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Updated Guidance for Using Intravenous Artesunate to Treat Severe Malaria in the United States

Clinician Outreach and Communication Activity (COCA) Webinar

Tuesday, December 10, 2019

Continuing Education

All continuing education for COCA Calls are issued online through the [CDC Training & Continuing Education Online system \(http://www.cdc.gov/TCEOnline/\)](http://www.cdc.gov/TCEOnline/).

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- 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.
- The presentation will not include any discussion of the unlabeled use of a product or a product under investigational use with the exception of Dr. Tan's discussion of intravenous (IV) antimalarial as there is no FDA-approved, commercially available intravenous (IV) antimalarial for the treatment of severe malaria in the United States. IV artesunate, the first-line drug for treatment of severe malaria in the United States, is not FDA approved but is available through CDC under an expanded use investigational new drug (IND) protocol. IV artesunate is the only option in the United States for treatment of severe malaria.
- CDC did not accept commercial support for this continuing education activity.

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- Using the Webinar System
 - Click on the **Q&A** button in the Zoom webinar system.
 - Type your question in the **Q&A** box.
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- 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.

Today's First Presenter

Katherine R. Tan, MD, MPH

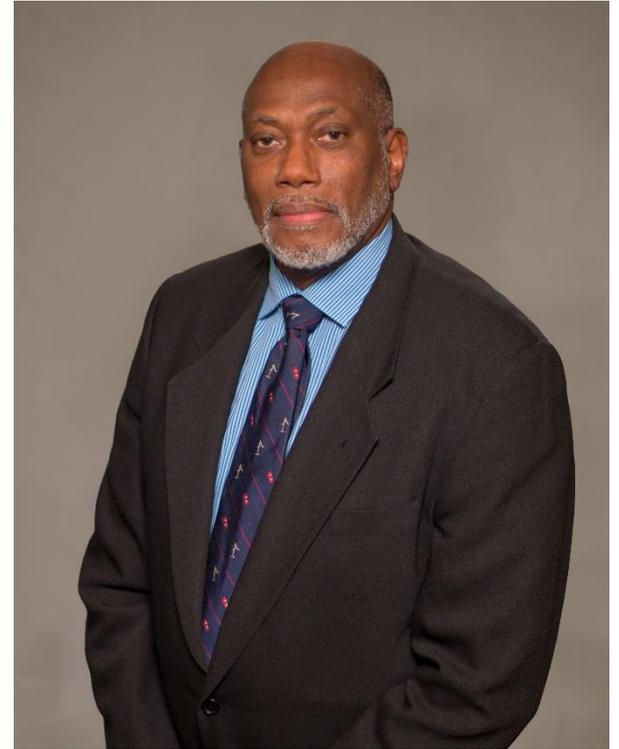
Chief, Domestic Response Unit, Malaria Branch
Division of Parasitic Diseases and Malaria
Center for Global Health
Centers for Disease Control and Prevention



Today's Second Presenter

Clive Brown, MBBS, MPH, MSc, DTM&H

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

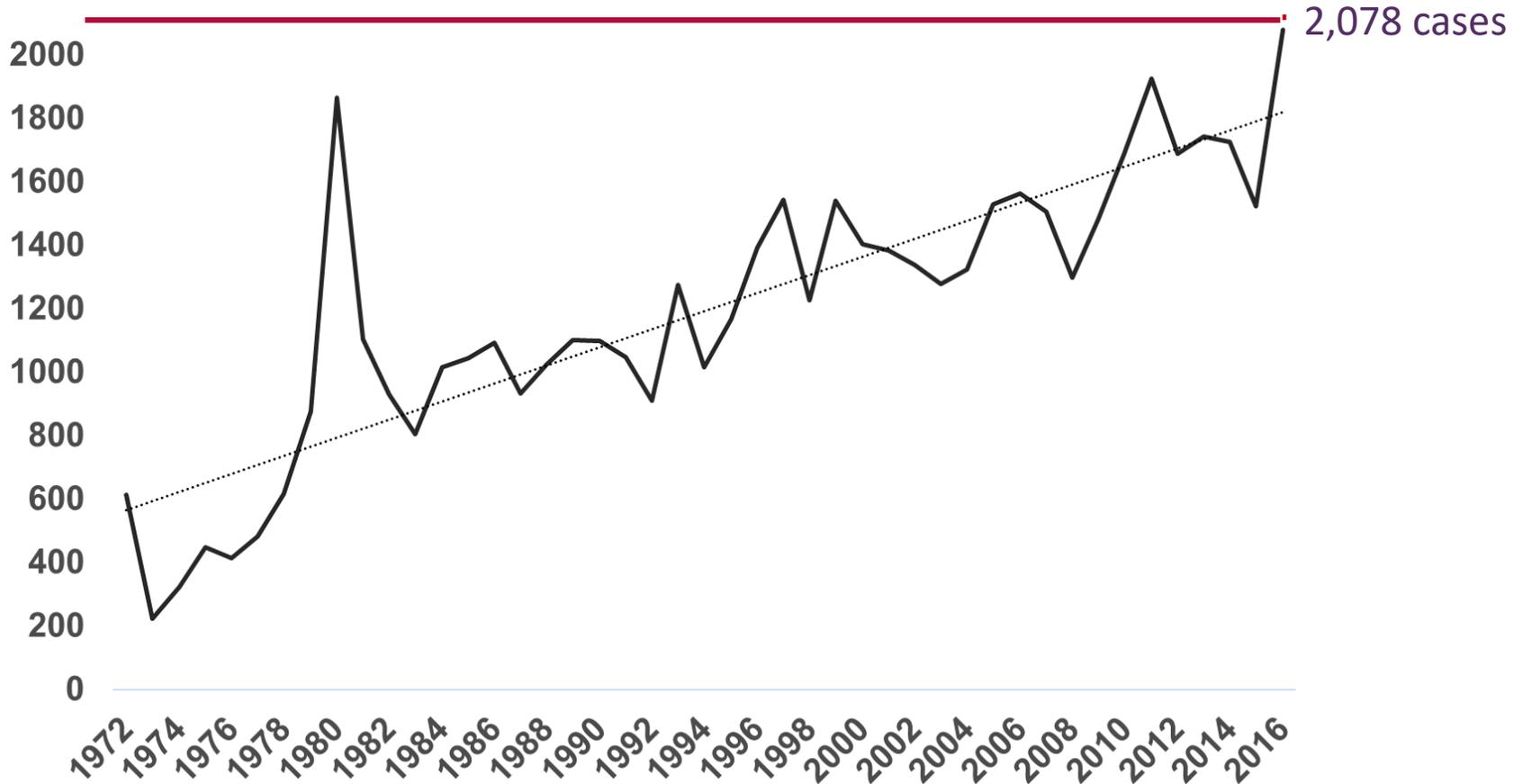




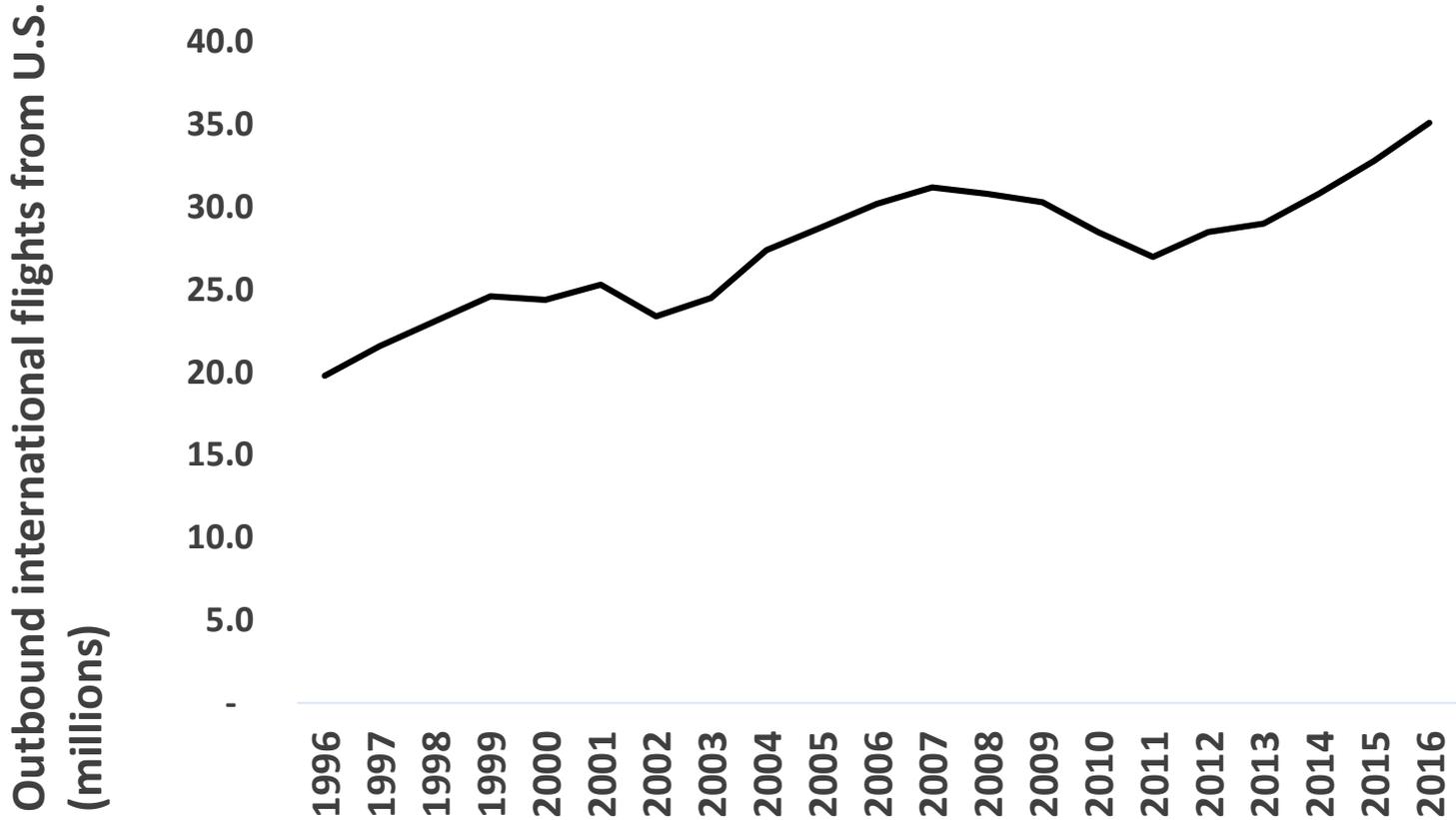
I.V. Artesunate as First-line for Severe Malaria in the United States

Kathrine R. Tan MD, MPH
Chief, Domestic Response Unit/Malaria Branch

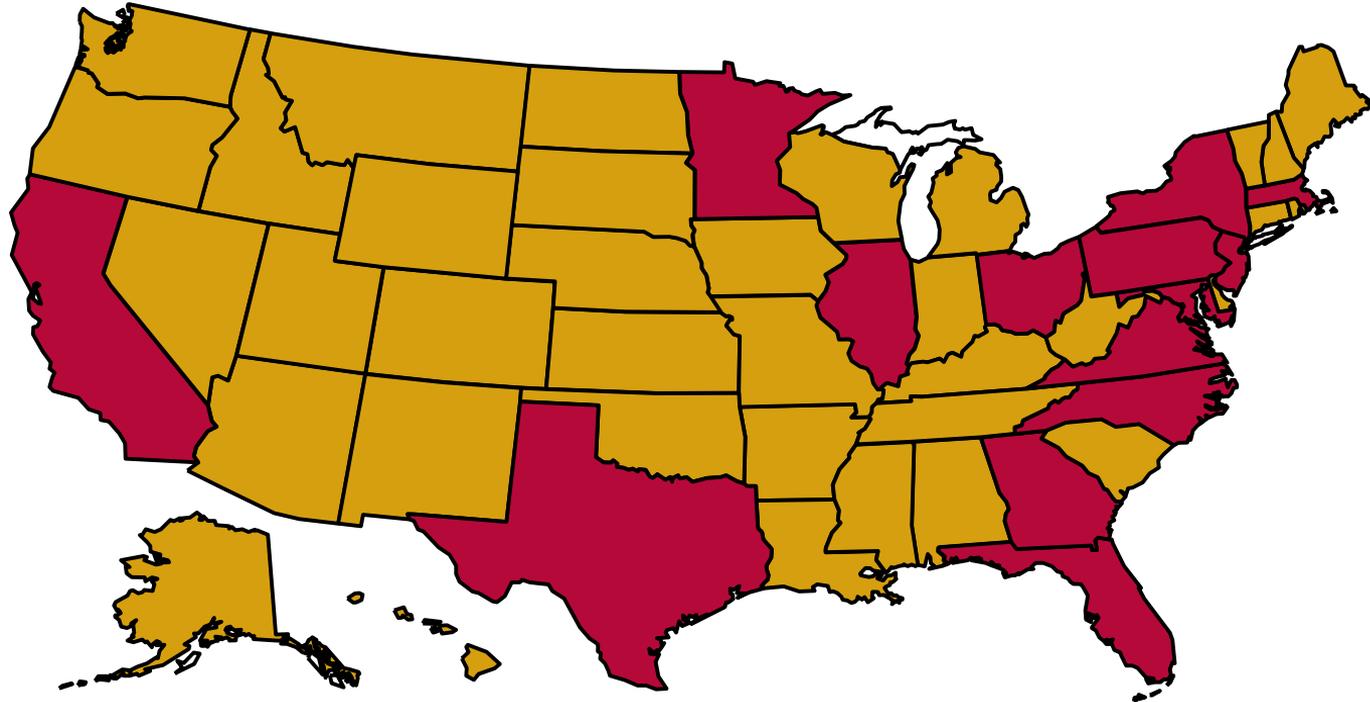
Highest Number of U.S. Malaria Cases Since 1972



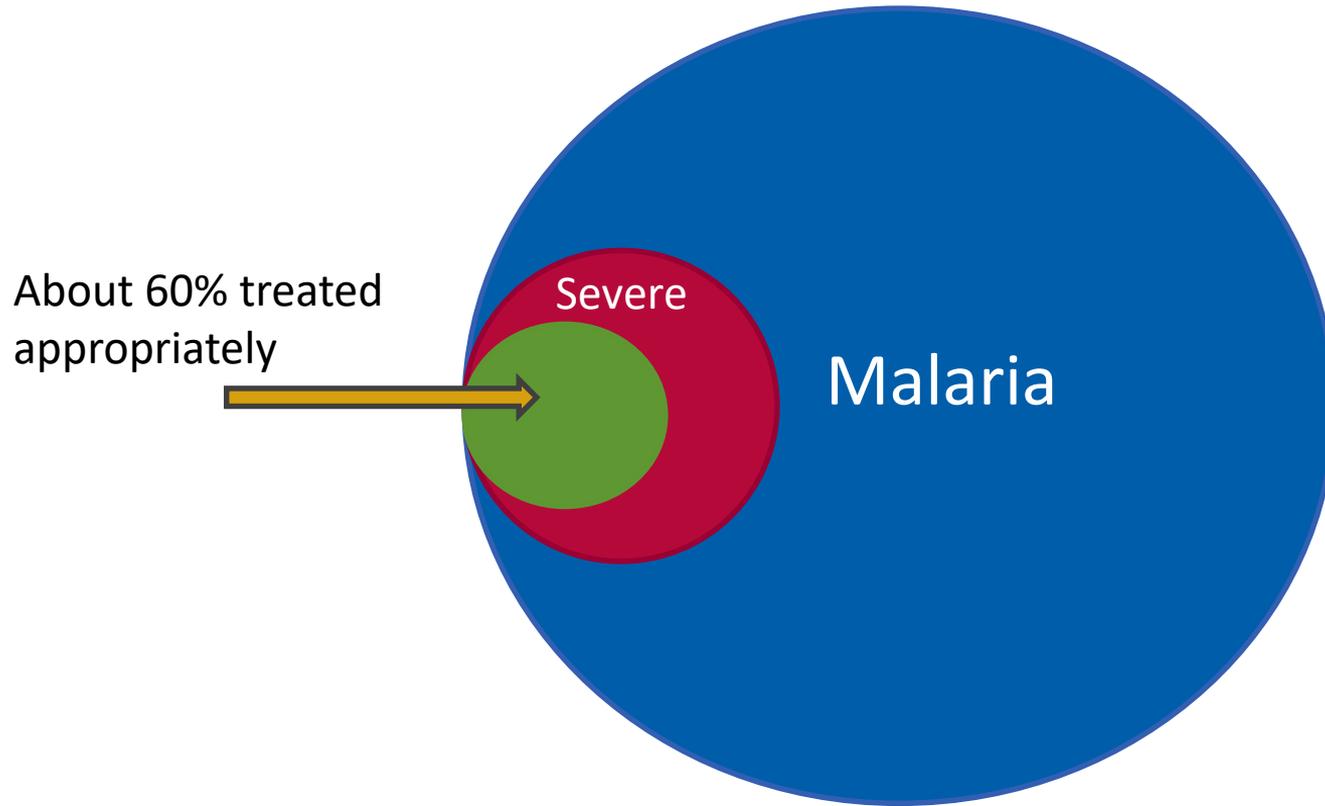
Increase in U.S. Resident International Travel



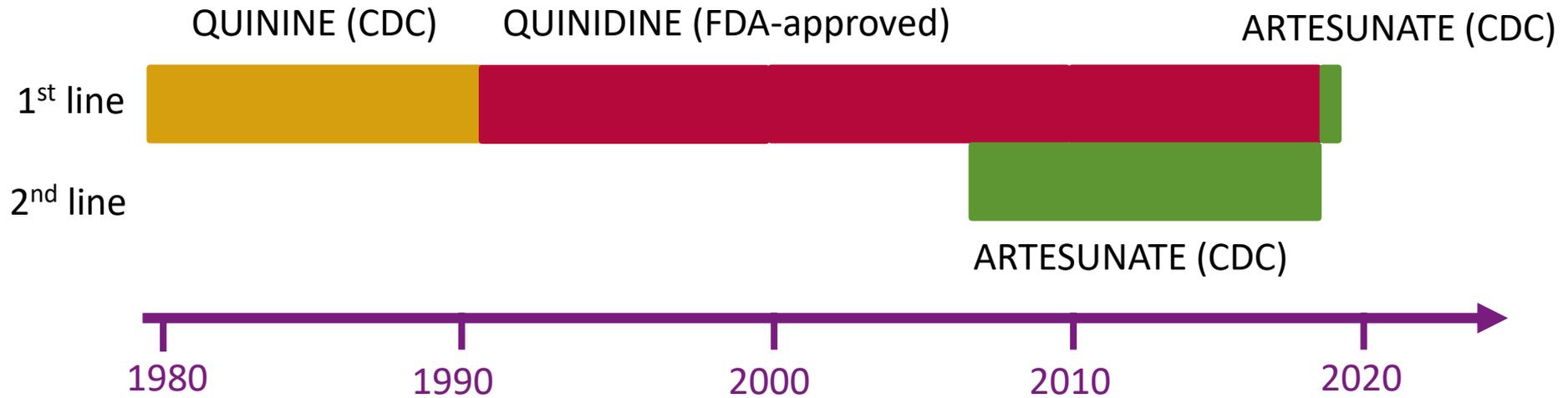
At Least 1 Case in Each State
15 Jurisdictions Have 75% of Cases



About 300 Cases of Severe Malaria Annually



Severe Malaria Treatment in the United States



IV Artesunate Availability in the United States (Jun 2007 – March 31, 2019)

- Artesunate developed and provided to CDC from Walter Reed Army Institute of Research and the U.S. Army Medical Materiel Development Activity
- CDC released drug under an expanded access investigational new drug (IND) protocol if:
 - Quinidine not available
 - Adverse events to quinidine
 - Quinidine failure
- Artesunate prepositioned at 9 CDC Quarantine Stations nationwide
- About 40-50 releases a year
 - Supply only enough for this volume of use

December 2017

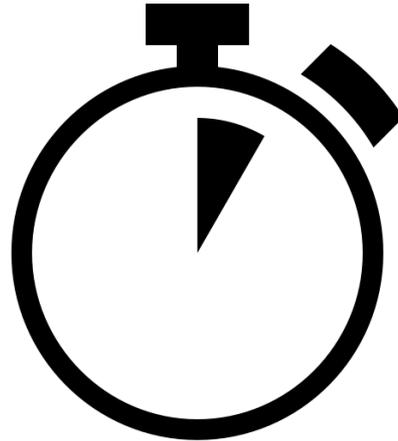


~~December 2017-April 2019~~

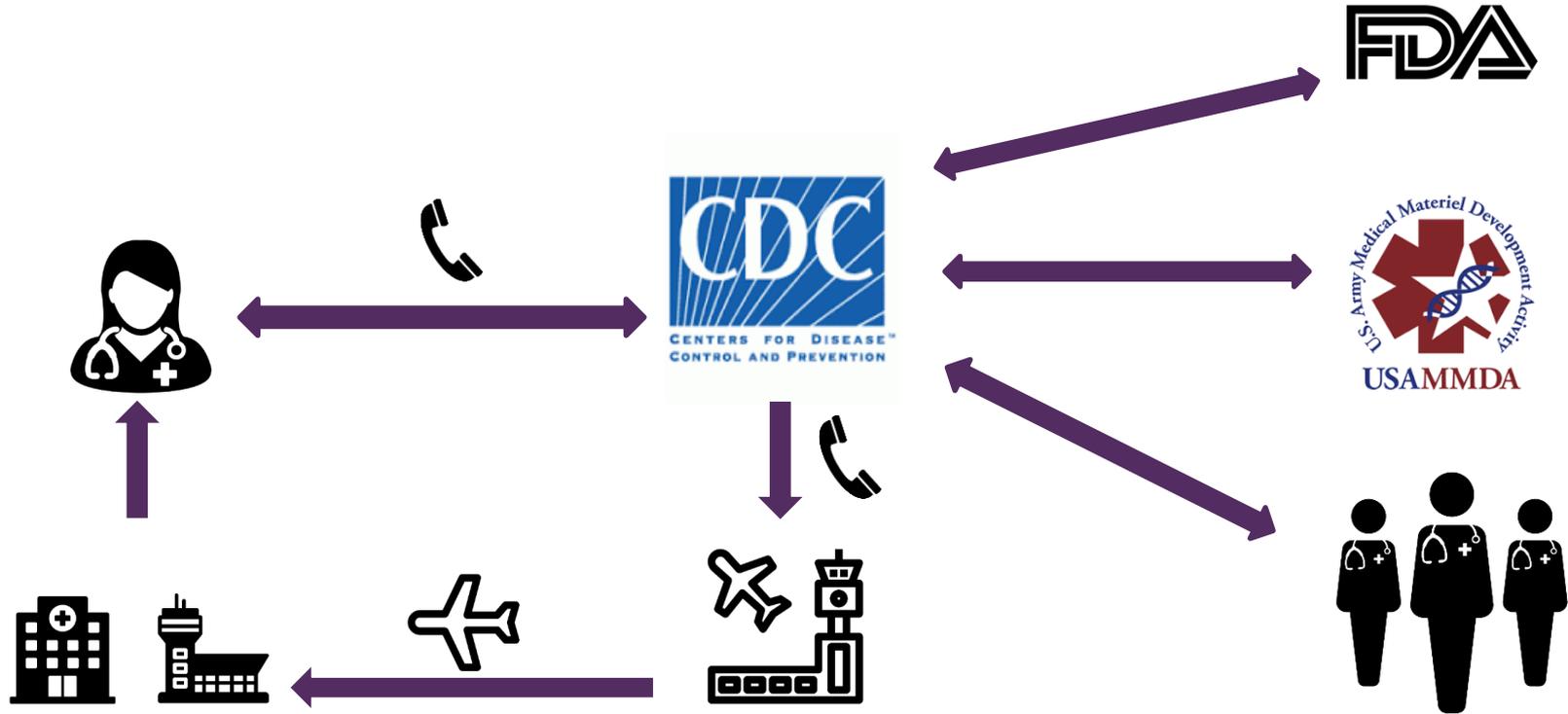


By April 2019

- Find supplier of IV antimalarial
- Obtain regulatory clearance from FDA (expanded access program)
- Procure IV antimalarial
- Expand distribution system
- Update guidelines
- Disseminate information



National Artesunate for Severe Malaria Program



Inclusion Criteria

- Severe malaria confirmed by smear
- Clinical severe malaria based on history, timely smear not available
- Uncomplicated malaria, unable to tolerate oral medications

Severe Malaria Criteria (At Least One)

- Parasitemia $\geq 5\%$
- Impaired consciousness (defined by inquiring clinician)
- Seizures
- Circulatory collapse/shock
- Acidosis
- Acute respiratory distress syndrome
- Acute kidney injury
- Disseminated intravascular coagulation
- Severe anemia
- Jaundice (seen with other signs/symptoms)

Updated Guidance: Treatment of Severe Malaria the in U.S.

INTERIM TREATMENT

Preferred:

- Artemether-lumefantrine (Coartem)

Other:

- Atovaquone-proguanil (Malarone) or quinine

Last resort:

- Mefloquine

ARTESUNATE



0 hours

12 hours

24 hours

REASSESSMENT OF PARASITE DENSITY

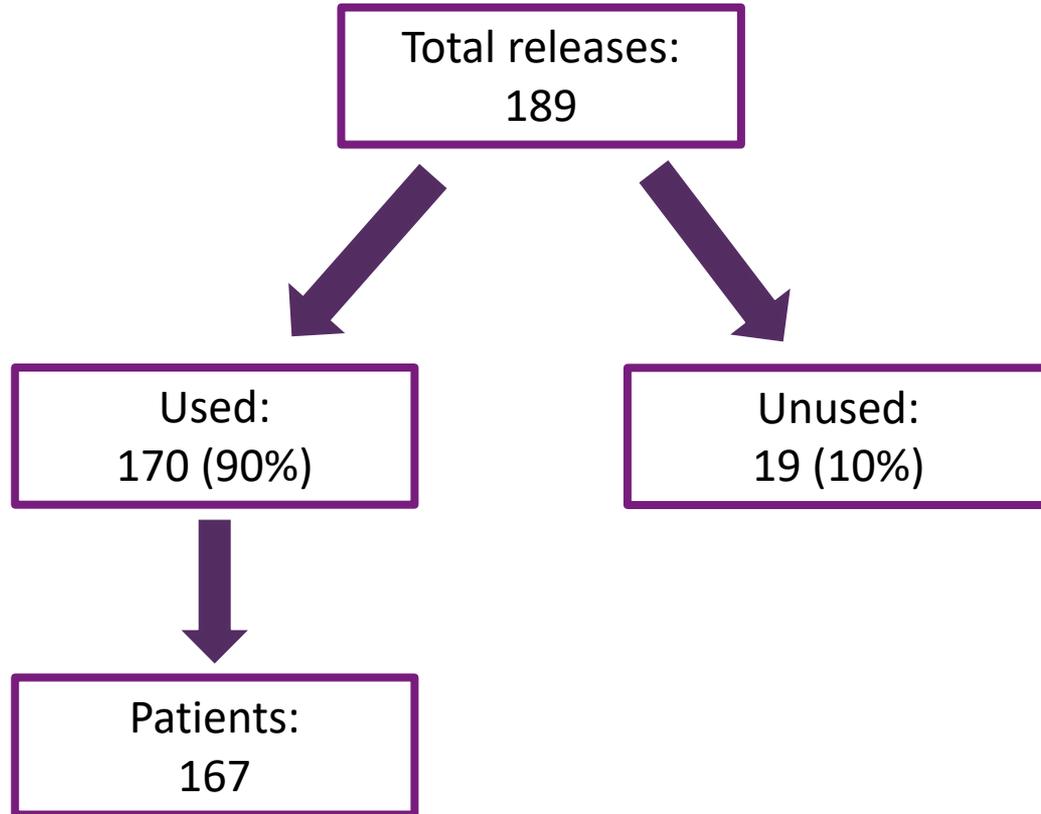
$\leq 1\%$ give oral regimen

$> 1\%$ Continue artesunate dosed once daily until $< 1\%$

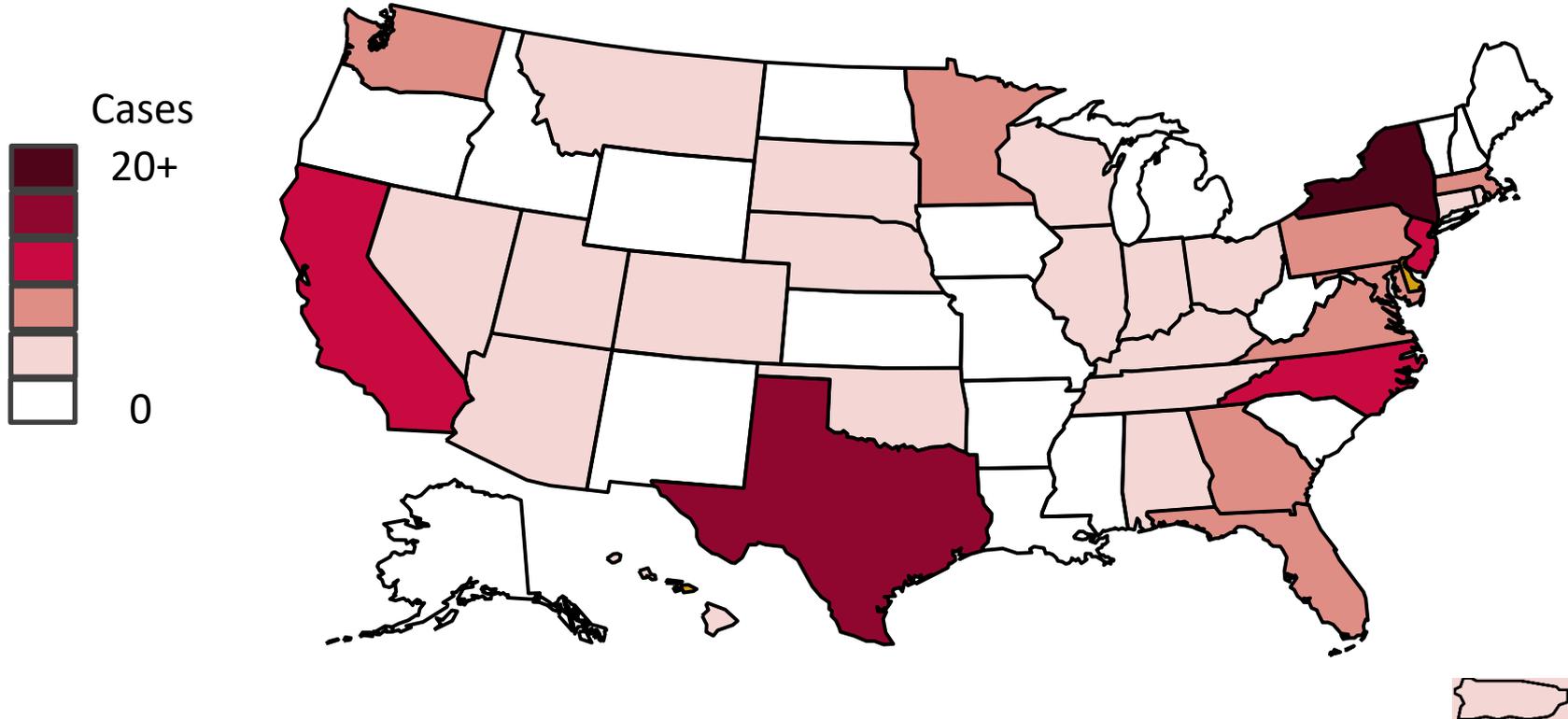
Adverse Event Reporting Required for IND

- 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

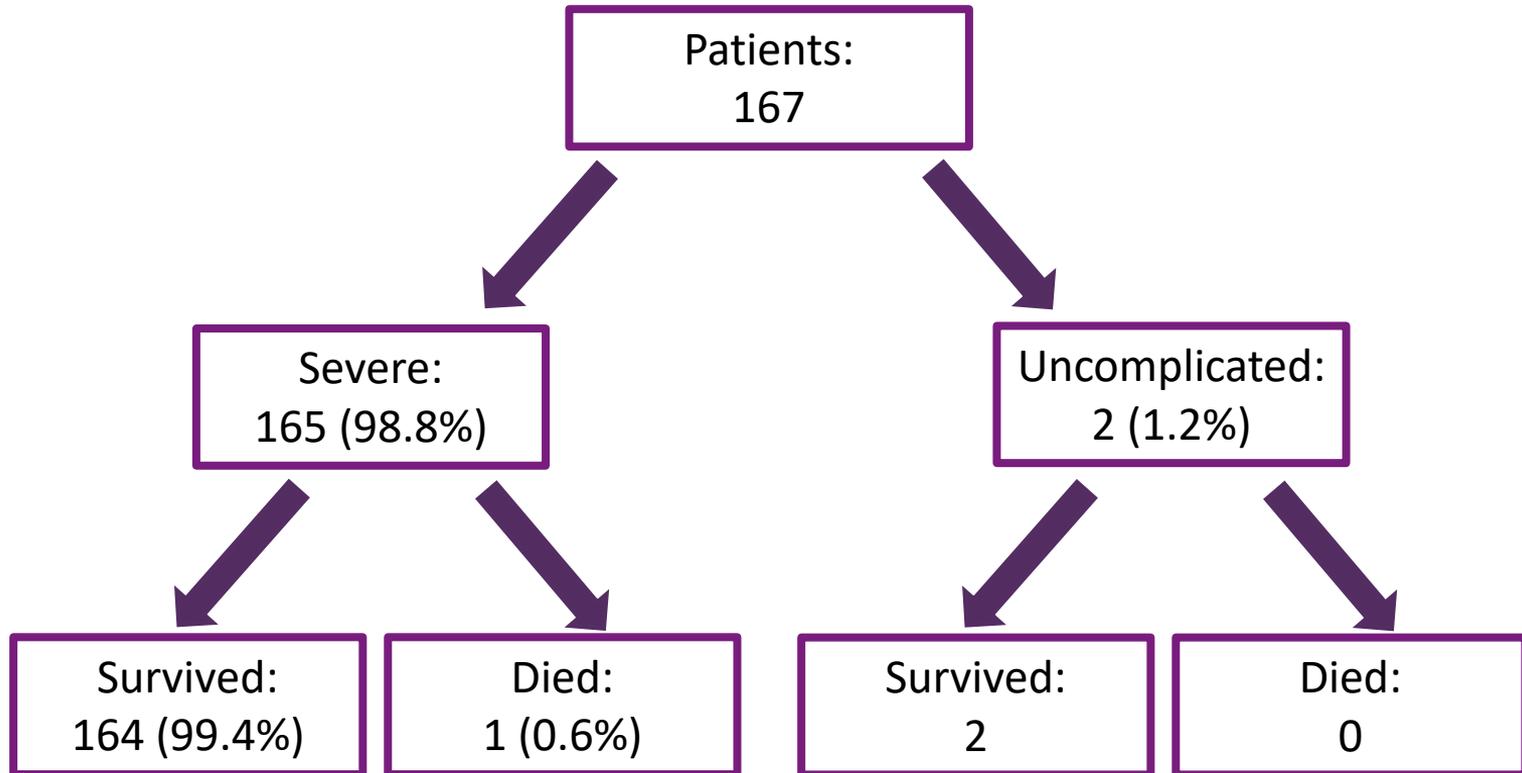
Artesunate Releases April 1 – October 31, 2019



Distribution of Patients With Severe Malaria April – October 2019



Patients Receiving Artesunate

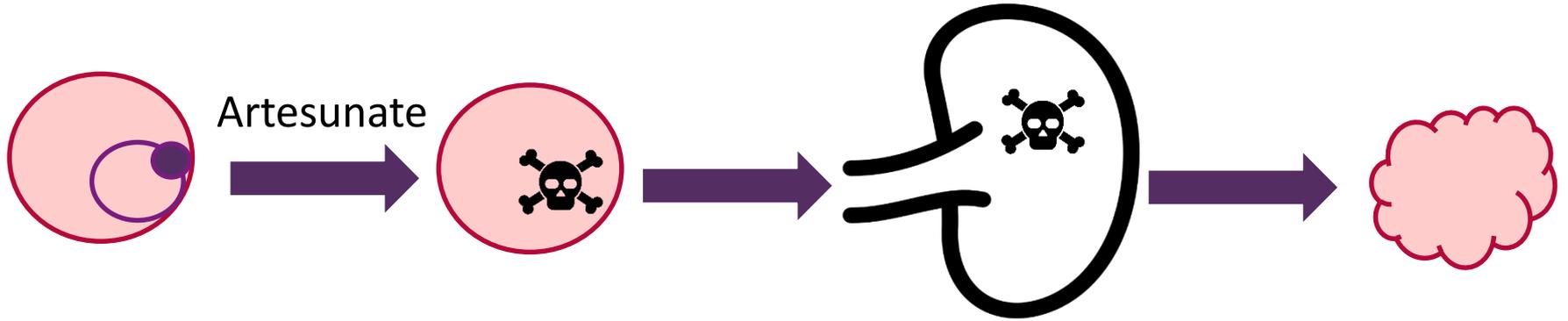


Adverse Events (April – September 2019)

Reported in 9/144 (6%)

- Post-artemisinin delayed hemolysis (PADH) 4 (3%)
- Suspected PADH 1 (0.7%)
- Ventricular Tachycardia 1 (0.7%)
- Rash and neutropenia 1 (0.7%)
- Death 1 (0.7%)

PADH: One Proposed Mechanism



Follow Up for PADH

- 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 $\geq 10\%$ over baseline
- Monitor for evidence of hemolytic anemia up to 4 weeks after treatment
- Higher parasitemia, higher risk

Future Direction

- Artesunate program
 - Monitor adverse events including PADH
 - Examine timeliness of receiving artesunate and patient outcomes
 - Monitor distribution closely
- Unknown when artesunate will be FDA approved
- Until then, CDC will continue to provide life-saving drug for patients who need it

CDC Contact Information for Artesunate

- CDC Malaria Hotline M-F 9am–5pm: (770) 488-7788
- CDC Emergency Operations Center (afterhours): (770) 488-7100
- Website for more information:
 - https://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html

Acknowledgements

- CDC:
 - Division of Global Migration and Quarantine
 - Division of Parasitic Diseases and Malaria
 - Drug Service
 - Malaria Branch
 - Quarantine and Border Health Services Branch
 - Regulatory Affairs
- FDA
- USAMMDA
- ASTMH



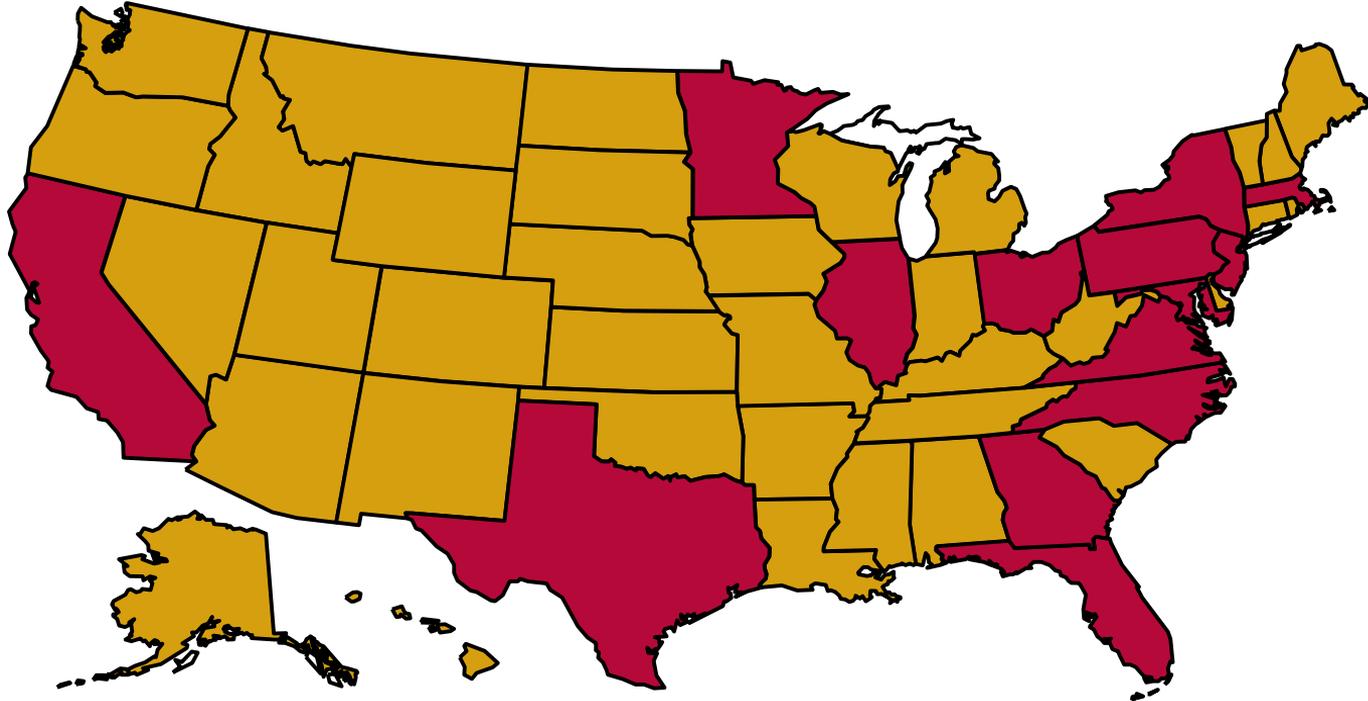
From Van to Vein

Artesunate Distribution from CDC Quarantine Stations

April 1 – October 31, 2019

Dr. Clive M Brown,
Chief, Quarantine and Border Health Services Branch
Division of Global Migration and Quarantine

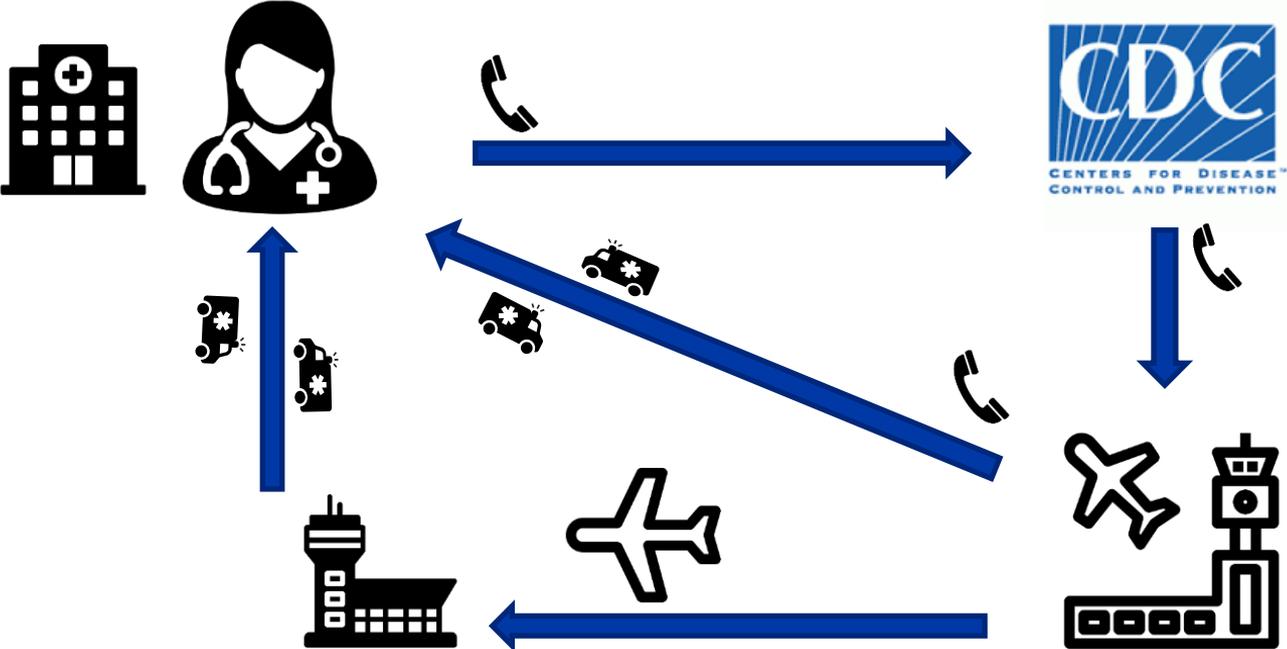
AT LEAST 1 CASE IN EACH STATE
15 JURISDICTIONS HAVE 75% OF CASES



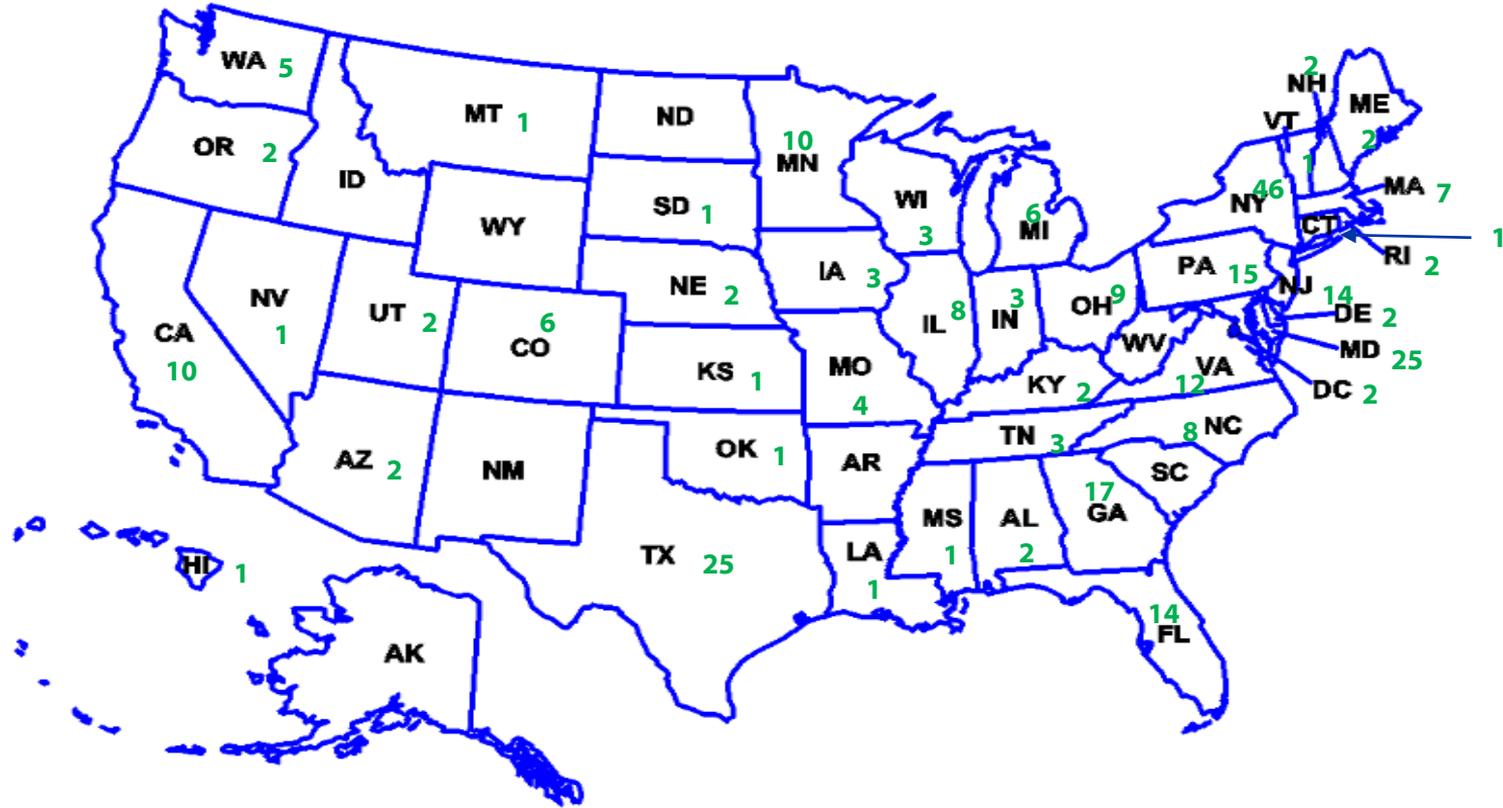
Update on Artesunate distribution by Quarantine Stations

- ❑ **Malaria Branch released IV artesunate via CDC Quarantine stations when quinidine could not be used**
 - **Prepositioned at 9 Quarantine Stations across the U.S. for timely distribution**
 - **About 50 courses were released each year**
- ❑ **Starting April 1, 2019, IV quinidine not available for treating severe malaria**
- ❑ **With no quinidine, CDC needed to expand IV artesunate distribution**
 - **Reviewed the distribution of severe malaria cases in the U.S.**
 - **Evaluated current malaria drug release process from quarantine stations:**
 - **Estimated impact of increased artesunate drug releases on current urgent station activities**

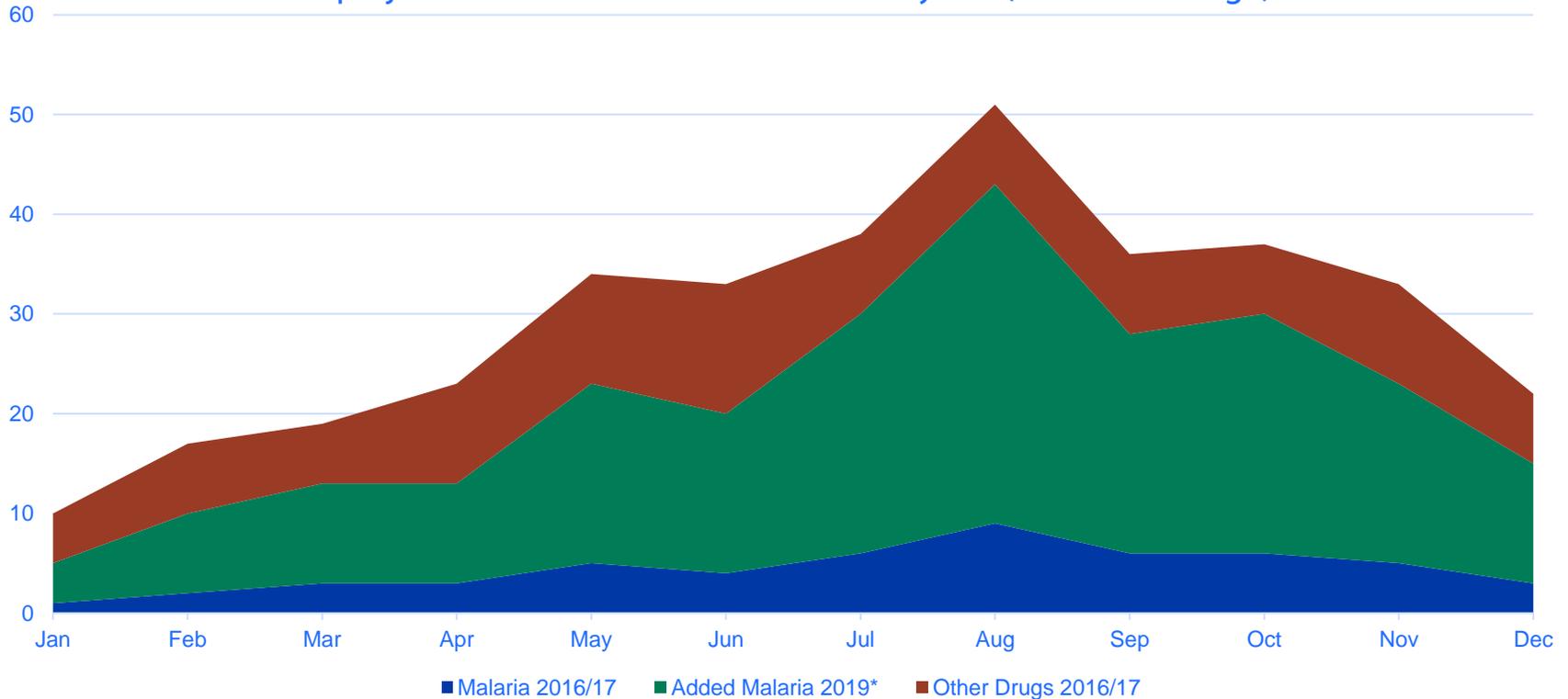
Artesunate Distribution Logistics



Severe Malaria per year, 2014 - 2016



Impact of added Malaria Drug Releases on Total Drug Release by month comparing projected increase for 2019 to baseline years (2016/17 average)



Changes to enhance timely distribution based on evaluation findings

- ❑ **About 50% of our current distribution occurs after the normal workday**
- ❑ **Increasing artesunate drug release increased (depending on station size):**
 - 2 or more drug releases occurring in a single day by four to six-fold.
 - 2 or more urgent events occurring in a single day from 1 in 10 to 1 in 5.
- ❑ **DC and neighboring states accounted for 14% of severe malaria cases (2nd to NY State)**
 - No distribution site in the DC area

Changes

- ❑ **Added Dulles to cover DC area** (increased from 9 to 10 Quarantine Stations);
- ❑ **Hired additional staff and added 2nd shift (plus on-call) for after-hours requests and weekend coverage**
- ❑ **Set delivery goal of 8 hours & tracked drug supply logistic challenges**
- ❑ **Implemented on-going evaluation plan with a dashboard for real-time data visualization and frequent reviews**
 - Recommend strategies to minimize identified gaps or challenges

Filters

Date Range

2019-04-01 to 2019-11-30

Only display releases from the last week

Quarantine Station

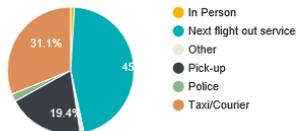
All Quarantine Stations

Only display releases where artesunate was received by the hospital 8+ hours after the request.

Transport Mode

- Display air and ground releases
- Only display air releases
- Only display ground releases (including helicopter)

Artesunate Release Transportation Modes



Download Data

Choose Dataset to Download

Q Station Summary Table for Selected Dates

Download



Quarantine Station Summary Table

	QStation	Artesunate_Release_Reports	Avg_Hours_Handoff_Time	Avg_Hours_Time_To_Hospital	Min_Hours_To_Hosp
1	Atlanta	32	2.87	7.14	
2	Chicago	25	2.67	7.66	
3	Honolulu	1	1.03	1.33	
4	Houston	23	1.86	5.49	
5	Los Angeles	11	2.08	5.85	

About this Dashboard

Metrics - All Quarantine Stations

206 releases
Number of Artesunate Releases

79%
Percent Received by Hospital Within 8 Hours

Q Station to Handoff | Q Station to Hospital

5.17 hours
Median Time of Release (Q Station to Hospital)

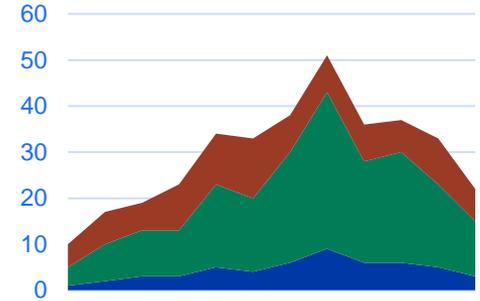
0.95 hours
Minimum Time of Release (Q Station to Hospital)

17.17 hours
Maximum Time of Release (Q Station to Hospital)

Artesunate Releases by Month April to October 2019



Artesunate Releases by Month April to October 2019

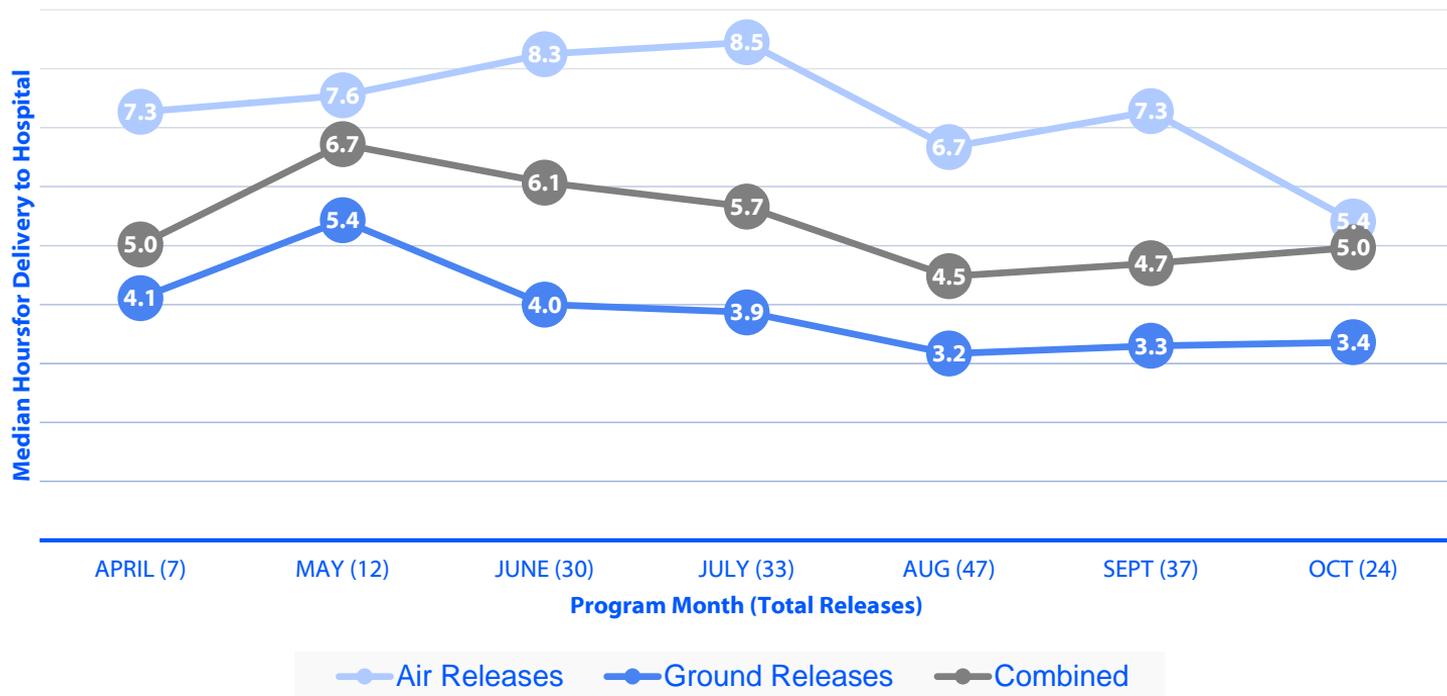


Artesunate Releases by Primary Points of Distribution (PPOD): April 1 – Oct 31, 2019

Q-Station	Air Releases	Ground Releases	Total
New York City (JFK)	8	43	51
Atlanta	22	6	28
Chicago	22	3	25
Houston (Bush)	16	6	22
DC (Dulles)	3	18	21
San Francisco	4	8	12
Los Angeles	6	5	11
Miami	6	4	10
Seattle	3	4	7
Honolulu	0	1	1
Total	90	100	190
Median time to hosp (hrs)	7.4 (4-15.4)	3.6 (1-17.2)	5.3 (1-17.2)
Over 8 hours	37 (41%)	5 (5%)	42 (22%)

Median Hours for Delivery for Air vs Ground Releases

April 1, 2019 - October 31, 2019



Factors associated with distribution times > 8 hours

- No timely flight from PPOD station, most frequent cause (>50%)
- Courier delay
- Difficulty finalizing plan with hospital
- Flight delayed
- Missed flight
- Closed cargo facility at distribution airport with outbound flight
- Other airline issue
- Cancelled flight
- Closed cargo facility at destination airport with inbound flight

Longer delivery times between 6pm to 2am and longer distances

Low resource options to reduce distribution times

- Secondary Points of Distribution (SPOD)
 - Drug release by other 8 q-stations
 - During normal working hours
 - Provided with refrigerators and stocks of artesunate
- SPOD drug releases rolled out July 22, 2019
 - Philadelphia: 1 release
 - Minneapolis-St. Paul: 1 release
- Hospital uses courier based near quarantine station airport for one-way drive times of about 4 to 5 hours
 - List of couriers drafted and kept by Q-stations, offered as an option to hospital when appropriate
 - **Not CDC endorsed**

Options to reduce distribution times that require resources

- Additional staff to enable MSP to be a PPOD station
- DGMQ staff at Colorado department of public health
 - No quarantine station in Denver
- Re-staffing Dallas Fort Worth and Boston quarantine stations
 - Texas ranked 3rd for number of severe malaria cases
 - DFW airport among top 5 with most domestic flights in U.S.
 - Boston Logan airport ranks 13th for most domestic flights in the U.S.
 - Both locations have high concentration of hospitals

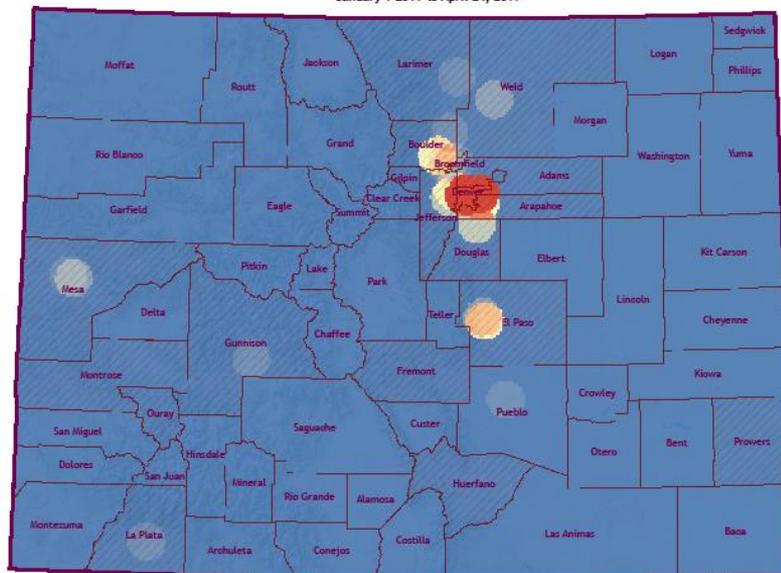
Distributions from Chicago vs MSP: April 1st – October 31

- Chicago received 25 artesunate requests
 - 8 (32%) shipments went to Minnesota
 - 2 (8%) shipments (1 each to SD and NE) went to hospitals in MSPs jurisdiction
 - Thus 10 (40%) of Chicago's artesunate requests could have been covered by MSP
 - Average delivery time from Chicago was 7.6 hours
 - distribution times for some shipments from MSP potentially would have been faster
 - SD – 7 hour delay due to weather;
 - 4 hour one-way drive via courier from MSP; or 1 hour ship time via air + pickup time
 - MN – 12 hour delay due to airline cargo closure
 - If distributed from MSP, 1-2 hour ship time
- MSP as a PPOD station could expedite some artesunate releases

Advantages with Artesunate in Denver, Colorado

Hospitalized Cases of Malaria by First-Admitted Hospital, per Km² Colorado, 2011-Present

January 1 2011 to April 24, 2019



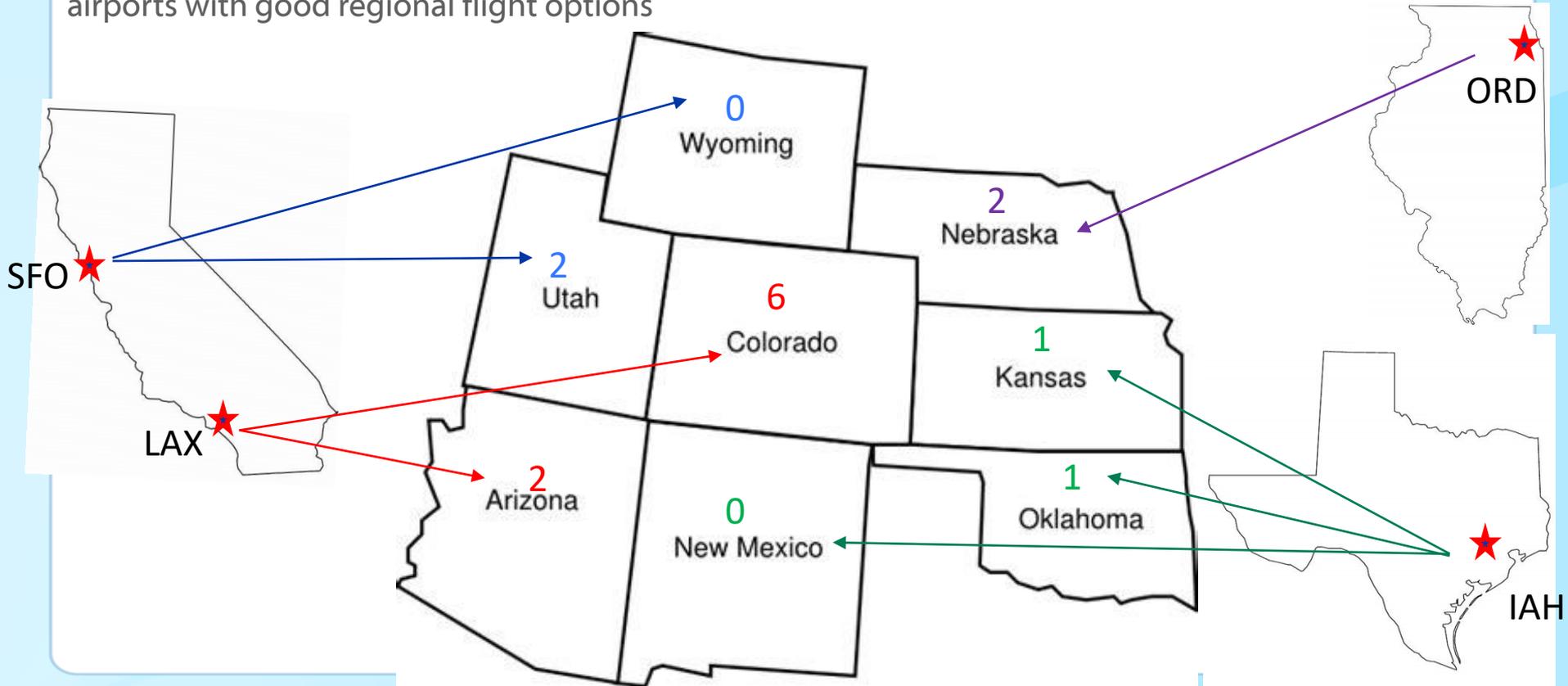
Colorado Counties with Hospitalized Malaria Cases Hospitalized Cases per km²
High : 0.15
Low : 0



- ~80% of Colorado's severe malaria cases managed in urban/metro areas
- Faster distribution within Colorado (ground and air)

Severe malaria cases Colorado and Neighboring states, 2014-2016

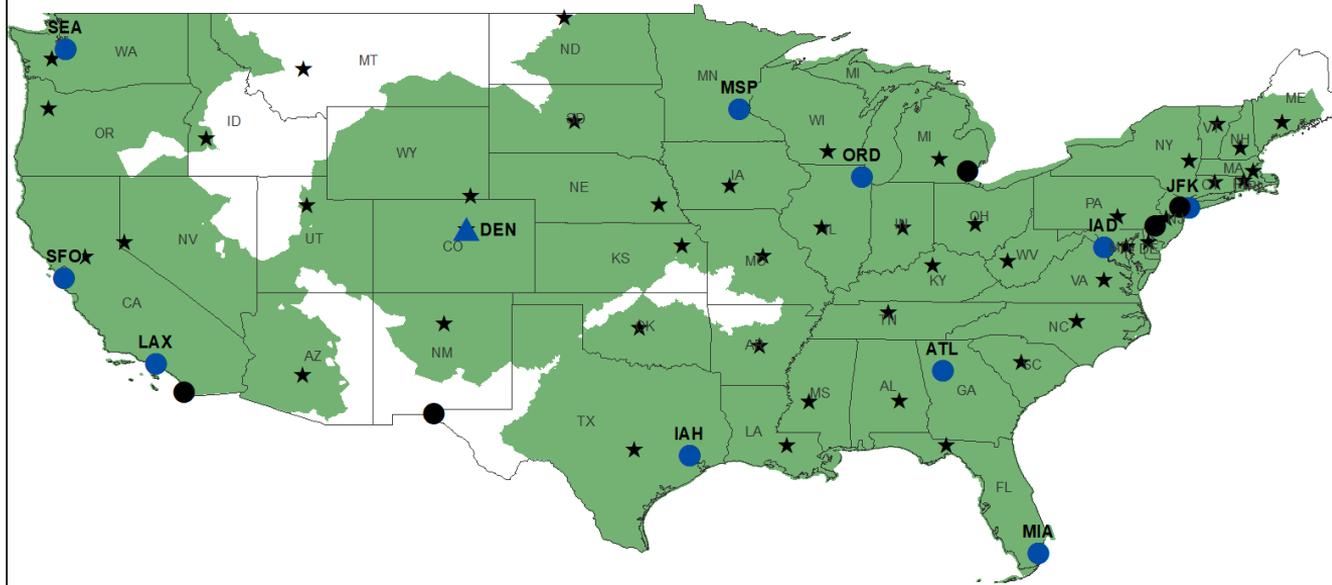
Potentially better distribution to bordering states: Denver International among top 5 busiest domestic airports with good regional flight options



Additional Approved changes post Evaluation Findings

- ❑ MSP approved as PPOD distribution station
 - Increases number of PPOD Quarantine Stations from 10 to 11
 - Started Nov 18, 2019
- ❑ Denver, Colorado approved as a regional distribution site
 - Partnership with the Colorado Dept of Public Health
- ❑ **19 total distribution sites**
 - 11 PPOD Quarantine Stations
 - Working 2 shifts and weekend coverage
 - 1 regional distribution site in partnership with state health dept
 - 7 SPOD quarantine stations

Drug Distribution Desert with staff at MSP and Denver



- Quarantine station; Primary release site
- Quarantine station; Secondary release site
- ▲ Colorado Department of Public Health and Environment; Primary release site
- ★ US state capitals
- 8-hour drive time service area

Drug delivery times would decrease in upper Midwest and Rocky Mountain

*Primary release site in Honolulu, HI and secondary release sites in Anchorage, AK and San Juan, PR not shown

Summary

- April 1, 2019, CDC started expanded artesunate distribution
- Based on evaluation of existing artesunate drug release process and other data:
 - Increased number of PPOD Quarantine Stations from 9 to 10
 - Added allowing a 2nd shift and weekend coverage, plus on-call
 - Implemented an on-going evaluation plan
- Based on findings from the evaluation plan
 - Other 8 q-stations became SPOD for artesunate
 - Encouraged hospitals to use ground delivery and use courier based near airport
 - MSP approved as PPOD; Denver, Colorado approved for regional distribution
- 19 total distribution sites (11 PPOD, 1 regional, and 7 SPOD)
- Many factors associated with longer distribution times; few within CDC's control
- CDC continues evaluation to identify strategies to minimize gaps and challenges

Acknowledgments

- ❑ **Entire Quarantine Branch especially quarantine station staff**
 - Krista Kornylo, Arnold Vang, Andy Klevos, Michelle Calio, Mahmoud Aboukheir, Ian Ruskey, Reena Gulati
 - Training Activity: Onalee Grady-Erickson, Federico Feldstein and many others
- ❑ **DGMQ-OD**
 - Brian Maskery, (OPRA), Heather Joseph (IDEA), Rachel Eidex, Marty Cetron
- ❑ **CDC Malaria Branch**
 - Kathrine Tan, Monica Parise
- ❑ **CDC Drug Service**
- ❑ **Denver Department of Public Health**

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What: Video with closed captioning

Where: On the COCA Call webpage at:

https://emergency.cdc.gov/coca/calls/2019/callinfo_121019.asp

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Upcoming COCA Call

Topic: “Update on Ebola Diagnostics at the State and Federal Levels in the United States”

Date: Thursday, December 19, 2019

Time: 2:00-3:00 PM EST

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As-needed messages that provide specific, immediate action clinicians should take. Contains comprehensive CDC guidance so clinicians can easily follow recommended actions.

COCA Products & Services



Monthly newsletter that provides updates on emergency preparedness and response topics, emerging public health threat literature, resources for health professionals, and additional information important during public health emergencies and disasters.



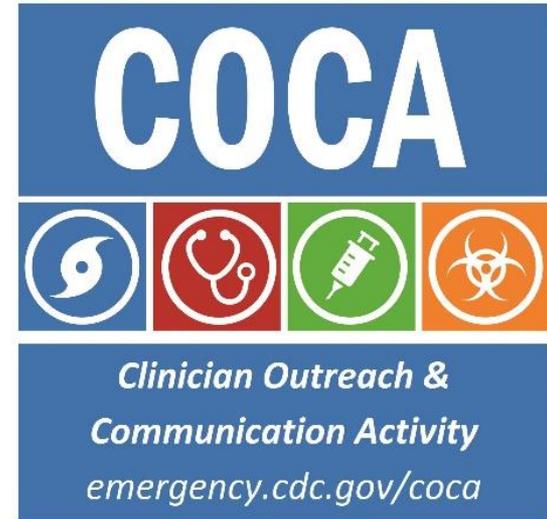
Informs clinicians of new CDC resources and guidance related to emergency preparedness and response. This email is sent as soon as possible after CDC publishes new content.



CDC's primary method of sharing 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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COCA

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Government Organization in Atlanta, Georgia
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