

COCA Call Information

- ❑ For the best quality audio, we encourage you to use your computer's audio.
- ❑ Webinar Link:
<https://zoom.us/j/275324866>
- ❑ If you cannot join through digital audio, you may join by phone in listen-only mode:
 - US: +1 646 876 9923 or +1 669 900 6833
 - Webinar ID: 275 324 866
- ❑ All questions for the Q&A portion must be submitted through the webinar system via the **Q&A button**. Please do not ask a question using the chat button.

Guidance for Using Intravenous Artesunate for Treating Severe Malaria in the United States

Clinician Outreach and Communication Activity (COCA) Webinar

emergency.cdc.gov/coca

March 28, 2019



Continuing Education for this COCA Call

All continuing education (CME, CNE, CEU, CECH, ACPE, CPH, and AAVSB/RACE) for COCA Calls are issued online through the **CDC Training & Continuing Education Online system** (<http://www.cdc.gov/TCEOnline/>).

Those who participated in today's COCA Call and who wish to receive continuing education should complete the online evaluation by **April 29, 2019** with the course code **WC2922**.

Those who will participate in the on demand activity and wish to receive continuing education should complete the online evaluation between **April 30, 2019** and **April 30, 2021** will use course code **WD2922**.

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Continuing Education Disclaimer

- ❑ **In compliance with continuing education requirements, CDC, our planners, our presenters, and their spouses/partners wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters.**
- ❑ **Planners have reviewed content to ensure there is no bias.**
- ❑ **This webinar will focus on the new treatment guidelines for severe malaria in the United States. Content will include discussion of the unlabeled use of a product and a product under investigational use. Starting April 1, 2019, there will be no FDA-approved, commercially available intravenous (IV) antimalarial for the treatment of severe malaria in the United States. IV artesunate, the WHO-recommended first-line drug for severe malaria, is not FDA approved but is available through CDC under an expanded access investigational new drug (IND) protocol. IV artesunate will be the only option in the United States for treatment of severe malaria.**
- ❑ **CDC did not accept commercial support for this continuing education activity.**

To Ask a Question

- ❑ **Using the Webinar System**
 - Click the **Q&A** button in the webinar.
 - Type your question in the **Q&A** box.
 - Submit your question.
 - Please do not submit a question using the chat button.
- ❑ **For media questions, please contact CDC Media Relations at 404-639-3286 or send an email to media@cdc.gov.**
- ❑ **If you are a patient, please refer your questions to your healthcare provider.**

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

- Identify the criteria for severe malaria;
- Describe treatment of severe malaria, including interim treatment, and use of IV artesunate; and
- Describe how to obtain IV artesunate from CDC.

Today's First Presenter

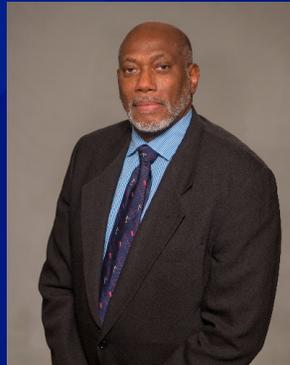


Kathrine Tan, MD, MPH

Chief, Domestic Response Unit/Malaria Branch
Division of Parasitic Diseases and Malaria
Center for Global Health
Centers for Disease Control and Prevention



Today's Second Presenter



Clive Brown, MBBS, MPH, MS

Branch Chief, Quarantine and Border Health Services Branch
Division of Global Migration and Quarantine
National Center for Emerging and Zoonotic Diseases
Centers for Disease Control and Prevention



IV Artesunate for Treatment of Severe Malaria in the United States

Kathrine Tan, MD, MPH

Unit Chief, Domestic Response Unit, Malaria Branch

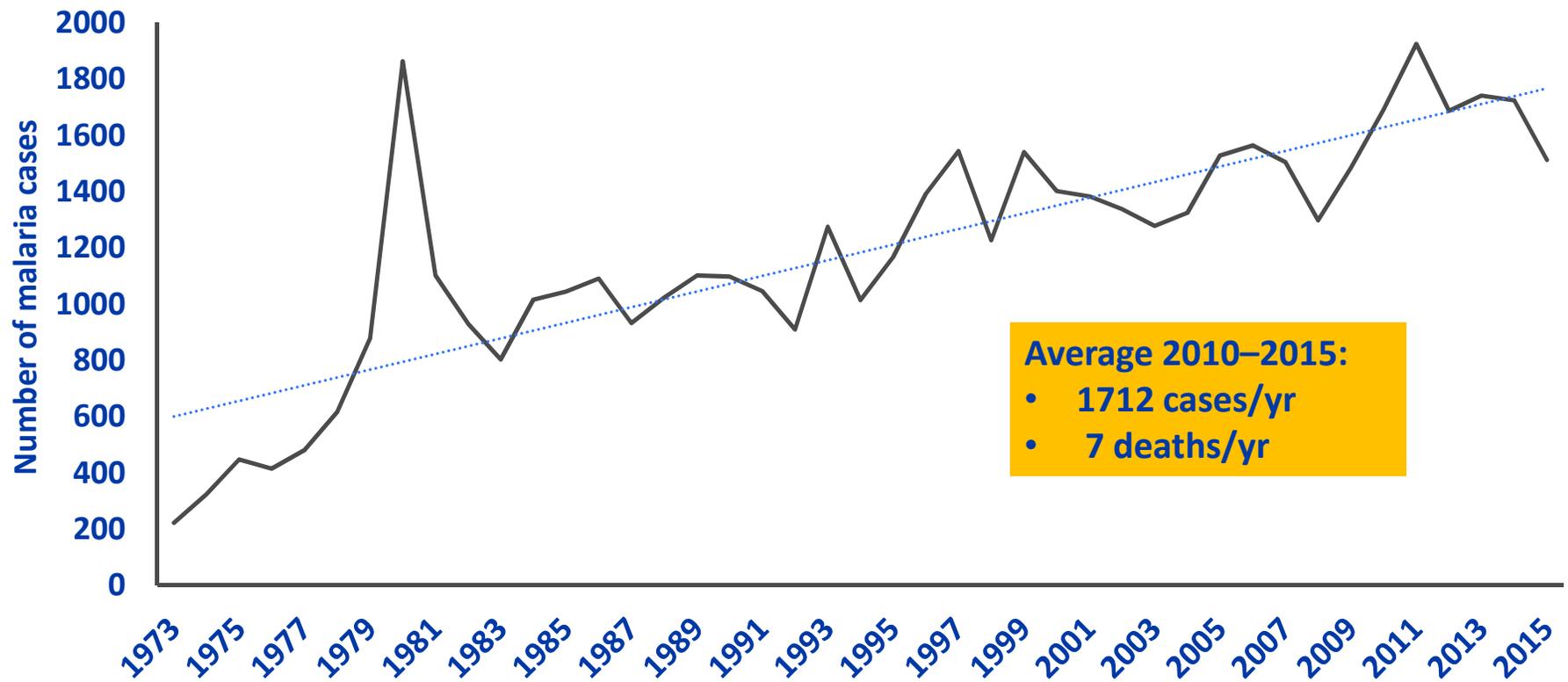
COCA Webinar

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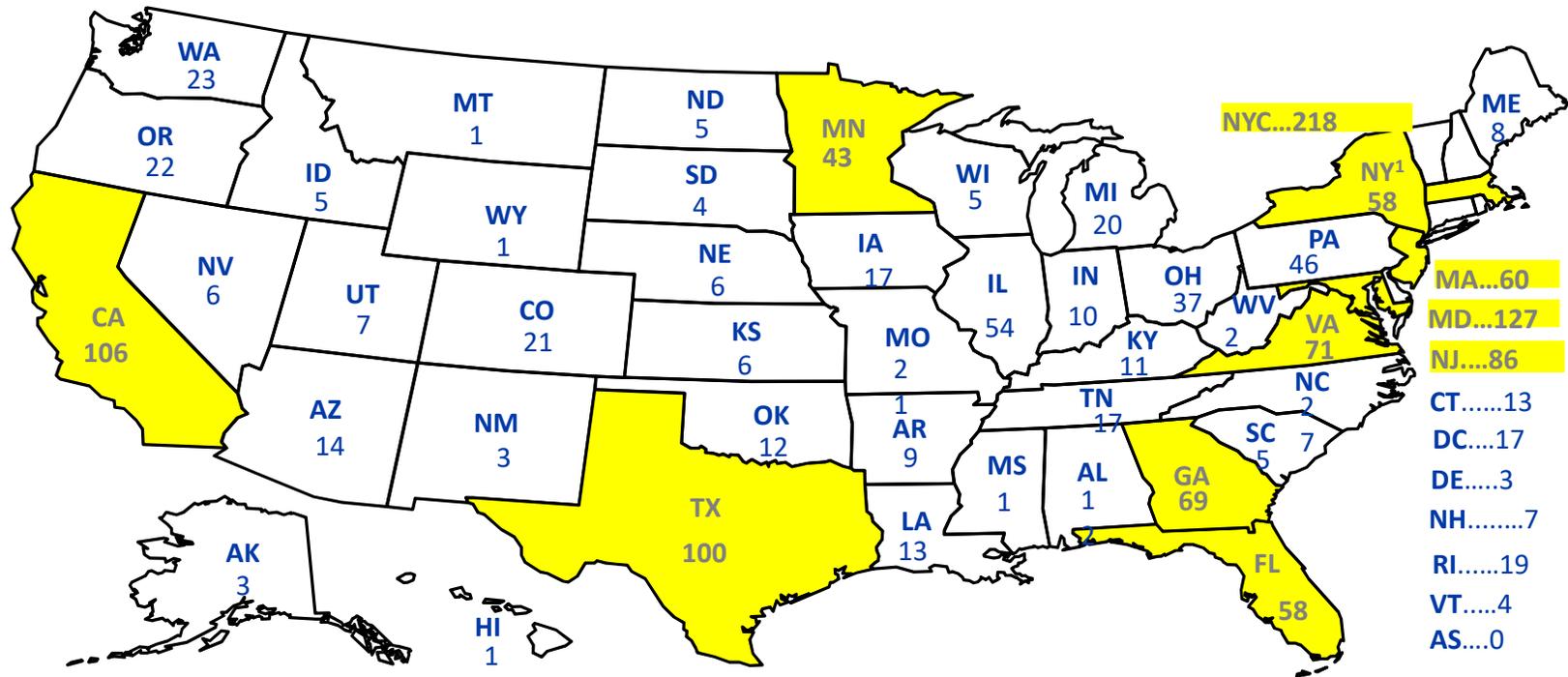
Center for Global Health
Division of Parasitic Diseases and Malaria



Increase in Malaria Cases Reported in the U.S. (1973–2015)



Eleven Jurisdictions Had 2/3 of Malaria Cases in 2015



➔ At least 1 malaria case each state

¹Cases in New York state do not include those from New York City (NYC)

Presentation of Malaria

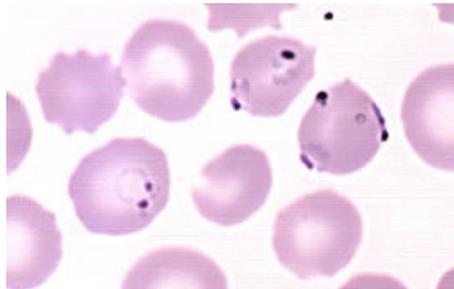
- **Non-specific symptoms: fever, chills, myalgias, headaches**
 - Mistaken for the flu or gastrointestinal illness
- **Acute illness most often within a month of returning from travel**
- **Relapses of malaria can occur with *P. vivax* and *P. ovale***
 - Hypnozoites can lie dormant in the liver, then emerge later

Diagnosis and Work Up

- **Think malaria if:**
 - Fever
 - History of travel to endemic area
- **Diagnostic test**
 - Thick and thin blood smears STAT
 - If negative, repeat every 12–24 hrs for a total of 3 sets
 - Thick smears best for detection of parasites
 - Thin smears for species identification and determining parasite density
 - Rapid diagnostic test if smear not immediately available (confirm with smear)
- **Other initial tests**
 - CBC, chemistry panel, other tests and studies as needed for differential

Thick and Thin Blood Smears

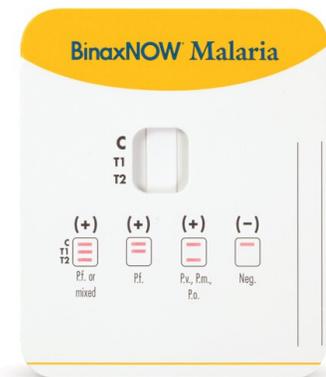
- **Speciation**
 - Different species of malaria have distinguishing characteristics on smears
 - Treatment can vary for different species
- **Parasitemia**
 - Number of infected cells per 100 red cells
 - Useful for identifying severe disease and monitoring therapy



P. falciparum

Additional Diagnostic Options

- **Rapid Diagnostic tests (RDTs)**
 - Antigen detection
 - Can rapidly establish diagnosis
 - Does not confirm species
 - No quantification
 - Must be confirmed by microscopy
- **PCR**
 - Can be more sensitive than microscopy
 - Results not available soon enough to establish diagnosis
 - More useful for species confirmation
- **Antibody testing — not helpful for acute management of malaria**



Severe Malaria Criteria (any one of the following)

- **Parasitemia >5%**
- **Cerebral malaria (seizures, impaired consciousness)**
- **Acute respiratory distress syndrome**
- **Disseminated intravascular congestion**
- **Sepsis (hypotension, acidosis)**
- **Acute kidney injury, hemoglobinuria**
- **Jaundice (usually seen with other signs/symptoms)**
- **Severe anemia (Hb<7)**

Severe Malaria in the United States

- **About 300 severe cases per year**
- **IV quinine from CDC Drug Service until 1991**
- **IV quinidine, stereoisomer of quinine**
 - FDA approved as an antiarrhythmic, available at hospitals, and effective antimalarial
 - 1991 – added treatment of severe malaria to label
- **IV quinidine — the only FDA-approved commercially available IV antimalarial in the United States**

IV Artesunate

- **Artesunate superior to quinine:**
 - SEQUAMAT (2005): Reduction of mortality by 34.7%
 - AQUAMAT (2010): Reduction of mortality by 22.5%
- **WHO-recommended, first-line drug for severe malaria**
- **Neither FDA approved nor commercially available in the United States**

Artesunate Development for the U.S.

- **Walter Reed Army Institute of Research (WRAIR) and the U.S. Army Medical Materiel Development Activity (USAMMDA) worked on research and development of artesunate**
- **Small batches made for expanded access investigational new drug (IND) protocol**

IV Artesunate Expanded Access IND (2007)

- **WRAIR/USAMMDA provides IV artesunate**
- **CDC releases drug if**
 - Quinidine not available
 - Quinidine intolerance
 - Quinidine failure
 - Contraindication to quinidine
- **Artesunate prepositioned at 9 quarantine stations**
- **About 40–50 releases a year**

Treatment of Severe Malaria in the United States before April 1, 2019

- **IV quinidine gluconate first line**
 - The only FDA-approved intravenous antimalarial in the U.S.
- **IV artesunate (first line per WHO)**
 - Not FDA approved, not commercially available in the U.S.
 - Available from CDC under an IND protocol

After April 1st, 2019
IV Artesunate will be the first-line drug for severe malaria

www.cdc.gov/malaria

- **Treatment guidance**
- **Expanded access IND protocol**
- **More information about artesunate**

Criteria for Release of IV Artesunate

Parenteral treatment required due to one or more:

- **High density parasitemia (>5%)**
- **Severe malaria based on:**
 - Impaired consciousness
 - Seizures
 - Circulatory collapse/shock
 - Pulmonary edema or acute respiratory distress syndrome
 - Acidosis
 - Acute kidney injury
 - Abnormal bleeding or disseminated intravascular coagulation
 - Jaundice (usually with other criteria)
 - Severe anemia (Hb < 7 g/dL)
- **Unable to take oral medications**

IV Artesunate Regimen

- **Artesunate: 4 doses total, given at 0, 12, 24, and 48 hours**
 - Adults and children $\geq 20\text{kg}$: 2.4 mg/kg per dose
 - Children $< 20\text{kg}$: 3.0 mg/kg per dose

FOLLOWED BY :

- **Artemether-lumefantrine (Coartem[®]) for 3 days OR**
- **Atovaquone-proguanil (Malarone[®]) for 3 days OR**
- **Doxycycline for 7 days OR**
- **Clindamycin (if doxycycline is contraindicated) for 7 days OR**
- **Mefloquine for 2 doses**
- **If unable to take oral medications after 3 days**
 - Continue IV artesunate up to 7 days OR
 - Switch to IV doxycycline or IV clindamycin

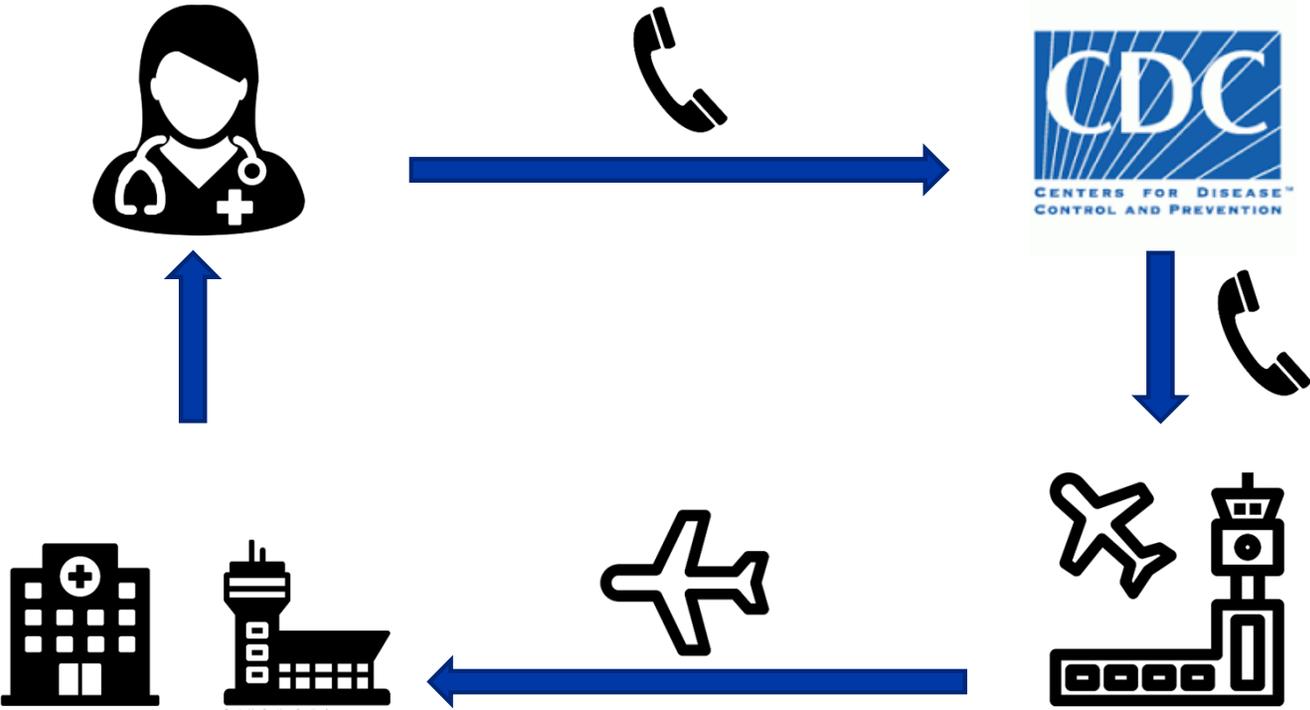
Dose Adjustments and Safety

- **Renal or hepatic dose adjustment not needed**
- **Use actual weight for dosing**
- **Can be used in pregnant and lactating women**
 - More limited data for 1st trimester, but no evidence of adverse outcomes – benefits outweigh risks

Interim Treatment While Waiting for Artesunate

- **Oral drug options**
 - Artemether-lumefantrine (Coartem®)
 - Atovaquone-proguanil (Malarone®)
 - Quinine
 - Mefloquine (if other drugs not available, and benefits outweighs risks)
- **May need to consider nasogastric tube, or anti-emetic prior to antimalarial**
- **Do not use: doxycycline, tetracycline, clindamycin — slow acting, limited benefit acutely**

Artesunate Logistics



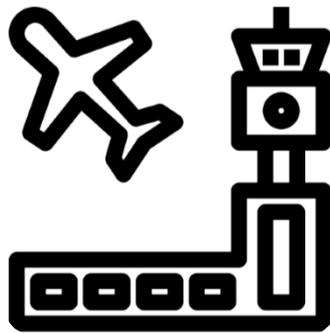
Expanded Access IND Protocol

- **FDA regulatory pathway that allows access to an investigational drug (i.e. non-FDA approved) under certain circumstances**
- **CDC “holds” IND protocol**
 - Ensure appropriate use of drug by releasing drug if inclusion criteria are met
 - Fulfill FDA reporting requirements
 - Adverse events
 - Annual reports
- **Artesunate IND protocol available online**

Local IRB Approval Not Needed

- **CDC IRB serves as central IRB**
- **CDC IRB determined that drug is being given for treatment, not research purposes, and Federal Wide Assurance not needed**

Release of Artesunate Is Not Dependent on Paperwork



Release

- Call CDC
- Criteria met or suspected



Consent

- Sign consent form (patient, kin, or doctor)
- Sign FDA 1572



Treat

- Report adverse events
- Complete report forms

Adverse Event Reporting

- **Clinician to CDC**
 - Serious adverse events: ≤ 24 hours by phone
 - All adverse events: ≤ 10 days via reporting form
- **CDC to FDA**
 - Unexpected fatal or life-threatening adverse reactions ≤ 7 days
 - Serious or unexpected adverse events ≤ 15 days
 - All adverse events: annual report

Post-Artemisinin Delayed Hemolytic Anemia

- **Case definition**
 - At least 7 days after initiation of IV artesunate
 - 10% or greater decrease in hemoglobin
 - Haptoglobin <0.1 g/L
 - LDH >390 U/L or ≥10% over baseline
- **Believed to be due to how artesunate works**
 - Artesunate kills malaria parasite
 - Parasite selectively removed from erythrocytes in the spleen
 - Cells with a reduced life span left circulating
- **Patients with higher parasitemias at higher risk**
- **Monitor for evidence of hemolytic anemia up to 4 weeks after treatment**

When Will Artesunate Be Approved by FDA?

- **Unknown**
- **A drug company must submit a new drug application to FDA to start the review process for approval**
- **Regulatory approval is beyond purview of CDC**

CDC Malaria Clinical Consultation Service

Questions about diagnosis or management of malaria?

CDC Malaria Branch staff available 24/7

Malaria Hotline (M-F 9a-5p EDT)

770-488-7788 or 855-856-4713 (Toll free)

Emergency, after-hours hotline

(770) 488-7100 or malaria@cdc.gov

Additional resources: www.cdc.gov/malaria

Laboratory services at CDC

- **Telediagnosis (dpdx@cdc.gov)**
- **Microscopy review**
- **PCR**
- **Drug levels**
- **Molecular markers for drug resistance**
- **Serology — not for acute diagnosis**
- **All photos or specimens should have a specimen submission form (CDC 50.34)**
 - Shipping instructions online: <https://www.cdc.gov/dpdx/contact.html>

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30329

Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Center for Global Health
Division of Parasitic Diseases and Malaria



To Ask a Question

□ Using the Webinar System

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- Submit your question.
- CDC Media: media@cdc.gov or 404-639-3286.
- Patients, please refer your questions to your healthcare provider.

Today's webinar will be archived

When: Soon after the live call

What: Video with closed captioning

Where: On the COCA Call webpage

https://emergency.cdc.gov/coca/calls/2019/callinfo_032819.asp

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Upcoming COCA Call

Topic: Travel-associated Rickettsioses Guidance: Pre-travel Counseling to Diagnosis, Treatment, and Reporting

Date: Tuesday, May 7, 2019

Time: 2:00-3:00pm EDT

COCA Products & Services

		COCA Call
		CDC Clinician Outreach and Communication Activity

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

		COCA Learn
		CDC Clinician Outreach and Communication Activity

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.

		Clinical Action
		CDC Clinician Outreach and Communication Activity

Provides comprehensive CDC guidance so clinicians can easily follow recommendations.

COCA Products & Services

		COCA Digest
		CDC Clinician Outreach and Communication Activity

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

		COCA Now
		CDC Clinician Outreach and Communication Activity

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.

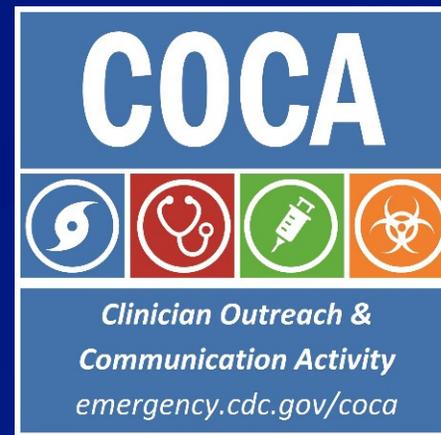


CDC's primary method of sharing cleared information about urgent public health incidents with public information officers; federal, state, territorial, and local public health practitioners; clinicians; and public health laboratories.

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- CDC public health activations
- Emerging health threats
- Emergency preparedness and response conferences and training opportunities



<http://emergency.cdc.gov/coca>

Join Us on Facebook!



The screenshot shows the Facebook profile for 'CDC Clinician Outreach and Communication Activity - COCA'. The profile picture features a diverse group of healthcare professionals. The cover photo shows a group of six people, including a woman in blue scrubs, a woman in a black blazer with a stethoscope, a man in a white lab coat, and others. The page includes a navigation menu on the left with options like Home, About, Posts, Photos, Events, and Community, along with a 'Create a Page' button. The main content area shows a 'Status' section with a text input field and a 'Posts' section featuring a recent event announcement: 'CDC Clinician Outreach and Communication Activity - COCA shared their event. October 31 at 1:18pm. Clinicians, you can earn FREE CE with this COCA Call! Join us for this COCA Call November 7, 2017 at 2:00PM.' The right sidebar displays the organization's location as 'Government Organization in Atlanta, Georgia', shows 21,420 likes and 21,217 followers, and includes a map of the location at 1600 Clifton Rd NE, Atlanta, Georgia 30333.

Thank you for joining!



**Centers for Disease Control and Prevention
Atlanta, Georgia**

<http://emergency.cdc.gov/coca>