IS PLAGUE A PROBLEM IN THE EGYPTIANS RETURNING BACK FROM LIBYA?

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Abstract

Many employees return home with fever with or without other accompanying symptoms. Fever can be a manifestation of a minor, self-limited process or can herald a progressive, life-threatening illness.

The assessment of this group is often hampered by the clinician's lack of familiarity with the types of infections that the patient may have encountered while traveling. The evaluation of such patients should focus on: What infections are possible given where the patient has lived or traveled and the time when exposures may have occurred? Which of these infections is more probable given the patient's clinical findings and potential exposures? Which of these infections is treatable or transmissible or both? On the other hand, the outbreak of plague at the Libyan-Egyptian borders and the high density rodents and their ecto-parasitic fleas in many Egyptian governorates should be embarked a control program to rodents and fleas and to raise the awareness of the concerned authorizes.

Key words: History, Plague, Libyan-Egyptian borders, Rodents, Fleas, Risk.

Historical Review

Davis (1953) reviewed the history of plague in Africa during the period 1935-49. Much of the information derives from a questionnaire sent to all African territories in 1950. The plague annual incidence declined, particularly from 1946 onwards. In 1949, fewer than 400 cases were reported, as compared with over 6,000 in 1935. By the end of 1949, plague was still active in the Belgian Congo, Kenya and Tanganyika, Madagascar, and southern Africa. No cases were reported from Egypt, Tunisia, Algeria, Morocco, Senegal, or Uganda during 1949. A comparison of the seasonal incidence of plague with prevailing atmospheric conditions in African territories showed that human plague was more frequent in warm moist weather (15°C-27°C) than in hot dry, or cold, weather-over (27°C) or under 15°C. The African and Madagascar highlands gave the optimum environment for persistence of plague on the domestic (murine) plane and the high-veld and Kalahari of southern Africa on the sylvatic one. \textit{Rattus rattus} and \textit{R. m. natalensis} and
fleas *Xenopsylla brasiliensis* and *X. cheopis* were mainly responsible for the reservoir persistence in the East African highlands; *R. rattus* and *X. cheopis* play this role in Madagascar. *Tatera* and *Desmodillus* and *X. philoxera* and *X. piriei* were the main reservoirs in southern Africa. So, *Pasteurella pestis* found the suitable environment for survival as those in India. Elsewhere in Africa such endemic centres do not appear to exist. Hussein (1955) stated that from 1899-1945, before the DDT introduction, plague was first reported in the ports and then spread rapidly inland; in contrast with previous epidemics, the prevalence was greater in Upper than in Lower Egypt. By 1937 all Lower Egypt had became plague-free, which, however, persisted in endemo-epidemic form in Upper Egypt until 1941. The reasons for the slighter severity of this third plague pandemic in Egypt compared with the previous history of the disease, particularly in connexion with the role played by rodents. In 1941 a control scheme was introduced for rats in river and canal craft to prevent the plague inland spread from the ports. So, none was reported inland from 1941 to 1945 despite an outbreak during that time in the Suez Canal Zone. Turning to the period 1946-51, after the introduction of DDT, he discussed the Alexandria epidemic of 1946-47, giving rat and flea counts and the control methods adopted using poison baits and DDT. Dusting both persons and rat burrows with DDT resulted in a sharp decrease in flea indices, and the periodical use of DDT and Gammexane in port areas since 1950 gave good results. Milleliri (1993) stated that an uncommon military campaign commanded by General Bonaparte aged of 29 led the French Army to Egypt. The history did not mark the role of the Military Health Service. But it was tremendous, in spite of its poor facilities because its strong subordination to the omnipotent Supply Services. Through the description of the conditions of the daily life of soldiers, he reviewed the measures to protect the troops against the usual troubles faced at the 18th Century end: thirst and hunger, long marches with heavy equipment, affective isolation increased by the battles roughness and plague that caused heavy casualties.

Mafart *et al.* (2004) stated that before the Second World War, the plague was still rife in North Africa but occurred only as sporadic cases or small outbreaks as in Egypt or Morocco. The permanent foci of infected wild rodent were the cause of these rural outbreaks. In 1943 & 1944, plague came back in several Mediterranean towns and ports and was considered as a serious danger for the Allied Forces. These resurgences were related to the World War, the overpopulation of the cities, regroupings and population movements, relaxation of prophylactic measures of the plague in sea transport. The Allied Forces medical officers then showed the resistance of *Y. pestis* to penicillin which they had been supplied with the effectiveness of sulphonides but mortality was high, but drastic fight against rodents and fleas (DDT) gave excellent results.
Khan (2004) reported that the first available record of the occurrence of this calamity, in humans, is from the Bible, in 1000 BC in Ashdod City. The first definitely identified pandemic originated in Egypt in ad 542 (the Justinian Plague) and caused about 100 million deaths. The second one lasted for three centuries and claiming over 25 million lives appeared in 1334 in China spreading too many spots on the globe. The third pandemic occurred in Europe from the 15th–18th century. The pandemic began around 1860, in the Chinese province Yunnan; it reached Hong Kong in 1894 killing 100,000 individuals. Within 20 years the disease spread from southern Chinese ports throughout the world resulting in more than 10 million deaths. Since the discovery of the causative agent in 1894, there have been remarkable advancements in immunoprophylaxis and chemoprophylaxis. However, the disease is still active in Africa, in Asia and in Americas and was classified as a re-emerging disease. A plague-free world will remain a dream for an indefinite period.

Ehrenkranz and Sampson (2008) reported that past disasters supplied insights to mitigate the recurrences impact. They offered a unifying causative theory of Old Testament plagues that has present day public health implications. They suggested that the root cause to have been an aberrant El Niño-Southern Oscillation teleconnection that brought unseasonable and progressive climate warming along the ancient Mediterranean littoral, including the coast of biblical Egypt, which initiated the serial catastrophes of biblical sequence-in particular arthropod-borne and arthropod-caused diseases. Located beyond the boundary of focal climate change, inland Goshen would not have been similarly affected. Implicit in this analysis is a framework to consider a possibility of present day recurrence of similar catastrophes and their impact upon essential public services.

Sabbatani and Fiorino (2010) said that in ancient times the term pestilence referred not only to infectious disease caused by *Yersinia pestis*, but also to several different epidemics. They explored the relations between references in the Bible and recent scientific evidence concerning some infectious diseases, especially the so-called Plague of the Philistines and leprosy. In addition, some considerations regarding possible connections among likely infectious epidemic diseases and the Ten Plagues of Egypt are reported. Evidence suggesting the presence of the rat in the Nile Valley in the II millennium BC is shown; a possible role of the rat in the plague spreading already in this historical period should be confirmed by these data. While the biblical tale in the Book of Samuel may well report an epidemic event resembling plague, as to date this disease remains unknown, and not conceivable to confirm leprosy in same age, because the little palaeopathologic evidence of the latter one, in a geographic area corresponding to Egypt and Palestine, is late, dating back only to the II century AD.

**Review and Discussion**

*Yersinia pestis*, etiologic agent of plague, is one of the few infectious or-
ganisms having an important impact on humanity. During the last pandemic Dr. Alexandre Yersin isolated the plague bacillus that was formerly called *Bac*terium *p*estis, *Bacillus pestis*, and then *Pasteurella pestis*, in current nomenclature is referred to as *Y. pestis*. Several forms of plague occur in humans, bubonic, septicemic, and pneumonic, which vary in clinical features, severity, and outcome (Perry and Fetherston, 1997). Three major pandemics have been recorded in human history: the first in the sixth century; the second in the fourteenth century followed the Black Death, which killed up to one-third of the European population; and the third at the end of nineteenth century followed the spread of infection from China. The activity of plague in various countries worldwide is the result of this last pandemic (Prentice and Rahalison, 2007).

*Yersinia* species are gram-negative coccobacilli are facultative anaerobes (Bottone, 1997). Three species of *Yersinia* produce human illness: *Y. pestis* (the causative agent of human plague), *Y. enterocolitica* (causative agent of yersinia), and *Y. pseudotuberculosis*. *Y. enterocolitica* and *Y. pseudotuberculosis* most commonly cause enterocolitis; *Y. enterocolitica* is the more common of the two species to cause disease.

**Types of Plague**

There are three generally recognized clinical syndromes associated with plague that vary in clinical features, severity, and outcome: Bubonic plague accounts for 80 to 95% of cases and has a mortality rate of 50 to 90 percent if untreated and 10 to 20% if treated Septicemic plague accounts for 10 to 20 percent of cases and has a mortality rate of 20 to 25% Pneumonic plague is generally rare and has a mortality rate of 100% if untreated and 50% if treated (Ratsitorahina et al. 2000).

Overall, the estimated mortality is 60 to 100% in untreated plague compared to less than 15 %with treatment. In a series of 23 cat-associated cases in the United States between 1977 & 1998, 17 of which were bubonic, five were fatal for a mortality rate of 22%. Mortality was associated with misdiagnosis or a delay in treatment.

Humans acquire plague by: 1- Bites by rodent fleas, 2-Exposure to pneumonic plague, 3- Handling of infected animal carcasses, 4- Scratches or bites from infected domestic cats, and 5- Exposure to aerosols.

**Clinical Manifestations**

The manifestations of plague vary with the type of disease. The incubation period is generally two to eight days.

1- Bubonic plague is the most common form and is characterized by the sudden onset of fever, chills, weakness, and headache. These symptoms are soon followed by intense pain and swelling in a lymph node bearing area (bubo), which may precede lymphadenopathy. The acute bubo is characterized by exquisite tenderness without
fluctuation, often associated with erythema and edema of the overlying skin. The inguinal region is the most frequently involved site, but the axillary or cervical regions may also be involved. In cat-associated bubonic plague, axillary, cervical, or epitrochlear buboes are the rule.

Without treatment, this initial stage is followed by disseminated infection that can lead to complications such as pneumonia (secondary pneumonic plague) and meningitis. Pneumonia can be the source of person-to-person transmission. Bacteremia occurred and some patients developed signs of sepsis (Prentice and Rahalison, 2007).

2- The septicemic form of plague may be particularly difficult to diagnose in a timely fashion because characteristic clinical clues, such as a bubo, are not present. Patients with the septicemic form are febrile and extremely ill, but do not have localizing signs or symptoms. Some patients develop prominent gastrointestinal symptoms including nausea, vomiting, diarrhea and abdominal pain. Hypotension, disseminated intravascular coagulation, and multiorgan failure develop in the later illness stages. The plague first emerged as a flea-borne septicemic disease with subsequent acquisition of the plasminogen activator gene enabling the bubonic form of disease (Sebbane et al, 2006).

3- Pneumonic plague is often secondary to bacteremia in bubonic or septicemic plague. However, primary pneumonic plague can occur, being acquired from inhalation of Y. pestis from another patient or animal, such as a domestic cat with pneumonic disease, or from inhalation of laboratory specimens of the organism (Butler, 1994). Primary pneumonic plague has a short incubation period, ranging from a few hours to a few days. Affected patients typically present with the sudden onset of dyspnea, high fever, pleuritic chest pain, and cough that may be accompanied by bloody sputum. It is rapidly fatal unless an appropriate antimicrobial agent is begun within the first day of illness.

There are no clinical or radiographic features that are diagnostic of plague pneumonia. The sputum may be clear, purulent, or hemorrhagic, and contains gram-negative rods.

Pneumonic plague may be the source of outbreaks in families or other close contacts. In a study from Madagascar, 13 of 154 (8.4%) contacts became infected with Y. pestis. Treatment of patients and prophylaxis of contacts stopped the outbreak. The ability to be spread as an aerosol makes Y. pestis a potential bio-terrorism agent.

Plague can cause a number of other manifestations. As an example, meningitis can occur in conjunction with any of the three forms of plague or as a "primary" meningeal infection. Symptoms tend to be similar to other bacterial meningitides and cerebrospinal fluid examination typically reveals a low glucose concentration, increased protein concentration, and a neutrophilic pleocytosis.

Other manifestations include a less common and potentially confusing presentation is pharyngitis and tonsilli-
tis, associated with anterior cervical lymphadenitis. Involvement of urinary tract or gastrointestinal tract was reported in 4/27 cases in one series and was the sole manifestation of Y. pestis infection. A minority of patients develop skin lesions such as purpura (Crook and Tempest, 1992).

Asymptomatic transient pharyngeal carriage of Y. pestis has been described in healthy contacts of bubonic plague cases. How often this occurred was not known (Chanteau et al. 2003).

**Pathogenesis**

The pathogenesis of plague involves two steps: transmission via fleas, and the host response. Transmission via fleas Fleas feed upon bacteremic animals to maintain continual transmission in the animal population. Y. pestis is not transmitted transovarially in the flea but rather relies upon a complex phenomenon known as blockage. After ingestion of an infected blood meal, the organism can survive in the midgut (stomach) of the flea. A plasmid-encoded phospholipase D appears to protect Y. pestis from digestion by a cytotoxic product of blood plasma in the flea gut.

Organisms multiply in the midgut, resulting in formation of dark brown masses containing bacilli, a fibrinoid-like material, and probably hemin. These masses extend from the stomach proximally into the esophagus through a sphencter-like structure with needle-like teeth called the proventriculus (Hinnebusch et al., 2002).

The blockage phenomenon in the flea is intimately associated with hemin storage (hms) genes in the bacterium, which are needed for the formation of a biofilm that permits colonization of the proventriculus (Hinnebusch et al., 1996). Y. pestis mutants in the hms locus are able to colonize the midgut of fleas but not the proventriculus; as a result, blockage does not occur and the organism is not transmitted efficiently. Bacteria grown within the biofilm are more resistant to human polymorphonuclear leukocytes than when those grown in vitro.

After blockage, the flea may live for several days before dying of starvation and dehydration. During this interval, the flea repeatedly tries to obtain a blood meal from hosts but, in the presence of the blockage, the blood can only mix with organisms in the esophagus. Material, including blood and organisms, is then regurgitated back into the mammalian host. Depending upon the species, the host becomes bacteremic and either dies or survives (Jarrett et al., 2004).

**Diagnosis**

A high index of suspicion must be maintained for the timely diagnosis of plague. Patients with fever and painful lymphadenopathy should be questioned about travel to areas of endemic disease, particularly in the southwestern United States. In addition, potential animal or rodent vector contact within the preceding ten days may provide clues that raise suspicion for the possible diagnosis of plague.

The diagnosis confirmation of plague is made by isolation of the organism in culture or by serologic testing. *Yersinia*
grows well on commonly used laboratory media. Microbiology personnel should be informed of any specimen suspected to harbor the organism so they may exercise proper precautions.

Blood cultures are positive in 27 to 96% of patients. Aspirates of buboes are also common sources for positive cultures, and the organism may be grown from sputum or cerebrospinal fluid. In one study, for example, cultures of bubo aspirates were positive in 10/13 cases. Injection of the bubo with saline and aspiration may be necessary to obtain an adequate specimen.

Examination of a peripheral blood specimen stained with Wright-Giemsa stain reveals rod-shaped organisms in up to 40 percent of cases, thereby permitting more rapid diagnosis. Staining of an aspirate from a bubo may also demonstrate the organism.

The fluorescent antibody or the Wayson's stain for identification of the organism are the most useful tests, but may not be immediately available. Wayson's stain demonstrates the typical bipolar staining, which resembles a closed safety pin. Gram's stain shows small gram-negative coccobacilli.

Serologic confirmation requires acute and convalescent serum, looking for at least a fourfold rise in antibody titers to the F-1 antigen of Y. pestis. A single titer of >1:16 using the passive hemagglutination test is suggestive of the diagnosis.

A new rapid diagnostic test (RDT) capable of detecting 0.5 ng/mL of the Y. pestis F1 antigen within 15 minutes has been developed and field tested in Madagascar. The test had 100 percent sensitivity and specificity against laboratory isolates of Y. pestis, other Yersinia spp., and other bacteria. Agreement between field testing and reference laboratory testing was 90 percent (Hinnebusch and Schwan, 1993).

The RDT was able to detect 42% more positive clinical specimens than culture and 31% more than ELISA with overall positive and negative predictive values of 91 & 87%, respectively. This test holds considerable promise for rapid diagnosis including in medically underserved areas of the world.

PCR using primers derived from the Y. pestis plasminogen activator gene has been used successfully to detect the organism in fleas but to our knowledge has not been applied to human specimens. Adaptation of PCR to human specimens could provide a diagnosis within hours.

No doubt, routine laboratory and radiologic studies do not provide specific data for plague. White blood cell counts may vary from 3000 to 100,000/μL. Chest radiographs may show bronchopneumonia, consolidation, or cavities; pleural effusions and hilar or mediastinal adenopathy have also been described (Wagle, 1948). The radiographic of plague pneumonia is not specific enough to be diagnosed. Differential diagnosis includes other acute bacterial, fungal or mycobacterial pneumonias and syndromes such as the hanta-virus pulmonary syndrome.

Treatment

Appropriate and timely therapy can markedly improve patient outcomes
and chemoprophylaxis can prevent spread. As mentioned, bubonic plague has a mortality rate of 50 to 90% if untreated and 10 to 20% if treated and pneumonic plague has mortality rate of 100% if untreated and 50% if treated.

Streptomycin is considered the drug of choice for plague based upon non-randomized studies from the 1940s and 1950s (Butler et al. 1974) and on treatment of thousands of patients in Vietnam in the period 1960 to 1975 (Wong et al., 2000). The usual dose is 30 mg/kg per day IM (up to a total dose of 2 g) in two divided doses for 10 days.

Because of the limited manufacture of streptomycin, and in vitro studies and a murine model of Y. pestis infection suggesting that other antimicrobials might be effective therapy, a randomized clinical trial for the treatment of plague was conducted in Tanzania (Mwengee et al. 2006).

In this trial, 65 adults and children with symptoms of bubonic, septicemic, or pneumonic plague were randomly assigned to gentamicin (2.5 mg/kg IM every 12 hours for seven days) or doxycycline (100 mg in adults or 2.2 mg/kg in children both PO every 12 hours for 7 days). Both therapies had high rates of a favorable response (94% for gentamicin and 97% for doxycycline) and low rates of adverse events (four patients treated with gentamicin had a serum creatinine concentration after treatment greater than 1.5 mg/dL [133 micromol/L]).

Based upon this study and clinical experience with other agents, alternative 7 to 10 day regimens include: Tetracycline (2 to 4 g/day in four divided doses orally). Doxycycline, 100 mg PO or IV twice daily and Chloramphenicol, 25 mg/kg IV as a loading dose followed by 60 mg/kg per day in 4 divided doses (Boulanger et al., 2004). Gentamicin is given as 2.5 mg/kg IM every 12 hours, and/or Trimethoprim-sulfamethoxazole, 160/800 mg twice daily (Nguyen et al., 1973).

While Y. pestis historically has responded well to these agents, multidrug resistant plague was described. An isolate from a 16 year-old boy in Madagascar in 1995 contained a plasmid that conferred resistance to ampicillin, chloramphenicol, kanamycin, streptomycin, spectinomycin, sulfonamides, tetracycline, and minocycline. Isolate remained sensitive to cephalosporins, other aminoglycosides, quinolones, and trimethoprim. Plasmid probably originated among Enterobacteriaceae, and was readily passed in vitro between Y. pestis strains (Guiyoule et al. 2001).

Although another isolate has been described with plasmid-mediated high-level streptomycin resistance, outbreaks of multidrug resistant plague have not been reported. Nevertheless, surveillance of resistance patterns is necessary, and modification of empiric therapy may be required to conform to local susceptibility patterns.

Data are not readily available for the management of plague in pregnancy. A few cases have been successfully treated with streptomycin with or without tetracycline or chloramphenicol.
Isolation: Patients suspected of having any form of plague should be placed on strict respiratory isolation until each of the following measures have been completed: Pneumonia has been ruled out at least 48 hours of effective antimicrobial therapy has been given. Sputum cultures are negative.

Optimal treatment strategies for Yersinia spp. infections are unclear. Although treatment appears not to impact mild intestinal disease, fecal shedding decreases following antimicrobial treatment. This by itself does not justify treatment, as person-to-person transmission is rare. However, antimicrobial treatment may be lifesaving in invasive infections.

There has been one controlled trial of antimicrobial therapy for Y. enterocolitica infection and one for Y. pseudo-tuberculosis gastroenteritis. Neither demonstrated a clinical benefit from treatment, though, in treated groups, the pathogen was rapidly cleared from feces. In addition to these studies, treatment recommendations are based on susceptibility data and clinical case series.

In vitro studies

Yersinia susceptibilities vary with the serotype, and therapeutic decisions should be guided by the susceptibility pattern of the clinical isolate. Y. enterocolitica serotype most commonly associated with illness (O:3) usually produces chromosomally-mediated beta-lactamases and thus is resistant to penicillin, ampicillin, and most first generation cephalosporins. Yersinia is also usually resistant to macrolides (Ostroff et al. 1992).

Clinically significant strains are usually susceptible to other beta-lactam agents, aminoglycosides, tetracyclines, chloramphenicol, trimethoprim-sulfamethoxazole, and fluoroquinolones (Capilla et al. 2003). In one series, strains were uniformly susceptible to piperacillin, imipenem, ceftazidime, cefepime, aminoglycosides, fluoroquinolones, and trimetho-primsulfamethoxazole (Capilla et al. 2004).

Fluoroquinolone resistance: Quinolone resistance, including resistance to nalidixic acid and reduced susceptibility to ciprofloxacin, has been documented in Spain, due to mutations in DNA gyrase and an efflux pump, which may limit the effectiveness of these agents. As Y. enterocolitica rarely spreads from person to person, this resistance is more likely due to the use of antimicrobials in agriculture than in human medicine (Fryden et al. 1990).

Enterocolitis: There are no controlled trials that indicate that antimicrobial treatment of acute, uncomplicated yersiniosis is beneficial. In a retrospective case series of Y. enterocolitica gastroenteritis from Norway (67 case-patients and 132 controls), treatment was not associated with a decreased duration of illness (18 versus 21 days). There also was no clinical benefit demonstrated in a small prospective, placebo-controlled trial of trimethoprim-sulfamethoxazole (10 mg/kg TMP and 50 mg/kg SMX per day in two divided doses) in 34 Canadian children. The initiation of therapy was significantly delayed in
both studies (>20 days after disease onset in Norway and 12 days in Canada), as the onset of yersiniosis is often insidious. It is unclear if earlier treatment would prove more beneficial.

However, rapid microbiologic clearance of the organism was observed following treatment in both of these studies (Marketon et al. 2005).

There was no clinical benefit from ampicillin in a prospective placebo-controlled trial in 136 pediatric patients with *Y. pseudotuberculosis* in Japan. Although there was no difference in clinical response between treatment and control groups, following five days of treatment, clearance of the organism was significantly greater in the ampicillin group (continued organism excretion 0 versus 90%, respectively). There is also no evidence that early antimicrobial therapy reduces the frequency or severity of chronic sequelae for either *Y. enterocolitica* or *Y. pseudotuberculosis* (Press et al., 2001).

In general, most cases of *Yersinia enterocolitica* do not merit treatment and no clinical benefit of treatment has been documented. Bearing in mind the lack of clinical efficacy data, should treatment of an individual case be judged clinically necessary because of clinical severity or underlying condition of the patient (eg, immunocompromised patients), we suggest a fluoroquinolone such as ciprofloxacin (500 mg twice daily) or trimethoprim-sulfamethoxazole for the pediatric patient (TMP 8 mg/kg per day and SMX 40 mg/kg per day in two divided doses).

Doxycycline or trimethoprim-sulfamethoxazole is alternatives to fluoroquinolones for complicated gastrointestinal infections or focal extra-intestinal infections (Cover and Aber, 1989).

Septicemia: Antibiotics are indicated for the treatment of complicated illness such as septicemia. Mortality associated with *Yersinia* bacteremia has decreased from 30% in the 1970s to less than 10% in the late 1980s, presumably as a result of improved therapy (Jensen et al. 1995).

In a retrospective case series of 43 patients with *Y. enterocolitica* septicemia, third generation cephalosporins with or without other antibiotics were effective in 85% of cases; fluoroquinolones alone or in combination, cured all of 15 infections. Ampicillin, amoxicillin, first-generation cephalosporins, and amoxicillin-clavulanate when used alone were not effective. The duration of therapy varied from two to six weeks, with a median of 22 days, intravenous followed by oral therapy (Gayraud et al. 1993).

In patients with septicemia or severe disease, recommend intravenous therapy with a third generation cephalosporin such as ceftriaxone (2 g per day in adults or 100 mg/kg per day in one or two divided doses in children, to a maximum dose of 4 g per day) combined with gentamicin (5 mg/kg per day in one to three divided doses). An alternative antibiotic to replace ceftriaxone is ciprofloxacin, if susceptible.

Duration of treatment: There have been no controlled trials examining the duration of antimicrobial therapy in
Yersinia spp. infections. The treatment recommendations are based on clinical case series. It is suggested that if enterocolitis is treated, patients should receive five days of oral antibiotics. It is suggested that more severe extraintestinal infections, including septicemia, receive three weeks of therapy; the patient can be switched to oral agents, once clinically improved, to complete therapy (Black and Slome, 1988).

**Prevention**

Reducing exposure is the best preventive measure. In known endemic areas, avoidance of handling dead rodent carcasses, use of insect repellents, and flea and rodent control may play a role in prevention.

Unprotected face-to-face contacts (ie, within two meters) of patients with known or suspected pneumonic plague who have not been treated with effective antimicrobial therapy for at least 48 hours should be provided chemoprophylaxis. Appropriate drugs tetracycline (15-30 mg/kg/day orally for 5-7 days), doxycycline, chloramphenicol, and trimethoprim-sulfamethoxazole

In the outbreak of pneumonic plague cited above, treatment of patients with streptomycin and prophylaxis of contacts with sulfadoxine stopped the outbreak. The infection rate in contacts was 8.4%.

In the event of pregnancy or children under the age of eight, trimethoprim-sulfamethoxazole has been recommended for five to seven days. Although data confirming efficacy is lacking in these settings, trimethoprim-sulfamethoxazole was recommended in a dose of one double-strength tablet twice daily in adults and 4 mg/kg of the trimethoprim component twice daily in children (Guiyoule et al, 2001).

A killed whole cell vaccine has been developed but is no longer commercially available in the United States. The efficacy of the vaccine has been difficult to evaluate. Much of the experience has been with vaccination of military personnel deployed to areas endemic for plague such as Vietnam.

It is a general feeling that vaccine provides some protection. The recommended regimen is a primary series of two injections one to three months apart, followed by a booster every six months for as long as the exposure lasts (Cavanaugh et al, 1974).

The concern about plague as a bioterrorism agent has led to the development of a number of newer vaccines, some of which are undergoing clinical testing (Morris, 2007).

**Reservoirs and Vectors**

Plague is a zoonosis primarily affecting rodents. Humans are accidental hosts who play virtually no role in the maintenance of Y. pestis as a persistent pathogen in the ecosystem. While transmission occasionally occurs by direct contact or ingestion, survival of the bacillus in nature is dependent upon the flea-rodent interaction (Drancourt et al, 2004).

Over 1500 species of fleas have been identified, but only about 30 are proven vectors of plague. The most efficient flea vector is *Xenopsylla cheopis*, the oriental rat flea but different flea vec-
tors may be important in different regions. The most important flea vector in North America is *Oropsylla montana* while *Pulex irritans*, the human flea, might play a marked role in Tanzania (Gage *et al.*, 1992).

More than 200 mammalian species in 73 genera have been reported to be infected with *Y. pestis*, but rodents are the most important hosts. Different species are more or less susceptible to death from *Y. pestis* infection; ground squirrels and prairie dogs, for example, are highly susceptible while other species are only moderately susceptible or even frankly resistant to fatal infection. Death in large numbers of animals in a susceptible species may herald an increase in plague activity in nature. Obviously, in order to survive in nature, the organism must not kill all hosts.

Flea blockage: It has been argued that the blockage paradigm, which consists of a lengthy incubation period followed by a short infectious window and then death of the flea, may not be sufficient to explain the rapid rate of spread during plague epidemics.

Support for this concern comes from a study of the flea *Oropsylla montana*, which is the major vector of human disease in North America. In contrast to the blockage model, *O. montana* is immediately infectious, transmitting the infection efficiently for at least four days, and may remain infectious for a prolonged period because the infected flea does not die from blockage. These characteristics meet the criteria required to drive a plague epidemic (Eisen *et al.*, 2006).

Host response: After the flea bite, *Y. pestis* disseminates from the site of inoculation into the lymphatic system by a process that may be facilitated by a plasmid-encoded plasminogen activator that produces local proteolysis (Prentice and Rahalison, 2007). In a mouse model, it has been estimated that the plasminogen activator lowers the median lethal dose of *Y. pestis* by one million-fold. This may enable the bubonic form of plague (Sodeinde *et al.*, 1992) and, by promoting rapid *Y. pestis* replication in the airways, the pneumonic form of plague (Lathem *et al.*, 2007).

Survival and replication within macrophages is probably of greatest importance in the early stages of infection. After dissemination, necrotic foci containing extracellular *Y. pestis* form and progressively increase in size. This progressive extracellular course is facilitated by impairment of local immune cell function via injection of bacterial Yop proteins into effector cells such as macrophages and neutrophils (Pujol and Bliska, 2005).

The minimum infectious dose for mammals is less than 10 organisms by the subcutaneous route, which is about the same number needed to kill 50% of susceptible animals.

**Routes of Transmission**

Humans acquire plague by several routes as bites by rodent fleas, exposure to humans with pneumonic plague handling of infected animal carcasses, scratches or bites from infected domestic cats or exposure to infective aerosols (Crook and Tempest, 1992).
Flea bites are the most common route of transmission of plague to humans, followed by contact with infected animals. In about 14% of cases, the source of infection is unknown. In the absence of epidemics, plague is largely a disease occurring in wild animals, with humans being an accidental victim (Weniger et al. 1984).

The most common animals to transmit plague in the United States are squirrels, rabbits, and prairie dogs, although undetermined species account for about one-third of cases. Of note is the role of domestic cats in the transmission of plague since 1977. Twenty-three cases of human plague associated with cats were collected by Centers for Disease Control and Prevention (CDC) from eight western states of the United States from 1977 through 1998, representing 8 percent of the reported cases of plague during that time. The incidence of infection did not increase during the summer months unlike cases of plague associated with fleas. Inhalation was found to be more common as a route of acquisition involving cats than in other cases of plague (5 of 23 patients versus 2 of 228, p<0.0001). Approximately 25% of the cases resulting from contact with cats have occurred in veterinarians and their assistants (Gage et al. 2000).

There has been a revival of concern about plague as a bioterrorism agent (Inglesby et al. 2000).

Food safety

The food industry plays a critical role in preventing yersiniosis. Reducing levels of contamination of raw pork products with Yersinia by improved hygiene at slaughter is important. Pasteurizing milk and maintaining high standards of sanitation in dairy plants prevents contamination of dairy products.

The most common food vehicles implicated in Yersinia transmission are pork and pork products, particularly chitterlings. A common route of transmission is indirect, via the hands of the person handling the raw food to the formula bottle of the infant. Separating the two tasks of preparing raw meat foods and caring for an infant is an important prevention measure.

Careful hand-washing, cutting boards and utensils with soap immediately after handling raw meats, as well as general measures to prevent cross contamination in the kitchen can help prevent transmission. Persons preparing pork should avoid eating raw or undercooked pork, even as part of adjusting spices while cooking. Measures to prevent Yersinia infection include safe food processing and preparation and hand washing after exposure to pigs or pork products. Pigs are the natural reservoir for Yersinia spp. and thus, particular care after handling these animals is warranted.

Waterborne transmission is prevented by routine municipal water treatment and disinfection.

Transfusion-transmitted: Testing units of packed red blood cells for the presence of bacterial endotoxin, and limiting the shelf-life of packed red cells may be helpful in preventing transfu-
sion-associated sepsis (Kuehnert et al., 1998).

**Geographic Distribution**

Foci of plague are present on most continents other than Australia. The largest enzootic plague area is in North America (mainly the southwestern United States and Pacific coastal area) followed by the former Soviet Union. Multiple stable foci exist in Africa, Asia, and South America. No foci are present in Western Europe (Marketon et al., 2005).

Between 1994 and 2003, 28,530 cases worldwide were reported to the WHO. In 2000 and 2001, more than 95% of reported cases came from Africa, including approximately 40% from Madagascar. Outbreaks of human plague, with numbers of cases ranging from 100 to more than 1000, have occurred since 1992 in Zaire, Peru, and India. Plague reappeared in 1994 in Malawi, Mozambique, and India, raising concerns that the disease may reemerge as a significant worldwide public health hazard (Butler, 1994). An increase in bubonic cases was noted in Uganda in 2006.

In the United States, plague is endemic in all of the western states and has extended north and east over the years. Ninety percent of human cases in the United States have occurred in four states: Arizona, California, Colorado, and New Mexico. Human disease has also been reported from Texas and Oklahoma. In addition, animal and/or flea plague has been identified in western North Dakota and Nebraska (Campbell and Hughes, 1995).

The rate of plague in the United States is low, probably because the affected areas are rural and largely uninhabited. Between 1987 and 2001, only 125 cases were reported in the United States to the WHO. In 2006, a total of 13 human plague cases were reported among the residents of four states: New Mexico, Colorado, California, and Texas; two cases were fatal.

**What about Libya?**

Misonne (1977) reported the presence of natural focus in Libya. Christie et al. (1980) reported that in 1976, in a small, remote Libyan village, one apparently sick camel was slaughtered and skinned, and the camel meat was distributed for human consumption. A few days later, 15 villagers suffered a severe febrile illness. Of the five individuals who had participated in the killing and dispensation of the camel, all were dead within four days. When sera from nine of the remaining patients were examined, seven were positive for plague by passive hemagglutination test. Another six persons became ill after killing two goats, and the serum of one goat contained antibodies to Y. pestis. Because all the patients except one were treated early enough, they recovered. These incidents confirm previous reports that the camel and the goat are susceptible to naturally occurring plague infection and have a significant role in the dissemination of human plague. Mollaret (1995) mentioned plague epidemics which have been negated or dissimulated in order to avoid isolation and quarantine: epidemics of Marseille (1720), San Francisco (1900), Mauretania (1963-1967),
Libya and Egypt (1984). Tarantola et al. (2009) stated that limited outbreak with five cases has recently been notified by the health authorities of the Libyan Arab Jamahiriya.

What about Egypt

In Egypt, so many authors dealt with rodents and their fleas from different aspects (Hoogstraal, 1956, 1963, 1965, 1966; Abdon and Samaan, 1962; Hoogstraal, 1956, 1963, 1965, 1966; Hoogstraal and Traub, 1963; Rifaat et al., 1969; Arafa et al., 1973; Osborn and Helmy, 1980; Morsy et al., 1981, 1982, 1986a, b, 1988a; Shoukry et al., 1986, 1987; Lewis, 1967; Zeese et al., 1990; Khalid et al., 1992; Bakr et al., 1996; El Kady et al., 1998; Allam et al., 2002; Loftis et al., 2006; Mahmoud et al., 2008; Soliman et al., 2010; Mikhail et al., 2011).

Conclusion and Recommendations

The control of rodents and their flea ectoparasites is a must particularly on the bordered and portal governorates. The measures to prevent Yersinia infection include safe food processing and preparation and hand washing after exposure to pigs or pork products.

There are no controlled trials indicating that antimicrobial treatment of acute, uncomplicated yersiniosis is beneficial. It is recommended not to treat enterocolitis with antibiotics unless the patient has severe disease or has an underlying comorbid illness (Grade 2B). If enterocolitis requires treatment, it is suggested treatment with a fluoroquinolone in adults (eg, ciprofloxacin 500 mg twice daily) or trimethoprim-sulfamethoxazole in children (TMP 8 mg/kg per day and SMX 40 mg/kg per day in two divided doses) (Grade 2C), typically treating with antibiotics for five days. It is recommended intravenous therapy for patients with septicemia or severe disease (Grade 1B). The preferred regimen is a 3rd generation cephalosporin as ceftriaxone (2g/day in adults or 100mg/ kg/day in one or two divided doses in children, to a maximum dose of 4gm/day) combined with gentamicin (5mg/kg/day in 1 to 3 divided doses). Ciprofloxacin (500mg twice daily) can be used in place of ceftriaxone in adults if the isolate is susceptible. The typical duration of treatment is three weeks.

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