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The association of ESBL-producing Enterobacteriaceae (ESBL-E) carriage in humans with pigs

To the Editor

This letter is a comment on the recent study by Fischer *et al.* who found no extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E) in the nares of 114 persons exposed to pigs. These results were surprising due to the high prevalence of ESBL-E in livestock [1]. They detected Enterobacteriaceae in the nares of 76/114 (66·7%) participants, none of which produced ESBL. No association between working hours per week on pig farms and nasal colonization with Enterobacteriaceae could be identified. The authors concluded that nares represent a negligible reservoir for carriage of ESBL-E in persons exposed to pigs.

Interestingly, Dohmen *et al.* found rectal colonization with ESBL-E in 27% (95% CI 10–44) of humans with daily exposure to ESBL-E-carrying pigs. [2]. Genetic similarities of ESBL genes, plasmid types and sequence types (STs) suggested a likely transmission between humans and pigs on the same farms. Further, human colonization with ESBL-E was associated with the number of working hours on a particular farm and with the ESBL carriage of the pigs. Dohmen and colleagues found evidence for transmission of rectal ESBL-E between pig farmers and their livestock. In this context, the rectum and not the nose seems to be the crucial reservoir for colonization of humans with ESBL-E after exposure to pigs.

We feel it necessary to add certain points to the well conducted discussion of Fischer *et al.* They stated that the northwestern area of Germany is one of the regions with the highest densities of pig production in Europe. Recent data from the German national nosocomial infections surveillance system (KISS) documented the highest – and significantly increasing – incidence of nosocomial infections with ESBL-E in this region [3]. This observation suggests a relationship between the production farming of pigs and the emergence of ESBL-E infections in the same regions. A Dutch study using whole genome sequencing (WGS) confirmed the similarity of epidemiologically linked strains from humans and pigs of the same farms [4]. Thus, in the case of human and animal contact, our 'farming theory' suggests dissemination of ESBL-E between pigs and pig farmers that causes rectal colonization of humans.

Not only contact with farm animals, but also consumption of meat might lead to human ESBL-E carriage. So far, the most often discussed source of ESBL-E from livestock is poultry [5]. Therefore, transmission from poultry to the human consumer was suspected. However, de Been *et al.* demonstrated by WGS that transmission of ESBL-producing *E. coli* between humans and poultry via the food chain seems unlikely [4]. They suggested that rather than whole bacteria, ESBL genes are disseminated between animals and humans by ESBL-carrying plasmids. However, it remains unclear how the transmission of these ESBL-carrying plasmids occurs. Consumption of raw contaminated meat might be an important source of transmission since plasmids are most likely destroyed by correct temperature during cooking. To our knowledge, there is no dish containing raw poultry meat in the European culture, but in Germany, for example, there are several dishes that contain raw pork. In 2012, we conducted a case-control study assessing the risk factors for community-associated colonization with ESBL-E in hospital patients [6]. Among other factors, we found that ESBL-E carriage was associated with frequent consumption of pork. In addition, data from KISS showed high incidences of nosocomial infections with ESBL-E in North Rhine-Westphalia and Thuringia [3]. Interestingly, these German federal

states are associated with high consumption of meat, mainly pork (German National Nutrition Study II, 2008). These findings lead to our 'food theory' suggesting that antibiotic resistance might be disseminated by mobile genetic elements following the consumption of raw pork.

Another important issue considered by Fischer *et al.* is differentiating between colonization and infection. In the literature and in our hospital, CTX-M-15 is described as the most common genotype (58%) in clinical ESBL-E isolates, while CTX-M-1 was found in only 22% of clinical isolates from *E. coli* bloodstream infections [7]. The latter ESBL genotype was found by Dohmen *et al.* in 66% (12/18) of ESBL-E-positive pig-farms [2] and was the predominant genotype in patients colonized with ESBL-E (45%, 37/83 patients carrying ESBL-E) [6]. This leads to the assumption that bacteria with the CTX-M-1 genotype, although found in the community quite frequently, cause infections less frequently. Furthermore, the *E. coli* ST commonly found in ESBL-E infections is ST131 [8]. In the study on rectal colonization with ESBL-E by Dohmen *et al*., this ST was found in neither pigs nor humans [2]. As a consequence, there might be a distinct difference between clinically associated ESBL genotypes and STs and those associated with frequent colonization in the community.

It is still not clear what role animal-to-human-transmission plays in the emergence of ESBL-E infections in humans. By this letter, we hope to stimulate the discussion of three issues. First, close contact with production animals including pigs represents an important risk factor for human ESBL-E carriage in the rectum, not nares. Second, transmission of antibiotic resistance via the food chain is most likely facilitated by ESBL-carrying plasmids and might be more likely for pork than poultry. Third, molecular analyses of ESBL genotypes and STs lead to the hypothesis that ESBL-E, which cause human infections, might originate mainly from sources other than the food chain or production animals. These could presumably include human-to-human-transmission, e.g. in hospitals or by selection after antibiotic consumption.

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Declaration of Interest

None.

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