Enterobacteriaceae

The **Enterobacteriaceae** is a large family of Gram-negative bacteria that includes, along with many harmless symbionts, many of the more familiarpathogens, such as *Salmonella*, *Escherichia coli*, *Yersinia pestis*, *Klebsiella* and *Shigella*. Other disease-causing bacteria in this family include*Proteus*, *Enterobacter*, *Serratia*, and *Citrobacter*. This family is the only representative in the order Enterobacteriales of the classGammaproteobacteria in the phylum Proteobacteria Phylogenetically, in the Enterobacteriales, several peptidoglycan-less insect endosymbionts form a sister clade to the Enterobacteriaceae, but as they are not validly described, this group is not officially a taxon; examples of these species are*Sodalis*, *Buchnera*, *Wigglesworthia*, *Baumannia* and *Blochmannia*, but not former rickettsias. Members of the Entero - bacteriaceae can be triviallyreferred to as enterobacteria, as several members live in the intestines of animals. In fact, the etymology of the family is enterobacterium with the suffix to designate a family (aceae) — not after the genus *Enterobacter* (which would be "Enterobacteraceae")— and the type genus is *Escherichia*.

Characteristics

Members of the Enterobacteriaceae are rod-shaped, and are typically 1-5 µm in length. Like other proteobacteria, enterobacteria have Gram-negativestains, and they are facultative anaerobes, fermenting sugars to produce lactic acid and various other end products. Most also reduce nitrate to nitrite, although exceptions exist (e.g.*Photorhabdus*). Unlike most similar bacteria, enterobacteria generally lack cytochrome C oxidase, although there are exceptions (e.g. *Plesiomonas shigelloides*). Most have many flagella used to move about, but a few genera are nonmotile. They are not spore-forming. Catalase reactions vary among Enterobacteriaceae.

Many members of this family are a normal part of the gut flora found in the intestines of humans and other animals, while others are found in water or soil, or are parasites on a variety of different animals and plants. *Escherichia coli* is one of the most important model organisms, and its genetics and biochemistry have been closely studied.

Most members of Enterobacteriaceae have peritrichous, type I fimbriae involved in the adhesion of the bacterial cells to their hosts. Some enterobacteria produce endotoxins. Endotoxins reside in the cell cytoplasm and are released when the cell dies and the cell wall disintegrates. Some members of the Enterobacteriaeceae produce endotoxins that, when released into the bloodstream following cell lysis, cause a systemic inflammatory and vasodilatory response. The most severe form of this is known as endotoxic shock, which can be rapidly fatal.

Identification

To identify different genera of Enterobacteriaceae, a microbiologist may run a series of tests in the lab. These include:

Phenol red

- Tryptone broth
- Phenylalanine agar for detection of production of deaminase, which converts phenylalanine to phenylpyruvic acid
- Methyl red or Voges-Proskauer tests depend on the digestion of glucose. The methyl red tests for acid endproducts. The Voges Proskauer tests for the production of acetylmethylcarbinol.
- Catalase test on nutrient agar tests for the production of catalase enzyme, which splits hydrogen peroxide and releases oxygen gas.
- Oxidase test on nutrient agar tests for the production of the enzyme oxidase, which reacts with an aromatic amine to produce a purple color.
- Nutrient gelatin tests to detect activity of the enzyme gelatinase.

In a clinical setting, three species make up 80 to 95% of all isolates identified. These are *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*.

Antibiotic resistance

Several Enterobacteriacea strains have been isolated which are resistant to antibiotics including carbapenem, which are often claimed as "the last line of antibiotic defense" against resistant organisms. For instance, some *Klebsiella pneumonia* strains are carbapenem resistant.

Examples/classification

The following inexhaustive list details bacterial genera classified as members of Enterobacteriaceae.

Genera

Alishewanella

- *Alterococcus*
- *Aquamonas*
- *Aranicola*
- *Arsenophonus*
- *Azotivirga*
- *Blochmannia*
- *Brenneria*
- *Buchnera*
- *Budvicia*
- *Buttiauxella*
- *Cedecea*
- *Citrobacter*
- *Cronobacter*
- *Dickeya*
- *Edwardsiella*
- *Enterobacter*
- *Erwinia*, e.g. *Erwinia amylovora*, *Erwinia tracheiphila*, *Erwinia carotovora*, etc.
- *Escherichia*, e.g. *Escherichia coli*
- *Ewingella*
- *Grimontella*
- *Hafnia*
- *Hamiltonella*
- *Klebsiella*, e.g. *Klebsiella pneumoniae*
- *Kluyvera*
- *Leclercia*
- *Leminorella*
- *Moellerella*
- *Morganella*

- *Obesumbacterium*
- *Pantoea*
- *Pectobacterium* see *Erwinia*
- *Candidatus* Phlomobacter
- *Photorhabdus*, e.g. *Photorhabdus luminescens*
- *Plesiomonas*, e.g. *Plesiomonas shigelloides*
- *Pragia*
- *Proteus*, e.g. *Proteus vulgaris*
- *Providencia*
- *Rahnella*
- *Regiella*
- *Raoultella*
- *Salmonella*
- *Samsonia*
- *Serratia*, e.g. *Serratia marcescens*
- *Shigella*
- *Sodalis*
- *Tatumella*
- *Trabulsiella*
- *Wigglesworthia*
- *Xenorhabdus*
- *Yersinia*, e.g. *Yersinia pestis*
- *Yokenella*

Escherichia coli

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Escherichia coli (/ˌɛrɪkiˌkoˈlaɪ/;commonly abbreviated ***E. coli***) is a Gram-negative, facultative anaerobic, rod-shaped bacterium that is commonly found in the lower intestine of warm-blooded organisms (endotherms). Most *E. coli* strains are harmless, but some serotypes can cause serious food poisoning in humans, and are occasionally responsible for product recalls due to food contamination. The harmless strains are part of the normal flora of the gut, and can benefit their hosts by producing vitamin K_2, and by preventing the establishment of pathogenic bacteria within the intestine.*E. coli* and related bacteria constitute about 0.1% of gut flora, and fecal–oral transmission is the major route through

which pathogenic strains of the bacterium cause disease. Cells are able to survive outside the body for a limited amount of time, which makes them ideal indicator organismsto test environmental samples for fecal contamination. There is, however, a growing body of research that has examined environmentally persistent *E. coli* which can survive for extended periods outside of the host

The bacterium can also be grown easily and inexpensively in a laboratory setting, and has been intensively investigated for over 60 years. *E. coli* is the most widely studied prokaryotic model organism, and an important species in the fields of biotechnology and microbiology, where it has served as the host organism for the majority of work with recombinant DNA.

History

The genera *Escherichia* and *Salmonella* diverged around 102 million years ago (credibility interval: 57–176 mya), which coincides with the divergence of their hosts: the former being found in mammals and the latter in birds and reptiles.[11] This was followed by a split of the escherichian ancestor into five species (*E. albertii*, *E. coli*, *E. fergusonii*, *E. hermannii* and *E. vulneris*.) The last*E. coli* ancestor split between 20 and 30 million years ago

In 1885, a German pediatrician, Theodor Escherich, discovered this organism in the feces of healthy individuals and called it *Bacterium coli commune* due to the fact it is found in the colon and early classifications of Prokaryotes placed these in a handful of genera based on their shape and motility (at that time Ernst Haeckel's classification of Bacteria in the kingdom Monera was in place *Bacterium coli* was the type species of the now invalid genus *Bacterium* when it was revealed that the former type species ("*Bacterium triloculare*") was missing. Following a revision of *Bacteria* it was reclassified as *Bacillus coli* by Migula in 1895and later reclassified in the newly created genus *Escherichia*, named after its original discoverer.

The genus belongs in a group of bacteria informally known as "coliforms", and is a member of the Enterobacteriaceae family ("the enterics") of the Gammaproteobacteria.

Biology and biochemistry

E. coli is Gram-negative, facultative anaerobic and non-sporulating. Cells are typically rod-shaped, and are about 2.0 micrometers(μm) long and 0.25-1.0 μm in diameter, with a cell volume of 0.6–0.7 $μm^3$. It can live on a wide variety of substrates. *E. coli* uses mixed-acid fermentation in anaerobic conditions, roducing lactate, succinate, ethanol, acetate and carbon dioxide. Since many pathways in mixed-acid fermentation produce hydrogen gas, these pathways require the levels of hydrogen to be low, as is the case when *E. coli* lives together with hydrogen-consuming organisms, such as methanogens or sulphate-reducing bacteria.

Optimal growth of *E. coli* occurs at 37 °C (98.6 °F) but some laboratory strains can multiply at temperatures of up to 49 °C(120 °F). Growth can be driven by aerobic or anaerobic respiration, using a large variety of redox pairs, including the oxidation of pyruvic acid, formic acid, hydrogen and amino acids, and the reduction of substrates such as oxygen, nitrate, fumarate,dimethyl sulfoxide and trimethylamine N-oxide.

Strains that possess flagella are motile. The flagella have a peritrichous arrangement.

E. coli and related bacteria possess the ability to transfer DNA via bacterial conjugation, transduction or transformation, which allows genetic material to spread horizontally through an existing population. This process led to the spread of the gene encoding shiga toxin from *Shigella* to E. coli O157:H7, carried by a bacteriophage.

Diversity

Escherichia coli encompasses an enormous population of bacteria that exhibit a very high degree of both genetic and phenotypic diversity. Genome sequencing of a large number of isolates of *E. coli* and related bacteria shows that a taxonomic reclassification would be desirable. However, this has not been done, largely due to its medical importanceand *E. coli* remains one of the most diverse bacterial species: only 20% of the genome is common to all strains In fact, from the evolutionary point of view, the members of genus *Shigella* (*S. dysenteriae*, *S. flexneri*, *S. boydii*, *S. sonnei*) should be classified as *E.*

coli strains, a phenomenon termed taxa in disguise Similarly, other strains of *E. coli* (e.g. the K-12 strain commonly used in recombinant DNA work) are sufficiently different that they would merit reclassification.

A strain is a sub-group within the species that has unique characteristics that distinguish it from other strains. These differences are often detectable only at the molecular level; however, they may result in changes to the physiology or lifecycle of the bacterium. For example, a strain may gain pathogenic capacity, the ability to use a unique carbon source, the ability to take upon a particular ecological niche or the ability to resist antimicrobial agents. Different strains of *E. coli* are often host-specific, making it possible to determine the source of fecal conta - mination in environmental samples. For example, knowing which *E. coli* strains are present in a water sample allows researchers to make assumptions about whether the contamination originated from a human, another mammal or a bird.

Serotypes

A common subdivision system of *E. coli*, but not based on evolutionary relatedness, is by serotype, which is based on major surface antigens (O antigen: part of lipopolysaccharide layer; H:flagellin; K antigen: capsule), e.g. O157:H7 It is however common to cite only the serogroup, i.e. the O-antigen. At present about 190 serogroups are known. The common laboratory strain has a mutation that prevents the formation of an O-antigen and is thus non-typeable.

Genome plasticity

Like all lifeforms, new strains of *E. coli* evolve through the natural biological processes of mutation, gene duplication and horizontal gene transfer, in particular 18% of the genome of the laboratory strain MG1655 was horizontally acquired since the divergence from *Salmonella*. In microbiology, all strains of *E. coli* derive from *E. coli* K-12 or *E. coli* B strains. Some strains develop traitsthat can be harmful to a host animal. These virulent strains typically cause a bout of diarrhea that is unpleasant in healthy adults and is often lethal to children in the developing world. More virulent strains, such as O157:H7 cause serious illness or death in the elderly, the very young or the immunocompromised

Genomics

The first complete DNA sequence of an *E. coli* genome (laboratory strain K-12 derivative MG1655) was published in 1997. It was found to be a circular DNA molecule 4.6 million base pairs in length, containing 4288 annotated protein-coding genes (organized into 2584 operons), seven ribosomal RNA (rRNA) operons, and 86 transfer RNA (tRNA) genes. Despite having been the subject of intensive genetic analysis for approximately 40 years, a large number of these genes were previously unknown. The coding density was found to be very high, with a mean distance between genes of only 118 base pairs. The genome was observed to contain a significant number of transposable genetic elements, repeat elements, cryptic prophages, and bacteriophage remnants.

Today, over 60 complete genomic sequences of *Escherichia* and *Shigella* species are available. Comparison of these sequences shows a remarkable amount of diversity; only about 20% of each genome represents sequences present in every one of the isolates, while approximately 80% of each genome can vary among isolates. Each individual genome contains between 4,000 and 5,500 genes, but the total number of different genes among all of the sequenced E. coli strains (the pan-genome) exceeds 16,000. This very large variety of component genes has been interpreted to mean that two-thirds of the *E. coli* pangenome originated in other species and arrived through the process of horizontal gene transfer.

Proteomics

Full sets of *E. coli* proteins and their interactions have also been isolated and studied. A 2006 study purified 4,339 proteins from cultures of strain K-12 and found interacting partners for 2,667 proteins, many of which had unknown functions at the time. A 2009 study found 5,993 interactions between proteins of the same *E. coli* strain though this data showed little overlap with that of the 2006 publicatio

Role in disease

Virulent strains of *E. coli* can cause gastroenteritis, urinary tract infections, and neonatal meningitis. In rarer cases, virulent strains are also responsible for hemolytic-uremic syndrome, peritonitis, mastitis, septicemia and Gram-negative pneumonia. UPEC (uropathogenic *E. coli*) is one of the main causes of urinary tract infections. It is part of the normal flora in the gut and can be introduced many ways. In particular for females, the direction of wiping after defecation (wiping back to front) can lead to fecal contamination of the urogenital orifices. Anal sex can also introduce this bacteria into the male

urethra, and in switching from anal to vaginal intercourse the male can also introduce UPEC to the female urogenital system. For more info see databases at the end of the article or UPEC pathogenicity.

In May 2011, one *E. coli* strain, *Escherichia coli* O104:H4, has been the subject of a bacterial outbreak that began in Germany. Certain strains of *E. coli* are a major cause of foodborne illness. The outbreak started when several people in Germany were infected with enterohemorrhagic *E. coli* (EHEC) bacteria, leading to hemolytic-uremic syndrome (HUS), a medical emergency that requires urgent treatment. The outbreak did not only concern Germany, but 11 other countries, including regions in North America. On 30 June 2011 the German *Bundesinstitut für Risiko-bewertung (BfR)* (*Federal Institute for Risk Assessment*, a federal, fully legal entity under public law of the Federal Republic of Germany, an institute within the German Federal Ministry of Food, Agriculture and Consumer Protection) announced that seeds of fenugreek from Egypt were likely the cause of the EHEC outbreak.

Klebsiella

Klebsiella is a genus of non-motile, Gram-negative, oxidase-negative, rod-shaped bacteria with a prominent polysaccharide-based capsule. It is named after the German microbiologist Edwin Klebs (1834–1913). Frequent human pathogens, *Klebsiella* organisms can lead to a wide range of disease states, notably pneumonia, urinary tract infections, septicemia, and soft tissue infections. *Klebsiella* species have also been implicated in the pathogenesis ofankylosing spondylitis and other spondyloarthropathies

Klebsiella species are ubiquitous in nature.

During the last 40 years, many trials for constructing effective Klebsiella pneumoniae vaccines have been tried. Currently, no Klebsiella vaccine has been licensed for use in the US. Klebsiella pneumoniae is the most common cause of nosocomial respiratory tract and premature intensive care infections, and the second most frequent cause of Gram-negative bacteraemia and urinary tract infections. Drug resistant isolates remain an important hospital-acquired bacterial pathogen, add significantly to hospital stays, and are especially problematic in high impact medical areas such as intensive care units.

Klebsiella pneumoniae

Klebsiella pneumoniae is a Gram-negative, non-motile, encapsulated, lactose-fermenting, facultative anaerobic, rod-shaped bacterium.

Although found in the normal flora of the mouth, skin, and intestines, it can cause destructive changes to human lungs if aspirated.

In the clinical setting, it is the most significant member of the *Klebsiella* genus of Enterobacteriaceae.

Seven species of the *Klebsiella* genus, with demonstrated similarities in DNA homology are known. These are (1) *Klebsiella pneumoniae*, (2)*Klebsiella ozaenae*, (3) *Klebsiella terrigena*, (4) *Klebsiella rhinoscleromatis*, (5) *Klebsiella oxytoca*, (6) *Klebsiella planticola*, and (7) *Klebsiella ornithinolytica*. Of these, *K oxytoca* and *K rhinoscleromatis* have also been demonstrated in human clinical specimens.

In recent years, klebsiellae have become important pathogens in nosocomial infections.

It is closely related to *K. oxytoca* from which it is distinguished by being indole-negative and by its ability to grow on both melezitose and 3-hydroxybutyrate. It naturally occurs in the soil, and about 30% of strains can fix nitrogen in anaerobic conditions. As a free-living diazotroph, its nitrogen fixation system has been much-studied.

Members of the *Klebsiella* genus typically express 2 types of antigens on their cell surface. The first, O antigen is a component of thelipopolysaccharide (LPS), of which 9 varieties exist. The second is K antigen, a capsular polysaccharide with more than 80 varieties. Both contribute to pathogenicity and form the basis for serogrouping.

Clinical significance[

K. pneumoniae can cause the disease Klebsiella pneumonia. They cause destructive changes to human lungs inflammation and hemorrhage with cell death (necrosis) that sometimes produces a thick, bloody, mucoid sputum (currant jelly sputum). These bacteria gain access typically after a person aspirates colonizing oropharyngeal microbes into the lower respiratory tract.

As a general rule, *Klebsiella* infections are seen mostly in people with a weakened immune system. Most often illness affects middle-aged and older men with debilitating diseases. This patient population is believed to have impaired respiratory host defenses, including persons with diabetes, alcoholism, malignancy, liver disease, Chronic obstructive pulmonary diseases (COPD),glucocorticoid therapy, renal failure, and

certain occupational exposures (such as paper mill workers). Many of these infections are obtained when a person is in the hospital for some other reason (a nosocomial infection).

The most common infection caused by *Klebsiella* bacteria outside the hospital is pneumonia, typically in the form of bronchopneumonia and also bronchitis. These patients have an increased tendency to develop lung abscess, cavitation, empyema, and ural adhesions. It has a high death rate of about 50% even with antimicrobial therapy. The mortality rate can be nearly 100% for persons with alcoholism and bacteremia.

In addition to pneumonia, *Klebsiella* can also cause infections in the urinary tract, lower biliary tract, and surgical wound sites. The range of clinical diseases includes pneumonia,thrombophlebitis, urinary tract infection (UTI), cholecystitis, diarrhea, upper respiratory tract infection, wound infection, osteomyelitis, meningitis, and bacteremia and septicemia. For patients with an invasive device in their body, contamination of the device becomes a risk; for example, respiratory support equipment and urinary catheters put patients at increased risk. Also, the use of antibiotics can be a factor that increases the risk of nosocomial infection with *Klebsiella* bacteria. Sepsis and septic shock can follow entry of the bacteria into the blood.

Two unusual infections of note that are from *Klebsiella* are rhino - scleroma and ozena. Rhinoscleroma is a chronic inflammatory process involving the nasopharynx. Ozena is a chronic atrophicrhinitis that produces necrosis of nasal mucosa and mucopurulent nasal discharge.

Research conducted at King's College, London has implicated molecular mimicry between HLA-B27 and two *Klebsiella* surface moleculars as the cause of ankylosing spondylitis. New antibiotic resistant strains of *K. pneumoniae* are appearing, and it is increasingly found as a nosocomial infection.

Klebsiella ranks second to *E. coli* for urinary tract infections in older persons. It is also an opportunistic pathogen for patients with chronic pulmonary disease, enteric pathogenicity, nasal mucosa atrophy, and rhinoscleroma. Feces are the most significant source of patient infection, followed by contact with contaminated instruments.

Resistant strains

Infection with carbapenem-resistant Enterobacteriaceae (CRE) or carbapenemase-producing Enterobacteriaceae is emerging as an important challenge in health-care settings. One of many carbapenem-resistant Enterobacteriaceae (CRE) is Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP). Over the past 10 years, a progressive increase in CRKP has been seen worldwide; however, this new emerging nosocomial pathogen is probably best known for an outbreak in Israel that began around 2006 within the healthcare system there. In the USA, it was first described in North Carolina in 1996; since then CRKP has been identified in 41 states; and is recovered routinely in certain hospitals in New York and New Jersey. It is now the most common CRE species encountered within the United States.

CRKP is resistant to almost all available antimicrobial agents, and infections with CRKP have caused high rates of morbidity and mortality, in particular among persons with prolonged hospitalization and those critically ill and exposed to invasive devices (e.g., ventilators or central venous catheters). The concern is that carbapenem is often used as a drug of last resort when battling resistant bacterial strains. The worry is that new slight mutations could result in infections for which there is very little, if anything, healthcare professionals can do to treat patients with resistant organisms.

There are a number of mechanisms of Carbapenem Resistance in Enterobacteriaceae. These include (1) Hyperproduction of ampC beta-lactamase with an outer membrane porin mutation (2) CTX-M extended-spectrum beta-lactamase with a porin mutation or drug efflux, and (3) Carbapenemase production. When Klebsiella pneumoniae bacteria produce the carbapenemase enzyme they are known as KPC-producing organisms or carbapenem-resistant Klebsiella pneumoniae (CRKP). Put another way, the most important mechanism of resistance by CRKP is the production of a carbapenemase enzyme, *blak*pc. The gene that encodes the *blak*pc enzyme is carried on a mobile piece of genetic material (a transposon; the specific transposon involved is called Tn4401), which increases the risk for dissemination. CRE can be difficult to detect because some strains that harbor *blak*pc have minimal inhibitory concentrations (MICs) that are elevated but still within the susceptible range for carbapenems. Because these strains are susceptible to carbapenems, they are not identified as potential clinical or infection

control risks using standard susceptibility testing guidelines. Patients with unrecognized CRKP colonization have been reservoirs for transmission during nosocomial outbreaks.

The extent and prevalence of CRKP within the environment is currently unknown. The mortality rate is also unknown but is suspected to be within a range of 12.5% to as high as 44%.The likelihood of an epidemic or pandemic in the future remains uncertain.

The Centers for Disease Control and Prevention (CDC) released guidance for aggressive infection control to combat CRKP.

Place all patients colonized or infected with CRE or carbapenemase-producing Enterobacteriaceae on contact precautions. Acute-care facilities are to establish a protocol, in conjunction with the guidelines of the Clinical and Laboratory Standards Institute (CLSI) to detect nonsusceptibility and carbapenemase production in Entero - bacteriaceae, in particular *Klebsiella* spp. and *Escherichia coli*, and immediately alert epidemiology and infection control staff members if identified. All acute-care facilities are to review microbiology records for the preceding 6--12 months to ensure that there have not been previously unrecognized CRE cases. If they do identify previously unrecognized cases, a point prevalence survey (a single round of active surveillance cultures) in units with patients at high risk (e.g., intensive-care units, units where previous cases have been identified, and units where many patients are exposed to broad-spectrum antimicrobials) is needed to identify any additional patients colonized with carbapenem-resistant or carba - penemase-producing *Klebsiella* spp. and *E. coli*. When a case of hospital-associated CRE is identified, facilities should conduct a round of active surveillance testing of patients with epidemiologic links to the CRE case (e.g., those patients in the same unit or patients having been cared for by the same health-care personnel).

One specific example of this containment policy could be seen in Israel in 2007. This policy had an intervention period from April, 2007 to May, 2008. A nationwide outbreak of CRE (which peaked in March, 2007 at 55.5 cases per 100,000 patient days) necessitated a nationwide treatment plan. The intervention entailed physical separation of all CRE carriers and appointment of a task force to oversee efficacy of isolation by closely monitoring hospitals and intervening when necessary. After the treatment plan (measured in May, 2008), the number of cases per 100,000 patient

days decreased to 11.7. The plan was effective because of strict hospital compliance, wherein each was required to keep detailed documentation of all CRE carriers. In fact, for each increase in compliance by 10%, incidence of cases per 100,000 patient days decreased by 0.6. Therefore, containment on a nationwide scale requires nationwide intervention.

In the United States, the reasons that the CDC is recommending the detection of carbapenem resistance or carbapenemase production only for *Klebsiella* spp. and *E. coli* are 1) this facilitates performing the test in the microbiology laboratory without the use of molecular methods and 2) these organisms represent the majority of CRE encountered in the United States.

Effective sterilization and decontamination procedures are important to keep the infection rate of this antibiotic resistant strain, CRKP as low as possible.

Treatment

As with many bacteria, the recommended treatment has changed as the organism has developed resistances. *Klebsiella* organisms are often resistant to multiple antibiotics. Current evidence implicates a plasmid as the source of the resistant genes. *Klebsiella* with the ability to produce extended-spectrum beta-lactamases ESBL are resistant to many classes of antibiotics. The most frequent resistances include resistance to aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicol, and trimethoprim/sulfamethoxazole

The choice of a specific antimicrobial agent or agents depends on local susceptibility patterns and on the part of the body that is infected. For patients with severe infections, a prudent approach is the use of an initial short course (48-72 h) of combination therapy, followed by a switch to a specific mono-therapy once the susceptibility pattern is known for the specific patient.

If the specific *Klebsiella* in a particular patient does not have antibiotic resistance, then the antibiotics used to treat such susceptible isolates include ampicillin/sulbactam, piperacillin/tazobactam,ticarcillin/clavulana te, ceftazidime, cefepime, levofloxacin, norfloxacin, gatifloxacin, moxiflo xacin, meropenem, and ertapenem. Some experts recommend the use of meropenem for patients with ESBL producing *Klebsiella*. The claim is that meropenem produces the best bacterial clearing.

The use of antibiotics is usually not enough. Surgical clearing (frequently done as interventional radiology drainage) is often needed after the patient is started on antimicrobial agents.

Yersinia pestis

Yersinia pestis (formerly *Pasteurella pestis*) is a type of bacterium. More specifically, it is a Gram-negative rod-shaped coccobacillus. It is a facultative anaerobe that can infect humans and other animals

Human *Y. pestis* infection takes three main forms: pneumonic, septicemic, and bubonic plagues. All three forms are widely believed to have been responsible for a number of high-mortality epidemics throughout human history, including the Justinianic plague of the sixth century and the Black Deaththat accounted for the death of at least one-third of the European population between 1347 and 1353. It has now been shown conclusively that these plagues originated in rodent populations in China More recently, *Y. pestis* has gained attention as a possible biological warfare agent and the CDChas classified it as a category A pathogen requiring preparation for a possible terrorist attack

Y. pestis was discovered in 1894 by Alexandre Yersin, a Swiss/French physician and bacteriologist from the Pasteur Institute, during an epidemic of plague in Hong Kong Yersin was a member of the Pasteur school of thought. Kitasato Shibasabur , a German-trained Japanese bacteriologist who practiced Koch's methodology, was also engaged at the time in finding the causative agent of plague. However, it was Yersin who actually linked plague with *Yersinia pestis*. Originally named *Pasteurella pestis*, the organism was renamed in 1967.

Every year, thousands of cases of plague are still reported to the World Health Organization, although, with proper treatment, the prognosis for victims is now much better. A five- to six-fold increase in cases occurred in Asia during the time of the Vietnam war, possibly due to the disruption of ecosystems and closer proximity between people and animals. Plague also has a detrimental effect on non-human mammals. In the United States of America, animals such as the black-tailed prairie dog and the endangered black-footed ferret are under threat from the disease.

Historical outbreaks

Plague of Justinian

During the mid 6th century, the pandemic known as the Plague of Justinian wiped out roughly one third of the Byzantine Empire's population, creating major military and financial difficulties. Modern historians named this plague incident after the Eastern Roman Emperor Justinian I, who held power in the Byzantine capital of Constantinople at the time of the initial outbreak. The primary years of the plague were 541–542 AD, although plague returned throughout the Mediterranean basin in successive generations, until about 750.

The waves of disease had a major effect on the future course of European history. The plague's social and cultural impact during the Justinian period is comparable to that of the Black Death.

The most commonly accepted cause of the pandemic has been bubonic plague. A genetic study suggests that the Plague of Justinian (and others from antiquity) arose from either now-extinct strains of *Y. pestis*, genetically distinct from the strain that broke out in the 14th century pandemic, or from pathogens entirely unrelated to bubonic plague.

Role in Black Death

Confirmed presence of *Y. pestis* indicates that it was a contributing factor in at least some of the European plagues.

In 2000, Didier Raoult and others reported finding *Y. pestis* DNA by performing a "suicide PCR" on tooth pulp tissue from a fourteenth-century plague cemetery in Montpellier

A study by an international team of researchers published in October 2010 confirmed that *Y. pestis* was the cause of the Black Death and later epidemics on the entire European continent over a period of 400 years. The team used ancient DNA and proteins recovered from the bodies of plague victims buried in Hereford in England, in Saint-Laurent-de-la-Cabrerisse in France, and Bergen op Zoom in the Netherlands to identify the pathogen.[12] They found two previously unknown, older strains of *Y. pestis* that had spread from China by two different routes, rather than the modern*Orientalis* and *Medievalis*.

Three biovars of *Y. pestis* were originally thought to correspond to one of the historical pandemics of bubonic plague. Biovar *Antiqua* is thought to correspond to the Plague of Justinian; it is not known whether this biovar also corresponds to earlier or smaller epidemics of bubonic plague, or

whether these were even truly bubonic plague. Biovar *Mediaevalis* was formerly thought to correspond to the Black Death, while Biovar *Orientalis* was thought to correspond to the Third Pandemic and the majority of modern outbreaks of plague. However, calculations of *Y pestis's* evolutionary age, found using the number of synonymous single nucleotide polymorphisms (SNPs) in conjunction with molecular clock rates, date the emergence of the biovars prior to any of the historical epidemics due to the length of time needed to accumulate such mutations Additional evidence against this hypothesis includes the fact that *Mediaevalis* is likely too young to have produced the Black Death due to its recent divergence from *Orientalis*.

General characteristics

Y. pestis is a rod-shaped facultative anaerobe with bipolar staining (giving it a safety pin appearance). Similar to other *Yersinia* members, it tests negative for urease, lactose fermentation, andindole. The closest relative is the gastrointestinal pathogen *Yersinia pseudotuberculosis*, and more distantly *Yersinia enterocolitica*.

Genome

The complete genomic sequence is available for two of the three sub-species of *Y. pestis*: strain KIM (of biovar Medievalis) and strain CO92 (of biovar *Orientalis*, obtained from a clinical isolate in the United States). As of 2006, the genomic sequence of a strain of biovar *Antiqua* has been recently completed. Similar to the other pathogenic strains, there are signs of loss of function mutations. The chromosome of strain KIM is 4,600,755 base pairs long; the chromosome of strain CO92 is 4,653,728 base pairs long. Like its cousins *Y. pseudotuberculosis* and *Y. enterocolitica*, *Y. pestis* is host to the plasmid pCD1. In addition, it also hosts two other plasmids, pPCP1 (also called pPla or pPst) and pMT1 (also called pFra) that are not carried by the other*Yersinia* species. pFra codes for a phospholipase D that is important for the ability of *Y. pestis* to be transmitted by fleas.[25] pPla codes for a protease, Pla, that activates plasminogen in human hosts and is a very important virulence factor for pneumonic plague. Together, these plasmids, and a patho - genicity island called HPI, encode several proteins that cause the pathogenesis, for which *Y. pestis* is famous. Among other things, these virulence factors are required for bacterial adhesion and injection of proteins into the host cell, invasion of bacteria in the host cell (via a Type

III secretion system), and acquisition and binding of iron that is harvested from red blood cells (via siderophores). *Y. pestis* is thought to be descendant from *Y. pseudotuberculosis*, differing only in the presence of specific virulence plasmids.

A comprehensive and comparative proteomics analysis of *Y. pestis* strain KIM was performed in 2006. The analysis focused on the transition to a growth condition mimicking growth in host cells.

Pathogenics and immunity

Oriental rat flea (*Xenopsylla cheopis*) infected with the *Yersinia pestis* bacteriumwhich appears as a dark mass in the gut. The foregut (*proventriculus*) of this flea is blocked by a *Y. pestis biofilm;* when the flea attempts to feed on an uninfected host, *Y. pestis* is regurgitated into the wound, causing infection.

In the urban and sylvatic (forest) cycles of *Y. pestis,* most of the spreading occurs between rodents and fleas. In the sylvatic cycle, the rodent is wild, but, in the urban cycle, the rodent is domestic. In addition, *Y. pestis* can spread from the urban environment and back. Every infected animal can transmit the infection to humans through contact with skin tissue. Humans can also spread the bacteria to other humans through sneezing, coughing, or direct contact with infected tissue.

In reservoir hosts

The reservoir commonly associated with *Y. pestis* is several species of rodents. In the steppes, the reservoir species is believed to be principally themarmot. In the United States, several species of rodents are thought to maintain *Y. pestis*. However, the expected disease dynamics have not been found in any rodent species. It is known that rodent populations will have a variable resistance, which could lead to a carrier status in some individuals. There is evidence that fleas from other mammals have a role in human plague outbreaks.

This lack of knowledge of the dynamics of plague in mammal species is also true among susceptible rodents such as the black-tailed prairie dog (*Cynomys ludovicianus*), in which plague can cause colony collapse, resulting in a massive effect on prairie food webs. However, the transmission dynamics within prairie dogs does not follow the dynamics of blocked fleas; carcasses, unblocked fleas, or another vector could possibly be important instead.

In other regions of the world, the reservoir of the infection is not clearly identified, which complicates prevention and early warning programs. One such example was seen in a 2003 outbreak in Algeria.

Infector

The transmission of *Y. pestis* by fleas is well characterized. Initial acquisition of *Y. pestis* by the vector occurs during feeding on an infected animal. Several proteins then contribute to the maintenance of the bacteria in the flea digestive tract, among them the hemin storage (Hms) system and *Yersinia* murine toxin (Ymt).

Although *Yersinia* murine toxin is highly toxic to rodents and was once thought to be produced to ensure reinfection of new hosts, it has been demonstrated that Ymt is important for the survival of *Y. pestis* in fleas. The Hms system plays an important role in the transmission of *Y. pestis* back to a mammalian host. While in the insect vector, proteins encoded by Hms genetic loci induce biofilm formation in the proventriculus, a valve connecting the midgut to the esophagus Aggregation in the biofilm inhibits feeding, as a mass of clotted blood and bacteria forms (referred to as "Bacot's block"[]). Transmission of *Y. pestis* occurs during the futile attempts of the flea to feed. Ingested blood is pumped into the esophagus, where it dislodges bacteria lodged in the proventriculus and is regurgitated back into the host circulatory system.

In humans and other susceptible hosts

Pathogenesis due to *Y. pestis* infection of mammalian hosts is due to several factors including an ability of these bacteria to suppress and avoid normal immune system responses such as phagocytosis and antibody production. Flea bites allow for the bacteria to pass the skin barrier. *Y. pestis* expresses the *yadBC* gene, which is similar to adhesins in other *Yersinia* species, allowing for adherence and invasion of epithelial cells. *Y. pestis* expresses a plasminogen activator that is an important virulence factor for pneumonic plague and that might degrade on blood clots in order to facilitate systematic invasion. Many of the bacteria's virulence factors are anti-phagocytic in nature. Two important anti-phagocytic antigens, named F1 (Fraction 1) and V orLcrV, are both important for virulence These antigens are produced by the bacterium at normal human body temperature. Furthermore, *Y. pestis* survives and produces F1 and V antigens while it is residing within white blood cells such

as monocytes, but not in neutrophils. Natural or induced immunity is achieved by the production of specific opsonic antibodies against F1 and V antigens; antibodies against F1 and V induce phagocytosis by neutrophils.

In addition, the Type III secretion system (T3SS) allows *Y. pestis* to inject proteins into macrophages and other immune cells. These T3SS-injected proteins are called Yops (Yersinia Outer Proteins) and include Yop B/D, which form pores in the host cell membrane and have been linked to cytolysis. The YopO, YopH, YopM, YopT, YopJ, and YopE are injected into the cytoplasm of host cells via T3SS into the pore created in part by YopB and YopD. The injected Yop proteins limit phagocytosis and cell signaling pathways important in the innate immune system, as discussed below. In addition, some *Y. pestis* strains are capable of interfering with immune signaling (e.g., by preventing the release of some cytokines).

Yersinia pestis proliferates inside lymph nodes where it is able to avoid destruction by cells of the immune system such as macrophages. The ability of *Yersinia pestis* to inhibit phagocytosisallows it to grow in lymph nodes and cause lymphadenopathy. YopH is a protein tyrosine phosphatase that contributes to the ability of *Yersinia pestis* to evade immune system cells. In macrophages, YopH has been shown to dephosphorylate p130Cas, Fyb (Fyn binding protein) SKAP-HOM and Pyk, a tyrosine kinase homologous to FAK. YopH also binds the p85 subunit ofphosphoinositide 3-kinase, the Gab1, the Gab2 adapter proteins, and the Vav guanine nucleotide exchange factor.

YopE functions as a GTPase activating protein for members of the Rho family of GTPases such as RAC1. YopT is a cysteine protease that inhibits RhoA by removing the isoprenyl group, which is important for localizing the protein to the cell membrane. It has been proposed that YopE and YopT may function to limit YopB/D-induced cytolysis. This might limit the function of YopB/D to create the pores used for Yop insertion into host cells and prevent YopB/D-induced rupture of host cells and release of cell contents that would attract and stimulate immune system responses.

YopJ is an acetyltransferase that binds to a conserved -helix of MAPK kinases. YopJ acetylates MAPK kinases at serines and threonines that are normally phosphorylated during activation of the MAP kinase

cascade. YopJ is activated in eukaryotic cells by interaction with target cell Phytic acid (IP6). This disruption of host cell protein kinase activity causes apoptosis of macrophages, and it has been proposed that this is important for the establishment of infection and for evasion of the host immune response. YopO is a protein kinase also known as Yersinia protein kinase A (YpkA). YopO is a potent inducer of human macrophage apoptosis.

Immunity

A formalin-inactivated vaccine once was available in the United States for adults at high risk of contracting the plague until removal from the market by the U.S. Food and Drug Administration. It was of limited effectiveness and could cause severe inflammation. Experiments with genetic engineering of a vaccine based on F1 and V antigens are underway and show promise. However, bacteria lacking antigen F1 are still virulent, and the V antigens are sufficiently variable, such that vaccines composed of these antigens may not be fully protective. United States Army Medical Research Institute of Infectious Diseases (USAMRIID) have found that an experimental F1/V antigen-based vaccine protect cynomolgus macaques but fails to protect African green monkeys. A systematic review by the Cochrane Collaboration found no studies of sufficient quality to make any statement on the efficacy of the vaccine.

Clinical aspects

Symptoms and disease progression
Bubonic plague

- Incubation period of 2–6 days, when the bacteria is actively replicating.
- General malaise
- Fever
- Headache and chills occur suddenly at the end of the incubation period
- Swelling of lymph nodes resulting in buboes, the classic sign of bubonic plague. The inguinal nodes are most frequently affected ("boubon" is Greek for "groin.")

- **Septicemic plague**

- Hypotension
- Hepatosplenomegaly
- Delirium
- Seizures in children
- Shock
- General malaise
- Fever
- Symptoms of bubonic or pneumonic plague are not always present
- Note: Patient may die before any symptoms appear

- **Pneumonic plague (Spread person to person)**
  - Fever
  - Chills
  - Coughing
  - Chest pain
  - Dyspnea
  - Hemoptysis
  - Lethargy
  - Hypotension
  - Shock
  - Symptoms of bubonic or septicemic plague are not always present
  - If this occurs with the classic buboes, this is considered primary, while secondary occurs after symptoms of bubonic or pneumonic infection. Since the bacteria are blood-borne, several organs can be affected, including the spleen and brain. The diffuse infection can cause an immunologic cascade to occur, leading to disseminated intravascular coagulation (DIC), which in turn results in bleeding and necrotic skin and tissue. Such a disseminated infection increases mortality to 22%.

With the exception of the buboes, the initial symptoms of plague are very similar to many other diseases, making diagnosis difficult.

ICD-9 codes for the diseases caused by *Y. pestis*:

- 020.0 Bubonic plague
- 020.2 Septicemic plague
- 020.5 Unspecified pneumonic plague

- 020.3 Primary pneumonic plague
- 020.4 Secondary pneumonic plague

Clinical determination

Gram's stains can confirm the presence of gram-negative rods, and in some cases the identification of the double-curved shape. An anti-F1 serology test can differentiate between different species of *Yersinia*, and Polymerase chain reaction (PCR) can be used to identify *Y. pestis*.

The protein H of the tail fiber of the bacteriophage *Yersinia phage L-413C* permits the differenciation between *Y. pestis* and *Y. pseudotuberculosis", the gastro-intestinal corrolary (Kane et al.)*.[52]

Treatment

The traditional first line treatment for *Y. pestis* has been streptomycin, chloramphenicol, tetracycline, and fluoroquinolones. There is also good evidence to support the use of doxycyclineor gentamicin. Resistant strains have been isolated; treatment should be guided by antibiotic sensitivities where available. Antibiotic treatment alone is insufficient for some patients, who may also require circulatory, ventilator, or renal support.

In an emergency department setting, Harrison's *Principles of Internal Medicine* outlines the following treatment course Antibiotics within the first 24 hours are very beneficial, with intravenous being preferred in pulmonary or advanced cases. Streptomycin or gentamicin are the first-line drugs, with chloramphenicol for critically ill patients, or rarely for suspected neuro-involvement.

Shigella

Shigella is a genus of Gram-negative, facultative anaerobic, nonspore forming, non-motile, rod-shaped bacteria closely related to *Salmonella*. The causative agent of human shigellosis, *Shigella* causes disease in primates, but not in other mammalsIt is only naturally found in humans and apes.[2] During infection, it typically causes dysentery. The genus is named after Kiyoshi Shiga, who first discovered it in 1898.

Phylogenetic studies indicate that *Shigella* is more appropriately treated as subgenus of *Escherichia*, and that certain strains generally considered *E. coli* – such as *E. coli* O157:H7 – are better placed in *Shigella* (see *Escherichia coli#Diversity* for details).

After invasion, Shigella multiply intracellularly and spread to neighboring epithelial cells, resulting in tissue destruction and characteristic pathology of shigellosis

Classification

Shigella species are classified by four serogroups:

- Serogroup *A*: *S. dysenteriae* (12 serotypes)
- Serogroup *B*: *S. flexneri* (6 serotypes)
- Serogroup *C*: *S. boydii* (18 serotypes)
- Serogroup *D*: *S. sonnei* (1 serotype)

Groups *A–C* are physiologically similar; *S. sonnei* (group *D*) can be differentiated on the basis of biochemical metabolism assays. Three *Shigella* groups are the major disease-causing species: *S. flexneri* is the most frequently isolated species worldwide, and accounts for 60% of cases in the developing world; *S. sonnei* causes 77% of cases in the developed world, compared to only 15% of cases in the developing world; and *S. dysenteriae* is usually the cause of epidemics of dysentery, particularly in confined populations such as refugee camps.

Pathogenesis

Shigella infection is typically via ingestion (fecal–oral contamination); depending on age and condition of the host, fewer than 100 bacterial cells can be enough to cause an infection. *Shigella* causes dysentery that results in the destruction of the epithelial cells of the intestinal mucosa in the cecum and rectum. Some strains produce the enterotoxin shiga toxin, which is similar to the verotoxin of *E. coli* O157:H7 and other verotoxin-producing Escherichia coli. Both shiga toxin and verotoxin are associated with causing hemolytic uremic syndrome. As noted above, these supposed *E. coli* strains are at least in part actually more closely related to *Shigella* than to the "typical" *E. coli*. It is also commonly known to cause large and painful bowel movements.

Shigella invade the host through the M-cells in the gut epithelia of the small intestine, as they cannot enter directly through the epithelial cells. Using a Type III secretion system acting as a biological syringe, the bacterium injects IpaD protein into cells, triggering bacterial

invasion and the subsequent lysis of vacuolar membranes using IpaB and IpaC proteins. It uses a mechanism for its motility by which its IcsA protein triggers actin polymerization in the host cell (via N-WASP recruitment of Arp2/3 complexes) in a "rocket" propulsion fashion for cell-to-cell spread. The most common symptoms are diarrhea, fever, nausea, vomiting, stomach cramps and flatulence. The stool may contain blood, mucus or pus. In rare cases, young children may have seizures. Symptoms can take as long as a week to appear, but most often begin two to four days after ingestion. Symptoms usually last for several days, but can last for weeks. *Shigella* is implicated as one of the pathogenic causes of reactive arthritis worldwide

Each of the *Shigella* genomes includes a virulence plasmid that encodes conserved primary virulence determinants. The *Shigella* chromosomes share most of their genes with those of *E. coli* K12 strain MG1655

Diagnosis

The diagnosis of Shigellosisis made by isolating the organism from diarrheal fecal samples submitted for culture.

Shigella species are negative fow motility and are not lactose fermenters. (However, *S. sonnei* can ferment lactose). They typically do not produce gas from carbohydrates (with the exception of certain strains of *S. flexneri*) and tend to be overall biochemically inert. *Shigella* should also be urea hydrolysis negative . When inoculated to a triple sugar iron (TSI) slant, they react as follows: K/A, gas -, H2S -. Indole reactions are mixed, positive and negative, with the exception of *S. sonnei*, which is always indole negative. Growth on *Hektoen enteric agar* will produce bluish-green colonies for Shigella and bluish-green colonies with black centers for *Salmonella*.

Prevention and treatment

Hand washing before handling food and thoroughly cooking all food before eating decreases the risk of getting *Shigella*.

Severe dysentery can be treated with ampicillin, TMP-SMX, or fluoroquinolones, such as ciprofloxacin, and of course rehydration.

Medical treatment should only be used in severe cases or for certain populations with mild symptoms (elderly, immunocompromised, food service industry workers, child care workers). Antibiotics are usually avoided in mild cases because some Shigella are resistant to antibiotics, and their use may make the germ even more resistant. Antidiarrheal agents may worsen the sickness, and should be avoided For *Shigella*-associated diarrhea,antibiotics shorten the length of infection.

 Shigella is one of the leading bacterial causes of diarrhea worldwide. Insufficient data exist, but conservative estimates suggest that *Shigella* causes approximately 90 million cases of severe dysentery with at least 100,000 of these resulting in death each year, mostly among children in the developing world

Currently, no licenced vaccine targeting *Shigella* exists. *Shigella* has been a longstanding World Health Organization target for vaccine development, and sharp declines in age-specific diarrhea/dysentery attack rates for this pathogen indicate that natural immunity does develop following exposure; thus, vaccination to prevent the disease should be feasible. Several vaccine candidates for *Shigella* are in various stages of development.

Enterobacter

Enterobacter is a genus of common Gram-negative, facultatively anaerobic, rod-shaped, non-spore-forming bacteria of the family Enterobacteriaceae. Several strains of these bacteria are pathogenic and cause opportunistic infections in immuno -compromised (usually hospitalized) hosts and in those who are on mechanical ventilation. The urinary and respiratory tracts are the most common sites of infection. The genus *Enterobacter* is a member of the coliform group of bacteria. It does not belong to the fecal coliforms (or thermotolerant coliforms) group of bacteria, as does Escherichia coli, because it is incapable of growth at 44.5°C in the presence of bile salts. Two clinically important species from this genus are *E. aerogenes* and *E. cloacae*.

Biochemical characteristics

The genus *Enterobacter* ferments lactose with gas production during a 48-hour incubation at 35-37°C in the presence of bile salts and detergents. It is oxidase-negative, indole-negative, and urease-negative.

Treatment

Note: Treatment is dependent on local trends of antibiotic resistance.

1. Cefepime, a fourth-generation cephalosporin from the beta-lactam antibiotic class.
2. Imipenem (carbapenems) is often the antibiotic of choice.
3. Aminoglycosides such as amikacin have been found to be very effective, as well
4. Quinolones can be an effective alternative.

5. Linked to obesity

A recent study has shown that the presence of *Enterobacter cloacae* B29 in the gut of a morbidly obese individual may have contributed to the patient'sobesity. Reduction of the bacterial load within the patient's gut, from 35% *E. cloacae* B29 to non-detectable levels, was associated with a parallel reduction in endotoxin load in the patient and a concomitant, significant reduction in weight. Furthermore, the same bacterial strain, isolated from the patient, induced obesity and insulin resistance in germfree C57BL/6J mice that were being fed a high-fat diet. The study concludes that *E. cloacae* B29 may contribute to obesity in its human hosts through an endotoxin-induced, inflammation-mediated mechanism.

Serratia

Serratia is a genus of Gram-negative, facultatively anaerobic, rod-shaped bacteria of the Enterobacteriaceae family. The most common species in the genus, *S. marcescens*, is normally the only pathogen and usually causes nosocomial infections. However, rare strains of *S. plymuthica*, *S. liquefaciens*, *S. rubidaea*, and *S. odoriferae* have caused diseases through infection. Members of this genus produce characteristic red pigment,prodigiosin, and can be distinguished from other members of the family Enterobacteriaceae by their unique production of three enzymes: DNase,lipase, and gelatinase Serratia may be correctly pronounced Ser-ra-shia (common) or Ser-rah-tee-a, although the latter is the correct pronunciation in Latin.

Infection of humans

In the hospital, *Serratia* species tend to colonize the respiratory and urinary tracts, rather than the gastrointestinal tract, in adults.

Serratia infection is responsible for about 2% of nosocomial infections of the bloodstream, lower respiratory tract, urinary tract, surgical wounds, and skin and soft tissues in adult patients. Outbreaks of *S. marcescens* meningitis, wound infections, and arthritis have occurred in pediatric wards

Serratia infection has caused endocarditis and osteomyelitis in people addicted to heroin.

Cases of *Serratia* arthritis have been reported in outpatients receiving intra-articular injections.

History

S. marcescens was once thought to be a nonpathogenic bacterium. Because of the red pigment it produces, it was widely used to trace bacterial transmission and to study settling and drifting of bacteria in air currents. In 1950, the US Navy conducted a secret experiment called "Operation Seaspray" to study wind currents that might carry biological weapons. They filled balloons with *S. marcescens* and burst them over San Francisco. Shortly thereafter, doctors in the area noted a drastic increase in pneumonia and urinary tract infections.

Citrobacter

Citrobacter isa genus of Gram-negative coliform bacteria inthe Enterobacteriaceae family.

The species *C. amalonaticus*, *C. koseri*, and *C. freundii* can use citrate as a sole carbon source. *Citrobacter* species are differentiated by their ability to convert tryptophan to indole, ferment lactose, and use malonate. *Citrobacter* shows the ability to accumulate uranium by building phosphate complexes.

Clinical significance

These bacteria can be found almost everywhere in soil, water, wastewater, etc. They can also be found in the human intestine. They are rarely the source of illnesses, except for infections of the urinary tract and infant meningitis and sepsis. *C. freundii* strains have inducible ampC genes encoding resistance to ampicillin and first-generation cephalosporins. In addition, isolates of *Citrobacter* may be resistant to many other antibiotics as a result of plasmid-encoded resistance genes.