CDC's Activities in Examining Adverse Events of Antimalarials

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Malaria in the U.S.

- About 1700 cases imported annually, and rising with increased travel
  - About 250 to 300 cases of severe malaria
- Malaria is deadly: 5–10 deaths annually
- Healthcare providers in the U.S. are not familiar with diagnosis and treatment of malaria
  - Limited resources for timely diagnosis of malaria
  - Limited availability of antimalarials
- Malaria is preventable
  - Chemoprophylaxis
  - Mosquito avoidant measures

Characteristics of antimalarials available for malaria chemoprophylaxis in the U.S.

Antimalarial	Dosing	Use in all areas	Use in Pregnancy	Use in Children
Atovaquone-proguanil (AP, Malarone)	Daily	✓	✗	✓ †
Chloroquine (CQ)	Weekly	✗	✓	✓
Doxycycline (DX)	Daily	✓	✗	✗
Mefloquine (MQ)	Weekly	✓ *	✓	✓
Primaquine (PQ)	Daily	✗ ‡	✗	✓

* Resistance in certain areas of Southeast Asia

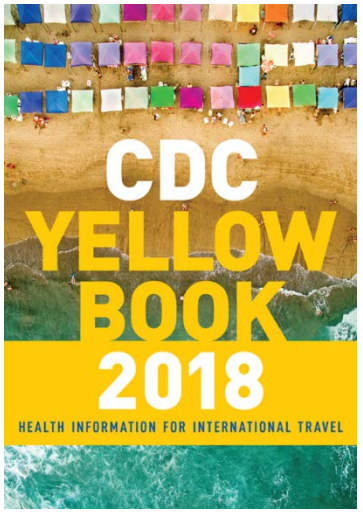
† Not in children <5 kg

‡ Only in areas with primarily *P. vivax*

CDC Malaria Branch: Protecting the health of the U.S. population from malaria

- Prevent
- Detect
- Treat
- Track

CDC Recommendations for Malaria Chemoprophylaxis



- Country-specific recommendations
  - Where transmission is occurring
  - Type of malaria
  - Presence or emergence of drug resistance
- Guidelines reflect most up to date evidence for efficacy and safety of medication
  - Efficacy: Presence or emergence of drug resistance
  - Safety: Drug label, published literature

Who monitors or studies adverse events for antimalarials after FDA approval?

- FDA
  - FDA Adverse Event Reporting System
- Drug companies
  - FDA-mandated postmarketing surveillance – for newly approved drugs for a defined period of time (ex: 5 yrs)
  - Ongoing surveillance: passively reported adverse events
- Others (Department of Defense, Travel Medicine groups)
  - Research, systematic literature reviews
- CDC
  - Postmarketing surveillance
  - Routine malaria case reports
  - Literature review
  - Research

Postmarketing surveillance

- Assisted with FDA-mandated adverse event surveillance in the years after approval (short-term)
  - Reports sent to FDA or drug manufacturer
    - Malarone ®(atovaquone-proguanil) for treatment of malaria
      - Focused on efficacy, used routine malaria case reporting data
    - Coartem ®(artemether-lumefantrine) for treatment of malaria
      - Active surveillance of patients treated with Coartem®for malaria

Routine Malaria Surveillance

Part II (to be complete 4 weeks after treatment)

Please list all prescription and over the counter medicines the patient had taken during the 2 weeks **before** starting their treatment for malaria.

Please list all prescription and over the counter medicines the patient had taken during the 4 weeks **after** starting their treatment for malaria.

Was the medicine for malaria treatment taken as prescribed? ☐ No, doses missed ☐ Yes, no doses missed ☐ Unknown

Did all signs or symptoms of malaria resolve without any additional malaria treatment within 7 days after treatment start?
☐ Yes ☐ No ☐ Unknown

If yes, did the patient experience a recurrence of signs or symptoms of malaria during the 4 weeks after starting malaria treatment?
☐ Yes ☐ No ☐ Unknown

Did the patient experience any adverse events within 4 weeks after receiving the malaria treatment? ☐ Yes ☐ No ☐ Unknown

(If Yes): Event description	Relationship to treatment suspected*	Time to Onset since treatment start	Fatal?	Life-Threatening?	Other Seriousness?**
1 _____	☐	_____	☐	☐	☐
2 _____	☐	_____	☐	☐	☐
3 _____	☐	_____	☐	☐	☐
4 _____	☐	_____	☐	☐	☐
5 _____	☐	_____	☐	☐	☐

* Suspected means that a causal relationship between the treatment and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

** A *serious* adverse event is defined as an event which is fatal or life-threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, is medically significant (i.e., jeopardizes the patient or may require medical or surgical intervention), or requires inpatient hospitalization or prolongation of existing hospitalization.

Limitations of adverse event reporting

- Passive reporting
  - Underreporting
  - Possible bias for reporting more severe adverse events
- Lack of denominator
  - Unknown how many are taking the drug for prophylaxis
- Adverse event reporting using malaria surveillance system data
  - Incomplete – on case report form, but not required, and not a main objective of malaria surveillance
  - Issues with timeliness

Research activities — primarily observational studies (1)

- Long-term malaria prophylaxis with weekly mefloquine (Lobel Lancet 1993)
- Compared effectiveness and safety of weekly MQ to CQ
- Methods:
  - Peace Corps Volunteers on malaria chemoprophylaxis for 1 year
    - Chemoprophylaxis is required for all Volunteers at risk
  - Adverse events reported by medical officers, and Volunteers received questionnaire every 4 months
  - Clinical data and blood test results in Volunteers with malaria
  - Denominator - numbers of Volunteers given particular antimalarial
- Conclusions:
  - No serous adverse reactions observed
  - Mild adverse events were equally frequent in MQ and CQ users
  - Weekly MQ more effective than CQ

Research activities — primarily observational studies (2)

- Long-term outcomes among Returned Peace Corps Volunteers (RPCVs) after malaria prophylaxis, 1995–2014 (Tan et al. Trav Med Inf Dis 2017)
- Compared prevalence of certain diseases between RPCVs who took chemoprophylaxis vs none
- Methods: Anonymous, internet-based survey of RPCVs
- Results: Slightly higher prevalence of very few diagnoses in exposed
  - Among all RPCV, MQ vs no MQ: Psychiatric side effects slightly more prevalent (PR 1.15)
  - Among those without prior psychiatric disease, MQ vs no MQ: no difference in prevalence of psychiatric diagnoses
- Conclusions: Malaria prophylaxis has very few latent effects
  - Avoid MQ use in those with prior psychiatric disease

Systematic literature review

- Objective: To inform malaria prophylaxis and treatment guidelines
- CDC Expert Meeting on Malaria Chemoprophylaxis
  - Atovaquone proguanil (Boggild et al. Am J Trop Med Hyg 2007)
  - Primaquine (Hill et al. Am J Trop Med Hyg 2006)
  - Doxycycline (Tan et al. Am J Trop Med Hyg 2011)
- Safety of atovaquone-proguanil in pregnancy (Andrejko et al. Trav Med Inf Dis, 2019)
- Efficacy and safety of artemether-lumefantrine for treatment of uncomplicated malaria in pregnant women (Ballard et al. MMWR, 2018)

A few limitations of published studies

- Dependence on self-report of exposure and outcomes
  - Travel Medicine studies often depend on surveys
- Limited use of standard screening tools or medical examination to verify neuropsychiatric outcomes
- Accounting for confounders
- Limitations of using administrative data

Self-report: possible influence of placebo effect or preconceptions of drug

Overbosch et al, CID, 2001. Randomized double blind trial comparing atovaquone-proguanil (AP) to mefloquine (MQ)

Event	Atovaquone-proguanil (n=493)	Mefloquine (n=483)
Any adverse event (regardless of plausible relationship to drug)	71%	67%
Any neuropsychiatric event*	14%	29%

*p<0.01

Limited use of standard screening tools to verify outcomes

Schlagenhauf et al, JTM, 2009: Randomized, double-blind four-armed trial (AP, MQ, DX, CQ)

- Used standardized "Profile of Mood States" to assess moods and feelings of travelers
- Findings:
  - Overall mood profiles similar across all arms
  - Of those on MQ: women reported fatigue and confusion slightly more than men
  - Regardless of antimalarial used: < 34 years old, reported slightly more "tension" and "fatigue" than those older

Accounting for confounders is challenging

- For the average traveler:
  - Physical and psychological stress of travel
    - Ex: Jet lag, unfamiliar food, unfamiliar environment
  - History of psychiatric illness
- For the soldier:
  - All of the above AND
  - Physical and psychological stress of deployment or combat

New studies consider confounders in soldiers (1): Eick-Cost, AJTMH, 2017

- Objective: Examine neuropsychiatric outcomes (NPO) and MQ
- Methods: Analysis of military medical and pharmacy data
  - Subgroup analyses: deployment and neuropsychiatric history
- Findings: MQ vs DX vs AP, no difference in risk of NPO
  - Deployed:
    - MQ vs AP tinnitus IRR 1.81 [1.18-2.79]
    - MQ vs DX: anxiety IRR 1.12 [1.01-1.24]
  - Nondeployed
    - MQ vs DX PTSD IRR 1.83 [1.07-3.14], tinnitus 1.51 [1.13-2.03]
  - Previous neuropsychiatric disorder: non-statistically significant, but slightly higher rates of 4 NPOs
- Conclusions: No association between MQ and NPO overall
  - Subcohorts increased anxiety, tinnitus and PTSD
  - Importance of screening for contraindication to MQ before use

New studies consider confounders in soldiers (2): Schneiderman, AJTMH, 2018

- Objective: Association of antimalarials and overall physical and mental health
- Methods: Analyzed data from a population-based study of US Veterans who served 2001–2008 (validated tools for outcomes)
- Findings:
  - Unadjusted: Any antimalarial use associated with poorer physical and mental health outcomes
  - Adjusted for deployment and combat exposure: no association between antimalarial use and outcomes
  - No significant association between MQ and mental health outcomes (but not powered for individual drugs)
  - Dose-response of combat exposure and poor outcomes
- Conclusions: Poor outcomes in vet population likely due to combat exposure

Limitations of administrative data

- Validation of exposure
  - Prescription filled, but was it taken?
  - Was medication for malaria prophylaxis?
    - Can be used for malaria treatment (all meds used for prophylaxis)
    - Use for other diseases (ex: doxycycline)
- Validation of outcome
  - Were diagnostic codes used correctly?
- Certain populations might not be represented
  - Care outside of military system
  - Dependents
  - Uninsured

Evidence gaps for safety of antimalarials for chemoprophylaxis

- Long term health effects after prolonged use of antimalarials
  - Some studies in Peace Corps Volunteers and military personnel
- Safety in certain populations
  - Pregnant women (AP)
  - Children (<5 kg AP, DX)

Thank you

Questions?

For more information please contact Centers for Disease Control and Prevention

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