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INTRODUCTION

A Working Group on Yersiniosis was convened in Paris from 1 to 3 June 1981. The meeting was opened by Dr B. Velimirovic, Regional Officer for Communicable Diseases, on behalf of the WHO Regional Director for Europe. Professor H.H. Mollaret was elected Chairman and Dr J.M. Alonso Rapporteur.

The purpose of the meeting was to study the problems posed by the growing incidence in the world, and especially in the northern hemisphere, of infections due to *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* subspecies *pseudotuberculosis* (hereafter referred to as *Y. pseudotuberculosis*).[a]

An earlier meeting, convened in 1979 as part of the WHO diarrhoeal diseases control programme, had reviewed present knowledge of enteric infections due to *Campylobacter, Yersinia, Salmonella* and *Shigella* spp., and made a number of recommendations for research (*1*).

More than 20 years of bacteriological, clinical and epidemiological research has greatly improved our knowledge of infections due to *Y. enterocolitica* and *Y. pseudotuberculosis*. From the bacteriological standpoint, criteria for identifying *Y. enterocolitica* and the related species *Y. frederiksenii, Y. intermedia* and *Y. kristensenii* have been clearly defined. Some of the symptoms in man, such as diarrhoeal disease (either alone or associated with joint pain), mesenteric adenitis and septicaemia, have been well characterized. The mode of infection through the digestive system and the multiple pathology of the disease have been clearly demonstrated. Much knowledge is still lacking, however, particularly with regard to epidemiology. The epidemiological situation in Europe, as well as the geographical distribution of the different *Yersinia* biotypes, is still unclear. Despite the large number of animal species found infected, there is as yet no proof of infection of man by animals, and the role of foodstuffs of animal or vegetable origin has yet to be established.

The main aims of the meeting were to:

— identify the infectious agents of yersiniosis bacteriologically and antigenically;

[a] *Note added in proof.* WHO has recently drawn attention to the potential hazard, particularly for laboratory personnel, associated with the new nomenclature for the etiological agents of plague and pseudotuberculosis, i.e. *Y. pseudotuberculosis* subsp. *pestis* and *Y. pseudotuberculosis* subsp. *pseudotuberculosis*, respectively. See *Bulletin of the World Health Organization*, **61**: 545–546 (1983).

— review the epidemiological situation in different countries;
— determine the present distribution of the different biotypes and serotypes;
— determine the relationships between the clinical forms of the disease in man and the different types of *Yersinia*;
— determine the relationships between the different types of *Yersinia* and the various animal species infected;
— clarify the nomenclature of human yersiniosis;
— review the present knowledge of diagnostic methods; and
— make recommendations on improving diagnostic methods, and on research requirements in the areas of epidemiology and physiopathology.

BACTERIOLOGICAL DEFINITION OF *Y. PSEUDOTUBERCULOSIS, Y. ENTEROCOLITICA* AND NEWLY DESCRIBED RELATED SPECIES

Cultivation and biochemical features

Y. pseudotuberculosis and *Y. enterocolitica* are Gram-negative, asporogenous, non-encapsulated bacteria that can be cultivated on normal media such as nutrient agar and peptone water. All are facultative anaerobes. They ferment glucose and reduce nitrates to nitrites, they are oxydase-negative and catalase-positive, and they show peritrichous flagella when cultivated at less than 30 °C. These characteristics place them in the family Enterobacteriaceae. Nevertheless, they differ from most members of that family by virtue of their slower growth which, on solid media, is apparent in the formation of colonies of 1 mm or less after 24 hours. The optimum temperature for growth is around 29 °C; incubation at 37 °C reduces the growth of the bacteria on artificial media, which in turn hinders and delays their isolation and identification.

Y. pseudotuberculosis and *Y. enterocolitica* are distinguished from the other members of the Enterobacteriaceae by a combination of the following characteristics: rapid urease, ONPG, motility evident solely at temperatures under 30 °C. *Y. enterocolitica* and related species may be distinguished biochemically from *Y. pseudotuberculosis* by fermentation of cellobiose.

Because *Y. pseudotuberculosis* is biochemically homogeneous, it cannot be divided into biotypes. *Y. enterocolotica* on the other hand, because of its biochemical heterogeneity, may at present be subdivided into six biotypes (Table 1).

Table 1. Differentiation of *Y. enterocolotica* from other *Yersinia* species[a]

Test	*Y. enterocolitica* biotype		S⁻ *Y. kristensenii*	Rh⁺ *Y. frederiksenii*	Mel⁺ *Y. intermedia*	X1	X2	*Y. pseudo-tuberculosis*
	1–4	5						
$NO_3 \rightarrow NO_2$	+	–	+	+	+	+	+	+
Voges-Proskauer	+	+	–	+	+	–	+	–
D-Cellobiose	+	+	+	+	+	+	–	–
Sucrose	+	V	–	+	+	–	–	–
D-Trehalose	+	–	+	+	+	+	+	+
L-Rhamnose	–	–	–	+	+	–	+	+
D-Melibiose	–	–	–	–	+	–	–	+
α-Methyl-D-glucoside	–	–	–	–	+	–	–	–
Ornithine decarboxylase	+	V	+	+	+	–	+	–
Indole	V	–	V	+	+	–	–	–
L-Sorbose	+	V	+	+	+	–	–	–
D-Sorbitol	+	–	+	+	+	–	+	–
D-Melitose	–	–	–	–	+	–	–	V (11%⁺)
Citrate (Simmons')	–	–	–	V	+	–	+	–
Maltose	+	+	+	+	+	+	–	+
β-Xylosidase (PNPX)	–	–	–	V	–	–	–	+

[a] From **Bercovier, H. et al.** (*2*).

\+ : 90% positive or more after 72 hours.
– : less than 10% positive after 72 hours.
V : 10.1–89.9% positive.
All incubations done at 28 °C.

Bercovier at al. (*2–4*) and Brenner et al. (*5,6*) showed that new species, previously classified as atypical *Y. enterocolitica,* are distinct genotypes. They include *Y. intermedia,* which is biochemically differentiated by fermentation of rhamnose and melibiose, *Y. frederiksenii,* whose distinguishing feature is fermentation of rhamnose, and *Y. kristensenii,* which does not ferment sucrose (Table 1).

Antigenic properties

Y. pseudotuberculosis is currently thought to comprise six O serogroups, and *Y. enterocolitica* and the related species *Y. intermedia, Y. frederiksenii* and *Y. kristensenii* a total of 57. In view of this extreme antigenic heterogeneity the profile should be expanded, especially in order to reflect "wild" strains isolated in systematic surveys among asymptomatic carriers or in the environment.

Phage typing

Diagnosis of *Y. pseudotuberculosis* may be supplemented by studying the lytic action of a phage that is also active on *Y. pestis.*

For full characterization of *Y. enterocolitica,* it is necessary to undertake phage typing as developed by Nicolle et al. (*7,8*); this involves studying the lytic action of a series of bacteriophages from lysogenic *Y. enterocolitica* strains, together with the lytic action of bacteriophages isolated from sewage of unknown origin.

GEOGRAPHICAL DISTRIBUTION

Determination of the incidence of *Y. pseudotuberculosis* and *Y. enterocolitica* infections, among and within countries, appears to depend mainly on the technical capabilities of bacteriologists and health authorities and on their interest in these diseases. Whether these diseases are notifiable, whether the diagnosis is centralized, for instance in a national or regional reference centre, and whether serodiagnosis is carried out in preference to bacteriological diagnosis or in place of it, are also determining factors. The attitude of physicians to conditions associated with yersiniosis also affects estimates of the incidence of these infections. For instance, although blood culture may be routinely performed for apparent septicaemia, digestive trouble will not necessarily, depending on the local practice, be thought to call for faecal culture; instead the patient may be referred for surgery or antibiotic therapy.

Yersinia pseudotuberculosis

Up to 1955–1960, *Y. pseudotuberculosis* was the only *Yersinia* species regularly isolated in Europe in man and animals. Gradually, however, there were fewer isolations of this species and more of *Y. enterocolitica.*

Reports presented to the meeting by participants provided much useful information. In Czechoslovakia, for instance, 845 strains of *Y. enterocolitica* were isolated in man from 1958 to 1971, but none of *Y. pseudotuberculosis;* from 1972 to 1980, some 3533 strains of *Y. enterocolitica* were isolated in man compared with only four of *Y. pseudotuberculosis.* In Hungary, 4598 human strains of *Y. enterocolitica* were isolated between 1969 and 1980, compared with only eight of *Y. pseudotuberculosis.* In the Federal Republic of Germany *Y. pseudotuberculosis* accounts for only 1% of isolations of *Yersinia,* and no isolations of *Y. pseudotuberculosis* have been reported in recent years in Norway or the Netherlands. In Belgium isolations are exceptional, in contrast to their frequency in the neighbouring districts of France (*9*). Human infection from *Y. pseudotuberculosis* remains common in Ireland and the United Kingdom, where 305 strains of *Y. pseudotuberculosis* and 463 of *Y. enterocolitica* were isolated between 1970 and 1980, and in France where half of the cases of mesenteric adenitis investigated are due to *Y. pseudotuberculosis;* septicaemia from *Y. pseudotuberculosis* is also common (11 cases in 1980).

The decrease in human infection from *Y. pseudotuberculosis* in most European countries, judging by the comparison of the number of strains of *Y. pseudotuberculosis* and *Y. enterocolitica,* should be interpreted in the light of the origin of the strains and the clinical forms observed when they were isolated. The dominant feature of human infection from *Y. pseudotuberculosis* remains mesenteric adenitis in which the bacterium, which is only rarely found in faeces, must be detected through ganglion biopsy. In eastern Bohemia systemic seeding of ganglia yielded four times as many *Y. pseudotuberculosis* as *Y. enterocolitica.* Ganglion biopsy is rarely carried out, however, and it is even more rare to send the specimen to a laboratory for culture.

Similarly, in the case of erythema nodosum or involvement of the joints, following a painful abdominal episode or diarrhoeal disease, *Y. pseudotuberculosis* can be isolated only occasionally in faeces while *Y. enterocolitica* can be demonstrated several weeks or even months after the initial episode. The brief period during which *Y. pseudotuberculosis* can be isolated in faeces may partially explain the disproportion in the numbers of isolations of the two organisms where the syndromes are the same.

If we take account not only of isolations but also of serological surveys, infection from *Y. pseudotuberculosis* would appear to be less of an exception in some countries; in Poland there were reports of 340 cases of infection from *Y. pseudotuberculosis* and 490 from *Y. enterocolitica*

between 1972 and 1980. In Sweden (Malmö) from 1964 to 1978, 1732 cases of *Y. enterocolitica* infection were detected by culture and serodiagnosis compared with 38 cases of *Y. pseudotuberculosis* infection detected by serodiagnosis alone. In Romania it is reported that one case of mesenteric adenitis out of eight is due to *Y. pseudotuberculosis.*

In animals *Y. pseudotuberculosis* infection is regarded as commonplace and hence not reported, and it is therefore difficult to assess its occurrence without systematic surveys. At the State Veterinary Laboratory in Stockholm 15 strains were isolated in 1977, 10 in 1978, 14 in 1979 and 4 in 1980, almost all in hares, compared with 0, 2, 2 and 2 strains of *Y. enterocolitica* reported for the same four years. In France *Y. pseudotuberculosis* is isolated from time to time in hares, rodents and birds. In Czechoslovakia 380 strains of *Y. pseudotuberculosis* were isolated in animals from 1978 to 1980, including 168 in hares and 112 in rabbits. In Poland isolations of strains of animal origin are also sporadic.

Yersinia enterocolitica

At present, human infection due to *Y. enterocolitica* has been recognized in all countries in Europe, apparently with higher rates in the north of the Region. The highest incidence occurs in Belgium and Scandinavia, but it is difficult to assess the epidemic situation because of the greater or lesser interest taken in systematic detection of the disease. Nevertheless, there appears to have been a real and generalized increase in incidence (see Fig. 1 and 2 and Table 2).

Fig. 1. Number of isolations of *Y. enterocolitica* in man, Belgium, 1963–1978

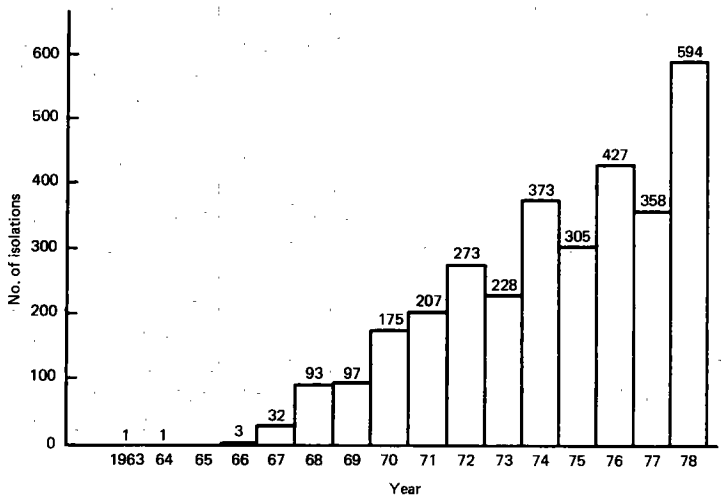
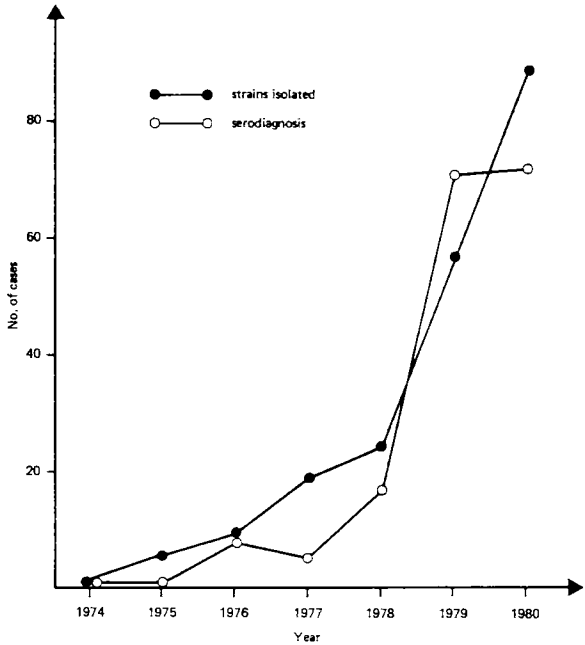


Fig. 2. Cases of *Y. enterocolitica* infection detected by isolation and serodiagnosis, Federal Republic of Germany, 1974-1980



There are appreciable geographical differences in the distribution of the different phenotypes of *Y. enterocolitica* isolated in man: serogroup O3 biotype 4 is the most widespread in Africa, Canada, Europe, Japan and Latin America. Phage typing makes it possible to distinguish, within serogroup O3 biotype 4, between European strains (phage type VIII), Canadian strains (phage type IXb) and South African strains (phage type IXa).

In Europe, strains of serogroup O3 biotype 4 (phage type VIII) are predominant by virtue of their prevalence in man. Moreover, they are the only phenotype of *Yersinia* in some countries, such as Czechoslovakia, Denmark, Hungary, Italy, Norway, Poland and Sweden.

Serogroup O9 biotype 2 (phage type X3) is the second most common in Europe, but its distribution is far more uneven; while it accounts for 30% of strains isolated in France and the Netherlands, the proportion is only 19% in the Federal Republic of Germany and 11% in Belgium and Romania. It has not yet been isolated in Czechoslovakia, Poland or the United Kingdom. Only a few strains have been isolated in Italy, Norway, Spain and Sweden, but in Belgium and France isolations of serogroup O9 strains have been increasing over the last two years.

Table 2. Number of isolations of *Y. enterocolitica*, Hungary, 1969-1980

Year	Number of positive cases	Number of strains
1969	1	1
1970	18	42
1971	40	59
1972	246	324
1973	345	438
1974	446	491
1975	479	516
1976	236	254
1977	363	447
1978	282	354
1979	545	762
1980	704	910
Total	3705	4598

Strains of serogroup O6 are also showing an increase although they are still rare; the rate ranges from 0.5% in France and the Federal Republic of Germany to 1.4% in Belgium. Strains of serogroup O6,30 are exceptionally common in the United Kingdom, where they account for 40% of isolations.

Strains of serogroup O5 account for no more than 1% of isolations in Belgium, France, the Federal Republic of Germany, Hungary, the Netherlands and Spain. They are common in the United Kingdom, where they account for 40% of isolations.

Serogroup O8 biotype 1, which predominates in the United States, is found only occasionally in Europe in human cases.

On the whole, strains of serogroups other than O3 and O9 appear to have been on the increase in Europe over the last two years. This trend is very clear in Belgium (see Table 3).

Importance of yersiniosis

The importance of *Y. enterocolitica* among the other agents of diarrhoea varies from one country to another. In Sweden the results of 11 000 faecal cultures for 7304 patients, carried out at the municipal laboratory in Malmö, placed *Y. enterocolitica* in third place after *Salmonella* and

Table 3. Trends in the distribution of *Y. enterocolitica*, Belgium, 1963-1980

Period	Serogroups						All serogroups
	03		09		Others		
	No.	%	No.	%	No.	%	No.
1963-1969	206	90.7	16	7.0	5	2.2	227
1970-1972	598	91.4	45	6.9	11	1.7	654
1973-1975	770	86.8	93	10.4	24	2.7	887
1976-1978	1073	77.8	212	15.4	94	6.8	1379
1979-1980	1244	67.8	485	26.4	106	5.8	1835
Total	3891	78.1	85.1	17.1	240	4.8	4982

Campylobacter. The same is true of Hungary. In Norway *Y. enterocolitica* has ranked immediately below *Salmonella* but above *Campylobacter* and *Shigella* in the last five years. In Czechoslovakia the rate of yersiniosis is only one sixtieth that of salmonellosis and shigellosis. In the Netherlands the number of isolations of *Yersinia* is between one sixth and one twentieth that of *Salmonella*. In the Federal Republic of Germany *Yersinia* is apparently isolated almost as often as *Salmonella*.

In general, as far as the etiology of digestive infections is concerned, *Y. enterocolitica* should be ranked immediately below *Salmonella* in the order of frequency, at the same level as *Shigella, Campylobacter* and *Escherichia coli*.

HUMAN PATHOLOGY

The predominant clinical forms of yersiniosis are mesenteric adenitis, appearing as disease of the right iliac fossa, enteritis, septicaemia and, more rarely, localized infections other than in the digestive system. Erythema nodosum and polyarthritis, which are diagnosed essentially by seroreaction, appear in fact to be secondary nonseptic forms of *Y. enterocolitica* infection.

There is a relationship between age and clinical symptoms and between serogroups and these symptoms (see Table 4).

Table 4. *Y. enterocolitica* in Belgium: main clinical diagnoses according to serogroup

Clinical diagnosis	Serogroups						All serogroups	
	O3		O9		Others			
	No.	%	No.	%	No.	%	No.	%
Gastroenteritis	2091	88.4	259	82.2	61	64.2	2411	86.9
Pseudoappendicitis	261	9.1	39	12.4	9	9.5	264	9.5
Septicaemia	9	0.4	3	1.0	0		12	0.4
Abcess	2	0.1	0		0		2	0.1
Healthy carrier	33	1.4	7	2.2	16	16.8	56	2.0
Other	15	0.6	7	2.2	9	9.5	31	1.1
Total	2366		315		95		2776	100.0

Mesenteric adenitis

Mesenteric adenitis used to be the main lesion in pseudotuberculosis due to *Y. pseudotuberculosis* (*10,11*). This infection now seems to be decreasing compared to mesenteric adenitis due to *Y. enterocolitica,* which has the same clinical features, including pseudotumoral forms (*12*). The incubation period of *Y. enterocolitica* adenitis is reported as 2–3 weeks; it is accompanied by abdominal pain so that the patient is often sent to the surgical department. The biological syndrome is one of inflammation with increase in the rate of sedimentation and neutrophilic polynucleosis, which cannot specifically be linked with yersiniosis. Surgery shows that the appendix is unaffected and that there is involvement of the ileocaecal ganglions, and often reveals the presence of terminal ileitis. Ileal involvement, limited to the last 10–15 cm in mesenteric adenitis due to *Y. pseudotuberculosis,* is normally more extensive in mesenteric adenitis due to *Y. enterocolitica.*

Enteritis

Enteritis is the predominant clinical form of *Y. enterocolitica* infection. It occurs mainly in children of either sex. The severity of the digestive disturbance varies, ranging from moderate painless diarrhoea to chronic enteritis associated with the discovery, should surgery be performed, of ileitis that may or may not be complicated by mesenteric adenitis. The patient's temperature is slightly raised or normal. Vomiting, serious impairment of general health or acute dehydration are rare. In most cases *Y. enterocolitica* enteritis is cured spontaneously.

As mentioned above, however, ileitis may be diagnosed clinically as appendicitis, so that the patient is referred for surgery.

The correlation between hepatic disorders that may be detected by biological examination and an acute abdominal syndrome has been observed by some surgeons, particularly in Norway. Small-scale epidemics of *Y. enterocolitica* enteritis have been reported in Hungary and the United Kingdom; in such cases infection from the same source, rather than direct man-to-man infection, has been suspected. In all cases, simple forms of the disease were involved and hospitalization was not required.

Diarrhoea of long duration due to serogroup O3 or O9 strains of *Y. enterocolitica* has been reported in Belgium in association with enteritis lasting 2–3 weeks, and in these cases *Y. enterocolitica* was re-isolated by faecal culture. Similarly, possible relapses, up to eight months after the primary infection, with bacteriological confirmation of the reactivation, have been observed in Belgium, the Federal Republic of Germany and Hungary. In some clinically cured patients, the *Y. enterocolitica* strain has been re-isolated one month after the initial episode of enteritis. Carrying of the organism by convalescents appears to be limited to persons who have not undergone antibiotic treatment, but the situation must be monitored since the possibility of reinfection in a non-immune patient cannot be excluded.

Septicaemia

The incidence of human septicaemia due to *Y. enterocolitica* varies considerably from one country to another. Five cases have been reported in the Federal Republic of Germany and the United Kingdom, 69 in France, 25 in Norway and 4 in Czechoslovakia. It occurs in adults with an immune deficiency that may be either constitutional (diabetes, cirrhosis, blood disease, etc.) or acquired (immunosuppressive treatment, intensive parenteral therapy, etc.). A special form of septicaemia due to *Y. enterocolitica* affects children or young adolescents suffering from β-thalassaemia. Two clinical pictures may be distinguished: either a febrile typhoid-like syndrome from the outset or a septicopyemic syndrome, accompanied by

hepatic pain and jaundice, identical to the classical picture of septicaemia due to *Y. pseudotuberculosis.* Mortality is estimated at 25%. True septicaemia of this kind is essentially due to serogroup O3 chemotype 4 strains of *Y. enterocolitica* and must be distinguished from certain infections which may already have been diagnosed as bacterial (septicaemia due to staphylococci, streptococci, meningitis, listeriosis, etc.) and during which *Y. enterocolitica* strains of biotype 1 and various serogroups or *Y. intermedia* were isolated by haemoculture. Where *Y. intermedia* is found, the presence of *Y. enterocolitica* in the blood suggests a superinfection, although it has still to be established whether or not *Y. enterocolitica* strains outside serogroups O3 or O9 are pathogenic.

Erythema nodosum

Erythema nodosum due to *Y. pseudotuberculosis* or *Y. enterocolitica* appears to be a complication of a digestive infection. Erythema nodosum due to *Y. pseudotuberculosis* has traditionally affected young males, whereas the *Y. enterocolitica* infection appears to affect adult women in 80% of cases.

The etiological diagnosis of erythema nodosum due to *Yersinia* is based on serology but it is possible to make a bacteriological confirmation through faecal culture in 20% of cases. The rate of erythema nodosum that can be attributed to yersiniosis is estimated at 30%. Certain observations have given grounds for suspecting the existence, alongside erythema nodosum, of a polymorphous erythema, or even disease (two cases in Sweden) suggestive of the "scarlatiniform fever" from which a *Y. enterocolitica* strain of serogroup O3 was isolated.

Polyarthritis due to *Yersinia*

Like erythema nodosum, this form of polyarthritis appears to be a non-septic complication of a digestive infection. Clinical and epidemiological data show that the condition occurs in the north of Europe and that there is a correlation with the human genotype HLA B 27; for instance, in Sweden 65% of patients with arthritis due to *Y. enterocolitica* are of this genotype. As in the case of erythema nodosum, etiological diagnosis is based on detection of *Y. enterocolitica* agglutins and their increase as the disease progresses. Faecal cultures, which remain positive for quite a long time (up to a few weeks) after the initial episode of diarrhoea, should be performed systematically. In Denmark, serodiagnosis detects *Y. enterocolitica* in 40–65% of mono- or poly-articular and 20% of arthralgia cases for which it is undertaken. Apparently 33% of cases of "chronic rheumatoid polyarthritis" are associated with a rise in antibodies to *Y. enterocolitica* serogroup O3. The rate of occurrence of arthritis during recovery from a

Y. enterocolitica infection has been estimated at 1 per 1000 in Denmark. This estimate should be modified, however, in view of the considerable infrequency or absence of bacteriological examinations (faecal culture) that would allow confirmation of the etiology of the arthropathy.

The kinetics of *Y. enterocolitica* agglutinins in arthritis ranges from two to three weeks, as in digestive infections, or may form a plateau curve with an average titre (1/200 or 1/500) persisting for several months. This phenomenon can be linked with the occurrence of acute arthritis or the onset of chronicity. At present it is difficult to assess the effectiveness of antirheumatismal treatment or to propose antibiotic therapy. Noncorticosteroid anti-inflammatory treatments appear to vary in efficacy. Early antibiotic therapy, in the absence of signs of infection, does not appear to alter the prognosis of impairment of the joints. On the other hand, it does seem that arthritis is more likely to occur after an infection not treated by antibiotics that are effective against *Yersinia.*

Reiter's syndrome

The association of eye involvment and inflammation of the joints during recovery for *Yersinia* infections has been suspected on the basis of positive serodiagnosis. As in the case of arthritis, there appears to be a correlation with the human genotype HLA B 27.

"Extra-mesenteric" forms

Forms localized in sites other than the digestive system and those where there is no suggestion of enteritis are quite variable and isolation of *Yersinia,* when it is undertaken, reveals phenotypes other than the serogroups O3 and O9 that are generally incriminated in human cases in Europe. Some deep suppurations may indicate an uncommon primary localization or a metastase of an infection due to a *Y. enterocolitica* strain of serogroup O3. Thus, *Y. enterocolitica* has been isolated from specimens taken in cases of acute meningitis, pleurisy, purulent arthritis and osteitis, from ascitic fluid, and from abcesses of the liver, spleen, colon and cerebellum. Isolations have been made in connection with post-operative suppurations in digestive surgery or gynaecology (abdominal fistula, parenteral drains).

Yersinia has also been isolated from urine, acute conjunctivitis tissue, sores on the hand, knee and scalp, ulcers on the leg, and impetigo lesions; about half of the strains belong to serogroups O3 and O9, and half to serogroups O5, O6, O7,8 and O10,K1.

Finally, nonseptic conditions suggestive of autoimmune pathology have been attributed to yersiniosis purely on the basis of a positive serodiagnosis; for instance there have been reports of glomerulonephritis,

where in some cases antigens to serogroup O3 strains of *Y. enterocolitica* were found during biopsies for myocarditis and pericarditis.

ANIMAL PATHOLOGY

Yersinia pseudotuberculosis

"Pseudotuberculosis" due to *Y. pseudotuberculosis,* although apparently less and less frequently diagnosed in man and virtually unknown in some countries such as Belgium, is still found occasionally in rodents and birds, especially in France and the United Kingdom.

Yersinia enterocolitica

Y. enterocolitica was first diagnosed in Europe in investigations of epizootics in chinchilla farms (*13*) and in hares (*14*).

Currently, the following animal species must be distinguished:

(*a*) those in which *Y. enterocolitica* has been shown to be pathogenic more or less regularly;

(*b*) those in which some isolated symptoms have been attributed to *Y. enterocolitica;* and

(*c*) those (the largest category) in which *Y. enterocolitica* has been isolated more or less frequently, without appearing to be pathogenic.

(*a*) The only species affected are chinchillas (*13*), hares (*14*) and sometimes monkeys in zoos. Occasional cases of "pseudotuberculosis" due to *Y. enterocolitica* have been reported in guinea pigs. In all these species, the disease normally takes the form of a fatal "pseudotuberculosis". The strains isolated in chinchillas were all of biotype 3, serogroups O1, O2a, O3 (phage type II). They seem specific to this species and otherwise have been isolated only once, in goats (*15*). The strains isolated in hares were of biotype 5 serogroup O2 (phage type XI) (*14*).

(*b*) There have been very occasional reports of mastitis in cows, endocarditis in bulls, and septicaemia in swine. These species are generally asymptomatic carriers.

(*c*) As a result of numerous prospective surveys to identify a natural animal reservoir, *Y. enterocolitica* has been isolated in nearly all of the vertebrate species examined, without any evidence of disease (Tables 5

Table 5. Animal species infected by *Y. enterocolitica*

Chinchilla	*Exceptionally:*	Goat
Hare		Bovines
Monkey (in zoos)		Dog
Guinea pig		Pig
		Birds

and 6). A distinction must be made between synanthropic species carrying strains of serogroups O3 or O9 that have been associated with human pathology, and a great variety of domestic or wild species in which strains of biotype 1 or *Y. intermedia, Y. frederiksenii* or *Y. kristensenii* have been isolated in the same way as they are isolated from the faecal flora of human subjects not showing any symptoms of disease.

ECOLOGY OF *YERSINIA*

Yersinia pseudotuberculosis

From the information now available concerning the ecology of *Y. pseudotuberculosis,* "pseudotuberculosis" can be regarded as a genuine zoonosis. Infection in animals may take the form of fatal septicopyemia (rodents, birds) or there may be no symptoms in certain domestic species (pets such as guinea pigs, hamsters and cats) that have subclinical lesions (mesenteric adenitis with faecal excretion) and are a source of infection for man. The disease may also be transmitted through the consumption of vegetables contaminated by soil, which appears to be a favourable biotype for conserving *Y. pseudotuberculosis* (*16*).

Yersinia enterocolitica

The ecology of *Y. enterocolitica* and related species (*Y. intermedia, Y. frederiksenii, Y. kristensenii*) encompasses a wide variety of hosts and environments. The most important feature is that a close correlation has been observed between the phenotype, habitat or host and the presence or absence of specific disease symptoms (see Table 7).

Table 6. Animal species identified as carriers of *Y. enterocolitica*

Large mammals	***Small mammals***	***Birds***
Pig	*Clethrionomys glareolus*	Chicken
Bovines	*Clethrionomys rutilus*	Goose
Horse	*Microtus arvalis*	Duck
Sheep	*Microtus agrestis*	Pigeon
Goat	*Microtus oeconomus*	Sparrow
Dog	*Microtus minutus*	Goldfinch
Cat	*Apodemus sylvaticus*	Canary
Fox	*Apodemus flavicolis*	*Lagopus* sp.
Mink	*Arvicola terrestris*	Yellow-hammer
Ocelot	*Rattus rattus*	Finch
Raccoon	*Mus musculus*	Lapwing
Camel	*Lemmus lemmus*	
Fallow deer	*Myocastor coypu*	***Freshwater fish***
Wapiti	*Castor fiber*	Trout
	Citellus citellus	Perch
	Sorex sp.	Roach
	Crocidura sp.	
	Talpa sp.	***Insects***
	Rhinolophus	Flea
		Other
		Frog
		Snail
		Oyster
		Mussel

The present data on *Y. enterocolitica* infection in man in Europe do not provide evidence of pathogenicity of strains other than those of serogroup O3 biotype 4 (phage type VIII) as well as serogroup O9 biotype 2 (phage type X3). As mentioned above, faecal excretion of *Y. enterocolitica* occurs in patients convalescing from enteritis due to *Y. enterocolitica* serogroups O3 or O9. These strains have been isolated increasingly in swine and *Rattus rattus* without any evidence of disease.

Systematic prospective surveys among domestic or wild animals (other than dogs, swine or rats) in aquatic environments, in the soil and in foodstuffs of animal origin such as milk and meat or of vegetable origin,

Table 7. Ecology of *Y. enterocolitica*

			Chemotype	AG O	Phage type	Host	Syndromes	Country
Yersinia enterocolitica urea +, tryptophane desaminase 0, phenyl alanine 0; ornithine decarboxylase +, VP + (20–29 °C), motile < 30 °C	indole +	rhamnose + melibiose 0[a] nitrate reductase type a	① (lipase variable)	1,7 or N[b]	X_0	man	healthy carriers and unusual syndromes (sores, abcesses, conjunctivitis, pharyngitis, urine)	USA
		rhamnose + melitose 0 nitrate reductase type b			X_2	man small mammals birds foodstuffs of animal origin (milk, meat)	healthy carriers healthy carriers healthy carriers	France Europe Europe Europe
		rhamnose + melibiose +[a] melitose +		variable or N[b]	X_2	water fish man	healthy carriers superinfection	Norway, Japan, France Europe France
		rhamnose 0		1 10,K1 2 13 4 13,7 5 14 6 15 7 16 8	X_2 sometimes X_0	small mammals birds foodstuffs (plant)	healthy carriers	Europe
						man	healthy carriers superinfection septicaemia and unusual syndromes	France Europe USA, France
			① (lipase 0)	9	X_3	man swine	"classic" syndromes: gastroenteritis, RIF syndromes, polyarthritis, Reiter's syndrome healthy carriers	Europe Europe (Scandinavia) Europe
			① — ③ indole variable[c]	5,27	X_2 or X_0	man swine monkey and carnivore species	variable healthy carriers "pseudotuberculosis" lesions	Canada (Ontario) Canada (Ontario) Canada (Ontario)
	indole 0	xylose +	①	1 1,2a 1,2a3	II	primates	"pseudotuberculosis" lesions (epizootics)	Europe (North America?)
		xylose 0	④	3	V	man — swine	man: "classic" syndromes (gastroenteritis), RIF syndromes, septicaemia swine: healthy carriers	Europe, Japan, Zaire, Brazil
					IX b	man — swine		Canada exclusively
					IX a	man — swine		South Africa exclusively[d]
		Y. enterocolitica VP 0 nitrate, 0, ODC 0 TDA 0 beta-galactosidase 0 sucrose 0	⑤	2a 2b 3	XI (sometimes III)	hare	"pseudotuberculosis" lesions (epizootics)	Europe

Source From **Mollaret, H.H.** Contribution à l'etude epidemiologique des infections à *Yersinia enterocolitica* III Bilan provisoire des connaissances *Medecine et maladies infectieuses* **6** (10bis): 442–448 (1976)

[a] The melibiose + strains are associated with *Y. intermedia*, and the melibiose 0 strains with *Y. frederiksenii*

[b] Strains that are not agglutinable by anti O:1 to O:34 sera

[c] Indole variable strains generally indole 0 in peptone water but often slightly indole + in urea-indole medium of the Pasteur Institute

[d] Strains of phage type IXa isolated in South Africa are beta-galactosidase 0. Some strains of this phage type have been isolated in Czechoslovakia and Hungary and are beta-galactosidase +

particularly those consumed raw, have not led to any isolations of *Y. enterocolitica* serogroups O3 or O9. We now have a picture of the distribution by host or ecosystem according to type of strain: *Y. intermedia* and *Y. frederiksenii* are often isolated from samples of water or fish gills, while *Y. kristensenii* is the main agent found in soil samples. *Y. enterocolitica* strains of biotype 1 and different serogroups appear to be present in the intestinal flora of virtually all land vertebrates in which systematic faecal culture has been carried out.

Presence of *Yersinia* in foodstuffs

Systematic surveys in Belgium, Czechoslovakia and France have shown the different foodstuffs in which *Yersinia* may be isolated.

Dairy products. Strains have been isolated in untreated milk, pasteurized milk, chocolate milk, dairy cream and ice cream, but none in cheese or yoghurt.

Vegetables. Strains have been isolated, by decreasing order of frequency, in carrots, tomatoes, radishes, lettuce, parsley, beetroot, celery and mushrooms. Surveys carried out in institutional settings have shown *Yersinia* in made-up dishes such as grated carrots, salad with dressing, celery with remoulade sauce, and hors d'oeuvres.

Meat. Wauters (*17*) found *Yersinia* in more than 50% of specimens of pork tongue offered for sale, but the percentage recorded in similar surveys in France was not so high. Strains have also been isolated in raw meat (hare, beef, lamb) and blood sausage. The strains are of all phenotypes.

Asymptomatic carriers

Y. enterocolitica biotype 1 may also be present in asymptomatic human carriers or even patients with diarrhoea, as shown by Wauters[a] in Belgium (Table 8).

Van Noyen[a] obtained similar results in Bonheiden, Belgium (Table 9).

Wauters in Belgium showed that, unlike cultures of the faeces of patients with enteritis due to *Y. enterocolitica* serogroups O3 or O9, examinations of clinically healthy subjects in which a biotype 1 strain is found initially will show, on making a further isolation, that the subject is the carrier of a biotype 1 strain belonging to a different serogroup than that of the strain previously isolated.

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[a] Unpublished paper presented to the meeting.

Table 8. Isolation of *Y. enterocolitica* biotype 1 in a group of patients with diarrhoea and in a clinically healthy group

	Patients	Healthy subjects
Numbers of carriers/subjects	43/618	15/240
Percentage	6.9	6.2

The hypothesis that biotype 1 strains found during systematic surveys are not pathologically significant is supported by the fact that serodiagnosis carried out in human or animal carriers, vis-à-vis their own strain, does not reveal any antibodies.

Table 9. Biotypes of *Y. enterocolitica* and related species isolated by culture of the faeces of patients or clinically healthy subjects.

Biotype or species	No. of strains in patients	No. of strains in contacts
4	41	1
2	14	2
1	25	18
3A	1	—
Y. frederiksenii	2	—
Y. intermedia	1	1
Y. kristensenii	1	
Total	85	22

Mode of transmission of *Yersinia*

Since the principal form of *Y. pseudotuberculosis* and *Y. enterocolitica* infection is digestive, the oral mode of transmission has naturally been incriminated. Transmission through the skin or mucosa is apparently responsible for local lesions (abcesses and/or peripheral adenitis) or systemic lesions, but certain observations of digestive infections following parenteral contamination give grounds to suspect that ingestion may not be the only mode of transmission involved in these digestive forms.

Populations at risk

Age and terrain are key factors in *Y. enterocolitica* infection: the groups at risk appear to be children and people with an immune deficiency, especially in the case of septicaemia in individuals suffering from cirrhosis, diabetes, cancer, blood diseases (generally thalassaemia), weight loss, neonatal distress, or patients undergoing immunosuppressive treatment.

Sources of human infection

Surveys have shown that *Y. enterocolitica* and the related *Y. intermedia, Y. frederiksenii* and *Y. kristensenii* are ubiquitous. Animals are an important reservoir.

Although strains of serogroups O3 and O9, which are responsible for human infection, have been isolated in swine and *Rattus rattus,* these animals cannot be regarded as the normal source of the infection in man; rather they appear to be asymptomatic carriers. The only foodstuff of animal origin in which strains of serogroup O3 have often been isolated is pork tongue (*17*). Pork may, in fact, depending on the country and bacteriological techniques used, be found to contain strains other than those of serogroups O3 or O9.

Although strains of *Y. enterocolitica* serogroup O3 have been isolated in *Rattus rattus,* an anthropophilic species, the strains found in *R. norvegicus,* which has less contact with man, are of biotype 1. These findings suggest that certain animal species closely associated with man might become infected in man's environment, but that this is merely the reflection of the endemicity of the disease and not its main source.

Other domestic (dogs, bovines, farmyard animals) or wild (rodents, insectivores, birds) species have been found to carry *Y. enterocolitica* strains of phenotypes that have not been associated with specific human disease (*18*). Surveys of foodstuffs of animal origin (fresh and prepared

meats, milk), as well as drinking-water, have shown strains of *Y. enterocolitica* biotype 1, *Y. intermedia* and *Y. frederiksenii* (samples of water or vegetable products) or *Y. kristensenii.*

The capacity of *Yersinia* to propagate at low temperatures (under 10 °C) appears to be the explanation for the enrichment of products contaminated by these bacteria during refrigeration. This psychrophilia appears to be the property mainly of biotype 1 strains.

Thus, there appear to be many potential sources of human infection by *Y. enterocolitica* in the broad sense. However, because strains of serogroups O3 and O9 appear at present to be the only ones involved in human infection that are invariably isolated in faecal culture during recovery from enteritis or mesenteric adenitis and haemoculture during septicaemia, swine and *Rattus rattus* are the only reservoirs that can be suspected where convalescents are concerned. As the mode of transmission from swine or rats to human populations that are normally susceptible to these conditions (children, immunosuppressed individuals) has not been established, human yersiniosis would appear to be the result of infection of the susceptible host by an asymptomatic carrier (small children and the newborn could therefore be seen as indicators of latent inapparent infection in adults in the immediate family circle).

The possibility of man-to-man transmission, either from a patient to a contact, or from a healthy carrier to a susceptible person, is suggested both by the existence of family episodes or epidemics affecting children in institutions, and by the high rate of enteritis in the newborn whose feeding is supervised and who have no direct contact with potential external sources of *Y. enterocolitica* infection.

Thus, *Y. enterocolitica* does not really appear to be a zoonosis. Observation of the carrying by synanthropic animals of strains that are "pathogenic" for man should for the time being be regarded as an epidemiological "tracer" in respect of human infection. The pathogenic capacity of strains in the environment should be monitored and has still to be demonstrated.

Seasonal incidence

A recrudesence of yersiniosis during cold and damp weather has been reported in Belgium, Czechoslovakia (particularly in Slovakia, since several annual peaks are observed in Bohemia), France, the Federal Republic of Germany, Hungary, the Netherlands, Norway and Poland (except in 1978 when two peaks were recorded in November and February). In three provinces of Spain isolations have been made throughout the year, but predominantly in January, February, May and November. In the other provinces few isolations are made in summer.

The greater frequency of yersiniosis during cold weather may be compared with the higher rate of *Salmonella* isolations during the summer.

DIAGNOSIS

Clinical diagnosis and further examinations

As described above, yersiniosis usually takes the form of a digestive infection or septicaemia which does not have specific symptoms and must be distinguished from bacterial enteric diseases such as salmonellosis and enteritis due to *Shigella, E. coli* or *Campylobacter.*

Radiological examinations of the digestive system are not pathognomonic, apart from certain images of follicular ileitis or compression due to mesenteric adenitis. The blood count and leukogram are normal and merely show (often only moderate) neutrophil polynucleosis. The rate of sedimentation is normal or moderately increased. Disturbances in hepatic functional tests may be observed transiently.

Bacteriological diagnosis

Isolation of Yersinia

Monocontaminated pathological substances such as blood do not pose any technical difficulty for culture of *Y. pseudotuberculosis* or *Y. enterocolitica;* the usual haemoculture media are suitable.

Y. pseudotuberculosis is rarely isolated by faecal culture even in genuine cases of mesenteric adenitis. Taking a ganglion specimen is the only means of isolating the species in pure culture, but this procedure is rarely undertaken.

Y. enterocolitica is generally sought in faeces or material from the appendix, like the other enteropathogenic bacteria. Selective techniques must be used for faecal culture.

Direct isolation for rapid diagnosis is carried out on selective media. Enrichment methods are used for systematic detection during surveys. The isolation procedure must be appropriate to the circumstances, whether it involves a faecal culture to determine the cause of a digestive or generalized syndrome, or systematic monitoring of human or animal carriers, or detection of *Yersinia* in the environment. At present it is not possible to propose a standard method.

Direct isolation. Most culture media containing factors that inhibit the growth of commensal aerobic bacteria of the alimentary canal are

suitable for isolating the *Y. enterocolitica* phenotypes normally encountered in human cases. These media have added bile salts, desoxycholate or citrate, and among the most commonly used are *Salmonella–Shigella,* MacConkey, lysine–sucrose–urea, Hektoen, and desoxycholate–citrate–lactose. The experience of various authors has shown that growth of *Y. enterocolitica* biotype 1, *Y. intermedia, Y. frederiksenii* and *Y. kristensenii* is hindered in these media as compared with *Y. enterocolitica* serogroups O3 and O9.

For the purpose of clinical diagnosis in the laboratory, a faecal culture may be made on a standard medium for the isolation of common enteropathogenic bacteria (*Salmonella, Shigella, E. coli*) and incubated at 37 °C for 18–24 hours; the culture should then be incubated for a further 24 hours at a temperature between 28 °C and 25 °C in order to detect colonies of *Y. enterocolitica.* If an incubator that can be set to these temperatures is not available, the medium must be left in the ambient temperature of the laboratory.

Enrichment methods. According to various authors, enrichment of *Y. enterocolitica* by exposure at +4 °C is rarely carried out in clinical bacteriology; on the other hand, enrichment in Rappaport medium (modified by Wauters), stored for two days at 25 °C, increases the rate of isolations of *Y. enterocolitica* serogroups O3 and O9 by about 20%.

Enrichment at +4 °C in liquid media (phosphate buffer or peptone water) apparently enhances selection of *Y. enterocolitica* biotype 1, *Y. intermedia, Y. frederiksenii* and *Y. kristensenii.* The value of this method in epidemiological surveys has been universally recognized. It is apparently not suitable, however, for the isolation of *Y. enterocolitica* serogroups O3 and O9.

Identification of Yersinia

The methods for bacteriological identification of *Yersinia* are the same as those used for the Enterobacteriaceae generally; the relevant characteristics are given in Table 1.

Serological diagnosis

It is unanimously recognized that serodiagnosis of yersiniosis must be seen as a supplementary procedure that can never replace isolation of the bacteria, which is the only technique that provides confirmation of the etiology. The causes of aseptic arthritis and erythema nodosum occurring after the infectious episode, however, cannot be investigated at present except by detection and titration of *Yersinia* antibodies, although in

arthritis due to *Y. enterocolitica* the strain can still be found in the faeces several weeks after the initial diarrhoea.

Sero-agglutination of complete bacterial antigens has emerged as a practical and reliable method advocated by most authors. Suspensions of living bacteria are no longer used. Most authors prefer suspensions that have been inactivated by ethanol or formol, as tests conducted with them can be standardized and reproduced, with less likelihood of cross-reactions.

Because the antigens used in different countries are not standardized, it is not possible at present to give a precise titre for positive serodiagnosis. At least two consecutive titrations should be made to evaluate the agglutinin reaction.

At present the selection of antigen types is limited to those serogroups that are known to be pathogenic for man; this selection must be adapted to changes in the disease that might be due to serogroups whose pathogenic capacity has not yet been demonstrated.

It is difficult to assess the extent of serological cross-reactions between yersiniosis and other infections. Cross-reactions between *Y. enterocolitica* serogroup O9 and *Brucella* are known to occur, and in doubtful cases certain immuno-enzymatic techniques can apparently be used to differentiate between these two types of infection. Immunological diagnostic techniques to determine cell-mediated immunity, such as the detection of retarded hypersensitivity reaction, especially in forms suggesting immunopathology, cannot be carried out in cases of *Y. enterocolitica* infection at present, but the possibility should be studied.

TREATMENT

Although cases of common enteritis should be monitored bacteriologically, they generally require only symptomatic treatment without antibiotics.

Deep or generalized forms should be treated with antibiotics. The betalactamines currently available are not effective; tetracycline and related drugs, although very potent, should be used only in adults as they may cause disturbances in children. Chloramphenicol, streptomycin and gentamicin should be reserved for severe forms. Combined trimethoprim-sulfamethoxazole is effective.

Pseudo-appendicitis syndromes of pain in the right iliac fossa, which are indicative of ileitis or mesenteric adenitis, generally require hospitalization of the patient for surgery; in cases of chronic adenitis, ablation of the lesion combined with antibiotic treatment generally cures the condition, although simple ablation of an apparently normal appendix also effects a cure without our being able to explain why.

The clinical course of post-infectious aseptic forms such as arthritis and erythema nodosum is not affected by antibiotics. On the other hand, the possibility that they might be prevented by antibiotic therapy should be investigated.

CLINICAL COURSE AND PROGNOSIS

In enteritic forms, the prognosis is generally good. Deep suppurative forms and septicaemia may be fatal, even with treatment. In most cases *Y. enterocolitica* infection occurs in persons with serious immunodeficiencies. Aseptic arthritis not associated with treatment of an infection appears to be difficult to treat. The effectiveness of non-steroidal anti-inflammatory agents varies, and the use of corticosteroids must still be considered dangerous in view of our lack of knowledge concerning the possibility of latent infection.

IMPORTANCE FOR PUBLIC HEALTH

The incidence of *Y. pseudotuberculosis* infection is difficult to assess owing to the complexity and our lack of knowledge of the bacteriological techniques involved. Over the last few years the incidence of *Y. enterocolitica* infection has reached a level where the condition now ranks second or third among the bacterial diarrhoeal diseases in Europe. Because of its growing importance, it merits the same attention as salmonellosis with which it shows certain similarities in terms of physiopathology and epidemiology. Prevention should be based on a common methodological approach to both types of infection. The cost of treating yersiniosis is high because of the associated complications (erythema nodosum and arthritis requiring long and difficult treatment) and the frequent need for surgery in certain digestive forms.

SURVEILLANCE

The WHO collaborating centre for *Y. enterocolitica,* at the Bacterial Ecology Unit, Pasteur Institute, Paris provides worldwide services for expert evaluation of bacterial strains, antigenic typing and phage typing. It

supplies corresponding institutions with reference strains and bacteriophages for diagnosis and phage typing. It maintains an updated list of bibliographical references concerning yersiniosis, and sends it to interested correspondents twice a year. To carry out surveillance, national facilities must be established for the detection and typing of strains and for the standardization of isolation, identification and immunological diagnostic techniques. It is essential that national centres and the WHO collaborating centre remain in contact in order to monitor the epidemiological situation.

RECOMMENDATIONS

Improvement of laboratory diagnostic methods

1. The media and techniques used for identification and isolation should be standardized according to the material analysed (pathological substances, foodstuffs, water or samples from the natural environment).

2. The enrichment media and procedures used for epidemiological investigations should be standardized to allow comparability of results.

3. There is an urgent need to complete the antigenic typing of *Y. enterocolitica, Y. intermedia, Y. frederiksenii* and *Y. kristensenii,* of which increasing numbers of strains are classified as nonagglutinable, in order to define epidemiological markers for these new phenotypes.

4. The titration procedures and antigens used for serological diagnosis should be standardized to allow reliable interpretation of results and reproducibility of examinations in the same patient, according to syndromes and countries.

Research

Epidemiology

1. The methods used for investigating sources of human infection should be standardized, especially those for the detection of *Yersinia* in swine and other animals closely associated with man.

2. To determine the rate of asymptomatic carriers of *Yersinia* in man, it will be necessary to undertake systematic surveillance of representative

samples of the population that would show the etiology and frequency of certain relatively nonspecific symptoms (erythema nodosum, arthritis, glomerulonephritis, carditis, thyroiditis, etc.) and provide a basis for determining the duration of the incubation phase and the infection index.

3. The relationship between *Yersinia* and Crohn's ileitis should be clarified.

4. Systematic investigations of *Yersinia,* made initially by faecal culture, should be extended to pharyngeal swab sampling and, in view of the possible neonatal implications, systematic screening for the organism in gynaecology and obstetrics.

Physiopathology

1. Research should be undertaken on the pathogenic mechanisms of the serogroups O3 and O9 that are mainly incriminated in human cases, modes of infection, target tissues in the host, and modes of transmission from an infected individual to one at risk. A laboratory animal model should be developed in order to study immune responses to yersiniosis and the effect of antibiotic therapy on this infection.

2. Strains of *Y. enterocolitica* biotype 1, *Y. intermedia, Y. frederiksenii* and *Y. kristensenii,* which are being isolated increasingly in samples from the external environment, and also in cases of superinfections in man or clinically healthy subjects, should be studied with reference to their virulence and their pathogenic mechanisms, as these are not known at present.

3. Inflammation of the joints, erythema nodosum and other tissue involvement with nonspecific symptoms are conditions that should be investigated with a view to clarifying the immunopathology of yersiniosis.

4. Antibiotic resistance of *Yersinia* strains should be studied not only by elucidating the chromosome mechanisms, but also through monitoring the development of resistance factors not involving the chromosomes.

5. The effect of antibiotic therapy on the occurrence of complications should be studied both in patients and experimentally with regard to the modification of symptoms, the establishment of a carrier state with faecal excretion in convalescents, and the development of resistance to secondary infection.

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Annex 1

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