OREGON HEALTH AUTHORITY
PUBLIC HEALTH DIVISION
ACUTE AND COMMUNICABLE DISEASE PREVENTION SECTION

Protocol for
Antimicrobial Prophylaxis in Setting of Exposure to *Yersinia pestis* Aerosol or To a Patient with Pneumonic Plague
November 4, 2021 version

I. OREGON MODEL PROTOCOL

1. Conduct an assessment of people presenting for prophylaxis against a known or potentially harmful biological agent.
2. Provide people information about plague and the preventive antibiotics prior to administration, answering any questions
3. Dispense antibiotic prophylaxis in accordance with prophylactic treatment guidelines (Tables 1-3) and within the restrictions of the guidelines of the Centers for Disease Control and Prevention (CDC) Medical Countermeasures Program.

   Accessed 18 October 2021: http://www.cdc.gov/phpr/stockpile/stockpile.htm

_____

Signature, Health Officer Date

II. People for whom prophylaxis may be dispensed

1. People who have a confirmed or highly suspect exposure to ***Yersinia pestis,*** as determined by the Local Health Officer, either through an intentional aerosol release or through contact with a person who has pneumonic plague.

2. People in a group for which the State Health Officer has activated the Health and Medical Annex (Annex F) of the State of Oregon Emergency Operations Plan and recommended plague post-exposure prophylaxis.

3. Pre-exposure prophylaxis is not considered necessary for first responders or healthcare personnel if standard and droplet precautions can be maintained.[1] During acute shortages of surgical masks or other crisis situations, pre-exposure prophylaxis might be warranted and could be dispensed using this protocol. Oregon Health Authority (OHA) will issue guidance if pre-exposure prophylaxis is recommended.

Tables 1-3: Post-exposure prophylaxis (PEP) [1, 2]

Post-exposure prophylaxis is indicated in persons with known exposure to a person with pneumonic plague or to an aerosol release. Duration of post-exposure prophylaxis to prevent plague is 7 days. Recommended antibiotic regimens for PEP of various people are as follows:

Table 1. Pre- and postexposure prophylaxis for adults and children potentially exposed to *Yersinia pestis* Return

Population	Category	Antimicrobial*,† *Class*	Dosage§
Adults aged ≥18 yrs	**First-line**	Ciprofloxacin *Fluoroquinolone*	500–750 mg every 12 hrs PO
		Levofloxacin *Fluoroquinolone*	500–750 mg every 24 hrs PO
		Moxifloxacin *Fluoroquinolone*	400 mg every 24 hrs PO
		Doxycycline *Tetracycline*	100 mg every 12 hrs PO
	Alternatives	Ofloxacin¶,**,†† *Fluoroquinolone*	400 mg every 12 hrs PO
		Gemifloxacin¶ *Fluoroquinolone*	320 mg every 24 hrs PO
		Tetracycline¶ *Tetracycline*	500 mg every 6 hrs PO
		Omadacycline¶ *Tetracycline*	300 mg every 24 hrs PO
		Minocycline¶ *Tetracycline*	100 mg every 12 hrs PO
		Trimethoprim-sulfamethoxazole¶ *Sulfonamide*	5 mg/kg (trimethoprim component) every 12 hrs PO
Children aged ≥1 mos to ≤17 yrs (unless otherwise noted)	**First-line**	Ciprofloxacin *Fluoroquinolone*§§	15 mg/kg every 12 hrs PO (maximum 750 mg/dose)
		Levofloxacin *Fluoroquinolone*§§	Body weight <50 kg: 8 mg/kg every 12 hrs PO (maximum 250 mg/dose) Body weight ≥50 kg: 500–750 mg every 24 hrs PO
		Doxycycline *Tetracycline*§§	Body weight <45 kg: 2.2 mg/kg every 12 hrs PO Body weight ≥45 kg: 100 mg every 12 hrs PO

Children aged ≥1 mos to ≤17 yrs (unless otherwise noted)	**Alternatives**	Moxifloxacin[¶¶] *Fluoroquinolone*[§§]	Infants and children aged ≥3 mos to ≤23 mos: 6 mg/kg every 12 hrs PO*** Children aged 2–5 yrs: 5 mg/kg every 12 hrs PO*** Children aged 6–11 yrs: 4 mg/kg every 12 hrs PO*** Children and adolescents aged 12 to ≤17 yrs: Body weight <45 kg: 4 mg/kg every 12 hrs PO*** Maximum dose for all children <45 kg: 200 mg/dose Body weight ≥45 kg: 400 mg every 24 hrs PO***
		Ofloxacin[¶,**,††] *Fluoroquinolone*[§§]	7.5 mg/kg every 12 hrs PO (maximum 400 mg/dose)
		Tetracycline[¶] *Tetracycline*[§§]	10 mg/kg every 6 hrs PO (maximum 500 mg/dose)
		Minocycline[¶] *Tetracycline*[§§]	2 mg/kg every 12 hrs PO (maximum 100 mg/dose)
		Trimethoprim-sulfamethoxazole[¶] *Sulfonamide*	Infants and children aged ≥2 mos to ≤17 yrs: 5 mg/kg (trimethoprim component) every 12 hrs PO

Abbreviations: PO = per os.
Note: All oral antimicrobials recommended in these guidelines can be administered via alternative enteral routes (e.g., nasogastric tube and gastric tube) except for ciprofloxacin.
* Prophylaxis with a single antimicrobial class is recommended for potentially exposed persons following a case of naturally acquired infection or intentional release of *Yersinia pestis,* with targeting of drug choice if engineered resistance is detected in the aftermath of a bioterrorism attack.
† Antimicrobials are not listed in order of preference within each category.
§ Pre-exposure prophylaxis can be discontinued 48 hours after the last perceived exposure. Recommended duration for postexposure prophylaxis is 7 days.
¶ Not approved by the Food and Drug Administration (FDA) for treatment of plague. In some instances, these antimicrobials have been used off label for the treatment of naturally occurring plague. Large-scale use of these antimicrobials during a bioterrorism response might be under FDA-issued Emergency Use Authorization.
** Additional fluoroquinolone alternatives, such as delafloxacin, also can be considered depending on drug availability.
†† Ofloxacin suspension for oral liquid administration is not available in the United States.
§§ Data on use of fluoroquinolones and tetracyclines in infants and young children are limited. Because of the risk for permanent tooth discoloration and tooth enamel hypoplasia, tetracycline and minocycline should only be used for children aged <8 years when other prophylaxis options have been exhausted.
¶¶ Moxifloxacin is not FDA approved for use in children aged ≤17 years but has been used off label (79). Data

on use in neonates and children aged ≤2 months are extremely limited; however, successful use in neonates has been reported (**Source:** Watt KM, Massaro MM, Smith B, Cohen-Wolkowiez M, Benjamin DK Jr, Laughon MM. Pharmacokinetics of moxifloxacin in an infant with *Mycoplasma hominis* meningitis. Pediatr Infect Dis J 2012;31:197–9). For children aged 12–17 years weighing ≥45 kg with risk factors for cardiac events, consider 200 mg twice daily to reduce risk for QT prolongation.
*** Although no commercial liquid formulation is available for moxifloxacin, hospitals and compounding retail pharmacies can use a published recipe to make liquid suspension.

Table 2. Pre- and post-exposure prophylaxis for pregnant women potentially exposed to *Yersinia pestis*

Return

Category	Antimicrobial*,† *Class*	Dosage§
First-line	Ciprofloxacin *Fluoroquinolone*	500 mg every 8 hrs PO or 750 mg every 12 hrs PO
	Levofloxacin *Fluoroquinolone*	750 mg every 24 hrs PO
Alternatives	Moxifloxacin *Fluoroquinolone*	400 mg every 24 hrs PO
	Ofloxacin¶,** *Fluoroquinolone*	400 mg every 12 hrs PO
	Tetracycline¶,†† *Tetracycline*	500 mg every 6 hrs PO
	Doxycycline *Tetracycline*	100 mg every 12 hrs PO
	Minocycline¶,†† *Tetracycline*	200 mg loading dose, then 100 mg every 12 hrs PO
	Trimethoprim-sulfamethoxazole¶ *Sulfonamide*	5 mg/kg (trimethoprim component) every 12 hrs PO

Abbreviations: PO = per os.
Note: All oral antimicrobials recommended in these guidelines can be administered via alternative enteral routes (e.g., nasogastric tube and gastric tube) except for ciprofloxacin.
* Prophylaxis with a single antimicrobial class is recommended for potentially exposed pregnant women following a case of naturally acquired infection or intentional release of *Yersinia pestis,* with targeting of drug choice if engineered resistance is detected in the aftermath of a bioterrorism attack.
† Antimicrobials are not listed in order of preference within each category.
§ Pre-exposure prophylaxis can be discontinued 48 hours after the last perceived exposure. Recommended duration for postexposure prophylaxis is 7 days.
¶ Not approved by the Food and Drug Administration (FDA) for treatment of plague. In some instances, these antimicrobials have been used off label for the treatment of naturally occurring plague. Large-scale use of these antimicrobials during a bioterrorism response might be under FDA-issued Emergency Use Authorization.
** Additional fluoroquinolone alternatives, such as gemifloxacin and delafloxacin, also can be considered depending on drug availability.
†† In utero exposure can lead to permanent discoloration of developing teeth in the fetus. This is more likely to occur following repeated or long-term exposure.

Table 3. Postexposure prophylaxis for neonates aged ≤28 days potentially exposed to *Yersinia pestis*

Category	Antimicrobial*,† *Class*	Dosage§
First-line	Ciprofloxacin *Fluoroquinolone*¶	15 mg/kg every 12 hrs PO
	Levofloxacin *Fluoroquinolone*¶	10 mg/kg every 12 hrs PO
	Doxycycline *Tetracycline*¶	2.2 mg/kg every 12 hrs PO
Alternatives	Gentamicin** *Aminoglycoside*	Neonates aged ≤7 days: 4 mg/kg every 24 hrs IM or IV Neonates aged 8–28 days: 5 mg/kg every 24 hrs IM or IV
	Ofloxacin**,†† *Fluoroquinolone*¶	7.5 mg/kg every 12 hrs PO

Abbreviations: IM = intramuscular; IV = intravenous; PO = per os.
Note: All oral antimicrobials recommended in these guidelines can be administered via alternative enteral routes (e.g., nasogastric tube and gastric tube) except for ciprofloxacin. Additional considerations for treatment and postexposure prophylaxis of neonates, depending on the clinical status of both neonate and mother, are included in Supplementary Appendix 2 (https://stacks.cdc.gov/view/cdc/107427).
* Antimicrobials are not listed in order of preference within each category.
† Postexposure prophylaxis with a single antimicrobial agent is recommended for potentially exposed neonates following a case of naturally acquired infection or intentional release of *Yersinia Pestis*, with targeting of drug of choice if engineered resistance is detected in the aftermath of a bioterrorism attack. Postexposure prophylaxis should be given to neonates orally when possible, unless the neonate is hospitalized and has existing intravenous access. For neonates with highly concerning exposure to *Y. pestis* who cannot take medications orally, IV or IM formulations of the drugs listed in this table can be given.
§ Recommended postexposure prophylaxis duration is 7 days.
¶ Data on use of fluoroquinolones and doxycycline in neonates are extremely limited; however, successful use of these antimicrobials in neonates has been reported (**Sources:** Kaguelidou F, Turner MA, Choonara I, Jacqz-Aigrain E. Ciprofloxacin use in neonates. Pediatr Infect Dis J 2011;30:e29–e37. Newby BD, Timberlake KE, Lepp LM, Mihic T, Dersch-Mills DA. Levofloxacin Use in the Neonate: A case series. J Pediatr Pharmacol Ther 2017;22:304–13. Forti G, Benincori C. Doxycycline and the teeth. Lancet 1969;1:782).
** Not approved by the Food and Drug Administration (FDA) for prophylaxis of plague. In some instances, these antimicrobials have been used off label for the prophylaxis of naturally occurring plague. Large-scale use of these antimicrobials during a bioterrorism response might be under FDA-issued Emergency Use Authorization.
†† Ofloxacin suspension for oral liquid administration is not available in the United States.

Tables adapted from: Nelson CA, Meaney-Delman D, Fleck-Derderian S, et al. Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response. MMWR Recomm Rep 2021;70(No. RR-3):1–27. DOI: http://dx.doi.org/10.15585/mmwr.rr7003a1

Plague Post-exposure Prophylaxis Dispensing Algorithm

The following algorithm guides antimicrobial selection and dosing for people requiring post-exposure prophylaxis or preventive treatment after exposure to *Yersinia pestis*, the bacterium that causes plague. Recommendations follow CDC guidance.[1]

Depending on availability, if there are no contraindications, either doxycycline or a first-line fluoroquinolone can be used for those who aren't pregnant. CDC notes that doxycycline might be preferred for those age 65 or older due to its more favorable adverse-effect profile in this population. First-line fluoroquinolones, as noted in Table 2 above, are preferred for prophylaxis in pregnant women.

Antimicrobial resistance is rare in naturally occurring strains of *Yersinia pestis*. Following an intentional release, if susceptibility testing suggests resistance to a particular class of antimicrobials, OHA will provide guidance on any needed modification of prophylaxis. All people who have been potentially exposed to *Y. pestis* should receive a 7-day course of drug therapy.

Recommendations for prophylaxis against plague must balance risks associated with prophylaxis against those posed by the illness. Children age 8 years or older generally can be treated with tetracycline antibiotics safely. In children younger than 8 years*, some tetracycline antibiotics may cause discolored teeth, and rare instances of retarded skeletal growth have been reported in infants. In the setting of exposure to plague, the potential benefits of these antimicrobials in the treatment of or prophylaxis against plague infection substantially outweigh the risks.

To prevent serious medical consequences associated with hypersensitivity reactions, underlying health conditions, and drug interactions, the OHA recommends that certain people be medically evaluated prior to dispensing. In the event that this is not possible due to extreme time constraints, following a non-medical model may be necessary.

If, based on screening using this algorithm, a person should not receive any of the antimicrobials available to you for dispensing, refer the person for prompt medical consultation to determine appropriate prophylaxis. If a medical screener is available on-site, and if there are concerns about possible drug interactions, a database for checking interactions between medications a person is taking can be found at: https://reference.medscape.com/drug-interactionchecker

---

*See table 1 on pages 2-3 for dosing of children younger than 8 years.

Plague Post-Exposure Prophylaxis Dispensing Algorithm
If Doxycycline Is Used

All persons to receive post-exposure prophylaxis start in the "express" line. Anyone with history of an allergic reaction to a tetracycline antimicrobial should be screened for possible prophylaxis with a fluoroquinolone. If there are contraindications to that, the person should be routed to a medical provider for evaluation and prophylaxis.

1. **Has the patient ever had an allergic reaction to a tetracycline class drug?**
   Allergic reactions may include: hives, redness of the skin, rash, difficulty breathing, or worsening of lupus after taking one of the tetracycline class drugs. Those licensed in the U.S. include demeclocycline (Declomycin®); doxycycline (Adoxa®, Bio-Tab®, Doryx®, Doxy®, Monodox®, Periostat®, Vibra-Tabs®, Vibramycin®); ervacycline (Xerava); minocycline (Arestin®, Dynacin®, Minocin®, Vectrin®); omadacycline (Nuzyra); sarecycline (Seysara); tetracycline (Achromycin V®, Sumycin®, Topicycline®, Helidac); and tigecycline (Tygacil). The following are not currently licensed in the U.S. or are seldom used: chlortetracycline (Aureomycin); oxytetracycline (Terak®, Terra-Cortril®, Terramycin®, Tija, Urobiotic-®250®); lymecycline (CycloPel, Lymelysal, Tetralysal); methacycline, and rolitetracycline (Kinteto, Syntetrin, Transcycline).

   Patients allergic to any tetracycline class drug should receive another form of prophylaxis such as a first-line fluoroquinolone.

2. **Is the patient pregnant or breast-feeding?**
   CDC recommends ciprofloxacin or levofloxacin as first-line medications for pregnant women. (See Table 2 on page 5.) Breastfeeding mothers can receive any of the first-line antimicrobials for prophylaxis, as all of them produce low concentrations in breast milk and have an acceptable safety profile. [1]

3. **Is this person an infant 28 days old or younger?**
   Select antimicrobial using Table 3, page 6.

4. **Is this person older than 28 days and less than 18 years old?**
   Weigh the person**.** Dosage by weight can be found in Table 1, pages 3-4, above.

5. **Is this person younger than 8 years?**
   Because of the risk for permanent tooth discoloration and tooth enamel hypoplasia, tetracycline and minocycline should only be used for children aged <8 years when other prophylaxis options have been exhausted.[1]

6. **People answering "no" to all of the above questions.**
   People answering "no" to all medical screening questions can receive doxycycline as described in Table 1. Duration of post-exposure prophylaxis to prevent pneumonic plague infection is 7 days.

Plague Post-exposure Prophylaxis If Ciprofloxacin or Another Fluoroquinolone Is Used

All people to receive post-exposure prophylaxis start in the "express" line. Anyone answering "yes" to any of the following questions should be routed to a medical screener for evaluation.

1. **Has this person ever had an allergic reaction to a fluoroquinolone medication?**
   Allergic reactions may include: difficulty breathing, rash, itching, hives, yellowing of the eyes or skin, swelling of the face or neck, cardiovascular collapse, loss of consciousness, hepatic necrosis (death of liver cells), or Stevens-Johnson Disease (a rare but severe skin reaction) after taking a quinolone class drug, including: ciprofloxacin (Cipro, Ciloxan), delafloxacin, gatifloxacin ophthalmic solution (Zymar), gemifloxacin, levofloxacin (Levaquin, Quixin, Iquix), moxifloxacin (Avelox, ABC Pak, Vigamox), and ofloxacin (Floxin, Ocuflox), which are licensed by FDA. Additional medications in this class are not licensed in the U.S. seldom used currently, or have been discontinued. They include: acrosoxacin or rosoxacin (Eradacil); cinoxacin (Cinobac); enoxacin (Penetrex); gatifloxacin by mouth (Tequin); grepafloxacin (Raxar); lomefloxacin (Maxaquin); nadifloxacin (Acuatim); norfloxacin (Chibroxin, Noroxin); nalidixic acid (NegGram); oxolinic acid; pefloxacin (Peflacine); rufloxacin; sparfloxacin (Zagam, Respipac); temafloxacin (Omniflox); trovafloxacin or alatrofloxacin (Trovan).

People who have had an allergic reaction to any medication in the quinolone class should be referred to a medical screener and receive another form of therapy such as doxycycline.

2. **Is this person pregnant or breast-feeding?**
   CDC recommends ciprofloxacin or levofloxacin as first-line medications for pregnant women. Breastfeeding mothers can receive any of the first-line antimicrobials for prophylaxis, as all of them produce low concentrations in breast milk and have an acceptable safety profile. [1]

3. **Is this person age 65 years or older?**
   CDC notes that doxycycline should be considered for those age 65 or older due to its more favorable adverse-effect profile in this population.[1]

4. **Is this person an infant 28 days old or younger?**
   Select antimicrobial using Table 3, page 6.

5. **Does the patient have known kidney insufficiency or failure?**
   This includes those receiving dialysis, with known kidney failure (end-stage renal disease) or who report they have reduced kidney function. If possible,

people who report kidney insufficiency should be referred to a medical screener for dosage adjustment if they will receive ciprofloxacin www.accessdata.fda.gov/drugsatfda_docs/label/2005/019537s057,020780s019lbl.pdf or levofloxacin www.accessdata.fda.gov/drugsatfda_docs/label/2005/020634s037,020635s038,021721s002lbl.pdf See "Dosage and Administration – Patients with impaired renal function" at the above links. If creatinine clearance is unknown, give ciprofloxacin 500 mg by mouth once a day, and refer the person to a healthcare provider for further assessment.

6. **Is this person older than 28 days and less than 18 years old?**
   Weigh the person**.** Dosage by weight can be found in Table 1, pgs. 3-4, above.

7. **Does this person have a history of myasthenia gravis?**
   Those with a history of myasthenia gravis should avoid use of fluoroquinolones if alternative antimicrobials are available.

8. **Does this person have a history of seizures or neurologic problems?**
   People with a history of seizures should avoid use of ciprofloxacin if alternative antibiotics are available.

9. **Is this person taking tizanidine?**
   Ciprofloxacin should be avoided in those taking tizanidine, a muscle relaxant, due to risk of severe hypotension.

10. **People answering "no" to all of the above questions**
    Person can receive a fluoroquinolone as described in Table 1 on pages 2-3.

If, based on screening, a person should not receive any of the antimicrobials available to you for dispensing, refer the person for prompt medical consultation to determine appropriate prophylaxis.

References

1. Nelson CA, Meaney-Delman D, Fleck-Derderian S, et al. Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response. MMWR Recomm Rep 2021;70(No. RR-3):1–27. DOI: http://dx.doi.org/10.15585/mmwr.rr7003a1 Accessed: 12 October 2021.
2. Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a Biological Weapon JAMA 2000;283:2281-90. Available at: http://jama.jamanetwork.com/article.aspx?articleid=192665 . Accessed 27 July 2018.
3. CDC. Plague. Resources for Clinicians. Available at: www.cdc.gov/plague/healthcare/clinicians.html . Accessed 12 October 2021.