

Review

Yersiniosis I: Microbiological and Clinicoepidemiological Aspects of Plague and Non-Plague *Yersinia* Infections

R.A. Smego, J. Frean, H.J. Koornhof

Introduction

The nature of a microorganism may be so fascinating and intellectually appealing that individuals are drawn to try and unravel the mysteries of its microbial past, present and future. Such would seem to be the case with the charismatic yersiniae as described by Bottone [1, 2]. Basic laboratory and clinicoepidemiologic investigations over the past two decades have sought to unravel the keys to the pathogenesis of these prototypic invasive and immunogenic pathogens. We have learned much about the molecular biological basis of yersinia, witnessed an evolving epidemiology of transmission and drug resistance capabilities, categorized the remarkable array of clinical manifestations caused by its human disease-causing species, and compared the historical contribution of yersiniae to the misery and suffering of mankind to the present-day scourges, tuberculosis and acquired immunodeficiency syndrome (AIDS).

This paper will review the microbiological, epidemiological, and clinical features of *Yersinia* species that characterize disease in humans. The species causing plague and non-plague yersiniosis will be discussed separately because of their historical and clinical uniqueness.

The Genus *Yersinia*

Laboratory Characterization. The genus *Yersinia* belongs to the *Enterobacteriaceae* family [3]. Yersiniae are therefore facultatively anaerobic, gram-negative,

non-sporing rods or coccobacilli. They are non-encapsulated except for *Yersinia pestis*, which develops an envelope at 37°C. They grow on MacConkey agar, are catalase positive and oxidase negative, and ferment glucose with the production of acid.

In Bergey's Manual of Systematic Bacteriology published in 1984, Bercovier and Molleret [3] described seven *Yersinia* species comprising the three pathogenic species, *Yersinia pestis*, *Yersinia pseudotuberculosis* and *Yersinia enterocolitica*, the three species *Yersinia intermedia*, *Yersinia frederiksenii* and *Yersinia kristensenii*, whose pathogenicity in humans and animals is not clearly established but which may cause opportunistic infections, and a seventh species called *Yersinia ruckeri*, which is a fish pathogen causing red mouth disease in rainbow trout [4, 5]. Subsequently, four other species, *Yersinia aldovae*, *Yersinia rohdei*, *Yersinia mollaretii* and *Yersinia bercovieri* were added to the list [6–8]. The latter two species were formerly classified as biogroup 3A and biogroup 3B, respectively [9]. These species demonstrate considerable DNA divergence as well as differences in pathogenicity for humans, ecology, and O and H antigenic patterns compared with *Yersinia enterocolitica* biovar 3 and other biovars of this species [8].

The biochemical reactions elicited by *Yersinia pestis* and *Yersinia pseudotuberculosis* [3, 10] are fairly homogeneous, but *Yersinia enterocolitica* strains were divided into biogroups by Knapp and Thal in 1972 [11]. Minor modifications have been subsequently proposed [8, 12], and at present five biovars are recognized. Table 1 illustrates microbiologic and biochemical features of *Yersinia* species and *Yersinia enterocolitica* biovars, which may be used for their differentiation in the laboratory [3, 10, 12]. Biovar 1 has been subdivided into 1A and 1B biogroups, based on failure to ferment salicin and inability to produce the enzyme pyrazinamidase by biogroup 1B [2]. Biogroup 1B isolates occur mainly in the USA, while biogroup 1A strains appear to be non-pathogenic or opportunistically pathogenic only [2, 12, 13].

R.A. Smego, J. Frean, H.J. Koornhof
Department of Clinical Microbiology and Infectious Diseases,
University of the Witwatersrand, and the South African
Institute for Medical Research, Johannesburg, Republic of
South Africa

R.A. Smego (✉)
Department of Clinical Microbiology and Infectious Diseases,
Faculty of Health Sciences, Room 3T02, 7 York Road,
Parktown, Johannesburg 2193, Republic of South Africa

Table 1 Results of laboratory tests for characterization of *Yersinia* species and biovars (modified data from references 1, 8 and 10)

Organism	Motility 22°C	Lipase 22°C	Orni- thine Decar- boxylase	Urease	Citrate (Sim- mons) 25°C	Voges- Pros- kauer	Indole	Xylose	Treha- lose	Su- crose	Rham- nose	Raffi- nose
<i>Y. pestis</i>	—	—	—	—	—	—	—	+	+	—	(+)	—
<i>Y. pseudotuberculosis</i>	+	—	—	+	—	—	—	+	+	—	+	—
<i>Y. enterocolitica</i>	+	v	v	+	—	v	v	v	+	v	—	v
Biovar 1 ^a	+	+	+	+	—	+	+	(+) ^c	+	+	—	v
Biovar 2	+	—	+	+	—	+	(+)	(+)	+	+	—	—
Biovar 3	+	—	+	+	—	+	—	(+)	+	+	—	—
Biovar 4	+	—	+	+	—	+	—	—	+	+	—	—
Biovar 5 ^b	+	—	v	+	—	v	—	v	—	v	—	—
<i>Y. intermedia</i>	+	v	+	+	v	+	v	(+)	+	+	(+)	(+)
<i>Y. frederiksenii</i>	+	v	+	+	v	+	+	(+)	+	+	(+)	—
<i>Y. kristensenii</i>	+	v	+	+	—	—	v	(+)	+	—	—	—
<i>Y. ruokeri</i>	+	v	+	—	(+)	v	—	—	+	—	—	—
<i>Y. aldovae</i>	+	v	+	+	v	+	—	(+)	+	—	+	—
<i>Y. rohdei</i>	+	—	+	+	+	—	—	+	+	+	—	v
<i>Y. mollaretti</i>	+	—	+	+	—	—	—	+	+	+	—	—
<i>Y. bercovieri</i>	+	—	+	+	—	—	—	+	+	+	—	—

^a Biovar 1 may be subdivided into biogroups 1 A and 1 B, the latter being unable to ferment salicin or to produce pyrazinamidase (II)

^b Biovar 5 is the only *Y. enterocolitica* biovar which fails to reduce nitrate

^c Positive only at 22°C–25°C
v, reaction variable

Antigenic Structure. Some antigens are shared by the three pathogenic species, including the common enterobacterial antigen found in gram-negative bacteria [14]. Recently, Aleksic [15] reported the presence of *Yersinia enterocolitica* antigens 0:3, 0:8 and 0:9 in different *Yersinia* species and described their corresponding H antigens and origins. The fraction 1 envelope antigen (F1) of *Yersinia pestis* produced at 37°C consists of a protein linked to polysaccharide (fraction 1A) which is complexed to a free protein fraction 1B [16], while the V and W antigens also optimally expressed at 37°C and first described in *Yersinia pestis* have, in addition, been demonstrated in *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* [16–18]. The somatic antigen of *Yersinia pestis* is rough (R-antigen) and is also present in *Yersinia pseudotuberculosis* [19]. Lawton et al. [20] found that *Yersinia pestis* and *Yersinia pseudotuberculosis* shared at least 11 antigens other than V and W. Two of the shared antigens were produced at 37°C but not at 26°C, suggesting that they represent virulence factors that were characterized later. Similarly, Barber and Eylan [21] have described several antigens common to *Yersinia pestis*, *Yersinia enterocolitica* and other members of *Enterobacteriaceae*.

Several other antigens, including antigen pH6, previously known as antigen 4, and the catalase antigen [16] as well as some virulence-related *Yersinia* outer proteins (YOPs) such as YOP H (formerly known as YOP 2b), are shared by the three human pathogenic species [22]. The antigenic scheme of Thal and Knapp [19, 23] for *Yersinia pseudotuberculosis* comprises six heat-stable serogroups and five heat-labile flagellar H antigens, some of which cross-react with *Salmonella*,

Escherichia coli (including O:55) and *Enterobacter* strains.

Wauters et al. [24] described 34 O antigen and 20 H antigen serogroups in *Yersinia enterocolitica*. This classification included *Yersinia intermedia* (O:17) and *Yersinia kristensenii* (O:11, O:12, O:28), while cross-reactions between serogroups 0:9 and *Brucella* species as well as serogroup O:12 and *Salmonella* O:47 have been demonstrated [3, 25]. There is a relationship between *Yersinia enterocolitica* serogroups and biovars and the ecological distribution of human pathogenic strains and strains isolated mainly from pigs, chinchillas and hares. This relationship is seen with isolates from the environment in Europe, the USA and Japan [2, 12].

Plague Yersiniosis

***Yersinia pestis* and Plague.** Plague is an acute bacterial infection caused by *Yersinia pestis*. It is a zoonosis, maintained primarily in populations of wild rodents and their fleas, and transmitted to humans under appropriate conditions. Around 1994, the 100th anniversary of the start of the third pandemic, plague came to prominence again in outbreaks in India and Mozambique; it is still endemic in many parts of the world, being regarded as a re-emerging infectious disease [26–28]. Between 1979 and 1993, 56% of all reported cases and 75% of deaths were in African countries [28].

History of Plague. Plague has been known since antiquity [29]. It is generally believed that there have been three pandemics of plague in recent history. The first was the Justinian plague, which occurred in cycles

between 541 and 750 AD, mainly in and around the Mediterranean basin. The first epidemic (1347–1351) of the second pandemic became known as the Black Death, but the pandemic itself lasted well into the 17th century in Europe. Most recently, the third pandemic began in China in 1855 and spread worldwide from the Chinese coast at the end of the 19th century [30]. In particular the devastating second pandemic convulsed the European cultural, social and economic order [29, 30]. The Black Death alone is estimated to have caused around 25 million deaths, representing 30–40% of the population of Europe [31]. As only historical records are available, there is some uncertainty surrounding any disease called plague as a number of conditions may have contributed to the large-scale depopulation typical of these epidemics [29]. Doubts have been raised about the uniformity of the aetiology of the earlier epidemics, including the Black Death in England [32, 33], and certain identification has only been possible since 1894 when Alexandre Yersin isolated and identified the plague bacillus in humans and rats in Hong Kong [34, 35]. The features of Shiba-saburo Kitasato's organism, announced as the agent of plague at the same time as Yersin's, were probably the result of contamination of cultures by pneumococcus [36]. Three years later Paul-Louis Simond established the role of fleas in transmission during the Indian epidemic [34, 35]. Steamships rapidly disseminated the disease from Hong Kong, and by 1900 it had spread to Africa, Australia, Russia, India, Japan, the Middle East, the Philippines, the USA and South America [29, 30, 36]. Today enzootic foci remain in Asia, Africa, and North and South America.

Bacteriological Characterization. *Yersinia pestis* is a gram-negative, non-motile, non-spore-forming coccobacillus (0.5–0.8 μm by 1–3 μm); bipolar staining with methylene blue-based stains (Giemsa or Wayson's) is characteristically seen in vivo and in fresh isolates. A high degree of pleomorphism is typical, especially when the organism is grown on unfavourable media such as 3% salt agar, with short chains, clubs, filamentous forms, coccoid and yeast-like forms [3, 37]. Growth is optimal at 28 °C, but the organism will grow at temperatures between 4 °C and 40 °C. Culture characteristics are discussed below. The structure of the cell wall is typical of *Enterobacteriaceae*, and the lipopolysaccharide lacks extended O-group side-chains [30]. *Yersinia pestis* is a facultative intracellular parasite and as such, is equipped with a variety of chromosomal- and plasmid-mediated virulence factors which enable it initially to survive and multiply within phagocytes, and later to disseminate widely in the susceptible host. There is no true capsule, but an antiphagocytic carbohydrate-protein envelope called the capsular or fraction 1 (F1) antigen is produced during growth at temperatures above 33 °C. Other virulence factors are V and W antigens, outer membrane proteins conferring dependence on calcium for growth at 37 °C, iron and haemin

transport systems, and temperature-dependent coagulase and fibrinolysin enzymes. Most *Yersinia pestis* strains carry three plasmids encoding for, amongst others, the F1 protein, pesticin, plasminogen activator, low calcium response stimulon, and murine toxin. Some of these virulence factors are common to other yersiniae, and relevant work by Perry and Fetherston [30] and Brubaker [16] is reviewed elsewhere in this article and in Part II, which will appear in EJCMIID, volume 18, number 2. The metabolic requirements of *Yersinia pestis* [3, 16, 37] are such that it is an obligate parasite and cannot exist as a saprophyte, although it may survive for limited periods in the environment (e.g. up to a year in rodent burrows) under favourable conditions [38].

Based on the presence or absence of nitrate reduction and glycerol fermentation, three biotypes or biovars (*antiqua*, *mediaevalis*, *orientalis*) of *Yersinia pestis* are distinguishable. Devignat [39] proposed that these biovars were responsible for the first, second and third pandemic, respectively. While this is impossible to verify for the first two pandemics, it is supported by evidence that biovar *orientalis* isolates have been confined to areas previously unaffected by plague and invaded during the third pandemic, while isolates from older foci have been of other biovars [40, 41]. Molecular techniques can provide a much higher resolution than biotyping in elucidating past and present plague. Ribotyping of 70 isolates of *Yersinia pestis* isolated in 16 geographical areas between 1908 and 1979 distinguished 16 different profiles, of which two accounted for 65.7% of the strains studied, and certain ribotypes consistently corresponded with certain biovars [42]. Ribotyping has shown that new ribotype variants, representing chromosomal rearrangements, evolve rapidly and spread and establish themselves in new ecosystems. This was confirmed by genomic restriction profiles and plasmid profiles [40].

Epidemiology of Plague. Plague is focally maintained in mammal, mainly rodent, reservoirs and transmission is via their fleas; *Yersinia pestis* does not exist freely in nature. The ecology is highly variable: foci of infection develop in different animals and fleas in different geographical locations. There is a complex interaction between the hosts, vectors and organism, influenced by factors such as host susceptibility, season, temperature, humidity, availability of food and transmission efficiency of fleas [29, 41]. When a flea feeds, blood is taken into the midgut (stomach) via the oesophagus and the proventriculus, a valve-like structure equipped with rearward-facing spines, which functions to prevent regurgitation of the meal and aids in rupture of the blood cells. If plague bacilli are present in the blood meal, they multiply over the next few days to produce gelatinous dark brown masses consisting of bacteria and fibrinoid material in the midgut, extending into the proventriculus and oesophagus [38, 43]. These may

eventually completely block the proventriculus and as the flea repeatedly attempts to feed, ingested blood, prevented from reaching the stomach and having mixed with the plague bacilli, is regurgitated into the wound. At environmental temperatures greater than 28–30 °C, there is less blockage of fleas, possibly due to temperature-dependent regulation of haemin storage and plasminogen activator (Pla protease) which controls fibrinolytic and coagulase activities [44]. Not all species of fleas are equally susceptible to blocking, the rate of which depends on frequency of feeding and the quantity of blood and bacilli ingested at a feed. The time until infectivity of a flea which has ingested plague bacilli varies with the flea species and external temperature and humidity, as does the survival time of fleas, which is also influenced by whether they are fed or not. Only about 30 of the approximately 3000 known species of fleas are proven plague vectors, although under the right circumstances any flea may potentially be a vector. *Xenopsylla cheopis* (the Oriental rat flea) is the prototypical vector, and one of the most effective. The cat and dog fleas (*Ctenocephalides felis* and *Ctenocephalides canis*, respectively) and the human flea (*Pulex irritans*) are poor vectors [29, 30, 38].

Animal Reservoirs. The important animal hosts for the maintenance of plague are primarily rodents, although many other mammals are naturally infected. Urban and domestic rats, *Rattus rattus* and *Rattus norvegicus*, were the predominant animal hosts early in the third pandemic, but their present importance is restricted to a few plague areas in the world, such as Madagascar [45], and they do not generally play a role in maintaining plague in the wild [29, 30]. Most human plague today is acquired in rural settings with wild animals forming the reservoir (sylvatic plague) [36]. A recent exception was the pneumonic plague outbreak in Surat, India, in 1994, which was preceded by increased rat mortality (the classical “rat fall”) in rural villages where bubonic plague broke out in humans [26, 30]. Urban plague has also been reported from Zaire and Madagascar recently [45–47].

Interepidemic/epizootic persistence of plague is still poorly understood. One possibility is that attenuated strains of *Yersinia pestis* persist in reservoir populations, to produce epizootics when they revert to virulence. Non-encapsulated strains have been suggested as candidates [48], but recent work has shown that F1-strains, either naturally occurring or experimentally mutated, maintain their virulence for mice and non-human primates [49], although this may not apply to plague infections in other animals. An experimentally constructed *Yersinia pestis* strain expressing the YadA outer membrane protein of *Yersinia pseudotuberculosis* partially lost virulence [50].

Yersinia pestis has been isolated by means of animal inoculation from unoccupied rodent burrow soil for up

to a year after an epizootic [38]. DNA hybridisation probes and polymerase chain reaction (PCR) methods should be able to demonstrate the presence of putative non-culturable organisms in the environment. Experimentally, the transition of the organism into a non-culturable form in soil extracts, with subsequent reversion by enrichment of the culture medium with serum, has been demonstrated [51]. Survival of enzootic animal hosts is, however, the most widely accepted scenario for interepizootic maintenance of plague. The hypothetical prototype enzootic reservoir host is probably a highly resistant animal which does not develop serious illness following infection [41]. Epizootic rodent hosts, on the other hand, are susceptible and there is a high mortality in these populations. Wild rodent “die-offs” are therefore characteristic of plague epizootics and a warning sign of possible spread of plague to domestic rodents and to humans and their livestock and pets. Related rodent species living in close association may respond differently to plague infection. For example, in southern Africa the multimammate mouse, *Mastomys natalensis* (sensu lato), forms a species complex comprising *Mastomys coucha* and its morphologically identical sibling species *Mastomys natalensis*, which have diploid chromosome numbers of 36 and 32, respectively. The former is highly susceptible to plague, and the latter highly resistant [52]. It was shown that splenic lymphocytes of *Mastomys coucha* were unable to proliferate in vitro in response to exposure to *Yersinia pestis* F1 capsular antigen, unlike those of *Mastomys natalensis* [53]. As *Mastomys coucha* is semi-commensal in man it forms an important link (a “Trojan horse”) between sylvatic and domestic hosts in southern Africa. Transmission of plague from animal to man is usually via the bite of an infected flea. Transmission pathways are illustrated in Figure 1. Humans may also acquire plague from direct contact with infected wild rodents or other animals and their predators, usually in the course of hunting or trapping. The majority of recent human cases in the southwestern USA have been acquired peridomestically, where rapid suburbanisation encroaches on active plague foci [54]. Domestic animals, which, like man, may intrude into wild plague foci [29, 54, 55] and acquire the infection via fleas or by eating infected rodents, are occasionally sources of human plague infections. Cats, in contrast to dogs, develop clinical plague [56], and a number of cases of direct cat-to-human transmission have been described [54–57]. Person-to-person spread of plague is almost invariably airborne, but fleaborne interhuman plague transmission, usually involving the human flea *Pulex irritans*, can occur and has a typical intrafamilial pattern of spread [31].

Clinical Features. The most characteristic and common presentation of plague is the bubonic form which follows the bite of an infected flea. The incubation period is between 2 and 8 days. There is typically a sudden onset of fever, chills, headache and weakness,

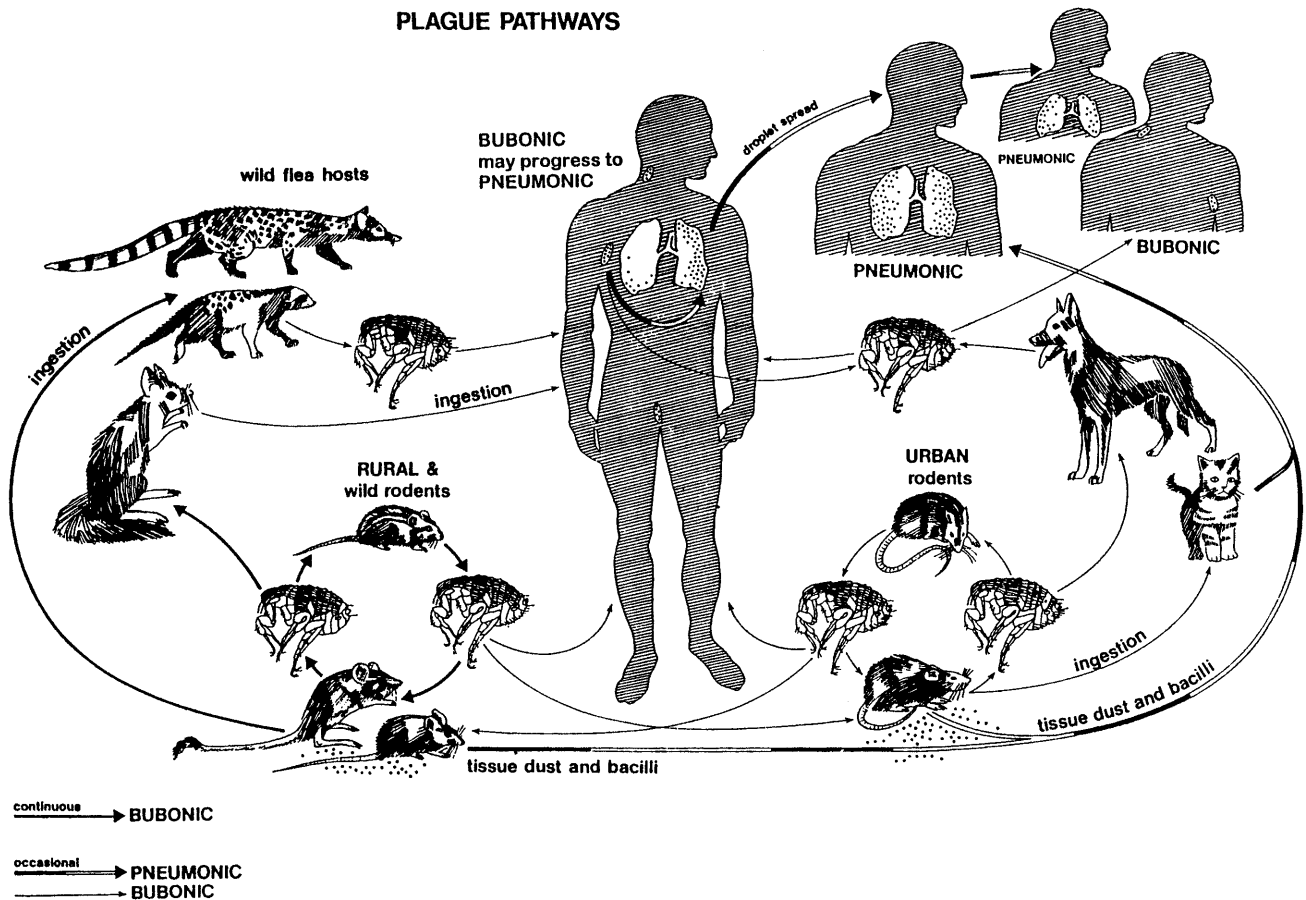


Figure 1 Life cycle of *Yersinia pestis* causing bubonic pneumonic plague

followed by intensely tender enlargement of regional lymph nodes (so-called buboes), usually in the groin, axilla or neck [36, 58]. There is often marked inflammation or cellulitis around the bubo. In a minority of cases in Vietnam there were pustules, vesicles, eschars or papules near or in the lymphatic drainage area of the bubo, presumably at the sites of flea bites [58]. Occasionally large carbuncles may develop at such sites [56]. Gastrointestinal symptoms such as abdominal pain, nausea, vomiting and diarrhoea may sometimes predominate [59]. All patients probably have intermittent bacteraemia in the early stage, and secondary septicaemia may develop, showing the typical clinical and laboratory features of gram-negative septicaemia and its complications, including shock, disseminated intravascular coagulation, peripheral gangrene and purpura [60]. A high-density bacteraemia is characteristic of moribund patients with plague [36, 58]. Primary septicaemic plague is characterised by absence of peripheral buboes and presents clinically as gram-negative septicaemia. It has been suggested that the mortality of this form of plague is high (30–50%) because antibiotics generally used to treat undifferentiated sepsis are not effective against plague [59].

Secondary pneumonic plague resulting from haematogenous spread from the bubo is a dreaded complication with a high mortality rate, presenting in patients as severe bronchopneumonia, cavitation, or consolidation with production of bloody or purulent sputum [36, 58]. This form of plague is highly contagious by the airborne route for close contacts, who are at risk for developing primary pneumonic plague within 1 to 3 days. It is usually fatal unless treated within a day of onset. Sick cats have been the main source of primary pneumonic plague in the USA recently [54, 57]. Plague meningitis and plague pharyngitis or tonsillitis associated with axillary and cervical buboes, respectively, are rare presentations of the disease [56, 59, 61].

Bubonic plague varies in clinical severity from case to case and from focus to focus; for example in Owambo, northern Namibia, plague is generally a mild illness [62]. Seroprevalence studies show that mild or inapparent infections are more common than realized in endemic areas [29, 61]. Rarely, it is possible to culture *Yersinia pestis* from the throats of healthy individuals, as reported in Vietnam [63]. Plague is readily treatable but a high index of suspicion is required to recognize the disease when transmission to humans is rare, when it reappears after long periods of quiescence in endemic areas, or when patients present outside endemic areas [59, 64].

Laboratory Diagnosis. Smears of clinical material can readily be prepared and are useful in the presumptive diagnosis of plague [65]. Blood, bubo aspirates, sputum and cerebrospinal fluid may be stained and cultured to detect the presence of *Yersinia pestis*. Plague bacilli are often present in large numbers in these specimens and typically show bipolar staining with Giemsa or Wayson's stain. *Yersinia pestis* will grow on a variety of routine culture media; solid and liquid culture media (e.g. blood agar and brain heart infusion broth) are inoculated and incubated at 27°C (for laboratory safety reasons). Growth is usually visible after 48 hours but plates should be incubated for up to 7 days before being considered negative. Colonies are opaque, smooth and round but sometimes have irregular edges. They may have a smooth or finely granular ("beaten copper") surface under magnification, with a raised center and flat periphery. There is no haemolysis on blood agar [37, 38]. Growth in nutrient broth is typically non-turbid, with a floccular deposit and later a delicate surface pellicle [3, 37].

The organism is identified by a typical battery of biochemical tests demonstrating presence of catalase but not oxidase; production of acid but not gas from glucose, mannitol or salicin; no acid reaction in sucrose, rhamnose or melibiose; and a negative Voges-Proskauer reaction [3, 37, 65]. Because it is slow-growing and biochemically relatively inactive, *Yersinia pestis* may not be correctly identified by miniaturized rapid biochemical test systems [66]. For confirmation, *Yersinia pestis* is lysed by a specific bacteriophage at 20°C [38]. Various virulence factors can be demonstrated using special media and methods but this is not required for routine diagnosis [38]. It is important that clinical specimens are taken before antimicrobial therapy is started. Overgrowth of the relatively slow-growing *Yersinia pestis* by other bacteria can be circumvented by animal inoculation. Ordinary white mice or guinea pigs may be used but Williams et al. [67] demonstrated the advantage of using laboratory-reared African multimammate mice (*Mastomys coucha* [Smith, 1834], 36 chromosome species) in the diagnosis of plague. Triturated reticuloendothelial organs of dead rodents, or other highly contaminated material collected in the course of surveillance activities, are usually best inoculated into laboratory animals as a first step in recovering *Yersinia pestis*. Successful use for this purpose of the selective CIN medium, originally developed for isolation of *Yersinia enterocolitica*, has been reported [68].

Serological tests can be used in the diagnosis of plague. Various techniques have been used [41], following the first specific plague passive haemagglutination (PHA) test described by Chen and Meyer [69]. Haemagglutinating antibodies appear towards the end of the first week of illness [29]. An enzyme immunoassay (EIA) to detect antibodies to F1 is more sensitive and specific

than PHA [70–72] and has the advantage of detecting IgG and IgM antibodies, but PHA has advantages of ease of use and economy in field surveillance [65]. In our laboratory, serological tests are performed on acute and convalescent (if available) serum specimens for F1 antibody and antigen detection by EIA, antigen detection being especially useful when antibiotics have been given before cultures are attempted [73]. Direct immunofluorescence to detect F1 antigen in clinical samples is often used in the USA but should complement, not replace, culture; false negative results have been recorded [59]. Other approaches to F1 antigen detection are a rapid chromatographic ("dip-stick") technique (personal communication, Dr. J. Burans, Naval Medical Research Institute, Bethesda, MD, USA), and a fibreoptic biosensor to detect bound immune complexes rapidly [74]. Although they are rare (only one human infection has been described [75]), strains lacking F1 would escape detection by all these serological methods. However, these variants are catered for in an immunoassay newly described in Russian literature [76].

Molecular techniques for diagnosis of clinical plague are not in routine use, although PCR is potentially attractive because of its sensitivity, specificity and speed, and a number of applications have been described [77–79]. The technique holds particular promise for studying the ecology and epidemiology of plague [51].

Treatment and Prevention. Untreated plague has a high mortality rate and effective antibiotic treatment is essential. A limited range of antimicrobial agents is used for treatment, namely streptomycin (alternatively gentamicin), chloramphenicol and tetracycline (or doxycycline) [29, 30, 36, 58, 80]. Streptomycin given for 10 days is still regarded as the drug regimen of choice, but because this drug is rapidly bactericidal, its use may precipitate endotoxic shock. However, this did not appear to be a problem in plague cases treated in Vietnam [60]. Most patients improve after 3 days, but 10 days of therapy is recommended to prevent relapses. Tetracycline or doxycycline is generally a satisfactory alternative for treatment of uncomplicated bubonic plague. In patients at risk for ototoxicity or renal toxicity, streptomycin therapy may be changed to tetracycline or doxycycline 3 days after defervescence. Chloramphenicol is used to treat plague meningitis and as an alternative to tetracycline or doxycycline in pregnant women and young children. Tetracycline or doxycycline is the usual choice for prophylaxis unless contraindicated for reasons of age or pregnancy, when trimethoprim-sulfamethoxazole is suggested [81]. Other agents which have been used previously for treatment but which are less satisfactory in terms of efficacy or toxicity include sulfonamides, trimethoprim-sulfamethoxazole, ampicillin and kanamycin [58]. Pneumonic plague is highly infectious and patients must be strictly

isolated with adequate precautions against airborne spread until 48 hours of antibiotic treatment has been given with a favourable response [82]. Bubonic plague cases should be observed for 24 hours under antibiotic therapy to detect incipient pneumonia.

The emergence in Madagascar of an isolate of *Yersinia pestis* showing plasmid-mediated high level resistance to multiple antibiotics (including all agents in use for plague prophylaxis and treatment) has suddenly highlighted the problem of a limited therapeutic armamentarium in need of supplementation [83]. The most active agents *in vitro* are extended-spectrum cephalosporins and fluoroquinolones [84, 85]. The potential use of quinolones for treatment of yersinial infections was proposed a number of years ago [86]. Ciprofloxacin prophylaxis was shown to be highly effective against intraperitoneal challenge with *Yersinia pestis* in mice compared to doxycycline, but ciprofloxacin post-infection treatment was less protective than prophylaxis in terms of mortality [87]. Ciprofloxacin prophylaxis and therapy was successful in a mouse pneumonic plague model for up to 24 hours after challenge, but not after 48 hours [88]. In two other studies, treatment of experimental murine plague with ofloxacin showed that it was as effective as streptomycin in reducing splenic bacterial counts [89], and both ofloxacin and ciprofloxacin were comparable to streptomycin for both early and late treatment (24 and 48 hours after challenge, respectively) of murine pneumonic plague [90]. It has been suggested that the fluoroquinolones are the most promising newer agents for treatment of plague, but information on clinical efficacy is required [84, 85]. Of concern is a report of rapid induction by nalidixic acid of *in vitro* resistance to quinolones (including ciprofloxacin), resulting in treatment failure of experimental infections in mice [91]. A new ketolide and a new penem have been shown to be active against *Yersinia pestis* *in vitro* and may warrant further investigation [84].

A whole-cell killed plague vaccine (Greer Laboratories, Lenoir, NC, USA) is available for those at high risk of exposure in epidemic situations, such as field control teams or laboratory workers. The latter are mainly at risk of acquiring plague via aerosolized infective material or accidental inoculation [41]. Side-effects of the vaccine are common and multiple boosters are required, and protection against pneumonic plague is not certain [58, 82]. F1 antigen is known to be a protective immunogen, suggesting its potential as a vaccine [92]. Experiments in mice showed that purified F1 provided better protection than the killed whole-cell vaccine for human use [49], but the finding that F1-mutants retain their virulence in mice implies that other immunogens which are also essential virulence factors are required in a vaccine [49]. A subunit vaccine containing F1 and V antigens, and a live recombinant vaccine (*Salmonella typhimurium* expressing an F1/V

fusion protein) have elicited protective efficacy in mice [93, 94].

Plague Surveillance and Control. Plague surveillance is aimed at identifying and enumerating potential mammalian hosts and flea vectors, demonstrating zoonotic plague infections in order to delineate plague foci [38, 41], and detecting or anticipating epizootics before they spill over into domestic rodent and human populations. Southern African experience has shown that the method of using the capture and bacteriological examination of rodents rarely yields positive results except during plague epizootics [95]; Shepherd and Leman [96] failed to culture *Yersinia pestis* from any of 4516 rodents of 27 species collected in surveillance activities during plague quiescence in South Africa. Serological methods can be used to detect the presence of zoonotic plague but when applied to susceptible rodents in plague foci usually yield few positive results, mirroring the bacteriological results. These species do not survive to carry *Yersinia pestis* or develop antibodies, making them unsuitable for monitoring purposes [95]. On the other hand, Rust et al. [97] showed that dogs are relatively resistant to plague and develop high titres of antibodies, ideal attributes of sentinel animals. Seropositivity rates in dogs can accurately identify epicenters and direction of spread of plague in outbreaks [98].

Plague ecology may alter in response to environmental changes, and continuous surveillance is required to detect changes in the pattern of animal reservoirs or flea vectors. For example, an interesting change in plague ecology has occurred in Madagascar, where *Rattus rattus*, while remaining the only reservoir in rural foci, has largely been replaced in the urban foci of Antananarivo by *Rattus norvegicus*. In the harbour city of Mahajanga, besides these rat species, the shrew *Suncus murinus* is now thought to play a key role [45]. Molecular typing of *Yersinia pestis* isolates can be used to trace the source or monitor the spread of plague. Ribotyping, pulsed-field gel electrophoresis, repetitive sequence analysis and plasmid restriction profile analysis are being applied to *Yersinia pestis* [40, 42].

In general, prevention of plague in humans rests on public education about its transmission, reducing domestic rodent access to food and shelter, personal measures to prevent flea bites (e.g. repellants), application of insecticides to home, work or recreational environments, elimination of fleas on pets, avoidance of sick or dead animals, and antibiotic prophylaxis for presumptive exposure [41, 81, 82]. Field plague control teams should be vaccinated and supplied with appropriate protective clothing to prevent flea bites. Insecticide application must always precede rodent control so as not to displace flea populations from dead hosts in search of new food sources, which are then at risk for plague. Rodent control (by trapping, gassing or poisoning) must be undertaken with caution as an over-

enthusiastic eradication campaign may create an ecological vacuum to be quickly filled by the same or other species, which may aggravate the plague risk [41].

Apart from rodent and flea control as mentioned above, measures to be taken when an epidemic is recognized include using trained teams to find and treat cases; isolation of pneumonic plague patients; tracing and surveillance of and antibiotic prophylaxis for contacts; and prevention of panic in local populations by providing accurate information [41, 82]. Likewise, appropriate information and recommendations concerning epidemics may be required in the international community because modern air travel provides the opportunity for rapid spread of pneumonic plague [99]. The numerous problems complicating the plague outbreak in India in 1994 (including public and media hysteria, an inappropriate international response, delayed recognition and misdiagnosis of plague, and inadequate public health measures) showed the powerful disruptive potential of epidemic plague [100–102].

Non-Plague Yersiniosis

Epidemiology and Occurrence. Human non-plague yersiniosis is caused by two species, *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*. The disease is zoonotic, capable of being transmitted from infected animals to man. The principal animal reservoirs of non-human *Yersinia enterocolitica* infection include domestic animals such as swine, goats, cattle and horses, rodents, and household pets such as dogs and cats [2, 103]. Man is an accidental host and is not necessary in the ongoing maintenance of transmission in nature. Pigs commonly harbour the organisms in their oropharynx and nasopharynx; during slaughter carcasses may become contaminated if infected heads are disposed of improperly. Pigs are the major reservoirs for human pathogenic strains of *Yersinia*, while non-porcine *Yersinia* are generally non-pathogenic. The majority of human pathogenic strains are found in distinct serogroups (e.g. O:3, O:5.27, O:8 and O:9). In addition to colonising the above-mentioned animal reservoirs as for *Yersinia enterocolitica*, *Yersinia pseudotuberculosis* resides in a number of avian species, including pigeons, turkeys, ducks, geese and canaries [58, 103–106]. Non-plague yersiniosis occurs more commonly in regions with temperate rather than tropical or subtropical climates.

The gastrointestinal tract is the portal of entry for most cases of yersiniosis. An inoculum of 10^9 organisms is typically required to cause clinical infection. Routes of transmission of *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* include fecal-oral spread via inges-

tion of contaminated food as the most common route [e.g. pork, pig intestines (chitterlings), soybean curd (tofu), chocolate milk and other dairy products, and shellfish]; consumption of contaminated water supplies; direct person-to-person contact; and animal-to-human contact [1, 2, 103]. Erythrocyte and platelet transfusions contaminated with *Yersinia enterocolitica* have also been described in the USA and Europe, Australia and New Zealand [2, 107–111]. Over the last decade, *Yersinia enterocolitica* has emerged as an increasingly important agent of foodborne gastrointestinal outbreaks in the USA and elsewhere [2, 112]. In addition, several hospital outbreaks of *Yersinia enterocolitica* gastroenteritis have been reported [113–115].

Most cases of yersiniosis occur sporadically without an apparent source. Yersiniosis is most often an age-related infection; disease caused by *Yersinia enterocolitica* is encountered in about two thirds of cases in infants and young children, while *Yersinia pseudotuberculosis* infection occurs most frequently in older children, adolescents and young adults, especially males [105, 106]. Yersiniosis is found more commonly in countries with temperate climates rather than in tropical and subtropical regions. In colder climates, *Yersinia* infections occur especially during winter months.

Clinical Features. Major clinical forms of yersiniosis can be caused by either *Yersinia enterocolitica* or *Yersinia pseudotuberculosis* and include gastroenterocolitis; acute mesenteric adenitis, often with associated terminal ileitis; reactive polyarthritis; erythema nodosum or, rarely, erythema multiforme; and systemic infection [2, 103, 116–120]. The site of human infection depends on a number of variables which include the age of the patient, the serogroup of the organism, and the presence or absence of underlying medical conditions. Gastrointestinal yersiniosis is the most frequently encountered form of *Yersinia enterocolitica*, occurring most commonly in infants and young children [1, 2, 120, 121]. The infection presents as an invasive diarrhoea characterized by fever, abdominal pain, mucus- and blood-containing stools, the presence of fecal leukocytes, and positive stool cultures. The incubation period for intestinal yersiniosis is about 3 to 7 days, and patients shed organisms in feces and remain infectious during the symptomatic period of about 2 to 3 weeks. Convalescent carriage of *Yersinia* in stool of untreated individuals may uncommonly extend for weeks to months in a small percentage of patients [2].

Intestinal yersiniosis may mimic acute appendicitis, presenting with fever, right lower quadrant abdominal pain and leukocytosis, usually without diarrhoea [105, 106, 120]. Macroscopically, there is acute mesenteric lymphadenitis and terminal ileitis, and a histologically normal or only mildly inflamed appendix. The differential diagnosis of acute mesenteric adenitis includes infections caused by *Mycobacterium tuberculosis*,

Salmonella typhi and non-typhoidal salmonellae, *Actinomyces* species, *Entamoeba histolytica* and *Balantidium coli*. Older children and adolescents are particularly prone to developing an acute appendicular syndrome with either *Yersinia enterocolitica* or *Yersinia pseudotuberculosis*, and acute mesenteric adenitis is the most frequent clinical presentation of *Yersinia pseudotuberculosis* [103]. In the evaluation of patients suspected of having acute appendicitis, computed tomographic scanning of the abdomen may help avoid exploratory laparotomy by revealing a normal appendix and enlarged mesenteric lymph nodes [122].

Yersinia are among multiple gastrointestinal and genitourinary pathogens capable of causing a post-infectious, reactive polyarthritis and occasionally a multi-system Reiter's syndrome [2, 103, 104]. The mechanism of reactive arthritis is presumably one of immunological mediation as Gram stains and cultures of synovial fluid from affected joints typically reveal no microorganisms. However, *Yersinia* antigens can be detected in synovial fluid cells from patients with reactive arthritis [123]. Joint inflammation involving the knees, ankles, toes, wrists and fingers usually develops days to months after the onset of acute diarrhoea, and may last from 1 to 12 months before subsiding spontaneously. A small number of patients may have residual low back pain due to sacroiliitis, but ankylosing spondylitis is rare. About 10% to 30% of adult cases of yersiniosis reported from Scandinavia have been complicated by reactive arthritis [120]. Patients possessing the histocompatibility gene HLA-B27 are at particular risk of developing *Yersinia*-related reactive polyarthritis and Reiter's syndrome, although the reasons underlying this predisposition are unclear. Secondary sequelae have generally been reported with *Yersinia enterocolitica* serogroup O:9, and less commonly with serogroup O:3 [2].

Like reactive polyarthritis, erythema nodosum, and less commonly, erythema multiforme, represent immunologically-mediated dermatological manifestations of yersiniosis. Adult women seem to be at particular risk for the development of erythema nodosum. Humoral and cellular responses to *Yersinia* infection have also been found in higher frequency than in control populations in persons with acute anterior uveitis and autoimmune thyroid disease [124–127]. Various *Yersinia enterocolitica* proteins appear to have common antigenicity and cross-reactivity with thyroid and retinal tissue [124–127]. However, immunological and molecular findings do not allow conclusions about a possible causal relationship to *Yersinia* in these conditions. Other rarely reported forms of post-infectious, presumably immune-mediated, extraintestinal yersiniosis include glomerulonephritis and myocarditis [1, 2].

Systemic or septicemic infection with *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* is characterized

by frequent bacteraemia and a metastatic potential for the development of focal suppurative, hematogenously-seeded lesions located in various tissues and organs. Previously described metastatic lesions include hepatic, splenic and renal abscesses [128–141], osteomyelitis and septic arthritis [139–146], meningitis [147], peritonitis [148–152], pulmonary infiltrates, lung abscess and empyema [145, 146, 153–156], mycotic aneurysms [157, 158], endocarditis [159, 160], endophthalmitis [147], and skin and soft tissue infections [161]. Exudative pharyngitis caused by *Yersinia enterocolitica* has also been described in recent years [162, 163].

Several underlying conditions have been associated with extraintestinal yersiniosis including iron overload syndromes (e.g. hemochromatosis, Bantu siderosis, and long-term iron therapy) [140, 150, 164–166] seen in about 60% of cases of systemic *Yersinia* infection; iron chelation therapy [167]; chronic haemolytic anemia such as thalassemia [143, 168, 169] or sickle cell anemia [170]; diabetes mellitus [165]; liver cirrhosis [58, 105, 106, 165]; malignancy [58, 105, 106]; and immunosuppression caused by corticosteroids, cytotoxic chemotherapy or AIDS [1, 2, 151, 171]. *Yersinia enterocolitica* is an iron-dependent bacterium that relies entirely on exogenous iron for growth. Treatment of iron overload syndromes with chelating agents may precipitate yersiniosis, as *Yersinia enterocolitica* can use exogenous siderophores such as desferrioxamine to acquire iron. Iron overload and iron chelation treatment are independent risk factors for systemic yersiniosis. Liver abscesses are a typical feature of yersiniosis associated with iron overload or desferrioxamine therapy, and are almost always multiple in location. Positive blood cultures are seen in over 70% of iron overload-associated hepatic abscesses, and mortality can approach 60% [165]. Systemic bacteraemia and portal vein bacteraemia originating from the gastrointestinal tract, as well as functional impairment of the liver secondary to excessive accumulation of iron in the liver parenchyma and Kupffer cells, are proposed to be the pathogenetic mechanisms in the development of multiple liver abscesses in these patients, and defective phagocytic killing of *Yersinia enterocolitica* by polymorphonuclear leukocytes has recently been documented [172]. Hepatic yersiniosis may disclose prior undetected primary hemochromatosis; when iron overload cannot be documented at the time of diagnosis of the liver abscess, long-term follow-up for determination of increasing iron stores is recommended [158].

Diagnosis. *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* can be isolated using routine blood culture media, and recovery of organisms from enclosed body fluids (e.g. cerebrospinal or peritoneal fluid) or tissue specimens (e.g. mesenteric lymph nodes or liver aspirates) uncontaminated by other microorganisms is not difficult [2, 173]. Cultural isolation of *Yersinia* from stool, however, is hampered by their slow growth and

by overgrowth of other fecal flora. As mentioned above, use of selective CIN or VYE media or Congo Red agar, or enteric media with cold enrichment in buffered saline at 25 °C or 4 °C for 2 to 3 weeks can optimize cultural recovery of *Yersinia* from stool specimens [174, 175]. Biochemical tests such as fermentation of salicin, hydrolysis of esculin and pyrazinamidase positivity can be helpful in differentiating pathogenic from non-pathogenic strains of *Yersinia*.

Serological diagnosis of non-plague yersiniosis may be accomplished through the use of EIA agglutination and immunoblotting techniques or by detection of specific IgG and IgA antibodies to *Yersinia* outer membrane proteins [173, 176, 177]. Although not very widely available commercially, antibody testing may be particularly useful in diagnosing the post-infectious, extraintestinal sequelae of yersiniosis where cultures of stool, blood and other specimens are characteristically negative [1, 2, 177]. Cross-reactive antibodies can be seen with *Salmonella*, *Brucella*, *Escherichia coli* and *Vibrio*, thus giving false-positive serological results. Antigen detection in tissue biopsy specimens or aspirated pus can also be performed using an immunofluorescent antibody [1, 2, 173].

Treatment. The antimicrobial susceptibility of *Yersinia* species is serogroup-specific. *Yersinia enterocolitica* serogroups O:3 and O:9 are generally resistant to penicillin G, ampicillin, carbenicillin and cephalothin, while serogroup O:8 and *Yersinia pseudotuberculosis* are sensitive to ampicillin. A number of antimicrobial agents are active in vitro and clinically against *Yersinia enterocolitica*. These include trimethoprim-sulfamethoxazole, chloramphenicol, newer fluoroquinolones such as ciprofloxacin and ofloxacin, tetracycline hydrochloride, doxycycline, aminoglycosides, imipenem and aztreonam [2, 178–183]. With the exception of third generation cephalosporins such as ceftriaxone and cefotaxime, beta-lactam antibiotics are generally inactive against *Yersinia* due to the chromosomally-mediated production of beta-lactamases (i.e. penicillinases and/or cephalosporinases). Most cases of *Yersinia* enterocolitis and acute mesenteric adenitis in immunocompetent hosts are self-limited, and supportive care including fluid and electrolyte replacement is usually sufficient. For more severe or protracted gastrointestinal or mesenteric nodal infection, especially in immunosuppressed individuals, and for bacteraemic and deep-seated tissue infections, selection of an appropriate antibiotic is dependent not only upon the activity of the drug but also upon its pharmacokinetic penetration. Trimethoprim-sulfamethoxazole, ciprofloxacin and aminoglycosides are effective in the treatment of septicaemic infection and tissue abscesses in liver and spleen. Ciprofloxacin is more appropriate for *Yersinia* osteomyelitis, and trimethoprim-sulfamethoxazole, chloramphenicol or a third-generation cephalosporin are preferable for central nervous infection.

Yersinia pseudotuberculosis is susceptible in vitro to all of the above-mentioned antibiotics active against *Yersinia enterocolitica*, as well as to ampicillin and earlier generation cephalosporins [58]. As for *Yersinia enterocolitica*, mild cases of acute mesenteric lymphadenitis probably do not routinely require antimicrobial therapy. More severe cases of mesenteric adenitis and terminal ileitis, and septicaemic *Yersinia pseudotuberculosis* infections require antimicrobial treatment, although the mortality of *Yersinia pseudotuberculosis* sepsis despite antibiotic therapy may be as high as 75%.

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