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*J Antimicrob Chemother* 2014

doi:10.1093/jac/dku054

Advance Access publication 26 February 2014

## The carbapenemase threat in the animal world: the wrong culprit

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**Keywords:** carbapenems, ESBLs, veterinary medicine, food chain

Sir,

We read with great interest two recent publications dealing with the same topic, i.e. the public health risk related to the occurrence of acquired carbapenemase-producing Gram-negative species in the animal world and the environment.<sup>1,2</sup> Woodford *et al.*<sup>1</sup> highlight the series of reports of carbapenemases found either in bacteria isolated from non-human sources or in *Salmonella enterica* subsp. *enterica*, a zoonotic species. This raises concern about the real spread of these threatening organisms in the food chain and other non-human sources of infection. Abraham *et al.*<sup>2</sup> focus on the possible role of companion animals as a source of carbapenemase-producing strains in humans, building their hypotheses on two studies reporting NDM-1-producing *Escherichia coli* isolates from dogs in the USA, and OXA-48-producing *E. coli* and *Klebsiella pneumoniae* isolates, also from dogs, in Germany. Both reports encourage public health authorities to implement measures to better evaluate the spread of carbapenemase-producing strains in animals, and reinforce efforts leading to a reduction of antibiotic consumption in veterinary practice.

We fully agree that the implementation of surveillance studies aimed to better evaluate and trace multidrug resistance in general, and carbapenem resistance in particular, is crucial in the fight against antibiotic resistance. We also agree that any effort towards a reduction of antibiotic consumption is valuable and must be sustained. However, we believe that the spread of carbapenemase-producing isolates among animals is not the main explanation for their occurrence in humans. Carbapenems are not registered for use in veterinary medicine, even though they may be used in specific circumstances in companion animals or horses when dealing with multidrug-resistant Enterobacteriaceae. This usage, at least in developed countries, remains rare.<sup>3</sup> The occurrence of carbapenemase-producing isolates in companion animals, as for extended-spectrum  $\beta$ -lactamase (ESBL) producers,<sup>4</sup> most probably results from contamination from the animal keeper, who is statistically more exposed to broad-spectrum antibiotics, and in particular to broad-spectrum  $\beta$ -lactams, than the animal itself. In this regard, an increasing and irresponsible use of carbapenems in companion animals might contribute to the selection and dissemination of carbapenem-resistant strains, and all efforts to avoid carbapenem use in veterinary practice should be pursued.<sup>3</sup>

The real threat related to carbapenemase resistance in humans comes from two main facts. The first corresponds to the increased consumption of carbapenems worldwide, as a consequence of an increased rate of resistance to broad-spectrum cephalosporins among human isolates. Therefore, carbapenems, although being last-resort antibiotics, are now considered to be first-line therapeutic options in certain geographical areas where multidrug resistance is endemic. The second main explanation comes from the overall increase in human population movements worldwide, including migration and tourism.<sup>5</sup>

In humans, carbapenemase-producing Enterobacteriaceae may be either hospital acquired (mostly *K. pneumoniae*), or community acquired (mostly *E. coli*), either as colonizers or infectious agents. Carbapenemase-producing *E. coli* are mainly the source of community-acquired infections or colonization.<sup>5</sup> Of note, *E. coli*, by contrast with *K. pneumoniae*, may be identified in the food chain. Numerous studies have been conducted over the past decade to evaluate the possible link between the occurrence of ESBL producers among food-producing animals on one hand, and in humans on the other. Despite the fact that the rate of colonization

of animals (poultry, pigs, cattle etc.) is high, there is still little evidence that ESBL producers are spreading mainly through the food chain.<sup>4</sup> Taking into account the paucity of reports of carbapenemase producers in animals, and the fact that carbapenems are not used in food-producing animals, the risk to public health remains marginal.

Nowadays, the major threat related to the spread of carbapenemase producers among humans is linked to a lack of hygiene, to contaminated drinking water and to poor control of antibiotic usage in some highly populated geographical areas.<sup>5</sup> As a consequence, some countries may become endemic not only for ESBL producers but also for carbapenemase producers. As examples, it is estimated that among isolates associated with intra-abdominal infections in India during 2008, 61% and 47% were ESBL-producing *E. coli* and *K. pneumoniae*, respectively.<sup>6</sup> In Pakistan, the faecal carriage of NDM-1-producing isolates among hospitalized patients was estimated at 15%–20%.<sup>7</sup>

In a country such as Switzerland, where the rate of patient colonization with ESBL-producing Enterobacteriaceae at admission has been evaluated to be 4%–5%,<sup>8</sup> while being 8.4% among the Swiss slaughter cattle population,<sup>9</sup> recent surveys have reported the lack of detection of carbapenemase-producing Enterobacteriaceae among farm animals and community patients.<sup>10,11</sup> The first case of colonization by a carbapenemase-producing *S. enterica* strain has recently been reported, being an OXA-48 producer recovered from a patient transferred from Libya to Switzerland.<sup>12</sup> Knowing that Libya is endemic for OXA-48-producing Enterobacteriaceae,<sup>13</sup> this case further highlights that the risk of acquisition of carbapenemase producers mainly comes from human endemic areas.

Rapid identification of carbapenemase producers by using easy-to-handle and affordable techniques will contribute to the recognition of infected and colonized patients at an early stage.<sup>14</sup> This will allow the rapid implementation of isolation and cohorting strategies, and the improvement of antibiotic stewardship to prevent the development of outbreaks. It may also contribute to better identification of the possible dissemination of carbapenemase producers, not only within the human population but also from a human source to animals.

## Funding

This work has been funded by the University of Fribourg, Switzerland.

## Transparency declarations

None to declare.

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*J Antimicrob Chemother* 2014

doi:10.1093/jac/dku075

Advance Access publication 20 March 2014

## Single- and multiple-dose pharmacokinetics and total removal of colistin in a patient with acute kidney injury undergoing extended daily dialysis

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