Salmonella: Clinical Importance and Evolution of Nomenclature

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Salmonella is an important pathogen for both humans and animals. Although the organism has been intensively studied during the last century, much remains to be learned about this pathogen. The complicated nomenclature system of *Salmonella* has long been a subject of discussion. In 2005, "*Salmonella enterica*" finally gained official approval as the type species of the genus *Salmonella*. The genus *Salmonella* also contains the species "*Salmonella bongori*" in addition to a new species, "*Salmonella subterranean*", which was recognized in 2005. Unlike other bacterial genera, *Salmonella* organisms are differentiated by serotyping analysis. Presently, new serotypes (serovars) are still being discovered each year, adding to the complexity of this large bacterial population. Despite the conserved genetic background, molecular analysis has indicated successful evolution of the *Salmonella* genome in response to the environment, particularly to the selective pressure from antimicrobial agents. Mechanisms of fluoroquinolone resistance in *Salmonella* are similar to the complex system reported for other members of the family *Enterobacteriaceae*. On the other hand, resistance to extended-spectrum cephalosporins is more likely to be mediated by bla_{CTX-M} or *ampC* genes that are carried on plasmids. Plasmid-borne genes have increased efficacy in the dissemination of resistance determinants, resulting in increased antimicrobial resistance. To provide clinicians with up-to-date information on this important pathogen, the evolving nomenclature and clinical importance of *Salmonella* are reviewed. *(Chang Gung Med J 2007;30:210-9)*

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Salmonella is a genus of the family *Enterobacteriaceae* and comprises a large and closely related population of medically important pathogens. It has long been associated with a wide spectrum of infectious diseases, including typhoid fever and nontyphoid salmonellosis, which cause public health problems worldwide. Despite recognition of *Salmonella* as an important pathogen, the sophisticated nomenclature system of *Salmonella* remains unfamiliar to clinicians. The present report aims to provide an overview of the evolving nomenclature of this organism as well as a brief introduction to the

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importance of *Salmonella* in medicine.

Ever-changing nomenclature system

Origin as multiple species

Salmonella is named after an American bacteriologist, D. E. Salmon, who first isolated *Salmonella choleraesuis* from porcine intestine in 1884.[1] The organism was originally called "*Bacillus choleraesuis*," which was subsequently changed to "*Salmonella choleraesuis*" by Lignieres in 1900. Based on the serologic classification determined using an array of specific antisera, many salmonellae were differentiated by their serotyping results. Although "serotype" and "serovar" were both frequently used, according to the Rules of the *Bacteriological Code* (1990 Revision) established by the Judicial Commission of the International Committee on the Systematics of Prokaryotes, the term "serovar" is preferred to the term "serotype". Kauffmann proposed that each serovar be considered a separate species.[2] Thus, *Salmonella* serovars identified after 1966 were designated mainly by their antigenic formula and multiple species within the genus *Salmonella* were generally accepted. However, some clinically important salmonellae identified before 1966 had been given specific names either according to the disease and/or the animal from which the organism was isolated, such as *S. typhi* and *S. typhimurium*, or by the geographical area where the strain was first isolated, e.g., *S. london* and *S. panama*. These names had been used for a number of years and therefore were adopted without being amended into the new antigenic formula system.

Sub-classification into subspecies

Because of the complexity of multiple *Salmonella* species, it was proposed that the genus *Salmonella* be subdivided into three species, *S. choleraesuis* (the type species), "*S. thphosa*" (*S. typhi*), and "*S. kauffmannii*," with the last containing all the other serovars.[3] Later, "*Salmonella enterica*" was proposed by Kauffman and Edwards to encompass all salmonellae.[4] In 1966 a similar three-species model was proposed, with "*Salmonella enteritidis*" representing all serovars other than *S. typhi* and *S. choleraesuis*.[5] Another proposal in 1970 recommended that Kauffmann's "subgenera" be considered a species, i.e., "*S. kauffmannii*" for "subgenus" I, *S. salamae* for "subgenus" II, *S. arizonae* for "subgenus" III, and *S. houtenae* for "subgenus" IV.[6] Serovars of "*S. kauffmannii*" would be designated by their species names followed by that of their serovar (e.g., "*S. kauffmannii*" serovar typhi), and serovars of the other three species would be designated by their species names followed by their antigenic formulae.

Emergence of one-species concept

In 1973, on the basis of DNA-DNA hybridization experiments, Crosa et al. demonstrated that all *Salmonella* strains should belong to a single species.[7] In 1982, on the basis of numerical taxonomy and DNA relatedness studies Le Minor et al. proposed the name "*Salmonella choleraesuis*" for the single *Salmonella* species and six subspecies were defined.[8] These authors also proposed that the name of serovars should be used without italicization or underlining (e.g., *Salmonella choleraeusis* subsp. *choleraesuis* ser. typhimurium). In 1989, a single exception was described: one of the subspecies, *Salmonella choleraesuis* subsp. *bongori*, was separated from the other subspecies as a unique *Salmonella* species due to differences demonstrated by DNA relatedness studies.[9]

Proposal of "*Salmonella enterica*" to replace "*Salmonella choleraesuis*" as the type species

Because of confusion caused by using "choleraesuis" as a name for both a species and a serovar, in 1986 "*Salmonella enterica*" was proposed again as the type species of *Salmonella* by the Subcommittee of *Enterobacteriaceae* of the International Committee on Systematic Bacteriology at the XIV International Congress of Microbiology.[10] The proposal was formally made to the Judicial Commission of the International Committee of Systematic Bacteriology in 1987 by Le Minor and Popoff of the World Health Organization (WHO) Collaborating Centre.[11] The epithet "enterica" was recommended because it has not been used previously for a serovar. They also proposed that the seven subgenera of *Salmonella* be referred to as subspecies (subspecies I, II, IIIa, IIIb, IV, V, and VI). Subgenus III was divided into IIIa and IIIb by DNA similarity and phenotypic characteristics. The suggestion was accepted by the Centers for Diseases Control and Prevention (CDC) and other experts and laboratories[12,13] but denied by the Judicial Commission due

to concerns that the status of *Salmonella* serovar Typhi might be overlooked. *S. choleraesuis* was thus retained as the legitimate type species pending an amended request for an opinion.[14] To comply with this ruling and also to support the proposal by Le Minor and Popoff, in 1999 Euzéby made an amended request to use "*Salmonella enterica*" as the type species of *Salmonella* and reserve the name "*Salmonella typhi*" to reflect its clinical importance.[15]

Approval of "*Salmonella enterica*" as the type species

In 2002, the Judicial Commission carefully discussed the request by Euzéby[15] and the others and issued an opinion (the Judicial Opinion 80) which finally approved that from January 2005, "*Salmonella enterica*" would replace "*Salmonella choleraesuis*" to become the type species of the genus *Salmonella*.[16] Furthermore, an accompanying commentary was written by Tindall et al. to help the bacteriologists better interpret both the nomenclatural and taxonomic consequences of Opinion 80.[17] According to the ruling of the Judicial Commission, the genus *Salmonella* consists of two species, "*Salmonella bongori*" and "*Salmonella enterica*". The latter includes six subspecies, "*arizonae*", "*diarizonae*", "*enterica*", "*houtenae*", "*indica*", and "*salamae*". In 2005, a new species, "*Salmonella subterranea*" was approved by the Judicial Commission.[18]

Names of some medically important *Salmonella* serovars such as "*Salmonella typhi*",[15,19] "*Salmonella typhimurium*",[19] and "*Salmonella enteritidis*",[19] have been used frequently and in 2000, Euzéby et al. proposed that these names be conserved. However, this proposal was not granted by the Judicial Commission. Furthermore, the proposal of Ezaki et al. to raise "*Salmonella choleraesuis* subsp. *choleraesuis* serovar Paratyphi A" to as a new species, "*Salmonella paratyphi*", was also not granted by the Judicial Commission.[20]

Current nomenclature system used by the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC) and the American Society for Microbiology (ASM)

The antigenic classification system of various *Salmonella* serovars used today has accumulated from many years of studies on antibody interactions with surface antigens of *Salmonella* organisms established by Kauffman and White almost a century ago. All antigenic formulae of recognized *Salmonella* serotypes are listed in a document called the Kauffmann-White scheme.[21] The WHO Collaborating Centre for Reference and Research on *Salmonella* at the Pasteur Institute, Paris, France is responsible for updating the scheme. Every year newly recognized serovars are reported in the journal Research in Microbiology by Popoff et al. In the latest report published in 2004, there were a total of 2,541 serovars in the genus *Salmonella* (Table 1).[22]

Currently, the nomenclature system used at the CDC for the genus *Salmonella* is based on recommendations from the WHO Collaborating Centre. According to the CDC system, the genus *Salmonella* contains two species, *S. enterica*, the type species,

Table 1. Current *Salmonella* Nomenclature

Taxonomic position (writing format) and nomenclature				No. of serotypes in each species or subspecies[22]
Genus (capitalized, italic)	Species (italic)	Subpecies (italic)	Serotypes (or serovars) (capitalized, not italic)*	
Salmonella	*enterica*	*enterica* (or subspecies I)	Choleraesuis, Enteritidis, Paratyphi, Typhi, Typhimurium	1504
		salamae (or subspecies II)	9,46:z:z39	502
		arizonae (or subspecies IIIa)	43:z29:-	95
		diarizonae (or subspecies IIIb)	6,7:l,v:1,5,7	333
		houtenae (or subspecies IV)	21:m,t:-	72
		indica (or subspecies VI)	59:z36:-	13
	bongori	subspecies V	13,22:z39:-	22
	subterranea[18]			

*: Some selected serotypes (serovars) are listed as examples.

and *S. bongori*. A third species "*Salmonella subterranea*" was recognized in 2005, and the CDC may incorporate it in their system in the near future. *S. enterica* consists of six subspecies:[21,23] I, *S. enterica* subsp. *enterica*; II, *S. enterica* subsp. *salamae*; IIIa, *S. enterica* subsp. *arizonae*; IIIb, *S. enterica* subsp. *diarizonae*; IV, *S. enterica* subsp. *houtenae*; and VI, *S. enterica* subsp. *indica*.

In subspecies I, serovars are designated by a name usually indicative of associated diseases, geographic origins, or usual habitats. In the remaining subspecies, as well as those of *S. bongori*, antigenic formulae determined according to the Kauffmann-White scheme[21] are used for unnamed serovars. Some members of these subspecies may have been named before 1966 and thus their names are retained and cited as those in subspecies I.

To avoid confusion between serovars and species, the serovar name is not italicized and starts with a capital letter. When cited the first time in a report, the genus name is given followed by the word "serotype" (or the abbreviation "ser.") and then the serotype name, e.g., *Salmonella* serotype or ser. Choleraesuis. Afterward the name may be shortened with the genus name followed directly by the serotype name, e.g., *Salmonella* Choleraesuis or *S.* Choleraesuis.[22] Because the type species name, *enterica*, was not approved before 2005, serotype names are used directly after the genus name without mention of the species. Following official approval of "*enterica*" as the type species name, further amendment to include the species name in the *Salmonella* nomenclature of the CDC may be expected.

For those designated by their antigenic formulae, the subspecies name is written in Roman letters (not italicized) followed by their antigenic formulae, including O (somatic) antigens, H (flagellar) antigens (phase 1), and H antigens (phase 2, if present). A colon is used between each antigen, e.g., *Salmonella* serotype II 39:z_{10}:z_6. For serotypes in *S. bongori* (which previously belonged to subgenus V), V is still used for consistency, e.g., *S.* V 13,22:z_{35}:–.[22]

In publications of the ASM, the *Salmonella* nomenclature used at the CDC was approved as the standard form by the publications board in 1999, and the "Instructions to Authors" of the journal was updated to include this information in 2000.[24] The 2006 ASM "Instructions to Authors" indicated that, for the species, "*Salmonella enterica*" is used at first mention, and "*S. enterica*" thereafter; for the subspecies, "*Salmonella enterica* subsp. *arizonae*" is used first, and "*S. enterica* subsp. *arizonae*" thereafter. Serovar names should be in Roman type with the first letter capitalized, e.g., *Salmonella enterica* serovar Typhimurium. After the first use, the serovar may be used without a species name, e.g., *Salmonella* Typhimurium.

Salmonella as an important human pathogen

Clinical features - from diarrhea to fatal diseases

Salmonella causes approximately 1.4 million human infections each year in the United States, resulting in 116,000 hospitalizations and 600 deaths.[25] Most *Salmonella* infection is limited to uncomplicated gastroenteritis that seldom requires antimicrobial treatment.[26] In fact, antimicrobial treatment does not reduce the duration or severity of gastroenteritis and instead may result in prolonged fecal excretion and emergence of resistant strains.[27] However, severe sequelae, such as bacteremia or meningitis, may develop in an approximately 5-10% of individuals infected with non-typhoid *Salmonella*.[28] Invasive *Salmonella* infections can be fatal[29,30] and antimicrobial treatment is essential in these circumstances.[31]

Those at risk of development of complications of extra-intestinal salmonellosis include patients at the two age extremes and those with immune suppression, or accompanying severe infections, such as meningitis, septic arthritis and osteomyelitis.[28,32-35] All *Salmonella* can cause extra-intestinal infections, but *S.* Typhi, *S.* Paratyphi, *S.* Choleraesuis and *S.* Dublin are the major serotypes which cause invasive salmonellosis in humans.[30,32,36-38] The other serotypes, such as *S.* Typhimurium, *S.* Enteritidis and *S.* Heidelberg, are associated with a relatively low proportion of invasive infections. However, the total number of invasive cases caused by these serotypes appears to be high, because they are relatively prevalent among the whole *Salmonella* population.[32] Among the invasive non-typhoid *Salmonella* serotypes, *S.* Choleraesuis is particularly rampant in Asian countries, including Taiwan, while *S.* Dublin is

much more prevalent in western countries.[32,36,37] Analysis of data from the Foodborne Diseases Active Surveillance Network (FoodNet) indicates that discrepancies remain between different races, even when all patients studied are from the same geographic area, such as the United States.[30]

The development of infectious endarteritis (also known as infectious aortitis or mycotic aneurysm) is a serious complication of *Salmonella* bacteremia in adults. The prevalence of endothelial infections in the presence of atherosclerosis was 25% among patients > 50 years old with *Salmonella* bacteremia.[39] Present data on the study of associated risk factors are usually from anecdotal reports or retrospective reviews. To obtain accurate risk factors, a prospective case-controlled study is required. Mycotic aneurysm caused by *Salmonella* was associated with a high mortality rate in the past, but early surgical intervention has been shown to effectively increase the survival of infected patients.[40-43] In addition, an extended course of antimicrobial therapy for 6 weeks or longer is recommended.[39,41,44]

The serotypes most commonly associated with *Salmonella* aortitis are *S.* Typhimurium, *S.* Enteritidis and *S.* Choleraesuis.[41-43] Interestingly, reports of infectious aortitis caused by *S.* Choleraesuis are mostly from Taiwan.[41-43] This corresponds with the high prevalence of *S.* Choleraesuis in Asian countries, including Taiwan. The high virulence of *S.* Choleraesuis in humans as well as its high prevalence may contribute to the high incidence of endovascular infection caused by this organism in Taiwan.

Increasing antimicrobial resistance - a global problem

Parenteral antimicrobial therapy is required for invasive salmonellosis.[45-47] Previously, appropriate drugs included ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole; unfortunately, resistance to these agents has increased to as high as 70% in many areas of the world, including Taiwan.[47,48] However, the resistance rate differs among serotypes. *S.* Enteritidis is generally more susceptible to antimicrobial agents, while *S.* Typhimurium exhibits a much higher resistance.[47,48] One of the major reasons for the higher antimicrobial resistance observed in *S.* Typhimurium may be the emergence of a distinct multidrug-resistant strain of definitive phage type 104 (DT104) *S.* Typhimurium in the United States and Europe in the early 1990s.[49] This unique strain is characterized by concomitant resistance to 5 antimicrobial agents, ampicillin (A), chloramphenicol (C), streptomycin (S), sulfonamide (Su), and tetracycline (T) (= R-type ACSSuT).[49] As of the mid-1990s, *S.* Typhimurium DT104 had become one of the most prevalent strains among human isolates of *Salmonella*, second only to *S.* Enteritidis strain PT4 in the United Kingdom.[50] In the United States, the prevalence of *S.* Typhimurium isolates of R-type ACSSuT had increased to 34% in 1996.[51] Another study by the National Antimicrobial Resistance Monitoring System (NARMS) conducted in 1997-1998 indicated that 65% of *S.* Typhimurium isolates of R-type ACSSuT were phage type DT104.[52] Molecular typing analysis revealed that most isolates of *S.* Typhimurium DT104 had very similar genetic fingerprints, suggesting that clonal spread may be responsible for the increasing prevalence of this unique resistant strain of *S.* Typhimurium.[51]

Problems aroused by the increasing antimicrobial resistance of *Salmonella* include not only difficulties in antimicrobial therapy but also the apparent predilection of the organism to cause serious diseases. In the United States, a recent report from the NARMS indicates that the risk of bloodstream infections in patients infected with antimicrobial resistant nontyphoid *Salmonella*, particularly *S.* Typhimurium, is 2-fold greater than in those infected with pan-susceptible strains.[53] Information from FoodNet also indicates a more than 4-fold risk of hospitalization in patients with resistant *Salmonella* infections.[53] Similarly, a Danish study reported that infection with quinolone-resistant *S.* Typhimurium was associated with a 3-fold higher risk of invasive illness or death within 90 days of infection, compared with that observed for infection with pan-susceptible strains.[54]

Fluoroquinolone resistance - a complex system

Fluoroquinolones are one of the alternatives in the treatment of invasive infections caused by *Salmonella* multiply resistant to traditional antibiotics.[45,46] However, resistance to fluoroquinolones has been frequently reported in many countries.[47] A particularly worrisome situation in Taiwan is that fluoroquinolone resistance was found in clinical isolates of *S.* Choleraesuis in 2000 and this resistance has increased rapidly, to approximately 70% in 2003[45,48]

and 96% in 2006 (Su LH, unpublished data).

As found in other bacterial species, acquired quinolone resistance in *Salmonella* is usually due to point mutations in the genes encoding DNA gyrase (GyrA, GyrB), or DNA topoisomerase IV (ParC, ParE),[47,55] which are essential enzymes for the maintenance of topology within the bacterial cell.[56] They also are the primary and secondary targets of quinolones. Modifications in the target genes protect the bacteria from being attacked by quinolones. A region called the quinolone resistance-determining region (QRDR) is found in both DNA gyrase and topoisomerase IV and is also the region where mutations usually occur. Some "hot-spots" are particularly prone to mutate. The most commonly described mutation sites are codon 83 (serine to phenylalanine, tyrosine, or alanine) and codon 87 (aspartic acid to glycine, asparagine, or tyrosine) in GyrA.[47,55] Other frequently reported mutation sites include: codon 464 (serine to phenylalanine) in GyrB;[57-60] and codon 57 (threonine to serine),[61-65] codon 80 (serine to isoleucine or arginine),[47,61,63-65] and codon 84 (glutamic acid to lysine) in ParC.[60,65,66] Recently, mutations in ParE have also been reported at various codons.[63-65]

Fluoroquinolone resistance is characterized by a step-wise process. A single mutation in any of the mutation sites described above may result in resistance to nalidixic acid but only a slightly reduced susceptibility to fluoroquinolones (MIC, < 4 μg/mL).[55] Full resistance to fluoroquinolones is achieved when double or more mutations are present concurrently.[61] However, together with the target gene mutations, concomitant over-expression of AcrAB-TolC efflux systems is also required to achieve high-level fluoroquinolone resistance (MIC, ≥ 32 μg/mL).[57] Furthermore, two global regulatory systems, *marRAB* and *soxRS*, have been associated with multiple antimicrobial resistance among members of *Enterobacteriaceae*, including *Salmonella*.[55] The *marA* and *soxS* genes code for homologous proteins that up-regulate the AcrAB-TolC efflux system, whereas the *marR* and *soxR* genes code for repressor proteins that down-regulate the expression of marA and soxS genes, respectively.[55] MarA and SoxS also up-regulate the production of an antisense RNA, *micF*, which is responsible for the reduced synthesis of a major porin, OmpF, resulting in decreased outer membrane permeability and thus increased resistance to multiple antibiotics, including fluoroquinolones.[55]

Resistance to extended-spectrum cephalosporins - bad news again

Extended-spectrum cephalosporins are also used for treatment of invasive infections caused by multidrug-resistant *Salmonella*.[45,46] Resistance to these antimicrobial agents, however, has also been on the rise among several *Salmonella* serotypes.[48] The major mechanism for this resistance is through the production of specific enzymes to hydrolyze the associated extended-spectrum cephalosporins. Molecular analysis indicates that the resistance genes, mostly $bla_{\text{CMY-2}}$ and $bla_{\text{CTX-M-3}}$, are plasmid-borne and can be transmitted among bacterial organisms of the same or different species, resulting in wide-spread resistance.[47,48]

A longitudinal investigation of the molecular evolution of multiresistance in nontyphoid *Salmonella* demonstrated that progressive acquisition and accumulation of plasmid-mediated resistance determinants through the exchange of plasmids or other mobile elements between *Salmonella* and/or other members of the family *Enterobacteriaceae* may have led to multiresistance.[67] In addition to the generally recognized selective pressure from antimicrobial use in food animals, *Salmonella* could acquire drug resistance plasmids from other enteric pathogens in the intestinal tract of individual patients.[68] Evidence of this from our own experience, was seen in a case in which an originally susceptible *Salmonella* isolate acquired a resistance plasmid *in vivo* and became resistant to ceftriaxone during treatment, resulting in the death of a patient.[69]

The most feared situation was the finding in 2002 that a bacteremic strain of *S.* Choleraesuis was simultaneously resistant to ceftriaxone and ciprofloxacin.[46] The ceftriaxone resistance was attributed to the presence of a plasmid-mediated $bla_{\text{CMY-2}}$ gene,[46,70] which was located on a transposon-like DNA element consisting of a specific *tnpA*-$bla_{\text{CMY-2}}$-*blc*-*sugE* structure.[46] Further investigation identified the same $bla_{\text{CMY-2}}$-carrying, transposon-like element among several bacterial species of the family *Enterobacteriaceae*.[71]

Conclusions

Throughout the years, the nomenclature of the

genus *Salmonella* has gone through many changes and is still evolving. Molecular analysis indicates successful genetic evolution of *Salmonella* in response to the environment. Advances in knowledge of this organism will improve the control of *Salmonella* infections. Research work is underway to further elucidate the mechanisms of the pathogenesis and antimicrobial resistance of *Salmonella*. Stringent antimicrobial prescription policies in both human and veterinary medicine, as well as improvements in public heath and infection control policies, are required to reduce the biological and economic burden of *Salmonella* infections.

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沙門氏菌：臨床重要性及其命名沿革

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沙門氏菌是人類及動物的重要致病菌，雖然已經被廣泛的研究了超過百年之久，這個麻煩的致病菌還有許多特性是值得再被深入探討的。沙門氏菌的命名系統相當複雜，也經常被拿來討論。在 2005 年，“*Salmonella enterica*”終於被承認是沙門氏菌屬的代表性種名 (type species)。而除了“*Salmonella bongori*”之外，“*Salmonella subterranean*”也已在 2005 年被公認爲沙門氏菌屬的第三個種 (species)。與其它細菌不一樣的地方是，不同的沙門氏菌是以它們的血清型來區分的。而且，直到目前，每年仍不斷有新的血清型被發現，使得這個龐大的細菌家族更形複雜。雖然沙門氏菌的基因多型性變化不大，分子生物學的分析指出，沙門氏菌的基因可以有效的因應環境的不同而改變，尤其是在面對各種抗生素所造成的選擇性壓力時。沙門氏菌對 fluoroquinolone 類抗生素的抗藥機制，與其他腸桿菌科的細菌並無不同。相對的，沙門氏菌對超廣效性乙醯胺酶的抗藥性，則主要是由帶在質體上，會產生 CTX-M 或 AmpC 的基因所造成。這種由質體傳播抗藥性基因的方式相當有效率，也使得沙門氏菌的抗藥性得以快速增加。這份綜論主要是針對沙門氏菌的命名沿革及臨床重要性作一番探討，希望可以提供臨床醫師最新的資訊，以有助於相關的診斷與處置。(長庚醫誌 2007;30:210-9)

關鍵詞：沙門氏菌，命名學，抗生素抗藥性，侵襲性感染，感染性動脈瘤

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