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Antibiotic consumption and resistance: Data from Europe and Germany

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ABSTRACT

The use of antibiotics – including the over- and misuse – in human and veterinary practices selected for resistant pathogens and led to their emergence and dissemination along with the transmission of resistant bacteria. The aim of this article is to prescribe the prerequisites for the surveillance of antibiotic use and bacterial resistance, to explain advantage and disadvantage of surveillance parameters used, to present new data from a surveillance network of intensive care units focusing on antibiotic use and resistance and to discuss the impact of antibiotic use on resistance.

The Surveillance System of Antibiotic Use and Bacterial Resistance in Intensive Care Units (SARI) is an on-going project that collects data from its network of intensive care units (ICU) in Germany. Antimicrobial use was expressed as daily defined doses (DDD) and normalized per 1000 patient-days (pd). ICU decided either to provide monthly data on antibiotic and resistant pathogens or they decided to provide only yearly data on antibiotic use without resistance data.

85% of all antibiotics used in Germany are administered in animals; 85% of the antibiotics used in humans are prescribed in the outpatient setting and 85% of the antibiotics used in hospitals are prescribed on non-ICUs wards. The mostly widely used parameter for the surveillance of resistance is the percentage of resistant pathogens which is important to guide empirical therapy but does not measure the burden of resistance which is of interest to the public health perspective. The burden of MRSA did not increase over the last 11 years in ICUs and was 4.2 MRSA/1000 pd in 2011. The burden of 3rd generation resistant *E. coli* and *K. pneumoniae* more than quintupled (up to 2.6 and 1.2 respectively) and was followed by a three times increased use of carbapenems and correlated with quinolone and 3rd generation cephalosporin use. The burden VRE *faecium* also increased dramatically from 0.1 to 0.8 within 11 years; VRE *faecium* showed no significant correlation to vancomycin use ($p = 0.190$) although glycopeptide use increased lately.

Antibiotic use in animals and humans correlates with the risk of resistant microorganisms in a multifactor and complex way; it is of upmost importance that surveillance and interventions focus on all sectors: animal use and in- and outpatient setting in humans.

Introduction

Antibiotic resistance is now considered as one of the top health challenges facing the 21st century and called the World Health Organization (WHO) into action. The WHO focused their strategy in 2012 on the five most important areas for the control of antibiotic resistance, which are: surveillance, rational use in humans, rational use in animals, infection prevention and control, and innovation.

The use of antibiotics – including the over- and misuse – in human and veterinary practices selected for resistant pathogens and led to their emergence and dissemination along with the transmission of resistant bacteria (Marshall et al., 2012).

However, the threat of antimicrobial resistance became virulent only in the last decades, i.e. some decades after the discovery and use of antibiotics in the beginning of the 20th century when antibiotics lost increasingly their effectiveness.

If nothing else, antibiotic resistance is an ancient and naturally occurring phenomenon: recently 30,000-year old genes encoding resistance to ß-lactams, vancomycin and tetracycline were collected from permafrost sediments in the North of Canada (D'Costa et al., 2011).

Soil is generally one of the largest and most diverse microbial habitats on earth and is a natural habitat for Streptomyces, whose species account for the majority of all naturally produced antibiotics (Forsberg et al., 2012). Soil is now recognized as a vast repository of antibiotic resistance genes (resistom) with evidence of recent exchange between soil bacteria and clinical pathogens (Forsberg et al., 2012). Direct exchange between soil microbes and

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human pathogens or indirect transfer via reservoirs such as the human intestinal microbiota is hypothesized.

The aim of this article is describing the prerequisites for the surveillance of antibiotic use and bacterial resistance, to explain advantage and disadvantage of surveillance parameters used, to present new data from a surveillance network of intensive care units focusing on antibiotic use and resistance and to discuss the impact of antibiotic use on resistance in a more global context.

We will look for published data from the European Surveillance of Antimicrobial Consumption (ESAC) and new data from the Surveillance System of Antibiotic Use and Bacterial Resistance in Intensive Care Units (SARI) as examples.

Methods

ESAC. The European Surveillance of Antimicrobial Consumption (ESAC now ESAC-net) project collects data on antimicrobial consumption in ambulatory care and hospital settings in Europe. In 2008, 36 countries participated in ESAC. Data on antimicrobial use were aggregated at the level of the active substance and according to the anatomical therapeutic chemical (ATC) classification and the defined daily dose (DDD) measurement unit (WHO Collaborating Centre for Drug Statistics Methodology, 2012). The hospital and the outpatient antibiotic use, expressed in DDD were normalized per 1000 inhabitants per day. The number of inhabitants in the participating countries was based on the midyear population in the country. In our study, only countries were included which reported data of both hospital and outpatient use according to the ESAC protocol.

SARI. The Surveillance System of Antibiotic Use and Bacterial Resistance in Intensive Care Units (SARI) is an on-going project launched in 2000 that collects data from its network of intensive care units (ICU) in Germany. SARI focuses on the critically ill because antimicrobial use in ICUs is among the highest in the hospital. Monthly data on antimicrobial use were obtained from the computerized pharmacy databases and also expressed as daily defined doses (DDD) – but normalized per 1000 patient-days. ICU decided either to provide monthly data on antibiotic and resistant pathogens or they decided to provide only yearly data on antibiotic use without resistance data. Copy strains – defined as an isolate of the same species showing the same susceptibility pattern throughout the period of one month in the same patient, no matter what the site of isolation – were excluded. The method is described in more detail elsewhere (Meyer et al., 2010).

Following a pilot phase, we first analyzed data at the beginning of 2001. A total of 98 SARI-ICUs reported monthly or annually antibiotic use. 68 ICUs provided not only antibiotic use data but additionally unit-based resistance data.

Statistical analysis. In SARI, the proportion of resistant isolates (RP) was calculated by dividing the number of resistant isolates by the total number of the isolates of the same species tested against the corresponding antibiotic multiplied by 100. The incidence density of resistant isolates (RD) was defined as being the number of resistant isolates per 1000 patient days (pd). For association of annual antibiotic use and resistance, Spearman correlation coefficient (cc) was calculated. Trends over time of antibiotic use were determined by linear regression with the yearly data. Trends for RP were determined by the Chochrane Armitage test. Significance level was $p < 0.05$ and all analysis were performed using IBM SPSS Statistics version 19; and SAS 9.2, SAS Institute Inc., Cary, NC, USA.

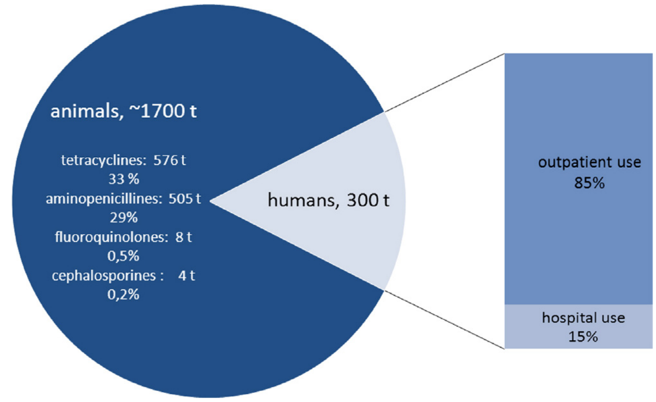

Fig. 1. Antibiotic use in tons per year, Germany. Antibiotic use data for humans from 2008 (GERMAP, 2008), from animals from 2011(Fleischatlas, 2013).

Results

Fig. 1 gives an overview how many tons of antibiotics are used per year in animals and humans in a Western European country (Germany). Of the total amount of antibiotics 85% are used in animals and 15% in humans (Fleischatlas, 2013; GERMAP, 2008) Animal use data from 2011 were published by the German ministry for consumer protection and food safety and outnumbered by far estimations by sales data retrieved from pharmaceutical companies (Fleischatlas, 2013). In the outpatient use in humans, amoxicillin was the most frequently prescribed agent and accounted for 80 tons, other betalactams for 35 tons and flouroquinolones for 25 tons (GERMAP, 2008). The majority (85%) of the antibiotics used in humans are administered in the outpatient setting and only 15% in hospitals (GERMAP, 2008).

These data give a rough impression on the extent of the antibiotic selective pressure in different areas of usage. Further conclusions will need a more detailed analysis with respect to classes of antibiotics and to indicator substances, and finally to daily dosages.

Furthermore, for matters of comparison denominator data are needed. Outpatient antibiotic use data are usually obtained by

Table 1
Measures for surveillance or report of antibiotic use in hospitals and bacterial resistance.

Measure	Advantage	Disadvantage
Antibiotic use		
In defined daily doses (DDD) (Methodology)	Internationally comparable	Often overestimates antibiotic use
In prescribed daily doses (PDD)	Reflect the usually prescribed dose	Lack of standardization
Patient days with antibiotic(s) per 100 pd	Monitors selection density over time	No information of intensity of use
Patient days with antibiotic(s) per 100 admissions	Estimates antibiotic selection pressure	No information of individual patients exposed
Proportion of patients on antibiotics	Percentage of exposed individuals	Correlation with resistance parameters not widely studied
Resistance (Schwaber et al., 2004) (without copy strains)		
Proportion (% resistance)	Useful for direction of empirical therapy; easy to collect	No conclusions can be drawn concerning how many patients with resistant pathogens
Incidence density of resistant isolates – number of resistant pathogens per 1000 pd	Accounts for occupancy	Does not account for turnover
Rate – number of resistant pathogens per hospital admission	Easy to interpret; accounts for turnover	Does not account for occupancy