Extended-spectrum β-lactamases in non-typhoidal *Salmonella* spp. isolated in the UK are now a reality: why the late arrival?

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In February 2004, we reported the first recognition of the presence of an extended-spectrum β-lactamase (ESBL) in non-typhoidal *Salmonella* spp. in the UK; the β-lactamase was TEM-52. Six months later, an SHV-derived ESBL (SHV-12) was detected in a salmonella strain isolated in York and 6 months after that we have just identified CTX-M-type β-lactamases in Scottish isolates of *Salmonella enterica* subsp. *enterica* serovar Typhimurium and *Salmonella* Virchow (unpublished results). A very recent retrospective study of UK isolates suggests that they may have been in the population for some years but have gone undetected. Even so, compared with reports of ESBLs in *Salmonella* spp. elsewhere, these results are suggestive of a delayed emergence of the ESBL phenotype in non-typhoidal *Salmonella* spp. in the UK. Should the British congratulate themselves on warding off the emergence of these important resistance mechanisms in *Salmonella* spp., or is the sudden revelation of three of the major ESBL types a cause for concern?

Keywords: ESBLs, emergence, TEM, CTX-M

Introduction

Non-typhoidal salmonellae are one of the principal pathogens implicated in food-borne gastroenteritis worldwide. Although antibiotics are not usually recommended in cases of salmonella enterocolitis, they are crucial if the infection spreads from the intestine. Invasive complications, including meningitis, sepsis and bacteremia are more common in infants and the elderly and in immunocompromised patients. In these potentially life-threatening cases, the antibiotics of choice are fluoroquinolones and extended-spectrum cephalosporins. *Salmonella* spp. resistant to extended-spectrum cephalosporins have been recognized since 1988, and are increasing in prevalence worldwide. This is of particular concern for the treatment of salmonellosis in children, because fluoroquinolones should not be used in this age group.

How does the situation in the UK compare with other European countries?

In 2003, over 14 400 human infections with *Salmonella* spp. in England and Wales were reported. In developed countries, the principal method of spread of these organisms to humans is through the food chain from reservoirs in food-producing animals. In Europe, the use of antibiotics in animal husbandry is the primary driving force for the selection of antibiotic resistance in non-typhoidal salmonellae.

Extended-spectrum cephalosporins (cefoperazone, cefuroxime, cefalonium, and the third and forth-generation cephalosporins, ceftiofur and cequinone) are prescription-only medicines approved in the UK for the treatment of diseases such as mastitis in dairy cattle, respiratory diseases in ruminants (cattle, sheep, goats) and cattle foot rot. Extended-spectrum cephalosporins are also licensed for the treatment of bacterial diseases in poultry, such as necrotic enteritis and colisepticaemia. Commonly the only practical method of treating these problematic diseases is mass oral medication.

Extended-spectrum β-lactamases (ESBLs) are most often found in *Escherichia coli* and *Klebsiella pneumoniae,* but have been detected in non-typhoidal salmonellae in France and Italy since 1989 and 1990, respectively. However, it was not until 14 years later that the first ESBL was actually reported in a salmonella isolate from the UK, a TEM-52 β-lactamase-containing strain isolated in Glasgow. Recently, Batchelor et al. retrospectively studied the reference laboratory collection of human clinical and food salmonellae from England and Wales for the presence of CTX-M-type enzymes. Of interest is that the isolates analysed in this study had been collected during 1992–2003, yet no isolates containing CTX-M enzymes were present in this extensive collection of 278 308 isolates until September 1997.

Why would resistance development vary between countries?

The delay in emergence of this resistance mechanism in the UK compared with other European countries may result from differences in cephalosporin usage, methods of detecting ESBL...
producers, prevalence of resistant serovars, or the import of resistant strains through travel.

Countries differ in the quantity of cephalosporins used, and the dosage and route of administration, as well as the duration of usage in that country. However, it has proved extremely difficult to obtain data on cephalosporin use in European countries. Many countries monitor sales of veterinary antibiotics, but comparison of sales between countries is confounded by differences in data collection and numbers of food-animal species per country.

In addition to differences in cephalosporin usage, countries may differ in the methods used to detect ESBL producers. In the UK, many laboratories use only ceftazidime resistance as an indicator of ESBL production.\(^\text{(10)}\) This may result in cefotaxime-resistant organisms, for which the ceftazidime MIC is in the susceptible range, being missed during ESBL screening tests, and is exemplified by the work of Batchelor et al.\(^\text{(10)}\) Similarly, screening for AmpC-type enzymes (which confer a broader spectrum of resistance than the ESBLs) is not routinely performed in the UK. As a result, the first identification of a salmonella isolate from the UK harbouring an AmpC-type enzyme was identified following a retrospective study on isolates collected during 1993–2003.\(^\text{(11)}\) These important studies indicate that we may be missing the opportunity to identify new resistance genes. According to Liebana et al.,\(^\text{(11)}\) there should be routine surveillance to identify emerging genes which may present a threat to the treatment of invasive pathogens.

The tendency of salmonellae to develop or acquire resistance mechanisms also depends on the particular serovar and sometimes phage type; antibiotic resistance is, for instance, relatively uncommon in Salmonella Enteritidis.\(^\text{(1)}\) During 1996–2000, the overall incidence of multidrug resistance (resistance to four or more antibiotics) in this serovar was <1% in England and Wales.\(^\text{(1)}\) In contrast, multidrug-resistant Salmonella Typhimurium, identified in the UK in 1964, has been responsible for several epidemics. These were caused by definitive phage type (DT) 29 in the late 1960s,\(^\text{(12)}\) DT 204 and DT 193 from 1975 until the mid-1980s,\(^\text{(13)}\) and DT 104 in the early 1990s.\(^\text{(14)}\) Therefore, differences in salmonella resistance between countries will also depend on the prevalence of specific serovars and phage types.

ESBL-harbouring salmonellae are frequently isolated from hospitals in North African countries, India and in South Korea. Travel from these areas has been linked with outbreaks of ESBL-harbouring salmonellae in France.\(^\text{(15,16)}\) A study in the UK of 41 906 human isolates of non-typhoidal salmonellae isolated during 1998–1999 also found a link between travel to developing countries and resistance to third-generation cephalosporins, although the presence of ESBLs in resistant isolates was not confirmed. However, only six of the 14 retrospective cases described by Batchelor et al.\(^\text{(10)}\) in 2005 were associated with travel abroad and there was no link between foreign travel and the outbreak of salmonellosis reported in Glasgow in 2004.\(^\text{(9)}\)

### Development of ESBL-harbouring salmonellae in the UK

The aetiological agent of the Glasgow outbreak in 2004 was a Salmonella Enteritidis strain carrying TEM-52. Six months after this report a salmonella isolate from York was found to harbour SHV-12.\(^\text{(17)}\) Recently, we have identified, in Scotland, two clinical salmonellae harbouring different CTX-M-type enzymes (C. M. Yates, D. J. Brown, A. Guleri and S. G. B. Amyes, unpublished results), again with no patient history of foreign travel. The study by Batchelor et al.\(^\text{(10)}\) revealed that the majority of the CTX-M-harbouring salmonella in England and Wales were isolated during 2001–2003. Is this increased detection of three different enzyme families in the last 5 years an indication that salmonellae harbouring ESBLs are emerging in the UK per se? Will these prove to be seminal incidences in the development of multidrug-resistant salmonellae?

Fortunately, ESBLs from Salmonella spp. in the UK have not yet been categorically identified to be of veterinary origin. Surveillance of antibiotic resistance in 5214 salmonellae isolated from animals and their environment in 2003 revealed that none was resistant to the third-generation cephalosporin ceftazidime.\(^\text{(18)}\) Food-producing animals are the primary reservoirs of salmonella, and so these results suggest that the presence of ESBLs in the UK clinical isolates arose by some other method, such as nosocomial acquisition from other Enterobacteriaceae. In Madrid, a nosocomial outbreak caused by a Salmonella Othmarschen was found to involve the dissemination of a single TEM-27-encoding plasmid among E. coli and Enterobacter cloaceae.\(^\text{(19)}\)

Although the epidemiology of the recent reports of ESBL-harbouring salmonellae in the UK is not clear, the detection of three different ESBL types in Britain means that we can no longer be complacent in the face of this serious human health issue. Continued surveillance of the presence of ESBLs in Enterobacteriaceae, and rapid elucidation of the mode of spread of these resistance genes in Salmonella spp., is essential to minimize the risks to future treatment that their widespread dissemination would create.

### References


