ORIGINAL ARTICLE

Global development of resistance

– secondary publication

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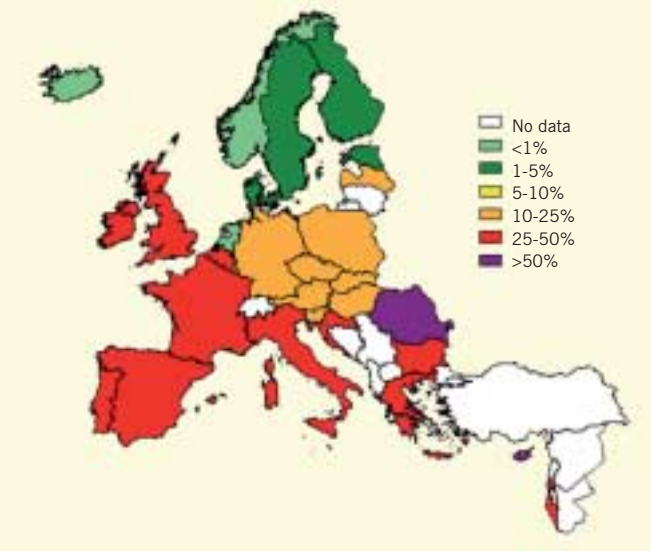
ABSTRACT

Antibiotic resistance is an increasing problem world wide, although in some areas the increase in resistance is slow, as in the Nordic countries. Multi-resistant staphylococci, *Enterobacteriaceae* and *Mycobacterium tuberculosis* are already causing increased morbidity, mortality and huge costs in health budgets. New effective antibiotics will not be available for the next 10-15 years, since the pharmaceutical industry has lost interest in antibiotics. The major determinant in this field, in order to save the activity of the known antibiotics, is the control of antibiotic use.

The frequency of resistance towards all important antibiotics in most human pathogenic bacteria is increasing world wide, however, at varying pace in different parts of the world. The largest increases outside Europe are being reported from Asia, South America and Africa and for some bacteria also from North America. In Europe an increasing gradient is obvious in direction from the north to the south, i.e. low resistance prevalences occur in the Nordic countries and the Netherlands while the frequencies of resistance reported from the southern European countries rank in the same order as those reported from high prevalence Third World countries.

Table 1 shows the frequency of resistance for selected antibiotics and important human pathogens in different parts of the World including countries which are often visited by Danish tourists. Thus, Denmark and Germany generally report low frequencies of resistance excepting ampicillin resistance in *Escherichia coli* and gentamicin high level resistance in enterococci. In addition, endemics and epidemics with multi-resistant bacteria are becoming increasingly common both in- and outside hospitals.

Methicillin-resistant *Staphylococcus aureus* (MRSA) which are often multi-resistant as well, have been almost absent in the Nordic countries for 30 years, while being prevalent in the rest of Europe (Figure 1 [1]). During the last 3-4 years, however, MRSA have increased epidemically in Scandinavia now occurring at the same prevalence in the community as in hospitals.



Figur 1. Percent methicillin resistant *Staphylococcus aureus* (MRSA) among *S. aureus* isolates from blood, Europe, 2005 [1].

Multi resistant tuberculosis is a problem in neighbouring countries such as the Baltic countries and Russia, but increasing problems are encountered in the USA as well.

Another worrying development is the rapidly increasing prevalence of the so-called *extended spectrum beta-lactamases* (ESBL) and metallobeta-lactamases in *Enterobacteriaceae* and *Pseudomonas* spp leading to resistance against older and newer penicillins and cephalosporins including the third generation cephalosporins (ceftazidime, cefotaxime and ceftriaxone), monobactams (aztreonam) and – as to the latter enzymes – also carbapenems. These broad-spectrum beta-lactamases are typically transferred easily by plasmids, and the bacteria often show co-resistance to fluoroquinolones and aminoglycosides.

There have lately been reports even on infections caused by pan-resistant *Enterobacteriaceae* with resistance against all known therapeutic antibiotics [2].

Antibiotic resistance leads to increased costs of treatment, increased morbidity as well as increased mortality [3]. Treatment of acute serious infections is based on empiric principles, i.e. the choice of antibiotics rests upon the experience from previous infections and the susceptibility of the pathogens involved. Increasing resistance leads to the choice of antibiotics with still broader spectrum, which again creates more resistant microorganims, a "circulus vitiosus" of resistance.

NEW ANTIBIOTICS?

During the 1960's and 1970's the development in the antibiotic field

Table 1. Percent resistance among invasive isolates (blood and spinal fluid) of frequent human pathogens in various countries in 2000-2004.

		Country								
Bacteria	**Resistance**	**Denmark**	**Germany**	**Spain**	**Greece**	**USA**	**Turkey**	**Egypt**	**Tunesia**	**Thailand**
Staphylococcus aureus	Methicillin-R (MRSA)	1	19	27	44	47	40	50	18	34
Streptococcus pneumoniae	Penicillin-R/I	3	1	29	18	33	22	27	44	54
	Macrolide-R/I	5	13	27	30	28	9	22	33	42
Escherichia coli	Aminopenicillin-R	30-50	55	60	46	–	68	73	66	–
	Aminoglycoside-R	2	4	8	6	2-9	28	58	21	–
	Fluoroquinolone-R	3	24	25	12	21	43	31	15	–
Enterococcus faecium	Aminoglycoside-R, high	61	61	17	52	–	59	–	64	–
	Vancomycin-R	1	11	2	20	72	3	–	0	–

R: resistant; R/I: resistant or intermediary.

could keep track of the development of resistance, and few worried about a future without effective antimicrobials. While the antibiotic market was extremely lucrative at that time, the trend after the 1990's has shown decreasing interest in this market due to falling profits for the pharmaceutical industry. Several of the leading companies have closed down their antiinfective research laboratories and have left the area for more profitable markets. Therefore, the supply line has been dwindling resulting in very few new effective antibiotics especially for the treatment of multi-resistant Gram-negative pathogens. Since 2004 the Food and Drug Administration in the USA has filed only five new antibiotics for registration, and four of these belong to already known classes of antibiotics [4].

New antibiotics are fundamental to our ability to treat the approaching multi-restistant pathogens, why there is an urgent need to focus upon how we can help or influence the pharmaceutical industry. Extending the duration of the patent on the compounds has been mentioned as one approach to help the companies retain their investment. A multitude of smaller companies showing interest in the antibiotic field has evolved. The problem for this type of industry is the huge investments needed to conduct the toxicity studies and clinical efficacy studies prior to registration of drugs, which may prevent such companies from following otherwise interesting leads. Perhaps society should step in and take over financial responsibilities at least in areas of life-saving drugs. The so-called *orphan drug* programmes are such examples of legislation easing the way for drugs through the registration process, if there is an urgent need for the compounds. The development of resistance being so closely related to the use of antibiotics, society cannot let mere profit rule the development of the antibiotic market but has to invest in the pharmaceutical industry, which can produce cheap narrow-spectrum drugs.

MONITORING ANTIBIOTIC RESISTANCE AND ANTIBIOTIC CONSUMPTION

Since no new drugs seem to be appearing it is even more important to secure the effect of the antibiotics, that we already have. No one – or only a few – doubt the causal relationship between the use of antibiotics and development of antibiotic resistance. In order to reduce or prevent antibiotic resistance it is therefore mandatory to know the level of antibiotic resistance in all important pathogens as well as the detailed consumption of antibiotics. Fortunately, the microbiological expertise has improved considerably during the last 20 years and now an increasing number of countries including Third World countries publicise – either via scientific journals or as parts of international monitoring programmes – details on frequencies of resistance in human pathogenic bacteria. The high levels of resistance reported from some Third World countries may be alarming, but they can also be viewed as positive signs of technical skills as well as increasing awareness of the problem.

The European countries have via EU research funding achieved the best resistance monitoring programme the European Antimicrobial Resistance Surveillance System (EARSS) [1]. Figure 1 illustrates one type of reporting from the EARSS. The European Surveillance of Antimicrobial Consumption (ESAC)-programme [5, www.ua.ac.be/esac/] is another EU-funded initiative with the purpose of collecting and reporting data on human antibiotic consumption in the EU member states, which is crucial in order to enable comparison among countries and provode benchmarking for countries outside the EU [5].

With a few exceptions, there is a huge and regrettable gap in our knowledge of the level and type of antibiotic consumption in countries outside the EU. Very few countries outside Scandinavia publish data on antibiotic consumption and resistance of production animals or pets. Denmark may be at the forefront of antibiotic monitoring in the veterinary field with the so-called VET-STAT programme [6]. The discussion continues to rage as to which degree humans obtain resistant bacteria or resistance genes from animals. While there is little doubt about this relationship as to classical zoonotic bacteria such as *Salmonella* and *Campylobacter*, the role of *E. coli* is under continued scrutiny.

WHAT CAN BE DONE?

In order to influence levels of antibiotic resistance it is necessary to have constant access to current data on antibiotic resistance and consumption at the local level. “Local” can mean department, hospital, county or country. Furthermore, antibiotic use must be controlled. How this control is enacted depends on a range of factors. The low frequencies of antibiotic resistance seen in the Scandinavian countries are the result of an early, i.e. already in the 1950's, understanding and focusing both from central health authorities and on the local hospital level on the importance of antibiotic consumption for development of resistance. Of crucial importance was the acceptance of clinical microbiology as a medical speciality and establishment of decentralised clinical microbiology laboratories in all countries. Further decentralisation was pursued by inducing via financial incitements the general practioners to conduct simple microbiological diagnostic procedures e.g. microscopy, culture and susceptibility testing of urine, rapid antigen-test for *Streptococcus* pyogenes etc.

The concept of prudent use of antibiotics has been lacking in the scientific medical literature. Figure 2 illustrates this fact by showing the number of hits over time in PubMed of various surrogate markers for antibiotic resistance and use. As shown in the figure one can since the advent of penicillin find over 40,000 hits on use of antibiotics, more than 10,000 hits on antibiotic resistance, while search for papers on the combined issue of antibiotic use and antibiotic resistance results in less than 400 hits. The term “antibiotic misuse” returns less than 500 hits in the same time period (not shown in the figure).

In 1998 Denmark hosted a first EU conference, The Microbial Threat, focusing on the increasing problems with antibiotic resistance [3]. The resulting Copenhagen Recommendations formed the platform for a range of initiatives in the EU including commissionary recommendations [7], guidelines, monitoring programmes and funding of research. The World Health Organization (WHO) and other international organisations have followed up with similar recommendations and guidelines [8-10]. Whether these initiatives have lead to more prudent use of antibiotics especially in countries with

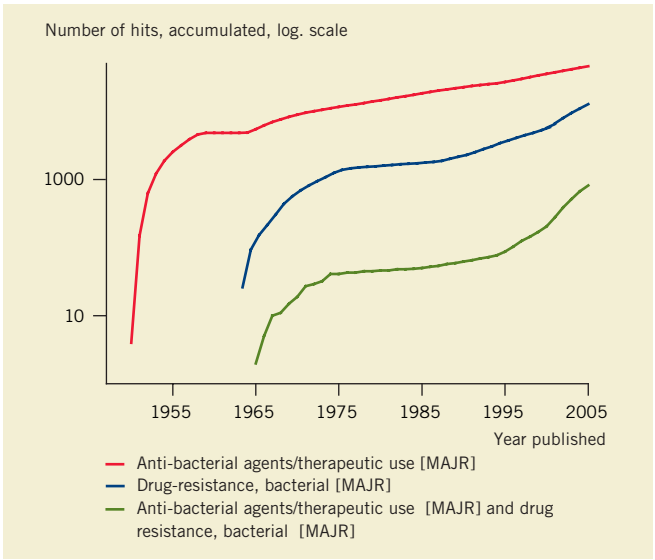


Figure 2. Number of hits found in MEDLINE/PubMed at www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed. Each of the three queries were performed for each of the years from 1947 to 2005. Queries were limited using Major Topic headings, which means that only articles in which the mentioned Medical Subject Headings term/subheading were one of the main points discussed are included. All queries were performed on 2006.04.28. The ordinate is logarithmic. More information on Medical Subject Headings is found at www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh.

high antibiotic consumption is a question of some urgency. Even in Denmark, a low consumption country, the antibiotic consumption increased around 20% from 1997 to 2005. Among several reasons are increased doses, increased activity in the hospital system with more surgical procedures requiring more antibiotics for prophylaxis, higher prevalences of nosocomial infections to mention a few. Although a monitoring programme is running in this country we still need to improve the methods how we translate the survey data to intervention.

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