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Antimicrobial resistance in the food chain and the AGISAR initiative

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Basic facts and context

Antimicrobial resistance is a major threat that medicine is now facing because bacteria have developed a strong defensive response to the increasing use of antibiotics. Bacteria have been able (i) to transfer to pathogens resistance genes naturally present in antibiotic producing organisms and the environment, and (ii) to evolve pre-existing enzymes to inhibit recently developed synthetic antibiotics. Resistance affects all types of antibiotics. In contrast, innovation in antibiotic research faded abruptly in the 1980s. Thus, we face situations in which bacteria resistant to most, if not all, antibiotics can cause serious infections.

Early demonstrations

The relationship between antibiotic usage and bacterial resistance is supported by chronological, biological, and epidemiological long known evidences. Commensal bacteria are first impacted by antibiotics during treatments [1]. Susceptible bacteria are replaced by resistant ones which disseminate to innate materials or other hosts and transfer resistance genes to pathogens.

Commensal resistant enteric bacteria can contaminate the food chain products during slaughtering [2] just as salmonella, campylobacter, listeria, or entero-haemorragic *Escherichia coli*. Also, because manure is often dispersed on vegetal cultures and crops, animal resistant bacteria can reach vegetarian food [3].

Meat and vegetables contain frequently significant amounts of resistant bacteria. Our gut is likely to be seeded daily with many new strains of resistant bacteria. When volunteers eat only sterile foods, their bowel flora rapidly changes so they then only carry low counts of resistant fecal *E. coli* [4].

Bacteria resistant to tetracycline rapidly emerged in chickens when they were feed with that drug, and these bacteria transmit from chicken to chicken and to men [5]. Decades ago it was already shown that when pigs were feed with a new antibiotic (streptotricin), bacteria containing specific resistance genes were readily isolated in

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all animals from the farm, then in the farmers, and in inhabitants of the village. Some women living nearby suffered from urinary tract infections caused by strains carrying that specific resistance gene [6].

However, doubts are still raised by some on the role of the food chain in resistance in human bacteria. They argue that contributor to resistance in humans is entirely the human use of antibiotics and that antibiotic use in animals and transmission of resistant animal strains, or genes, through the food chain could only be a marginal phenomenon, if ever it occurs.

Recent evidences

Recently, evidences of impact of antimicrobial use in food animals on human health have been reviewed [7]. Genetic rearrangements in bacteria are frequent with bacteria transferred between animals and humans. Thus, resistant bacteria and genetic constructions are often different in the donor animals and in the recipient humans. This leads to the erroneous conclusion that no transfer has occurred. In this field, ''no proof of transfer'' is not the same as ''a proof of no transfer''. The debate relationship on the role of animal antibiotics to resistance in humans is protracted, particularly in the United States, where action lags far behind that of the European Union, where the ''precautionary principle,'' is a guiding tenet of public health, even though the Swann report [8] from the UK showed in the 1960s a clear link between antibiotic use in food animals and human disease and deaths and made many important recommendation to curb antibiotic use in food animals. Things might however be changing [9].

Recent studies and evidence is best focussed on (i) frequency of enterobacteria producing extended spectrum beta-lactamases (E-ESBL) or resistant to fluoroquinolones (both major threat for humans) in food chain animals (FCA), (ii) role of density of fecal E-ESBL in terms of risks, (iii) evidences for transfer between animals and humans, and (iv) characteristics of organic FCA in terms of resistance.

Resistant *Escherichia coli* in food chain animals

E. coli causes not only very common community infections such as urinary tract infections (UTI), but yearly also millions of severe and life threatening infections such as blood stream infections. In Australia, fluoroquinolones have been used in people for over 30 years but the use of fluoroquinolones is banned in food production animals. Levels of fluoroquinolone resistance in both community and healthcare acquired *E. coli* infections are low (~5%) in contrast to nearly all other countries where fluoroquinolone resistance rates are often very much higher. This is despite the overall use of antibiotics per capita being relatively high in Australia [10]. Also, there is also almost no fluoroquinolone resistance in food-borne infections with salmonella and campylobacter acquired domestically. In Europe there is a clear association between the levels of antibiotic resistant *E. coli* causing blood stream infections in different countries and the levels of resistance in poultry and pig *E. coli* isolates [11].

Colonization of food chain animals by *E. coli*-ESBL is quite high and increasing. In Switzerland in 2011, it was of 15% in pigs, which is over that of the local human population [12] and as high a 25% in calves and 63% in chicken which might be in relation with specific usage of cephalosporins in these animals. The widespread practice of injecting 3rd generation cephalosporin (e.g. ceftiofur) into eggs just before they hatch appears to be the major contributor to this problem [13]. In Germany, 38% of the chicken were colonized with a variety of ESBL genes and retail chicken meat might be a reservoir for strains or ESBL genes for humans [14]. In Spain the prevalence of *E. coli*-ESBL in poultry meat increased from 62.5% in 2007 to 93.3% in 2010. Consumption of retail meat by women is associated with a threefold risks that strain are resistant in case of UTI [15].

Density of colonization

Densities of ESBL strains in the feces of colonized animals can vary greatly by several orders of magnitude some being categorized as high density shedders or super shedders [16]. In humans high densities of colonization is associated with increase dissemination [17]. Thus, consequences of such variations in food chain animals should be investigated in further details.

Genetic evidences of transfer

When looking at the distribution of enzymes that cause the ESBL phenotypes, striking differences are observed depending on the origin of the strains (animal or humans, or between animal species) [18]. Some, such as CTX-M1 are however found across all species, suggesting that some transmission does indeed occur. Differences observed between species in the distribution of ESBL enzymes

are not greater than those observed between fecal and blood isolates in humans [19]. Plots of the phylogenetic relationships between ESBL *E. coli* from chicken, human feces and human blood show no clear differential patterns suggesting that transfer does indeed occur with a significant rate. High resolution power genetic tools with increased resolution power are highly conclusive that food chain animals can be the source of EBSL in humans but cannot estimate the precise rate of transfer [20]. This is currently addressed for instance by the EvoTar 7th European Union Research program (http://www.evotar.eu) which characterizes antibiotic resistance genes from the human microbiome and elucidates its interactions with environmental, animal and food reservoirs of resistance.

Organic food

Whether organic products are less likely than conventional ones to carry resistant bacteria is a frequently asked by consumers. In France, there were no significant differences in rates and densities of colonization by resistant bacteria between organic and conventional fruits and vegetables eaten raw [3]. This however is not be the same for meat, ESBL contamination appearing significantly less frequent and less dense in organic than in conventional retail chicken meat [21]. When resistant bacteria are widespread in food animals, it is very likely that soil and waterways contaminated with fecal material and effluent from farm animals will carry resistant bacteria. These can then go onto colonize fruits and vegetables, even if raised organically. Certainly more studies are needed in the field.

The AGISAR initiative

It is obvious that food chain animals are a significant reservoir of resistance for human pathogens. Although the magnitude of this source in comparison of the direct selection of resistance due to antibiotic use in humans remains unknown and will vary for different groups of bacteria, this obvious important factor certainly needs to be taken into account at a time where no new antibiotic are available, which forces to consider those on the market as a ''limited resource'' to be preserve for infected patients who need it.

This is in this context that has been launched in December 2008 the WHO-AGISAR (World Health Organization Advisory Group on Integrated Surveillance of Antimicrobial Resistance) initiative. It was established to support WHO's effort to minimize the public health impact of antimicrobial resistance associated with the use of antimicrobials in food animals. In particular, the Advisory Group will assist WHO on matters related to the integrated surveillance of antimicrobial resistance and the containment of food-related antimicrobial resistance. The terms of reference of WHO-AGISAR are (i) Develop harmonized schemes for monitoring antimicrobial resistance in zoonotic and enteric bacteria using appropriate sampling, (ii) Support WHO capacity-building activities in Member countries for antimicrobial resistance monitoring (AMR training modules for Global Foodborne Infections Network (GFN) training courses), (iii) Promote information sharing on AMR, (iv) Provide expert advice to WHO on containment of antimicrobial resistance with a particular focus on Human Critically Important Antimicrobials, (v) Support and advise WHO on the selection of sentinel sites and the design of pilot projects for conducting integrated surveillance of antimicrobial resistance and (vi) Support WHO capacity-building activities in Member countries for antimicrobial usage monitoring. The WHO-AGISAR comprises over 20 internationally renowned experts in a broad range of disciplines relevant to antimicrobial resistance, appointed following a web-published call for advisers, and a transparent selection process. WHO-AGISAR holds quarterly telephone conferences and annual face-to-face meetings.

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