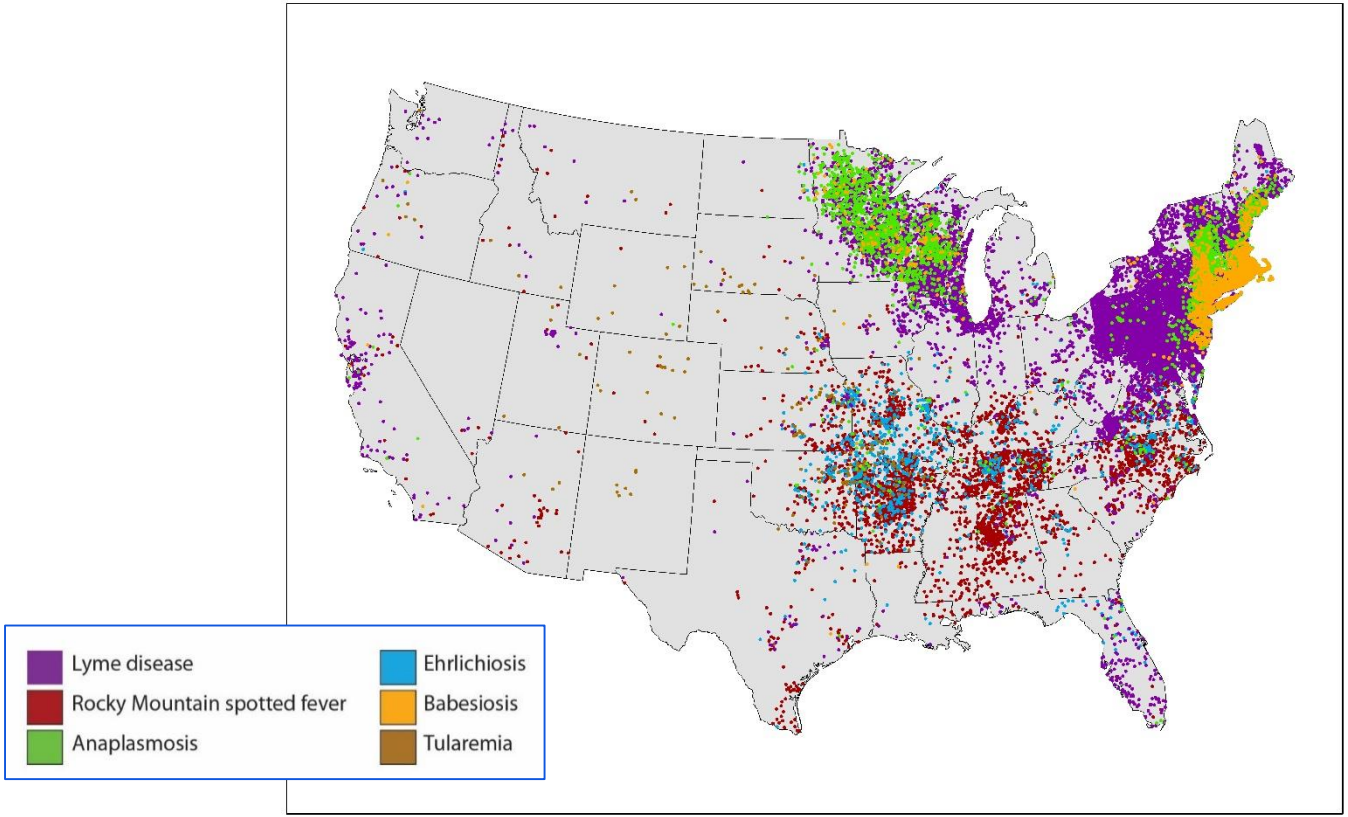
Tickborne Diseases

Leading Tickborne Diseases in US

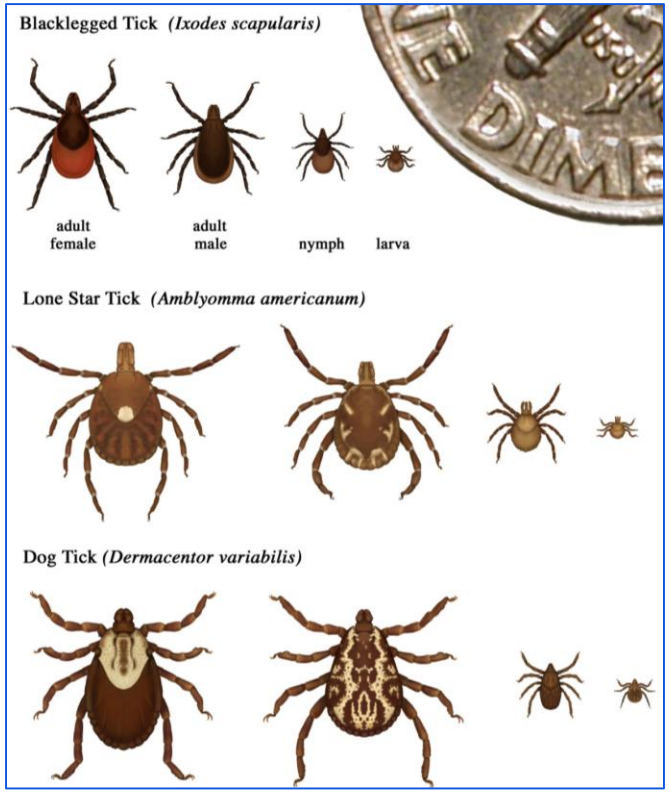
- Lyme disease (*Borrelia burgdorferi*)
- Rocky Mountain spotted fever (*Rickettsia rickettsii*)
- Anaplasmosis (*Anaplasma phagocytophilum*)
- Ehrlichiosis (*Ehrlichia chaffeensis,* others)
- Babesiosis (*Babesia microti*)



Distribution of Key Tickborne Diseases, 2016



Selected Ticks and Life Stages



Rocky Mountain spotted fever (RMSF)

Rocky Mountain spotted fever

- Caused by *Rickettsia rickettsii*
  - Gram-negative intracellular bacterium
  - Tickborne
- Endemic throughout Western Hemisphere
- Rapidly fatal, yet difficult to diagnose

American Dog Tick (*Dermacentor variabilis*)

- Tularemia
- Rocky Mountain spotted fever

Rocky Mountain Wood Tick (*Dermacentor andersoni*)

- Tularemia
- Rocky Mountain spotted fever
- Colorado tick fever virus

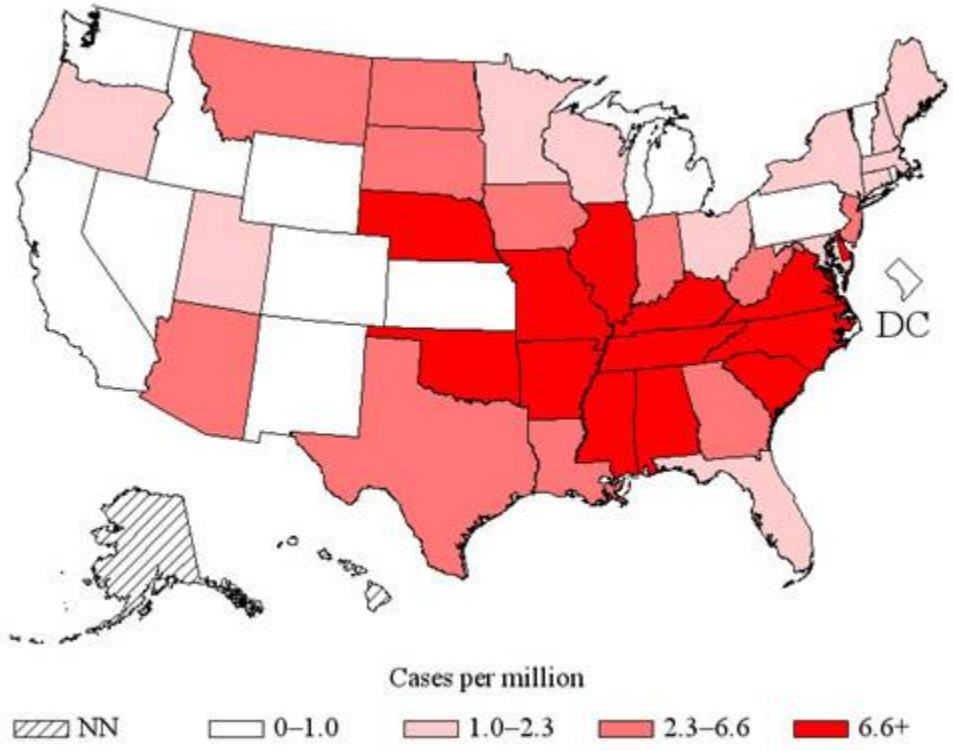
Brown Dog Tick (*Rhipicephalus sanguineus*)

- Rocky Mountain spotted fever

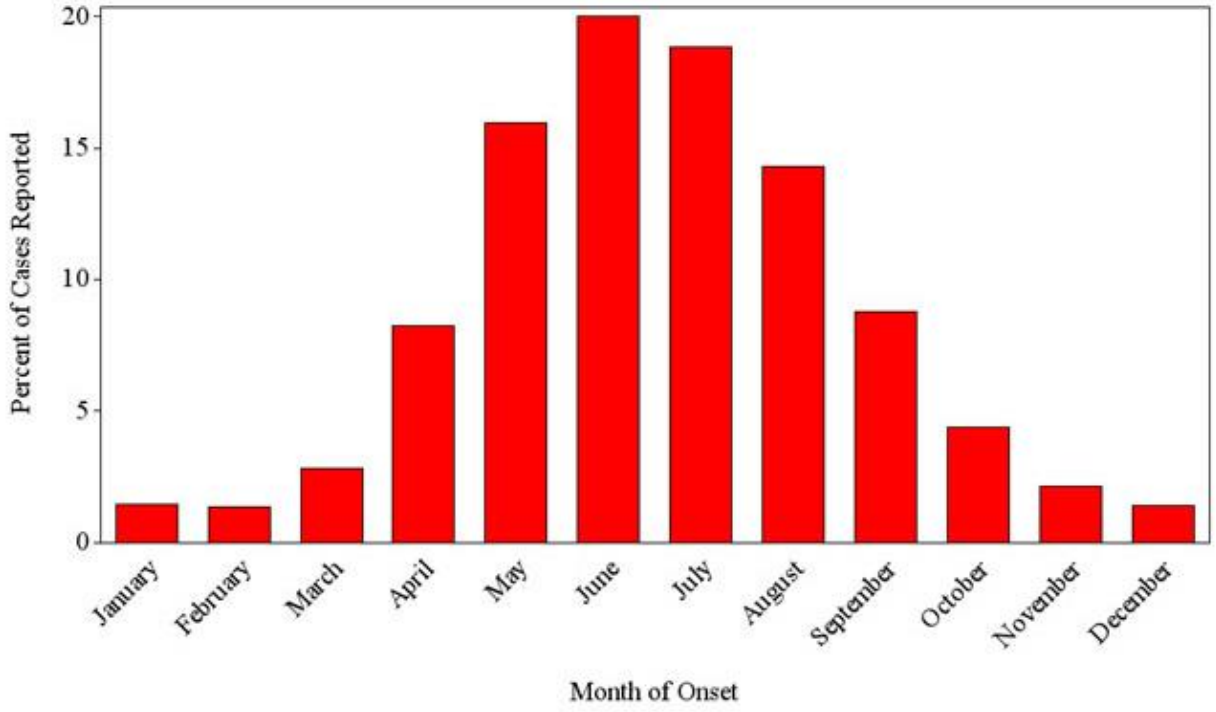
Rh. sanguineus is the primary vector for *R. rickettsii* transmission in the southwestern U.S. and along the U.S.-Mexico border. It is unknown to what extent it contributes to *R. rickettsii* transmission in other parts of the U.S.

In 2016, 4,269 cases of spotted fever rickettsiosis (including RMSF) were reported in the US.

Incidence of Spotted Fever Rickettsiosis in the United States, 2014



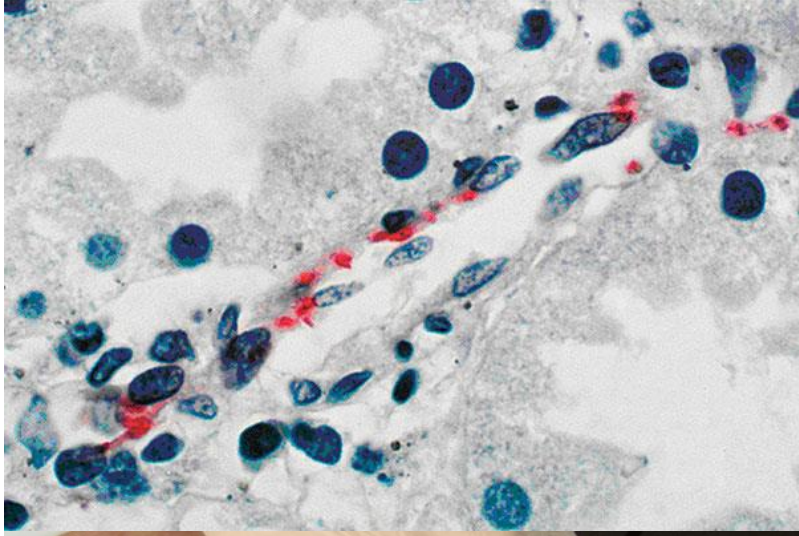
Spotted Fever Rickettsiosis Cases by Month of Onset, 1993 through 2014



Clinical

Rocky Mountain spotted fever

- Causative organism is *Rickettsia rickettsii*
  - Gram negative intracellular bacterium
  - Primarily infects vascular endothelial cells
  - Leads to advancing vascular damage throughout the body



Initial Illness (Days 1-2)

- **Signs and Symptoms**
  - Abrupt onset of high fever
  - Headache, myalgia, and malaise

- **Laboratory Indicators**
  - Often within normal limits

Early Illness (Days 2-4)

- **Signs and Symptoms**
  - Respiratory signs (cough, pneumonia)
  - GI signs (nausea, abdominal pain)
  - Rash may appear

- **Laboratory Indicators**
  - Mildly elevated transaminases
  - Mild thrombocytopenia
  - WBC typically within normal limits

Early Rash (Days 2-4)

Never wait for the rash to begin treatment

Moderate to Late Illness (Days 5-7)

- **Signs and Symptoms**
  - High fever
  - Worsening abdominal pain
    - Can mimic appendicitis or cholecystitis
  - Worsening respiratory status
  - Rash becomes petechial and more widespread
  - CNS manifestations (coma)

- **Laboratory Indicators**
  -  Transaminases
  -  Platelets
  -  Sodium

Progression of Rash (Days 5-7)

Late Illness (Days 7-9)

- **Signs and Symptoms**
  - Septic shock
  - Cerebral edema
  - Pulmonary edema (ARDS)
  - Myocarditis and cardiac arrhythmias
  - Coalescent rash forming purpura
  - Necrosis of digits and peripheral gangrene

- **Laboratory Indicators**
  -  WBC
  -  Platelets
  -  Creatinine, CK, Lactic acid

20-25% of untreated cases of RMSF will be fatal with most deaths occurring within the 7^{th} to 9^{th} day of illness

Sequelae (Long-term Effects)

- **Necrosis necessitating amputation**
- **Permanent organ damage**
- **Profound neurologic deficits (especially in children)**
  - Hearing loss
  - Paralysis
  - Mental disability

Treatment

Doxycycline is the treatment of choice for all age groups and is most effective at preventing severe illness and death if administered within the first 5 days of symptoms

Recommended by:

American Academy of Pediatrics

Centers for Disease Control and Prevention

Outcome by Day of Treatment, Arizona (2002–2011)

Day of treatment (N)	# Hospitalized (%)	# ICU (%)	# Fatal (%)
Day 1 (6)	1 (17)	0 (0)	0 (0)
Day 2 (11)	3 (27)	0 (0)	0 (0)
Day 3 (9)	5 (56)	1 (11)	0 (0)
Day 4 (7)	4 (57)	1 (14)	0 (0)
Day 5 (8)	6 (75)	4 (50)	0 (0)
Day 6 (9)	9 (100)	5 (55)	3 (33)
Day 7 (11)	11 (100)	4 (36)	3 (27)
Day 8 (5)	4 (80)	2 (40)	2 (40)
Day 9 (4)	4 (100)	4 (100)	2 (50)

Outdated Perceptions: Doxycycline in Pediatric Patients

- In 1970, FDA placed a warning label on all tetracycline-related medications, including doxycycline
  - Believed to be associated with enamel hypoplasia and tooth discoloration

Doxycycline and Tooth Staining, Arizona

- 2013 Study examined the erupted teeth of 58 children who received doxycycline before 8 years old
  - NO staining or hypoplasia, even with multiple short courses
  - NO significant difference in objective tooth shade between exposed and unexposed children
- CDC and the American Academy of Pediatrics (AAP) recommend doxycycline as **first line** treatment for suspected RMSF in children

Treat Early!

- **Delay in treatment is the single most important predictor of fatal outcome**
- Doxycycline within the first 5 days of illness reduces severe morbidity and mortality
- Mortality rate in children < 10 years of age is 5 times higher than adults

Doxycycline: Dosing

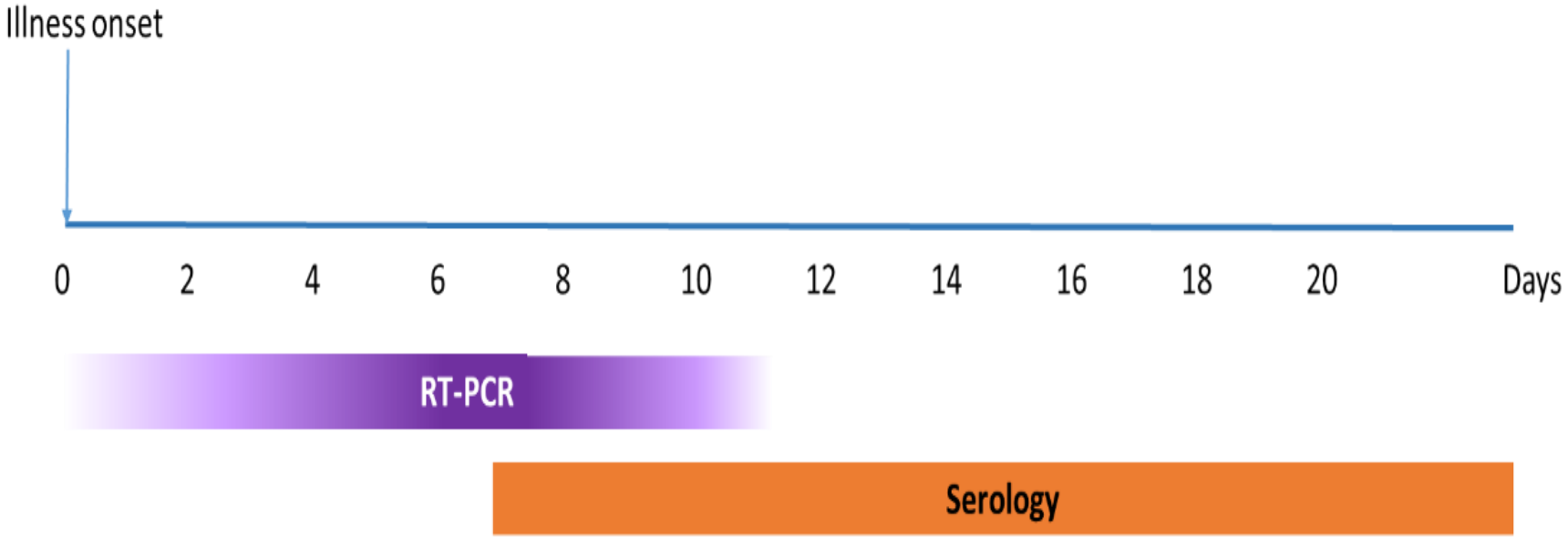
- Dosing:
  - Adult or child ≥ 45 kg: 100 mg twice daily
  - Child < 45 kg: 2.2 mg/kg/day twice daily
  - Pregnant adult or tetracycline allergy: consult infectious diseases specialist, in severe cases doxycycline may be warranted
- Duration of treatment: 5-7 days (or 3 days past defervescence)

Diagnostics

Laboratory Diagnosis

- Serology (serum)
  - Four-fold change in IgG-specific antibody titer by indirect immunofluorescence antibody (IFA) assay in paired serum samples
    - Acute: first week
    - Convalescent: 2 to 4 weeks later
- Molecular diagnostics (whole blood, biopsy)
  - Sensitivity can be low during early acute illness
    - New assays with improved detection
- IHC staining of organism from skin or tissue biopsy specimen

Estimated Utility of Diagnostic Tests Over Time



Rickettsia species RT-PCR Assay

- FDA 510(k)-cleared
- Now available through Laboratory Response Network (LRN) Laboratories
  - More than 20 state and regional labs have already requested the test
- Whole blood only
- Limitations
  - *Rickettsiae* found in the endothelial cells
  - Decreased sensitivity following doxycycline administration
- Treatment is still recommended based on clinical signs and symptoms

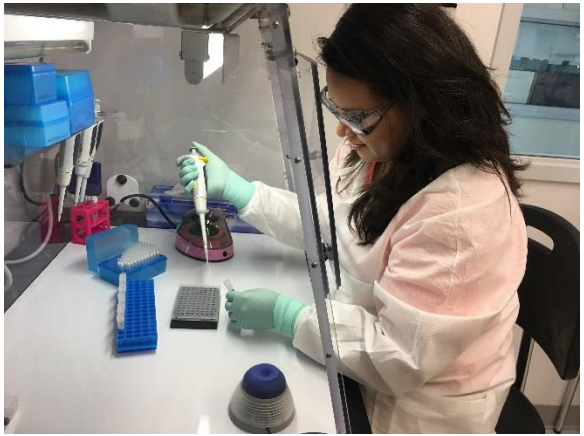


Image courtesy of Cecilia Kato and Ida Chung

Key Points

- Rapidly progressing and may be fatal
- Nonspecific early clinical signs making it difficult to diagnose
- Increasing incidence

But…

- Treated with doxycycline in all age groups
- Antibiotic treatment is very effective if initiated early (within the first 5 days of illness)

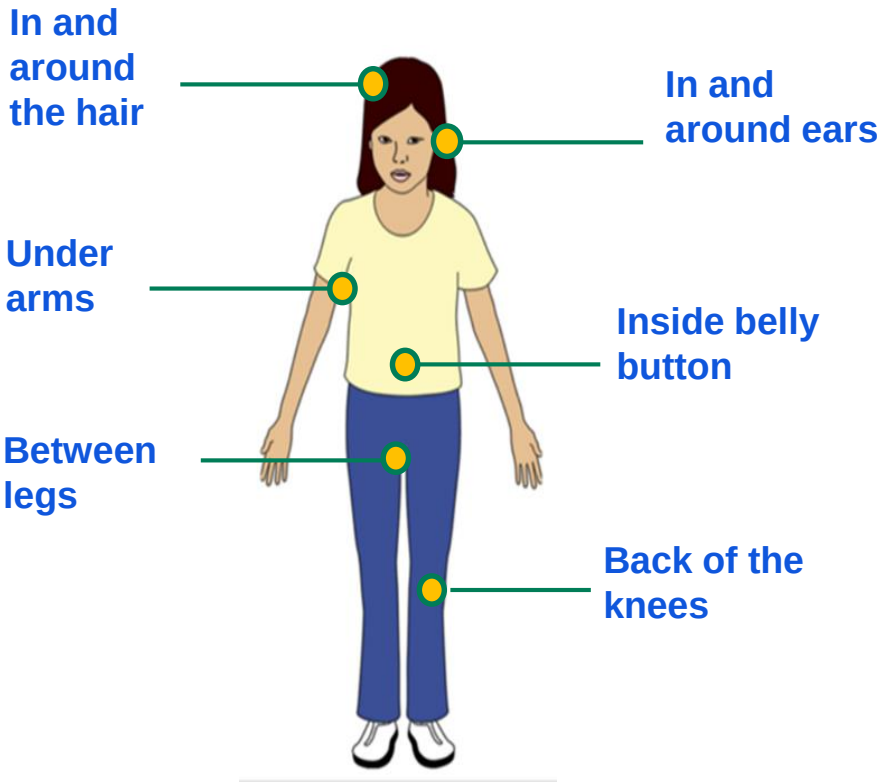
Prevention

Before You Go Outdoors

- Know where ticks live and avoid tick habitats
- Treat clothing with 0.5% permethrin
- Use Environmental Protection Agency (EPA)-registered insect repellents containing DEET, picaridin, IR3535, oil of lemon eucalyptus (OLE), para-menthane-diol (PMD), or 2-undecanone
- Treat your pets for ticks

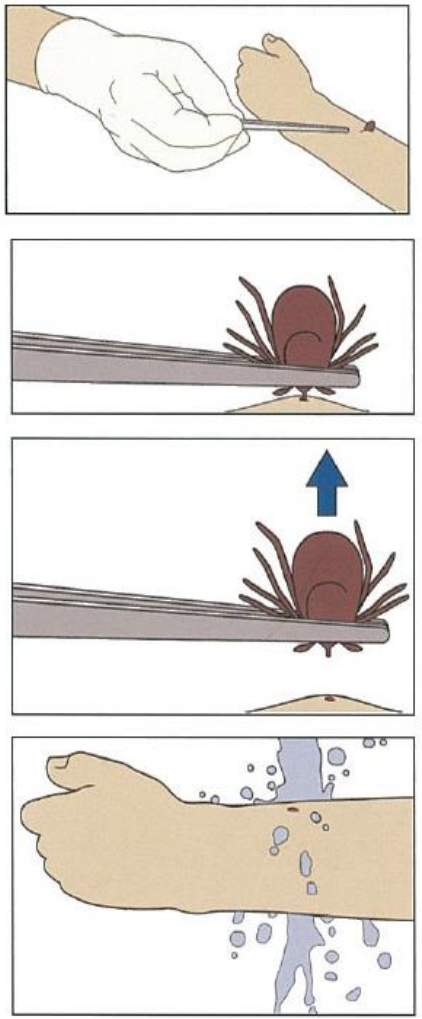
After You Come Indoors

- Check your clothing and gear for ticks
  - Tumble clothes in the dryer on high heat for 10 minutes
  - Damp clothes may need longer
- Shower soon after being outdoors
  - Washes away unattached ticks
- Check your body for ticks
  - Get someone to help
- Quickly remove attached ticks



Removing an Attached Tick

- Use fine-tipped tweezers to grasp the tick as close to the skin's surface as possible.
- Pull upward with steady, even pressure.
- Clean the bite area and your hands with rubbing alcohol, an iodine scrub, or soap and water.
- Never crush a tick with your fingers.



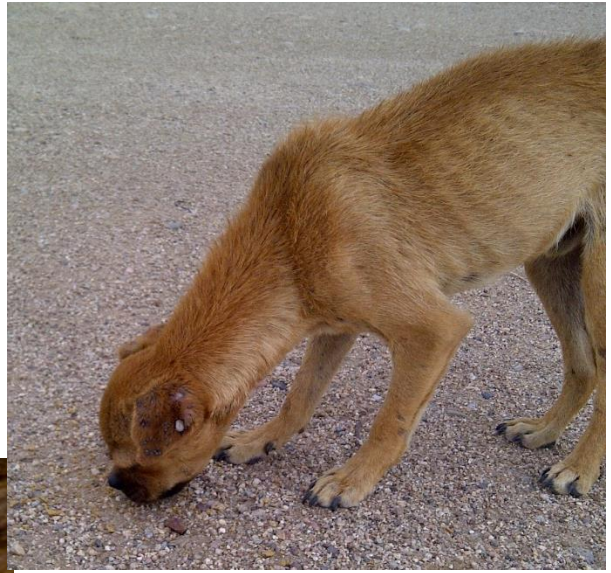
Epidemic RMSF

RMSF in Arizona, 2003-2017

- 2003 death of a 1 yr old American Indian child who had not left his community
- Investigations revealed RMSF spread by different tick vector
  - *Rhipicephalus sanguineus* (brown dog tick)
- Epidemic levels of disease
  - 388 cases and 23 deaths
  - Incidence approximately 150 times the national average
- Half of cases and deaths in children <10 years

Different Tick: Different Epidemiology

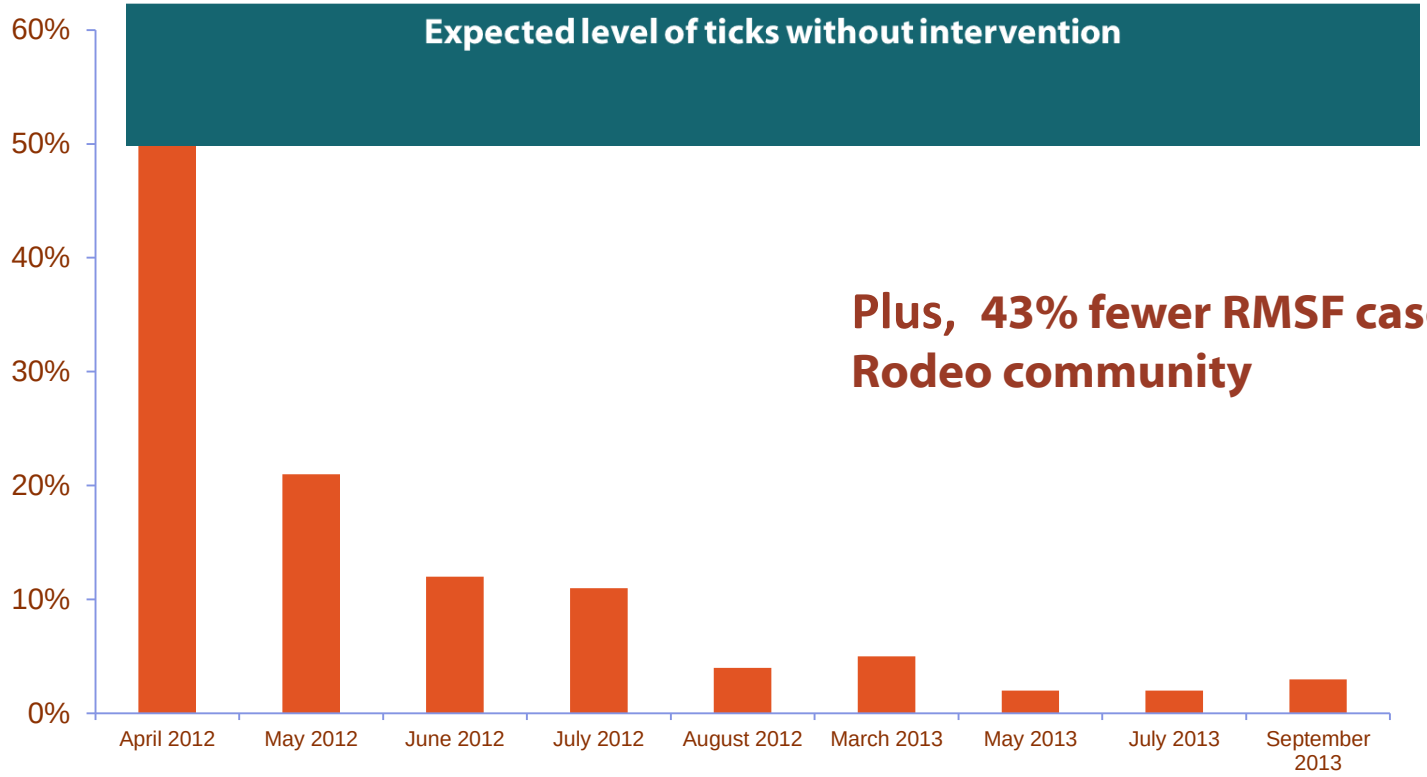
- Preferentially feeds and breeds on domestic dogs at all life stages
- Adapted for peri-domestic infestations
- Active year-round in Arizona
- All life stages can transmit *R. rickettsii*
- High rates of infection
  (~5%, compared to <1% *D. variabilis*)
- Dog-centered life-cycle creates opportunity for host-targeted control



An Ounce of Prevention: the RMSF Rodeo

- Integrated pest management techniques
- 600 home community, ~1000 dogs
- Methods:
  - Monthly yard treatments
  - Long-lasting tick collars on all dogs
  - Free spay and neuter opportunities
  - Community education

Tick Counts on Dogs at RMSF Rodeo Homes



Plus, 43% fewer RMSF cases in the Rodeo community

RMSF Rodeo Success

- Pilot program demonstrated that by targeting the tick on the dog, in the environment, and before it can bite people effectively reduced the incidence of RMSF
- Methods have been adapted and used in other impacted communities
- Significant progress has been made, however, tribes are limited by cost, infrastructure, and scale of interventions needed

RMSF—A Binational Issue

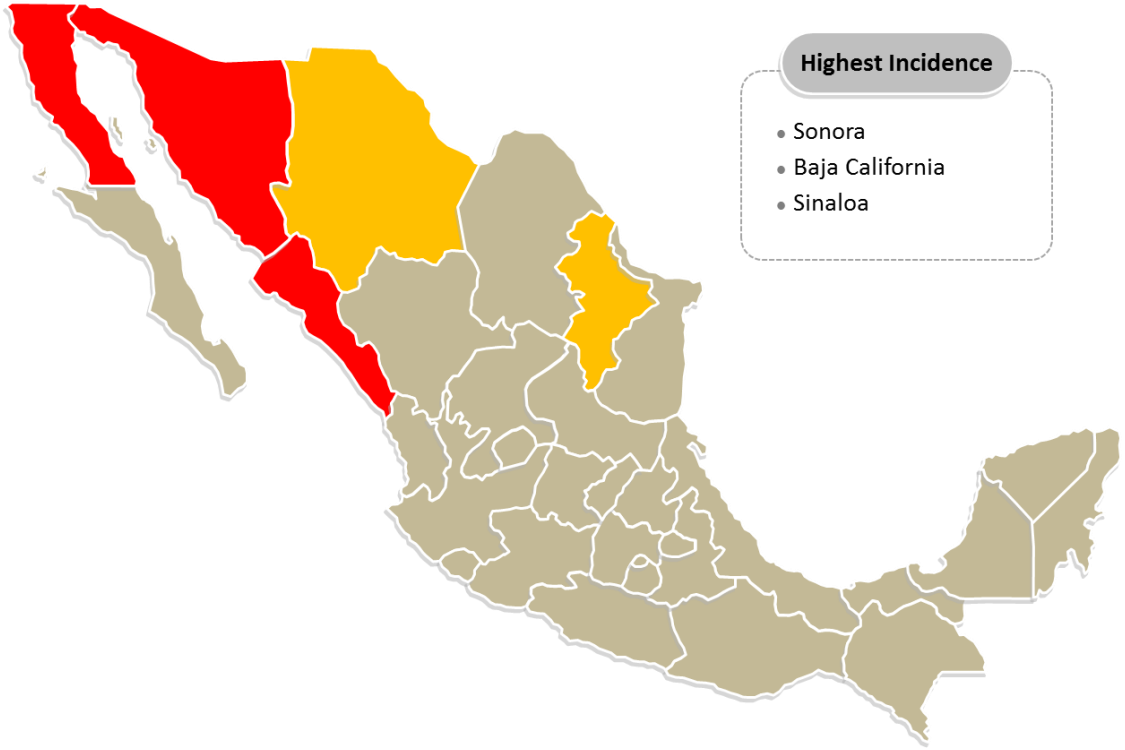
Figure 1: Locations of historical and contemporary outbreaks of Rocky Mountain spotted fever in Mexico and collection sites of ticks infected with *Rickettsia rickettsii*

http://thelancet.com/journals/laninf/article/PIIS1473-3099(17)30173-1/abstract

RMSF in Mexico

- Re-emergence of disease in early 2000s particularly states bordering the US
- Modern day case fatality rates as high as 55%
- Cases occur in impoverished communities with free-roaming dogs
- RMSF spread by the brown dog tick
- Fatal binational cases have been documented

Different country, same ecology

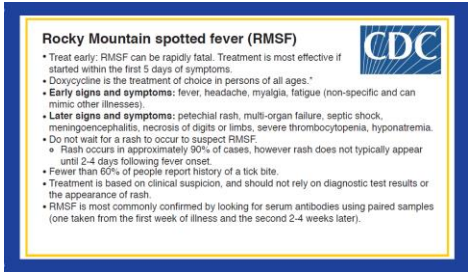


Conclusions

- RMSF starts with non-specific symptoms, rapidly fatal
- Early treatment is essential to prevent severe morbidity and death
- Doxycycline is the treatment in all age groups
- Epidemics of RMSF are occurring in Arizona tribal communities and parts of Mexico spread by the brown dog tick
- **Prevention is key no matter where you are**

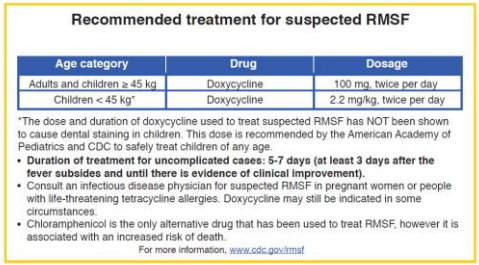
New Provider Resources for RMSF

- Pocket cards



Rocky Mountain spotted fever (RMSF)

- Treat early: RMSF can be rapidly fatal. Treatment is most effective if started within the first 5 days of symptoms.
- Doxycycline is the treatment of choice in persons of all ages.*
- **Early signs and symptoms:** fever, headache, myalgia, fatigue (non-specific and can mimic other illnesses).
- **Later signs and symptoms:** petechial rash, multi-organ failure, septic shock, meningoencephalitis, necrosis of digits or limbs, severe thrombocytopenia, hyponatremia.
- Do not wait for a rash to occur to suspect RMSF.
  - Rash occurs in approximately 90% of cases, however rash does not typically appear until 2-4 days following fever onset.
- Fewer than 60% of people report history of a tick bite.
- Treatment is based on clinical suspicion, and should not rely on diagnostic test results or the appearance of rash.
- RMSF is most commonly confirmed by looking for serum antibodies using paired samples (one taken from the first week of illness and the second 2-4 weeks later).



Recommended treatment for suspected RMSF

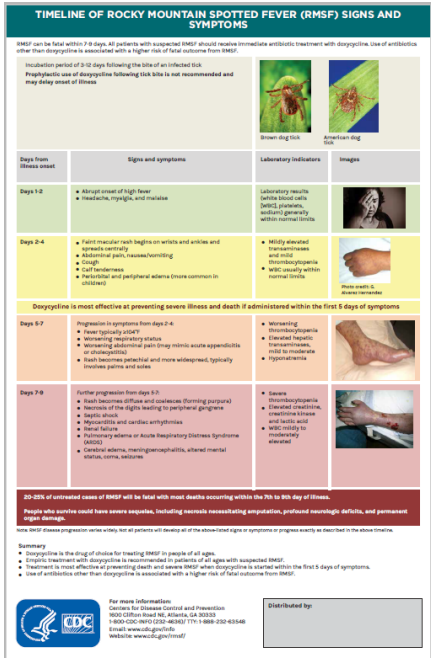
Age category	Drug	Dosage
Adults and children ≥ 45 kg	Doxycycline	100 mg, twice per day
Children < 45 kg*	Doxycycline	2.2 mg/kg, twice per day

*The dose and duration of doxycycline used to treat suspected RMSF has NOT been shown to cause dental staining in children. This dose is recommended by the American Academy of Pediatrics and CDC to safely treat children of any age.

- **Duration of treatment for uncomplicated cases: 5-7 days (at least 3 days after the fever subsides and until there is evidence of clinical improvement).**
- Consult an infectious disease physician for suspected RMSF in pregnant women or people with life-threatening tetracycline allergies. Doxycycline may still be indicated in some circumstances.
- Chloramphenicol is the only alternative drug that has been used to treat RMSF, however it is associated with an increased risk of death.

For more information, www.cdc.gov/rmsf

- Timeline



TIMELINE OF ROCKY MOUNTAIN SPOTTED FEVER (RMSF) SIGNS AND SYMPTOMS

RMSF can be fatal within 7-9 days. All patients with suspected RMSF should receive immediate antibiotic treatment with doxycycline. Use of antibiotics other than doxycycline is associated with a higher risk of fatal outcome from RMSF.

Incubation period of 3-12 days following the bite of an infected tick

Prophylactic use of doxycycline following tick bite is not recommended and may delay onset of illness

Brown dog tick — American dog tick

Days from illness onset	Signs and symptoms	Laboratory indicators	Images
Days 1-2	• Abrupt onset of high fever • Headache, myalgia, and malaise	Laboratory results (white blood cells [WBC], platelets, sodium) generally within normal limits	
Days 2-4	• Faint macular rash begins on wrists and ankles and spreads centrally • Abdominal pain, nausea/vomiting • Cough • Calf tenderness • Periorbital and peripheral edema (more common in children)	• Mildly elevated transaminases and mild thrombocytopenia • WBC usually within normal limits	Photo credit: G. Alvarez Hernandez

Doxycycline is most effective at preventing severe illness and death if administered within the first 5 days of symptoms

Days 5-7	Progression in symptoms from days 2-4: • Fever typically ≥104°F • Worsening respiratory status • Worsening abdominal pain (may mimic acute appendicitis or cholecystitis) • Rash becomes petechial and more widespread, typically involves palms and soles	• Worsening thrombocytopenia • Elevated hepatic transaminases, mild to moderate • Hyponatremia	
Days 7-9	Further progression from days 5-7: • Rash becomes diffuse and coalesces (forming purpura) • Necrosis of the digits leading to peripheral gangrene • Septic shock • Myocarditis and cardiac arrhythmias • Renal failure • Pulmonary edema or Acute Respiratory Distress Syndrome (ARDS) • Cerebral edema, meningoencephalitis, altered mental status, coma, seizures	• Severe thrombocytopenia • Elevated creatinine, creatinine kinase and lactic acid • WBC mildly to moderately elevated	

20-25% of untreated cases of RMSF will be fatal with most deaths occurring within the 7th to 9th day of illness.

People who survive could have severe sequelae, including necrosis necessitating amputation, profound neurologic deficits, and permanent organ damage.

Note: RMSF disease progression varies widely. Not all patients will develop all of the above-listed signs or symptoms or progress exactly as described in the above timeline.

Summary

- Doxycycline is the drug of choice for treating RMSF in people of all ages.
- Empiric treatment with doxycycline is recommended in patients of all ages with suspected RMSF.
- Treatment is most effective at preventing death and severe RMSF when doxycycline is started within the first 5 days of symptoms.
- Use of antibiotics other than doxycycline is associated with a higher risk of fatal outcome from RMSF.

For more information:
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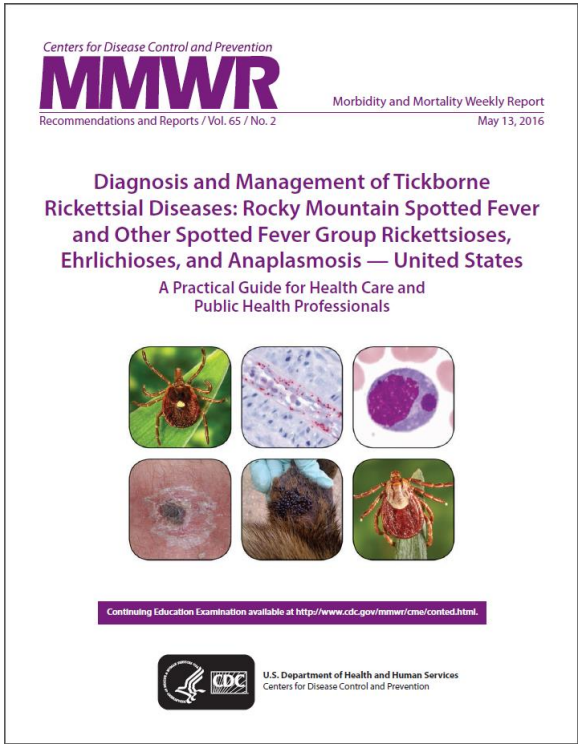

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Upcoming COCA Call

"Recommendations for the Use of Herpes Zoster Vaccines"

Thursday, May 10, 2018

2:00-3:00 ET

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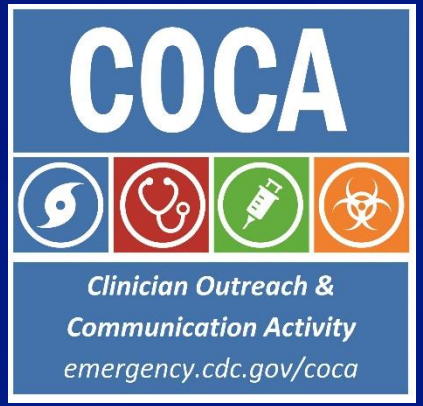
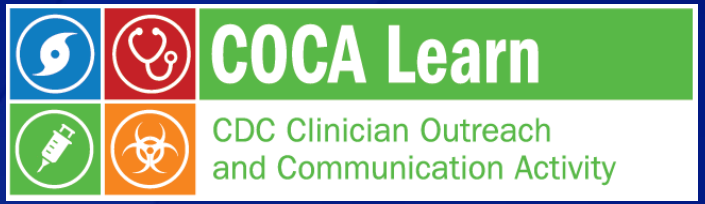
- Emerging health threats
- Emergency preparedness and response conferences and training opportunities



http://emergency.cdc.gov/coca

COCA Products & Services

Promotes COCA Calls and contains all information subscribers need to participate in COCA Calls. COCA Calls are done as needed.

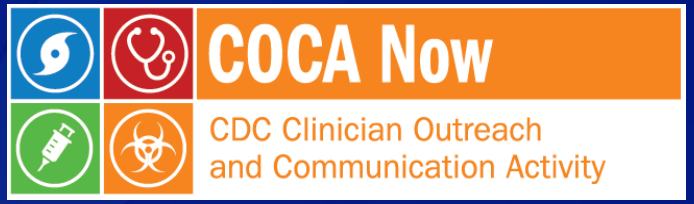


Monthly email that provides information on CDC training opportunities, conference and training resources located on the COCA website, the COCA Partner Spotlight, and the Clinician Corner.

Provides comprehensive CDC guidance so clinicians can easily follow recommendations.

COCA Products & Services

Monthly email that provides new CDC & COCA resources for clinicians from the past month and additional information important during public health emergencies and disasters.



Informs clinicians of new CDC resources and guidance related to emergency preparedness and response. This email is sent as soon as possible after CDC publishes new content.

CDC's primary method of sharing cleared information about urgent public health incidents with public information officers; federal, state, territorial, and local public health practitioners; clinicians; and public health laboratories.

CDC Clinician Outreach and Communication Activity - COCA

@CDCClinicianOutreachAndCommunicationActivity

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CDC Clinician Outreach and Communication Activity - COCA shared their event.

October 31 at 1:18pm

Clinicians, you can earn FREE CE with this COCA Calll Join us for this COCA Call November 7, 2017 at 2:00PM.

Thank you for joining!

Centers for Disease Control and Prevention
Atlanta, Georgia
http://emergency.cdc.gov/coca