Speaker 1 (00:05):

Welcome to part two of CDC's training on plague response for healthcare providers. This video provides an overview of treatment recommendations for the different clinical forms of plague. Guidance for pre and post-exposure prophylaxis and considerations following a known or suspected bioterrorism attack. For a review of the epidemiology and different clinical forms of plague, please see part one of this series. Treatment of plague depends on several factors, including clinical form, patient age, severity of illness, considerations, such as pregnancy status, and whether the illness originates from a suspected bioterrorism attack or a naturally occurring source. The list shown here provides an overview of the recommended first-line antimicrobials for treatment of plague in patients 18 years of age or older. As well as alternative treatments, if the first-line therapies are contraindicated or unavailable. The first-line agents for all clinical forms of plague are the fluoroquinolones, ciprofloxacin, moxifloxacin, and levofloxacin.

The aminoglycosides, streptomycin and gentamicin are also acceptable first-line agents for all clinical forms except plague meningitis. Doxycycline is a first-line therapy for bubonic and pharyngeal plague only. Alternative antimicrobials for bubonic and pharyngeal plague include the fluoroquinolones, aminoglycosides, amphenicols, sulfonamides, and additional tetracycline shown here. For pneumonic and septicemic plague, doxycycline is not first-line, but is an appropriate alternative treatment if first-line antimicrobials are not available. Additional tetracycline are not recommended as alternative treatments for pneumonic, septicemic or meningitic plague. As mentioned earlier, patient age is a factor when making treatment decisions. Recommendations differ slightly when treating children between the ages of one month and 18 years.

The major differences between treatment recommendations for children versus adults are as follows. Number one, moxifloxacin is not a first-line agent for children, since it is not FDA approved for this age group. Number two, gemifloxacin and plazomicin are not recommended as alternative agents in children. For children as with adults, doxycycline is recommended as a first-line option for the treatment of bubonic and pharyngeal plague only. Doxycycline may be safely administered to children under the age of eight, as there is no evidence of too staining when given in short courses of two weeks or less and prompt treatment of plague is life saving. A loading dose of doxycycline should be administered for both children and adults.

For pneumonic or septicemic plague, first-line antimicrobials are the fluoroquinolones and aminoglycosides shown here. For detailed information on weight-based dosing including maximum doses for children, please consult the full treatment guidelines published in CDC's MMWR. Plague meningitis has some specific treatment considerations. If plague meningitis is suspected, the first-line therapy for both adults and children is chloramphenicol, plus either levofloxacin or moxifloxacin. Although chloramphenicol has a long history of successful use in plague meningitis, it is not readily available in the United States. If chloramphenicol is not available, a suggested alternative is a first line fluoroquinolone, plus streptomycin or gentamycin. Severity of illness can also be a consideration when treating patients with plague. Consider using oral antimicrobials, if possible, for patients with mild to moderate disease. In patients with severe disease or for patients unable to tolerate oral medications, intravenous antimicrobials are appropriate. Both fluoroquinolones and tetracyclines have good oral bio availability. Additional advantages of oral antimicrobials include: ease of administration, preservation of IV medical supplies in the event of a bioterrorism attack, decreased risk of hospital-acquired infections in patients and reduced risk to healthcare workers. For example, by needle stick injury.

Next, let's touch briefly on pre-exposure prophylaxis of plague. Pre-exposure prophylaxis of plague in the clinical setting is not necessary as long as standard and droplet precautions can be maintained. However, in the event of personal protective equipment shortages, poor ventilation or

hospital overcrowding, preexposure prophylaxis can be considered for frontline healthcare workers caring for patients with pneumonic plague. Pneumonic plague is the only clinical form that can be transmitted from person to person. Therefore, healthcare workers caring for patients with other clinical forms of plague do not require preexposure prophylaxis. The optimal duration for preexposure prophylaxis is not known and has not been studied in clinical trials. However, based on animal models and our knowledge of *Yersinia pestis*, it is reasonable to discontinue preexposure prophylaxis 48 hours after the last perceived exposure to a person or animal with pneumonic plague. Now let's move on to post exposure prophylaxis or PEP, which is warranted in four major scenarios.

In the first scenario, people who have sustained close contact with a person who had known or suspected pneumonic plague and were not wearing appropriate personal protective equipment should receive post exposure prophylaxis. This situation can apply to any close contact of a person with pneumonic plague, including healthcare personnel. The second scenario involves laboratory personnel exposed to infectious materials or potentially infectious clinical specimens while not wearing appropriate personal protective equipment. The third scenario applies to a person not wearing appropriate personal protective equipment, who had direct contact with infected animals, including animals who died of plague or any carcass in a mass die off scenario in a plague endemic area. The fourth scenario in which post exposure prophylaxis is warranted, would be following a bioterrorism attack. In which people may have been exposed to intentionally release *Y. pestis* or may have had close sustained exposure to people who are sick with pneumonic plague and coughing. Additional treatment considerations specific to bioterrorism attacks will be discussed in a later section.

Fever watch may be considered as an alternative to PEP for people who had low risk exposure. However, there are no set criteria for determining who should be managed by fever watch versus immediate PEP. Factors to consider when deciding between PEP or fever watch, include the nature of the exposure, the incubation period of *Y. pestis* and the person's level of concern. For laboratory personnel, working with the organism on the bench is lower risk than sniffing a plate or accidentally coming into contact with the bacteria. People who recall an exposure that occurred more than seven days ago may be outside of the incubation period for *Y. pestis*. The recommended antimicrobials and appropriate dosing for pre or post-exposure prophylaxis are shown here.

The recommended duration for post-exposure prophylaxis is seven days. For prophylaxis, antimicrobials should be administered orally. Note that aminoglycosides are not recommended as they are not available in an oral formulation. Now we will discuss considerations for the treatment and prophylaxis of plague in the event of a bioterrorism attack. As discussed in part one of this training, *Y. pestis* has long been used or considered as a bioweapon. An outbreak of plague following the release of *Y. pestis* as a bioweapon could look quite different from naturally occurring plague. Additionally, the release mechanism would influence the clinical manifestations that develop. For example, an attack with aerosolized *Y. pestis* would likely result in people developing pneumonic plague. A release of infected fleas would result in bubonic plague. And contamination of food or water supplies would likely lead to exposed people developing pharyngeal or septicemic plague. However, it is important to note that any method of release could result in multiple clinical forms of plague. Clinicians would need to maintain a high index of suspicion in the wake of an intentional release.

Following a bioterrorism attack, two different classes of antimicrobials should be administered to patients with suspected plague. The rationale for using two different classes is that *Y. pestis* strains used in a bioterrorism attack may have been engineered to be resistant to antimicrobials. Some possible treatment combinations include a recommended fluoroquinolone and doxycycline, a recommended fluoroquinolone and a recommended aminoglycoside or a recommended aminoglycoside and doxycycline. Note that both antimicrobials used do not necessarily need to be first-line, but ideally at

least one should be. Due to the risk of engineered resistance, antimicrobial susceptibility testing should be obtained if a bioterrorism attack is suspected. However, do not wait for confirmation of the diagnosis or results of susceptibility testing to begin treatment. Following a bioterrorism attack, people who are exposed but have not yet developed illness should be provided post exposure prophylaxis. PEP with one antimicrobial class is recommended using the antimicrobials listed previously and referenced in the plague clinical treatment guidelines. Use of one antimicrobial is recommended to reduce the risk of adverse reactions.

If testing indicates that the intentionally released strain of *Y. pestis* is resistant to the initial PEP antimicrobial, the PEP antimicrobial should be changed. If a person develops symptoms of plague while taking PEP, they should begin receiving antimicrobial treatment with two different antimicrobial classes. Finally, we will discuss considerations for antimicrobial therapy in certain populations. This discussion will focus only on key differences in recommended treatment. Consult the full CDC guidelines published in MMWR for complete details. If a pregnant patient develops plague, concerns about fetal safety should not preclude treatment or prophylaxis. Pregnant patients who contract plague have worse outcomes than the general population. Even with appropriate treatment, there is a high rate of fetal loss or preterm birth. If an aminoglycoside is prescribed, gentamicin is preferred over streptomycin for pregnant patients, due to lower risk of ototoxicity. Plague in neonates has been rarely described. Generally, antimicrobial should be administered intravenously whenever possible.

Oral formulations are not recommended due to the immature intestinal system of neonates. Despite the risk of gray baby syndrome, chloramphenicol should be considered for neonates with plague meningitis due to the severity of this disease. Although it has not been studied in detail, there are no reports of *Y. pestis* transmission by breast milk. Therefore, mothers with bubonic or septicemic plague and mothers taking antimicrobial prophylaxis after exposure to *Y. pestis* can continue to breastfeed their infants if able. Lactating mothers with pneumonic plague should avoid direct breastfeeding until they have received antimicrobial treatment for at least 48 hours and have demonstrated clinical improvement. Unless the breastfeeding infant is also receiving antimicrobial treatment or prophylaxis, in which case breastfeeding may continue. The majority of antimicrobials recommended for *Y. pestis* treatment or prophylaxis produce low concentrations in breast milk and have an acceptable safety profile. Note that because chloramphenicol has the potential for serious adverse reactions in infants, including gray baby syndrome, other drugs should be used preferentially for lactating mothers when possible.

People who are underweight or obese may require special dosing considerations. Differing volumes of distribution for medications can result in either decreased efficacy or increased risk of toxicity. In particular, aminoglycosides have a narrow therapeutic window and require careful dose adjustments. In underweight patients, the aminoglycoside dose should be based on total body weight. The aminoglycoside dose for obese patients should be based on adjusted body weight. Measuring serum aminoglycoside levels is helpful in ensuring effective therapeutic levels and avoiding toxicity. Note that chloramphenicol should always be dose based on total body weight, regardless of body mass index. Serum concentration monitoring should be performed when available. For obese adults, ciprofloxacin should be dosed at the upper end of the dose range. Also, for obese adults, trimethoprim-sulfamethoxazole should be dosed according to adjusted body weight when prescribing doses more than eight milligrams per kilogram per day.

Finally, although immunocompromised patients and patients age 65 and over may develop more severe manifestations of plague, there are no differences in the recommended antimicrobials or dosing. However, treatment duration may need to be extended if an appropriate clinical response is not seen after 10 to 14 days. Clinicians should also be aware of the risks of polypharmacy in

immunocompromised patients or patients age 65 and over. For example, there is an increased possibility of severe injury and hyperemia if trimethoprim-sulfamethoxazole is administered with an ACE inhibitor, angiotensin receptor blocker or potassium sparing diuretic. For post-exposure prophylaxis of patients aged 65 and over, clinicians should consider using doxycycline over fluoroquinolones due to the risks for QTc prolongation, neuropsychiatric disturbances, including dizziness and imbalance, and damage to connective tissues. In an emergency, the CDC Emergency Operations Center can be reached 24 hours a day, seven days a week at 800-232-4636. Thank you for watching part two in this series.