Eur J Clin Microbiol Infect Dis (1999) 18:1–15

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	Ornithine Decarboxylase	Urease	Citrate (Simmons) 25 °C	Voges-Proskauer	Indole	Xylose	Trehalose	Sucrose	Rhamnose	Raffinose
Y. pestis	−	−	−	−	−	−	−	+	+	−	(+)	−
Y. pseudotuberculosis	+	−	−	+	−	−	−	+	+	−	+	−
Y. enterocolitica	+	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	−	−
Y. intermedia	+	v	+	+	v	+	v	(+)	+	+	(+)	(+)
Y. frederiksenii	+	v	+	+	v	+	+	(+)	+	+	(+)	−
Y. kristensenii	+	v	+	+	−	−	v	(+)	+	−	−	−
Y. ruokeri	+	v	+	−	(+)	v	−	−	+	−	−	−
Y. aldovae	+	v	+	+	v	+	−	(+)	+	−	+	−
Y. rohdei	+	−	+	+	+	−	−	+	+	+	−	v
Y. mollaretti	+	−	+	+	−	−	−	+	+	+	−	−
Y. bercovieri	+	−	+	+	−	−	−	+	+	+	−	−

[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 *Enterobacteriaciae*.

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-stabile 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 Shibasaburo 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 dependency 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 EJCMID, 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, eithernaturally 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,

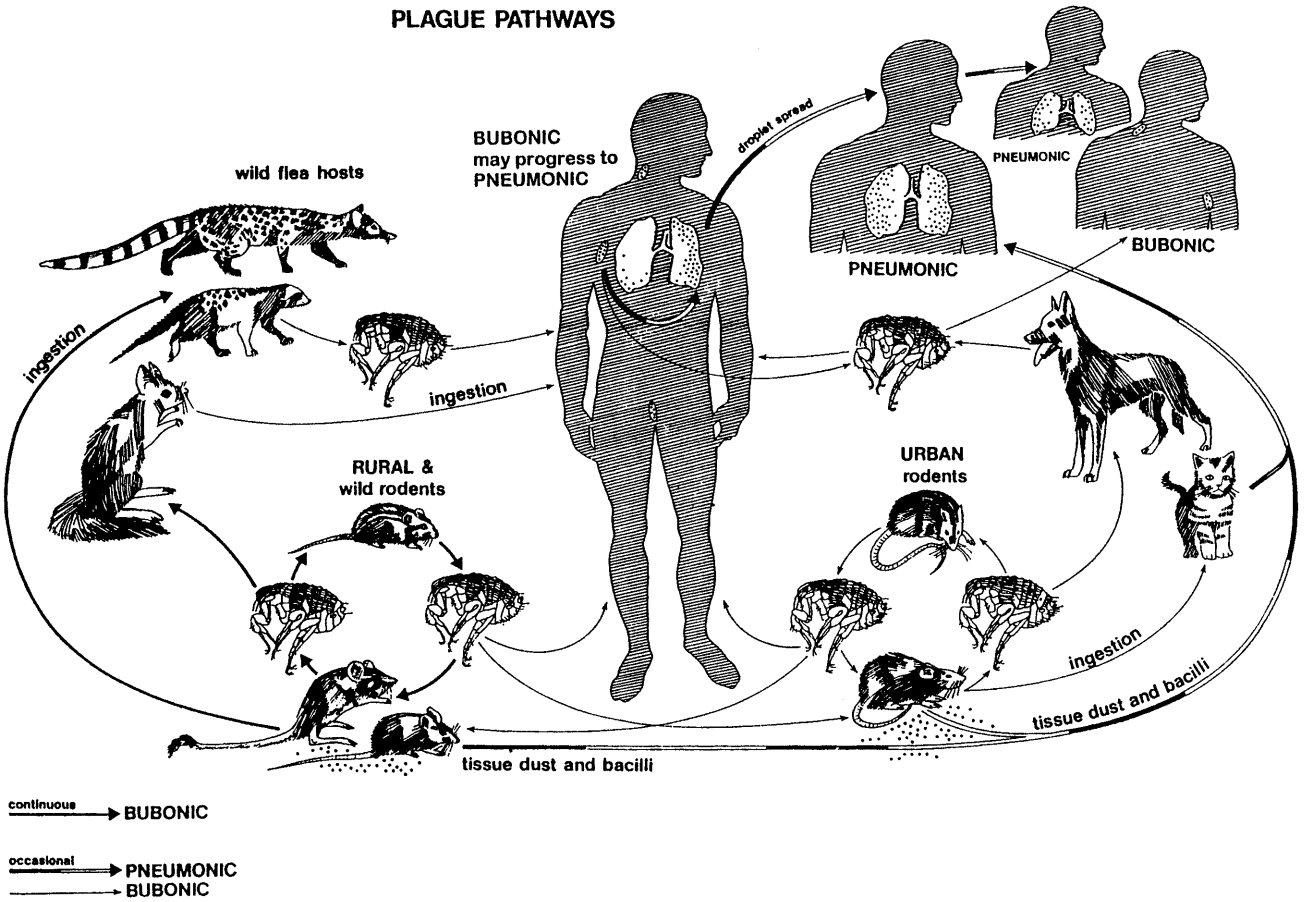

Figure 1 Life cycle of *Yersinia pestis* causing bubonic pneumonic plague

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 Yersinioisis

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 ingestion 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 multisystem 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 Scandanavia 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. hemachromatosis, 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 hemachromatosis; 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%.

Acknowledgements We thank the South African Department of Health for providing Figure 1 on the plague.

References

1. Bottone EJ: *Yersinia enterocolitica*: A panoramic view of a charismatic microorganism. CRC Critical Reviews in Microbiology (1977) 5:211–241
2. Bottone EJ: *Yersinia enterocolitica:* the charisma continues. Clinical Microbiology Reviews (1997) 10:257–276
3. Bercovier H, Mollaret HH: Genus XIV *Yersinia* van Loghem 1944, 15AL. In: Krieg NR, Holt JG (eds): Bergey's Manual of Systematic Bacteriology. Williams & Wilkins, Baltimore (1984) pp 498–506
4. Kapperud G: Studies on the pathogenicity of *Yersinia enterocolitica* and *Yersinia enterocolitica*-like bacteria. Enterotoxin production at 221C and 371C by environmental and human isolates from Scandinavia. Acta Pathologica Microbiologica et Scandinavica (1980) 88:287–291
5. Rucker RR: Redmouth disease in rainbow trout *(Salmo gairdneri).* Bulletin of the Office of International Epizoology (1966) 65:825–830
6. Bercovier H, Steigerwalt AG, Guiyoule A, Huntley-Carter G, Brenner DJ: *Yersinia aldovae* (formerly *Yersinia enterocolitica*-like group X2) a new species of *Enterobacteriaceae* isolated from aquatic ecosystems. International Journal of Systematic Bacteriology (1984) 34:166–172
7. Aleksic S, Steigerwalt AG, Bockemühl J, Huntley-Carter GP, Brenner DJ: *Yersinia rohdei* sp *nov* isolated from human and dog feces and surface water. International Journal of Systematic Bacteriology (1987) 37:327–332
8. Wauters G, Janssens M, Steigerwalt AG, Brenner DJ: *Yersinia mollaretii,* sp *nov* and *Yersinia bercovieri* sp *nov* formerly called *Yersinia enterocolitica* biogroups 3A and 3B. International Journal of Systematic Bacteriology (1988) 38:324–429
9. Bercovier H, Brault J, Barré N, Treignier M, Alonso JM, Mollaret HH: Biochemical, serological and phage typing characteristics of 459 *Yersinia* strains isolated from a terrestrial ecosystem. Current Microbiology (1978) 1:353–357
10. Barrow GI, Feltham RKA (eds): Cowan and Steel's manual for the identification of medical bacteria. Cambridge University Press, Cambridge (1993) pp 146–148
11. Knapp W, Thal E: Differentiation *Yersinia enterocolitica* by biochemical reactions. Contributions in Microbiology and Immunology (1973) 2:10–16
12. Wauters G, Kandolo K, Janssens M: Revised biogrouping scheme of *Yersinia enterocolitica.* Contributions in Microbiology and Immunology (1987) 9:14–21
13. Cornelis G, Laroche Y, Ballingad G, Sory M, Wauters G: *Yersiniae enterocolitica,* a primary model for invasiveness. Reviews in Infectious Diseases (1987) 9:64–87
14. Maeland JA, Digranes A: Common enterobacterial antigen in *Yersinia enterocolitica.* Acta Pathologica Microbiologica et Scandinavica Section B (1975) 83:382–386

15. Aleksic S: Occurrence of *Yersinia enterocolitica* antigens 0:3, 0:9 and 0:8 in different *Yersinia* species, their corresponding H antigens and origin. Contributions in Microbiology and Immunology (1995) 13:89–92
16. Brubaker RR: Factors promoting acute and chronic diseases caused by yersiniae. Clinical Microbiology Reviews (1991) 4:309–324
17. Gemski P, Lazere JR, Casey T: Plasmid associated with pathogenicity and calcium dependency of *Yersinia enterocolitica.* Infection and Immunity (1980) 27:682–695
18. Gemski P, Lazere JR, Casey T, Wohlhieter I: Presence of a virulence-associated plasmid in *Yersinia pseudotuberculosis.* Infection and Immunity (1980) 28:1044–1047
19. Thal E, Knapp W: A revised antigenic scheme of*Yersinia pseudotuberculosis.* Progress in Immunologic Standardization (1971) 15:219–222
20. Lawton WD, Fukui GM, Surgalla MJ: Studies on the antigens of *Pasteurella pestis* and *Pasteurella pseudotuberculosis.* Journal of Immunology (1960) 84:475–479
21. Barber C, Eylan E: Immunochemical relations of *Yersinia enterocolitica* with *Yersinia pestis* and their connection with other *Enterobacteriaceae.* Microbios Letter (1976) 3:25–29
22. Heesemann J, Eggers C, Schröder J: Serological diagnosis of yersiniosis by immunoblot technique using virulence-associated antigen of enteropathogenic yersiniae. Contributions in Microbiology and Immunology (1987) 9:285–289
23. Knapp W: Serologische kreuzreaktionen zwischen *Pasteurella pseudotuberculosis* (Syn *Yersinia pseudotuberculosis), Escherichia coli* und *Enterobacter cloacae.* Progress in Immunological Standardization (1968) 2:179–186
24. Wauters G, Le Minor L, Chalon A, Lassar J: Supplement au schema antigénique de *Yersinia enterocolitica.* Annals of the Institute Pasteur (1972) 122:951–956
25. Hurvell B, Lindberg AA: Serological cross-reactions between *Brucella* species and *Yersinia enterocolitica* type 9. Contributions in Microbiology and Immunology (1973) 2:159–168
26. World Health Organization: Plague - India. Weekly Epidemiological Record (1995) 70:35
27. Barreto A, Aragon M, Epstein PR: Bubonic plague outbreak in Mozambique. Lancet (1995) 345:983–984
28. World Health Organization: Human plague in 1993. Weekly Epidemiological Record (1995) 70:45–48
29. Christie AB, Corbel MJ: Plague and other yersinial diseases. In: Parker MT, Collier LH (eds): Topley and Wilson's principles of bacteriology, virology and immunity. Edward Arnold, London (1990) vol. 3, pp 400–408
30. Perry RD, Fetherston JD: *Yersinia pestis* – etiologic agent of plague. Clinical Microbiology Reviews (1997) 10:35–66
31. Pollitzer R: Plague. World Health Organization, Monograph Series, No. 22, WHO, Geneva (1954) pp 1–698
32. Twigg G: Bubonic plague: doubts and diagnoses. Journal of Medical Microbiology (1995) 42:383–385
33. Twigg G: Plague in India. Lancet (1995) 345:258
34. Solomon T: Alexandre Yersin and the plague bacillus. Journal of Tropical Medicine and Hygiene (1995) 98:209–212
35. Gross L: How the plague bacillus and its transmission through fleas were discovered: reminiscences from my years at the Pasteur Institute in Paris. Proceedings of the National Academy of Sciences of the USA (1995) 92:7609–7611
36. Butler T: Plague and other *Yersinia* infections. In: Greenough WB, Merigan TC (eds): Current topics in infectious disease. Plenum, New York (1983) pp 1–220
37. Corbel MJ: *Yersinia.* In: Parker MT, Collier LH (eds): Topley and Wilson's principles of bacteriology, virology and immunity. Edward Arnold, London (1990) vol. 2, pp 496–510
38. Bahmanyar M, Cavanaugh DC: Plague Manual. World Health Organization, Geneva (1976) pp 1–76
39. Devignat R: Variétés de léspèce *Pasteurella pestis.* Nouvelle hypothèse. Bulletin de l'Organisation Mondial de la Santé (1951) 4:247–263
40. Guiyoule A, Rasoamanana B, Buchrieser C, Michel P, Chanteau S, Carniel E: Recent emergence of new variants of *Yersinia pestis* in Madagascar. Journal of Clinical Microbiology (1997) 35:2826–2833
41. Isaäcson M: A review of some recent developments in human plague with special reference to southern Africa. Ecology of Disease (1984) 2:161–171
42. Guiyoule A, Grimont F, Iteman I, Grimont PAD, Lefèvre M, Carniel E: Plague pandemics investigated by ribotyping of *Yersinia pestis* strains. Journal of Clinical Microbiology (1994) 32:634–641
43. Cavanaugh DC: Specific effect of temperature upon transmission of the plague bacillus by the oriental rat flea, *Xenopsylla cheopis.* American Journal of Tropical Medicine and Hygiene (1971) 20:264–273
44. McDonough KA, Falkow S: A *Yersinia pestis*-specific DNA fragment encodes temperature-dependent coagulase and fibrinolysin-associated phenotypes. Molecular Microbiology (1989) 3:767–775
45. Chanteau S, Ratsifasoamanana L, Rasoamanana B, Rahalison L, Randriambelosoa J, Roux J, Rabeson D: Plague, a reemerging disease in Madagascar. Emerging Infectious Diseases (1998) 4:101–104
46. Butler G, de Graaf P, van de Wijk J: Urban plague in Zaire. Lancet (1994) 343:536
47. Rasolomaharo M, Rasoamanana B, Andrianirina Z, Buchy P, Rakotoarimanana N, Chanteau S: Plague in Majunga, Madagascar, Lancet (1995) 346:1234
48. Williams JE, Cavanaugh DC: Chronic infections in laboratory rodents from inoculation of nonencapsulated plague bacilli *(Yersinia pestis).* Experimentia (1983) 39:408
49. Friedlander AM, Welkos SL, Worsham PL, Andrews GP, Heath DG, Anderson GW, Pitt MLM, Estep J, Davis K: Relationship between virulence and immunity as revealed in recent studies of the F1 capsule of *Yersinia pestis*. Clinical Infectious Diseases (1995) 21, Supplement 2:178–181
50. Rosqvist R, Skurnik M, Wolf-Watz H: Increased virulence of *Yersinia pseudotuberculosis* by two independent mutations. Nature (1988) 334:522–525
51. Suchkov IG, Khudiakov IV, Emel'ianenko EN, Levi MI, Pushkareva VI, Suchko II, Litvin VI, Kulesh EV, Zotova RS, Gintsburg AL: The possibility of preserving the causative agent of plague in soil in resting (nonculturable) form (in Russian). Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii (1997) 4:42–46
52. Isaäcson M, Arntzen L, Taylor P: Susceptibility of members of the *Mastomys natalensis* species complex to experimental infection with *Yersinia pestis.* Journal of Infectious Diseases (1981) 144:80
53. Arntzen L, Wadee AA, Isaäcson M: Immune responses of two *Mastomys* sibling species to *Yersinia pestis.* Infection and Immunity (1991) 59:1966–1971
54. Centers for Disease Control and Prevention: Human plague – United States, 1993–1994. Morbidity and Mortality Weekly Report (1994) 43:242–246
55. Centers for Disease Control and Prevention: Fatal human plague – Arizona and Colorado, 1996. Morbidity and Mortality Weekly Report (1997) 46:617–620
56. Isaäcson M, Levy D, Pienaar BJ, Bubb HD, Louw JA, Genis DK: Unusual cases of human plague in southern Africa. South African Medical Journal (1973) 47:2109–2113
57. Doll JM, Zietz TS, Ettestad P, Bucholtz AL, Davis T, Gage K: Cat-transmitted fatal pneumonic plague in a person who travelled from Colorado to Arizona. American Journal of Tropical Medicine and Hygiene (1994) 51:109–114
58. Butler T: *Yersinia* infections: centennial of the discovery of the plague bacillus. Clinical Infectious Diseases (1994) 19:655–663

59. Crook LD, Tempest B: Plague. A clinical review of 27 cases. Archives of Internal Medicine (1992) 152:1253–1256
60. Butler T: A clinical study of bubonic plague. Observations of the 1970 Vietnam epidemic with emphasis on coagulation studies, skin histology and electrocardiograms. American Journal of Medicine (1972) 53:268–276
61. Butler T, Levin J, Ngoc Linh N, Minh Chau D, Adickman M: *Yersinia pestis* in Vietnam. II. Quantitative blood cultures and detection of endotoxin in the cerebrospinal fluid of patients with meningitis. Journal of Infectious Diseases (1976) 133:493–499
62. Isaäcson M, Jamison JR: Epidemiological and clinical aspects of plague in southern Africa. In: Gear JHS (ed): Medicine in a tropical environment. Proceedings of the International Symposium, AA Balkema, Cape Town (1977) pp 479–486
63. Marshall JD, Quy DV, Gibson FL: Asymptomatic pharyngeal plague in Vietnam. American Journal of Tropical Medicine and Hygiene (1967) 16:175–177
64. McClean KL: An outbreak of plague in northwestern province, Zambia. Clinical Infectious Diseases (1995) 20:650–652
65. Arntzen L, Frean J: The laboratory diagnosis of plague. Belgian Journal of Zoology (1997) 127, Supplement 1:91–96
66. Wilmoth BA, Chu MC, Quan TJ: Identification of *Yersinia pestis* by BBL Crystal enteric nonfermenter identification system. Journal of Clinical Microbiology (1996) 34:2829–2830
67. Williams JE, Arntzen L, Isaäcson M: Advantages and use of laboratory-reared African multimammate mice *(Mastomys coucha)* in the diagnosis of plague. Annales de la Societe Belge de Médecine Tropicale (1982) 62:247–251
68. Rasoamanana B, Rahalison L, Raharimanana C, Chanteau S: Comparison of *Yersinia* CIN agar and mouse inoculation assay for the diagnosis of plague. Transactions of the Royal Society of Tropical Medicine and Hygiene (1996) 90:651
69. Chen TH, Meyer KF: Studies on immunization against plague. VII. A haemagglutination test with the protein fraction of *Pasteurella pestis.* Journal of Immunology (1954) 72:282–298
70. Williams JE, Arntzen L, Robinson DM, Cavanaugh DC, Isaäcson M: Comparison of passive haemagglutination and enzyme-linked immunosorbent assay for serodiagnosis of plague. Bulletin of the World Health Organization (1982) 60:777–781
71. Shepherd AJ, Leman PA, Hummitzsch DE, Swanepoel R: A comparison of serological techniques for plague surveillance. Transactions of the Royal Society of Tropical Medicine and Hygiene (1984) 78:771–773
72. Rasoamanana B, Leroy F, Boisier P, Rasolomaharo M, Buchy P, Carniel E, Chanteau S: Field evaluation of an immunoglobulin G anti-F1 enzyme-linked immunosorbent assay for serodiagnosis of human plague in Madagascar. Clinical and Diagnostic Laboratory Immunology (1997) 4:587–591
73. Williams JE, Arntzen L, Tyndal GL, Isaäcson M: Application of enzyme immunoassays for the confirmation of clinically suspect plague in Namibia, 1982. Bulletin of the World Health Organization (1986) 64:745–752
74. Cao LK, Anderson GP, Ligler FS, Ezzell J: Detection of *Yersinia pestis* fraction 1 antigen with a fibre optic biosensor. Journal of Clinical Microbiology (1995) 33:336–341
75. Winter CC, Cherry WB, Moody MD: An unusual strain of *Pasteurella pestis* isolated from a fatal human case of plague. Bulletin of the World Health Organization (1960) 23:408–409
76. Devdariani ZL, Fedorova VA, Solodovnikov NS, Plotnikov OP, Shuligina IV: An immunoenzyme test system for the identification of typical and atypical strains of the plague microbe. Meditsinskaia Parazitologiia i Parazitarnya Bolezni (1997) 1:31–33
77. Campbell J, Lowe J, Walz S, Ezzell J: Rapid and specific identification of *Yersinia pestis* by using a nested polymerase chain reaction procedure. Journal of Clinical Microbiology (1993) 31:758–759
78. Hinnebusch J, Schwan TG: New method for plague surveillance using polymerase chain reaction to detect *Yersinia pestis* in fleas. Journal of Clinical Microbiology (1993) 31:1511–1514
79. Norkina OV, Kulichenko AN, Gintsburg AL, Tuchkov IV, Popov YA, Aksenov MU, Drosdov IG: Development of a diagnostic test for *Yersinia pestis* by the polymerase chain reaction. Journal of Applied Bacteriology (1994) 76:240–245
80. Meyer KF: Modern therapy of plague. Journal of the American Medical Association (1950) 144:982–985
81. Centers for Disease Control and Prevention: Prevention of plague: recommendations of the Advisory Committee on Immunization Practices. Morbidity and Mortality Weekly Report (1996) 45(RR-14):1–15
82. Benenson AS (ed): Plague. In: Control of Communicable Diseases Manual. American Public Health Association, Washington, DC (1995) pp 353–358
83. Galimand M, Guiyoule A, Gerbaud G, Rasoamanana B, Chanteau S, Carniel E, Courvalin P: Multidrug resistance in *Yersinia pestis* mediated by a transferable plasmid. New England Journal of Medicine (1997) 337:677–780
84. Frean JA, Arntzen L, Capper T, Bryskier A, Klugman KP: In vitro activities of 14 antibiotics against 100 human isolates of *Yersinia pestis* from a southern African plague focus. Antimicrobial Agents and Chemotherapy (1996) 40:2646–2647
85. Smith MD, Vinh DX, Hoa NTT, Wain J, Thung D, White NJ: In vitro antimicrobial susceptibilities of strains of *Yersinia pestis.* Antimicrobial Agents and Chemotherapy (1995) 39:2153–2154
86. Hoogkamp-Korstanje JAA: The possible role of quinolones in yersiniosis. Drugs (1987) 34:134–138
87. Russell P, Eley SM, Bell DL, Manchee RJ, Titball RW: Doxycycline or ciprofloxacin prophylaxis and therapy against experimental *Yersinia pestis* infections in mice. Journal of Antimicrobial Chemotherapy (1996) 37:769–774
88. Russell P, Eley SM, Green M, Stagg AJ, Taylor RR, Nelson M, Beedham RJ, Bell DL, Rogers D, Whittington D, Titball RW: Efficacy of doxycycline and ciprofloxacin against experimental *Yersinia pestis* infection. Journal of Antimicrobial Chemotherapy (1988) 41:301–305
89. Bonacorsi SP, Scavizzi MR, Guiyoule A, Amouroux JH, Carniel E: Assessment of a fluoroquinolone, three beta-lactams, two aminoglycosides, and a cycline in treatment of murine *Yersinia pestis* infection. Antimicrobial Agents and Chemotherapy (1994) 38:481–486
90. Byrne WR, Welkos S, Pitt ML, Davis KJ, Brueckner RP, Ezzell JW, Nelson GO, Vaccaro JR, Battersby LC, Friedlander AM: Antibiotic treatment of experimental pneumonic plague in mice. Antimicrobial Agents and Chemotherapy (1998) 42:675–681
91. Ryzhko IV, Shcherbaniuk AI, Samokhodkina ED, Tsuraeva RI, Mishnikin BN, Kasatkina IV, Zhigalova TA: Virulence of rifampicin and quinolone resistant mutants of strains of plague microbe with Fra^+ and Fra^- phenotypes. Antibiotiki i Khimioterapiia (1994) 39:32–36
92. Anderson GW, Worsham PL, Bolt CR, Andrews GP, Welkos SL, Friedlander AM, Burans JP: Protection of mice from fatal bubonic and pneumonic plague by passive immunization with monoclonal antibodies against the F1 protein of *Yersinia pestis.* American Journal of Tropical Medicine and Hygiene (1997) 56:471–473
93. Williamson ED, Eley SM, Stagg AJ, Green M, Russell P, Titball RW: A sub-unit vaccine elicits IgG in serum, spleen cell cultures and bronchial washings and protects immunized animals against pneumonic plague. Vaccine (1997) 15:1079–1084

94. Leary SEC, Griffin KF, Garmory HS, Williamson ED, Titball RW: Expression of an F1/V fusion protein in attenuated *Salmonella typhimurium* and protection of mice against plague. Microbial Pathogenesis (1997) 23:167–179
95. Isaäcson M: Plague and cholera surveillance in southern Africa. South African Medical Journal (1986) 70, Supplement to 11 Oct issue: 43–46
96. Shepherd AJ, Leman PA: Bacterial surveillance of South African rodents. South African Journal of Science (1985) 81:302–308
97. Rust JH, Cavanaugh DC, O'Shita R, Marshall JD: The role of domestic animals in the epidemiology of plague. I. Experimental infection of dogs and cats. Journal of Infectious Diseases (1971) 124:522–526
98. Cruikshank JG, Gordon DH, Taylor P, Naim H: Distribution of plague in Rhodesia as demonstrated by serological methods. Central African Journal of Medicine (1976) 22:127–130
99. Fritz CL, Dennis DT, Tipple MA, Campbell GL, McCance CR, Gubler DJ: Surveillance for pneumonic plague in the United States during an international emergency: a model for control of imported emerging diseases. Emerging Infectious Diseases (1996) 2:30–36
100. Mavalankar DV: Plague in India. Lancet (1994) 344:1298
101. Kumar S: Confirmation of Indian plague outbreak? Lancet (1995) 345:443
102. Cook GC: Plague in India: an inappropriate media response. Current Opinions in Infectious Diseases (1994) 639–643
103. Benenson AS: Yersiniosis. In: Control of Communicable Diseases Manual. American Public Health Association Washington, DC (1995) pp 524–526
104. Cover TL, Aber RC: *Yersinia enterocolitica.* New England Journal of Medicine (1989) 321:16–24
105. Butler T: *Yersinia enterocolitica* infections. In: Strickland GT (ed): Hunters Tropical Medicine. WB Saunders Co, Philadelphia (1994) pp 384–385
106. Butler T: *Yersinia* species. In: Mandell GL, Bennett JE, Douglas RG (eds): Principles and Practice of Infectious Diseases. John Wiley, New York (1979) pp 1797–1800
107. Centers for Disease Control and Prevention: Update – *Yersinia enterocolitica* bacteremia and endotoxin shock associated with red blood cell transfusions – United States, 1991. Morbidity and Mortality Weekly Report (1991) 40:176–178
108. Centers for Disease Control and Prevention: Red blood cell transfusion contaminated with *Yersinia enterocolitica* B United States, 1991–1996. Morbidity and Mortality Weekly Report (1997) 46:553–555
109. Kuehnert MJ, Jarvis WR, Schaffer DA, Chaffin DJ: Platelet transfusion reaction due to *Yersinia enterocolitica.* Journal of the American Medical Association (1997) 20:278
110. Theakston EP, Morris AJ, Streat SJ, Baker BW, Woodfield DG: Transfusion-transmitted *Yersinia enterocolitica* infection in New Zealand. Australian and New Zealand Journal of Medicine (1997) 27:62–67
111. Gibb AP, Poling N, Murphy WG: Failure to kill *Yersinia enterocolitica* by plasma diluted to the concentration found in red cell units. Journal of Clinical Pathology (1996) 49:434–436
112. Ostroff S: *Yersinia* as an emerging infection: epidemiologic aspects of yersiniosis. Contributions in Microbiology and Immunology (1995) 13:5–10
113. Toivanen P, Toivanen A, Olkkonen L, Aantaa S: Hospital outbreak of *Yersinia enterocolitica* infection. Lancet (1973) i:801–803
114. Ratnam S, Mercer E, Picco B, Parsons S, Butler R: A nosocomial outbreak of diarrheal disease due to *Yersinia enterocolitica* serotype O:5 biotype 1. Journal of Infectious Diseases (1982) 145:242–247
115. McIntyre M, Nnochiri E: A case of hospital-acquired *Yersinia enterocolitica* gastroenteritis. Journal of Hospital Infection (1986) 7:299–301
116. alMohsen I, Luedtke G, English BK: Invasive infections caused by *Yersinia enterocolitica* in infants. Pediatric Infectious Diseases Journal (1997) 16:253–255
117. Lee LA, Taylor J, Carter GP, Quinn B, Farmer JJ III, Tauxe RV: *Yersinia enterocolitica* O:3:an emerging cause of pediatric gastroenteritis in the United States. Journal of Infectious Diseases (1991) 163:660–663
118. Jensen KT, Arpi M, Frederiksen W: *Yersinia enterocolitica* septicemia in Denmark 1972–1991. Contributions in Microbiology and Immunology (1995) 13:11–15
119. Lee JH, Rhee PL, Lee JK, Lee KT, Son HJ, Kim JJ, Koh KC, Paik SW, Lee WJ, Lim HK, Rhee JC: The etiology and clinical characteristics of mesenteric adenitis in Korean adults. Journal of Korean Medical Sciences (1997) 12:105–110
120. Stolk-Engelaar VM, Hoogkamp-Korstanje JA: Clinical presentation and diagnosis of gastrointestinal infections by *Yersinia enterocolitica* in 261 Dutch patients. Scandinavian Journal of Infectious Diseases (1996) 28:571–575
121. Kapperud G, Ostroff SM, Nesbakken T, Hutwagner LC, Bean NH, Lassen J, Taux RV: Risk factors for sporadic *Yersinia enterocolitica* infections in Norway. Contributions in Microbiology and Immunology (1995) 13:25–28
122. Rao PM, Rheu JT, Novelline RA, Mostafavi AA, McCabe CJ: Effect of computed tomography of the appendix on treatment of patients and use of hospital resources. New England Journal of Medicine (1998) 338:141–146
123. Granfors K, Jalkanen S, von Essen R, Lahesman-Rantala R, Isomaki O, Pekkola-Heino K, Toivanen A: *Yersinia* antigens in synovial-fluid cells from patients with reactive arthritis. New England Journal of Medicine (1989) 320:216–221
124. Tanaka T, Yamakawa N, Yamaguchi H, Okada AA, Konoeda Y, Ogawa T, Kamiya S, Usui M: Common antigenicity between *Yersinia enterocolitica*-derived heat shock protein and the retina, and its role in uveitis. Ophthalmic Research (1996) 8:284–288
125. Careless DJ, Chiu B, Rabinovitch T, Wade J, Inman RD: Immunogenetic and microbial factors in acute anterior uveitis. Journal of Rheumatology (1997) 24:102–108
126. Wenzel BE, Peters A, Zubaschev I: Bacterial virulence antigens and the pathogenesis of autoimmune thyroid diseases (AITD). Experimental and Clinical Endocrinology and Diabetes (1996) 104, Supplement 4:75–78
127. Zhang H, Kaur I, Niesel DW, Seetharamaiah GS, Peterson JW, Prabakar BS, Klimpel GR: Lipoprotein from *Yersinia enterocolitica* contains epitopes that cross-react with the human thyrotropin receptor. Journal of Immunology (1997) 158:1976–1982
128. Beeching NJ, Hart HH, Synek BJ, Bremner DA: A patient with hemosiderosis and multiple liver abscesses due to *Yersinia enterocolitica.* Pathology (1985) 17:530–532
129. Ismail MHA, Hodkinson HJ, Patel M, Koornhof HJ: Multiple liver abscesses caused by *Yersinia enterocolitica:* a case report. South African Medical Journal (1987) 72:291–292
130. Leighton PM, MacSween HM: *Yersinia* hepatic abscesses subsequent to long-term iron therapy. Journal of the American Medical Association (1987) 257:964–965
131. Leyman P, Baert AL, Marchal G, Fevery J: Ultrasound and CT of multifocal liver abscesses caused by *Yersinia enterocolitica.* Journal of Computer Assisted Tomography (1989) 13:913–915
132. Mantse L, West J, Cosman HH, Mullens JE: Liver abscess due to *Yersinia enterocolitica.* Canadian Medical Association Journal (1978) 119:992–993
133. Rabson AR, Koornhof HJ, Notman J, Maxwell WG: Hepatosplenic abscesses due to *Yersinia enterocolitica.* British Medical Journal (1972) 4:341
134. Ryan ME, Burke PJ, Novinger QT, Shah NR: Hepatic abscesses due to *Yersinia enterocolitica.* American Journal of Diseases of Children (1979) 133:961–962

135. Viteri AL, Howard PH, May JL, Ramesh GS, Roberts JW: Hepatic abscess due to *Yersinia enterocolitica* without bacteremia. Gastroenterology (1981) 81:592–593
136. Fothergill J, Mulira AEJL, Skirrow MB: Liver abscess due to an unusual strain of *Yersinia enterocolitica.* Postgraduate Medicine (1982) 58:371–372
137. Hopwood AH, Riddle BW: *Yersinia enterocolitica* hepatic abscesses. Journal of the Kentucky Medical Association (1986) 84:13–15
138. Khanna R, Levendoglu H: Liver abscess due to *Yersinia enterocolitica*: case report and review of the literature. Digestive Diseases and Sciences (1989) 34:636–639
139. Nemoto H, Murabayashi K, Kawamura Y, Sasaki K, Makata N, Kinoshita M, Furube M: Multiple liver abscesses secondary to *Yersinia enterocolitica.* Internal Medicine (1992) 31:1125–1127
140. Schuchmann M, Helmberger T: Images in hepatology. Hepatic abscesses in a patient with yersiniosis and iron overload. Journal of Hepatology (1997) 26:215
141. Olesen LL, Ejlertsen T, Paulsen SM, Knudsen PR: Liver abscesses due to *Yersinia enterocolitica* in patients with haemochromatosis. Journal of Internal Medicine (1989) 225:351–354
142. Thirumoothi MC, Dajani AS: *Yersinia enterocolitica* osteomyelitis in a child. American Journal of Diseases of Children (1978) 132:578–580
143. Hewstone AS, Davidson GP: *Yersinia enterocolitica* septicaemia with arthritis in a thalassaemic child. Medical Journal of Australia (1972) 1:1035–1038
144. Spira TJ, Kabins SA: *Yersinia enterocolitica* septicemia with septic arthritis. Archives of Internal Medicine (1976) 136:1305–1308
145. Sebes JI, Maybry EH, Rabinowitz JG: Lung abscess and osteomyelitis of rib due to *Yersinia enterocolitica.* Chest (1976) 69:546–548
146. Tallor BG, Zafarzai MZ, Humphries DW, Manfredi F: Nodular pulmonary infiltrate and septic arthritis associated with *Yersinia enterocolitica* bacteremia. American Review of Respiratory Disease (1977) 116:525–529
147. Sonnewirth AC: Bacteremia with and without meningitis due to *Pseudomonas enterocolitica, Edwardsiella tarda, Commamonas terrigena,* and *Pseudomonas maltophilia*. Annals of the New York Academy of Sciences (1980) 174:444–502
148. Boemi G, Chiesa C, Diorenzo M, Patti G, Marrocco G, Midulla M: *Yersinia enterocolitica* peritonitis in idiopathic hemochromatosis. Gastroenterology (1984) 87:1372–1375
149. De Cuenca-Morn B, Solis-Herruzo JA, Moreno D, Guijarro C, Gentil AA, Castellano G: Spontaneous bacterial peritonitis due to *Yersinia enterocolitica* in secondary alcoholic hemochromatosis. Journal of Clinical Gastroenterology (1989) 11:675–678
150. Capron J-P, Capron-Chivrac D, Tossou H, Delamarre J, Eb F: Spontaneous *Yersinia enterocolitica* peritonitis in idiopathic hemochromatosis. Gastroenterology (1984) 87:1372–1375
151. Flament-Saillour M, de Trachis P, Risbourg M, Nordmann P: *Yersinia enterocolitica* peritonitis in a patient infected with the human immunodeficiency virus. Clinical Infectious Diseases (1996) 18:655–656
152. Reed RP, Robins-Browne RM, Williams ML: *Yersinia enterocolitica* peritonitis. Clinical Infectious Diseases (1997) 254:1468–1469
153. Bigler RD, Atkins RR, Wing EJ: *Yersinia enterocolitica* lung infection. Archives of Internal Medicine (1981) 141:1529–1530
154. Clarridge J, Roberts C, Peters J, Musher D: Sepsis and empyema caused by *Yersinia enterocolitica.* Journal of Clinical Microbiology (1983) 17:936–938
155. Portnoy D, Martinez LA: *Yersinia enterocolitica* septicemia with pneumonia. Canadian Medical Association Journal (1979) 120:61–62
156. Sodervik H, Syrjala H, Raisanen S: lnterstitial pneumonia and sepsis by *Yersinia enterocolitica* serotype 3. Scandinavian Journal of Infectious Diseases (1986) 18:241–243
157. Donald K, Woodson J, Hudson H, Menzoian JO: Multiple mycotic pseudoaneurysms due to *Yersinia enterocolitica.* Annals of Vascular Surgery (1996) 10:573–577
158. Plotkin GR, O'Rourke JN: Mycotic aneurysm due to *Yersinia enterocolitica.* American Journal of Medical Sciences (1981) 28:35–42
159. Appelbaum JS, Wilding G, Morse LJ: *Yersinia enterocolitica* endocarditis. Archives of Internal Medicine (1983) 143:2150–2151
160. Urbano-Marquez A, Estruch R, Agusti A, Jimenez De Ant MT, Ribalta T, Grau JM, Rozman C: Infectious endocarditis due to *Yersinia enterocolitica.* Journal of Infectious Diseases (1983) 148:910
161. Abramovitch H, Butas CA: Septicemia due to *Yersinia enterocolitica.* Canadian Medical Association Journal (1973) 109:1112–1115
162. Rose FB, Camp CJ, Antes EJ: Family outbreak of fatal *Yersinia enterocolitica* pharyngitis. American Journal of Medicine (1987) 82:636–637
163. Tackett CO, Davis BR, Carter GP, Randoff JR, Cohen ML: *Yersinia enterocolitica* pharyngitis. Annals of Internal Medicine (1983) 99:40–42
164. Cauchie P, Vincken W, Peeters O, Charels K: Hemochromatosis and *Yersinia enterocolitica* septicemia. Digestive Diseases and Sciences (1987) 32:1438
165. Vadillo MN, Corbello X, Pac V, Fernandez-Viladrich P, Pujol R: Multiple liver abscesses due to *Yersinia enterocolitica* discloses primary hemachromatosis: three case reports and review. Clinical Infectious Diseases (1994) 18:938–941
166. Shibuya H, Ando M, Kuroda K, Naoe S, Maruyama T: Fatal *Yersinia enterocolitica* septicemia complicated by unique hemosiderosis: a case report. Acta Patholologica of Japan (1988) 381:1461–1472
167. Robins-Browne RM, Prpic JK: Desferrioxamine and systemic yersiniosis. Lancet (1983) 2:1372
168. Periola R, Petracca M, De Rinaldis C, Perrone A, Pizzolante MA: Severe case of *Yersinia enterocolitica* infection in a thalassemic patient. Italian Journal of Gastroenterology and Hepatology (1997) 29:82–83
169. Cherchi GB, Cossellu S, Pacifico L, Gallisai D, Ranucci A, Zanetti S, Fadda G, Chiesa C: Incidence and outcome of *Yersinia enterocolitica* infection in thalassemic patients. Contributions in Microbiology and Immunology (1995) 13:16–18
170. Stoddard JJ, Wechsler DS, Natatro JP, Casella JF: *Yersinia enterocolitica* infection in a patient with sickle cell disease after exposure to chitterlings. American Journal of Pediatric Hematology and Oncology (1994) 16:153–155
171. Cohen JI, Rodday P: *Yersinia enterocolitica* bacteremia in a patient with the acquired immunodeficiency syndrome. American Journal of Medicine (1989) 86:254–255
172. Cantinieaux B, Boelaert J, Hariga C, Fondu P: Impaired neutrophil defense against *Yersinia enterocolitica* in patients with iron overload who are undergoing dialysis. Journal of Laboratory and Clinical Medicine (1988) 111:524–528
173. Stolk-Englaar V, Hoogkamp-Korstanje J: Diagnosis in *Yersinia enterocolitica* infection. Contributions in Microbiology and Immunology (1995) 13:137–139
174. Prpic JK, Robins-Browne RM, Davey B: Differentiation between virulent and avirulent *Yersinia enterocolitica* isolates by using Congo red agar. Journal of Clinical Microbiology (1983) 18:486–490
175. Schiemann DC: Synthesis of a selective agar medium for *Yersinia enterocolitica.* Canadian Journal of Microbiology (1979) 25:1298–1304

176. Kihlstrom E, Foberg U, Bengtsson A, Fryden A, Svenungsson B, Schvarcz R, Lindblom B, Castor B: Intestinal symptoms and serological response in patients with complicated and uncomplicated *Yersinia enterocolitica* infections. Scandinavian Journal of Infectious Diseases (1992) 24:57–63
177. Maki-Ikola O, Heesemann J, Toivanen A, Granfors K: High frequency of *Yersinia* antibodies in healthy populations in Finland and Germany. Rheumatology International (1997) 16:227–229
178. Preston M, Brown S, Borczyk A, Riley G, Krishnan C: Antimicrobial susceptibility of pathogenic *Yersinia enterocolitica* isolated in Canada from 1972 to 1990. Contributions in Microbiology and Immunology (1995) 13:175–179
179. Scavizzi MR, Gayraud M, Hornstein MJ, Jupeau-Vessieres AM, Bronner FD, Elbhar A: *In vitro* and *in vivo* activities of antibiotics on *Yersinia enterocolitica.* Journal of Antimicrobial Agents and Chemotherapy (1996) 38:1108–1109
180. Stolk-Englelarr V, Meis J, Mulder J, Loeffen F, Hoogkamp-Korstanje J: Activity of 24 antimicrobials against *Yersinia enterocolitica.* Contributions in Microbiology and Immunology (1995) 13:172–174
181. Graninger W, Zebtwitz-Liebenstein K, Laferl H, Burgmann H: Quinolones in gastrointestinal infections. Chemotherapy (1996) 1, Supplement 42:43–53
182. Gayraud M, Scavizzi MR, Mollaret HH, Guillevin L, Hornstein MJ: Antibiotic treatment of *Yersinia enterocolitica* septicemia: a retrospective review of 43 cases. Clinical Infectious Diseases (1993) 17:405–410
183. Zhang Y, Toivanen A, Toivanen P: Experimental *Yersinia*-triggered reactive arthritis: effect of a 3-week course of ciprofloxacin. British Journal of Rheumatology (1997) 36:541–546