The interaction between human antimicrobial use and the risk of foodborne zoonotic bacteria

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 general overview of the discovery of antimicrobials, and the development and mechanisms of antimicrobial drug resistance in Salmonella, C. jejuni, and C. coli are described in chapter 2. Several features of the epidemiology, sources of infection, antimicrobial resistance, and surveillance of Salmonella and Campylobacter are described in chapter 3 and 4, respectively.

The history of human use of antimicrobial drugs in relation to acquiring an infection with Salmonella or Campylobacter, and the subsequent risk of the causalative pathogen being 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.

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-typhoid 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 a 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 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 effect, occurring when a person is exposed to a pathogen resistant to the antimicrobial taken. This increases the risk of infection further due to the selective pressure put on other bacteria susceptible to the drug taken.

Between 1999 – 2005, a total of 31,899 cases of Campylobacter were laboratory confirmed in Denmark, and thus enrolled in the study. We found that being diagnosed with Campylobacter was associated with an increased odds of exposure to a course of fluoroquinolones, macrolides, broad spectrum penicillins, tetracyclines, and sulphonamides and trimethoprim, up to one year before onset of disease. The risk was highest for taking fluoroquinolones (OR 2.4, 95%CI: 2.0 – 3.0). Due to the low number of Campylobacter isolates being tested for other antimicrobial drugs than fluoroquinolones and macrolides, it was only possible to calculate the interaction term (or selective effect) for these two drugs. For fluoroquinolones, we found an effect modification of the strain additionally being resistant to the drug taken (OR 1.6, 95%CI: 1.1 – 2.3). The odds of being exposed to a course of fluoroquinolones was 2.4 times higher for cases diagnosed with a fluoroquinolone-sensitive Campylobacter than for controls whereas the odds of being exposed to a fluoroquinolone was 3.8 (2.4*1.6) times higher for cases with a fluoroquinoloneresistant Campylobacter than for controls. For macrolides, the interaction term was not significant (OR 1.0, 95%CI: 0.7 – 1.5). However, when we performed cubic spline plots of the OR of being exposed to a course of antimicrobials we found that being exposed to a course of macrolides provided a protective effect for being diagnosed with Campylobacter, up to one month before diagnosis. This effect is likely to be caused by the fact that the metabolites and active compound of macrolides are trapped into lysosomes of phagocytic cells, and get released at a very low rate and provide prolonged protection against invasive bacteria such as Campylobacter.

In Manuscript III, the relation between clinical outcomes of infection with S. Typhimurium and the antimicrobial resistance profile of the causative strain was assessed, together with the association between outcome of infection and previous antimicrobial use. A prospective case-case study was performed, using data obtained through telephone-conducted interviews, which were merged with data from the NREP and the Civil Registry System. Data were analysed using logistic regression. The interviews were conducted between January-June 2010, and a total of 150 S. Typhimurium cases were enrolled in the study. Cases were divided into three different groups according to the resistance pattern of the strain they
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 focussed 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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