Acquired carbapenemases pose one of the most pressing public health threats relating to antibiotic resistance. In most countries, the number of carbapenemase-producing bacteria from human clinical specimens is rising, and the epidemiological status of these multiresistant bacteria is progressively worsening. Furthermore, there is a growing number of reports of carbapenemases found either in bacteria isolated from non-human sources or in \textit{Salmonella enterica} subsp. \textit{enterica}, a zoonotic species. However, carbapenemases are not yet systematically sought in bacteria from non-human sources, reports of them are largely observational, and there is limited investigation of carbapenemase-positive bacteria in animals and possible links with people who may have acted as potential sources. Active surveillance and monitoring for carbapenem-resistant bacteria in the food chain and other non-human sources is urgently needed, with an enhanced and rigorous follow-up of all positive results. The carbapenems are currently our last good defence against multiresistant Gram-negative bacteria. Our ability to limit the rise and spread of carbapenemase producers, which occur only at basal levels in many countries at present, should serve as a key performance indicator for the success or failure of the efforts that have been called for by international organizations and governments to reduce the impact of antibiotic resistance.

**Keywords:** KPC, NDM, VIM, OXA-48, rivers, pets, food chain, \textit{Salmonella enterica}

**Introduction**

Acquired carbapenemases pose one of the most pressing public health threats relating to antibiotic resistance. They confer resistance not just to carbapenems, but to almost all \(\beta\)-lactams, our most widely used class of antibiotic, and are encoded by genes that are transferable between bacteria. Furthermore, most carbapenemase-producing isolates of Enterobacteriaceae and non-fermenters (predominantly, but not exclusively, \textit{Pseudomonas} spp. and \textit{Acinetobacter} spp.) are resistant to multiple other classes of antibiotics, which severely limits therapeutic options even after the antibiogram of an infecting strain has been determined; the chance of empirically prescribing an appropriate antibiotic (or combination) is highly unlikely, which impacts on mortality.

Rates of acquired carbapenem resistance in most bacterial species and in most countries of the European Economic Area (EEA) are below the thresholds needed to register on the maps arising from surveillance schemes such as EARS-Net.\(^1\) In consequence almost all countries in the EEA appear ‘green and pleasant’, but this masks a reality in which the actual number of carbapenemase-producing bacterial isolates is rising and the epidemiological status of these bacteria (sporadic versus local or regional spread versus national endemicity) is progressively worsening.\(^2\) Here, it is important to mention that the carbapenem MICs for some carbapenemase-producing bacteria do not categorize them as resistant, irrespective of the clinical breakpoints used. Such non-susceptible isolates may not be considered in some prevalence studies.

We have had endemic carbapenemases (KPC and VIM types) in Greece and Cyprus for some time,\(^2,3\) and the ease with which other countries can succumb is illustrated by Italy, where carbapenem resistance among blood culture isolates of \textit{Klebsiella pneumoniae} rose from 1.3% in 2009 to 27% in 2011,\(^4\) reflecting a nationwide outbreak of KPC producers.\(^4\) Even more worryingly, about 13% of carbapenemases detected by Public Health England’s Antimicrobial Resistance and Healthcare Associated Infections Reference Unit are in isolates of \textit{Escherichia coli} (N. Woodford, unpublished data), which are the perfect vehicles for taking these enzymes
out of the hospital and establishing them in the community setting, where they will impact on primary care. The warnings about resistance from the Chief Medical Officer for England have come at a critical time. We must act now to prevent carbapenemases becoming as established as extended-spectrum β-lactamases (ESBLs). Rates must be kept low because these are some of the most resistant bacteria that we face.

Spread of strains, plasmids and genes

For any Gram-negative resistance issue, especially situations involving the Enterobacteriaceae, one must consider not just the spread of resistant strains, but also the spread of their resistance genes between plasmids and the spread of those plasmids between strains, species and genera. Furthermore, any antibiotic use (whether appropriate or not) provides selective pressure for resistant strains, and of course that use is not limited to humans. We need to consider the role of any non-human reservoirs of resistance genes and strains, which have the potential to be a public health threat. The problem is that although these reservoirs represent a theoretical hazard, quantifying the actual risk and the contribution to the burden of human disease is difficult. However, the potential for the transfer of bacteria between reservoirs, as well as both to and from man, is amply illustrated by considering non-typhoidal Salmonella, irrespective of its resistance.

About a decade ago, ESBL-producing E. coli with CTX-M enzymes emerged and spread internationally to become a substantial cause of community-acquired/community-onset urinary tract infections, bacteraemias and healthcare-associated infections. We have since discovered that ESBL-producing E. coli can also be found in food production animals, raw meat, companion animals and the environment, but after 10 years of intense global research and discussion, we still lack an indisputable assessment of the risk that these sources of resistant E. coli represent to human health. Rather, the evidence is fragmentary and suggests substantial differences between countries. For example, the E. coli strains, ESBLs and plasmids found in food animals and meat in the UK are distinct from those that cause the vast majority of human infections, whereas closer associations between the food chain and human disease have been identified in the Netherlands. The debate is still unresolved for ESBL-producing E. coli, and it is only just starting for carbapenemase-producing bacteria, for which the body of evidence is far less substantial.

Non-human carbapenem use

Carbapenem antibiotics have never been licensed for veterinary use in any country worldwide, as far as we are aware. There are no legally ‘safe’ limits for carbapenems in meat because no maximum residue limit has been defined in Europe, so any food production animals treated with them could not enter the food chain, which effectively precludes their use in the agricultural sector. However, in the UK, vets can prescribe carbapenems to treat ‘resistant’ infections in companion animals, based on clinical judgement and as part of the cascade mechanism. In the authors’ experience, this is limited in the UK to the occasional use of imipenem by veterinary surgeons to treat dogs with highly resistant urinary tract infections. However, national figures on such usage are not collected, and the British Small Animal Veterinary Association advises that there is a strong argument that ‘last-resort’ antimicrobials, such as imipenem, should not be used for veterinary patients.

By contrast, the prescribing of carbapenems is escalating in humans, as a consequence of the rising numbers of ESBL producers and other multiresistant Gram-negative organisms. So the bulk of carbapenem prescribing occurs in human medicine, and this is currently the major sector reporting carbapenemase producers; but multidrug resistance means, of course, that many antibiotic classes, not just carbapenems and other β-lactams, have the potential to select indirectly for carbapenemase producers.

Carbapenemases from non-human sources

There is a growing number of reports of carbapenemases found either in bacteria isolated from non-human sources or in Salmonella enterica subsp. enterica, a zoonotic species (Table 1). The spread of OXA-48 and VIM-2 to Salmonella serovar Kentucky ST198-X1 has raised concerns as this strain is widely distributed in North Africa. S. enterica strains carrying carbapenem resistance genes are frequently resistant to fluoroquinolones, limiting treatment options, and also often display relatively low carbapenem MICs, making them difficult for laboratories to detect. Where do such strains originate, and do they represent a public health risk?

The precise origins of the genes encoding most acquired carbapenemases remain undefined, but they have all escaped from environmental bacteria into species with clinical relevance. Exceptions and examples are (i) the OXA-48 family of enzymes, which occur naturally in Shewanella spp., a genus that inhabits lake sediments, and (ii) OXA-23 carbapenemase, which is almost entirely restricted to Acinetobacter baumannii and originates from the environmental species Acinetobacter radioresistens. For these reasons, finding carbapenemase genes by PCR or metagenomic approaches in environmental samples has limited value if the identity of the host species is not determined. Reports of carbapenemases in sewage and waste water (Table 1) have often sampled downstream of hospitals, so the discovery of resistance in clinically relevant species is not surprising in this setting. We are contaminating the environment, releasing a concentrated supply of resistant bacteria that can spread their resistance genes into many different species. The extent of this contamination can be dramatic in countries with poor sanitation, as exemplified by the widely publicized report of NDM carbapenem in water samples taken from multiple sites around New Delhi.

Other reports have documented the detection in environmental samples of carbapenemases that have rarely (IMI enzyme) or never (BIC-1 enzyme) been isolated from clinical isolates. By contrast, OXA-23 enzyme is undoubtedly a significant clinical concern, but detecting it in ‘clinically inconsequential’ Acinetobacter species from animals may well represent further gene escape events from A. radioresistens. They seem unlikely to pose any substantial public health threat even to those in direct contact with the animals for four reasons: (i) the vast majority of human Acinetobacter infections are caused by A. baumannii; (ii) most non-hospitalized people would not be susceptible to infection by this genus; (iii) it is exceptional to find A. baumannii even as a colonist in people outside the hospital environment so gene transfer events to this species are unlikely; and (iv) the bulk of...
carbapenem-resistant strains of this species belong to three successful and hospital-adapted international lineages.

The so-called ‘big five’ carbapenemases (KPC and OXA-48 non-metallo-carbapenemases as well as the IMP, NDM and VIM metallo-carbapenemases) collectively cause the greatest clinical concern. So recent reports of ‘enterobacteria’ with NDM, VIM or OXA-48 enzymes from food production animals or companion animals are worrying, but the reasons for their occurrence have usually not been investigated or reported. The retrospective investigation that often takes place in such cases can be problematic and complicates the analysis, where the smoking gun has essentially ceased to smoke or is no longer at the scene. The significance of these facts is uncertain and it may be that the resistant bacteria were derived from human sources, either directly or indirectly. This seems especially likely for companion animals, although details of the owners have not been disclosed (recent hospitalization, etc.). Transmission of a single K. pneumoniae strain with OXA-48 carbapenemase to several dogs in a veterinary clinic illustrates that hand hygiene is as important here as in human medicine to prevent and control infections and to limit the spread of resistant bacteria.

On the other hand, the presence of Salmonella and E. coli isolates carrying VIM-1 carbapenemase has been reported in food-producing animals in Germany. In this case, investigations showed that once the bacteria are on the farm or in the farm environment, they can be maintained there, may be widely spread among animals (including insects and rodents) and can reach the environment via manure. In addition, the role of wild birds as a reservoir for carbapenemase-encoding genes Account...
should be taken into account, as Salmonella producing NDM-1 has been isolated from a black kite.31

A need for wider screening

There are currently no reports of carbapenemases in bacteria from retail meat or other foodstuffs, but the possibility needs to be considered. Would food that tested positive for carbapenemase producers be deemed fit for human consumption given the low prevalence in normal healthy people and the potential for resistance genes to be transferred to species resident in the gut flora from bacteria ingested with improperly cooked meat or raw vegetables or in ready-to-eat food? Testing foodstuffs for carbapenem-resistant bacteria is not currently a legal requirement. The European Food Safety Authority has acknowledged that “the carbapenems...are assuming importance as ‘last-resort’ antimicrobials in the treatment of certain highly-resistant Gram-negative infections in humans, and their inclusion also needs to be considered when panels of antimicrobials are reviewed” and is currently working on a scientific opinion on carbapenem resistance in food animal ecosystems. In addition, European legislation is currently being revised and it seems likely that a significant extension in the monitoring of carbapenemases is occurring.32 Such active surveillance and monitoring for carbapenem-resistant bacteria in animals and possible links to human populations are strongly welcome. The few ad hoc reports of carbapenemases in animals are essentially meaningless in the absence of widespread, large-scale and proficient testing.

Concluding remarks

In summary, carbapenemases in bacteria from non-human sources are not yet being systematically sought; proposals to enhance and extend such monitoring are to be strongly welcomed. At the current time, reports of them are largely observational, and there is limited systematic investigation of the occurrence of carbapenem-positive bacteria in animals and possible links with people (e.g. owners of animals, farmers, vets) who may have risk factors for infection or colonization (including prior exposure, hospitalization, antibiotic use, healthcare contact and/or travel overseas) and so may have acted as potential sources. Such active surveillance and monitoring for carbapenem-resistant bacteria in the food chain and other non-human sources is urgently needed, with an enhanced and rigorous follow-up of all positive results. The carbapenems are currently our last good defence against multiresistant Gram-negative bacteria. Our ability to limit the rise and spread of carbapenemase producers, which occur only at basal levels in many countries at present, should serve as a key performance indicator for the success or failure of the efforts that have been called for by international organizations and governments to reduce the impact of antibiotic resistance.

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