The interaction between human antimicrobial use and the risk of foodborne zoonotic bacteria - DTU Orbit (31/10/2018)

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Salmonella enterica, Campylobacter jejuni and Campylobacter coli are the most common causes of foodborne bacterial infections worldwide. Both bacterial species have many modes for transmission in the food chain through which humans can be infected. The widespread use of antimicrobial drugs for food animals and the consequent dissemination of antimicrobial drug resistance have been well described in literature. Much less investigated is the association between human antimicrobial drug use and the adverse consequences it may have on human infections. This thesis addresses the relation between antimicrobial drug use in humans, and the acquisition of infection with antimicrobial resistant non-typhoidal Salmonella, Campylobacter coli (C. coli), and Campylobacter jejuni (C. jejuni). The main objectives were:

1) To assess if the history of human use of antimicrobial drugs is a risk factor for acquiring infection with an antimicrobial Salmonella or Campylobacter strain.
2) To compare clinical outcome of disease for patients infected with Salmonella Typhimurium having different antimicrobial susceptibility profiles (i.e. pansusceptible, resistant or multidrug-resistant).
3) To examine how clinical outcome of an infection is affected by previous antimicrobial exposure.

A total of 22,609 Salmonella cases that were laboratory confirmed between 1997 - 2005, were enrolled in the study. The analyses were performed separately for Salmonella Typhimurium (S. Typhimurium, 4,534 cases), Salmonella Enteritidis (S. Enteritidis, 4,195 cases), and all other Salmonella serotypes combined (5,776 cases). We found that treatment with trimethoprim, sulphonamides, broad-spectrum penicillins, tetracyclines and fluoroquinolones, during one year before diagnosis, was associated with an increased risk of non-typhoidal Salmonella infection. Overall, the highest risk was associated with the prior use of fluoroquinolones. The risk increased as the time-window of exposure approached the infection date. The Odds Ratios (OR) for previous use of fluoroquinolones were OR 4.6 (95% confidence interval (CI): 3.8 – 5.5) for other Salmonella serotypes, an OR 2.2 (95%CI: 1.7 – 2.9) for S. Typhimurium, and an OR 2.1 (95%CI: 1.8 – 2.4) for S. Enteritidis. Additionally for fluoroquinolones, we found an interaction term for the pathogen being resistant to fluoroquinolones and a history of fluoroquinolone use; OR 3.6 (95%CI: 1.2 – 10.3) for S. Typhimurium and OR 2.7 (95%CI: 1.2 – 5.9). Meaning that the risk for being diagnosed with a fluoroquinolone resistant S. Typhimurium after treatment with this drug in up to one year before diagnosis was 7.2 (2.0*3.6) times higher for patients than for controls. For S. Enteritidis the corresponding risk was 4.5 (1.7*2.7) times higher for cases than for controls. These findings are ascribed to the competitive and the selective effect of acquiring antimicrobial resistance, respectively. The competitive effect occurs when a course of antimicrobials taken disrupts the natural barrier effect of the gut flora. The selective effect is an additional competitive and the selective effect of acquiring antimicrobial resistance, respectively. The competitive effect occurs when a person is exposed to a pathogen resistant to the drug taken previously and unrelated to the infection in question was assessed in Manuscript I and Manuscript II. Both studies had the same study design: registry based case-control study, for which several of the Danish registries were merged using the unique Civil Registration Number (CPR), and approximately ten controls were matched to each patient on sex, age, and county of residence. Data on history of antimicrobial use was derived from the National Prescription database; cases enrolled in the study were retrieved from the National Registry for Enteric Patients (NREP); the Integrated Database on Labour Market Research provided data on socio-demographics of cases and controls; and the Civil Registry System was used to derive the CPR numbers, date of birth, and residential area of cases and controls.

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were infected with: pansusceptible (S), resistant (R) to 1-3 antimicrobials, or multidrug-resistant (MR), i.e. resistant to 4 or more antimicrobials. We found that previous antimicrobial use, unrelated to the current S. Typhimurium infection, was associated with a higher odds of weight loss (OR 2.4, 95%CI: 1.1 – 5.5), hospital admission (OR 2.0, 95%CI: 1.0 – 4.1), and antimicrobial therapy for the current salmonellosis (OR 7.9, 95%CI: 2.8 – 16.8). The study focused on short-term outcomes of disease (diarrhoea, nausea, etc.), and patients were interviewed relatively shortly after notification in the NREP. This may explain why this study, in contrast to other studies that focussed more on long-term outcome of disease (mortality, bacteraemia, etc.), did not find other more serious disease outcomes to be related to resistance profile. Also, it is possible that, due to our study design, we missed out on the most severely ill people, simply because they were too ill to participate in the interviews.

We also found that patients with a resistant (R) susceptibility profile had a higher odds of being hospitalised due to their salmonellosis (OR 2.5, 95%CI: 1.0 – 6.0), experience abdominal pain (OR 2.9, 95%CI:1.3 – 6.5), and feeling nauseated (OR 2.6, 95%CI: 1.1 – 6.2), than patients with a pansusceptible Salmonella. We found no increasing trend with increasing antimicrobial resistance (S versus MR). These findings may be an extension of the competitive and selective effect of antimicrobial treatment (Manuscript I and Manuscript II), where past antimicrobial treatment depletes or changes the composition of the gut flora in a way that increases severity of infection. Alternatively, a past history of treatment could be an indicator or proxy of a vulnerable patient.

The overall conclusion of this thesis is that human antimicrobial use interacts in many ways with the risk of being infected with antimicrobial-drug resistant strains of Salmonella and Campylobacter, and that treatment with antimicrobials may be associated with severity of infection as well. The protective role of macrolides as observed for Campylobacter infection adds another layer to the complexity of these interactions. Prudent use of antimicrobial drugs should always be advocated in human health practices. Future studies should point out whether the associations found in this thesis also applies to other pathogens.

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