

## OREGON HEALTH AUTHORITY

### IMMUNIZATION with BioThrax® (AVA)<sup>1</sup> & ANTI-MICROBIAL PROTOCOL for POST-EXPOSURE ANTHRAX PROPHYLAXIS in a

#### Mass Dispensing Setting

Updates: November 2016

1. Ciprofloxacin and Doxycycline are equivalent first-line antimicrobial agents for PEP in most situations. See tables on pages 3–5 for recommended alternate antimicrobials due to allergy or unavailability of first-line antimicrobials.
2. Addition of recommendations for pregnant, postpartum and lactating women, see IV.A page 3–4
3. Addition of recommendations for children, see IV.A page 4
4. Appendix A for doxycycline conversion of pills to liquid, pages 12–13

#### I. ORDER:

1. Screen client for contraindications to fluoroquinolones, doxycycline and anthrax vaccine.
2. Provide initial 10 days of 60–day course of antimicrobial, followed by the balance of the medication at a follow-up visit 7–10 days later. If the medication is not available on-site, a prescription can be called or sent to the recipient's pharmacy of choice. The prescription should include the following elements: the recipient's name, full name of the authorizing prescriber, the name, strength and dosage form of the medication, the route and frequency of administration, and the amount to be dispensed.
3. Schedule follow-up appointment to continue protocol.
4. Review current Vaccine Information Statement (VIS), answering any questions.<sup>2</sup>
5. Complete the anthrax Vaccine Administration Record (VAR).
6. Shake BioThrax® (AVA) vial thoroughly to ensure homogeneous suspension during withdrawal.
7. Inspect visually for particulate matter or discoloration. If present, discard vial.
8. Give 0.5mL subcutaneously (SC) at day 0, week 2 and week 4 using a 1– or 1½- inch 23– or 25 gauge needle, selecting a different injection site (e.g., alternating arms) for each sequential injection.
9. Observe client for 15 minutes after vaccination to monitor for and address any acute reaction.

Note: To maximize the benefits of vaccine, the first dose should be within 10 days of exposure.<sup>3</sup>

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Signature Health Officer

Date

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Signature Health Officer

Date

**This standing order expires July 31, 2017**

**II. LICENSED ANTHRAX VACCINE ADSORBED<sup>1</sup>**

PRODUCT NAME	VACCINE COMPONENTS	ACCEPTABLE AGE RANGE	PRESERVATIVES
BioThrax® Anthrax Virus Adsorbed (AVA)	83kDa <i>B. anthracis</i> protective antigen protein  1.2mg/mL aluminum hydroxide	≥6 weeks of age <sup>9</sup>	25µ/mL benzethonium chloride  100µ/mL formaldehyde
BioThrax® does not contain either dead or live bacteria. <sup>1</sup>			

**III. RECOMMENDATIONS FOR USE<sup>1, 3, 6A</sup>**

Recommended post-exposure vaccination schedules for anthrax vaccine adsorbed				
Type of prophylaxis*	Vaccination Status	Schedule	Route	Dose
Anthrax Vaccine Adsorbed	Unvaccinated <sup>◇</sup>	3 doses (0, 2, and 4 wks.)	Subcutaneous	0.5mL
	Partially vaccinated <sup>§</sup>	Continue with vaccine schedule	IM	0.5mL
	Fully vaccinated <sup>§</sup>	Continue annual boosters	IM	0.5mL

\*Everyone exposed to aerosolized *B. anthracis* should receive a full 60 days of antimicrobial PEP regardless of vaccination status.<sup>6A</sup>

<sup>◇</sup> In conjunction with 60-day antimicrobial post-exposure prophylaxis.<sup>3</sup>

<sup>§</sup>Continue antimicrobial PEP at least 30 days after any type of disruption of respiratory protection.<sup>3</sup>

#### IV. A. RECOMMENDED INITIAL ANTIMICROBIAL AGENT AND ANTHRAX VACCINE DOSAGES FOR POST-EXPOSURE PROPHYLAXIS (PEP)

Population	Antimicrobials for 60-day* PEP <i>Give one of the following for 10 days; give balance of 60-day course at follow-up visit in 7–10 days.</i> <b>Note: Amoxicillin<sup>7</sup> or Penicillin VK<sup>8b</sup> <sup>∞</sup> could be used under an investigational new drug protocol for balance of course if organism has proved sensitive to penicillins and there is no allergy to penicillin.<sup>7</sup></b>	Anthrax vaccine dosage and route <sup>∞</sup>  AVA would be considered under an investigational new vaccine protocol for individuals <18 and >65 years of age. <sup>1, 4, 5</sup>
Non-pregnant Adults ≥19 years of age <sup>6a,6b</sup>	<p><b>Preferred Choices</b></p> <p>Ciprofloxacin, 500 mg orally twice daily</p> <p>Doxycycline, 100 mg orally twice daily</p> <p>(Ciprofloxacin and doxycycline are equally recommended for PEP in non-pregnant adults)</p> <p>Second-line options (<i>if preferred choices unavailable or contraindicated</i>)</p> <p>Levofloxacin<sup>§</sup> 750mg orally every 24 H</p> <p>Moxifloxacin 400 mg orally every 24 H</p> <p>Clindamycin<sup>‡</sup> 600 mg orally every 8 H</p> <p>If susceptibility confirmed, Amoxicillin 1 gm every 8 H or Penicillin VK<sup>8b</sup> 500mg every 6 H could be considered.<sup>∞</sup></p>	3-dose subcutaneous (SC) series: first dose administered as soon as possible, second and third doses administered 2 and 4 weeks after first dose.
Pregnant, postpartum and lactating women <sup>**</sup>	<p><b>Ciprofloxacin is preferred</b>, 500 mg orally twice daily</p> <p>Second-line options</p> <p>Levofloxacin<sup>§</sup> 750mg orally every 24 H</p> <p>Moxifloxacin 400 mg orally every 24 H</p> <p>Clindamycin<sup>‡</sup> 600 mg orally every 8 H</p> <p>Doxycycline<sup>**</sup>, 100 mg orally twice daily</p>	3-dose SC series; first dose administered as soon as possible, second and third doses administered 2 and 4 weeks after first dose. AVA Pregnancy registry: 1-619-553-9255 <sup>1</sup>

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Original: 2006

	<p>If susceptibility confirmed, Amoxicillin 1gm every 8 H or Penicillin VK<sup>8b</sup> 500mg every 6 H could be considered.<sup>∅∅</sup></p>	
<p>Children (≤18 years of age<sup>8</sup>)<sup>∅∅</sup></p> <p>AVA would be considered under an investigational new vaccine protocol for individuals &lt;18 years of age.<sup>1, 4, 5</sup></p>	<p><b>Preferred Choices</b></p> <p>Ciprofloxacin<sup>§§</sup> 15 mg/kg orally every 12 H. (not to exceed 500mg/dose)<sup>3,7,9</sup></p> <p><b><i>Oral suspension of ciprofloxacin is available in limited supply in the SNS.</i></b></p> <p>Doxycycline<sup>§§</sup> (not to exceed 100 mg/dose)<sup>3</sup></p> <p>&gt;8 yrs and &gt;45 kg: 100 mg every 12 H</p> <p>&gt;8 yrs and ≤45 kg: 2.2 mg/kg every 12 H</p> <p>≤8 yrs: 2.2 mg/kg every 12 H</p> <p>(Ciprofloxacin and doxycycline are equally recommended for PEP in children.)<sup>3</sup></p> <p>Second-line options</p> <p>Levofloxacin<sup>§</sup></p> <p><b>&lt;50 kg:</b> 8 mg/kg by mouth, every 12 H (not to exceed 250mg per dose)</p> <p><b>&gt;50 kg:</b> 500mg by mouth every 24 H</p> <p>[If susceptibility confirmed, Amoxicillin or Penicillin VK could be considered.]<sup>∅∅</sup></p>	<p>All exposed children 6 weeks and older should receive 3 doses of AVA subcutaneously at 0, 2, and 4 weeks in addition to 60 days of antimicrobial chemoprophylaxis.</p> <p>Children younger than 6 weeks should immediately begin antimicrobial prophylaxis but delay starting the vaccine series until they reach 6 weeks of age<sup>9</sup></p>

\* Antimicrobial should continue for 14 days after administration of the third dose of vaccine.<sup>3</sup>

∅AVA used for PEP must be administered subcutaneously.<sup>1</sup>

§Levofloxacin is a second-line antimicrobial agent for PEP in persons aged ≥6 mos with medical issues (e.g., tolerance or resistance to ciprofloxacin) that indicate its use. Safety data on extended use of levofloxacin in pediatric populations are limited beyond 14 days of therapy, and in adults are limited beyond 30 days of use; therefore, levofloxacin PEP should only be used when the benefit outweighs the risk.<sup>9</sup>

‡Based on *in vitro* susceptibility data, rather than studies of clinical efficacy.<sup>8b</sup>

\*\*The antimicrobial of choice for initial prophylaxis among pregnant women is ciprofloxacin. Doxycycline should be used with caution in asymptomatic pregnant women and only when other appropriate antimicrobial drugs are contraindicated, particularly before the third trimester. Although tetracyclines are not recommended during pregnancy, their use might be indicated for life-threatening illness.<sup>8a, 8b</sup>

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∞If susceptibility testing demonstrates an amoxicillin Minimum Inhibitory Concentration  $\leq 0.125 \mu\text{g/mL}$ , use of oral amoxicillin could be considered under an investigational new drug protocol.<sup>7</sup> Pregnant women, adults, and pediatric patients  $\geq 40\text{kg}$  = 1000 mg every 8 hours. Because of the lack of data on amoxicillin dosages for anthrax prophylaxis and the associated high mortality rate with inhalational disease, AAP recommends a dosage for pediatric patients  $< 40\text{kg}$  of 25mg/kg every 8 H, not to exceed 1gm per dose.<sup>7, 8b, 9</sup> Penicillin VK 16.6mg–25mg/kg orally every 6 H or 12.5mg–18.75mg/kg every 8 H<sup>9</sup>. Recipients should be carefully monitored for side effects from long-term treatment.<sup>9</sup>

§§Use of tetracyclines and fluoroquinolones in children can have adverse effects. These effects must be weighed carefully against the risk for developing life-threatening disease. If exposure to *B. anthracis* is confirmed, children may receive either ciprofloxacin or doxycycline as prophylaxis. However, amoxicillin is preferred for antimicrobial PEP in children when susceptibility testing indicates that the *B. anthracis* isolate is susceptible to penicillins.<sup>7, 9</sup>

#### IV. CONTRAINDICATIONS

**1. Anthrax Vaccine Adsorbed (AVA)**<sup>1</sup> is contraindicated for persons who have experienced an anaphylactic reaction after a previous dose of AVA or any of the vaccine components.

**2. Ciprofloxacin:**<sup>10</sup>

- a. Allergy to fluoroquinolones
- b. Concomitant use with Tizanidine (If one has been exposed to anthrax, and ciprofloxacin is all that's available for prophylaxis, it might be a good time to taper off the Tizanidine!)

**3. Doxycycline:**<sup>11</sup>

- a. Allergy to Tetracyclines

#### V. PRECAUTIONS and WARNINGS

**The CDC strongly discourages the use of fluoroquinolones, including Cipro, in individuals with myasthenia gravis due to the potential to exacerbate muscle weakness.**<sup>10C</sup>

**Anthrax Vaccine Adsorbed:**<sup>1</sup>

- A. **Latex Allergy:** The vial stopper contains dry, natural rubber latex. Use caution when administering the vaccine to persons with a latex allergy.

**B. History of Anthrax Disease:** A history of anthrax disease might increase the potential for severe local adverse reactions after AVA administration.

**Ciprofloxacin:** <sup>10a, 10b</sup>

**A. Central Nervous System or Seizure Disorders:** decreased seizure threshold

**B. Co-administration with theophylline** or other medicine metabolized by CYP1A2: increased serum levels

**C. Renal impairment:** altered dosage regimen indicated

**Doxycycline:** <sup>11</sup>

**A. Pregnancy:** Evidence of human fetal risk, but use in pregnancy may be acceptable if benefits out-weigh risks.

**B. Use at age <8 years** may affect tooth development.

**VII. SIDE EFFECTS AND ADVERSE REACTIONS**

Ciprofloxacin <sup>10a</sup>	<p>Nausea, vomiting, diarrhea, stomach pain, headache, dizziness, joint pain and rash.</p> <p>Long-term fluoroquinolone use has been associated with tendinitis and tendon tears.</p>
Doxycycline <sup>11</sup>	<p>Photosensitivity of skin, nausea, vomiting, diarrhea and rash.</p> <p>Effect on tooth development in fetus if taken during last half of pregnancy or in children if taken during initial 8 years of life.</p> <p>Bismuth subsalicylate (Pepto Bismol) may reduce absorption of tetracyclines<sup>11</sup></p>

<b>AVA S.Q. INJECTION<sup>1</sup>:</b> n= 259	<b>Dose 1</b> %	<b>Dose 2</b> %	<b>Dose 3</b> %
Warmth	29	41	32
Tenderness	64	72	48
Itching	3	16	23
Pain	16	22	12
Arm motion limitation	8	12	5
Erythema	53	64	57
Induration	26	35	28
Edema	17	33	31
Nodule	39	42	36
Bruise	6	7	6
Presence of any large local adverse reaction <sup>§</sup>	0	1	4
Presence of any systemic adverse reaction	16	20	18
Fatigue	9	12	8
Muscle ache	5	8	4
Headache	7	9	8
Fever >104	0	0	0
Tender/painful axillary adenopathy	0	1	2
Presence of any moderate / severe systemic adverse reactions <sup>*,<sup>◇</sup></sup>	2	5	4
<p>*Moderate = causes discomfort and interferes with normal daily activities;  Severe = incapacitating and completely prevents performing normal daily activities.  <sup>◇</sup>Women report a higher rate of adverse events than men. ACIP concluded there is no evidence that the risk for serious adverse events after administration of anthrax vaccine is higher in children.  <sup>§</sup>Large = an occurrence of induration, erythema, edema, nodule and bruise with a largest diameter greater than 120mm.</p>			
Note: Adapted from Anthrax Vaccine Adsorbed package insert, 2015 p.9–10 <sup>1</sup>			

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## VIII. OTHER CONSIDERATIONS

1. Adverse Events: epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be available for immediate use in case of anaphylactic or acute hypersensitivity reaction.<sup>12</sup>
2. Military Personnel: If an adult has a record of military service and does not have records available, providers can assume that the person has received all vaccines recommended by the military at the time of service entry. Serologic testing might be helpful in clarifying immune status if questions remain because at different times and depending on military assignments, there might be inter-service and individual differences.<sup>12</sup>
3. Immunocompromised: individuals with altered immunocompetence may have reduced immune responses.<sup>1</sup>
4. The serum elimination half-life of ciprofloxacin in subjects with normal renal function is approximately 4 hours. Elimination half-life is only slightly (~20%) prolonged in the elderly.<sup>10a</sup>
5. Continue antimicrobial PEP for 14 days after the third dose of vaccine, even if the initial vaccine administration is delayed and therefore antimicrobial is used for >60 days.<sup>3</sup>
6. Anthrax Vaccine Adsorbed (AVA) for exposed children aged >6 weeks of age and older.<sup>4, 5, 9</sup>
7. Duration of AVA protection in humans after the initial priming series is unknown.<sup>1</sup>
8. There is no biologic reason to suggest that breast-feeding women or breast-fed infants have an increased risk for adverse events after vaccination with AVA<sup>8a</sup>.
9. When the strain *B. anthracis* is found to be susceptible to amoxicillin, use of amoxicillin can be considered under an investigational new drug protocol for pregnant, postpartum or lactating women, and children.<sup>8a, 8b, 9</sup>
10. A shorter course (<60 days) of antimicrobial therapy, even when combined with a 3-dose AVA series, is not approved for use by the FDA.<sup>3</sup>
11. Anthrax Virus Adsorbed vaccine may be administered to persons who have a mild illness with or without a low-grade fever.<sup>3</sup>

**IX. STORAGE AND HANDLING**

Vaccine	Temperature	Storage Issues	Notes
<b>BioThrax®<sup>1</sup></b> (Anthrax Vaccine Adsorbed):	Store at 2°–8°C (36°F–46°F)	Do not use if vaccine has been frozen.  Do not use after the expiration date on the printed label.	The stopper of the vial contains natural rubber latex.

**X. ADVERSE EVENTS REPORTING**

Public providers are to complete the Vaccine Adverse Events Reporting System (VAERS) report online at <https://vaers.hhs.gov/esub/step1>.

- Save a copy of the report number for your records
- Send copies of the report and VAERS ID number to the Oregon Immunization Program Vaccine Safety Coordinator via confidential email at [ORVAERS.Reports@state.or.us](mailto:ORVAERS.Reports@state.or.us) or fax (971-673-0278).

Private providers are to report events directly to VAERS and can read about options on how to do so at <http://vaers.hhs.gov/index>.

To request this material in an alternative format (e.g., Braille) or to clarify any part of the above order, contact the Oregon Health Authority Immunization Program at 971.673.0300 and 711 for TTY. For other questions, consult with the vaccine recipient's primary health care provider or a consulting physician.

Electronic copy of this standing order is available at:

<http://1.usa.gov/OregonStandingOrders>

Report to the FDA MedWatch program at <http://www.fda.gov/Safety/MedWatch/default.htm>

## REFERENCES

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2. CDC. Vaccine Information Statement. Anthrax Vaccine. What you need to know. (2010). Available at: [www.cdc.gov/vaccines/hcp/vis/vis-statements/anthrax.pdf](http://www.cdc.gov/vaccines/hcp/vis/vis-statements/anthrax.pdf). Accessed 08 March 2016.
3. CDC. Use of anthrax vaccine in the United States; Recommendations of the Advisory Committee on Immunization Practices (ACIP) 2009. MMWR 2010. 59 RR-6. Available at [www.cdc.gov/mmwr/preview/mmwrhtml/rr5906a1.htm?s\\_cid=rr5906a1\\_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5906a1.htm?s_cid=rr5906a1_w) Accessed 07 March 2016.
4. Office of Counterterrorism Policy and Planning. Guidance---Emergency Use Authorization of medical products; 2016. Available at [www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm) Accessed 07 March 2016.
5. Food and Drug Administration. Emergency Preparedness and Response. Emergency Use Authorization: Available\* at [www.fda.gov/emergencypreparedness/counterterrorism/ucm182568.htm](http://www.fda.gov/emergencypreparedness/counterterrorism/ucm182568.htm) Accessed 07 March 2016.

\*Anthrax is just past half-way down the page.

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7. U.S. Food and Drug Administration. Protecting and promoting your health. Commentary on Non-labeled dosing of oral amoxicillin in adults and pediatrics for post-exposure inhalational anthrax. (2015). Available at: [www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismAndDrugPreparedness/ucm072106.htm#Pediatric\\_patients](http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismAndDrugPreparedness/ucm072106.htm#Pediatric_patients) Accessed 08 March 2016.
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- 10A. Ciprofloxacin package insert: Revised February, 2015: [aidsinfo.nih.gov/drugs/458/ciprofloxacin/0/professional#ID\\_2be6ecba-598a-489b-9a0e-f2f5f7b02f28](http://aidsinfo.nih.gov/drugs/458/ciprofloxacin/0/professional#ID_2be6ecba-598a-489b-9a0e-f2f5f7b02f28)
- 10B .Cipro Medication Guide: Revised March, 2015: [www.fda.gov/downloads/Drugs/DrugSafety/ucm246794.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/ucm246794.pdf)
- 10C. Fluoroquinolones and Myasthenia Gravis. CDC. EUI. Available at: <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm495126.htm#cipro> Accessed 07 November 2016.
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12. CDC. General Recommendations on Immunizations. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011; 60 (RR-2). Available at: [www.cdc.gov/mmwr/pdf/rr/rr6002.pdf](http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf) Accessed 09 March 2016.

For more information or to clarify any part of the above order, consult with the vaccine recipient's primary health care provider, a consulting physician, or contact Oregon State Acute and Communicable Disease Program at (971) 673–1111.

APPENDIX A

# In an Emergency: How to Prepare Doxycycline for Children and Adults Who Cannot Swallow Pills

## Mixing Doxycycline Hyclate 100mg Tablets with Food

Once you have been notified by your federal, state or local authorities that you need to take doxycycline for a public health emergency, it may be necessary to prepare emergency doses of doxycycline for children and adults who cannot swallow pills.

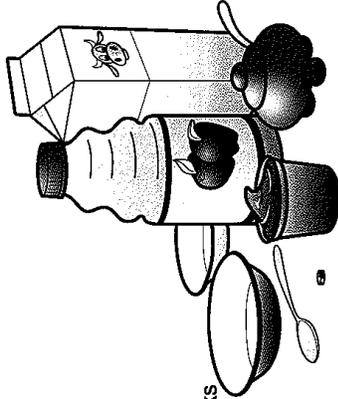
June 2008  
Prepared by the U.S. Food and Drug Administration

### 1

#### Supplies You Will Need

You will need these items to make doses of doxycycline for adults and children who cannot swallow pills:

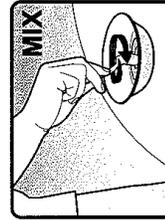
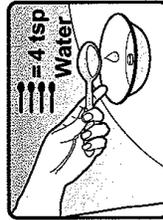
- 1 doxycycline pill (100 mg)  
*(Do not take doxycycline if you are allergic to tetracyclines)*
- a metal teaspoon
- 2 small bowls
- Water
- one of these foods or drinks to hide the bitter taste of crushed doxycycline:
  - milk or chocolate milk
  - chocolate pudding
  - apple juice and sugar



### 2

#### Crushing the Pill and Mixing with Water

1. Put 1 doxycycline pill in a small bowl.
2. Add 4 full teaspoons of water to the same bowl.
3. Let the pill soak in the water for 5 minutes so it will be soft.
4. Use the back of a metal teaspoon to crush the pill in the water. Crush the pill until no visible pieces remain.
5. Stir the pill and water so it is well mixed.

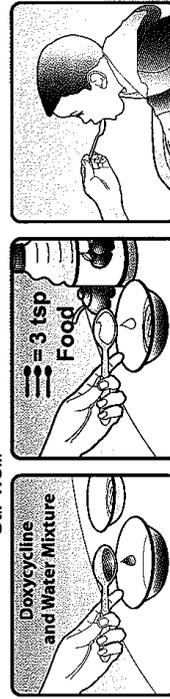


**You have now made the Doxycycline and Water Mixture.**

- 3 Adding Food to the Doxycycline and Water Mixture to Make It Taste Better**
- Child's weight: \_\_\_\_\_
1. Weigh your child.
  2. Find your child's weight on the left side of the chart below.
  3. Next, look on the right side of the chart to find the amount of the Doxycycline and Water Mixture to mix with food. The chart shows you the amount to give your child for 1 dose. (For a ½ teaspoon dose, fill the metal teaspoon half way. It is better to give a little more of the medicine than not enough).

Child's Weight	Amount of Doxycycline and Water Mixture	Teaspoons
12 pounds or less	½ teaspoon	1
13 to 25 pounds	1 teaspoon	1
26 to 38 pounds	1½ teaspoons	1½
39 to 50 pounds	2 teaspoons	2
51 to 63 pounds	2½ teaspoons	2½
64 to 75 pounds	3 teaspoons	3
76 to 88 pounds	3½ teaspoons	3½
89 pounds or more and adults	Use the entire mixture	Entire Mixture

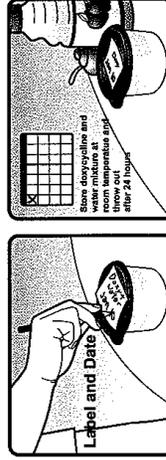
4. Add the right amount of the Doxycycline and Water Mixture from the chart above to the second bowl. For adults and children 89 pounds and more, use the entire mixture.
5. Add 3 teaspoons of milk or chocolate milk or chocolate pudding or apple juice to the second bowl. If you use apple juice, also add 4 teaspoons of sugar to the second bowl.
  - Stir well.



6. Go to Step 4 for dosing.

- 4 Dosing the Doxycycline and Water Mixture Mixed With Food**
1. Give all of the Doxycycline and Water and food mixture in the second bowl. This is one dose.
  2. Each child or adult should take 1 dose in the morning and 1 dose at night each day.

- 5 Storing the Doxycycline and Water Mixture (If There Is Enough for Another Dose)**
- If you have enough leftover doxycycline and water mixture for another dose, you can keep it for the next dose.
  - The doxycycline and water mixture can be stored in a covered bowl or cup. Label and date.
  - Keep the mixture in a safe place out of the reach of children.
  - Store the Doxycycline and Water Mixture at room temperature for up to 24 hours.
  - Throw away any unused mixture after 24 hours and make a new Doxycycline and Water Mixture before the next dose.



Do not take doxycycline if you have an allergy to tetracyclines. Get emergency help if you have any signs of an allergic reaction including hives, difficulty breathing, or swelling of your face, lips, tongue or throat. Doxycycline may cause diarrhea, skin reaction to the sun, loss of appetite, nausea and vomiting. Birth control pills may not work as well if you take doxycycline.



Report any reaction to the medication to MedWatch at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or 1-800-FDA-1088