Model Post-Exposure Prophylaxis Protocol

Anthrax Vaccine (BioThrax®) and Antibiotic Dispensing	
Last Reviewed	6 July 2021
Last Revised	6 July 2021
This order expires	31 July 2023

Table of contents

1. What's new

Updated information on uses of anthrax vaccine adsorbed in mass-exposure situations, including option for intramuscular administration, possible use of dose-sparing regimens in scarcity settings, and reduced duration of antimicrobial prophylaxis in certain settings. Updated links. Minor edits for clarity.

2. Oregon immunization model protocol

A. Check the ALERT Immunization Information System (IIS) to determine whether the patient needs this vaccine and any other vaccines.

B. Screen clients for contraindications to fluoroquinolones, doxycycline, and anthrax vaccine, as well as risk factors noted under *Warnings and Precautions*.

C. 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. In immunocompetent adults (e.g., healthy, nonpregnant adults aged 18–65 years), antimicrobial prophylaxis can be stopped 42 days after initiating vaccine if anthrax vaccine is administered on the recommended schedule. This is also true if a dose-sparing vaccine schedule is used.[3]

D. 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.

E. Schedule follow-up appointment to continue protocol.

F. Provide a current Vaccine Information Statement[2] (VIS), answering any questions.

G. Record all required data elements in the client's permanent health record.

H. Verify needle length for SQ injection.

I. Shake BioThrax® (AVA) vial thoroughly to ensure homogeneous suspension during withdrawal.

J. Inspect visually for particulate matter or discoloration. If present, discard vial.

K. Give 0.5mL SC.

L. Observe client for 15 minutes after vaccination to monitor for and address any acute reaction.

Health Officer Signature Date

Health Officer Signature Date

3. Post-exposure schedule for anthrax[3]

Anthrax vaccine			
Dose and Route: 0.5-mL, SQ*			
Unvaccinated			
Dose	**Preferred age**	**Minimum acceptable age**	**Minimum acceptable spacing¶**
1	N/A	18 years#	
2			2 weeks dose 1 to 2
3			4 weeks dose 2 to 3
Partially vaccinated			
Complete primary series of three doses.			
Fully vaccinated			
Provide annual booster doses for persons at high-risk			

*During a large-scale emergency response, initial dose can be given IM if the SC route poses significant materiel, personnel, or clinical challenges that might delay or preclude vaccination. Persons who had adverse events from an SC AVA dose may elect to receive subsequent doses IM after consulting with a healthcare provider.[3]

#Anthrax vaccine may be made available to children ≥ 6 weeks of age under an Investigational New Drug protocol when necessary.[10]

¶ACIP recommends use of dose-sparing PEP regimens if the anthrax vaccine supply is insufficient to vaccinate all potentially exposed persons. The 2 full-dose strategy will expand the existing vaccine supply by 50%, and the 3 half-dose strategy will expand the supply by 100%. Immediately after a wide-area aerosolized release of *B. anthracis* spores, the preferred dose-sparing PEP regimen, if needed, will be announced and authorized under an EUA. All dose-sparing PEP-Vx regimens are estimated to provide high levels of protection 2 weeks after the last dose.[3]

Recommended Initial Antimicrobial Regimens* Give one of the following for 10 days; give balance of course at follow-up visit in 7–10 days.				
Population	**Preferred medication choices**	**Dosage**	**Second line options**	**Dosage**
Non-pregnant adults ≥19 years of age	Ciprofloxacin	500 mg orally twice daily	Levofloxacin†	750mg orally every 24 H
	Doxycycline	100 mg orally twice daily	Moxifloxacin	400 mg orally every 24 H
	Ciprofloxacin and doxycycline are equally recommended for PEP in non-pregnant adults		Clindamycin#	600 mg orally every 8 H
			Consider only if susceptibility is confirmed	
			Amoxicillin	1 gm every 8 H
			Penicillin VK[8]	500mg every 6 H‡
Population	**Preferred medication choices**	**Dosage**	**Second line options**	**Dosage**
Pregnant, postpartum and lactating women**	Ciprofloxacin	500 mg orally twice daily	Levofloxacin†	750mg orally every 24 H
			Moxifloxacin	400 mg orally every 24 H
			Clindamycin#	600 mg orally every 8 H
			Doxycycline**	100 mg orally twice daily
			Consider only if susceptibility confirmed	
			Amoxicillin	1gm every 8 H
			Penicillin VK[8]	500mg every 6 H.‡
Population	**Preferred medication choices**	**Dosage**	**Second line options**	**Dosage**

<table>
<tr><td rowspan="3">Children≤18 years of age[10] ††</td><td>Ciprofloxacin,†† 15 mg/kg orally every 12 H. (not to exceed 500mg/dose)[3,7]

Oral suspension of ciprofloxacin is available in limited supply in the Strategic National Stockpile.

Doxycycline††
(not to exceed 100 mg/dose)[3]
>8 years and >45 kg: 100 mg every 12 H
>8 years and ≤45 kg: 2.2 mg/kg every 12 H
≤8 years: 2.2 mg/kg every 12 H</td><td rowspan="3">Levofloxacin†</td><td><50 kg: 8 mg/kg by mouth, every 12 H
(not to exceed 250 mg per dose)</td></tr>
<tr><td>Ciprofloxacin and doxycycline are equally recommended for PEP in non-pregnant adults</td><td>>50 kg: 500mg by mouth every 24 H</td></tr>
</table>

* **N.B**.: In immunocompetent adults (e.g., healthy, nonpregnant adults aged 18–65 years), PEP-Abx given with either standard or dose-sparing PEP-Vx regimens can be stopped 42 days after initiating vaccine if AVA is administered on the recommended schedule. If the AVA series can't be completed, antimicrobial therapy should continue for 60 days.[3] Antimicrobial should continue for 14 days after administration of the third dose of vaccine.[3]

†Levofloxacin is a second-line antimicrobial agent for PEP in persons aged ≥6 months 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.[8]

#Based on *in vitro* susceptibility data, rather than studies of clinical efficacy.[7]

‡If susceptibility testing demonstrates an amoxicillin Minimum Inhibitory Concentration ≤0.125 μg/mL, use of oral amoxicillin could be considered under an investigational new drug protocol.[8] Pregnant women, adults, and pediatric patients ≥40kg = 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 <40kg of 25mg/kg every 8 H, not to exceed 1gm per dose.[8, 10] Penicillin VK 16.6mg–25mg/kg orally every 6 H or 12.5mg–18.75mg/kg every 8 H.[8] Recipients should be carefully monitored for side effects from long-term treatment.[8]

**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.[9]

††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.[8,10]

4. Licensed anthrax vaccine

Product Name	Vaccine Components	Presentation	Acceptable Age Range	Thimerosal
BioThrax[1]	83kDa B. anthracis protective antigen protein1.2mg/mL aluminum hydroxide	5 mL multidose vial	18 years to 65 years	None

5. Recommendations for use

See section 3 above.

6. Contraindications

Vaccine:

A. Anaphylactic reaction to a previous dose of anthrax vaccine or any component of the vaccine.

Vaccine	Vaccine Excipient Summary[16]
BioThrax	Aluminum hydroxide, sodium chloride, benzethonium chloride, formaldehyde

Ciprofloxacin:

A. Allergy to fluoroquinolones

B. Concomitant use of Tizanidine.

Doxycycline:

A. Allergy to tetracyclines.

7. Warnings and precautions

Vaccine:[1]

A. Hypersensitivity to latex. Vial stopper contains dry, natural rubber latex.

B. History of anthrax. Severe local reactions after vaccination in persons with a

history of anthrax disease.

Ciprofloxacin:[11,13]

A. Use of fluoroquinolones, including Cipro, is strongly discouraged in individuals with myasthenia gravis because it may exacerbate muscle weakness.[13]

B. Central nervous system or seizure disorders. Cipro may decrease seizure threshold.

C. Co-administration of theophylline or other drugs metabolized by CYP1A2 may result in increased serum levels.

D. Renal impairment. Altered dosage regimen indicated.

Doxycycline:[14]

A. Pregnancy. Evidence of human fetal risk, but use may be acceptable if benefits outweigh risks.

B. Children under 8 years of age. Use may affect tooth development.

8. Other considerations

A. Anthrax vaccine injections should use alternating injection sites (e.g. alternate arms) for each sequential injection.[3]

B. Persons who experienced adverse events from AVA that was administered SC may elect to receive subsequent vaccine doses IM after consultation with a healthcare provider.[3]

C. During a large-scale emergency response, anthrax vaccine for post-exposure prophylaxis can be administered using an IM route if the SC route poses significant materiel, personnel, or clinical challenges that might delay or preclude vaccination.[3]

D. 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.[15]

E. 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.[12]

F. 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.[3]

G. In case of exposure, anthrax vaccine may be used for children 6 weeks of age and older under an Investigational New Drug protocol.[10]

H. Duration of anthrax vaccine protection in humans after the initial priming series is unknown.[1]

I. Anthrax vaccine may be used in breastfeeding women when indicated.[9]

J. 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.[9,10]

K. Anthrax vaccine may be administered to persons who have a mild illness with or without a low-grade fever.[15]

9. Side effects and adverse reactions

Adverse Events – BioThrax[1]	**Frequency**
Any local reaction – pain, redness, induration or swelling at injection site.	Very common, up to 65%
Moderate to severe local reactions	Uncommon, up to 4%
Any systemic reaction—fever, malaise, muscle aches, headache	Common, up to 20%
Tenderness in axillary lymph nodes	Uncommon, up to 2%
Moderate to severe systemic reactions	Uncommon, up to 5%
Adverse Events – Ciprofloxacin[11]	
Nausea, vomiting, diarrhea, stomach pain, headache, dizziness, joint pain and rash.	
Long-term fluoroquinolone use has been associated with tendinitis and tendon tears.	
Adverse Events – Doxycycline[14]	
Photosensitivity of skin, nausea, vomiting, diarrhea and rash.	
Effect on tooth development in fetus if taken during last half of pregnancy or in children if taken during initial 8 years of life.	
Bismuth subsalicylate (Pepto Bismol) may reduce absorption of tetracyclines.	

10. Storage and handling

All clinics and pharmacies enrolled with the Vaccines for Children (VFC) Program must immediately report any storage and handling deviations to the Oregon Immunization Program at 971-673-4VFC (4823).

Vaccine	Temp	Storage Issues	Notes
BioThrax[1]	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.

11. Adverse events reporting

Report suspected vaccine adverse events to the Vaccine Adverse Events Reporting System (VAERS) online at https://vaers.hhs.gov/reportevent.html. VAERS Reporting Table: https://vaers.hhs.gov/resources/infoproviders.html

Report suspected medication adverse events to the FDA MedWatch Program at http://www.fda.gov/Safety/MedWatch/default.htm

12. References

1. Emergent BioSolutions. 2015 BioThrax® (Anthrax Vaccine Adsorbed) package insert. Available at: https://www.fda.gov/media/71954/download Accessed 30 June 2021.
2. CDC. Vaccine Information Statement. Anthrax Vaccine. What you need to know. (2020). Available at: www.cdc.gov/vaccines/hcp/vis/vis-statements/anthrax.pdf. Accessed 30 June 2021.
3. CDC. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2019. MMWR 2019. 68 RR-4 www.cdc.gov/mmwr/volumes/68/rr/rr6804a1.htm Accessed 10 June 2021.
4. Office of Counterterrorism Policy and Planning. Guidance---Emergency Use Authorization of medical products; 2017. Available at www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm Accessed 30 June 2021.
5. Doxycycline for Post-exposure prophylaxis of anthrax. Emergency Use Instructions for Healthcare Providers. 2018. Available at:

https://www.fda.gov/media/97089/download Accessed 30 June 2021.

6. Ciprofloxacin for Post-Exposure Prophylaxis of Anthrax. Emergency Use Instructions for Healthcare Providers. 2018. Available at: https://www.fda.gov/media/97098/download Accessed 30 June 2021.
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8. 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 Accessed 30 June 2021.
9. Meaney-Delman, D et. al. Special considerations for prophylaxis for and treatment of anthrax in pregnant and postpartum women. Emerging Infectious Diseases: (2014);20(2); e1–e6. Available at: https://wwwnc.cdc.gov/eid/article/20/2/13-0611_article Accessed 30 June 2021.
10. Bradley JS, et al. Clinical Report. Pediatric anthrax clinical management: Executive summary. Appendix 1. American Academy of Pediatrics: 2014; 133(5):e1411–e1436. Available at: pediatrics.aappublications.org/content/pediatrics/early/2014/04/22/peds.2014-0564.full.pdf Accessed 30 June 2021.
11. Ciprofloxacin package insert: Revised March, 2020: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/019537s090,020780s047lbl.pdf Accessed 10 June 2021.
12. Cipro Medication Guide: Revised July 2016, page 41: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019537s087,020780s044lbl.pdf#page=41 Accessed 30 June 2021.
13. CDC. Anthrax Emergency: How to Take Ciprofloxacin to Prevent Anthrax. EUI. August 2017. Available at: https://www.cdc.gov/anthrax/pdf/cipro-eui-recipients-H.pdf Accessed 30 June 2021.
14. Doxycycline Hyclate package insert: Reviewed May 2018: www.drugs.com/pro/doxycycline.html Accessed 30 June 2021.
15. Kroger A, Bahta L, Hunter P. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). www.cdc.gov/vaccines/hcp/acip-recs/general-

recs/downloads/general-recs.pdf Accessed on 30 June 2021.

16. CDC. Vaccine Excipient Table. February 2020. Available at: hwww.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf. Accessed 30 June 2021.

For more information or to clarify any part of the above protocol, 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.

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: standing orders

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

Mixing Doxycycline Hyclate 100mg Tablets with Food

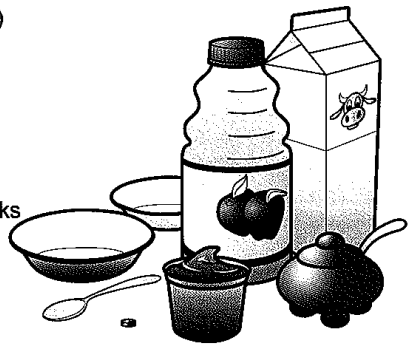
Once you have been notified by your federal, state or local authorities that you need to take doxycycline for a public health emergency, it may be necessary to prepare *emergency* doses of doxycycline for children and adults who cannot swallow pills.

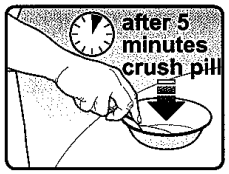
June 2008
Prepared by the U.S. Food and Drug Administration

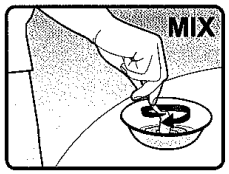
1 Supplies You Will Need

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.

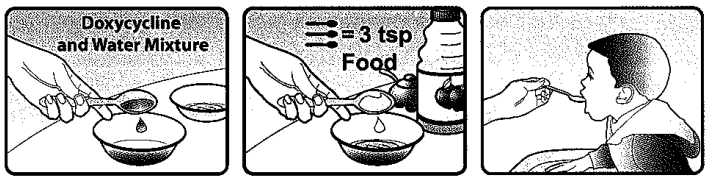
Child's weight: _____

3 Adding Food to the Doxycycline and Water Mixture to Make It Taste Better

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	
13 to 25 pounds	1 teaspoon	
26 to 38 pounds	1½ teaspoons	
39 to 50 pounds	2 teaspoons	
51 to 63 pounds	2½ teaspoons	
64 to 75 pounds	3 teaspoons	
76 to 88 pounds	3½ teaspoons	
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.



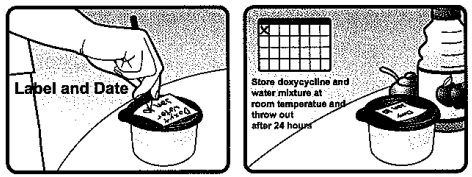
6. Go to Step 4 for dosing.

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 or 1-800-FDA-1088

14. Appendix B – Dose-sparing regimens

Postexposure prophylaxis with anthrax vaccine adsorbed dose-sparing regimens[3]		
Dose	Route of administration	Dosing schedule
0.5 mL (full dose)	SC or IM*	2 doses: 0 and 2-4 weeks
0.25 mL (half dose)	SC or IM*	3 doses: 0, 2, and 4 weeks

* Can be administered IM if the SC route of administration poses significant materiel, personnel, or clinical challenges that might delay or preclude vaccination.

15. Appendix C -EUA Manual

EUA Manual January 2017:

Doxycycline-specific protocol 04-2016. Available at: https://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/UCM495925.pdf Accessed 02 April 2019.

Emergency Use Authorization of Medical Products and Related Authorities. Guidance for Industry and Other Stakeholders. U.S. Department of Health and Human Services. Food and Drug Administration. January 2017 Expiration Date 08/31/2019. Available at: https://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/UCM493627.pdf Accessed 02 April 2019.