

Disease Planning Guide - Plague

Mass Post Exposure Prophylaxis

I. Disease-specific guidance:

The following guide should only be used in events where a plague epidemic has been identified, an Emergency Use Authorization from the Food and Drug Administration has been issued and a state and local emergency declaration has been issued by the proper authorities.

Step 1) Complete Screening Form and Print Voucher

DISPENSE ASSIST

VOUCHERS FOR: Anthrax Medication Consent Form

FOR: Anthrax, Influenza, Plague, Tularemia

Personal Information

First Name: [Text Field]
 Last Name: [Text Field]
 Address: [Text Field]
 City/State/Zip: [Text Field] Kansas [Dropdown]
 Telephone: (555) 555-5555
 Date of Birth: [Text Field]
 Height (in): [Text Field]
 Sex: [Text Field]

Medical Information

1. Is this person allergic to Doxycycline, Tetracycline or any other "tetracycline" drug? Yes No
2. Is this person allergic to Clarithromycin, Levofloxacin or any other "fluoroquinolone" drug? Yes No
3. Does this person have kidney disease or kidney? Yes No
4. Is this person currently taking "Tetracycline (Zinbax)"? Yes No
5. Does this person take any other "antibiotic" pills? Yes No

You have been offered a copy of the [Dispense Assist User Guide](#). By checking the "I agree" box, I consent to receive the user guide to print it out for my personal use only. I understand that I will not receive the user guide if I do not check the "I agree" box.

Sign: [Text Field]

[Print] [Close Form]

Step 2) Bring Voucher to Dispensing Site

BRING THIS VOUCHER WITH YOU

Dispense Assist
 National Post-Exposure Prophylaxis Voucher

Medication: Doxycycline

FACT SHEET: FDA EUA Doxycycline Drug Information Sheet

Label:

Dispensing Site Information:

Dispensing Site: [Text Field] Telephone: (555) 555-5555
 Last Name: [Text Field] DOB: [Text Field]
 Address: [Text Field] Height: [Text Field]
 City, St, Zip: [Text Field] State: [Text Field]

Health History Information:

1. Is this person allergic to Doxycycline, Tetracycline or any other "tetracycline" drug? Yes No
2. Is this person allergic to Clarithromycin or any other "fluoroquinolone" drug? Yes No
3. Is this person pregnant? Yes No
4. Does this person have kidney disease or kidney? Yes No
5. Is this person currently taking "Tetracycline (Zinbax)"? Yes No
6. Does this person take any other "antibiotic" pills? Yes No
7. Is this person less than 18 years old? Yes No

I, the undersigned, with that all of the above information is correct to the best of my knowledge, I hereby authorize the recipient of this document to share this information with public health entities at the local, state and federal level for purposes of ensuring medication efficacy and safety. I have been offered a copy of folder of information practices.

Client Signature: [Text Field] Date Signed: [Text Field]

Point of Dispensing Site Only:

Medication Provided: Doxycycline Clarithromycin

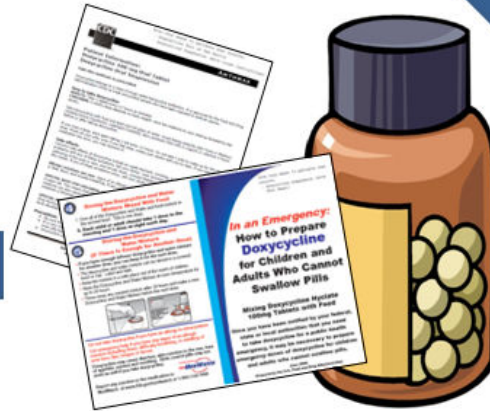
Printed at [Text Field]

Dispensing Location/Store Name: [Text Field] Date Dispensed: [Text Field]

Dispenser's Initials: [Text Field]



Step 4) Scan Voucher into Database



Step 3) Dispense Pills and Fact Sheets Affix Lot# Sticker to Voucher

Clients will arrive at dispensing sites with a voucher indicating which medication, if any, they should receive. Specific guidance related to dispensing is shown in red.

This voucher permits the individual named below to receive this medication

D **BRING THIS VOUCHER WITH YOU**

Dispense Assist
Post Exposure Prophylaxis Voucher

Medication: Doxycycline

Fact sheet: FDA EUA Doxycycline Drug Information Sheet

Demographic Information

First Name:	Alisha	Telephone:	(913) 477-8332
Last Name:	Griswold	DOB:	7/15/1982
Address:	11875 S. Sunset	Weight:	150
Address 2:	Disease Containment Division	Sex:	Female
City, St Zip:	Olathe, KS 66061		

Health History Information

1. Is this person allergic to Doxycycline, Tetracycline or any other "cycline" drug?
2. Is this person allergic to Ciprofloxacin or any other "floxacin" drug?
3. Is this person pregnant?
4. Does this person have seizure disorder or epilepsy?
5. Is this person taking Tizanidine (Zanaflex ©)?
6. Does this person have difficulty swallowing pills?
7. Is this person less than 18 years old?

I, the undersigned, certify that all of the above information is correct to the best of my knowledge. I hereby authorize the recipient of this document to share this information with public health entities at the local, state and federal level for purposes of ensuring medication efficacy and safety. I have been offered a copy of Notice of Information Practices.

Client Signature: _____ Date Signed: _____

Point of Dispensing Use Only:

Medication Provided: Doxycycline Ciprofloxacin

Place Lot # Sticker Here

Dispensing Location/Site Name: _____

Dispenser Signature: _____ Date Dispensed: _____

QR code contains all demographic data and health history information listed above.

Bold icon in upper left corner indicates which medication should be dispensed.
D = Doxycycline C = Ciprofloxacin
X = Do Not Dispense Medication


Dispensers should provide clients with the fact sheets listed here

Answers will reflect responses to follow-up questions to prevent false contraindicators.

- No
- No
- No
- No
- No
- No
- No

Dispensers will organize vouchers according to Lot # for records purposes.

Clients that present this voucher will not receive medication for the individual named on the form. Dispensers may collect "Do Not Dispense Medication" vouchers for records purposes.



DO NOT DISPENSE MEDICATION!

← Bold icon and instructions indicate no meds are to be dispensed

Thank you for submitting your medication form. Unfortunately, your answers indicate that you are unable to receive any of the medications that are currently available. Please contact your health care provider or your local health department for additional information.

Demographic Information

First Name: Alisha	Telephone: (913) 477-8332
Last Name: Griswold	DOB: 7/15/1982
Address: 11875 S. Sunset	Weight: 150
Address2: Disease Containment Division	Sex: Female
City, St Zip: Olathe, KS 66061	


Health History Information

1. Is this person allergic to Doxycycline, Tetracycline or any other "cycline" drug?	Yes
2. Is this person allergic to Ciprofloxacin or any other "floxacin" drug?	Yes
3. Is this person pregnant?	Yes
4. Does this person have seizure disorder or epilepsy?	Yes
5. Is this person taking Tizanidine (Zanaflex ©)?	Yes
6. Does this person have difficulty swallowing pills?	Yes
7. Is this person less than 18 years old?	No

I, the undersigned, certify that all of the above information is correct to the best of my knowledge. I hereby authorize the recipient of this document to share this information with public health entities at the local, state and federal level for purposes of ensuring medication efficacy and safety. I have been offered a copy of Notice of Information Practices.

Client Signature: _____ Date Signed: _____

Point of Dispensing Use Only:



← QR code contains all client data if record of non-dispense is needed

← No place for dispenser's signature helps ensure that no meds are dispensed

II. PERSONS FOR WHOM PROPHYLAXIS MAY BE ORDERED

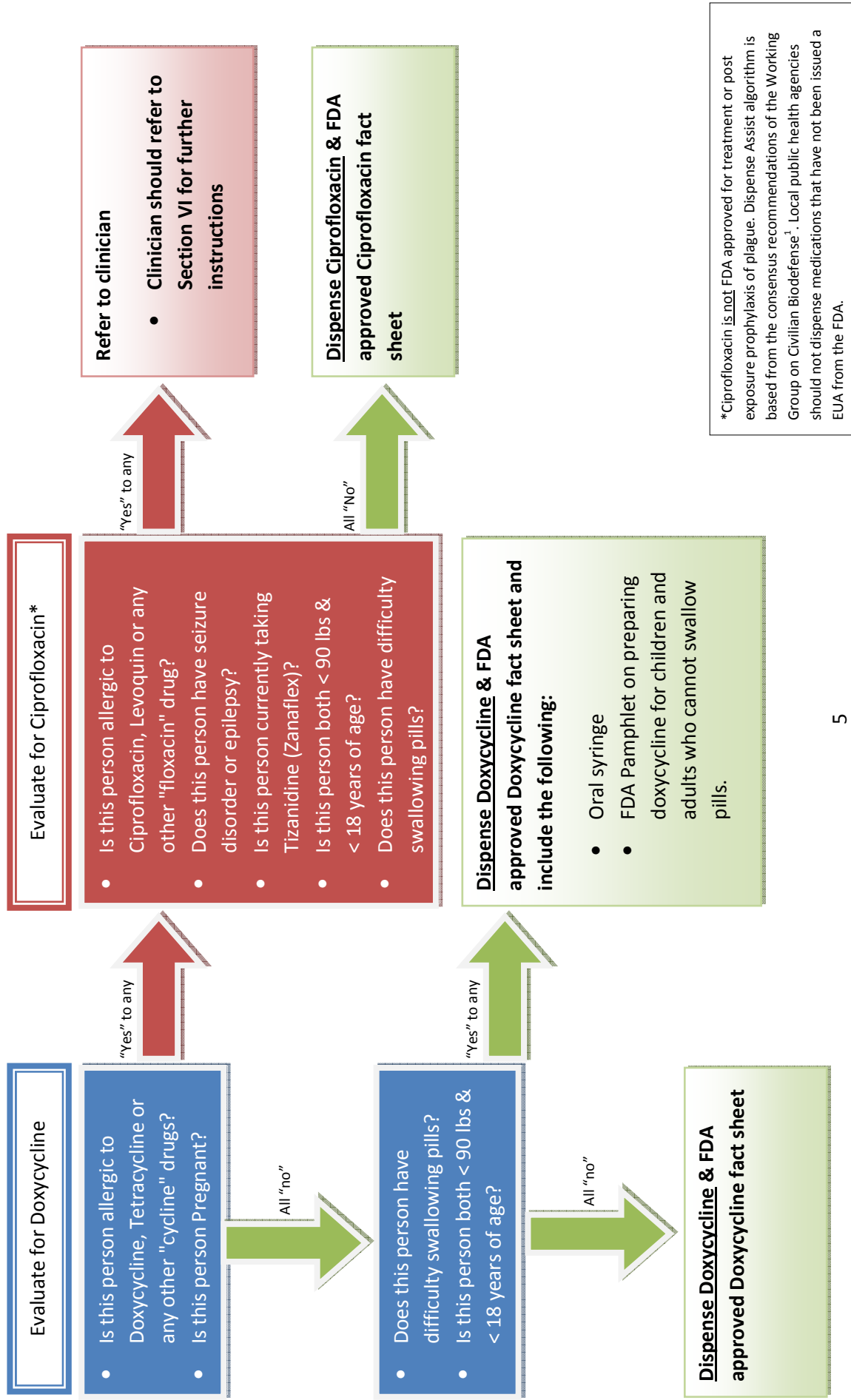
Persons who have a confirmed or suspect exposure to *Yersinia pestis*, the causative agent of plague, as determined by the local or State Health Officer.

Table 1: Recommended Post-Exposure Prophylaxis for Inhalational Plague

Patient Category	Therapy Recommendation	Duration
Adults	Doxycycline , 100 mg PO BID <i>or</i> Ciprofloxacin , 500 mg PO BID	10 days
Children	Ciprofloxacin , 15 mg/kg PO BID, max 500 mg/dose <i>or</i> Doxycycline : >45 kg: 100 mg PO BID ≤45 kg: 2.2 mg/kg PO BID ***** If susceptibility to penicillin has been confirmed: Amoxicillin : >20 kg: 500 mg PO TID ≤20 kg: 80 mg/kg/day PO divided TID	10 days
Pregnant women	Doxycycline , 100 mg PO BID <i>or</i> Ciprofloxacin , 500 mg PO BID ***** If susceptibility to penicillin has been confirmed: Amoxicillin 500 mg PO TID	10 days
Immunocompromised	Doxycycline , 100 mg PO BID <i>or</i> Ciprofloxacin , 500 mg PO BID	10 days
Adapted from: <i>Working Group on Civilian Biodefense</i> . ¹		

III. Post Exposure Prophylaxis Screening Questionnaire and Algorithm

Figure 1: Doxycycline Dominant Dispensing Algorithm



*Ciprofloxacin is not FDA approved for treatment or post exposure prophylaxis of plague. Dispense Assist algorithm is based from the consensus recommendations of the Working Group on Civilian Biodefense¹. Local public health agencies should not dispense medications that have not been issued a EUA from the FDA.

IV. Dispensing Rationale

Need for Rapid Initiation of Mass Prophylaxis

→ ***Goal is to deliver effective antimicrobials to entire population within 48 hours.***

Antimicrobial prophylaxis should occur as soon as possible following exposure. Symptoms would appear 1-6 days following exposure and death would follow about 2-6 days following exposure.

Duration of Plague PEP

→ ***Minimum 7 days***

POD will dispense medication sufficient for the first 10 days of PEP.

Rationale is based largely on reports on treatment of human disease, studies in animal models, reports on in vitro susceptibility testing and antibiotic safety. The Working Group on Civilian Biodefense has recommended that in a community experiencing a pneumonic plague mass casualty situation individuals should be provided doxycycline or ciprofloxacin prophylaxis for seven days. However, local public health agencies will dispense 10 day regimens because that is what is stockpiled in the Strategic National Stockpile.

Antibiotic Susceptibility: Doxycycline, Ciprofloxacin,

- Doxycycline has been used for the treatment and prophylaxis of plague and is FDA approved for this purpose.
- The Working Group on Civilian Biodefense recommends the use of doxycycline as the first choice antibiotic for postexposure prophylaxis.
- Ciprofloxacin has been demonstrated to be at least as efficacious as tetracyclines in studies of mice with experimentally induced pneumonic plague.
- In vitro studies also suggest equivalent or greater activity of ciprofloxacin against *Y. pestis* when compared with tetracyclines. However there have been no clinical trials of fluoroquinolones in human plague.

V. Explanation and Rationale of Antibiotic Algorithms

(Note: this is the rationale for the algorithm. See subsequent sections for instructions on what to do with persons that the algorithm sends to Medical consultation).

1. Allergy to Doxycycline, Tetracyclines, Ciprofloxacin, or Quinolones (“-floxacin”)

Definition of Allergy:

By “allergic” we mean:

- a medical professional said the person is allergic; OR
- the person had a life-threatening reaction to one of these drugs

Quinolone drugs include: acrosoxacin or rosoxacin (Eradacil); cinoxacin (Cinobac); ciprofloxacin (Cipro, Ciloxan); gatafloxacin (Tequin); grepafloxacin (Raxar); levafloxacin (Levaquin, Quixin); lomefloxacin (Maxaquin); moxifloxacin (Avelox, ABC Pak); nadifloxacin (Acuatim); norfloxacin (Chibroxin, Noroxin); nalidixic acid (NegGram); ofloxacin (Floxin, Ocuflax); oxolinic acid; pefloxacin (Peflaxine); rufloxacin; sparfloxacin (Zagam, Respipac); temafloxacin; trovafloxacin or alatrofloxacin (Trovan).

Tetracycline drugs include: demeclocycline (Declomycin); doxycycline (Adoxa, Bio-Tab, Doryx, Doxycycline, Monodox, Periostat, Vibra-Tabs, Vibramycin); minocycline (Arestin, Dynacin, Minocin, Vectrin); oxytetracycline (Terak, Terra-Cortril, Terramycin, Urobotic-250); tetracycline (Achromycin V, Sumycin, Topicycline, Helidac).

2. Pregnancy

According to the CDC, **ciprofloxacin is the drug of choice for pregnant women** as it is “unlikely to be associated with a high risk for structural malformations in fetal development,” according to the MMWR.⁷ There is agreement on this from both the FDA and the American College of Obstetrics & Gynecology (ACOG)

Doxycycline is normally to be avoided during pregnancy, however the Working Group on Civilian Biodefense has endorsed its use for post exposure prophylaxis in pregnant women.

3. Breastfeeding

Breastfeeding does not factor into the antibiotic selection. The American Academy of Pediatrics considers ciprofloxacin and tetracyclines (including doxycycline) to be usually compatible with breastfeeding because the amount of either drug absorbed by infants is small.

See: www.cdc.gov/mmwr/preview/mmwrhtml/mm5045a5.htm
aappolicy.aappublications.org/cgi/content/full/pediatrics;108/3/776

A more recent publication reviewed the risk of using both ciprofloxacin and doxycycline during pregnancy and lactation, and found that the teratogenic potential of ciprofloxacin and doxycycline are unlikely, based on careful review of peer-reviewed literature and drug safety databases.⁹

Some experts recommend that use of tetracycline or doxycycline by a lactating mother be avoided, if possible, because of the potential for staining of the infant's unerupted teeth.¹⁰ However, these risks of teeth staining are clearly outweighed by the potential morbidity and mortality from plague. Additionally, some studies detailed in the next section below demonstrate that giving a 10 day course of doxycycline to children does not cause tooth staining.

Mothers concerned about the use of ciprofloxacin or doxycycline for antimicrobial prophylaxis during lactation should consider expressing and then discarding breast milk so that breastfeeding can be resumed when antimicrobial prophylaxis is completed.

4. Children Age Less Than 9 Years

In children <9 yrs old, ciprofloxacin is preferred, as concerns about the effect of doxycycline on tooth enamel in young children outweigh the risk of possible ciprofloxacin-mediated arthropathy. The American Academy of Pediatrics supports first-line use of ciprofloxacin rather than doxycycline.^{7,11}

In children age \geq 9 yrs, doxycycline is preferred. Doxycycline is not believed to affect tooth enamel in this age group, but children up to age 18 still face the possible risk of arthropathy with ciprofloxacin.

Despite the preference for ciprofloxacin in children \leq 9 years of age, the SNS vendor-managed inventory may contain little to no ciprofloxacin suspension. If ciprofloxacin suspension is available, it may be used. The FDA has not approved **crushing ciprofloxacin tablets at home and creating a ciprofloxacin suspension and is not a viable substitute for commercially-produced ciprofloxacin suspension.** Crushed ciprofloxacin tablets are extremely unpalatable, even when mixed with syrup, pudding, chocolate, or other foods that children normally enjoy. It is so unpalatable that the Bay Area Mass Prophylaxis Working Group believes that no child would comply with prophylaxis.

Therefore, if the SNS vendor managed inventory has sufficient amounts of commercially-produced ciprofloxacin suspension, children will be assigned to receive ciprofloxacin if they are <9 years of age. In the event that there is insufficient ciprofloxacin suspension in the SNS VMI, the algorithm is designed to have children receive doxycycline regardless of age.

Commercially-produced doxycycline suspension may or may not be available in the SNS VMI. If it is not available, or is available only in insufficient quantities, crushing doxycycline tablets and creating a doxycycline suspension at home is recommended. The FDA has published "Public Health Emergency Home Preparation Instructions for Doxycycline".

See: www.fda.gov/cder/drug/infopage/penG_doxy/home_prep.htm

Two studies demonstrate that giving 10 days of doxycycline to children 2-7 yrs of age does not cause significant tooth discoloration.^{12,13} One study demonstrated that up to 5 courses could be given without causing tooth staining.¹⁴

Since there may be insufficient amounts ciprofloxacin suspension in the SNS, it is reasonable to plan to give doxycycline to all children including those <9 yrs old, for the first 10 days of PEP. Depending on antibiotic susceptibility and other antibiotic availability, for the following 50 days of PEP, one could consider switching to ciprofloxacin or amoxicillin suspension.

Weight was used instead of age as a cutoff for doxycycline and ciprofloxacin dosing, as the most recent CDC growth charts, published in 2000, may not reflect current average weights (http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm). Pediatric doxycycline doses are 2.2 mg/kg/dose to the maximum dose of 100 mg. The maximum pediatric dose is reached at ~90 lbs (45 kg). Pediatric ciprofloxacin is given as a 15 mg/kg/dose to a maximum dose of 500 mg. The maximum pediatric dose is reached at ~73 lbs (33 kg), but the cutoff weight was set at 62 pounds (28 kg) to have more children go through the express line, as higher ciprofloxacin dosing (up to 20 mg/kg/dose) has been safely used in pediatric cystic fibrosis patients with pseudomonas lung infections.^{15, 16}

5. History of Seizures or Epilepsy

Quinolone antibiotics can act as GABA-receptor antagonists, lowering the seizure threshold, particularly in those with underlying seizure disorders or epilepsy. The seizure risk with quinolones is widely recognized, and even though experts feel it is low risk, the algorithm flags those with epilepsy or seizures before they are given ciprofloxacin.¹⁷ Seizures can occur within hours of receiving ciprofloxacin in those with underlying seizure disorders.¹⁸

Other neurological diseases that can predispose to seizures, such as stroke and traumatic brain injury (TBI), may also interact with quinolones, but the associated seizure risk is felt to be too low to include them as contraindications to ciprofloxacin, as the percentage of patients with stroke who develop post stroke epilepsy is only 2-4%, and the percentage of patients with TBI who develop seizures is 0.5 to 10%.¹⁹⁻²³

6. Drug-Drug Interactions

Issues:

- There are many drug-drug interactions for doxycycline and especially for ciprofloxacin. The number of drug names involved runs into the hundreds. This makes it impractical for members of the public to self-screen for every possible drug-drug interaction before receiving their antibiotics, as the list of potential interactions would be overwhelming to many.
- Time is of the essence in getting antibiotics to all members of the public. Taking the time to have medical personnel elicit and evaluate each potential drug-drug interaction for individuals at PODs would impede POD flow and delay antibiotic distribution.
- The federal government has sanctioned the “postal plan” whereby doxycycline would be distributed door-to-door by letter carriers, without regard to drug-drug interactions. According to this plan, the extent of morbidity caused by drug-drug interactions in a minority of individuals is a much lesser consideration than the timely receipt of effective prophylaxis by the majority.

- Strong warnings about drug-drug interactions could discourage people from taking their prophylaxis. The message needs to be clear that certain interactions need to be evaluated, but that this should not stop people from starting their life-saving PEP.
- Professional drug interaction references (Micromedex, Lexi-Comp, Cerner-Multum, American Hospital Formulary Services, and PDR) differ in their assessment of the severity of drug-drug interactions and their recommendations for managing those interactions. This makes it difficult to define a concise set of drug-drug interactions that physicians would universally agree are the most important.

Our antibiotic algorithm tries to negotiate all these competing issues and, as such, is imperfect. It relegates nearly all drug-drug interactions to follow-up monitoring with community physicians, rather than addressing them all at the POD.

The algorithm screens for drug-drug interactions which are contraindicated per the FDA-approved product label. The only drug that is specifically contraindicated with Ciprofloxacin is Tizanidine (Zanaflex®). There are no specific drugs that are contraindicated with Doxycycline.

Other drugs carry strong warnings per the FDA-approved product label or pose a significant risk of toxicity. These drug interactions are dealt with in the post-dispensing instructions. When drug-drug interactions are present, patients are instructed to contact a physician **within 48 hours** because, with the exception of Tizanidine, the onset of serious adverse effects of drug-drug interactions has been reported at 48 hours or later. For example:

Drug	Interacts with	Type of toxicity	Time until toxicity	Source
Oral retinoids	Doxycycline	Pseudotumor cerebri	3 weeks	24
Methotrexate	Doxycycline	Hematologic and GI toxicity	48 hours for high IV chemotherapy doses (25 mg/mL)	25
Tizanidine	Ciprofloxacin	CNS and respiratory depression	"Hours"	26
Theophylline	Ciprofloxacin	Seizures	3 days	27

The antibiotic instruction sheets given to patients at the PODs instruction sheets will contain a list of drug interactions and the instruction:

“Start taking _____ (Ciprofloxacin or Doxycycline) now but talk to your doctor within 48 hours. You may need a change in drug or drug dose, special monitoring, or special testing.”

Instructions for physicians in regard to drug-drug interactions and monitoring will be distributed to the medical community pre-event and during event through mass facsimile programs, local websites and health alert network systems.

7. SPECIAL NOTES:

Those Concurrently Taking Tetracyclines or Quinolones

POD attendees may already be taking a tetracycline- or quinolone-class drug. These individuals will receive an antibiotic at the POD, subject to all the usual considerations. Their use of concurrent tetracyclines or quinolones will not affect which antibiotic they receive at the POD; dispensing will proceed according to the usual algorithm.

Post-dispensing instructions will be provided recommending consultation with their physician within 2 days to review their antibiotic coverage.

“Start taking _____ (Ciprofloxacin or Doxycycline) now but talk to your doctor within 48 hours. You may need a change in drug or drug dose, special monitoring, or special testing.”

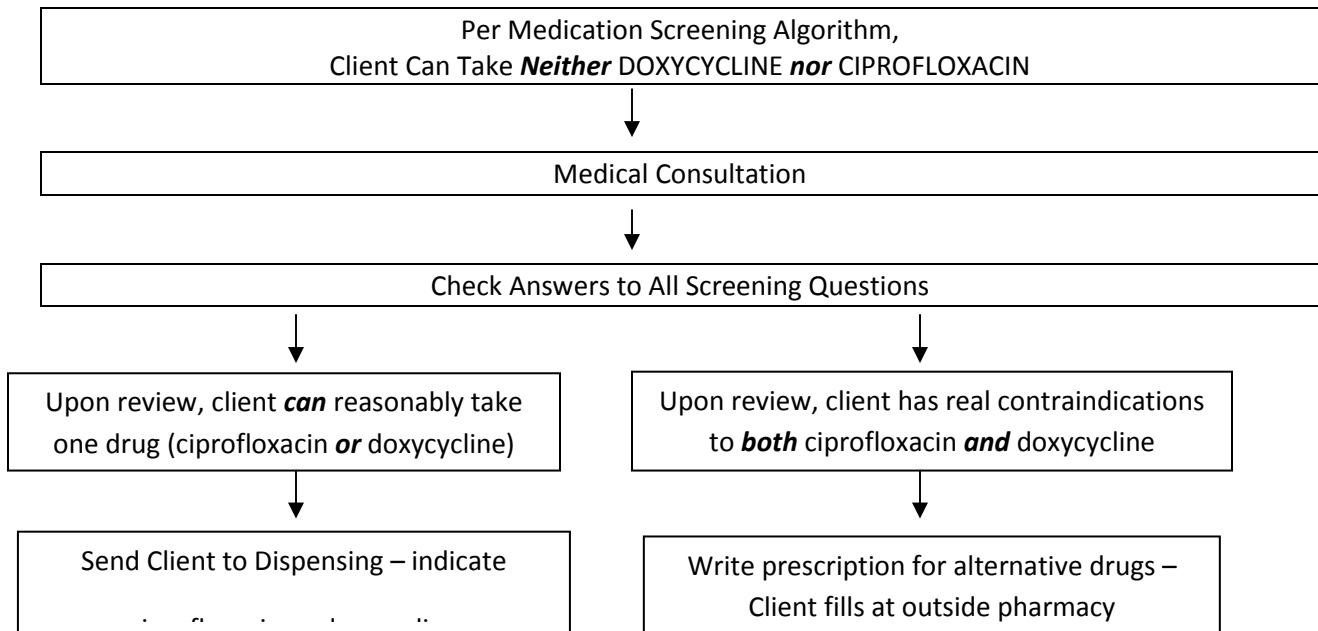
Rationale:

- Determining the dose, duration, and indication for those on concurrent antibiotics will consume Medical consultant time and potentially impede POD flow. Even if a determination can be made quickly, the accuracy of the information will be in question. Patients often do not know the precise reason for prescribing a particular antibiotic, such as the results of antibiotic sensitivity testing
- Even if information can be gathered quickly and accurately, the consultant may still not have enough information or expertise to determine the best course of action for these individuals
- Overall, the potential negative consequences of temporarily duplicating antibiotic coverage seems lesser than inappropriately discontinuing an individual’s medication or withholding doxycycline or ciprofloxacin at the POD

Kidney Failure or Dialysis

Ciprofloxacin is excreted primarily by renal metabolism. Dosage modification is recommended by the manufacturer for those with severe renal impairment (ClCr <30 mL/min). Post-dispensing instructions will be provided recommending those with kidney failure or who are on dialysis to reduce the ciprofloxacin dosing interval from Q12 to Q24 hours and to consult with their physician.

VI. Managing Clients Assigned to Consultation: Overview



- **Every POD client must exit the POD with an appropriate antibiotic in hand or with a prescription for an appropriate antibiotic (if no physician is available at the POD refer clients to one)**
- **Primary task of the MD Consultant is to finalize the selection and dose of antibiotic for clients who are routed to Consultation by the screening process**
- **Clients who report contraindications to BOTH ciprofloxacin AND doxycycline should be managed as follows (unless the Kansas City/Kansas CRI local health jurisdiction, in consultation with state and federal authorities adopts different recommendations):**
 1. **Amoxicillin monotherapy is presumed ineffective and should not be prescribed unless the *Y. pestis* strain is confirmed penicillin-sensitive**
 2. **Instead, the Medical Consultant should evaluate the reported contraindications and determine which agent, ciprofloxacin or doxycycline, would be the least toxic option**
 3. **However, clients with bona fide hypersensitivity to BOTH ciprofloxacin AND doxycycline should not be given either agent; but should instead receive combination therapy with Amoxicillin + a Second Antibiotic**

VII. Evaluating Reported Contraindications to Ciprofloxacin and Doxycycline

Clients going to Medical consultation have self-reported contraindications to BOTH ciprofloxacin AND doxycycline. However, they may have erred in interpreting the screening questions. As a first step, the Medical consultant should review each screening question with client, since if the client was mistaken, s/he may in fact be able to take doxycycline or ciprofloxacin. Here is a step-by-step guide to assessment.

Allergies

Confirm drug allergy to tetracyclines and/or quinolones. Ask about symptoms of the reaction, name of drug, how was allergy diagnosed, etc. Gather details of the history and decide if drug allergy to one or both drugs is present.

Age

Confirm age (verbal report OK, no need to check ID).

Pregnant

Confirm pregnancy: Clients who think they are pregnant because they have: a) tested positive; b) are having typical symptoms; or c) have missed periods; should be considered pregnant. The mere theoretical possibility of pregnancy or history of unprotected sex is not sufficient to consider client pregnant. Clients who are still concerned can be instructed to get a pregnancy test and then talk to their doctor.

History of seizures or epilepsy

Confirm whether the client understands these terms and whether the condition is or was present. In adults, history of childhood febrile seizures (that have since resolved) does not count. Clients who have a history of seizures but have been seizure-free for several years while off medication may or may not still have a lowered seizure threshold, and so this is a relative but not an absolute contraindication to receiving ciprofloxacin.

Tizanidine

Confirm concurrent use of the drug. Past use is irrelevant.

VIII. Managing Clients with Contraindications to BOTH Ciprofloxacin and Doxycycline

If the Medical assessment confirms that the client has contraindications to both ciprofloxacin and doxycycline, **and** there has been no confirmation that the *Y. pestis* strain is penicillin-sensitive, then the following recommendations apply:

	DOXYCYCLINE CONTRAINDICATIONS		
	Tetracycline allergy	<9 years old	Pregnant
CIPROFLOXACIN CONTRAINDICATIONS			
Quinolone allergy	AMOX + 2 nd Drug	DOXYCYCLINE	DOXYCYCLINE
Seizures or Epilepsy	CIPROFLOXACIN or AMOX + 2 nd Drug	DOXYCYCLINE	DOXYCYCLINE
Tizanidine	AMOX + 2 nd Drug or CIPROFLOXACIN	DOXYCYCLINE	DOXYCYCLINE

Allergic to Both: Persons who seem truly allergic to both Quinolones and Tetracyclines should be given a prescription for Amoxicillin plus a second antimicrobial.

Children age <9 years: It is permissible to give doxycycline to children age <9 years if they have a contraindication to ciprofloxacin. In the setting of plague PEP, doxycycline is FDA-approved for children of any age. The FDA and other authorities recognize that while tooth discoloration is a risk, it is outweighed by the need to administer effective antimicrobial prophylaxis for a serious infection such as inhalational plague. Therefore, unless the organism is known to be Penicillin-sensitive, doxycycline is a better choice for PEP for these individuals than Amoxicillin + 2nd Drug.

Pregnant: It is permissible to give doxycycline to pregnant women if they have a contraindication to ciprofloxacin. In the setting of plague PEP, doxycycline is FDA-approved for pregnant women. The FDA and other authorities recognize that while tooth discoloration is a risk, it is outweighed by the need to

administer effective antimicrobial prophylaxis for a serious infection such as inhalational plague. Therefore, unless the organism is known to be Penicillin-sensitive, doxycycline is a better choice for PEP for these individuals than Amoxicillin + 2nd Drug.

Seizures or Epilepsy: Seizures or epilepsy are a relative, not absolute contraindication to ciprofloxacin. A person who is doxycycline-allergic and who has had increased seizure activity with quinolones in the past could be a candidate for Amoxicillin + 2nd agent. Since this regimen is possibly less effective against plague, however, ciprofloxacin is an acceptable choice if the person is warned of the risks and can consult with their physician within 2 days.

Tizanidine: With Tizanidine, ciprofloxacin is contraindicated. Ciprofloxacin should not be given if the person can take doxycycline. A person who is doxycycline-allergic who cannot reduce the Tizanidine dose or discontinue Tizanidine could be a candidate for Amoxicillin + 2nd agent. Since this regimen is possibly less effective against plague, however, ciprofloxacin is an acceptable choice if the person is warned of the risks and agrees to consult with their physician immediately regarding reduction or discontinuation of Tizanidine.



Adding a Second Antimicrobial to Amoxicillin

A physician should prescribe a treatment for individuals that cannot take both doxycycline and ciprofloxacin.

REFERENCES:

- 1) Working Group on Civilian Biodefense. Inglesby et al, *JAMA* 2002; 287(17):2236-52 and correction in *JAMA* 2002; 288 (15):1849
- 2) Friedlander A, et al. *JID* 1993;167:1239.
- 3) Inglesby TV, et al. *JAMA* 1999; 281:1735
- 4) Brouillard, JE et al; *Pharmacotherapy* 2006; 26(1):3
- 5) Athamna A et al; *J Antimicrob Chemother* 2004; 53:247
- 6) Bell DM et al; *Emerg Infect Dis* 2002; 8(2):222
- 7) *MMWR* 2001; 50(43): 960
- 8) **Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks.** [Nahum GG](#), [Uhl K](#), [Kennedy DL](#). *Obstet Gynecol.* 2006 May;107(5):1120-38.
- 9) ACOG Committee Opinion number 268, February 2002. Management of asymptomatic pregnant or lactating women exposed to plague. American College of Obstetricians and Gynecologists. [Obstet Gynecol.](#) 2002 Feb;99(2):366-8.
- 10) Red book
- 11) *PEDIATRICS* 2006; 118(3): 1287
- 12) *CLINICAL PEDIATRICS* 2007; 46(2): 121-126
- 13) *PEDIATRIC INFECTIOUS DISEASE JOURNAL* 1998; 17(5): 429-431
- 14) *Pharmacotherapy* 1997; 31(4):492-4
- 15) [Schaefer HG](#), [Stass H](#), [Wedgwood J](#), [Hampel B](#), [Fischer C](#), [Kuhlmann J](#), [Schaad UB](#) Pharmacokinetics of ciprofloxacin in pediatric cystic fibrosis patients. [Antimicrob Agents Chemother.](#) 1996 Jan;40(1):29-34
- 16) [Rajagopalan P](#), [Gastonguay MR](#). Population pharmacokinetics of ciprofloxacin in pediatric patients. [J Clin Pharmacol.](#) 2003 Jul;43(7):698-710
- 17) Goldstein & Harden: Infectious states. In: Ettinger & Devinsky; Managing epilepsy and co-existing disorders; 2002; 83
- 18) Kushner, et al *Annals of Pharmacotherapy* 200; 35; 1194-1198
- 19) *Postgrad. Med. J.* 2006;82;568-572
- 20) *Epilepsia*, 46(8):1246–1251, 2005
- 21) Aggarwal et al *Clinical Neurology and Neurosurgery* 2006; 108: 433-439
- 22) *Epilepsia*, 44 (Suppl 10): 11-17 2003
- 23) *Curr Opin Neurol* 17:731–735
- 24) **Pseudotumor cerebri after treatment with tetracycline and isotretinoin for acne.** [Lee AG](#).[Cutis.](#) 1995 Mar;55(3):165-8.
- 25) Tortajada-Ituren, J et al. *Annals of Pharmacotherapy* _ 1999; 33: 804-808
- 26) [Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism.](#) Granfors MT, Backman JT, Neuvonen M, Neuvonen PJ. *Clin Pharmacol Ther.* 2004 Dec;76(6):598-606.
- 27) Semel, J and Allen, N. *Southern Medical Journal* 1991; 84(4): 465-468.
- 28) *MMWR* 2001; 50(42)
- 29) *MMWR* 2001; 50(42): 909;
- 30) Athamna A et al. *J Antimicrob Chemother* 2004; 53(2) 247-51.